The role of an extended Self-Regulatory Model in predicting adherence to Highly Active Anti-Retroviral Therapy (HAART) among adults with HIV-infection

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A thesis submitted in partial fulfilment of the requirements of the University of Brighton for the degree of Doctor of Philosophy

July 2004

University of Brighton

ABSTRACT

The success of Highly Active Anti-Retroviral Therapy (HAART) requires a high rate of adherence to a complex regimen. Even small variations in adherence compromise treatment efficacy and can lead to viral resistance. Low levels of adherence to HAART continue to pose a major barrier to the success of these treatments. Studies investigating adherence to HAART have focused on practical barriers, yet studies in other illness groups suggest that patients' perceptions of their illness and treatment have a strong influence.

This thesis is concerned with furthering our understanding of non-adherence to HAART. It begins with a review of HIV and its treatment. A critical review of the literature was conducted using systematic techniques. This identifies outstanding questions relating to the antecedents of adherence to HAART.

The aim of this investigation was primarily to test the Self-Regulatory Model (SRM) and extensions to it to incorporate treatment perceptions (perceptions of personal necessity for HAART and concerns about adverse effects) in predicting adherence to HAART.

Consecutive patients were recruited from HIV clinics in Brighton. A prospective, longitudinal design was employed, using validated questionnaires to explore the impact of patients' perceptions of HIV and HAART on adherence. The empirical section of this investigation comprised three studies. Study 1 explored the influence of patients' perceptions of HIV and HAART, elicited before initiating treatment, on subsequent adherence. Study 2 explored the ways in which patients' appraisals of their symptom experiences impacted on adherence. Study 3 explored how perceptions of HIV and HAART changed over the treatment process, and the relationships between these changes and adherence.

The results provide support for the utility of an extended Self-Regulatory Model in predicting adherence to HAART. Patients' initial perceptions of HIV and HAART predicted subsequent adherence. Furthermore, beliefs about HAART were related to perceptions of HIV in a way that is broadly consistent with the extended SRM. Beliefs about HAART changed dramatically once patients had initiated their treatment. There was a sharp decrease in the strength of patients' concerns about adverse effects of HAART. Perceived necessity for HAART was initially high but decreased over time. Experiencing a decline in necessity was associated with low adherence. Consistent with an extended SRM, patients used their symptom experiences to appraise their treatment. Those whose symptoms did not improve over time reported low adherence. Perceived necessity for HAART mediated the relationship between symptom experiences and adherence.

The findings are discussed in relation to the development of interventions to support adherence to HAART.

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ACKNOWLEDGMENTS

Thanks primarily to my supervisors, Professors Rob Horne and John Weinman. Thanks to Rob for giving me the opportunity to run such an interesting and rewarding research project and for his invaluable feedback, support and advice over the process. Thanks for giving me the confidence to present and encouraging me to write from the outset, and for introducing me to the wider research community within the fields of HIV and Health Psychology. Thanks to John for his invaluable feedback and advice.

Thanks to my colleagues and friends who have been great company and made me laugh over the past four years: Jane Clatworthy for friendship, food, formatting, entertainment, advice and for keeping me company by working similar long hours in 'the field', Grace Gellaitry for invaluable help with the study, keeping me enthusiastic and motivated, and for being a great friend, Susanne Hughes for her realistic and humorous approach, Jennie Brierley, Cara Davis, David Claxton, Natalie Lambert, and Keri Peters for their work on the study, Matthew Hankins for his excellent statistics advice, Lida Graupner and Kate Perry for proof-reading and helpful suggestions.

I'm grateful to Martin Fisher for access to patients at the Lawson Unit and Elton John Centre, for his constant interest and useful advice, and to all the doctors who referred patients to the study and who maintained their interest over the years. Thanks to Heather Leake-Date for her help and interest in the study and to Claire Smyth for allowing me access to pharmacy records, keeping me up to date with new drugs and trials, and for introducing me to patients. Thanks to David Johnson for going out of his way to help and to Eddie Knibbs, Vanessa Simmons and all the other Lawson Unit and Elton John Centre Staff for making me welcome.

Thanks to Perry French at THT South and Rob Davis at Social Services for their advice and interest, and to Brighton Body Positive for allowing me to conduct the pilot study on their premises.

Special thanks to the participants, who freely gave their time to fill in questionnaires and share their experiences, and whose input kept me motivated.

Thanks to my mum, grandparents and sister who have been incredibly supportive in many ways and who have been a gentle source of motivation to finish. Thanks to Rob W for listening, being understanding and for looking after Lucas while I worked, and to Lucas for being a lovely baby, who slept for large chunks of time in the office. Thanks finally to my friends, especially Sarah, Bee and Simon, for entertainment and encouragement.

Chapter 1
HISTORY AND EPIDEMIOLOGY OF HIV

1.1 History of HIV

A series of events in the early 1980s led to the discovery of a new disease. In 1981, reports described a constellation of unusual infections among young, previously healthy gay men in the USA. In the spring, a drug technician at the Centre for Disease Control (CDC) in the USA noted an unusual number of requests by doctors for a rarely used drug, Pentamidine, to treat Pneumonocytis Carinii Pneumonia (PCP; McGinn, 2001). This particularly virulent pneumonia was usually found in people with extremely weakened immune systems, yet reports later in the year identified several cases of PCP among young, gay men in Los Angeles and New York, who had no particular history of illness (Masur et al., 1981; Gottleib et al., 1981). Shortly afterwards, several cases of Karposi's Sarcoma, a form of cancer, were identified among the gay population in New York and California (Friedman-Kein, 1981; CDC, 1981b). Persistent, unexplained lymphadenopathy (enlarged lymph glands) was also noted (Masur et al., 1981; Gottleib et al., 1981; Friedman-Kein, 1981). Common to each of these patients was a distinct impairment of cellular immune response, resulting from a loss of 'T-helper' cells, with the CD4 marker (Masur et al., 1981; Gottleib et al., 1981).

The fact that these symptoms and diseases appeared to be found exclusively in gay men lead to suggestions that certain facets of a homosexual lifestyle (including the use of amyl nitrate or other recreational drugs, a high number of sexual partners, a preference for receptive anal intercourse, a history of sexually transmitted diseases or a combination of these factors) were accountable (Goedert et al., 1982; Sonnabend et al., 1983). As a result, the name 'GRID: Gay Related Immune Defiency' was coined to describe the syndrome. However, the theory was refuted and the name was changed to AIDS (Acquired Immune Deficiency Syndrome) when the syndrome was observed in other groups, including female partners of bisexual men, intravenous drug users, recipients of blood transfusions, people with haemophilia, and babies (CDC, 1982b,c,d,e,f; Poon et al., 1983). The clustering of AIDS cases in these groups could only be explained if the disease was caused by an infectious agent that was transmitted

through blood or blood products, by sexual contact or from mother to baby (CDC, 1982; Francis et al., 1983; Curran et al., 1984).

1.1.1 The discovery of HIV

Research into AIDS began to take off in 1983, when scientists at the Pasteur Institute in France lead by Luc Montagnier provided the first experimental evidence for an association between a retrovirus and AIDS (Barre-Sinoussi et al., 1983). This virus was named Lymphadenopathy-Associated Virus (LAV). In 1984, researchers at the National Cancer Institute in the USA identified a retrovirus: HTLV-III, which was isolated from a number of individuals with AIDS (Gallo et al., 1984). This virus was identical to LAV, and in 1986, the International Committee on the Taxonomy of Viruses ruled that both names should be dropped in favour of HIV (Human Immunodeficiency Virus).

In 1984, the first test for detecting antibodies to HIV was developed and licensed by the U.S. Food and Drug Administration. Testing revealed that only a small percentage of people with the virus had developed AIDS. However, since all patients with AIDS were found to carry antibodies to HIV, HIV was identified as the likely cause of AIDS (Gallo et al., 1984). These findings suggested that outcomes associated with HIV infection could be seen along a continuum, with asymptomatic disease at one endpoint and AIDS at the other.

1.2 Epidemiology of HIV

Although initially identified among gay men, by the mid 1980s, the spread of AIDS had begun to change. In New Jersey, USA, half of all cases reported were among intravenous drug users (IVDU), while in Los Angeles and New York, AIDS was reported predominately among gay men. Transmission in Africa was predominately through heterosexual contact. In Europe, epidemics occurred among gay men who had visited the USA, males and females who had visited Africa, people who had received treatment with blood products and intravenous drug users. By 1985, when heat treatment was implemented to inactivate the virus in blood products, most haemophilia patients with HIV had had their infections diagnosed. Since then the main routes of infection in the UK have been sex between men, heterosexual sex and

injecting drug use. The percentage of infections transmitted by IVDU has been much lower in the UK compared to many other European countries. While sex between men had been the dominant route of transmission in the UK, heterosexual exposure has been the major transmission risk since 1999, and accounted for 63% of new cases in 2002 (PHLS data, Health Protection agency, 2003).

Two distinct viruses (HIV-1 and HIV-2) have been found to cause AIDS. The vast majority of infections worldwide are caused by HIV-1. HIV-2 is more common in West Africa, with individual cases found thoughout the rest of Africa, Europe, North and South America and India. Most cases of HIV-2 have been linked to West Africa. These viruses have the same modes of transmission, although HIV-2 may be less easily spread than HIV-1 with a slower progression to AIDS (Grant & De Cook, 2001).

At the end of 2002, statistics from UNAIDS (Joint United Nations Programme on HIV/AIDS) and the World Health Organisation estimated that the number of people living with HIV/AIDS worldwide was 42 million. There were 5 million new cases of HIV infection and 3.1 million AIDS deaths in 2002. Since the start of the pandemic, 21.8 million people with AIDS have died. The major burden of the pandemic has been in the developing world, particularly Sub-Saharan Africa, South-East Asia and South America. Prevalence in several southern African countries now exceeds 30%. The impact of the HIV epidemic in Lesotho, Swaziland and Zimbabwe is so severe that current food crises have been linked to the toll of the HIV epidemic on the lives of young, productive adults. In 2002, there were sharp increases in the incidence of HIV in the Baltic states, the Russian Federation and several Central Asian republics. In vast, densely populated Asian countries such as China, India and Indonesia, low national prevalence rates mask serious localised epidemics that are affecting millions (UNAIDS/WHO, 2002).

Data to the end of 2002 show that there have been approximately 54,215 cases of HIV infection reported in the UK, with 19,167 diagnoses of AIDS. 12,544 (65%) of those diagnosed with AIDS have died, and a further 2455 have died without having been diagnosed

with an AIDS defining condition. The regions most affected are London and the South-East of England. There has been a gradual increase in new diagnoses of HIV reported each year since the mid 1990s, and 2001 saw the highest number of new infections since reporting began. However, there has been a dramatic decline in AIDS diagnoses and reported deaths from AIDS since the widespread use of Highly Active Anti-Retroviral Therapy (HAART) in 1997 (Health Protection Agency, 2003), although this trend has begun to level off over the last two years, perhaps due to poor adherence and the emergence of drug resistant strains of HIV Tthese issues are discussed in more detail later in this chapter.

1.3 Transmission and prevention of HIV

HIV has been detected in blood, semen, vaginal fluid, breast milk, saliva, tears, cerebrospinal fluid and peritoneal fluid. In some body fluids HIV is present in such small concentrations that it does not present a risk. The major routes of transmission are through sexual intercourse, sharing unsterilized needles or syringes, unscreened or untreated blood or blood products and vertical transmission inutero, during labour or through breast-feeding.

In the UK, major prevention efforts followed the discovery that HIV is transmitted through blood, semen and vaginal fluids. In 1986, the Government launched a campaign with the slogan 'don't die of ignorance'. Educational leaflets were sent to every household. In the USA, laws were passed banning immigrants and short-term visitors with HIV from entering the country. Needle exchanges were set up to curb the spread of HIV among intravenous drug users (IVDUs).

Despite the successes of early prevention efforts especially among the gay community, increases in levels of unsafe sex have been documented among men who have sex with men, and high risk behaviours, less frequent condom use and higher rates of sexually transmitted infections including gonorrhoea, syphilis and chlamidya have more than doubled in the UK since 1995 (UNAIDS/WHO, 2002).

1.4 Origins of HIV

The origins of HIV are unknown. One group of researchers claim that HIV-1 descends from the Simian Immune deficiency Virus (SIV) found in a species of chimpanzee in central Africa called Pan troglodytes trolglodytes (Gao et al., 1999). Researches in America, France and Japan have found a virus in these chimpanzees that combines elements of SIV with those of HIV. This virus does not appear to cause illness in the chimpanzees. HIV-2 has been isolated from macaques and sooty mangabeys. Researchers believe that these viruses have been present in primates for thousands of years and no longer harm them, however, when SIV crosses into other species, it causes illness.

Theories concerning the possible transmission from monkeys to humans include malaria experiments with blood transfusions (Gilks, 1991) and contaminated polio vaccines in the 1950s (Kyle, 1992). However, a recent report suggests that the crossover from monkeys to humans occurred during the 1930s, and that the virus subsequently mutated and led to HIV (Vandamme et al., 2000). The oldest confirmed case of HIV-1 was found in a plasma sample taken from an adult Bantu man in 1959, living in what is now the Democratic Republic of the Congo (Zhu et al., 1998). Available data suggest that the current pandemic started in the mid-to-late 1970s, and had spread to at least five continents (Africa, Australia, Europe, North America and South America) by 1980 (Mann, 1992).

1.5 Structure of HIV

Within the retrovirus family, HIV is classified as a lentivirus. Lentiviruses have also been identified in animals, including cats, primates, cows, goats, sheep and horses. They are also called 'slow viruses' because of the long intervals between initial infection and the onset of serious symptoms (Chiu et al., 1985). Lentiviruses primarily infect cells of the immune system and often cause immunodeficiency, neurodegeneration and death in their hosts (Haase, 1986). In common with all retroviruses, the genes of HIV are composed of RNA (ribonucleic acid) while human genes (along with those of most other organisms) are made of DNA (deoxyribonucleic acid). As viruses can only replicate within host cells using the cell's genetic equipment to reproduce, HIV enters the cell and uses an enzyme (reverse transcriptase) to

convert its RNA into DNA, which can then be incorporated into the genes within the human cell. In this way, the virus replicates itself thousands of times over, producing up to a million new virions each day (Perelson et al., 1996).

Figure 1.1: Structure of HIV

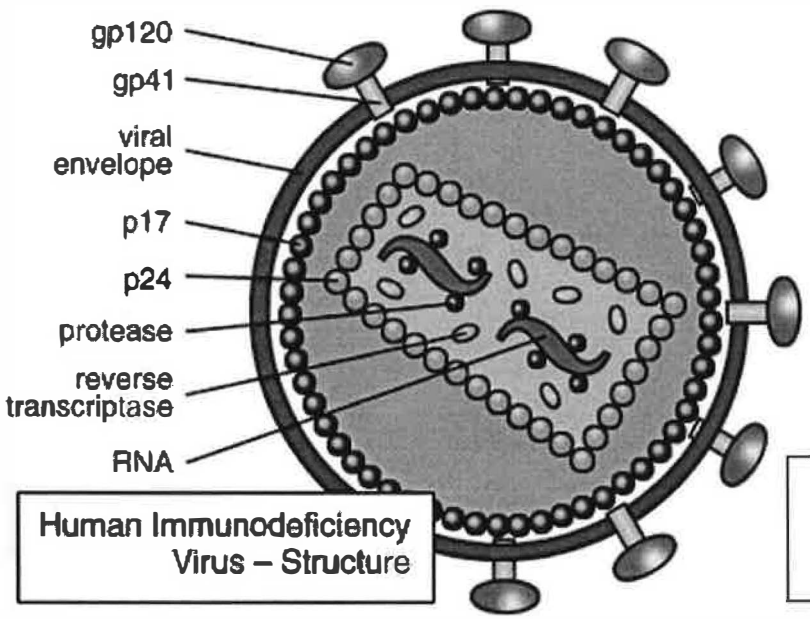


Photo credit: © AVERT
www.avert.org/virus.htm

1.6 Action of HIV

The GP120 receptor on the viral envelope attaches to the CD4 cell receptor on the human cell. Fusion then occurs and the virus deposits RNA. Once inside the cell, the viral envelope is removed by protease enzymes, leaving the viral core free in the cytoplasm of the cell. Here, HIV reverse transcriptase converts viral RNA to DNA. This DNA then moves to the cell nucleus, where HIV integrase helps incorporate the viral DNA into the host cell DNA. The activated cell copies DNA back to RNA by a process called transcription. This RNA, called messenger RNA (mRNA) is then transported to the cell's cytoplasm and makes the viral proteins of the HIV virus, using the mRNA as a template. This is translated into the RNA and proteins comprising the envelope and core of the virus. Viral protease then cuts the gene products of translation into those that make up the final virus. The virus can then 'bud' (Levy, 1993). Once free of the cell, the virus is infectious and can make thousands of infectious particles of HIV.

1.6.1 The impact of HIV on the immune system

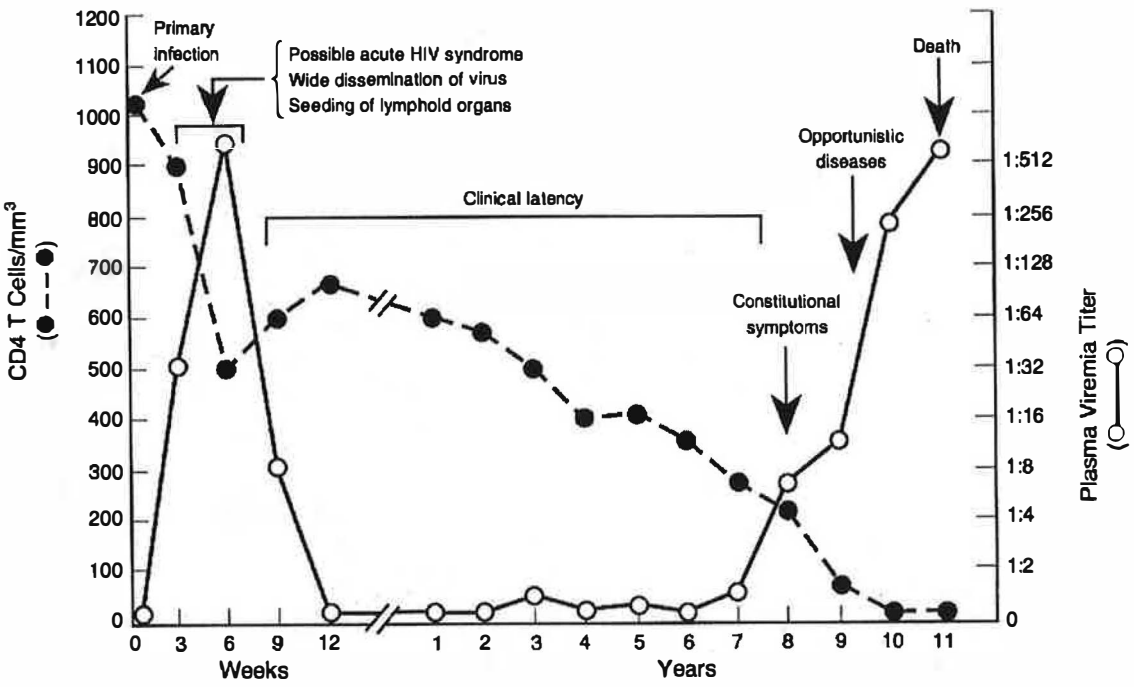
Because HIV infects cells expressing the CD4+ marker, disabling and destroying these immune cells, and decreasing the production of new cells, HIV infection is characterised by a gradual decline in the host's immune system (Fahey et al., 1990). The predominant targets of HIV are CD4+ T helper cells, however, the virus can enter any cells that have a CD4 receptor. These other cells, including the long-lived cells, monocytes and macrophages, can act as reservoirs of HIV (Ho, 1998). Most healthy individuals have a CD4 T-cell count between 800-1200 cells per mm3 of blood. When the number of CD4 cells drops below 500 cells per mm3 of blood, the individual may be susceptible to minor, non life-threatening conditions, such as cold sores, wart infections, and fungal infections. Under 200 CD4 cells per mm3 of blood, the individual becomes vulnerable to the serious opportunistic infections (including PCP, toxoplasmosis, cytomeglovirus infections, toxoplasmosis, chronic severe diarrhoea and wasting) and cancers (Karposi's Sarcoma (KS), invasive cervical cancer and lymphomas) that define AIDS (Pantaleo et al., 1993). The CDC devised a 3-stage clinical classification system for adolescents and adults. Clinical Category A refers to 'asymptomatic HIV infection' and includes acute HIV illness and persistent generalised lymphadenopathy (PGL), Category B 'symptomatic HIV infection' is defined by persistent HIV related symptoms such as bacterial infections and constitutional symptoms such as fever or diarrhoea, and Category C 'AIDS' consists of AIDS defining infections and cancers and wasting syndrome due to HIV (CDC December ,1992).

1.6.2 Progression of HIV

Following exposure to HIV, 50 – 90% of people experience symptoms, typically flu-like illness and a rash, and an illness called Acute Retroviral Syndrome which is non-specific but can include fever, sweats, malaise, myalgias, anorexia, nausea, diarrhoea, sore throat, stiff neck, headaches and light sensitivity. These symptoms can occur at any time between one and six weeks after exposure to the virus are due to the initial rapid replication of HIV, which produces a burst of virus affecting every lymph node. Medical examinations at this time show general swollen lymph nodes, and sometimes an enlarged liver and spleen. During this initial

infection the patient looses CD4 and CD8 cells rapidly. The CD4 count rebounds as the immune system strives to control the infection. However, this immunity is not enough to completely suppress the virus, probably due to reservoirs of HIV in the lymph nodes. After primary infection the clinical course of HIV is usually characterised by a prolonged period of latency, lasting an average of six years. Although clinically latent (the patient may not experience symptoms) the vast majority of patients show a gradual depletion of CD4 T-helper cells over this time, showing that there is activity at a micorobiological level. Clinically apparent disease and AIDS defining illness typically follow the latent period.

Figure 1.2: Typical Course of HIV Infection (Pantaleo et al., 1993)



Individuals differ in the speed at which their HIV infection progresses. This was demonstrated early on in studies of Hepititis B transmission. Of over 6000 homosexual and bisexual men recruited to the studies, 341 retrospectively tested positive for HIV. While 81% of those developed symptomatic HIV infection or died over the following eleven years, the remainder stayed asymptomatic. Half of those who did not progress retained CD4 counts of over 500 (Rutherford et al., 1990). Those remaining asymptomatic with CD4 counts over 500 for a

number of years have been termed 'long term survivors' or 'long-term non-progressors.' The reasons for long-term non-progression have not yet been clarified.

1.7 Detection of HIV

HIV is diagnosed by the detection of antibodies to the virus. Antibodies are detectable from three to twelve weeks following infection. The standard screening test uses an enzyme linked immunosorbent assay (ELISA). These antibody tests have been in widespread use since 1985. Since then, the tests have been improved and are usually confirmed using a second ELISA test. More recently, ELISA testing has been combined with p24 antigen detection tests, which detect the HIV virus itself. However, p24 antigen tests are insufficient as a single test, as there are times at which the HIV antigens may be undetectable.

1.8 Surveillance of disease progression

Because the majority of people infected with HIV experience few or no symptoms for a number of years after initial infection, surrogate markers of disease progression are frequently monitored in order to track the progression of disease, estimate vulnerability to infection and guide treatment decisions. These tests primarily include the viral load test and CD4 count.

The viral load test was developed in 1996, to measure the concentration of HIV ribonucleic acid (RNA) in the plasma. These tests can detect to a lower limit of 50 copies of HIV per ml, therefore a viral load reading of below 50 is termed 'undetectable'. Viral load has been found to correlate with prognosis, where a high viral load predicts a poor outcome, while clinical benefit is derived from a reduction in viral load after initiation of antiretroviral treatment. A reduction in viral load leads to an increase in CD4 cell count, with the greatest changes seen in those with sustained viral load reduction to undetectable levels (Staszewski et al., 1999). Data from pharmaceutical trials suggest that changes in HIV plasma viremia explain the major part of treatment benefit (O'Brien et al., 1996). For patients who are taking antiretroviral therapy, viral load tests are frequently carried out in order to determine the efficacy of treatment. The aim of antiretroviral therapy is to reduce the viral load to undetectable. After six months of treatment, patients who do not achieve an undetectable viral load, and those

whose viral load rebounds from below 50 and becomes sustained above 50 are said to be experiencing 'virological failure'.

The level of immunosuppression is measured using the CD4 count, which measures the number of CD4 lymphocytes present in the patients' peripheral blood. While the normal range varies between 500-1200 cells/μl, patients with HIV infection usually become susceptible to particular infections at predictable CD4 counts. The CD4 count has been found to be a better indicator of the risk of developing AIDS defining conditions than viral load (Miller et al., 2000).

1.9 Treatment of HIV

The first effective anti-retroviral treatments were introduced following the discovery that HIV was the aetiological agent of AIDS (Barre-Sinoussi et al., 1983, Gallo et al., 1984). In 1987, zidovudine (AZT) was approved and became widely available (Fischl et al., 1987). AZT was the first of a class of antiretroviral agents called nucleoside analogues (NARTIs) to be used in the treatment of HIV and AIDS.

A clinical trial showed that AZT increased CD4 counts and improved survival when compared to placebo in a group of highly immunocompromised patients with advanced HIV disease and AIDS (Fischl et al., 1987). However, the Concorde trial (Concorde Co-ordinating Committee, 1994) reported no sustained difference in survival or disease progression between groups of assymptomatic patients administered AZT or placebo. The development of additional nucleoside analogues, including ddi (didanasone), d4t (stavudine), ddC (zalcitabine) and 3TC (lamivudine) gave clinicians more options in treating patients who developed resistance or who were intolerant to AZT. Switching to ddI (Kahn et al, 1992) or stavuidine (Spruance et al., 1997) often benefited AZT experienced patients. As a result, early management of HIV often consisted of a series of single agents, in high doses. However, the clinical benefits of monotherapy were limited and transient, while side effects were diverse and sometimes severe. It soon became clear that the benefits of monotherapies were short-lived and seriously hindered by the ability of HIV to develop 'resistance' to single antiretroviral therapies. Viral resistance has been defined as 'any increase in the ability of the virus to grow

in the presence of the antiretroviral drug' (Gulick, 1997). Up until the mid 1990s, treatment options for HIV remained limited.

The Delta trial (1996) compared DDI and AZT, and DDC and AZT, to AZT monotherapy. AZT in combination with another agent was found to reap greater benefits, especially among patients who had had no prior antiretroviral treatment. Side effects were no more severe than with monotherapy (Hammer et al., 1996). This research suggested that effective treatment was achieved by using combinations of two antiretroviral agents and by earlier intervention. However, the efficacy of these dual therapies was also found to be transient.

1.9.1 The emergence of combination therapy or Highly Active Antiretoviral Therapy (HAART)

The increase in quality of life and rates of survival for people with HIV in resource rich countries was accelerated by the introduction of protease inhibitors. Studies showed that adding protease inhibitors to nucleoside analogue antiretroviral therapy resulted in significant decreases in plasma viremia, and was associated with distinct clinical improvement and increased survival for people infected with HIV (Deeks et al, 1997). A combination including saquinavir, AZT and ddC demonstrated modest superiority over controls of either AZT and saquinavir or AZT and ddC, however the clinical effectiveness was found to be temporary due to the limited bio-availability of saquinavir in its initial formulation (Collier et al., 1996). Using a combination of indinavir, AZT and 3TC, 80% of a group of antiretroviral-experienced patients experienced a reduction in viral load to undetectable for over a year (Gulick et al., 1997). A large clinical trial demonstrated a 50% reduction in progression to AIDS and death among anti-retroviral experienced patients with advanced HIV disease who added Ritonavir to their existing nucleoside analogue regimen (Cameron et al., 1996), while significant clinical effects were also demonstrated among antiretroviral-naïve patients receiving nelfinavir, AZT and 3TC (Hammer et al., 1997). On the basis of these and other studies, combinations containing at least three agents from at least two different classes of drugs were recommended for the treatment of HIV infection. Combinations of three or more drugs became known as combination therapy or Highly Active Antiretroviral Therapy (HAART).

1.9.2 Types of antiretroviral drugs

Currently there are 18 antiretrovial drugs in clinical use in the UK (see Table 1.2). These drugs fall into five classes: nucleoside analogues (NARTIs), nucleotide analogues (NtRTIs), protease inhibitors (PIs), non-nucleoside reverse transcriptase Inhibitors (NNRTIs), and fusion inhibitors (FIs).

1.9.2.1 Nucleoside analogue reverse transcriptase inhibitors (NARTIs)

Abacavir, Didanosine (ddI), Lamivudine (3TC), Stavudine (d4T) Zalcitabine (ddC), Zidovudine (AZT), and combinations of 2 or more drugs Combivir (AZT, 3TC) and Trizivir (AZT, 3TC, Abacavir) belong to a class of drugs called nucleoside analogue reverse transcriptase inhibitors (NARTIs). Most patients starting therapy will have at least two of these drugs in their regime. Inside the cell the drug is phosphorylated into its active form, and works by inhibiting the viral reverse transcriptase enzyme, which is essential to the process of viral replication. Thus, these drugs prevent the virus from converting its viral RNA into the DNA needed to replicate within the human cell. Side effects differ between individual agents but include headache, diarrhoea, nausea, tiredness, anaemia, myopathy and peripheral neuropathy. More severe conditions include lactic acidosis, pancreatitis, liver problems and a hypersensitivity reaction to abacavir. Most NARTIs do not carry food restrictions, with the exception of ddI, which should be taken on an empty stomach.

1.9.2.2 Nucleotide analogue reverse transcriptase inhibitors (NtRTIs)

Tenovavir is a relatively new drug that has been approved for treatment-experienced adults in the UK. It belongs to the nucleotide analogue group of drugs, which, like the nucleoside analogues, inhibit the enzyme reverse transcriptase, which is essential to the process of viral replication. The advantage of NtRTIs over NARTIs is that they contain extra phosphate, which means they do not have to be phosphylated inside the cell, and hence are present in a more active form that may be active in more types of cells within the human body. Tenofavir should be taken with food to increase absorption. Common side effects include diarrhoea and nausea. Longer term toxicities have not yet been established.

1.9.2.3 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Nevirapine was the first non-nucleoside reverse transcriptase inhibitors (NNRTI) class to be licensed by the FDA in America in 1996. The licensing of Effavirenz (Sustiva) followed. NNRTIs bind to the active site of the reverse transcriptase enzyme, blocking it and thereby inhibiting its action. Because they are able to act upon cell-free virions as well as infected cells, these drugs are useful in post-exposure prophylaxis combinations, or to prevent vertical transmission from mother to child. NNRTIs are considered to be easy to use because they do not carry food restrictions. They are recommended in UK guidelines for use in first line therapy for treatment naïve patients (BHIVA, 2001), but are hampered by their resistance profile, whereby resistance can develop quickly and usually extends to all drugs within this class (Davies et al., 2001). Common side effects are also quick to appear, these include psychological effects, insomnia, vivid dreams, depression and suicidal thoughts, dizziness, diarrhoea and headaches associated with effavirenz, and skin rash, fatigue, liver problems, muscle pain and depression associated with nevirapine.

1.9.2.4 Protease Inhibitors (PIs)

Protease inhibitors (PIs) prevent the maturation of newly produced virions by binding to the active site of the HIV-1 protease enzyme. They work by preventing protease from cutting long chains of protein into the shorter chains that HIV needs to manufacture new virus particles. This prevents these virions from infecting other cells. Protease inhibitors currently in use include Amprenavir, Indinavir, Lopenavir/Ritonavir (Kaletra), Nelfinavir, Ritonavir and Saquinavir. The main drawbacks of PIs are the number of doses currently required per day and the need to adhere to food restrictions. Side effects are also common and include diarrhoea, vomiting, nausea, stomach pain, kidney stones, dry lips and skin, weakness and taste abnormalities and fatigue. Long term metabolic conditions such as lipodystrophy and diabetes are frequently experienced by patients taking PI-based combinations.

1.9.2.5 Fusion Inhibitors (FIs)

T20 (enfuvirtide) is the first of a new class of drugs called fusion inhibitors. These drugs bind onto the gp41 protein on the surface of the HIV, preventing the virus from binding to and entering human cells. T20 is currently recommended only for treatment experienced patients. Because the drug is readily broken down by the digestive system it is only available in an injection form, requiring patients to prepare and inject the drug sub-cutaneously twice a day. Injection site reactions are the most commonly reported side effects to T20. Decreased appetite, vomiting, nausea, diarrhoea, peripheral neuropathy have also been associated with the drug (Lalezari et al., 2003). Longer-term toxicities are not yet known.

1.9.3 Aims of HAART

The goal of antiretroviral therapy is to reduce the amount of replicating virus in the body for as long as possible in order to improve immunity and thereby increase the quality and duration of life (BHIVA treatment guidelines, 2001). By reducing the amount of replicating virus, antiretroviral treatment prevents the virus from infecting further immune cells and allows the immune system to rebuild itself.

1.9.4 Effectiveness of HAART

There is overwhelming evidence that the dramatic decrease in AIDS related mortality and opportunistic infections in countries where antiretroviral treatment is available is associated with the advent of HAART. Results from EuroSIDA, a prospective European, multicentre cohort study of 4270 HIV positive patients from 1994-1998, showed that the death rate for patients who were not taking antiretroviral treatment was 65.4 per 100 person years of follow-up, compared to 7.5 per 100 person years of follow-up for those taking dual therapy and 3.4 per 100 person years of follow-up for patients taking HAART (Mocroft et al., 1998). These findings were paralleled in a US study of 1255 patients, which found mortality declined from 29.4 per 100 person years in 1995 to 8.8 per 100 in 1997. Furthermore, the incidence of opportunistic infections declined from 21.9 per 100 person years to 3.7 per 100 person years. Combination therapy, especially with the inclusion of protease inhibitors, was associated with greater benefit (Palella et al., 1998). A sharp decline in the incidence of opportunistic

infections, including oesophageal candidiasis, cytomeglovirus disease, Karposi's Sarcoma, lymphoma, wasting syndrome and PCP was noted amongst patients attending a London clinic between 1987-1998 (Mocroft et al., 1999). A study conducted among 2,466 patients in the USA between 1996-1997 also demonstrated an improvement in the mental health of HIV positive patients, even those who are not taking antiretroviral treatment, a finding that the authors attribute to 'optimism about the future and quality of life' (Chan et al., 2003).

1.9.5 Access to treatment

It should be noted that there are enormous inequalities in access to HAART. While HAART is available to all patients who need it in the UK, in the developing world, currently less than 5% of people who are estimated to need treatment have access to antiretroviral drugs. WHO figures show that 230,000 people in the developing world receive antiretroviral treatment, half of whom are concentrated in Brazil. In Africa, where HIV has hit hardest, less than 2% of those who need treatment have access to it (WHO, 2002).

1.9.6 When to start therapy

Not all patients with HIV are recommended treatment with HAART. Treatment recommendations are usually made on the basis of symptomatic disease or AIDS, or on the basis of surrogate markers of disease progression for those who are asymptomatic. Early treatment may be offered to those who have recently seroconverted to HIV.

All patients with symptomatic HIV, or who have been diagnosed with AIDS or have severe, recurrent HIV related illnesses or a tumour should be offered HAART regardless of their CD4 count (BHIVA, 2001). In the absence of symptoms, surrogate markers of disease progression are used to guide treatment recommendations. For many years, decisions about when to start anti-retroviral therapy were made primarily on the basis of viral load, however recent research indicates that small differences in viral load do not substantially affect response to treatment but that CD4 count is the crucial factor. Data from short-term cohort studies suggest increased mortality among patients who start treatment with a CD4 count of <200 cells/μL (Hogg et al., 2001, Sterling et al., 2001; Kaplan et al., 2001). This has lead to the resurgence

of emphasis on CD4 count as the determinant of when to start treatment (BHIVA, 2001; Centre for Disease Control, 2001). However, high viral load can also be used to guide treatment decisions in those with asymptomatic conditions with CD4 between 200-350, since a viral load of above 55,000 copies predicts a faster rate of decline in CD4 cells (Mellors et al., 1997).

Table 1.1 Summary of recommendations (BHIVA, 2001)

Presentation	Surrogate markers	Recommendation
Primary HIV infection		If treatment considered, start as soon as possible, certainly within 6 months of contracting HIV; clinical trial if available
Established asymptomatic HIV infection	CD4 count >350 cells/μL and any viral load	Defer treatment
	CD4 count 200-350 cells/μL	Start treatment within this range, taking into account the rate of CD4 decline, patient's wishes and viral load
	CD4 count <200 cells/μL and any viral load	Treat
Serious/recurrent HIV related illness or AIDS		Treat

1.9.7 Practical problems with HAART

Despite their clinical effectiveness, early studies with protease inhibitors uncovered a range of practical difficulties with their potential for impact on the quality of life of patients. Taking protease inhibitors often entails a large number of capsules taken twice or more daily. Because of food and drug interactions, protease inhibitors often have special requirements. Different absorption characteristics between drugs mean that each of the drugs have different dietary requirements, for example indinivir requires concurrent fasting or a low fat meal while saquinavir requires a high fat high protein meal. In addition, PIs are metabolised by the liver, so drug interactions are common. Drug toxicities and side effects vary widely between

individual PIs. Moreover, it was noted at an early stage that because PIs bind reversibly to the HIV protease enzyme, when drug levels fall, the virus resumes its replication and resistance can occur (Danner et al., 1995, Condra et al., 1995). Similar difficulties extend to other classes of antiretroviral agents, and are a major consideration for many patients contemplating the risks and benefits of treatment.

1.9.8 Side effects and long term effects

Increasing attention has been paid to the toxicity of HAART. Toxicity issues are particularly important since the treatment is potentially life-long. Because the licensing of many antiretroviral drugs was accelerated because of the severity of the HIV epidemic, the long-term safety of many medications was initially unknown (Carr & Cooper, 2000). Furthermore, patients are required to take these pills for long periods of time although they may not have previously experienced any symptoms of HIV. Therefore, while greatly improving quality of life for many, taking antiretrovirals may be associated with decreased quality of life for others.

Antiretroviral drugs of all classes can cause side effects and adverse events are common, sometimes requiring more medication. Side effects range in severity and impact on patients' lives. For some, they are a nuisance or minor inconvenience, for others they can be intolerable, debilitating or life threatening. For a list of common and severe side effects associated with each antiretroviral agent available in the UK, please see Table 1.2. Diagnoses of many of the conditions related to drug side effects is difficult since patients who are receiving these drugs are likely to be taking other drugs with side effects that can overlap. In addition, patients can suffer a hypersensitivity reaction to several antiretroviral agents including (more commonly) all NNRTIs, the NARTI abacavir and the protease inhibitor amprenavir (Carr & Cooper, 2000), and several deaths have been attributed to restarting abacavir after a hypersensitivity reaction.

In 1998, the syndrome of lipodystrophy was described in Australia (Carr et al., 1998). This syndrome is characterised by selective loss of subcutaneous fat from the face arms and legs, and accumulation of fat around the neck, upper back, stomach and chest. Lipodystrophy is

associated with insulin resistance and associated metabolic abnormalities, including glucose intolerance, diabetes and hypertriglyceridemia (Max & Sherer, 2000). Carr et al (2000) reported that 68% of patients treated with protease inhibitor-containing therapy for an average of eleven months showed signs of fat redistribution, in contrast to only 1 (3%) of 32 patients not taking a PI. However, Mallal et al (2000) showed that even patients receiving PI sparing regimens were at risk of the syndrome. In the study by Carr et al (1998), lipodystrophy was related to the amount of time on PIs, where those who had been treated longer were at higher risk of the syndrome.

1.9.9 The problem of resistance

Resistance to antiretroviral agents among treatment experienced patients was noted by investigators comparing patients who were simultaneously started on AZT, 3TC and indinivir, and those who initiated treatment with AZT and 3TC with indinivir added 24-52 weeks later. Of those who started all drugs together, 78% had a durable virological response, compared to only 33% of those who started their drugs sequentially (Gulick et al., 1998). Similarly, Montaner et al. (1998) found a sustained virological response to a combination of AZT, ddI and nevirapine in treatment naïve patients, while D'Aquila et al. (1996) found only a transient effect of the same combination in those who were pre-treated with nucleoside analogues. These studies suggest that patients who had previously been exposed to drugs were more likely to experience virological failure because of the emergence of drug resistance and cross-resistance between drugs in the same class.

Resistance occurs when the virus becomes less susceptible to antiretroviral drugs. If optimal concentrations of antiretroviral drugs are not maintained, viral replication may continue in the presence of the drug. This results in the development of mutations within the protease and reverse transcriptase genes, changing the structure of the protease and reverse transcriptase enzymes, so that they are less susceptible to inhibition by the drugs (Deeks et al., 2000). The consequence is reduced drug efficacy and an increase in viral load. Cross-resistance can also occur among drugs in a therapeutic class, severely limiting future treatment possibilities for the individual (Harrigan & Larder, 2002).

Resistance testing is now available in clinics and is recommended for use in all patients undergoing a change of treatment to ensure the choice of more appropriate and effective drugs (BHIVA, 2001). Use of this technology has demonstrated the fact that drug resistant strains of HIV can be transmitted to others. One recent report showed that 14% of recently infected patients had one or more mutations associated with drug resistance, and that the risk of being infected with drug-resistant HIV was increasing 1.74 fold each year. These authors estimated a prevalence of drug resistance of 27% in individuals who were infected in the UK in 2000 (UK Collaborative group on Monitoring the Transmission of HIV Drug Resistance; Pillay et al., 2002).

1.9.10 Adherence and resistance to antiretroviral drugs

The clinical success of HAART depends upon extremely strict adherence, maintained over an infinite period of time. If the drugs being taken are highly potent, and adherence is perfect, viral replication is shut off, so that resistant mutations are unable to arise. However, low rates of adherence create the ideal conditions for resistance to occur, since the drug is present, but not in large enough quantities to suppress the virus (Friedland & Williams, 1999). Sub-optimal drug levels in the context of imperfect adherence allow the HIV virus to resume its typical rapid replication and quickly develop resistant mutations to the drugs being taken (Perelson et al., 1996).

Low adherence is not the only reason for sub-therapeutic drug levels, resistance selection or treatment failure, which can also be caused by poor drug absorption, rapid metabolism and interactions with other drugs (Andrews & Friedland, 2000). Furthermore, even in the context of perfect adherence, HAART may be ineffective if resistant virus is already present. However, there is unequivocal evidence that very high and enduring rates of adherence are critical to ensure treatment efficacy over the long-term.

Unlike treatments for other diseases and conditions, HIV requires the continual presence of potent antiretroviral therapy. Treatment adherence therefore needs to be exceptionally high.

The patient not only needs to take almost all his/her drugs, but to adhere strictly to frequency and timing of doses, as well as food and drug restrictions. Several investigators have shown strong associations between low adherence and virological failure, where undetectable viral load is not achieved or maintained (Mannheimer et al., 2002; Knobel et al., 2001). In the INCAS trial, previously antiretroviral naïve patients receiving AZT, ddI and nevirapine were more likely to have a detectable viral load after six months of treatment if their adherence was inadequate (Montaner et al., 1998). Deeks et al. (1999) showed that participants reporting poor adherence were 15 times less likely to obtain an undetectable viral load than those reporting high adherence. Paterson et al (2000) confirmed widely divergent rates of success at different levels of adherence: 78% of participants with adherence of 95% or greater showed complete viral suppression, compared with 39% of those with 80-94.9% adherence and 20% of those with less than 80% adherence. Furthermore, none of the group of participants demonstrating at least 95% adherence died or developed opportunistic infections during the follow-up period and they spent fewer days in hospital compared to those with less than 95% adherence (2.6 days compared to 12.9 days per 1000 days of follow-up respectively).

1.9.11 Consequences of low adherence

The studies described above show that for the individual patient, low rates of adherence and subsequent virological failure result in limited clinical benefit (Maher et al., 1999). Treatment failure invariably means progression to increasingly complex and difficult drug regimens (BHIVA treatment guidelines, 2001). Wider public health consequences of low adherence stem from the fact that drug resistant strains of HIV can be transmitted to others, leading to the increased incidence of new infections that are already resistant to some or all available antiretroviral drugs. This is of particular concern in the light of evidence that risky sexual behaviour is elevated among patients who are non-adherent to their drugs (Kalichman & Rompa, 2003). A recent study conducted in Brazil suggests that high rates of adherence to antiretrovirals decreases the risk of transmission. Barroso et al. (2003) showed that adherence was the most consistent predictor of undetectable seminal viral load after six months of HAART. Patients who reported taking at least 80% of doses were twelve times more likely to have undetectable viral load in their semen.

To date there is a dearth of research into the cost of adherence or non-adherence. However, testimony to the cost efficacy of sustained adherence is provided by Scalera et al. (2002) who acknowledge that although other factors (poor absorption, development of resistance and reservoirs of HIV) can contribute, adherence is a precursor of treatment failure. They cite evidence to show that treatment failure is associated with significantly increased direct costs to the health service (including hospitalisations; pharmacy; laboratory testing; skilled nursing care and professional care costs). Mullins et al. (2000) estimated annual indirect costs for patients depending on their symptomatic status. They found that costs were substantially lower if patients could be maintained at earlier stages of HIV infection for longer periods of time.

While newer drugs and more manageable formulations of old drugs have been introduced to combat some of the obstacles presented by HAART, adherence remains a significant problem. There are substantial difficulties in measuring adherence, and perhaps as a consequence, studies report widely divergent adherence rates. However, there is consensus among clinicians and researchers that adherence levels are consistently sub-optimal. The aim of this thesis is therefore to explore factors associated with non-adherence to HAART among HIV positive adults.

Table 1.2 Antiretroviral drug chart

Drug class	Name	Regimen	Common side effects	Rare side effects
NARTI Nucleoside analogues	3TC, lamivudine Epivir™,	One tablet twice a day, no food restrictions	Headache, tiredness	Rash, diarrhoea, nausea, abdominal pain, blood disorders, peripheral neuropathy, insomnia, liver problems
	Abacavir, Ziagen™	One tablet twice a day, no food restrictions	Nausea and vomiting, headaches, weakness, diarrhoea, insomnia, dizziness, abdominal pain	An allergic reaction often involving fever of rash in 3% of people, usually within 4 weeks. Abacavir should never be restarted after this hypersensitivity reaction. Liver problems
	AZT, zidovudine, Retrovir™	One tablet twice a day, 12 hours apart	Nausea, vomiting, fatigue, headache, insomnia, blood disorders	Liver problems
	combined AZT and 3TC, Combivir™	One tablet twice a day	As for constituent drugs (above)	As for constituent drugs (above)
	combined AZT, 3TC & abacavir, Trizivir™	One tablet twice a day	As for constituent drugs (above)	As for constituent drugs (above)
	d4T, stavudine, Zerit™	One tablet twice a day	Peripheral neuropathy, headache, nausea, diarrhoea or constipation	Pancreatitis, liver problems
	ddC, zalcitabine, Hivid™	One tablet three times a day	Peripheral neuropathy, mouth ulcers, diarrhoea, nausea, rash	Pancreatitis (very rare), liver problems
	ddI, didanosine, Videx™, VidexEC™	Four large tablets once daily or two enteric coated tablets once daily. Take on empty stomach at least two hours after eating and wait half hour before eating again. Crush and dissolve large tablets in water or apple juice. Many interactions with other drugs	Diarrhoea, peripheral neuropathy, nausea	Pancreatitis (greater risk if high alcohol consumption), liver problems

PI Protease Inhibitors	Amprenavir, Agenerase ™	8 capsules twice a day. With or without food. Many drug interactions.	Headache, nausea, vomiting, diarrhoea, rash, fatigue, tingling around the mouth, lipodystrophy and metabolic abnormalities. Oral solution may also cause seizure, stupor, fast heart beat, blood disorders	
	Indinivir, Crixivan ™	Two capsules every eight hours, on empty stomach. Avoid food 2 hours before and 1 hour after indinavir. Increase fluid intake. Many drug interactions	Kidney stones, pain when urinating, tiny stones in urine, dry lips and skin, liver abnormalities, nausea, lipodystrophy, metabolic abnormalities	diabetes
	lopinavir/ritonavir, Kaletra ™	3 orange capsules, twice daily. Take with food. Many drug interactions	Diarrhoea and loose stools, headache, nausea, vomiting, stomach pain, fatigue, rash, metabolic abnormalities, lipodystrophy possible	
	Nelfinavir, Viracept ™	3 tablets, 3 times a day. Take with food. Many drug interactions	Diarrhoea, nausea, lipodystrophy, metabolic abnormalities	
	Ritonavir, Norvir ™	6 capsules twice a day. Or 7.5ml liquid. Take with food. Many drug interactions	Diarrhoea, stomach pain, nausea, vomiting, weakness, taste abnormalities, loss of appetite, numbness around the mouth, lipodystrophy and metabolic abnormalities	Kidney problems, diabetes
	Saquinavir, Invirase ™ (hard gel) Fortovase ™ (soft gel)	3 capsules twice a day or 6 capsules three times a day within two hours of food, grapefruit juice increases absorption. Many drug interactions	Diarrhoea, stomach pain, nausea, lipodystrophy, metabolic disorders	diabetes

NNRTI Non-nucleoside reverse transcriptase inhibitors	Efavirenz, Sustiva ™	3 capsules once a day (1x 600mg tablet in development, not yet licensed in European Union). Many drug interactions	Dizziness, diarrhoea, headache, rash. Psychological effects, most common during first 4 weeks include 'feeling out of sorts', vivid dreams, euphoria, suicidal thoughts, psychotic episodes	Stevens Johnson Syndrome (very rare), alcohol intolerance, fever, asthma, aches and pains, fatigue, dry mouth, raised total cholesterol, pancreatitis, blurred vision
	Nevirapine, Viramune ™	One tablet twice a day, with or without food, many drug interactions	Rash, fatigue, liver problems, muscle pain, depression	Steven's Johnson Syndrome
	Delavirdine, Rescriptor ™	Experimental dosage: four white tablets three times a day. With or without food. Can be dissolved in cola or water. Many drug interactions	Mild skin rash, fever, headache, fatigue, nausea, skin problems, diarrhoea, liver abnormalities	
NtRTI Nucleotide analogue reverse transcriptase inhibitors	Tenofavir, Viread ™	One tablet once daily. Take with food to increase absorption	Diarrhoea, nausea	Longer term side effects not yet established
Fusion inhibitors	T20	The recommended adult dosage is 90mg injected twice daily.	Reactions around the injection site, headache, insomnia, peripheral neuropathy, and eosinophilia (an increase in the number of immune cells known as eosinophils).	Longer term side effects not yet established

Adapted from NAM: http://www.aidsmap.com

Chapter 2
CRITICAL REVIEW

Correlates and predictors of adherence to HAART: A critical review of the literature

2.1 Introduction

The advent of HAART in 1996 transformed the landscape of HIV. In countries where treatment is widely available, a dramatic decrease in mortality and incidence of AIDS-defining illness has been documented (Mocroft et al., 2000; Law et al., 2000). As a result, the perception of HIV as an uncompromising, progressive disease has given way to that of a chronic, treatable condition.

Despite its successes, HAART has brought obstacles of its own. Drug regimens can be complex, sometimes involving a large number of pills, frequent dosing, conflicting food requirements, and specific storage instructions. More drugs are often taken to prevent or treat opportunistic infections. Patients are required to take pills for long periods of time although they may not have previously experienced any symptoms of HIV. Yet side effects to all classes of antiretroviral agents are common and can be severe, sometimes requiring still more medication (Carr & Cooper, 2000). Recent studies have shown that long-term use can lead to lipodystrophy, a syndrome characterised by selective loss of subcutaneous fat from the face and extremities, and accumulation of fat around the neck, upper back, stomach and chest. Lipodystrophy is associated with insulin resistance and associated metabolic abnormalities, including glucose intolerance, diabetes and hypertriglyceridemia (Max & Sherer, 2000). Carr et al (2000) reported that 68% of patients treated with HAART including a protease inhibitor (PI) for an average of eleven months showed signs of fat redistribution, while Mallal et al (2000) showed that even patients receiving PI sparing regimens were at risk of the syndrome.

In spite of the challenges posed by HAART, clinical success depends upon extremely strict adherence, maintained over an infinite period of time. Several investigators have shown strong associations between low adherence and virological failure, where undetectable viral load is not achieved or maintained (Mannheimer et al., 2002; Knobel et al., 2001). Deeks et al. (1999) showed that participants reporting poor adherence were 15 times less likely to obtain an undetectable viral load. Paterson et al (2000) confirmed widely divergent rates of success at different levels of adherence: 78% of participants with adherence of 95% or greater showed complete viral suppression, compared with 39% of those with 80-94.9% adherence and 20% of those with less than 80% adherence. Furthermore, none of the group of participants demonstrating at least 95% adherence died or developed opportunistic infections during the follow-up period and they spent fewer days in hospital compared to those with less than 95% adherence (2.6 days compared to 12.9 days per 1000 days of follow-up respectively).

Low rates of adherence to HAART have serious implications on three levels: for the individual patient, public health and health economics. For the individual patient, low rates of adherence and subsequent virological failure result in limited clinical benefit (Maher et al., 1999) and progression to increasingly complex drug regimens (BHIVA treatment guidelines, 2001). Moreover, sub-optimal drug levels in the context of imperfect adherence allow the HIV virus to resume its typical rapid replication (Perelson et al., 1996). Resistant mutations to the drugs being taken can develop quickly, while cross-resistance can extend to other drugs within a therapeutic class, compromising future treatment options (Harrigan & Larder, 2002).

Public health consequences of low adherence stem from the fact that drug resistant strains of HIV can be transmitted to others, although it should be acknowledged that low adherence is not exclusively responsible for viral resistance, which can also be caused by low drug absorption, rapid metabolism and interactions with other drugs (Andrews & Friedland, 2000). One recent report showed that 14% of recently infected patients had one or more mutations associated with drug resistance, and that the risk of being infected with drug-resistant HIV was increasing 1.74 fold each year. These authors estimated a prevalence of drug resistance

of 27% in individuals who were infected in the UK in 2000 (UK Collaborative group on Monitoring the Transmission of HIV Drug Resistance; Pillay et al., 2002).

To date there is a dearth of research into the cost of adherence or non-adherence. Scalera et al. (2002) based their findings on the premise that adherence is a precursor of treatment failure. They showed that treatment failure is associated with significantly increased direct costs to the health service (including hospitalisations; pharmacy; laboratory testing; skilled nursing care and professional care costs). Mullins et al. (2000) estimated annual indirect costs for patients depending on their symptomatic status. They found that costs were substantially lower if patients could be maintained at earlier stages of HIV infection for longer periods of time.

Newer drugs and more manageable formulations of old drugs have been introduced to combat some of the obstacles presented by HAART. However, adherence remains a significant problem. There is consensus among clinicians and researchers that adherence levels are consistently sub-optimal. A plethora of studies have been carried out to uncover determinants of non-adherence to HAART in order to identify targets for interventions to promote adherence. The aim of this review was to critically evaluate this research.

2.2 Methods

2.2.1 Search procedures and inclusion criteria

A literature review was conducted on MEDLINE, PsychINFO, Cinahl and Embase library databases of articles published in English prior to September 2003, using combinations of the keywords: adher*, compl* crossed with antiretroviral*, HAART, protease inhibitor* and with HIV, AIDS, HIV/AIDS. Exclusion criteria included: children or adolescents under the age of 18, pregnant or postpartum women, recipients of post-exposure prophylaxis (PEP), studies conducted in resource poor countries, case studies and review articles. Conference abstracts were not included in the review because of the possibility of missing or incomplete data. The number of articles retrieved from each database is presented in Table 2.1. In total, 727 articles were generated from the search. One article was obtained through personal

communication with the authors. Qualitative and quantitative studies reporting original data on predictors and correlates of adherence and interventions to improve adherence were reviewed. Studies exclusively investigating outcomes or measurement of adherence, or interventions to improve adherence were not included. One hundred and eleven articles describing correlates and predictors of adherence were selected for review using the systematic search. One article was accessed through personal communication.

2.2.2 Coding of adherence correlates

Reports were coded using a computerised table to extract information on the setting and context, population characteristics, design, definition of adherence, measurement of adherence, rates and correlates of adherence. Every correlate of adherence measured was extracted from the report. This generated a list of 424 variables. The variables were sorted into categories by two researchers by a process of consensus and conciliation. These were further condensed into eight groups of variables: Clinical status, Socio-demographic characteristics, Treatment regimen, Lifestyle factors, Perceptions of illness and treatment, Knowledge and information, Psychosocial characteristics and Characteristics of the Health Service. The principal variables making up each of these categories are described in Table 2.5. Table 2.5 describes the number of studies reporting each variable, the number reporting significant associations with adherence or non-adherence and those reporting trends or qualitative findings (associations), as well as the number reporting no association.

2.3 Results

2.3.1 Descriptive characteristics of reviewed studies

2.3.1.1 Definition of adherence

Most studies defined non-adherence in terms of the number or percentage of missed doses over a given time period (ranging from 1 day to 12 months). Some computed a composite measure to include missed doses, timing and special instructions, e.g. food restrictions. Three studies included self-reported adherence, having an undetectable viral load and keeping clinic appointments in their composite adherence score. One study defined adherence solely in terms of frequency of meeting dosing requirements. Many set criteria where adherence was

defined according to a minimum threshold of doses consumed of those prescribed. This threshold ranged from 50% to 100% (median = 80%). Several described adherence as a continuum, usually denoting the percentage of pills taken, or the number of missed doses (as measured by self report or number of medication event monitoring system (MEMS cap) openings) or the percentage of prescriptions refilled on time over a specified time period. Others used Likert scales, where participants were required to state how frequently they missed doses according to a scale where adherence was typically defined as 'never' or 'very rarely' missing doses, or to rate the percentage of pills taken as prescribed on a visual analogue scale. Two studies defined adherence in terms of the length of time participants spent on antiretrovirals: those who discontinued therapy without their prescribing physician's advice were defined as non-adherent.

2.3.1.2 Measurement of adherence

Adherence measures could be grouped into three categories: 1) Subjective measures: Self report, interview and review of medical files, 2) Objective measures: Electronic monitoring, pharmacy refills, pill count, and 3) Biological and clinical markers: undetectable viral load, plasma drug levels and macrocytosis. Table 2.2 shows the number of studies using each type of measure. By far the most widely used measure was subjective (83.3%), including validated and unvalidated questionnaires, interviews and review of medical files. It should be noted that several studies used multiple measures of assessment, and almost half (43.2%) validated their measures against viral load.

2.3.1.3 Adherence rates

The percentage of participants defined as non-adherent varied enormously between studies, ranging from 9%-93%. The median percentage of participants reporting non-adherence was 33.0%. Thirty-seven percent of studies did not provide this data.

2.3.1.4 Patterns of adherence over time

The majority of longitudinal and prospective studies either reported adherence at a single follow-up, or averaged adherence across all follow-ups. All those who compared adherence

across more than one time-point (n=9) reported changes in adherence over time. One study reported a significant increase in adherence to antiretrovirals over the first four weeks of adjustment to a methadone maintenance programme, and a subsequent decline. The remainder described significant decreases in adherence over time. Two studies clearly illustrated the inaccuracy of labelling patients 'adherent' or 'non-adherent.' They provided evidence to suggest that adherence is a dynamic behaviour and that few patients are adherent or non-adherent all the time. Carrieri et al. (2001) measured adherence after four, twelve and twenty months of treatment. While the prevalence of adherence remained relatively stable at each visit, the longitudinal analysis of individual adherence patterns showed that only 31.4% of the sample remained highly adherent at all three visits, while 51.6% were only sometimes highly adherent. Half of those who were 'sometimes' highly adherent reported high adherence at 4 months but not at follow-up, while half were not initially highly adherent, but became so at either the 12-month or 20-month follow-up. Duran et al. (2001) selected only patients who reported taking 100% of their medicines as prescribed at a 4-month follow-up. By the 20-months follow-up, 30% had not maintained this high level of adherence. These studies show not only that adherence rates change over time, but that most individuals cannot be reliably labelled 'adherent' or 'non-adherent'. Many studies lacked information on patterns of adherence among those who changed therapy and frequently neglected to report reasons for discontinuing treatment or changing drugs. Often patients who changed drugs or discontinued therapy were not included in the final analysis. As a consequence, patterns of non-adherence over time may be obscured or underestimated. The longest period of follow-up was 20 months. There was a notable lack of research investigating patterns and correlates of adherence over the longer term.

2.3.1.5 Methodology

Table 2.3 summarises the methodological characteristics of the studies reviewed. The majority (68.8%) of studies were conducted in the USA, and most (69.0%) accessed populations from hospital clinics. Eighty percent of the studies have been published since the beginning of the year 2000. Sample sizes ranged from 11 to 5073, with a median of 111.0 participants per study. Most studies (81.3%) used quantitative, statistical methods of analysis,

however 18.7% were primarily qualitative in nature. Although many studies were cross-sectional (70.0%), almost a third utilised prospective or longitudinal designs allowing causal relationships between correlates and adherence to be explored. There was a notable lack of theory-based research: only ten studies (11.2%) tested components of theoretical models of adherence. Of these, seven measured constructs proposed in the health belief model (HBM; Rosenstock, 1966; Becker & Rosenstock, 1984) and three explored constructs developed from the self-regulation model (SRM: Leventhal et al., 1980) or extensions to it proposed by Horne (1997, 2003).

2.3.1.6 Characteristics of study participants

Characteristics of study participants are shown in Table 2.4. The percentage of male participants ranged from 0-100. The median percentage of male participants per study was 72.9%. Six studies (5.4%) consisted of exclusively male populations and 11 (9.8%) were exclusively female. The average age ranged from 28.0 – 54.5, the mean age was 39.2, (S.D. = 4.7). Thirty-two percent of studies were missing average age data. Participants in most studies (71.4%) were using HAART regimens, 20.5% were taking a mixture of HAART or mono- or dual therapy regimens and 8.1% were taking exclusively non-HAART regimes. The majority transmission risk was men who have sex with men (MSM) in 22 (19.6%) of studies, IVDU in 31 (27.7%) of studies and heterosexual in 7(6.3%) of studies. Data regarding transmission risk factors was missing almost half (46.4%) of the studies reviewed.

2.3.1.7 Conceptual groupings of correlates of adherence

Findings for each of the conceptual groupings are presented in Table 2.5. The first set relates to clinical status, the second to socio-demographic characteristics, the third to the complexity of the regimen, the fourth to patients' lifestyles, the fifth to patients' perceptions of illness and treatment, the sixth to knowledge and information, the seventh to psychosocial factors, the eighth to characteristics of the health service.

2.3.2 Findings of studies measuring correlates of adherence

2.3.2.1 Clinical status

Clinical status was reflected in various measures, including markers of disease progression such as viral load and CD4 count, CDC symptomatic classification, length of HIV diagnosis, and treatment history.

2.3.2.1.1 Viral load

Overall, 44 studies investigated the relationship between adherence and viral load, of which 38 (86.4%) reported significant findings. All reported relationships in the expected direction: higher adherence was associated with lower viral load, a steeper decline in viral load or greater likelihood of obtaining an undetectable viral load.

2.3.2.1.2 CD4 count

The relationship was weaker for CD4 count, however 46.9% of studies exploring the relationship between adherence and CD4 count found that higher CD4 count was associated with greater adherence, while 53.1% found no significant relationship. Prospective studies indicate that CD4 count and viral load prior to initiating treatment are not predictive of subsequent adherence (Spire et al., 2002; Duran et al., 2001; Lucas et al., 2001; Singh et al., 1999). However, one study found that lower viral load at baseline was predictive of consistent adherence over 12 months of follow-up (Roca et al., 2000).

2.3.2.1.3 Disease severity

Of 23 studies, only 6 (26.1%) reported significant relationships between disease stage and adherence, with inconsistent findings. Four found that patients with more severe disease were more adherent to their treatment: Singh et al. (1996) found that having had an opportunistic infection prior to study entry was associated with subsequent adherence, and Durante et al (2003) found that having been hospitalised during the past three months was associted with high adherence. Molassitosis et al (2002) found that stage C disease (AIDS diagnosis) was independently associated with higher adherence. Moreover, Gao et al. (2000) found that more severely ill patients (those in stages B and C) were more adherent to their medications than

those in stage A, and that those in stage C were more likely to perceive that their disease would get worse if they were not adherent to their treatment. These authors propose that having a diagnosis of AIDS or opportunistic infections increases patients' perceptions of severity of their disease and thereby motivates them to adhere. However, these findings may have been confounded by the use of cross-sectional methodologies. In prospective studies, Paterson et al (2000) found less than 95% adherence was associated with the emergence of AIDS defining illness over 6-month follow-up and Ostrop et al (2000) found that having had an AIDS diagnosis was associated with lower adherence over a 12 month follow-up.

2.3.2.1.4 Treatment experience

This category included factors relating to previous experience of treatment including being naïve to antiretrovirals prior to study entry, the number antiretroviral drugs prescribed previously and problems with adherence to prior antiretroviral treatment. Of ten studies reporting on these variables, five (55.6%) reported significant associations with subsequent adherence. Three prospective studies found that participants who were naïve to antiretrovirals at study entry reported higher levels of adherence at follow-up (Mannheimer et al., 2002; Carrieri et al., 2001; Duran et al., 2001). A fourth reported that being naïve at study entry, or having been adherent to prior combinations was associated with better adherence at 6-month follow-up (Matthews et al. 2002), and Spire et al. (2002) found that those who indicated that they had previously had adherence problems were likely to be non-adherent at a four-month follow-up. Conversely, Arnsten et al (2002) found that having been prescribed more than four antiretroviral drugs in the past was not associated with subsequent adherence among current and former drug users, Moatti et al (2000) discovered that being antiretroviral naïve had no significant impact on adherence within a sample of 164 patients receiving treatment for opiate addiction and others found neither the length of time on treatments, nor the number of previous combinations was associated with adherence (Carrieri et al., 2003; Kleeberger et al., 2001; Gordillo et al., 1999). No studies controlled for reasons for stopping or changing previous therapies, although it could be hypothesised that those who stopped under medical supervision would be more likely to be adherent to subsequent treatments than those who stopped without their doctors' endorsement.

2.3.2.1.5 Time since diagnosis of HIV

Twelve studies reported on the length of time since HIV diagnosis. Most (91.7%) found no relationship with adherence. Paterson et al (2000) found patients with 95% or greater adherence had been infected with HIV for a longer time, however this relationship was not maintained in their multivariate analysis.

2.3.2.2 Social and demographic factors

2.3.2.2.1 Age

Evidence for an effect of age on adherence was weak. Of 47 studies, 20 (42.6%) reported an association, the majority of which found that younger participants were more likely to be non-adherent. Prospective studies found that older participants tended to maintain high levels of adherence over time more frequently than younger participants (Carrieri et al., 2001; Moatti et al., 2000). Conversely, Gordillo et al. (1999) found that those aged between 32 and 35 were more compliant than either younger or older participants, and Stone et al (2001) found younger age was independently associated with reduced likelihood of missing doses. To date, no studies have explored mediators of the relationship between age and adherence.

2.3.2.2.2 Gender

There was scant evidence for a gender effect on adherence. Only 19.5% of studies found an association with adherence. Six studies reported that men were more adherent than women while one found women were more adherent than men (Roca et al., 2000). Arnsten et al. (2002) found a significant interaction between gender and depression, indicating that women who were depressed were less adherent. Three qualitative studies illustrated unique problems relating to adherence among women who were caring for children, such as lacking appropriate childcare (Roberts & Mann, 2000) and concealing their HIV status from their children (Sankar et al., 2002; Siegel et al., 2000).

2.3.2.2.3 Ethnicity

Relationships between ethnicity and adherence were reported in 35 studies, of which a minority (37.1%) found associations. Most of these revealed that participants from ethnic minorities were less adherent than white participants, while one study found that participants from ethnic minorities were more adherent than white Americans (Van-Servellen et al., 2002). Frequently, relationships between ethnicity and adherence were identified in univariate statistics but not maintained in multivariate statistics, suggesting that the relationship is due to shared variance with other variables. Furthermore all studies identifying a significant relationship between ethnicity and adherence were conducted in the USA. In an attempt to explain race differences, Singh et al (1999) compared non-Caucasian and Caucasian participants on all the measures included in their study. They found no differences in socio-demographics, disease status, drug use, depression or type of antiretroviral regime, however non-Caucasians reported significantly lower satisfaction with overall and information support and were more likely to use emotion-focused coping and cognitive coping strategies. Manheimer et al. (2002) found non-white participants (African Americans and Latinos) were more likely than white individuals to report confidentiality concerns and side effects as reasons for missing doses, while white participants reported forgetfulness more often. Furthermore, Ferguson et al (2002) found no differences between Caucasian and African American participants in terms of adherence levels, however, barriers to adherence differed between the two groups. Caucasian participants were more likely to maintain that antiretroviral medicines are not convenient to take and that they were taking more medication than desired. African Americans were more likely to maintain that they did not take antiretroviral medications when they felt well, that they were embarrassed to obtain refills of their treamtne, and that they had nowhere to store their drugs.

2.3.2.2.4 Transmission risk group

Twenty-five studies explored differences in adherence rates depending on transmission risk, the majority of which (82.7%) reported no relationship. One study found significantly higher adherence among gay men compared to heterosexual men and heterosexual women (Wagner et al., 2002). Three studies found lower adherence among those whose

transmission risk was IVDU. Gordillo et al. (1999) found that compliance was twice as high for those whose transmission route was other than IVDU. In a longitudinal study, Roca et al. (1999) reported higher adherence in non-IVDUs, however, the relationship reached significance at only one of four follow-ups. Kemppainen et al (2001) found that participants with a history of IVDU were less likely than others to use reminders and cues to facilitate adherence and more likely to attribute decreased adherence to symptoms, lifestyle factors (such as homelessness) and interactions with providers, family or friends. Few studies comparing groups by transmission risk controlled for current drug use or treatment for drug abuse, yet these factors could be hypothesised to differentiate adherence levels among those whose HIV risk was IVDU.

2.3.2.2.5 Education

Of the 32 studies reporting on education, nine (28.1%) found significant relationships, seven of these were in the predicted direction, where lower levels of education were associated with non-adherence. Indeed, Kalichman et al. (1999) found those with less than 12 years of education were between 3 and 4 times more likely than others to have missed a dose in the two days prior to the study. However, one study found the lowest adherence in those with the highest level of education (Van Servellen et al., 2002). There is a shortage of research exploring possible mechanisms by which education is linked to adherence.

2.3.2.2.6 Income

With regard to income, only six (37.5%) of sixteen studies found a significant relationship with adherence, where higher income was related to higher adherence, while lower income, or receiving social security was related to non-adherence (Gifford et al., 2000; Kempainnen et al., 2001; Kleeberger et al., 2001; Paterson et al., 2000; Spire et al., 2002; Wagner et al., 2002).

2.3.2.2.7 Employment

Twenty studies investigated associations between employment and adherence, of which 35.0% found a relationship. Being employed outside the home was associated with higher

adherence in five studies (Howard et al., 2002; Ammassari et al., 2001; Schuman, 2001; Wagner et al., 2001 and Gordillo et al., 2000;), and identified as a risk for non-adherence in another (Chesney et al., 2000). Qualitative studies shed light on some of the difficulties faced by those in employment, including side effects, storage requirements, food restrictions and disclosure of HIV status (Golin et al., 2002; Meystre-Augostoni et al., 2000). Methods used to overcome these barriers included switching to a simpler regime with no problematic mid-day dose.

2.3.2.2.8 Housing and social instability

There was a consistent relationship between housing conditions and adherence. Of eleven studies, nine (77.8%) identified significant associations, indicating that poor or unstable housing and homelessness are associated with lower adherence. In a qualitative study, Stone et al. (1998) described problems accessing medications on time among people living in institutional settings such as hostels, halfway houses or prisons. Gebo et al. (2003) found no association between homlessness and adherence, however, other indicators of social instability such as eating less than two meals a day and running out of money for essential items during the past ninety days were associated with non-adherence to antiretrovirals. It is likely that rather than homelessness per se, some of the factors associated with social instability are responsible for low rates of adherence among those with unstable housing conditions. Further research is required in order to identify these factors.

2.3.2.2.9 Living status

With regard to living status, four of eight studies (50%) found an significant effect on adherence: Arnsten et al. (2001) and Pratt et al. (2001) found those living alone were more likely to be non-adherent, while Wagner et al. (2002) found that those living with their partner were more adherent to their medicines. Results from Spire et al (2002) were more ambiguous: participants who were cohabitating were more likely to be non-adherent than married couples, while Carrieri et al (2003) found those living in a stable relationship were more adherent. While these relationships may have been mediated by the availability of social support, no studies explored potential mechanisms fuelling the relationship.

In conclusion, socio-demographic variables were weak and inconsistent predictors of adherence. A persons housing situation was the only consistent predictor, where unstable housing and homelessness were associated with lower adherence. There has been scant research into possible mediators of relationships between socio-demographics and adherence, yet this would be necessary in order to appropriately target interventions, since most socio-demographic variables (with the exception of housing) cannot be modified. These findings suggest that attempts should be made to ensure that individuals eligible for HAART should be adequately housed and that treatment should not be withheld from patients on the basis of socio-demographic stereotypes.

2.3.2.3 Factors related to the treatment regimen

2.3.2.3.1 Antiretroviral regimen

This category included studies reporting on adherence according to antiretroviral class (e.g. PI Vs NNRTI) or specific drugs within a class (e.g. type of PI), or type of regime (e.g. Dual therapy Vs combination therapy). Of 18 such studies, only 5 (27.8%) reported significant relationships with adherence. In a randomised clinical trial, Mannheimer et al. (2002) found patients receiving regimens containing an NNRTI were significantly more likely to report 100% adherence than those who received PI-containing combinations, however reasons for non-adherence were not compared between groups. Howard et al (2002) found lower adherence among women whose combination included a PI, however these data may have been confounded by the fact that those receiving a PI were also more likely to be on thrice-daily regimens, which was also a significant predictor of low adherence. Stein et al. (2000) compared participants receiving dual therapy with those receiving triple therapy, and found that those taking triple therapy were half as likely to take a drug holiday and third as likely to skip pills the previous day. Furthermore, Schuman et al. (2001) found that participants receiving either monotherapy or combination therapy without a protease inhibitor were less adherent than those receiving a protease inhibitor. Reasons for these associations have not been defined, although Schuman et al. (2001) found the type of regimen was not related to reporting either side effects or forgetting as interfering with adherence. In a randomised,

open-label, prospective study comparing two protease inhibitors, Roca et al. (2000) found patients taking Nelfinavir were significantly more likely to be adherent than patients taking Indinavir. Non-adherence was attributed to side effects significantly more often in the Indinavir group. Finally, it would appear that when lapses in adherence occur, they usually apply to all the drugs in the regimen, rather than to a specific medication. Wilson et al. (2001) showed that within person variability explained only a small amount of variability of reported adherence: most of the variance in adherence scores was due to between-subjects variability.

2.3.2.3.2 Regimen complexity

Regimen complexity was described in several ways, including the number of pills, number of doses per day and special instructions such as food and drug restrictions. Thirty-one studies explored associations between regime complexity and adherence. Of those, two-thirds identified significant relationships. Most of these showed that more complex dosing schedules were associated with lower adherence, although some showed the opposite to be true. In a randomised trial, Eron et al (2000) found that adherence to Combivir, a combination of two nucleoside analogues, in combination with a protease inhibitor, was higher than adherence to conventional doses of its constituent drugs, 3TC and AZT, in combination with a protease inhibitor. This is consistent with the premise that taking fewer tablets facilitates adherence. Indeed, a dose-response relationship between the number of antiretrovirals prescribed and non-adherence has been identified (Kleeberger et al., 2001). Matthews et al. (2002) showed that a lower number of drugs in the regimen was associated with better adherence, however this relationship was not maintained in their multivariate analysis. A further two studies reported seemingly contradictory findings. Singh et al. (1996) found that while the type of antiretrovirals did not differ between compliant and non-compliant participants, compliant patients were taking a significantly higher number of total daily prescription medications. One explanation for this finding was that the investigators combined antiretrovirals with other medications in their analysis, raising the possibility that those who were adherent to combination therapy may be more likely to accept and/or consume additional prescribed medications. However, Wutoh et al. (2001) also found that patients taking more medications were more compliant. Possible explanations for this relationship were not explored.

The number of doses per day also seemed to impact on adherence. Eldred et al (1998) and McNabb et al (2003) reported higher adherence to twice daily compared to three times daily dosage while Pratt et al (2001) found a greater number of dose events in 24 hours was significantly associated with poorer adherence. Stone et al. (2001) found medicines with three or more daily doses and those that needed to be taken on empty stomach were most likely to have been skipped in previous three days, while Carrieri et al. (2003) found that neither food restrictions nor having to take antiretrovirals on an empty stomach were associated with non-adherence.. Gifford et al. (2000) showed that while the characteristics of the regime such as more pills or more frequent dosing instructions did not impact on adherence, participants' perceptions of the convenience of their drug regimen and its 'fit' with routine or daily activities was independently related to increased adherence.

Niewkerk et al (2001) confirmed the reduced efficacy of HAART in the context of non-adherence to food and timing instructions. Patients who were non-adherent to food and timing instructions, yet did not miss doses, were more likely to have a detectable viral load. In spite of this, there was a dearth of quantitative studies directly comparing adherence to combinations with or without special instructions. Insights from qualitative studies suggest that food restrictions are a barrier to adherence. Patients were often faced with a dilemma, needing to eat to keep weight on, yet having to fast to ensure optimal absorption of antiretrovirals (Kemppainen et al., 2001; Meystre-Augustoni et al., 2000). Others found it difficult to get food in time (Siegel et al., 2000). Further difficulties were experienced as a result of inconvenient timing as well as problems with the size, shape, smell, taste, and the sheer number of pills that patients were required to take (Murphy et al., 2000; Ostrop et al., 2000; Proctor et al., 1999; Roberts & Mann, 2002; Roberts 2000). Sian et al. (2001) found reasons given for non-adherence included having trouble with altering the timing of the regimen when abroad, and storage problems such as refrigeration of protease inhibitors: one person reported missing doses because his drugs melted on holiday. Participants reported that fewer doses, fewer pills, and improved physical properties such as size and shape of the pills would facilitate their adherence (Wagner et al., 2002).

Drawing conclusions from the studies pertaining to the type and complexity of the drug regimen is difficult on several levels. There is a lack of evidence from randomised, controlled trials. Data collection spanned a period over which there were momentous changes in treatments for HIV, both in terms of the improved effectiveness of newer combination therapies and more manageable treatment formulations. A potentially confounding variable is the patients' previous treatment experience: a patient taking a complex salvage regimen will have experienced treatment failure of less demanding regimens in the past, which may have been due to sub-optimal adherence. Furthermore the vast majority of these studies were conducted in the USA, where prescribing guidelines differ from UK (US guidelines advocate initiating most patients on treatment with a PI- based regimen, a typically more complex regimen than the NNRTI-based regimen usually recommended in the UK (BHIVA, 2001)). Further research is needed to tease apart mechanisms by which aspects of the treatment regimen impact on adherence and to identify adaptive coping mechanisms by which some patients manage a high level of adherence to extremely complex drug schedules. Moreover, there is little research investigating the potential impact of complexity over the long-term, yet it is possible that maintaining a high level of adherence to a demanding schedule for an indefinite duration of time contributes to a phenomenon known as 'treatment fatigue.'

2.3.2.4 Lifestyle factors

2.3.2.4.1 Substance use

Thirty studies investigated associations between adherence and drug use and 23 measured associations with alcohol use and abuse. Most of these studies (69.0% and 63.6% respectively) found significant associations in the expected direction: current drug and heavy alcohol use were negatively associated with adherence. In a study conducted at treatment centres for drug rehabilitation, Stein et al. (2000) found participants reporting current alcohol abuse and those who admitted to intravenous drug use in the past six months were more likely to have missed doses of antiretrovirals the previous day. In a longitudinal study involving current and former drug users, Arnsten et al (1996) found that active cocaine use and a tendency to use drugs or alcohol to cope with stress was associated with lower

adherence. Paterson et al (2000) found a link between alcohol abuse and less than 95% adherence, while Moatti et al (2000) showed that the risk of being non-adherent increased 20% for each additional 25 units of alcohol consumed per month. Matthews et al (2002) discovered differential results depending on the substance under investigation: Neither lifetime nor current alcohol intake was related to adherence, however higher adherence was associated with absence of current cocaine use and less than seven days' lifetime amphetamine use. Similarly Halkitis et al (2003) found that of a list of recreational drugs, only crack cocaine use was related to non-adherence. Marijuana use has not been related to adherence (Lucas et al., 2001). Two studies explored changes in drug and alcohol use over time: Spire et al (2002) found that increases in alcohol and tobacco consumption from baseline to four-month follow-up were associated with lower rates of adherence at four months. Lucas et al (2001) found that participants who remained free from drug and heavy alcohol use were more likely than others to show continued or improved adherence over time. Studies investigating relationships between adherence and more distant drug or alcohol use tended to find no relationship (Avants et al., 2001; Matthews et al., 2002).

One interview-based study suggests that current alcohol or drug use does not always preclude high rates of adherence. Malcolm et al (2003) found that participants who reported very high levels of adherence often differed from those reporting sub-optimal adherence in terms of their beliefs and behaviour while taking alcohol or drugs. Those reporting high adherence maintained that they continued to take their antiretrovirals even when using drugs or alcohol, while those with lower adherence generally did not take their HAART medicaitions when drugs or alcohol were in their system because they believed the antiretrovirals would not be effective, or because they did not want to think about it at that time.

These studies provide valuable insights for the development of interventions to support sustained adherence over time. They show that current but not lifetime abuse tends to impair adherence, and that failure to maintain adherence over time is associated with patterns of increasing drug and alcohol use. Further research is needed to elucidate the nature of the relationship between adherence and substance use, since it could be that relapse into

substance use impairs adherence, or that both substance use and non-adherence are fuelled by the same mechanism: for example social instability, side effects, treatment fatigue, personality, stress or depression.

2.3.2.4.2 Treatment for substance abuse

In four out of five studies, being on a drug treatment programme was associated with improved adherence. Turner et al. (2003) found that men who received regular treatment for drug use were more likely to be adherent to their medication. Moatti et al (2000) compared three groups of patients infected with HIV through IVDU. Those continuing active IVDU were about five times more likely to be non-adherent than those on drug abuse maintenance therapy (DMT) with buprenorphine and ex-IDU. Moreover, there was a statistical trend for IDU on DMT to report higher adherence than ex-IDU, even among those taking DMT who continued injecting drugs. Sambamoorthi et al. (2000) found that consistent participation in methadone maintenance treatment (MMT) was associated with a 10% increase in the proportion of time on antiretrovirals, compared to those currently using heroin. However, Schuman et al (2001) found that both women who reported recent IVDU, and those on MMT reported significantly lower rates of adherence compared to others, and that rates of non-adherence were similar for both groups. Finally, Avants et al. (2001) found that rates of non-adherence decreased significantly over four weeks of methadone stabilisation. While these results suggest that receiving treatment for drug abuse improves adherence, none of the studies were controlled, samples were biased and mechanisms responsible have not been identified.

2.3.2.4.3 Sexual risk behaviours

Six studies explored relationships between non-adherence to HAART and risky sexual behaviours. All found significant associations with non-adherence. Wilson et al. (2002) found that women who reported less than 95% adherence were more likely to report inconsistent use of condoms than those reporting more than 95%. Wagner et al. (2002) found that unprotected sex in the previous two months was a risk factor for non-adherence among HIV sero-discordant gay and heterosexual couples. Aversa et al (2001) found that receiving

money for sex was associated with lower rates of adherence to antiretrovirals. Kalichman & Rompa (2003) found people who had missed at least one dose of their antiretrovirals in the last week reported more sexual partners and a greater frequency of unprotected sex compared to those who had taken all their medication. In a study of current drug users, Williams et al (2002) found nonadherence was associated with trading sex for drugs, but not with trading sex for money. Halkitis et al (2003) found that drinking alcohol or being intoxicated before sex were related to non-adherence to antiretrovirals. Further investigation is required to identify similarities and differences between the mechanisms or belief systems underlying both risky sexual behaviour and low adherence. If a consistent relationship is found, it would imply that interventions to increase adherence should also focus on reducing risky sexual behaviour.

2.3.2.4.4 Health protective behaviours

Five studies explored reported on relationships between health protective behaviours (using complementary treatments, exercising, following a healthy diet) and adherence. Two found positive relationships, two found no relationship, and one had mixed results. Manfriedi et al (2000) explored links between the use of non-conventional treatments for HIV in two cohorts. They found that poor adherence was associated with a greater tendency to use alternative treatments in 1996 (pre-HAART), but that adherence had significantly improved and was no longer associated with the use of alternative treatment in 1998. More recently, Gifford et al. (2000) identified a positive relationship between healthy dietary behaviour and self-reported adherence, while Knippels & Weiss (2000) found those using complementary medicines were more adherent to their antiretrovirals. However, the cross-sectional design of these studies means that causality could not be ascertained. In a prospective study, Spire et al (2002) reported no relationship between having regularly practised exercise or relaxation, or having used alternative medicines in the previous six months and subsequent adherence. However, they did not report on the evolution of these behaviours from baseline to follow-up in relation to adherence. Wutoh et al (2001) found no significant difference in adherence scores based on the use of complementary therapies. Studies differed in their definition of alternative or complementary treatments, making comparisons between studies difficult. Future research is

needed to define what types of behaviour are relevant and to determine how the use of health protective behaviours impacts on adherence. For example, these behaviours might promote adherence by alleviating side effects or reducing anxiety. Alternatively, similar patient characteristics might underlie both adherence and other health protective behaviours.

2.3.2.5 Perceptions of HIV and antiretroviral treatment

2.3.2.5.1 Symptoms and side effects

Thirty studies explored relationships between symptom experiences and adherence. Most used questionnaires asking participants to rate the symptoms they were experiencing from a list of common antiretroviral side effects. Fewer studies addressed symptoms attributed to HIV and fewer still asked patients to distinguish between symptoms they associated with HIV and those they attributed to their treatment, yet these might be hypothesised to have differential effects on adherence. Nevertheless, the vast majority of studies (86.7%) identified relationships between symptoms and adherence. Only five studies found no relationship (Duong et al., 2001; Halkitis et al., 2003; Lopez-Suarez et al., 1998; Paterson et al., 2000; Singh et al., 1999). Most found that patients who reported more or more severe symptoms were less adherent, while one reported a positive association between lipodystrophy-related symptoms and adherence. In addition, Aversa & Kimberlain (1996) found that 64% of those who had discontinued their therapy cited side effects or adverse events as their primary reason for doing so.

The cross-sectional design of the majority of studies precludes the inference of causal relationships. Recent prospective, longitudinal studies illuminate the data. In a prospective study over 20 months, Carrieri et al (2001) found that the risk of non-adherence at follow-up increased six-fold for each additional HAART-related symptom. Moreover, these investigators found no relationship between medically reported side effects and adherence at any of the five follow-ups, suggesting that patients' perceptions of symptoms are more important than their clinical significance. Duran et al (2001a) followed patients one and four months after initiating a PI-containing regimen and found that those reporting more symptoms a month after initiating treatment were more likely to be non-adherent at the four month follow-up.

Again, adherence was not associated with physician estimates of side effects. Furthermore, only those who were adherent at four months reported a significant reduction in symptoms between one and four months, suggesting that the alleviation of symptoms over time promotes higher adherence. Similarly, Spire et al. (2002) found that while perceptions of symptoms at baseline did not predict adherence at four month follow-up, those who were non-adherent at four months declared a higher number of symptoms at four months and were more likely to rate the symptoms as disturbing. They also found that evolution of symptoms between baseline and four months was important: those whose symptoms remained high at both follow-ups, and those whose symptoms increased from limited to high were more likely to be non-adherent than those whose symptoms decreased from high to low or remained low. These studies suggest a dynamic relationship between symptoms and adherence.

For lipodystrophy related symptoms, the association with adherence was not so clear-cut. Duran et al (2001b) selected participants who reported 100% adherence four months after initiating treatment. Patients' reports of lipodystrophy-related symptoms were independently associated with failure to maintain adherence at 20 months, suggesting the experience of symptoms caused non-adherent behaviour. Conversely Vergis et al. (2001) found that participants with adherence levels of more than 80% at a 12-month follow-up (assessed by pharmacy prescription redemption) had more medical symptoms of lipodystrophy compared to those with less than 80% adherence, suggesting that higher adherence causes lipodystrophy. However, they did not measure patient reports of symptoms. It is possible that the difference in measures (self report versus medical assessment) and follow-up period accounts for the differences between these two sets of results.

Several qualitative studies confirmed the link between symptoms and non-adherence, and some provided additional insights. Unanticipated side effects (such as body-weight changes) were identified as barriers to adherence in two studies (Abel et al., 2003; Barton Laws et al., 2000). Siegel et al. (1999) reported a 'dose-response' relationship between side effects and adherence, where patients would take less of their antiretroviral therapy in order to alleviate side effects and were prepared to accept the trade-off of less clinical benefit. Participants

often held the belief that symptoms are a sign of illness and as such, should be ameliorated by treatment. They felt that if medicines caused symptoms it was a sign that they were doing more harm than good. For some, non-adherence was a way of regaining control over their illness.

None of the studies reviewed provided data on the effects of changing treatments, or reasons for changing treatment on symptoms and adherence. Few explored possible differential relationships between adherence and symptoms depending on whether patients attribute them to HIV, HAART or other illnesses, although results from one study suggest that both those reporting more HIV and those reporting more HAART symptoms were less adherent to their treatment (Ammassari et al., 2001). Overall, these data provide a convincing case for incorporating the continued identification and aggressive management of symptoms and side effects into the design of interventions to support adherence.

2.3.2.5.2 Perceptions of CD4 count and viral load

Three qualitative studies explored patients' perceptions of their laboratory test results in relation to adherence. Siegel et al (2000) found that many participants questioned the validity of blood test results especially when they did not meet their expectations, or did not reflect their physical well-being, while some believed that missing doses was acceptable if their viral load was undetectable. Other investigators found that perceiving good laboratory test results motivated participants to adhere (Roberts, 2000; Stone et al.,1998). No quantitative studies assessed patients' perceptions of their CD4 count and viral load in relation to adherence.

2.3.2.5.3 Subjective assessment of health

Eleven out of eighteen studies (61.1%) found that patients' subjective assessments of their health or quality of life were associated with adherence. Five cross-sectional studies found non-adherent participants reported lower quality of life or poorer health status (Penedo et al., 2003; Catz et al., 2001; Kastriossis et al., 1998; Wilson et al., 2002; Aversa & Kimberlain, 1996). However, these studies were unable to determine causal relationships between quality of life and adherence. In a longitudinal study, Singh et al (1996) reported a greater decline in

quality of life between baseline and 12 months for non-adherent patients. Data from Spire et al. (2002) suggest a dynamic relationship between patients' perceptions of their health and adherence. Although perceptions of physical health at baseline did not predict adherence four months later, those who felt that their health had improved or remained good were significantly more likely to be adherent than those whose subjective assessment of health had decreased from good to bad or maintained bad. However, it is also possible that patients' perceptions of their health changed as a consequence of their adherence or non-adherence. In a qualitative study, Roberts et al (2000) found that participants who believed that their health had improved were more adherent. Conversely, others found that feeling better was endorsed as a reason for missing doses (Murphy et al., 2000; Proctor et al., 1999; Chesney et al., 2000). Further prospective research utilising quantitative research methods to establish the nature of relationships between subjective assessment of health and adherence.

2.3.2.5.4 Perceptions of treatment efficacy

A series of studies investigated relationships between patients' beliefs about the extent to which HAART is beneficial or effective and adherence. Of 17 studies, 15 (88.2%) reported associations with adherence, these were all in the expected direction. Several cross-sectional studies showed that those who perceived antiretrovirals to be effective, beneficial, or reliable, and those who held a greater degree of trust in the treatment or who believed that the treatment would increase longevity or prevent illness were more likely to be adherent to their treatment, while those who were more sceptical were more likely to be non-adherent (Atlice et al., 2001; Aversa & Kimberlain, 1996; Catz et al., 2000; Gebo et al., 2003; Martini et al., 2000; Murphy et al., 2003; Murphy et al., 2000; Nannis et al., 1993; Sternhell & Corr, 2002; Wagner et al., 2002). In a longitudinal study, Martini et al. (2002) found that patients who perceived antiretrovirals as 'protective' or 'reliable' at baseline were more likely to be adherent 12 months later, while results from another prospective study suggest that patients' perceptions of the effectiveness of antiretrovirals stem from their experiences of treatment. Spire et al (2002) found that beliefs about the effectiveness of HAART before initiating treatment did not predict later adherence, however, patients whose beliefs were maintained high or increased from low to high were more adherent at 4 months than those whose beliefs were maintained

low or decreased from high to low. No studies investigated which aspects of experience were associated with beliefs about effectiveness.

2.3.2.5.5 Adherence self-efficacy

Adherence self-efficacy, the belief that one is capable of taking their medicines as prescribed, was a consistent predictor of adherence. All of seven studies investigating the construct found significant positive associations adherence (Catz et al., 2000; Chesney et al., 2000; Duong et al., 2001; Eldred et al., 1998; Gifford et al., 2000; Molassiotsis et al., 2002). All were cross-sectional in design, precluding the investigation of causal relationships. Prospective studies are required to determine whether adherence self-efficacy is predictive of adherence, or whether it is an artefact of adherence behaviour: 'I believe I can adhere because I'm adhering'.

2.3.2.5.6 Beliefs relating to initial decision making

Nannis et al (1993) found that participants who felt that their initial decision to initiate AZT was made without undue pressure were more likely than others to continue with their treatment. This was echoed in two qualitative studies where patients explained that they were motivated to adhere because they were reluctant to break the commitment they felt they had made to taking antiretrovirals (Roberts, 2000; Murphy et al., 2000). Since these studies were conducted pre-HAART or soon after its introduction, further research is required to determine whether these beliefs are relevant to adherence in the era of new treatments.

2.3.2.5.7 Concerns about antiretrovirals

Twenty-four studies investigated the relationship between a range of concerns about antiretrovirals and adherence. Of these, 22 (91.7%) found negative relationships between patients' concerns and adherence. One study used a validated measure assessing the degree to which patients held a range of concerns about the potential harmful effects of their treatment including concerns about side effects, problems with timing and disruption to daily life as well as more abstract concerns stemming from fears about potential long-term effects and embarrassment about taking antiretrovirals. They found a significant negative

relationship, where patients with stronger concerns about their treatment were more likely to be non-adherent to dosage instructions (Horne et al., in press). Most studies used interviews or single statements rated on Likert scales to assess patients' concerns. These concerns were grouped into four categories.

The first set of concerns related to harmful effects of taking HAART on the body. Qualitative studies found that barriers to adherence included patients' perceptions of their medicines as being too strong (Siegel et al., 1999) or not thoroughly tested (Siegel et al., 2000). Laws et al. (2000) found that some participants took drug holidays to 'detox' or to rid the body of the powerful effects of their drugs. Indeed, some patients feared that their treatment (AZT) accelerated deterioration, and were less likely to adhere (Aversa & Kimberlain, 1996). The second set of concerns was related to patients' perceptions of negative consequences of taking antiretrovirals on various aspects of daily life including work, daily routines and social life, as barriers to adherence (Meystre-Augostoni et al., 2000; Roberts et al., 2000; Siegel et al., 2000; Stein et al., 2000; Schilder et al., 2001; Barton-Laws et al., 2000). The third set of concerns was associated with the impact of taking HAART on the person's self-identity: Catz et al (2000) found that the most frequently endorsed barrier to HAART adherence (acknowledged by 89% of participants) was the statement 'treatment reminds me of my HIV status'. This was reinforced in a qualitative study investigating barriers to adherence (Roberts, 2000), where participants indicated that they felt that taking antiretroviral medication took them 'out of normality and into sickness', and felt stigmatised by having a diagnosis of HIV. The emotional trauma of dealing with diagnosis and treatment for HIV along with the associated stigma was also identified as a barrier to adherence among focus groups with women (Abel et al., 2003). The fourth category included fears that taking antiretrovirals would lead to disclosure of HIV status at work, in public and to children (Murri et al., 2001; Sankar et al., 2002; Siegel et al., 2000; Murphy et al., 2000; Roberts et al., 2000). The overwhelming majority of these studies used qualitative and cross-sectional methodologies. While these studies suggest that patients hold a wide range of concerns that constitute barriers to adherence, further research is needed to determine what types of concerns predict adherence, how concerns about HAART evolve over the treatment process, to what extent

patients' concerns about HAART are associated with adherence over time, and what methods patients use to overcome or cope with their concerns, in order to identify targets for intervention.

2.3.2.5.8 Health beliefs

There was a consistent relationship between health beliefs and adherence. Of 26 studies, 22 (84.6%) identified associations with adherence, however concepts were ill defined and in general, lacked a theoretical framework. Of seven studies that operationalised aspects of the Health Belief Model (HBM), six found significant associations between at least one component of the model and adherence. However, five of the studies were cross-sectional, precluding the determination of causality between beliefs and adherence. Aversa & Kimberlain (1996) found significant differences between those who adhered to their treatment (AZT) and those who discontinued on four constructs: perceived benefits/barriers of AZT, susceptibility to illness, perceived severity (the extent to which HIV is perceived as a serious disease) and pessimism about antiretrovirals. There were fewer statistically significant differences between non-adherent participants (who did not discontinue their treatment), and those who adhered. Gao et al. (2000) found that patients perceiving a higher chance of getting worse if not taking their medication as prescribed ('severity-inaction') were more likely to adhere to their treatment. However, perceived severity (defined as the severity of HIV in comparison to other illnesses) benefits and barriers, and 'susceptibility-action' (the perceived chance of disease aggravation if adherent to the treatment) were not related to adherence. In a study of adherence to AZT monotherapy, Morse et al. (1991) found no relationship between increased susceptibility/severity and adherence, however they found a significant relationship between certain 'perceived barriers' and non-adherence. Ferguson et al (2002) also found some of a list of barriers to adherence, including the inconvenience of the regimen, feeling well and stigma associated with HIV to be related to non-adherence, however only this one facet of the HBM was explored. Malcolm et al (2003) based an interview around concepts of the HBM and found that patients' 'attitudes and beliefs' were associated with adherence. Unfortunately, these attitudes were vague and were not defined or discussed in terms of the HBM constructs. In a prospective study, Matthews et al. (2002) found greater adherence to

HAART among participants who held the belief that HIV medications are important for personal health, and who had a low degree of pessimism about taking antiretrovirals. These relationships reached statistical significance in bivariate but not multivariate statistics. Mostashari et al. (1998) defined the construct 'susceptibility' in terms of CD4 count, presence of HIV related symptoms and the belief that health will worsen over the next year. None of these variables were associated with adherence. While these studies lend some support to the Health Belief Model, concepts were poorly defined and not comparable across studies. Only one study found consistent relationships between HBM constructs and adherence.

A consistent relationship was apparent between patients' behaviour and their perceptions of the need for adherence in order to prevent illness or to stave off the emergence of viral resistance, in that non-adherent patients were less sure of the link (Chesney et al., 2000; Gifford et al., 2000; Molassitosis et al., 2002; Stein et al.,2000; Siegel et al., 2000; Smith et al., 1997). This relationship was consolidated in a prospective study, where patients' perceptions of the risks of reducing prescribed doses of antiretrovirals before initiating treatment were predictive of subsequent adherence (Spire et al., 2002).

Three studies provided some support for components of the Self-Regulation Model (Leventhal et al., 1980) or extensions to it proposed by Horne (1997, 2003), which propose that patients' 'common sense' perceptions of their illness and treatment guide the procedures they use to cope with their illness (such as adherence to medication). Using a qualitative methodology, Siegel et al (2000) found that the attributions patients made for their symptoms (to HIV, antiretrovirals or unrelated illnesses or aging) influenced whether patients adhered to their antiretroviral regimes. Those who experienced symptoms that they associated with their treatment or failed to detect any improvement in symptoms they attributed to HIV were less adherent, even when their viral load and CD4 responses indicated that their treatment was working. Horne et al (in press) found that patients were more likely to report taking pills within two hours of the time recommended if their beliefs about their personal need or 'necessity' for HAART outweighed their concerns. Walsh et al (2001) conducted a principal component analysis of 20 reasons endorsed by participants for missing doses. They found that a factor

labelled 'having a 'low priority for medication' was independently associated with non-adherence.

Several miscellaneous health beliefs were identified. One study showed that participants possessing the belief that they could influence the course of their disease were more adherent than others (Molassiotis et al., 2002). Another found those who perceived that AIDS is no longer a serious disease since the advent of new treatments were less adherent (Williams et al., 2000). Participants who perceived that HIV interfered with their daily lives were more likely to take pills off schedule (Stein et al., 2000) and those who believed that they had been infected with HIV as a punishment or that antiretrovirals were a punishment for getting HIV were more likely to be non-adherent (Safren et al., 2001).

While studies show consistent relationships between beliefs and adherence, the majority lack of a theoretical framework. Those that have tested components of psychological models have been unanimously cross-sectional in design, and to a large extent the concepts specified in the models have been poorly defined with little consistency of measurement between studies. Since it is clear that rates of adherence change over time, prospective, longitudinal studies are required to explore whether beliefs also change over the treatment process and how these changes relate to adherence.

2.3.2.6. Knowledge/ Information

2.3.2.6.1 Knowledge about HIV/HAART and adherence

Twenty-five studies explored aspects of participants' knowledge of antiretrovirals, HIV or adherence, use and satisfaction with information. Of those, two thirds (68.0%) found associations with adherence. These were all in the predicted direction – a higher degree of knowledge was associated with increased levels of adherence. Several studies found that a greater degree of knowledge about antiretrovirals (knowledge about different drug classes and tests of antiretroviral effectiveness) and personal treatment regimen (such as ability to recall the name, colour or timing of drugs, understanding of the treatment regimen) was associated with higher adherence (Ammassari et al., 2001; Durante et al., 2003; Gifford et

al.2000; Jones et al., 2003; Laws et al, 2000; Miller et al., 2003; Roberts et al. 2000, Wagner et al. 2002, Stein et al., 2000). HIV-related knowledge (knowing one's CD4 count and viral load, being better informed about HIV in general) was not related to adherence in three studies (Durante et al., 2003; Gordillo et al.,1999; Sternhell et al., 2002) but was significantly related to higher adherence in another Jones et al., 2003). With regard to knowledge about adherence, Chesney et al. (2000) found that 22% of participants taking PI based regimens requiring adherence to special instructions were unaware of them. Others found that greater knowledge of the consequences of nonadherence was associated with higher adherence (Stone et al., 2000; Wagner et al., 2002).

2.3.2.6.2 Use and satisfaction with information

There was very little research on patients' use of information, and even less regarding their perceptions of the information they had received. Kalichman et al.(1999) found those who had lower 'health literacy' or ability to understand written instructions on prescriptions were almost four times as likely as others to be non-adherent to their antiretrovirals. This was echoed in a qualitative study where patients often had to ask other HIV positive people to explain aspects of their medication, or bring their friends along to consultations to decipher the doctors' dialogue (Schuman et al., 2001). Pratt et al. (2001) found that 14% of participants did not feel sufficiently informed to make decisions about their treatment. Adherence was negatively related to participants' rating of the difficulty of following doctors' instructions on the antiretrovirals: patients who perceived the instructions as more difficult to follow were less adherent to their treatment (Gao et al., 2000; Catz et al., 2001). In another qualitative study, participants asserted that the instructions from their doctors were in conflict with the written instructions provided with their medicines (Murphy et al., 2000).

Pratt et al. (2001) found that patients who reported having been influenced by the general and HIV-specific media were less adherent to their antiretroviral regimen. This was echoed in a qualitative study (Sankar et al., 2002) who found that negative messages about antiretrovirals on the television and in patient support groups were associated with lower levels of adherence.

In a qualitative study, Malcolm et al (2003) found that participants who reported excellent adherence to their medication often commented that their commitment to take HAART consistently was reinforced by receiving positive information about their health at each visit.

In a prospective study, Spire et al (2002) found no differences in subsequent adherence among participants who had received prior information about their treatment or those who had previously discussed taking antiretrovirals with their doctor, when compared to those who had not utilised these information sources.

In conclusion, research to date has heavily relied on qualitative methodologies. There was very little consistency between studies in terms of the type of information under investigation, so comparison between studies is impossible. No consistent differences between adherent and non-adherent patients have been identified in their knowledge of HIV, HAART or adherence, or in their usage or satisfaction with information.

2.3.2.7 Psychosocial characteristics

This category includes positive and negative affect, experience of stress and negative life events, the availability and satisfaction with social support, diagnosis of psychiatric illness, use of coping strategies, locus of control and cognitive and neurological variables. Overall, 78.3% of studies exploring psychosocial characteristics identified associations with adherence to antiretrovirals.

2.3.2.7.1 Negative affect

This category included depression, anxiety, and other negative emotions. Of 37 studies, 32 (86.5%) found negative associations between negative affect and adherence. There was a consistent relationship depression and adherence, all but five studies found significant inverse correlations (Arnsten et al; 1996; Avants et al. 2001; Catz et al., 2000; Holzemer et al.,1999; Kalichman et al.,1999 Kleeberger et al., 2001; Malcolm et al., 2003; Nannis et al., 1993; Pratt et al 2001; Schuman et al.; 2001; Sian et al., 2001; Rabkin et al., 2000; Simioni et al., 2002;

Singh et al., 1996; Van Servellen et al., 2002). Turner et al. (2003) found depression to be associated with increased adherence, perhaps due to diagnosed depression being associated with use of mental health services. Gordillo et al. (1999) found that both depression and an interaction between depression and social support were associated with adherence: those who were not depressed and who perceived that they had good social support were more adherent. Another study found an interaction between gender and depression (Arnsten et al., 2002). Women who were depressed were more likely than other women or men to be non-adherent.

While many of these studies were cross-sectional, prospective research has been conducted in order to determine whether negative affect prior to initiating treatment predicts subsequent adherence. These studies have mixed findings. Singh et al. (1996) found that depression as measured by the Beck Depression Inventory (BDI) did not predict adherence 12 months later, however 'mood disturbance' determined by high scores on the Profile of Mood States (POMS) predicted non-adherence at follow-up. Using the BDI, Matthews et al. (2002) found that participants who failed to complete 30 days of using MEMS-caps were more depressed at baseline than those completing the follow-up, however amongst those who completed, there was no difference in scores between adherent and non-adherent participants. Another study suggests a dynamic relationship between experience of HAART and depression. In a prospective, longitudinal study where depression was assessed at baseline and four months later, Spire et al (2002) showed that the evolution of depressive symptoms (measured by the Centre for Epidemiological Studies Depression Scale: CES-D) over time was particularly important. While depression at baseline did not predict non-adherence, those who reported an increase in depressive symptomatology between baseline and four months were more likely to be non-adherent at four months. No studies explored which aspects of taking HAART impacted on depression.

A range of other negative emotions were associated with non-adherence. Kalichman et al (1999) found that patients who reported taking less than 100% of doses in the past two days reported more psychological distress on the Brief Symptom Inventory which includes items

pertaining to somatic anxiety, obsessive-compulsive thoughts, depression, anxiety, hostility and paranoia. Murri et al (2001) found that confusion and poor psychological well-being were associated with lower pre-dose PI levels. Others found negative relationships between anxiety and adherence (Amassari et al., 2001; Catz et al., 2001; Molassiotis et al., 2002 & Van Servellen et al., 2002). Singh et al (1999) found non-adherence was associated with loss of motivation and more negative feelings about the future. In a study using focus groups, Proctor et al (1999) identified anger, denial and rebellion as being barriers to adherence.

These results suggest a strong relationship exists between negative affect and adherence. However, the direction of causality has not been clarified, since some prospective research suggests that negative affect at baseline predicts later adherence, while others have found that evolution over the treatment process is more important. While the majority of studies used standardised scales to measure depression, the diversity of measures makes it difficult to compare results across studies. Moreover, most studies reported symptoms as a continuum and did not report clinical cut-offs for depression or anxiety, so the clinical significance of these symptoms could not be ascertained. No studies investigated the possible impact of receiving treatment for depression or anxiety on adherence. Further research is required in order to determine which aspects of taking HAART are associated with negative affect. Studies to date indicate that negative affect should be monitored prospectively across the treatment process.

2.3.2.7.2 Positive affect

Included in this category was a range of positive emotions, planning for the future, hope for the future, optimism and positive self-assessment. Although the investigation of different concepts makes comparison across studies difficult, all of nine studies found significant relationships between positive affect and adherence. In eight of the nine studies, there were positive relationships between positive affect and adherence. Duong et al., (2001) found positive feelings about personal life and trust in personal skills were associated with better adherence. Holzemer et al. (1999) found participants who reported having a meaningful life, cherishing the environment, using time wisely and making time for important things were

more adherent to their antiretrovirals, more likely to follow instructions and keep appointments. Planning for the future was associated with adherence in one study (Pratt et al., 2001) and having a higher degree of hope for the future was an independent predictor of non-adherence in another (Van Servellen et al., 2002). Williams et al. (2000) found that experience of 'joy' was associated with higher adherence. Pratt et al. (2001) reported that those who evaluated themselves positively were more adherent to their treatment. Conversely, Holmes et al. (2002) found that participants who were optimistic about their life expectancy reported lower adherence to their medication. All studies were cross sectional, future prospective research is required to explore the direction of relationships between positive affect and adherence over time.

2.3.2.7.3 Psychiatric illness

Of eight studies, four identified significant relationships between psychiatric disorders and adherence. Two studies showed that lower adherence was related to probable psychiatric disorder as measured by the General Health Questionnaire (GHQ-28) (Paterson et al., 2000; Sternhell & Corr, 2001). Sternhell & Corr (2001) found that participants who had been prescribed psychotrophic medicine in the past were more likely to be non-adherent, however having had a past psychiatric admission was not related to adherence. In a review of case notes, patients with recorded psychiatric problems were less likely to stay on treatment for more than a month and more likely to be rated as a poor complier by their physician (Broers et al., 1994). Conversely, a retrospective review of 7744 case notes found that a diagnosis of schizophrenia was independently associated with more consistent use of antiretrovirals (Walkup et al., 2001). No studies explored possible mechanisms linking psychiatric disorder with adherence or non-adherence, nor did they explore the impact of receiving treatment for psychiatric treatment on adherence.

2.3.2.7.4 Stress and negative life events

Of eleven studies reporting on life stress, ten (90.9%) found that perception of stress or experience of negative life events was negatively related to adherence. Most studies used validated measures. Catz et al., (2001) found that life stress associated with problems

common among people with HIV (including loss, financial problems and discrimination) was significantly higher in those with low adherence. In a study of French IVDUs, Moatti et al. (2000) found non-adherence to HAART was associated with retrospectively reporting a higher number of negative life events over the preceding six months. The risk of non-adherence increased 20% for each additional negative life event. Major financial problems and confrontation with the police were the single events that contributed most to the group difference in overall life event scores. Gebo et al. (2003) found running out of money for essential items and feeling as though pressures outside the clinic affected the patient's ability to take antiretroviral treatment as prescribed were associated with low adherence. Halkitis et al (2003) detected significant increases in both missed doses and suboptimal adherence to timing instructions after September 11th, 2001, when terrorists flew two planes into the twin towers in New York. This increase in non-adherence could not be explained by socio-demographic variables, drug or alcohol use. However, the mechanisms which linked the events of September 11th with non-adherence to HAART were not examined.

Relationships between adherence and perceived stress were less consistent: Gifford et al (2000) found non-adherent patients had higher scores on the Perceived Stress Scale. Using the same measure, Chesney et al (2000) found a trend for non-adherent participants to report higher perceived stress, while Duong et al (2001) reported no association between perceived stress and adherence. The impact of stress on adherence was also illustrated in an interview-based study (Proctor et al., 1999). Prospective studies are required to investigate directions of causality between stress and adherence, and to identify possible mediators of this relationship.

2.3.2.7.5 Social support

Of thirty-one studies, twenty-four (77.4%) found that having or perceiving good social support was associated with higher adherence, while six found no relationship. Social support was usually measured using one of several validated social support scales. Several cross-sectional studies showed that higher perceived support or higher satisfaction with support was associated with higher adherence, or low perceived social support or need for social

support was associated with low adherence (Atlice et al., 2001; Catz et al., 2000; Holzemer et al.,1999; Kalichman et al., 1999; Malow et al., 1998; Power et al., 2003; Pratt et al., Simioni et al., 2002; Stein et al.,2000; Mostashari et al.,1998; Safren et al., 2001). Two studies specifically measured perceived social support for using medications, with conflicting results. Gifford et al. (2001) found that better social support for using medications was associated with higher adherence, while Molassiotis et al. (2002) found that those receiving less help from families in remembering to take medication were more adherent. Prospective studies suggest that the availability or satisfaction with social support before initiating treatment predicts subsequent adherence (Duran et al., 2001; Singh et al., 1999; Spire et al., 2002).

Two studies found that the relationship between social support and adherence was mediated by additional variables. Simioni et al (2002) found that the need for social support was related to non-adherence, and that this relationship was mediated by self-efficacy and depressive symptoms. Gordillo et al (1999) found that an interaction between social support and depression predicted adherence. Those without depression and with good social support had an adherence score of nearly twice that of participants who were depressed and lacking social support.

Some studies found differential effects for specific types of social support. Singh et al. (1999) found that non-adherence was associated with less satisfaction with overall social support, tangible social support and informational social support but not emotional social support. Pratt et al (2001) found that heavily relying and gaining practical help from a close confident were correlates of higher adherence, however, being comforted in somebody's arms every day and having a non-professional person identified as a caregiver were not related to adherence. Mostashari et al (1998) showed that while those who were less adherent were less likely to seek help from others when they were feeling down, receiving 'HIV-related support' from a friend was not associated with adherence. In a qualitative study, those reporting high adherence were more likely to report receiving strong social support from family, friends and support groups, while sub-optimal adherers were more secretive about their HIV status, lacking family support and avoiding support groups, preferring to preserve their privacy

regarding their HIV status (Malcolm et al., 2003). Halkitis et al. (2003) found that having more HIV positive friends was related to higher adherence among gay men, and Durante et al. (2003) found that living with other HIV-positive people was associated with higher adherence, however the mechanisms responsible for these relationships are not clear.

In an interview-based study, Murphy et al. (2003) found some participants' family and friends discouraged them from taking their antiretroviral medication, saying that it was bad for them. These investigators also found that 'having someone to live for' such as a child, was often a motivator to take medication. Malcolm et al. (2003) suggested that taking HAART for the sake of others was not always conducive to high adherence rates. They found that participants reporting high adherence were more likely to mention themselves as their primary motivation for taking their medication while those who were less adherent were more likely to say they were taking their drugs for the sake of others, such as their children or spouses.

2.3.2.7.6 Coping

Eight studies explored relationships between the use of coping strategies and adherence. All found significant associations with adherence. Active behavioural or problem focussed coping strategies (the tendency to use behaviour to minimise sources of stress) were associated with greater adherence. Using alcohol or drugs to cope with HIV was associated with lower adherence (Dorz et al., 2003; Power et al., 2003). Molassiotis et al. (2002) also found the use of avoidance-denial coping (denying that the problem exists, or avoiding confrontation) was associated with higher adherence, while the others found that using avoidance coping, coping by denial, mental or behavioural disengagement was associated with lower adherence (Dorz et al., 2003; Jones et al., 2003; Singh et al., 1996; Singh et al., 1999). These differences may be due to differences in study populations (e.g. Hong Kong Vs USA). Singh et al (1999) found differences in the use of coping strategies between African-American and white Americans. No research has sought to explain how coping styles or strategies influence adherence behaviour.

It has been suggested that a concept known as 'sense of coherence' (SOC) may be a prerequisite for an individual's coping capacity. SOC has three elements: comprehensibility, manageability and meaningfulness. High scores on these variables are thought to lead to successful stress management. Cederfjall et al. (2002) found that HIV positive patients reporting >=95% adherence to HAART had higher scores on this variable compared to those reporting low adherence.

2.3.2.7.7 Locus of control

Locus of control is a psychological construct, which refers to an individual's expectancy of the degree to which they have control over what happens to them. 'Internal locus of control' refers to the belief that the individuals own behaviour determines what happens to them, while 'external locus of control' involves the belief that fate or chance or 'powerful others' (such as physicians) are responsible for what happens. Three studies investigated relationships between locus of control and adherence. All found significant relationships. Molassiotis et al. (2002) found higher adherence was associated with internal locus of control. Aversa and Kimberlain (1996) reported that patients who were non-adherent but continued with their mono-therapy reported a more internal locus of control than those who discontinued, however there were no significant group differences on measures of 'chance' or 'powerful others' locus of control. Spire et al (2002) found those who scored higher on 'powerful others' locus of control at baseline were more adherent to their treatment four months later, while internal and chance locus of control did not predict subsequent adherence. While all three studies reported significant associations between locus of control and adherence, the results are inconsistent. If locus of control is a useful concept, the mechanisms by which it impacts on adherence need to be identified.

2.3.2.7.8 Cognitive/neurological dysfunction

Hinkin et al (2002) found that poor adherence was associated with deficits in memory, attention and executive function. Furthermore, these investigators found that cognitive compromise interacted with regimen complexity, such that cognitively impaired participants

who were taking HAART medications three times daily were at greatest risk of non-adherence.

2.3.2.7.9 Personality

One study investigated the influence of personality type and adherence (Penedo et al., 2003). The investigators found no significant differences between high and low adherence groups in terms of neuroticism, extraversion, openness, agreeableness and conscientiousness.

2.3.2.8 Characteristics of the health service

The final category of correlates encompasses the various facets of the health service that have been investigated in relation to adherence. Most of this research focuses on patients' perceptions of their relationship with their doctor, but also includes satisfaction with medical services more generally, access to healthcare and medication, and the accuracy of health care professionals ratings of adherence. The use and impact of props or facilitators to enhance adherence was also included in this category.

2.3.2.8.1 Doctor-Patient Relationship

The relationship between doctor and patient was consistently related to adherence. Of twenty studies, sixteen (80.0%) found that patients who perceived that they had a better relationship with their prescribing physician and other key health care workers were more adherent to their antiretroviral medicines than those who were less satisfied with the relationship. Studies used single items or a scale to measure satisfaction with the doctor-patient relationship. Atlice et al. (2001) reported an 8% increase in adherence for each unit increase on a 'trust in physician' scale. Webb et al. (2001) found that patients who perceived a high degree of 'treatment-related empowerment' reported lower levels of intentional non-compliance. Similarly, Pratt et al (2001) found that participants who believed their health care provider supported their decisions, were accessible, helped them understand things about their care and involved them as a partner in their care were more likely to be adherent. Bakken et al. (2000) found greater adherence among patients who reported greater 'engagement' with their health care provider. In a prospective study, Spire et al (2002) found that those who reported that they

regularly talked about personal problems with their physician prior to starting treatment were less likely to be non-adherent four months later, as were those who reported having complete trust in their relationship with their prescribing physician. Despite significant associations with adherence, comparison between these studies is clearly hindered by the use of diverse concepts and measures.

Using focus groups to elicit barriers and facilitators of adherence to HAART, Golin et al. (2002) found many participants stressed the importance of the role health care professionals play in helping patients take and adhere to their medication. In focus groups involving gay, bisexual and transsexual men, having a gay physician was deemed helpful, while having an open, on-going dialogue and being able to discuss problems was important (Schilder et al., 2001). This was echoed in a study which found that being involved in decision making, being allowed time to ask questions and to disclose adherence problems were important features of a good patient-provider relationship (Murphy et al., 2000). Using in-depth interviews to explore themes associated with adherence, Roberts et al. (2000) found that being satisfied with the Dr-patient relationship, feeling that the doctor believes in antiretrovirals, and being able to disclose information to a non-judgemental doctor were important facilitators to adherence. Conversely, non-adherence was associated with a less than optimal doctor-patient relationship, feeling that the doctor was inaccessible or not listening and not trusting the doctor and as a result, not trusting the medicines. Abel et al. (2003) also found that communication with health care providers was a key facilitator of adherence.

2.3.2.8.2 Use of medical services

This category encompassed any other aspects of the patient's use of the health service, including attendance at clinic appointments, consultations with medical professionals other than the HAART prescriber and enrolment in pharmaceutical research trials. A lower likelihood of keeping outpatient appointments was associated with non-adherence in three studies (Chesney et al., 2000; Fong et al., 2003; Kleeberger et al., 2001), however, in another neither attending for regular medical care, nor HIV focused care was associated with improved adherence (Turner et al., 2003). These differences may be due to differences in

samples, since those in the Turner et al. study were predominately drug users who may need adjunctive services such as drug treatment to improve adherence.

Spire et al. (2002) found that participants who had talked to medical professionals outside the hospital clinic at which they received their medical about their treatment were less likely to be non-adherent compared to those who had not benefited from this extra medical follow-up. Kleeberger et al. (2001) reported a statistical trend for higher adherence to drugs that were monitored in a research trial setting versus a non-trial setting. Chesney et al. (2000) found that patients were more likely to be non-adherent if they reported having entered a clinical trial specifically to gain access to a particular drug, although reasons for this relationship were not offered.

2.3.2.8.3 Access to healthcare

Van Servellen et al. (2002) measured access to healthcare on a scale including items encompassing difficulty paying for medication, difficulty getting dental or other medical services, and difficulties with transportation to and from medical appointments. They found participants who indicated that they had poorer access to healthcare were more likely to be non-adherent. In two USA based-studies, participants in focus groups discussed having problems obtaining refills of their antiretroviral medicines, due to their health insurance policies (Murphy et al., 2000) or because the pharmacy had run out of the medicines (Proctor et al., 1999). Halkitis et al. (2003) found no relationship between whether the participant received public or private healthcare and adherence.

2.3.2.8.4 The clinical setting

Neither of the two studies found that aspects of clinical setting were related to adherence. Nieuwkerk et al (2001) reported non-adherence levels ranging from 38% to 63% across nine different healthcare sites, however differences in adherence between sites were not statistically different. Schuman et al (2000) found no difference in reported adherence between women who reported having a regular healthcare site and those who did not have a regular healthcare site.

2.3.2.8.5 Adherence facilitators

Ostrop et al. (2000) explored antiretroviral drug adherence with respect to use of adherence tools. They found that 60.9% of patients used at least one adherence tool including individualised schedules, dosette boxes and electronic reminder devices. Adherence did not differ with respect to overall tool use, use of schedules, or use of dosette boxes. However, the absence of a control group meant that it was impossible to determine the impact of adherence facilitators on adherence. In an interview-based study, respondents reported that reminder aids such as beepers could help improve adherence (Wagner et al., 2002). Only one study compared the use of strategies to promote adherence to antiretrovirals between adherent and non-adherent patients (Catz et al., 2000). They found no differences between the groups.

2.4 Discussion

This review identified one hundred and twelve publications investigating correlates and predictors of adherence, spanning the last ten years. These studies yielded over four hundred variables that were analysed for an association with adherence. Based on a conceptual sort of the variables, eight broad categories of adherence related factors were identified. These were: clinical status, socio-demographic variables, factors related to the treatment regimen, health risk and health protective behaviours, perceptions of HIV and antiretroviral treatment, knowledge and information, psychosocial characteristics of the patient and characteristics of the health service.

Older studies tended to use exploratory research methods and were largely cross-sectional in design. More recently, there has been a surge of prospective studies allowing the investigation of predictors of adherence before starting treatment, as well as facets of the treatment experience that impact on adherence. These data confirm that there is no such thing as a 'non-adherent patient,' and that most people are neither consistently adherent nor consistently non-adherent. Moreover, they show that adherence is a dynamic, multi-faceted behaviour that cannot be reliably predicted on the basis of apriori clinical and socio-demographic characteristics of patients or aspects of the treatment regimen. Fewer than half

of the studies investigating links between these variables and adherence found significant relationships.

There were notable exceptions within these categories. Viral load was consistently associated with adherence, however, prospective studies confirmed that rather than being predictive, lower viral load was an outcome of high adherence. Indeed most prospective studies found no relationship between baseline viral load and subsequent adherence. Moreover, the data suggested that caution should be exercised in interpreting undetectable viral load as synonymous with high adherence. The flip-side of the data in the seminal study by Paterson et al. (2000) was that 20% of those with less than 80% adherence (measured by MEMS caps) and 39% of those with 80-94.9% adherence had an undetectable viral load. Further research is required to explore patients' perceptions of laboratory test results and their role in adherence.

The single socio-demographic characteristic that was consistently associated with non-adherence was poor or insecure housing. This suggests that efforts should be made to ensure that patients eligible for HAART are adequately housed. Where relationships between other socio-demographic variables and adherence were found, most studies failed to investigate the mechanisms linking them to adherence. Yet is likely that these mechanisms are more important than a person's age, ethnicity, transmission risk or gender per se. For example, UK-based research has shown that black African patients (who make up the second largest HIV positive group in London) are less likely to take up antiretroviral treatment than other groups, and that uptake is hindered by concerns about side effects, fears about being experimented upon, concerns about drugs being tested only on white men, negative experiences of the health service and discrimination (Erwin & Peters, 1999).

Despite the lack of evidence, there has been concern that prescribing decisions are sometimes based on unrealistic stereotypes of 'the non-adherent patient'. In the USA, Bogart et al. (2001) presented 495 HIV physicians with clinical scenarios depicting HIV positive patients. Scenarios varied information according to the patient's gender, disease severity,

ethnicity and transmission risk group. Physicians were asked to predict who they thought would be non-adherent and whether they would start the patient on HAART. The results suggested that doctors were apt to perceive that patients with less severe disease, those whose transmission risk was IVDU and African American men would be less likely to adhere. Both perceived adherence and disease severity impacted on their treatment decisions. However, the review suggests that these variables are poor predictors of adherence, and should not form the basis of prescribing decisions.

Drawing conclusions about relationships between adherence and the type or complexity of the regimen is hindered by the lack of randomised controlled trials and the presence of confounding variables such as previous treatment experience (patients might be taking more demanding regimens as a consequence of previous treatment failure, which in turn, could have been the result of sub-optimal adherence). From the studies reviewed, it would seem that the type and complexity of the treatment regimen were poor predictors of adherence. However, the complexity of the regimen seemed to be more important than the type of drug regimen, and number of doses per day more important than number of medications. While few studies investigated relationships between the presence or absence of food restrictions and adherence, there was little doubt from qualitative findings that patients perceive them as barriers. The studies reviewed suggest that those who manage to fit the regimen around their lifestyles are more successful at maintaining a high degree of adherence, indicating that efforts to improve or sustain adherence should focus on the individual's daily routine and their perceptions of convenience. To this end, a recent conference paper found that patients who perceived their treatment as being more intrusive on their daily lives were less likely to be highly adherent to their treatment (Newell et al., 2002).

Over half the studies investigating knowledge and information and those exploring characteristics of the health service found associations with adherence. These components are contained within a 'cognitive hypothesis' model of compliance proposed by Ley (1981, 1989), which claims that compliance can be predicted by satisfaction with the consultation process as well as understanding and recall of the information given. With regard to the first

category, it is perhaps not surprising that patients who lacked a good understanding of their disease and treatment were less likely to adhere to their treatment. Indeed, one randomised controlled intervention to improve adherence to antiretrovirals (not covered by this review) showed that providing patients with educational counselling significantly improved adherence to HAART compared to conventional dispensing (Haddad et al., 2000). However, despite a dearth of research into information provision and satisfaction, this review suggests that solely providing information or ensuring adequate knowledge would not be adequate, since 30% of studies found no significant association between these variables. With regard to health service characteristics, the perceived quality of the doctor-patient relationship, having good access to treatment and use of other medical services were all consistently related to high adherence, while aspects of the clinical setting itself did not appear to have an impact. The research suggests feeling involved and empowered in treatment decision-making, and being able to relate to and discuss treatment issues with the HAART prescriber facilitates adherence. Interventions to improve adherence should focus on the individual, tailoring information to ensure that they have sufficient knowledge, and feel adequately empowered in treatment decisions. Although there was a lack of evidence to suggest that use of adherence facilitators such as dosette boxes, alarms or bleepers is associated with higher adherence, the studies reviewed indicate that many patients find them helpful.

While caution should be exercised in making inferences from a fairly arbitrary categorisation process, it is interesting to note that the categories showing the most consistent relationships with adherence or non-adherence to antiretrovirals (perceptions of HIV and antiretroviral treatment, psychosocial characteristics and engaging in health risk and health protective behaviours) are all amenable to change. Indeed, data from prospective, longitudinal studies show that these variables often have a dynamic relationship with adherence. One of the most illuminating studies in this respect showed that beliefs, behaviour and psychological well-being varied within the same individual over the treatment process and that these evolutions influenced adherence over and above baseline characteristics (Spire et al., 2002). These findings suggest that any intervention to improve or support continued adherence should monitor these variables over time. These categories are discussed below.

Adherence or non-adherence to antiretroviral treatment did not occur in a vacuum, but within the context of a person's daily life. Perhaps not surprisingly, studies showed that low adherence was often associated with other health risk and health protective behaviours. For example, current use of alcohol or recreational drugs was associated with non-adherence to a greater extent than more distant use. Indeed, prospective studies that explored changes in substance use and adherence over the treatment process showed that increases in usage were related to decreases in adherence, while decreases in substance use were related to improved adherence. Further research is required to explore the nature of these relationships, since it could be that relapse into substance abuse impairs adherence, or that both behaviours are fuelled by the same mechanism (for example side effects, stress or depression). Nonetheless, the findings suggest that efforts to improve or maintain adherence should monitor and address issues surrounding substance use.

It was interesting to note an association between non-adherence and engaging in sexual transmission risk behaviours in the few studies that explored these links. If these findings are confirmed they are of particular concern, since non-adherence to HAART increases the chances of transmitting drug-resistant strains of HIV. These associations may be fuelled by erroneous perceptions of treatment efficacy. Several studies have shown that a significant number of HIV positive men and women believe that decreased viral load in the blood reduces the risk of sexual transmission of HIV (e.g. Kelly et al., 1998). However, studies have shown that these beliefs are often misinformed, for example, Kalichman et al. (2001) found no correlation between levels of HIV in the blood and semen. These associations indicate the need for integrating perceptions of sexual risk behaviours into interventions to support and improve adherence.

Despite measurement problems, psychosocial characteristics (e.g. positive and negative affect, the availability of social support, experience of stress and life events) were often related to adherence behaviour. Again the question of causality arises, for example, whether non-adherence results from motivational or cognitive features of depression, or whether

particular aspects of the treatment process (such as side effects) are related to increases in depressive symptoms. Although studies incorporating assessments of psychological characteristics before initiating HAART and over the treatment process were scarce, they suggested that both were important. Further research is required to explore which aspects of treatment impact on psychological well-being. It would also appear that the availability of adequate social support buffers the relationship between depressive symptomatology and non-adherence. The research suggests that efforts should be made provide psychological support where required, both before initiating treatment, and across the treatment process.

Patients' perceptions of their illness and treatment were the most reliable correlates of adherence. A plethora of studies showed that experiencing symptoms, particularly those attributed to treatment, was associated with non-adherence. Data from prospective studies indicated that experiencing symptoms over the long term was particularly problematic. Further research is needed to explore possible differential effects on adherence depending on whether symptoms are attributed to HIV or HAART, and what happens when symptoms are ameliorated or worsen over the treatment process. None of the studies reviewed assessed the impact of interventions to alleviate or counteract side effects, or the effect of changing therapy. Furthermore, no studies explored protective mechanisms by which some people coped with symptoms while others reacted to them by reducing doses or stopping treatment.

The majority of the studies reviewed failed to provide a theoretical framework. Those that operationalised components of the Health Belief Model (HBM) failed to provide any convincing support for the model as a whole. Reference to the more general theoretical literature shows that HBM has been criticised for its static approach to health beliefs. Schwarzer (1992) asserted that beliefs within the HBM are described as occurring simultaneously, with no room for change. The applicability of this model to a dynamic behaviour such as adherence must therefore be questioned.

Rather than persisting with attempts to isolate a single variable or set of variables that predicts adherence, data from prospective studies advocate an approach that integrates the

patients' own ideas about their illness and treatment. In line with the SRM (Leventhal et al., 1980), which proposes that people use 'common sense' models of illness to guide their adherence behaviour, a qualitative study showed that those who experienced symptoms that they attributed to HAART side effects perceived that their treatment was doing more harm than good and reduced their doses accordingly. Furthermore, two questionnaire-based studies showed that harbouring concerns about HAART and perceiving a lack of personal need or necessity for treatment were associated with non-adherent behaviour. This is in accordance with extensions to the SRM proposed by Horne (1997; 2003), which incorporates beliefs about prescribed medicines as well as illness representations. These data substantiate findings from studies conducted with other illness groups including asthma, diabetes, renal disease and cancer (Horne and Weinman, 1999) and suggest that the extended SRM is a valid framework within which to study adherence to HAART. This model may be particularly relevant to adherence to HAART, since unlike other social cognition models, it acknowledges that beliefs and behaviour may be modified by experience and incorporates change over time.

2.5 Limitations

Although estimated adherence rates were higher than those found in the general adherence literature, they were consistently lower than levels required for effective treatment with HAART (Patterson et al., 2000). The most obvious and fundamental drawback of the studies concerns the measurement of adherence. Many studies did not offer an explicit definition of adherence and tended to calculate adherence as a continuum, while neglecting to categorise 'adherent' or 'non-adherent' behaviour according to an accepted level required for suppression of HIV to undetectable levels (95% or greater: Paterson et al., 2000). Studies relied heavily on self-report measures of adherence, which are believed to over-estimate adherence compared to electronic monitoring systems, due to recall bias and a tendency to give socially desirable responses (Miller & Hays, 2000). The use of multiple measures of adherence has been advocated, since no single measure of adherence is thought to be sufficiently accurate (Arnsten et al., 2001). However, the vast majority of studies did not use multiple measures. Nonetheless, approximately half validated their adherence measure against reduced or undetectable viral load.

Nearly a third of studies used prospective, longitudinal designs, however adherence rates were often averaged over the entire follow-up or measured at only one time-point, precluding the investigation of predictors of change. Furthermore, considering HAART is a potentially life-long treatment, follow-up periods were short. Very little is known about how long-term effects of taking HAART, such as lipodystrophy, treatment fatigue or feeling better impact on adherence in the long term.

The review covered articles published over the last ten years. This time period has seen momentous changes in the treatment of HIV, from mono-therapy through dual therapies to current treatment with HAART. Some of the disparities in the data may reflect these changes. Adherence issues faced by individuals starting antiretroviral treatment in the HAART era may differ from those encountered by individuals starting early treatments with AZT.

The vast majority of the research was conducted in the USA. While similarities in HIV care exist throughout western Europe and America, most notably the widespread availability of treatment, differences that render the direct application of US findings to UK populations imprudent include characteristics of the healthcare service (e.g. NHS versus medical insurance), differences in the epidemiology of HIV (such as the ethnic composition of HIV positive populations), and differences in HIV prescribing guidelines, specifically, when to start treatment and with which drugs.

A possible sampling bias stems from the fact that those who agree to take part in adherence research and complete assessments, particularly those who consent to take part in clinical trials, may be more likely to adhere to their treatment. This problem is exacerbated in longitudinal studies, where participants are required to complete assessments on several occasions. Very few studies used intention to treat analyses, which would help to overcome the problem by classifying those who did not complete the study as non-adherent in the data analyses. Consequently, not only is it likely that adherence rates were inflated, but that

correlates of adherence and non-adherence among those who do not complete the research were overlooked.

2.6 Conclusions

Over the past ten years, investigators have generated a surfeit of correlates and predictors of adherence. Generally these findings show that adherence is a dynamic behaviour that cannot be reliably predicted by the socio-demographic or clinical characteristics of the patient. While efforts to ease the burden of complex drug regimens will no doubt facilitate adherence, the research shows that particular attention should be paid to psychological, behavioural and cognitive factors fuelling adherence or non-adherence. Far from being a passive recipient of treatment, the patient actively processes their experiences and their adherence behaviour often reflects their beliefs. Interventions aimed at supporting or improving adherence should continually monitor the patients' experiences of treatment and their impact on daily life. The major drawback of research to date is its failure to provide or test a coherent theoretical framework within which to explore the relationships between these variables. However the studies have identified multiple correlates of adherence, suggesting need to amass psychological, physical and social resources to promote adherence and ensure treatment success.

Table 2.1: Articles generated from each database

	Medline	PsychINFO	Cinahl	Embase	Personal communication	Total
Number of studies identified	298	98	94	237	1	728
Number rejected	219	70	93	234	0	616
Number used in review	79	28	1	3	1	112

Table 2.2: Types of adherence measures

	Main adherence measure	N
Subjective measures	Self-report	70 (83.3%)
	Review of medical files	2 (2.4%)
Objective measures	MEMS caps	4 (4.8%)
	Pharmacy records	7 (8.3%)
Biological measures	Plasma drug levels	1 (1.2%)

Table 2.3: Methodological characteristics of included studies (n = 112)

Country of research	
USA	77 (68.8%)
UK	7 (6.3%)
France	8 (7.1%)
Italy	6 (5.4%)
Spain	4 (3.6%)
Canada	3 (2.7%)
Netherlands	3 (2.7%)
Switzerland	2 (1.8%)
Sweden	1 (0.9%)
Australia	1 (0.9%)
Research setting	
Hospital clinics	77(68.8%)
Community	25 (22.3%)
Prison	2 (1.8%)
Missing	7 (7.1%)
Sample size	
Average	Median 101.0
Range	15-1095
Data type	
Quantitative	67 (79.8%)
Qualitative	17 (20.2%)
Methodology	
Cross sectional	57 (67.8%)
Longitudinal	2 (2.4%)
Prospective	25 (29.8%)
Retrospective	2 (1.8%)
Model	
Used theoretical model	11 (9.8%)
Year of publication	
<2000	22 (19.6%)
2000	24 (21.4%)
2001	24 (21.4%)
2002	22 (19.6%)
2003	20 (17.9%)

Table 2.4: Characteristics of study participants

	Median (range)
Number of participants	111.0 (11-5073)
Age	
Average age	39.4 (28.0-54.50)
Missing age data	36 (32.1%)
Sex	**N (%)**
Average % male	72.9 (0-100%)
100% male	6 (5.4%)
100% female	11 (9.8%)
Type of antiretroviral therapy	**N (%)**
Mono- or dual therapy	9 (8.1%)
Mixture	23 (20.5%)
HAART	80 (70.2%)
Transmission risk	**N (%)**
Men who have sex with men	22 (19.6%)
IVDU	23 (27.7%)
Heterosexual	7 (6.3%)
Missing data	52 (46.4%)

Table 2.5: Correlates of adherence

	Number of studies reporting variable	Number of studies reporting significant finding	Number of studies reporting association	Number of studies reporting no association
Clinical status: 43.2% found associations with adherence				
Viral load	44	38	0	6
CD4 count	32	15	0	17
Symptom classification	23	5	0	18
Treatment history	10	5	0	5
Time since diagnosis of HIV	15	1	0	14
Social and demographic factors: 33.2% found associations with adherence				
Age	57	20	3	34
Gender	50	8	1	34
Ethnicity	43	12	2	29
Transmission risk	27	5	0	22
Education	38	9	0	29
Income	18	5	1	12
Employment	25	6	2	17
Housing	14	8	3	3
Living status	11	4	1	6
Factors related to the treatment regime: 45.9% found associations with adherence				
Antiretroviral class	21	5	1	15
Regimen complexity	38	13	11	14
Health risk and health protective behaviour: 76.9% found associations with adherence				
Substance use	64	36	8	20
Treatment for substance use	6	4	1	1
Sexual risk behaviour	6	5	1	0
Health protective behaviours	5	2	1	2
Perceptions of HIV and HAART: 88.9% found associations with adherence				
Symptoms and side effects	35	18	12	5
Subjective assessment of health	18	7	4	7
Perceptions of CD4 count and viral load	2	0	2	0
Perceptions of treatment efficacy	17	10	5	2
Adherence self-efficacy	7	7	0	0

	Number of studies reporting variable	Number of studies reporting significant finding	Number of studies reporting association	Number of studies reporting no association
Beliefs relating to initial decision	3	1	2	0
Concerns about antiretrovirals	24	10	12	2
Health beliefs	26	12	10	4
Knowledge and information: 71.5%				
Knowledge of HIV/ARVs/adherence	25	10	7	8
Use and satisfaction with information	12	5	4	3
Psychological characteristics: 78.3%				
Negative affect	37	23	9	5
Positive affect	9	5	4	0
Stress and life events	11	5	5	1
Social support	31	18	6	7
Psychiatric illness	8	4	1	4
Coping	8	8	0	0
Locus of control	3	3	0	0
Cognitive/Neurological dysfunction	1	1	0	0
Personality	1	0	0	1
Characteristics of the health service: 58.0%				
Dr-patient relationship	20	8	8	4
Use of medical services	10	4	2	4
Access to healthcare	3	2	1	0
Clinical setting	2	0	0	2
Facilitators of adherence	8	0	6	2

Chapter 3
THE SELF-REGUALTORY MODEL (SRM)

The critical review of the HIV adherence literature described in Chapter 2 exposed a lack of a theory driven research into adherence to HAART. This is an important omission if the goal of research is to inform the design of interventions to improve adherence. Advances in health psychology have lead to the adoption of several theoretical frameworks to explain health and illness related behaviours such as adherence to treatment. Many of these models fall into the category of Social Cognition Models (SCMs). This chapter will briefly describe the most commonly used models and their application to adherence behaviour. The remainder of the chapter will focus on the description and application of the self-regulatory model proposed by Leventhal et al. (1980).

3.1 Social cognition models

This section will briefly describe and review the main social cognition models that have been applied to adherence.

3.1.1 The Health Belief Model (HBM)

The Health Belief Model (HBM: Hochbaum, 1956, Rosenstock, 1966, Becker, 1974, Becker & Rosenstock, 1987) was originally developed to explain preventative health behaviour. It has also been used to predict the behaviour of patients with chronic and acute illnesses. The model proposes that the likelihood of engaging in a particular action (such as adherence to medication) is a function of two main factors:

1 Health threat: The degree to which the individual perceives a threat to their health, which causes a state of readiness to act. The perception of a health threat is influenced by the individuals' perception of their susceptibility to illness, the perceived seriousness of the illness, a more general concern and motivation towards health and illness and perceived control over the illness.

2 Response effectiveness: The perception that the proposed course of action will reduce the threat, which provides the preferred course of action. Whether

the person believes the proposed action will reduce the threat depends on their perception of potential costs and benefits of the proposed action, and an assessment of whether the perceived benefits outweigh the costs.

It is proposed that these concepts are modified by individual differences such as personality and demographic variables. Whether or not the behaviour is actually carried out is also thought to be due to 'cues to action' (Becker & Maiman, 1975). These cues can be internal (such as experiencing symptoms of illness) or external (such as a health awareness campaign or the advice of a doctor). The components of the HBM are illustrated in Figure 3.1.

The Health Belief Model has been criticised on the grounds that the components are not clearly defined and the absence of rules as to how they should be combined (Sheeran & Abraham, 1996). Although a review of 46 studies showed correlations between all HBM concepts and behaviour (Janz & Becker, 1984), a later meta-analysis showed that the effect sizes were small (Harrison et al., 1992). Furthermore, the concepts of 'cues to action' and 'health motivation' have not been adequately operationalised or tested (Amitage & Conner, 2000). In a review of the HBM, Sheeran & Abraham (1996) concluded that the weak predictive validity of the HBM was due to the poor definition of concepts with no evidence that the concepts differ from variables proposed in other models. Researchers utilising the model have used a variety of measures, combinations of variables and analyses, making comparison between studies difficult. One of the most potent criticisms of the HBM is that it neglects the idea of change in behaviour over time (Schwarzer, 1992), limiting its utility for the investigation of adherence.

In spite of its limitations, studies applying the health belief model to adherence identify some of the cognitions that might be salient, providing support for the influence of certain beliefs on adherence, if not for the HBM as a whole. Higher adherence rates have been associated with the perception of being highly susceptible to becoming ill if one does not take treatment (Kelly et al., 1987; Nelson et al.; 1978, Taylor, 1979). Adherence decisions have also been related

to a cost-benefit analysis in which the benefits of treatment are weighed up against perceived barriers (Kelly et al., 1987; Nelson et al.; 1978, Taylor, 1979).

3.1.2 The Theories of Reasoned Action and Planned Behaviour (TRA: Ajzen & Fishbein, 1980; Fishbein & Ajzen, 1975); TPB: Ajzen, 1988)

Within the Theory of Reasoned Action (TRA), intention is proposed to be the proximal determinant of behaviour. The more one intends to carry out a particular behaviour, the more likely they are to do so. Within this model, intention is determined by attitudes and subjective norms or 'normative beliefs'. The TRA was developed to deal with simple behaviours that only required intention in order to perform them, rather than personal resources or environmental factors, and as such, lacked the complexity to deal with more complex behaviours that were not completely under voluntary control (Armitage & Connor, 2000). The Theory of Planned Behaviour (TPB) extends the TRA by including the concept of perceived behavioural control (PBC) as the determinant of both intentions and behaviour. PBC stems from the idea that the easier a behaviour is perceived to be, the more likely one will intend to perform it. The TPB is illustrated in Figure 3.2.

The TPB has been applied to the prediction of a range of health related behaviours, including adherence to medication. In a review, Godin & Kok (1996) found that the TPB accounted for 41% of the variance in behavioural intentions and 34% of the variance in behaviours. However, evidence from meta-analyses suggest that the TPB should be extended in order to encompass the additional concepts of self-identity and moral norms (Conner & Armitage, 1998), since these variables independently predict intention. There is some support for the TRA/TPB in relation to adherence behaviour. The perceived views of others including family, friends and doctors (normative beliefs) have been associated with adherence (Cochran & Gitlin, 1988; Reid & Christensen, 1988; Reid et al., 1985).

The main criticisms of research using SCMs are that there has been very little consistency across studies in terms of the concepts measured, and the variance in adherence explained by these models has been small (Marteau, 1995). A fundamental problem with the application

of the HBM and TPB to the investigation of adherence behaviour is the fact that within these models, adherence is viewed as a static, one off decision, yet evidence suggests that adherence is a changeable behaviour and that adherence decisions are made in stages (Schwarzer, 1992). These SCMs seem to be more relevant to one-off decisions about preventative health measures than to explaining adherence to treatment for chronic conditions (Connor & Norman, 1996).

3.2 The Self-Regulatory Model (SRM: Leventhal et al., 1980)

The SRM is a dynamic model that takes account of changes in personal perceptions of illness and coping responses due to continual appraisal of adherence behaviours over time (Leventhal et al., 1980; 1992). Unlike social cognition models, the SRM specifies the content of beliefs that precede behaviour as well as the process by which they influence behaviour (Leventhal et al., 2003).

3.2.1 Background to SRM

The Self-Regulatory Model (SRM: Leventhal & Nerenz, 1980; Leventhal & Cameron, 1987) also called the Common Sense Model (CSM: Leventhal et al., 2003) was designed to describe and predict how individuals respond and cope with health threats. The model takes account of both the individual's cognitive and emotional response to a health threat. It stems from work investigating the impact on fear on attitude and behaviour change. A series of studies investigating the impact of fear arousing messages on health prevention behaviours (see Leventhal et al., 1997) showed that fear aroused by the threat of illness was not an adequate motivation to engage in health protective behaviour. In order to be effective, fear messages needed to be accompanied by an 'action plan', for example, providing clear instructions about how to successfully complete the preventative action or reviewing the individual's schedule to help the individual to incorporate the action into their daily routine. This combination of fear message and action plan resulted in significant increases in uptake of tetanus vaccinations (Leventhal et al., 1965, 1966) and reductions in cigarette smoking (Leventhal et al., 1967). Leventhal (1970) proposed that this combination of fear arousal and action were linked by the "cognitive representation" of the health threat. Interest became

focused on how individuals perceive health threats, and how these cognitive representations of health threats are linked to behaviour.

3.2.2 Overview of the SRM

Self regulation has been defined as:

"A systematic process involving conscious efforts to modulate thoughts, emotions and behaviours in order to achieve goals within a changing environment" (Zneider et al., 2000)

The Self-Regulatory Model (SRM: Leventhal et al., 1980; Leventhal & Cameron, 1987) conceptualises the patient as an active problem solver, who chooses a particular course of action (or inaction) in an attempt to reduce the perceived discrepancy between their current health and a future goal state. Within self-regulatory models, goals are set, strategies to achieve goals are developed and acted upon, the successes (or failures) of these strategies are appraised and revisions of goals and strategies are made. The individual's chosen response to a health threat is shaped by the way they interpret and evaluate the illness, consequently individuals may differ in their response to the same health threat. Whether to take a particular course of action or 'coping response' is determined by whether it makes sense in terms of the individual's perceptions of the illness and their personal experience of symptoms. Within the SRM, adherence or non-adherence to treatment is conceptualised as one of several possible behaviours or coping responses that may be adopted to cope with an illness threat. There are broadly three stages of processing within the SRM, occurring in parallel at cognitive and emotional levels. These stages are shown in Figure 3.3 and described below:

1. The individual builds a cognitive representation of the threat, from internal cues such as experience of symptoms, and/or from external cues such as information.
2. The individual develops an action plan or 'coping procedure' (for example to take medication), which is implemented in order to deal with the threat.

3. The outcome of the action plan is appraised.

These stages are dynamic rather than discreet, so that while the utilisation of a coping procedure (I'll stay off work and rest) may arise from a particular representation of the health threat (it's just a bug that's going round), the perceived outcome of the coping procedure at the appraisal stage (my symptoms have got worse) may feed back and result in the selection of an alternative coping strategy (I'll see the doctor) or change the representation (it might be bowel cancer).

Within the SRM, emotional processes run parallel to cognitive mechanisms (Leventhal et al., 2001). Health threats generate emotional states of fear or distress and a need to manage these emotions (fear control), as well as the need for managing the threat of illness (danger control). Because the individual is motivated to minimise fear, they may use seemingly irrational coping procedures to deal with their representation of illness. This is exemplified by a patient who believes that a lump in her chest is a tumour, but who delays seeking help because she is frightened of the diagnosis (Phelan et al., 1992). In terms of the SRM, her coping response (to delay seeking help) is an attempt to cope with the emotion (fear) aroused by her cognitive representation of breast cancer (Horne & Weinman, 1998).

3.2.3 The central role of symptom perception in the SRM

Leventhal (1982) proposed a central role for symptom perceptions in the formulation of illness representations and the selection of coping procedures. In an interview-based study, Meyer et al (1985) found that the vast majority of patients receiving treatment for hypertension believed that they could tell (through their experience of symptoms) when their blood pressure was high, however, when asked a general question about whether most people can tell when their blood pressure is up, nearly all participants indicated that it was not possible. Leventhal (1982) proposed that that their personal representation of hypertension was comprised of a combination of symptoms and a label. Several other studies show that this combination of symptoms and label is central to representations of a variety of illness conditions (Lau & Hartman, 1983, Nerenz et al., 1982, Bishop, 1991).

Leventhal (1982) proposed that patients use symptoms to appraise the effectiveness of their treatment and often drop out of treatment, even if the treatment is successful in clinical terms, if it does not have a postitive impact on their symptoms. Leventhal (1982) summised that in the patient's view, effective treatment should alleviate symptoms, an ineffective treatment will not change the symptom and a 'dangerous' treatment will make the symptom worse or cause its own. The individual taking treatment may also use symptoms to mark the onset of disease and to isolate the cause.

3.2.4 Illness representations

While symptoms have been shown to be central to the experience of a health condition, several studies utilising either open ended interviews or factor analytic techniques across a range of illnesses including the common cold, hypertension and pulmonary disease contributed to the discovery of a further four domains of illness representations which help patients make sense of their symptoms, assess risks to their health and direct their actions during recovery (Lau & Hartman, 1983; Lau et al., 1989, Bauman & Leventhal; 1985; Meyer et al., 1985; Lacroix et al., 1991). Bishop et al. (1991) presented participants with descriptions of specific sets of symptoms and asked them what else would be experienced by individuals suffering them. They found 90% of participants' responses could be attributed to five coherent themes or components: identity, cause, timeline, consequences and cure. Identity refers to the specific concrete symptoms the individual associates with the disease, and an abstract name or label for them. Cause relates to how the individual believes one acquires the disease. Timeline refers to the individual's beliefs about the likely course and duration of illness, consequences are the physical, social and psychological outcomes the individual would expect as a result of having the condition and control/cure refers to the extent to which the individual believes the condition to be amenable to cure, or control by medicines or other means (Leventhal et al., 1992, 1997). These themes or components are known as 'illness perceptions' or 'illness representations.' These terms will be used interchangeably throughout this thesis. Although the structure of illness representations is constant across illnesses and contexts, their content varies between individuals (Leventhal et al., 1985). A range of

influences on these concepts have been proposed, including the views of significant others and past experience (Leventhal et al., 1992) as well as cultural norms (Farmer, 1988, Farmer and Good, 1991).

3.2.4.1 Measurement of illness perceptions

In a review of studies assessing illness perceptions between 1985-1995, Sharloo & Kaptein (1997) found that the majority of researchers used open-ended or semi-structured interviews to assess illness representations. Typically, researchers analysed this interview data in terms of codes or categories. While this type of analysis has the benefit or tapping into illness perceptions directly, without forcing participants to respond to predefined categories, it is disadvantaged by methodological problems including time constraints and ensuing low sample sizes, difficulty generalising results and social desirability. Indeed, even open-ended interview questions may be subtly biased (Leventhal & Nerenz, 1985).

Sharloo & Kaptein (1997) found quantitative measures had been used to measure beliefs about control, causes, consequences, identity and timeline, however, most studies measured only one or two of these dimensions and usually used separate instruments to do so. The development of the Illness Perceptions Questionnaire, a self-report measure developed to assess the five components of illness representation proposed by the SRM (identity, cause, timeline consequences and cure/control: Weinman et al., 1996) facilitated the empirical investigation of the model and was the catalyst for a surge of research interest in the utility of the SRM for predicting illness and treatment behaviours and outcomes in chronic disease. Three additional components of illness representation have been added to the revised version of this questionnaire: illness coherence or the degree to which the individual perceives they understand or can make sense of their condition, cyclical timeline which refers to the perception of symptoms as changeable, unpredictable or having periods of remission, and emotional representations or the degree of anger, anxiety and depression the individual associates with their condition (IPQ-R; Moss-Morris et al., 2002).

3.2.5 Empirical support for the SRM

Several cross-sectional studies have linked illness perceptions to coping and outcome over a range of acute and chronic illnesses including arthritis, breast cancer, diabetes, osteoarthritis, haemophilia, Huntington's disease, asthma, chronic fatigue syndrome and recovery from myocardial infarction (Llewellyn et al., 2003; Helder et al., 2002; Edwards et al., 2001; Sharpe et al., 2001; Byer & Myers, 2000; Orbell et al., 1998; Hampson, 1997; Buick, 1997; Petrie et al., 1996). Results from studies applying illness perceptions to different types of outcomes (functional outcomes, psychological response to illness and self-management of chronic illness) are outlined below.

3.2.5.1 Illness perceptions and functional outcomes

Beliefs about the identity, timeline, consequences and control of illness have been linked to functional outcome following treatment. Using a longitudinal research design, Petrie et al (1996) showed that illness perceptions on admission to hospital were related to outcome after myocardial infarction (MI). Specifically, those who believed that their illness would last for a short time and that it had less serious consequences were more likely to return to work within six weeks of the acute event. Possessing the belief that MI has serious consequences was associated with subsequent disability at home and work, as well as in recreational and social activities, while perceiving a stronger illness identity on admission was associated with sexual dysfunction after three and six months post MI. Orbell et al. (1998) found that perceptions of cause and control of osteoarthritis elicited before surgery predicted functional activity at follow-up. Perceptions of identity, consequences and control have been associated with physical functioning in patients with chronic fatigue syndrome and Addison's disease (Moss-Morris et al., 1996; Heijmans & de Ridder, 1998; Heijmans, 1999). In a prospective study, McCarthy et al. (2003) showed that patients' expectations of recovery following oral surgery predicted recovery over and above medical factors.

3.2.5.2 Illness perceptions and psychological response to illness

Identity, cause, control, timeline and consequences have been related to mental health and psychological adjustment to illness (Heijmans & deRidder, 1998; Heijmans, 1998, Moss-

Morris et al. (1996). Murphy et al. (1999) found depression in patients with rheumatoid arthritis (RA) was associated with viewing the consequences of RA negatively and a perceived lack of control over the illness. However, the nature of the relationship between depression and illness perceptions has not been clarified to date. While the studies above have conceptualised depression as an outcome variable, they have used cross-sectional research designs. Consequently, it is not possible to determine whether depression leads to a negative view of illness, or whether a negative view of illness and perceived lack of control over it leads to depression. There is clearly a need for a prospective study in order to clarify the nature of relationships between illness representations and negative affect.

3.2.5.3 The SRM and adherence to treatment

Within the SRM, adherence to medication is conceptualised as a coping response, chosen by the individual to deal with the illness threat (Leventhal & Cameron, 1987, Leventhal et al., 1992). Leventhal et al. (1992) proposed that patients are more likely to adhere to their medication if it makes common sense in terms of their current symptoms and/or past experiences and their representation of the illness. Few studies have investigated the role of illness perceptions in explaining adherence however, there is some empirical evidence that the SRM is a useful model within which to frame adherence decisions. Meyer et al (1985) showed that compliance to anti-hypertensive medication was related to patients' perceptions of the treatment as effectively controlling the symptoms they associated with their condition. In two studies, beliefs about the controllability of MI, elicited at baseline, predicted subsequent attendance at rehabilitation classes (Petrie et al., 1996; Cooper et al., 1999).

In a cross sectional study of adherence to clotting factor medication among individuals with severe haemophilia, Llewellyn et al. (2003) found higher adherence to the frequency of prophylactic infusions of clotting factor among patients reporting stronger perceptions of illness identity, while those who perceived the personal consequences associated with their condition to be less severe were more likely to under-treat. Similarly, in a study of adherence to preventer medication among patients with asthma, Horne & Weinman (2002) found that patients who perceived the consequences of their condition to be more severe were less

likely to adhere to their prophylactic medication. The direction of these findings is contrary to hypotheses generated from the SRM, which would predict higher adherence among those with more catastrophic illness perceptions. It is possible that rather than causing non-adherence, higher perceptions of negative consequences may have been the result of uncontrolled haemophilia or asthma stemming from earlier non-adherence. There is a dearth of prospective research into the relationships between illness perceptions and adherence, which is required in order to illuminate the direction of these relationships.

3.2.6 Treatment beliefs and the SRM

Horne (1997, 2003) proposed that in addition to perceptions of their condition, patients hold beliefs about the coping procedures that they adopt. He asserts that the ability of the SRM to explain treatment decisions would be improved by incorporating beliefs about treatment into the model. In a review of studies exploring patients' perceptions of medications, Horne (1997) noted that similar beliefs were held across studies carried out in the UK, USA and Europe. Horne et al. (1999) presented a sample of 524 patients with asthma, renal disease, diabetes, heart disease and psychiatric disorders with statements elicited from open-ended interviews with patients receiving treatment for chronic illness and others identified in the literature. The patients were required to rate the extent to which they agreed or disagreed with each statement. Using a principal component analysis (PCA), core constructs regarding beliefs held about specific prescribed medicines and more general beliefs about medicines as a whole were identified. Two core themes related to specific medicines were perceptions of personal necessity or need for the treatment in order to preserve health or recover from illness, and concerns about the potential adverse effects of taking it (including concerns about side effects, dependence or adverse long-term effects from continued use). The 'concerns' dimension encompasses both emotional and cognitive representations of medication, similar to the parallel processing proposed by the SRM with regard to illness representations (Leventhal et al., 1980). The PCA showed that beliefs about medicines in general could be organised into two themes 'general overuse' containing items stemming from views that doctors prescribe medicines too readily and 'general harm' referring to beliefs that medicines are inherently poisonous or detrimental to health.

Horne (1999) proposed that while patients' perceptions of their illness help them to make sense of their experience and guide their adoption of coping response (e.g. whether or not to take medication), their choice of coping procedure might also be influenced by their views about their personal necessity of the procedure as well as concerns about the potential adverse effects. Within this extended SRM (eSRM, Horne, 2003; see Figure 3.4), treatment beliefs are influenced by illness perceptions in a logically consistent way. The nature of these proposed relationships are described below.

3.2.6.1 Necessity beliefs

3.2.6.1.1 Symptoms and necessity beliefs

Within this extended SRM (Horne, 1997, 2003), perceptions of symptoms guide treatment necessity through several possible mechanisms. While severe symptoms might serve as a concrete reminder of the illness and thereby reinforce the need for treatment, their absence may lead one to believe that their condition is less serious than it is and as a result, to doubt the necessity for treatment (Siegel & Gorey, 1997). Appraisal of the cause of symptoms may also influence treatment beliefs: need for continued treatment may be questioned where it is perceived as having failed to alleviate symptoms of disease, while concerns may be aroused where symptoms are attributed to side effects (Leventhal et al., 1986; Horne, 2003).

3.2.6.1.2 Illness representations and necessity beliefs

If the proposed treatment is perceived to be appropriate for the illness, patients' perceptions of treatment efficacy may be be correlated with their perception of personal necessity for treatment. However, it is possible that a patient can perceive a treatment as effective, yet not necessarily believe that they need to take it (Horne et al., 1997). Beliefs about personal need for treatment may also be influenced by perceptions of timeline (whether the condition is perceived to be acute, chronic or cyclical). For example, patients perceiving their symptoms to be cyclical may doubt the need for their medicine at times at which when they are not experiencing symptoms they associate with the illness (Horne et al., 2003). Similarly one who perceives the physical, social and psychological consequences of their condition to be

minimal may doubt the necessity for medical intervention. It is also possible that beliefs about the likely cause of a condition may influence the perceived need for a particular treatment. For example a patient who perceives that their depression is caused by a biological imbalance may be more likely to take antidepressant medication than one who believes their condition is the result of a transient social situation.

3.2.6.2 Concerns about adverse effects

3.2.6.2.1 Concerns and beliefs about medicines in general

Previous negative experiences of treatment as well as negative views about medicines in general, such that they are intrinsically harmful or overused by doctors, may ignite concern about a particular prescribed medicine (Horne, 2003). Pre-held negative beliefs about a treatment may also increase readiness to attribute ambiguous symptoms to medication rather than some other cause such as the underlying illness, or to possible non-illness causes such as anxiety or ageing (Siegel et al., 1999), and may contribute to the 'nocebo effect' where patients in clinical trials taking placebo have reported side effects to the inactive substance (Crow et al., 1999). Some patients perceive themselves to be particularly sensitive or susceptible to the potential adverse effects of medicines in general and are more predisposed to concerns about the medicines they have been prescribed (Horne, 1997).

3.2.6.3 Support for the extended SRM proposed by Horne (1997; 2003)

Treatment perceptions have been related to outcome in chronic illness. In a longitudinal study, Buick (1997) found that breast cancer patients who had strong concerns about the potential adverse effects of chemotherapy or radiation were more likely to experience subsequent negative physical and emotional consequences. Using the Beliefs about Medicines Questionnaire (Horne et al., 1999) to measure necessity and concerns constructs, recent studies have provided preliminary support for the utility of this extended model in explaining adherence to medicines among patients with chronic illnesses. In particular, the degree of necessity or need for treatment has been related to adherence to asthma medication (Byer & Myers, 2000) and the frequency of prophylactic infusions among patients with haemophilia (Llewellyn et al., 2003), while the strength of patients concerns about

adverse effects of medication have been associated to low adherence to Highly Active Antiretroviral Medicines among patients with HIV/AIDS (Horne et al., in press).

A recent study of adherence to preventer medication among patients with asthma lends further support to the model (Horne & Weinman, 2002). Patients reporting low adherence reported lower necessity beliefs and stronger concerns about their treatment. Furthermore, perceptions of asthma and treatment were related in a way that was consistent with the model: necessity beliefs were positively related to asthma timeline and asthma consequences, while concerns were not related to either timeline or consequences. Although illness and treatment beliefs combined accounted for 30% of the variance in adherence over and above that explained by clinical and demographic variables, structured equational modelling showed that treatment necessity was largely responsible for the variation in adherence scores, while illness perceptions exerted a more indirect influence on adherence by influencing patients perceptions of necessity.

3.2.6.4 Key questions for future research

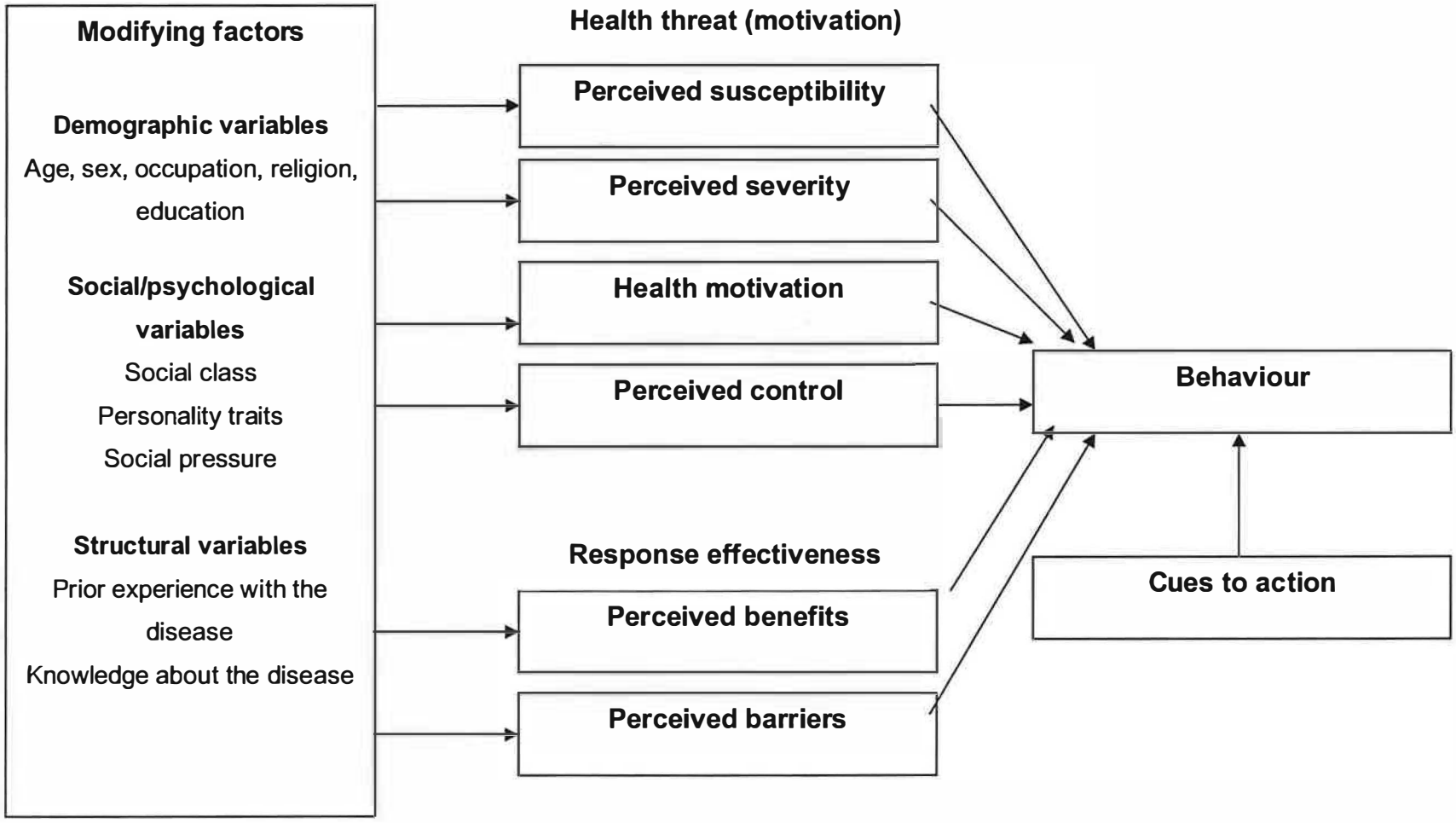
The complexity of the SRM in relation to other models increases its explanatory power but also makes it difficult to operationalise and test empirically. To date, the SRM has not been tested in its entirety. Perhaps the most important advantage of the SRM over the TPB and HBM in terms of its application to adherence is that it conceptualises the relationship between beliefs and adherence as dynamic rather than static, by including a feedback loop whereby patients appraise the impact of taking or not taking their treatment and adjust their beliefs or behaviour accordingly (Leventhal et al., 1984). However, very little research to date has operationalised this appraisal mechanism. Studies to date have been constrained by their reliance on cross-sectional research methodologies.

An important yet under-researched question with regard to the utility of theoretical models of adherence is whether the components proposed to account for behaviour are amenable to change, and whether changing components of the model influence outcome. In the only published study of its kind, Petrie et al. (2002) showed that introducing an intervention to

change illness perceptions improved outcome post MI. Patients were randomised to receive either standard rehabilitation care given by nurses or an intervention aimed at changing their illness perceptions. Those in the intervention group reported positive changes in their views of MI, were better prepared for leaving hospital and returned to work significantly faster than controls. Those who received the intervention also reported significantly lower rates of angina at the three-month follow-up. However there has been very little work investigating how perceptions of illness or treatment change over time or in relation to medical interventions such as receiving treatment for chronic illness, nor how changes in illness perceptions impact on adherence and outcome.

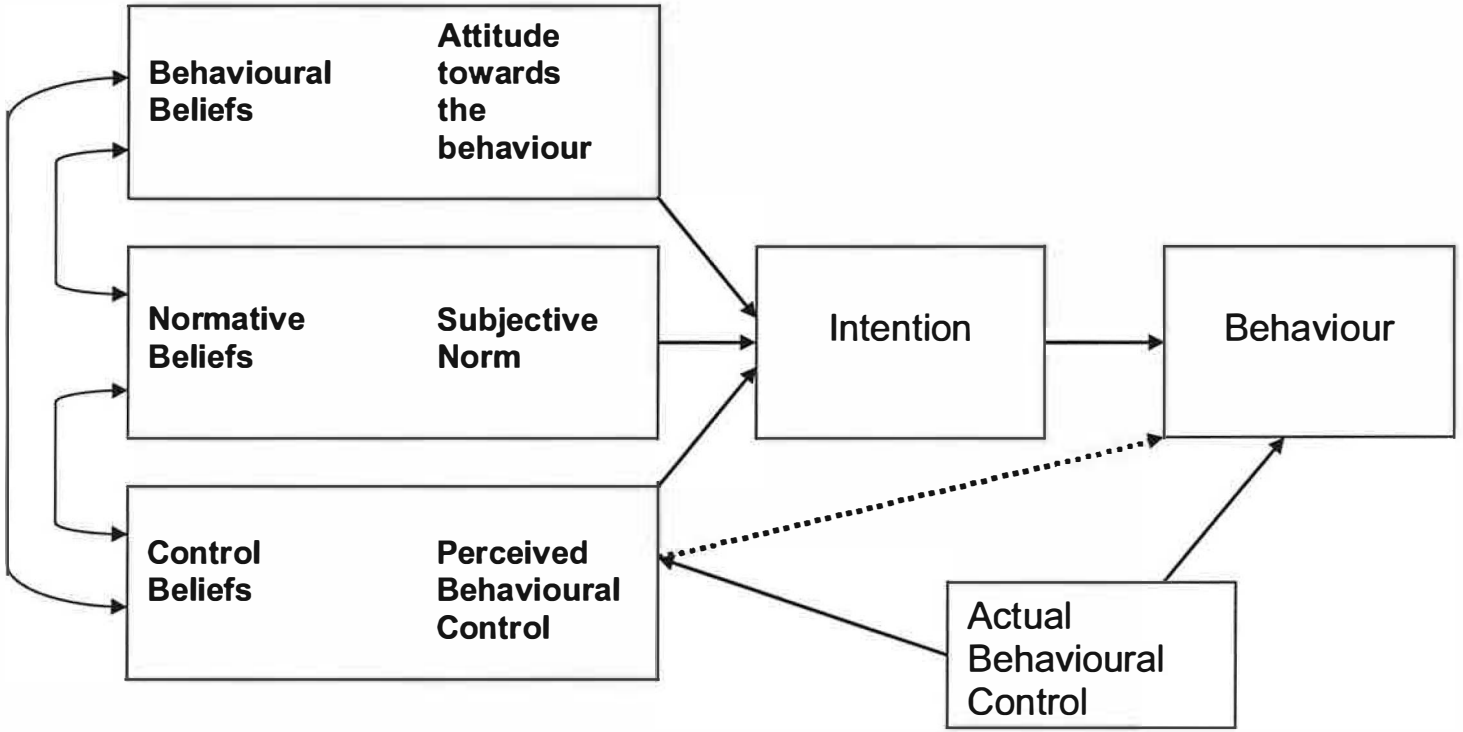
Horne (2003) proposed possible antecedents of necessity and concerns. Necessity beliefs were proposed to stem from patients perceptions of their illness (identity, timeline, consequences) and its amenability to control. In addition, he suggests that laboratory test results may feed back into patients' perceptions of necessity for treatment. These relationships have received little empirical investigation to date. Furthermore no published studies to date have explored the ways in which previous experiences of medicine impact on concerns.

Figure 3.1: The Health Belief Model (HBM)



Adapted from Connor, M & Norman, P. Health behaviour in Predicting Health Behaviour, Connor, M & Norman, P (Eds.) (1996)

Figure 3.2: The Theory of Planned Behaviour (TPB)



From Icek Aizen, 2002 (http://www-unix.oit.umass.edu/%7Eaizen/index.html)

Figure 3.3: The Self-Regulatory Model: Leventhal et al (1980)

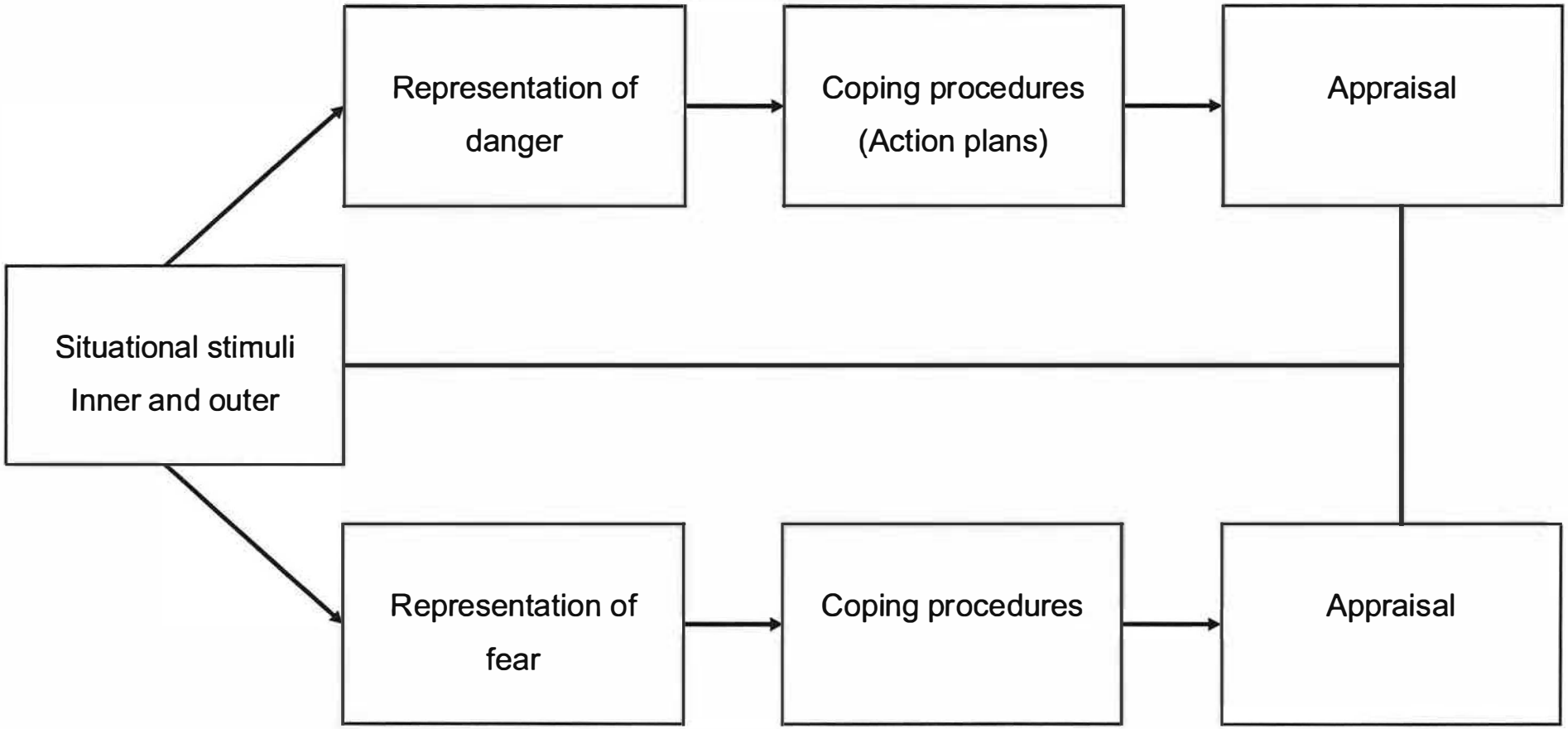
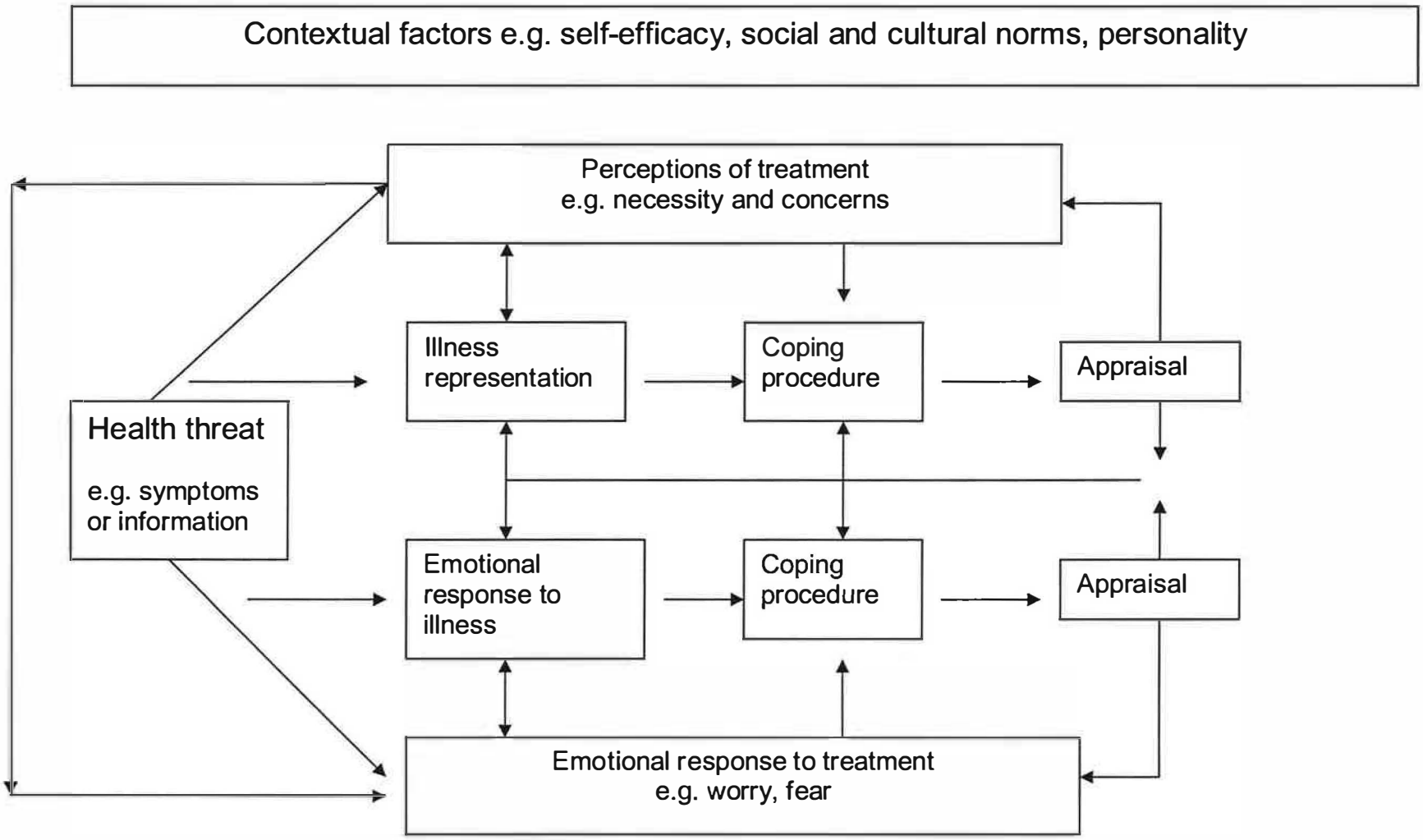


Figure 3.4: Treatment perceptions and the Self-Regulatory Model (Horne, 2003)



Chapter 4
RATIONALE AND RESEARCH AIMS

4.1 Rationale for empirical work

This section provides a summary of the introductory chapters, a rationale for the studies contained within the thesis, and an outline of research questions to be addressed.

4.1.1 Summary of preceding chapters

Chapter 1 outlined the history of HIV and antiretroviral treatments to date. In summary, while recent years have seen dramatic decreases in mortality and increases in quality of life among HIV positive patients living in the UK, the success of HAART rests heavily on strict adherence to demanding drug regimens. Recent clinical studies show that at least 95% of HAART medications need to be taken on time each day in order to achieve and sustain undetectable viral load (Patterson et al., 2000), and thereby improve immunity and prevent disease. The consequences of low adherence to HAART are severe. In addition to the lack of clinical benefit, viral resistance can quickly develop and extend to whole classes of drugs, reducing future treatment options. Furthermore, multi-drug resistant HIV may be transmitted to others, causing a serious public health risk. The levels of adherence required for the clinical success of HAART are unprecedented in chronic illness and evidence from studies to date show that average adherence rates fall vastly short of this figure.

The results of a critical review of the HIV adherence literature formed the second chapter of this thesis. While research studies to date have unveiled a plethora of correlates of high and low adherence, many of these studies focused on associations between socio-demographic variables and adherence behaviour. While some significant relationships have been identified, these findings in isolation are cannot be used to inform efforts to increase adherence, since socio-demographic variables are not amenable to change. Recent prospective, longitudinal studies showed that adherence was not a static behaviour but tended to fluctuate over time. The most consistent predictors and correlates of adherence to HAART were psychological,

behavioural and cognitive in nature. The major drawback of research to date was its failure to provide or test a coherent theoretical framework within which to explore the relationships between these variables.

Chapter 3 outlined the major social cognition and self-regulatory models that have been proposed as theoretical frameworks within which to investigate health behaviours. While social cognition models have been applied to the study of adherence, with some success, they have been criticised for lacking consistency across studies in terms of the concepts measured, explaining very little of the variation in adherence, and viewing adherence as a static, once-off decision. The Self-Regulatory Model (SRM) proposed by Leventhal et al., (1980) was deemed to be more applicable to the study of adherence, since the emphasis is on the patient as an active problem solver, who responds to threats to their health based on their interpretations and evaluations of the illness. Within the SRM, adherence is framed as a type of coping behaviour used to deal with the threat of illness. Horne (1997, 2003) proposed that patients' beliefs about their treatment should be added to the SRM in order to operationalise the model in relation to adherence to treatment. In particular, he suggested that patients' perceptions of their personal necessity for treatment and concerns about adverse effects would be directly related to adherence. Within this extended SRM, illness perceptions would be related to necessity and concerns in a logically consistent way. The utility of this extended SRM (referred to as the eSRM throughout this thesis) as a framework for predicting adherence to HAART will be explored in this thesis.

4.1.2 The problem to be addressed

Advances in the measurement of illness perceptions and beliefs about medicines have lead to a plethora of research studies testing the utility of the SRM in relation to coping and outcome among patients with acute and chronic illness. Fewer studies have explored the model in relation to adherence. While some studies provide support for the model by identifying relationships between illness perceptions, beliefs about treatment and adherence, the majority of studies to date have used cross-sectional research designs. A major drawback of

this type of research design is that cause and effect cannot be inferred, since beliefs could predict adherence, or vice versa.

This thesis was designed to test the utility of the SRM (Leventhal et al., 1980) and the extended model proposed by Horne (1997; 2003) in predicting adherence to HAART. The empirical section of this thesis will be split into three studies. The first will address the question of causality, in order to find out whether perceptions of HIV and beliefs about HAART, elicited before initiating a new treatment, predict subsequent adherence. Moreover, the model has not been tested in its entirety. The SRM proposes a feedback mechanism whereby patients appraise their illness and the procedures they have selected to cope with it (such as whether or not to adhere to medication), and adapt their behaviour and beliefs accordingly. Leventhal et al. (1982) and Horne (2003) suggest that patients' primary means of treatment appraisal are their experiences of concrete symptoms, and whether the symptoms they are experiencing are attributed to their illness or treatment. The second section of the thesis will investigate the role of symptom appraisal and attribution in relation to adherence to HAART, and will explore how patients' appraisals of their symptoms over time feed back into their perceptions of HIV and HAART.

Finally, there has been very little published research to date exploring how perceptions of illness and treatment change or evolve over time or in response to medical intervention such as initiating a new treatment regimen. Furthermore, it is not known how these changes over time are related to adherence. The third section of the study was designed to explore relationships between perceptions of HIV and HAART and adherence over the treatment process.

4.2 Overview of research aims

AIM 1: To evaluate the impact of patients' perceptions of HIV and beliefs about HAART *before starting their treatment* on subsequent adherence.

It was expected that illness representations would influence adherence directly. This was a direct test of the original SRM (Leventhal et al., 1980) in which coping procedures such as adherence to treatment recommendations are influenced by patients' representations of their illness. In order to operationalise the SRM in relation to adherence to treatment, Horne (1997; 2003) incorporated necessity and concerns within this model. Within this extended model, patients' perceptions of their personal necessity for HAART and their concerns would be directly related to adherence.

AIM 2: To explore antecedents of beliefs about personal necessity for HAART and concerns about potential adverse effects HAART in order to test hypotheses generated by the extended Self Regulatory Model (eSRM: Horne et al., 1997; 2003).

It was expected that patients' representations of their illness would influence their perceived necessity for treatment, while perceptions of medicines in general and past experiences would influence concerns.

AIM 3: The third general aim was to evaluate patients' appraisals of their symptom experiences in relation to their adherence and perceptions of HIV and HAART.

It was expected that symptom appraisal would be directly related to adherence, with patients who experience a lack of improvement in the symptoms they attribute to HIV, or persistent HAART-related symptoms, being less adherent to their treatment. Furthermore, it was expected that patients' appraisals of their symptoms would be related to perceived necessity for treatment and to concerns about adverse effects of treatment in a logically consistent way, with symptoms attributed to illness and those attributed to treatment side effects impinging differentially on necessity beliefs and concerns.

AIM 4: The fourth general aim was to explore how perceptions of HIV and HAART change over the first six months of treatment, and how these changes impact on adherence.

It was expected that adherence to HAART would be influenced not only by baseline perceptions of illness and treatment but also by the degree to which these perceptions changed over time.

Study 1 addressed Aims 1 and 2; Study 2 addressed Aim 3 and Study 3 addressed Aim 4. Specific hypotheses relating to these aims can be found in the individual studies.

Chapter 5
MEASUREMENT OF ADHERENCE

This chapter gives a brief overview of the methods available to measure adherence, and includes empirical research relevant to measuring adherence to HAART.

5.1 Difficulties associated with the measurement of adherence

The measurement of adherence is fraught with difficulties, most of which arise from 'self-presentational' or 'reactivity' biases on the part of the patient. These biases refer to the tendency of people tend to behave in a socially desirable way if they think they are being observed. Many people want to be thought of as a 'good patient' and are reluctant to admit to non-adherence because they risk the disapproval of their doctor. Therefore patients may under-report non-adherence or take more than normal immediately prior to adherence testing.

There are two broad categories of adherence measurement. Direct measures involve directly observing the ingestion of the drug or detecting its presence in body fluids. Indirect measures assume ingestion of the drug based on a proxy measure such as patient self-report, pharmacy records or pill counts. Some of the commonly used direct and indirect methods for measuring adherence to HAART are described below.

5.2 Direct measures of adherence

5.2.1 Directly observed therapy (DOT)

The patient's medication taking behaviour is observed by a clinician, researcher or significant other. This method is usually impractical in research situations and is clearly open to reactivity bias. However, there has been some success in improving adherence to antiretrovirals using these methods in interventions where patients who have problems with adherence have been randomised to receive voluntary supervision of treatment (Stenzel et al., 2001; Wall et al., 1995).

5.2.2 Measurement of drug concentrations in body fluids

The concentration of a drug is measured in body fluids as evidence that the medication has been taken. The advantage of this over other methods is that it confirms that the drug has actually been ingested. However, there is often little correlation between the amount of medication taken and the concentration found in body fluids, with considerable variation between individuals in terms of drug absorption, distribution, metabolism and elimination. Furthermore these processes can differ within the same person over time. Another disadvantage is that tests will usually be arranged in advance, giving the patient the opportunity to alter their adherence behaviour. Thus the reliability of this method is disputable. Moreover, this technique gives little indication of how the individual is actually taking their drugs in terms of the timing of dosages, which can be crucial to the success of many antiretroviral agents. The method is also expensive and impractical for longitudinal research studies, where repeated measurement of adherence is necessary.

5.3 Indirect measures of adherence

5.3.1 Patient diary cards

This method entails asking patients to keep diaries of their medication use each day. However, keeping a diary may well influence adherence by serving as a reminder, and those who are more adherent to their pills may be more likely to fill in the diary.

5.3.2 Pill count

The number of tablets left in the container are compared to the number that would have been left if the patient had followed the instructions. However, a tablet removed from the container has not necessarily been ingested. For example, the tablet may have been taken out and put in a pill or dosette box, or removed to give the impression that it has been taken prior to monitoring. Another potential problem is that the date of dispensing may not be the same as the date on which the prescription was started.

5.3.3 Prescription redemption records

The frequency with which the patient collects prescriptions from the pharmacy is compared with the expected frequency if the patient was using the medication as prescribed. Disparities between the expected and actual usage indicate non-adherence. This type of measure can be used to detect taking too little or too much medication, however, it doesn't take into account that the patient may have lost medication, be keeping an extra supply, or obtaining medication from elsewhere. Furthermore it is not possible to gain information regarding the frequency of dosing or adherence to special instructions such as diet or drug restrictions using this method. Researchers often use pharmacy prescription redemption records as a way of cross-checking the validity of self-report.

5.3.4 Clinician estimates

Clinician estimates of adherence are notoriously inaccurate, and tend not to improve with professional experience or familiarity with the patient. In one study of 196 patients who had been HIV-infected through injecting drug use (Escaffre et al., 2000), physicians classified 60% of all patients who self-reported non-adherence to HAART as adherent and tended to make assumptions of the likelihood of patients adhering to their treatment based on social stereotypes as well as clinical experience, with women, older patients, healthier patients and those perceived as free of injecting drug use being more likely to be perceived as adherent to their antiretroviral treatment regimens. Furthermore, physicians were found to equate markers of clinical efficacy such as detectable viral load with non-adherence, while ignoring other potential causes. In a study of homeless or marginally housed patients receiving antiretroviral therapy, Bansberg et al (2001) found that health care providers' estimations of adherence categorised only 26% of the variation in adherence assessed by pill count, while patient self-report explained 72%. In a prospective study, Miller et al (2002) found that clinicians tended to overestimate adherence, and inadequately detect non-adherence. The probability of clinicians correctly identifying a non-adherent patient was between 24% and 62%, depending on the non-adherence cut-off, with greater clinician inaccuracy being associated with higher CD4 count, younger patient age, and number of previous visits to the clinic.

In an innovative study, Bogart et al (2001) sent clinical scenarios to a sample of 495 US clinicians, in which they described HIV positive patients, varying patient characteristics of gender, disease severity, ethnicity and risk group. Physicians predicted that African American men, former IVDUs, and those with less severe disease would be less likely to adhere to antiretroviral treatment. These results show that clinicians are at risk of using social stereotypes, which have not been borne out of empirical evidence, to inform their judgements of non-adherence. In conclusion, there is little support for the validity of clinician assessment of non-adherence.

5.3.5 Electronic monitors

This technique involves fitting electronic devises inside the lid of medicine container to record the time and date of usage. These devices provide a detailed profile of medication taking by recording the date and time of each bottle opening, which is potentially extremely useful for adherence to antiretroviral medications, where clinical benefit depends on adherence to complex timing as well as dosage instructions. However, because the bottle is opened, it doesn't necessarily follow that the dose was taken out or ingested. The devices are expensive and data accuracy may be limited if the patient is required to take any more than one dose at a time, or needs to be taken in liquid form.

Electronic monitors such as Medication Event Monitoring Systems (MEMS-caps) are regarded by many conducting research into HAART-adherence as the 'gold standard' of adherence measures. However, they may underestimate or overestimate adherence. HAART regimens usually involve more than one tablet, and often more than two, with non-antiretroviral medications such as PCP prophylaxis and anti-sickness drugs often being taken as well. Carrying many special containers may compromise the privacy of patients who often decant their medicines into pill-boxes, dosette boxes or other smaller containers. They may also overestimate adherence, since the patient may open the container for reasons other than to take a dose (e.g. to show someone the tablets, to check a dose has been taken). For these reasons, it is necessary to include a self-report measure into the study in addition to the electronic monitor in order to determine how the monitor was used (Chesney et al., 2000).

Further issues including cost, loss and malfunctioning of monitors have also lead to fewer patients completing adherence assessments, introducing the possibility of sample bias and underpowered studies (Vanhove et al., 1996).

5.3.6 Therapeutic outcome

In order to use therapeutic outcome as a measure of adherence, it is necessary to equate clinical benefit with high adherence and lack of clinical benefit with low adherence. Unfortunately, there is rarely a quantifiable, linear relationship between adherence and clinical benefit. While for people taking HAART, there is a strong correlation between undetectable viral load and adherence (Paterson et al., 2000), it is important to note that high levels of adherence do not guarantee benefit. There are several reasons why viral load might remain detectable in a highly adherent individual, including viral resistance, HIV viral load at the start of therapy and potency of antiretroviral regimens (Murri et al., 1999). Conversely, a minority of people who are not highly adherent may have an undetectable viral load (Paterson et al., 2000). Thus, while viral load may be used as a means of measurement validation (with lower viral load expected amongst patients reporting high levels of adherence), it is not reliable as a measure of adherence in isolation.

5.3.7 Patient self-report

Self-report measures are widely used in adherence research. They are practical, quick and can cover several aspects of adherence that may be pertinent (dosage, timing, special instructions). However, reliance on self-reports of adherence has come under heavy criticism. One criticism is related to the accuracy of recall, since adherence questionnaires are often completed at a time and place that is distant from the actual event, which can result in a tendency to recall the good things that one has done and to forget the bad. Moreover, it is well known that patients tend to under-report non-adherence. While it is generally accepted that self-reported accounts of low adherence are valid (Bansberg et al., 2001), there are often disparities between the number of patients self-reporting high adherence and high adherence as measured by other methods.

Investigators have attempted to minimise self-presentational bias by phrasing questions in a non-threatening way, in order to permit non-adherence. Self-presentational bias may also be reduced if questions are presented by a 'neutral' researcher, rather than a clinician or other person involved in the patients' care. In adherence research, it is important to ensure that patients are assured that their responses are anonymous and confidential, and will not be seen by medical staff or impact on their care.

Furthermore, the accuracy of self-report questionnaires may also be improved by presenting patients with a likert scale with a range of possible responses, rather than categorical 'yes/no' response options. Using a range of response options has been found to improve the accuracy of the self-report assessment of adherence (Haynes et al., 1980).

Patient self-report is the most widely used measure in studies of adherence to antiretroviral therapy. Several questionnaires have been proposed, probably the most widely used of these was developed by the Adult AIDS Clinical Trials group (Chesney et al., 2000). However, the validity of many of these measures is questionable, since the data generated have not been compared against objective measures of adherence. Given the problems that may be associated with self-report measures of adherence, it is essential that new measures are validated against more objective measures. The Medication Adherence Self-Report Inventory (MASRI: Walsh et al., 2002) was developed in the UK for use with HIV positive adults taking HAART. The validity of responses to the MASRI was ensured by comparison against two objective measures: pill count and electronic monitoring. The MASRI questionnaire contains 12 items encompassing missed doses and timing over the past few days, past two weeks and past month. Participants are also required to rate the percentage of medication they have taken as prescribed over the preceding month on a visual analogue scale (VAS). Of the 12 items, responses on the VAS were most strongly associated with adherence measured by both electronic monitoring and pill count. This scale is quick and easy to administer while providing a valid means of measuring adherence to HAART.

5.4 Use of multiple adherence measures

The summary provided in this chapter shows that while there are clear advantages and disadvantages to all measures of adherence, no single measure is error-proof. As a result, researchers recommend the use of multiple measures of adherence in studies of adherence to HAART in order to validate the measure employed (Arnsten et al., 2001).

Chapter 6
GENERAL METHODOLOGY

6.1 Overview of empirical section

This chapter provides an overview of studies, sample characteristics, measures and procedures. More detailed study designs and procedures can be found in the relevant chapters.

6.2 Author contribution

The data contained within this thesis was collected alongside a larger investigation of psychological predictors of uptake of and adherence to HAART over 12 months, which was funded by Abbott Laboratories, Bristol Myers Squibb, Boeringer Ingleheim, GlaxoSmithKline and Pharmacia. The author was responsible for all stages of research, from designing the longitudinal study, selecting, revising and piloting questionnaires, recruiting participants, collecting data, setting up and managing databases and independently designed and conducted all statistical analyses for the studies contained within this thesis. After a year of being solely responsible for recruitment and data collection, the author was responsible for managing two research assistants who were employed to help recruit, collect and input data. The data used within this thesis was collected from a sub-sample of participants who accepted a treatment offer and initiated HAART. The larger study also followed up patients who declined a treatment recommendation and those who were not clinically eligible for a treatment recommendation.

6.3 Plan of empirical work

The empirical section of this PhD consists of three studies. These studies were designed to investigate the role of an extended self-regulatory model in adherence to HAART. Study 1 was conducted to determine whether patients' perceptions of HIV and HAART before initiating treatment predicted subsequent adherence. Study 2 explored the concept of 'symptom appraisal' in relation to adherence, perceptions of HIV and beliefs about HAART. Study 3

explored how perceptions of HIV and HAART evolved over the treatment process, and whether changes in beliefs over time were associated with adherence. Inter-relationships between perceptions of illness and beliefs about treatment were also explored in studies 1 & 3 in order to test hypotheses generated by the extended SRM. All studies utilised a prospective, longitudinal research design, with participants derived from the same sample. Participants initiating HAART completed assessments before starting treatment (Baseline assessment: T0), after one month (T1), three months (T2) and six months (T3) of taking HAART. Six months was chosen as the last follow-up because treatment is deemed to be clinically successful if undetectable viral load is reached by this time, thus a major clinical outcome of optimal adherence is reached by this stage (Paterson et al., 2000).

6.4 General methods (Studies 1, 2 & 3)

6.4.1 Ethical approval

Ethics approval for this study was gained from the East Sussex, Brighton and Hove Health Authority in November, 1999 (Ref: (B) 99/82).

6.4.2 Participants

6.4.2.1 Access to patients

Participants were recruited from the Lawson Unit, an outpatient HIV clinic in Brighton with permission from Dr. Martin Fisher, Consultant Physician in HIV/AIDS. All patients receiving care for HIV-infection in Brighton are treated through this centre.

6.4.2.2 Inclusion/Exclusion criteria

HIV positive patients who attended the Lawson Unit at the Royal Sussex County Hospital between January 2000 and June 2002 were eligible for recruitment into the larger prospective study if they were not currently taking treatment, were able to understand sufficient written English language to comprehend the study information sheet and able to complete the questionnaires. Only patients who received a recommendation of HAART and initiated treatment were eligible for the studies contained within this thesis. Patients who were changing part or all of their existing combination were not eligible for the study as it is likely that they represented a biased sample whose views may have been influenced by their

treatment experience and reason for changing drugs (e.g. side effects, treatment failure, practical difficulties or adherence problems). Therefore eligibility required having not taken any antiretroviral medication for at least a month. Pregnant women and individuals initiating post-exposure prophylaxis (PEP) were not eligible for the study because treatment is recommended on the basis of different guidelines and may be short-term, therefore predictors and correlates of adherence may differ among these groups. Those who started treatment as part of an emergency inpatient admission were not eligible as it was not possible to complete the questionnaires before initiating treatment. Patients who had been involved in the pilot study were not approached for recruitment into the adherence study.

6.4.2.3 Referral and recruitment

Recruitment procedures were the same for all studies. Each week, a multidisciplinary HIV team including doctors, research staff, pharmacists and community nurses met to discuss the clinical status of patients before their clinic appointments. The purpose of these meetings was to monitor recent blood test results and to identify patients recording a detectable viral load in order for the medical team to make decisions regarding their clinical care. During these meetings, all patients who were not currently taking antiretroviral treatment were discussed in terms of their eligibility for HAART on the basis of British HIV Association (BHIVA) guidelines. The author attended these weekly clinical meetings in order to identify patients who were eligible for a treatment recommendation at their next appointment. Referral to the study was made through the patients' HIV physician. Prior to each clinic (9 clinics, 5 days per week), medical files of patients who were eligible for the study were flagged up by attaching a reminder to the patient's HIV physician. Each clinic doctor (n = 6) referred eligible patients to the researcher. Reasons for non-referral were recorded whenever possible. The purpose of the research and details of participation were explained by the researcher who also gave the participant a written information leaflet (see Appendix 2). The leaflet explained details of what taking part would entail, stressing that all information given would be confidential, and that whether the individual chose to take part or not would not affect their treatment at the clinic. Those who agreed to participate were asked to complete a patient consent form and contact details (see Appendix 2). Patients who accepted the treatment recommendation and initiated

HAART formed the study sample for this thesis. Those who declined or deferred treatment were followed up as part of the larger, prospective study.

Patients were not told that the purpose of the study was to investigate their adherence to medication, as this knowledge might have influenced their subsequent adherence behaviour. This practice is considered ethically justifiable in order to avoid research bias (Wadeley, 1991). Participants were informed that this was an investigation of patients' views about and experiences of HIV and HAART. Participants were assured that they were not committed to the research project and could decide to discontinue their participation at any time without having to give a reason.

6.4.2.4 Recruitment figures

Table 6.1: Recruitment to the study from January 2000 to June 2002

		% of patients lost to recruitment at each stage
Total number of patients eligible	156	N/a
Patients not referred to study	32	20.5%*
Patients referred but not recruited to study	10	6.4%**
Total number of study eligible patients recruited	114	73.1%

*see table two for breakdown of reasons for non-referral

**see table three for breakdown of reasons for non-recruitment following referral

Table 6.2: Breakdown of reasons for non-referral to study by clinicians

Reasons for non-referral by clinician (n=32)		
No reason given	3	9.4%
Patient DNA or cancellation	10	31.3%
Doctor forgot	7	21.9%
Poor literacy or English	3	9.4%
Dr considered patient too upset/depressed	2	6.2%
Too many things going on at that appointment	4	12.5%
Patient refusal	3	9.4%

Table 6.3: Breakdown of reasons for non-recruitment to study following clinician referral

Reasons for non-recruitment following referral to study (n=10)		
Patient declined (no reason given)	7	70%
Patient moving/ going travelling	2	20%
Patient in prison (concern about disclosure)	1	10%

Table 6.4: Breakdown of reasons for drop-out from study following recruitment

Reasons for drop-out (n=28)		
Patient didn't want to continue (no reason given)	5	17.9%
Too ill to continue	1	3.6%
Baseline questionnaire not returned/ unable to contact patient	11	39.3%
Patient moved care to another hospital	6	21.4%
Patient too depressed	3	10.7%
Patient too busy	1	3.6%
Patient died	1	3.6%

To ensure representative sampling, those completing the study were compared to those who did not complete the study on baseline demographic and clinical data.

Table 6.5: Demographic and clinical characteristics of sample recruited (n=114), comparing those who completed the study with those who dropped out or died during follow-up.

Clinical/demographic feature		Completed study n=86	Dropout/ died n=28	Significance level
Age	Mean (SD)	38.6 (8.8)	39.8 (8.8)	p>0.1
Male		83 (96.5%)	25 (89.3%)	p>0.1
Employed		51 (59.3%)	14 (50.0%)	p>0.1
Ethnic origin: White UK		76 (88.4%)	24 (85.7%)	p>0.1
Transmission risk: gay man		**78 (90.7%)**	**21 (75.0%)**	**p<0.05**
Years since HIV diagnosis	Median (range)	3.2 (0-17)	1.8 (0-17)	p>0.1
Asymptomatic HIV		26 (30.2%)	7 (25.0%)	p>0.1
Symptomatic HIV		35 (40.7%)	13 (46.4%)	p>0.1
AIDS		25 (29.1%)	8 (28.6%)	p>0.1
Clinical trial		**35 (40.7%)**	**4 (14.3%)**	**p<0.05**
Prior experience of ARVs		31 (36.0%)	11 (39.3%)	p>0.1
CD4 count	Mean (SD)	200.6 (134.9)	164.9 (106.8)	p>0.1
Viral load $\log^{10}$	Median (range)	5.3 (3.4-6.0)	5.4 (3.6-6.0)	p>0.1

Gay men were more likely than those with other HIV transmission risks to complete the study (χ^2= 4.56, df = 1, $p < 0.05$), as were those who had been enrolled to receive their treatment as part of a clinical trial (χ^2= 6.5, df = 1, $p < 0.05$). No other clinical or demographic characteristics distinguished those who completed from those who dropped out of the study.

Consistent with the HIV clinic population in Brighton in comparison to the overall UK population, gay men and those describing their ethnic origin as white UK were over-represented in the final sample.

6.4.3 Measures

6.4.3.1 Pilot study

A pilot study was conducted to assess the validity of the Illness Perception Questionnaire (IPQ) and Beliefs about Medicines Questionnaire (BMQ) within this sample, to check the acceptability of the wording of questions, and to make appropriate revisions to the measures. Ten HIV positive adults who were not taking antiretroviral treatment volunteered for the pilot study at Brighton Body Positive, a volunteer run complementary therapy centre for HIV positive individuals. Modifications to the scales based on analyses of this data and conversations with each of the individuals were incorporated into the revisions made to the scales. These revisions are shown under the descriptions of individual measures.

6.4.3.2 Illness Perceptions Questionnaire-Revised version (IPQ: Weinman et al., 1996; IPQ-R; Moss-Morris et al., 2002)

The IPQ (Weinman et al., 1996) was developed in order to quantify the five components of illness representation proposed by (Leventhal et al., 1984, 1997; and Lau et al., 1989). These were: *identity* (patients' ideas about the disease label and symptoms) *consequences* (patients' ideas about the impact of the disease on physical, social and psychological functioning), *causes* (patients' ideas about what caused the condition), *timeline* (the likely duration of illness) and *cure/control* (the extent to which the patient believes his/her condition to be amenable cure or control). Recently, the measure has been revised to improve its measurement properties and extend its scope (Moss-Morris et al., 2002). There were three major revisions: First, the cure/control component was separated into two separate factors, one concerned with beliefs about personal control and self-efficacy (*personal control*), the other assessing beliefs about the efficacy of prescribed treatment or recommended advice (*treatment control*). Second, in addition to the original acute/chronic timeline, a '*cyclical timeline*' scale was added, in order to aid research into conditions where experience of illness cannot be adequately described on a simple acute/chronic dimension. Third, the IPQ was extended to include two new scales. These were measures of '*illness coherence*' (how much the patient understands the condition or to what extent the illness 'makes sense' to the patient) and '*emotional representations*,' which was added to measure the patient's emotional reaction to their illness. The IPQ and IPQ-R scales have been shown to have acceptable

validity and reliability (Weinman et al., 1996; Moss-Morris et al., 2002). The IPQ-R was adapted for the sample by replacing the words 'my illness' with 'my condition' or 'HIV' (as appropriate), and by adding HIV-specific items to the core items of the scales (see Appendices 3 and 4).

6.4.3.2.1 Identity

The Identity scale comprises 23 symptoms, twelve of which are 'core symptoms', common to any illnesses (pain, nausea, breathlessness, weight loss, fatigue, stiff joints, sore eyes, headaches, upset stomach, sleep difficulties, dizziness, loss of strength). Additional items specific to the illness under investigation may be added to this list. Eleven specific HIV symptoms were added: sore throat, wheezing, night sweats, diarrhoea, feeling faint, fever, sexual problems, loss of appetite, skin problems, stomach pain and altered sensation in hands or feet.

Participants were asked to rate whether they experienced any of these symptoms *as part of their HIV condition*, and were asked to rate only those they believed to result from HIV. The scoring was conducted by asking whether the person was experiencing the symptom (yes/no). The scale was adapted for this study by asking the participant to rate the severity of each symptom they experienced on a scale of 1-5, where 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe. The scale was then used in two ways – 1) to give a dichotomous score where 'no' was scored 0 and any of the five other possible responses was scored 1, giving a minimum score of 0 and maximum score of 23; and 2) In order to reflect the severity of symptoms, a 'symptom severity index' was calculated by categorising very mild, mild or no symptoms as 'low severity' and moderate, severe or very severe symptoms as 'high severity', again giving a minimum score of 0 and maximum score of 23, but representing only those symptoms the participant perceived to be moderate, severe or very severe.

6.4.3.2.2 Symptoms attributed to HAART

A second symptom scale was developed so that it was possible to distinguish symptoms the patient associated with HIV and those they associated with their treatment. This scale was

included in all follow-up assessments. The scale was similar to the identity scale, including identical symptoms so that a direct comparison could be made. The instructions asked the participant to *rate only the symptoms they attributed to their anti-HIV therapy,* and not those they believed were due to their HIV condition or any other cause. Again, two scoring procedures were followed, one representing the total number of HAART related symptoms experienced, the other reflecting only those symptoms the participant regarded to be moderate, severe or very severe.

6.4.3.2.3 Illness representations

For all other scales, items were rated on a scale of 1 to 5, where 1 = strongly disagree, 2=disagree, 3 = neither agree nor disagree, 4 = agree and 5 = strongly agree. Appropriate items were reversed scored and totals were generated for each of the scales (timeline = 1 item, cyclical timeline = 4 items, consequences = 7 items, treatment control = 6 items, personal control = 6 items, coherence = 5 items, emotional representations = 6 items). Total scores were then divided by the number of items to give a total score of 1-5 for each scale.

6.4.3.2.4 Alterations to IPQ-R scales based on the pilot study

Items were deducted from the timeline scale on the basis of the pilot study which showed ceiling effects for the following items: 'my illness will last a long time;' 'I expect to have this illness for the rest of my life,' and 'my illness is likely to be permanent rather than temporary'; and floor effects for 'my illness will last a short time' and 'this illness will pass quickly,' suggesting that people with HIV are very aware that they will have the illness for the rest of their lives. The item 'this treatment will be effective in curing my condition' was dropped from the treatment control scale because of floor effects and two extra items were added: 'Anti-HIV medication can control the progress of my HIV infection' and 'I'll get ill when my time comes whether I'm taking anti-HIV medication or not'. Patients unanimously attributed the cause of the HIV to be a germ or virus, with no other causal attributions endorsed. Causal attributions were therefore not measured in this study.

6.4.3.3 Beliefs about Medicines Questionnaire

6.4.3.3.1 BMQ-HAART

Perceptions of HAART were assessed using the Beliefs about Medicines Questionnaire-HAART specific version (BMQ-HAART; Horne et al., 1999), which has been validated for use in HIV samples. The BMQ comprises two scales: a HAART-*necessity* scale assessing patients' beliefs about their personal need for HAART for controlling HIV and maintaining health, the other assessing their *concerns* about the potential adverse effects of HAART. The *concerns* scale brings together a range of separate concerns about the potential adverse effects of HAART that have been identified across studies (Cooper et al., 2002a; Cooper et al., 2002b). Individuals' concerns about HAART are scored according to the extent to which they endorse each of the items representing different beliefs about the potential adverse effects of HAART. The items include worries about short term and long-term side effects and the disruptive effects of the HAART regimen on social and work life and more abstract worries about becoming too dependent on HAART. These items represent common concerns about HAART.

Participants are presented with a series of statements about which they are told: 'these are statements that other people have made about combination therapy.' They are then asked to rate their level of agreement with each item on a scale, where responses range from strongly agree (scored 5) to strongly disagree (scored 1). Scores for the individual items within each scale are summed to give a total scale score. In this study, participants completed a BMQ-HAART questionnaire for every antiretroviral medicine in their combination. Scores for each scale were totalled and divided by the number of medicines. In order to facilitate comparison of scores between scales, a mean score was computed by dividing each scale by the number of items, giving a range of 1 to 5 for both *necessity* and *concerns* scales. High scores indicate stronger perceptions of necessity or concerns.

6.4.3.3.2 Adjustment to BMQ-HAART for pre-HAART assessment

Two versions of the BMQ-HAART were used in this study, since the questionnaire was completed both prior to initiating treatment and over the treatment experience. The pre-

HAART version contained 6 necessity items and 7 concerns, while the on HAART version contained 8 necessity items and 12 concerns. Six items were dropped from the pre-HAART version because they were specific to the experience of taking HAART. These included: 'Missing this medication for a day won't matter in the long run', 'Using these medicines is embarrassing,' 'I am unlikely to get a bad side effect from this medication in the next month®','Missing this medication for a day won't matter in the long run®,'Taking this medication has been much worse than expected' and 'The taste of this medication makes me feel unwell'. The wording of remaining items was changed subtly to reflect hypothetical statements rather than those based on experience for example 'taking these medicines *gives me* unpleasant side effects' was changed to 'taking this medicine *would give* me unpleasant side effects'.

6.4.3.3.3 Beliefs about Medicines in General (BMQ-General)

The BMQ-General measures representations about medicines in general. There are two sub-scales: general *harm* refers to the tendency of individuals to believe that medicines in general are intrinsically harmful or poisonous, while general *overuse* refers to the belief that medicines are too readily prescribed by doctors. Participants are presented with a series of statements asking them about their views about medicines in general. They are asked to rate their level of agreement with each item on a scale, where responses range from strongly agree (scored 5) to strongly disagree (scored 1). Scores for the individual items within each scale are summed to give a total scale score. In order to facilitate comparison of scores between scales, a mean score was computed by dividing each scale by the number of items, giving a range of 1 to 5 for both *harm* and *overuse* scales. Higher scores indicate more negative beliefs.

6.4.3.4 Sensitive Soma (SENSOMA) Scale

The Sensitive Soma (SENSOMA) Scale (Diefenbach, Leventhal & Leventhal, 1996) consists of five items assessing perceptions of personal sensitivity to potential adverse effects of medication (e.g. 'Even small amounts of medicines can upset my body'). Responses are scored on a five-item Likert scale and the individual item scores are summed to provide a

total Sensitive Soma score ranging from 5 to 25. In order to facilitate comparison of scores between scales, a mean score was computed by dividing each scale by the number of items, giving a range of 1 to 5. High scores indicate a high level of perceived sensitivity to potential adverse effects of medication.

6.4.3.5 The Medical Outcomes Short Form Questionnaire (SF-12: Ware et al.,1996)

The Medical Outcomes Short Form Questionnaire (SF-12) was used to measure health status. This measure was developed for use in large samples and longitudinal studies of health outcomes. It contains either one or two items from the following health concepts: physical functioning, role limitations arising from problems with physical health, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations arising from emotional problems and mental health (psychological distress and well-being). The measure generates two scales: physical component summary (PCS-12) and mental component summary (MCS-12). After reverse scoring appropriate items, indicator variables were created and weighted using regression weights. These scores were then transformed to norm-based scores based on the US general population. Possible scores range from 0–100, where higher scores indicate better health. The scale has demonstrated acceptable validity and reliability (McHorney, Kosinski & Ware, 1994; Ware, Kosinski & Keller, 1996).

6.4.3.6 Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

This is a brief measure of state anxiety (7 items) and depression (7 items), which was developed for the purpose of detecting clinical cases of anxiety and depression and the severity of anxiety and depression in patients attending outpatient clinics without contamination of scores by reporting of physical symptoms. Items are scored from 0 to 3, with possible total scores on each scale ranging from 0 to 21. Higher scores indicate greater anxiety or depression. Scores from 8-10 on each subscale are taken to indicate possible clinical disorder and scores from 11-21 indicate probable clinical disorder. The scale has been shown to have good psychometric properties in studies of medical outpatients and people with cancer (Moorley et al., 1991; Zigmond & Snaith, 1983).

6.4.3.7 The Medication Adherence Self-report Inventory (MASRI: Walsh, Mandaila & Gazzard, 2002)

A visual analogue scale (VAS) was adapted from the Medication Adherence Self-report Inventory (MASRI; Walsh, Mandaila & Gazzard, 2002) in order to measure adherence. This scale has been validated using Medication Event Monitoring System (MEMS) caps and found to be equally predictive of viral load (Walsh, Mandaila & Gazzard, 2002). Patients were asked to estimate on a scale from 0 -- 100 the percentage of medication they had taken as prescribed over the previous month. In an attempt to reduce the pressure on patients to underreport adherence, questions were worded carefully to minimise connotations of blame and patients were assured that their responses were confidential. Adherence was rated for each antiretroviral medication the patient was taking, however correlations between individual drugs indicated very little variance in adherence scores (r = 0.97-0.99). Therefore adherence was summed for all antiretrovirals in the combination (n = 1-6) and divided by the total number of medicines. Combined drugs such as combivir and trizivir were rated as one medication. This measure generated two adherence indices: a continuous variable with possible range from 0-100, and a categorical variable, where patients reporting 0-94% adherence were categorised into a 'low adherence' group and those reporting 95-100% adherence were categorised into a 'high adherence' group. This categorisation was based on studies showing that patients demonstrating at least 95% adherence had a significantly elevated probability of achieving optimal clinical outcomes on HAART (Paterson et al., 2000).

6.4.3.7.1 Composite adherence measure

Participants who made a unilateral decision to stop their treatment were categorised into the 'low adherence' group. In order to ensure that these participants were not lost to analysis (since their behaviour represents an extreme of non adherence, or taking zero percent of their medication as prescribed), these participants were grouped together with those taking less than 95% of their medication as prescribed according to the MASRI-VAS.

6.4.3.7.2 Validation of adherence measures

Pharmacy records of the first 38 participants to initiate HAART were tracked over six months in order to validate the adherence measure. All antiretroviral medications for patients attending Brighton HIV clinics are distributed from the Sussex Eye Hospital Pharmacy at the Royal Sussex County Hospital, so it was possible to track prescription and collection dates for each participant. Predicted collection dates were estimated from the date of starting medication and the length of supply of each drug prescribed. A score representing the number of days early or late was estimated on the basis of prescriptions coinciding with the follow-up assessments to reflect possible change in adherence behaviour over time. The score represented the estimated date of collection minus the actual date of collection. Patients were classified into two groups: those who picked up their prescriptions on time or early (those with a positive or zero score) were labelled adherent, while those who collected their prescriptions late (those with a negative score) were labelled non-adherent.

Those who were late picking up their medicines (n=6) reported lower adherence scores on the MASRI VAS (mean adherence = 87.2%, SD = 17.8) compared to those who collected them early or on time (n = 32, mean adherence = 95.2%, SD = 7.72). This difference was statistically significant (Mann Whitney U test: $Z = -3.03$, $p < 0.01$).

There was also a significant negative correlation between the composite adherence score and log transformed viral load at six months indicating that the adherence measure was predictive of clinical outcome ($r = 0.41$, $p < 0.001$).

6.4.3.8 Clinical and demographic information

Clinical and demographic information was obtained from medical records. Information recorded at baseline included age, sex, ethnic origin, current employment, CD4 count and viral load, symptomatic status (asymptomatic HIV, symptomatic HIV and AIDS), number of months since first diagnosis of HIV, most likely route of HIV transmission (as the most likely transmission risk for approximately 90% of the clinic population is homosexual contact, we compared gay men with those citing all other risks: IVDU, heterosexual contact and infected

blood products), details of previous antiretroviral treatment (whether the person had previously been prescribed antiretrovirals, how many previous combinations they had taken and reasons for stopping). Details of the new antiretroviral regimen were also recorded (name, type and number of medicines).

Follow-up clinical information was obtained at the 1 month, 3 month and 6 month assessments. This included CD4 counts, viral loads and details of changes to any of the medications. Participants initiating HAART at the Lawson unit routinely have their bloods taken after 2, 4, 12 and 24 weeks, so it was possible to collect blood test results (CD4 and viral load) that coincided with the study assessments.

6.4.4 Data entry

Two databases were set up by the author to record study information: A password protected 'contacts database' in Microsoft Access was used to monitor the progression of each participant through the study. This database included the participants name, contact details, subject number, clinic number, date of recruitment, date of treatment offer, therapy start date, date of each assessment and details of data obtained and pending. Questionnaire, clinical and demographic data was entered into SPSS Version 11.0 along with the participant identification number. Questionnaire data was either entered by the author or by a research assistant. All data input was counter-checked for accuracy.

6.4.4.1 Missing data

Every effort was made to contact participants where missing responses were found in questionnaire data. However, if it was not possible to contact the participant, the following procedures were followed:

1. If one item from a scale was missing a response, an average scale score was calculated by adding the remaining items and dividing by their total.
2. If more than one item was missing a missing data value was inserted.

Missing data values were recorded as '999' if the data was missing and '888' if the question was not applicable to the participant.

6.5 Procedures

Following recruitment to the study, participants were given the baseline questionnaire and were encouraged to complete the questionnaire at the clinic. However, in cases where this was not possible, a stamped addressed envelope was supplied for its return. Participants were informed that it was important that they completed the questionnaire before starting their treatment, and were followed up with a reminder phone call after one week and if necessary two weeks until the questionnaire was returned. Pharmacy records were checked weekly to monitor the date participants collected their first prescription of antiretroviral medications. Three weeks after the date of prescription, participants were telephoned and a one-month follow-up was arranged at a time convenient to the patient. The vast majority of follow-up assessments took place at the patients' home. Where this was not convenient for the participant, (for example if they were undergoing respite, had been admitted as an in-patient, or preferred the appointment to coincide with a clinic appointment), space was provided at the Lawson Unit, the Elton John Centre (a specialised HIV centre for clinical research clinics, outpatient care and inpatient ward) or the Sussex Beacon (an inpatient respite ward) to conduct the assessment. Follow-up assessments consisted of a questionnaire booklet and an interview with a researcher. A stamped addressed envelope was provided for the return of the questionnaire, and if necessary reminder telephone calls were made weekly until the questionnaire was returned. The same procedure was followed for the three and six month assessments. If the questionnaire was not returned within three weeks it was recorded as missing data.

6.5.1 Procedures for those who stopped treatment

Since the decision to stop treatment rarely coincided with study follow-up assessments, those who stopped their treatment (n=9) did not complete further questionnaires. However, since making a unilateral decision to stop HAART medications was categorised as low adherence, these patients were included in the final analysis for Study 1 in which baseline predictors of adherence were investigated.

6.6 Sample variation across Studies 1, 2 and 3

Conducting a prospective follow-up study facilitated separate analyses to test different aspects of the extended SRM as described in the Studies 1, 2 and 3. The study samples are derived from the same study population, however sample size varies across the three studies. Study 1 explored baseline predictors of adherence at six months. IPQ questionnaire data was only required from T0 assessments. The sample (N = 86) contained nine participants who provided data at baseline but subsequently stopped their treatment, therefore did not provide data for all follow-up assessments. A further seven participants were missing data on symptom subscales at T1. The final number of participants in Study 2 was therefore 70. In order to explore patterns of change in IPQ and BMQ variables across the entire follow-up, Study 3 utilised IPQ and BMQ data from all four time-points (T0, T1, T2 and T3). A further three participants were missing data at on IPQ or BMQ variables at T2 and were excluded from the analyses in this study.

6.7 Power analysis

A priori power analyses were carried out to determine the sample size required to avoid unacceptable type II error rates. Studies are considered adequately powered if power is above 50%, with a desirable power rate of 80%. The power calculation was conducted on the basis of obtaining a medium effect size, which was estimated using the results of a study exploring the utility of an extended self-regulatory model for predicting uptake of HAART (Horne & Cooper, *in preparation*). The number of participants required and power estimations obtained for each of the three studies included in this thesis are outlined below:

6.7.1 Power analysis for Study 1

The number of participants required to obtain 80% power was 114 for multiple regression with nine predictor variables and 98 for the multiple regression with six predictor variables, 102 for the ANOVA and ANCOVA, 102 for t-tests and non-parametric equivalents, 88 for the chi square analyses and 64 for the correlations. The actual number of participants who provided data for Study 1 was 86. Overall the power of the study was between 64-89%. The actual power estimation was 64-73% for the multiple regression analyses, 74% for the ANOVA, t-

tests and their non-parametric equivalents, at least 74% for the ANCOVA, 80% for the chi-square tests, and 89% for correlations and partial correlations.

While it would have been desirable to include a logistic regression in this study to isolate independent predictors of adherence, the study was vastly underpowered for such an analysis, which would require a minimum of 50-100 cases per variable (Aldrich & Nelson, 1984) in order to have statistical power, that is, to avoid the type II error of accepting the null hypothesis when it is false.

6.7.2 Power analysis for Study 2

The number of participants required to obtain 80% power was 102 for the t-tests, univariate ANOVA and ANCOVA and their non-parametric equivalents, 64 for the repeated measures ANOVA and 64 for the correlations. The actual number of participants providing data for Study 2 was 70. Overall the power of the study was between 66-83%. The actual power estimation was 66% for the univariate ANOVAs and t-tests, at least 66% for the ANCOVA and 83% for the correlations and repeated measures ANOVA.

6.7.3 Power analysis for Study 3

The number of participants required to obtain 80% power was 64 for the correlations, repeated measures ANOVA and repeated measures ANCOVA. The actual number of participants providing data for Study 3 was 67. Overall the power of this study was 80%. The actual power estimation was 80% for the repeated measures ANOVA, at least 80% for the ANCOVA and 80% for the partial correlations.

6.8 Statistics

Statistical analyses are described in individual studies.

Chapter 7

STUDY 1

Predicting adherence to HAART: The role of patients' illness and treatment perceptions before starting treatment.

7.1 Introduction

This study was designed to address questions proposed by the SRM (Leventhal et al., 1980) and extensions to it proposed by Horne (eSRM: 1997; 2003) with respect to adherence to HAART. Within these models, the individual's choice of coping procedure (for example whether or not to adhere to their treatment regimen) is determined by their perceptions of the illness threat and their beliefs about the prescribed treatment. While previous research has suggested that perceptions of HIV and HAART are related to adherence to HAART (e.g. Catz et al., 2000; Spire et al., 2002), these studies have lacked a coherent theoretical framework within which to investigate non-adherence to HAART. Furthermore, the conclusions that can be made from these studies are limited by their reliance on cross-sectional research methodologies that preclude the determination of cause and effect. For example, several cross-sectional studies have found a positive relationship between HIV positive patients' perceptions of treatment efficacy and adherence (Atlice et al., 2001; Aversa & Kimberlain, 1996; Catz et al., 2000; Nannis et al., 1993). However, it is not clear whether patients miss doses as a result of their belief that the treatment is ineffective, or whether reduced clinical benefit is a result of previous non-adherence. This study utilises a prospective, longitudinal design in order to establish causality.

The SRM (Leventhal et al., 1992) proposes that patients' selection of coping procedures are determined by their perceptions of their illness. Consistent with this model, those who perceive their condition as being more symptomatic and chronic, with more severe personal consequences would be more likely to take their medication as prescribed. Consistent with the HIV literature (Atlice et al., 2001; Aversa & Kimberlain, 1996; Catz et al., 2000; Nannis et al., 1993), it is expected that patients who perceive HIV as being amenable to control will also be more likely to adhere to HAART.

Horne (1997; 2003) proposed that treatment beliefs should be included in the SRM in order to predict adherence behaviour. Within this extended SRM, beliefs about specific prescribed medications are proposed to have a direct impact on adherence. Indeed studies conducted with patients from several illness groups (asthma, diabetes, cardiac disease and cancer) found that non-adherence was associated with patients' doubts about their personal necessity for their prescribed treatment and concerns about its potential adverse effects (Horne & Weinman, 1999). In a recent cross-sectional study, Horne et al. (in press) found that the strength of patients' concerns about adverse effects of taking HAART were significantly related to adherence. To date, the direction of these relationships has not been ascertained.

Preliminary studies have investigated the relationship between illness and treatment perceptions, identifying relationships that are broadly consistent with the theoretical prediction that illness perceptions relate to beliefs about medicines (Horne, 1997; 2003). Specifically, patients' perceptions of their personal necessity for treatment have been related to perceptions of illness severity, with patients who perceive their condition to have few adverse consequences or to be neither chronic nor persistently problematic harbouring more doubts about their personal necessity for continuous treatment (Horne & Weinman, 2002). However, not all of the components appear to be relevant. This raises the question of whether other types of illness perception may be related to treatment perceptions and adherence. For example, the representation of illness impact as measured by patient reported quality of life measures might, in this respect, be conceptualised as a form of illness representation. Furthermore, perceptions of necessity may be influenced by feedback of clinical and biological data (Cooper et al., 2002b). Concerns about potential adverse effects of prescribed medicines are believed to be more strongly related to the perceptions and experiences of whole classes of treatment than to perceptions of illness (Horne et al., 1999).

This chapter sets out to explore the role of perceptions of HIV and beliefs about HAART, elicited before initiating treatment on subsequent adherence. In addition, since depression has been identified as one of the most consistent predictors of non-adherence to antiretroviral

treatment (Catz et al., 2000; Pratt et al., 2001; Simioni et al., 2002; Spire et al., 2002) and in the light of research that shows more negative perceptions of illness among depressed and anxious individuals (Murphy et al., 1999), the relationships between negative affect and perceptions of HIV and HAART and adherence will be explored.

7.2 Aims and hypotheses

AIM 1: The general aim of this section of the thesis was to evaluate the impact of patients' perceptions of HIV and beliefs about HAART *before starting their treatment* on subsequent adherence. Specifically:

To determine whether beliefs about HAART elicited before starting treatment predict subsequent adherence after six months of treatment as suggested by Horne (1997; 2003)

To determine whether perceptions of HIV elicited before starting HAART predict subsequent adherence, as specified within the SRM (Leventhal et al., 1980)

To determine whether negative affect (depression and anxiety) mediates the relationship between illness and treatment perceptions and adherence

AIM 2: To explore antecedents of perceptions of personal necessity for HAART and concerns about potential adverse effects of HAART in order to test hypotheses derived from the extended SRM (Horne, 1997; 2003).

Specific research questions and hypotheses relating to these aims are outlined below:

Research question 1: Do beliefs about HAART, elicited before starting treatment, predict subsequent adherence?

To answer this question the following hypothesis was tested:

Hypothesis 1: Patients' beliefs about their personal necessity and concerns about potential adverse effects of HAART, elicited before starting treatment, will predict adherence after six months of taking HAART. Specifically, low adherence will be predicted by:

H1.1 Doubts about personal necessity for HAART

H1.2 Stronger concerns about potential adverse effects of taking HAART

Research question 2: Do perceptions of HIV, elicited before starting HAART, predict subsequent adherence?

To answer this question the following hypotheses were tested:

Hypothesis 2: Low adherence at six months follow-up (T3) will be predicted by:

H2.1 Reporting fewer and less severe HIV-related symptoms

H2.2 Reporting less severe negative personal consequences associated with HIV

H2.3 Anticipating greater improvement over time

H2.4 Perceiving a more cyclical timeline

H2.5 Perceiving less personal control over HIV

H2.6 Doubting that HIV can be controlled by HAART

H2.7 A more negative emotional representation of HIV

H2.8 Less illness coherence (as indicated by a higher illness coherence score)

In addition to IPQ-illness representations low adherence will be predicted by:

H2.9 A more positive perception of physical health (as shown by a higher score on the SF-12 physical health scale)

Research question 3: Does negative affect (depression and anxiety) mediate the relationship between illness and treatment perceptions and adherence?

To answer this question the following hypotheses were tested:

H3.1 The relationships between treatment perceptions and adherence will be mediated by negative affect

H3.2 The relationships between illness perceptions and adherence will be mediated by negative affect

Research question 4: Are perceptions of HIV related to perceptions of personal necessity for HAART and concerns about adverse effects in a way that is consistent with hypotheses generated by the extended SRM (Horne 2003)?

To achieve this aim the following hypotheses were tested:

With respect to *necessity* beliefs:

Hypothesis 4: Higher perceived necessity for HAART will be associated with:

H4.1 lower subjective assessment of physical health (SF-12 physical health score)

H4.2 more frequent/severe HIV-related symptoms

H4.3 perceiving greater negative consequences of HIV

H4.4 anticipating less improvement over time

H4.5 perceiving a less cyclical timeline

H4.6 a greater conviction that the progression of HIV can be controlled by HAART

In addition, necessity beliefs may be associated with feedback about disease progression obtained from laboratory test results. Results from a qualitative study (Cooper et al., 2002b) showed that patients who accepted HAART following a clinically indicated treatment recommendation tended to express views consistent with the prescribing guidelines for HAART, where CD4 count was associated with perceptions of need for treatment. It was therefore hypothesised that necessity beliefs would be related to clinical indicators of disease progression. Specifically, higher perceived necessity will be related to:

H4.7 lower CD4 count

H4.8 higher viral load

With respect to *concerns* about potential adverse effects of HAART

H5: Stronger concerns about potential adverse effects of HAART will be associated with:

H5.1 perceptions of being personally susceptible to the adverse effects of medicines in general (higher SENSOMA score)

H5.2 holding negative beliefs about medicines in general (higher BMQ-General overuse and higher BMQ-General harm scores)

In addition to beliefs about more general classes of treatment, it is proposed that concerns about potential adverse effects of taking HAART stem from negative previous experiences of antiretroviral treatment (Cooper et al., 2002). It is therefore expected that low adherence will be associated with:

H5.3 having stopped a previously prescribed regimen of antiretroviral treatment

7.3 Statistics

Continuous variables were examined for normal distribution using sample data (Q-Q plots) and estimates of population normality (Shapiro-Wilk tests). A log transformation was carried out to establish a linear scale of measurement for viral load data. Cronbach's alpha was used to explore internal consistency of scales. In line with recommendations for good practice (Nunnally, 1978), a Cronbach's alpha of 0.7 or above was considered acceptable.

The adherence categorisation was validated against pharmacy prescription redemption data and undetectable viral load using the chi-square statistic. Cochran's Q and McNemar's tests were used to explore changes in the number of participants reporting low adherence over the one, three and six-month follow-ups (T1, T2 and T3). These tests are suitable for testing the hypothesis that related dichotomous variables have the same mean. Cochran's Q test was used to analyse differences in rates of adherence within groups over the three time-points, while McNemar's test was used to explore changes within groups over two time-points. Non-parametric tests were used in this instance because there was very little variation in adherence at T1 and T2. A non-parametric test (Mann Whitney U-test) was also used to explore differences in viral load (log^{10}) between the groups because viral load remained negatively skewed at six months because of the large number of people with an undetectable viral load (recorded as 50, as standard). All other clinical and demographic predictors of adherence were explored using chi-square test with odds ratios and 95% confidence

intervals, t-tests or one-way analysis of variance (ANOVA). Two-tailed tests were used throughout.

Comparisons of illness perceptions and beliefs about medicines between high and low adherence groups were carried out in three stages:

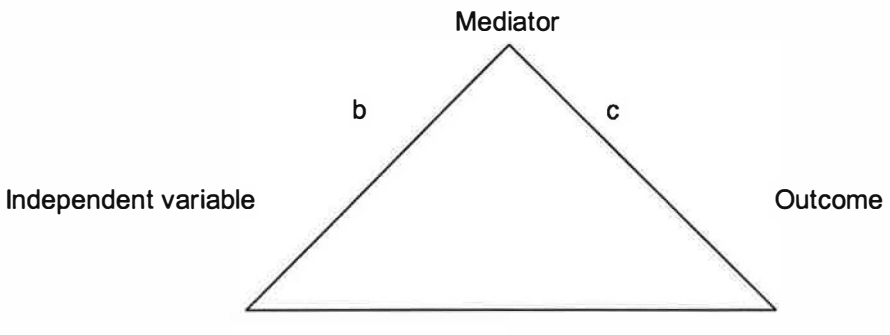
1. *Unadjusted scores:* Patients reporting high adherence were compared to those reporting low adherence using univariate ANOVA.

2. *Control for negative affect:* Previous studies have identified strong links between depression and low adherence to HAART (e.g. Avants et al. 2001; Catz et al., 2000; Kalichman et al.,1999; Nannis et al., 1993; Pratt et al 2001; Schuman et al.; 2001; Sian et al., 2001; Simioni et al., 2002; Singh et al., 1996). Furthermore, negative illness perceptions have been linked to depression and anxiety (Murphy et al., 1999). In order to identify relationships between beliefs and adherence that were independent of negative affect, the analyses were repeated controlling for HADS Anxiety and Depression. These analyses were carried out using ANCOVA.

3. *Control for past experience of antiretroviral treatment*: Previous studies have found that those who have previously been prescribed antiretroviral therapy are more likely to report non-adherence to their current treatment (Mannheimer et al., 2002; Carrieri et al., 2001; Duran et al., 2001). The study sample consisted of both antiretroviral naïve and experienced individuals, therefore ANCOVA was used to control for previous treatment use in analyses comparing high and low adherence groups.

In order to test the hypothesis that negative affect *mediates* the relationship between perceptions of HIV/HAART and adherence, mediational analyses were conducted in accordance with the recommendations of Baron & Kenny (1986), who propose that a variable functions as a mediator when the following conditions are met:

Figure 7.1: Mediational analysis



Adapted from Baron & Kenny (1986)

a. The independent variable is significantly associated with outcome
b. The independent variable is significantly associated with the proposed mediator
c. The mediator is significantly associated with outcome
d. When controlling for the proposed mediator, the previously significant association between the independent variable and the proposed mediator becomes non-significant

Pearson's correlations were used to assess relationships between the independent variable and negative affect. Point bi-serial correlations were used when assessing relationships between adherence (a categorical variable) and beliefs or negative affect.

Correlations assessing relationships between illness representations and beliefs about HAART were carried out in two stages:

1. *Unadjusted scores*: Relationships between continuous variables were carried out using Pearson's correlations.

2. *Control for negative affect:* In order to identify relationships that might be mediated by negative affect, the analyses were repeated controlling for anxiety and depression using partial correlations.

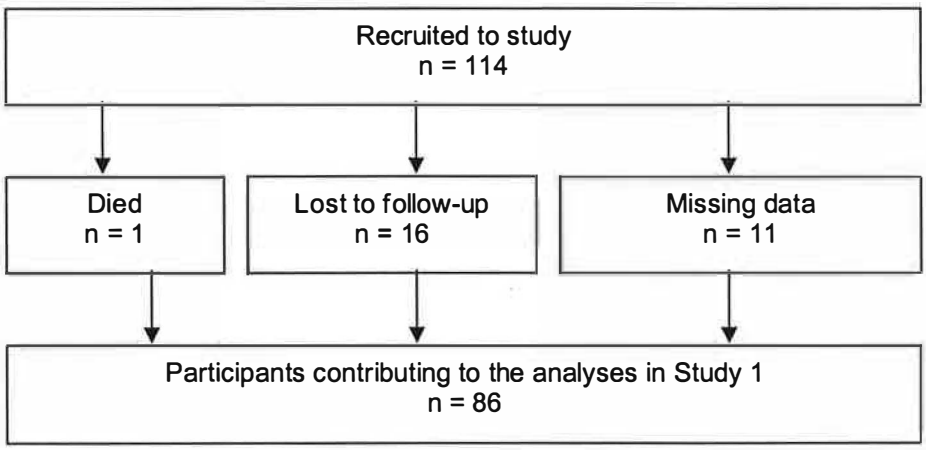
Stepwise multiple regression was used to explore independent predictors of perceived necessity for HAART and concerns about adverse effects. Candidate variables for these analyses were chosen on the basis of significant relationships identified in univariate analyses.

7.4 Methods

7.4.1 Participants

Of the 114 patients recruited to the study who initiated HAART, eighty-six (75.4%) provided data for this study and were included in the final analyses. Twenty-eight were lost to follow-up. Data regarding reasons for attrition and sample representativity are presented in the General Methodology. These are summarised below:

Figure 7.2: Flow chart showing recruitment, drop-out and sample contributing to the analyses in Study 1.



7.4.2 Measures

7.4.2.1 Core questionnaires

All measures are described in the General Methodology. The questionnaire booklet given at baseline (T0) contained the Illness Perceptions Questionnaire (IPQ), the Beliefs about Medicines Questionnaire (BMQ-HAART and BMQ-General), the Sensitive Soma (SENSOMA), the Hospital Anxiety and Depression Scale (HADS) and the MOS Short-Form 12-item health assessment inventory (SF-12).

7.4.2.2 Measurement of adherence

In addition to the core questionnaires, the booklet given at the one-month (T1), three-month (T2) and six-month (T3) follow-ups contained a visual analogue scale adapted from the Medication Adherence Self Report Inventory (MASRI). This questionnaire is described in the General Methodology. For this study, participants were split into high and low adherence groups. The distinction between high and low adherence was made according to recent research which suggests that at least 95% adherence to HAART is required for clinical efficacy (Patterson et al., 2000). The overall percentage of antiretroviral medication taken as prescribed was calculated by adding together the percentage adherence reported on the MASRI for each antiretroviral drug in the patient's combination, and dividing by the total number of drugs in the regime. Participants were divided into low and high adherence groups on the basis of whether their average adherence score on the MASRI was 95% or above (high adherence) or below 95% (low adherence). Those who had made a unilateral decision to stop their treatment prior to each follow-up were categorised into the low adherence group. Adherence at six months was selected as the main outcome for this study.

7.4.2.3 Clinical and demographic information

Once consent had been gained, clinical and demographic information (age, sex, ethnic origin, employment status, date of first positive HIV test, most likely HIV transmission risk, Centre for Disease Control (CDC) severity classification (asymptomatic HIV, symptomatic HIV or AIDS), whether the individual had previously been prescribed antiretroviral treatment, details of new antiretroviral combination (type of treatment, number of medications and whether treatment

had been prescribed as part of a clinical research trial) was recorded from patients medical files. Laboratory test results (CD4 count and viral load) were recorded from medical files at T0, T1 and T3.

7.5 Results

7.5.1 Sample characteristics

The majority of the sample described their ethnic origin as white UK (76, 88.4%), 4 (4.7%) as black African, 4 (4.7%) as white other and 2 (2.3%) as black Caribbean. Eighty-three (96.5%) were male, of whom 78 (94.0%) described their most likely transmission risk as sex with a man. The mean age of the sample was 38.6 (SD = 8.8). Fifty-one participants (59.3%) were employed outside the home. The mean number of years since diagnosis of HIV ranged from 0-17, with a median of 3.2. In terms of CDC classification, 26 (30.2%) were asymptomatic, 35 (40.7%) were symptomatic and 25 (29.1%) had a diagnosis of AIDS. Over a third of the sample (36.0%) had previously been prescribed antiretroviral therapy. The mean CD4 count before initiating treatment was 200.6 (SD = 134.9), with a median viral load (log10) of 5.3 (3.4-6.0).

7.5.2 Regimen characteristics

The majority of the sample (n=63; 73.3%) was initiated on a HAART combination with an non-nucleoside reverse transcriptase inhibitor (NNRTI) backbone plus either two or three nucleoside analogues (NRTIs). The single most common antiretroviral regimen was Combivir and Effavirenz (n=41, 47.7%) consistent with the prescribing guidelines for first line therapy at the Brighton clinic. Twenty-three participants (26.7%) were prescribed a combination including at least one protease inhibitor of whom six (7.0%) were prescribed a combination including at least one protease inhibitor together with at least one NNRTI. The median number of medicines in the combination (where combinations of two or more drugs in one tablet or capsule counts as one) was 3 (range 2-5). Thirty-five (40.7%) participants were enrolled into a clinical trial, the majority of whom (33 (94.2%)) were previously naïve to antiretroviral treatment.

7.5.3 Adherence

7.5.3.1 Patterns of adherence over time

Table 7.1: Levels of adherence at 1 month (T1), 3 months (T2) and 6 months (T3)

	MASRI <95%	Stopped treatment	Composite adherence score: low adherence
1 month (T1)	**8 (9.3%)**	**3 (3.5%)**	**11 (12.8%)**
3 months (T2)	**11 (12.8%)**	**6 (7.0%)**	**17 (19.8%)**
6 months (T3)	**19 (22.1%)**	**9 (10.5%)**	**28 (32.6%)**

Scores on the MASRI ranged from 80-100% at one month (T1), 60-100% at three months (T2) and 70-100% at six months (T3). The median score at all three follow-ups was 100%. Table 7.1 shows rates of adherence at T1, T2 and T3. When participants were split into high adherence and low adherence groups, only 12.8% reported low adherence at T1, increasing to 19.8% at T2 and 32.6% at T3. This increase in the number of participants reporting low adherence over time was statistically significant (Cochran's Q = 22.0, df= 2, $p<0.001$). The increase in the number of participants reporting low adherence between T1 and T2 was not statistically significant (McNemar's test: $p>0.1$), however there was a significant increase in low adherence between T2 and T3 (McNemar's test: $p<0.005$). By six months, a third of the sample reported a low level of adherence to their treatment. Adherence at six months (T3) was the outcome variable in this study.

7.5.3.2 Validity of adherence classification

The validity of the adherence classification used for this study was established by comparison with prescription redemption data and clinical outcome, as highlighted in the General Methodology.

7.5.3.2.1 Prescription redemption

Pharmacy prescription redemption data was collected for the first 38 participants (44.2% of the sample). Concordance between the two adherence measures was high: 96% of those who reported high adherence at T3 collected their antiretroviral medications early or on time compared to only 60% of those in the low adherence group ($\chi^2 = 8.6$, df =1, $p<0.005$).

7.5.3.2.2 Clinical outcome

Viral load (log^{10}) at six months was compared between those in high and low adherence groups. Consistent with previous research (Patterson et al., 2000), those in the high adherence group reported a significantly lower mean viral load (log^{10}) of 1.8 (SD=0.5) at six months compared to 2.5 (SD=1.2) in the low adherence group (Mann Whitney U test, Z = -2.4, $p<0.05$).

The adherence categorisation was also predictive of successful clinical outcome as indicated by undetectable viral load: those reporting high adherence at one month (T1) were significantly more likely than those reporting low adherence to obtain an undetectable viral load at six months ($\chi^2 = 8.2$, df = 1, $p<0.005$). Three-quarters (75.8%) of those reporting high adherence at three months had an undetectable viral load at six months compared to only 37.5% of those reporting low adherence. ($\chi^2 = 8.7$, df = 1, $p<0.005$). Furthermore, 74.5% of those reporting high adherence at the six month follow-up obtained an undetectable viral load at six months, compared to only 57.1% of those reporting low adherence. This relationship did not reach statistical significance at the 95% level ($\chi^2 = 2.6$, df = 1, $p>0.05$). The lack of a significant association between adherence and viral load at six months is probably due to the close proximity of the viral load test to the adherence measure, where the impact of low adherence on viral load was not yet discernable.

7.5.4 Scale characteristics

For Q-Q-plots and histograms showing distribution of scores for all scales please see Appendix 1.

7.5.4.1 Beliefs about treatment

7.5.4.1.1 BMQ-Necessity

Scores on the *necessity* scale ranged from 2.5 –5-0, with a mean of 3.9 (SD = 0.6). Scores were approximately normally distributed. The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.96, df = 86, $p<0.005$) but visual inspection of the normal Q-Q plot revealed

only small unsystematic deviations from the expected normal distribution. Cronbach's alpha was acceptable (0.8) indicating that the scale was internally consistent.

7.5.4.1.2 BMQ-Concerns

Scores on the BMQ-*concerns* subscale ranged from 2-5, with a mean of 3.1 (SD = 0.6). Visual inspection of the normal Q-Q plot revealed the expected normal distribution and this was confirmed by a non-significant Shapiro-Wilk statistic (Shapiro Wilk Statistic = 0.98, df = 86, p>0.1). Cronbach's alpha was acceptable (0.8), indicating that the scale was internally consistent. Examination of the distribution of scores on individual items on the concerns scale showed that worries about the potential long-term effects of HAART, risk of side effects and concerns about disruption to routine were particularly prevalent. Sixty-four percent of participants agreed with the statement "I worry about the long term effects of taking HAART," 45% agreed with the statement "Taking HAART would give me unpleasant side effects," and 41% agreed with the statement "Taking HAART would disrupt my life".

7.5.4.1.3 BMQ General Harm

Scores on the General Harm scale ranged from 1-4, with a mean of 2.5 (SD = 0.5). The scale was normally distributed (Shapiro Wilk statistic = 0.97, df = 72, p>0.05). Cronbach's alpha was unsatisfactory (0.4). Since the scale lacked an acceptable level of internal consistency, it was not included in the study.

7.5.4.1.4 BMQ General Overuse

Scores on the BMQ general overuse scale ranged from 1-5, with a mean score of 3.0 (SD = 0.7). The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.98, df = 72, p<0.05) but visual inspection of the normal Q-Q plot revealed the expected normal distribution. Cronbach's alpha was satisfactory (0.7) indicating that the scale was internally consistent.

7.5.4.1.5 Sensoma

Scores on the Sensoma scale ranged from 1-5, with a mean score of 2.1 (SD = 0.7). Cronbach's alpha was good (0.9) indicating that the scale was internally consistent. The

Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.95, df = 70, $p<0.01$) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution.

7.5.4.2 Illness perceptions

7.5.4.2.1 IPQ-Identity: HIV-related symptoms

Cronbach's alpha was good (0.9) indicating that the scale was internally consistent. Scores on IPQ-symptom frequency scale ranged from 0-23, with a mean of 10.2 (SD = 6.2). Visual inspection of the normal Q-Q plot revealed that scores were skewed towards lower scores, and the Shapiro Wilk test confirmed that the scale was not normally distributed (Shapiro Wilk Statistic = 0.97, df = 86, $p<0.05$). Where possible, results from analyses involving this scale were repeated using a non-parametric equivalent test.

7.5.4.2.2 IPQ- Identity: Moderate to severe HIV-related symptoms

Cronbach's alpha was good (0.9) indicating that the scale was internally consistent. Scores on IPQ-symptom frequency scale ranged from 0-21, with a mean of 5.8 (5.0). As before, visual inspection of the normal Q-Q plot revealed that scores were negatively skewed. The Shapiro Wilk test confirmed that the scale was not normally distributed (Shapiro Wilk Statistic = 0.91, df = 86, $p<0.05$). Where possible, results from analyses involving this scale were repeated using a non-parametric equivalent test.

7.5.4.2.3 IPQ-Consequences

Cronbach's alpha was acceptable (0.8) indicating that the scale was internally consistent. Scores were approximately normally distributed. The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.97, df = 86, $p<0.005$) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution. Scores ranged from 2-5, with a mean of 3.7 (0.8).

7.5.4.2.4 IPQ-Timeline

This was a single-item scale, therefore Cronbach's alpha was not applicable. Scores ranged from 1-5, with a mean of 3.1 (1.0). Scores were approximately normally distributed. The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.90, df = 86, $p<0.005$) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution.

7.5.4.2.5 IPQ- Cyclical timeline

Cronbach's alpha was acceptable (0.8) indicating that the scale was internally consistent. Scores ranged from 1-5, with a mean of 3.7 (SD = 0.8). Visual inspection of the normal Q-Q plot revealed the expected normal distribution and this was confirmed by a non-significant Shapiro-Wilk statistic (Shapiro Wilk Statistic = 0.98, df = 86, $p>0.1$).

7.5.4.2.6 IPQ- Personal control

Cronbach's alpha was acceptable (0.8) indicating that the scale was internally consistent. Scores ranged from 2-5, with a mean of 3.8 (SD = 0.6). Scores were approximately normally distributed. The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.96, df = 86, $p<0.05$) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution.

7.5.4.2.7 IPQ- Treatment control

Cronbach's alpha was acceptable (0.7) indicating that the scale was internally consistent. Scores ranged from 2-5, with a mean of 3.9 (SD =0.6). Scores were approximately normally distributed. The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.96, df = 86, $p<0.05$) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution.

7.5.4.2.8 IPQ-Illness coherence

Cronbach's alpha was acceptable (0.8) indicating that the scale was internally consistent. Scores ranged from 1-5, with a mean score of 2.5 (0.8). Visual inspection of the normal Q-Q

plot revealed the expected normal distribution and this was confirmed by a non-significant Shapiro-Wilk statistic (Shapiro Wilk Statistic = 0.97, df = 86, p>0.05).

7.5.4.2.9 IPQ-Emotional representations

Cronbach's alpha was good (0.9) indicating that the scale was internally consistent. Scores ranged from 1-5, with a mean score of 3.3. Visual inspection of the normal Q-Q plot revealed the expected normal distribution and this was confirmed by a non-significant Shapiro-Wilk statistic (Shapiro Wilk Statistic = 0.98, df = 86, p>0.1).

7.5.4.3 SF-12 Self-rated physical health

Cronbach's alpha was acceptable (0.7) indicating that the scale was internally consistent. Scores ranged from 15-62, with a mean of 39.7 (SD = 11.4). The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.96, df = 86, p<0.05) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution.

7.5.4.4. HADS Anxiety and Depression

7.5.4.4.1 HADS Anxiety

Cronbach's alpha was good (0.9) indicating that the scale was internally consistent. Scores ranged from 0-20, with a mean of 8.2 (5.0). The Shapiro-Wilk statistic was significant (Shapiro Wilk Statistic = 0.97, df = 86, p<0.05) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution. The HADS manual proposes a cut-off for possible and probable clinical disorder. According to this criteria, 48 (56%) of participants had anxiety scores indicating possible clinical disorder, 29 (34%) of whom had probable clinical disorder.

7.5.4.4.2 HADS Depression

Cronbach's alpha was good (0.9) indicating that the scale was internally consistent. Scores ranged from 0-20, with a mean of 5.7 (4.6). Visual inspection of the normal Q-Q plot revealed that scores were negatively skewed. The Shapiro Wilk test confirmed that the scale was not normally distributed (Shapiro Wilk Statistic = 0.92, df = 86, p<0.01). According to the HADS

criteria, 31 (36%) of participants met the threshold for possible clinical depression with 11 (13%) reporting scores indicating probable clinical disorder.

7.5.5 Predictors of adherence

7.5.5.1 Clinical and demographic predictors of adherence

Baseline clinical and demographic data for those reporting high adherence and those and reporting low adherence at T3 are shown in Table 7.2. The odds of participants who reported high adherence at T3 being in employment before starting treatment were three times greater than those for participants who reported low adherence (χ^2 = 6.9, df =1, p<0.01; OR = 3.4; CI = 1.3-8.8). Participants who reported low adherence had been diagnosed significantly longer than those reporting high adherence (t=-2.0, df = 84, p<0.05); and the odds of having previously been prescribed antiretroviral treatment were eight times higher for those reporting low adherence (χ^2 = 18.2, df = 1, p<0.001; OR = 8.1, CI = 2.9-22.4). No other baseline clinical (CDC symptomatic status, CD4 count, viral load) or demographic characteristics (age, sex or transmission risk) measured at baseline were associated with subsequent adherence (all p>0.1).

Table 7.2: Baseline clinical and demographic characteristics of participants reporting high adherence and those reporting low adherence at 6 months (T3)

Baseline clinical/demographic feature		High adherence n = 58	Low adherence n = 28	p
Age	Mean (SD)	39.7 (9.0)	36.2 (8.1)	p >0.05
Male	Number (%)	56 (96.6)	27 (96.4)	p >0.1
White UK	Number (%)	49 (84.4)	27 (96.4)	p>0.1
Employed	**Number (%)**	**40 (69.0)**	**11 (39.3)**	**p<0.01**
Transmission risk: gay man	Number (%)	52 (89.7)	26 (92.9)	p >0.1
Months since HIV diagnosis	**Median (range)**	**20.0 (0-197)**	**66.5 (0-202)**	**p<0.05**
Asymptomatic HIV	Number (%)	20 (34.5)	6 (21.4)	p >0.1
Symptomatic HIV	Number (%)	21 (36.2)	14 (50.0)	p >0.1
AIDS	Number (%)	17 (29.3)	8 (28.6)	p >0.1
Prior experience of ARVs	**Number (%)**	**12 (20.7)**	**19 (67.9)**	**p<0.001**
CD4 count	Mean (SD)	201.5 (141.6)	198.7 (122.9)	p >0.1
Viral load $\log^{10}$	Mean (SD)	5.3 (0.5)	5.2 (0.6)	p>0.1

7.5.5.2 Characteristics of the regimen

Table 7.3 shows characteristics of the treatment regimen for high and low adherence groups. Participants reporting low adherence to HAART were significantly less likely to be receiving their HAART regimen as part of a clinical trial (χ^2= 9.0, df = 1, p<0.005; OR = 0.2; CI = 0.1-0.6), significantly more likely to be taking three or more antiretroviral medications (χ^2= 7.7, df = 1, p<0.005), and significantly more likely to be taking a protease inhibitor (χ^2= 4.1, df = 1, p<0.05; OR = 2.8; CI=1.0-7.5).

Table 7.3: Characteristics of the treatment regimen among participants reporting high adherence and those reporting low adherence at 6 months (T3)

Type of regimen		High adherence n = 58	Low adherence n = 28	p
Clinical trial	**Number (%)**	**30 (51.7%)**	**5 (17.9%)**	**p<0.005**
>=3 drugs	**Number (%)**	**25 (43.1%)**	**21 (75.0%)**	**p<0.005**
Contains PI	**Number (%)**	**11 (19.0%)**	**11 (39.3%)**	**p<0.05**

Caution should be exercised when drawing conclusions from these results, since all regimen variables were strongly associated with having previous experience of antiretroviral treatment. The majority of clinical trials available to patients at the time of recruitment were recruiting antiretroviral naïve patients. In this study previously naïve patients were significantly more likely to have been recruited to a clinical trial than those who had previously been prescribed antiretrovirals (χ^2= 23.6, df = 1, p<0.001; OR = 0.05 (CI = 0.01-0.21). Consistent with prescribing guidelines at the Brighton clinic at the time of the study, the majority of previously naïve patients initiating HAART were offered a two-medicine combination of Combivir and Effavirenz, while those starting their second or subsequent treatment would usually need to take combinations entailing more medicines, since few combination drugs were available. Indeed, patients taking two medicines were significantly more likely to have been previously naïve to antiretrovirals compared to those taking more than two (χ^2= 18.0, df = 1, p<0.001; OR =9.1; CI=3.0 - 27.4). Finally, in line with current BHIVA guidelines, most previously naïve patients in the UK are offered an NNRTI based regimen, while subsequent therapies may contain a protease inhibitor (BHIVA, 2003). In the current study, those taking a protease inhibitor were significantly more likely to have been prescribed antiretroviral treatment in the past compared to those not taking a protease inhibitor (χ^2= 32.5, df = 1, p<0.001; OR = 27.4; CI=7.0-107.9).

7.5.5.3 Negative affect

Table 7.4 shows HADS depression and anxiety scores for high and low adherence groups. Depression and anxiety at baseline were significant predictors of adherence at six months. Those reporting high adherence at six months had significantly lower depression scores ($t = -2.8$, $df = 84$, $p<0.01$) and lower anxiety scores ($t = -3.2$, $df = 84$, $p<0.005$) at baseline when compared to those reporting low adherence at six months.

Table 7.4: Baseline depression and anxiety among participants reporting high adherence and those reporting low adherence at 6 months (T3)

	High adherence		Low adherence			
	Mean	SD	Mean	SD	t	p
Depression	**4.8**	**(4.1)**	**7.6**	**(5.0)**	**-2.8**	**<0.01**
Anxiety	**7.1**	**(4.6)**	**10.5**	**(5.1)**	**-3.2**	**<0.005**

7.5.5.4 Beliefs about HAART

Research Question 1: Do beliefs about HAART, elicited before starting treatment, predict subsequent adherence?

To answer this question the following hypothesis was tested:

Hypothesis 1: Patients' beliefs about their personal necessity and concerns about potential adverse effects of HAART, elicited before starting treatment, will predict adherence after six months of taking HAART. Specifically low adherence will be predicted by:

H1.1 Doubts about personal necessity for HAART

H1.2 Stronger concerns about potential adverse effects of taking HAART

Table 7.5 shows means and standard deviations for BMQ and Sensoma scores for participants reporting high adherence and those reporting low adherence at T3. Contrary to

H1.1, baseline BMQ-*Necessity* scores did not significantly differentiate between those reporting high and those reporting low adherence at T3 (p>0.1). However, in line with H1.2, those in the low adherence group reported significantly stronger *concerns* about potential adverse effects from taking HAART compared to those in the high adherence group (F (1,84) = 7.2, p<0.001).

After controlling for negative affect, there were no significant differences in perceptions of personal necessity for HAART or concerns about potential adverse effects between those who reported high and low adherence at six months (both p>0.1). This suggests that the relationship between concerns and adherence may have been mediated by negative affect. When previous use of antiretroviral treatment was controlled in the analysis, the relationship between concerns and low adherence at six months remained significant, indicating that the result was independent of past treatment experience.

Table 7.5: Baseline beliefs about medicines among participants reporting high adherence and those reporting low adherence at 6 months (T3)

			Unadjusted scores		Control for negative affect		Control for past ARV	
Scale	High adherence	Low adherence	F	p	F	p	F	p
BMQ-Necessity	4.0 (0.6)	3.8 (0.6)	2.6	>0.1	2.5	>0.1	2.1	>0.1
BMQ-Concerns	**2.9 (0.6)**	**3.3 (0.7)**	**7.2**	**<0.01**	0.7	>0.1	**3.6**	**<0.05**
BMQ-Overuse	3.0 (0.6)	3.0 (0.7)	0.04	>0.1	0.7	>0.1	0.0	>0.1
Sensoma	**2.0 (0.7)**	**2.4 (0.9)**	**4.0**	**<0.05**	0.2	>0.1	0.6	>0.1

7.5.5.5 Beliefs about medicines in general

Relationships between beliefs about medicines in general at baseline and subsequent adherence are shown in Table 7.5. There were no differences between high and low adherence groups in the extent to which they perceived medicines to be overused by doctors. However, individuals who perceived themselves to be particularly vulnerable to adverse

reactions to medicines as a whole (as indicated by higher scores on the sensitive soma scale) were more likely to report low adherence after six months of treatment ($F(1,84) = 4.0$, $p<0.05$). This relationship was rendered insignificant when controlling both negative affect and past experience of antiretroviral treatment. Further analyses revealed that patients who had previously stopped antiretroviral treatment reported higher scores on the sensitive soma (mean = 2.6, SD = 0.8) compared to those who were previously naïve to antiretroviral treatment (mean = 1.9, SD = 0.6; $t = -3.6$, $p<0.001$).

7.5.5.6 Perceptions of HIV

Research Question 2: Do perceptions of HIV, elicited before starting HAART, predict subsequent adherence?

To answer this question the following hypothesis was tested:

Hypothesis 2: Low adherence at six months follow-up (T3) will be predicted by:

- **H2.1** **Reporting fewer and less severe HIV-related symptoms**
- **H2.2** **Reporting less severe negative personal consequences associated with HIV**
- **H2.3** **Anticipating greater improvement over time**
- **H2.4** **Perceiving a more cyclical timeline**
- **H2.5** **Perceiving less personal control over HIV**
- **H2.6** **Doubting that HIV can be controlled by HAART**
- **H2.7** **A more negative emotional representation of HIV**
- **H2.8** **Less illness coherence (as indicated by a higher illness coherence score)**

In addition to IPQ-illness representations low adherence will be predicted by:

- **H2.9** **A more positive perception of physical health (as shown by a higher score on the SF-12 physical health scale)**

Table 7.6: Baseline perceptions of HIV and self-rated health among participants reporting high adherence and those reporting low adherence at 6 months (T3)

			Unadjusted scores		Control for negative affect		Control for past ARV use	
	High adherence	Low adherence	F	p	F	p	F	p
HIV related symptoms	**9.2 (5.9)**	**12.4 (6.5)**	**4.8**	**<0.05**	0.3	>0.1	3.0	>0.05
Moderate-severe HIV symptoms	**4.8 (4.7)**	**7.7 (5.2)**	**6.8**	**<0.01**	0.7	>0.1	**4.0**	**<0.05**
Consequences	**3.5 (0.8)**	**3.9 (0.8)**	**5.8**	**<0.05**	0.7	>0.1	**5.7**	**<0.05**
Timeline	**2.9 (1.0)**	**3.5 (0.9)**	**6.8**	**<0.01**	**3.4**	**<0.05**	**6.2**	**<0.05**
Cyclical timeline	**3.2 (0.8)**	**3.7 (0.8)**	**7.3**	**<0.01**	0.5	>0.1	**4.4**	**<0.05**
Personal control	3.9 (0.5)	3.7 (0.8)	1.2	>0.1	0.0	>0.1	2.6	>0.1
Treatment control	3.9 (0.5)	3.7 (0.7)	2.6	>0.1	0.6	>0.1	1.7	>0.1
Coherence	2.5 (0.7)	2.6 (1.0)	0.2	>0.1	1.4	>0.1	1.0	>0.1
Emotional representations	**3.3 (0.9)**	**3.4 (1.0)**	0.6	>0.1	**5.5**	**<0.05**	1.0	>0.1
Self-rated physical health	**42.3 (11.4)**	**36.8 (10.8)**	**4.4**	**<0.05**	0.5	>0.1	**4.4**	**<0.05**

Means and standard deviations for baseline perceptions of HIV and self-rated health among low and high adherence groups are shown in Table 7.6. Contrary to hypothesis H2.1, low adherence at T3 was associated with a *greater* frequency of HIV-related symptoms ($F(1,84) = 4.8$, $p<0.05$) and with a *greater* frequency of HIV-related symptoms rated moderate, severe or very severe ($F(1,84) = 6.8$, $p<0.01$). Furthermore, contrary to hypotheses H2.2 and H2.3, participants who reported low adherence at T3 perceived *more severe* social and psychological consequences associated with HIV ($F(1,84 = 5.8$, $p<0.05$) and were *less* likely to perceive that their illness would improve in time ($F(1,84) = 6.8$, $p<0.01$). Those reporting low adherence were also *more* likely to report that their symptoms were cyclical in nature ($F(1,84) = 7.3$, $p<0.01$).

Participants reporting low adherence did not differ significantly from those reporting high adherence in the extent to which they perceived HIV to be amenable to control: contrary to expectations neither perceptions of personal control (H2.5) nor perceptions of treatment control (H2.6) at baseline predicted adherence (both $p>0.1$). Low and high adherence groups did not differ in the degree to which they held a coherent picture of their illness (H2.8) or in the extent to which participants held a negative emotional representation of their condition (H2.7) (both $p>0.1$).

Contrary to the direction of results predicted by H2.9, those in the low adherence group at T3 perceived themselves to be in *poorer* physical health at baseline (as indicated by a lower score on the SF-12 physical health scale: $F(1,84) = 4.4$, $p<0.05$).

7.5.5.6.1 Relationships between illness perceptions and adherence when controlling for negative affect

When HADS depression and anxiety were controlled in the analyses, HIV-related symptoms, consequences, cyclical timeline and self-rated physical health were no longer significant predictors of adherence (all $p>0.1$), indicating that depression and anxiety mediate the relationship between these baseline beliefs and subsequent adherence. Timeline remained a significant predictor of adherence, with those in the high adherence group reporting more optimism that their condition would improve with time prior to initiating HAART ($F(1,82) = 3.42$, $p<0.05$). When controlling for depression and anxiety, a significant difference emerged between those in high and low adherence groups in terms of emotional representations of HIV ($F(1,82) = 5.45$, $p<0.05$): those reporting low adherence at T3 reported a more negative emotional reaction to their diagnosis at baseline.

7.5.5.6.2 Relationships between illness perceptions and adherence when controlling for past experience of antiretrovirals

When controlling for the possible influence of past treatment experience, low adherence at six months remained significantly associated with baseline perceptions of more severe consequences ($F(1, 83) = 5.65$, $p<0.05$), a more negative timeline ($F(1,83) = 6.23$, $p<0.05$),

a more cyclical timeline (F (1, 83) = 4.38, p<0.05), perceiving a greater frequency of moderate to severe HIV related symptoms (F (1, 83) = 4.05, p<0.05) and poorer self-rated physical health (F (1,83) = 4.4, p<0.05). The frequency of HIV related symptoms per se no longer predicted adherence, suggesting that having past experience of antiretroviral treatment may have mediated this relationship.

7.5.5.7 Negative affect as a mediator between perceptions of HIV/HAART and adherence

Research question 3: Does negative affect (depression and anxiety) mediate the relationship between illness and treatment perceptions and adherence?

To answer this question the following hypotheses were tested:

H3.1 The relationships between illness perceptions and adherence will be mediated by negative affect

H3.2 The relationships between treatment perceptions and adherence will be mediated by negative affect

The analyses in the preceding sections have shown that depression and anxiety were significantly related to adherence, and that controlling for depression and anxiety eliminated many of the relationships between illness and treatment perceptions and adherence. In order to directly test the mediational hypotheses above, it was necessary to show the following (Baron & Kenny, 1996):

1. The belief variable was significantly related to negative affect (see Table 7.7)
2. Negative affect was significantly related to adherence (see Table 7.4)
3. The belief variable was significantly related to adherence (see Table 7.8)
4. When controlling for negative affect, the belief variable was no longer related to adherence (see Table 7.8)

Table 7.7: Relationships between beliefs (illness and treatment perceptions) and negative affect (depression and anxiety)

	Anxiety		Depression	
	r	p	r	p
HIV related symptoms	**0.53**	**<0.001**	**0.46**	**<0.001**
Moderate-severe HIV symptoms	**0.54**	**<0.001**	**0.49**	**<0.001**
Consequences	**0.58**	**<0.001**	**0.64**	**<0.001**
Timeline	**0.21**	**<0.05**	**0.38**	**<0.001**
Cyclical timeline	**0.62**	**<0.001**	**0.53**	**<0.001**
Personal control	**-0.28**	**<0.01**	**-0.42**	**<0.001**
Treatment control	**-0.36**	**<0.001**	**-0.47**	**<0.001**
Coherence	**0.31**	**<0.005**	**0.54**	**<0.001**
Emotional representations	**0.63**	**<0.001**	**0.58**	**<0.001**
Self-rated physical health	**-0.34**	**<0.005**	**-0.42**	**<0.001**
BMQ-Necessity	-0.05	>0.1	-0.02	>0.1
BMQ-Concerns	**0.54**	**<0.001**	**0.61**	**<0.001**
BMQ-Overuse	0.09	>0.1	**0.24**	**<0.05**
SENSOMA	**0.45**	**<0.001**	**0.38**	**<0.001**

7.5.5.7.1 Does negative affect mediate the relationship between treatment perceptions and adherence?

Table 7.8 shows relationships between beliefs about HAART and adherence when controlling for depression and anxiety. Consistent with H3.1, negative affect mediated the relationship between concerns and adherence and between SENSOMA and adherence. When controlling for anxiety and depression, concerns about potential adverse effects and perceiving oneself to be at heightened sensitivity to the adverse effects of medicines no longer significantly predicted adherence. When controlling for negative affect, beliefs about personal necessity for HAART and the perception that medicines in general are over-prescribed remained unrelated to adherence.

Table 7.8: Relationships between beliefs (illness and treatment perceptions) and adherence showing unadjusted scores and controlling for negative affect (depression and anxiety)

	Unadjusted scores		Control for NA	
	r	p	r_p	p
HIV related symptoms	**0.24**	**<0.05**	0.08	>0.1
Moderate-severe HIV symptoms	**0.27**	**<0.01**	0.06	>0.1
Consequences	**0.25**	**<0.05**	0.08	>0.1
Timeline	**0.28**	**<0.01**	**0.22**	**<0.05**
Cyclical timeline	**0.28**	**<0.01**	0.07	>0.1
Personal control	-0.14	>0.1	-0.05	>0.1
Treatment control	-0.18	>0.1	-0.08	>0.1
Coherence	0.05	>0.1	-0.16	>0.05
Emotional representations	0.09	>0.1	**-0.22**	**<0.05**
Self-rated physical health	**-0.22**	**<0.05**	-0.64	>0.1
BMQ-Necessity	-0.17	>0.05	-0.17	>0.05
BMQ-Concerns	**0.28**	**<0.01**	0.12	>0.1
BMQ-Overuse	-0.03	>0.1	-0.14	>0.1
SENSOMA	**0.24**	**<0.05**	0.06	>0.1

7.5.5.7.2 Does negative affect mediate the relationship between illness perceptions and adherence?

Table 7.8 shows relationships between illness perceptions and adherence when controlling for negative affect. Many of the previously seen relationships between illness perceptions and adherence were rendered insignificant when anxiety and depression were partialled out of the analyses. Adherence remained significantly associated with timeline scores. It also became significantly associated with emotional representations, suggesting that depression and anxiety had previously obscured this relationship. Previously significant associations between adherence and symptoms, consequences, cyclical timeline and self-rated health no longer reached statistical significance when controlling for anxiety and depression in the analyses. Personal control, treatment control and coherence remained unrelated to adherence.

7.5.6 Antecedents of necessity and concerns

Research question 4: Are perceptions of HIV and physical health related to perceptions of personal necessity for HAART and concerns about adverse effects in a way that is consistent with hypotheses generated by the extended SRM (Horne 2003)?

To achieve this aim the following hypotheses were tested:

Hypothesis 4: Higher perceived necessity for HAART will be associated with:

- **H4.1 lower subjective assessment of physical health (SF-12 physical health score)**
- **H4.2 more frequent/severe HIV-related symptoms**
- **H4.3 perceiving greater negative consequences of HIV**
- **H4.4 anticipating less improvement over time**
- **H4.5 perceiving a more cyclical timeline**
- **H4.6 perceiving more personal control over HIV**
- **H4.7 greater conviction that the progression of HIV can be controlled by HAART**

In addition, necessity beliefs may be associated with feedback about disease progression obtained from laboratory test results. Results from a qualitative study (Cooper et al., 2002b) showed that patients who *accepted* HAART following a clinically indicated treatment recommendation tended to express views consistent with the prescribing guidelines for HAART, where CD4 count was associated with perceptions of need for treatment. It was therefore hypothesised that *necessity* beliefs would be related to clinical indicators of disease progression. Specifically, higher perceived necessity will be related to:

- **H4.8 lower CD4 count**
- **H4.9 higher viral load**

Hypothesis 5: Stronger concerns about potential adverse effects of HAART will be associated with:

H5.1 patients' perceptions of being personally susceptible to the adverse effects of medicines in general (higher SENSOMA score)

H5.2 holding negative beliefs about medicines in general (higher BMQ-General overuse and higher BMQ-General harm scores)

7.5.6.1 Predictors of necessity at baseline

7.5.6.1.1 Relationships between necessity beliefs and perceptions of HIV

Table 7.9 shows correlations between beliefs about HAART and perceptions of HIV. In line with H4.1, there was a significant negative correlation between self-rated physical health and necessity beliefs ($r = -0.37$, $df = 85$, $p<0.001$), indicating that those who perceived themselves to be in poorer physical health were more convinced of their personal need for treatment. Contrary to H4.2, neither the frequency nor the severity of HIV related symptoms was associated with patients' perceptions of their personal necessity for HAART ($p>0.1$). Contrary to Hypotheses H4.3-H4.6, there were no significant relationships between necessity beliefs and consequences, timeline, cyclical timeline or personal control over HIV (all $p>0.1$). In line with H4.7, there was a significant positive correlation between the degree to which patients felt that HAART would be effective in controlling HIV and their perception of personal necessity for the treatment ($r = 0.45$, $df = 85$, $p<0.001$).

Relationships between necessity beliefs and perceptions of HIV controlling for negative affect

When the analyses were repeated controlling for negative affect (HADS depression and anxiety), treatment control ($r = 0.52$, $df = 82$, $p<0.001$) and subjective rating of physical health ($r = -0.43$, $df = 82$, $p<0.001$) remained significantly associated with necessity beliefs.

Table 7.9: Correlations between necessity beliefs and perceptions of HIV

Scale		Unadjusted scores		Control for negative affect	
		r	p	r_p	p
IPQ	HIV related symptoms	0.08	>0.1	0.11	>0.1
IPQ	Moderate-severe HIV symptoms	0.06	>0.1	0.10	>0.1
IPQ	Consequences	0.07	>0.1	0.10	>0.1
IPQ	Timeline	-0.14	>0.1	-0.16	>0.1
IPQ	Cyclical timeline	0.00	>0.1	0.05	>0.1
IPQ	Personal control	0.18	>0.1	0.19	>0.05
IPQ	**Treatment control**	**0.45**	**<0.001**	**0.52**	**<0.001**
IPQ	Coherence	-0.07	>0.1	-0.06	>0.1
IPQ	Emotional representations	-0.02	>0.1	-0.00	>0.1
SF12	**Physical health**	**-0.37**	**<0.001**	**-0.43**	**<0.001**

7.5.6.1.2 Relationships between necessity beliefs, clinical and demographic variables and negative affect

Table 7.10 shows relationships between necessity beliefs, clinical and demographic variables and negative affect. Contrary to H4.9, necessity beliefs were not significantly associated with viral load (log_{10}). There was a trend for higher necessity beliefs among those with a lower CD4 count, although this relationship did not reach significance at the 5% level ($r = -0.21$, $df = 85$, $p<0.1$). In addition, there was a significant negative correlation between necessity and the number of months since diagnosis ($r = -0.28$, $df = 85$, $p<0.01$) indicating that participants who had been diagnosed with HIV for a longer period of time were more likely to doubt their personal need for treatment. Necessity beliefs were not significantly associated with age, previous use of antiretrovirals, CDC symptom classification or negative affect (all $p>0.1$).

Table 7.10: Relationships between necessity beliefs, clinical and demographic variables and negative affect

		Unadjusted BMQ-necessity scores	
		r	p
	Age	0.10	>0.1
	CD4 count (log_{10})	**-0.21**	**<0.1**
	Viral load (log_{10})	0.18	>0.1
	Months since diagnosis of HIV	**-0.28**	**<0.01**
	Previous use of antiretrovirals	-0.08	>0.01
HADS	Depression	-0.02	>0.1
HADS	Anxiety	-0.05	>0.1

	CDC symptom classification	Asymptomatic		Symptomatic		AIDS		p
		Mean	SD	Mean	SD	Mean	SD	
BMQ	Necessity	3.91	0.58	3.81	0.57	4.03	0.66	>0.1

7.5.6.1.3 Independent predictors of baseline necessity beliefs

In order to isolate independent predictors of necessity beliefs, variables were entered into a stepwise linear regression. The results of this analysis are shown in Table 7.11. The eSRM (Horne, 1997; 2003) asserts that necessity beliefs are influenced by patients' beliefs about their illness. In order to control for possible interference by other variables, the analysis was conducted entering clinical and demographic variables on the first step, depression and anxiety on the second step and illness perceptions on the third step. In order to reduce the number of variables included in the analysis, only illness perceptions, clinical and demographic variables that were associated with adherence in the bivariate analyses were included. Overall this model accounted for 49% of the variance in necessity beliefs. Clinical variables accounted for 11% of the variance in *necessity* beliefs. Number of months since HIV diagnosis was the only significant independent predictor within this group (beta = -0.22 $p<0.01$). Negative affect accounted for only a further 2% of variance. Neither depression nor anxiety were significantly associated with necessity beliefs. In line with the eSRM, the majority (36%) of the variation in necessity scores was explained by illness perceptions and self-rated

physical health. Specifically, IPQ-treatment control (beta = 0.54, p<0.001) and SF-12 physical health (beta = -0.38, p<0.001) emerged as significant independent predictors of necessity. Overall, these results provide support for the eSRM, and suggest that patients' models of HIV are more influential in determining their perceptions of personal necessity for treatment than clinical indicators of disease progression.

Table 7.11: Stepwise linear regression: Predictors of baseline necessity beliefs

Variable	R^2	Adjusted R^2	Sig	ΔR^2	β	p
Block 1: Clinical variables	**0.11**	**0.09**	**<0.005**	**0.11**		
Time HIV					**-0.22**	**<0.01**
CD4 count (log^{10})					-0.12	>0.1
Block 2: Negative affect	**0.13**	**0.08**	**<0.05**	**0.02**		
Anxiety					-0.12	>0.1
Depression					0.18	>0.1
Block 3: Illness representations	**0.49**	**0.45**	**<0.001**	**0.36**		
Treatment control					**0.54**	**<0.001**
Physical health					**-0.38**	**<0.001**

7.5.6.2 Correlates of concerns at baseline

Hypothesis 5: Stronger concerns about potential adverse effects of HAART will be associated with:

H5.1 **perceptions of being personally susceptible to the adverse effects if medicines in general (higher SENSOMA score)**

H5.2 **holding negative beliefs about medicines in general (higher BMQ-General overuse and higher BMQ-General harm scores)**

In addition to perceptions of more general classes of treatment, it is proposed that concerns about potential adverse effects of taking HAART stem from negative previous experiences of antiretroviral treatment (Cooper et al., 2002). It is therefore expected that low adherence will be associated with:

H5.3 having stopped a previously prescribed regimen of antiretroviral treatment

7.5.6.2.1 Relationships between concerns about HAART and beliefs about medicines in general

Correlations between concerns about HAART and beliefs about medicines in general are shown in Table 7.12. In line with H5.1 and H5.2, there were significant positive correlations between concerns about potential adverse effects of taking HAART and both a general perception of being personally susceptible to adverse effects of taking medicines ($r = 0.55$, $p<0.001$), and the perception that medicines are over-prescribed by doctors ($r = 0.34$, $p<0.005$).

7.5.6.2.2 Relationships between concerns about HAART and beliefs about medicines in general controlling for negative affect

The relationships between concerns about HAART and a general perception of being personally susceptible to adverse effects of taking medicines ($r = 0.39$, $p<0.001$) and the perception that medicines are over-prescribed by doctors ($r = 0.26$, $p<0.05$) remained significant when controlling for negative affect.

7.5.6.2.3 Relationships between concerns about HAART and perceptions of HIV

In addition to the relationships proposed in H5, significant positive correlations were observed between concerns and the frequency of HIV related symptoms ($r = 0.40$, $df = 85$, $p<0.001$), the frequency of moderate to severe HIV related symptoms ($r = 0.45$, $df = 85$, $p<0.001$), perceiving more severe consequences associated with having HIV ($r = 0.53$, $df = 85$, $p<0.001$), perceiving a more negative timeline ($r = 0.45$, $df = 85$, $p<0.001$), perceiving a more cyclical timeline ($r = 0.45$, $df = 85$, $p<0.001$) and holding a negative emotional representation of HIV ($r = 0.60$, $df = 85$, $p<0.001$). There were significant negative correlations between

concerns and perceived personal control over HIV (r = -0.36, df = 85, p<0.001), beliefs about the effectiveness of HAART in controlling HIV (r = -0.47, df = 85, p<0.001) and perceiving a less coherent understanding of HIV (indicated by higher illness coherence scores) (r = 0.50, df = 85, p<0.001).

Table 7.12: Relationships between concerns, perceptions of HIV and beliefs about medicines in general

		Unadjusted concerns scores		Controlling for negative affect	
		r	p	r_p	p
IPQ	**HIV related symptoms**	**0.40**	**<0.001**	0.07	>0.1
IPQ	**Moderate-severe HIV symptoms**	**0.45**	**<0.001**	0.13	>0.1
IPQ	**Consequences**	**0.53**	**<0.001**	0.16	>0.1
IPQ	**Timeline**	**0.45**	**<0.001**	**0.31**	**<0.005**
IPQ	**Cyclical timeline**	**0.45**	**<0.001**	0.10	>0.1
IPQ	**Personal control**	**-0.36**	**<0.001**	-0.13	>0.1
IPQ	**Treatment control**	**-0.47**	**<0.001**	**-0.25**	**<0.05**
IPQ	**Coherence**	**0.50**	**<0.001**	**0.27**	**<0.05**
IPQ	**Emotional representations**	**0.60**	**<0.001**	**0.31**	**<0.01**
SF12	Physical health	-0.17	>0.1	0.14	>0.1
BMQ	**General overuse**	**0.34**	**<0.005**	**0.26**	**<0.05**
	SENSOMA	**0.55**	**<0.001**	**0.39**	**<0.001**

7.5.6.2.4 Relationships between concerns about HAART and perceptions of HIV controlling for negative affect

When controlling for negative affect, several of the relationships previously observed between concerns and illness perceptions no longer reached statistical significance. Symptoms, consequences, cyclical timeline and personal control were no longer significantly related to concerns (all p>0.1). However, the previously observed correlations between concerns and

timeline, treatment control, coherence and emotional representations were reduced in size but remained significant (all <0.05; see table 7.12), suggesting that these relationships were independent of negative affect.

7.5.6.2.5 Relationships between concerns about HAART, clinical and demographic variables and negative affect

Relationships between clinical and demographic variables and concerns about HAART were assessed using Pearson's correlations. Contrary to H5.3, concerns were not related to having previously been prescribed antiretroviral treatment (p>0.1). Age was significantly associated with concerns, specifically younger participants were more suspicious of their treatment (r = -0.23, df = 85, p<0.05). Concerns were not associated with clinical markers of disease progression. There were positive correlations between concerns and depression (r = 0.61, df = 85, p<0.001) and anxiety (r = 0.54, df = 85, p<0.001), indicating that patients reporting more negative affect had stronger concerns about their treatment.

Table 7.13: Relationships between concerns, clinical and demographic variables and negative affect

		Unadjusted BMQ-concerns scores	
		r	p
	Age	**-0.23**	**<0.05**
	CD4 count (log_{10})	0.11	>0.1
	Viral load (log_{10})	0.10	>0.1
	Months since diagnosis of HIV	0.15	>0.1
	Previous use of antiretrovirals	0.15	>0.1
HADS	**Depression**	**0.61**	**<0.001**
HADS	**Anxiety**	**0.54**	**<0.001**

		Asymptomatic		Symptomatic		AIDS		p
		Mean	SD	Mean	SD	Mean	SD	
BMQ	Concerns	3.02	0.63	3.10	0.54	3.00	0.79	>0.1

7.5.6.2.6 Independent predictors of concerns about potential adverse effects of HAART

Stepwise linear regression was used to isolate independent correlates of concerns. The results of this analysis are shown in Table 7.14. In order to reduce the number of variables entered into the analyses, only those that predicted concerns independently of negative affect in the bivariate analyses were included. Age was entered on Step 1, depression and anxiety on Step 2, treatment control, timeline, emotional representations and illness coherence on Step 3, and SENSOMA and general overuse on Step 4. The model accounted for 54% of the variance in concerns scores. Age accounted for 7% of variance in concerns, however in the final model age did not emerge a significant independent predictor of concerns ($p>0.1$).

Depression and anxiety were entered on the second step and accounted for a further 38% of variance, although again, neither reached statistical significance in the final model ($p>0.1$), indicating shared variance with other measures. Illness perceptions (timeline, coherence, emotional representations and treatment control) were entered on Step 3 and accounted for a further 9% of the variance. There was a trend for timeline (beta = 0.16, $p<0.1$) and coherence (beta = 0.22, $p<0.1$) to be associated with concerns, however treatment control and emotional representations did not significantly predict concerns ($p>0.1$).

Finally beliefs about medicines in general (general overuse and SENSOMA) were added on step 4, accounting for a further 5% of the variance in concerns. The perception of being particularly sensitive to adverse effects of taking medicine (SENSOMA scores) emerged as the only statistically significant independent predictor of concerns (beta = 0.30, $p<0.01$), indicating that participants who believe they have a heightened sensitivity to medicines as a whole are likely to harbour strong concerns about the potential adverse effects of taking HAART.

Table 7.14: Stepwise linear regression: Predictors of baseline concerns

Variable	R^2	Adjusted R^2	Sig	ΔR^2	β	p
Block 1: Clinical/ demographics	**0.07**	**0.06**	**<0.05**	**0.07**		
Age					-0.09	>0.1
Block 2: Negative affect	**0.45**	**0.43**	**<0.001**	**0.38**		
Anxiety					0.11	>0.1
Depression					0.18	>0.1
Block 3: Illness representations	**0.54**	**0.49**	**<0.05**	**0.09**		
Timeline					**0.16**	**<0.1**
Treatment control					-0.07	>0.1
Coherence					**0.22**	**<0.1**
Emotional reps					0.03	>0.1
Block 4: General medicine beliefs	**0.66**	**0.57**	**<0.001**	**0.05**		
Overuse					0.07	>0.1
SENSOMA					**0.30**	**<0.01**

7.6 Discussion

The aim of this study was to twofold: first, to explore the ability of patients' perceptions of HIV and HAART, elicited before initiating a new HAART regimen, to predict subsequent adherence, and second, to examine relationships between perceptions of HIV and beliefs about HAART stemming from the SRM (Leventhal et al., 1980) and the extended SRM proposed by Horne (1997, 2003).

7.6.1 Patterns of adherence over time

There was a significant decrease in adherence over follow-up, with the number of participants reporting low adherence increasing from only twelve percent at one month to a third by the

six-month follow-up. Consistent with previous research (Paterson et al., 2000), low adherence to HAART was associated with sub-optimal clinical outcome. Only a third of participants who reported low adherence at three months obtained an undetectable viral load at six months, compared to three quarters of those who reported high adherence. These results confirm the utility of the adherence measure used within the study and reinforce the need for an unusually high level of adherence to HAART to ensure clinical efficacy. Although rates of adherence remained high until the three-month follow-up, the results suggest that interventions to support adherence in order to ensure clinical efficacy (undetectable viral load after six months of treatment with HAART) should begin as soon as patients initiate treatment, since low adherence as early as one month was predictive of clinical 'failure' (detectable viral load) at six months.

7.6.2 Baseline beliefs about HAART and subsequent adherence

7.6.2.1 Concerns about potential adverse effects of taking HAART

Consistent with expectations, possessing strong concerns about potential adverse effects of taking HAART before initiating treatment was a significant predictor of subsequent low-adherence. This finding is in accordance with cross-sectional research which has found that patients who hold negative views about their antiretroviral treatment are less likely to adhere (Horne et al., in press; Catz et al., 2000; Siegel et al., 2000; Siegel et al., 1999; Aversa & Kimberlain, 1996), and extends previous findings by emphasising the relevance of patients' concerns about HAART before they initiate treatment to later adherence. This finding emphasises the importance of eliciting and addressing patients' concerns about HAART before they initiate treatment. The results suggest that concerns about a wide range of adverse effects are relevant, including the possibility of side effects and negative long-term consequences of taking treatment as well as worries about the difficulty of keeping to a rigid treatment regime and more abstract concerns about the stigma associated with taking HAART.

As having previous experience of antiretroviral treatment was a strong predictor of adherence in this study, the analyses of the relationships between concerns and adherence were

repeated controlling for this variable. Controlling for the possible influence of previous antiretroviral treatment did not eliminate the relationship between baseline concerns about HAART and low adherence, therefore the results suggested that the association could not be explained in terms of negative previous experience of taking HAART. Indeed, contrary to expectations derived from the extended SRM (Horne, 2003), concerns about HAART were not related to having had previous experience of treatment. Unfortunately, reasons for stopping previous antiretroviral treatments were not ascertained as part of this study, and it is possible that some participants stopped previous treatments for positive reasons, such as feeling better or on the advice of a clinician. Further research is required in order to determine whether previous negative experiences of treatment are related to stronger concerns about subsequent antiretroviral treatment regimens.

Controlling for negative affect in the analyses eliminated the significance of the relationship between baseline concerns and adherence. Since there was a strong correlation between concerns and negative affect, and between negative affect and adherence, it was concluded that negative affect mediates the relationship between concerns and adherence. This finding raises the question of whether interventions to increase adherence to HAART should focus on addressing patients' concerns about adverse effects, or whether they should focus on reducing anxiety and depression to ameliorate concerns and improve subsequent adherence. It should be noted that the findings of this study do not clarify the nature of the relationship between concerns and negative affect. While negative affect could lead to a higher level of concern about treatment, holding concerns about a prescribed treatment could lead to high levels of depression and anxiety. Since negative affect and treatment perceptions were measured at the same assessment, it was not possible to tease out causal mechanisms. Either way, over three-quarters of patients held strong concerns about HAART prior to initiating their treatment which should be elicited and addressed in order to ensure high adherence and subsequent clinical benefit. The role of negative affect as a mediator between beliefs and adherence is further addressed in Section 7.6.5 of this discussion.

7.6.2.2 Perceptions of personal necessity for HAART

Participants' beliefs about their personal necessity for HAART were high at baseline. The vast majority of participants starting HAART perceived their treatment to be necessary (all but one participant reporting scores over the scale mid-point) and it is perhaps not surprising that necessity beliefs did not predict subsequent adherence. These findings are contrary to those of cross sectional studies conducted across a range of illness conditions (Horne & Weinman, 1999, 2002; Llewellyn et al., 2003) in which strong perceptions of personal necessity for treatment were related to high rates of adherence. They suggest that the relationships observed in cross-sectional studies may be due to the closer temporal proximity of adherence and belief measures. Rather than causing future adherence problems, necessity beliefs may be the result of non-adherence, in that patients might report beliefs that are congruent with their behaviour. Alternatively, perceptions of personal necessity for treatment might decline over time and predict adherence. Study 3 will monitor changes in necessity beliefs over time, in order to assess whether a decrease in perceived need for HAART is associated with subsequent low adherence, as predicted by an extended self-regulatory model (Horne, 2003). The study will also investigate predictors of change in patients' perceptions of necessity for HAART over time.

7.6.3 Relationships between perceptions of HIV and subsequent adherence to HAART

Low adherence at six months was predicted by illness identity (both frequency of symptoms per se, and frequency of moderate-severe symptoms), consequences, timeline and cyclical timeline at baseline, while personal control, treatment control, coherence and emotional representations were not associated with subsequent adherence. Within a 'common sense' model of adherence (SRM: Leventhal, 1982), more negative illness representations are proposed to predict higher adherence, so that a person who is experiencing more frequent, persistent and severe symptoms or who believes the consequences of their condition to be more catastrophic will be more likely to adhere to their prescribed medication. However, the current study showed that in contrast with expectations proposed by the SRM, those with more *negative* perceptions of their illness before initiating treatment (perceiving more and

more severe symptoms, more negative consequences associated with HIV, and a more chronic timeline and more cyclical symptoms) were more likely to be subsequently non-adherent.

One explanation for these findings might be that the relationship between negative illness perceptions and adherence is mediated by negative affect. Indeed, there were positive correlations between negative affect and identity, timeline and consequences, and negative correlations among negative affect and control beliefs. Furthermore, when depression and anxiety were partialled out of the analyses, only the relationship between *timeline* and adherence remained significant, showing that negative affect mediated the relationships between adherence and identity, consequences and control beliefs. The role of negative affect as a mediator is addressed in Section 7.6.5 of this discussion.

After controlling for negative affect, the relationship between perceiving a more chronic timeline and low adherence remained statistically significant. A possible reason for the difference between the results of the current study and those of studies conducted with patients with other illnesses (e.g. asthma: Horne & Weinman, 2002) is that an adapted timeline scale was used in this study. While timeline has typically been conceptualised as the extent to which an individual perceives their condition to be chronic or acute, the scale was modified for the present study and comprised a single item, 'my illness will improve in time'. Given that the participants included in this study had recently decided to accept a treatment offer and were about to initiate HAART, endorsement of this item may represent an optimistic attitude towards the benefits of treatment (or treatment efficacy). Viewing the 'timeline' item in this light makes sense in terms of previous research, which shows that optimists perform health promoting behaviour, including adherence to treatment, more often than pessimists (Scheier & Carver, 1985; Scheier et al., 1989; Taylor et al., 1992; Mann, 2001).

7.6.4 Relationships between beliefs about medicines in general and subsequent adherence to HAART

Possessing the belief that medicines in general are over-prescribed by doctors was not directly related to adherence to HAART. However, there was a negative relationship between scores on the Sensitive Soma scale and adherence, with participants reporting low adherence at the six month perceiving themselves to be more susceptible to adverse effects of medicines as a whole before starting treatment. Interestingly, this relationship no longer reached statistical significance when controlling for past experience of antiretroviral treatment. This might be because participants who experience adverse effects from taking HAART on repeated occasions perceive themselves to be particularly vulnerable to adverse reactions to medicines in general and respond by not taking their treatment. This hypothesis could not be tested in the current study, as there was no information regarding reasons for stopping previous treatments. Negative affect was also found to mediate the relationship between SENSOMA scores and adherence. The role of negative affect is discussed below.

7.6.5 The role of negative affect in relationships between beliefs and adherence

Consistent with hypotheses, negative affect mediated many of the relationships between perceptions of illness and treatment and adherence. However, there are several reasons why the observed relationships between beliefs and adherence should not be dismissed as merely a symptom of a more general negative mood. Firstly, since negative affect, illness perceptions and beliefs about HAART were measured cross-sectionally in the current study, it was not possible to deduce the direction of the relationship. It is possible that negative cognitive processes preceded depression (Smith et al., 1994), thus harbouring negative perceptions of HIV may lead to both negative affect and non-adherence. Secondly, the majority of participants did not meet the suggested cut-off scores for probable clinical disorder of depression or anxiety, so it would be inaccurate to assume that a clinical diagnosis of depression or anxiety disorder accounts for the relationship between illness perceptions and adherence. Indeed there is no evidence to date that treatment for depression or anxiety changes illness perceptions, although treating depression has shown to improve adherence to interferon treatment among patients with multiple sclerosis (Mohr et al., 1999). Finally, a

high level of depressive symptomatology has been noted among people who have been diagnosed with HIV (Cruess et al., 2003; Starace et al., 2002). There are many facets of HIV that might be relevant to the aetiology of depression among HIV positive adults including psychological influences stemming from the diagnosis, onset of symptoms, progression of disease, young age and associated rejection by family, society and work (Maj, 1990). Receiving a recommendation of HAART usually means that there has been recent deterioration in health, a decrease in CD4 count indicating viral progression, or a recent diagnosis of HIV at a stage at which the disease necessitates treatment. Patients' perceptions of their illness and treatment at this time may well contribute to a negative mood state prior to initiating HAART and may be a valid target for intervention to both improve mood and subsequent adherence problems.

7.6.6 Clinical and demographic predictors of adherence

7.6.6.1 Previous experience of antiretroviral treatment

Being naïve to antiretroviral therapy was the strongest independent predictor of adherence in the current study. Patients who had previously been prescribed antiretroviral treatment were about eight times as likely to report low adherence to HAART after six months of treatment compared to those who were previously naïve to antiretrovirals, and were more likely to have a poor clinical outcome in terms of detectable viral load. These findings concur with previous longitudinal research, which has identified higher adherence at follow-up among participants who were previously naïve to antiretrovirals (Mannheimer et al., 2002; Carrieri et al., 2001; Duran et al., 2001).

Several studies show that previous adherence is strong predictor of subsequent adherence. Matthews et al (2000) found that participants who were naïve to antiretroviral treatment at study entry and those who reported high adherence to previous treatment at study entry were more adherent at follow-up. Spire et al. (2002) found that patients who indicated that they had had adherence problems in the past were more likely to be non-adherent. No information was available regarding reasons for stopping previous combinations in the current study, but it

could be speculated that the reasons for stopping previous antiretroviral treatment and for low adherence to the current combination may have been similar.

It was hypothesised that having previous experience of taking antiretrovirals would be associated with stronger concerns about potential adverse effects before initiating another treatment. This hypothesis was based on the rationale that most people stop HAART of their own volition rather than under medical recommendation (personal communication, Fisher, 2002). However, this hypothesis was not substantiated: there was no significant relationship between concerns and having previous experience of antiretroviral treatment. However, it is of note that having previous antiretroviral experience mediated the relationship between sensitive soma and adherence but not other relationships between adherence and illness perceptions or other beliefs about medicines. This suggests a possible mediational pathway between having previously used antiretrovirals and low adherence. Patients who have previously stopped antiretroviral treatment may see themselves as more vulnerable to the potential adverse effects of medicines as a whole, and be more likely to respond to this belief by missing doses or stopping their treatment. Further research is required to establish the direction of causality, since perceiving oneself to be particularly sensitive to the effects of medicines may increase the likelihood of stopping HAART, on the other hand experiencing adverse effects from taking HAART may influence beliefs about a whole class of treatment.

It is also of note that, consistent with prescribing guidelines, participants who were initiating their second, third, fourth or fifth combination were taking more complicated regimens, with more drugs, and more likely to be taking a protease inhibitor. These regimen variables were also correlated with adherence. Unfortunately the sample in the current study was not large enough to explore the impact of regimen complexity on adherence among solely antiretroviral naïve patients, although this presents an area of interest for future studies.

7.6.6.2 Employment

Consistent with previous studies (Gordillo et al., 2000; Ammassari et al., 2001; Schuman, 2001; Wagner et al., 2001), being in employment was associated with higher adherence to HAART. To date, the mechanisms linking unemployment to low adherence have received

little investigation. It is likely that the links between employment and adherence go beyond practical barriers to drug taking within the workplace suggested by previous work (Chesney et al., 2000). In the current study there was a crude distinction between employment unemployment, with no further information on types of unemployment (for example whether the person was on sickness benefits, jobseeker's allowance, looking after dependents etc.). Further research is required to explore possible psychological factors, such as depression and perceptions of illness, which might link unemployment and low adherence.

7.6.6.3 Duration of HIV diagnosis

Participants who had been diagnosed with HIV for longer were also more likely to report low adherence. This result is in contrast to previous findings (e.g. Paterson et al., 2000) where participants who had been infected with HIV for a longer time showed higher adherence rates according to MEMS Caps. Previous studies have found that patients who have been diagnosed with HIV for longer were more likely to decline a clinically recommended offer of HAART and were more sceptical of their personal need for treatment (Cooper et al., 2001). The nature of the relationship in the present study may be further explained in the light of a qualitative study, where patients who had been diagnosed with HIV for a number of years often explained that their concerns about HAART stemmed from early negative experiences of HIV treatments such as AZT monotherapy (Cooper et al., 2002). The link between time since diagnosis and adherence warrants further investigation.

7.6.6.4 Age

There was also a weak positive relationship between age and adherence, where older patients were more likely to report high adherence. This is in accordance with previous prospective studies that found that older participants tended to maintain high levels of adherence over time more frequently than younger participants (Carrieri et al., 2001; Moatti et al., 2000). To date, no studies have explored mediators of the relationship between age and adherence. In the present study, there was a significant negative correlation between age and concerns about HAART, indicating that younger participants were more suspicious of the treatment.

7.6.7 Predictors of necessity beliefs

7.6.7.1 Relationships between necessity and perceptions of HIV

The multiple regression showed that almost half the variance in necessity scores was accounted for by clinical variables and illness perceptions, with illness perceptions independently accounting for over a third of the variance. This provides strong support for the relationships predicted by extensions to the SRM (eSRM) proposed by Horne (1997, 2003).

In line with expectations generated by the eSRM, perceiving a stronger personal necessity for HAART was associated with a greater conviction that HIV can be controlled by HAART. In contrast with hypotheses, necessity was not significantly associated with identity, consequences, timeline or cyclical timeline scores.

Hypotheses derived from the eSRM predicted that those experiencing more frequent and severe symptoms they associate with HIV would perceive a greater personal necessity for HAART. This was demonstrated in two qualitative studies of HAART refusal, where HIV positive gay men who rejected a clinically recommended treatment offer of HAART questioned their need for treatment when they had experienced few or none of the symptoms they associated with HIV or AIDS (Cooper et al., 2002; Siegel & Gorey, 1997). Within the current study, however, the symptom scales were not correlated with perceptions of necessity. There are several possible reasons why this might be the case. One relates to the identity scale itself in relation to the HIV condition. HIV is characterised by its heterogeneity of clinical presentation. While the identity scale was modified for this study to include both generic illness symptoms and HIV-specific symptoms, it could not encompass the huge diversity of symptoms and illnesses experienced by people with HIV. For example, the scale may minimise the importance of one very severe or disabling symptom, or over-inflate the importance of several minor symptoms. In the current study, attempts were made to reflect differences in symptom severity by including a second identity scale, where only symptoms rated moderate to severe were counted. However, neither identity scale was correlated with necessity beliefs. In order to measure the impact of symptoms on daily functioning, self-rated physical health, measured by the SF-12, was included in the study. There was a significant

negative correlation between patients' subjective ratings of their physical health and necessity beliefs, indicating that those who rated their health as more severely compromised perceived a higher necessity for HAART. Indeed, patients' subjective assessments of their physical health as measured by the SF-12, accounted for about a fifth of variance in necessity beliefs. The physical health rating assessed by the SF-12 encompasses the subjective impact of symptoms on various areas of functioning including work and daily chores, social life and vitality. This broader rating of health status seems to be more relevant than symptom frequency and severity in determining patients' perceptions of their need for HAART.

7.6.7.2 Relationships between necessity for HAART and clinical variables

Contrary to expectations, neither clinical markers of disease severity (CDC classification) nor laboratory markers of disease progression (CD4 count and viral load) were significantly associated with patients' perceptions of their personal necessity for HAART. It is of note that over recent years, treatment guidelines have endorsed the use of CD4 count and symptomatic status, over and above viral load counts, to inform clinical decisions to initiate therapy (BHIVA, 2001). To an extent this was a homogenous subset of HIV positive individuals, in that they were all eligible to initiate treatment. However, even within this subset there was a wide range of severity as reflected in clinical markers of immune suppression, virologic progression and symptom classification. It would appear that abstract clinical markers and classifications are less salient in determining patients' perceptions of necessity for HAART than their personal beliefs about the extent to which treatment is effective in controlling HIV and their own subjective assessment of their physical health. This is in line with Leventhal (1992) who highlights the difficulties associated with integrating tangible symptom experiences with more abstract information from healthcare professionals.

The negative correlation between *necessity* beliefs and the number of years since HIV diagnosis is consistent with previous research, which shows that many 'long term survivors' of HIV are reluctant to initiate therapy on the basis of constantly changing treatment guidelines. This group of patients have often remained in good health for a number of years with no antiretroviral intervention, despite having been recommended treatment repeatedly over that

time (Cooper et al., 2002). The present findings suggest that even those who decide to initiate treatment remain more sceptical about their need for HAART than more recently diagnosed individuals. An alternative explanation for this finding is that several participants had been recently diagnosed with severe disease and therefore perceived their personal need to be more urgent (Cooper et al.,2002b).

7.6.8 Predictors of concerns about HAART

7.6.8.1 Relationships between beliefs about medicines in general and concerns about HAART

According to the eSRM (Horne, 1997; 2003), individuals who perceive themselves to be particularly sensitive or susceptible to the adverse effects of medicines in general have stronger concerns about the potential adverse effects of their prescribed medicines. Horne (2003) proposes that ideas about vulnerability to medicines in general may stem from one's own past experiences of medication or those of other people. In line with this model, patients' scores on the Sensitive Soma, a scale developed to measure individual differences in perceptions of sensitivity to medicines as a whole, were independently related to concerns about HAART. Concerns about HAART were also related to the belief that doctors over-prescribe medicines in general.

7.6.8.2 Relationships between concerns about HAART, clinical and demographic variables

Contrary to expectations, concerns about HAART were not associated with having previously taken antiretroviral treatment. However, it was not possible to gain information regarding reasons for stopping previous antiretroviral treatments in this study. It may be hypothesised that patients who had made the decision to stop previous treatments because of side effects may be more likely to hold stronger concerns about subsequent treatments, than those who stopped for other reasons.

7.6.8.3 Relationships between concerns about HAART and perceptions of HIV

There were several significant relationships between concerns about HAART and perceptions of HIV. Concerns were positively correlated with identity (more frequent symptoms and more

frequent moderate to severe symptoms), more severe consequences, a more chronic and cyclical timeline, stronger emotional representations, lower illness coherence and lower perceptions of control. Even after controlling for negative affect, significant relationships remained between concerns and timeline, treatment control, illness coherence and emotional representations of HIV. The direction of these relationships indicate that patients who have stronger concerns about HAART also have more negative beliefs about their condition and its treatment. These relationships make sense in terms of a 'common sense' model, where patients who are about to initiate a treatment that they have strong concerns about, hold a more negative picture of their illness and its likely outcome, have a less coherent picture of their condition and a more negative emotional reaction to HIV. However, since illness perceptions and beliefs about HAART were elicited at the same time, this study cannot answer questions of causality.

7.7 Limitations

7.7.1 Sample size

Adherence was framed as a dichotomous variable in this study in order to be clinically meaningful (Paterson et al., 2000). However, the study was under powered for logistic regression, which requires a minimum of 50 cases per predictor variable (Aldrich & Nelson, 1984) in order to have statistical power, that is, to avoid the type II error of accepting the null hypothesis when it is false. A much larger sample would allow the use of logistic regression to predict adherence in order to determine the relative contribution of perceptions of HIV and HAART against negative affect, clinical and demographic variables.

7.7.2 Sample bias

White, gay men were over-represented among the population receiving HIV care at the Lawson Unit in Brighton. The most likely HIV transmission route for 86.8% of participants recruited to this study was sex between men. Of those reporting their transmission risk as sex between men, 91.9% described their ethnic origin as 'white UK'. Figures from the Communicable Disease Surveillance Centre (July 2003) show that the cumulative percentage of HIV infection acquired as a result of sex between men in the UK from 1993 to the end of

June 2003 was 51.7%. Therefore the results of this study may not be directly applicable to the population of HIV positive adults in the UK as a whole.

7.7.3 Measures

7.7.3.1 Timeline measure

Although 'timeline' was a significant independent predictor of adherence, it should be noted that the timeline scale of the IPQ was reduced to a single item "my illness will improve in time" for this study. This item may not reflect the chronic/acute timeline in the original sense of the timeline scale. The scale was adapted for this study because the pilot study indicated that people living with HIV unanimously view their condition as chronic, therefore there would be no variation in timeline scores. The single item was retained because people differed in terms of their expectations, some felt they would improve, some felt their health would be maintained at a certain level and others felt they would get worse in time. However, since these were patients who were initiating a new treatment regimen, the item could reflect treatment optimism. Treatment optimism has been related to adherence to medication in other illness groups (Schier & Carver, 1985; Schier et al., 1989; Taylor et al., 1992). Further development of the timeline scale is required to adapt the scale for use with HIV populations.

7.7.3.2 IPQ-Identity

The symptom scales used for this study were based on a list of twelve generic symptoms common to any illness and eleven additional common HIV-related symptoms, as recommended by the authors of the IPQ (Weinman et al., 1996). However, symptoms of HIV are wide ranging and it is possible that participants may have been experiencing additional severe symptoms that were not included on the symptom checklist. Furthermore there is a myriad of possible HAART-related symptoms that were not included on the symptom lists. A more comprehensive list of symptoms may be useful for future studies.

7.7.3.3 BMQ-Concerns about HAART

Insights from recent interview-based studies suggest concerns about this treatment might be more complex than those currently covered by the BMQ-HAART. In a study of gay men who

had received a clinically recommended treatment offer of HAART (Cooper et al., 2002a; 2002b), a range of additional concerns were uncovered. These included patients' fears that the drugs would make them worse, accelerate the progression of HIV, or decrease their quality of life; worries about potential adverse effects of the drugs on libido and sex-life; concerns that treatments have not been thoroughly tested by drug companies or feelings of being experimented upon; fears that taking treatment would have a negative effect on self-identity because it is an unwelcome, daily reminder of HIV, or because it signifies a personal failure to fight the virus; concerns about future treatment options as a result of becoming resistant to all classes of antiretrovirals; concerns about the potentially life-long commitment to taking treatment and concerns stemming from previous negative experiences of taking antiretrovirals. It is possible that revising the BMQ-concerns scale to include these items may increase its predictive power by encompassing a more comprehensive range of the types of concerns encountered by patients who are faced with decisions about HAART and which might impact on adherence.

7.7.4 The role of depression and anxiety in the SRM

While it was evident that negative affect mediated many of the relationships between illness and treatment perceptions and adherence, the direction of relationships between illness beliefs and negative affect were not clarified in the current study. The direction of causality between perceptions of illness and treatment and negative mood warrants further investigation.

7.7.5 Previous treatment experience

Having previous experience of taking antiretrovirals was a strong predictor of adherence. Contrary to expectations, this variable was not significantly related to concerns about potential adverse effects of HAART. However, reasons for terminating previous combinations of antiretrovirals were not ascertained in this study. Further research is needed to determine whether having negative experiences of treatment in the past leads to a higher level of concern about subsequent treatment.

7.8 Implications for interventions and clinical practice

The key findings from the study indicate that patients' perceptions of their illness and concerns about HAART should be elicited and addressed before they initiate HAART in order to ensure subsequent adherence.

7.8.1 Concerns about potential adverse effects

Patients' concerns about potential adverse effects of taking HAART, elicited before they initiated treatment, predicted subsequent adherence. These findings indicate that attempts should be made to elicit and address patients' concerns about HAART *before* they initiate treatment. These concerns may include worry about side effects, adverse long-term effects, practical difficulties such as timing and disruption to routine, as well as more abstract worries about the stigma or embarrassment surrounding the medication.

7.8.2 Beliefs about medicines in general

Participants who scored high on the SENSOMA at baseline reported low adherence at follow-up, indicating that patients' perceptions of their personal vulnerability to adverse effects of medication in general should be elicited and addressed before they initiate treatment. The fact that this relationship was mediated by past treatment experience indicates that for many, these perceptions stem from previous negative experiences of taking HAART. Interventions to promote high adherence should therefore elicit patients' previous experiences of antiretroviral treatment to determine how these experiences might relate to the patients' current belief systems.

7.8.3 Illness perceptions

Adherence six months after initiating HAART was predicted by patients' perceptions of their illness identity, consequences, timeline and cyclical timeline at baseline. Those with more negative perceptions of their illness and its outcome were more likely to report low adherence. Interventions aimed at supporting high adherence should aim to elicit and address perceptions of HIV before the patient initiates treatment. The aim of the intervention would be to challenge any unrealistic or unduly pessimistic perceptions of HIV.

7.8.4 Negative affect

Depression and anxiety mediated many of the relationships between perceptions of HIV/HAART and adherence including concerns, identity, consequences and cyclical timeline. Further research is required to identify the direction of causality between negative affect and beliefs, and to determine whether treating depression and anxiety has a positive impact on beliefs among those with a clinically defined mood disorder. However, since depression and anxiety independently predicted low adherence, interventions to improve adherence should incorporate the detection and reduction of depression and/or anxiety.

7.9 Conclusions

In summary, consistent with hypotheses derived from the SRM (Leventhal et al., 1980) and extensions to it to include treatment perceptions (eSRM; Horne 1997; 2003), patient's perceptions of HIV (identity, timeline, cyclical timeline and consequences) and beliefs about treatment (concerns about HAART and perceptions of susceptibility to adverse effects of medicines in general), elicited before initiating treatment, predicted subsequent adherence.

Negative affect mediated several of the relationships between perceptions of illness and treatment and adherence. However, the direction of causality between negative affect and beliefs could not be ascertained. In common with previous research, having previous experience of antiretroviral medication was a strong predictor of adherence, and this relationship appeared to be independent of beliefs about HIV and HAART. However, the relationship between treatment experience and adherence was associated with perceptions of personal susceptibility to adverse effects of medicines in general. This finding suggests that people with repeated experiences of HAART perceive themselves to be more vulnerable to adverse side effects and respond with non-adherent behaviour.

Beliefs about HAART were related to perceptions of HIV and beliefs about medicines in general in a way that is broadly consistent with the extended SRM proposed by Horne (1997; 2003). Specifically, stronger perceptions of necessity for HAART were associated with a

greater conviction that perceptions that HAART can effectively control HIV and perceiving poorer physical health. Contrary to expectations, perceptions of necessity for HAART were not related to illness identity, consequences or timeline, nor were they related to clinical markers of disease progression (CD4 count and viral load). Concerns were associated with more negative perceptions of medicines in general and negative affect, but were not associated with previous experience of antiretroviral treatment. Concerns about HAART were also related to more negative illness perceptions. These relationships were discussed in relation to the extended SRM.

Adherence was initially extremely high but decreased significantly over follow-up. This suggests that the drivers of adherence may also change in response to experience. Patients' perceptions of their illness and treatment may alter significantly over the treatment process and impact on adherence. This interaction between beliefs and behaviour over time will be investigated in the remainder of this thesis.

Chapter 8

STUDY 2

Appraisal of symptoms over six months of treatment: Impact on adherence, perceptions of HIV and beliefs about HAART

8.1 Introduction

Study 1 showed that patients' perceptions of HIV and beliefs about HAART, elicited before initiating treatment, predicted subsequent adherence. However, adherence is not a static behaviour. Longitudinal studies have noted a decline in adherence to HAART over time (Carrieri et al., 2001; Duran et al., 2001). It is therefore likely that the beliefs fuelling adherent or non-adherent behaviour also change over the treatment process. Central to the Self Regulatory Model (SRM) is the idea that perceptions of illness and treatment are dynamic concepts, which change in response to individuals' evaluations or appraisals of their experience (Leventhal et al., 1980; 1992; Horne, 2003). If illness perceptions and beliefs about treatment are amenable to change, and if change predicts adherence, this provides an important target for interventions to support and improve adherence.

Leventhal et al (1980; 1982) view symptoms as a readily accessible and continual source of information through which patients monitor and appraise the impact of their illness and prescribed medication. They propose that patients use their concrete experiences of symptoms to evaluate or appraise their chosen coping procedure (for example whether or not to adhere to treatment) and to guide their subsequent behaviour. Despite the central role of symptom appraisal in the SRM, there has been surprisingly little empirical research investigating how patients' experiences of symptoms change over time or in response to medical procedures.

In a qualitative study, Meyer et al. (1985) found that patients who were undergoing treatment for hypertension were more likely to adhere to their treatment if they perceived that their treatment was effectively keeping the symptoms that they associated with their condition at

bay. However, this data was anecdotal, and there has been a dearth of empirical research into the impact of symptom appraisal on adherence.

Furthermore, it is not clear whether and how patients' attributions of symptoms to their illness or treatment differentially impact on their adherence. In the patient's common sense view, an effective treatment should alleviate symptoms associated with illness, an ineffective treatment will not change the symptom and a dangerous treatment will make the symptom worse or cause symptoms of its own (Leventhal et al., 1982). Thus, patients' attributions of their symptom experiences (to HIV or to HAART) over time may differentially impact on their adherence behaviour, depending on how they are interpreted and evaluated.

There are two broad mediational pathways through which symptom appraisal may impact on adherence. Horne (2003) proposed that treatment perceptions might mediate the relationship between symptom appraisal and adherence. Specifically, symptoms attributed to illness might impact on adherence through patients' beliefs about their *necessity* for treatment while symptoms attributed to treatment might impact on adherence through patients' *concerns* about adverse effects (Horne, 2003). Thus, a patient who perceives that their treatment has not been effective in alleviating the symptoms they associate with their HIV condition may doubt the need for strict adherence. In the same way, the perception that treatment has caused persistent and severe symptoms of its own may activate a plethora of concerns about HAART, including worries about the long-term consequences of taking drugs, as well as the more practical day-to-day inconvenience and stigma associated with the treatment which might in turn impact on adherence. These mediational pathways have not been empirically tested to date.

The second pathway through which symptom appraisal may influence adherence is through patients' representations of their illness (Leventhal et al., 1982). For example a patient who sees their condition as acute may expect their treatment to alleviate symptoms and therefore stop adhering to their treatment when their symptoms have returned to normal. Weak evidence for this suggestion comes from a qualitative study in which hypertensive patients

held an acute model of their disorder where they expected their blood pressure would drop when they initiated treatment, and that they could then stop their treatment and be cured (Meyer et al., 1980). However, no empirical studies in the published literature to date have investigated links between symptom appraisal, illness perceptions and adherence.

8.2 Aims and research questions

The aim of this section of the study was to use a prospective, longitudinal research design to evaluate patients' appraisals of their symptom experiences in relation to adherence, perceptions of HIV and HAART, in order to test hypotheses generated by the SRM (Leventhal et al., 1980) and extensions to it proposed by Horne (1997; 2003). Specifically:

- To explore how patients' perceptions of HIV and HAART related symptoms change over the first six months of taking HAART.
- To examine the impact of changes in patients' perceptions of symptoms over time impact on adherence.
- To explore relationships between changes in patients' perceptions of symptoms over time, perceptions of HIV and beliefs about HAART proposed by the SRM and eSRM.
- To determine whether beliefs about HAART mediate relationships between changes in patients' perceptions of symptoms over time and adherence.

Research Question 1: How do patients' perceptions of HIV and HAART related symptoms change over the first six months of taking HAART?

There has been little empirical research in this area, therefore these hypotheses are exploratory:

Hypothesis 1.1: There will be a significant change in patients' perceptions of the frequency of HIV related symptoms over the first six months of taking HAART.

Hypothesis 1.2: There will be a significant change in patients' perceptions of the frequency of HAART-related symptoms over the first six months of treatment.

Research Question 2

Are patients' perceptions of change in HIV and HAART related symptoms over the first six months of taking HAART related to their adherence behaviour?

In the patient's common sense view, an effective treatment should alleviate symptoms they attribute to illness, an ineffective treatment will not change the symptom and a dangerous treatment will cause symptoms of its own (Leventhal et al., 1982). Furthermore, patients' appraisals of their symptoms impact on adherence. Therefore:

Hypothesis 2.1: Patients who experience an improvement in the symptoms they attribute to HIV over the first six months of treatment will be more adherent to their treatment than those who experience persistent HIV related symptoms.

Hypothesis 2.2: Patients who experience persistent or worsening symptoms they attribute to HAART side effects over the first six months of treatment will be less adherent to their treatment than those who experience an improvement in the symptoms they attribute to HAART side effects.

Research Question 3

How do patients interpret and evaluate changes in symptom experiences over time?

The SRM and eSRM propose that patients' experiences of symptoms feed back into their perceptions of illness and treatment. Therefore:

Hypothesis 3.1: Experiencing persistent, severe symptoms after six months of treatment will stimulate concerns about the treatment if the symptoms are perceived as being caused by HAART side effects (Horne, 2003).

Hypothesis 3.2: Experiencing a lack of improvement or worsening of symptoms attributed to HIV between T0 and T3 will lead to a decrease in perceptions of personal necessity for HAART (Horne, 2003; Cooper et al., 2003).

Hypothesis 3.3: Patients who report little improvement, or worsening of the symptoms they attribute to HIV or HAART after six months of taking HAART will have more negative views of their illness compared to those who perceive that their symptoms have improved over the treatment process. Specifically, they will:

- Perceive more severe personal consequences associated with their diagnosis
- Be less convinced that their symptoms will improve with time (timeline)
- Perceive a more cyclical timeline
- Be less convinced that HIV is amenable to control, either through HAART (treatment control) or by other means (personal control)
- Hold a less coherent picture of their illness (less illness coherence)
- Have a more negative emotional representation of HIV

Research Question 4: Do beliefs about HAART mediate the relationship between symptom change and adherence in a way that is consistent with the eSRM?

The extended SRM proposed by Horne (2003) predicts that patients' beliefs about HAART, specifically their perceptions of personal necessity for HAART and concerns about adverse effects, mediate relationships between symptom experiences and adherence.

Hypothesis 4.1: Patients' perceptions of their personal necessity for HAART after six months of treatment will mediate the relationship between experiencing persistent HIV-related symptoms and adherence. Specifically, those who believe that the symptoms they associate with HIV have not improved over time will be less adherent to their treatment if they perceive a low necessity for HAART.

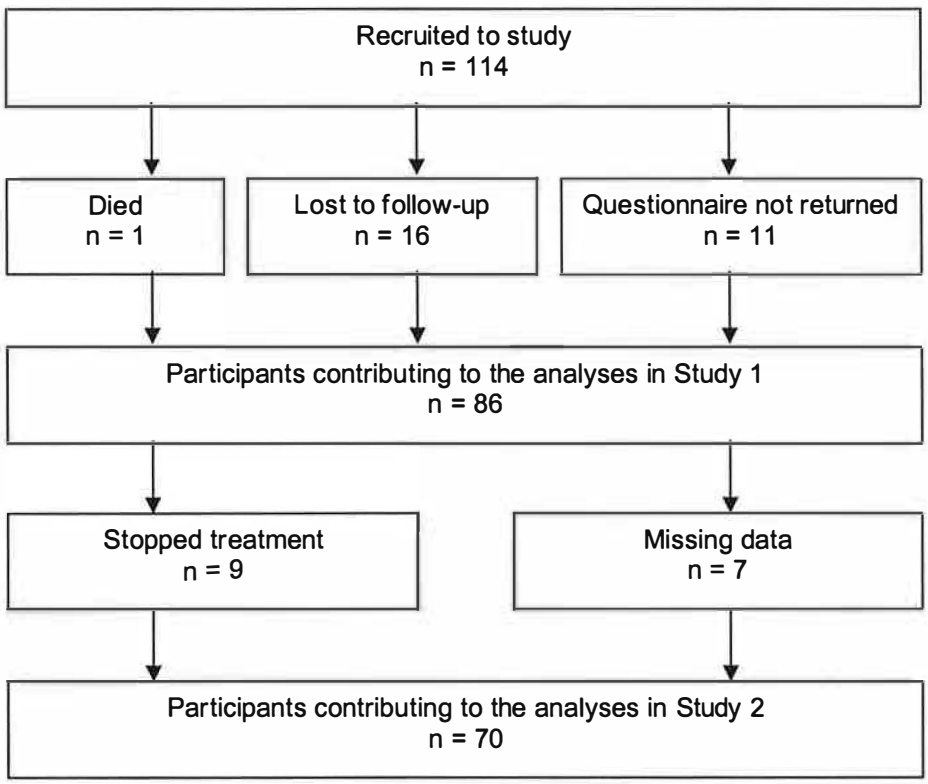
Hypothesis 4.2: The degree to which patients hold concerns about the adverse effects of taking HAART will mediate the relationship between experiencing persistent HAART-related symptoms and adherence. Specifically, those who are experiencing persistent symptoms they associate with HAART will be less adherent if they hold strong concerns about their treatment.

8.3 Methods

8.3.1 Participants

Of the eighty-six participants described in Study 1, nine had stopped their treatment before the six-month follow-up (T3). Although this group comprised a sub-sample of participants who met the definition for low adherence using the composite score utilised in Study 1, these participants did not complete the six-month (T3) questionnaires (in line with study protocol: see General Methodology), therefore it was not possible to use their data in the analyses in Study 2. A further seven participants had missing data. The final sample for the present study therefore comprised seventy participants (see Figure 8.1).

Figure 8.1: Flow chart showing recruitment, drop-out and sample contributing to analyses.



8.3.2 Procedure

The procedure was described in the General Methodology. In summary, patients who were not taking HAART were recruited to study through their HIV clinician. The author attended weekly clinical meetings in order to identify participants who were eligible for a HAART recommendation on the basis of British HIV Association (BHIVA) guidelines. Those who accepted a treatment recommendation were given a questionnaire to complete before starting treatment (T0), and again after one month (T1), three months (T2) and six months (T3) of their treatment.

8.3.3 Measures

All measures are described in detail in the General Methodology. The questionnaire booklet given at T0, T1, T2 and T3 contained the Illness Perceptions Questionnaire (IPQ), the Beliefs about Medicines Questionnaire (BMQ), Hospital Anxiety and Depression Scale (HADS) and the MOS Short-Form 12-item health assessment inventory (SF-12). As stronger relationships were found between perceptions of *moderate-severe* symptoms (rather than frequency of symptoms per se) and outcome in Study 1, the HIV and HAART related symptom (*identity*) scales used in this part of the study were computed to represent the frequency of symptoms rated moderate to severe. In addition to these core questionnaires, the booklet given at the one, three and six month follow-ups contained a visual analogue scale adapted from the Medication Adherence Self Report Inventory (MASRI). Two measures of adherence were used. Firstly, the overall percentage of antiretroviral medication taken as prescribed was calculated by adding together the percentage adherence to each antiretroviral drug in the patient's regimen and dividing by the total number of drugs in the regime. Secondly, patients were divided into low and high adherence groups on the basis of whether their average adherence score on the MASRI was 95% or above (high adherence) or below 95% (low adherence). This adherence categorisation was informed by recent research, which suggests that at least 95% adherence to HAART is required for clinical efficacy (Patterson et al., 2000). Clinical information at T0 and T3 was recorded from medical files.

8.4 Statistics

Estimations of population normality and homogeneity of variance for IPQ, BMQ, HADS and SF-12 scales were described in Study 1. Participants were categorised into high and low adherence groups on the basis of MASRI scores as described above, and changes in the number of participants reporting high and low adherence were calculated using Cochrane's Q and McNemar's tests. As before, a log transformation was carried out to establish a linear scale of measurement for viral load and CD4 count data.

In order to establish whether the results from the sample could be generalised to the population as a whole, clinical, demographic and adherence data were compared between those who completed all assessments and those who had stopped treatment or who were missing data. Baseline clinical and demographic data was compared between groups reporting high and low adherence at six months using chi square statistics with odds ratios and confidence intervals for categorical data, t-tests for continuous data meeting parametric assumptions and Mann Whitney U tests for continuous data that did not meet assumptions for parametric tests.

Pearson's correlations were used to examine linear relationships between variables where assumptions of normality were met. Partial correlations were used to examine linear relationships between variables when controlling for possible confounding variables (negative affect and baseline beliefs). T-tests were used to investigate differences between low and high adherence groups. Univariate analyses of co-variance (ANCOVA) were used to investigate differences in illness perceptions and medication beliefs between high- and low-adherence groups when controlling for possible confounding variables. Repeated measures ANOVAs were used to assess changes in symptom experiences over time for high and low adherence groups. Since the focus of this study was on change in symptoms over the entire follow-up, changes in HIV-related symptoms were examined between T0 and T3, and changes in HAART-related symptoms were examined between T1 and T3.

Residualised change scores (RCS) were calculated to represent the change in symptoms over time. RCS are calculated by regressing baseline scores (or 1 month scores for HAART-related side effects) onto subsequent time-points. Using RCS had three advantages. First, the score represents change but does not suffer from regression to the mean. Second, the RCS analysis is sensitive to change, because not only does it remove variance due to baseline scores, it also removes any errors that are correlated between the scores, i.e. measurement error, so that any remaining variance is due to change over time. Third, although the raw symptom scores were skewed, RCS were approximately normally distributed. A higher RCS for HIV and HAART related symptoms indicated less improvement in symptoms over time: symptoms that have worsened over time have the highest score, while those that have improved have the lowest scores. Univariate ANOVA was used to investigate the impact of symptom change on adherence. These tests were repeated controlling for the possible influence of previous adherence (at 1 month and 3 months) on symptom evolution scores using ANCOVA, since symptom change could be either a cause or effect of previous adherence. The symbol 'Δ' was used to represent change.

Analyses exploring differences in symptom change scores between high and low adherence groups, and those exploring relationships between symptom change scores, illness perceptions and beliefs about HAART were conducted in three stages:

1. The analyses were conducted without controlling for any possible confounding variables
2. The analyses were repeated controlling for beliefs about HAART at baseline. Partialling baseline beliefs about HAART out of the analyses allowed the impact of symptom evolution on beliefs to be explored independently of pre-existing beliefs about HAART. The question of how symptom evolution impacts on patients' beliefs about their need for treatment and concerns about adverse effects could thereby be addressed.
3. Analyses were repeated controlling for negative affect at baseline. Since depression and anxiety scores at baseline were associated with symptom

evolution (those with greater negative affect tended to report less improvement in symptoms over time), partialling depression and anxiety out of the analyses allowed the relationships between symptom evolution, perceptions of HIV and beliefs about HAART to be explored without the potential confounding effect of negative affect.

Mediational analyses (Baron & Kenny, 1986) as described in Study 1 were used to assess the impact of beliefs about HAART on the relationship between symptom appraisal and adherence. Point bi-serial correlations were used when assessing relationships with adherence (a categorical variable).

8.5 Results

8.5.1 Sample characteristics

This was a sub-sample of participants included in Study 1. Nine participants stopped their treatment between baseline and six months, a further seven had missing data or failed to complete assessments at the six-month follow-up. A total of seventy participants therefore provided the data for this study. The majority of the sample described their ethnic origin as white UK (62 (88.6%)), 3 (4.3%) as black African, 3 (4.3%) as white other and 2 (2.6%) as black Caribbean. Sixty-seven participants (95.7%) were male, of whom 63 (94.0%) described their most likely transmission risk as sex with a man. The mean age of the sample was 40.1 (SD = 8.6). Forty-three participants (61.4%) were employed outside the home. The median number of years since diagnosis of HIV ranged from 0-17, with a median of 2.5. In terms of CDC classification, 22 (31.4%) were asymptomatic, 29 (41.4%) were symptomatic and 19 (27.1%) had a diagnosis of AIDS. Approximately a third of the sample (n=21, 30.0%) had previously been prescribed antiretroviral therapy. The mean CD4 count before initiating treatment was 204.8 (SD = 136.0), with a median viral load (log^{10}) of 5.3 (3.4-6.0).

In order to establish whether the results from this sample could be generalised to the population as a whole, clinical, demographic and adherence data were compared between those who completed all assessments (n=70) and those who provided data in Study 1 but had

stopped treatment or had missing data (n=16). Descriptive statistics for both groups are shown in Tables 8.1 and 8.2.

Table 8.1: Comparison of baseline demographic and clinical characteristics of participants who completed all assessments and those who stopped their treatment or had missing data

Baseline clinical/demographic feature		Completed study n=70	Missing data n=16	p
Age	**Mean (SD)**	**40.1 (8.6)**	**31.9 (6.3)**	**<0.001**
Male		67 (95.7%)	16 (100%)	>0.1
Employed		43 (61.4%)	8 (50.0%)	>0.1
Transmission risk: gay man		63 (90.0%)	15 (93.8%)	>0.1
Years since HIV diagnosis	Median (range)	2.5 (0-17)	4.0 (0-17)	>0.1
Asymptomatic HIV		22 (31.4%)	4 (25.0%)	>0.1
Symptomatic HIV		29 (41.4%)	6 (37.5%)	>0.1
AIDS		19 (27.1%)	6 (37.5%)	>0.1
Clinical trial		**32 (45.7%)**	**3 (18.8%)**	**<0.05**
Prior experience of ARVs		**21 (30.0%)**	**10 (62.5%)**	**<0.05**
CD4 count at treatment offer	Mean (SD)	204.8 (136.0)	172.5 (136.3)	>0.1
Viral load $\log^{10}$ at treatment offer	Median (range)	5.3 (3.4-6.0)	5.3 (4.6-5.8)	>0.1

Table 8.2: Comparison of T3 clinical outcomes of participants who completed all assessments and those who stopped their treatment or had missing data

Clinical outcome		Completed study n=70	missing data n=16	p
CD4 count at T3	Mean (SD)	355.4 (243.7)	261.5 (176.3)	>0.1
Viral load $\log^{10}$ at T3	**Median (range)**	**1.7 (0.8-2.6)**	**1.9 (1.7-5.7)**	**0.05**

Participants who completed all assessments were more likely to be older (t=3.56, df=84, $p<0.001$), to have had prior antiretroviral treatment ($\chi^2= 5.97$, df =1, $p <0.05$) and to be enrolled in a clinical trial ($\chi^2= 5.96$, df =1, $p<0.05$) compared to those who were missing data. The latter two findings are probably not mutually exclusive because eligibility criteria for many of the clinical trials being conducted over this period included being naïve to antiretroviral treatment. Those who had stopped their treatment or who were missing data had significantly higher viral loads at six months ($z = -2.39$, $p<0.05$). Since those who had completely stopped their treatment represented, by definition, a biased sample of non-adherent patients, this finding was in line with expectations.

8.5.2 Scale characteristics

For Q-Q plots and histograms of scores for all IPQ, BMQ, HADS and SF-12 scales please see Appendix 1. These scales are described in Study 1.

8.5.2.1 Residualised change scores (RCS)

8.5.2.1.1 RCS-HIV

Change scores for symptoms attributed to HIV between T0 and T3 were calculated as described in the statistics section. Scores on this scale ranged from –4.7 to 13.3, with a mean of 3.4 (SD = 3.7). The Shapiro-Wilk statistic was significant (Shapiro-Wilk Statistic = 0.91, $p<0.01$) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution.

8.5.2.1.2 RCS-HAART

Change scores for symptoms attributed to HIV between T0 and T3 were calculated as described in the statistics section. Scores on this scale ranged from –3.8 to 10.1, with a mean of 3.5 (SD = 2.9). The Shapiro-Wilk statistic was significant (Shapiro-Wilk Statistic = 0.95, $p<0.01$) but visual inspection of the normal Q-Q plot revealed only small unsystematic deviations from the expected normal distribution.

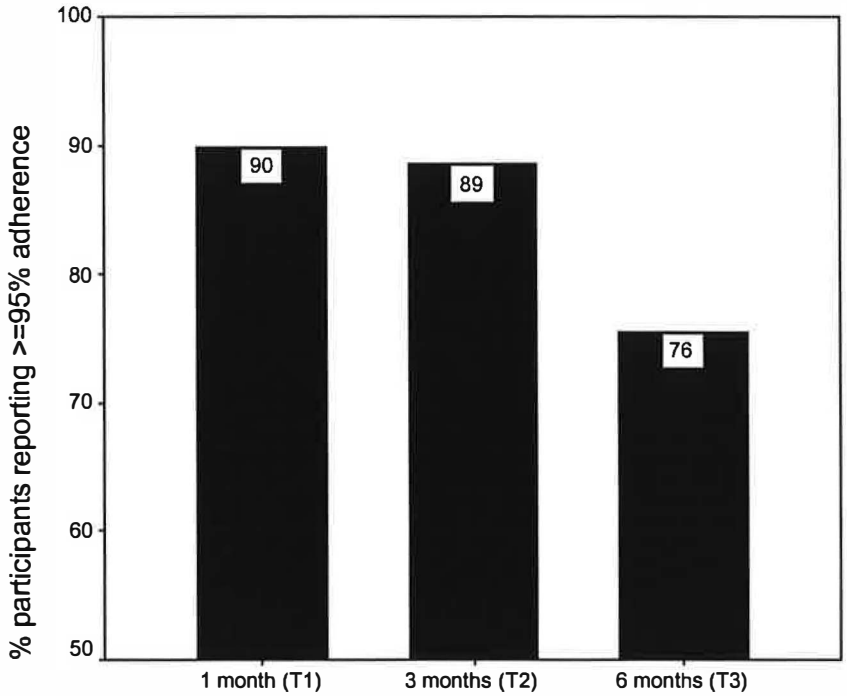
8.5.3 Patterns of adherence over time

Table 8.3: Levels of adherence at one, three and six month follow-ups

	High adherence >=95%	Low adherence <95%
1 month (T1)	63 (90.0%)	7 (10.0%)
3 months (T2)	62 (88.6%)	8 (11.4%)
6 months (T3)	53 (75.7%)	17 (24.3%)

Table 8.5.3 shows the number of participants categorised into high and low adherence groups at each assessment. The number of participants reporting less than 95% adherence declined significantly over the follow-up (Cochran's Q = 14.0, $p<0.001$). A series of McNemar's tests showed no significant change in the percentage of participants reporting low adherence between one and three months, but identified a decline in adherence between three and six months on treatment (McNemar's test, $p<0.005$), and between one and six months (McNemar's test, $p<0.001$).

Figure 8.2: Percentage of participants reporting high adherence over 6 months



8.5.4 Validation of adherence measure

As in Study 1, the adherence categorisation was validated against clinical outcome and pharmacy prescription redemption data. Table 8.4 shows CD4 counts and viral loads for patients reporting high adherence and those reporting low adherence after six months of taking HAART. In line with expectations, low adherence at T3 was associated with significantly higher viral load ($t=-3.46$, $df=65$, $p<0.05$). Pharmacy prescription redemption data was collected for the first half of the sample. According to prescription redemption data, 50% of the low adherence group collected their prescriptions late compared to only 4% of the high adherence group. This difference was statistically significant ($\chi^2 = 10.39$, $df = 1$, $p<0.01$).

Table 8.4: Clinical outcome among participants reporting high adherence and those reporting low adherence at T3.

Clinical/demographic feature		High adherence n = 53	Low adherence n = 17	Significance level
T3 CD4 count	Mean (SD)	366.0 (260.7)	323.8 (186.6)	Ns
T3 Viral load $\log^{10}$	**Mean (SD)**	**1.8 (0.2)**	**2.3 (1.1)**	**P<0.05**

8.5.5 Predictors of adherence

8.5.5.1 Clinical and demographic predictors of adherence

As in Study 1, patients reporting low adherence at T3 were less likely to be in employment than those reporting high adherence ($\chi^2 =3.9$, $df=1$, $p<0.05$; OR = 3.0; CI = 1.0-9.3). They had been diagnosed with HIV for a longer period of time ($Z=-2.0$, $p<0.05$) and were more likely to have previously been prescribed antiretroviral medication in the past ($\chi^2 =8.9$, $df=1$, $p<0.005$; OR = 5.5; CI = 1.7-17.6). In contrast to Study 1, those reporting low adherence at six months

were not significantly more likely to be enrolled in a clinical trial (p>0.1). These results are shown in Table 8.5.

Table 8.5: Baseline clinical and demographic characteristics of participants reporting high adherence and those reporting low adherence at T3.

Clinical/demographic feature		High adherence n = 53	Low adherence n = 17	Significance level
Age	Mean (SD)	40.6 (8.6)	38.5 (8.8)	p>0.1
Male	n (%)	51 (96.2%)	16 (94.1%)	p>0.1
Employed	n (%)	**36 (67.9%)**	**7 (41.2%)**	**p<0.05**
Transmission risk: gay man	n (%)	48 (90.6%)	15 (88.2%)	p>0.1
# Years HIV	Median (range)	**3.5 (0-16)**	**6.4 (0-17)**	**p<0.05**
Asymptomatic HIV	n (%)	17 (32.0%)	5 (29.4%)	p>0.1
Symptomatic HIV	n (%)	21 (39.6%)	8 (47.1%)	p>0.1
AIDS	n (%)	15 (28.3%)	4 (23.5%)	p>0.1
Clinical trial	n (%)	27 (56.3%)	5 (31.3%)	p>0.1
Prior experience of ARVs	n (%)	**11 (20.8%)**	**10 (58.8%)**	**p<0.005**
T0 CD4 count	Mean (SD)	197.3 (141.9)	227.8 (117.3)	p>0.1
T0 Viral load $\log^{10}$	Mean (SD)	5.3 (0.5)	5.1 (0.6)	p>0.1

8.5.6 Changes in symptom experiences over time

Research Question 1: How do patients' perceptions of HIV and HAART related symptoms evolve over the first six months of taking HAART?

Hypothesis 1.1: There will be a significant change in patients' perceptions of the frequency of moderate to severe HIV related symptoms over the first six months of taking HAART.

Hypothesis 1.2: There will be a significant change in patients' perceptions of the frequency of moderate to severe HAART-related symptoms over the first six months of taking HAART. Table 8.6 shows means and standard deviations for symptoms attributed to HIV and HAART at baseline (HIV) or one month (HAART) and six months among participants reporting high adherence and those reporting low adherence at six months.

Table 8.6: Means and standard deviations for symptoms attributed to HIV and HAART at T0 (HIV) or T1 (HAART) and T3 for high adherence and low adherence groups

	HIV		HAART	
	High adherence Mean (SD)	Low adherence Mean (SD)	High adherence Mean (SD)	Low adherence Mean (SD)
T0/T1 symptoms	4.8 (4.7)	7.3 (4.2)	3.4 (4.4)	5.4 (4.7)
T3 symptoms	2.4 (3.8)	5.9 (5.3)	2.5 (4.2)	6.3 (5.4)

Table 8.7: Repeated measures ANOVA exploring changes in HIV symptoms between T0 and T3

MODERATE-SEVERE HIV SYMPTOMS	F	p
Within groups (time)	**10.3**	**<0.05**
Between groups (high or low adherence)	**8.1**	**<0.01**
Group x Time interaction	1.3	>0.1

Table 8.7 shows the results of repeated measures ANOVA exploring the change in symptoms attributed to HIV between baseline and six-month assessments. There was a significant main effect of time on HIV symptoms ($F(1, 67) = 2.85$, $p<0.05$) indicating an overall decline in the number of moderate to severe symptoms attributed to HIV between baseline (T0) and the six-month follow-up (T3). There was also a significant main effect for group ($F(1, 67) = 4.15$, $p < 0.05$), where the mean number of HIV-related symptoms was significantly higher among those in the low adherence group compared to those in the high adherence group. Figure 8.3

shows a steeper decline in symptoms related to HIV from T0 to T3 for the high adherence group, although the group x time interaction was not significant.

Figure 8.3: Line graph showing changes in moderate to severe HIV-related symptoms between T0 and T3 for high and low adherence groups

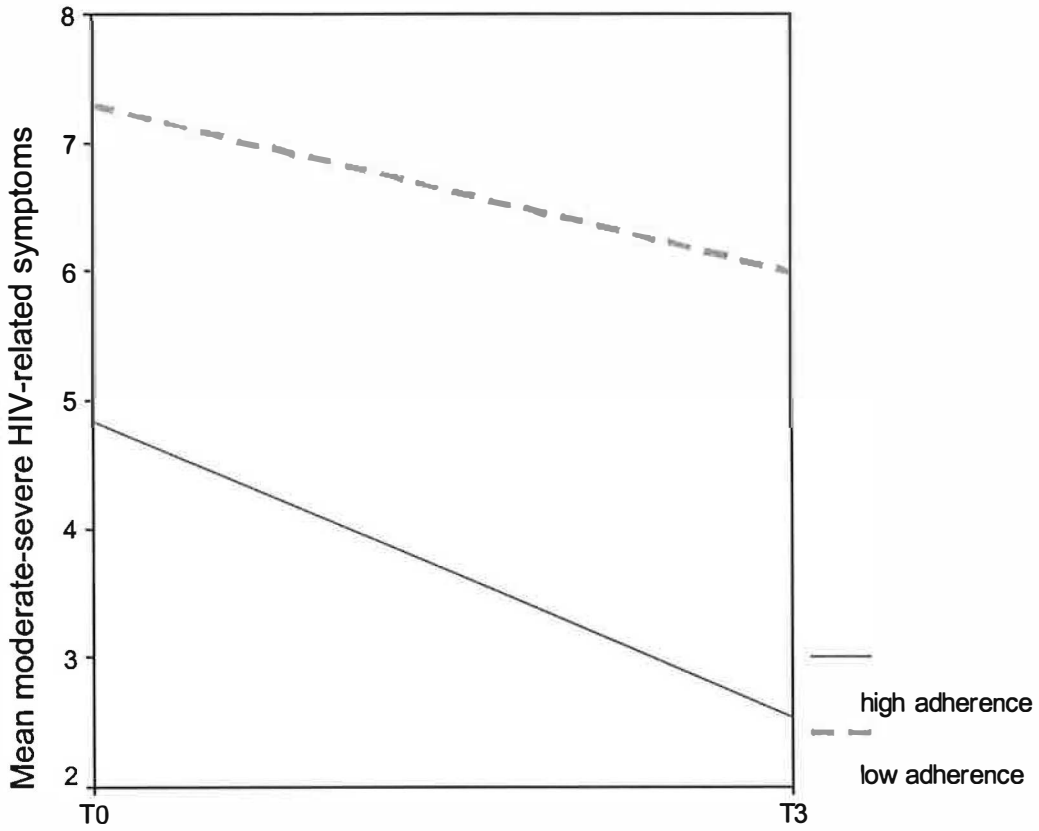
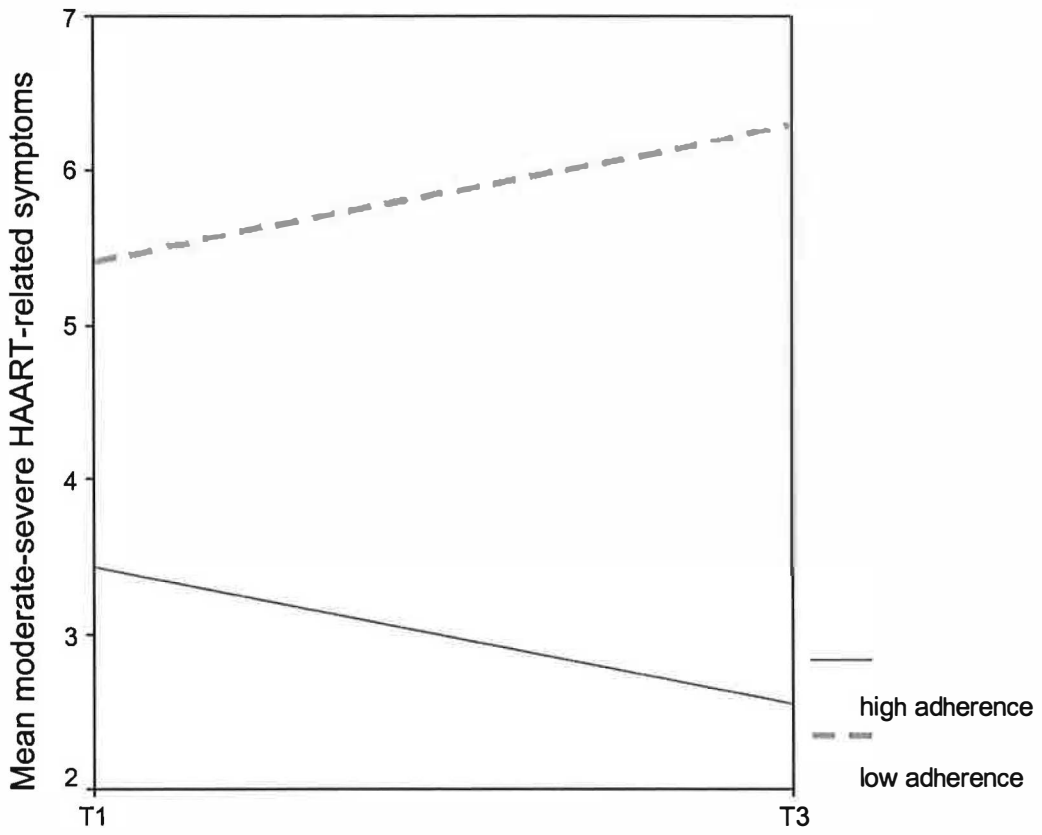


Table 8.8: Repeated measures ANOVA exploring changes in HAART-related symptoms between T1 and T3

MODERATE-SEVERE HAART SYMPTOMS	F	p
Within groups (time)	0.00	>0.1
Between groups (high or low adherence)	**5.89**	**<0.05**
Group x Time interaction	**4.76**	**<0.05**

Table 8.8 shows the results of repeated measures ANOVA exploring the change in symptoms attributed to HAART between one-month and six-month assessments. There was no main effect of time on HAART-related symptoms ($F(1, 68) = 0.00$, $p>0.1$), indicating that for the sample as a whole, the number of HAART related symptoms reported did not change significantly between T1 and T3. However, there was a significant main effect for group ($F(1, 68) = 5.89$, $p<0.05$), where HAART-related symptom scores were significantly higher for those in the low adherence group compared to those in the high adherence group. There was also a significant group x time interaction ($F(1, 68) = 4.76$, $p<0.05$). Paired t-tests within low adherence and high adherence groups confirmed that while there was no significant change in HAART-related symptom scores between T1 and T3 for those in the low adherence group ($t= -1.14$, $df = 16$, $p>0.1$), there was a significant decrease in symptoms for those in the high adherence group ($t = 2.30$, $df = 52$, $p<0.05$). These results are illustrated in Figure 8.4.

Figure 8.4: Line graph showing changes in moderate to severe HAART-related symptoms between T1 and T3 for high and low adherence groups



8.5.7 Changes in symptoms over time as predictors of adherence

Research Question 2

Are patients' perceptions of change in HIV and HAART related symptoms over the first six months of taking HAART related to adherence?

Hypothesis 2.1: Patients who experience an improvement in the symptoms they attribute to HIV over the first six months of treatment will be more adherent to their treatment than those who experience persistent HIV related symptoms.

Hypothesis 2.2: Patients who experience persistent symptoms they attribute to HAART over the first six months of treatment will be less adherent to their treatment than those who experience an improvement in HAART related symptoms.

Hypotheses 2.1 and 2.2 were tested by comparing residualised change scores (RCS) for HIV and HAART related symptoms between high and low adherence groups (see Table 8.9). The RCS reflects the frequency of symptoms reported at six months after controlling for symptoms at baseline, so that a higher score represents less improvement in symptoms. The results are illustrated in Figure 8.5 and 8.6. They showed a greater improvement in moderate to severe HIV-related symptoms between T0 and T3 among patients in the high adherence group ($F(1,67) = 4.0$ $p<0.05$). Furthermore, patients in the low adherence group reported significantly less improvement in their experience of HAART-related side effects ($F(1,67) = 7.3$, $p<0.01$).

Table 8.9: Means and standard deviations showing change in HIV and HAART-related symptoms over time for high and low adherence groups

	Low adherence	High adherence	Unadjusted scores		Control for NA		Control for T1 and T2 adherence	
	Mean (sd)	Mean (sd)	F	p	F	p	F	p
RCS HIV	**4.9 (4.3)**	**2.9 (3.4)**	**4.0**	**<0.05**	1.8	>0.1	**3.7**	**<0.05**
RCS HAART	**5.0 (3.2)**	**3.0 (2.6)**	**7.3**	**<0.01**	**5.1**	**<0.05**	**3.3**	**<0.05**

Figure 8.5: Means and 95% confidence intervals showing change in HIV-related symptoms from T0-T3 for participants reporting high adherence at T3 and those reporting low adherence at T3

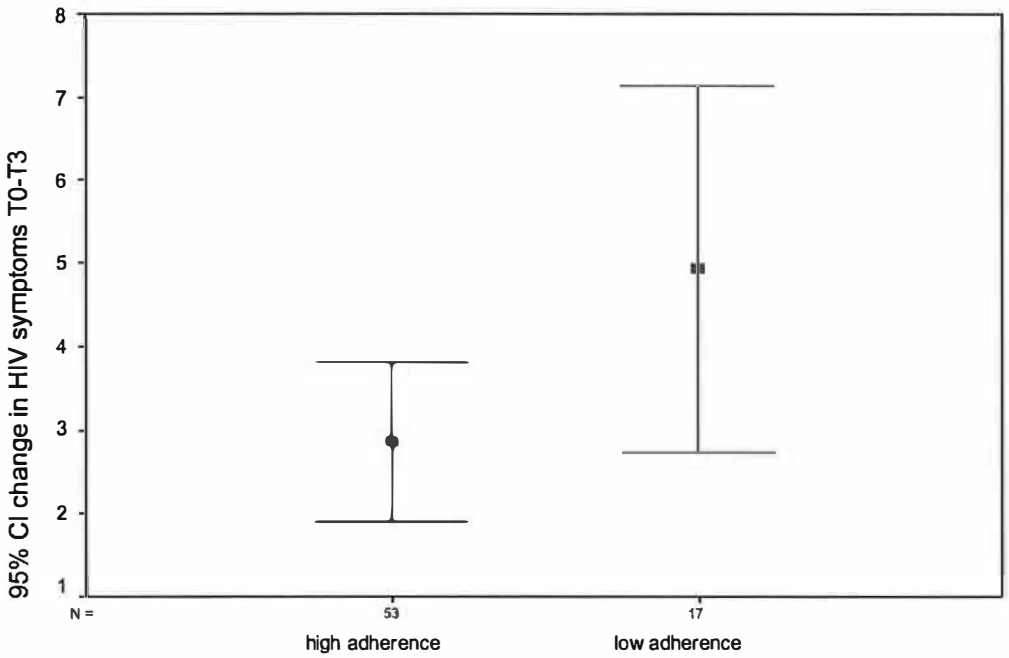
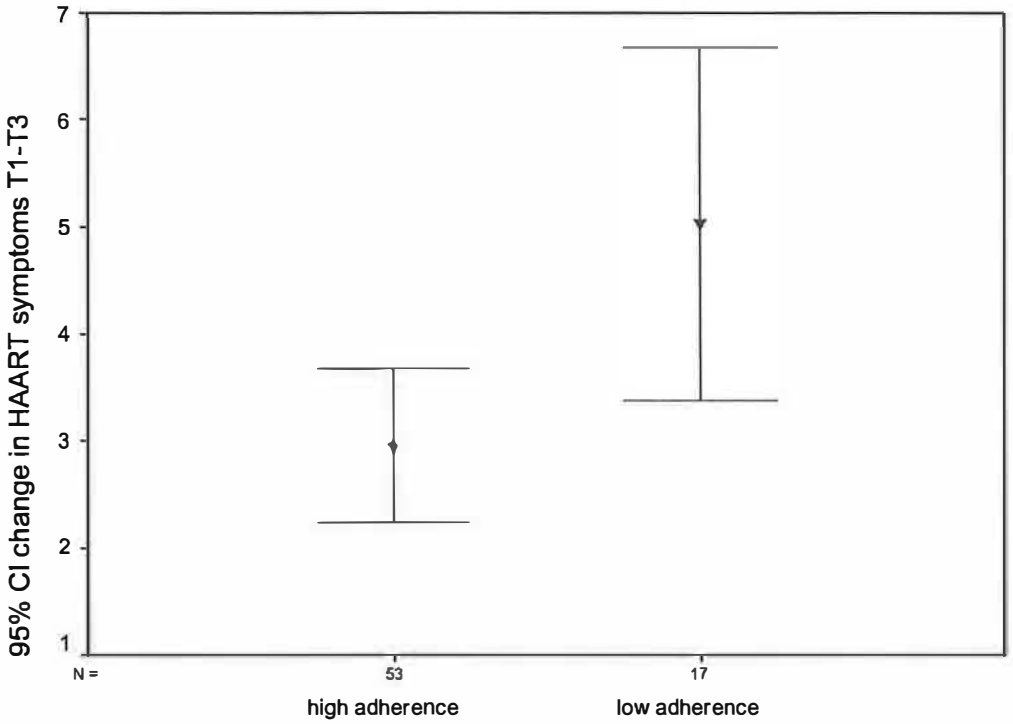


Figure 8.6: Means and 95% confidence intervals showing change in HAART-related symptoms between T1 and T3 for participants reporting high adherence at T3 and those reporting low adherence at T3



When the analyses were repeated controlling for baseline (T0) negative affect (NA), the previously identified relationship between improvement HIV-related symptoms and adherence was no longer significant ($F(1, 67) = 1.8$, $p>0.1$). This suggests that patients who were experiencing higher negative affect before initiating HAART were more prone to respond to a lack of symptom improvement with non-adherence. However, controlling for negative affect at baseline did not eliminate the relationship between experiencing a lack of improvement in HAART related symptoms and low adherence ($F(1,67) = 5.1$, $p<0.05$), indicating that this relationship was true regardless of the level of negative affect experienced at baseline.

Differences in symptom change between low and high adherence groups remained significant when controlling for adherence at T1 and T2 for both HIV related symptoms ($F(1, 67) = 3.7$, $p<0.05$) and HAART-related symptoms ($F(1,67) = 3.3$, $p<0.05$). This indicates that the impact

of symptom change on adherence was not the consequence of previous adherence, but that the change in symptoms over time predicted subsequent adherence.

8.5.8 Predictors and correlates of change in HIV and HAART-related symptoms

The relationships between change in HIV and HAART related symptoms, clinical and demographic variables, negative affect and adherence at T1 and T2 were assessed in order to eliminate the possibility that perceived changes in symptoms over time were the result of disease variables, negative affect or earlier adherence, so that appropriate analyses could be conducted to control for the possible influences of these variables where necessary, in further analyses.

8.5.8.1 Clinical and demographic correlates of change in HIV and HAART-related symptoms over follow-up

Baseline clinical and demographic characteristics of patients were not associated with symptom evolution. Furthermore neither the change in HIV- or HAART-related symptoms over six months was related to clinical outcome. These results are summarised below and shown in Table 8.10.

Neither the change in HIV related symptoms between T0 and T3 nor the change in HAART related symptoms between T1 and T3 was significantly related to clinical or demographic variables. Change scores for HIV related symptoms were not related to baseline CD4 count, baseline viral load, CD4 count at six months, viral load at six months, age, number of months since HIV diagnosis, CDC disease categorisation or past treatment experience.

Table 8.10: Relationships between symptom change scores and clinical and demographic variables

	RCS HIV		RCS HAART	
	r	**p**	**r**	**p**
T0 CD4	-0.02	>0.1	0.03	>0.1
T0 viral load	-0.13	>0.1	0.00	>0.1
T3 CD4	-0.11	>0.1	-0.10	>0.1
T3 viral load	0.08	>0.1	0.10	>0.1
Time HIV	0.17	>0.1	0.12	>0.1
Age	0.09	>0.1	0.06	>0.1
	F	**p**	**F**	**p**
CDC classification	0.09	>0.01	1.75	>0.1
Past ARV	0.05	>0.1	0.05	>0.1

8.5.8.2 Relationships between negative affect and change in HIV and HAART-related symptoms over follow-up

There were significant positive correlations between depression and anxiety scores at T0 and symptom evolution between T0 and T3. Specifically, participants who reported higher depression scores before they initiated treatment were more likely to report both a lack of improvement in HIV-related symptoms ($r = 0.27$, $p<0.05$) and to experience a lack of improvement in HAART related symptoms ($r = 0.31$, $p<0.01$) over time. Those who reported higher anxiety scores before initiating treatment were also more likely to experience a lack of improvement in HIV related symptoms over time ($r = 0.34$, $p<0.005$), however level of anxiety before initiating treatment did not predict subsequent evolution of HAART related symptoms ($r = 0.19$, $p>0.1$). These results are illustrated in Table 8.11.

Table 8.11: Associations between symptom change scores and baseline negative affect

	RCS HIV		RCS HAART	
	r	p	r	p
T0 Depression	**0.27**	**<0.05**	**0.31**	**<0.01**
T0 Anxiety	**0.34**	**<0.005**	0.19	>0.1

8.5.8.3 Relationships between adherence at T1 and T2 and change in HIV and HAART-related symptoms over follow-up

Adherence at T1 did not have a statistically significant impact on change scores for either HIV-related symptoms or HAART-related symptoms. Furthermore adherence at T2 did not significantly impact on change scores for either HIV-related symptoms or HAART related symptoms. These results are illustrated in Table 8.12.

Table 8.12: Relationships between symptom change scores and adherence T1 and T2

	RCS HIV		RCS HAART	
	t	**p**	**t**	**p**
Adherence at 1 month (T1)	-1.8	>0.05	-1.2	>0.1
Adherence at 3 months (T2)	-0.61	>0.1	-1.9	>0.05

8.5.9 Impact of symptom change on beliefs about HAART

Research Question 3

How do patients interpret and evaluate changes in their symptom experiences over time?

Hypothesis 3.1: Experiencing persistent, severe symptoms after six months of treatment will stimulate concerns about the treatment if the symptoms are perceived as being caused by HAART side effects (Horne, 2003).

Hypothesis 3.2: Patients who experience persistent, severe symptoms they associate with HIV (i.e. perceiving little improvement or worsening of symptoms between T0 and T3) may doubt the necessity for its continued use (Horne, 2003; Cooper et al., 2003).

Associations between symptom change scores and beliefs about HAART (necessity and concerns) are shown in Tables 8.13 and 8.14. In line with Hypothesis 3.1, there was a significant positive correlation between concerns at T3 and change scores for HAART related

symptoms (r = 0.21, p<0.05), indicating that a lack of improvement in HAART related symptoms between T0 and T3 was also associated with stronger concerns about the treatment. Furthermore, there was a significant positive correlation between change scores for HIV-related symptoms and concerns scores at T3 (r= 0.45, p<0.001), indicating that patients who were experiencing persistent symptoms they attributed to HIV had stronger concerns about HAART six months after they started their treatment.

In line with hypothesis 3.2, there was a significant negative correlation between the perceived change in HIV related symptoms between T0 and T3 and beliefs about personal necessity for HAART (r =-0.24, p<0.05). This suggests that patients may doubt their personal necessity for a treatment that they perceive as having little or no impact on the symptoms they associate with their illness. There was also a significant negative correlation between change in HAART-related symptoms and necessity beliefs at T3 (r = -0.32, p<0.01), where patients who perceived that their treatment was causing persistent symptoms of its own were also more likely to doubt the necessity for its continued use.

Table 8.13: Relationships between treatment beliefs at the six-month follow-up (T3) and evolution of HIV-related symptoms since baseline (T0-T3)

	RCS HIV					
	Unadjusted scores		Control NA		Control T0 beliefs	
Treatment beliefs at T3	r	p	r	p	r	P
Necessity	**-0.24**	**<0.05**	**-0.24**	**<0.05**	-0.16	>0.1
Concerns	**0.45**	**<0.001**	**0.34**	**<0.005**	**0.41**	**<0.001**

Table 8.14: Relationships between treatment beliefs at the six month follow-up (T3) and evolution of HAART-related symptoms since one-month follow-up (T1-T3)

	RCS HAART					
	Unadjusted scores		Control NA		Control T0 beliefs	
Treatment beliefs at T3	r	p	r	p	r	P
Necessity	**-0.32**	**<0.05**	**-0.33**	**<0.005**	**-0.27**	**<0.05**
Concerns	**0.21**	**<0.001**	0.09	>0.1	0.08	>0.1

8.5.9.1 Relationships between symptom change and beliefs about HAART controlling for beliefs about HAART at baseline

When controlling for concerns about HAART at baseline, the relationship between change in symptoms associated with HIV and concerns at T3 remained significant ($r = 0.41$, $p<0.001$), suggesting that experiencing a lack of improvement in HIV-related symptoms over time leads to stronger concerns about HAART. However, when controlling for baseline concerns, the relationship between change in HAART-related symptoms and concerns at T3 was no longer statistically significant ($r = 0.08$, $p>0.1$), suggesting that the previously observed relationship between symptom change and concerns at T3 was influenced by the strength of patients' concerns about potential adverse effects before they initiated treatment.

When controlling for baseline necessity beliefs, the relationship between change in HIV symptoms and necessity beliefs at T3 was no longer significant ($r = -0.16$, $p>0.1$). This indicates that the relationship was influenced by beliefs about personal necessity for HAART before initiating treatment. The relationship between necessity beliefs and change in HAART-related symptoms however remained significant when controlling for baseline necessity beliefs ($r = -0.27$, $p<0.05$). This suggests that experiencing persistent HAART-related side effects has a negative impact on patients' perceptions of their personal need for treatment.

8.5.9.2 Relationships between symptom change and beliefs about HAART controlling for negative affect

When controlling for baseline negative affect, the relationship between change scores for symptoms associated with HAART and concerns became non-significant ($r = 0.09$, $p>0.1$). This suggests that negative affect mediates the relationship between experiencing persistent HAART-related side effects and concerns about HAART, i.e. that the relationship is influenced by the level of negative affect reported before treatment was initiated. However, the relationship between HIV symptoms and concerns remained significant when controlling for negative affect ($r=0.34$, $p<0.005$). This suggests that the relationship between

experiencing persistent symptoms related to HIV and stronger concerns about HAART is independent of negative affect at baseline.

When controlling for negative affect at T0, the association between change in HIV symptoms and necessity beliefs at T3 remained significant ($r = -0.24$, $p < 0.05$), as did the relationship between change in HAART related symptoms and necessity beliefs at T3 ($r = -0.33$, $p < 0.005$). This suggests that the relationship between necessity beliefs and symptom change is independent of depression and anxiety symptoms before initiating treatment.

8.5.10 Impact of symptom change on perceptions of HIV

Hypothesis 3.3: Patients who report persistent, severe HIV or HAART related symptoms after six months of taking HAART will have more negative views of their illness (specifically, they will perceive more severe personal consequences associated with their diagnosis, be less convinced that their symptoms will improve with time, perceive a more cyclical timeline, will be less convinced that HIV is amenable to control, either through HAART or by other means, hold a less coherent picture of their illness and have a more negative emotional reaction to HIV

Hypothesis 3.3 was approached by assessing associations between change scores for symptoms attributed to HIV (RCS-HIV) and those attributed to HAART (RCS-HAART) with illness representations. Correlations between illness representations and change scores for symptoms attributed to HIV (RCS-HIV) are shown in Table 8.15, and correlations between illness representations and change scores for symptoms attributed to HAART (RCS-HAART) are shown in Table 8.16.

Table 8.15: Relationships between perceptions of HIV at the six-month follow-up (T3) and evolution of HIV-related symptoms since baseline (T0-T3)

	RCS HIV					
	Unadjusted scores		Control NA		Control T0 beliefs	
Illness perceptions at T3	r	p	r	p	r	p
Consequences	**0.31**	**<0.01**	0.13	>0.1	0.19	>0.05
Timeline	**0.47**	**<0.001**	**0.39**	**<0.001**	**0.38**	**<0.001**
Cyclical timeline	**0.44**	**<0.001**	**0.30**	**<0.01**	**0.47**	**<0.001**
Personal control	**-0.30**	**<0.01**	**-0.25**	**<0.05**	**-0.23**	**<0.05**
Treatment control	**-0.46**	**<0.001**	**-0.37**	**<0.001**	**-0.40**	**<0.001**
Coherence	**0.25**	**<0.05**	0.14	>0.1	0.18	>0.05
Emotional representations	**0.43**	**<0.001**	**0.29**	**<0.01**	**0.40**	**<0.001**
Self-assessment of physical health	**-0.43**	**<0.001**	**-0.30**	**<0.01**	**-0.43**	**<0.001**

Table 8.16: Relationships between perceptions of HIV at the six-month follow-up (T3) and evolution of HAART-related symptoms since the one-month follow-up (T0-T3)

	RCS HAART					
	Unadjusted scores		Control NA		Control T0 beliefs	
Illness perceptions at T3	r	p	r	p	R	p
Consequences	**0.33**	**<0.01**	0.18	>0.05	0.14	>0.1
Timeline	**0.29**	**<0.01**	**0.24**	**<0.05**	**0.23**	**<0.05**
Cyclical timeline	**0.30**	**<0.01**	0.18	>0.05	**0.29**	**<0.01**
Personal control	**-0.43**	**<0.001**	**-0.38**	**<0.001**	**-0.34**	**<0.005**
Treatment control	**-0.46**	**<0.001**	**-0.40**	**<0.001**	**-0.36**	**<0.001**
Coherence	0.18	>0.05	0.05	>0.1	0.12	>0.1
Emotional representations	**0.33**	**<0.005**	**0.23**	**<0.05**	**0.35**	**<0.001**
Self-assessment of physical health	**-0.38**	**<0.001**	**-0.32**	**<0.005**	**-0.34**	**<0.005**

Correlations between illness representations and change scores for symptoms attributed to HIV (RCS-HIV) are shown in Table 8.15. Patients who experienced a lack of improvement in HIV-related symptoms had more negative representations of HIV. Specifically, they perceived a more chronic and cyclical timeline and more severe personal consequences associated with their condition. Furthermore, those whose symptoms did not improve perceived a lack of control over HIV, and believed that their treatment was not effectively controlling the

progression of the virus. In line with expectations, experiencing a lack of improvement in HIV related symptoms between T0 and T3 was also associated with a more negative emotional reaction to HIV and less illness coherence.

The results were similar for HAART-related symptoms (see Table 8.15): Participants who experienced persistent or worsening symptoms they attributed to HAART side effects between T1 and T3 perceived a more chronic and more cyclical timeline, and attributed more severe personal consequences to their condition. Change scores for HAART-related symptoms were negatively correlated with perceptions of treatment control and personal indicating that patients who experienced persistent or worsening symptoms they attributed to HAART after six months of treatment perceived a lack of control over HIV, and felt that their treatment was not effectively controlling their condition. In line with expectations, experiencing persistent or worsening HAART related symptoms between T1 and T3 was associated with a more negative emotional reaction to HIV, however change scores for HAART-related symptoms were not significantly related the degree of illness coherence perceived by the patient.

8.5.10.1 Relationships between symptom change and illness representations at T3 controlling for illness perceptions at T0

When controlling for illness perceptions at baseline, the relationships between change scores for HIV-related symptoms and consequences and coherence were no longer statistically significant. The relationships between change scores for HAART related symptoms and consequences and coherence also became non-significant. All other correlations remained consistent.

8.5.10.2 Relationships between symptom change and illness representations at T3 controlling for negative affect

When controlling for baseline negative affect, change scores for HIV-related symptoms and consequences and coherence became non-significant. The relationship between change in

HAART-related symptoms and consequences, coherence and cyclical timeline also became non-significant. All other relationships remained consistent.

8.5.11 Necessity and concerns as mediators of the relationship between symptom appraisal and adherence to HAART

Research Question 4: Do beliefs about HAART mediate the relationship between symptom change and adherence in a way that is consistent with the extended SRM proposed by Horne (1997; 2003)?

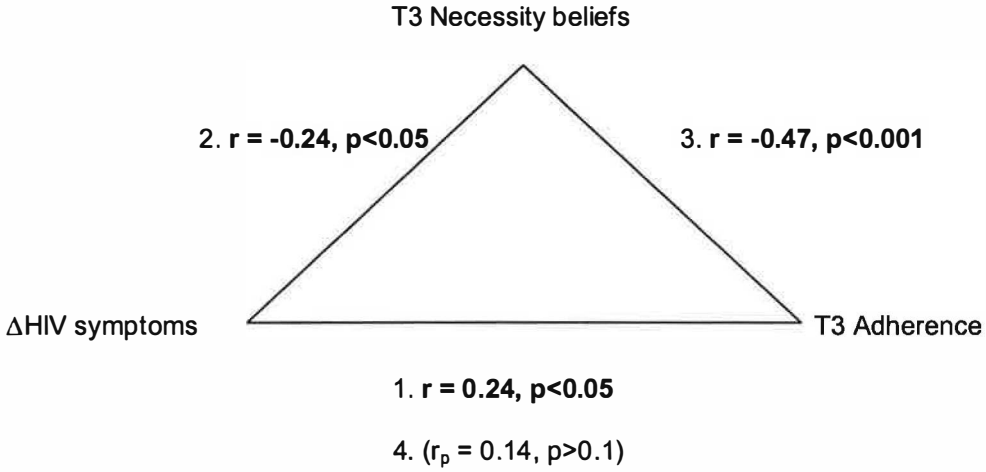
Hypothesis 4.1: Patients' perceptions of their personal *necessity* for HAART will mediate the relationship between experiencing persistent HIV-related symptoms and adherence. Specifically, those who believe their symptoms have not improved over time will be less adherent to their treatment *if they perceive a low personal necessity for HAART*.

Hypothesis 4.2: The degree to which patients hold *concerns* about the adverse effects of taking HAART will mediate the relationship between experiencing persistent HAART-related symptoms and adherence. Specifically, those who are experiencing persistent, severe symptoms they associate with HAART will be less adherent *if they hold strong concerns about their treatment*.

Mediational relationships were explored between change in symptom scores and beliefs about HAART at T3. These analyses are illustrated in Figures 8.7 - 8.10.

8.5.11.1 Do *necessity* beliefs mediate the relationship between HIV-related symptoms and adherence?

Figure 8.7: Necessity beliefs as a mediator between changes in HIV related symptoms over time and adherence

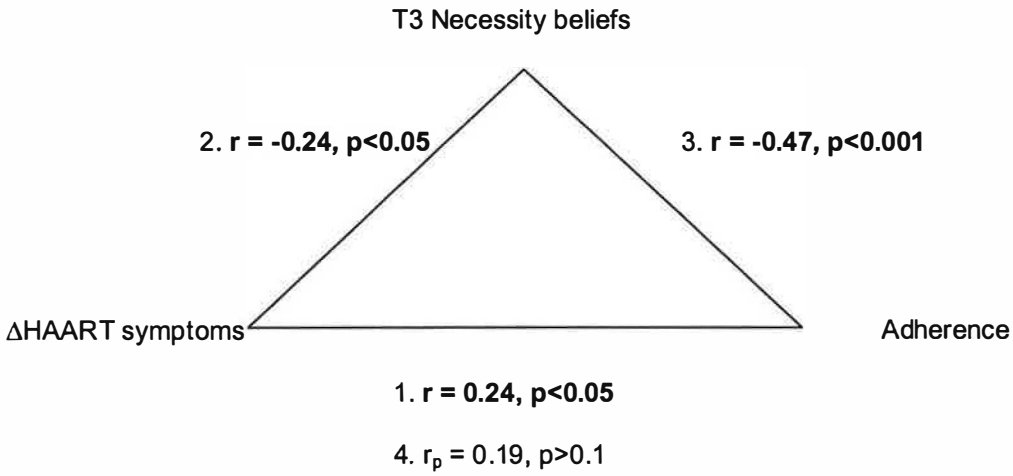


1. Low adherence at T3 was significantly associated with experiencing a lack of improvement in HIV-related symptoms (r = 0.24, p<0.05)
2. There was a negative correlation between change scores for HIV related symptoms and necessity beliefs, indicating that a lack of improvement in HIV-related symptoms over time was associated with lower necessity for HAART (r = -0.24, p<0.05)
3. There was a significant negative correlation between T3 necessity and adherence, showing that those with lower necessity scores at T3 were less adherent (r = -0.47, p <0.001)
4. When controlling for necessity beliefs, change in HIV symptoms was no longer related to adherence (r_p = 0.14, p>0.1)

These results are consistent with *necessity* beliefs mediating the relationship between HIV related symptoms and adherence, supporting the hypothesis generated by the eSRM.

8.5.11.2 Do *necessity* beliefs mediate the relationship between experiencing persistent HAART-related symptoms and adherence?

Figure 8.8: Necessity beliefs as a mediator between changes in HAART-related symptoms over time and adherence

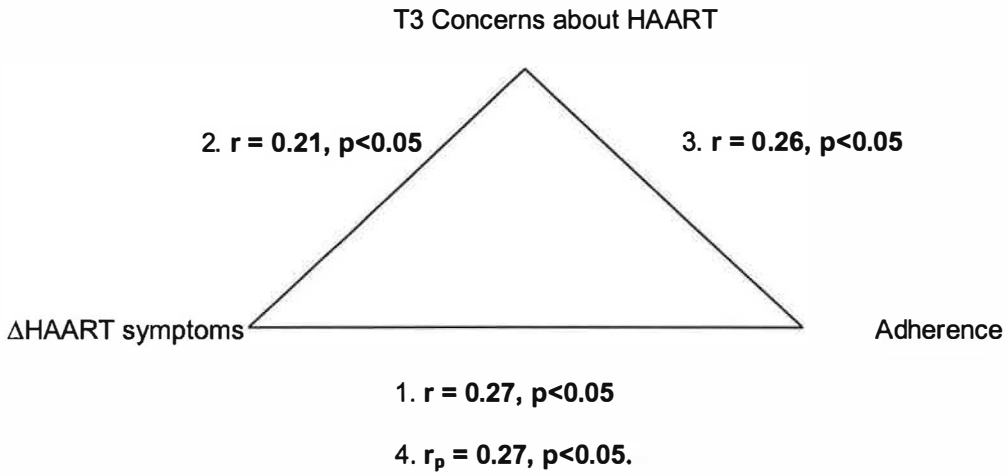


1. Low adherence at T3 was significantly associated with a lack of improvement in HAART-related symptoms (r = 0.31, p<0.01)
2. There was a significant negative correlation between experiencing a lack of improvement in HAART-related symptoms over time and beliefs about personal necessity for HAART at T3 (r = -0.32, p<0.01), indicating that those who believed that their HAART-related symptoms had not improved were less convinced of their need for treatment.
3. Low adherence at T3 was significantly associated with perceiving a lack of personal necessity for HAART at T3 (r = -0.47, p <0.01)
4. When controlling for T3 necessity beliefs, change in HAART-related symptoms was no longer related to adherence (r_p = 0.19, p>0.1)

This is consistent with *necessity* beliefs mediating the relationship between change in HAART-related symptoms and adherence.

8.5.11.3 Do concerns about HAART mediate the relationship between experiencing persistent HAART-related symptoms and adherence?

Figure 8.9: Concerns as a mediator between changes in HAART-related symptoms over time and adherence



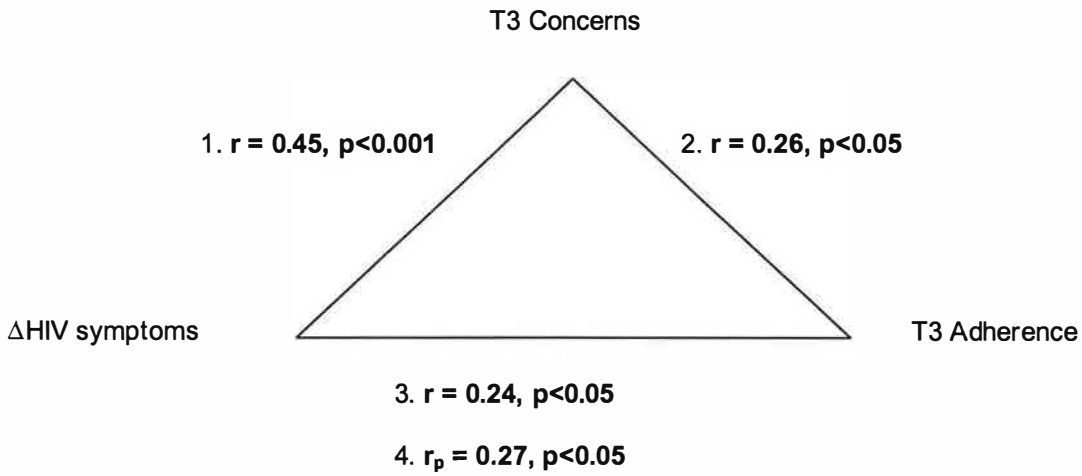
For this analysis, the item relating to patients' experiences of side effects was removed from the *concerns* scale. The scale retained an acceptable Cronbach's alpha (0.7).

1. Low adherence was significantly associated with experiencing a lack of improvement in HAART-related symptoms over time (r= 0.27, p<0.05)
2. Experiencing a lack of improvement in HAART-related symptoms between T1 and T3 was significantly related to stronger concerns at T3 (r=0.21, p<0.05)
3. Concerns about HAART at T3 were significantly associated with low adherence (r_s = 0.26, p<0.05)
4. When controlling for T3 concerns scores, reporting a lack of improvement in HAART-related symptoms remained significantly associated with low adherence (r_p = 0.27, p<0.05).

Therefore, contrary to Hypothesis 4.2, the relationship between experiencing persistent HAART-related symptoms and adherence was independent of patients' concerns about HAART.

8.5.11.4 Do concerns about HAART mediate the relationship between experiencing a lack of improvement in HIV-related symptoms and adherence?

Figure 8.10: Concerns as a mediator between changes in HIV-related symptoms over time and adherence



1. Low adherence at T3 was significantly associated with experiencing lack of improvement in HIV-related symptoms (r = 0.24, p<0.05)
2. There was a significant positive correlation between RCS HIV and concerns, indicating that experiencing a lack of improvement in HIV related symptoms was related to stronger concerns about HAART (r = 0.45, p<0.001)
3. Higher concerns were significantly associated with low adherence (r_s 0.26, p<0.5)
4. When controlling for T3 concerns, change in HIV-related symptoms remained significantly related to adherence (r_p = 0.27, p<0.05)

Therefore the relationship between change in HIV symptoms over time and adherence is independent of patients' concerns about HAART.

8.6 Discussion

The aim of this study was to explore the role of symptom appraisal and attribution in adherence to HAART over the first six months of a new treatment, in order to test hypotheses driven by the SRM (Leventhal et al., 1980) and extensions to it proposed by Horne (1997, 2003).

8.6.1 Patterns of adherence over follow-up

First, patterns of adherence were explored across the follow-up. Adherence was initially very high. However, there was a significant decrease in adherence levels between three and six months on HAART, with a quarter of the sample reporting less than adequate adherence at the six month follow-up according to current clinical recommendations (Paterson et al, 2000). Low adherence after six months of treatment was significantly associated with a poorer clinical outcome (higher viral load). This was a relatively short time on HAART in view of the fact that treatment is potentially life-long. The decline in adherence at this early stage mirrors findings from other longitudinal studies of adherence to HAART (Carrieri et al., 2001; Duran et al., 2001) and emphasises the need to identify risk factors for low adherence early in the treatment process. This is especially pertinent because viral replication in the event of sub-optimal viral suppression can be rapid (Perelson et al., 1996). The results from this study augment those from Study 1 and suggest that any intervention to promote adherence should be initiated very early in the treatment process.

8.6.2 Symptom appraisal in relation to adherence

The results provided strong support for the Self-Regulatory Model (SRM: Leventhal et al., 1980), showing that patients' appraisals of their symptoms over time were related to their adherence behaviour. There was a significant decrease in the frequency of moderate to severe symptoms patients attributed to HIV between baseline and six months for the group as a whole. Furthermore patients reporting low adherence experienced a significantly greater frequency of symptoms at each follow-up. The pattern of results for moderate to severe symptoms attributed to HAART side effects was slightly different. For the group as a whole there was no overall decline in the number of symptoms they attributed to HAART over six

months. However, when patterns of symptoms were compared between high and low adherence groups it was evident that while there was a significant decrease in HAART-related symptoms between one and six months for the high adherence group, the mean number of symptoms actually increased slightly for those who reported low adherence at six months. In line with expectations, symptom change scores were related to adherence: Patients reporting low adherence after six months of taking HAART reported less of an improvement in both HIV and HAART related symptoms over time.

It is unlikely that the lack of improvement in symptoms among those reporting low adherence at six months an artefact due to reduced clinical effect stemming from earlier non-adherence, since neither adherence at one month nor adherence at three months was significantly associated with the evolution of HIV or HAART related symptoms over six months. Neither changes in HIV nor changes in HAART related symptoms over time were associated with clinical markers of disease progression, before starting treatment or at the six-month follow-up. This suggests that patients' perceptions of their symptoms over time were not influenced by the actual clinical efficacy of their treatment.

However, symptom appraisal was associated with negative affect at baseline. Experiencing higher levels of anxiety and depression before initiating treatment was associated with less improvement in HIV-related symptoms over the six-month follow-up. Furthermore, higher levels of depression (but not anxiety) at baseline were associated with persistent or worsening HAART-related symptoms over time. Since the measure of negative affect used in this study was chosen because of its lack of overlap with physical symptomatology, it is unlikely that the relationship is due to overlap between symptoms of physical and psychological nature. It could be that depressive and anxious symptomatology is associated with a perceived lack of improvement because of a general negative or pessimistic orientation (Peterson & Bossio, 1991) or a greater tendency to attend to somatic symptoms (Watson & Pennebaker, 1991). Conversely, depression and anxiety before starting treatment may influence the adoption of other health promoting behaviours, not measured in this study, which in turn may impact on perceptions of symptom evolution over time.

Associations between patients' experiences of symptoms and adherence have been identified in several previous cross-sectional studies (Ammassari et al., 2001; Catz et al., 2000; Chesney et al., 2000; Gifford et al., 2000). In a prospective study, Spire et al. (2002) found that patients who perceived that their HAART-related side-effects remained high or increased from limited to high over four months of follow-up were significantly more likely than others to report low adherence. There is a dearth of research exploring differential relationships between adherence and symptoms depending on whether patients attribute them to HIV, HAART or other illnesses, although results from one cross-sectional study suggested that both those reporting more HIV and those reporting more HAART symptoms were less adherent to their treatment (Ammassari et al., 2001). The current study adds to this body of research, suggesting that experiencing either a lack of improvement in HIV-related symptoms or HAART-related side effects over time is associated with low adherence.

8.6.3 Impact of symptom appraisal on beliefs about HAART

8.6.3.1 Perceptions of necessity for HAART

Having established that symptom appraisal is associated with adherence in a causative fashion, the next step was to identify the mechanisms by which symptom appraisal impacts on adherence in order to test hypotheses driven by self-regulatory models. Within an extended SRM framework (Horne, 2003), experiencing a lack of improvement in symptoms associated with illness should lead to perceptions of low necessity for the prescribed treatment and subsequent non-adherence. This hypothesis was tested by correlating symptom change scores against patients' perceptions of their personal necessity for HAART, elicited at the six-month follow-up. In line with expectations, those who perceived an improvement in the symptoms they associated with HIV perceived a higher necessity for their treatment. This pattern of results was similar for HAART-related symptoms. Those who perceived an improvement in the symptoms they attributed to their treatment also perceived a higher necessity for HAART after six months of treatment.

The next question was whether these relationships were fuelled by patients' perceptions of necessity for HAART before initiating treatment, or whether their appraisal of symptoms over

time impacted on their perceptions of need over the six months of treatment. Partialling baseline beliefs about HAART out of the analyses allowed the impact of symptom evolution on beliefs to be explored independently of pre-existing beliefs about HAART. The question of how symptom evolution *impacts* on patients' beliefs about HAART could thereby be addressed. When controlling for baseline necessity beliefs, the relationship between experiencing an improvement in HIV related symptoms and necessity beliefs at six months no longer reached statistical significance.

There are several possible reasons for this finding. It may be speculated that for some, experiencing an improvement in the symptoms they attributed to HIV actually *reduced* their perceptions of necessity between baseline and six months. While for some participants, experiencing an improvement in symptoms appeared to reinforce their perceived need for treatment, for others the consequence of perceiving an improvement in symptoms related to HIV may have been a *decrease* in their perceptions of need for HAART. This reduction in perceptions of necessity in response to improved health was illustrated in the results of a parallel interview-based study in which a sub-sample of participants in the current study were interviewed about their experiences of taking HAART after six months of treatment (Cooper et al., 2003). One theme associated with low adherence was doubting the need for continued treatment once the patient had started to feel better. This is illustrated by the following quote from a participant who reported low adherence:

"I've been complacent in the way that my health is at the moment. I feel fine and well, so you can almost forget you have HIV when you are well. When I started taking the drug therapy and there were symptoms, there was always a reminder there that you had HIV and to take your tablets and stuff like that. Now it's pretty much out of sight, out of mind." *Presented at AIDS Impact, July, 2003.*

The relationship between experiencing an improvement in *HAART*-related symptoms over time and perceived necessity for HAART remained statistically significant when controlling for baseline necessity beliefs. This indicates that experiencing a lack of improvement in the

symptoms patients attributed to HAART side effects led to decrease in perceived need for treatment. This makes intuitive sense, the self-regulating patient who experiences persistent or worsening side effects may begin to doubt that the treatment is actually necessary, since the treatment itself makes them ill.

Finally, it was proposed that necessity beliefs would mediate the relationship between symptom appraisal and adherence. Necessity beliefs at six months were found to mediate the relationships between both HIV related symptoms and HAART related side effects and adherence. When necessity was partialled out of the analyses, symptom appraisal was no longer significantly related to adherence. This finding provides strong support for the extended SRM proposed by Horne (2003). It suggests that interventions to promote adherence to HAART should focus on maintaining strong perceptions of personal necessity for HAART among patients who are experiencing persistent symptoms or side effects. One way of maintaining strong necessity for HAART among these patients might be to encourage the use of laboratory test results (such as HIV-viral load and CD4 count) in patients' evaluations of their treatment.

8.6.3.2 Concerns about adverse effects

Next, relationships between symptom appraisal, concerns about HAART and adherence were explored. Within the extended self-regulatory framework proposed by Horne (2003), experiencing persistent symptoms should stimulate concerns about the prescribed medication if the symptoms are interpreted as treatment side effects. This hypothesis received support in the current study. Patients who did not experience an improvement in the symptoms they attributed to the side effects of HAART between one month and six months held stronger concerns about their treatment after six months of treatment.

When controlling for concerns about HAART at baseline, experiencing an improvement in HIV related symptoms remained significantly associated with concerns, however, experiencing an improvement in HAART related symptoms was no longer related to concerns. Observing that HAART was not alleviating symptoms the patient associated with their condition may

stimulate new concerns about the adverse effects of taking HAART. If the patient perceives the treatment to be ineffective in alleviating the symptoms of HIV, perhaps day-to-day regimen complexities, stigma and embarrassment surrounding antiretroviral treatment as well as worries about longer-term difficulties become increasingly salient.

It was further proposed that concerns about HAART would mediate the relationship between experiencing persistent, severe HAART-related symptoms and adherence, i.e. that the relationship between experiencing persistent side effects and adherence was due to the activation of a range of concerns about adverse effects of taking HAART, including worries about long-term side effects, concerns about the treatment regimen and disruption to daily routine, as well as more abstract worries about the stigma and embarrassment of taking HAART. This hypothesis was not supported: the relationship between change in HAART related symptoms over time and adherence remained significant when controlling for concerns in the analysis. This indicates that the relationship was independent of the strength of concerns participants held about their treatment. These findings suggest that, although concerns about the adverse effects of taking HAART were elevated among patients who were experiencing persistent side effects, they did not have a causative role in terms of their adherence behaviour. With respect to HIV-related symptoms, patients who experienced a lack of improvement in the symptoms they attributed to their condition over six months of treatment also held stronger concerns about HAART. However, again the strength of patients' concerns about HAART did not mediate the relationship between HIV related symptoms and adherence.

It is interesting that the relationship between the evolution of HIV-related symptoms and concerns was considerably stronger than the relationship between the evolution of symptoms attributed to HAART side effects and concerns ($r = 0.45$ compared to $r = 0.21$, respectively). The concerns scale includes a range of items addressing concerns about potential long-term effects of taking HAART, disruption to routine, difficulty with timing of pills, stigma associated with taking the treatment and general worry about antiretroviral medication. It would seem that these concerns are activated to a greater degree by the perception that the treatment is not

effectively alleviating symptoms of the virus itself than by the perception that HAART is causing persistent symptoms of its own. The burden of HAART may become greater if it is not perceived as being effective in relieving the symptoms that the patient associates with HIV.

8.6.4 Impact of symptom appraisal on perceptions of HIV and self-rated health

It was expected that patients' appraisals of their symptoms over the treatment process would impact on their perceptions of HIV, in line with the original SRM (Leventhal et al., 1980; 1982). In order to ensure that the relationships were not confounded by pre-existing illness perceptions or negative affect, corresponding perceptions of HIV, depression and anxiety at baseline were partialled out of the analyses. Consistent with the SRM, experiencing an improvement in symptoms associated with HIV or HAART over time was associated with greater optimism among patients that their condition would improve in time, and a decrease in the perception of symptoms recurring in a cyclical fashion. Furthermore, symptom appraisal appeared to be central to patients' appraisals of the effectiveness of their treatment: those reporting an improvement in the symptoms they associated with their virus or its treatment over time reported greater perceptions of control over HIV at six months relative to baseline. These patients also reported improved physical health and a less negative emotional reaction to HIV compared to baseline. However, the evolution of HIV and HAART related symptoms was not associated with changes in perceived personal consequences associated with living with HIV, nor with the extent to which patients felt they held a coherent picture of HIV.

Consistent with the original SRM proposed by Leventhal et al. (1980; 1982), these findings suggest that patients use their symptom experiences to generate their representations of illness, particularly perceptions of control and timeline. These findings are important because they suggest that patients might be erroneously judging the efficacy of their treatment on the basis of their symptom experiences. The clinical aim of HAART is to reduce viral load to undetectable levels in order to promote a healthy immune system and prevent opportunistic infections (BHIVA treatment guidelines, 2001). HAART may not therefore be expected to alleviate all the symptoms the patient associates with their illness, and is well known to cause side effects of its own (Carr & Cooper, 2000). These findings indicate that efforts should be

made to focus patients' attention on clinical indicators of HAART-efficacy, such as HIV viral load in determining the efficacy of their treatment, rather than their experiences of symptoms.

8.6.5 The role of negative affect

When controlling for depression and anxiety at baseline, experiencing an improvement in HIV-related symptoms was no longer significantly related to adherence. Since depression and anxiety were significantly related to both low adherence and symptom appraisal, it can be concluded that negative affect mediated the relationship between HIV symptom appraisal and adherence. This suggests that patients who were experiencing high levels of negative affect before they began treatment were more likely to respond to a lack of improvement in the symptoms they attributed to their illness with low adherence. This may be due to a general negative orientation, where patients experiencing a more negative mood may feel negatively about a treatment that is not improving the symptoms they attribute to their illness and respond by missing doses. Negative affect did not, however, mediate the relationship between HAART-related symptom appraisal and adherence. This indicates that patients responded to a lack of improvement in HAART related side effects by missing doses, regardless of their initial level of depressive or anxious mood. While isolating 'pure' relationships between symptom appraisal and adherence may be useful for the development of theory, it is difficult to envisage how these findings should be incorporated into interventions that aim to improve high adherence, especially given the high incidence of depression in HIV (Cruess et al., 2003). Moreover, it is not yet known whether improving negative mood would improve adherence. Further research is needed to address these questions.

In conclusion, this study has shown that changes in patients' perceptions of symptoms over time predict adherence to HAART over the first six months of treatment as suggested by self-regulatory models (Leventhal et al., 1980, Horne et al., 2003). It suggests that patients use their experience of symptoms as a primary means of appraising the impact of their treatment, and illustrates some of the mechanisms through which symptom appraisal impacts on

adherence. The study both supports existing research showing links between symptom experiences and adherence to HAART, and extends this body of knowledge in several ways.

First, while previous cross-sectional studies have tended to show links between HAART-side effects and adherence, or not differentiated between symptoms attributed to HAART and those attributed to HIV (Ammassari et al., 2001; Catz et al., 2000; Chesney et al., 2000; Gifford et al., 2000), this study shows that both types of symptoms impact on adherence. Second, by using a prospective, longitudinal research design, it was possible to show that the associations between symptoms and adherence were not due to the tendency of particular patients to over or under-report symptoms, but to the evolution of symptom experiences over time. By controlling for the variance accounted for by symptom experiences prior to initiating treatment (HIV) or in the early stages of treatment (HAART), the results showed that those who experienced an improvement in symptoms over time reported high levels of adherence, while those experiencing persistent or worsening symptoms over time were more likely to respond with less than optimal adherence. These results are consistent with the SRM (Leventhal et al., 1980; 1982), suggesting that patients expect HAART to alleviate symptoms of HIV, and not to cause its own. Third, the study provides support for extensions to the SRM proposed by Horne (1997, 2003), by showing how patients' beliefs about their personal *necessity* for HAART mediate the relationships between symptom experiences and adherence. These results suggest that patients who experience a decrease in both HIV and HAART-related symptoms over time are likely to be adherent to their treatment because they perceive a stronger need to take it. Finally, the data lend support to the theoretical framework proposed by Leventhal et al. (1980; 1982), showing a dynamic relationship between patients' appraisals of their symptoms over the first six months of taking HAART and their perceptions of HIV, with those experiencing an improvement in symptoms over time reporting more optimistic beliefs about the likely outcome of their condition, stronger perceptions of control over HIV, and less negative emotional representations of HIV at six months, compared to baseline. They also show improved physical health among those who experienced an improvement in symptoms.

The data generated by this study extend research the HIV-adherence literature by specifying some of the mechanisms by which symptom experiences impact on adherence, thus enabling clinicians and researchers to develop appropriate interventions to maintain high levels of adherence to HAART. The results are also relevant to the understanding of theory that may be applicable to other illness groups, by specifically addressing the previously under-researched appraisal mechanism proposed by the SRM and mechanisms through which symptom appraisal impacts on adherence proposed by Horne (1997; 2003).

8.6.6 Limitations

8.6.6.1 Sample bias

Participants who completed Study 2 were compared to those completing Study 1 in order to establish sample whether the results could be generalised to the study population as a whole. There were some differences between the two cohorts in terms of clinical and demographic characteristics. Those who failed to complete the assessments necessary for inclusion in Study 2 were younger, less likely to be in a clinical trial and to have had prior experience taking ARVs, compared to those who completed assessments for Study 1. It is worthy of note that over half of those with missing data had stopped their treatment before the six-month follow-up, therefore the Study 2 assessments were not applicable for these patients. In order to overcome the problem of attrition in studies investigating adherence to HAART, many investigators employ an 'intention to treat' analysis, where patients who fail to complete the study are classified as non-adherent. However, this analysis was not feasible in the current study, which required questionnaires to be completed at all time-points, not only at baseline. Since those who made the decision to stop their treatment represent a sample of non-adherent patients, it is not surprising that they also had a significantly higher viral load at six months compared to those who completed the Study 2 assessments.

With regard to the wider UK population of HIV positive adults, this Brighton-based sample over-represent white gay men. The findings require replication within a range of HIV populations in order to develop intervention based on a more representative sample.

8.6.6.2 Measurement of symptoms

The symptom measure used in this study was crude and not encompassing of the wide spectrum of symptoms that may be experienced by patients with HIV and those using HAART. It is therefore possible that some participants could have been experiencing one or more severe symptom that was not covered by the measure. Furthermore, because of the relatively short follow-up it was not possible to investigate patients' appraisals of side effects that occur with longer-term use of HAART, such as lipodystrophy, or the impact of these long-term adverse effects on adherence.

8.6.7 Implications for intervention and clinical practice

The data suggest that symptom experiences are key to patients' appraisals of their antiretroviral treatment. The change in symptoms over time appears to be particularly important. The risk of low adherence is increased if patients experience a lack of improvement in the symptoms they attribute to HIV, or if they experience persistent or worsening symptoms attributed to HAART. Clinicians and researchers should be aware that patients' appraisals of their symptom experiences over time impact on their adherence behaviour. Although alleviating symptoms and side effects would be desirable, this is unlikely to be possible for every patient. There has been very little research into the most effective ways of managing persistent symptoms and side effects among people with HIV. Where pharmacological treatment of symptoms is not possible, effective or desirable, psychological interventions might help patients to develop coping skills that reduce the distress caused by persistent symptoms. Further research is required in order to explore the impact of physical, psychological and practical interventions to alleviate or manage symptoms on adherence to HAART among people with HIV.

The study identified some of the mechanisms by which symptom experiences impact on adherence to HAART. In particular, patients' perceptions of their personal necessity for HAART mediated the relationships between both HIV and HAART related symptom appraisal and adherence. These results suggest that eliciting and addressing patients' beliefs about their continued necessity for HAART may be an effective way of maintaining high levels of

adherence among patients whose HIV-related symptoms have not improved on treatment, and those experiencing persistent side effects. The findings also indicate that efforts should be made to focus patients' attention on clinical indicators of HAART-efficacy, such as HIV viral load in determining the efficacy of their treatment, rather than their experiences of symptoms.

Chapter 9

Study 3

Changes in perceptions of HIV and beliefs about HAART over six months of treatment: Impact on adherence.

9.1 Introduction

Study 2 showed that patients' experiences of symptoms changed over six months of treatment and that these changes fed back into representations of illness and treatment and impacted on adherence. Although central to the theoretical structure of the SRM (Leventhal et al., 1980) and extended SRM (Horne, 1997; 2003), very few studies to date have explored changes in perceptions of illness or beliefs about treatment over time or in response to a new treatment. Although recent studies have identified links between illness perceptions and adherence to treatment (Cooper et al., 1999; Horne & Weinman, 1998; 2002; Llewellyn et al., 2003; Horne et al. (in press)), these studies have used cross sectional designs, so it was not possible to determine the nature of causality between beliefs and adherence. Consequently, little is known about how perceptions of illness and treatment change over time and whether such changes are associated with adherence. This is an important omission, since patients' experiences over the months following the initiation of a new treatment for chronic illness may have a profound influence on their beliefs and impact on the degree to which they adhere to their prescribed treatment regimen.

One recent study suggests that perceptions of illness do indeed change over time and that these changes predict behaviour and clinical outcome. Petrie et al (2002) found that patients who were randomised to receive an intervention following their first myocardial infarction (MI) reported significant positive changes in their views of their MI and were better prepared for leaving hospital compared to patients in the control group. Furthermore, those who received the intervention reported a significantly lower rate of angina symptoms three months later.

If little is known about how perceptions of illness change over time, still less is known about the evolution of beliefs about medicines. To date, studies utilising the extended SRM (Horne

& Weinman, 2002; Llewellyn et al., 2003; Horne et al., 2003 (in press)) have been cross-sectional in design. Subsequently, there is a dearth of information concerning how patients' perceptions of their personal necessity for treatment or their concerns about adverse effects evolve over the treatment process, or whether these changes predict adherence.

This final part of the thesis explored how patients' perceptions of HIV and HAART evolved over time, from before initiating a new antiretroviral treatment regimen, over the following six months. The aim was to determine whether changes in perceptions of HIV and HAART over time predicted adherence. The prospective, longitudinal design of the study also provided the opportunity to explore what factors are associated with the change in beliefs over time, in order to provide targets for the content of interventions to maintain the unusually high levels of adherence to HAART that are required for clinical success.

9.2 Aims and research questions

The overall aim of this study was to explore how perceptions of HIV and HAART change over the first six months of treatment, and how these changes impact on adherence. Specifically:

1. To explore how perceptions of HIV and HAART evolve over the first six months of treatment
2. To determine whether patients' perceptions of HIV and beliefs about HAART are associated with adherence
3. To determine whether *changes* in patients' perceptions of HIV and beliefs about HAART over the first six months of treatment are associated with adherence
4. To examine relationships between changes in perceptions of HIV and beliefs about HAART over the treatment process
5. To determine whether perceptions of HIV mediate relationships between changes in beliefs about HAART and adherence over time

Research Question 1: How do patients' perceptions of HIV and beliefs about HAART evolve over the first six months of treatment?

Very little previous work has looked at change in beliefs about HIV or HAART in response to initiating a new treatment. Therefore these hypotheses are exploratory.

Hypotheses

Hypothesis 1.1: There will be significant changes in patients' beliefs about HAART over the first six months of treatment

Hypothesis 1.2: There will be significant changes in patients' perceptions of HIV over the first six months of treatment

Research question 2: Are patients' perceptions of HIV and beliefs about HAART associated with adherence?

Study 1 showed relationships between *baseline* perceptions of HIV and beliefs about HAART and subsequent adherence. This question addresses the question of whether these beliefs are associated with adherence across the entire treatment process.

Hypothesis 2.1: Beliefs about HAART will be associated with adherence. Specifically, low adherence will be associated with:

H2.1.1 lower perceived *necessity* for treatment

H2.1.2 stronger *concerns* about adverse effects of taking HAART

Hypothesis 2.2: Perceptions of HIV will be associated with adherence. Specifically, low adherence will be associated with perceiving:

H2.2.1 less negative personal consequences of having HIV

H2.2.2 a more optimistic timeline

H2.2.3 a less cyclical timeline

H2.2.4 less personal control over HIV

H2.2.5 doubting that HAART can effectively control HIV

H2.2.5 greater illness coherence

H2.2.6 a less negative emotional representation of HIV

H.2.2.7 a more positive perception of physical health

Research question 3: Are *changes* in patients' perceptions of HIV and beliefs about HAART over six months of treatment associated with adherence?

Having already addressed the question of whether baseline beliefs impact on subsequent adherence (Study 1), and whether there is a relationship between beliefs and adherence across the entire follow-up (RQ2, this study), this question addressed the interaction between time and adherence, in order to find out whether the degree to which perceptions of illness and treatment changed over time impacted on adherence.

Hypothesis 3.1: Changes in beliefs about HAART over the first six months of treatment will be associated with adherence. Specifically:

H3.1.1: low adherence will be associated with a greater decline in *necessity* beliefs

H3.1.2: high adherence will be associated with a greater decline in *concerns*

Hypothesis 3.2: Changes in perceptions of HIV over the first six months of treatment will be associated with adherence. The general expectation is that increases in perceived control over HIV (treatment control and personal control) will be associated with high adherence while increases in consequences, timeline, cyclical timeline, emotional representations and illness coherence will be associated with low adherence. It was also expected that an increase in self-rated health over time would be associated with high adherence.

Research question 4: Are changes in perceptions of personal necessity for HAART over the treatment process associated with changes in perceptions of HIV in a way that is consistent with the extended SRM?

Hypothesis 4.1: Reporting a decrease in perceptions of personal necessity for HAART across the treatment process will be associated with an increase in negative perceptions of

HIV (symptoms related to HIV and HAART, consequences, timeline, cyclical timeline, illness coherence and emotional representations) and a decrease in perceptions of control over HIV (treatment control and personal control). It is also expected that self-rated health will decline as perceptions of necessity decline.

Research question 5: Do perceptions of HIV mediate relationships between beliefs about personal necessity for HAART and adherence?

H5.1 The relationship between changes in beliefs about HAART and adherence will be mediated by changes in illness perceptions

9.3 Methods

9.3.1 Participants

Of the eighty-six participants described in the General Methodology, nine had stopped their treatment before the six-month follow-up (T3). Although this group comprised a sub-sample of participants who met the definition for low adherence using the composite score utilised in Study 1, these participants did not complete the six-month (T3) questionnaires (in line with study protocol: see General Methodology), therefore it was not possible to use their data in the analyses in Study 3. A further seven participants were missing data at the one-month (T1) assessment, and three were missing data at the three-month (T2) assessment. The final sample for the present study therefore comprised sixty-seven participants. The sample is described in the Results section.

9.3.2 Procedure

The procedure for Study 3 is described in the General Methodology. In summary, patients who were not taking HAART were recruited to the study through their HIV clinician. The author attended weekly clinical meetings in order to identify participants who were eligible for a HAART recommendation on the basis of British HIV Association (BHIVA) guidelines. Those who accepted a treatment recommendation were given a questionnaire to complete before

starting treatment (T0), and again after one month (T1), three months (T2) and six months (T3) of taking their HAART regimen.

9.3.3 Measures

All measures are described in detail in the General Methodology. The questionnaire booklet given at T0, T1, T2 and T3 contained the Illness Perceptions Questionnaire (IPQ), the Beliefs about Medicines Questionnaire (BMQ), Hospital Anxiety and Depression Scale (HADS) and the MOS Short-Form 12-item health assessment inventory (SF-12). As stronger relationships were found between perceptions of *moderate-severe* symptoms (rather than frequency of symptoms per se) the HIV and HAART related symptom (*identity*) scales used in this section of the thesis represented the frequency of symptoms rated moderate to severe. In addition to these core questionnaires, the booklet given at the one, three and six month follow-ups contained a visual analogue scale adapted from the Medication Adherence Self Report Inventory (MASRI). Patients were divided into 'low adherence' and 'high adherence' groups on the basis of whether their average adherence score on the MASRI was 95% or above (high adherence) or below 95% (low adherence). This adherence categorisation is in accordance with the findings of recent clinical research, which suggests that at least 95% adherence to HAART is required for clinical efficacy (Patterson et al., 2000). Clinical information was recorded from medical files at T0 and T3.

9.3.4 Statistics

Estimations of population normality and homogeneity of variance for IPQ, BMQ, HADS and SF-12 scales have already been described (See Chapter 7). Participants were categorised into high and low adherence groups on the basis of MASRI scores as described above, and changes in the number of participants reporting high and low adherence were calculated using Cochrane's Q and McNemar's tests. Non-parametric tests were used in this instance because adherence was extremely high with very little variation in scores at T1 and T2. In order to determine whether the study sample was representative of the study population, participants who provided data for this study were compared with those with missing data on clinical and demographic variables. As before, a log transformation was carried out to

establish a linear scale of measurement for viral load data. Between groups comparisons were made using independent samples t-tests for continuous data and chi-square tests for categorical data. The adherence categorisation was validated against clinical outcome using a t-test.

An omnibus repeated measures ANOVA was used to investigate differences in mean scores for IPQ (consequences, timeline, cyclical timeline, personal control, treatment control, coherence, and emotional representations of HIV), BMQ (HAART-necessity and concerns) and SF-12 (physical health) variables across the four timepoints (T0, T1, T2 and T3) and between high and low adherence groups. The results of the ANOVA were used to identify:

1. Within groups differences (time): whether patients' perceptions of HIV and HAART changed significantly over the four time-points
2. Between groups differences (adherence): whether there were significant differences between those high and low adherence in terms of their perceptions of HIV and HAART
3. Interaction effects (adherence x time): whether high and low adherence groups differed significantly in terms of patterns of change over time

Because negative affect at baseline has already been identified as a predictor of adherence (See Study 1), it was possible that depression and anxiety mediated the relationship between perceptions of HIV and HAART and adherence. In order to determine which relationships were mediated by negative affect, and which were independent of negative affect, the analyses of variance were repeated controlling for possible effects of anxiety and depression using repeated measures ANCOVA. Where the ANOVA or ANCOVA identified significant effects of time, paired samples t-tests were used to locate differences between means at individual time-points. Significant group by time interaction effects were explored within high and low adherence groups using Friedman's Test. Friedman's test was chosen in this instance because it is less sensitive than ANOVA to the disparity in group size between high and low adherence groups. Results were illustrated using error bars (to show the pattern of

change over time for the group as a whole) and line graphs (to show change over time for high Vs low adherence groups). Scales measuring patients' perceptions of HIV and HAART related symptoms were not included in these analyses, since symptom appraisal over the six months of treatment was the subject of Chapter 8. Perceptions of HIV and HAART-related symptoms were, however, included in the analyses of predictors and correlates of changes in beliefs about HAART over the treatment process.

Partial correlations were used to examine relationships between changes in beliefs about HAART and perceptions of HIV. These analyses were conducted by partialling out the variance that could be attributed to perceptions of HIV and beliefs about HAART at baseline, so that the dynamic relationship between evolutions of these beliefs over time could be assessed. The symbol 'Δ' was used to represent change.

Mediational analyses were conducted in order to assess whether perceptions of HIV mediated the relationship between perceived necessity for HAART and adherence. These mediational analyses were conducted in accordance with the recommendations of Baron & Kenny (1986), as described in Study 1. A series of partial correlations were used to assess relationships between variables and proposed mediators. Candidates for the mediational analyses were chosen post-hoc on the basis of results generated by statistics in Sections 2 and 4 of this study, because mediational analyses are only relevant where there is a significant relationship between the proposed mediator, the independent variable and the dependent variable. Point bi-serial correlations were used when assessing relationships between adherence (a categorical variable) and illness perceptions or treatment beliefs.

9.4 Results

9.4.1 Sample characteristics

This was a sub-sample of participants described in Studies 1 and 2. The sample are essentially the seventy participants described in Study 2 minus three participants, who were missing data at the three-month follow-up (T2). A total of sixty-seven participants provided the data for this study. The majority of the sample described their ethnic origin as white UK (59

(88.1%)), 3 (4.5%) as black African, 3 (4.5%) as white other and 2 (3.0%) as black Caribbean. Sixty-four participants (95.5%) were male, of whom 60 (93.8%) described their most likely transmission risk as sex with a man. The mean age of the sample was 40.3 (SD=8.8). Forty-three participants (62.7%) were employed outside the home. The median number of years since diagnosis of HIV ranged from 0-17, with a median of 2.3 years. In terms of CDC classification, 21 (31.3%%) were asymptomatic, 27 (40.3%) were symptomatic and 19 (28.4%) had a diagnosis of AIDS. Over a quarter of the sample (n=18, 26.9%) had previously been prescribed antiretroviral therapy. The mean CD4 count before initiating treatment was 202.4 (SD = 138.0), with a median viral load ($\log^{10}$) of 5.3 (SD=0.4).

In order to establish whether the results from this sample could be generalised to the population as a whole, clinical, demographic and adherence data were compared between those who completed all assessments (n=67) and those who had stopped treatment or who were missing data (n=19). Descriptive statistics for both groups are shown in Tables 9.1 and 9.2.

As before, those who completed all assessments were more likely to have had prior antiretroviral treatment (χ^2= 11.1, df =1, p<0.001) and to be enrolled in a clinical trial (χ^2= 7.9, df =1, p<0.005) and to be older (t=3.6, df=84, p<0.001) compared to those who had missing data or who had stopped their treatment.

Those who had stopped their treatment or who were missing data had significantly higher viral loads at six months (t = -3.2, df=84, p<0.001). Since those who had completely stopped their treatment represented, by definition, a biased sample of non-adherent patients, this finding was in line with expectations.

Table 9.1: Comparison of baseline demographic and clinical characteristics of participants who completed all assessments and those who stopped their treatment or had missing data

Baseline clinical/demographic feature		Completed study n=67	Missing data n=19	p
Age	Mean (SD)	**40.3 (8.8)**	**32.6 (6.1)**	**<0.001**
Male		64 (95.5)	19 (100%)	>0.1
Employed		42 (62.7%)	9 (47.7%)	>0.1
Transmission risk: gay man		60 (89.6%)	18 (94.7%)	>0.1
Years since HIV diagnosis	Median (range)	2.3 (0-17)	4.4 (0-17)	>0.1
Asymptomatic HIV		21 (31.3%)	5 (26.3%)	>0.1
Symptomatic HIV		27 (40.3%)	8 (42.1%)	>0.1
AIDS		19 (28.4%)	6 (31.6%)	>0.1
Clinical trial		**32 (51.6%)**	**2 (12.5%)**	**<0.005**
Prior experience of ARVs		**18 (26.9%)**	**13 (68.4%)**	**<0.001**
CD4 count at treatment offer	Mean (SD)	202.4 (138.0)	194.0 (126.7)	>0.1
Viral load log^{10} at treatment offer	Mean (SD)	5.3 (0.4)	5.2 (0.6)	>0.1

Table 9.2: Comparison of clinical outcomes among participants who completed all assessments and those who stopped their treatment or had missing data

Clinical outcome		Completed study n=67	Missing data n=19	p
CD4 count at T3	Mean (SD)	345.8 (243.1)	309.4 (187.7)	>0.1
Viral load log^{10} at T3	**Mean (SD)**	**1.9 (0.6)**	**2.6 (1.4)**	**<0.005**

9.4.2 Characteristics of scales

For Q-Q plots and histograms of scores for all IPQ, BMQ, HADS and SF-12 scales please see Appendix 1. These scales have already been described (See Chapter 7).

9.4.3 Patterns of adherence over follow-up

Table 9.3: Levels of adherence at one, three and six month follow-ups

	High adherence >=95%	Low adherence <95%
	n (%)	n %
1 month (T1)	61 (91.0%)	6 (9.0%)
3 months (T2)	60 (89.6%)	7 (10.4%)
6 months (T3)	53 (79.1%)	14 (20.9%)

Table 9.3 shows the number of participants categorised into high and low adherence groups at each assessment. As before, the number of participants reporting less than 95% adherence declined significantly over the follow-up (Cochrane's Q Test: $\chi 2= -10.4$, $p<0.01$). A series of McNemar's tests showed that the percentage of participants reporting low adherence did not change significantly between one and three months ($p>0.1$), but identified a significant decrease in adherence between three and six months on treatment (McNemar's test, $p<0.01$), and between one and six months (McNemar's test, $p<0.05$). In line with expectations, those in the low adherence group had a significantly higher viral load log^{10} (mean =2.3, SD = 1.1) compared to those in the high adherence group (mean =1.8, SD = 0.2; $t=-3.4$, $df = 62$, $p<0.001$).

9.4.4 Changes in perceptions of HIV and HAART over time

RQ1: How do patients' perceptions of HIV and beliefs about HAART evolve over the first six months of treatment?

Table 9.4 shows means and standard deviations for perceptions of HIV and beliefs about HAART at baseline, 1, 3 and 6-month follow-ups for the group as a whole, Table 9.5 shows means and standard deviations for perceptions of HIV and beliefs about HAART at baseline, 1, 3 and 6-month follow-ups for the high adherence group and Table 9.6 shows means,

standard deviations for perceptions of HIV and beliefs about HAART at baseline, 1, 3 and 6-month follow-ups for the low adherence group.

Table 9.4: Perceptions of HIV and beliefs about HAART at T0, T1, T2 and T3 for the group as a whole (n = 67)

	T0	T1	T2	T3
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Necessity	3.9 (0.5)	3.8 (0.6)	3.8 (0.6)	3.7 (0.7)
Concerns	3.0 (0.6)	2.6 (0.6)	2.4 (0.6)	2.4 (0.6)
Consequences	3.6 (0.8)	3.5 (0.8)	3.5 (0.8)	3.5 (0.8)
Timeline	3.0 (1.0)	2.9 (1.0)	3.1 (0.9)	3.2 (1.0)
Cyclical timeline	3.2 (0.8)	3.0 (0.8)	2.9 (0.8)	3.0 (0.9)
Personal control	3.8 (0.6)	3.9 (0.5)	3.9 (0.5)	3.8 (0.5)
Treatment control	3.9 (0.5)	4.5 (0.5)	4.4 (0.6)	4.3 (0.7)
Illness coherence	2.4 (0.7)	2.3 (0.7)	2.3 (0.7)	2.4 (0.7)
Emotional representations	3.3 (0.9)	3.1 (0.9)	3.1 (0.9)	3.1 (0.9)
SF-12 physical health	40.7 (11.4)	43.2 (11.2)	44.9 (11.5)	43.6 (12.3)

Table 9.5: Perceptions of HIV and beliefs about HAART at T0, T1, T2 and T3 among participants reporting high adherence to HAART (n = 53)

	T0	T1	T2	T3
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Necessity	4.0 (0.5)	3.9 (0.5)	3.9 (0.5)	3.8 (0.6)
Concerns	2.9 (0.6)	2.5 (0.7)	2.4 (0.6)	2.4 (0.5)
Consequences	3.5 (0.8)	3.4 (0.8)	3.4 (0.8)	3.4 (0.8)
Timeline	2.9 (1.0)	2.9 (1.1)	3.0 (0.9)	3.1 (1.0)
Cyclical timeline	3.2 (0.8)	3.0 (0.8)	2.8 (0.9)	3.0 (0.9)
Personal control	3.9 (0.5)	3.9 (0.5)	3.9 (0.5)	3.8 (0.5)
Treatment control	4.0 (0.5)	4.5 (0.5)	4.5 (0.6)	4.4 (0.7)
Illness coherence	2.4 (0.7)	2.2 (0.7)	2.2 (0.7)	2.3 (0.6)
Emotional representations	3.3 (0.9)	3.0 (0.9)	3.0 (0.9)	3.1 (0.9)
SF-12 physical health	41.6 (11.3)	44.0 (11.7)	46.4 (11.7)	45.4 (12.1)

Table 9.6: Perceptions of HIV and beliefs about HAART at T0, T1, T2 and T3 among participants reporting low adherence to HAART (n = 14)

	T0	T1	T2	T3
Necessity	3.8 (0.5)	3.5 (0.7)	3.4 (0.8)	3.2 (0.7)
Concerns	3.2 (0.6)	2.6 (0.6)	2.6 (0.7)	2.6 (0.6)
Consequences	4.0 (0.7)	3.9 (0.7)	4.0 (0.7)	3.6 (0.8)
Timeline	3.5 (0.9)	3.0 (1.0)	3.4 (0.8)	3.3 (1.0)
Cyclical timeline	3.5 (0.8)	3.1 (0.7)	3.4 (0.6)	3.4 (1.0)
Personal control	3.6 (0.8)	3.8 (0.5)	3.8 (0.6)	3.6 (0.6)
Treatment control	3.8 (0.6)	4.3 (0.5)	4.2 (0.7)	3.9 (0.7)
Illness coherence	2.4 (0.9)	2.6 (0.8)	2.6 (0.7)	2.5 (0.7)
Emotional representations	3.2 (0.9)	3.3 (0.9)	3.4 (0.9)	3.3 (0.9)
SF-12 physical health	38.5 (12.0)	41.4 (9.1)	39.5 (9.5)	37.3 (10.2)

Table 9.7 shows the results of an omnibus repeated measures ANOVA exploring changes in beliefs about HAART and perceptions of HIV over time (within groups effects), differences between high and low adherence groups in terms of their beliefs about HAART and perceptions of HIV (between groups effects) and differences between high and low adherence groups in terms of changes in their beliefs about HAART and perceptions of HIV over time (group x time interaction).

Table 9.7: Repeated measures ANOVA and ANCOVA exploring changes in beliefs about HAART and perceptions of HIV between T0, T1, T2, T3 and their impact on adherence

	Unadjusted scores		Controlling for NA	
NECESSITY	**F**	**p**	**F**	**p**
Within groups (time)	**8.4**	**<0.001**	**4.0**	**<0.01**
Between groups (high or low adherence)	**9.6**	**<0.005**	**10.2**	**<0.005**
Group x Time interaction	**4.5**	**<0.05**	**5.0**	**<0.05**

CONCERNS				
Within groups (time)	**26.8**	**<0.001**	**11.3**	**<0.001**
Between groups (high or low adherence)	1.7	>0.1	0.0	>0.1
Group x Time interaction	0.4	>0.1	0.3	>0.1
IPQ CONSEQUENCES				
Within groups (time)	**3.0**	**<0.05**	1.5	>0.1
Between groups (high or low adherence)	3.8	>0.05	0.7	>0.1
Group x Time interaction	2.0	>0.1	1.7	>0.1
IPQ TIMELINE				
Within groups (time)	2.0	>0.1	0.2	>0.1
Between groups (high or low adherence)	1.6	>0.1	0.2	>0.1
Group x Time interaction	2.2	>0.1	3.1	>0.05
IPQ CYCLICAL TIMELINE				
Within groups (time)	**4.3**	**<0.01**	1.7	>0.1
Between groups (high or low adherence)	2.6	>0.1	0.0	>0.1
Group x Time interaction	1.0	>0.1	0.5	>0.1
IPQ PERSONAL CONTROL				
Within groups (time)	2.6	>0.05	1.7	>0.1
Between groups (high or low adherence)	2.2	>0.1	0.1	>0.1
Group x Time interaction	0.2	>0.1	0.9	>0.1
IPQ TREATMENT CONTROL				
Within groups (time)	**20.0**	**<0.001**	**9.2**	**<0.001**
Between groups (high or low adherence)	**3.1**	**<0.05**	0.8	>0.1
Group x Time interaction	2.6	>0.1	1.8	>0.1
IPQ ILLNESS COHERENCE				
Within groups (time)	0.12	>0.1	1.7	>0.1
Between groups (high or low adherence)	1.1	>0.1	0.4	>0.1
Group x Time interaction	1.6	>0.1	2.2	>0.1
IPQ EMOTIONAL REPRESENTATIONS				
Within groups (time)	0.3	>0.1	0.4	>0.1
Between groups (high or low adherence)	0.6	>0.1	1.5	>0.1
Group x Time interaction	3.2	>0.05	3.8	>0.05
SF-12 PHYSICAL HEALTH				
Within groups (time)	1.9	>0.1	2.4	>0.1
Between groups (high or low adherence)	2.8	>0.05	0.6	>0.1
Group x Time interaction	3.1	>0.05	1.9	>0.1

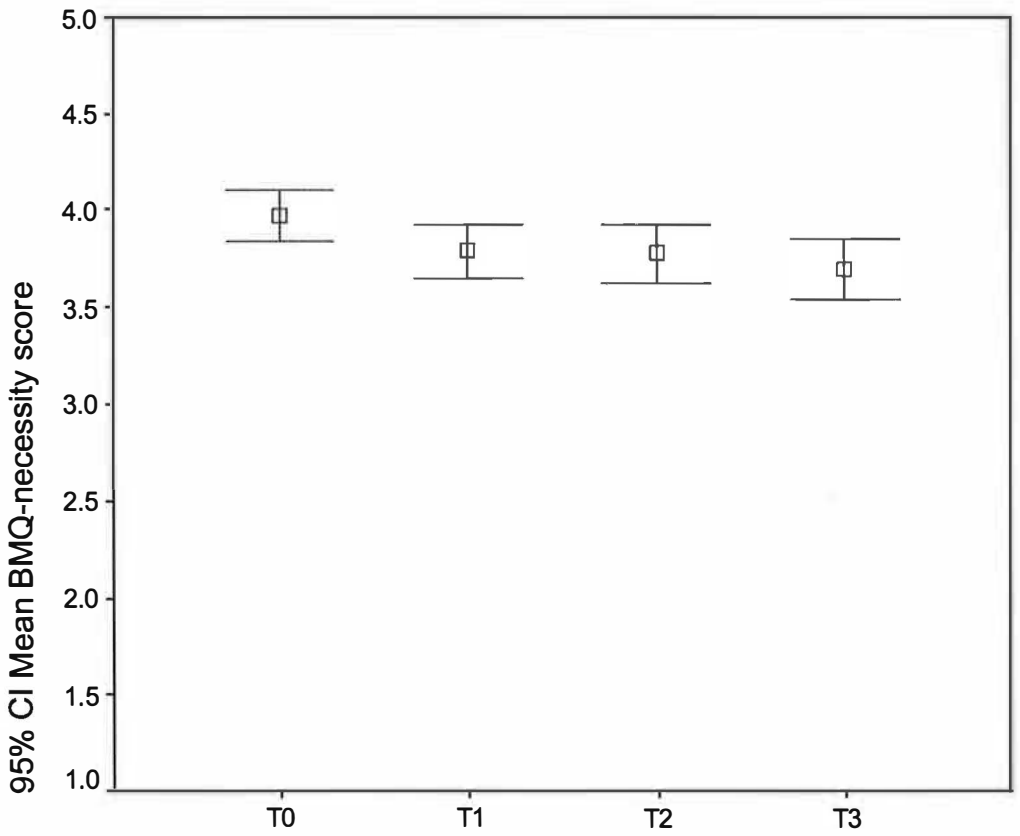
9.4.4.1 Changes in beliefs about HAART over time

Hypothesis 1.1: There will be significant changes in patients' perceptions of HAART over the first six months of treatment

9.4.4.1.1 BMQ-Necessity

Patients' perceptions of their personal necessity for HAART were initially high but declined significantly over the six months of follow-up ($F(3, 65) = 8.4$, $p<0.001$). The decline in necessity beliefs over time was independent of negative affect ($F(3, 63 = 4.0$, $p<0.01$). Figure 9.1 shows that the decline in necessity beliefs was linear over the four time-points. Paired t-tests showed that when comparing change over individual time-points, the only significant changes occurred over the first month of treatment (T0-T1: $t = 2.9$, $df = 66$, $p<0.01$) and over the entire follow-up (T0-T3: $t = 3.8$, $df = 66$, $p<0.001$).

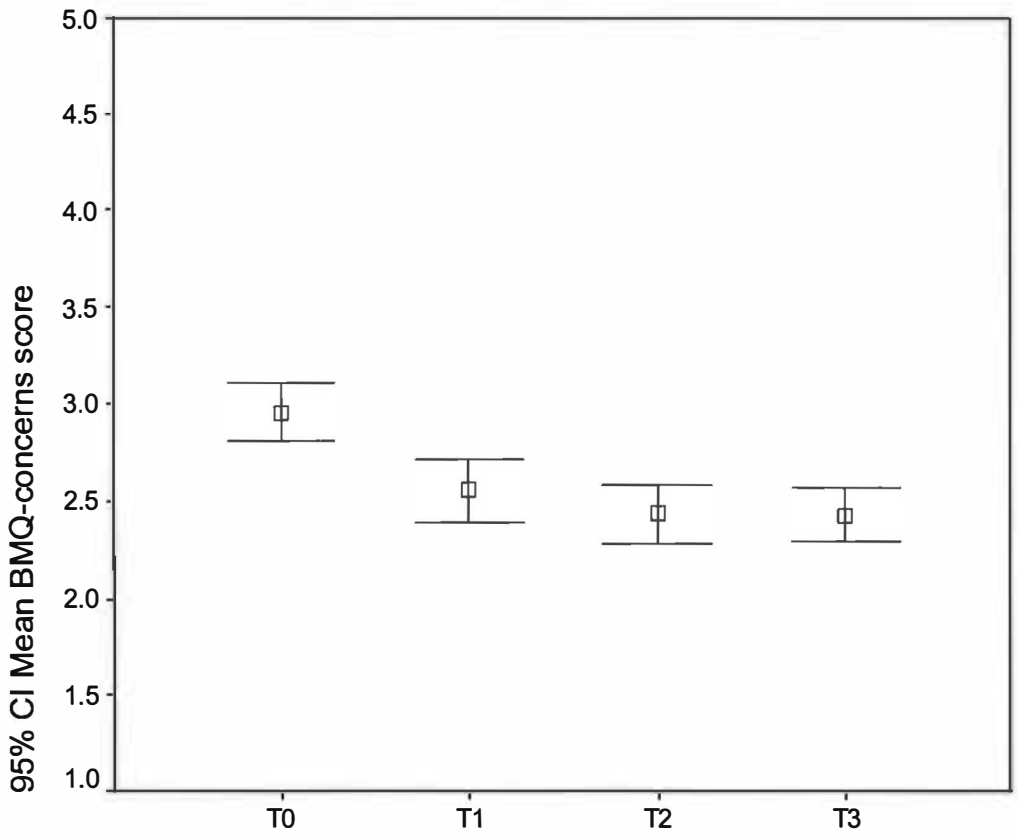
Figure 9.1: Perceptions of necessity over six months of taking HAART



9.4.4.1.2 BMQ-Concerns

There was a significant decrease in the strength of concerns about adverse effects of HAART over the follow-up period ($F(3,65) = 26.8$, $p<0.001$). The decline in concerns over time was independent of negative affect ($F(3, 63) = 11.3$, $p<0.001$). These results are illustrated in Figure 9.2. They show a dramatic decline in concerns scores between T0 and T1 ($t = 5.8$, $df = 66$, $p<0.001$) indicating that patients' concerns about taking HAART started to decrease almost as soon as they initiated treatment. There was also a significant decline in concerns between T1 and T2 ($t = 2.0$, $df = 66$, $p<0.001$). Level of concern about taking HAART remained consistent between T2 and T3 ($t = 0.4$, $df = 66$, $p>0.1$).

Figure 9.2: Concerns over six months of taking HAART



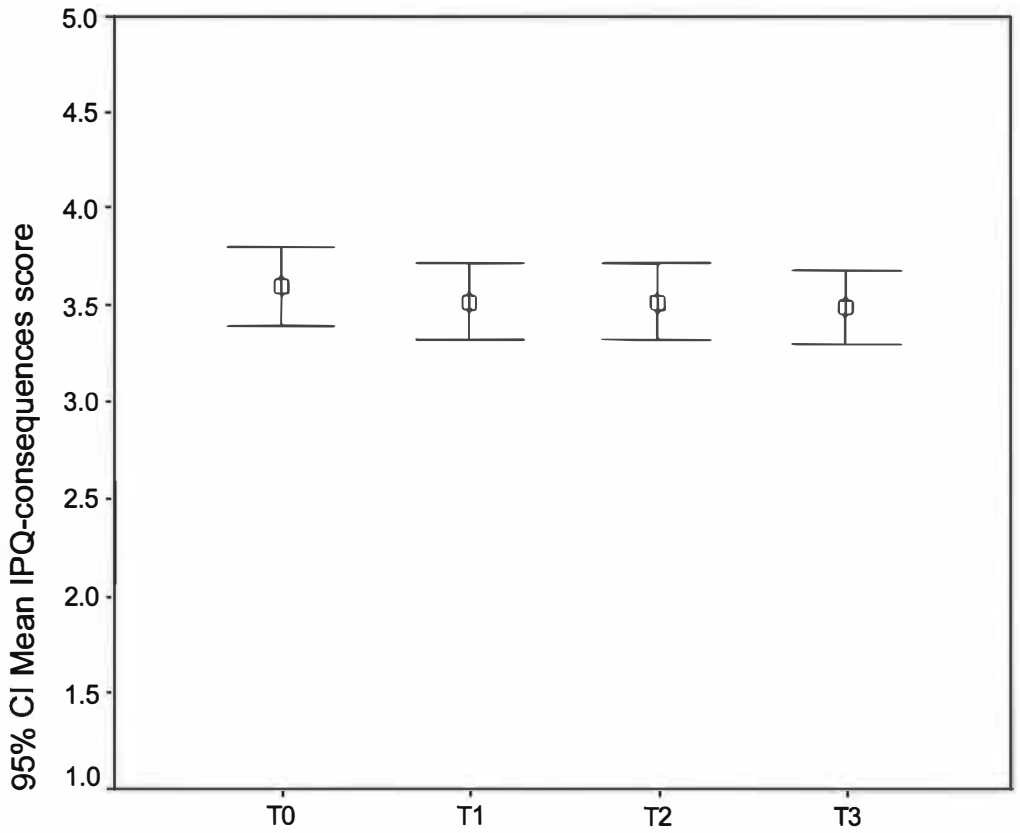
9.4.4.2 Illness perceptions

Hypothesis 1.2: There will be significant changes in perceptions of HIV over time

9.4.4.2.1 IPQ-Consequences

Patients' perceptions of negative personal consequences associated with HIV declined significantly over the first six months of treatment ($F(3, 65) = 3.0$, $p<0.05$). However this relationship no longer reached statistical significance when controlling for negative affect ($F(3, 63) = 1.5$, $p<0.1$). Figure 9.3 shows that scores declined between T0 and T1 and then remained constant over the rest of the follow-up. However, a series of paired t-tests failed to show significant changes in consequences scores between any of the individual time-points (all $p>0.1$).

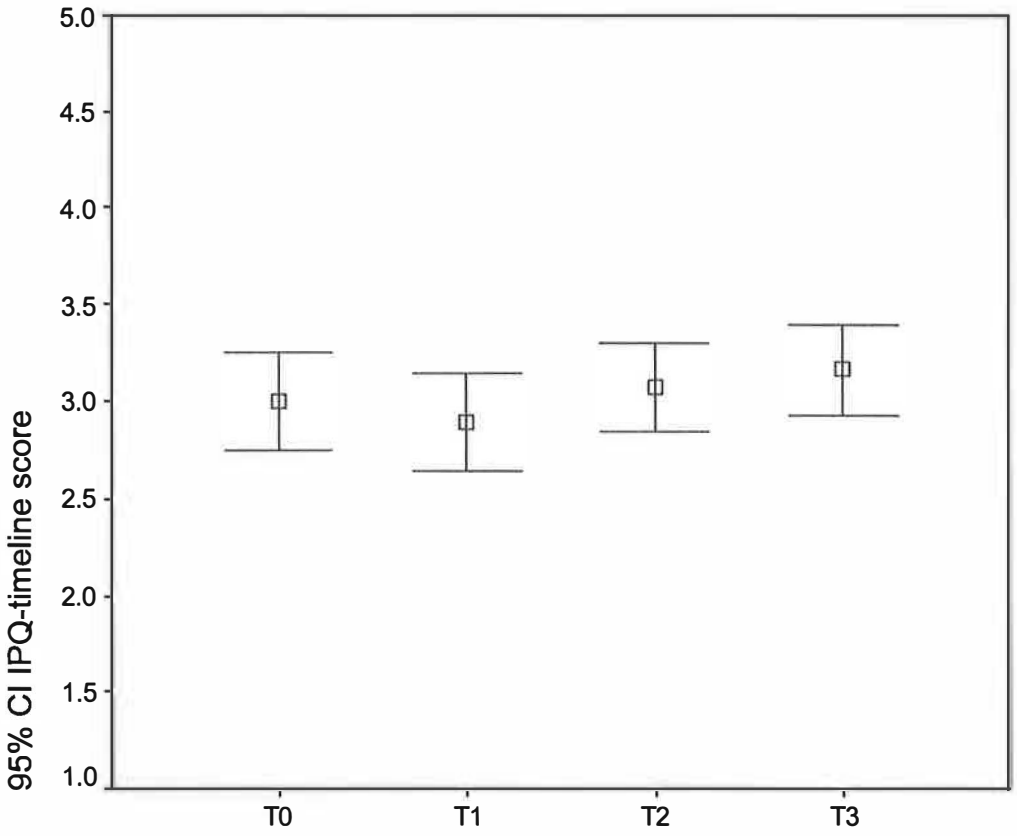
Figure 9.3: Perceptions of personal consequences associated with living with HIV over six months of HAART



9.4.4.2.2 IPQ-Timeline

Figure 9.4 shows the means and 95% confidence intervals for perceptions of timeline over the follow-up. Patients' perceptions that their HIV condition would not improve in time decreased between T0 and T1, then increased at T2 and T3. However, these changes were not statistically significant (all p>0.1).

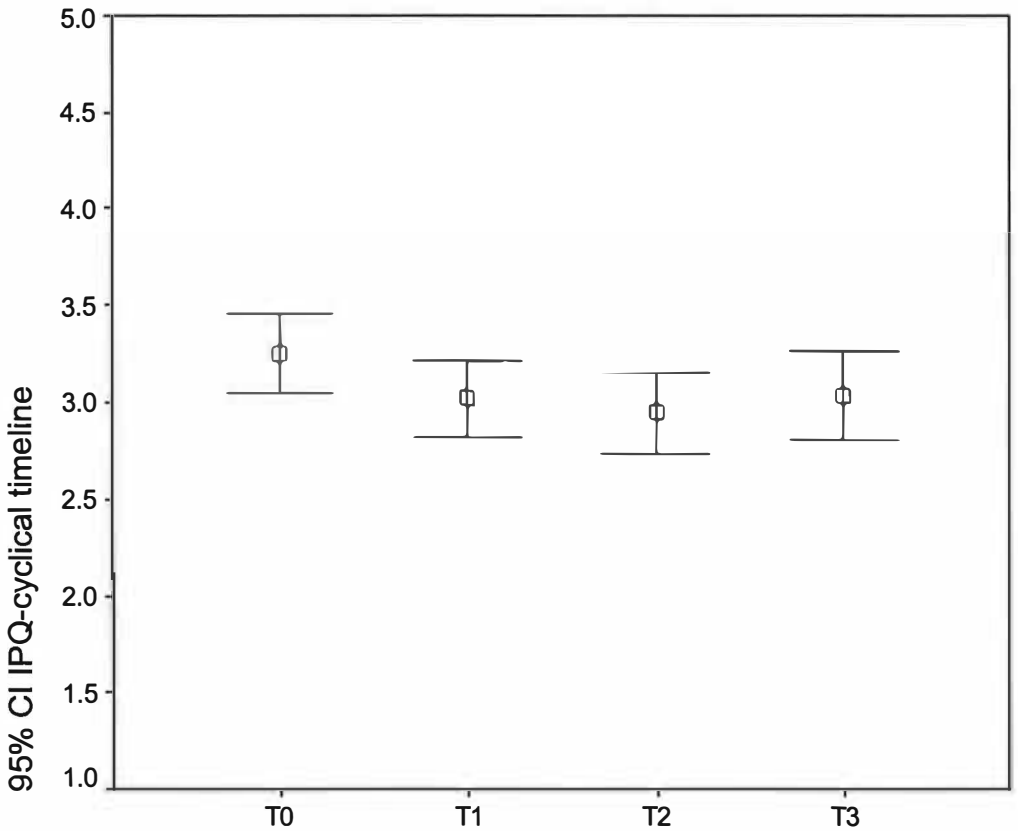
Figure 9.4: Perceptions of timeline over six months of HAART



9.4.4.2.3 IPQ-Cyclical timeline

There was a significant change in cyclical timeline scores over the follow-up period ($F(3,65) = 4.3$, $p<0.01$). The means for individual time-points are shown in Figure 9.5. Scores declined significantly between T0 and T1 ($t = 3.2$, $df = 66$, $p<0.01$) and between T1 and T2 and increased between T2 and T3, although these changes did not reach statistical significance (both $p>0.1$). The change in perceived cyclical timeline over the follow-up period was no longer statistically significant when negative affect was controlled in the analyses ($F(1,63 = 1.7$, $p>0.1$), suggesting patients with initial negative mood were more likely to experience a change in the extent to which they experienced a recurrence of symptoms over time.

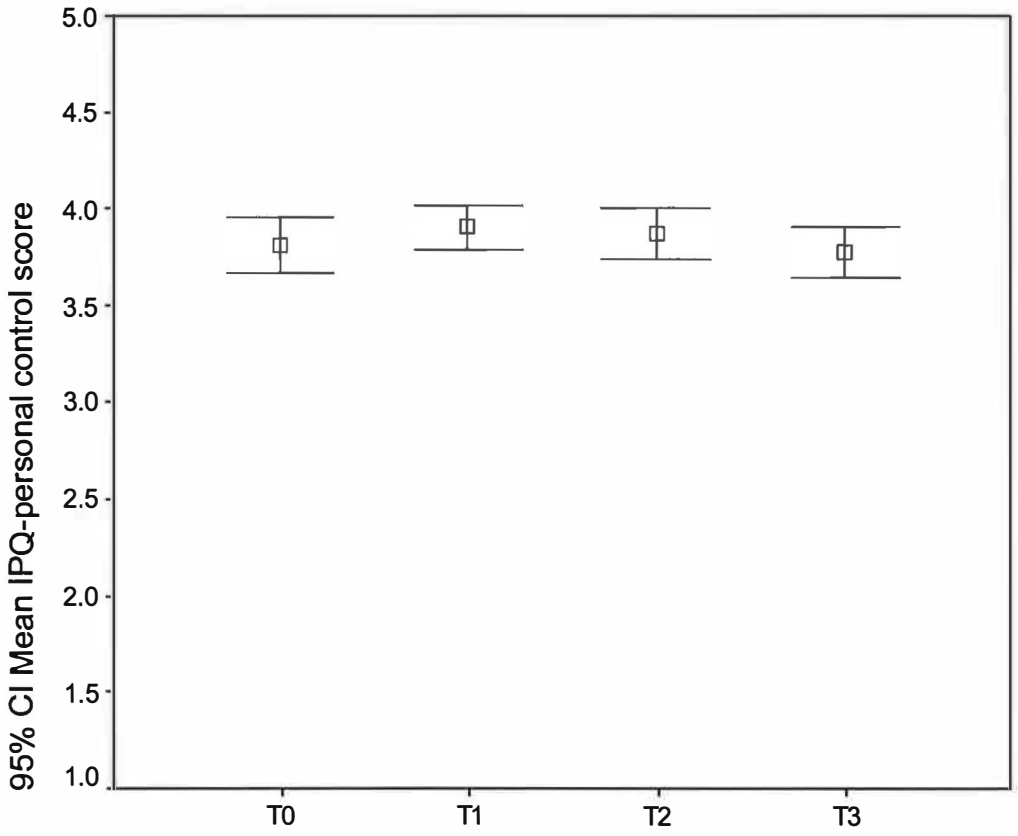
Figure 9.5: Perceptions of cyclical timeline over six months of HAART



9.4.4.2.4 IPQ-Personal control

The means and 95% confidence intervals for personal control are illustrated in Figure 9.6. There were no significant changes in patients' perceptions of the degree to which they had personal control their condition over the six months of follow-up ($F(3, 65) = 2.6$, $p > 0.1$).

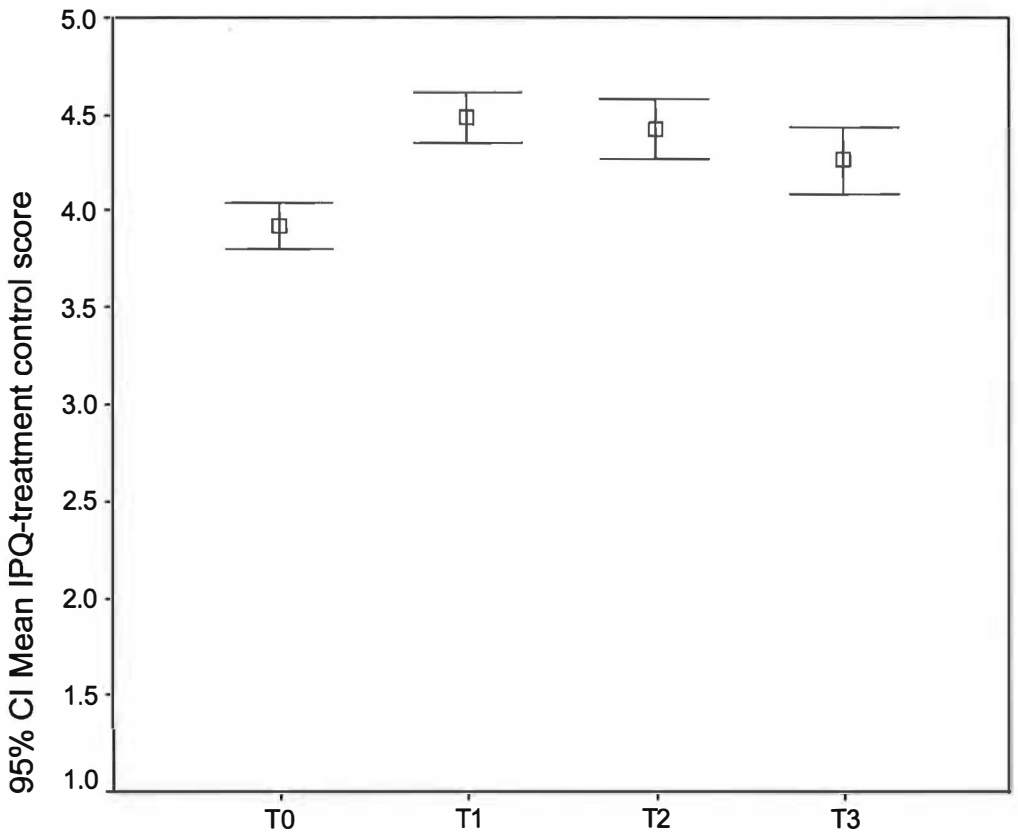
Figure 9.6: Perceptions of personal control over the progression of HIV over six months of HAART



9.4.4.2.5 IPQ-Treatment control

There was a significant increase in the strength of patients' perceptions that HIV could be controlled by treatment over follow-up ($F(3,65) = 20.0$, $p<0.001$). This relationship remained significant after controlling for negative affect ($F(3,63) = 9.2$, $p<0.001$). Figure 9.7 shows a sharp increase in perceptions of treatment control between the first month of taking HAART, and subsequent analyses showed that this increase reached statistical significance ($t = -9.9$, $df = 66$, $p<0.001$). The strength of patients' perceptions that HAART could effectively control the progression of their HIV-infection decreased between T1 and T2 (although this decrease was not statistically significant: $p>0.1$), and again between T2 and T3 ($t = 2.6$, $df = 66$, $p<0.01$).

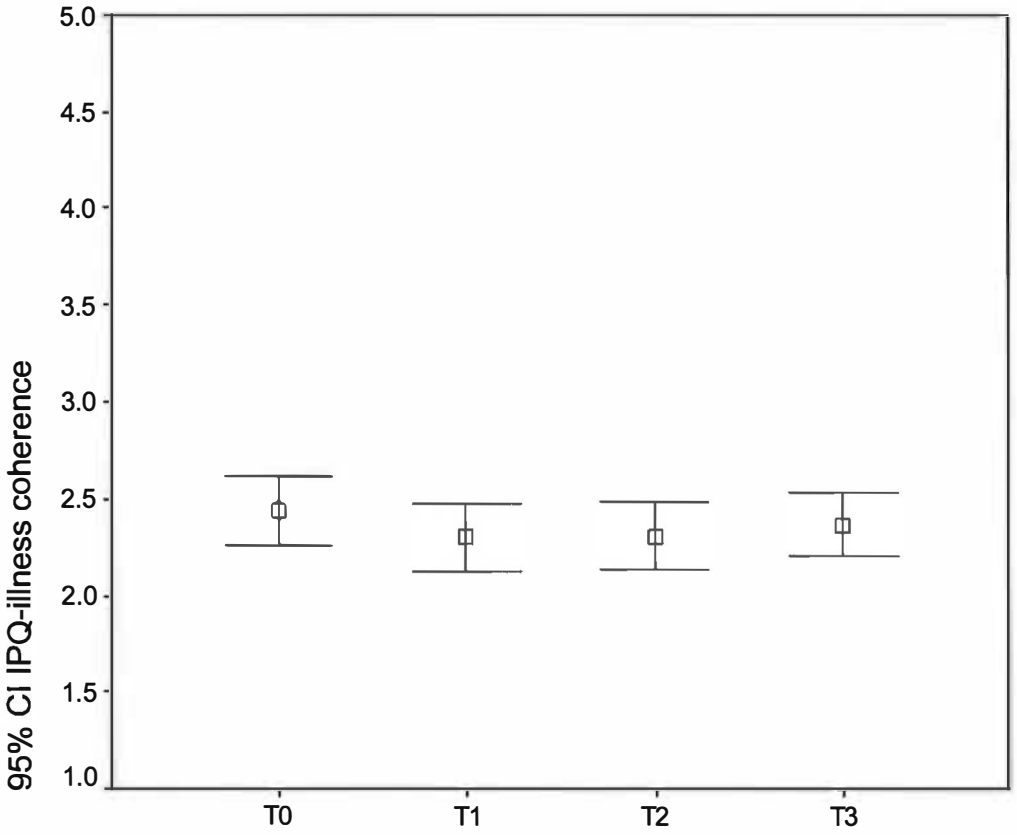
Figure 9.7: Perceptions of treatment control over six months of HAART



9.4.4.2.6 IPQ-Illness coherence

Figure 9.8 shows that perceptions of illness coherence declined over the first month of treatment, indicating that patients felt they had a greater understanding of their condition after a month of taking HAART. However, perceptions of illness coherence increased again between T2 and T3, indicating that the effect was short-lived. The magnitude of these changes in illness coherence over follow-up was not statistically significant ($F(3, 65) = 0.1$, $p>0.1$).

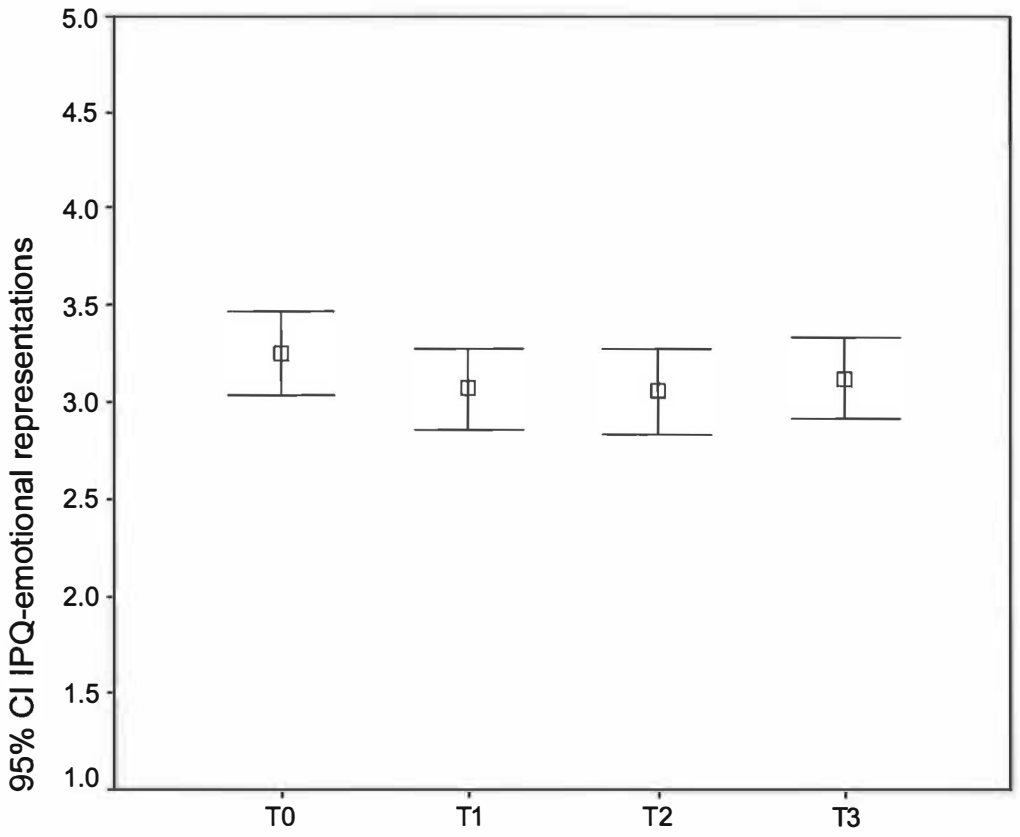
Figure 9.8: Perceptions of illness coherence over six months of HAART



9.4.4.2.7 IPQ-Emotional representations

Figure 9.9 shows that there was a decrease in perceived negative emotional representations over the first month of taking HAART, indicating that patients perceived a less negative emotional response to HIV after a month on treatment. However, results from the repeated measures ANOVA showed no significant changes in emotional representations of HIV over follow-up ($F(3,65) = 0.3$, $p>0.1$).

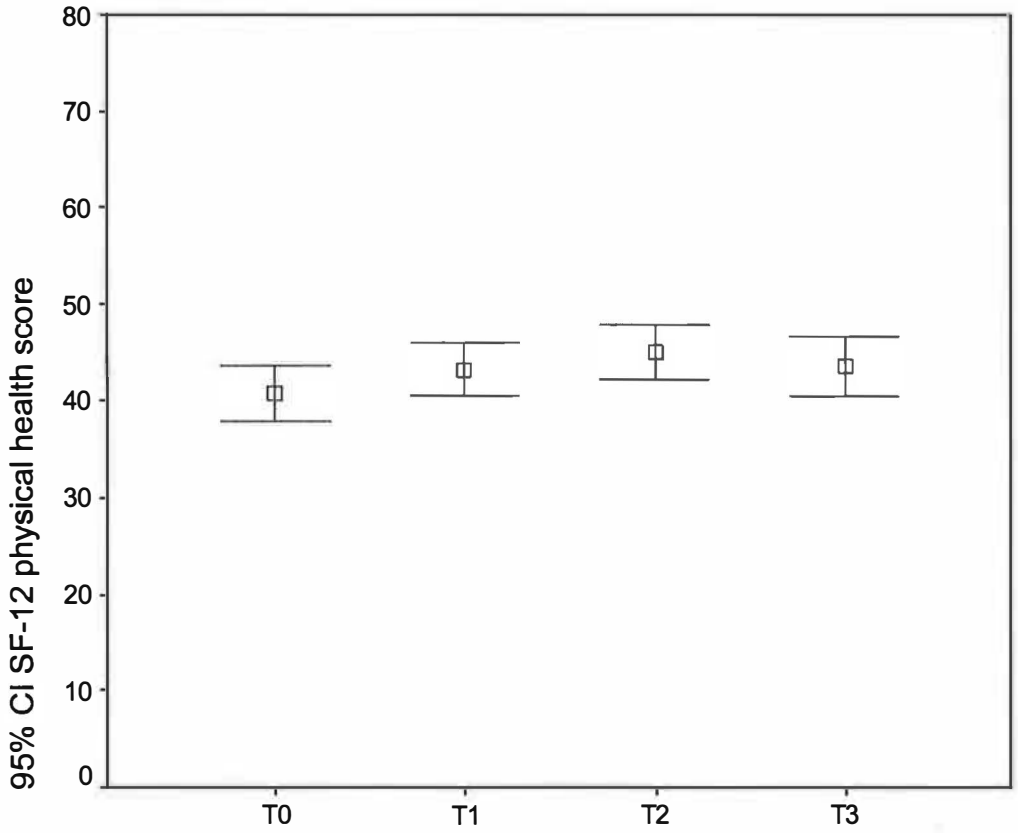
Figure 9.9: Emotional representations of HIV over six months of HAART



9.4.4.2.8 SF-12 Self-rated physical health

Figure 9.10 shows that patients' subjective ratings of their physical health increased between T0 and T1, and again between T1 and T2, before declining again between T2 and T3. However, changes in perceptions of physical health did not reach statistical significance ($F(3,65) = 1.9$, $p>0.1$).

Figure 9.10: Self-rated physical health over six months of HAART



9.4.5 Relationships between perceptions of HIV/HAART and adherence

9.4.5.1 Perception of HAART

Research question 2: Are patients' perceptions of HIV and beliefs about HAART associated with adherence?

Hypothesis 2.1: Beliefs about HAART will be associated with adherence. Specifically, low adherence will be associated with:

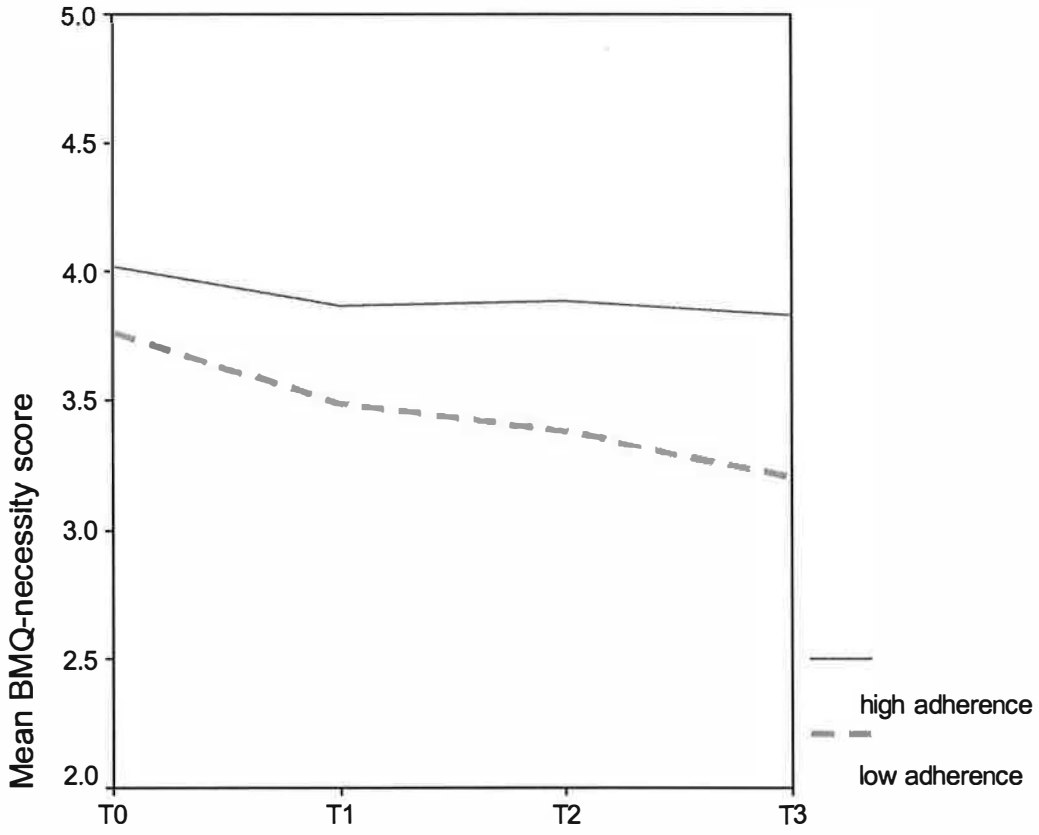
H2.1.1 Lower perceived *necessity* for treatment

H2.1.2 Stronger *concerns* about adverse effects of taking HAART

9.4.5.1.1 BMQ-Necessity

There was a significant main effect of adherence group on necessity beliefs ($F(1,65) = 9.6$, $p<0.005$). This relationship remained statistically significant after controlling for negative affect in the analysis ($F(1,63) = 10.2$, $p<0.005$). Figure 9.11 shows higher perceptions of personal necessity for HAART among those in the high adherence group at all time-points. A series of univariate ANCOVAs (controlling for negative affect) identified significant differences in necessity beliefs between high and low adherence groups at T1 ($F(1,63) = 5.0$, $p<0.05$), T2 ($F(1,63) = 8.6$, $p<0.005$) and T3 ($F(1,63) = 13.3$, $p<0.001$).

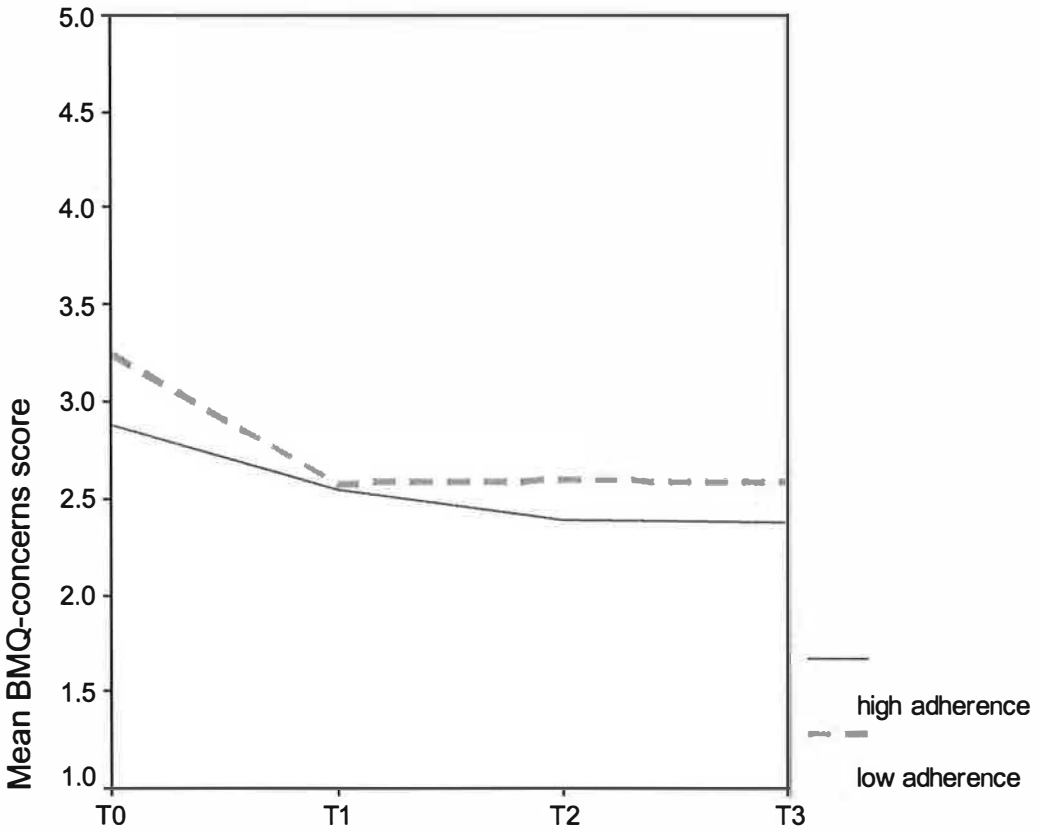
Figure 9.11: Mean necessity scores for high and low adherence groups over six months of taking HAART



9.4.5.1.2 BMQ-Concerns

Figure 9.12 shows concerns scores for high and low adherence groups across the four time-points. Although at all follow-ups concerns were stronger among those reporting low adherence, there was no main effect of group ($F(1,65) = 1.7$, $p>0.1$).

Figure 9.12: Mean concerns scores for high and low adherence groups over six months of taking HAART



9.4.5.2 Perception of HIV

Hypothesis 2.2: Perceptions of HIV will be associated with adherence. Specifically, low adherence will be associated with perceiving:

- **H2.2.1 Less severe personal consequences of having HIV**
- **H2.2.2 A more optimistic timeline**
- **H2.2.3 A less cyclical timeline**

H2.2.4 Greater perceived control over HIV

H2.2.5 Greater illness coherence

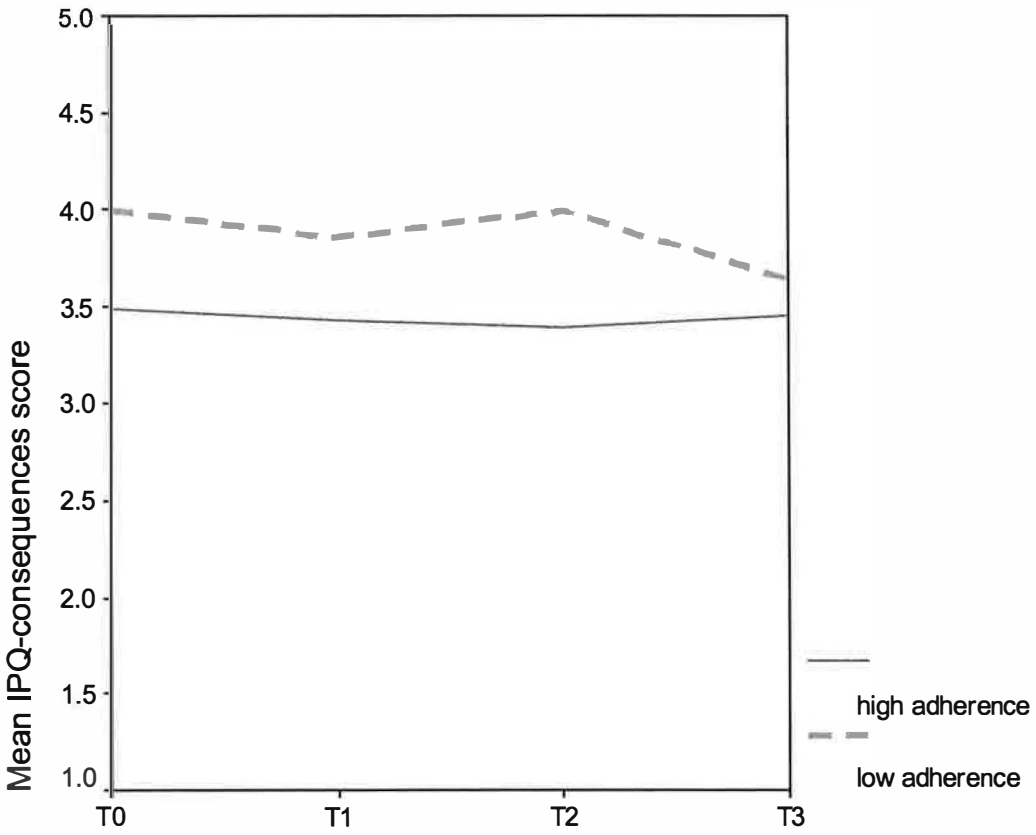
H2.2.6 A less negative emotional representation of HIV

H2.2.7 A more positive perception of physical health

9.4.5.2.1 IPQ-consequences

Figure 9.13 shows consequences scores for high and low adherence groups across the four time-points. Although the mean scores show that those in the low adherence group reported consistently higher scores, indicating that they perceived more negative personal consequences of living with HIV, there was no significant main effect of group ($F(1,65) = 3.8$, $p>0.05$).

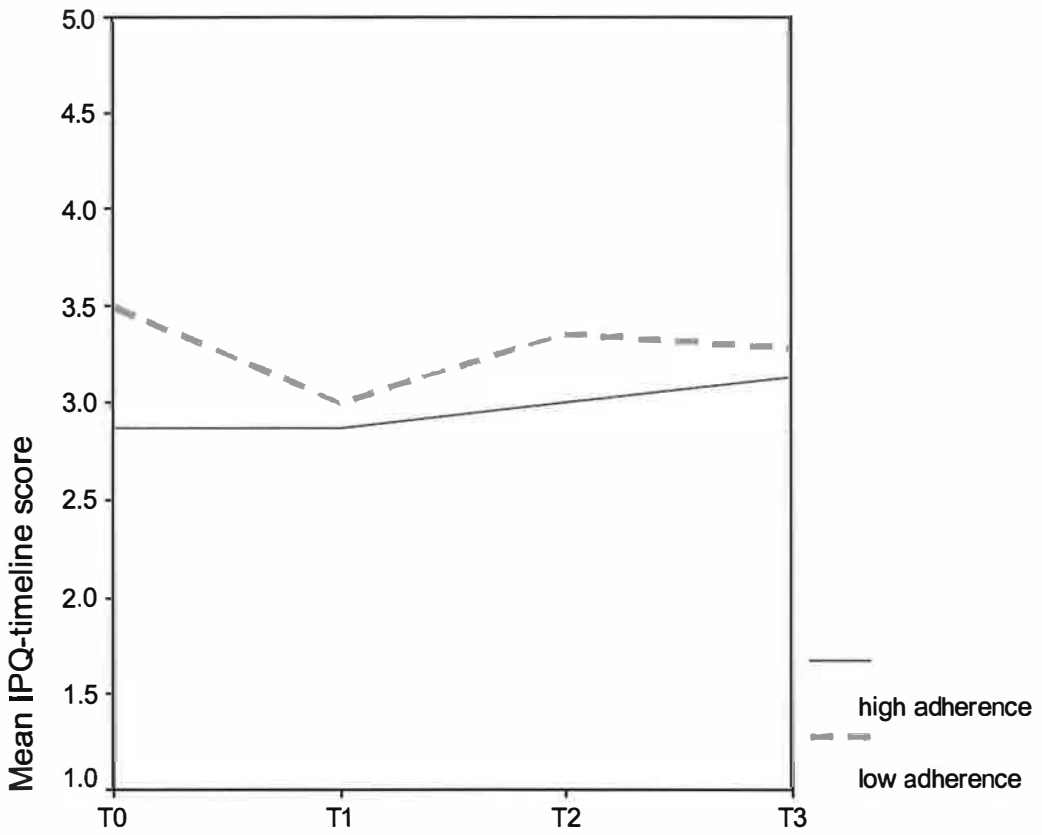
Figure 9.13: Mean IPQ-consequences scores for high and low adherence groups over six months of taking HAART



9.4.5.2.2 IPQ-timeline

Figure 9.14 shows timeline scores for high and low adherence groups across the four time-points. Scores for those in the low adherence group were consistently higher than scores for those in the high adherence group at each follow-up, indicating that those who were more pessimistic about their prognosis were more likely to report low adherence. However, there was no significant main effect of group on timeline scores ($F(1,65 = 1.6, p>0.1)$ indicating no significant effect of patients' perceptions of the degree to which their illness would improve in time on their adherence behaviour.

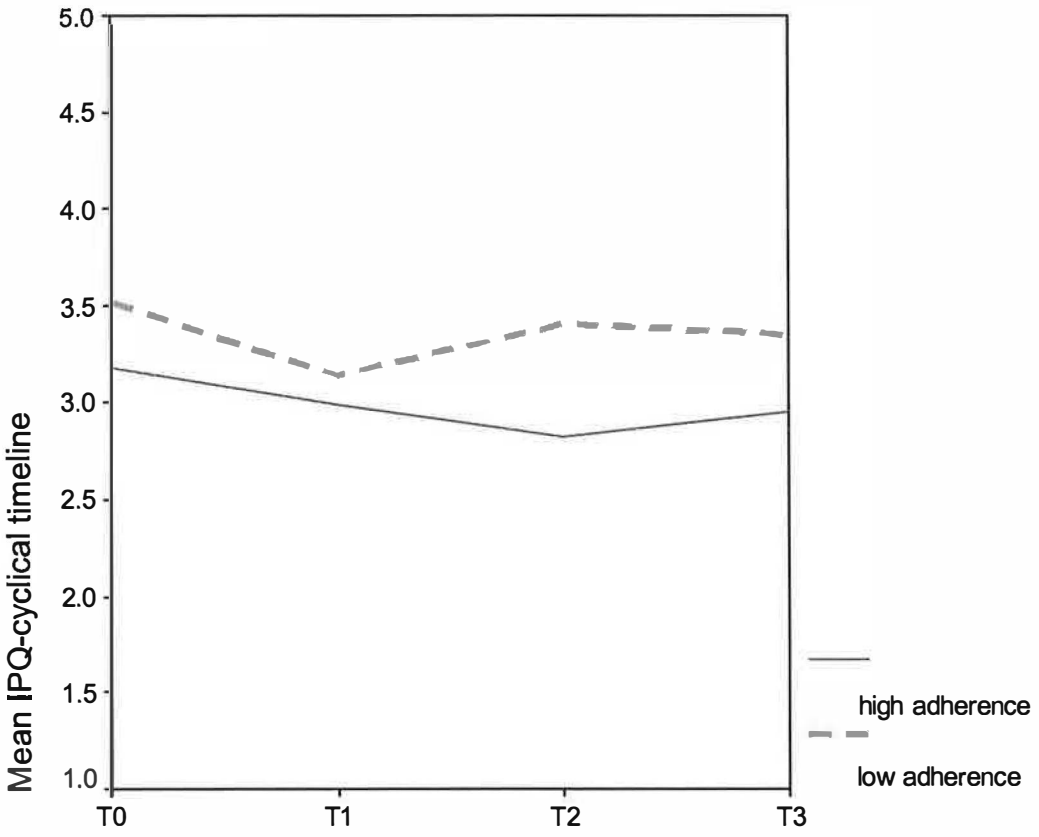
Figure 9.14: Mean IPQ-timeline scores for high and low adherence groups over six months of taking HAART



9.4.5.2.3 IPQ-cyclical timeline

Figure 9.15 shows cyclical timeline scores for high and low adherence groups across the four time-points. Scores for those in the low adherence group appeared to be higher than scores for those in the high adherence group at each follow-up, indicating that low adherence was associated with stronger perception that symptoms come and go in cycles. However, there was no significant main effect of group on cyclical timeline scores ($F(1,65 = 2.6, p>0.1)$).

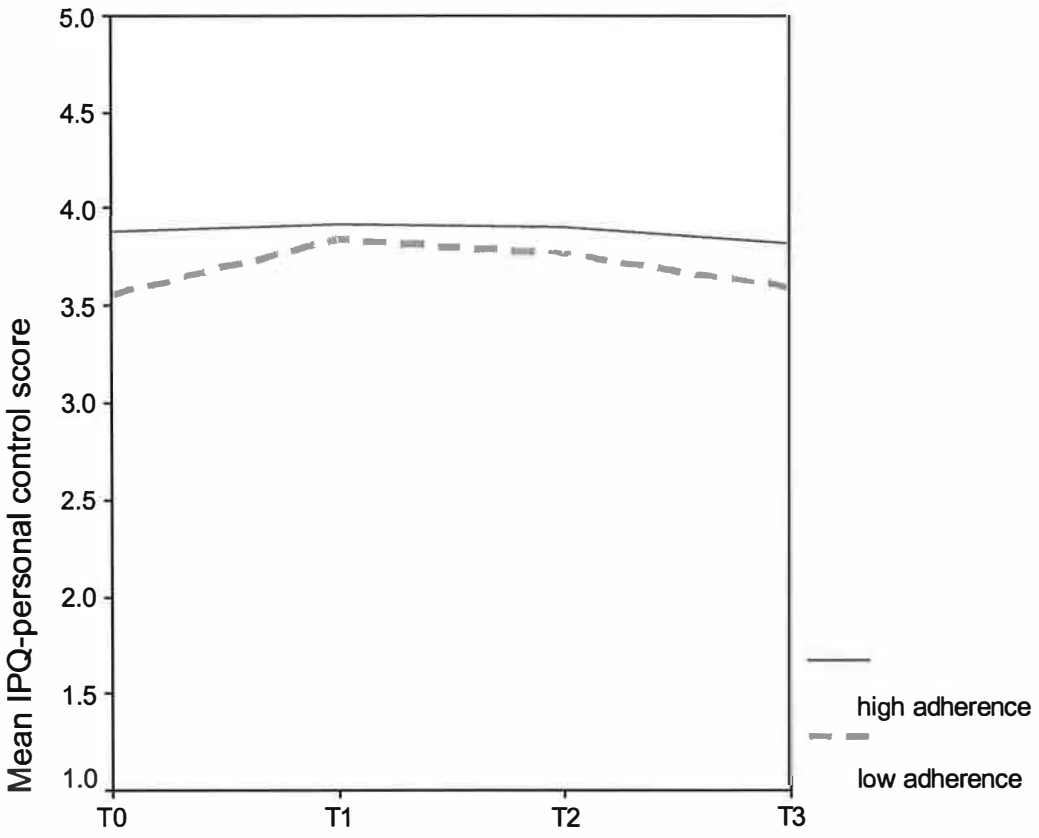
Figure 9.15: Mean IPQ-cyclical timeline scores for high and low adherence groups over six months of taking HAART



9.4.5.2.4 IPQ-personal control

Figure 9.16 shows personal control scores for high and low adherence groups across the four time-points. Although scores for those in the high adherence group appear slightly higher than those for participants in the low adherence group, there was no significant main effect for group across the follow-up (F (1, 65) = 2.2, $p>0.1$), indicating that adherence was not significantly related to patients' perceptions of the degree to which they were able to control the progress of their condition.

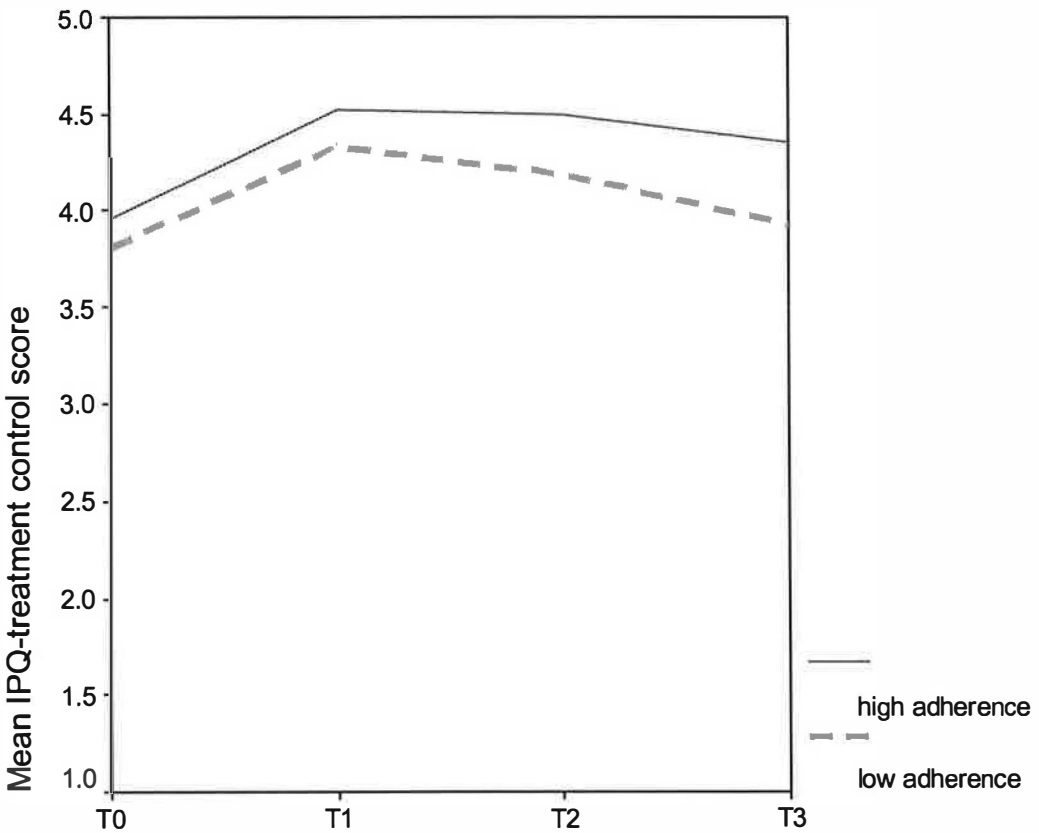
Figure 9.16: Mean IPQ-personal control scores for high and low adherence groups over six months of taking HAART



9.4.5.2.5 IPQ-treatment control

Figure 9.17 shows treatment control scores for high and low adherence groups across the four time-points. Those in the low adherence group reported lower treatment control scores at all time-points. There was a significant main effect of group ($F(1,65) = 3.1$, $p<0.05$). A series of independent t-tests showed that only the difference between high and low adherence groups at T3 was significant ($t = 2.0$, $df = 65$, $p<0.05$). The results indicate that participants reporting low adherence were less convinced that HAART was effective in controlling the progression of HIV. However, this relationship no longer reached statistical significance with controlling for negative affect in the analyses ($F(1, 63) = 0.7$, $p>0.1$).

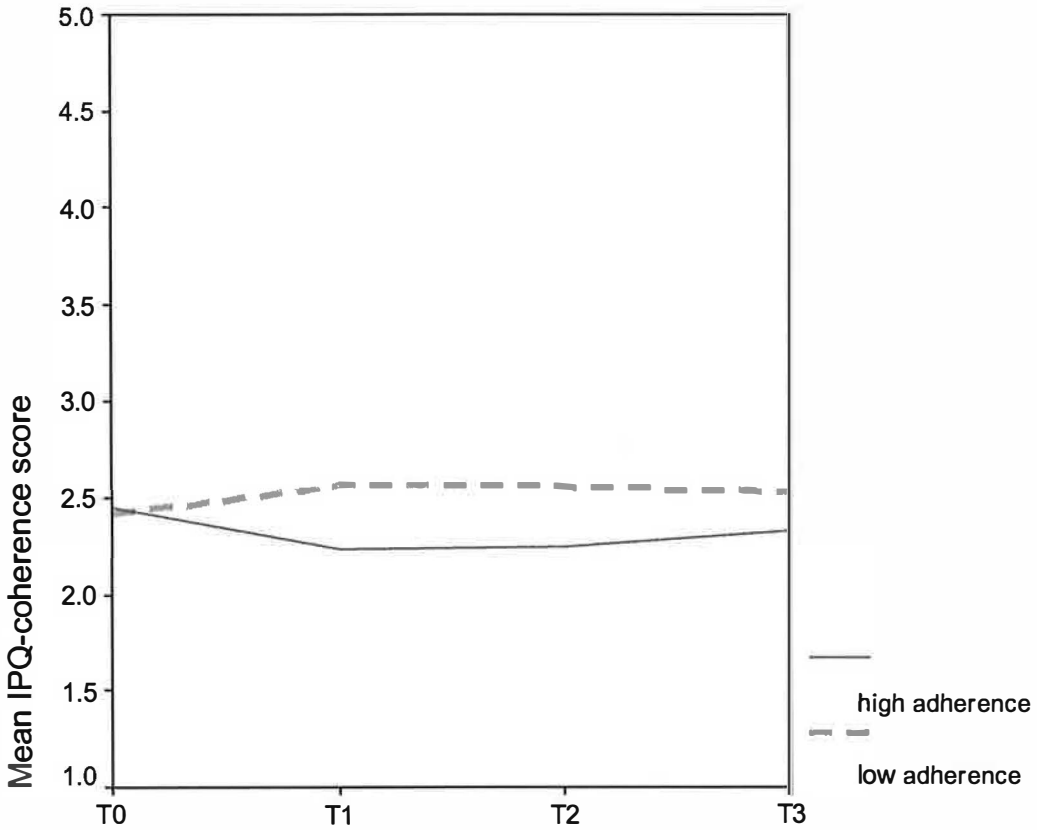
Figure 9.17: Mean IPQ-treatment control scores for high and low adherence groups over six months of taking HAART



9.4.5.2.6 IPQ-illness coherence

Figure 9.18 shows illness coherence scores for high and low adherence groups across the four time-points. Scores for those in the low adherence group appeared to be higher than those for participants in the high adherence group. However, there was no significant main effect on group ($F(1, 65) = 1.1$, $p>0.1$), indicating that adherence was not associated with patients' perceptions of the degree to which they held a coherent picture of their condition.

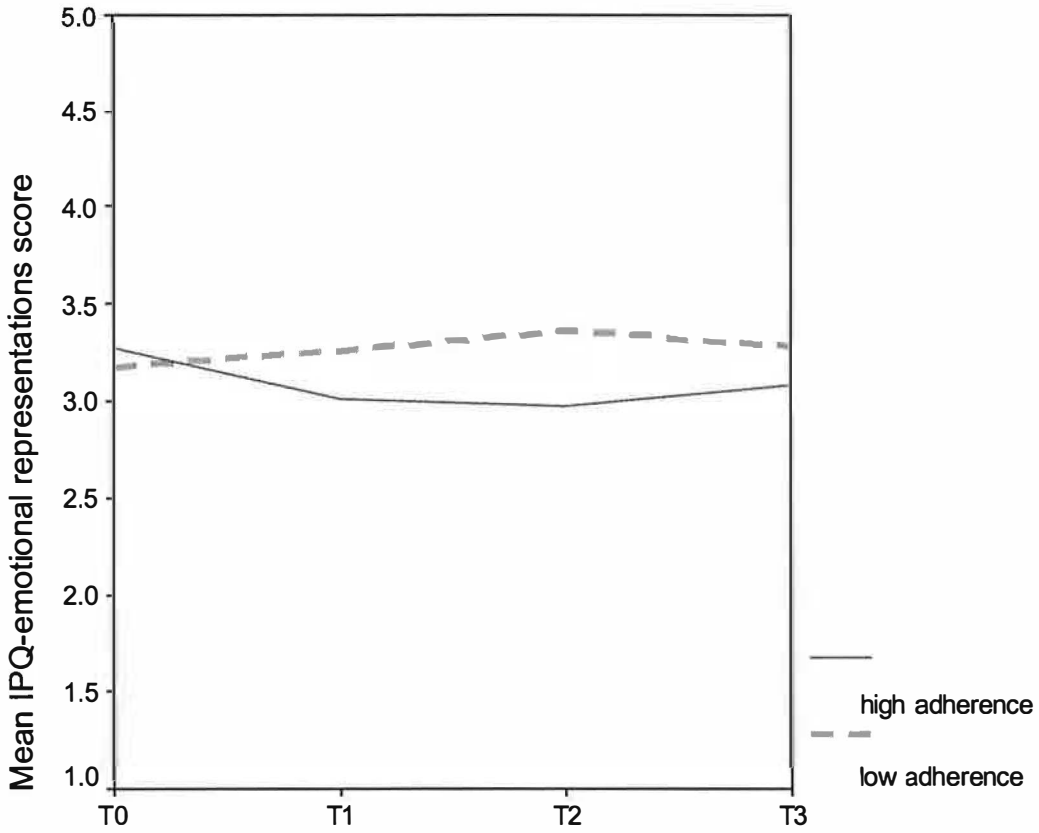
Figure 9.18: Mean IPQ-illness coherence scores for high and low adherence groups over six months of taking HAART



9.4.5.2.7 IPQ-emotional representations

Figure 9.19 shows emotional representations scores for high and low adherence groups across the four time-points. Scores for those in the low adherence group appear slightly higher than those for participants in the high adherence group, however there was no significant main effect for group across the follow-up ($F(1, 65) = 0.6$, $p>0.1$). The results indicate that adherence was not associated with the degree to which patients held a negative emotional representation of HIV.

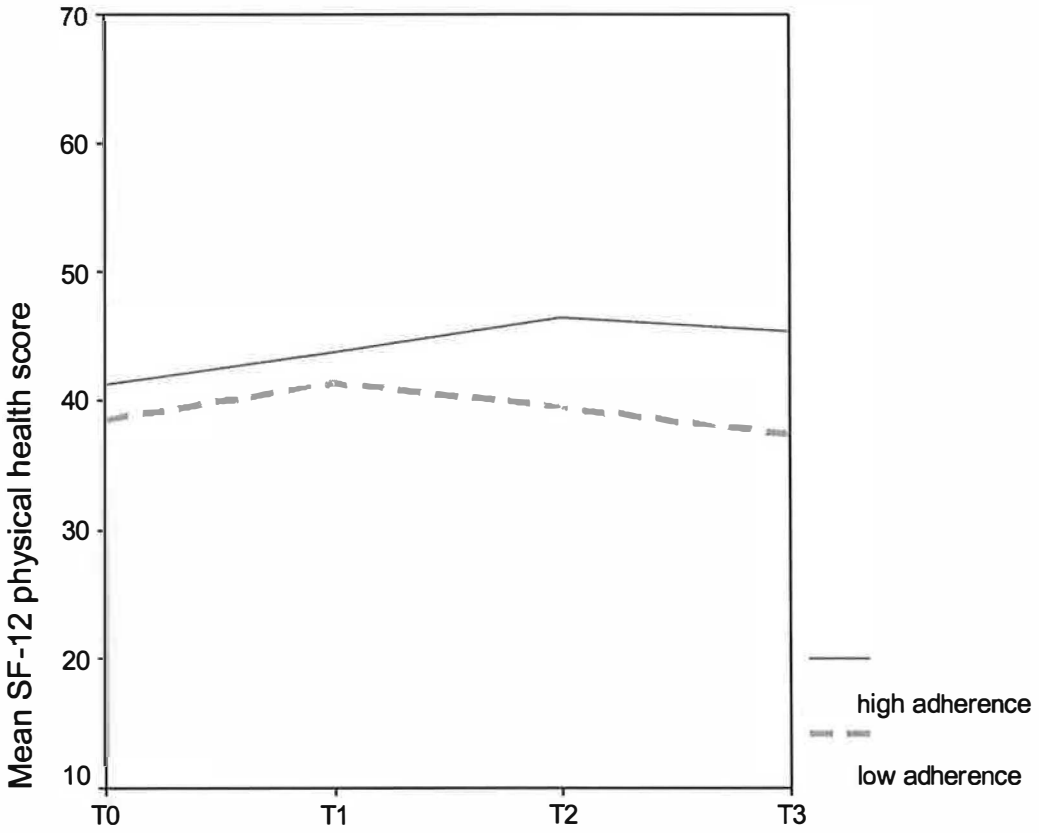
Figure 9.19: Mean IPQ-emotional representations scores for high and low adherence groups over six months of taking HAART



9.4.5.2.8 SF-12 Self-rated physical health

Figure 9.20 shows perceptions of physical health for high and low adherence groups across the four time-points. Patients reporting low adherence consistently rated their physical health as lower than those for participants in the high adherence group. However, the results of the ANOVA showed no significant main effect for group across the follow-up ($F(1, 65) = 0.6$, $p>0.1$), indicating that adherence was not associated with patients' subjective perceptions of their physical well-being.

Figure 9.20: Mean SF-12 physical health scores for high and low adherence groups over six months of taking HAART



9.4.6 Relationships between changes in perceptions of HIV/HAART and adherence

Research question 3: Are *changes* in patients' perceptions of HIV and beliefs about HAART over six months of treatment associated with adherence?

9.4.6.1 Changes in beliefs about HAART over time and adherence

Changes in beliefs about HAART over the entire follow-up were assessed using the repeated measures ANOVA shown in Table 9.7. This shows interaction effects between adherence group and time, thus indicating where the pattern of change over time differed significantly for participants reporting high adherence and those reporting low adherence.

Hypothesis 3.1: Changes in beliefs about HAART over the first six months of treatment will be associated with adherence. Specifically:

H3.1.1: Low adherence will be associated with a greater decline in *necessity* beliefs

H3.1.2: High adherence will be associated with a greater decline in *concerns*

There was a significant interaction between necessity beliefs and adherence ($F(1,65) = 4.5$, $p<0.05$), which remained significant when controlling for negative affect in the analyses ($F(1, 63) = 5.0$, $p>0.05$). This indicates that the pattern of results over time was different for those in the high adherence and those in the low adherence groups. Visual inspection of the mean necessity scores over the four follow-ups (Figure 9.11) suggests a steeper decline in perceived need for HAART among those in the low adherence group. Friedman Tests were conducted to explore changes over the four time-points within high adherence and low adherence groups. They confirmed that the decline in necessity beliefs over follow-up reached statistical significance within the low adherence group ($\chi^2 = 10.4$, $df = 3$, $p<0.05$) but not within the high adherence group ($\chi^2 = 3.7$, $df = 3$, $p>0.1$).

Visual inspection of mean concerns scores across time (Figure 9.12) shows a decline in concerns about negative affects of taking HAART across the first month of treatment,

especially among those in the low adherence group. However, the results of the repeated measures ANOVA show no interaction between group and concerns when all four time-points were included in the analyses ($F(1,65) = 0.4$, $p>0.1$). This indicates that the decline in concerns over time was similar for high and low adherence groups.

9.4.6.2 Changes in perceptions of HIV over time and adherence

Hypothesis 3.2: Changes in perceptions of HIV over the first six months of treatment will be associated with adherence.

The general expectation was that increases in perceived control over HIV (treatment control and personal control) would be associated with high adherence while increases in consequences, timeline, cyclical timeline, emotional representations and illness coherence would be associated with low adherence. It was also expected that a decline in self-rated health over time would be associated with low adherence.

Table 9.7 shows interaction effects between group and time. There were no significant interactions between adherence and perceptions over time for any of the IPQ illness perceptions or self-rated health. These findings indicate that the pattern of change in illness perceptions over time does not differ significantly between high and low adherence groups. The results suggest that changes in illness perceptions over the treatment process are not significant independent predictors of adherence.

Having established that changes in beliefs about personal necessity HAART, but not changes in perceptions of HIV, influenced adherence, the next step was to identify predictors and correlates of changes in beliefs about personal necessity for HAART. This section looks at whether changes in necessity beliefs over the treatment process were related to perceptions of HIV in a way consistent with the eSRM (Horne, 1997, 2003).

9.4.7 Predictors of change in beliefs about HAART over time

9.4.7.1 Relationships between changes in necessity and perceptions of HIV over time

Research question 4: Are changes in perceptions of personal necessity for HAART over the treatment process associated with changes in perceptions of HIV in a way that is consistent with the extended SRM?

Hypothesis 4.1: Reporting a decrease in perceptions of personal necessity for HAART across the treatment process will be associated with an increase in negative perceptions of HIV (symptoms related to HIV and HAART, consequences, timeline, cyclical timeline, illness coherence and emotional representations) and a decrease in perceptions of control over HIV (treatment control and personal control). It is also expected that self-rated health will decline as perceptions of necessity decline.

Partial correlations showing relationships between change in necessity beliefs and illness perceptions are shown in Table 9.8.

9.4.7.1.1 HIV-related symptoms

There was a significant negative correlation between change in necessity beliefs between T0 and T3 and the frequency of moderate to severe HIV symptoms at T3 (r_p = -0.23, $p<0.05$), indicating that those who experienced a greater decline in perceptions of need for HAART over time were experiencing a greater number of symptoms at six months. However, this relationship no longer reached statistical significance after controlling for the influence of HIV symptoms at baseline (r_p= -0.16, $p>0.05$), suggesting that rather than being the result of perceiving a lack of improvement in symptoms over time, the observed decline in perceptions of necessity over time may have been influenced by pre-treatment HIV-related symptomatology.

9.4.7.1.2 HAART-related symptoms

The frequency of moderate to severe HAART-related symptoms reported at T3 was not significantly correlated with change in necessity from T0-T3 (r_p = -0.20, p>0.05). However, the relationship gained statistical significance when the influence of HAART-related symptoms reported at T1 was controlled in the analyses (r_p = -0.27, p<0.05). This suggests a causal relationship between reporting a higher frequency of HAART-related symptoms after six months of treatment and a decline in necessity beliefs, where patients who perceived a lack of improvement in the symptoms they associated with their treatment over six months were more likely to report a decline in their perceived need for treatment.

9.4.7.1.3 Consequences

Experiencing a decline in perceptions of personal necessity for HAART over time was not associated with perceived personal consequences associated with HIV at six months, nor with the evolution of consequences between T0 and T3 .

9.4.7.1.4 Timeline

The degree to which participants perceived that their condition would improve in time was not related to the decline in necessity beliefs at six months, or to changes in perceptions of timeline over time.

9.4.7.1.5 Cyclical timeline

There was a significant negative correlation between the perception that symptoms were cyclical in nature at T3 and necessity beliefs (r_p = -0.23, p<0.05), indicating that a decrease in necessity beliefs was associated with a stronger perception that symptoms were cyclical in nature. This relationship remained statistically significant when controlling for cyclical timeline scores at baseline (r_p = -0.23, p<0.05), suggesting a dynamic relationship between perceived necessity and perceptions of the degree to which symptoms come and go in cycles.

9.4.7.1.6 Personal control and treatment control

There was a significant positive correlation between the evolution of necessity beliefs over time and perceptions of both personal control (r_p = 0.22, $p<0.05$) and treatment control (r_p = 0.39, $p<0.001$) at T3. The direction of these correlations indicate that those who perceived they had more control over their condition after six months of treatment were less likely to have experienced a decline in necessity beliefs between T0 and T3. Both relationships remained significant when perceptions of control at baseline were controlled in the analyses (personal control: r_p = 0.21, $p<0.05$; treatment control: r_p= 0.34, $p<0.001$). The results suggest that rather than being driven by beliefs prior to initiating HAART, there was a dynamic relationship between the evolution of control beliefs and the evolution of necessity beliefs over time, where an increase in perceptions of necessity for HAART was related to an increase in perceptions of control over HIV.

9.4.7.1.7 Illness coherence

Illness coherence at T3 was not significantly correlated with the change in necessity beliefs between T0 and T3 (r_p = -0.12, $p>0.1$). However, this relationship became statistically significant when coherence scores at baseline were controlled in the analysis (r_p = -0.26, $p<0.05$). This indicates that experiencing a decrease in perceived necessity for HAART was associated with a decline in perceived coherence between T0 and T3.

9.4.7.1.8 Emotional representations

Neither emotional representations of HIV at six months (r_p = 0.12, $p>0.1$), nor the evolution of emotional representations over time (r_p = 0.10, $p>0.1$) were significantly associated with the evolution of necessity beliefs over time.

9.4.7.1.9 Self-rated health

There was a significant positive correlation between patients' perceptions of their physical health at six months and the evolution of necessity beliefs between T0 and T3 (r_p = 0.23, $p<0.05$), indicating that those who perceived themselves to be more healthy after six months of treatment were less likely to have experienced a decline in necessity beliefs over the

preceding six months. However, this relationship did not retain statistical significance after controlling for perceptions of physical health at baseline (r_p= 0.10, p>0.1), suggesting that the relationship was not independent of patients' perceptions of their physical health before initiating treatment.

Table 9.8: Partial correlations showing relationships between change in necessity beliefs and illness perceptions

	Δ necessity		Δ necessity controlling for T0 illness perceptions	
	r_p	p	r_p	p
HIV symptoms	**-0.23**	**<0.05**	-0.16	>0.05
HAART symptoms*	-0.20	>0.05	**-0.27**	**<0.05**
Consequences	0.03	>0.1	0.03	>0.1
Timeline	-0.15	>0.1	-0.18	>0.05
Cyclical timeline	**-0.23**	**<0.05**	**-0.23**	**<0.05**
Personal control	**0.22**	**<0.05**	**0.21**	**<0.05**
Treatment control	**0.39**	**<0.001**	**0.34**	**<0.005**
Coherence	-0.12	>0.1	**-0.26**	**<0.05**
Emotional representations	0.12	>0.1	-0.08	>0.1
Self-assessment of physical health	**0.23**	**<0.05**	0.10	>0.1

9.4.7.2 Relationships between changes in necessity and clinical variables over time

Partial correlations showing relationships between change in necessity beliefs and clinical variables are shown in Table 9.9.

Table 9.9: Partial correlations showing relationships between change in necessity beliefs and clinical variables

	Δ necessity		Δ necessity controlling for T0 clinical variables	
CD4 count	0.02	>0.1	0.09	>0.1
Viral load	**-0.31**	**<0.01**	**-0.32**	**<0.01**
Previous use of antiretrovirals	-0.26	<0.05	N/A	N/A

CD4 count was not related to the evolution of necessity scores over time. There was a significant negative correlation between viral load at T3 and the evolution of perceived necessity for HAART between T0 and T3 (r_p = -0.31, p<0.01). This relationship remained statistically significant when controlling for the possible influence of viral load at baseline (r_p = -0.32, p<0.01) and suggests that a decrease in perceptions of necessity over time is related to a worse clinical outcome after six months on HAART. It is likely that adherence to HAART mediates this relationship. This hypothesis is tested below.

9.4.7.2.1 Adherence as a mediator between decreased necessity and viral load

Hypothesis: Adherence to HAART mediates the relationship between decreased necessity over time and clinical outcome after six months on HAART

The four steps of this mediational analysis are shown below:

1. Experiencing an increase in viral load between baseline and six months was associated with a decline in necessity beliefs over time (r_p = -0.32, p<0.01)
2. Low adherence at six months was significantly associated with a decrease in perceived necessity for HAART over time (r_p =-0.36 , p<0.005)
3. Experiencing an increase in viral load between baseline and six months was associated with low adherence at six months (r_p = 0.41, p<0.001)
4. When controlling for adherence at six months, the relationship between decreased necessity and increased viral load was no longer statistically significant (r_p -0.18, p>0.1)

These results indicate that adherence mediates the relationship between a decline in necessity beliefs and sub-optimal clinical outcome.

There was also a significant negative correlation between the evolution of necessity scores and having previously been prescribed antiretroviral treatment (r_p = -0.26, p<0.05). The direction of this relationship shows that patients who had previously been prescribed antiretroviral treatment were more likely than those who were previously naïve to antiretroviral

treatment to report a decline in their perceptions of personal need for HAART over the follow-up.

9.4.8 Mediators of the relationship between change in necessity and adherence

Research question 5: Do perceptions of HIV mediate relationships between beliefs about personal necessity for HAART and adherence in line with hypotheses driven by the eSRM?

Illness perceptions that were associated with both adherence and change in necessity (HAART related symptoms and treatment control beliefs) were chosen as candidates for the mediational analyses.

Hypothesis 5.1 The relationship between changes in perceptions of necessity for HAART and adherence will be mediated by changes in:

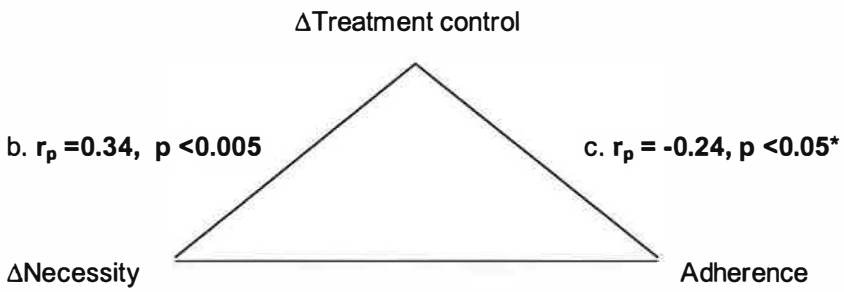
H5.1.1 Perceptions of treatment control

H5.1.2 Perceptions of HAART-related symptoms

9.4.8.1 Perceptions of treatment control

The results of this mediational analysis are shown in Figure 9.21.

Figure 9.21 Change in perceptions of treatment control as a mediator of the relationship between necessity and adherence



** because adherence is a dichotomous variable, r is a point bi-serial correlation*

a. ΔNecessity was significantly related to adherence (r_p = -0.41, p <0.001)

b. ΔNecessity was significantly associated with Δtreatment control (r_p =0.34, p <0.005)

c. ΔTreatment control was significantly associated with adherence (r_p = -0.24, p <0.05)

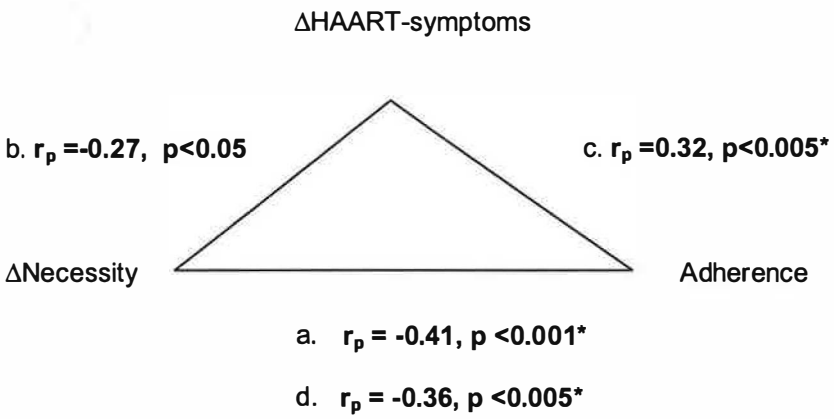
d. When controlling for treatment control, the relationship between Δnecessity and adherence remained significant (r = -0.34, p<0.005).

This indicates that the relationship between experiencing a decline in necessity over time and adherence is not mediated by changes in perceptions of treatment control.

9.4.8.2 Perceptions of HAART-related symptoms

The results of this mediational analysis are shown in Figure 9.22.

Figure 9.22 Change in experience of HAART-related symptoms as a mediator of the relationship between necessity and adherence



** because adherence is a dichotomous variable, r is a point bi-serial correlation*

a. ΔNecessity was significantly related to adherence (r_p = -0.41, p <0.001)

b. ΔNecessity was significantly related to ΔHAART symptoms (r_p =-0.27, p <0.005)

c. ΔHAART symptoms was significantly related to adherence (r_p = -0.32, p <0.005)

d. When controlling for ΔHAART symptoms, the relationship between Δnecessity and adherence remained significant (r = -0.36, p<0.005).

This indicates that the relationship between experiencing a decline in necessity and adherence is not mediated by patients' experiences of HAART-related symptoms.

9.5 Discussion

The process of change in perceptions of illness and beliefs about HAART over time and in response to medical procedures and interventions is central to self-regulation models, yet has received very little empirical investigation to date. This part of the thesis used a prospective, longitudinal design to explore how patients' perceptions of HIV and HAART changed over the first six months of treatment and to determine whether these changes were related to adherence. The results are discussed first in relation to beliefs about HAART and second in relation to perceptions of HIV.

9.5.1 The impact of changes in beliefs about HAART over time on adherence

9.5.1.1 Necessity

Mean scores for BMQ variables were compared across baseline, one-month, three-month and six-month follow-ups. For the group as a whole, there were significant changes in beliefs about HAART over the treatment process, with a significant decline in both beliefs about personal necessity for HAART and concerns about potential adverse effects over time.

Scores on the necessity scale were high before patients initiated HAART, but there was a significant decline in their perceptions of need over time. This decline in perceived necessity for HAART over time indicates that patients' models of their personal necessity for HAART differ from the current medical opinion that continued use HAART is necessary for clinical success. Although research is currently underway into the feasibility of structured treatment interruptions (STIs), these are not yet recommended in routine clinical practice in the UK (BHIVA, 2003).

There was a strong relationship between perceptions of necessity for HAART and adherence. Although perceptions of necessity at baseline did not predict subsequent adherence, necessity beliefs reported as early as one month after starting treatment predicted adherence

at six months. Furthermore, there was a dynamic relationship between perceptions of necessity and adherence over time. Perceptions of necessity for HAART remained high over the six months among patients reporting high adherence, while those reporting low adherence reported a significant decrease in their perceptions of necessity over time. Furthermore, reporting a decrease in necessity beliefs over time was predictive of sub-optimal clinical outcome (higher viral load). Mediational analyses (Baron & Kenny, 1986) showed that the relationship between the decline in necessity over time and higher viral load was dependent on low adherence. This is in accordance with the SRM in which Leventhal et al. (1980) proposes that illness representations lead to coping procedures, which in turn, impact on health outcomes.

These findings extend those from previous cross-sectional studies that have linked necessity beliefs to adherence (Llewellyn et al., 2003; Horne & Weinman, 2002) and provide important targets for clinicians and for interventions that aim to promote and maintain high levels of adherence to HAART. They suggest that patients' perceptions of their personal necessity for HAART should be elicited and addressed soon after they start treatment in order to maintain adherence over the long-term.

Having established that experiencing a decline in necessity over time predicts low adherence, the next step was to find out what variables were associated with a decline in perceived necessity, in order to identify targets for intervention. Horne (2003) proposed that symptom appraisal is central to patients' perceptions of their personal need for treatment. Consistent with this theory, reporting lack of improvement in HAART related symptoms over time was associated with a decline in necessity beliefs. Furthermore, patients who reported a decline in perceived necessity for HAART over time reported a greater number of HIV symptoms at six months. However, this relationship was no longer statistically significant when perceptions of HIV symptoms before initiating HAART were controlled for in the analysis. This indicates that patients who were experiencing more symptoms that they attributed to HIV per se (as opposed to whether their symptoms got better or worse over the six months they were taking

HAART) were more likely to report a decline in their perceived need for HAART over time. The same pattern was true for self-reported physical health.

These findings make sense in the light of an extended self-regulatory model, in which patients formulate 'common sense' models of their illness and treatment (Horne, 1997; 2003). They indicate that patients who perceive a higher frequency of moderate to severe symptoms that they attribute to their HIV-infection, and those who experience poorer physical well-being after six months of taking HAART often begin to question the necessary of continuing their treatment with HAART. Furthermore, perceiving a lack of improvement or worsening of HAART-related symptoms over time leads to a decrease in perceived need for HAART.

The results suggest that clinicians and those designing interventions that aim to maintain high levels of adherence among patients receiving HAART should monitor patients' perceptions of their symptom experiences and perceptions of their physical health throughout the treatment process. Those who experience poor physical health or more symptoms they associate with HIV at any time over the treatment process may begin to doubt their continued need for HAART, and respond by missing doses. Those who experience a lack of improvement or worsening of the symptoms they attribute to HAART-side effects over time are also likely to begin to doubt their continued need for HAART. These results suggest that interventions should aim to alleviate or help patients to cope with symptoms while they are taking HAART.

Relationships between illness perceptions measured by the IPQ were assessed in relation to changes in necessity beliefs over the treatment process. The perception that symptoms come and go in a cyclical fashion (cyclical timeline) was associated with the evolution of necessity beliefs, with patients who reported more recurrence of symptoms being more likely to experience a decline in their perceptions of need for treatment. This relationship was independent of perceptions of cyclical timeline elicited before initiating treatment, indicating a dynamic relationship between perceptions of cyclical timeline and necessity for HAART, where perceptions of necessity decrease when symptoms recur. This relationship suggests that within patient's models of HIV, experiencing a recurrence of symptoms may signal that

the treatment is no longer necessary, while experiencing less recurrence of symptoms over the treatment process (compared to baseline) may increase their perceptions of necessary.

Control beliefs were also associated with the change in perceptions of necessity over time. Stronger perceptions of necessity for HAART were maintained among those who perceived greater personal control over the progression of HIV, and those who were more convinced that HAART was effective in controlling their HIV (treatment control). These relationships were independent of baseline perceptions of control, indicating a dynamic relationship between perceived control over HIV and perceptions of need for treatment, where perceptions of necessity increased as perceptions of control increased.

There was an interesting relationship between illness coherence and the evolution of perceived necessity for HAART. Coherence beliefs elicited at six months were not significantly related to the change in perceived need over time. However, this relationship became statistically significant when the influence of coherence beliefs elicited at baseline was controlled in the analysis. This indicates that the change in perceived coherence over time was related to the change in perceived necessity. The direction of this relationship shows that those who reported a decline in necessity began to feel that their condition no longer made sense to them. This suggests that necessity beliefs are more likely to remain high if patients' retain a coherent picture of their illness in the light of their treatment experience.

Clinical and demographic variables were also associated with changes in perceptions of personal necessity for HAART over the treatment process. Having previously been prescribed antiretroviral treatment was associated with a decline in perceived necessity for HAART over the six months of treatment. This relationship may provide important clues into why patients with treatment experience are more likely to report non-adherence (see Study 1). It may be speculated that patients who repeatedly start and stop their treatment possess different models of HAART to those initiating HAART for the first time. It could be hypothesised that those who had previously stopped one or more combinations of antiretroviral treatment were more likely to view HAART as a short-term intervention, rather than as a potentially life-long

treatment. This view of HAART was endorsed by a small number of participants in a qualitative study of HAART uptake (Cooper et al., 2002). Unfortunately, the scales included in the current study did not address patients' perceptions of how long they would need to take their treatment. These expectations of 'treatment timeline' warrant further research, particularly in view of the sensitive resistance profiles and limited treatment options that are characteristic of these drugs.

It was further hypothesised that the relationship between changes in perceptions of necessity for HAART and adherence would be mediated by change in illness perceptions. Candidates for these mediational analyses were HAART-related symptoms and treatment control beliefs, since these variables were associated with both necessity and adherence. However, neither the evolution of HAART-related symptoms over time, nor the evolution of treatment control beliefs over time, mediated the relationship between the evolution of necessity beliefs over time and adherence. These results provide strong support for the extended self-regulation model proposed by Horne, 1997, 2003) in which beliefs about HAART are primary predictors of adherence. Although perceptions of HIV are related to treatment perceptions, the relationship between treatment perceptions and adherence is not dependent on illness perceptions. The results highlight the importance of eliciting and addressing patients' beliefs about their personal necessity for HAART across the treatment process in order to support and maintain the high levels of adherence that are required for clinical success of this treatment.

9.5.1.2 Concerns

There was a significant, linear decline in the strength of patients' concerns about adverse effects of taking HAART across the six months of treatment. There was a dramatic decline in concerns scores between baseline and one month, suggesting that concerns about HAART were alleviated on initiating treatment. Concerns scores declined again between one and three months, after which they remained constant. The decline in concerns over time was independent of negative affect and was not related to the decline in perceptions of HAART-related side effects over time. The results suggest that patients' worries about the potential

adverse effects of taking HAART prior to initiating treatment might be out of proportion to their actual experience.

Two unpublished studies found patients' concerns about their anti-hypertension medication also declined over time (James, 1999; Miller, 2003). The tendency of patients' concerns about HAART to be alleviated rather than exacerbated by experience is of interest in view of research that shows that the decision to decline a clinically recommended treatment offer of HAART was influenced by the strength of patients' concerns about potential adverse effects of HAART (Horne et al., 2001). The items included in the concerns scale encompass concerns about the complexity of the regimen and disruption to lifestyle, the stigma/embarrassment of taking HAART as well as concerns about side effects, long-term effects and dependency. One possible explanation for the fact that patients' concerns prior to initiating HAART outweigh those arising from experience is that recent developments in the formula of antiretroviral agents have reduced the complexity of antiretroviral treatment regimens and improved their tolerability over the past few years. It is possible that some of patients' concerns about HAART before initiating treatment may originate from knowledge or experience of early treatments, which may not be applicable to some of the new combinations which the majority of participants in this study were taking. Indeed, in a recent qualitative study, patients who declined a clinically recommended treatment offer HAART often attributed their decision to their early experiences of complex drug regimens and ineffective treatments with early antiretroviral regimens (Cooper et al., 2002), which may not be applicable to some of today's drug schedules. Alternatively, the decline in concerns following treatment initiation may be attributed to a psychological phenomena known as 'cognitive dissonance,' which refers to the tendency of individuals to report beliefs that are consistent with their behaviour (Albarracin & Wyer, 2000). Perhaps a more plausible explanation for the decline in concerns over time is that patients find ways of dealing or coping with some of the everyday difficulties involved with taking HAART over the course of their treatment. The ways in which patients cope with side effects, practical difficulties and more abstract concerns about HAART warrants further research.

There was no significant main effect of concerns on adherence. This finding is interesting in the light of the results described in Study 1 in which the strength of patients' concerns about HAART before initiating treatment was predictive of adherence at six months. Study 1 included patients who had stopped treatment (as well as those taking less than 95% of their drugs as prescribed) within the low-adherence group, which could have affected the results. It is possible that possessing strong concerns about HAART was more predictive of stopping treatment altogether than other forms of low adherence such as taking less medication than prescribed or neglecting to take medication within the prescribed timing restrictions. However, this seems unlikely in view of the pattern of means in the current study which shows stronger concerns at baseline among those reporting low adherence at six months, with differences between high and low adherence groups becoming minimal after one month of treatment.

These findings conflict with those from a cross-sectional study in which a significant negative relationship was found between concerns and adherence (Horne et al., in press). Differences between the two studies include the adherence measure, sample characteristics and study design. Within the Horne et al. study, patients had been taking their treatment for longer period of time and were less likely to be antiretroviral naïve, with over half the sample taking a protease inhibitor. Being on treatment (especially with more complex protease inhibitor-based regimens) for a longer time period increases the chances of adverse long-term effects such as metabolic complications (e.g. lipodystrophy). Furthermore, data were collected between January and May 1999, while data for the current study was collected from Jan 2000 to Jan 2003. There have been considerable treatment advances over this time period in terms of reducing the complexity of drug regimens and the frequency of daily dosages required. The adherence measure used within the Horne et al. study required patients to rate the degree to which they adhered to timing recommendations. This adherence measure may have been more strongly associated with concerns about HAART among a sample where the majority were taking complex protease inhibitor regimens. The majority of participants in the current study were taking twice-daily regimens of NNRTI based combinations, which are less disruptive and have a different side effect profile.

9.5.2 Patterns of illness perceptions over time

On the whole, patients' perceptions of HIV remained stable over the treatment process. Where they changed, the general pattern was that perceptions of HIV became more positive over time. These changes were minimal and most did not reach statistical significance, with one exception. There was a notable increase in treatment control beliefs over the follow-up, which was independent of negative affect. This indicates that patients' perceptions of the extent to which HIV can be controlled by treatment improve once treatment is initiated. The reasons why perceptions of treatment control increase over time are not clear from this study, but may be related to experiencing benefits from taking HAART such as positive feedback from the doctor in terms of blood test results. No information regarding patients' perceptions of their blood test results was collected in the current study although this would be an interesting area of inquiry for future investigations.

Perceptions of treatment control at six months were significantly higher among those reporting high adherence at six months, however there was no interaction between group and time, indicating that the increase in treatment control beliefs over time did not predict adherence.

In summary, patients' beliefs about HAART (necessity and concerns), and perceptions of treatment control changed dramatically over the first months of initiating a new treatment regimen. This change was particularly dramatic over the first month, while patients adapted to their new regimen. Interestingly as patients' concerns about their treatment declined dramatically, so did their perceived need for treatment. The decline in necessity beliefs was found to be a strong, independent predictor of adherence to HAART. This has implications for interventions to improve and maintain high adherence to HAART.

The findings of this study provide support for the utility of an extended SRM (Horne, 1997; 2003) as a theoretical framework within which to explore adherence to HAART. This prospective data clearly illustrate the dynamic nature of illness and treatment perceptions, and emphasise the need to study adherence within a theoretical framework that incorporates

change over time. The findings support the view of the patient as an active information processor who makes sense of his or her illness experiences by developing and reassessing his or her beliefs about illness and treatment, which in turn, influence adherence decisions and impact on clinical outcome. The data support the theoretical framework provided by the SRM (Leventhal et al., 1980) and extensions to it suggested by Horne (1997, 2003).

9.5.3 Limitations

9.5.3.1 Sample bias

The sample that completed this part of the study (n = 67) were compared to the overall study population (n = 86) in order to establish sample representativity. There were some differences in terms of clinical and demographic characteristics. As before, those who failed to complete this part of the study were younger, less likely to be enrolled in a clinical trial, and more likely to have previously been prescribed antiretroviral treatment compared to those who completed the study. Possible ways of dealing with missing data have already been discussed (see Chapter 8). It should be noted that nine of the nineteen participants with missing data had stopped their treatment before the six-month follow-up, and therefore were not eligible for the assessments completed for this part of the study.

9.5.3.2 Repetition of questionnaires

Participants were required to answer the same questionnaire on four occasions. Oppenheim (1998) suggests that this might introduce a source of bias, because people aim to complete questionnaires consistently. However, this does not seem to have been applicable to the present study, where change over time was evident on some scales, but not on others.

9.5.3.3 Length of follow-up

The length of follow-up was restricted to six months for practical and economic reasons, however it would be interesting to explore change in illness perceptions, beliefs about HAART and adherence over the longer term, especially as HAART is a potentially life-long treatment. One question that warrents further research is whether perceptions of necessity for HAART continue to decrease over time, and whether patients who continue to experience a decrease

in their perceptions of necessity are at risk of stopping their treatment completely. It might be hypothesised that the predictors and correlates of necessity for HAART change over the longer term. For instance, those reporting *more* benefit from their treatment might become *less* convinced that they need to continue treatment once they feel better (Cooper et al., 2003). It would also be interesting to explore the content of patients' beliefs such as their concerns about HAART over the longer-term, especially with regard to lipodystrophy and other long-term metabolic complications that have been associated with long-term use of HAART (Carr & Cooper, 2000).

9.5.3.4 Implications for intervention and clinical practice

These data show that experiencing a decline in perceived necessity for HAART over time is a strong predictor of adherence to HAART among HIV positive adults. This finding suggests that efforts to increase and maintain perceptions of necessity for HAART should be incorporated into clinical practice and into the design of interventions that aim to improve adherence to HAART.

These findings suggest that in order to maintain strong perceptions of necessity for HAART, interventions need to address patients' perceptions of control over HIV, and their beliefs in the efficacy of their treatment. Since it is possible that patients sometimes mistakenly use their symptom experiences to guide their perceptions of the efficacy of their treatment, efforts should be made to alert the patient to changes in clinical markers of disease progression, such as viral load, in evaluating their treatment. Alleviating or helping patients to cope with the symptoms they associate with their HIV condition and those they attribute to HAART-side effects might help to maintain strong perceptions of necessity. Finally, patients who experience a decrease in perceptions of necessity for HAART begin to feel that their condition does not make sense in the light of their treatment. Interventions should aim to help patients to understand their illness and treatment experience.

Patients who had previously been prescribed antiretroviral medication were particularly prone to experiencing a decline in perceived necessity for HAART over the treatment process.

Another target for intervention would be to address necessity beliefs in this group, since it could be that patients who repeatedly start and stop antiretroviral treatment perceive HAART as a short-term treatment, in contrast to the medical opinion.

This study also provides information regarding the timing of interventions to promote adherence. The fact that beliefs changed dramatically over the first month of taking HAART suggest that the intervention should be administered both before initiating treatment, and soon afterwards (i.e. one month later) in order to address patients' early experiences of treatment in relation to their expectations.

Chapter 10
General discussion

10.1 Overview of thesis

Recent years have seen major developments in the pharmacological treatment of HIV, resulting in vastly improved life expectancy and quality of life for many. However, because the antiretroviral agents that make up these potent drug combinations (HAART) have a short half-life, extremely high levels of adherence are required in order to suppress the virus and prevent the development of viral resistance. A critical review of the literature (see Chapter 2) showed that low levels of adherence to HAART continue to pose a major barrier to the success of these treatments. Studies to date have identified a plethora of correlates of adherence and suggest that psychological variables, including beliefs about illness and treatment, are strongly related to adherence. However, researchers have relied heavily on cross-sectional methodologies, precluding the determination of causality. Furthermore, few studies have attempted to frame adherence within a theoretical framework, which would aid the development of interventions to promote and maintain high levels of adherence.

This thesis was designed primarily to test the utility of the SRM (Leventhal et al., 1980) and extensions to it to incorporate treatment perceptions (perceptions of personal necessity for HAART and concerns about potential adverse effects: Horne, 1997; 2003) in predicting adherence to HAART. The fundamental questions addressed within the thesis were whether the necessity/concerns framework suggested by Horne (1997; 2003) predicted adherence, and whether incorporating the necessity/concerns framework into Leventhal's SRM increases our understanding of non-adherence to HAART. This thesis therefore represents a primary test of the extended SRM, based on the following hypotheses:

- It was expected that illness representations would influence adherence directly. This was a direct test of the original SRM (Leventhal et al., 1980) in which coping procedures such as adherence to treatment recommendations are influenced by patients' representations of their illness.

- In order to operationalise the SRM in relation to adherence to treatment, Horne (1997; 2003) incorporated necessity and concerns within this model. Within this extended model, patients' perceptions of their personal necessity for HAART and their concerns would be directly related to adherence.

- Patients' representations of their illness would influence their perceived necessity for treatment, while perceptions of medicines in general and past experiences would influence concerns.

- Symptom appraisal would be directly related to adherence, with patients who experience a lack of improvement in the symptoms they attribute to HIV, or persistent HAART-related symptoms, being less adherent to their treatment.

- Patients' appraisals of their symptoms would be related to perceived necessity for treatment and to concerns about adverse effects of treatment in a logically consistent way, with symptoms attributed to illness and those attributed to treatment side effects impinging differentially on necessity beliefs and concerns.

- Adherence to HAART would be influenced not only by baseline perceptions of illness and treatment but also by the degree to which these perceptions changed over time.

Conducting a prospective follow-up study facilitated separate analyses to test these aspects of the model as described in Studies 1, 2 and 3.

10.2 Summary of main findings

In general the necessity/concerns framework proposed by Horne (1997, 2003) was found to be a useful predictor of adherence. Moreover, relations between illness perceptions, beliefs about medicines and adherence over time were consistent with predictions based on Leventhal's SRM and Horne's proposed operationalisation of the extended model (eSRM).

Patients' initial perceptions of HIV and HAART predicted subsequent adherence. Specifically, low adherence was predicted by stronger concerns about potential adverse effects of taking HAART, experiencing more symptoms attributed to HIV and poorer physical health, perceiving more negative personal consequences associated with HIV and being less convinced that illness would improve over time.

Beliefs about HAART were related to perceptions of HIV in a way that is broadly consistent with the extended SRM. Perceptions of personal necessity for HAART were strongly associated with illness perceptions, specifically the perception that HAART is effective in controlling the progression of HIV and poorer self-rated health. Perceptions of necessity were not significantly related to clinical variables or negative affect. Concerns about HAART were associated with perceptions of personal susceptibility to the adverse effects of medicines, the belief that medicines in general are over-prescribed and more negative illness perceptions. However, strong relationships between concerns and negative affect warrant further investigation in order to determine the direction of causality.

Consistent with the SRM (Leventhal et al., 1980) and extended SRM (Horne et al., 1997; 2003), patients' symptom experiences and attributions both predicted adherence and fed back into perceptions of HIV and HAART. Symptoms changed significantly over time and changes in symptom reporting predicted adherence. Specifically, patients who experienced a lack of improvement in the symptoms they attributed to HIV, or persistent symptoms they attributed to HAART, over the treatment process reported low adherence. Furthermore, patients' perceptions of their personal necessity for HAART mediated the relationship between change in both HIV and HAART related symptoms and adherence.

Beliefs about HAART changed dramatically over time. Concerns declined over time but this change did not predict adherence. Perceptions of personal necessity for HAART also declined over time. Furthermore, experiencing a decline in necessity beliefs over time predicted adherence. Patients who maintained strong perceptions of necessity for HAART reported high adherence to HAART, while perceptions of necessity declined amongst those

who reported low adherence. Predictors of the decline in perceptions of necessity over time were identified.

On the whole, patients' perceptions of HIV remained stable over the treatment process, with one exception. Perceptions of treatment control increased significantly over time, but this increase did not predict adherence.

The specific findings relating to each of the main tenants of the theory outlined above are discussed in this chapter.

10.3 Patterns of adherence over six months of HAART

Adherence was measured one, three and six months after starting a new HAART regimen. Levels of adherence remained extremely high over the first three months of treatment but declined significantly between three and six months. Low adherence as early as one month predicted sub-optimal clinical outcome (virologic failure at six months). The initial high levels of adherence identified in this study exceed those in many cross-sectional studies of adherence (Arnsten et al., 2002; Atlice et al., 2001; Niewkerk et al., 2001; Chesney et al., 2000; Ostrop et al., 2000). While it is possible that the sample were predisposed to high adherence, perhaps due to referral or sample bias (see Limitations of Study), this initial high level of adherence has also been evident in other prospective, longitudinal studies of adherence (Tuldra et al., 2000; Spire et al., 2002, Duran et al., 2001). These studies have also shown high levels of adherence over the first few months of treatment followed by a gradual decrease over time. The fact that adherence fluctuates over time suggests that predictors and correlates of adherence also change over the first few months of treatment. These findings have implications for the timing of interventions aimed at improving and maintaining adherence over the long-term, suggesting that a single intervention would not be sufficient to maintain adherence over the long-term. Implications for the timing of interventions will be discussed further in Section 10.6 of this discussion.

experience of antiretroviral treatment and subsequent adherence is of particular concern in view of increasingly limited treatment options once viral resistance occurs. Previous studies have also identified having previously started and stopped combinations of antiretroviral therapy as a risk factor for non-adherence (Mannheimer et al., 2002; Carrieri et al., 2001; Duran et al., 2001). Possible mechanisms fuelling the relationship between having past treatment experience and low adherence were explored in the current study. It was hypothesised that those who had stopped their antiretroviral treatment in the past would have stronger *concerns* about the potential adverse effects of taking HAART. However, the data did not support this hypothesis: having previously received antiretroviral treatment was not significantly associated with any of the perceptions of HIV or beliefs about HAART measured at baseline.

Two possible mechanisms linking past treatment experience to subsequent adherence were identified. The first stemmed from the finding that those who had previously been prescribed antiretroviral treatment were more likely to perceive that they were sensitive to adverse effects from medicines in general compared to those who were antiretroviral naïve. The fact that those who previously stopped antiretroviral medication view themselves as being highly susceptible to adverse effects of medicines in general, but do not have significantly stronger concerns about HAART in particular, reflects a negative attitude towards medicines as a whole rather than to HAART per se in this group. However, the direction of this relationship was not clarified in this study, since the belief could be either the cause, or the effect, of previous non-adherence. The second mechanism linking previous experience of antiretroviral treatment to subsequent adherence was a greater decline in perceptions of personal necessity for HAART over the treatment process among those who had previously been prescribed antiretroviral treatment. This finding indicates that interventions to promote and maintain high levels of adherence to HAART should focus on maintaining strong perceptions of need for treatment over the long term among patients who have previous experience of antiretroviral treatment. It may be speculated that this finding reflects an erroneous belief among this group, who may perceive their need for HAART as only short-term. Addressing

10.4 Clinical and demographic predictors of adherence

Transmission risk group, sex and ethnicity were highly skewed in this population (the majority of the sample were white, gay men). Not surprisingly, these variables did not predict adherence. Age was not associated with adherence. Participants who were not in employment at baseline were at greater risk for low adherence at follow-up. This is consistent with previous findings (Ammassari et al., 2001; Schuman et al., 2001; Wagner et al., 2001; Gordillo et al., 2000). However, the mechanisms by which employment status impacts on adherence behaviour have not been clarified and warrant further research. It may be that a third variable such as negative affect or severity of illness mediates the relationship between employment and adherence. In common with other prospective studies (Spire et al., 2002; Duran et al., 2001; Lucas et al., 2001) the clinical severity of the participant's disease at baseline (CD4 count, viral load, CDC symptomatic status) did not predict subsequent adherence.

Participants who had been diagnosed with HIV for a longer duration of time reported lower adherence at follow-up. The results suggest that the relationship between length of diagnosis and adherence was mediated by psychological factors rather than disease severity. This is consistent with findings from a study of uptake of HAART in which patients who had been diagnosed longer were more likely to decline a clinically indicated treatment recommendation and had stronger concerns about HAART (Cooper et al., 2001). This finding is further illuminated by a qualitative study exploring reasons for declining a clinically recommended treatment offer. Participants who had been diagnosed with HIV for a number of years often reported scepticism about HAART, which stemmed from early experiences of HIV treatments such as AZT monotherapy (Cooper et al., 2002). However the pathways through which a longer duration of HIV diagnosis impacts on *adherence* to HAART were not addressed in this thesis, and warrant further investigation.

10.4.1 Past experience of antiretrovirals

The strongest predictor of low adherence identified at baseline was having previously received a prescription for antiretroviral treatment. The relationship between having previous

this belief may prevent viral resistance to antiretroviral agents from occurring from starting and stopping treatment without medical supervision.

The view of HAART as a short-term treatment was also elicited in a qualitative study in which a minority of patients indicated that they were initiating treatment to boost their immune system, and expected to stop the treatment when they felt better, or when clinical markers of disease progression indicated that their HIV was under control (Cooper et al., 2002). Neither the IPQ nor BMQ questionnaires used in this study addressed this concept of 'treatment timeline'. However, exploring the length of time patients expect to be taking their treatment in relation to adherence and perceptions of illness and treatment may be an interesting route of investigation for future prospective studies.

10.4.2 Regimen complexity

The participants in this study were taking a range of HAART regimens of varying complexitiy. The complexity of the prescribed antiretroviral regimen (whether the regimen contained protease inhibitors, the number of tablets and frequency of dosing) was found to be associated with adherence. However these relationships are likely to be confounded by previous treatment experience. In line with current UK prescribing guidelines (BHIVA 2003), antiretroviral regimens prescribed to previously treatment naïve patients are relatively simple compared to those prescribed to patients who have previous antiretroviral treatment experience. Typically, the prescribed regimen becomes more complex when resistance to these drugs has occurred, therefore regimen complexity could indirectly result from previous low adherence as well as being a potential cause of future low adherence. Indeed it was shown in the present study that all aspects of the regimen that were associated with adherence (whether the regimen contained protease inhibitors, the number of tablets and frequency of dosing) were confounded by past treatment experience. It is of note that the complexity of the regimen has also been identified as a barrier to adherence to HAART in several previous studies (Matthews et al., 2002; Atlice et al., 2001; Pratt et al., 2001; Barton-Laws et al., 2000; Eldred et al., 1998). However none of these studies contained exclusively anti-retroviral naïve participants. Over recent years, efforts have been made by the

manufacturers of antiretroviral agents to improve their formulation and reduce the complexity of dosing schedules. However, the results of interview-based studies investigating patients views of their treatment in relation to adherence (Cooper et al., 2003; Siegel et al., 2000; Meystre-Agustoni et al., 2000; Roberts, 2000) suggest that issues surrounding the complexity of the regimen are only one facet of patients' concerns about HAART and that, although simplifying complex drug regimens might facilitate medication taking, it will not solve the problem of non-adherence.

10.5 Testing the extended SRM in relation to adherence to HAART

The first aim of this thesis was to evaluate the impact of patients' perceptions of HIV and HAART, elicited before initiating treatment, on subsequent adherence.

10.5.1 Illness and treatment perceptions as predictors of adherence

There was support for a causal relationship between perceptions of HIV/HAART and adherence, where beliefs elicited *before* initiating treatment predicted subsequent adherence. Several significant relationships were found between pre-HAART beliefs and adherence after six months of treatment.

10.5.1.1 Necessity and concerns as predictors of adherence

The strength of patients' concerns about potential adverse effects of taking HAART and the perception of being particularly sensitive to adverse effects of medicines in general were associated with low adherence at follow-up, while perceptions of personal necessity for HAART and the belief that doctors overuse medicines in general were not significantly related to adherence.

Horne (1997; 2003) proposed that the strength of patients' perceptions of their personal necessity for treatment and their concerns about potential adverse effects would predict adherence. While previous cross-sectional studies with different illness groups have identified relationships between patients' perceptions of necessity for treatment and their concerns about adverse effects and adherence behaviour (Horne & Weinman, 1999; 2002; Llewellyn et

al., 2003), no published studies to date have explored these relationships within a prospective, longitudinal design. The finding that the strength of patients' concerns about their treatment before initiating HAART predicts adherence augments those from cross-sectional studies conducted with patients with a range of chronic diseases including HIV (Horne et al., *in press*; Horne et al., 1999; Horne & Weinman, 2002), and suggests that the relationship might be causal in nature, where patients' decisions not to take their medication as prescribed arise as a consequence of their concerns about potential adverse effects.

Contrary to expectations stemming from the findings of Horne & Weinman (2002) and Llewellyn et al. (2003), participants' perceptions of their personal *necessity* for HAART did not predict subsequent adherence. The difference in design between these previous cross-sectional studies and the current prospective study might account for this difference. In the current study, very high levels of perceived need for HAART were found amongst participants before they initiated treatment. Indeed, this high level of perceived need for HAART predicted uptake of HAART amongst this sample (Horne et al., 2002; Cooper et al., 2002a). The fact that necessity beliefs did not predict adherence is likely to be due to the lack of variation in perceived necessity for HAART at baseline. This finding led to the hypothesis that reporting a decrease in perceived necessity over time would be associated with low adherence. Empirical support for this hypothesis was generated. These data are discussed further in Section 10.5.4.1 of this chapter.

10.5.1.2 Beliefs about medicines in general as predictors of adherence

No published studies to date have explored relationships between perceiving oneself to be particularly sensitive to the adverse effects of medicines in general and adherence to a specific, prescribed treatment. In this study, scores on the Sensitive Soma scale, which measures patients' perceptions of their personal sensitivity to medicines, were higher amongst those who subsequently reported low adherence. This indicates that patients who perceived themselves to be more vulnerable to suffering adverse effects of medicines in general were less likely to take their treatment as prescribed. It could be hypothesised that these patients were attempting to avoid sensitivity reactions to their medication by taking less

of their treatment than the amount prescribed (e.g. skipping doses to minimise side effects: Siegel et al., 2000). Contrary to expectations, higher scores on this scale were not related to the strength of patients' concerns about potential adverse effects of HAART per se. This could be because the concerns scale of the BMQ measures concerns about several aspects of the HAART regimen, including practical difficulties associated with taking the drugs and more abstract concerns such as embarrassment about taking antiretroviral treatment. Patients who perceive themselves to be more susceptible to side effects may not also possess strong concerns about other aspects of the regimen.

Interestingly, the relationship between Sensitive Soma scores and adherence was mediated by past treatment experience. When the variance in adherence due to previous use of antiretrovirals was removed from the analysis, Sensitive Soma scores were no longer related to adherence. This finding suggests a possible mechanism by which past experience of treatment might impact on adherence to HAART, thus identifying a possible target for intervention. However it was not possible to ascertain whether perceptions of personal susceptibility to medicines in general arose from previous negative experiences of HAART, or whether the patient stopped their previous combination as a result of feeling at increased risk of adverse reaction to the treatment. Reasons for stopping previous combinations (e.g. whether it was because of side effects) were not ascertained in this study, but would certainly be of relevance to future investigations.

10.5.1.3 Perceptions of HIV and self-rated health as predictors of adherence

Consistent with the original SRM (Leventhal et al., 1980) in which coping procedures such as adherence to treatment recommendations are influenced by patients' representations of their illness, perceptions of HIV and self-rated health before initiating HAART were related to subsequent adherence. Specifically, experiencing a greater number of HIV-related symptoms or a greater frequency of moderate to severe HIV-related symptoms, perceiving more severe personal consequences associated with HIV, being less convinced that one's condition would improve in time, perceiving a more cyclical timeline and perceiving oneself to be in poorer physical health were all significant predictors of low adherence at the six-month follow-up.

Control beliefs, illness coherence and emotional representations of HIV were not significantly related to subsequent adherence.

Few prospective studies to date have explored the role of illness perceptions as predictors of adherence. Two studies found links between illness perceptions and attendance at rehabilitation classes post MI (Petrie et al., 1996; Cooper et al., 1999). Specifically those who attended the rehabilitation classes reported stronger beliefs on admission that their illness could be cured or controlled. Control beliefs elicited prior to initiating treatment did not predict subsequent adherence to HAART in the current study. This lack of consistency between studies may be due to differences between the outcomes measured (adherence to medication versus attendance at rehabilitation classes) or to differences between the illness conditions. Myocardial Infarction may be perceived as an acute condition with a distinct onset and possibility for complete cure, while HIV may be perceived as a chronic condition with possibility for control but no known cure.

These results confirm and elaborate findings previous findings from cross-sectional studies linking illness perceptions to adherence to medication. Llewellyn et al. (2003) and Horne & Weinman (2002) found significant relationships between perceptions of negative *consequences* of illness and adherence to medication. However, the direction of the relationship differed between studies. Llewellyn et al (2003) found greater levels of non-adherence to prophylactic treatment among patients who perceived *less* severe negative illness consequences associated with severe haemophilia, while Horne & Weinman (2002) found that low adherence to preventer medication for asthma was associated with perceiving *more* severe negative consequences of illness. The current study also found more negative perceptions of illness consequence among those reporting low adherence. It is not clear why the direction of relationships differs between the three studies. Horne & Weinman (2002) suggest that patients in their study might have reported more negative illness consequences as a result of experiencing more disability from asthma, which may have been the result of previous non-adherence to their preventative medication. However the results of the present study suggest a *causal* relationship between beliefs and behaviour, where perceiving more

negative personal consequences of HIV before initiating treatment predicted low adherence at follow-up. It might be speculated that patients who perceive more negative personal consequences associated with their HIV diagnosis might be more likely to lack optimism in their treatment and give up. This might be due to a general negative mood. Indeed, negative affect mediated the relationship between illness consequences and adherence. These findings are discussed further in Section 10.5.1.4.

Low adherence at follow-up was also predicted by perceiving a stronger illness identity, perceiving oneself to be in poorer physical health and perceiving a more cyclical timeline before initiating treatment. The direction of these relationships (where poorer perceived health and more frequent and cyclical symptom experiences predicted lower adherence) was also contrary to that proposed by the SRM (Leventhal et al., 1980). Indeed, *greater* adherence to dose recommendations for prophylactic medications was found among patients with haemophilia who had a stronger illness identity (Llewellyn et al., 2003). It was proposed that the relationship between beliefs and adherence in the current study might be mediated by negative affect, where those with more negative mood were more likely to hold negative views about their illness and to respond with low adherence. Support for this hypothesis was gained and will be discussed below.

10.5.1.4 The role of negative affect in relationships between baseline perceptions of HIV/HAART and adherence

There was a strong relationship between both depression and anxiety at baseline and low adherence at follow-up. Depression and anxiety were also strongly associated with negative perceptions of HIV and HAART at baseline. It was therefore hypothesised that negative affect mediated the relationships between perceptions of HIV, beliefs about HAART and low adherence. Indeed, when depression and anxiety were partialled out of the analyses, only 'timeline' remained significantly related to adherence. Relationships between treatment beliefs (concerns and sensitive soma), illness perceptions (identity, cyclical timeline, consequences) and subjective assessment of physical well-being (SF-12 physical health) at baseline and subsequent adherence appeared to be the result of shared variance with negative affect.

Within the SRM, Leventhal et al. (2001) suggest that the individual is motivated to minimise fear, therefore may use seemingly irrational coping procedures to deal with their representation of illness. Consistent with this model, the non-adherent patient might be using a seemingly irrational coping procedure (non-adherence) to deal with the fear or anxiety aroused by his or her representation of the illness or concerns about the treatment.

The role of negative affect in the SRM has received very little empirical investigation to date. There are at least two ways in which negative affect might be related to negative illness and treatment perceptions. Depression and anxiety could either cause a more negative view of illness and treatment, or be the effect of viewing one's illness and available treatment in a negative way. Few studies utilising the SRM have explicitly tested the nature of the relationship between illness or treatment perceptions, negative affect and adherence. Several cross-sectional studies investigating the role of illness perceptions in adjustment to chronic illness have framed depression and anxiety as outcome variables, showing that more negative illness perceptions are related to more negative mood: In cross-sectional studies, Jopson & Moss-Morris (2003) found that illness perceptions were significantly related to anxiety and depression in a group of 168 patients with multiple sclerosis, Fortune et al. (2002) found illness perceptions were associated with anxiety and depression in 225 patients with psoriasis and Edwards et al. (2001) found illness perceptions accounted for around 30% of the variance in depression and anxiety among patients with chronic fatigue syndrome. In prospective studies, Sharloo et al (1999) found that patients who reported a greater number of symptoms associated with rheumatoid arthritis were more likely to be depressed one year later, while the belief that the illness would last for a long time predicted higher anxiety scores at one year follow-up. Conversely, Leventhal et al (1996) found negative mood states reliably predicted somatic complaints (such as common cold), and Diefenbach et al (1996) found significant cross-sectional relationships between negative affect and flu-like symptoms in elderly people following flu jab or placebo, but no long-term relationships between negative affect and symptoms. No clear pattern emerges from these studies in terms of the direction of causality. Further prospective research is required to investigate the direction of relationships

between negative affect and perceptions of illness and treatment, and the impact of these relationships on adherence.

Although negative affect mediated relationships between baseline treatment beliefs (concerns and sensitive soma), illness perceptions (identity, cyclical timeline, consequences) and self-rated health and subsequent adherence, there are several reasons why these relationships remain important in terms of their clinical utility. First, high levels of depression and anxiety have been found among people living with HIV (Cruess et al., 2003; Starace et al., 2002). Furthermore, psychological distress is likely to be elevated when patients start a new treatment, because treatment recommendations normally follow a deterioration in health or in clinical indicators of disease progression (BHIVA, 2003). Removing the variance due to negative affect in the analyses may obscure the relationships between illness perceptions and adherence that are true in reality. Second, as already discussed, the data do not clarify the direction of causality between negative affect, illness and treatment perceptions, since depression and anxiety could lead to negative views of illness, alternatively, holding negative views of illness and treatment could lead to depression and anxiety. Third, this study did not explore the impact of a clinically defined mood disorder on beliefs, and there is no evidence to suggest that treating depression or anxiety would lead to more positive perceptions of illness or treatment. Therefore, although it is of interest theoretically to identify 'pure' relationships between negative affect, perceptions and adherence, relationships that are mediated by negative affect should still be targeted in interventions that aim to promote adherence.

10.5.2 Relationships between illness perceptions and beliefs about HAART

The second aim of the thesis was to explore the antecedents of beliefs about HAART. Understanding the origins of perceived necessity for HAART and concerns about adverse effects is important in order to aid the design of interventions which aim to promote adherence by changing these beliefs (Horne, 2003).

10.5.2.1 Relationships between perceived *necessity* for HAART and illness perceptions

Horne (1997, 2003) proposed that patients' perceptions of their personal necessity for treatment arise from their perceptions of their illness and of the efficacy of the treatment. Key questions for the patient who is faced with decisions about treatment are whether their illness warrants treatment, and whether the suggested treatment is appropriate. It was expected that stronger illness *identity, consequences, timeline* and *treatment control* beliefs would be associated with stronger *necessity* beliefs. The results of the multiple linear regression showed that thirty-six percent of the variance in *necessity* beliefs was accounted for by patients' perceptions of their illness. Consistent with these hypotheses, patients' perceptions of their personal necessity for HAART were positively correlated with treatment control beliefs. This relationship was independent of negative affect, and indicates that those who perceived HAART to be effective in controlling the progression of their HIV were more likely to believe that they need to take it.

Contrary to expectations and in contrast to previous findings among patients with asthma (Horne & Weinman, 2002), neither illness consequences nor timeline were related to necessity beliefs. It is possible that the difference between studies was due to differences between the illness conditions. While asthma is characterised by discrete episodes of illness with the potential for severe, immediate consequences, HIV is a chronic condition with long-term negative consequences. Also contrary to expectations, illness identity (the frequency of symptoms patients attributed to HIV) was not related to necessity beliefs. This might be due to patients' models of HIV being congruent with medical models i.e. treatment necessity may be gauged by laboratory markers of disease progression such as CD4 count to a greater extent than non-specific symptoms as measured by the Identity scale. However, patients' subjective assessments of their physical health as indicated by their scores on the SF-12 were negatively correlated with their necessity beliefs, where those who perceived their health to be poorer were more likely to perceive a strong personal necessity for HAART. It is possible that the illness *identity* scale, consisting of a list of generic illness symptoms and HIV-specific symptoms, may not encompass the array of possible symptoms that patients

associate with HIV and related illnesses. Furthermore, rating symptoms on a simple scale might minimise the importance of one very severe or disabling symptom, or over-inflate the importance of several more minor symptoms. In the current study, attempts were made to minimise this possibility by including a second identity scale in which only symptoms patients rated as moderate to severe were included. However, this scale was not related to treatment necessity beliefs either. Patients' subjective ratings of their physical health on the SF-12, a health outcome measure, accounted for approximately a fifth of the variance in necessity beliefs. This rating encompasses the subjective impact of illness on a variety of areas of functioning, including work, daily chores, social life and vitality. This broader rating of health status may be more relevant to determining patients' perceptions of their need for treatment than symptom frequency, since the gross impact of the HIV condition on daily functioning might be more salient to the individual than the severity of individual symptoms. For subsequent analyses, the SF-12 was used as a proxy illness perception measure representing the impact of HIV on daily functioning, although this is not conventional in illness perceptions research.

10.5.2.2 Clinical and demographic predictors of necessity beliefs

Qualitative findings suggest that patients' views of their laboratory markers of disease progression may differ from the medical model. In a study of HAART uptake (Cooper et al., 2002), many participants believed that their blood test results were inaccurate, invalid, or that they did not adequately reflect their subjective well-being. Horne (2003) suggested that one of the factors that patients might use to evaluate their personal need for medication is the results of laboratory tests or clinical markers of disease progression. These relationships have received little investigation to date. In the current study, having a lower CD4 count was associated with stronger perceptions of necessity for HAART, however this relationship did not reach statistical significance. The fact that viral load was not related to perceptions of necessity is consistent with the latest UK clinical guidelines for treatment, which now base decisions about treatment initiation primarily on CD4 count (BHIVA, 2003). The absence of a significant association between CD4 count and treatment necessity provides some support for Leventhal et al. (1982), who proposed that patients often have difficulty integrating abstract

information from health care professionals regarding their health status into their personal models of illness and treatment. However, it should be noted that all participants in this study were clinically eligible to receive HAART, and that the results could be explained by the fact that necessity beliefs were extremely high in this sample. However, the results suggest that patients' perceptions of their physical well-being may be more relevant to their perceptions of necessity for HAART than their laboratory test results.

10.5.2.3 Relationships between concerns about HAART and beliefs about medicines in general

The extended SRM (Horne, 1997, 2003) proposes that concerns about adverse effects of specific, prescribed medicines are fuelled by patients' perceptions of medicines in general. Support for this hypothesis was obtained in the current study. Stronger concerns about HAART were associated with perceptions that medicines in general are over-prescribed by doctors and perceptions of being personally susceptible to experiencing adverse effects of medicines. These relationships were independent of negative affect.

It would appear that some individuals hold a negative view about medicines as a whole which influences their perceptions of specific prescribed medications (Horne, 2003). Although the origins of this schema have received little investigation to date, Horne (1999, 2001) found that many people had negative views about medicines in general that were linked to their unnatural, chemical origins, and perhaps to a broader suspicion in western cultures of science, medicine and technology (Petrie & Wessely, 2002).

10.5.2.4 Relationships between concerns about HAART and perceptions of HIV

Participants' who reported strong concerns about HAART had more negative perceptions of HIV, including a greater number of symptoms, which recurred in cycles (cyclical timeline). These patients perceived a lack of control over the progression of their virus (personal control), harbouring doubts that their treatment was effective (treatment control), and were pessimistic about the possibility of their condition improving in time (timeline). They also experienced a negative emotional representation of their illness (emotional representations),

and felt that it did not make sense (illness coherence). Since concerns about HAART were also related to higher anxiety and depression scores, it was hypothesised that these relationships were mediated by negative affect. However, after controlling for depression and anxiety, timeline, treatment control, coherence and emotional representations remained significantly associated with concerns about HAART. Although previous studies have not published relationships between illness perceptions and concerns, these relationships may be understood in the light of a common sense model. It makes coherent sense that an individual who believes that HAART cannot effectively control the progression of their HIV disease (as shown by lower treatment control scores), and who believes that their condition will not improve on their new treatment (indicated by higher timeline scores) would have stronger concerns about the potential adverse effects associated with taking HAART. Similarly, it makes sense that possessing strong concerns about a treatment that one is about to initiate would be associated with a weaker sense of illness coherence and a more negative emotional representation of illness. Further prospective research is required in order to determine whether concerns about the available treatment lead to negative perceptions of illness, or whether possessing negative illness perceptions leads to concerns about the available treatment.

10.5.2.5 Relationships between concerns about HAART and negative affect

There were strong, positive relationships between concerns about HAART and negative affect, with depression and anxiety accounting for 38% of the variance in concerns scores. Again, because concerns, depression and anxiety were measured at the same assessment it was not possible to determine causal relationships: having strong concerns about a treatment one is about to initiate might lead to negative mood, conversely the presence of a negative mind-set might lead to more negative views about both illness and treatment. Few previous studies have explored relationships between beliefs about medicines and negative affect. Further research using a prospective design is needed to tease out causal relationships between negative mood and concerns about adverse effect of treatment in order to identify targets for intervention and clinical practice.

10.5.2.6 Relationships between concerns, clinical and demographic variables

Horne (2003) has suggested that having negative experiences with medicines in the past may lead to concerns about a specific prescribed treatment. However, concerns about HAART were not significantly related to having previously been prescribed antiretroviral treatment in this study. Unfortunately, reasons for stopping previous antiretroviral treatment were not ascertained in this study, so it is possible that not all participants stopped because of adverse experiences. Further research is needed to directly test this hypothesis.

Age was significantly related to concerns about HAART: younger patients had stronger concerns about their treatment. This finding is contrary to the results of a study of patients with inflammatory bowel disease in which older patients had stronger concerns about their medication (Horne, 2003). It is not clear why younger participants had stronger concerns about HAART, but it could be speculated that younger people may feel less able or willing to keep to a rigid treatment regimen that may have negative impact on their social or personal lives. In line with expectations, concerns about HAART were not related to laboratory markers of disease progression or symptomatic status.

10.5.3 The role of symptom appraisal in adherence to HAART

The third aim of the thesis was to evaluate patients' appraisals of their symptom experiences over time, in relation to adherence. Specifically, the study aimed to gauge how patients' experiences of symptoms changed over the first six months of treatment, whether changes in patients' perceptions of the symptoms they attributed to HIV or HAART over time predicted adherence, whether and how their appraisals of their symptoms over time had an impact on their perceptions of HIV and HAART and finally, whether perceptions of HIV and HAART mediated relationships between symptom appraisal and adherence.

Consistent with expectations stemming from the self-regulatory model (SRM: Leventhal et al., 1980), and extensions to the SRM to include treatment perceptions (Horne, 2003), patients' perceptions of their symptoms changed significantly over time and these changes were related to adherence. Those who experienced an improvement in the symptoms they

attributed to HIV over six months of treatment were more likely to report high adherence to HAART, while those who experienced persistent or worsening symptoms they attributed to HAART side effects over time reported low adherence. These relationships remained significant when controlling for earlier adherence in the analyses, suggesting that symptom changes were not the result of lack of clinical benefit arising from earlier non-adherence.

Many published studies in the HIV literature have linked treatment side effects to low rates of adherence, however, the majority have been hindered by their reliance on cross-sectional research designs. Two prospective studies identified significant relationships between symptoms and subsequent adherence to HAART: Duran et al (2001) found that patients who reported a greater number of HAART-related symptoms after one month of treatment were less adherent at four months, while Spire et al. (2002) found that patients who reported a lack of improvement in symptoms over time more likely to be non-adherent compared to those who reported that their symptoms had remained low or improved. This study both confirms and extends previous research, by using a prospective design to explore the impact of patients' attributions of their symptoms to HIV or HAART on adherence, and identifying mediators of this relationship.

Few empirical studies utilising the SRM have explicitly explored the role of symptom appraisal in relation to treatment adherence. Although one cross-sectional study linked scores on the identity scale to adherence (Llewellyn et al., 2003), this remains a scarcely researched area of inquiry. It may be that changes in symptoms over time are key determinants of adherence. In an interview-based study, Meyer et al. (1980) found that patients often stopped treatment when the symptoms that they associated with hypertension were alleviated, because they felt their anti-hypertensive medication had cured their illness and therefore that they no longer needed to keep taking treatment. Leventhal et al. (1982) propose that this finding stems from patients' perceptions of hypertension as an acute illness. Within the acute illness schemata, disease is perceived as a 'discrete, concrete entity with specific causal agents, symptoms, breakdowns in physiological process and curative interventions' (page 74, Leventhal et al., 1982). Patients viewing their illness this way expect treatment to cure their high blood

pressure, therefore they stopped the treatment when the symptoms they perceived as being associated with their condition had been alleviated.

In the current study, it was recognised early on (in the pilot study) that patients unanimously perceived their HIV condition to be chronic. Within the chronic illness schemata, Leventhal et al (1982) propose that patients are driven to minimise the extent to which their condition interferes with their everyday life activities. Consistent with this model of HIV, the patients in the current study were more likely to respond with a high level of adherence if they perceived that the symptoms they associated with their condition were being alleviated by their treatment. Few previous studies have explored links between symptoms associated with treatment side effects and adherence over time within a self-regulatory framework. Consistent with Leventhal (1982), patients who perceived that their treatment was causing persistent, severe symptoms of its own were more likely to respond with low adherence. This is in line with a common-sense approach of trying to minimise the risk of side effects by taking less medication.

10.5.3.1 Mechanisms by which symptom appraisal impacts on adherence

Having determined that changes in symptom experiences over time predicted adherence to HAART, the next step was to identify the mechanisms by which symptom appraisal impacted on adherence. These findings are discussed below.

10.5.3.1.1 Relationships between symptom appraisal and perceptions of HIV

Consistent with hypotheses derived from the SRM (Leventhal et al., 1980), patients' concrete symptom experiences influenced their perceptions of HIV. Those who experienced an improvement in symptoms over time had more positive representations of their illness and rated their physical health more favourably than those who reported that their symptoms had not improved. After controlling for baseline illness perceptions and negative affect in the analyses, the majority of these relationships remained statistically significant, suggesting that patients' appraisals of their symptoms impact on their perceptions of HIV in a causal way. Specifically, patients who experienced an improvement in the symptoms they attributed to

HIV experienced increased perceptions of control over HIV, less recurrence of symptoms, a more optimistic outcome, and a less negative emotional reaction to HIV after six months of treatment, compared to baseline. Conversely, experiencing a lack of improvement or worsening of HAART-related symptoms over time led patients to perceive of a lack of control over HIV, less optimism that their condition would improve in time, and a stronger negative emotional reaction to HIV at six months, compared to baseline.

10.5.3.1.2 Relationships between symptom appraisal and beliefs about HAART

Horne (1997, 2003) suggested that patients' appraisals of their symptom experiences impact on adherence because the appraisal process feeds back into their perceptions of the treatment (necessity and concerns). To date, this appraisal mechanism has received little empirical investigation. Hypotheses derived from the extended SRM proposed that experiencing an improvement in the symptoms attributed to HIV leads to adherence because symptom relief reinforces a strong sense of personal necessity for the treatment. Conversely, the model suggests that experiencing a lack of improvement in symptoms attributed to HAART-related side effects leads to low adherence because it activates a spectrum of concerns about the treatment, including concerns about potential long-term effects, practical barriers to taking medication such as timing and disruption to routine and more abstract concerns regarding the stigma and embarrassment surrounding antiretroviral treatment.

Consistent with the first hypothesis, participants who reported an improvement in HIV-related symptoms over the follow-up reported stronger perceptions of their personal necessity for HAART at six months. This relationship was independent of negative affect. However, this relationship did not retain statistical significance when baseline perceptions of necessity were controlled for in the analysis. This implies that holding stronger beliefs about personal necessity for HAART might, to some extent, be a cause of subsequent improvement in HIV symptoms. In other words, patients who held stronger perceptions of necessity before they initiated HAART might have expected a greater improvement in HIV related symptoms and this expectation might have lead to improved outcome. The tendency for expectations to predict outcome is known as the 'placebo effect'. This has previously been demonstrated in

work related to illness perceptions including studies of return to work following MI (Petrie et al., 1996) and quality of healing following oral surgery (McCarthy et al., 2003). Similarly, although those who reported persistent HAART-related symptoms over the follow-up reported stronger concerns about their treatment at six months, this relationship was not independent of concerns at baseline. This indicates that the relationship between experiencing persistent HAART-related side effects and adherence at six months was, to some extent, predicted by the strength of patients' concerns before they initiated HAART. In other words, patients who had stronger concerns about HAART or more negative mood before initiating their treatment were more likely to experience persistent side effects over the treatment process.

It was further hypothesised that experiencing an improvement in *HAART*-related symptoms over time would be associated with stronger beliefs about personal *necessity* for HAART, while a lack of improvement in *HIV*-related symptoms over time would be associated with stronger *concerns* about HAART. These hypotheses were supported by the data. Those who experienced an improvement in HAART-related symptoms perceived a stronger personal necessity for HAART at six months relative to baseline. Moreover, those experienced an improvement in HIV related symptoms over time reported a reduction in the strength of their concerns about HAART between baseline and six months. The results suggest that if the symptoms an individual attributes to their HIV fail to improve on treatment, a whole spectrum of concerns about HAART may be activated. Similarly, if HAART is perceived to be causing persistent symptoms of its own, the patient may begin to question his or her perceived need for the treatment. These findings make intuitive sense in the light of a common sense model. Indeed Horne (2003) proposed that concerns might be activated when symptoms attributed to illness fail to improve. Furthermore, although not explicit in the eSRM, it follows that an individual who is experiencing persistent side effects they believe to be caused by their prescribed treatment might question their need to keep taking it. These relationships have not previously been identified and have implications for the development of the eSRM.

10.5.3.2 Beliefs about HAART as mediators of the relationships between symptom appraisal and adherence

Having established that symptom appraisal was related to necessity and concerns, the next step was to test a mediational model, where symptom appraisal impacts on adherence via beliefs about HAART (necessity and concerns). In line with the model, the strength of patients' perceptions of their personal *necessity* for HAART at six months mediated the relationships between both change in HIV symptoms and change in HAART symptoms and adherence. These results showed that if HAART alleviated symptoms the patient associated with their HIV, or did not cause persistent symptoms of its own, patients perceived a strong personal necessity for their treatment, which in turn, had a direct impact on their adherence decisions. Necessity beliefs were central to the relationship between symptom change and adherence. If necessity beliefs were partialled out of the analyses, symptom change was no longer significantly related to adherence. This finding provides support for the extended SRM in explaining adherence to HAART. It implies that interventions to improve adherence should aim to maintain strong perceptions of need for HAART in patients who experience a lack of symptomatic benefit, and those who are experiencing persistent or worsening side effects from their treatment.

Concerns about HAART were also hypothesised to mediate the relationships between symptom change and adherence. However, although concerns were significantly elevated among those experiencing persistent HIV related symptoms and those experiencing persistent HAART-related side effects, and were associated with low adherence at six months, they did not play a causative role in the relationship between symptom change and adherence. When concerns were partialled out of the analyses, change in both HIV and HAART related symptoms remained significantly associated with adherence. In other words, experiencing persistent symptoms attributed to either HIV or HAART led to low adherence regardless of the strength of patients' concerns about HAART.

These results provide evidence for an appraisal pathway through which patients' concrete symptom experiences operate. They provide support for the theoretical structure of the SRM

proposed by Leventhal et al (1980), showing that the perceived outcome of adherence (whether or not symptoms are alleviated) feeds back into perceptions of HIV. They expand upon previous research in this area by empirically testing the appraisal processes emphasised in the SRM framework. They also support extensions to the model proposed by Horne (1997, 2003), by showing that treatment perceptions (necessity and concerns) mediate the relationship between symptom appraisal and adherence. Theoretical models that do not encompass change in symptom experiences over time may be unsuitable for complex behaviours such as adherence to long-term treatment regimens. Overall, these findings provide strong support for the extensions to the SRM proposed by Horne (2003). In particular, they highlight the fundamental role of *necessity* beliefs as a mediator of the relationship between symptom appraisal and adherence to HAART.

These results expand upon previous research into adherence to HAART in several ways. First, by using a prospective design to track the evolution of patients' perceptions of their symptoms over time in relation to adherence, it was possible to show that perceptions of symptoms changed over the treatment process and that these changes predicted adherence. Second, by exploring differential relationships between symptoms and adherence depending on whether patients attributed their symptoms to HIV or to HAART side effects it was possible to show stronger relationships between HAART side effects and adherence and that these relationships were mediated through similar mechanisms as HIV-related symptoms. Third, by utilising a theoretical framework within which to model relationships between symptoms and adherence to HAART, mediators of the relationships between symptoms and adherence (perceptions of personal necessity for HAART) have been identified. The results suggest that efforts to promote high adherence to HAART over the long-term should aim to help patients cope with symptoms in order to maintain strong perceptions of necessity for HAART.

10.5.4 Impact of changes in perceptions of HIV and HAART over time on adherence

The fourth aim of the empirical section of this thesis was to explore how perceptions of HIV and HAART change over the treatment process, how these changes impact on adherence to HAART, and how changes in beliefs about HIV and HAART relate to each other over time.

10.5.4.1 Changes in perceived necessity for HAART

Overall, patients' perceptions of their personal necessity for HAART declined over time. Furthermore the extent to which perceived necessity for HAART declined over time predicted adherence. Those who experienced a significant decrease in their perceptions of necessity for HAART over the six-month follow-up reported low adherence at six months, while necessity beliefs remained high among those who reported high adherence. This is the first study to explore the dynamic relationships between necessity beliefs and adherence over time. It has implications for the design of adherence interventions and clinical practice, suggesting that maintaining strong perceptions of necessity for HAART will promote high levels of adherence among patients. In order to inform interventions which aim to increase perceptions of necessity for HAART, it was necessary to find out why perceptions of necessity declined over time.

10.5.4.2 Predictors of the decline in necessity beliefs over time

10.5.4.2.1 Illness perceptions

The next step was to discover why patients' perceptions of their need for HAART declined over the treatment process. Consistent with hypotheses derived from the extended SRM proposed by Horne (1997; 2003), reporting a decrease in perceived necessity for HAART between baseline and six months was predicted by illness perceptions. Specifically, a decline in patients' perceptions of personal necessity for HAART was associated with a greater frequency of HIV-related symptoms and poorer self-rated health at six months. However, these relationships were no longer significant when controlling for HIV-related symptoms and self-rated health at baseline. This suggests that patients' perceptions of HIV-related symptoms and overall physical health before initiating treatment might impact on the decline in perceptions of necessity for HAART over time. Baseline perceptions of symptoms and physical health in general should therefore be targeted before patients initiate HAART, in order to maintain high perceptions of necessity.

As already discussed, patients who experienced an increase in the symptoms they attributed to HAART side-effects over the treatment process reported a decline in necessity for HAART. Experiencing a greater recurrence of symptoms over time predicted a decline in necessity, presumably because these patients felt that the treatment was not effectively controlling their HIV. Indeed, those who reported a decline in necessity for HAART over time became less convinced that HIV was amenable to control. In line with expectations, there was a particularly strong relationship between a decline in perceived necessity and perceptions of HAART efficacy (treatment control beliefs), where those who experienced a decline in necessity beliefs over time reported a decline in the belief that HAART was effectively controlling their HIV.

These relationships are consistent with hypotheses derived from the extended SRM proposed by Horne (1997; 2003). They suggest that in order to maintain strong perceptions of necessity for HAART, interventions need to focus on alleviating or coping with symptoms, especially those the patient attributes to his or her treatment. The findings also show that patients' faith in the efficacy of their treatment needs to be maintained over time. One potential way of maintaining strong perceptions of control over HIV might be to focus patients' attention on clinical markers of treatment efficacy (such as viral load) rather than symptoms, since their experience of symptoms may not always reflect the clinical benefit they have obtained.

10.5.4.2.2 Clinical/demographic variables

Experiencing a decline in perceptions of necessity for HAART over time was related to sub-optimal clinical outcome (detectable viral load). Further analyses showed that, consistent with the theoretical foundations of the SRM (Leventhal et al., 1980), which stipulate that illness perceptions mediate the relationship between coping and outcome, adherence mediated the relationship between necessity beliefs and viral load. In other words, rather than causing a high viral load, a decline in necessity beliefs over time led to low adherence, which, in turn impacted on viral load.

Experiencing a decrease in perceived necessity for HAART was not predicted by changes in CD4 count over time. This suggests that patients' cognitive models of HIV have a stronger influence on their perceived necessity for treatment than more abstract clinical information. Patients who had previously been prescribed antiretroviral treatment were more likely to experience a decrease in their perceptions of necessity for HAART over time than those who were anti-retroviral naive. This is interesting in the light of the finding that having previously been prescribed antiretroviral treatment was a strong predictor of adherence. It suggests a mediational pathway by which having previously been prescribed antiretroviral treatment might impact on subsequent adherence: patients who start and stop treatment may have models of their disease and treatment that are incongruent with the medical view. Specifically, these patients may perceive that HAART is only necessary for the short term. This view was evident in an interview-based study in which a some patients who accepted a clinically recommended treatment offer explained that they had made the decision to take HAART but that they intended to stop their treatment when they felt better or when their clinical markers of disease progression had stabilised (Cooper et al., 2002). Maintaining strong perceptions of necessity for HAART over the long-term constitutes an important target for HIV clinicians and interventions, in order to maintain high adherence among individuals who have previous antiretroviral experience.

10.5.4.3 Mediators of the relationship between perceived necessity for HAART and adherence

Finally, mediational analyses showed that the relationship between decline in necessity beliefs over time and adherence was independent of the change in treatment control beliefs, and independent of the change in HAART-related symptoms over time. The decline in necessity beliefs was therefore shown to be a strong independent predictor of adherence to HAART. This provides strong support for the utility of the extended SRM (Horne 1997, 2003) in explaining adherence to HAART.

10.5.4.4 Changes in concerns about adverse effects

Concerns about adverse effects of HAART decreased dramatically over the first month of treatment, although this decrease in concerns did not predict adherence. This finding is of relevance because the strength of patients' concerns about HAART elicited before initiating treatment predicted subsequent adherence. There was a rapid decline in the strength of concerns about HAART over the first month of treatment. This suggests that eliciting and addressing patients' concerns about potential adverse effects of HAART *before* they initiate treatment may improve subsequent adherence, since it would appear that expectations prior to initiating treatment were more negative than the actual experience of taking HAART.

10.5.4.5 Changes in illness perceptions over time

On the whole, patients' perceptions of HIV remained stable over the treatment process. Where they changed, the general pattern was that perceptions of HIV became more positive over time. These changes were minimal and most did not reach statistical significance. However, there was a notable increase in treatment control beliefs over the follow-up, which was independent of negative affect. This indicates that patients' perceptions of the extent to which HIV can be controlled by treatment tend to improve once treatment is initiated. The reasons why perceptions of treatment control increase over time are not clear from this study, but may be related to experiencing benefits from taking HAART such as positive feedback from the doctor in terms of blood test results. No information regarding patients' perceptions of their blood test results was collected in the current study, although this would be an interesting area of inquiry for future investigations.

The finding that perceptions of treatment control increase over time is also interesting in view of the decrease in necessity beliefs over time. It was hypothesised that participants' perceptions of necessity might be influenced by the degree to which they perceive their treatment to be effectively controlling the progression of their condition, so that as the patient perceives their treatment to be gaining control over their illness, their perceived need to keep taking it decreases. However this hypothesis was not supported by the data. Those who reported a *decrease* in perceived necessity for HAART also reported a *decrease* in

perceptions of treatment control. This suggests that those who do not perceive treatment to have been effective are less likely to maintain strong perceptions of need for HAART.

Perceptions of treatment control at six months were significantly higher among those reporting high adherence at six months, however there was no interaction between group and time, indicating that the increase in treatment control beliefs over time was similar for high and low adherence groups.

In summary, patients' beliefs about HAART (necessity and concerns), and perceptions of treatment control changed dramatically over the first months of initiating a new treatment regimen. This change was particularly dramatic over the first month, while patients adapted to their new regimen. Interestingly as patients' concerns about their treatment declined dramatically, so did their perceived need for treatment. The decline in necessity beliefs was found to be a strong, independent predictor of adherence to HAART. This has implications for interventions to improve and maintain high adherence, which will be discussed in Section 10.6.

10.5.5 Summary of findings in relation to the Self-Regulation Model (SRM)

In summary, the findings of this study illustrate the utility of the SRM as a theoretical framework within which to explore adherence to HAART. This prospective data clearly demonstrate the dynamic nature of illness and treatment perceptions, and emphasise the need to study adherence within a theoretical framework that incorporates change over time. The findings support the view of the patient as an active information processor who makes sense of his or her illness experiences by developing and reassessing his or her beliefs about illness and treatment, which in turn, influence adherence decisions and impact on clinical outcome. The data support the theoretical framework provided by the SRM (Leventhal et al., 1980) the specific operationalisation of the model in relation to adherence suggested by Horne (1997, 2003).

10.5.5.1 The value and limitations of the extended SRM in view of experimental results

The results of the three studies that form the experimental section of this thesis have both confirmed and extended many aspects of the original SRM suggested by Leventhal et al. (1980) and the extended SRM suggested by Horne (1997, 2003). They have also provided data that are contrary to some of the hypotheses stemming from these models. Table 10.1 lists these hypotheses, and indicates which of the hypotheses were upheld by the experimental results of this thesis and which were not. The three studies described in Chapters 7, 8 and 9 utilised a prospective, longitudinal design to address several hypotheses that have not been previously tested in relation to adherence. The first set of hypotheses addressed the predictive value of the model by exploring the impact of patients' beliefs about HIV and HAART, elicited prior to initiating HAART, on subsequent adherence. The second set of hypotheses explored relationships between beliefs about HAART and perceptions of HIV proposed by Horne (1997; 2003). The third set of hypotheses explored the role of symptoms in patients' appraisals of their treatment and the fourth set of hypotheses investigated the evolution of illness perceptions and beliefs about HAART over the first six months of treatment. The value and limitations of the extended SRM with respect to the findings of this thesis are discussed below.

Table 10.1: Hypotheses proposed and tested showing whether or not each hypothesis was upheld by the experimental results.

Hypothesis			Was the hypothesis upheld?
Study 1			
RQ1	**Do beliefs about HAART, elicited before starting treatment, predict subsequent adherence?**		
	H1.1	Low adherence will be predicted by doubts about personal necessity for HAART	NO*
	H1.2	Low adherence will be predicted by stronger concerns about potential adverse effects	YES
RQ2	**Do perceptions of HIV, elicited before starting treatment, predict subsequent adherence?**		
	H2.1	Low adherence will be predicted by reporting less severe HIV-related symptoms	NO** – MORE SEVERE
	H2.2	Low adherence will be predicted by reporting less severe negative personal consequences associated with HIV	NO** – MORE SEVERE
	H2.3	Low adherence will be predicted by anticipating greater improvement over time	NO** – LESS IMPROVEMENT
	H2.4	Low adherence will be predicted by perceiving a less cyclical timeline	NO** – MORE CYCLICAL
	H2.5	Low adherence will be predicted by perceiving less personal control over HIV	NO
	H2.6	Low adherence will be predicted by doubts that HIV can be controlled by HAART	NO
	H2.7	Low adherence will be predicted by a more negative emotional representation of HIV	NO
	H2.8	Low adherence will be predicted by less illness coherence (as indicated by a higher illness coherence score)	NO
	H2.9	Low adherence will be predicted by a more positive perception of physical health	NO** – POORER HEALTH
RQ3	**Does negative affect mediate the relationship between perceptions of illness and treatment and adherence?**		
	H3.1	Relationships between treatment perceptions and adherence will be mediated by negative affect	YES
	H3.2	Relationships between illness perceptions and adherence will be mediated by negative affect	YES (except timeline)

* attributed to ceiling in necessity scores

** illness perceptions related to adherence but in opposite direction to hypotheses

RQ4	**Are perceptions of HIV related to perceptions of personal necessity for HAART and concerns about adverse effects in a way that is consistent with hypotheses generated by the extended SRM proposed by Horne (2003)?**		
	H4.1	Stronger perceptions of necessity for HAART will be associated with lower self-rated physical health	YES
	H4.2	Stronger perceptions of necessity for HAART will be associated with more severe HIV-related symptoms	NO
	H4.3	Stronger perceptions of necessity for HAART will be associated with more severe negative consequences	NO
	H4.4	Stronger perceptions of necessity for HAART will be associated with anticipating less improvement over time	NO
	H4.5	Stronger perceptions of necessity for HAART will be associated with a less cyclical timeline	NO
	H4.6	Stronger perceptions of necessity for HAART will be associated with greater personal control	NO
	H4.7	Stronger perceptions of necessity for HAART will be associated with greater treatment control	YES
	H4.8	Stronger perceptions of necessity for HAART will be associated with lower CD4 count	NO
	H4.9	Stronger perceptions of necessity for HAART will be associated with higher viral load	NO
	H5.1	Stronger concerns about HAART will be associated with feeling highly susceptible to adverse effects of medicines	YES
	H5.2	Stronger concerns about HAART will be associated with negative beliefs about medicines in general	YES
	H5.3	Stronger concerns about HAART will be associated with having previously taken anti-retroviral treatment	NO
Study 2			
RQ1	**How do patients' perceptions of HIV and HAART related symptoms change over the first six months of taking HAART?**		
	H1.1	There will be a significant change in patients' perceptions of HIV-related symptoms over six months of HAART	YES
	H1.2	There will be a significant change in patients' perceptions of HAART-related symptoms over six months of HAART	NO
RQ2	**Are patients' perceptions of change in HIV and HAART related symptoms related to adherence?**		
	H2.1	Patients who experience an improvement in HIV-related symptoms over time will be more adherent	YES
	H2.2	Patients who experience persistent HAART-related symptoms will be less adherent	YES

RQ3	**How do patients interpret and evaluate changes in symptom experiences over time?**		
	H3.1	Experiencing persistent HAART-related symptoms will be associated with stronger concerns about HAART	YES
	H3.2	Experiencing persistent HIV-related symptoms will be associated with lower perceived necessity for HAART	YES
	H3.3	Experiencing a lack of improvement in symptoms will be associated with more negative perceptions of HIV	YES
RQ4	**Do beliefs about HAART mediate relationships between symptom change and adherence?**		
	H4.1	Necessity beliefs will mediate the relationship between HIV-related symptoms and adherence	YES
	H4.2	Concerns will mediate the relationship between HAART-related symptoms and adherence	NO
Study 3			
RQ1	**How do patients' perceptions of HIV and concerns about HAART change over the first six months of treatment?**		
	H1.1	There will be significant changes in patients' beliefs about HAART over time	YES
	H1.2	There will be significant changes in patients' perceptions of HIV over time	NO (treatment control only)
RQ2	**Are patients' perceptions of HIV and beliefs about HAART across the treatment process associated with adherence?**		
	H2.1.1	Low adherence will be associated with lower perceived necessity for HAART	YES
	H2.1.2	Low adherence will be associated with stronger concerns about adverse effects	NO
	H2.2.1	Low adherence will be associated with less negative personal consequences	NO
	H2.2.2	Low adherence will be associated with anticipating greater improvement over time	NO
	H2.2.3	Low adherence will be associated with a less cyclical timeline	NO
	H2.2.4	Low adherence will be associated with less personal control over HIV	NO
	H2.2.5	Low adherence will be associated with doubting that HAART can control HIV	YES
	H2.2.6	Low adherence will be associated with a less negative emotional representation of HIV	NO
	H2.2.7	Low adherence will be associated with a more positive perception of physical health	NO

RQ3	**Are changes in patients' perceptions of HIV and beliefs about HAART over time associated with adherence?**		
	H3.1.1	Low adherence will be associated with a decline in perceived necessity for HAART	YES
	H3.1.2	Low adherence will be associated with an increase in concerns about adverse effects	NO
	H3.2.1	Low adherence will be associated an increase in perceptions of negative personal consequences	NO
	H3.2.2	Low adherence will be associated with a decline in the expectation of improvement over time	NO
	H3.2.3	Low adherence will be associated with an increase in cyclical timeline	NO
	H3.2.4	Low adherence will be associated with a decrease in perceptions of personal control over HIV	NO
	H3.2.5	Low adherence will be associated with a decrease in perceptions that HAART can effectively control HIV	NO
	H3.2.6	Low adherence will be associated with an increase in negative emotional representations of HIV	NO
	H3.2.7	Low adherence will be associated with a decline in physical health	NO
RQ4	**Are changes in perceptions of necessity over time associated with changes in perceptions of HIV over time?**		
	H4.1	Decreased necessity will be associated with an increase in HIV-related symptoms	NO
	H4.2	Decreased necessity will be associated with an increase in HAART-related symptoms	YES
	H4.3	Decreased necessity will be associated with an increase in negative personal consequences	NO
	H4.4	Decreased necessity will be associated with a decline in the expectation of improvement over time	NO
	H4.5	Decreased necessity will be associated with an increase in cyclical timeline	YES
	H4.6	Decreased necessity will be associated with a decrease in perceptions of personal control over HIV	YES
	H4.7	Decreased necessity will be associated with an increase in doubts that HAART can effectively control HIV	YES
	H4.8	Decreased necessity will be associated with a decrease in illness coherence	YES

10.5.5.1.1 The role of the extended SRM in predicting adherence

The prospective, longitudinal design of the study offered the unique opportunity to explore the contribution of patients' perceptions of their illness and treatment both before initiating treatment, and over time, on subsequent adherence, extending previous findings from cross-sectional studies.

The results strongly support the utility of the Necessity-Concerns framework proposed by Horne (1997; 2003) in explaining adherence to HAART. There was also general support for Horne's suggestion that the inclusion of the Necessity-Concerns framework within an extended SRM (eSRM: Horne, 1997; 2003) would enhance the predictive power of the SRM in explaining adherence to HAART. In line with hypotheses generated from this extended SRM (see Table 10.1), treatment perceptions were more proximal determinants of adherence than illness perceptions. Patients who reported stronger concerns about potential adverse effects of taking HAART before they initiated their treatment were more likely to report subsequent non-adherence. Contrary to hypotheses, patients' perceptions of necessity for HAART before initiating treatment were not related to subsequent adherence. This was probably due to the fact that perceptions of HAART were extremely high among this sample before they initiated treatment, with little variation in scores. Indeed, patients' perceptions of necessity for HAART declined dramatically over time, and experiencing a decrease in perceived need for HAART over time was associated with low adherence. Furthermore, patients' interpretations of their symptoms and representations of HIV influenced treatment beliefs in a way that was consistent with the eSRM. The results emphasised the importance of concrete symptom experiences over more abstract information regarding disease progression (CD4 count and viral load test results) in determining adherence decisions.

However, the results were contrary to specific hypotheses regarding the direction of relationships between patients' perceptions of their illness before initiating treatment and subsequent adherence. Specifically, it was hypothesised that patients who perceived a stronger illness identity, more negative personal consequences of their diagnosis and a more

chronic and cyclical timeline would subsequently be more adherent to their treatment. The findings showed that the opposite was true (see Table 10.1). Those who experienced *more* symptoms, who perceived *more* negative personal consequences associated with HIV and who felt that their illness would *not* improve in time, before initiating their treatment, were less likely to be highly adherent after six months of treatment.

One of the possible explanations for these results was the confounding influence of negative affect, as negative affect mediated many of the relationships between illness perceptions and adherence (as discussed in Section 10.5.1.4). However, negative affect did not explain the relationship between timeline and adherence. Patients who perceived that their HIV would not improve reported low adherence. This may have been due to an artefact of assessment in that the operationisation of the timeline construct resembles a treatment expectation (as discussed in Section 10.6.2).

10.5.5.1.2 Relationships between baseline illness perceptions and beliefs about HAART proposed by the extended SRM

Few previous studies have empirically tested the relationships between illness and treatment perceptions suggested by the eSRM (Horne, 1997; 2003). According to this model, patients' perceptions of necessity for treatment stem from their perceptions of illness (identity, timeline, and consequences) and their beliefs about the effectiveness of the proposed treatment (treatment control), while concerns about a specific prescribed treatment stem from negative beliefs about medicines as a whole, and previous negative experiences of treatment. The results of Study 1 provided support for some, but not all of these hypotheses (see Table 10.1).

Illness perceptions and health-related quality of life

Consistent with the model, perceptions of treatment control were independently related to necessity beliefs, where patients who believed their treatment to be effective in controlling the progression of HIV were more likely to believe that they needed to take it. Contrary to

expectations, neither timeline nor consequences were associated with patients' perceptions of their necessity for HAART. Patients' symptom experiences before initiating treatment were not related to their perceptions of necessity for HAART, however, poorer self-rated physical health, as measured by the SF-12, was associated with stronger perceptions of necessity. This finding indicates that patients' perceptions of their necessity for HAART may have been determined by to a greater extent by the subjective impact of HIV on a variety of areas of functioning than by their experience of specific symptoms attributed to HIV. Relationships between this broader health rating and perceptions of necessity for treatment have not previously been tested. These results suggest that health-related quality of life measures such as the SF-12 function as an indication of the subjective impact of the illness and in this respect may be considered to be a form of illness representation.

The role of CD4 count and viral load

The relationships between treatment necessity and more abstract indicators of disease progression (CD4 count and viral load) proposed by the eSRM (Horne, 2003) have not been previously explored. Contrary to expectations, no significant relationships between CD4 count or viral load test results and necessity beliefs were identified. This indicates that individuals with HIV may use their subjective experiences of physical health to inform their perceptions of necessity for HAART, to a greater extent than more either symptom experiences or objective laboratory test results. This finding is important in relation to clinical practice and in the development of interventions to promote adherence to HAART.

Past treatment experience and beliefs about medicines in general

Hypotheses generated from the eSRM proposed that the strength of patients' concerns about HAART would be influenced by beliefs about medicines in general and having previous negative experience of taking antiretroviral treatment. These hypotheses received partial support: perceiving oneself to be highly susceptible to adverse effects from taking medicines and perceiving medicines in general to be over-prescribed were related to stronger concerns about HAART. Contrary to hypotheses, however, having previously been prescribed

antiretroviral treatment was not significantly related to concerns about adverse effects. Further research is required in order to confirm this finding, because having previously stopped antiretroviral treatment is only a valid indicator of negative treatment experience if the treatment was stopped due to problems with the treatment. It is possible that some patients may have stopped for a more positive reason, such as feeling better or on the advice of their physician.

10.5.5.1.3 The influence of time and repeated measures on the predictive value of the eSRM

Previous studies exploring the role of the eSRM in adherence to medication have been hindered by their use of cross-sectional research designs (Horne & Weinman, 2002; Llewellyn et al., 2003; Horne et al. 2004). The prospective, longitudinal design of the current study made it possible to explore the influence of time and repeated measures on the predictive value of the SRM and eSRM. The results of these studies (Studies 2 and 3) provided support for the appraisal mechanism proposed by these models, confirming that patients use concrete symptom experiences as their primary means of appraising their treatment and guiding their adherence decisions. Furthermore, the results showed that patients' symptom experiences fed back into their perceptions of illness as proposed by the original SRM (Leventhal et al., 1980; 1982) and extensions to the model incorporating beliefs about treatment (eSRM: Horne, 1997; 2003). In summary, patients who experienced an improvement in the symptoms they attributed to their HIV condition over time were more likely to be highly adherent to their treatment, while those who experienced persistent or worsening symptoms they attributed to HAART responded by missing doses. The way in which patients appraised their symptom experiences over the treatment process impacted on their perceptions of illness and beliefs about HAART. Consistent with hypotheses generated from the eSRM (see Table 10.1), necessity beliefs mediated the relationship between symptom appraisal and adherence, indicating that necessity beliefs were essential to this relationship. Contrary to hypotheses generated from the eSRM, the relationship between HAART symptom appraisal and adherence was not dependent on the strength of patients' concerns about HAART.

This research goes further than any previous studies by not only confirming the relationship between symptom appraisal and adherence, but also specifying the pathways by which these symptom experiences impacted on adherence. The findings highlight the central role of necessity beliefs in the relationship between symptom experiences and adherence to HAART in accordance with the extended model proposed by Horne (eSRM: 1997; 2003), paving the way for the design of evidence-based interventions to improve adherence among this group (as discussed in Section 10.7).

The final set of hypotheses (see Table 10.1) predicted that perceptions of illness and beliefs about HAART would change significantly over time, in accordance with the SRM (Leventhal et al., 1980) and eSRM (Horne et al., 1997; 2003). Of the illness perceptions measured, only symptoms and treatment control beliefs changed significantly over time. There were no significant changes in consequences, timeline, cyclical timeline, personal control or illness coherence over the six months of HAART. These results present a challenge to the original SRM proposed by Leventhal et al. (1980), which proposed that illness perceptions are dynamic, and that changes in these constructs would impact on coping procedures such as adherence to treatment. Few previous studies have explored changes in illness perceptions over time. If these results can be replicated within different illness groups it is recommended that the model should be reviewed in the light of this finding. The fact that perceptions of timeline, consequences and identity *before* treatment is initiated impacted on subsequent adherence suggests that interventions aimed at improving adherence would benefit from addressing these perceptions before treatment is initiated, rather than at later time-points.

While identifying little variation in illness perceptions, the results of Study 3 provide support for hypotheses stemming from the extended SRM proposed by Horne (1997; 2003) (see Table 10.1), which proposed that beliefs about HAART (necessity and concerns) change over time and predict adherence. Dramatic changes in both necessity and concerns were seen over time. The data confirmed that patients' perceptions of necessity declined over the treatment process, and furthermore, that experiencing a decline in necessity was predictive of non-

adherence. These findings suggest that interventions to maintain high levels of adherence among patients receiving HAART should focus on maintaining strong perceptions of necessity across the treatment process. Moreover, the findings showed dynamic relationships between necessity beliefs and illness perceptions. Consistent with hypotheses, the decline in necessity beliefs over time was associated with an increase of symptoms attributed to HAART side effects, an increase in recurrence of symptoms over time (cyclical timeline), a decrease in perceptions of control over HIV (treatment control and personal control) and a decrease in illness coherence. Contrary to hypotheses derived from the eSRM, experiencing a decline in necessity beliefs over time was not associated with changes in consequences or timeline, suggesting that the model should be revised in view of these findings.

The strength of patients' concerns about HAART also declined significantly over time, but the decline in concerns over time was not associated with adherence. It appears therefore that concerns and necessity beliefs impacted on adherence in different ways: concerns about HAART before treatment was initiated led to subsequent non-adherence, while pre-treatment perceptions of necessity did not impact on subsequent adherence. Conversely, while the decline in necessity beliefs over time led to non-adherence, the decline in concerns over time did not impact on adherence. These findings have important implications both in terms of the modification and development of the eSRM, and for the content and timing of interventions aimed at supporting adherence among those receiving HAART.

10.5.5.2 New knowledge that has been gained as a result of this thesis

In summary, the empirical section of the thesis extends previous research and provides major contributions to the future development of the SRM. The results give a better understanding of the determinants of adherence to HAART and emphasise the utility of the Necessity-Concerns framework. They provide an evidence base for the inclusion of patients' beliefs about HAART in interventions to support adherence to treatment. In this respect, they offer the potential to augment existing interventions in this area. Finally the results contribute to the development of theory, in particular the eSRM, as summarised below.

First, this thesis provides general support for the utility of Horne's Necessity-Concerns framework, and his suggestion that applying this framework enhances the predictive power of Leventhal's SRM when it is applied to adherence (Horne, 2003). The results showed that treatment beliefs exerted both direct influences on adherence (where strong concerns about HAART before initiating treatment, and experiencing a decline in perceptions of necessity over time, led to low adherence) and indirect influences on adherence (where necessity beliefs mediated the relationships between symptom appraisal and adherence). Second, many of the direct relationships between illness perceptions and adherence that were predicted by the original SRM were not upheld by the results: contrary to hypotheses, more positive perceptions of illness (rather than more negative perceptions of illness) were related to high adherence, and control beliefs were not directly related to adherence to HAART. However, it should be acknowledged that the SRM is not a prescriptive model, and that the principle of the model is that in order to understand variations in behaviour, we need to understand patients' illness perceptions (Leventhal et al., 1980). Third, the results confirmed relationships between illness perceptions and treatment beliefs proposed by Horne (1997; 2003). Specifically, perceived necessity for HAART was associated with strong perceptions of treatment control and poor subjective physical health, but not with other illness perceptions or with more objective laboratory test results (CD4 count or viral load), while concerns about HAART were related to negative beliefs about treatment in general, but not to having previous negative experience of HAART. Fourth, the results provided evidence for an appraisal mechanism whereby patients' used their experiences of symptoms to guide their adherence decisions, with changes in HIV and HAART related symptoms over time feeding back into their perceptions of HIV and HAART. Fifth, the results showed that beliefs about treatment (but not illness perceptions) changed significantly over the treatment process, and that experiencing a decline in necessity beliefs, but not concerns, over time predicted non-adherence. Finally, the results provided evidence of dynamic relationships between necessity beliefs and adherence over time, and for interrelationships between perceptions of HIV and HAART over time that were consistent with hypotheses derived from the extended SRM. Despite the major contributions of this research to the development of the eSRM, outstanding

questions remain which should be addressed by future research, including the role of negative affect and past experience of treatment in the model.

These findings have important implications for HIV-clinical practice and for the development of interventions to promote and maintain adherence to HAART. These are discussed in Section 10.7.

10.6 Limitations of empirical section

It is acknowledged that this study has several limitations, which should be taken into account when drawing conclusions from the findings. These limitations are discussed below.

10.6.1 Methodological issues

10.6.1.1 Sample size

Adherence was framed as a dichotomous variable in this study in order to be clinically meaningful (Paterson et al., 2000). However, the study was underpowered for logistic regression, which requires a minimum of 50 cases per predictor variable (Aldrich & Nelson, 1984) in order to have statistical power, that is, to avoid the type II error of accepting the null hypothesis when it is, in fact, false. A much larger sample would allow the use of logistic regression to predict adherence in order to determine the relative contribution of perceptions of HIV and HAART against negative affect, clinical and demographic variables. In this way it would also be possible to estimate how much of the variance in adherence could be accounted for by baseline predictors, and how much could be explained by changes in beliefs across the treatment process. Replication with a much larger sample would be needed to answer this question.

10.6.1.2 Sample bias

White, gay men were over-represented among the population receiving HIV care at the Lawson Unit in Brighton. The most likely HIV transmission route for 86.8% of participants recruited to this study was sex between men. Of those reporting their transmission risk as sex between men, 91.9% described their ethnic origin as 'white UK'. Figures from the Communicable Disease Surveillance Centre (July 2003) show that the cumulative percentage

of HIV infection acquired as a result of sex between men in the UK from 1993 to the end of June 2003 was 51.7%. Therefore the results of this study may not be directly applicable to the population of HIV positive adults in the UK as a whole. In order to inform a nationally applicable intervention to enhance adherence to HAART, the study requires replication with other populations of HIV positive adults in the UK, including men and women who have been infected with HIV through heterosexual sex with partners from Africa and those whose route of transmission stems from intravenous drug use.

10.6.1.3 Attrition

Of 114 participants recruited to the study, only 60% provided complete data. In order to ensure that these populations were representative of the Brighton clinic as a whole, the demographic and clinical characteristics of each sample was compared to the overall study population. Few differences were found, however gay men and those who were receiving their antiretroviral as part of a clinical trial were more likely to complete the study. It is therefore likely that even within the Brighton population, gay men were over-represented in the study sample. Reasons for increased participation among gay men are not clear, although it could be speculated that the gay population in Brighton might be generally more open about HIV or more used to participating in research compared to women, heterosexual men or those who acquired HIV through intravenous drug use. Those who consent to clinical research trials may be less likely to be lost to follow-up, since patients who consent to receive their treatment as part of a clinical trial may be more motivated to engage in research more generally (Enstrom et al., 2000). Because clinical trial participants are followed up more closely, they usually attend the clinic more frequently than those receiving routine care. This gives the patient a greater opportunity to complete questionnaires in the waiting room, and the researcher a greater opportunity to follow up missing questionnaires.

A concerted effort was made to avoid attrition. The majority of attrition occurred before the first assessment was completed. In a typical scenario (40% of drop-out cases) the participant consented to the study but failed to return the baseline questionnaire. Telephone reminders were made as set out in the General Methodology but the questionnaire was not returned

before the participant initiated treatment. One of the greatest disadvantages of attrition from adherence studies is the possibility that those who fail to complete assessments may also be more likely to be non-adherent to their medication, thus creating a biased sample. Although it was not possible to gain adherence information on those who did not complete any adherence assessments, it was possible to collect follow-up clinical information for those whose clinical care remained at the Lawson Unit. A proxy measure of adherence: undetectable viral load six months after initiating HAART, was collected. Those who dropped out of the study were no more likely to have a detectable viral load six months after initiating treatment than those who provided data for the study. It is therefore unlikely that the sample retained were biased in terms of non-adherence.

10.6.1.4 Sampling bias

Patients were referred to the study by their HIV physician at the Lawson Unit. Inspection of the recruitment figures, illustrated in the General Methodology, shows that 32 (21%) of those receiving a treatment recommendation were not referred to the study. While half of those were not referred for reasons beyond the doctor's control including patient refusal or non-attendance at appointment, the other half were not referred because the doctor forgot, was too busy, considered the patient to be too upset or depressed to participate or for unspecified reasons. Physician non-referral could introduce a sampling bias: it is possible that patients who were not referred to the study may have been more likely to be non-adherent. Non-adherence to clinic appointments has previously been related to non-adherence to medication (Chesney, 2000). Referral through a nurse or other clinic worker might be advantageous in future studies, since patients may have more frequent contacts with nurses. For example in Brighton patients may 'drop-in' to give blood samples, or may make an unplanned appointment to see a doctor, at which time they might also see the nurse. These unplanned visits are likely to be more frequent than a pre-booked clinic appointment.

10.6.1.5 Ensuring greater completion of questionnaires

One method of ensuring greater completion of questionnaires would be to give out and collect questionnaires in the clinic, so that there was no postal option. This was not always possible

for the baseline questionnaire in the current study, where patients were referred to the study by their clinician following their clinic appointment, and often did not have time after their appointment to complete the questionnaire. If referral was made through another member of staff, such as a nurse or other clinic worker, the patient might have more time prior to their clinic appointment to complete the questionnaire. The subsequent questionnaires (T1, T2 and T3) were routinely posted back in a stamped addressed envelope. In future studies, it might be advantageous to approach the participant in the clinic waiting room at a time corresponding to a routine clinic appointment, so that the participant is able to complete the questionnaire while at the clinic.

10.6.2 Measures

Further limitations to the study may have been related to the measures used. These limitations are discussed below.

10.6.2.1 IPQ-Timeline scale

The *timeline* scale of the IPQ was reduced to a single item "my illness will improve in time" for this study. This item may not reflect the chronic/acute timeline in the original sense of the timeline scale. The scale was adapted for this study because the pilot study indicated that people living with HIV unanimously view their condition as chronic, therefore there would be no variation in timeline scores. The single item was retained because people differed in terms of their expectations, some felt they would improve, some felt their health would be maintained at a certain level and others felt they would get worse in time. However, since these were patients who were initiating a new treatment regimen, the item could reflect treatment optimism. Treatment optimism has been related to adherence to medication in other illness groups (Schier & Carver, 1985; Schier et a., 1989; Taylor et al., 1992). Further development of the timeline scale is required to adapt the scale for use with HIV populations.

10.6.2.2 IPQ-Identity

The symptom scales used for this study were based on a list of twelve generic symptoms common to any illness and eleven additional common HIV-related symptoms, as recommended by the authors of the IPQ (Weinman et al., 1996). However, symptoms of HIV

are wide ranging and it is possible that participants may have been experiencing additional severe symptoms that were not included on the symptom checklist. Furthermore there is a myriad of possible HAART-related symptoms that were not included on the symptom lists. A more comprehensive list of symptoms may be useful for future studies. Please see Appendix 5.

10.6.2.3 Symptom severity/ Impact on daily functioning

Rating symptoms on a simple scale might minimise the importance of one very severe symptom or over-inflate the importance of several minor symptoms. In an attempt to overcome this problem, a severity scale was added for the current study, where participants were required to rate the severity of each symptom they experienced on a scale from 1-5. A second identity scale was calculated to include only symptoms that patients rated as moderate, severe or very severe. Although at baseline this scale showed stronger relationships with adherence, scores were not related to perceptions of treatment necessity, as predicted by the eSRM. The SF-12 physical health scale was included in this study in order to assess the impact of symptoms on daily functioning. Patients' subjective ratings of their physical health on the SF-12 accounted for approximately a fifth of the variance in necessity beliefs. This scale encompasses the subjective impact of illness on a variety of areas of functioning, including work, daily chores, social life and vitality. This broader rating of health status may be more relevant to determining patients' perceptions of their necessity for treatment than scales assessing symptom frequency or severity. The results highlight the utility of this measure used alongside symptom scales for future HIV research.

10.6.2.4 Attribution of symptoms to HIV or HAART

The current study extended previous research by asking participants whether they attributed their symptoms to their illness or treatment and investigating whether attribution of symptoms to HIV or HAART impacted differentially on adherence. Participants were presented with two identical lists of symptoms and asked to rate those they attributed to HIV and those they attributed to HAART in terms of their severity. In order to avoid confusion or fatigue due to repetition, a single, more comprehensive list of symptoms could be included in future studies,

where patients would be asked to rate the symptoms they attributed to HIV only, those they attributed to HAART only, those they attributed to neither HIV nor HAART and those they are not sure whether are due to HIV and/or HAART. Please see Appendix 5 for a suggested symptom scale.

10.6.2.5 IPQ-Causal scale

The causal scale of the IPQ was omitted from the current study because the results of the pilot study showed that patients unanimously attributed the cause of their HIV to a germ or virus. The lack of variation in causal attributions rendered the use of this scale invalid. However, the causal scale could be revised for use with HIV populations by adapting the scale instructions to refer not to the cause of HIV itself but to factors associated with the progression of the virus. The results of a study investigating causal attributions and immune decline among HIV-positive gay men suggest that this might be an interesting route of investigation. Segerstrom et al. (1996) found that participants' attributions about the causes of events to negative beliefs about themselves significantly predicted subsequent decline in CD4 count, and that this relationship was independent of depression. A potentially interesting line of enquiry for future research would be to gauge whether attributions of HIV progression to biological, emotional, environmental and psychological factors differentially impact on patients' use of coping procedures including adherence to HAART. For example, it might be hypothesised that patients who attribute the progression of their disease to purely biological factors would be more likely to adhere to their medication than those who attribute the progression of their disease to emotional factors, while those who attribute the progression of HIV to emotional factors would be more likely to skip doses if taking the medication made them feel depressed or anxious.

10.6.2.6 BMQ-Concerns about HAART

Insights from recent interview-based studies suggest concerns about this treatment might be more complex than those currently covered by the BMQ-HAART. In a study of gay men who had received a clinically recommended treatment offer of HAART (Cooper et al., 2002a; 2002b), a range of additional concerns were uncovered. These included patients' fears that

the drugs would make them worse, accelerate the progression of HIV, or decrease their quality of life; worries about potential adverse effects of the drugs on libido and sex-life; concerns that treatments have not been thoroughly tested by drug companies or feelings of being experimented upon; fears that taking treatment would have a negative affect on self-identity because it is an unwelcome, daily reminder of HIV, or because it signifies a personal failure to fight the virus; concerns about future treatment options as a result of becoming resistant to all classes of antiretrovirals; concerns about the potentially life-long commitment to taking treatment and concerns stemming from previous negative experiences of taking antiretrovirals. Revising the BMQ-concerns scale to include these items may increase its predictive power by encompassing a more comprehensive range of the types of concerns encountered by patients who are faced with decisions about HAART and which might impact on adherence.

10.6.2.7 Perceptions of laboratory markers of disease progression

The hypothesis that patients' perceptions of their personal need for HAART would be influenced by their CD4 counts was not fully supported by the data. Although lower CD4 count was associated with stronger perceptions of need for HAART, this relationship did not reach statistical significance. This lack of a relationship between CD4 and necessity could be due to the fact that in clinical terms, all patients who took part in this study were eligible for HAART (which is often determined by CD4 count: BHIVA, 2003). However, recent research suggests that patients' *perceptions* of their laboratory test results often differ from those of their doctors. For example, two recent interview-based studies found that participants often believed that too much emphasis was placed in abstract clinical markers, which did not reflect their subjective experiences of their health (Cooper et al., 2002a; Siegel et al., 2000). Furthermore, patients who had been taking HAART for six months sometimes interpreted an undetectable viral load as a sign that treatment had completed its purpose, and consequently believed that continuing to take HAART was no longer so important (Cooper et al., 2003). Patients' interpretations of their laboratory test results may therefore differ from the medical view and yet inform their personal perceptions of necessity for HAART. A measure of patients' *perceptions* of their CD4 count and viral load could be incorporated into HAART-specific BMQ scales in future. Suggested items are included in Appendix 5.

10.6.2.8 Adherence measure

Adherence to HAART was measured using a single visual analogue scale adapted from the MASRI (Walsh et al., 2000) which required patients to estimate the percentage of medicine they had taken as prescribed over the preceding month. Although self-report measures of adherence have been criticised because of the tendency of participants to over-report adherence, this measure showed good validity against viral load and pharmacy prescription redemption data in the current study. Other advantages of this measure were that it was quick to administer and easily understood by patients. More information regarding specific adherence problems, such as adherence to timing or food restrictions, might be useful in future studies, in order to pinpoint areas of difficulty among those reporting low adherence.

10.6.3 Procedure

10.6.3.1 Repetition of questionnaires

Participants were required to answer the same questionnaire on four occasions. Oppenheim (1992) suggests that this might introduce a source of bias, because people aim to complete questionnaires consistently. However, this does not seem to have been applicable to the present study, where change over time was evident on some scales, but not on others.

10.6.3.2 Length of follow-up

The follow-up of this study was limited to six months on HAART, due to time and funding restrictions. Six months of HAART represents a therapeutic landmark in HIV, by which most patients experience clinical benefit of their treatment in terms of achieving an undetectable viral load (Lepri et al., 2001). However, the relatively short length of follow-up meant that many of the factors or beliefs that might impact on adherence over the longer term could not be investigated. These include long term toxicities such as metabolic disorders particularly lipodystrophy which have previously been related to adherence (Ammassari et al., 2002), as well as other possible factors associated with adherence in the long-term such as settling into a routine, encountering problems due to inconvenient treatment regimens or having to change treatment due to viral resistance (Montaner, 2003). The long-term effects of taking HAART

are particularly salient at the present time, since many patients have been taking HAART regimens for several years. Various aspects of long-term exposure to HAART may impact on quality of life and adherence. This is an important area for future research, since to date, the longest follow-up found in the published literature was twenty months (Duran et al., 2001).

10.6.4 Advantages and limitations of the statistical approaches taken to this work

This study utilised multiple statistical tests to examine relationships between variables. The advantage of using multiple statistical tests in this study was that the results were unlikely to be affected by type II error. Type II error is the probability of accepting the null hypothesis (i.e. finding no relationship between variables) when it is, in fact, false (i.e. the variables are significantly related). However, the major disadvantage of using multiple statistical tests is that they may be affected by type I error. Type I error is the probability of rejecting the null hypothesis (i.e. finding a significant relationship between variables) when it is, in fact, true (i.e. the relationship identified was due to chance). The probability of a type I error for each test is the 'p'-value, which, in the studies contained within this thesis, was set at 95%. The capacity to avoid type II error is known as the study's power, which in this study ranged between 60-80%. The study lacked the power to conduct logistic regression with an acceptable degree of confidence, since the sample size was too small. Multiple statistical tests were therefore carried out in all of the studies included in this thesis.

The large number of statistical tests carried out in these studies increased the possibility of type I error, because each test has 5% probability of type 1 error. One way of adjusting is the Bonferroni correction, which means changing the level of significance to a lower value. However this inevitably increases the type II error rate. As the type II error rate is already quite high (ranging 20 – 40%), the level of significance was maintained at 95%, with a risk that some of the results may be subject to type I error.

10.6.4.1 The need for Structural Equational Modelling (SEM)

The results of this study provide insights into relationships between illness perceptions, beliefs about HAART and adherence as suggested by the eSRM. The statistics used in this study are not, however, the optimal method of determining the nature of these relationships.

Standard tests such as correlations, t-tests and ANOVA which were used in this study simply look at linear combinations of variables and can therefore only test simple hypotheses, such as whether perceptions of illness and treatment are related to adherence. Structured Equational Modelling (SEM) is a more sophisticated statistical technique, which could be used to test the model in its entirety, given a much larger study population. This technique takes into account measurement error, clarifying the distinction between the measured variables and the constructs one is attempting to measure ('latent variables', such as adherence). In order to test the fit of the eSRM to adherence, a sample of 300-400 would be required. The use of SEM within a large prospective study of adherence is now a priority, in order to provide a more definitive test of the utility of the eSRM. Such a study is justified by the findings of this thesis, which lend preliminary support to the model.

10.6.4.2 Estimation of variance in adherence accounted for by the eSRM at baseline and over time

Although it was not possible to carry out multivariate statistics with an acceptable degree of confidence, due to the strong possibility of type II error stemming from an inadequate sample size, logistic regression showed that approximately 44.9% of the variance in adherence could be attributed a model that included baseline perceptions of HIV and HAART. A further 30.1% of the variance in adherence could be attributed to the change in symptoms (HIV and HAART) and necessity beliefs over time.

10.6.5 Variables not tested in the model, which could be important determinants of outcome

It is acknowledged that several other factors, not measured in this thesis, may have contributed further to the variation in adherence.

10.6.5.1 Social support and coping strategies

The results of the critical review in Chapter 2 showed that additional psychological variables, such as social support and coping strategies have been related to adherence. As well as

exerting a direct influence on adherence, it is possible that these variables might mediate relationships between perceptions of HIV/HAART and adherence. Social support has been shown to 'buffer' the negative psychological effects of illness (Schneiderman et al., 1992). It is possible that access to adequate social resources may also impact on adherence, either directly, or via the individuals' perceptions of their illness and treatment. For example, adherence may be improved by allowing the patient to express his or her concerns about HAART, or by providing support, reassurance or information concerning side effects.

The importance of constructs such as social support is acknowledged within the SRM (Leventhal et al., 2001) and eSRM (Horne, 2003) but these variables are generally viewed as 'background variables'. A key priority for the development of the model is to achieve a more coherent and detailed view about the role of social support within the SRM. This is essential given the proven efficacy of interventions utilising social support to enhance coping and self-management of HIV/AIDS (Antoni et al., 1996; 1991).

10.6.5.2 Repeated measurement of affect beyond the baseline observation

Further variation in adherence may be due to anxiety and depression. In the current study, these variables were only measured at the baseline assessment. Future research would benefit from repeated measurement and analysis of these variables, since it is likely that anxiety and depression at the time of the adherence assessment would have an impact on adherence at that time (Arnsten et al., 1996; Avants et al., 2001; Kleeberger et al., 2001; Pratt et al., 2001; Simioni et al., 2002). Furthermore, changes in anxiety and depression over time might affect adherence to medication. For example, adherence might improve among patients who receive successful treatment for depression, or worsen among those who become more depressed over time (Kleeberger et al., 2004). Although depression and anxiety were combined into a single 'negative affect' construct in the current study, it is likely that these variables impact on adherence through different pathways. Patients who are depressed might experience difficulties with adherence as the result of impaired motivation or memory, while high levels of anxiety might have a negative impact on adherence because of heightened perceptions of sensitivity to side effects (Watson & Pennebaker, 1989). Indeed, interventions

aimed at improving coping among HIV positive patients appear to reduce anxiety and depression through different mediational pathways (Lutgendorf et al., 1998), with reductions in depression attributed to changes in coping strategies, and reductions in anxiety related to improved social support utilisation. The separate influences of depression and anxiety certainly warrant further investigation in relation to the further development of the eSRM, and in the development of interventions to support high levels of adherence to HAART.

10.7. Implications of findings for the development of interventions to promote and maintain adherence to HAART

This section will explore ways in which the findings of this thesis might inform the development of interventions to support adherence to HAART.

Few interventions to date have successfully improved adherence or health outcomes among patients taking HAART. Of those that have shown improvements in adherence, the mechanisms by which the intervention promotes adherence have not been identified (Saffren et al., 2001; Pradier et al., 2003; Tuldra et al., 2000). The published literature to date lacks evidence-based or theory-driven interventions, and randomised controlled trials are urgently needed to determine what type of intervention can increase adherence to HAART. The results of this thesis have important implications for the design of a theory driven intervention aimed at increasing adherence to HAART among patients with HIV.

10.7.1 Structure of intervention

A literature search revealed only one study that focused on changing illness perceptions in order to influence outcome (Petrie et al., 2003). The intervention stemmed from work which showed that patients' perceptions of their myocardial infarction (MI), elicited soon after the acute event, were associated with various aspects of their recovery including return to work (Petrie et al., 1996) and attendance at cardiac rehabilitation classes (Petrie et al., 1996, Cooper et al., 1999). This intervention comprised a first session in which the pathophysiology of MI was explained and patients' beliefs about the causes of their MI were explored, since

many patients attributed their MI to stress and not to lifestyle factors. The second session involved developing a plan to minimise future MI risk by altering risk factors and increasing patients' perceptions of control. Patients' scores on the timeline and consequences scales of the IPQ were used to identify maladaptive beliefs, which were challenged in the session, and an individualised recovery plan was developed. The third session involved a review of the recovery plan, a discussion of symptoms that were attributed to recovery and those which might be warning signs of a future MI, and exploration of patients' concerns about their medication. The results showed significant differences between controls and intervention participants on consequences, timeline, control/cure and symptom distress scales at discharge from hospital. Timeline and cure control scores remained significantly more positive in the intervention group three months later. Intervention participants were less likely to report angina pains at three months. When controlling for disease-related factors, the intervention group returned to work significantly faster than controls.

The results of this thesis indicate that a similarly structured intervention, aimed at changing perceptions of HIV and HAART, may be applicable to efforts to improve and maintain adherence to HAART. The findings of the study described in this thesis could be used to inform specific targets for intervention.

10.7.2 Targets for intervention

The results of this thesis indicate that interventions aimed at changing perceptions of HIV and HAART may increase adherence. Proposed targets for intervention, stemming from the major findings of this thesis, are highlighted below.

10.7.2.1 Perceptions of illness and treatment

10.7.2.1.1 Concerns about potential adverse effects of HAART

Patients' concerns about potential adverse effects of taking HAART, elicited before they initiated treatment, predicted subsequent adherence. The strength of patients' concerns about HAART declined steeply over the first month of taking HAART, suggesting that their expectations of adverse effects exceeded their subsequent experience. These findings

indicate that attempts should be made to elicit and address patients concerns about HAART *before* they initiate treatment. These concerns may include worry about side effects, adverse long-term effects, practical difficulties such as timing and disruption to routine, as well as more abstract worries about the stigma or embarrassment surrounding the medication.

10.7.2.1.2 Perceptions of necessity for HAART

Reporting a decline in perceptions of personal necessity for treatment over time was associated with low adherence to HAART. This finding indicates that efforts to improve adherence to HAART should focus on maintaining strong perceptions of personal necessity for treatment among participants. Predictors of decline in perceived necessity for HAART over time were identified in this study and may provide a useful focus for intervention. These included experiencing a lack of improvement in HAART related symptoms, experiencing a decline in the expectation that one's condition would improve in time, experiencing a decline in perceptions of control over HIV and experiencing a decline in illness coherence. Furthermore, changes in CD4 count and viral load were not related to the decline in necessity over time. These results suggest that patients' perceptions of necessity may be improved by a psych-educative intervention focusing on increasing patients' attention to clinical markers of disease progression in evaluating the efficacy and continued necessity for their treatment.

10.7.2.1.3 Perceptions of personal sensitivity to adverse effects

Participants who scored high on the SENSOMA at baseline reported low adherence at follow-up, indicating that patients' perceptions of their personal vulnerability to adverse effects of medication in general should be elicited and addressed before they initiate treatment. The fact that this relationship was mediated by having had past experience of antiretroviral treatment indicates that for many, these perceptions stem from previous negative experiences of taking HAART. Interventions to promote high adherence should therefore elicit patients' previous experiences of antiretroviral treatment and address they ways in which these experiences might relate to the patients' current belief systems and future adherence behaviour.

10.7.2.1.4 Illness perceptions

Adherence six months after initiating HAART was predicted by patients' perceptions of their illness identity, consequences, timeline, cyclical timeline at baseline. Those with more negative perceptions of their illness and its likely course were more likely to report low adherence. Adherence was not significantly related to changes in illness perceptions over time. These results indicate that interventions aimed at supporting high adherence should aim to elicit and address patients' perceptions of HIV before they initiate treatment. The aim of the intervention would be to challenge any unrealistic or unduly pessimistic perceptions of HIV.

10.7.2.1.5 Symptom appraisal

The results from this thesis show that patients who experience a lack of improvement in the symptoms they associate with their illness, despite taking HAART, or who experience persistent side effects from their treatment are likely doubt the continued necessity for their treatment and respond with low adherence. The results also show that a lack of symptomatic improvement over time was associated with stronger concerns about adverse effects of HAART. Efforts should be made to alleviate symptoms associated with both HIV and HAART over the treatment process. Because it would not always be possible to eliminate or alleviate symptoms pharmacologically, efforts should be made to help patients to cope with their symptoms (e.g. using psychological techniques or complementary therapies). It might be beneficial to provide participants with information regarding what they should expect to happen in relation to their symptoms and what to do if symptoms worsen or are not alleviated. Since perceptions of necessity were found to mediate relationships between symptom change and adherence, the intervention should aim to enhance perceptions of necessity for HAART amongst those experiencing persistent or worsening symptoms. The intervention should encompass an education module, which ensures that patients attend to clinical markers of their disease progression and treatment success (CD4 count and viral load) in order to ensure that symptoms are not used erroneously to gauge the clinical success of HAART.

10.7.2.2 Baseline depression and anxiety

Measurement of depression and anxiety over time, or at the adherence assessment, was not included in the current study. However, strong correlations existed between anxiety or depression at baseline and subsequent non-adherence. These relationships indicate that interventions to improve adherence should aim to reduce anxiety and depression among patients who are initiating HAART. Although levels of depression and anxiety were high in this group, they often fell short of the clinical cut-off for probable mood disorder. Therefore, it is unlikely that pharmacological treatment for depression and anxiety would be indicated for the majority of those initiating HAART. The non-pharmacological approaches described below appeared to be fruitful.

Levels of depression and anxiety are likely to be high among patients who are initiating HAART, partly because a clinical recommendation of HAART often follows a decline in health or a recent diagnosis of HIV. Starting treatment is an extremely stressful time for many people. Previous randomised controlled trials suggest some of the most effective interventions to improve or protect against depression and anxiety among HIV-positive groups. Many of these interventions have been administered in a group format. Antoni et al. (1991) found a group-based, cognitive-behavioural stress-management intervention (CBSM) protected against increases in anxiety and depression among a group who received notification of their HIV test results. This intervention involved techniques to build awareness of stress and negative thoughts, cognitive restructuring techniques, relaxation and imagery techniques, coping skills training, interpersonal skills training and techniques to enhance social support.

Mulder et al. (1994) found each of two different group-based interventions improved mood and decreased depression among HIV positive men, compared to waiting-list controls. Both interventions were given for 15 weeks. One of the interventions used cognitive behavioural therapy (CBT), involving training in cognitive restructuring, exercise and relaxation, health behaviour change, assertiveness skills and coping with controllable and uncontrollable

stressors. The other intervention used experiential therapy (ET), focusing on increasing awareness of the here and now, dealing with a shortened life expectancy, anxiety about death and finding a purpose in life. It was not clear how these interventions improved distress and depression, since there was no difference between the interventions in terms of changes in coping style, social support or emotional expression.

Kelly et al. (1993) compared group based CBT to a socially supportive (SS) group intervention. The CBT condition included cognitive and behavioural techniques to reduce stress and to make social and behavioural changes in their lives, muscle relaxation training, and to establish a social support network. The SS participants were asked to describe their feelings about having HIV, to share feelings and to provide support to other group members. Those receiving the interventions were compared to a standard of care control condition. Both intervention groups reported reductions in depression across the eight-week intervention. Those receiving the SS intervention also reported reduced psychological distress at a 3-month follow-up, which was attributed to the opportunity for emotional expression in a supportive environment.

Lutgendorf et al. (1998) examined the psychosocial mechanisms underlying reductions in anxiety and depression in HIV positive gay men receiving cognitive behavioural stress management (CBSM) interventions. These investigators found improvement in active coping, positive reframing and acceptance, in total social support and specific aspects of social support in those receiving the intervention compared to waiting-list controls. These results also suggested that different mechanisms underlie the improvements in depression and anxiety. Changes in coping were related to lower depression and total mood disturbance, while changes in social support were related to anxiety reduction. This study suggests that the impact of CBSM interventions on anxiety and depression is mediated by different pathways.

In summary, group-based interventions appear to be effective in reducing depression and anxiety among patients with HIV. Allowing emotional expression in a supportive environment appears to be key to improving mood and decreasing distress among patients with HIV (Antoni et al., 2000). This research suggests that cognitive behavioural stress management interventions successfully reduce anxiety and depression among patients with HIV, through the development of adaptive coping mechanisms and improved social support. This type of intervention seems to be particularly applicable to patients who are initiating HAART, since it has been shown to effectively protect against increased distress and depression among patients experiencing a stressful event (notification of HIV test results: Antoni et al., 1991). The impact of this type of intervention in reducing anxiety and depression among those initiating HAART, and its subsequent impact on beliefs and adherence to treatment would be an interesting avenue for future research. No studies to date have reported on changes in adherence following intervention to improve depression or anxiety.

10.7.3 Format of intervention

Given the large number of patients who initiate HAART, individual-based interventions may prove incredibly expensive and labour-intensive. There is no published information on the relative effectiveness of group versus individual based interventions to improve adherence in HIV. In addition to being cost effective, group-based interventions may enhance social support utilisation, which has been shown to mediate the effects of stress on anxiety levels (Lutgendorf et al., 1998). Providing a supportive group format might serve to improve utilisation of social support and thereby reduce buffer against increases in anxiety at the time at which treatment is initiated, and across the treatment process. The results of the current study also indicate that maintaining strong perceptions of necessity across the treatment process should form a major part of the intervention. The intervention would include a psycho-educative element to provide information regarding the continued necessity for treatment. This could easily be administered in a group format. A group setting might also provide a supportive setting allowing patients to voice their concerns about HAART and share their

experiences of symptoms and side-effects. A possible disadvantage of this format, however, is the possibility that some individuals may be inhibited from fully expressing their concerns about HAART, because of issues of confidentiality, stigma or embarrassment. A potential solution to this problem would be to administer the bulk of the intervention in a group format, with a back-up, one-to-one discussion to ensure the individual was able to express their all of their concerns about their treatment and to discuss the progression of individual symptoms and side-effects, in order to ensure the patients' individual treatment issues are elicited and addressed.

10.7.4 Timing of intervention

The results of this study suggest that low rates of adherence to HAART are fuelled by patients' beliefs about their illness and treatment, both before they initiate treatment and over the treatment process. They indicate that interventions to prevent the decline seen in adherence between three and six months should begin *before* the patient initiates treatment, with follow-up after 1 month and 3 months of HAART, since the beliefs fuelling non-adherence change significantly over the first month, with a significant decline in adherence about three months into treatment. The prospective, longitudinal design of this research informed the optimal timing of interventions to address the various targets for intervention. The timing of each aspect of the intervention is discussed in this section.

10.7.4.1 Concerns about HAART

Patients who expressed stronger concerns about HAART before they initiated their treatment were more likely to report low adherence at follow-up. This indicates that patients' concerns about HAART should be elicited and addressed *before they begin treatment*. A supportive group format would allow patients to openly discuss their worries, experiences and for information and advice to be given. This should be backed up with an individual session to ensure that all the patients' concerns have been elicited and addressed.

10.7.4.2 Necessity beliefs

Patients' perceptions of necessity were extremely strong before they initiated HAART, and these baseline perceptions of necessity did not impact on subsequent adherence. However, necessity beliefs declined dramatically between the baseline and one-month assessments. This indicates that increasing patients' awareness of their continued need for treatment once treatment has begun will improve adherence. Intervention to maintain strong perceptions of necessity should begin very soon after treatment has begun. Weekly psycho-educative group sessions should address perceptions of necessity for HAART across the first month of treatment, and perhaps continue on a monthly basis, since perceptions of necessity continued to decline among the low-adherence group. The current study identified several significant relationships between necessity and illness perceptions, indicating that these sessions should encompass patients' perceptions of treatment effectiveness and control over HIV, their experiences of HIV-related symptoms, HAART-related side effects and overall well-being, as well as their perceptions of laboratory test results.

10.7.4.3 Symptoms and side effects

The empirical studies within this thesis showed that patients used their experiences of symptoms, both before initiating treatment, and over time, to guide their adherence decisions. Changes in patients' experiences of symptoms they attributed to HIV and those they associated with HAART side effects over time were found to impact on adherence. Those who did not experience an improvement in the symptoms they attributed to their HIV condition between baseline and six months were less adherent to their HAART medication. Those who reported persistent or worsening side effects of HAART over time were also less likely to adhere to their treatment. These findings indicate that patients' experiences of both HIV- and HAART-related symptoms should form part of the intervention, both at baseline, and once treatment has been initiated. It is likely that patients' expectations of the impact of HAART on the symptoms they associate with HIV are not being met. These expectations could be elicited at baseline, so that unrealistic expectations can be addressed. Some of the ways in which symptoms might be addressed are discussed in Section 10.7.2.1.5 of this discussion.

10.7.4.4 Perceptions of HIV

Baseline perceptions of timeline, consequences, cyclical timeline, emotional representations, self-rated physical health all impacted on subsequent adherence. Most of these relationships were mediated by depression and anxiety, suggesting that intervention to improve depression and anxiety at baseline would eliminate the impact of these beliefs on subsequent adherence. However, patients' expectations of the likely outcome of their condition (timeline) remained predictive of subsequent adherence even after controlling for depression and anxiety. Improving patients' expectancies of a positive outcome on treatment should be included in the baseline intervention. The fact that perceptions of HIV did not change significantly over time, (with the exception of treatment control, which became more positive over time, and did not impact on adherence), indicates that there is no need to target perceptions of HIV at subsequent time-points.

10.7.4.5 Depression and anxiety

Depression and anxiety were only measured at the baseline assessment in this study, which limits the implications for the design of interventions to improve adherence. The finding that baseline depression and anxiety were strongly associated with subsequent adherence to HAART indicates that reducing depression and anxiety should be the target of intervention before treatment is initiated. Previous research suggests that group-based interventions utilising cognitive-behavioural stress-management techniques would be beneficial in reducing anxiety and depression before treatment is initiated (See Section 10.7.2.2). Further research is required in order to indicate whether depression and anxiety should be the focus of interventions at subsequent time-points.

10.7.5 Evaluation of intervention

Patients should be randomised to receive intervention or control condition so that comparisons can be made both within and between groups. The major outcome of interest would be adherence to HAART after six months of treatment. Other outcomes include change in beliefs over time, specifically, increasing necessity beliefs and perceptions of treatment control in the intervention group.

10.8 Implications for future research

The findings of this thesis have illuminated several areas that warrant further research. These are outlined below.

10.8.1 The role of depression and anxiety in the eSRM

While it was evident that negative affect at baseline predicted subsequent adherence, and that depression and anxiety mediated many of the relationships between illness and treatment perceptions and adherence, further research is required in order to determine the impact of depression and anxiety at the time of the adherence assessment on adherence and beliefs. Furthermore, the direction of relationships between perceptions of HIV/HAART and negative affect were not clarified in the current study. The direction of causality between perceptions of illness and treatment and negative mood warrants further investigation. Further research is also required to explore the possible separate influences of depression and anxiety on adherence and beliefs in order to develop effective interventions to support adherence.

10.8.2 The role of social support in the eSRM

The importance of constructs such as social support is acknowledged within the SRM (Leventhal et al., 2001) and eSRM (Horne, 2003) but these variables are generally viewed as 'background variables'. A key priority for the development of the model is to achieve a more coherent and detailed view about the role of social support within the SRM. This is essential given the proven efficacy of interventions utilising social support to enhance coping and self-management of HIV/AIDS (Antoni et al., 1996; 1991).

10.8.3 Patients' perceptions of blood test results

While clinical guidelines advocate the use of viral load testing to evaluate the efficacy of HAART, there has been little empirical investigation of how HIV positive individuals perceive their laboratory test results (CD4 count and viral load). Patients' perceptions of their blood test

results might feed back into perceptions of HIV/HAART and influence adherence. Qualitative studies suggest that this might be a useful route of inquiry (Cooper et al., 2002; 2003).

10.8.4 Coping with symptoms and side effects

Results from the current study showed that patients' experiences of symptoms attributed to HIV and side effects attributed to HAART were associated with low adherence. There has been very little research into the most effective ways of managing persistent symptoms and side effects among people with HIV. Further research is required in order to explore the impact of physical, psychological and practical interventions to alleviate or manage symptoms on adherence to HAART and quality of life among people with HIV.

10.8.5 Patterns and predictors of adherence over the long-term

The follow-up in the current study was limited to six months. Little is known about patterns or predictors of adherence over the long-term. Further research is required in order to gain more detailed information regarding patients' experiences of taking HAART over time. This data is required in order to inform interventions to support patients (e.g. to cope with long-term side effects and the psychological impact of taking long-term treatments) and to enable them to continue with treatment.

10.8.6 Replication studies

The current study reflects the clinic population in Brighton of approximately 90% gay men. It is likely that other groups have distinct or additional beliefs about HAART. Since these beliefs may be associated with adherence to HAART, the findings require replication within a range of HIV populations in order to develop intervention based on a more representative sample.

10.8.7 The impact of structured treatment interruptions on adherence and beliefs

The growing clinical interest in the feasibility of structured treatment interruptions (STIs) for patients with undetectable viral load presents an area of interest for future psychological research. Limited research has been conducted into the psychological consequences of treatment interruptions and re-instatement, however, data from one study suggests that

patients experience increased well-being and quality of life when treatment is stopped with a subsequent decline when it is re-introduced (Tuldra et al., 2001). The impact of STIs on patients' perceptions of their illness and treatment and on adherence over the long-term would be of considerable interest.

10.9 Conclusions

The studies contained within this thesis have increased our understanding of patients' perspectives of HIV and HAART. They demonstrate how patients' perceptions of their illness and its treatment impact on their adherence decisions, and validate the extended SRM as a useful model within which to frame adherence to HAART among patients with HIV-infection. The results support the view of the patient as an active information processor, who makes sense of his or her illness experiences by developing and reassessing his or her beliefs about illness and treatment, which in turn, influence adherence decisions and clinical outcome. The data support the theoretical framework provided by the SRM (Leventhal et al., 1980) and the specific operationalisation of the model in relation to adherence suggested by Horne (1997; 2003). As well as providing insights into the further development of the eSRM in relation to adherence, this thesis has highlighted areas for future research, including the role of depression, anxiety and social support in the eSRM.

If the findings of this thesis can be replicated with larger samples and more representative clinic populations, they have important implications for the design of evidence-based interventions to maintain high levels of adherence to HAART. Targets for intervention include treating depression and anxiety, eliciting and addressing negative perceptions of HIV and concerns about HAART, maintaining strong perceptions of necessity for HAART, and helping patients to cope with negative symptom experiences. This type of intervention may be combined with existing approaches to support patients by facilitating effective coping and self-management of HIV/AIDS.

References

Abel, E. & Painter, L. (2003). Factors that influence adherence to HIV medications: perceptions of women and health care providers. *Journal of the Association of Nurses in AIDS Care, 14,* 61-69.

Ajzen, I. & Fishbein, M. (1980). *Understanding attitudes and predicting social behaviour*. Englewood Cliffs, NJ: Prentice-Hall.

Ajzen, I. (1988). *Attitudes, personality, and behavior.* (xiv, 175pp. ed.). Milton Keynes: Open University Press.

Albarracin D. & Wyer, R.S. Jr. (2000) The cognitive impact of past behaviour: influences on beliefs, attitudes, and future behavioural decisions. *Journal of Personality and Social Psychology. 79 (1)*: 5, July.

Aldrich, J. & Nelson, F. (1984). *Linear Probability, logit and probit models*. California: Sage.

Altice, F. L., Mostashari, F., & Friedland, G. H. (2001). Trust and the acceptance of and adherence to antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 28,* 47-58.

Ammassari, A., Antinori, A., Cozzi-Lepri, A., Trotta, M. P., Nasti, G., Ridolfi, A. L. et al. (2002b). Relationship between HAART adherence and adipose tissue alterations. *Journal of Acquired Immune Deficiency Syndromes, 31,* s140-s144.

Ammassari, A., Murri, R., Pezzotti, P., Trotta, M. P., Ravasio, L., De Longis, P. et al. (2001). Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 28,* 445-449.

Ammassari, A., Starace, F., Aloisi, M. S., Trotta, M. P., Murri, R., d'Arminio, M. A. et al. (2003). Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. *Neurology, 61,* 723.

Ammassari, A., Trotta, M. P., Murri, R., Castelli, F., Narciso, P., Noto, P. et al. (2002a). Correlates and predictors of adherence to HAART: overview of published literature. *Journal of Acquired Immune Deficiency Syndromes, 31,* s123.

Andrews, L. & Friedland, G. (2000). Progress in HIV therapeutics and the challenges of adherence to antiretroviral therapy. *Infectious Disease Clinics of North America* 14[4], 901-928.

Antoni, M.H., Baggett, L., Ironson, G., August, S., LaPerriere, A., Klimas, N., Schneiderman, N. & Fletcher, M.A. (1991). Cognitive behavioural stress management intervention buffers distress responses and immunologic changes following notification of HIV-1 seropositivity. *Journal of Consulting and Clinical Psychology, 59*, 906-915.

Antoni, M.H., Lutgendorf, S., Ironson, G., Fletcher, M.A., & Shneiderman, N. (1996). CBSM intervention effects on social support, coping, depression and immune function in systematic HIV-infected men. *Psychosomatic Medicine, 58*, 86.

Antoni, M.H., Wagner, S., Cruess, D., Kumar, M., Lutgendorf, S., Ironson, G., Dettmer, E., Williams, J., Kilmas, N., Fletcher, M.A., & Schneiderman, N. (2000). Cognitive behavioural stress management reduces distress and 24-hour urinary free cortisol among symptomatic HIV-infected gay men. *Annals of Behavioral Medicine, 22,* 29-37.

Armitage, C. & Conner, M. (1999). The theory of planned behaviour: Assessment of predictive validity and 'perceived control'. *British Journal of Social Psychology, 38,* 35-54.

Arnsten, J., Demas, P., Farzadegan, H., Grant, R., Gourevitch, M., & et al (2001). ARV therapy adherence and viral suppression in HIV infected drug users: Comparison of self-report and electronic monitoring. *Clinical Infectious Diseases, 33,* 1417.

Arnsten, J., Demas, P., Grant, R., Gourevitch, M., Farzadegan, H., Howard, A. et al. (2002). Impact of Active drug use on ARV therapy adherence and viral suppression in HIV-infected drug users. *Journal of General Internal Medicine, 17,* 377.

Avants, S. K., Margolin, A., & Warburton, L. (2001). Predictors of nonadherence to HIV-related medication regimens during methadone stabilization. *American Journal on Addictions, 10,* 78.

Aversa, S. L. (1996). Psychosocial aspects of antiretroviral medication use among HIV patients. *Patient Education & Counseling, 29*(2), 219.

Bakken, S., Holzemer, W. L., Brown, M. A., Powell-Cope, G. M., Turner, J. G., Inouye, J. et al. (2000). Relationships between perception of engagement with health care provider and demographic characteristics, health status, and adherence to therapeutic regimen in persons with HIV/AIDS. *AIDS Patient Care & STDs, 14,* 189-197.

Bangsberg, D. R., Hecht, F. M., Clague, H., Charlebois, E. D., Ciccarone, D., Chesney, M. et al. (2001). Provider assessment of adherence to HIV antiretroviral therapy. Journal of Acquired Immune Deficiency Syndromes 26[5], 435-442.

Baron, R. M. & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. *Journal of Personality and Social Psychology, 51,* 1173-1182.

Barre-Sinoussi, F., Chermann, J., Rey, F., Nugeyre, M., & et al (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science, 220,* 868-871.

Barroso PF et al. (2003) Adherence to antiretroviral therapy and persistence of HIV RNA in semen. *JAIDS 32*: 435-440

Barton Laws, M., Wilson, I. B., Bowser, D. M., & Kerr, S. E. (2000). Taking antiretroviral therapy for HIV infection: learning from patients' stories. Journal of General Internal Medicine 15[12], 848-858.

Baumann, L. J. & Leventhal, H. (1985). "I can tell when my blood pressure is up, can't I?". *Health Psychology, 4,* 203-218.

Becker, M. H. & Rosenstock, I. M. (1987). Comparing social learning theory and the health belief model. In W.B.Ward (Ed.), *Advances in Health Education and Promotion* (pp. 245-249). Greenwich, CT: JAI.

Becker, M. H. & Rosenstock, I. M. (1984). Compliance with medical advice. In A.Steptoe & A. Mathews (Eds.), *Health Care and Human Behaviour.* London: Academic Press.

Becker, M. H. & Maiman, L. A. (1975). Sociobehavioural determinants of compliance with health and medical care recommendations. *Medical Care, 13,* 10-24.

Becker, M. H. (1974). The health belief model and personal health behaviour. *Health Education Monographs, 2,* 324-508.

BHIVA Guidelines Co-ordinating Committee (2001). BHIVA guidelines for the treatment of HIV-infected adults with antiretroviral therapy. *HIV Medicine, 1,* 76-101.

BHIVA writing committee on behalf of the BHIVA Executive Committee. (2002). British HIV Association Guidelines for the treatment of HIV-infected adults with antiretroviral therapy. *HIV Medicine 2*, 276-313.

BHIVA writing committee on behalf of the BHIVA Executive Committee. (2003). British HIV Association Guidelines for the treatment of HIV-infected adults with antiretroviral therapy. http://www.bhiva.org/guidelines/2003/hiv/.

Bishop, G. D. (1991). Understanding the understanding of illness: lay disease representations. In J.A.Skelton & R. T. Croyle (Eds.), *Mental Representation in Health and Illness* (pp. 32-60). New York: Springer-Verlag.

Bogart, L. M., Catz, S. L., Kelly, J. A., & Benotsch, E. G. (2001). Factors influencing physician's judgements of adherence and treatment decisions for patients with HIV disease. Medical Decision Making 21[1], 28-36.

Broers, B., Morabia, A., & Hirschel, B. (1994). A cohort study of drug users' compliance with zidovudine treatment. *Archives of Internal Medicine, 154,* 1121-1127.

Buick, D. (1997). Illness representation and breast cancer: coping with radiation and chemotherapy. In K.J.Petrie & J. A. Weinman (Eds.), *Perceptions of Health and Illness* (pp. 379-410). London: Harwood Academic.

Byer, B. & Myers, L. (2000). Psychological correlates of adherence to medication in asthma. *Psychology Health & Medicine, 5,* 389.

Cameron, B., Heath-Chiozzi, M., Uravcik, S., Mills, R., & Potthoff, A. e. a. (1996). Prolongation of life and prevention of AIDS in advanced HIV immunodeficiency with Ritonavir. 3rd Conference on Retroviruses and opportunistic Infections Washington, Abstract No. LB69.

Carr, A., Samaras, K., Burton, S., & et al (1998). A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitor. *AIDS, 12,* 1857-1858.

Carr, A. & Cooper, D. A. (2000). Adverse effects of ARV therapy. *Lancet, 356,* 1423.

Carrieri, M. P., Chesney, M. A., Spire, B., Loundou, A., Sobel, A., Lepeu, G. et al. (2003). Failure to maintain adherence to HAART in a cohort of French HIV-positive injecting drug users. *International Journal of Behavioral Medicine, 10,* 1-14.

Carrieri, M. P., Cailleton, V., Le Moing, V., Spire, B., Dellamonica, P., Bouvet, E. et al. (2001). The dynamic of adherence to HAART : results from the French National APROCO cohort. *Journal of Acquired Immune Deficiency Syndromes, 28,* 232.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology, 19,* 124-133.

Catz, S. L., Heckman, T. G., Kochman, A., & DiMarco, M. (2001). Rates and correlates of HIV treatment adherence among late middle-aged and older adults living with HIV disease. *Psychology, Health and Medicine, 6,* 47-58.

Cederfjaell, C., Langius-Ekloef, A., Lidman, K., & Wredling, R. (2002). Self-reported adherence to antiretroviral treatment and degree of sense of coherence in a group of HIV-infected patients. *AIDS Patient Care & STDs, 16,* 609-61

Centre for Disease Control (2001) Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *Morbidity and Mortality Weekly Report,* June 29, 50; 1-4

Centre for Disease Control (1992). 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report, 41,* 961-962.

Centre for Disease Control (1982f). CDC task force on Kaposi's sarcoma and opportunistic infections. *New England Journal of Medicine, 306,* 248-252.

Centre for Disease Control (1981). Kaposi's sarcoma and Pneumocytis pneumonia among homosexual men - New York city and California. *Morbidity and Mortality Weekly Report, 30,* 305-308.

Centre for Disease Control (1982e). Opportunistic infections and Kaposi's sarcoma among Haitians in the United States. *Morbidity and Mortality Weekly Report, 31,* 353-361.

Centre for Disease Control (1982c). Pneumocytsis carinii pneumonia among persons with haemophilia. *Morbidity and Mortality Weekly Report, 31,* 365-367.

Centre for Disease Control (1982d). Possible transfusion-associated acquired immune deficiency syndrome (AIDS) - California. *Morbidity and Mortality Weekly Report, 31,* 353-361.

Centre for Disease Control (1982b). Update on acquired immune deficiency syndrome (AIDS) - United States. *Morbidity and Mortality Weekly Report, 31,* 507-514.

Chan, K. J., Orlando, M., Joyce, G., & et al (2003). Combination arv therapy and improvements in mental health: Results from a nationally representative sample of persons

undergoing care for HIV in the US. *Journal of Acquired Immune Deficiency Syndromes, 33,* 104-111.

Chesney, M., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J., Zwickl, B. et al. (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: The AACTG Adherence Instruments. *AIDS Care, 12*(3): 255-66.

Chiu, I., Yaniv, A., Dahlberg, J., & et al (1985). Nucleotide sequence evidence for relationship of AIDS retrovirus to lentiviruses. *Nature, 317,* 366-368.

Cochran, S. D. & Gitlin, M. J. (1988). Attitudinal correlates of lithium compliance in bipolar affective disorders. *Journal of Nervous and Mental Disease, 176,* 457-464.

Collier, A., Coombs, R., & et al (1996). Treatment of HIV with saquinavir, zidovudine and zalcitabine. *New England Journal of Medicine, 334,* 1011-1018.

Concordance Coordinating Committee (1994). MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet, 343,* 871-881.

Condra, J., Schleif, W., & et al (1995). In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors. *Nature, 374,* 494.

Conner, M. & Armitage, C. (1998). Extending the Theory of planned behaviour: A review and avenues for further research. *Journal of Applied Social Psychology, 28,* 1429.

Conner, M. & Norman, P. (1996). *Predicting health behaviour: research and practice with social cognition models*. Buckingham: Open University Press.

Conner, M. & Norman, P. (1996). The role of social cognition in health behaviours. In M.Conner & P. Norman (Eds.), *Predicting health behaviour: research and practice with social cognition models* (pp. 1-22). Buckingham: Open University Press.

Cooper, A., Lloyd, G., Weinman, J., & Jackson, G. (1999). Why patients do not attend cardiac rehabilitation: role of intentions and illness beliefs. *HEART, 82,* 234-236.

Cooper, V., Buick, D., Horne, R., Lambert, N., Gellaitry, G., Leake, H. et al. (2001). Perceptions of HAART among those who have declined a treatment offer: preliminary results from an interview-based study. Oral presentation at the 5th International Conference of AIDS Impact: Biopsychosocial aspects of HIV infection, July 8-11, Brighton & Hove, UK.

Cooper, V., Buick, D., Horne, R., Lambert, N., Gellaitry, G., Leake, H. et al. (2002). Perceptions of HAART among gay men who declined a treatment offer: Preliminary results from an interview-based study. *AIDS Care, 14,* 319-328.

Cooper, V., Horne, R., Gellaitry, G., Lambert, N., & Fisher, M. (2002a). Perceptions of HAART among HIV-positive men who have been recommended treatment. *HIV Medicine, 3,* 157-194.

Cooper, V., Horne, R., Gellaitry, G., & Fisher, M. (2002b). Perceptions of highly active antiretroviral therapy (HAART) among HIV positive men who accepted a treatment recommendation. Proceedings of the International Congress on Behavioural Medicine, Helsinki, Finland, August 28-31.

Cooper, V., Gellaitry, G., Fisher, M., Horne, R. (2003) Appraising the efficacy of HAART: Use of symptoms, interpretation of blood test results and relationships with adherence over the first six months of treatment. Paper presented at AIDS Impact Biopsychosocial Aspects of HIV Infection. 6th International Conference, Milan, July 7–10.

Cooper, V., Horne, R., Gellaitry, G., & Fisher, M. Perceptions of HAART among HIV positive men who accepted a treatment recommendation: Insights from an interview-based study. (Submitted for publication).

Crow, R., Gage, H., Hampson, S., Hart, J., Kimber, A., & Thomas, H. (1999). The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. *Health Technology Assessment, 3.*

Cruess, D., Evans, D., Repetto, M., Gettes, D., Douglas, S., & Petitto, J. M. (2003). Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. *Biological Psychiatry, 54,* 307.

Curran, J., Lawrence, D., Jaffe, H., Kaplan, J., & et al (1984). Acquired immunodeficiency syndrome (AIDS) associated with transfusions. *New England Journal of Medicine, 310,* 69-75.

D'Aquila, R., Hughes, M., Johnson, V., Fischl, M. A., Sommadossi, J., Liou, S. et al. (1996). Nevirapine, Zidovudine, and Didanosine Compared with Zidovudine and Didanosine in Patients with HIV-1 Infection: A Randomized, Double-Blind, Placebo-Controlled Trial. *Annals of Internal Medicine, 124,* 1019.

Danner, S. A., Carr, A., Leonard, J., & et al (1995). A short term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. *New England Journal of Medicine, 333,* 1528-1534.

Davies, E., Morlese, J. F., Bower, M., & Pozniak, A. (2001). Drug treatment of HIV and AIDS. *Hospital Pharmacist, 8,* 96-104.

Deeks, S., Smith, M., Holodniy, M., & Kahn JO (1997). HIV-1 protease inhibitors: a review for clinicians. *JAMA, 277,* 145.

Deeks, S., Hecht, F. M., Swindells, S., & et al (1999). HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy. *AIDS, 13,* F35-F43.

Deeks, S. G. (2000). Determinants of virological response to antiretroviral therapy: implications for long-term strategies. Clinical Infectious Diseases, *30*[2], 177-184.
Ref Type: Journal (Full)

Diefenbach, M., Leventhal, H., & Leventhal, E. (1996). The Sensitive Soma Scale. Personal Communication.

Diefenbach, M. A., Leventhal, E. A., Leventhal, H., & Patrick-Miller, L. (1996). Negative affect relates to cross-sectional but not longitudinal symptom reporting: Data from elderly adults. *Health Psychology, 15,* 282-288.

Duong, M., Piroth, L., Peytavin, G., Forte, F., Kohli, E., Grappin, M. et al. (2001). Value of patient self-report and plasma human immunodeficiency virus protease inhibitor level as markers o adherence to antiretroviral therapy: relationship to virologic response. Clinical Infectious Diseases *33*[3], 386-392.

Duran, S., Solas, C., Spire, B., Carrieri, P., Fuzibet, J. G., Costagliola, D. et al. (2001). Do HIV-infected drug users over-report adherence to highly active antiretroviral therapy? A comparison between patients' self-reports and serum protease inhibitor concentrations in the French Manif 2000 cohort study. *AIDS, 15,* 153-159.

Duran, S., Saves, M., Spire, B., Cailleton, V., Sobel, A., Carrieri, P. et al. (2001a). Failure to maintain long-term adherence to HAART: the role of lipodystrophy. *AIDS, 15,* 2441-2444.

Duran, S., Spire, B., Raffi, F., Walter, V., Bouhour, D., Journot, V. et al. (2001b). Self-reported symptoms after initiation of a protease inhibitor in HIV-infected patients and their impact on adherence to HAART. *HIV Clinical Trials, 2,* 38-45.

Durante, A. J., Bova, C. A., Fennie, K. P., Danvers, K. A., Holness, D. R., Burgess, J. D. et al. (2003). Home-based study of anti-HIV drug regimen adherence among HIV-infected women: feasibility and preliminary results. *AIDS Care, 15,* 103-115.

Edwards, R., Suresh, R., Lynch, S., Clarkson, P., & Stanley, P. (2001). Illness perceptions and mood in chronic fatigue syndrome. *Journal of Psychosomatic Research, 50,* 65.

Eldred, L. J., Wu, A. W., Chaisson, R. E., & Moore, R. D. (1998). Adherence to antiretroviral and pneumocystis prophylaxis in HIV disease. Journal of Acquired Immune Deficiency Syndromes 18[2], 117-125.

Enstrom, I., Pennert, K., & Lindholm, L. H. (2000). Durability of improvement achieved in a clinical trial. Is compliance an issue? *Journal of Family Practice, 49,* 634-637.

Eron, J. J., Yetzer, E. S., Ruane, P. J., Becker, S., Sawyer, G. A., Fisher, R. L. et al. (2000). Efficacy, safety and adherence with a twice-daily combination lamivudine/zidovudine tablet formulation, plus a preotease inhibitor, in HIV infection. AIDS *14*[6], 671-681.

Erwin, J. & Peters, B. (1999). Treatment issues for HIV positive Africans in London. Social Science & Medicine *49*, 1519-1528.

Escaffre, N., Morin, M., Bouhnik, A. D., Fuzibet, J. G., Gastaut, J. A., Obadia, Y. et al. (2000). Injecting drug users' adherence to HIV antiretroviral treatments: Physicians' beliefs. *AIDS Care, 12,* 723-730.

Fahey, J. L., Taylor, J. M., Detels, R., Hofmann, B., Melmed, R., Nishanian, P. et al. (1990). The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1.[see comment]. *New England Journal of Medicine, 322,* 166-172.

Farmer, P. (1988). Bad blood, spoiled milk: bodily fluids as moral barometers in rural Haiti. *American Ethnologist, 15,* 61-83.

Farmer, P. & Good, B. J. (1991). Illness representations in medical anthropology: A critical review and a case study of the representation of AIDS in Haiti. In J.A.Skelton & R. T. Croyle (Eds.), *Mental representations in health and illness* (pp. 132-162). New York: Springer-Verlag.

Ferguson, T. F. (2002). Patient-perceived barriers to antiretroviral adherence: Associations with race. *AIDS Care, 14,* 607-617.

Fischl, M. A., Richmann, D. D., Grimes, J., & et al (1987). The efficacy of AZT in the treatment of patients with AIDS and AIDS-related complex. *New England Journal of Medicine, 317,* 185-191.

Fishbein, M. & Ajzen, I. (1975). *Belief, attitude, intention and behavior: an introduction to theory and research*. Reading, MA: Addison Wesley.

Fong, O. W., Ho, C. F., Fung, L. Y., Lee, F. K., Tse, W. H., Yuen, C. Y. et al. (2003). Determinants of adherence to highly active antiretroviral therapy (HAART) in Chinese HIV/AIDS patients. *HIV Medicine, 4,* 133-138.

Fortune, D., Richards, H., Griffiths, C., & Main, C. (2002). Psychological stress, distress and disability in patients with psoriasis: consensus and variation in the contribution of illness perceptions, coping and alexithymia. *British Journal of Clinical Psychology, 41,* 157.

Francis, D., Curran, J., & Essex, M. (1983). Epidemic acquired immune deficiency syndrome: epidemiologic evidence for a transmissible agent. *Journal of the Natural Cancer Institute, 71,* 1-4.

Friedland, G. & Williams, A. (1999). Attaining higher goals in HIV treatment: The central importance of adherence. *AIDS, 13,* S61-S72.

Friedman-Kein, A. (1981). Disseminated Kaposi's sarcoma syndrome in young homosexual men. *Journal of the American Academy of Dermatology, 5,* 468-471.

Gallo, R., Salahuddin, S., Popovic, M., & Shearer, G. (1984). Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science, 224,* 500-503.

Gao, F., Bailes, E., Robertson, D. L., Chen, Y., Rodenburg, C. M., Michael, S. F. et al. (1999). Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes.[see comment]. *Nature, 397,* 436-441.

Gao, X., Nau, D. P., Rosenbluth, S. A., Scott, V., & Woodward, C. (2000). The relationship of disease severity, health beliefs and medication adherence among HIV patients. *AIDS Care, 12,* 387-398.

Gebo, K. A., Keruly, J., & Moore, R. D. (2003). Association of social stress, illicit drug use, and health beliefs with nonadherence to antiretroviral therapy. *Journal of General Internal Medicine, 18,* 104-111.

Gifford, A. L., Bormann, J. E., Shively, M. J., Lee, M., Capparelli, E., Richman, D. D. et al. (2001). Effects of group HIV patient education on adherence to ARV's: a randomized controlled trial. Proceedings of the eighth Conference on Retroviruses and opportunistic Infections, San Diego. February 4-8. Abstract no. 470.

Gifford, A. L., Bormann, J. E., Shively, M. J., Wright, B. C., Richman, D. D., & Bozzette, S. A. (2000). Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 23,* 386-395.

Gilks, C. (1991). AIDS, monkeys and malaria. *Nature, 354,* 262.

Godin, G. & Kok, G. (1996). The theory of planned behavior: a review of its applications to health-related behaviors. *American Journal of Health Promotion, 11,* 87-98.

Goedert, J., Neuland, C., & Wallen, W. (1982). Amyl Nitrite may alter T lymphocytes in homosexual men. *Lancet, 1,* 412-416.

Golin, C., Isasi, F., Bontempi, J. B., & Eng, E. (2002). Secret pills: HIV-positive patients' experiences taking antiretroviral therapy in North Carolina. *AIDS Education & Prevention, 14,* 318-329.

Gordillo, V. & Gonzalez-Lahoz, J. (2000). Psychological variables and adherence to antiretroviral treatment. Anales de Medicina Interna *17*[1], 38-41.

Gordillo, V., del Amo, J., Soriano, V., & Gonzalez-Lahoz, J. (1999). Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS, 13,* Sep-1769.

Gottlieb, M. S. S. R., Schanker, H. M., & et al (1981). 'Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency'. *The New England Journal of Medicine, 305,* 1425-1431.

Grant, A. & De Cock, K. (2001). HIV infection and AIDS in the developing world. *BMJ, 322,* 1475-1478.

Gulick, R. (1997). Current antiretroviral therapy: An overview. *Quality of Life Research, 6,* 474.

Haase, A. (1986). Pathogenesis of lentivirus infections. *Nature, 322,* 130-136.

Haddad, M., Inch, C., Glazier, R. H., Wilkins, A. L., Urbshott, G., Bayoumi, A. et al. (2000). Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. Cochrane database of systematic reviews 3[CD001442].

Halkitis, P. N., Kutnick, A. H., Rosof, E., Slater, S., & Parsons, J. T. (2003). Adherence to HIV medications in a cohort of men who have sex with men: impact of September 11th. *Journal of Urban Health, 80,* 161-166.

Hammer, S. M., Squires, K., Hughes, M., Grimes, J., Demeter, L., Currier, J. et al. (1997). A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Eng J Med, 337,* 725-733.

Hammer, S. M., Katzenstein, D., Hughes, M. D., & et al (1996). A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimetre. *New England Journal of Medicine, 335,* 1081-1090.

Hampson, S. E. (1997). Illness representations and the self-management of diabetes. In K.J.Petrie & J. Weinman (Eds.), *Perceptions of health and illness* (pp. 323-348). Amsterdam: Harwood Academic.

Harrigan, P. & Larder, B. (2002). Extent of Cross-Resistance between Agents Used To Treat Human Immunodeficiency Virus Type 1 Infection in Clinically Derived Isolates. *Antimicrobial Agents and Chemotherapy, 46,* 909-912.

Harrison, J. A., Mullen, P. D., & Green, L. W. (1992). A meta-analysis of studies of the health belief model with adults. *Health Education Research, 7,* 107-116.

Haynes, R. B., Taylor, D. W., Sackett, D. L., Gibson, E. S., Bernholtz, C. D., & Mukherjee, J. (1980). Can simple clinical measures detect patient noncompliance? Hypertension *2*[6], 757-764.

Health Protection agency's HIV and sexually transmitted division, Scottish Centre for infection and Environmental Health, Institute of Child Health, & UK Haemophilia Centre Doctors' Organisation (2003). AIDS and HIV infection in the UK: monthly report (July 2003). *CDR Weekly, 13*. Available: http://www.hpa.org.uk/cdr/PDFfiles/2003/cdr3003.pdf.

Health Protection agency. (2003). AIDS/HIV Quarterly Surveillance tables. 10/03. Health protection agency and the Scottish Centre for infection & Environmental health. Available: http://www.hpa.org.uk/infections/topics_az/hiv_and_sti/hiv/epidemiology/files/quarterly.pdf.

Health Protection agency. (2003). HIV and other sexually transmitted infections in the United Kingdom in 2002 Annual Report, November 2003. Available: http://www.hpa.org.uk/infections/topics_az/hiv_and_sti/publications/annual2003/annual2003.pdf.

Heijmans, M. & De Ridder, D. (1998). Assessing illness representations of chronic illness: Explorations of their disease-specific nature. *Journal of Behavioral Medicine, 21,* 485.

Heijmans, M. (1999). The role of patients' illness representations in coping and functioning with Addison's disease. *British Journal of Health Psychology, 4,* 137-149.

Helder, D. (2002). *Living with Huntington's disease: a study on illness perceptions, coping mechanisms, and well-being of patients and their partners.* (Thesis).

Hinkin, C. H., Castellon, S. A., Durvasula, R. S., Hardy, D. J., Lam, M. N., Mason, K. I. et al. (2002). Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. *Neurology, 59,* 1944-1950.

Ho, D. D. (1998). Toward HIV eradication or remission: The tasks ahead. *Science, 280,* 1866-1867.

Hochbaum, G. M. (1956). Why people seek diagnostic X-rays. *Public Health Reports, Washington, 71, 377-380.*.

Hogg, S. & Yip, B. (2001). Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA, 286,* 2568-2577.

Holmes, W. C. & Pace, J. L. (2002). HIV-seropositive individuals' optimistic beliefs about prognosis and relation to medication and safe sex adherence. *Journal of General Internal Medicine, 17,* 677-683.

Holzemer, W. L., Corless, I. B., Nokes, K. M., Turner, J. G., Brown, M. A., Powell-Cope, G. M. et al. (1999). Predictors of self-reported adherence in persons living with HIV disease. *AIDS Patient Care & STDs, 13,* 185-197.

Horne, R. (2003). Treatment perceptions and self regulation. In L.D.Cameron & H. Leventhal (Eds.), *The self-regulation of health and illness behaviour* (pp. 138-153). London: Routledge.

Horne, R. (2001). Compliance, adherence and concordance. In K.Taylor & G. Harding (Eds.), *Pharmacy Practice* (pp. 165-184). London: Taylor and Francis.

Horne, R. (1999). Patient's beliefs about treatment: The hidden determinant of treatment outcome? *Journal of Psychosomatic Research, 47,* 491-495.

Horne, R. (1997). Representations of medication and treatment: Advances in theory and measurement. In K.J.Petrie & J. A. Weinman (Eds.), *Perceptions of Health and Illness : Current Research and Applications* (pp. 155-188). London: Harwood Academic Press.

Horne, R., Buick, D., Fisher, M., Leake, H., & Weinman, J. Low adherence to HAART is related to doubts about necessity and concerns about adverse effects. *International Journal of HIV and AIDS,* (in press).

Horne, R., Cooper, V., Fisher, M., & Buick, D. (2001). Beliefs about HIV and HAART and the decision to accept or reject HAART. *HIV Medicine, 2,* 195. Seventh Annual Meeting of the British HIV Association (BHIVA), 27-29 April 2001, Brighton, UK.

Horne, R., Cooper, V., Gellaitry, G., Lambert, N., & Fisher, M. (2002a). Predicting acceptance of highly active antiretroviral treatment (HAART): The role of patients' perceptions of illness and treatment. Proceedings of the XIV International AIDS Conference, Barcelona, Spain, July 7-12.

Horne, R., Cooper, V., Weinman, J., & Fisher, M. (2002b). Predicting acceptance of highly active antiretroviral treatment (HAART): The utility of an extended self-regulatory theory. Proceedings of the International Congress on Somatoform Disorders: New approaches to classification and treatment, February 21-24, Marburg.

Horne, R. & Weinman, J. (2002). Self-regulation and self-management in asthma: Exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychology and Health, 17,* 17-32.

Horne, R. & Weinman, J. (1999). Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *Journal of Psychosomatic Research, 47,* 555-567.

Horne, R. & Weinman, J. (1998). Predicting treatment adherence: An overview of theoretical models. In L.Myers & K. Midence (Eds.), *Adherence to Treatment In Medical Conditions* (pp. 25-50). London: Harwood Academic.

Horne, R. & Weinman, J. (1998a). Treatment beliefs and treatment adherence in a sample of haemodialysis recipients. Proceedings of the Division of Health Psychology Annual Conference, University of Wales, Bangor, UK.

Horne, R., Weinman, J., & Hankins, M. (1999). The Beliefs about Medicines Questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology and Health, 14,* 1-24.

Howard, A. A. (2002). A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS, 16,* 2175-2182.

James, D. (1999). *The Role of Patients' Perceptions of Illness and Treatment in Myocardial Infarction.* Doctoral Thesis: University of Brighton.

Janz, N. K. & Becker, M. H. (1984). The health belief model: a decade later. *Health Education Quarterly, 11,* 1-47.

Johnson, J. & Leventhal, H. (1974). Effects of accurate expectations and behavioural instructions on reactions during a noxious medical examination. *Journal of Personality and Social Psychology, 29,* 710.

Johnson, J. (1975). Stress reduction through sensation information. In I.Sarason & C. Speilberger (Eds.), *Stress and anxiety (Vol. 2).* Washington: Hemisphere publishing corporation.

Joint United Nations Programme on HIV/AIDS (UNAIDS) & World Health Organization (WHO) (2002). AIDS epidemic update. Available:*http://www.unaids.or*.

Jones, D. L., Ishii, M., LaPerriere, A., Stanley, H., Antoni, B., Ironson, G. et al. (2003). Influencing medication adherence among women with AIDS. *AIDS Care, 15,* 463-474.

Jopson, N. & Moss-Morris, R. (2003). The role of illness severity and illness representations in adjusting to multiple sclerosis. *Journal of Psychosomatic Research., 54,* 503.

Kahn JO et al. (1992). A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *New England Journal of Medicine, 327,* 581-587.

Kalichman, S. C., Ramachandran, B., & Catz, S. L. (1999). Adherence to combination antiretroviral therapies in HIV patients of low health literacy. Journal of General Internal Medicine 14[5], 267-273.

Kalichman, S. C., Cage, M., Barnett, T., Tharnish, P., Rompa, D., Austin, J. et al. (2001). Human immunodeficiency virus in semen and plasma: Investigation of sexual transmission risk behavioral correlates. *AIDS Research & Human Retroviruses, . 17.*

Kalichman, S. & Rompa, D. (2003). HIV treatment adherence and unprotected sex practices in people receiving ARV therapy. *Sexually Transmitted Infections, 79,* 59-61.

Kaplan, J., Hanson, D., Karon, J., Cohn, D., Thompson, M., Buskin, S. et al. (2001). Late initiation of ARV therapy (at CD4+ Lymphocyte Count <200 Cells/Ml) is associated with increased risk of death. Abstract presented at the 8th Conference on Retroviruses and Opportunistic Infections.

Kastrissios, H., Suarez, J. R., Hammer, S. M., Katzenstein, D., & Blaschke, T. F. (1998). The extent of non-adherence in a large AIDS clinical trial using plasma dideoxynucleoside concentrations as a marker. AIDS 12, 2305-2311.

Kelly, G. R., Mamon, J. A., & Scott, J. E. (1987). Utility of the health belief model in examining medication compliance among psychiatric outpatients. *Social Science & Medicine, 25,* 1205-1211.

Kelly, J., Murphy, D., Bahr, G., Koob, J., Morgan, M., Kalichman, S., Stevenson, L., Brashfield, T., Bernstein, B. & St. Lawrence, J. (1993). Factors associated with severity of depression and high-risk sexual behaviour among persons diagnosed with human immunodeficiency virus (HIV) infection. *Health Psychology, 12,* 215-219.

Kelly, J. A., Otto-Salaj, L. L., Sikkema, K. J., Pinkerton, S. D., & Bloom, F. R. (1998). Implications of HIV treatment advances for behavioral research on AIDS: Protease inhibitors and new challenges in HIV secondary prevention. *Health Psychology, 17,* 310-319.

Kemppainen, J. K., Levine, R. E., Mistal, M., & Schmidgall D (2001). HAART adherence in culturally diverse patients with HIV/AIDS: A study of male patients from a Veteran's Administration hospital in Northern California. *AIDS Patient Care & STDs, 15,* 117-127.

Kleeberger, C.A., Buechner, J., Palella, F., Detels, R., Riddler, S., Godfrey, R. & Jackobson, L.P. (2004). Changes in adherence to highly active antiretroviral therapy medications in the Multicentre AIDS Cohort Study. *AIDS, 18[4],* 683-688.

Kleeberger, C. A., Phair, J. P., Strathdee, S. A., Detels, R., Kingsley, L., & Jacobson, L. P. (2001). Determinants of heterogeneous adherence to HIV antiretroviral therapies in the Multicentre AIDS Cohort Study. *Journal of Acquired Immune Deficiency Syndromes* 26[1], 82-92.

Knippels, H. M. A. & Weiss, J. J. (2000). Use of alternative medicine in a sample of HIV-positive gay men: And exploratory study of prevalence and user characteristics. *AIDS Care, 12,* 435-446.

Knobel, H., Guelar, A., Carmona, A., Espona, M., Gonzalez, A., Lopez-Colmes, J. L. et al. (2001). Virologic outcome and predictors of virologic failure of highly active antiretroviral therapy containing protease inhibitors. *AIDS Patient Care & STDs 15*[4], 193-199.

Kyle, W. (92 A.D.). Simian Retroviruses, Poliovaccine, and Origin of AIDS. *Lancet, 339,* 600.

Lacroix, M. J. (1991). assessing illness schemata in patient populations. In J.A.Skelton & R. Croyle (Eds.), *Mental Representation in Health and Illness* (pp. 193-219). New York: Springer-Verlag.

Lalezari, J. & et al (2003). Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Eng J Med, 348,* 2175-2185.

Lau, R. R. & Hartman, K. A. (1983). Common Sense Representations of Illness. *Health Psychology, 2,* 167-185.

Lau, R. R., Bernard, T. M., & Hartman, K. A. (1989). Further explorations of common-sense representations of common illnesses. *Health Psychology, 8,* 195-219.

Law, M. G., Yueming, L., McDonald, A., Cooper, D. A., & Kaldor, J. M. (2000). Estimating the population impact in Australia of improved antiretroviral treatment for HIV infection. AIDS 14, 197-201.

Lepri, A. C., Miller, V., Phillips, A. N., Rabenau, H., Sabin, C. A., & Staszewski, S. (2001). The virological response to highly active antiretroviral therapy over the first 24 weeks

of therapy according to the pre-therapy viral load and the weeks 4 - 8 viral load. AIDS 15[1], 47-54.

Leventhal, H. (1965). Fear communications in the acceptance of preventive health practices. *Bulletin of the New York Academy of medicine, 2,* 20.

Leventhal, H. (1970). Findings and theory in the study of fear communications. In L.Berkowitz (Ed.), *Advances in Experimental Social Psychology* (pp. 119-186). New York: Academic Press.

Leventhal, H. (1992). I know distraction works even though it doesn't! [editorial]. *Health Psychology., 11,* 208-209.

Leventhal, H., Benyamini, Y., Brownlee, S., Diefenbach, M., Leventhal, E. A., Patrick-Miller, L. et al. (1997). Illness representations: Theoretical foundations. In K.J.Petrie & J. Weinman (Eds.), *Perceptions of health and illness: Current research and applications.* (pp. 19-46). London: Harwood Academic.

Leventhal, H., Brissette, I., & Leventhal, E. (2003). The common-sense model of self-regulation of health and illness. In L.D.Cameron & H. Leventhal (Eds.), *The self-regulation of health and illness behaviour* (pp. 42). NY: Routledge.

Leventhal, H. & Cameron, L. (1987). Behavioral theories and the problem of compliance. *Patient Education and Counseling, 10,* 117-138.

Leventhal, H. & Cleary, P. D. (1980). The smoking problem: A review of research and theory in behavioural risk modification. *Psychological Bulletin, 88,* 370-405.

Leventhal, H., Diefenbach, M., & Leventhal, E. A. (1992). Illness cognition: Using common sense to understand treatment adherence and affect cognition interactions. Special Issue: Cognitive perspectives in health psychology. *Cognitive Therapy and Research, 16,* 143-163.

Leventhal, H., Easterling, D. V., Coons, H. L., Luchterhand, C. M., & Love, R. R. (1986). Adaption to chemotherapy treatments. In B.L.Andersen (Ed.), *Women with Cancer: Psychological Perspectives* (pp. 172-203). New York: Springer Verlag.

Leventhal, H. & et al (1967). Effects of fear and instructions on how to cope with danger. *Journal of Personality and Social Psychology, 6*, 313.

Leventhal, H., Leventhal, E., & Cameron, L. (2001). Representations, procedures, and affect in illness self-regulation: a perceptual-cognitive model. In A.Baum, T. A. Revenson, & J. Singer (Eds.), *Handbook of health psychology* (pp. 19). New Jersey: Pergamon Press.

Leventhal, H., Leventhal, E. A., & Schaefer, P. M. (1992). Vigilant coping and health behavior. In Marcia G.Ory, Ronald Peter Abeles, & P. Darby-Lipman (Eds.), *Aging, health, and behavior* (pp. 109-140). Newbury Park, CA, US: Sage Publications.

Leventhal, H., Meyer, D., & Nerenz, D. (1980). The common sense representation of illness danger. In S.Rachman (Ed.), *Contributions to Medical Psychology* (pp. 7-30). Oxford: Pergamon Press.

Leventhal, H. & Nerenz, D. R. (1996). Illness representations and coping with health threats. In A.Baum (Ed.), *Handbook of Psychology and Health* (4 ed., pp. 219-252).

Leventhal, H. & Nerenz, D. (1985). The assessment of illness cognition. In P.Karoly (Ed.), *Measurement Strategies in Health Psychology* (1 ed., pp. 517-555). New York: Wiley and Sons.

Leventhal, H., Nerenz, D. R., & Steele, D. J. (1984). Illness Representations and coping with health threats. In *Handbook of psychology and health* (4 ed., pp. 219-252). New Jersey: Laurence Erlbaum Associates.

Leventhal, H., Nerenz, D. R., & Sraus, A. (1982). self regulation and the mechanisms for symptom appraisal. In D.Michanic (Ed.), *Symptoms, Illness Behavior and help seeking* (pp. 55-86). New York: Watson Academic Publishers.

Leventhal, H. & Watts, J. (1966). Sources of resistance to fear-arousing communications on smoking and lung cancer. *Journal of Personality, 34,* 155.

Leventhal, H., Zimmerman, R., & Gutmann, M. (1984a). Compliance: a self-regulatory perspective. In D.Gentry (Ed.), *Handbook of Behavioural Medicine* (pp. 369-434). New York: Pergamon Press.

Levy, J. (1993). Pathogenesis of human immunodeficiency virus infection. *Microbiological Reviews, 57,* 183-289.

Ley, P. (1989). Improving patients' understanding, recall, satisfaction, and compliance. In A.Broome (Ed.), *Health Psychology.* London: Chapman and Hall.

Ley, P. (1981). Professional non-compliance: A neglected problem. *British Journal of Clinical Psychology, 20*, 151.

Llewellyn, C., Miners, A., Lee, C., Harrington, C., & Weinman, J. (2003). The illness perceptions and treatment beliefs of individuals with severe haemophilia and their role in adherence to home treatment. *Health Psychology, 18*, 185-2000.

Lopez-Suarez, A., Fernandez-Gutierrez del Alam, & Perez-Guzman, E. (1998). Adherence to antiretroviral treatment in asymptomatic HIV-infected patients. *AIDS 12*[6], 685-686.

Lutgendorf, S., Antoni, M.H.., Ironson, G., Starr, K., Costello, N., Zuckerman, M., Klimas, N., Fletcher, M.A. & Schneiderman, N. (1998) Changes in cognitive coping skills and social support mediate distress outcomes in symptomatic HIV-seroposensitive gay men during a cognitive behavioural stress management intervention. *Psychosomatic Medicine, 60,* 204-214.

Maher, K., Klimas, N., & Fletcher, M. (1999). Disease progression, adherence and response to PI therapy for HIV infection in an urban veterans affairs medical centre. *Journal of Acquired Immune Deficiency Syndromes, 22*, 358.

Maj, M. (1990). Psychiatric aspects of HIV-1 infection and AIDS. *Psychological Medicine, 20,* 547.

Malcolm, S. E., Ng, J. J., Rosen, R. K., & Stone, V. E. (2003). An examination of HIV/AIDS patients who have excellent adherence to HAART. *AIDS Care, 15,* 251-261.

Mallal, S., John, M., Moore, C., James, I., & McKinnon, E. (2000). Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS, 14,* 1309-1316.

Malow, R. M., Baker, S. M., Klimas, N., Antoni, M. H., Schneiderman, N., Penedo, F. L. et al. (1998). Adherence to complex combination antiretroviral therapies by HIV-positive drug abusers. *Psychiatric Services 49*[8], 1021-2.

Manfredi, R. & Chiodo, F. (2000). The effects of alternative treatments for HIV disease on recommended pharmacological regimens. *International journal of antimicrobiological agents, 13,* 281-285.

Mann, J. (1992). AIDS - the second decade: a global perspective. *Journal of Infectious Diseases, 165,* 245-250.

Mann, T. (2001). Effects of future writing and optimism on health behaviors in HIV-infected women. *Annals of Behavioral Medicine, 23,* 26-33.

Mannheimer, S., Friedland, G., Matts, J., Child, C., & Chesney, M. (2002). The Consistency of Adherence to Antiretroviral Therapy Predicts Biologic Outcomes for Human Immunodeficiency Virus Infected Persons in Clinical Trials. *Clinical Infectious Diseases, 34,* 1115.

Marteau, T. M. (1995). Heath beliefs and attributions. In A.Broome & S. Llewellyn (Eds.), *Health psychology: processes and applications* (2nd ed., pp. 3-20). London: Chapman & Hall.

Martini, M., D'Eila, S., Paoletti, F., Cargnel, A., Adriani, B., Carosi, G. et al. (2002). Adherence to HIV treatment: results from a 1-year follow-up study. *HIV Medicine 3*, 62-64.

Martini, M., Nasta, P., Ricci, E., Parazzini, F., & Agnoletto, V. (2000). Perceptions of disease and therapy are factors influencing adherence to ARV therapy. *HIV Medicine, 3,* 62.

Masur H., Michelis M.A., Greene J.B., Onorato I., ,Stouwe R.A., Holzman R.S., Wormser G., Brettman L.., Lange M., Murray H.W., and Cunnigham-Rundles S. (1981). An Outbreak of community acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. *The New England Journal of Medicine, 305,* 1431-1438.

Mathews, W. C., Mar-Tang, M., Ballard, C., Colwell, B., Abulhosn, K., Noonan, C. et al. (2002). Prevalence, predictors, and outcomes of early adherence after starting or changing antiretroviral therapy. *AIDS Patient Care & STDs, 16,* 157-172.

Max, B. & Sherer, R. (2000). Management of the adverse effects of antiretroviral therapy and medication adherence. *Clinical Infectious Diseases 30*[2], 96-116.

McCarthy, S., Lyons, A., Weinman, J., Talbot, R., & Purnell, D. (2003). Do expectations influence recovery from oral surgery? An illness representation approach. *Psychology & Health, 18,* 109-126.

McGinn, D. (2001). 'MSNBC: AIDS at 20: Anatomy of a plague; an oral history', Newsweek Web Exclusive. Available:http://www.avert.org/his81_86.htm.

McHorney, C. A., Kosinski, M., & Ware, J. E. J. (1994). Comparisons of the costs and quality of norms for the SF-36 health survey collected by mail versus telephone interview: results from a national survey. *Med.Care, 32,* 551-567.

McNabb, J. J., Nicolau, D. P., Stoner, J. A., & Ross, J. (2003). Patterns of adherence to antiretroviral medications: the value of electronic monitoring. *AIDS, 17,* 1763-1767.

Mellors, J., Munoz, A., & et al (1997). Plasma viral load and CD4 Lymphocytes as prognostic makers of HIV-1 infection. *Annals of Internal Medicine, 126,* 946-954.

Meyer, D., Leventhal, H., & Gutmann, M. (1985). Common-sense models of illness: the example of hypertension. *Hlth Psychol, 4(2),* 115-135.

Meystre-Agustoni, G. (2000). Antiretroviral therapies from the patient's perspective. *AIDS Care, 12,* Dec-721.

Miller, L. G. & Hays, R. D. (2000). Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. *AIDS Reader 10*[3], 177-185.

Miller, L. G., Liu, H., Hays, R. D., Golin, C. E., Beck, C. K., Asch, S. M. et al. (2002). How well do clinicians estimate patients' adherence to combination antiretroviral therapy? *Journal of General Internal Medicine, 17,* 1-11.

Miller, L. G., Liu, H., Hays, R. D., Golin, C. E., Ye, Z., Beck, C. K. et al. (2003). Knowledge of antiretroviral regimen dosing and adherence: a longitudinal study.[comment]. *Clinical Infectious Diseases, 36,* 514-518.

Miller, J. (2003). *The Role of Patients' Perceptions of Illness and Treatment in Myocardial Infarction.* Doctoral Thesis: University of Brighton.

Moatti, J. P., Carrieri, M. P., Spire, B., Gastaut, J. A., Cassuto, J. P., & Moreau, J. (2000). Adherence to HAART in French HIV-infected injecting drug users: the contribution of buprenorphine drug maintenance treatment. The Manif 2000 study group. *AIDS 14*[2], 151-155.

Mocroft, A., Katlama, C., Johnson, A. M., Pradier, C., Antunes, F., Mulcahy, F. et al. (2000). AIDS across Europe, 1994-1998: the EuroSIDA study. *Lancet, 356,* 291-296.

Mocroft, A., Vella, S., Benfield, T., Chiesi, A., Miller, V., Gargalianos, P. et al. (1998). Changing patterns of mortality across Europe in patients infected with HIV-1. *The Lancet, 352,* 1725-1730.

Mohr, D., Goodkin, D., Likosky, W., Gatto, N., & Baumann, K. (1999). Treatment of Depression Improves Adherence to Interferon Beta -1b Therapy for Multiple Sclerosis. *Archives of Neurology, 54,* 531-533.

Molassiotis, A., Nahas-Lopez, V., Chung, W. Y., Lam, S. W., Li, C. K., & Lau, T. F. (2002). Factors associated with adherence to antiretroviral medication in HIV-infected patients. *International Journal of STD & AIDS, 13,* 301-310.

Montaner, J., Reiss, P., Cooper, D. A., Vella, S., Harris, M., Conway, B. et al. (1998). A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS trial. *JAMA, 279,* 930.

Montaner, J. S. G. (2003). Patient expectations and outcomes: Overcoming the challenges of adherence. *Advanced Studies in Medicine, 3,* 10B.

Moorey, S., Greer, S., Watson, M., Gorman, C., Rowden, L., Tunmore, R. et al. (1991). The factor structure and factor stability of the Hospital Anxiety and Depression Scale in patients with cancer. *British Journal of Psychiatry, 158,* 255-259.

Morse, E. V. (1991). Determinants of subject compliance within an experimental anti-HIV drug protocol. *Social Science & Medicine, 32,* 1161-1167.

Moss-Morris, R., Petrie, K. J., & Weinman, J. (1996). Functioning in Chronic Fatigue Syndrome: do illness perceptions play a regulatory role? *British Journal of Health Psychology, 1,* 15-25.

Moss-Morris, R., Weinman, J., Petrie, K., Horne, R., Cameron, L., & Buick, D. (2002). The revised illness perception questionnaire (IPQ-R). *Psychology and Health, 17,* 1-16.

Mostashari, F., Riley, E., Selwyn, P. A., & Altice, F. L. (1998). Acceptance and adherence with antiretroviral therapy among HIV-infected women in a correctional facility. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology, 18,* 341-348.

Mulder, C.L., Emmelkamp, P., Antoni, M.H., Mulder, J., Sandfort, T. & de Vries, M. (1994). Cognitive-behavioral and experimental group psychotherapy fof HIV-infected homosexual men: A comparative study. *Psychosomatic Medicine, 56,* 423-431.

Mullins, C., Whitelaw, G., Cooke, J., & Beck, E. (2000). Indirect cost of HIV infection in England. *Clinical Therapeutics, 22,* 1333.

Murphy, D. A., Roberts, K. J., Hoffman, D., Molina, A., & Lu, M. C. (2003). Barriers and successful strategies to antiretroviral adherence among HIV-infected monolingual Spanish-speaking patients. *AIDS Care, 15,* 217-230.

Murphy, D. A., Roberts, K. J., Martin, D. J., Marelich, W., & Hoffman, D. (2000). Barriers to antiretroviral adherence among HIV-infected adults. *AIDS Patient Care & STDs, 14,* 47-58.

Murphy, H., Dickens, C., Creed, F., & Bernstein, R. (1999). Depression, illness perception and coping in rheumatoid arthritis. *Journal of Psychosomatic Research, 46,* 155.

Murri, R., Ammassari, A., De Luca A., Cingolani, A., & Antinori, A. (1999). Definition and measurement of adherence to ARV drugs in HIV-1 -infected patients (Letter to the Editor). *The Lancet, 353,* 1974.

Murri, R., Ammassari, A., De Luca A., Cingolani, A., Marconi, K., Wu, A. et al. (2001). Self-reported nonadherence with ARV drugs predicts persistent condition. *HIV Clinical Trials, 2,* 323.

Nannis, E., Temoshok, L., Smith, M., & Jenkins, R. (1993). Perceptions of AZT: Implications for adherence to medical regimens. *Journal of Applied Biobehavioral Research, 1,* 39-54.

National Aids Manual (NAM) http://www.aidsmap.com/

Nelson, E. C., Statson, W. B., & Neutra, R. R. (1978). Impact of patient perceptions on compliance with treatment for hypertension. *Medical Care, 16,* 893-906.

Nerenz, D. R., Leventhal, H., & Love, R. R. (1982). Factors contributing to emotional distress during cancer chemotherapy. *Cancer, 50,* 1020-1027.

Newell, A., Mendes, S., & Horne, R. (2002). Assessing the psychological and therapy-related barriers to optimal adherence: an observational study. Proceedings of the Sixth International Congress on Drug Therapy in HIV Infection, Glasgow, UK.

Nieukerk, P. T., Sprangers, M. A., Burger, D. M., Hoetelmans, R. M., Hugen, P. W., Danner, S. A. et al. (2001). Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Archives of Internal Medicine 161*[16], 1962-1968.

Nunnally, J. C. (1978). *Psychometric Theory*. New York: McGraw-Hill.

O'Brien, W., Hartigan, P., Martin, D., Esinhert, J., Hill, A., & et al (1996). Changes in plasma HIV-1 RNA and CD4+ Lymphocyte counts and the risk of progression to AIDS. *The New England Journal of Medicine, 334,* 426-431.

Oppenheim, A. N. (1992). *Questionnaire Design, Interviewing and Attitude Measurement*. London: Pinter.

Orbell, S., Johnston M, Rowley, D., Espley, A., & Davey, P. (1998). Cognitive representations of illness and functional and affective adjustment following surgery for osteoarthritis. *Social Science & Medicine, 47,* 93.

Ostrop, N. J. & Gill, M. J. (2000). Antiretroviral medication adherence and persistence with respect to adherence tool usage. *AIDS Patient Care & STDs 14*[7], 351-358.

Ostrop, N. J., Hallet, K. A., & Gill, M. J. (2000a). Long-term patient adherence to antiretroviral therapy. *Annals of Pharmacotherapy, 34*[June], 703-709.

Palella, F., Delaney, K., et, & et al. (1998). Declining morbidity and mortality among patients with advanced HIV. *New England Journal of Medicine, 338,* 853-860.

Pantaleo, G., Graziosi, C., & Fauci, A. (1993). The immunopathogenesis of human immunodeficiency virus infection. *New England Journal of Medicine, 328,* 327-335.

Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C. et al. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine 133*[1], 21-30.

Penedo, F. J. (2003). Personality, quality of life and HAART adherence among men and women living with HIV/AIDS. *Journal of Psychosomatic Research, 54,* 271-278.

Perelson, A., Neumann, A., Markowitz, M., Leonard, J., & Ho, D. D. (1996). HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science, 271,* 1582-1586.

Peterson, C. & Bossio, L. M. (1991). *Health and optimism.* New York: Free Press

Petrie, K., Cameron, L., Ellis, C., Buick, D., & Weinman, J. (2002). Changing illness perceptions following myocardial infarction: an early intervention randomized controlled trial. *Psychosomatic Medicine, 64,* 580.

Petrie, K., Weinman, J., Sharpe, N., & Buckley, J. (1996). Role of patients view of their illness in predicting return to work and functioning after myocardial infarction: longitudinal study. *BMJ, 312,* 1191-1194.

Petrie, K. J. (2003). Assessing illness behaviour: what condition is my condition in? *Journal of Psychosomatic Research, 54,* 415-416.

Phelan, M., Dobbs, J., & David, A. S. (1992). 'I thought it would go away': patient denial in breast cancer. *J.R.Soc.Med., 85,* 206-207.

Poon, M., Landay, A., Prasthofer, E., & Stagno, S. (1983). Acquired immunodeficiency syndrome with Pneumocystis carinii pneumonia and Mycobacterium avium-intracellulare infection in a previously healthy patient with classic haemophilia. Clinical, immunologic, and virologic findings. *Annals of Internal Medicine, 98,* 287-290.

Pradier, C., Bentz, L., Spire, B., Tourette-Turgis, C., Morin, M., Souville, M. et al. (2003). Efficacy of an educational and counseling intervention on adherence to HAART: French prospective controlled study. *HIV Clinical Trials, 4,* 121.

Pratt, R. J., Robinson, N., Loveday, H. P., Pellowe, C. M., Franks, P. J., Hankins, M. et al. (2001). Adherence to antiretroviral therapy: Appropriate use of self-reporting in clinical practice. *HIV Clinical Trials, 2,* 146-159.

Proctor, V. E., Tesfa, A., & Tompkins, D. C. (1999). Barriers to adherence to highly active antiretroviral therapy as expressed by people living with HIV/AIDS. *AIDS Patient Care & STDs 13*[9], 535-44.

Rabkin, J. G., Rieppi, R., McElhiney, M., & Sewell, M. (2000). Relationships among apathy, depression and cognitive impairment in HIV/AIDS. *Journal of Neuropsychiatry and Clinical Neurosciences, 12,* 451-457.

Ried, D. & Christensen, D. (1988). A psychosocial perspective in the explanation of patients' drug-taking behaviour. *Soc Sci.Med., 27,* 277.

Ried, L. D., Oleen, M., Martinson, O., & Pluhar, R. (1985). Explaining intention to comply with antihypertensive regimens: the utility of health beliefs and the theory of reasoned action. *Journal of Social and Administrative Pharmacy, 3,* 42.

Roberts, K. J. (2000). Barriers to antiretroviral medication adherence in HIV-infected women. *AIDS Care, 12,* Aug-386.

Roca, B., Gomez, C. J., & Arnedo, A. (2000). Adherence, side effects and efficacy of stavudine plus lamivudine plus nelfinavir in treament experienced HIV-infected patients. *Journal of Infection 41*[1], 50-54.

Rosenstock, I. (1966). Why people use health services. *Milbank Memorial fund quarterly, 44,* 94.

Rutherford, G. W., Lifson, A. R., Hessol, N. A., Darrow, W. W., O'Malley, P. M., Buchbinder, S. P. et al. (1990). Course of HIV-I infection in a cohort of homosexual and bisexual men: an 11 year follow up study. *BMJ, 301,* 1183-1188.

Safren, S. A., Otto, M. W., Worth, J. L., Saloman, E., Johnson, W., Mayer, K. et al. (2001). Two strategies to increase adherence to HIV antiretroviral medication: Life-steps and medication monitoring. *Behaviour Research and Therapy, 39,* 1151-1162.

Sambamoorthi, U., Warner, L. A., Crystal, S., & Walkup, J. (2000). Drug abuse, methadone treatment and health services use among infection drug users with AIDS. *Drug and Alcohol Dependence 60*[1], 77-89.

Sankar, A., Luborsky, M., Schuman, P., & Roberts, G. (2002). Adherence discourse among African-American women taking HAART. *AIDS Care, 14,* 203.

Scalera, A., Bayoumi, A. M., Oh, P., Risebrough, N., Shear, N., & Tseng, A. L. I. (2002). Clinical and economic implications of non-adherence to HAART in HIV infection. *Disease Management & Health Outcomes, 10.*

Scharloo, M. & Kaptein, A. A. (1997). Measurement of illness perceptions in patients with chronic somatic illness: A review. In K.Petrie & J. Weinman (Eds.), *Perceptions of health and illness* (pp. 103). Reading: Harwood Academic Publishers.

Scharloo, M., Kaptein, A. A., Weinman, J., Hazes, J., Breedveld, F., & Rooijmans, H. (1999). Predicting functional status in patients with rheumatoid arthritis. *Journal of Rheumatology, 26,* 1686.

Scheier, M. F., Matthews, K., Owens, J., Magovern, G., Lefebvre, R., Abbott, R. et al. (1989). Dispositional optimism and recovery from coronary artery bypass surgery: The beneficial effects on physical and psychological well-being. *Journal of Personality and Social Psychology, 57,* 1024.

Scheier, M. F. & CARVER, C. S. (1985). Optimism, coping and health: Assessments and implications of generalised outcome expectancies. *Health Psychology, 55,* 169-210.

Schilder.A.J., Kennedy, C., Goldstone, I. L., Ogden, R. D., Hogg, R. S., & O'Shaughnessy, M. V. (2001). "Being dealt with as a whole person." Care seeking and adherence: The benefits of culturally competent care. *Social Science & Medicine, 52,* 1643-1659.

Schneiderman, N., Antoni, M., Ironson, G., LaPerriere, A. & Fletcher, M.A. (1992). Applied psychosocial science and HIV-1 spectrum disease. *Journal of Applied and Preventative Psychology, 1,* 67-82.

Schuman, P., Ohmit, S. E., Cohen, M., & Sacks, H. (2001). Prescription of and adherence to antiretroviral therapy among women with AIDS. *AIDS & Behavior, 5,* Dec-378.

Schwarzer, R. (1992). Self-efficacy in the adoption and maintenance of health behaviors: theoretical approaches and a new model. In R.Schwarzer (Ed.), *Self-efficacy: thought control of action* (pp. 217-243). London: Hemisphere.

Segerstrom, S., Taylor, S., Kemeny, M., Reed, G., & Visscher, B. (1996). Causal attributions predict immune decline in HIV seropositive gay men. *Health Psychology, 15,* 485.

Sharpe, L., Sensky, T., & Allard, S. (2001). The course of depression in recent onset rheumatoid arthritis: the predictive role of disability, illness perceptions, pain and coping. *Journal of Psychosomatic Research, 51,* 713.

Sheeran, P. & Abraham, C. (1996). The health belief model. In M.Conner & P. Norman (Eds.), *Predicting health behaviour; research and practice with social cogniton models* (pp. 23-61). Buckingham: Open University Press.

Sian, A. K. (2001). Encouraging adherence to antiretroviral drug regimes. *Family Practice, 18,* 463.

Siegel, K. & Gorey, E. (1997). HIV infected women: Barriers to AZT use. *Social Science Medicine, 45,* 15-22.

Siegel, K., Schrimshaw, E., & Dean, L. (1999). Symptom interpretation and medication adherence among late middle-age and older HIV infected adults. *Journal of Health Psychology, 4,* 247-257.

Siegel, K., Schrimshaw, E. W., & Raveis, V. H. (2000). Accounts for non-adherence to antiviral combination therapies among older HIV-infected adults. *Psychology, Health and Medicine, 5,* 29-42.

Simoni, J. M. (2002). Mediators of social support and antiretroviral adherence among an indigent population in New York City. *AIDS Patient Care & STDs, 16,* Sep-439.

Singh, N., Berman, S., Swindells, S., Justis, J., Mohr, J., Squier, C. et al. (1999). Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. *Clinical Infectious Diseases, 29,* 824-830.

Singh, N., Squier, C., Sivek, C., Wagener, M., Nguyen, M. H., & Yu, V. L. (1996). Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care 8*[3], 261-269.

Smith, M. Y., Rapkin, B. D., Morrison, A., & Kammerman, S. (1997). Zidovudine adherence in persons with AIDS. The relation of patient beliefs about medication to self-termination of therapy. *Journal of General Internal Medicine, 12,* 216-223.

Smith, S. L., Colenda, C. C., & Espeland, M. A. (1994). Factors determining the level of anxiety state in geriatric primary care patients in a community dwelling. *Psychosomatics, 35,* 50-58.

Sonnabend, J., Witkin, S. S., & Purtilo, D. T. (1983). Acquired immunodeficiency syndrome, opportunistic infections, and malignancies in male homosexuals. A hypothesis of etiologic factors in pathogenesis. *JAMA, 249,* 2370-2374.

Spire, B., Duran, S., Souville, M., Leport, C., Raffi, F., & Moatti, J. P. (2002). Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. *Social Science & Medicine, 54,* 1481-1496.

Spruance, M., Spotswood, L., & Pavia, A. e. a. (1997). Clinical efficacy of monotherapy with stavudine compared with zidovudine in HIV-infected, zidovudine-Experienced patients. *Annals of Internal Medicine, 126,* 355-363.

Starace, F., Ammassari, A., Trotta, M. P., & et al (2002). Depression Is a Risk Factor for Suboptimal Adherence to Highly Active Antiretroviral Therapy. *Journal of Acquired Immune Deficiency Syndromes, 31,* s136.

Staszewski, S., Miller, V., Sabin, C. A., Carlebach, A., Berger, A., Weidman, E. et al. (1999). Virological response to protease inhibitor therapy in an HIV clinic cohort. *AIDS, 13,* 367-373.

Stein, M. D., Rich, J. D., Maksad, J., Chen, M. H., Hu, P., Sobota, M. et al. (2000). Adherence to antiretroviral therapy among HIV-infected methadone patient: effect of ongoing illicit drug use. *American Journal of Alcohol and Drug abuse 26*[2], 195-205.

Stenzel, M. S., McKenzie, M., Adelson Mitty, J., & Flanigan, T. P. (2001). Enhancing adherence to HAART: a pilot program of modified directly observed therapy. *AIDS Reader, 11,* 317-328.

Sterling, T., Chaisson, R., & Moore, R. (2001). HIV-1 RNA, CD4 T-lymphocytes, and clinical response to HAART. *AIDS, 15,* 2251-2257.

Sternhell, P. S. & Corr, M. J. (2002). Psychiatric morbidity and adherence to antiretroviral medication in patients with HIV/AIDS. *Australian & New Zealand Journal of Psychiatry, 36,* 528-533.

Stone, V. E., Hogan, j., Schuman, P., Rompalo, A., Howard, A., Korkontzelou, C. et al. (2001). ARV regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the her study. *Journal of Acquired Immune Deficiency Syndromes, 28,* 124-131.

Stone, V. E., Clarke, J., Lovell, J., Steger, K. A., Hirschhorn, L. R., Boswell, S. et al. (1998). HIV/AIDS patients' perspectives on adhering to regimens containing protease inhibitors. *Journal of General Internal Medicine, 13,* 586-593.

Taylor, D. W. (1979). A test of the Health Belief Model in hypertension. In R.B.Haynes, D. L. Sackett, & D. W. Taylor (Eds.), *Compliance in Health Care* (pp. 103-109). Baltimore and London: John Hopkins University Press.

Taylor, S., Kemeny, M., Aspinwall, L., Schneider, S., Rodriguez, R., & Herbert, M. (1992). Optimism, coping psychological distress, and high-risk sexual behaviours among men at risk for AIDS. *Journal of Personality and Social Psychology, 63,* 460.

Tuldra, A., Fumaz, C. R., Ferrer, M. J., Bayes, R., Arno, A., Balague, M. et al. (2000). Prospective randomised two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes 25*[3], 221-228.

Turner, B. J., Laine, C., Cosler, L., & Hauck, W. W. (2003). Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users. *Journal of General Internal Medicine, 18,* 248-257.

UK collaborative Group on monitoring the transmission of HIV drug resistance (2001). Analysis of prevalence of HIV-1 drug resistance in primary infections in the UK. *BMJ, 322,* 1087-1088.

van Servellen, G., Chang, B., Garcia, L., & Lombardi, E. (2002). Individual and system level factors associated with treatment nonadherence in human immunodeficiency virus-infected men and women. *AIDS Patient Care & STDs, 16,* 269-281.

Vandamme, A., Hall, W., Lewis, M., Goubau, P., & Salemi, M. (2000). Origins of HTLV-1 in South America. *Nature Medicine, 6,* 232-233.

Vanhove, G. F., Schapiro, J. M., Winters, M. A., Merigan, T. C., & Blaschke, T. F. (1996). Patient compliance and drug failure in protease inhibitor monotherapy [6]. *Journal of the American Medical Association, 276,* 1955-1956.

Vergis, E. N., Paterson, D. L., Wagener, M. M., Swindells, S., & Singh, N. (2001). Dyslipidaemia in HIV-infected patients: association with adherence to potent antiretroviral therapy. *International Journal of STD and AIDS, 12,* 463-468.

Wadeley, A. (1991). *Ethics in psychological research and practice*. Leicester: BPS.

Wagner, G. J., Remien, R. H., Carballo-Dieguez, A., & Dolezal, C. (2002). Correlates of adherence to combination antiretroviral therapy among members of HIV-positive mixed status couples. *AIDS Care, 14,* 105-109.

Wagner, J., Justice, A., Chesney, M., Sinclair, G., Weissman, S., & Rodriguez-Barradas, M. (2001). Patient- and provider-reported adherence: toward a clinically useful approach to measuring ARV adherence. *Journal of Clinical Epidemiology, 54,* s91.

Walkup, J., Sambamoorthi, U., & Stephen, C. (2001). Incidence and consistency of antiretroviral use among HIV-infected Medicaid beneficiaries with schizophrenia. *Journal of Clinical Psychiatry 62*[3], 174-178.

Wall, T. L., Sorensen, J. L., Batki, S. L., Delucchi, K. L., London, J. A., & Chesney, M. A. (1995). Adherence to zidovudine (AZT) among HIV-infected methadone patients: A pilot study of supervised therapy and dispensing compared to usual care. *Drug & Alcohol Dependence, 37*.

Walsh, J. C. & Gazzard, B. G. (2000). A visual analogue scale based questionnaire on patient self reported adherence to HAART shows good correlation with objective measures. Proceedings of the European Conference on Clinical Aspects and Treatment of HIV infection, 27 October, Lisbon.

Walsh, J. C., Horne, R., Dalton, M., Burgess, A. P., & Gazzard, B. G. (2001). Reasons for non-adherence to antiretroviral therapy: Patients' perspectives provide evidence of multiple causes. *AIDS Care, 13,* 709-720.

Walsh, J., Mandalia, S., & Gazzard, B. (2002). Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS, 16,* 269.

Ware, J. E. & Sherbourne, C. D. (1992). The MOS 36-item Short Form Health Survey (SF-36), conceptual framework and item selection. *Medical Care, 30,* 473-483.

Ware, J. Jr., Kosinski, M., & Keller, S. (1996). A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Medical Care, 34,* 220-233.

Watson, D. & Pennebaker, J.W. (1989). Health complaints, stress and disease: Exploring the central role of negative affectivity. *Psychological Review, 96*, 234-254.

Webb, D. G., Horne, R., & Pinching, A. J. (2001). Treatment-related empowerment: Preliminary evaluation of a new measure in patients with advanced HIV disease. *International Journal of STD and AIDS, 12,* 103-107.

Weinman, J. (2003). Making sense of illness and treatment: A self-regulatory approach. Oral presentation at the 17th European Health Psychology Conference, 24-27 September, Kos, Greece.

Weinman, J., Petrie, K., Moss-Morris, R., & Horne, R. (1996). The Illness Perception Questionnaire: A new method for assessing the cognitive representation of illness. *Psychology and Health, 11,* 431-445.

Williams, M., Bowen, A., Ross, M., Freeman, R., & Elwood, W. (2000). Perceived compliance with AZT dosing among a sample of African-American drug users. *International Journal of STD & AIDS, 11,* 57-63.

Wilson, I., Tchetgen, E., & Spiegelman, D. (2001). Patterns of adherence with ARV medications: an examination of between-medication differences. *Journal of Acquired Immune Deficiency Syndromes, 28,* 259.

Wilson, T., Barron, Y., Cohen, M., Richardson, J., Greenblatt, R., Sacks, H. et al. (2002). Adherence to ARV therapy and its association with sexual behaviour in a national sample of women with HIV. *Clinical Infectious Diseases, 34,* 529.

Wutoh, A. K., Brown, C. M., Kumoji, E. K., Daftary, M. S., Jones, T., Barnes, N. A. et al. (2001). Antiretroviral adherence and use of alternative therapies among older HIV-infected adults. *Journal of the National Medical Association 93*[7-8], 243-250.

Zeider, M., Boekaerts, M., & Pintrich, P. (2000). Self-regulation: directions and challenges for future research. In M.Boekaerts, P. R. Pintrich, & M. Zeider (Eds.), *Handbook of self-regulation*. California: Academic Press.

Zhu, T., Korber, B., & Nahinias, A. E. (1998). An African HIV-1 Sequence from 1959 and Implications for the Origin of the Epidemic. *Nature, 391,* 594.

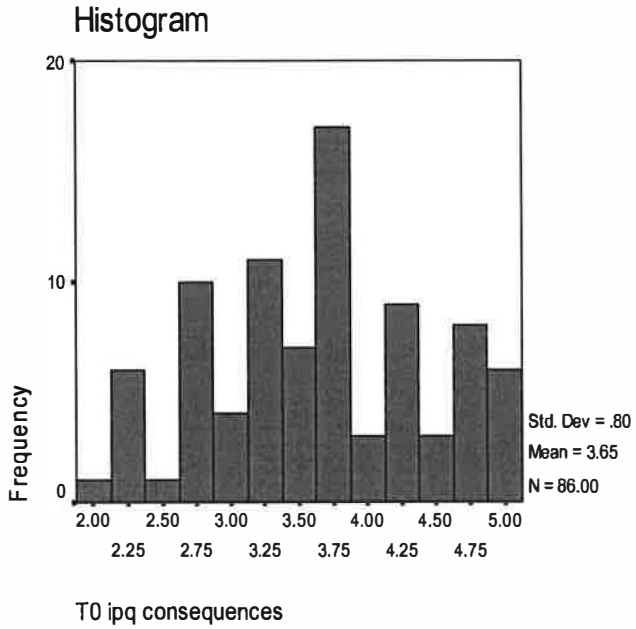
Zigmond, A. S. & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica, 67,* 361-370.

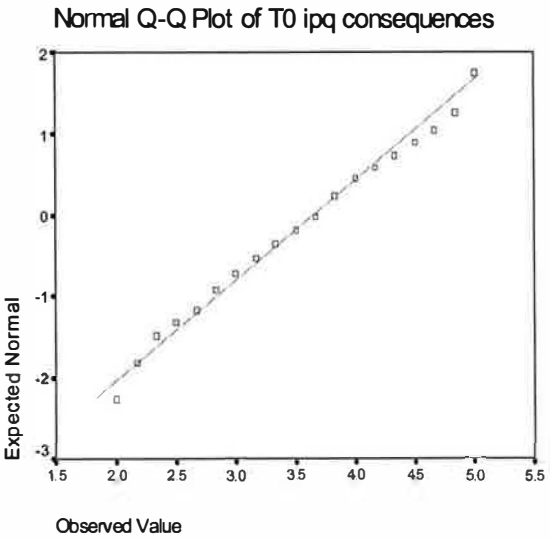
APPENDIX 1

Distribution of scales

1.1 Distributions of IPQ variables

1.1.1 IPQ-consequences





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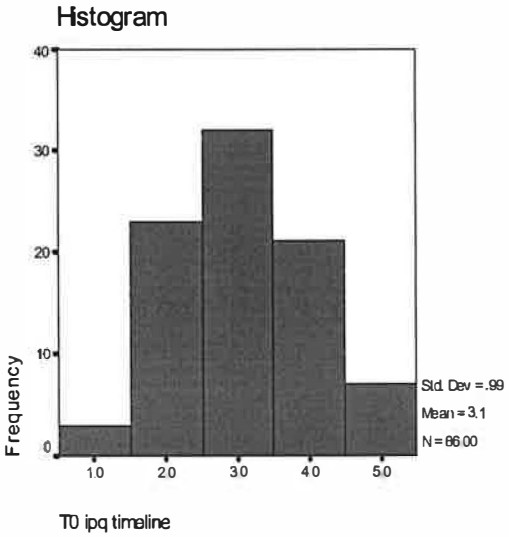

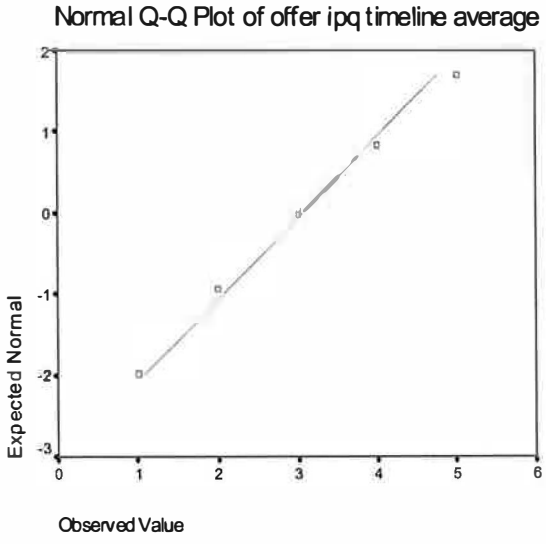

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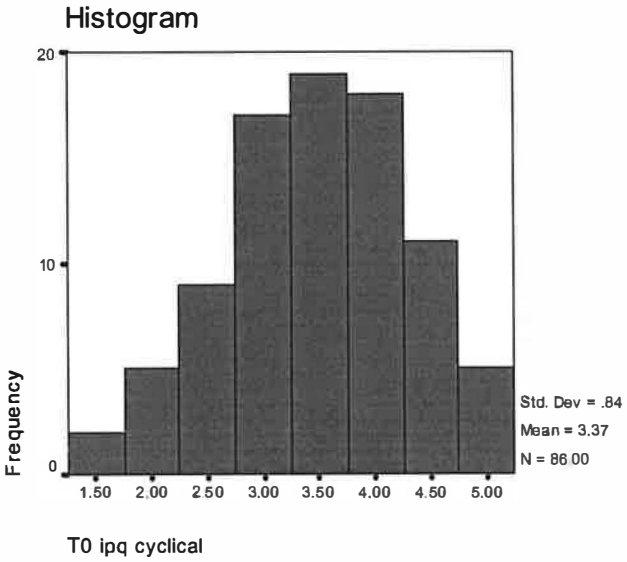

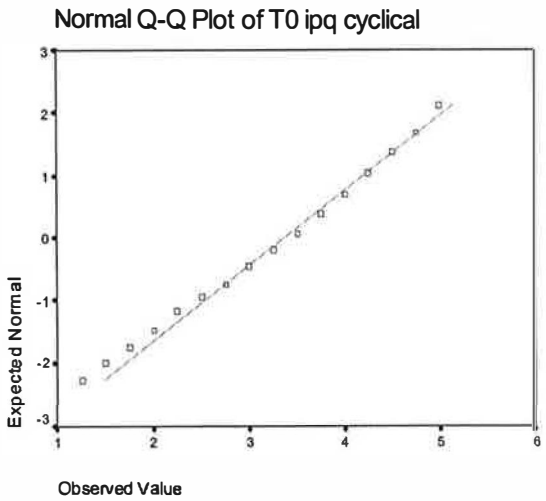

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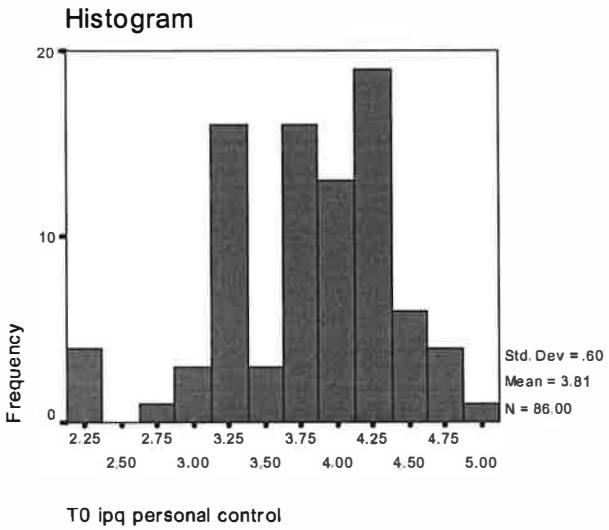

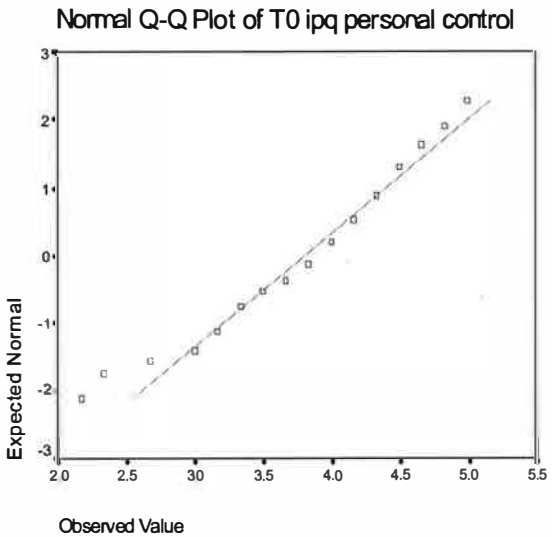

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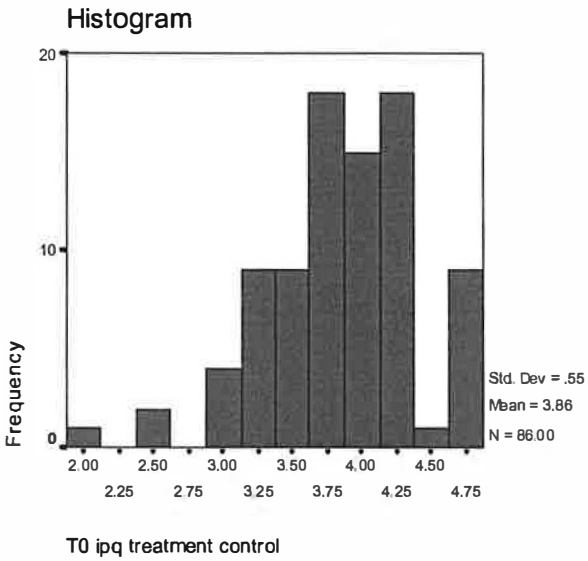

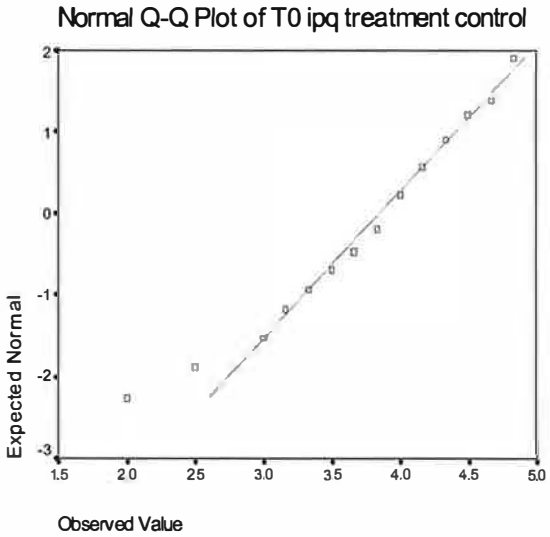

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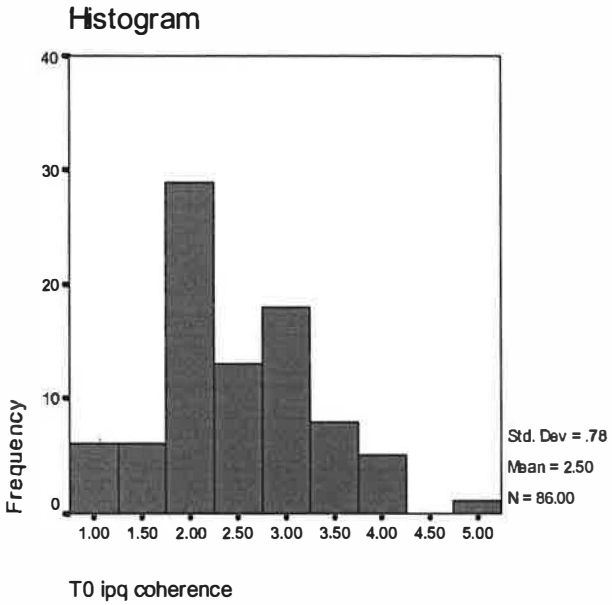

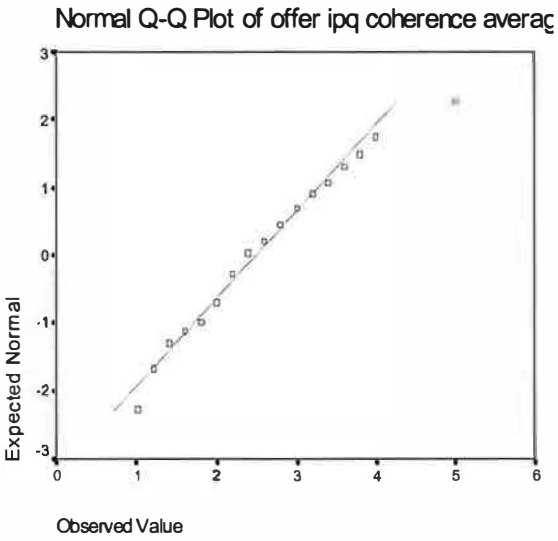

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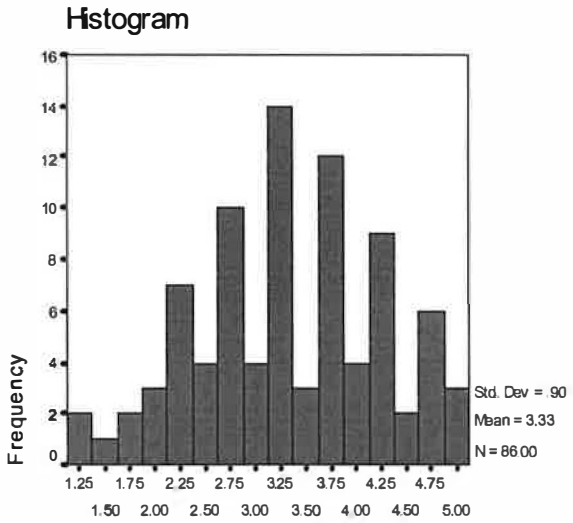
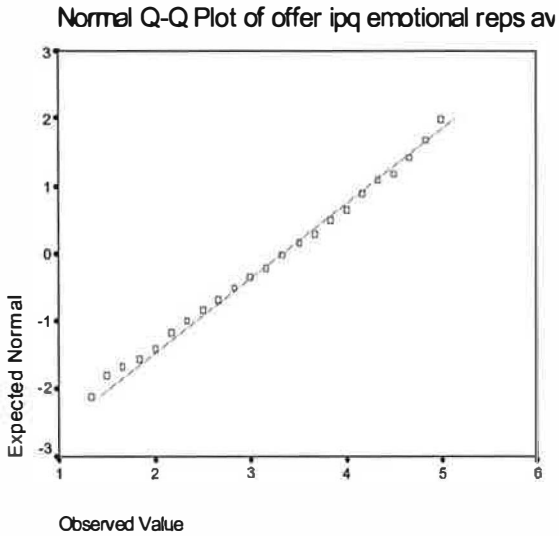
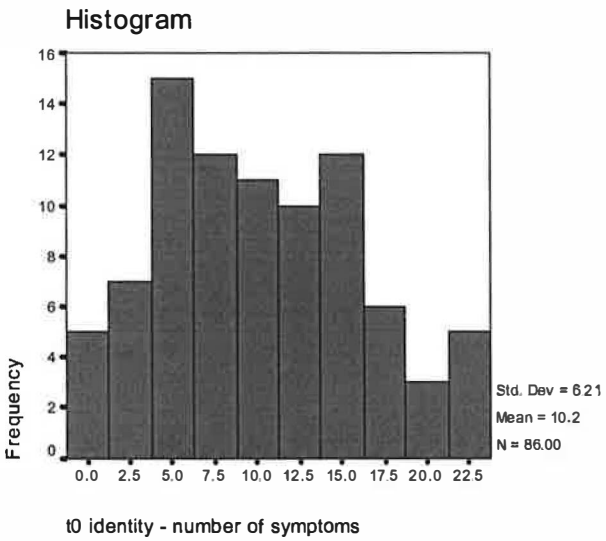
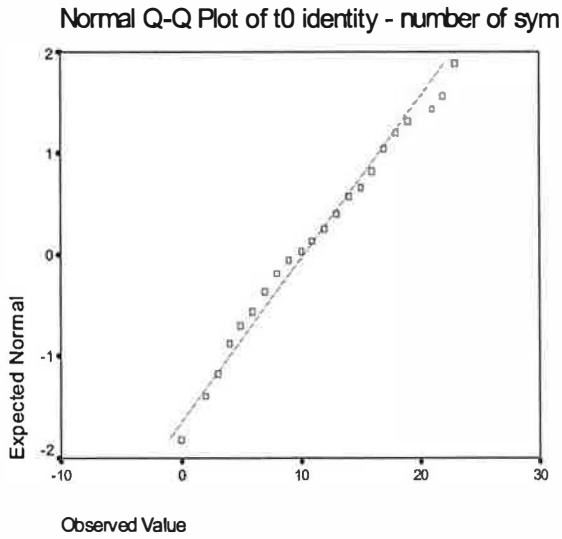


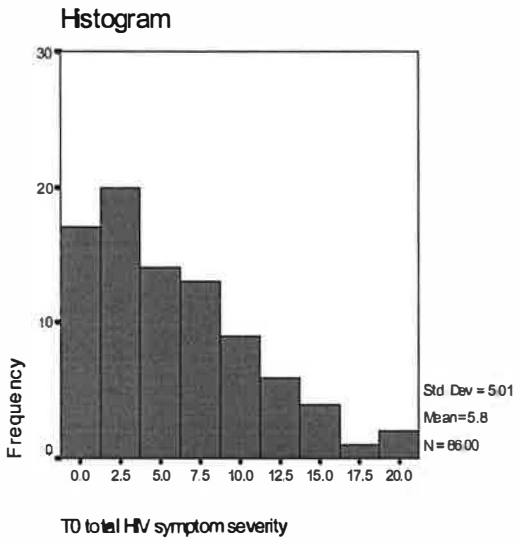


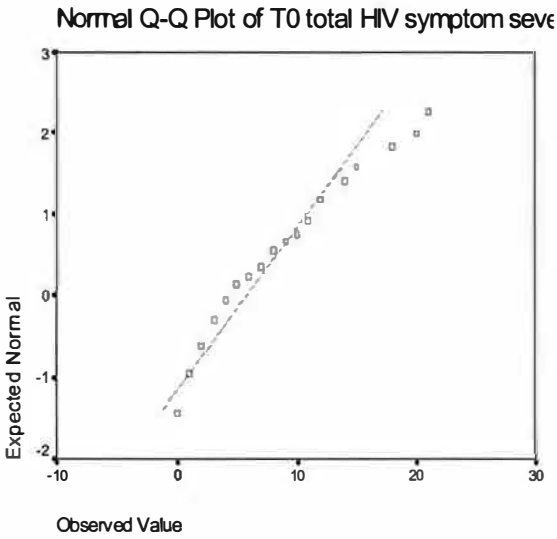
1.1.8 IPQ-identity





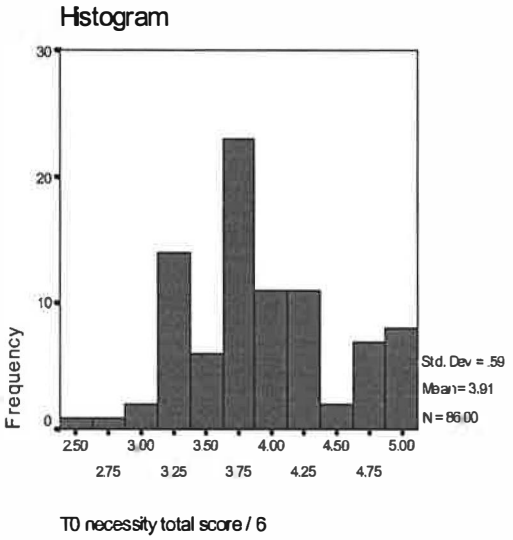
1.1.9 IPQ-identity moderate-severe symptoms

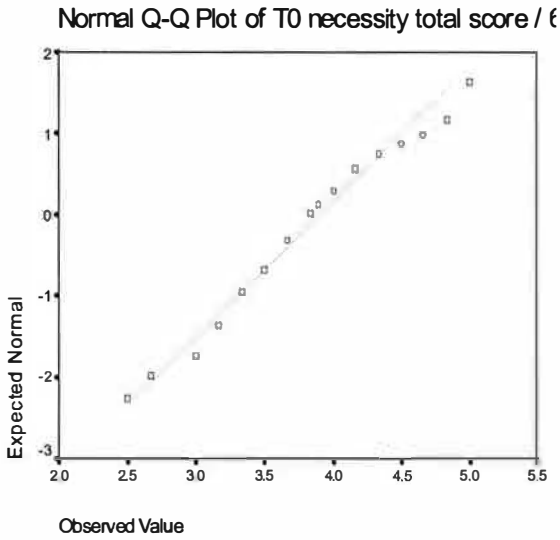




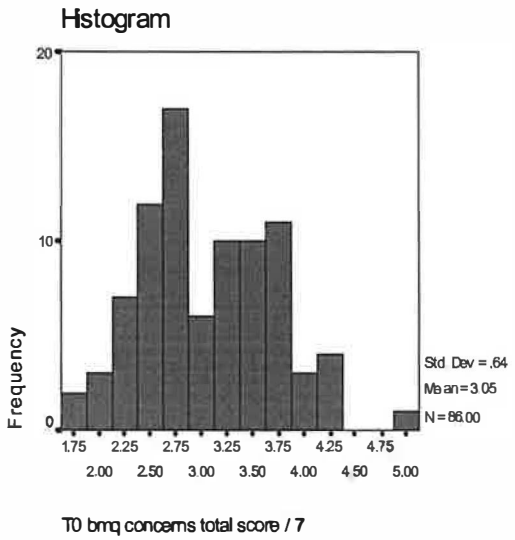
1.2 Distributions of BMQ variables

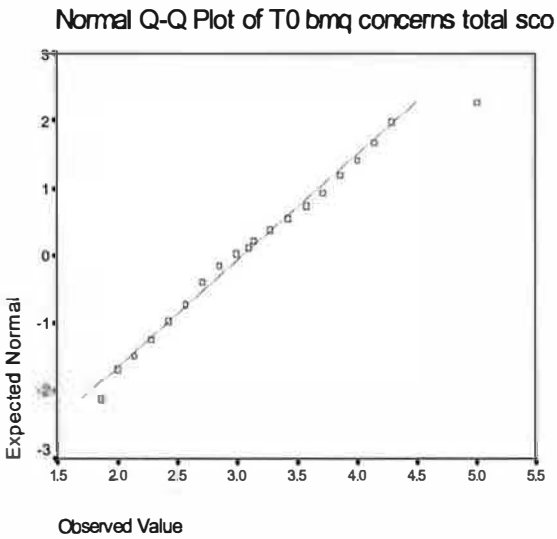
1.2.1 BMQ-Necessity





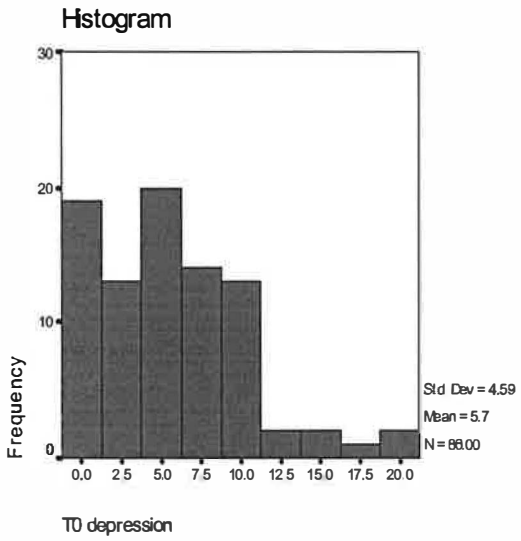
1.2.2 BMQ-Concerns

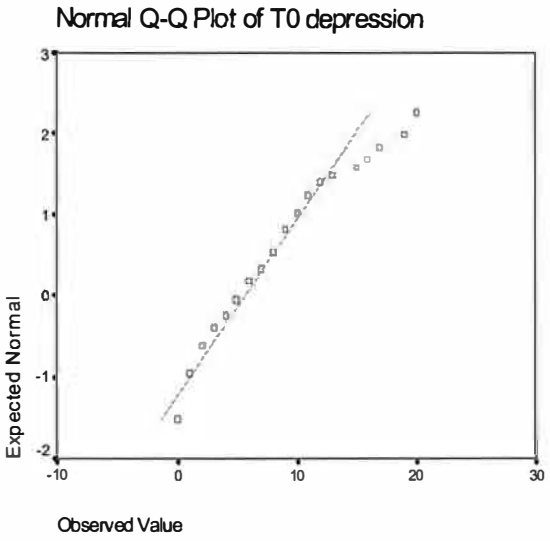




1.3 Distributions of HADS variables

1.3.1 HADS-depression





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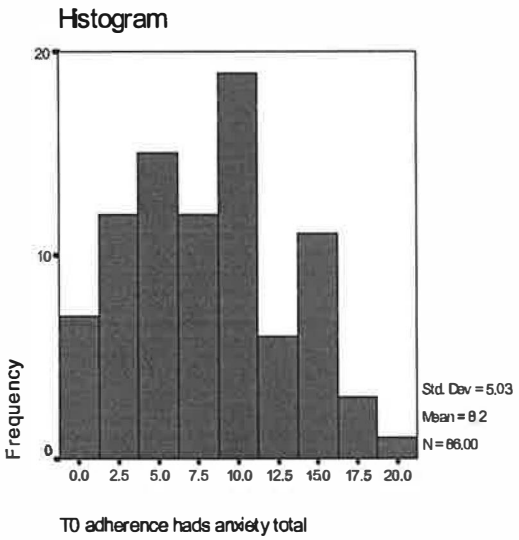
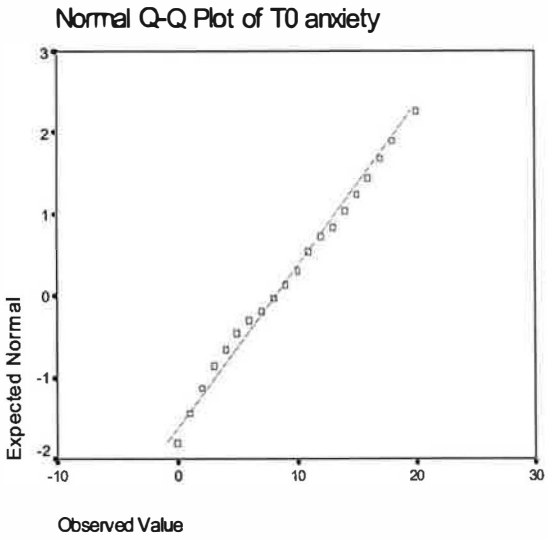
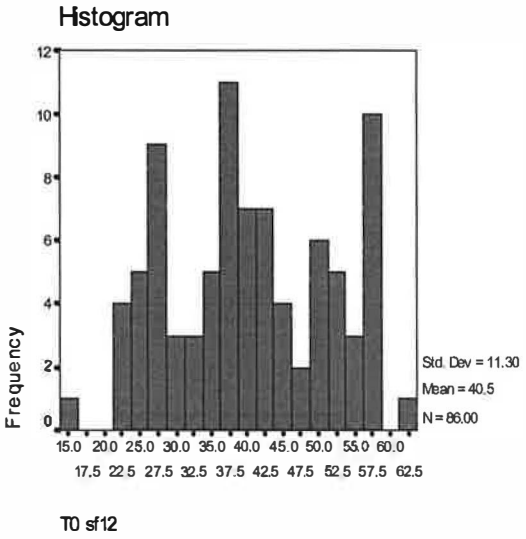
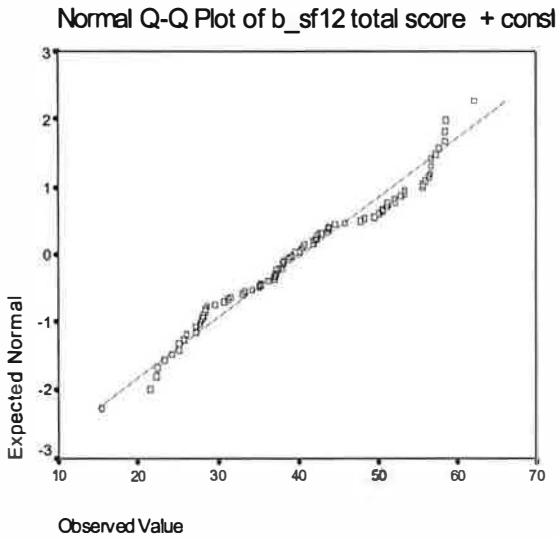




1.4 Distributions of SF12 physical health





APPENDIX 2
Information sheet, consent form and contact details

Consent form
Contact details

Patient information booklet

University of Brighton

Consent form

Your views about HIV and combination therapy

Hospital number.....

I fully and freely consent to participate in the study named above. I understand that my participation will involve an interview with a researcher and filling out a questionnaire booklet on up to 5 occasions over a 12 month period, as outlined on the information sheet.

I have been given an information sheet, which I have read and understand, and which I can keep for future reference.

I acknowledge that it is solely my decision whether or not to take part in this research and that I am free to withdraw from the study at any time without having to explain my decision to anyone. I understand that taking part will not affect any aspect of my continued care, and that the information I provide is confidential and will be used only for the purposes of research. I am aware that my participation is anonymous and that none of the information I provide will be linked to my name.

I have been given the opportunity to ask any questions.

***Signature of participant*.....**

***Initials of participant*.....**

Date of consent.....

***Signature of interviewer*.....**

Date.....

Thank you for consenting to take part in our research

University of Brighton

Contact form

Your views about HIV and combination therapy

I would like to find out more about the research project investigating people's views about HIV and combination therapy. I give my consent to be contacted by the research group at the University of Brighton.

Please write your details below and we will contact you as soon as we can.

Telephone number: .....

Contact name: .....

Signed: .....

Date: .....

May we telephone you?.....YES / NO

May we leave a message?.....YES / NO

May we write to you at your home address?.....YES / NO

Thank you for your interest in our research.

University of Brighton

Your views about HIV and Combination Therapy

Information about a Brighton based study

You are invited to take part in a research study being carried out collaboratively by the Centre for Health Care Research at the University of Brighton, with support from the Lawson Unit at the Royal Sussex County Hospital and the Elton John Centre at Brighton General Hospital.

Advances in treatment for HIV infection have had a major impact on the lives of many people. However, there is currently little research into people's feelings towards and views about treatment for HIV. The aim of this study is to try to get a better understanding of how you and others make decisions regarding treatment and to collect your views and/or experiences of combination therapy. The information we obtain will help your doctors and other health care workers to improve services for HIV positive individuals, whether or not they are currently taking combination therapy.

You will not directly benefit from this study, therefore it is important that before deciding whether or not to take part, you should read this information sheet carefully. If there is anything you do not understand, or if you require further information regarding the study please feel free to ask the research staff. Your participation in this study is entirely voluntary and you are free to withdraw from the study at any time without having to explain your decision to anyone. Your medical care will not be affected whatever decision you make.

What will taking part involve?

All patients attending the Lawson Unit and Elton John Centre, who are not receiving anti-retroviral therapy will be asked to participate in this study. The research will be conducted over a period of twelve months. If you agree to participate, we would like to arrange up to five appointments with you over this time. Taking part simply involves filling out some questionnaires, which you could take home to complete if you prefer. Filling out the questionnaire booklet takes approximately 30 - 45 minutes. As we are interested in hearing your views, we would also like to arrange a short interview with you. We anticipate the completion of the questionnaires and interview together will take approximately one hour on each occasion, so being involved in the study with all five appointments will amount to approximately five hours of your time over the period of a year.

Confidentiality

The questionnaires will be analysed by a researcher who will also have access to your medical information such as medication history, length of HIV diagnosis, CD4 count, etc. Your doctor will not be aware of your responses to the questions (unless you wish to tell him/her). Results from this study may be published in medical journals, but your identity would not be revealed. You are assured that your confidentiality will be maintained at all times.

What do I do now?

The researchers will be happy to answer any questions you have about this study. If you would like to be included in the study or would like to discuss the project further before you decide, please speak to one of the researchers (Vanessa or Grace) at the Lawson Unit. Or complete and sign the contact form attached and hand the form in at reception. We will contact you as soon as we can.

If you have any queries or would like to discuss any aspect of this study, please do not hesitate to contact us. You can telephone us on 01273 643961. Or write to us at the Centre for Health Care Research, University of Brighton, 2-3 Turnpike Piece, Falmer Campus, Brighton, BN1 9PH. Or you can e-mail us;

Vanessa Cooper v.cooper@brighton.ac.uk
Grace Gellaitry g.gellaitry@brighton.ac.uk

Thank you for considering taking part in our research.

APPENDIX 3

Baseline questionnaire booklet

Illness Perception Questionnaire

SF-12

Beliefs about Medicines Questionnaire – HAART

Beliefs about Medicines Questionnaire – General

Sensitive Soma

Hospital Anxiety and Depression Scale

University of Brighton

Your views about HIV and combination therapy

Baseline Questionnaire Booklet

Participant number: .....

Date: .....

YOUR EXPERIENCE OF SYMPTOMS ASSOCIATED WITH HIV

- **Listed below are a number of symptoms that you may or may not have experienced since being diagnosed as HIV positive.**
- **We are interested in how you are feeling AT PRESENT.**
- **Please rate the severity of any symptoms you are currently experiencing by circling the appropriate number on the scale, where 1 indicates very mild and 5 indicates very severe.**
- **Please only rate the symptoms *that you believe are a result* of *HIV* and not those that you believe are due to your medication.**

	Are you currently experiencing this symptom as a result of having HIV?			*If yes, please rate the symptom severity*				
				very mild	**mild**	**moderate**	**severe**	**very severe**
a_ie1	Pain	Yes	No	1	**2**	**3**	**4**	**5**
a_ie2	Sore throat	Yes	No	1	2	3	4	5
a_ie3	Nausea	Yes	No	1	2	3	4	5
a_ie4	Breathlessness	Yes	No	1	**2**	**3**	**4**	**5**
a_ie5	Weight loss	Yes	No	1	2	3	4	5
a_ie6	Fatigue	Yes	No	1	**2**	**3**	**4**	**5**
a_ie7	Stiff Joints	Yes	No	1	2	3	4	5
a_ie8	Sore eyes	Yes	No	1	**2**	**3**	**4**	**5**
a_ie9	Wheezing	Yes	No	1	2	3	4	5
a_ie10	Headaches	Yes	No	1	2	3	4	5
a_ie11	Upset stomach	Yes	No	1	**2**	**3**	**4**	**5**
a_ie12	Sleep difficulties	Yes	No	1	2	3	4	5
a_ie13	Dizziness	Yes	No	1	**2**	**3**	**4**	**5**
a_ie14	Loss of strength	Yes	No	1	2	3	4	5
a_ie15	Night sweats	Yes	No	1	**2**	**3**	**4**	**5**
a_ie16	Diarrhoea	Yes	No	1	2	3	4	5
a_ie17	Feeling faint	Yes	No	1	2	3	4	5
a_ie18	Fever	Yes	No	1	**2**	**3**	**4**	**5**
a_ie19	Sexual problems	Yes	No	1	2	3	4	5
a_ie20	Loss of appetite	Yes	No	1	**2**	**3**	**4**	**5**
a_ie21	Skin problems	Yes	No	1	2	3	4	5
a_ie22	Altered sensation in hands or feet	Yes	No	1	**2**	**3**	**4**	**5**
a_ie23	Stomach pain	Yes	No	1	2	3	4	5

YOUR VIEWS ABOUT LIVING WITH HIV

- **We are interested in your views about living with HIV.**
- **Below are some statements that other people have made.**
- **Please show how much you agree or disagree with each of the following statements by ticking the appropriate box.**

	YOUR VIEWS ABOUT HIV	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree
a_ctx1	Anti HIV medication can control the progress of my HIV infection					
a_er6	Having HIV makes me feel anxious					
a_ic3	I don't understand enough about HIV					
a_ti5	I expect to have HIV for the rest of my life					
a_ct6	There is nothing which can help my condition					
a_er1	I get depressed when I think about having HIV					
a_cy5	I go through cycles in which my condition gets better and worse					
a_ic5	I have a clear picture or understanding of my condition					
a_cp6	I have the power to influence the course of my condition					
a_ct3	Anti-HIV treatment will be effective in curing my illness					
a_cp7	My actions will have no affect on the outcome of my condition					
a_ctx2	I'll get ill when my time comes whether I'm taking Anti HIV medication or not					
a_cq8	The fact that I have HIV causes difficulties for those who are close to me					
a_cy3	My condition is very unpredictable.					
a_cq4	Having HIV does not have much effect on my life					
a_er5	Having HIV does not worry me					
a_ic4	Having HIV doesn't make any sense to me					
a_cq2	Having HIV has major consequences on my life					
a_cq6	Having HIV has serious financial consequences					

YOUR VIEWS ABOUT LIVING WITH HIV

	YOUR VIEWS ABOUT HIV	Strongly disagree	Disagree	Neither agree nor disagre	Agree	Strongly agree
a_ic2	The HIV virus is a mystery to me					
a_cq1	**My illness is a serious condition**					
a_ti2	**My condition is likely to be permanent rather than temporary**					
a_er8	**Having HIV makes me feel afraid**					
a_er4	**Having HIV makes me feel angry**					
a_cq5	**Having HIV strongly affects the way others see me**					
a_ti1	**My condition will improve in time**					
a_cy2	**My symptoms come and go in cycles**					
a_cp5	**Nothing I do will affect my illness**					
a_cp4	**The course of my condition depends on me**					
a_ct4	**The negative effects of my illness can be prevented by Anti HIV therapy**					
a_ic1	**The symptoms of my condition are puzzling to me**					
a_cy1	**The symptoms of my condition change a great deal from day to day**					
a_cp1	**There is a lot which I can do to control my condition**					
a_ct2	**There is very little that can be done to improve my condition**					
a_cp2	**What I do can determine whether my condition gets better or worse**					
a_er3	**When I think about having HIV I get upset**					
a_ct5	**Anti HIV medication can control my condition**					

QUESTIONS ABOUT YOUR GENERAL HEALTH

- **We would like to ask you about your overall health.**
- **Please read each question and answer by ticking one of the boxes.**

a_Sfgh1	In general, would you say your health is:
Excellent	
Very Good	
Good	
Fair	
Poor	

- **The following questions are about activities you might do during a typical day.**
- **We would like to know if your health limits you in these activities.**
- **Please show HOW MUCH YOUR HEALTH LIMITS YOU IN EACH OF THE FOLLOWING ACTIVITIES by ticking one of the boxes.**

	ACTIVITIES	YES limited a lot	YES limited a little	NO not limited at all
a_Sfpf 1	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
a_Sfpf 2	Climbing several flights of stairs			

- **We would now like to ask you about problems that you may have had with your work or regular daily activities during the past four weeks.**
- **Please show whether you have had any of the following problems AS A RESULT OF YOUR PHYSICAL HEALTH during the past four weeks, by ticking one of the boxes.**

	AS A RESULT OF YOUR PHYSICAL HEALTH, HAVE YOU:	YES	NO
a_sfrp1	Accomplished less than you would like?		
a_sfrp2	Been limited in the kind of work or other activities you could do?		

QUESTIONS ABOUT YOUR GENERAL HEALTH

- **Please show whether you have had any of the following problems AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious) during the past four weeks, by ticking one of the boxes.**

	AS A RESULT OF ANY EMOTIONAL PROBLEMS, HAVE YOU:	YES	NO
a_sfre1	Accomplished less than you would like?		
a_sfre2	Not been able to do work or other activities as carefully as usual?		

a_sfbp1	During the past four weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
Not at all	
A little bit	
Moderately	
Quite a bit	
Extremely	

- **We would now like to ask you about how you have been feeling during the past four weeks.**
- **Please show how much of the time during the past four weeks you have been feeling each of the following ways by ticking one of the boxes.**

	How much of the time:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a_sfmh1	Have you felt calm and peaceful?						
a_sfvt1	Did you have a lot of energy?						
a_sfmh2	Have you felt downhearted and low?						

a_sfsf1	During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends and relatives or going to groups)?
All of the time	
Most of the time	
Some of the time	
A little of the time	
None of the time	

YOUR VIEWS ABOUT COMBINATION THERAPY

- We would like to ask you about your personal views about combination therapy
- These are statements other people have made about combination therapy
- Please show how much you agree or disagree with them by ticking the appropriate box

There are no right or wrong answers.
We are interested in your personal views

	Views about COMBINATION THERAPY:	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
a_sn1	My health depends on these medicines					
a_sc1	Having to take these medicines would worry me					
a_sn2	My life would be impossible without these medicines					
a_sc2	I would worry about long-term effects of these medicines					
a_sn3	Without these medicines I would become very ill					
a_sc3	These medicines are a mystery to me					
a_sn4	My health in the future will depend on these medicines					
a_sc4	These medicines would disrupt my life					
a_sc5	I would worry about becoming too dependent on these medicines					
a_snx1	Taking these medicines would keep my HIV under control					
a_sc6	These medicines would give me unpleasant side effects					
a_scx1	It would be difficult for me to take the tablets on time each day					
a_snx2	These medicines are the best hope for the future					

YOUR VIEWS ABOUT MEDICINES IN GENERAL

- Below is a list of statements that other people have made about medicines in general.
- Please show the extent to which you agree or disagree with each of the statements below, by ticking one of the boxes.

	YOUR VIEWS ABOUT MEDICINES IN GENERAL	Strongly Agree	Agree	uncertain	Disagree	Strongly Disagree
a_go1	**Doctors use too many medicines**					
a_gh1	**People who take medicines should stop their treatment for a while every now and again**					
a_gb1	**Medicines help many people to live better lives**					
a_gh2	**Most medicines are addictive**					
a_go2	**Natural remedies are safer than medicines**					
a_gb2	**In most cases the benefits of medicines outweigh the risks**					
a_gb3	**In the future medicines will be developed to cure most diseases**					
a_gh3	**Most medicines are poisons**					
a_gh4	**Medicines do more harm than good**					
a_gb4	**Medicines help many people to live longer**					
a_go3	**Doctors place too much trust in medicines**					
a_go4	**If doctors had more time with patients they would prescribe fewer medicines**					

- **Below are statements that other people have made about the ways in which medicines have affected them in the past**
- **Please show how true each statement is for you, by ticking the box that most accurately describes your experiences of medicines**

	YOUR VIEWS ABOUT MEDICINES IN GENERAL	Strongly Agree	Agree	uncertain	Disagree	Strongly Disagree
a_s1	**My body is very sensitive to medicines**					
a_s2	**My body over-reacts to medicines**					
a_s3	**I usually have stronger reactions to medicines than most people**					
a_s4	**I have had a bad reaction to medicines in the past**					
a_s5	**Even very small amounts of medicine can upset my body**					

QUESTIONS ABOUT HOW YOU FEEL

- **This part of the questionnaire contains statements about feelings.**
- **Below each statement are four possible responses.**
- **Please read each statement carefully and place a tick in the box next to the reply that comes closest to how you have been feeling during the past week, including today.**
- **Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought out response.**

a_hax1	*I FEEL TENSE OR 'WOUND UP'*	
Most of the time		
A lot of the time		
From time to time, occasionally		
Not at all		
a_hdp1	*I STILL ENJOY THE THINGS I USED TO ENJOY*	
Definitely as much		
Not quite so much		
Only a little		
Hardly at all		
a_hax2	*I GET A FRIGHTENED FEELING AS IF SOMETHING AWFUL IS ABOUT TO HAPPEN*	
Yes, definitely and quite badly		
Yes, but not too badly		
A little, but it doesn't worry me		
Not at all		
a_hdp2	I CAN LAUGH AND SEE THE FUNNY SIDE OF THINGS	
As much as I always could		
Not quite so much now		
Definitely not so much now		
Not at all		
a_hax3	WORRYING THOUGHTS GO THROUGH MY MIND	
A great deal of the time		
A lot of the time		
From time to time but not too often		
Only occasionally		
a_hdp3	I FEEL CHEERFUL	
Not at all		
Not often		
Sometimes		
Most of the time		

a_hax4	I CAN SIT AT EASE AND FEEL RELAXED	
Definitely		
Usually		
Not often		
Not at all		
a_hdp4	I FEEL AS IF I AM SLOWED DOWN	
Nearly all the time		
Very often		
Sometimes		
Not at all		
a_hax5	I GET A SORT OF FRIGHTENED FEELING LIKE 'BUTTERFLIES' IN THE STOMACH	
Not at all		
Occasionally		
Quite often		
Very often		
a_hax5	I HAVE LOST INTEREST IN MY APPEARANCE	
Definitely		
I don't take as much care as I should		
I may not take quite as much care		
I take just as much care as ever		
a_hax6	I FEEL RESTLESS AS IF I HAVE TO BE ON THE MOVE	
Very much indeed		
Quite a lot		
Not very much		
Not at all		
a_hdp6	I LOOK FORWARD WITH ENJOYMENT TO THINGS	
As much as I ever did		
Rather less than I used to		
Definitely less than I used to		
Hardly at all		
a_hax7	I GET SUDDEN FEELINGS OF PANIC	
Very often indeed		
Quite often		
Not very often		
Not at all		
a_hdp7	I CAN STILL ENJOY A GOOD BOOK OR TV PROGRAMME	
Often		
Sometimes		
Not often		
Very rarely		

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

APPENDIX 4

Follow-up questionnaire booklet

Illness Perception Questionnaire

SF-12

Hospital Anxiety and Depression Scale

Beliefs about Medicines Questionnaire – HAART version

MASRI

HAART-symptom scale

University of Brighton

Your views about HIV and combination therapy

Questionnaire Booklet

1 month follow-up

Participant number: .....

Date: .....

YOUR EXPERIENCE OF SYMPTOMS ASSOCIATED WITH HIV

- **Listed below are a number of symptoms that you may or may not have experienced since being diagnosed as HIV positive.**
- **We are interested in how you are feeling AT PRESENT.**
- **Please rate the severity of any symptoms you are currently experiencing by circling the appropriate number on the scale, where 1 indicates very mild and 5 indicates very severe.**
- **Please only rate the symptoms *that you believe are a result of HIV* and not those that you believe are due to your medication.**

	Are you currently experiencing this symptom as a result of having HIV?			*If yes, please rate the symptom severity*				
				very mild	mild	moderate	severe	very severe
a_ie1	Pain	Yes	No	1	**2**	**3**	**4**	**5**
a_ie2	Sore throat	Yes	No	1	2	3	4	5
a_ie3	Nausea	Yes	No	1	2	3	4	5
a_ie4	Breathlessness	Yes	No	1	**2**	**3**	**4**	**5**
a_ie5	Weight loss	Yes	No	1	2	3	4	5
a_ie6	Fatigue	Yes	No	1	**2**	**3**	**4**	**5**
a_ie7	Stiff Joints	Yes	No	1	2	3	4	5
a_ie8	Sore eyes	Yes	No	1	**2**	**3**	**4**	**5**
a_ie9	Wheezing	Yes	No	1	2	3	4	5
a_ie10	Headaches	Yes	No	1	2	3	4	5
a_ie11	Upset stomach	Yes	No	1	**2**	**3**	**4**	**5**
a_ie12	Sleep difficulties	Yes	No	1	2	3	4	5
a_ie13	Dizziness	Yes	No	1	**2**	**3**	**4**	**5**
a_ie14	Loss of strength	Yes	No	1	2	3	4	5
a_ie15	Night sweats	Yes	No	1	**2**	**3**	**4**	**5**
a_ie16	Diarrhoea	Yes	No	1	2	3	4	5
a_ie17	Feeling faint	Yes	No	1	2	3	4	5
a_ie18	Fever	Yes	No	1	**2**	**3**	**4**	**5**
a_ie19	Sexual problems	Yes	No	1	2	3	4	5
a_ie20	Loss of appetite	Yes	No	1	**2**	**3**	**4**	**5**
a_ie21	Skin problems	Yes	No	1	2	3	4	5
a_ie22	Altered sensation in hands or feet	Yes	No	1	**2**	**3**	**4**	**5**
a_ie23	Stomach pain	Yes	No	1	2	3	4	5

YOUR VIEWS ABOUT LIVING WITH HIV

- **We are interested in your views about living with HIV.**
- **Below are some statements that other people have made.**
- **Please show how much you agree or disagree with each of the following statements by ticking the appropriate box.**

	YOUR VIEWS ABOUT HIV	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree
a_ctx1	Anti HIV medication can control the progress of my HIV infection					
a_er6	Having HIV makes me feel anxious					
a_ic3	I don't understand enough about HIV					
a_ti5	I expect to have HIV for the rest of my life					
a_ct6	There is nothing which can help my condition					
a_er1	I get depressed when I think about having HIV					
a_cy5	I go through cycles in which my condition gets better and worse					
a_ic5	I have a clear picture or understanding of my condition					
a_cp6	I have the power to influence the course of my condition					
a_ct3	Anti-HIV treatment will be effective in curing my illness					
a_cp7	My actions will have no affect on the outcome of my condition					
a_ctx2	I'll get ill when my time comes whether I'm taking Anti HIV medication or not					
a_cq8	The fact that I have HIV causes difficulties for those who are close to me					
a_cy3	My condition is very unpredictable.					
a_cq4	Having HIV does not have much effect on my life					
a_er5	Having HIV does not worry me					
a_ic4	Having HIV doesn't make any sense to me					
a_cq2	Having HIV has major consequences on my life					
a_cq6	Having HIV has serious financial consequences					

YOUR VIEWS ABOUT LIVING WITH HIV

	YOUR VIEWS ABOUT HIV	Strongly disagree	Disagree	Neither agree nor disagre	Agree	Strongly agree
a_ic2	The HIV virus is a mystery to me					
a_cq1	My illness is a serious condition					
a_ti2	My condition is likely to be permanent rather than temporary					
a_er8	Having HIV makes me feel afraid					
a_er4	Having HIV makes me feel angry					
a_cq5	Having HIV strongly affects the way others see me					
a_ti1	My condition will improve in time					
a_cy2	My symptoms come and go in cycles					
a_cp5	Nothing I do will affect my illness					
a_cp4	The course of my condition depends on me					
a_ct4	The negative effects of my illness can be prevented by Anti HIV therapy					
a_ic1	The symptoms of my condition are puzzling to me					
a_cy1	The symptoms of my condition change a great deal from day to day					
a_cp1	There is a lot which I can do to control my condition					
a_ct2	There is very little that can be done to improve my condition					
a_cp2	What I do can determine whether my condition gets better or worse					
a_er3	When I think about having HIV I get upset					
a_ct5	Anti HIV medication can control my condition					

QUESTIONS ABOUT YOUR GENERAL HEALTH

- **We would like to ask you about your overall health.**
- **Please read each question and answer by ticking one of the boxes.**

a_Sfgh1	In general, would you say your health is:
Excellent	
Very Good	
Good	
Fair	
Poor	

- **The following questions are about activities you might do during a typical day.**
- **We would like to know if your health limits you in these activities.**
- **Please show HOW MUCH YOUR HEALTH LIMITS YOU IN EACH OF THE FOLLOWING ACTIVITIES by ticking one of the boxes.**

	ACTIVITIES	YES limited a lot	YES limited a little	NO not limited at all
a_Sfpf 1	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
a_Sfpf 2	Climbing several flights of stairs			

- **We would now like to ask you about problems that you may have had with your work or regular daily activities during the past four weeks.**
- **Please show whether you have had any of the following problems AS A RESULT OF YOUR PHYSICAL HEALTH during the past four weeks, by ticking one of the boxes.**

	AS A RESULT OF YOUR PHYSICAL HEALTH, HAVE YOU:	YES	NO
a_sfrp1	Accomplished less than you would like?		
a_sfrp2	Been limited in the kind of work or other activities you could do?		

QUESTIONS ABOUT YOUR GENERAL HEALTH

- **Please show whether you have had any of the following problems AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious) during the past four weeks, by ticking one of the boxes.**

	AS A RESULT OF ANY EMOTIONAL PROBLEMS, HAVE YOU:	YES	NO
a_sfre1	Accomplished less than you would like?		
a_sfre2	Not been able to do work or other activities as carefully as usual?		

a_sfbp1	During the past four weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
Not at all	
A little bit	
Moderately	
Quite a bit	
Extremely	

- **We would now like to ask you about how you have been feeling during the past four weeks.**

- **Please show how much of the time during the past four weeks you have been feeling each of the following ways by ticking one of the boxes.**

	How much of the time:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a_sfmh1	Have you felt calm and peaceful?						
a_sfvt1	Did you have a lot of energy?						
a_sfmh2	Have you felt downhearted and low?						

a_sfsf1	During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends and relatives or going to groups)?
All of the time	
Most of the time	
Some of the time	
A little of the time	
None of the time	

QUESTIONS ABOUT HOW YOU FEEL

- **This part of the questionnaire contains statements about feelings.**
- **Below each statement are four possible responses.**
- **Please read each statement carefully and place a tick in the box next to the reply that comes closest to how you have been feeling during the past week, including today.**
- **Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought out response.**

a_hax1	I FEEL TENSE OR 'WOUND UP'
Most of the time	
A lot of the time	
From time to time, occasionally	
Not at all	
a_hdp1	I STILL ENJOY THE THINGS I USED TO ENJOY
Definitely as much	
Not quite so much	
Only a little	
Hardly at all	
a_hax2	I GET A FRIGHTENED FEELING AS IF SOMETHING AWFUL IS ABOUT TO HAPPEN
Yes, definitely and quite badly	
Yes, but not too badly	
A little, but it doesn't worry me	
Not at all	
a_hdp2	I CAN LAUGH AND SEE THE FUNNY SIDE OF THINGS
As much as I always could	
Not quite so much now	
Definitely not so much now	
Not at all	
a_hax3	WORRYING THOUGHTS GO THROUGH MY MIND
A great deal of the time	
A lot of the time	
From time to time but not too often	
Only occasionally	
a_hdp3	I FEEL CHEERFUL
Not at all	
Not often	
Sometimes	
Most of the time	

QUESTIONS ABOUT HOW YOU FEEL

a_hax4	I CAN SIT AT EASE AND FEEL RELAXED	
Definitely		
Usually		
Not often		
Not at all		
a_hdp4	I FEEL AS IF I AM SLOWED DOWN	
Nearly all the time		
Very often		
Sometimes		
Not at all		
a_hax5	I GET A SORT OF FRIGHTENED FEELING LIKE 'BUTTERFLIES' IN THE STOMACH	
Not at all		
Occasionally		
Quite often		
Very often		
a_hax5	I HAVE LOST INTEREST IN MY APPEARANCE	
Definitely		
I don't take as much care as I should		
I may not take quite as much care		
I take just as much care as ever		
a_hax6	I FEEL RESTLESS AS IF I HAVE TO BE ON THE MOVE	
Very much indeed		
Quite a lot		
Not very much		
Not at all		
a_hdp6	I LOOK FORWARD WITH ENJOYMENT TO THINGS	
As much as I ever did		
Rather less than I used to		
Definitely less than I used to		
Hardly at all		
a_hax7	I GET SUDDEN FEELINGS OF PANIC	
Very often indeed		
Quite often		
Not very often		
Not at all		
a_hdp7	I CAN STILL ENJOY A GOOD BOOK OR TV PROGRAMME	
Often		
Sometimes		
Not often		
Very rarely		

YOUR VIEWS ABOUT
YOUR ANTI-HIV MEDICINES

- **We would now like to ask you to tell us your views about your anti-HIV medicines.**

- **Combination therapy comprises a number of individual medicines. We are interested in your views about each separate medicine.**

- **In the next section, we will ask you a series of questions about each individual medicine in your combination therapy regimen.**

- **This might seem a bit repetitive because we will ask you the same questions about each medicine. This is because we are interested in your personal ideas about each medicine, even if you feel the same way about all of them.**

Please could you help us by:

1. **Writing the name of one of your medicines in the space provided on the front page of each section, so that we know which medicine you are referring to.**

2. **Using a different section for every drug in your combination.**

For example: If your combination contains DDI, D4T and Nevirapine, you might fill out Section A for DDI, Section B for D4T and Section C for Nevirapine.

It does not matter in what order you fill out the sections.

YOUR VIEWS ABOUT
YOUR ANTI-HIV MEDICINES

Section A

Medicine 1

- **Please write the name of one of the medicines in your combination in the box below.**

d_m1**Name of Medicine 1.....**

NB. All of the questions in this section refer only to this particular medicine.

Please ensure that you answer all of the questions in this section.

There are no right or wrong answers.

We are interested in your personal views.

YOUR VIEWS ABOUT
MEDICINE 1

- **We would like you to tell us your views about this particular medicine.**
- **Below is a list of statements that other people have made about their anti-HIV medicines.**
- **Please show how much you agree or disagree with them by ticking the appropriate box.**

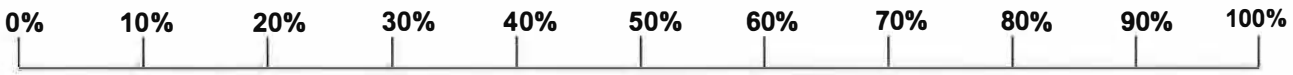
		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
d1_sn1	My health at present depends on this medicine					
d1_sc1	Having to take this medicine worries me					
d1_sn2	My life would be impossible without this medicine					
d1_sc2	I sometimes worry about the long-term effects of this medicine					
d1_sn3	Without this medicine I would be very ill					
d1_sc3	This medicine is a mystery to me					
d1_sn4	My health in the future will depend on this medicine					
d1_sc4	This medicine disrupts my life					
d1_sc5	I sometimes worry about becoming too dependent on this medicine					
d1_sc7	This medicine keeps my HIV under control					
d1_sc6	This medicine gives me unpleasant side effects					
d1_sx1	Using this medicine is embarrassing					
d1_sx2	Missing this medicine for a day won't matter in the long run					
d1_sx3	This medicine is the best hope for the future					
d1_sx4	I am unlikely to get a bad side effect from this medicine in the next month					
d1_sx5	Taking this medicine has been much worse than expected					
d1_sx6	I have received enough information about this medicine					
d1_sx7	This medicine keeps me alive					
d1_sx8	The taste of this medicine makes me feel unwell					

QUESTIONS ABOUT USING

MEDICINE 1

- **It's well known that many people who need to be on tablets for a long time experience difficulties taking them**
- **Many people find a way of using their medicines that suits them**
- **This may differ from the instructions on the label or what their doctor has said**
- **We would like to ask you about how you use this medicine**

Please put a cross on the line below at the point showing your best guess about how much of the prescribed amount of this medicine you have taken in the last month



YOUR VIEWS ABOUT
YOUR ANTI-HIV MEDICINES

Medicine 2

- **Please write the name of one of the medicines in your combination in the box below.**

d_m1**Name of Medicine 2**.....

NB. All of the questions in this section refer only to this particular medicine.

Please ensure that you answer all of the questions in this section.

There are no right or wrong answers.

We are interested in your personal views.

YOUR VIEWS ABOUT MEDICINE 2

- **We would like you to tell us your views about this particular medicine.**
- **Below is a list of statements that other people have made about their anti-HIV medicines.**
- **Please show how much you agree or disagree with them by ticking the appropriate box.**

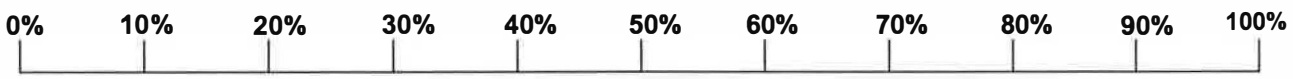
		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
d1_sn1	My health at present depends on this medicine					
d1_sc1	Having to take this medicine worries me					
d1_sn2	My life would be impossible without this medicine					
d1_sc2	I sometimes worry about the long-term effects of this medicine					
d1_sn3	Without this medicine I would be very ill					
d1_sc3	This medicine is a mystery to me					
d1_sn4	My health in the future will depend on this medicine					
d1_sc4	This medicine disrupts my life					
d1_sc5	I sometimes worry about becoming too dependent on this medicine					
d1_sc7	This medicine keeps my HIV under control					
d1_sc6	This medicine gives me unpleasant side effects					
d1_sx1	Using this medicine is embarrassing					
d1_sx2	Missing this medicine for a day won't matter in the long run					
d1_sx3	This medicine is the best hope for the future					
d1_sx4	I am unlikely to get a bad side effect from this medicine in the next month					
d1_sx5	Taking this medicine has been much worse than expected					
d1_sx6	I have received enough information about this medicine					
d1_sx7	This medicine keeps me alive					
d1_sx8	The taste of this medicine makes me feel unwell					

QUESTIONS ABOUT USING

MEDICINE 2

- **It's well known that many people who need to be on tablets for a long time experience difficulties taking them**
- **Many people find a way of using their medicines that suits them**
- **This may differ from the instructions on the label or what their doctor has said**
- **We would like to ask you about how you use this medicine**

Please put a cross on the line below at the point showing your best guess about how much of the prescribed amount of this medicine you have taken in the last month



YOUR VIEWS ABOUT
YOUR ANTI-HIV MEDICINES

Medicine 3

- **Please write the name of one of the medicines in your combination in the box below.**

d_m1 **Name of Medicine 3.....**

NB. All of the questions in this section refer only to this particular medicine.

Please ensure that you answer all of the questions in this section.

There are no right or wrong answers.

We are interested in your personal views.

YOUR VIEWS ABOUT MEDICINE 3

- **We would like you to tell us your views about this particular medicine.**
- **Below is a list of statements that other people have made about their anti-HIV medicines.**
- **Please show how much you agree or disagree with them by ticking the appropriate box.**

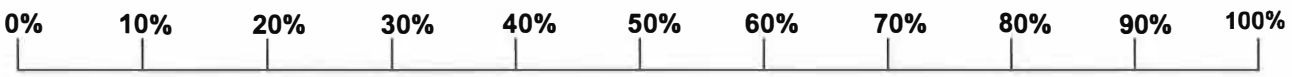
		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
d1_sn1	My health at present depends on this medicine					
d1_sc1	Having to take this medicine worries me					
d1_sn2	My life would be impossible without this medicine					
d1_sc2	I sometimes worry about the long-term effects of this medicine					
d1_sn3	Without this medicine I would be very ill					
d1_sc3	This medicine is a mystery to me					
d1_sn4	My health in the future will depend on this medicine					
d1_sc4	This medicine disrupts my life					
d1_sc5	I sometimes worry about becoming too dependent on this medicine					
d1_sc7	This medicine keeps my HIV under control					
d1_sc6	This medicine gives me unpleasant side effects					
d1_sx1	Using this medicine is embarrassing					
d1_sx2	Missing this medicine for a day won't matter in the long run					
d1_sx3	This medicine is the best hope for the future					
d1_sx4	I am unlikely to get a bad side effect from this medicine in the next month					
d1_sx5	Taking this medicine has been much worse than expected					
d1_sx6	I have received enough information about this medicine					
d1_sx7	This medicine keeps me alive					
d1_sx8	The taste of this medicine makes me feel unwell					

QUESTIONS ABOUT USING

MEDICINE 3

- **It's well known that many people who need to be on tablets for a long time experience difficulties taking them**
- **Many people find a way of using their medicines that suits them**
- **This may differ from the instructions on the label or what their doctor has said**
- **We would like to ask you about how you use this medicine**

Please put a cross on the line below at the point showing your best guess about how much of the prescribed amount of this medicine you have taken in the last month



YOUR VIEWS ABOUT
YOUR ANTI-HIV MEDICINES

Medicine 4

- **Please write the name of one of the medicines in your combination in the box below.**

d_m1 **Name of Medicine 4.....**

NB. All of the questions in this section refer only to this particular medicine.

Please ensure that you answer all of the questions in this section.

There are no right or wrong answers.

We are interested in your personal views.

YOUR VIEWS ABOUT MEDICINE 4

- **We would like you to tell us your views about this particular medicine.**
- **Below is a list of statements that other people have made about their anti-HIV medicines.**
- **Please show how much you agree or disagree with them by ticking the appropriate box.**

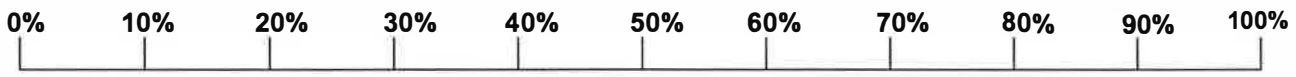
		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
d1_sn1	My health at present depends on this medicine					
d1_sc1	Having to take this medicine worries me					
d1_sn2	My life would be impossible without this medicine					
d1_sc2	I sometimes worry about the long-term effects of this medicine					
d1_sn3	Without this medicine I would be very ill					
d1_sc3	This medicine is a mystery to me					
d1_sn4	My health in the future will depend on this medicine					
d1_sc4	This medicine disrupts my life					
d1_sc5	I sometimes worry about becoming too dependent on this medicine					
d1_sc7	This medicine keeps my HIV under control					
d1_sc6	This medicine gives me unpleasant side effects					
d1_sx1	Using this medicine is embarrassing					
d1_sx2	Missing this medicine for a day won't matter in the long run					
d1_sx3	This medicine is the best hope for the future					
d1_sx4	I am unlikely to get a bad side effect from this medicine in the next month					
d1_sx5	Taking this medicine has been much worse than expected					
d1_sx6	I have received enough information about this medicine					
d1_sx7	This medicine keeps me alive					
d1_sx8	The taste of this medicine makes me feel unwell					

QUESTIONS ABOUT USING

MEDICINE 4

- **It's well known that many people who need to be on tablets for a long time experience difficulties taking them**
- **Many people find a way of using their medicines that suits them**
- **This may differ from the instructions on the label or what their doctor has said**
- **We would like to ask you about how you use this medicine**

Please put a cross on the line below at the point showing your best guess about how much of the prescribed amount of this medicine you have taken in the last month



YOUR VIEWS ABOUT
YOUR ANTI-HIV MEDICINES

Medicine 5

- **Please write the name of one of the medicines in your combination in the box below.**

d_m1**Name of Medicine 5.....**

NB. All of the questions in this section refer only to this particular medicine.

Please ensure that you answer all of the questions in this section.

There are no right or wrong answers.

We are interested in your personal views.

YOUR VIEWS ABOUT
MEDICINE 5

- **We would like you to tell us your views about this particular medicine.**
- **Below is a list of statements that other people have made about their anti-HIV medicines.**
- **Please show how much you agree or disagree with them by ticking the appropriate box.**

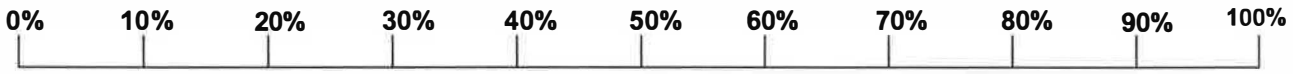
		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
d1_sn1	My health at present depends on this medicine					
d1_sc1	Having to take this medicine worries me					
d1_sn2	My life would be impossible without this medicine					
d1_sc2	I sometimes worry about the long-term effects of this medicine					
d1_sn3	Without this medicine I would be very ill					
d1_sc3	This medicine is a mystery to me					
d1_sn4	My health in the future will depend on this medicine					
d1_sc4	This medicine disrupts my life					
d1_sc5	I sometimes worry about becoming too dependent on this medicine					
d1_sc7	This medicine keeps my HIV under control					
d1_sc6	This medicine gives me unpleasant side effects					
d1_sx1	Using this medicine is embarrassing					
d1_sx2	Missing this medicine for a day won't matter in the long run					
d1_sx3	This medicine is the best hope for the future					
d1_sx4	I am unlikely to get a bad side effect from this medicine in the next month					
d1_sx5	Taking this medicine has been much worse than expected					
d1_sx6	I have received enough information about this medicine					
d1_sx7	This medicine keeps me alive					
d1_sx8	The taste of this medicine makes me feel unwell					

QUESTIONS ABOUT USING

MEDICINE 5

- **It's well known that many people who need to be on tablets for a long time experience difficulties taking them**
- **Many people find a way of using their medicines that suits them**
- **This may differ from the instructions on the label or what their doctor has said**
- **We would like to ask you about how you use this medicine**

Please put a cross on the line below at the point showing your best guess about how much of the prescribed amount of this medicine you have taken in the last month



YOUR VIEWS ABOUT
YOUR ANTI-HIV MEDICINES

Medicine 6

- **Please write the name of one of the medicines in your combination in the box below.**

d_m1 **Name of Medicine 6.....**

NB. All of the questions in this section refer only to this particular medicine.

Please ensure that you answer all of the questions in this section.

There are no right or wrong answers.

We are interested in your personal views.

YOUR VIEWS ABOUT
MEDICINE 6

- **We would like you to tell us your views about this particular medicine.**
- **Below is a list of statements that other people have made about their anti-HIV medicines.**
- **Please show how much you agree or disagree with them by ticking the appropriate box.**

		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
d1_sn1	My health at present depends on this medicine					
d1_sc1	Having to take this medicine worries me					
d1_sn2	My life would be impossible without this medicine					
d1_sc2	I sometimes worry about the long-term effects of this medicine					
d1_sn3	Without this medicine I would be very ill					
d1_sc3	This medicine is a mystery to me					
d1_sn4	My health in the future will depend on this medicine					
d1_sc4	This medicine disrupts my life					
d1_sc5	I sometimes worry about becoming too dependent on this medicine					
d1_sc7	This medicine keeps my HIV under control					
d1_sc6	This medicine gives me unpleasant side effects					
d1_sx1	Using this medicine is embarrassing					
d1_sx2	Missing this medicine for a day won't matter in the long run					
d1_sx3	This medicine is the best hope for the future					
d1_sx4	I am unlikely to get a bad side effect from this medicine in the next month					
d1_sx5	Taking this medicine has been much worse than expected					
d1_sx6	I have received enough information about this medicine					
d1_sx7	This medicine keeps me alive					
d1_sx8	The taste of this medicine makes me feel unwell					

QUESTIONS ABOUT USING

MEDICINE 6

- **It's well known that many people who need to be on tablets for a long time experience difficulties taking them**
- **Many people find a way of using their medicines that suits them**
- **This may differ from the instructions on the label or what their doctor has said**
- **We would like to ask you about how you use this medicine**

Please put a cross on the line below at the point showing your best guess about how much of the prescribed amount of this medicine you have taken in the last month

YOUR EXPERIENCE OF SYMPTOMS ASSOCIATED WITH ANTI-HIV MEDICINES

- **Listed below are a number of symptoms that you may or may not have experienced since starting your anti-HIV medicines.**
- **We are interested in how you are feeling AT PRESENT.**
- **Please show the severity of any symptoms that you are currently experiencing by circling a number on the scale below, where 1 is very mild and 7 is very severe.**
- **Please only rate the symptoms *that you believe are a consequence of taking anti-HIV medicines.***

Are you currently experiencing this symptom as a result of taking anti-HIV medicines?				*If yes, please rate the symptom severity*				
				very mild	**mild**	**moderate**	**severe**	**very severe**
a_ie1	Pain	Yes	No	1	2	3	4	5
a_ie2	Sore throat	Yes	No	1	2	3	4	5
a_ie3	Nausea	Yes	No	1	2	3	4	5
a_ie4	Breathlessness	Yes	No	1	2	3	4	5
a_ie5	Weight loss	Yes	No	1	2	3	4	5
a_ie6	Fatigue	Yes	No	1	2	3	4	5
a_ie7	Stiff Joints	Yes	No	1	2	3	4	5
a_ie8	Sore eyes	Yes	No	1	2	3	4	5
a_ie9	Wheezing	Yes	No	1	2	3	4	5
a_ie10	Headaches	Yes	No	1	2	3	4	5
a_ie11	Upset stomach	Yes	No	1	2	3	4	5
a_ie12	Sleep difficulties	Yes	No	1	2	3	4	5
a_ie13	Dizziness	Yes	No	1	2	3	4	5
a_ie14	Loss of strength	Yes	No	1	2	3	4	5
a_ie15	Night sweats	Yes	No	1	2	3	4	5
a_ie16	Diarrhoea	Yes	No	1	2	3	4	5
a_ie17	Feeling faint	Yes	No	1	2	3	4	5
a_ie18	Fever	Yes	No	1	2	3	4	5
a_ie19	Sexual problems	Yes	No	1	2	3	4	5
a_ie20	Loss of appetite	Yes	No	1	2	3	4	5
a_ie21	Skin problems	Yes	No	1	2	3	4	5
a_ie22	Altered sensation in hands or feet	Yes	No	1	2	3	4	5
a_ie23	Stomach pain	Yes	No	1	2	3	4	5

APPENDIX 5

Development of questionnaires for future research

Experience of symptoms associated with HIV and HAART

Perceptions of CD4 count

Perceptions of viral load

YOUR EXPERIENCE OF SYMPTOMS ASSOCIATED WITH HIV & ANTI-VIRAL TREATMENT

- Listed below are a number of symptoms that you may or may not be experiencing.
- We are interested in how you are feeling AT PRESENT.
- Please rate the severity of any symptoms you are currently experiencing by circling the appropriate number on the scale, where 1 indicates very mild and 5 indicates very severe.
- Additionally, please indicate whether you attribute the symptoms to HIV, anti-viral treatment, both or neither.

Are you currently experiencing this symptom?				*If yes, please circle the symptom's severity*					*Tick box to indicate what you think caused the symptom*			
				very mild	mild	moderate	severe	very severe	HIV	HIV anti-viral treatment	Both HIV & HIV anti-viral treatment	Neither HIV or HIV anti-viral treatment
	Pain	Yes	No	1	2	3	4	5				
	Sore throat	Yes	No	1	2	3	4	5				
	Nausea	Yes	No	1	2	3	4	5				
	Breathlessness	Yes	No	1	2	3	4	5				
	Weight loss	Yes	No	1	2	3	4	5				
	Fatigue	Yes	No	1	2	3	4	5				
	Stiff Joints	Yes	No	1	2	3	4	5				
	Sore eyes	Yes	No	1	2	3	4	5				
	Wheezing	Yes	No	1	2	3	4	5				

Are you currently experiencing this symptom?				*If yes, please circle the symptom's severity*					*Tick box to indicate what you think caused the symptom*			
				very mild	mild	moderate	severe	very severe	HIV	HIV anti-viral treatment	Both HIV & HIV anti-viral treatment	Neither HIV or HIV anti-viral treatment
	Headaches	Yes	No	1	2	3	4	5				
	Upset stomach	Yes	No	1	2	3	4	5				
	Sleep difficulties	Yes	No	1	2	3	4	5				
	Dizziness	Yes	No	1	2	3	4	5				
	Loss of strength	Yes	No	1	2	3	4	5				
	Night sweats	Yes	No	1	2	3	4	5				
	Diarrhoea	Yes	No	1	2	3	4	5				
	Feeling faint	Yes	No	1	2	3	4	5				
	Fever	Yes	No	1	2	3	4	5				
	Sexual problems	Yes	No	1	2	3	4	5				
	Loss of appetite	Yes	No	1	2	3	4	5				
	Skin problems	Yes	No	1	2	3	4	5				
	Altered sensation in hands or feet	Yes	No	1	2	3	4	5				
	Stomach pain	Yes	No	1	2	3	4	5				
	Anxiety	Yes	No	1	2	3	4	5				
	Blackouts	Yes	No	1	2	3	4	5				
	Fits	Yes	No	1	2	3	4	5				
	Bruising	Yes	No	1	2	3	4	5				

Are you currently experiencing this symptom?				*If yes, please circle the symptom's severity*					*Tick box to indicate what you think caused the symptom*			
				very mild	mild	moderate	severe	very severe	HIV	HIV anti-viral treatment	Both HIV & HIV anti-viral treatment	Neither HIV or HIV anti-viral treatment
	Coughing	Yes	No	1	2	3	4	5				
	Dry mouth	Yes	No	1	2	3	4	5				
	Gum problems	Yes	No	1	2	3	4	5				
	Hearing loss	Yes	No	1	2	3	4	5				
	Memory loss	Yes	No	1	2	3	4	5				
	Mouth ulcers	Yes	No	1	2	3	4	5				
	Thrush/ candida	Yes	No	1	2	3	4	5				
	Mouth infections	Yes	No	1	2	3	4	5				
	Numbness	Yes	No	1	2	3	4	5				
	Skin rashes	Yes	No	1	2	3	4	5				
	Visual problems	Yes	No	1	2	3	4	5				
	Swallowing difficulties	Yes	No	1	2	3	4	5				
	Walking difficulties	Yes	No	1	2	3	4	5				
	Vomiting	Yes	No	1	2	3	4	5				
	Weakness	Yes	No	1	2	3	4	5				
	Changes in body shape	Yes	No	1	2	3	4	5				
	Dry lips	Yes	No	1	2	3	4	5				
	Pain when urinating	Yes	No	1	2	3	4	5				

Are you currently experiencing this symptom?				*If yes, please circle the symptom's severity*					*Tick box to indicate what you think caused the symptom*			
				very mild	mild	moderate	severe	very severe	HIV	HIV anti-viral treatment	Both HIV & HIV anti-viral treatment	Neither HIV or HIV anti-viral treatment
	Itching	Yes	No	1	2	3	4	5				
	Vivid dreams	Yes	No	1	2	3	4	5				
	Depression	Yes	No	1	2	3	4	5				

- **If you have experienced any other symptoms recently, please write them in the space below.**
- **As before, please rate the severity of any symptoms by circling the appropriate number on the scale, where 1 indicates 'very mild' and 5 indicates 'very severe'**
- **Additionally, please indicate whether you attribute the symptoms to HIV, HIV anti-viral treatment, both or neither.**

Symptom		*Please rate the symptom's severity*					*Please indicate what you think caused the symptom*			
		very mild	mild	moderate	severe	very severe	HIV	HIV anti-viral treatment	Both HIV & HIV anti-viral treatment	Neither HIV or HIV anti-viral treatment
		1	2	3	4	5				
		1	2	3	4	5				
		1	2	3	4	5				
		1	2	3	4	5				
		1	2	3	4	5				
		1	2	3	4	5				

QUESTIONS ABOUT
YOUR CD4 COUNT

- **We would like to ask some questions about your CD4 count**
- Please tick the appropriate boxes below

Have you received a CD4 count today?	Yes ☐		No ☐	
What was your most recent CD4 count? (please write it in the box)				
Was the CD4 count any better or worse than you expected?	Better ☐	Worse ☐	Same ☐	No expectations ☐
How did your CD4 count compare to the result you received at your last appointment?	Better ☐	Worse ☐	Same ☐	Don't know ☐
How did you feel about the CD4 count you received today?	Pleased ☐	Disappointed ☐	Neither pleased or disappointed ☐	

- **Below is a list of statements that other people have made about their CD4 counts.**
- **Please indicate the extent to which you agree with each statement.**

MY CD4 COUNT INDICATES THAT	**Strongly Agree**	**Agree**	**Uncertain**	**Disagree**	**Strongly Disagree**
My HIV anti-viral treatment Is being effective	☐	☐	☐	☐	☐
My adherence to my HIV anti-viral treatment has been good enough	☐	☐	☐	☐	☐
Strict (100%) adherence to my HIV anti-viral treatment is vital for me	☐	☐	☐	☐	☐
I can afford to be slightly less strict with my anti-HIV medicines	☐	☐	☐	☐	☐
I need to keep taking my HIV anti-viral treatment exactly as It Is prescribed	☐	☐	☐	☐	☐
If I miss a few doses, my HIV anti-viral treatment will still work for me	☐	☐	☐	☐	☐
I need to be more strict with my HIV anti-viral treatment	☐	☐	☐	☐	☐
My count goes up and down regardless of how I take my pills	☐	☐	☐	☐	☐
The count Is less Important to me than how I feel within myself	☐	☐	☐	☐	☐

QUESTIONS ABOUT

YOUR VIRAL LOAD

- **We would like to ask some questions about your most recent blood test results**
- **Please tick the appropriate boxes below**

Have you received a viral load test today?	Yes ☐		No ☐	
What was your most recent viral load result? (please write it in the box)	☐			
Was the viral load result count any better or worse than you expected?	Better ☐	Worse ☐	Same ☐	No expectations ☐
How did your viral load result compare to the result you received at your last appointment?	Better ☐	Worse ☐	Same ☐	Don't know ☐
How did you feel about the viral load result you received today?	Pleased ☐	Disappointed ☐	Neither please or disappointed ☐	

- **Below is a list of statements that other people have made about their viral load test results.**
- **Please indicate the extent to which you agree with each statement.**

MY VIRAL LOAD INDICATES THAT	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
My HIV anti-viral treatment is being effective	☐	☐	☐	☐	☐
My adherence to my HIV anti-viral treatment has been good enough	☐	☐	☐	☐	☐
Strict (100%) adherence to my HIV anti-viral treatment is vital for me	☐	☐	☐	☐	☐
I can afford to be slightly less strict with my HIV anti-viral medicines	☐	☐	☐	☐	☐
I need to keep taking my HIV anti-viral treatment exactly as it is prescribed	☐	☐	☐	☐	☐
If I miss a few doses, my HIV anti-viral treatment will still work for me	☐	☐	☐	☐	☐
I need to be more strict with my HIV anti-viral treatment	☐	☐	☐	☐	☐
My viral load goes up and down regardless of how I take my HIV anti-viral treatment	☐	☐	☐	☐	☐
The viral load result is less important to me than how I feel within myself	☐	☐	☐	☐	☐

APPENDIX 6

LIST OF PUBLICATIONS RELATING TO THE THESIS

Publications in peer reviewed journals

COOPER, V., BUICK, D., HORNE, R., GELLAITRY, G., LAMBERT, N., FISHER, M (2002) Perceptions of HAART among gay men who declined a treatment offer: Preliminary results from an interview-based study *AIDS Care*, 14 (3), 319-328.

Presentations at national and international conferences

COOPER V., GELLAITRY, G., HANKINS, M., FISHER, M., HORNE, R. (2003) Changes in experience and interpretation of symptoms over time: Effects on adherence. 17th Annual Conference of the European Health Psychology Society, Kos (Greece). September 24-27.

COOPER V., GELLAITRY, G., HANKINS, M., FISHER, M., HORNE, R. (2003) Changes in experience and interpretation of symptoms over time: Effects on adherence. BPS Division of Health Psychology Annual Conference, Staffordshire University, September 3–5.

COOPER, V., GELLAITRY, G., FISHER, M., HORNE, R. (2003) Appraising the efficacy of HAART: Use of symptoms, interpretation of blood test results and relationships with adherence over the first six months of treatment. Paper presented at AIDS Impact Biopsychosocial Aspects of HIV Infection. 6th International Conference, Milan, July 7–10.

COOPER, V., GELLAITRY, G., HANKINS, M., FISHER, M., HORNE, R. (2003) Changes in symptom experiences over time predict adherence to HAART: Results from a prospective study. Paper presented at AIDS Impact Biopsychosocial Aspects of HIV Infection. 6th International Conference, Milan, July 7–10.

COOPER, V., GELLAITRY, G., FISHER, M., HORNE, R. (2003) Changes in symptom experiences and interpretation over time: effects on adherence. 9th Annual Conference of the British HIV Association (BHIVA), 25-26 April 2003, University of Manchester, Institute of Science and Technology (UMIST), Manchester, UK

COOPER, V., HORNE, R., GELLAITRY, G. & FISHER, M. (2002) Perceptions of highly active antiretroviral therapy (HAART) among HIV positive men who accepted a treatment recommendation. International Congress on Behavioural Medicine, 28-31 August, Helsinki, Finland

COOPER, V., HORNE, R., GELLAITRY, G. & FISHER M. (2002) Perceptions of highly active antiretroviral therapy (HAART) among HIV positive men who have been recommended treatment. XIV International AIDS Conference, Barcelona, July 7-12.

COOPER, V., HORNE, R., GELLAITRY, G. & FISHER M. (2002) Perceptions of highly active antiretroviral therapy (HAART) among HIV positive men who have been recommended treatment. 8th Annual Conference of the British HIV Association (BHIVA) York, 19- 21 April.

COOPER, V., FISHER M., & HORNE R. (2001) Differences in perceptions of HAART between people diagnosed before and after the advent of combination therapy. Poster presented at the 7th Annual Conference of the British HIV Association (BHIVA) Brighton, 27th - 29th April.

COOPER V., BUICK, D., HORNE R., LAMBERT, N., GELLAITRY G., LEAKE H. & FISHER M. (2001) Perceptions of HAART among those who have declined a treatment offer: Preliminary results from an interview-based study. Oral presentation at the 5th International Conference of AIDS Impact: Biopsychosocial Aspects of HIV Infection. 8-11 July, Brighton, UK.