Predicting adherence to antiretroviral therapy and retention to HIV care: Effects of baseline biopsychosocial status and neuropsychological functioning

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DECLARATION

This thesis is presented in fulfillment of the requirements for the Degree of Thesis presented for the Degree of Doctor of Philosophy (PhD) in the Department of Psychology, Faculty of Humanities, University of Cape Town.

The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university.

The contents of this thesis are entirely the work of the candidate (except where acknowledgements indicate otherwise).

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GLOSSARY OF ABBREVIATIONS

3TC: lamivudine
AIDS: acquired immune deficiency syndrome
ADC: AIDS dementia complex
ALT: amino alanine transferase
ART: antiretroviral therapy
ART-CC: ART Cohort Collaboration
ART-LINC: Antiretroviral Therapy in Lower Income Countries
ARV: antiretroviral
AST: aspartate amino transferase
AUDIT: Alcohol Use Disorders Identification Test
AZT: zidovudine
BDI: Beck Depression Inventory
CBT: cognitive behavioural therapy
CES-D: Centre for Epidemiological Studies in Depression Scale
CNS: central nervous system
CVLT: California Verbal Learning Test
D-KEFS: Delis-Kaplan Executive Function System
d4T: stavudine
ddI: didanosine
DG: disability grant
DOT: directly observed therapy
DTHC: Desmond Tutu HIV Centre
EFV: efavirenz
EMD: electronic monitoring device
ENT: ear, nose and throat
FBC: full blood count
HAART: highly active antiretroviral therapy
HAD: HIV-1-associated dementia
HCTC: Hannan Crusaid Treatment Centre
HIV: human immuno-deficiency virus

HIVDR: HIV drug resistance
IDU: injection drug use(r)
IQR: interquartile range
LFT: liver function test
LOC: loss of consciousness
LPV/r: lopinavir/ritonavir
LTFU: loss to follow-up
MEMS: Medication Events Monitoring System
MI: motivational interviewing
MSM: men who have sex with men
NGO: non-governmental organization
NVP: nevirapine
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
PAWC: Provincial Administration Western Cape
PEPFAR: President's Emergency Plan for AIDS Relief
PHC: primary health care
PI: protease inhibitor
PIT: Pill Identification Test
PMTCT: prevention of mother-to-child transmission
QA: quality assurance
QALY: quality-adjusted life-year
RAT: rapid assessment tool
RNA: ribonucleic acid
SASSA: South African Social Security Agency
sd-NVP: single-dose nevirapine
SSC-HIV-rev: Sign and Symptom Checklist for persons living with HIV disease-revised
STD: sexually transmitted disease
TAC: treatment action campaign
TB: tuberculosis
TBM: tuberulosis meningitis
TDF: tenofovir
TDM: therapeutic drug monitoring

TFO: transfer(red) out

TNR: true negative rate

TPR: true positive rate

UNAIDS: Joint United Nations Programme on HIV/AIDS

UNDP: United Nations Development Programme

VAS: Visual Analogue Scale

VCT: voluntary counseling and testing

WAIS-R: Wechsler Adult Intelligence Scale-Revised

WHO: World Health Organization

WMS-III: Wechsler Memory Scale – Third Edition

ZAR: South African Rands

ABSTRACT

Predicting adherence to antiretroviral therapy and retention to HIV care: Effects of baseline biopsychosocial status and neuropsychological functioning

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Introduction: The introduction and scale-up of antiretroviral therapy has dramatically improved the clinical outcomes of HIV infection. These drugs have demonstrated efficacy in improving immune function and reducing HIV-related morbidity and mortality, and while a cure is not available, patients on treatment may live longer, healthier lives. However, early optimism has been tempered by the growing recognition that meticulous adherence is a prerequisite for optimal clinical response and prevention of drug resistance. In this context, it is critical that systematic research be conducted to identify valid and reliable correlates of nonadherence and loss to follow-up in clinical settings in sub-Saharan Africa, so that solutions to these challenges can be implemented in the most affected region.

Methods: Patients were recruited from a community clinic in a peri-urban settlement near Cape Town, South Africa. Demographic and biopsychosocial data were collected through file reviews, interviews and neuropsychological testing at treatment initiation. Pill count adherence was measured across the first 16 weeks of treatment and retention and virological suppression assessed at 96 weeks. Bivariate and multiple logistic regression analyses were used to investigate the association of each factor with adherence outcomes.

Results: 150 patients were recruited. Sixty-three percent were female and 73% unemployed. 39% showed depressive symtomatology and 41% hazardous or harmful alcohol consumption. 75% achieved ≥90% pill count adherence across 16 weeks, and 71% were retained in care and 77% of those retained achieved virological suppression at 96 weeks. Factors associated with nonadherence, nonsuppression and/ or loss to follow-up were younger age, unemployment, holding/ having applied for a disability grant, lower CD4+ cell count, heamatological or ophthalmic but not dermatological or urological symptoms, able to name just some of the medications in the prescribed

regimen, alcohol abuse, poor neurocognitive performance, unmarried or in non-cohabiting relationship, disclosure to broader family or friends, less people known on antiretrovirals, living in households of three or more, no planned use of cell phone alarm as adherence aid and greater length of time spent traveling to the clinic.

Conclusion: High depression and alcohol abuse rates call for early identification and treatment of mental health disorders in this population. Special attention should be paid to younger and unemployed patient groups in adherence counseling. HIV symtomatology should be assessed and symptoms treated aggressively. Adaptation of treatment guidelines for earlier treatment initiation would minimize cognitive compromise in initiating populations. Mechanical reminders like cell phone alarms have proven successful in this sample and may be especially beneficial to those with cognitive dysfunction. Patients should be counseled to choose appropriate confidantes for disclosure and supportive relationships should be encouraged. Clinic visit burden should be minimized through home visits, flexible clinic hours and discounted transportation.

CHAPTER 1

Medication adherence and loss to follow-up in the HIV era

The HIV/AIDS pandemic

Global

Human immuno-deficiency virus (HIV) infection is one of the biggest health challenges facing humanity today. While there have been steps towards preventing new infections and decreasing the number of acquired immune deficiency syndrome (AIDS)- related deaths, the number of people living with the virus continues to increase. There are now an estimated 32.8 million people living with HIV worldwide: 30.3 million adults and 2.5 million children. Each day, an estimated 7,100 people become infected, amounting to 2.6 million new infections per year. AIDS-related illnesses remains one of the leading causes of mortality worldwide; annually, there are 1.8 million AIDS-related deaths (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2010b).

Sub-Saharan Africa

With an adult HIV prevalence of 5% and accounting for 22.5 million persons infected with HIV (up from 20.3 million in 2001), sub-Saharan Africa is home to the majority (68%) of the global total. In 2009, 1.8 million adults and children were newly infected with HIV in the region, accounting for 67% of all new infections. In the same year, there were 1.3 million deaths due to AIDS in sub-Saharan Africa, comprising 72% of the world's AIDS-related deaths (UNAIDS, 2010b). The impact on households and communities is staggering; just over 14.1 million children in sub-Saharan Africa have lost one or both parents to AIDS-related illnesses (UNAIDS & World Health Organization [WHO], 2009).

The scale and trends of the HIV/AIDS pandemic in the sub-Saharan region vary widely, with Southern Africa most seriously affected. The nine countries with the world's highest HIV prevalence (all over 10%) are located in Southern Africa (UNAIDS & WHO, 2009). In 2009, this sub-region accounted for just over a third (34%) of the world's HIV infections and the same percentage of its AIDS deaths (UNAIDS, 2010b).

South Africa

As the country with the largest number of infected individuals in the world, South Africa is at the epicentre of the pandemic. In 2009, there were 5.6 million people living with HIV in South Africa, accounting for 17% of the global total, i.e. one in six people living with HIV in the world today lives in South Africa (UNAIDS, 2010b). This is in contrast to South Africa's population size, which is just 0.7% of the world's total population (UNAIDS, 2010a).

The most recent national population-based household survey found the national HIV prevalence across all age groups to be 10.6%. General adult age 15–49 years HIV prevalence was estimated at 16.9%, increasing from 16.2% in 2005. One in three women (32.7%) age 25–29 years is HIV-positive, and one in four men (25.8%) age 30–34 years is infected (Shisana et al., 2009). The most recent National Antenatal Sentinel HIV and Syphilis Prevalence Survey conducted in 2008 in all nine provinces showed the overall national HIV prevalence among pregnant women aged 15–49 years to be 29.3%, similar to the rates of 29.1%, 29.4% and 29.3% seen in the previous three years. This data suggests that the prevalence rate amongst pregnant woman has stabilized, albeit at a very high level (Department of Health, 2009).

The numbers continue to grow. In 2009, there were an estimated 1,500 new infections daily, and 409,000 new infections throughout the year (UNAIDS, 2010a). The predominant mode of HIV transmission in the country is heterosexual sex, followed by mother-to-child transmission, with drivers including intergenerational sex, multiple concurrent partners, low condom use, high alcohol use and low rates of male circumcision (Department of Health, 2010c).

In 2009, more than 270,000 South Africans died of HIV-related causes, representing 42% of all national deaths. Recent reports show that between 1.4 and 2.1 million children have lost one or both parents to the disease (Department of Health, 2009; Statistics South Africa, 2010). As of mid-2010, life expectancy at birth was estimated at just 53.3 years for males and 55.2 years for females (Statistics South Africa, 2010). South Africa is one of the few countries in the world whose child mortality rates have worsened since the 1990's (UNAIDS, 2010b), and are currently estimated at 46.9 per 1,000 lives births (Statistics South Africa, 2010)

Western Cape

In 2008, there were approximately 241,000 persons living with HIV/AIDS in the Western Cape (Department of Health, 2009). General adult age 15–49 years HIV prevalence is 5.3% in the province (Shisana et al., 2009). While the Western Cape has the lowest antenatal prevalence in South Africa at 16.1%, it is one of the five provinces that has shown an (in this case slight) increase in prevalence, while the other provinces decreased or remained static in 2008; the overall antenatal HIV prevalence had increased from 15.1% in 2006 to 16.1% in 2008 (see Figure 1). A close analysis of the 2008 Western Cape data confirms the difference in HIV prevalence by race. The HIV results in this province show that 29.4% of Africans are infected compared with 3% of Coloureds (Department of Health, 2009).

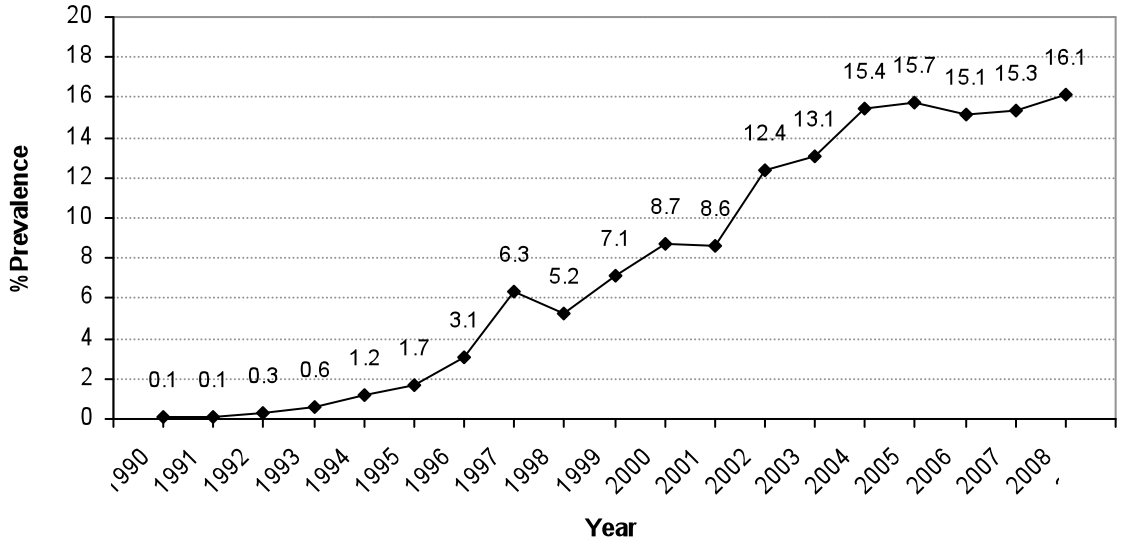

Figure 1. HIV prevalence among pregnant women curve, Western Cape, 1990 to 2008 (Department of Health, 2009).

According to the ASSA2003 AIDS and Demographic model, which uses several data sources, including the antenatal clinic survey results and deaths from the population register, it was estimated that in the Western Cape in 2010, there would be 318,115 people living with HIV, 31,338 people with AIDS-defining conditions, cumulative AIDS-related deaths since 1990 of 109,803 and 59,926 maternal orphans due to AIDS (Dorrington, Johnson, Bradshaw, & Daniel, 2006.)

Antiretroviral therapy (ART)

Since the first AIDS cases of 1979 until the late 1990's, a diagnosis was considered the first step in a steady downward progression leading to certain death as a result of opportunistic infections. Medications were available to treat opportunistic infections, and later, antiretroviral (ARV) medications like Zidovudine (AZT) could temporarily suppress HIV levels until the virus' rapid replication cycle allowed it to develop resistance to the single antiretroviral medication. In 1996, a significant shift in HIV medical care and disease prognosis occurred, with the development and roll-out of a new type of antiretroviral drug class called protease inhibitors that were to be used in combination with existing reverse transcriptase inhibitors (Catz, Kelly, Bogart, Benotsch & McAuliffe, 2000).

The development of multi-drug combination therapy has been heralded as one of the greatest success stories of modern medicine (Delaney, 2006). The introduction and scale-up of highly active antiretroviral therapy (HAART) has dramatically improved the clinical outcomes of HIV infection. HAART consists of the use of at least three ARV drugs to suppress the virus and halt disease progression. HAART has demonstrated efficacy in suppressing HIV viral load levels (the amount of virus circulating in the blood), improving immune system functioning (Autran et al., 1997; Lederman et al, 1998), and reducing HIV-related morbidity and mortality (Palella et al., 1998; Jacobson & French, 1998; Murphy et al., 2001), and while a cure for HIV has not been found, patients on HAART may go on to live longer, healthier lives. Thanks to the scientific advances that include HAART and HIV disease monitoring, for the first time since the start of the pandemic, clinicians can now effectively treat HIV disease. When ARV's are taken correctly, HIV viral load may be reduced to a level that is below the limits of detection (less than 50 copies/mL or less than 400 copies/mL, depending on the test) of commercially available assays. The ASSA2003 model projected that approximately 100,000 AIDS deaths could be prevented in 2010 alone in South Africa due to ART (Dorrington et al., 2006).

HAART is now being rapidly scaled up across the globe, particularly in resource-limited settings with high HIV prevalence and previous low access like Africa, Asia, South

America, Central America and the Caribbean. The Group of Eight countries and the United Nations member states all sanctioned the global goal of universal access by 2010 (United Nations Development Programme [UNDP], 2010). While this goal has not yet been reached, major strides have been undertaken. In 2009, 1.2 million people began antiretroviral therapy, a 30% increase in the number of people on treatment in just one year (UNAIDS, 2010b). An estimated 2.9 million lives have been saved because of antiretroviral therapy, 1.2 million of these from sub-Saharan Africa. Approximately 11.7 million life-years were added globally between 1996 and 2008 due to antiretroviral therapy (UNAIDS & WHO, 2009). The WHO, UNAIDS, the Global Fund to Fight AIDS, Tuberculosis and Malaria and the United States President's Emergency Plan for AIDS Relief (PEPFAR) have all committed to supporting ART expansion. Despite this progress, global antiretroviral coverage remains relatively low as new infections outpace the response rate; with 10 million people who need ART not receiving such services and just over 5 million on treatment, only a third in need are covered (UNAIDS, 2010b).

ART scale-up in developing countries is based on WHO guidelines (modified by country) and consists of one first-line regimen consisting of one non-nucleoside reverse transcriptase inhibitor (NNRTI) supported by two nucleoside/ nucleotide reverse transcriptase inhibitors (NRTI's). The use of three ARV medications is currently the standard treatment for HIV disease, in order to achieve best possible clinical outcomes. An alternative regimen, involving a different NNRTI, and/ or a different NRTI, can be substituted if required because of factors like drug interactions, toxicity or other health conditions. A second-line regimen, consisting of a protease inhibitor (PI), ideally boosted by Ritonavir, and two NRTI's is used when the first regimen fails. In resource-limited countries, selection of drugs is based largely on availability and affordability (in addition to criteria like efficacy, durability and tolerability that are also used in resource-rich countries).

Barriers to antiretroviral success

Treatment access

Despite the dramatic benefits of ART, there remain some major obstacles to overcome. Initially, the biggest challenge facing optimization of ART and the fulfillment of its benefits for HIV-positive individuals was structural; treatment access in many developing

countries, including South Africa, has and continues to be a major issue. South Africa's slow response to curbing the growth of the pandemic and delays in implementing antiretrovirals meant that deaths in the country doubled between 1997 and 2005. According to a 2008 Harvard University study, approximately 330,000 AIDS-related deaths could have been prevented had the government acted sooner in providing ART to those with HIV-related illness and pregnant women (UNAIDS, 2010a). Senior government officials questioned the link between HIV and AIDS and expressed mistrust in antiretroviral efficacy. The South African Department of Health's HIV/AIDS/sexually transmitted disease (STD) strategic plan for South Africa 2000–2005 (Department of Health, 2000) did not include the provision of ART to HIV-positive persons, inciting a national movement and legal proceedings initiated by the Treatment Action Campaign (TAC). Ultimately, the Constitutional Court ordered that the strategic plan be adapted to include ART provision to all HIV-infected pregnant women. In 2003, the South African Department of Health announced the National Comprehensive HIV and AIDS Care, Management and Treatment Plan (Department of Health, 2003), a strategy for HIV care that included ART, and in 2004, two ART regimens became available free of cost in the South African public health sector.

Since then, ART provision has seen a large national scale-up. This has coincided with increasing affordability of the medications, largely due to global efforts towards expanding access and availability. South Africa now has the largest antiretroviral therapy programme in the world. By the end of 2009, there were approximately one million people receiving treatment at public health facilities (n = 919,923, including eight provinces and excluding all deaths, losses to follow-up and transfers out) and an additional 51,633 individuals receiving treatment through the private and non-governmental organisational (NGO) sectors. In early 2010, antiretrovirals were being dispensed through approximately 500 accredited public sector health facilities, primarily hospitals but also community health centers and clinics (Department of Health, 2010c).

In the Western Cape, the most recent estimate of antiretroviral coverage (the number of patients receiving ART divided by the number needing treatment) was 71.7% in 2008 (Adam & Johnson, 2009), but numbers on treatment in the province have increased significantly since that report. As of July 2010, there were a total of 76,345 adults and 6,026 children (total 82,371) on ART in the Western Cape. In July alone, 2,445 adults

and 87 children (total 2,532) initiated ART in the province (unpublished Department of Health internal report dated July 2010: Western Cape ART Monthly Summary for July 2010).

While scale-up has been ongoing, the need remains great. In 2009, it is estimated that 1.5 million adults and 106,000 children actually needed treatment in South Africa (UNAIDS, 2010a), meaning that antiretroviral coverage for those who were in need was at approximately 56% (Department of Health, 2010c). Depending on the definition used for required treatment initiation, the year before, coverage was at 40.2% (using the Department of Health treatment criteria at the time of WHO stage IV or CD4+ cell count <200 cells/μL) (Department of Health, 2004) or just 22.2% (using the Southern African HIV Clinicians Society guidelines of WHO stage IV or CD4+ cell count <350 cells/μL), with 430,000–1.79 million people awaiting treatment. These figures are a substantial improvement from coverage in 2004, which was at just 4.9% (Adam & Johnson, 2009), but remain fairly low, with approximately half of those who need treatment actually receiving ART.

In 2010, the estimate of those in need moved up to 1.6 million (Statistics South Africa, 2010). By this year, it is estimated that 2.75 million South Africans with HIV need antiretroviral therapy. On 24 April 2010, President Zuma launched a national campaign that aims to scale up treatment to 1.5 million people by June 2011, reaching 80% coverage of those who need treatment. This would represent a dramatic 50% increase in the country's current antiretroviral patient base (UNAIDS, 2010a). The plan is to further decentralize care to primary health care (PHC) facilities, move to a largely nurse-driven model and increase the number of health care centers providing ART approximately tenfold to 4,000 (Department of Health, 2010c, 2010b). In April 2010 alone, over 500 new health centers began dispensing ARV's (UNAIDS, 2010a).

Limited resources

Obstacles to ART access are being dismantled and ARV medicines are becoming increasingly available and affordable – ART is being scaled up rapidly and treatment is reaching more and more patients in the country. Despite the absolute necessity for and obvious benefits of these developments, they too are a structural challenge: the expansion is taxing given the region's inadequate health infrastructure and facilities, lack

of appropriately trained health care workers and related personnel, and insufficient laboratory capacity (Department of Health, 2010c). In 2009, several of South Africa's nine provinces exceeded their health care budgets, and there were reports of antiretroviral drug stock short supplies in seven. South African Health Minister, Aaron Matsoaledi has said, 'We are aware that the health system is not working well, we can't hide it... Some call it a collapse, others call it a crisis', listing 'human resource capacity, and supply and logistical problems' as key challenges (UNAIDS, 2010a, p.76).

The fundamental question that has emerged is how to ensure programme effectiveness with a rapid scale-up, and a growing patient base, in the context of a resource-limited setting.

Medication adherence

Aside from the structural challenges of treatment access and resource limitations, in the past few years, early optimism about HAART has been tempered by the growing recognition that a fairly substantial proportion of patients does not achieve or sustain virological suppression, and significant rates of HIV-related morbidity and mortality have persisted (Bisson et al., 2006; Deeks, Beatty, Cohen, Grant & Volberding, 1998; Djomand et al., 2003; Karcher, Omondi, Odera, Kunz & Harms, 2007; Parruti et al., 2006; Seyler et al., 2003; Weidle et al., 2002). This is true of both developed (Paredes et al., 2000; Parruti et al., 2006) and developing (Bisson et al., 2006; Djomand et al., 2003; Karcher et al., 2007; Seyler et al., 2003; Weidle et al., 2002) contexts, including settings where access to HIV treatment is available free of charge (Karcher et al., 2007; Sterling, Chaisson, Keruly & Moore, 2003). Whilst certain biomedical factors like varying potency of regimens, ARV history and disease stage do impact patients' physical response to treatment (Altice & Friedland, 1998; Deeks, 2000), by far the most critical determinant of ART success is patients' adherence to the medication regimen (Altice & Friedland, 1998; Bangsberg et al., 2000; Paterson et al., 2000; Raboud et al, 2002).

The classic definitions of *adherence* and its alternate term *compliance* can be found in an oft cited text by Haynes, Taylor & Sackett (1979, p.1–2):

> 'Compliance… is defined simply as the extent to which a person's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice. The term adherence may be used

> interchangeably with compliance. The definition is intended to be non-judgmental… the term compliance is troublesome to many people because it conjures up images of patient or client sin and serfdom.'

Thus, while the term *compliance* may contain a value judgment (Chesney, Morin & Sherr, 2000), *adherence* is generally preferred for its recognition of the patient as an active partner in selecting and maintaining a medical regimen (Altice & Friedland, 1998; Lerner, Gulick & Dubler, 1998).

It has been said that many health care providers now consider adherence as important as regimen potency (Stone, Jordan, Tolsen, Miller & Pilon, 2004). What we are being confronted with is the distinction between efficacy and effectiveness: what works in randomized controlled trials in highly adherent patients (Chesney et al, 2000) might not work (or not work as well) in the real world of diverse patient populations with competing challenges. Sometimes referred to as the Achilles' heel of antiretroviral therapy (Simoni, Frick, Pantalone & Turner, 2003), adherence to medication is an issue across all diseases (Wright, 2000). For instance, it was shown in the 1950's that patients with streptococcal pharyngitis seldom complete 10-day courses of penicillin (Mohler, Wallin & Dreyfus, 1955). Adherence in the context of chronic, life-long medication is particularly challenging as evidenced by observational cohorts reporting decreases in adherence rates with time (Carrieri et al., 2003; Parruti et al., 2006; Roco, Gomez & Arnedo, 1999).

ART literature reports highly variable adherence rates; among HIV-positive individuals, estimates of mean adherence levels range from 71% to 100% (Lima et al., 2009; Weidle et al., 2006). In one Ugandan study, 99% of patients were found to be adherent to HAART (Weidle et al., 2006); a similarly high rate of adherence was noted in a study in Malawi, where 84% of participants were adherent (van Oosterhout et al., 2005). This contrasts with a Canadian study in which only 129 of the 278 patients participating in the study (46%) were shown to be adherent (Palepu et al., 2006).

As outlined earlier, HAART involves the simultaneous administration of multiple ARV medications, including PI's, NRTI's and NNRTI's. Typically, patients are prescribed two or three ARV medications, each of which is dosed once or twice daily; at each dose, between one and four pills is consumed, adding up to as many as twelve pills per day. Moreover, each drug has specific, often compound administration instructions. For

instance, Didanosine (ddI) must be taken on an empty stomach (at least an hour before, or at least two hours after, a meal), should not be taken with other ARV medications, and should be dissolved in at least 30ml of water or clear apple juice (no other juice may be used). The magnitude of effort required to sustain adherence to regimens with such high dose burdens and complexities is considerable and should not be underestimated. Of course, many patients also receive treatments for various conditions, side effects and comorbidities that relate to their HIV status (e.g. antiemetics for drugs that commonly cause vomiting) and others that do not (e.g. anti-hypertensives or insulin), each of which comes with its own set of dosing and administration instructions.

Helping patients to optimize antiretroviral adherence in clinical settings is crucial for several reasons related to the patient's own welfare and to public health. First, for the potential of antiretroviral treatment to be optimized, meticulous adherence is necessary. Without good adherence, antiretroviral medications are not maintained at sufficient concentrations to suppress HIV viral replication and to lower HIV plasma viral load. Historically, in most chronic diseases (such as hypertension), sufficient and even optimal adherence has been defined as 80% or more of prescribed doses taken (Christensen et al., 1997; Gebo, Keruly & Moore, 2003; Sackett et al., 1975; Sherr, 2000) and in early antiretroviral work, the 80% threshold was used (Roco, Gomez & Arnedo, 1999).

However, subsequent findings indicated that antiretrovirals are less 'forgiving' than other chronic medications, and do not provide sufficient coverage at the 80% level. Near-perfect adherence is required to facilitate the best possible short- and long-term treatment outcomes, including maximum and durable reduction of viral load, reduced destruction of CD4+ cells, promotion of immune reconstitution, and slowed disease progression, certainly for PI therapy. For instance, Paterson et al.'s (2000) pioneer study showed that in order for virological outcomes of patients to be optimized, adherence of at least 95% is necessary. This is the equivalent of missing only one pill per month for a once-daily regimen, and three pills per month for a twice-daily regimen. In their prospective observational study of 81 patients, a dose-response effect was clearly evident: as adherence decreased, HIV ribonucleic acid (RNA) levels increased sharply. The virological failure rate was just 22% for patients with adherence of 95% or greater, a dramatic increase to 61% for patients with adherence between 80% and 94% (an adherence rate that would have led to treatment success in many medical conditions),

and 80% for patients with adherence less than 80%. In addition, no opportunistic infections or deaths occurred in patients with 95% or greater adherence. The authors concluded that 95% or greater was the required level of adherence necessary to optimize treatment outcome. Comparable findings are available elsewhere (Orrell, Bangsberg, Badri & Wood, 2003; Tuldra et al., 2000).

Recently however, Bangsberg (2006) reported that while ≥95% adherence is indeed necessary for viral suppression on unboosted PI therapy, more potent NNRTI regimens may lead to viral suppression at more moderate levels of adherence. Thus, while the precise minimum threshold of adherence for clinical effectiveness of HAART has been a point of discussion and seems to be dependent on the regimen concerned, experts agree that excellent adherence is crucial to the success of ARV treatment, and findings continue to show the predictable and dramatic relationship between ART adherence and HIV outcomes (Bangsberg, Moss & Deeks, 2004; Hogg et al., 2006; Spire et al., 2002; Wood et al., 2004). Thus, at an individual level, antiretroviral therapy – compared with therapy for most other medical conditions – requires an unprecedented high level of adherence to be maintained for an indefinite time period in order for optimum outcome to be achieved.

Second, treatment is in itself an important prevention modality. Evidence from studies in serodiscordant couples shows that virological suppression (as achieved by good antiretroviral adherence) can significantly reduce infectiousness and thereby decrease the risk of HIV transmission to sexual partners (Padian, Buve, Balkus, Serwadda & Cates, 2008). A meta-analysis published in 2009 showed that the transmission rate drops from 5.6 per 100 person-years in patients not on ART to just 0.5 per 100 person-years for patients on ART (Attia, Egger, Muller, Zwahlen & Low, 2009). In a recent prospective cohort study of 3381 serodiscordant couples across seven African countries (South Africa, Botswana, Kenya, Rwanda, Tanzania, Uganda and Zambia), Donnell et al. (2010) found a transmission rate of 0.37 (95% CI 0.09–2.04) per hundred person-years in those who had initiated ARV treatment, compared with a transmission rate of 2.24 (95% CI 1.84–2.72) in those who had not, a 92% reduction (adjusted incidence rate ratio 0.08, 95% CI 0.00–0.57, p=.004). Hence, good antiretroviral adherence is necessary to prevent transmission of the virus to sexual partners.

Third, the consequences of poor adherence include not only reduced efficacy, but also the development of resistance. HIV is highly adaptive; it evolves and mutates rapidly in the human body. The success of HAART is contingent upon the constant and invariable suppression of HIV viral load to such low levels that the virus cannot replicate rapidly enough to develop resistance to the medication (Catz et al., 2000). The only way this can occur is through daily or bi-daily dosing of multiple ARV medications to maintain optimal plasma drug levels. Any variation, however modest or occasional, from this frequent and regular consumption can not only greatly diminish treatment efficacy, but lead to viral replication and resistance. Poor adherence leads to suboptimal drug levels, treatment failure and ultimately drug resistance. During ART, HIV strains containing mutations associated with resistance can emerge within days if treatment is interrupted and sufficient drug levels are not maintained. Once resistant strains emerge, they begin to replicate, and will persist indefinitely. A study by Sethi (2004) set out to determine the adherence cut-off point for minimizing the risk of drug resistance, and found that while no resistance was noted in patients who were less than 60% adherent (no plasma drug levels), the greatest risk occurred in those patients who were 70–89% adherent (inadequate plasma drug levels). Thus, while very poor adherence may lead to virological failure, in terms of resistance, at highest risk is the reasonably but not perfectly adherent patient.

Moreover, mutations conferring resistance to one drug often confer cross-resistance to other drugs within the same class that are not yet prescribed; patients become resistant to entire classes of antiretroviral agents, thereby rendering those classes ineffective (Temesgen, Warnke & Kasten, 2006). There is a particularly high degree of cross-resistance between NNRTI's, which form the basis of the South African Department of Health's antiretroviral treatment protocol (Department of Health, 2010b), and providing a second NNRTI after resistance has developed would be unlikely to provide any clinical benefit (Max & Sherer, 2000). The world has seen this occur in tuberculosis (TB) care; poor adherence has led to the emergence of multi-drug resistant strains of the disease (Lerner et al., 1998). In a resource-constrained setting like South Africa, with its limited treatment options, minimizing antiretroviral resistance is especially important. The goal is for treatment programmes to successfully keep patients on uninterrupted first-line therapy for as long as possible, which is simpler to administer, associated with higher adherence levels, and less costly than second-line therapy. Patients who fail first-line

therapy must move on to second-line, with its more complex pill-taking requirements and higher cost.

At present, if patients then fail their second-line therapy, there are no further standard treatment options in the public sector (Department of Health, 2010b). What usually occurs in South Africa is that second-line therapy is continued until there is no longer clinical benefit to its use, or the patient and provider choose to switch to palliative care. The latest Department of Health clinical guidelines for HIV/AIDS management stipulate the following for cases of second-line treatment failure: '…If viral load remains high, refer where possible, but maintain [sic] on failing regimen' (Department of Health, 2010b, p.9). Salvage ART regimens (for use in those cases of second-line regimen failure) are rare in most low- and middle-income countries and are unlikely to become available in resource-limited countries within the next few years largely due to cost (Bennet, Bertagnolio, Sutherland & Gilks, 2008) as even second-line regimens costs three times more than first-line regimens (Orrell et al., 2007) and require more complex monitoring systems and challenging supply chain management. Thus, non-adherence must be minimized in order to maintain virological suppression on first-line therapy, especially in resource-limited settings like South Africa.

Fourth and finally, the prospect of resistance is not just relevant at an individual level, but is a public health threat. Resistant strains of the virus may actually be transmitted to others through high risk activities, leading to new infections which are unresponsive to currently available treatments and the further spread of resistant strains of HIV across society. Widespread HIV drug resistance (HIVDR) is a real fear, and its prevention an international priority. One longitudinal study conducted in North America among newly-infected patients who had not yet received treatment, found that the frequency of high-level resistance to one or more drugs had increased from 3.4 percent during the period from 1995 to 1998 to 12.4 percent during the period from 1999 to 2000 (p=.002) (Little et al., 2002). The prevalence of transmitted HIVDR in a society is a function of the extent of ART coverage, length of use/ availability and the prevalence of primary resistance (Bennet et al., 2008).

In South Africa, as coverage expands and length of use/ availability increases, primary resistance must be kept at the absolute minimum possible so as to avert the emergence

of widespread transmitted HIVDR. Facilitating ART adherence is one of the most important strategies for suspending emergence of resistant strains of the virus and ensuring durability of the currently available regimens. Hence, adherence to ARV drugs is crucial to both individual and public health. The WHO's recommended strategy for prevention and assessment of HIVDR in resource-limited countries suggests targets of >90% of ART patients taking >90% of each of their prescribed drugs at each clinic visit and >70% of patients, who, at 12 months, have an HIV RNA level of less than the detection limit of the test used (Bennet et al., 2008).

Retention to HIV care

Retention in ART programmes is a precursor to medication adherence and essential for programme success, but has received far less attention (Cornell et al., 2010; Rosen, Fox & Gill, 2007). Studies to date have tended to focus on describing adherence, laboratory and clinical outcomes of those patients who are retained in care, sidestepping the often substantial proportion of the patient base who are lost to care, with many reporting on-treatment rather than intention-to-treat analyses (Carrieri et al., 2001; Golin et al., 2002; Spire et al., 2002; Tesoriero et al., 2003). This may be a result of the significant costs associated with tracking missing patients, and also that while adherence research can examine very short pill-taking periods (with some recall surveys spanning as little as a few days) (Spire et al., 2002; Tesoriero et al., 2003; Wagner, 2002; Wagner, Iguchi, Schneider, Scott & Anderson, 2002), retention research requires longer-term monitoring periods.

Antiretroviral treatment requires frequent clinic visits, long-term counseling, regular clinical and immunological staging and ongoing monitoring, all of which are resource-intensive for both the health care system and the patient (Dalal et al., 2008). Loss to follow-up (LTFU) from ART programmes raises many of the same issues as described with regard to ART adherence; it is a potential source of patient illness and death, HIV transmission, and single- and multi-drug resistance for similar reasons. Keeping rates of LTFU in ART programmes to a minimum is key to ensuring continuity of treatment so that patients reap the survival benefits of ART, halt disease transmission and minimize both their own and society-wide resistance. LTFU rates, like adherence levels, vary widely across studies, contexts and patient groups. Studies in Uganda (Kabugo et al., 2005) and Cameroon (Guiard-Schmid et al., 2004) report LTFU rates as high as 39.3%

and 38.5%, while a study from Khayelitsha, South Africa (Coetzee et al., 2004) reported an extremely low rate of 0.3%.

In a meta-analysis of 74,289 ART patients across 33 cohorts in 13 sub-Saharan countries (Rosen, Fox & Gill, 2007), at 24 months retention was at just 60%, largely due to LTFU. A recent cohort analysis of 44,177 ART patients from eight public sector programmes across South Africa reported a higher retention rate of 71% at 24 months (Cornell et al., 2010). Of note was the finding that LTFU increased with expansion of the ART programme (from just 1% at 12 months in 2002/ 2003 to 13% at 12 months in 2006), and that with each additional year on ART, failure to retain patients in the programme was increasingly attributable to LTFU compared with mortality (at 6 months, 5% had died and 9% were LTFU; at 36 months, 10% had died and 30% were LTFU). The authors concluded that LTFU is playing an increasing role in the South African national ART programme, presenting a major threat to its effectiveness, and attributed the observed LTFU rates to the size and pace of ART scale-up. The WHO's recommended strategy for prevention and assessment of HIVDR in resource-limited countries suggests a target of <20% LTFU in first year of ART (Bennet et al., 2008).

Consequently, with as many as one million patients currently on ART and approximately 500,000 new patients due to start by June 2011, South Africa now faces the dual challenges of ensuring medication adherence and retention to care in the context of a massive programme scale-up. We are entering a new phase of the HIV pandemic, one termed by Altice and Friedland (1998), the 'era of adherence'.

Next steps

In the face of the supremely difficult task of maintaining near-perfect adherence indefinitely to a daily medication regimen and frequent clinic visits, some of the early optimism around ART has decreased. The considerable variability in domestic and international antiretroviral adherence and loss to follow-up rates show an overwhelming potential for individual and public health to be compromised. If 'real world' patients are to truly benefit from the medical advances of HAART, and a sub-pandemic of treatment-resistant HIV is to be averted, it is critical that we conduct systematic research to identify valid and reliable correlates of antiretroviral medication nonadherence and LTFU in clinical settings in sub-Saharan Africa, so that solutions to these challenges can be put

forward and implemented in the most affected region. These correlates are likely to be a complex interaction of disease, health system, social and individual patient characteristics, and are poorly understood.

The purpose of this research is to identify baseline demographic, biomedical and psychosocial factors that may predict adherence to ART and retention to care in a cohort of adult HIV-infected patients in South Africa in order to provide data for planning, monitoring and evaluation of response activities. The results will be available for use in three important ways to help lessen the impact of HIV on individuals and communities:

1) To develop effective treatment readiness/ preparation programmes

The latest Department of Health clinical guidelines for HIV/AIDS management (Department of Health, 2010a, p.12) stipulate the conduct of 'a basic psychological assessment to document social issues and current psychological state, focusing on factors that impact adherence' at the first visit, before treatment initiation. The guidelines are based on the assumption that baseline psychosocial factors impact subsequent adherence, but do not specify how these factors should be determined, who should conduct the assessment, or which measures should be used. The document goes on to recommend 'evaluat(ing) psychosocial support' and the conduct of an 'information and education session' at subsequent pre-treatment visits; this time the underlying assumption is that baseline social support and knowledge impact adherence, and specifics like how social support should be defined or measured or what information is most important to convey in the education session are not described. Finally, at the ART commencement visit, the guidelines suggest that 'the multidisciplinary team should reassess ART readiness criteria', including 'patient's understanding of their HIV status, the need for ART, importance of adherence and the link to treatment outcomes, specifically virological suppression, and commitment to scheduled visits.' The focus of this final assessment is therefore levels of knowledge, with the underlying assumption again that increased knowledge would lead to better adherence behaviour.

In certain settings, treatment readiness programmes have included other forms of knowledge transfer, such as possible side effects to be expected and their management (Highstein, Willey & Mundy, 2006), 'mock' adherence trials using co-trimoxazole, multivitamins or jelly beans (Balfour et al., 2006; Bekker, Myer, Orrell, Lawn & Wood,

2006), home visits to assess and promote social support (Coetzee et al., 2004; Koenig, Leandre & Farmer, 2004), encouragement of disclosure and even a 'treatment buddy' or 'treatment assistant' (Coetzee et al., 2004), identification of reminder strategies like alarms and medication diaries (Andrade et al., 2005), and diagnosis and treatment of depression (Balfour et al., 2006). While on-ART adherence intervention research is scarce, pre-initiation adherence interventions are even less available (Balfour et al., 2006).

Since providing interventions once patients are already on treatment may be too late to prevent early resistance or to modify already set behaviour patterns, for the benefits of HAART to be realized and resistance averted, the field needs theory-based strategies to prepare patients before their antiretroviral initiation and for these strategies to be incorporated into the national guidelines. For this to occur, valid and reliable baseline predictors of adherence behaviour are needed for the South African context.

2) To develop effective adherence and retention support programs

The latest Department of Health guidelines (Department of Health, 2010a, p.17) advise a large number of on-treatment adherence interventions: 'explaining the link between virological suppression and clinical outcome, and adherence', 'provide ongoing education to patients on their disease, including any new diagnoses, unexplained symptoms or opportunistic infections', 'reassure on the transient nature of nausea and vomiting, if a patient experiences that at treatment initiation', 'address adverse events, interim illness, issues around stigma and disclosure', 'treat depression and substance abuse', 'identify food insecurity and actively address this through government support programmes', 'ensure communication between clinic visits and referral points', 'enlist support of family/ friends/ partners/ support group members/ community adherence support workers', 'home visits', 'use reminders and reinforce with adherence tools', 'spend time with the patient and explain the disease, the goals of therapy and why the need for adherence', 'consider monitoring of medications such as co-trimoxazole prior to ART initiation', 'negotiate a treatment plan that the patient can understand and to which he/ she commits', 'explain to patients how to avoid adverse drug reactions', 'encourage attendance and participating in a support group – these should ideally be run by community members but might need to be supported by the clinic staff or adherence/ therapeutic counselors or social workers', 'arrange home visits… to facilitate access to

drug and alcohol counseling, social welfare for grant access, emergency relief for nutritional support and support with disclosure', 'reinforce the use of adherence tools e.g. pill boxes and/ or daily dosing diary', consider using a 'treatment buddy' or even directly observed therapy for an agreed period'. Given the overburdened and under-resourced health care system, and the country's rapidly growing ART patient base, this intervention list is unfeasible to action in the South African context. Instead of over-recommending a litany of interventions that may or may not prove effective in this context, the guidelines should be adapted to include only a few interventions that target valid and reliable predictors of nonadherence and loss to follow-up.

A small number of on-ART adherence interventions have been investigated and implemented globally with varying success, such as motivational interviewing (MI), cognitive behavioural therapy (CBT) and other counseling types (Bekker et al., 2003; Dilorio et al., 2003; Martin et al., 2001; Safren, Otto & Worth, 1999; Safren et al., 2001), education sessions of varying lengths and formats (Goujard et al., 2003; Remien et al., 2005); use of electronic devises such as beepers, pagers, wrist watches and cellular phone alarms (Dunbar et al., 2003; Bamberger et al., 2000; Holzemer, Henry, Portillo & Miramontes, 2000), reminder phone calls (McCance-Katz et al., 2002), pill boxes (Holzemer et al., 2000), treatment of concomitant mental health and substance abuse (Murphy, Lu, Hoffman & Marelich, 2002) and even cash reinforcement (Bamberger et al., 2000; Rigsby et al., 2000). Each of these interventions has a different focus, intending to modify either knowledge levels, attitudes, mental health, substance abuse, or social relationships, with the eventual aim of impacting medication adherence and/ or retention to care. This final aim will only be realized if the target of change is actually a significant correlate of adherence behaviour, something which has not been reliably determined. Thus, efforts to support adherence and retention are hampered by the current lack of knowledge of the predictors of adherence and retention, and what helps to sustain them over time.

The costs associated with interventions to increase ART adherence are minimal compared with the costs of the treatment itself (Altice & Friedland, 1998). Moreover, given the high costs of HIV-associated morbidity and mortality, the implementation of effective adherence programs would prove highly cost-effective. Using a simulation model to perform a cost analysis of various adherence support programmes, Goldie et

al. (2003) found that even intensive interventions (such as home- or clinic-based supervised medication administration, including all medical, personnel and transportation costs) proved cost-effective. This was particularly true of the model's advanced disease (mean CD4+ cell count 87 cells/μL) patients, who were the most representative within the model of South Africa's HIV population initiating treatment. For these patients, providing an intervention that even modestly improved HIV RNA suppression (e.g. from 60% to 78% of the cohort) meant quality-adjusted life expectancy gains of 5.5 months to more than 42.7 months at cost effectiveness ratios below $50,000 per quality-adjusted life-year (QALY), which is the commonly suggested threshold. Given this, the development and implementation of effective evidence-based national, population-specific adherence and retention interventions should be a priority; the first step of which will be to identify the biomedical, psychological or social factors that they should target.

3) To offer stratified adherence and retention support dependent on who will benefit most

South Africa's urgent need for rapid scale-up and context of low health system resources makes impractical the ART provision model seen in resource-rich countries, which involves intensive and personalized patient management through highly specialized staff, extensive treatment options and expensive laboratory monitoring. Locally, patients are provided basic HIV care at PHC level, and referred on to hospital centers if necessary. While HIV has meant increased patients numbers and responsibilities, in many cases this has not translated into increased personnel. At PHC level, health care practitioners are faced with heavy workloads, competing tasks and priorities, lack of sufficient human resources and training, and major time constraints (Ruud, Toverud, Radloff & Srinivas, 2010). In South Africa, as treatment scales up and the patient base increases, the goal is a system that can cope with high patient numbers while maintaining quality of care at the lowest cost possible. In seeking to make maximum use of limited resources and human capital, it is pertinent to consider a model of stratified retention and adherence support, wherein, instead of all patients receiving low to moderate levels of adherence and retention support, patients who would benefit most from intensified and targeted support would receive it. In the absence of such profiling, clinics are forced to use limited resources to offer uniform low- or moderate-level support – insufficient for those in need, and a misuse of resources for those that are not.

For such a model to be actualized, patients would need to be screened and accurately identified as at high or low risk for nonadherence and/ or loss to follow-up so that they could be positioned in the appropriate adherence support stream. In order for this screening to be both effective and feasible in a low-resource, high volume context, it would need to have the following features and properties:

- *Administered at first clinic presentation*

Unlike many of the adherence interventions designed to date (Bamberger et al., 2000; Dilorio et al., 2003; Dunbar et al., 2003; Goujard et al., 2003; Holzemer et al., 2000; Martin et al., 2001; McCance-Katz et al., 2002; Murphy et al., 2002; Remien et al., 2005; Rigsby et al., 2000; Safren et al., 1999; Safren et al., 2001), the screening and stratification should occur as patients enter the treatment system (i.e. at the first clinic visit), rather than once they are already on-treatment. At present, what usually occurs is that all patients receive the same (if any) adherence/ retention support, until the first elevated viral load or low-intake pill count result suggests nonadherence or the patient is LTFU, at which point intensified formal or informal adherence/ retention support kicks in. The benefit of screening and stratification at the first clinic visit would be to flag high-risk patients and provide timely treatment support before treatment onset, without delay and time for resistance to emerge or early patient fall-off.

- *Evidence-based*

The focus of the screening would need to be the assessment of those factors that have been observed – in systematic, methodologically-sound and rigorous observational research – to reliably predict adherence behaviour in the South African context.

- *Reliable*

The screening would ideally have high sensitivity (true positive rate [TPR] or the probability that an at-risk patient will be identified as at risk) and high specificity (true negative rate (true negative rate [TNR] or the probability that a patient not at risk will be identified as not at risk), but since its primary function is screening rather than confirmation, and given the over-arching aim of providing increased support to all of those that need it, high sensitivity should be prioritized.

- *Standardized*

The screening would need to be standardized for three reasons. First, in scaling up ART to the maximum number of persons in need, and decentralizing care to non-specialized clinic level, it is necessary to have clear, standardized protocols and guidelines for each aspect of patient management in order to maintain quality of care. Second, with South

Africa's current (and growing) ART patient load, health care workers should not be further burdened with the additional task of making individualized support-profiling assessments. Third and finally, it has been repeatedly shown that health care providers typically are poor predictors of patient medication adherence (Gerbert, Bronstone, Clanon, Abercrombie & Bangsberg, 2000; Miller et al., 2002; Paterson et al., 2000; Weiser et al., 2003), tending to overestimate adherence (in the Miller et al. [2002] study, in 60% of cases and by 8.9% on average) and insufficiently detect poor adherence. For example, in a prospective observational study of 88 patients, physicians predicted adherence incorrectly for 41% of patients, and nurses predicted incorrectly for 30% of patients (Paterson et al., 2000). This may be a function of the nature of the predictors of adherence. As the following chapter will show, while some literature has confirmed the validity of certain demographic and biomedical factors as predictors of medical adherence in certain contexts (Ammassari et al., 2004; Cornell et al., 2010; Gordillo, del Amo, Soriano & Gonzalez-Lahoz, 1999; Hill et al., 2010), much of the research has pointed to psychological and/ or social constructs, attributes that do not fall within the traditional domain of medical assessments in practice. This further points to the need for an objective measure; without standardized assessment, clinicians are unlikely to accurately identify patients at risk of suboptimal adherence, missing the opportunity for targeted interventions.

- *Designed for use in routine ART clinics and primary care facilities in resource-constrained environments: suitable for use by lay counselors or personnel, user-friendly for staff and patients, quick to administer, and inexpensive to set up and maintain*

The South African Department of Health's most recent UNGASS report (Department of Health, 2010c, p.65) outlined the department's plan to 'formally adopt, and invest sufficient resources in, task-shifting and down-referral policies so that patients on ART can be seen at the lowest appropriate level in the health system.' The aim is to enable healthcare workers with non-specialized training to deliver HIV care to considerable numbers of patients. It is estimated that there are just 26 medical practitioners for every 100,000 South Africans (Day & Gray, 2008), meaning that approaches to minimize dependence on highly skilled providers is critical. At many PHC facilities, doctors and pharmacists are not permanently on staff, so delegation to various auxiliary health care workers is key where possible. Due to limited health care resources, it must be assumed that no clinical psychological, psychiatric or neuropsychological services will be available

to conduct the assessment at PHC level. Lay counselors are one of the primary health care system's greatest resources, significantly outnumbering other personnel types. Any intervention intended for routine widespread use in public facilities in this country would have the best chance of being utilized if targeted at lay counselors. This means the screening needs to be simple and easy to administer as many lay counselors are appointed to work without prior medical or professional standardized training (Ruud et al., 2010). With such high patient numbers, the screening should also be streamlined and quick to administer, with the level of effort required for administration possible between routine activities in a busy clinic. This is also necessary to minimize the burden on patients, who often spend much time waiting at busy clinics, losing casual wages and delegating childcare responsibilities. Finally, the screening should be inexpensive to set up and utilize, meaning that in addition to lay administration (reducing burden on high-cost medical personnel), it should be paper-based and involve no additional laboratory or other high assessment costs.

For all of these features to be realized, the most useful form would be a an evidence-based, highly sensitive, paper Rapid Assessment Tool (RAT), administered at first clinic presentation, in order to identify patients at highest risk for non-adherence and LTFU, and utilized to trigger adherence support measures from the onset. This is one of the primary goals of this project.

Summation, aim and objectives

In sum, while HAART has the potential to dramatically improve HIV outcomes at an individual and population level, turning the tide of HIV in this country, significant barriers to its effectiveness still exist. One of the primary barriers is patient adherence and LTFU, and effective treatment readiness and on-treatment support programmes are sorely needed. For such interventions to be designed and implemented, there is an urgent need for systematic data collection and analysis to identify valid and reliable predictors of nonadherence and LTFU in the South African population. The goal of this project is twofold: to determine these predictors through systematic and rigorous methodology, in order to provide evidence-based recommendations for the development of effective treatment readiness and adherence support programmes; and to develop an effective RAT for patient risk profiling and stratification of such programmes.

Study aim

The aim of this study is to identify baseline demographic, biomedical and psycho-social factors that may predict adherence to ART and retention to care in a cohort of adult HIV-infected patients in South Africa, in order to provide data for planning, monitoring and evaluation of response endeavors.

Specific objectives

- To describe the demographic and biopsychosocial profile of adult patients accessing ART in a primary health care clinic in South Africa
- To determine the prevalence of nonadherence to HAART and loss to follow-up in the sample
- To examine the effects of various demographic, biomedical, psychological and social factors on key laboratory (virological suppression) and behavioural (pill count, retention to care) endpoints indicative of adherence, and to make this information available for guideline-development, advocacy and the development of focused strategic treatment readiness, adherence and retention programmes
- To develop a treatment success prediction rapid assessment tool (RAT), based on the findings above, suitable for routine clinical use by lay counselors in resource-limited settings, in order to facilitate the detection of patients at high risk for nonadherence and loss to follow-up and in need of increased adherence support

CHAPTER 2

Predictors of antiretroviral adherence and retention to HIV care: State of the science

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Across diseases, medication adherence and retention to care are complex and dynamic human behaviours, resulting not only from individual attitudes, thoughts and behaviors, but also relevant health systems, socioeconomic conditions, disease- and drug-related factors. The goal of this review chapter is to describe the state of the science in emerging predictors of medication adherence and retention to care, focusing on HIV treatment antiretroviral adherence and retention to HIV care in particular. Using search and extraction methodology, information from literature across the field has been collected and synthesized for presentation here.

Theoretical framework

The biopsychosocial model is derived from an established body of psychological and behavioural research and theory and posits that psychological and social processes must be considered alongside biomedical symptoms, conditions and treatments in our attempts to understand health-related behaviours. Unlike the biomedical model (which is reductionist in its perception of illness and treatment as low-level processes, focusing only on such as aspects as bacteria and surgical interventions) (Edelmann, 2000), the biopsychosocial model recognizes the role played by individual habits, emotions and motivations as well as social context and circumstance in addition to biomedical processes in determining disease course and treatment efficacy.

It is the premise of this research that health-related actions and treatment adherence can only be understood by examining individual psychological factors like attitudes or affective state and broader social relationships and realities like marital and employment status alongside biological signs and symptoms.

Studies reviewed

This review covers a number of complex subject areas and themes. Space limitations preclude full and complete presentations of each topic, but representative articles are drawn together and cited, with a focus on recent literature.

Methodology of published studies

Because the study of antiretroviral adherence and its predictors is fairly new, study methodologies, methods of adherence measurement, durations of follow-up and endpoints vary widely, making comparisons of results challenging.

Most studies are conducted in developed nations, particularly the United States and Europe, with relatively few conducted in developing countries (Bisson et al., 2006; Byakika-Tusiiime et al., 2005; Caluwaerts et al., 2009; Cornell et al., 2010; Dalal et al., 2008; Do et al., 2010; Karcher et al., 2007; Laniece et al., 2003; Lubega et al., 2010; Maskew, Macphail, Menezes & Rubel, 2007; Nam et al., 2008; Ncama et al., 2008; Richard, Simon, Joseph, Fred & Violet, 2009; van Oosterhout et al., 2005; Weidle et al., 2006; Weiser et al., 2003; Wools-Kaloustian et al., 2006; Zachariah et al., 2008). As a result, little is known about predictors of adherence in Africa and particularly sub-Saharan Africa, which is sadly paradoxical as this is where the HIV pandemic continues to have its most devastating impact.

Most research is done with patients already on HAART, with just a few studies conducted among those initiating treatment (Bisson et al., 2006; Caluwaerts et al., 2009; Carrieri et al., 2006; Cornell et al., 2010; Dalal et al., 2008; Golin et al., 2002; Laniece et al., 2003; Lime et al., 2009; Parruti et al., 2006; Roco et al., 1999; Spire et al., 2002; Weidle et al., 2006; Zachariah et al., 2008), limiting their ability to identity at-risk patients before they have already begun treatment. While most studies are conducted in general adult populations made up of various transmission groups, some studies are conducted in special populations like injection drug users (IDU's) (Arnsten et al., 2007; Kerr et al., 2005; Turner & Hecht, 2003) or the incarcerated (Roberson, White & Fogel, 2009), and it is unclear how applicable each set of findings is to other population groups.

Some studies assess only self-reported reasons for poor adherence or loss to follow-up (Abel & Painter, 2003; Lubega et al., 2010; Maskew et al., 2007; Morse, Simon, Besch & Walker, 1995; Murphy, Roberts, Martin, Marelich & Hoffman, 2000; Nam et al., 2008; Roberson et al., 2009; Vervoort et al., 2010), rather than testing for associations between these factors and observed adherence. Of those studies that do test for associations, most do not use objective methods of assessing adherence (such as pill counts, HIV RNA level tests, electronic monitoring devices, pharmacy records or therapeutic drug monitoring); the most common form of assessing adherence across the literature is self-report (Ammassari et al., 2004; Arnsten et al., 2007; Byakika-Tusiime et al., 2005; Carrieri et al., 2006; Catz et al., 2000; Chesney et al., 2000; Corless, Nicholas, Davis, Dolan & McGibbon, 2005; Do et al., 2000; Gebo et al., 2003; Golin et al., 2002; Gordillo et al., 1999; Laniece et al., 2003; Malcolm, Ng, Rosen & Stone, 2003; Murphy et al., 2000; Murphy et al., 2010; Ncama et al., 2008; Parruti et al., 2006; Roco et al., 1999; Spire et al., 2002; van Oosterhout et al., 2005; Wagner, 2002; Weiser et al., 2003; Wools-Kaloustian et al., 2006), which is prone to bias.

Most studies are cross-sectional (Ammassari et al., 2004; Arnsten et al., 2007; Byakika-Tusiime et al., 2005; Catz et al., 2000; Chesney et al., 2000; Corless et al., 2005; Do et al., 2010; Gebo et al., 2003; Gordillo et al., 1999; Hinkin et al., 2002; Malcolm et al., 2003; Murphy et al., 2010; Ncama et al., 2008; Richard et al., 2009; van Oosterhout et al., 2005; Weiser et al., 2003); comparatively few studies incorporate a follow-up assessment period of adherence and/ or retention outcomes. Of those that do, most durations of follow-up are shorter than two years (Bisson et al., 2006; Caluwaerts et al., 2009; Dalal et al., 2008; Golin et al., 2002; Hinkin et al., 2004; Karcher et al., 2007; Roco et al., 1999; Spire et al., 2002; Wagner, 2002; Weidle et al., 2006; Wools-Kaloustian et al., 2006; Zachariah et al., 2008). While operationally simpler, cross-sectional designs are limited in their inability to evaluate cause-effect associations, which must be longitudinally tested. As such, some of the factors identified as 'determinants' of non-adherence may actually be outcomes of non-adherence. For instance, high rates of depression in poor adherers in cross-sectional studies may instead indicate the impact of non-consumption of ART and associated progressing illness on mood states. Likewise, correlations between adherence self-efficacy (i.e. patients' belief in their ability to take their medication as prescribed) and adherence behaviour may, instead of underscoring the significance of self-confidence and beliefs in determining adherence

patterns, reflect the impact of past adherence behaviour on self-perceived ability to adhere. Authors of cross-sectional studies agree that longitudinal designs are needed to more definitively establish the direction of these relationships (Ammassari et al., 2004; Catz et al., 2000; Corless et al., 2005; Hinkin et al., 2002) and call for the conduct of longitudinal investigations.

Few studies (Corless et al., 2005; Malcolm et al., 2003) use a theoretical framework to guide their choice of factors to investigate. Many assess only demographic, clinical, immunological and virological data (Bisson et al., 2006; Byakika-Tusiime et al., 2005; Caluwaerts et al., 2009; Cornell et al., 2010; Dalal et al., 2008; Hill et al., 2010; Karcher et al., 2007; Laniece et al., 2003; van Oosterhout et al., 2005; Weidle et al., 2006; Wools-Kaloustian et al., 2006; Zachariah et al., 2008), with no psychological or social evaluations. This is likely due to the fact that demographic, clinical and laboratory data are routinely collected in ART programmes, whereas the time and costs associated with collecting psychosocial data would necessitate special provisions. Only a handful of studies include cognitive testing (Albert et al., 1999; Ammassari et al., 2004; Avants, Margolin, Warburton, Hawkins & Shi, 2001; Hinkin et al., 2002; Hinkin et al., 2004; Levine et al., 2005; Wagner, 2002; Waldrop-Valverde et al., 2006); of those that do, most have sample sizes of less than 150 participants (Albert et al., 1999; Ammassari et al., 2004; Avants et al., 2001; Hinkin et al., 2002; Hinkin et al., 2004; Waldrop-Valverde et al., 2006) and are conducted in the United States (Albert et al., 1999; Avants et al., 2001; Hinkin et al., 2002; Hinkin et al., 2004; Levine et al., 2005; Wagner, 2002; Waldrop-Valverde et al., 2006), likely a function of the level of expertise, training and time required to perform such testing.

Biopsychosocial predictors of antiretroviral adherence and retention to HIV care

While medication adherence has been the focus of research for many years, interest in adherence has intensified in the era of ART. The seriousness and implications of non-adherence to ART has sparked increased attention; however, rigorous empiric investigations are sorely lacking. This emerging body of literature links certain demographic, biomedical, psychological and social constructs with adherence to ART and retention to care. These constructs include factors related to the patient (including demographics like age, gender, ethnicity, education and employment; levels of

understanding about, attitudes towards and concerns about HIV and ART; mental illness, which may or may not predate HIV-infection; concomitant substance abuse; comorbid conditions; adherence self-efficacy), factors related to HIV (primarily perceived HIV symtomatology) and its treatment (regimen complexity and perceived treatment side effects), and factors related to the patient's environment (disclosure; family and other social support; professional support and relationship with health care provider), but an almost equal literature set refutes each association.

Differences in reported results are likely a function of two factors: significant methodological variations, and differences in study populations. As outlined earlier, the literature uses various study designs (cross-sectional versus longitudinal; quantitative versus qualitative; reported versus observed behaviour), measures (subjective versus objective assessment of adherence, various viral load assays with different limits of detection), definitions (percentage of pill to be consumed for adherence to be considered acceptable, length of time absent to be considered lost to follow-up, viral load level to be considered suppressed). These methodological differences are likely to significantly impact study results. For certain constructs, the conflicting findings and variability of identified predictors of adherence by study may result from differences in study populations and settings, with studies conducted in both developed and developing countries, each with its own culture, circumstances and clinical settings (e.g. ART requiring payment or available free of charge), focusing on different population groups (general adult populations versus special subpopulations), and clinical settings (prisons, inpatient, outpatient). For instance, Hinkin et al. (2002) found older age to be associated with better adherence in a broad sample of HIV-infected patients, while Avants et al. (2001) found no association between age and adherence in a sample of HIV-infected injection drug users. Findings from Gebo et al.'s (2003) cross-sectional study of ART patients at an urban hospital clinic in the United States illustrate this point: in multivariate analyses, social pressures outside of the clinic were a significant predictor of nonadherence only in patients without a history of injection drug use. Even those studies that focus on general adult populations have significantly different sample characteristics, due to country and setting differences (for instance, men who have sex with men [MSM] populations in the United States versus heterosexual populations in Africa). Other differences may be explained by a time span across studies of approximately fifteen years, with divergent results reflecting changing patient

populations, ART regimens, clinical guidelines and social norms. This further justifies the need for methodologically-sound, locally-relevant, current antiretroviral adherence research.

Demographic predictors

Demographic features were some of the earliest variables to be examined as potential characteristic indicators of risk for nonadherence or loss to follow-up (Chesney et al., 2000) (see Table 1), although the data has generally found inconsistent and context-dependent associations. Female gender has been identified as a determinant of good ART adherence in some previous research (Wagner, 2002), as has male gender (Turner, Laine, Cosler & Hauck, 2003). Wagner (2002) noted better adherence in women than men according to medication diary, and Turner et al. (2003) showed that women were less adherent than men according to pharmacy refill records. Spire et al. (2002) however, found no relationship between gender and medication adherence in a cohort of HAART-initiating patients in France; nor did Catz et al. (2000), Do et al. (2010), Gebo et al. (2003), Golin et al. (2002); Parruti et al. (2006) or Weiser et al. (2003) in various observational studies.

The same inconsistencies exist in retention research. In a cohort study of 435 adolescents and adults (age 13 and older) initiating ART at a district hospital in Kenya, Zachariah et al. (2008) found a significantly higher proportion of females to have been lost to care. However, Hill et al. (2010) found that potential loss to follow-up (defined as 12 months without CD4+ cell count, the equivalent of 2–4 missed clinic appointments) was independently associated with male sex. Maskew et al. (2007), Mocroft et al. (2008) and Wools-Kaloustian et al. (2006) also found males to be significantly more likely to be lost to follow-up than females. However, Caluwaerts et al. (2009), Dalal et al. (2008), Karcher et al. (2007) and Kerr et al. (2005) found no relationship between gender and retention to care. Those that have found relationships between gender and adherence behaviour have attributed them to differences in attitudes to health and health-seeking behaviour, socio-cultural beliefs and patterns, and differences in employment levels and the associated impact on ability to attend clinic visits.

While some studies investigating the relationship between age and medication adherence (Bisson et al., 2006; Catz et al., 2000; Do et al., 2010; Gebo et al., 2003;

Parruti et al., 2006; Turner et al., 2003; Weiser et al., 2003) or loss to follow-up (Dalal et al., 2008; Maskew et al., 2007; Zachariah et al., 2008) have reported no association, each study that has seen a relationship has reported that younger patients are significantly less likely to adhere (Carrieri et al., 2006; Golin et al., 2002; Gordillio et al., 1999; Hinkin et al., 2002; Hinkin et al., 2004; Spire et al., 2002; Wagner, 2002) or be lost to follow-up (Caluwaerts et al., 2009; Cornell et al., 2010; Hill et al., 2010; Karcher et al., 2007; Kerr et al., 2005; Lanoy et al., 2006; Mocroft et al., 2008) than older patients. In Hinkin et al.'s (2002) cross-sectional investigation of 137 HAART patients in the United States, younger age was associated with a 4.6 times greater risk of adherence failure. The authors concluded that younger patients may have less prior experience adhering to daily medications, and that the lifestyle changes necessary for managing a high-burden medication regimen may be more challenging for younger individuals. In Hinkin et al.'s (2004) subsequent longitudinal study, wherein 148 patients were followed with electronic adherence monitoring for one month, younger patients again adhered more poorly (78.3% versus 87.5%), and were three times less likely to be adherent. Caluwaerts et al. (2009) found that young adult ARV patients age 16–35 years were at greater risk of being lost to follow-up than those older than 35 years, and Hill et al. (2010) found that patients age 25 and younger had a markedly higher risk of permanent loss to follow-up.

However, studies examining the impact of age on adherence underscore the importance of conducting locally-relevant research as opposed to applying international findings to the South African population: the definition used by Hinkin et al. (2002) and Hinkin et al. (2004) in their United States studies for 'younger' was <50 years. In a recent meta-analysis of 74,289 ART patients across 33 cohorts in 13 sub-Saharan countries (Rosen et al., 2007) the weighted mean age of the sample was 35.5 years (range 31–41 years).

There are a few studies that have addressed the association between education and adherence (Arnsten et al., 2007; Catz et al., 2000; Do et al., 2010; Golin et al., 2002; Gordillio et al., 1999; Karcher et al., 2007; Spire et al., 2002; Wagner, 2002; Weiser et al., 2003). Higher level of education has been reported to both positively influence adherence (Arnsten et al., 2007; Golin et al., 2002; Gordillo et al., 1999; Wagner, 2002) and negatively influence adherence (Weiser et al., 2003). For instance, in Wagner's (2002) investigation of 180 HAART patients in the United States, having at least some college education was associated with greater electronic-monitored adherence, whereas

in Weiser et al.'s (2003) cross-sectional study of 109 patients in Botswana, patients who did not complete secondary school were 3.87 times more likely to adhere than those with higher levels of education. However, according to Spire et al. (2002), level of education (defined in their cohort as ≥ a high school certificate) had no bearing on HAART adherence. Similar nonsignificant results are available elsewhere for medication adherence (Catz et al., 2000; Do et al., 2010) and retention (Karcher et al., 2007) research.

Past research has linked unemployment with poor antiretroviral adherence (Chesney et al., 2000; Gordillo et al., 1999; Morse et al., 1995). In a series of interviews conducted with 18 clinicians at various community centers conducting ARV drug trials, the most frequently mentioned barrier to patient recruitment, retention and adherence was unemployment (endorsed by 45% of clinicians) (Morse et al., 1995). Gordillo et al. (1999) concur; in their cross-sectional study of 366 patients on HAART in Spain, having a job was associated with better adherence (OR, 2.24; 95% CI, 1.27–2.73). Interestingly, one study of 75 HAART patients in the United States showed the opposite: less adherent patients were more likely to be employed outside the home for pay than adherent patients (Chesney et al., 2000). The authors hypothesized that employed patients may be too busy or forget to carry medications with them to their place of work. Results of other observational studies show no association between unemployment and adherence (Do et al., 2010; Golin et al., 2002; Parruti et al., 2006; Wagner, 2002) or retention to care (Karcher et al., 2007).

Economic barriers like low income (Byakika-Tusiime et al., 2005; Golin et al., 2002; Richard et al., 2009) and poor material living conditions (Gebo et al., 2003; Parruti et al., 2006; Spire et al., 2002) have been associated with poor adherence to ART. One study in France showed that patients with poor housing conditions were more likely to be non-adherent ($p < .01$) (Spire et al., 2002), underscoring the negative influence of low socio-economic status. Another in Italy associated homelessness with a 1.95 times higher likelihood of adherence failure ($p < .05$) (Parruti et al., 2006). Gebo et al. (2003) noted that patients who reported running out of money in the past ninety days for life essentials were 2.21 times more likely to be nonadherent. Low socio-economic status may prevent patients from being able to afford transportation to clinics or preoccupy them with more

immediate concerns (Mehta, Moore & Graham, 1997). One study however saw no link between socio-economic status and ART adherence (Weiser et al., 2003).

Factor	Significant result	Non-significant result
Gender	Hill et al., 2010 Maskew et al., 2007 Mocroft et al., 2008 Turner et al., 2003 Wagner, 2002 Wools-Kaloustian et al., 2006 Zachariah et al., 2008	Caluwaerts et al., 2009 Catz et al., 2000 Dalal et al., 2008 Do et al., 2010 Gebo et al., 2003 Golin et al., 2002 Karcher et al., 2007 Kerr et al., 2005 Parruti et al., 2006 Spire et al., 2002 Weiser et al., 2003
Age	Caluwaerts et al., 2009 Carrieri et al., 2006 Cornell et al., 2010 Golin et al., 2002 Gordillo et al., 1999 Hill et al., 2010 Hinkin et al., 2002 Hinkin et al., 2002 Karcher et al., 2007 Kerr et al., 2005 Lanoy et al., 2006 Mocroft et al., 2008 Spire et al., 2002 Wagner, 2002	Bisson et al., 2006 Catz et al., 2000 Dalal et al., 2008 Do et al., 2010 Gebo et al., 2003 Maskew et al., 2007 Parruti et al., 2006 Turner et al., 2003 Wesier et al., 2003 Zachariah et al., 2008
Education	Arnsten et al., 2007 Golin et al., 2002 Gordillo et al., 1999 Wagner, 2002 Wesier et al., 2003	Catz et al., 2000 Do et al., 2010 Karcher et al., 2007 Spire et al., 2002
Employment	Chesney et al., 2000 Gordillo et al., 1999 Morse et al., 1995	Do et al., 2010 Golin et al., 2002 Karcher et al., 2007 Parruti et al., 2006 Wagner, 2002
Socio-economic status and living conditions	Byakika-Tusiime et al., 2006 Gebo et al., 2003 Golin et al., 2002 Parruti et al., 2006 Spire et al., 2002	Weiser et al., 2003

Table 1. Demographic factors assessed for impact on adherence behaviour in literature.

Biomedical predictors

Several biomedical factors have been identified as having the potential to impede adherence (see Table 2). More advanced immunological stage of HIV disease, as

measured by CD4+ cell count, has been associated with decreased adherence to HAART treatments (Ammassari et al., 2004; Gordillo et al., 1999; Weidle et al., 2006). CD4 cells (white blood cells) are a key measure of strength of the immune system; because HIV targets CD4 cells specifically, the lower the CD4+ cell count, the greater the damage HIV has done. The relationship between CD4+ cell count and adherence has been observed using CD4+ cell count cut-off of 100 cells/μL (Weidle et al., 2006) and 200 cells/μL (Gordillo et al., 1999) for advanced immunological disease. Contrarily, other cohorts (Bisson et al., 2006; Spire et al., 2002; Wagner, 2002) and cross-sectional studies (Catz et al., 2000; Gebo et al., 2003; Hinkin et al., 2002) have shown no relationship between CD4+ cell count and medication adherence.

Some previous literature has linked CD4+ cell count with retention to care (Caluwaerts et al., 2008; Cornell et al., 2010; Hill et al., 2010; Lanoy et al., 2006; Mocroft et al., 2008; Zachariah et al., 2008). Lanoy et al. (2006) and Zachariah et al. (2008) reported a significantly higher proportion of patients with CD4+ cell counts under 200 cells/μL to be lost to follow-up than those with better immune functioning, as did Caluwaerts et al. (2008) and Mocroft et al. (2008) for patients with CD4+ cell counts less than 50 cells/μL. Hill et al. (2010) and Cornell et al. (2010) found the opposite – patients with CD4+ cell counts 50–499 cells/μL were at lower risk of potential loss to follow-up (defined earlier) than those with CD4+ cell counts greater than 500 cells/μL in the Hill et al. (2010) study, and patients with CD4+ cell counts 50–199 cells/μL were less likely to be lost to follow-up than those with CD4+ cell counts greater than or equal to 200 cells/μL in the Cornell et al. (2010) study. Finally, Karcher et al. (2007) found no association between CD4+ cell count and loss to follow-up.

Viral load (the amount of virus in the blood) may also play a role in medication adherence and/ or retention to HIV care (Hill et al., 2010; Lanoy et al., 2006; Mocroft et al., 2008; Weidle et al., 2006). Weidle et al. (2006) reported that a viral load level at baseline of 100,000 copies/mL or more was significantly associated with non-suppression at six and 12 months, and Mocroft et al. (2008) noted that a 1 $\log_{10}$copies/mL higher viral load level was associated with a 19% increased incidence of loss to follow-up in a large European cohort. Conversely, Hill et al. (2010) observed that a viral load of 50 copies/mL or less meant a lower risk of potential loss to follow-up

(definition earlier). Finally, Bisson et al. (2006), Gordillo et al. (1999), Spire et al. (2002) and Wagner (2002) reported no association between viral load and adherence.

WHO stage has been associated with adherence to ARV's (Lima et al., 2009). In 1993, the WHO developed a system which characterized and staged HIV disease based on clinical symptoms (WHO International Collaborating Group for the study of the WHO Staging System, 1993). While the first two stages are largely asymptomatic, stage III includes symptoms like weight loss and oral infections, and stage IV more severe conditions like pneumonia, TB and wasting (Dorrington et al., 2006). The system is still in use today, and is used as a guide for medical decision-making and reporting. Lima et al. (2009) showed that a significantly higher proportion of those with an AIDS diagnosis at baseline were adherent to therapy. However, others have shown that WHO/CDC stage is not related to HAART adherence (Parruti et al., 2006; Spire et al., 2002; Wagner, 2002) or retention to care (Caluwaerts et al., 2009; Karcher et al., 2007).

The length of time between HIV diagnosis and ART initiation may be related to adherence and loss to follow-up (Lanoy et al., 2006; Vervoort et al., 2010). In a qualitative study using individual interviews and focus groups to explore nurse consultants' strategies to promote adherence among their HIV-positive patients, one of the themes that emerged was the belief that adherence was most likely to be compromised when patients needed to start treatment soon after hearing the HIV diagnosis (Vervoort et al., 2010). However, Spire et al. (2002) observed no difference between self-reported adherence rates at four months on HAART between those who had been diagnosed more than a year before initiation and those less than a year. Similarly, Catz et al. (2000) found no relationship between length of time since HIV diagnosis and self-reported adherence in a cohort of HAART patients with a mean length of time on treatment of 15 months.

Poor health and HIV symptoms at the time of ARV initiation can either act a strong motivator for adherence, or make clinic visits and medication routine following challenging. Conversely, feeling well and healthy may either lead to complacency, making antiretroviral medications or clinic visits feel unnecessary, or allow patients the strength to attend the clinic and take the necessary actions to ensure adherence. For instance, in the same recent study, 43% of the sample listed feeling sick as a reason for

missing medication, whilst 35% of the sample mentioned feeling good as a reason for nonadherence (Gardenier et al., 2010). Supporting the association between HIV symptomatology and difficulty with adherence, in Wagner's (2002) study of 180 patients on HAART in the United States, patients who reported a greater number of symptoms and patients who reported higher symptom severity were less likely to adhere well, as evidenced by scores on electronic monitoring, self-report and medication diaries. Severity of certain symptoms in particular – insomnia, headaches, poor concentration, anxiety and diarrhea – was associated with lower adherence levels. Similarly, in a study by Corless et al. (2005), the degree to which patients were bothered by symptoms ('bothersomeness') was significantly associated with forgetting to take ARV medications (p=.003), difficulty taking the medications (p=.04) and discontinuing medications when feeling better (p=.007); symptom intensity was also associated with discontinuing medications when feeling better (p=.047). Other studies have documented the relationship between good health and nonadherence (Murphy et al., 2000). A patient in Murphy et al.'s (2000, p.52) investigation of common barriers to antiretroviral adherence explained, 'I think a lot of this probably has to do with how good a person feels. If a person feels like they're healthy and they [miss], they're like, "Well, if I missed my dose, that's okay, as long as I feel good or as long as I get a good report on my health."' However, in a small pilot study assessing a motivational interviewing ART adherence intervention, Dilorio et al. (2003) found that only 6% of these on-treatment participants reported 'feeling good' as a reason for missing doses.

Cohort studies have examined the impact of transmission group (heterosexual, MSM or IDU's on adherence rates, and some have found significant relationships (Ammassari et al., 2004; Gebo et al., 2003; Gordillio et al., 1999; Hill et al., 2010; Lanoy et al., 2006). For example, route of HIV transmission was associated with antiretroviral adherence in studies by Ammassari et al. (2004) and Gordillo et al. (1999), with suboptimal adherence found in patients with IDU as their mode of HIV acquisition. Hill et al. (2010) found that potential loss to follow-up (defined earlier) was less frequent among MSM as compared with the heterosexual group and those with nonsexual risks for infection (comprising 66% IDU's). Gebo et al. (2003) also reported positive results for MSM, who were more likely to adhere to their antiretroviral regimen than patients with an HIV risk factor of high-risk heterosexual activity. The authors hypothesized that MSM had more social support to take ART as prescribed and felt less social stigma attached to taking the

medication in public. However, Spire et al. (2002) investigated a cohort of 445 adult patients initiating HAART in France and found that transmission group (heterosexual exposure, MSM exposure, IDU or other) did not predict ARV adherence at four months follow-up. Similar nonsignificant results are available elsewhere (Parruti et al., 2006).

Previous studies have found that patients with comorbid conditions like TB (Caluwaerts et al., 2009), Kaposi's sarcoma (Caluwaerts et al., 2009) and pneumonia (Turner et al., 2003) have higher nonadherence and lost to follow-up rates than others. Other studies have found no relationship between various chronic conditions like hepatitis and ART adherence (Parruti et al., 2006).

Patients who have already experienced difficulty adhering to previous ART might logically be more likely to adhere poorly to newly-prescribed regimens, and this has been confirmed in a number of investigations (Carrieri et al., 2006; Spire et al., 2002). Interestingly, while Spire et al. (2002) observed no difference in adherence rates at four months on HAART between patients who had been exposed to previous ART before HAART initiation and those that had not (p=.70), the authors found that those who self-reported adherence difficulties with the previous regimens were more often non-adherent with HAART at month four than those who had also been exposed to previous ART but who did not report such difficulties (p=.001).

Complex ART regimens, high pill burden and high dose frequency are inconvenient and can lead to patient difficulty incorporating the medication into daily life or schedule (Abel & Painter, 2003; Mehta et al., 1997; Murphy et al., 2000). Unfortunately, considering the relatively short half-lives of the NNRTI's and PI's, reduction of dosing frequency is unlikely to occur in the short-term (Chesney, 2000). Patients may also be more unlikely to take prescribed medications with inconvenient requirements, such as the need to take a medication on an empty stomach (Murphy et al., 2000). The taste and size of specific pills may also play a role (Murphy et al., 2000). There have been some study results that correlate prescribed regimen with antiretroviral adherence (Ammassari et al., 2004; Carrieri et al., 2006; Golin et al., 2002; Hinkin et al., 2002; Laniece et al., 2003; Lima et al., 2009). Lima et al. (2009) found that among adult patients initiating ARV treatment in Canada, those first prescribed non-boosted PI's were at significantly greater risk of non-adherence than those prescribed NNRTI's or boosted PI's. A study from Senegal found

that adherence tended to be better with efavirenz than with indinavir (Laniece et al., 2003). Contrarily, Spire et al. (2002) investigated various dimensions of regimen prescription and their relationship with adherence, including whether a PI was included in the regimen, the mean daily number of prescribed pills and whether the regimen was to be taken on an empty stomach, and found none of these factors to be significant. Others (Gebo et al., 2003; Parruti et al., 2006; Wagner, 2002; Weiser et al., 2003) have also found no association between regimen, pill burden or dosing schedule and ART adherence.

Factor	**Significant result**	**Non-significant result**
CD4+ cell count	Ammassari et al., 2004 Caluwaerts et al., 2009 Cornell et al., 2010 Gordillo et al., 1999 Hill et al., 2010 Lanoy et al., 2006 Mocroft et al., 2008 Weidle et al., 2006 Zachariah et al., 2008	Bisson et al., 2006 Catz et al., 2000 Gebo et al., 2003 Hinkin et al., 2002 Karcher et al., 2007 Spire et al., 2002 Wagner, 2002
Viral load	Hill et al., 2010 Lanoy et al., 2006 Mocroft et al., 2008 Weidle et al., 2006	Bisson et al., 2006 Gordillo et al., 1999 Spire et al., 2002 Wagner, 2002
WHO stage	Lima et al., 2009	Caluwaerts et al., 2009 Karcher et al., 2007 Parruti et al., 2006 Spire et al., 2002 Wagner, 2002
Time since HIV diagnosis	Lanoy et al., 2006 Vervoort et al., 2010	Catz et al., 2000 Spire et al., 2002
HIV symptomatology	Corless et al., 2005 Gardenier et al., 2010 Murphy et al., 2000 Wagner, 2002	Dilorio et al., 2003 Gardenier et al, 2010
Transmission group	Ammassari et al., 2004 Gebo et al., 2003 Gordillo et al., 1999 Hill et al., 2010 Lanoy et al., 2006	Spire et al., 2002 Parruti et al., 2006
Comorbid conditions	Caluwaerts et al., 2009 Turner et al., 2003	Parruti et al., 2006
Treatment experience	Carrieri et al., 2006 Spire et al., 2002	-

Regimen/ regimen complexity	Abel & Painter, 2003 Ammassari et al., 2004 Carrieri et al., 2006 Golin et al., 2002 Hinkin et al., 2002 Laniece et al., 2003 Lima et al., 2009 Mehta et al., 1997 Murphy et al., 2000	Gebo et al., 2003 Parruti et al., 2006 Spire et al., 2002 Wagner, 2002 Weiser et al., 2003

Table 2. Biomedical factors assessed for impact on adherence behaviour in literature. WHO, World Health Organisation.

Psychological predictors

Several psychological barriers have been linked to nonadherence to antiretroviral regimens (see Table 3). Low levels of knowledge and understanding of HIV illness, the benefits and risks of ARV treatment, and the need for strict adherence may be an individual-level risk factor for ART adherence problems (Chesney et al., 2000; Malcolm et al., 2003; Spire et al., 2002; Wagner, 2002). Spire et al. (2002) reported results of a longitudinal observational study in which patients who believed at baseline that taking less than the prescribed doses of medications in general was not risky, were more often non-adherent to HAART at follow-up than those who thought it was (p=.03). Wagner (2002) had similar findings, with greater knowledge of HIV treatment and adherence positively correlated with electronically-monitored adherence. Patients who understood the meaning of drug resistance were more adherent according to both electronic monitoring and medication diaries. In Chesney et al.'s (2000) investigation, nonadherent patients were less sure about the statement that 'if I do not take the medications exactly as directed, the HIV in my body could become resistant to HIV medications' (19% versus 53% were 'very sure', p=.009). However, some studies have contradictory findings. Among HIV-positive adolescents (age 16–24 years) in the United Sates, health literacy (the degree to which they were found to have the 'capacity to obtain, process and understand basic health information') was not associated with antiretroviral adherence (Murphy et al., 2010, p.25). Similarly, levels of HIV knowledge were found to have no association with ART adherence levels in cross-sectional studies in Botswana (Weiser et al., 2003) and Spain (Gordillo et al., 1999).

Logically, several studies (Abel & Painter, 2003; Arnsten et al., 2007; Catz et al., 2000; Gebo et al., 2003; Kerr et al., 2005; Malcolm et al., 2003; Murphy et al., 2000) have

linked belief in or skepticism about ART drug efficacy and ART adherence. Catz et al. (2000) found that a checklist item 'I do not think treatments will help anyway' was cited as a barrier to adherence more often by nonadherent patients. In their cross-sectional study of 196 HIV-infected patients prescribed at least one antiretroviral medication, Gebo et al. (2003) found that strongly holding any of the following beliefs positively impacted antiretroviral adherence: the medication would increase longevity, sickness would result if medications were not taken, medications prevented hospitalization, and medication prevented HIV symptoms. A patient in Murphy et al.'s (2000, p.53) focus group discussions on factors impacting ART adherence stated, 'I find [taking ART] very easy because what motivates me to take it is that I want to live. And that alone helps me to remember to take my medication.' Surprisingly, others (Golin et al., 2002; Spire et al., 2002; Wagner, 2002) have noted no relationship between beliefs about antiretrovirals and antiretroviral adherence.

Patients might choose not to take prescribed ARV regimens because of concerns about anticipated side effects, or to control unwanted experienced side effects, whether or not the reported symptoms are truly established as medical and related to HAART. Qualitative and quantitative studies using interview, focus group and survey methodologies to elicit reasons for non-adherence and LTFU have confirmed this (Abel & Painter, 2003; Gardenier et al., 2010; Kerr et al., 2005; Murphy et al., 2000; Spire et al., 2002; Weiser et al., 2003), as have cross-sectional (Ammassari et al., 2004; Simon et al., 2009; Catz et al., 2000) and longitudinal (Carrieri et al., 2006; Parruti et al., 2006; Roco et al., 1999; Wagner, 2002) observational studies. A HAART patient in Abel & Painter's (2003) qualitative study explained, 'The medication makes me so sick till I say "God, it's not worth it"' (p.65).

Concerns about side effects are justified. Fellay et al. (2001) assessed the prevalence of adverse events in 1160 patients who were receiving ART, and found 70% of the sample to have experienced a clinical adverse event that was possibly (23%), probably (31%) or certainly (16%) attributable to ART, and 78% of the sample to have experienced a laboratory adverse event that was possibly (51%), probably (23%) or certainly (4%) due to ART. Applicable to this sample was the finding that the use of stavudine was independently associated with headache, lipodystrophy and a rise in serum concentrations of urate, creatine phosphokinase, lactate, cholesterol and triglyceride,

lamivudine with mood disorders and lipodystrophy, efavirenz with mood and sleep disorders, nevirapine with a rise in serum transaminase concentrations, didanosine with an increase in urate and lactate concentrations and zidovudine a trend towards an association with anaemia. Similarly, Spire et al. (2002) reported that 89.1% of their sample of 445 patients initiating HAART reported experiencing at least one symptom in the four weeks prior to the 4-month follow-up visit after initial HAART prescription, and 39.7% declared five symptoms or more. The majority (63.4% of the total sample) reported that these symptoms had been 'quite' or 'a lot' disturbing for them. Similar results showing high levels of treatment-related side effects are available elsewhere (van Oosterhout et al., 2005). Despite the prevalence of side effects associated with antiretrovirals, some investigations have found no relationship between either pre-initiation anticipation of and concern about side effects (Spire et al., 2002) or on-treatment perceived bad experience of side effects (Maskew et al., 2007) and adherence to medication or care.

In those patients who have not accepted their HIV status, medication-taking may act as an unwanted reminder of that status, and thus be intentionally or unconsciously avoided. In a number of qualitative investigations eliciting barriers to adherence, acceptance or denial of HIV status has emerged as a major factor (Abel & Painter, 2003; Catz et al., 2000; Murphy et al., 2000; Nam et al., 2008; Roberson et al., 2009; Vervoort et al., 2010). When Catz et al. (2000) elicited barriers to treatment adherence from a sample of 72 HAART patients, treatment as a reminder of HIV status was cited by 89% of participants as an adherence barrier. In Murphy et al.'s (2000) analysis of barriers to HAART adherence, 32% of patients listed 'want(ing) to forget the whole thing' as an adherence barrier. One patient in Abel & Painter's (2003) qualitative study with women on ART explained, 'When you take the medicine it's reminding [you] that you're sick' (p.65). Nam and colleagues (2008) had similar results; in their series of 32 interviews with patients on HAART for six months or more, the key concept described by participants as associated with good or excellent adherence was acceptance of HIV status. Participants explained how those who had accepted their status were able to develop a new perception of themselves as living with the virus, saying HIV was 'within me, so how can I forget?' (p.303), as compared with those who had not fully adapted to their HIV status or denied it in some way and therefore could not develop a positive and proactive relationship towards it or its treatment. One participant explained: 'The break

[in medication-taking] was caused by not accepting myself… I was just, like, curious on myself, asking to myself, why did it happen to me? Is it true that it's there?', and another 'They were looking for me at work… I was staying [away] because I was sort of embarrassed by my own things. I was embarrassed by my own fate (p.303)'. Health care practitioners agree; in the qualitative analysis of nurse consultants outlined earlier (Vervoort et al., 2010), nurses expressed that they were convinced that non-acceptance of HIV status was a risk factor for nonadherence, in that treatment could act as a confrontation of the diagnosis.

Patients' confidence or doubt in their ability to adhere, as measured by adherence self-efficacy self-rating scales, has been identified as a determinant of their antiretroviral treatment adherence in previous research (Arnsten et al., 2007; Catz et al., 2000; Chesney et al., 2000; Kerr et al., 2005). For example, a cross-sectional investigation of antiretroviral adherence found that treatment-adherent patients had higher levels of treatment adherence self-efficacy than patients who reported missing a HAART dose once per week or more during the past three months (Catz et al., 2000). Chesney et al. (2000) also found low adherence self-efficacy to be associated with nonadherence: nonadherent patients were less sure (56% versus 85%) that they would be able to take all or most of the medications as directed. Other research has not confirmed the association between medication self-efficacy and antiretroviral adherence (Golin et al., 2002; Wagner, 2002).

A major factor in treatment with HAART medication that has also been explored in several studies is depressed mood, as measured by self-report rating scales. Studies have generally found a predictive relationship, with depressive symptoms acting as a challenging barrier to achieving adherence (Ammassari et al., 2004; Arnsten et al., 2007; Carrieri et al., 2006; Catz et al., 2000; Do et al., 2010; Gordillo et al., 1999; Wagner, 2002); although this has not always been the case (Spire et al., 2002). In a study by Ammassari et al. (2004) among 135 HAART patients in Italy, patients who showed depressive symptoms were three times as likely as persons without depressive symptoms to be nonadherent to their regime. Wagner (2002) found that those patients with a current major depressive disorder had significantly lower adherence compared to others (86% versus 95%) although depressive symptomatology as measured by the Beck Depression Inventory (BDI) was not related to adherence. Studies assessing

patient-reported barriers to antiretroviral adherence have also linked depression to nonadherence (Gardenier et al., 2010; Malcolm et al., 2003; Murphy et al., 2000).

Depression is common among persons living with HIV/AIDS. In an assessment of 395 HIV-positive patients naïve to HAART, Starace et al. (2002) found the prevalence of prominent depressive symptomatology to be 15.5% across the sample, and 35.2% in those with full-blown AIDS. Ammassari et al. (2004) found depressive symtomatology in 24% of their sample of on-HAART patients. HAART (or its associated medical improvements) has been shown to curb HIV-associated depression (Low-Beer et al., 2000; Judd et al., 2000; Brechtl, Breitbart, Galietta, Krivo & Rosenfeld, 2001; Starace et al., 2002). For instance, Starace et al. (2002) observed a significant difference in the prevalence of depressive symptomatology between patients on HAART (14%) and those not on HAART (23.8%, p=0.05).

Perhaps unsurprisingly, various studies among ART-initiating (Spire et al, 2002) and on-treatment patients (Chesney et al., 2000; Do et al., 2010; Golin et al., 2002) have shown a strong association between alcohol use and/ or abuse and ability to adherence to the medication. Considering that substance abuse is a major risk factor for HIV acquisition, and the high rates of alcohol abuse in HIV-positive populations, this is a matter of concern. Golin and colleagues (2002) conducted a 48-week prospective cohort study with 140 HAART patients at a hospital HIV clinic and observed that patients who drank no alcohol in the last three days took 74.6% of their antiretroviral doses, while those who had drunk alcohol took 65.5% of theirs (p=.008). In Chesney et al.'s (2000) assessment of 75 HAART patients enrolled in clinical trials, nonadherent patients had a higher median consumption of alcoholic drinks over the past month (9 versus 2, p=.03). Patient-reported barriers to ART medication adherence concur (Malcolm et al., 2003; Ncama et al., 2008). One patients from Malcolm et al.'s (2003) qualitative interviews with patients on HAART for three months or more stated, 'When I'm drinking, I won't take the medications… they're not going to work' (p.258). On the other hand, some observational studies have found no distinctions in adherence with regard to alcohol abuse (Catz et al., 2000; Gebo et al., 2003; Hinkin et al., 2004; Parruti et al., 2006; Turner et al., 2003).

The importance of illicit drug use as a predictor of adherence behaviour has been highlighted in studies as well in Canada (Kerr et al., 2005; Lima et al., 2009), Italy

(Ammassari et al., 2004), France (Lanoy et al., 2006), Spain (Roco et al., 1999) and the United States (Gebo et al., 2003; Golin et al., 2002; Hinkin et al., 2004; Malcolm et al., 2003; Turner et al., 2003). Injection and other illicit drug users have – barring a few exceptions (Spire et al., 2002) – consistently poorer ART adherence and clinic attendance patterns than non-drug users (Ammassari et al., 2004; Gebo et al., 2003; Golin et al., 2002; Hinkin et al., 2004; Lanoy et al., 2006; Lima et al., 2009; Malcolm et al., 2003; Roco et al., 1999; Turner et al., 2003). Roco et al. (1999) compared medication adherence, clinic attendance and clinical outcomes in IDU's versus non-IDU's and noted a significant difference between the two groups at six months follow-up. In Golin and colleagues' (2002) prospective study of 140 ART patients at a public hospital-affiliated clinic, patients actively using drugs took 59% of their ART doses compared with the adherence rate of 72% for nonusers. These findings were corroborated by Gebo et al. (2003) who found that while IDU as the mode of HIV transmission was not associated with nonadherence, active illicit drug use in the past six months conferred a 2.75 times greater risk of nonadherence, heroin use a 4.46 times greater risk and binge drug use a 3.92 times greater risk.

A number of investigations have examined the impact of HIV-associated neurocognitive dysfunction on ART adherence (Albert et al., 1999; Ammassari et al., 2004; Avants et al., 2001, Hinkin et al., 2002; Hinkin et al., 2004; Levine et al., 2005; Wagner, 2002; Waldrop-Valverde et al., 2006) through objective neuropsychological testing. Not surprisingly, all but one (Ammassari et al., 2004) of these investigations report an association between neurocognitive performance and ARV adherence. The specific cognitive domains implicated are attention (Hinkin et al., 2002), speed of information processing (Albert et al., 1999; Hinkin et al., 2004; Wagner, 2002; Waldrop-Valverde et al., 2006), executive functioning (Albert et al., 1999; Avants et al., 2001; Hinkin et al., 2002; Hinkin et al., 2004; Wagner, 2002) and verbal memory (Albert et al., 1999; Hinkin et al., 2002; Hinkin et al., 2004; Wagner, 2002). Hinkin and colleagues (2002) found a mean adherence rate of 73% in their globally cognitively impaired group compared with 84% in their cognitively intact group. The study showed that global neuropsychological compromise was associated with a 2.3 times greater risk and memory dysfunction a 2.25 greater risk of adherence failure. Results of Wagner's (2002) assessment of 180 HAART patients showed that those patients with cognitive impairment indicated by at least one of the administered neuropsychological tests (California Verbal Learning Test

[CVLT], the Trail Making Test [TRAILS A and B] and the Digit Symbol subscale of the Wechsler Adult Intelligence Scale-Revised [WAIS-R]) were more likely to have lower adherence levels according to electronic monitoring, with a mean adherence of 82% as compared with 91% in those who were unimpaired.

As outlined in the previous chapter, recommended ART regimens are often complex, including two or three different drugs at specific dosages and with specific administration instructions. This excludes the often significant number of additional medications patients are also required to take, both related and unrelated to their HIV status. This complex and demanding pharmacologic regimen places high demands on cognitive and motivational factors, and thus may be particularly challenging for patients with cognitive dysfunction. Hinkin and colleagues' (2002) assessment of neurocognitive functioning and medication adherence found a significant interaction effect between cognitive impairment and regimen complexity, with cognitively impaired patients on more complex dosing schedules (defined as three doses daily as opposed to one or two) evidencing the lowest adherence rates. This was true of global cognitive impairment (across all of the cognitive domains assessed) as well as executive dysfunction and higher order attentional compromise in isolation. Typically, the simplest regimens are first line treatment. With treatment failure – which is generally due to poor adherence – regimens are switched to second and third line treatment. The upshot is therefore that those patients with a history of poor adherence are ultimately placed on the most complex regimens (Murphy et al., 2000).

Patients' own perceptions of their barriers to medication adherence also underscore the importance of cognitive functioning as a predictor of medication adherence. By far the most common reason cited by patients for nonadherence across the interviews, focus groups and surveys conducted with HIV-positive patients to elicit perceived facilitators of, and barriers to adherence is 'forgetting' to take the medications (Brigado et al., 2001; Chesney et al., 2000; Do et al., 2010; Golin et al., 2002; Murphy et al., 2000; Pienaar et al., 2006; Roberts, 2000; Spire et al., 2002; Weidle et al., 2006). For instance, Brigado et al. (2001) used surveys to elicit the main reasons for missing doses in 182 HIV-1-infected patients, and found 'forgetfulness' to be the most frequent response (48% of the sample). Murphy et al. (2000) conducted focus groups with 39 HIV-infected patients and reported that 40% of patients said they 'simply forgot' to take their medication, and a

further 21% said that while they remembered that they were required to self-medicate, they forgot how many pills they had already taken. Also using qualitative methodology, Roberts (2000) conducted a series of interviews with 28 patients on multi-drug regimens, and identified common themes expressed by participants in discussions around barriers to adherence. 'Forgetfulness' was the most frequently mentioned obstacle. Other studies have reported cognitive barriers to treatment adherence other than forgetfulness, including confusion over how many pills of each kind to take (Catz et al., 2000; Murphy et al., 2000), confusion about the appearance of the different medications and difficulty understanding complex medication instructions (Catz et al., 2000).

These findings are expected. HIV affects almost all organ systems, including the central nervous system (CNS). It is estimated that between 75% and 90% of patients will have some CNS involvement before they die, either due to the primary HIV infection (i.e. the direct effects of HIV-1 disease on the CNS that is not due to infections, tumours, cerebrovascular complications or metabolic disorders), the effects of CNS infections or neoplasms secondary to HIV-related immunocompromise, or both. In the later stages of HIV, the most common neurological condition is a chronic encephalitis. Cerebral changes tend to show on MRI as multiple small diffuse or larger bilateral subcortical – mostly white matter, but also deep gray matter – lesions and general atrophy (Lezak, 1995; Victor & Ropper, 2001). This encephalitis presents as a type of frontal-subcortical dementia, most frequently termed HIV-1-associated dementia (HAD) or AIDS dementia complex (ADC).

A considerable body of literature has documented the adverse neuropsychological consequences of HIV disease, the spectrum of presentation ranging from subtle neurocognitive complaints to frank dementia (Baldewicz et al., 2004; Castellon, Hinkin & Myers, 2000; Hinkin, Castellon, Atkinson & Goodkin, 2001; Krikorian & Wrobel, 1991; Maruff et al., 1994; Navia & Rostasy, 2005; McArthur et al., 2003; Paul, Cohen & Stern, 2002; Portegies et al., 1992; Reger, Welsh, Razani, Martin & Boone, 2002; Starace et al., 2002). Consistent with damage to subcortical regions, HIV-infected patients may present with decreased curiosity and spontaneity, disturbances of attention, and slowed mental processing (Baldewicz et al., 2004; Maruff et al., 1994; Paul et al., 2002; Reger et al., 2002;). In addition, executive dysfunction has been reported (Castellon et al., 2000; Krikorian & Wrobel, 1991), likely due to disruption of frontal-subcortical pathways. By

contrast, cortical processes like language, praxis and gnosis remain intact (Krikorian & Wrobel, 1991). Verbal memory deficits have also been shown to be associated with HIV disease. The pattern of memory deficits seen in HIV-positive patients is typical of subcortical dysfunction – evidenced on free recall tests due to poor retrieval, but improved with cueing. It has been estimated that neurocognitive impairment may be detectable in as many as 28% of asymptomatic individuals (Villa et al., 1996) and up to 40–50% of symptomatic individuals (Heaton et al., 1995).

The prevalence and severity of cognitive dysfunction due to HIV/AIDS increase as a function of disease progression (Reger et al., 2002; Starace et al., 2002; Baldewicz et al., 2004). While a few studies have noted observable cognitive disturbances in early disease (Villa et al., 1996; White, Heaton & Monsch, 1995), most report the early stages of HIV to be notably asymptomatic (Damos, John, Parker & Levin, 1997; Grassi et al., 1999; Miller et al., 1990; Selnes et al., 1995). While the conflicting findings on early disease may be difficult to reconcile, studies across the board agree that patients with later disease perform significantly worse on global and specific-domain neuropsychological testing than individuals in earlier stages. As the disease progresses, patients present with increased cognitive dysfunction. For instance, in their assessment mentioned earlier of 395 HIV-positive patients naïve to HAART, Starace et al. (2002) found the global prevalence of neurocognitive impairment (defined as an impaired performance on at least two neuropsychological tests) to be 18% across the sample, and 35% in those with full-blown AIDS.

HAART is able to achieve enduring suppression of HIV replication, resulting in dramatic improvements in HIV-related diseases (Paredes et al., 2000). However, many of the antiretroviral agents currently available do not penetrate the blood-brain-barrier (Gartner, 2000). While ziduvodine, stavudine and lamivudine have relatively high levels of CNS penetration, PI's are highly protein bound and have been shown to have poor CNS penetration (Dore et al., 1999). Some literature suggests that since HAART decreases systemic HIV viral load, the CNS may serve as a sanctuary for the virus and neurological dysfunction (such as HIV dementia) may result when the CNS serves as a reservoir for virological escape (Anderson, 1996; Melton, Kirkwood & Ghaemi, 1997; Portegies, 1997).

The literature on the impact of HAART on improving HIV-associated cognitive dysfunction has yielded some contradictory findings. Some studies have shown that cognitive dysfunction persists, despite HAART initiation (Starace et al., 2002). Consequently, patients on HAART may remain susceptible to HIV-associated cognitive impairment despite viral suppression in other tissues (Deutsch et al., 2001), meaning that should HIV-associated cognitive dysfunction impact upon capacity to adhere, there is good reason to anticipate that this relationship would persist beyond the initiation of ARV treatment. In their evaluation of HIV-positive patients naïve to HAART as mentioned earlier, Starace et al. (2002) found that patients on HAART did no better on neuropsychological testing than those not on HAART. In fact, and surprisingly, cognitive dysfunction was more prevalent in those on HAART, although the authors suggested the plausible explanation that those patients presenting with neuropsychological symptoms may have been initiated sooner onto HAART than their cognitively intact counterparts, making the two groups within the observational cohort (on and off HAART) qualitatively different to begin with.

Factor	Significant result	Non-significant result
HIV/ ART knowledge and health literacy	Chesney et al., 2000 Malcolm et al., 2003 Spire et al., 2002 Wagner, 2002	Gordillo et al., 1999 Murphy et al., 2010 Weiser et al., 2003
Attitudes towards HIV/ ART	Abel & Painter, 2003 Arnsten et al., 2007 Catz et al., 2000 Gebo et al., 2003 Kerr et al., 2005 Malcolm et al., 2003 Murphy et al., 2000	Golin et al., 2002 Spire et al., 2002 Wagner., 2002
Concerns about/ perceived side effects	Ammassari et al., 2004 Abel & Painter, 2003 Carrieri et al., 2006 Catz et al., 2000 Gardenier et al., 2010 Kerr et al., 2005 Murphy et al., 2000 Parruti et al., 2006 Roco et al., 1999 Simon et al., 2009 Spire et al., 2002 Wagner, 2002 Weiser et al., 2003	Maskew et al., 2007 Spire et al., 2002

Denial/ acceptance of HIV status	Abel & Painter, 2003 Catz et al., 2000 Murphy et al., 2000 Nam et al., 2008 Roberson et al., 2009 Vervoort et al., 2010	-
Self-efficacy	Arnsten et al., 2007 Catz et al., 2000 Chesney et al., 2000 Kerr et al., 2005	Golin et al., 2002 Wagner, 2002
Depression	Ammassari et al., 2004 Arnsten et al., 2007 Carrieri et al., 2006 Catz et al., 2000 Do et al., 2010 Gardenier et al., 2010 Gordillo et al., 1999 Malcolm et al., 2003 Murphy et al., 2000 Wagner, 2002	Spire et al., 2002
Alcohol use	Chesney et al., 2000 Do et al., 2010 Golin et al., 2002 Malcolm et al., 2003 Ncama et al., 2008 Spire et al., 2002	Catz et al, 2000 Gebo, Keruly & Moore, 2003 Hinkin et al, 2004 Parruti et al, 2006 Turner et al, 2003
Illicit drug use	Ammassari et al., 2004 Gebo et al., 2003 Golin et al., 2002 Hinkin et al., 2004 Kerr et al., 2005 Lanoy et al., 2006 Lima et al., 2009 Malcolm et al., 2003 Roco et al., 1999 Turner et al., 2003	Spire et al, 2002
Neurocognitive functioning	Albert et al., 1999 Avants et al., 2001 Brigado et al., 2001 Catz et al., 2000 Chesney et al., 2000 Do et al., 2010 Golin et al., 2002 Hinkin et al., 2002 Hinkin et al., 2004 Levin et al., 2005 Murphy et al., 2000 Pienaar et al., 2006 Roberts et al., 2000 Spire et al., 2002 Wagner, 2002 Waldrop-Valverde et al., 2006 Weidle et al., 2006	Ammassari et al, 2004

Table 3. Psychological factors assessed for impact on adherence behaviour in literature.

Social predictors

Various social factors have been linked with adherence behaviour (see Table 4). Some investigations have shown that people who are not married have more difficulty adhering to antiretroviral regimens (Parruti et al., 2006; Spire et al., 2002), whereas others have observed higher adherence rates in those who are single (Wagner, 2002). Using patient self-report and pharmacy records as adherence outcomes, Parruti et al. (2006) followed 171 patients in Italy for a minimum of 24 weeks and up to eight years to assess the impact of various potential predictors on adherence rates, and showed that those patients who were married were two times less likely to experience adherence failure (p=.03). By contrast, some studies have reported no association between marital or relationship status and ART adherence (Golin et al., 2002; Weiser et al., 2003) or loss to follow-up (Zacariah et al., 2008). Clearly, this is an area requiring further investigation.

Lack of disclosure has also been reported as a barrier to adherence (Abel & Painter, 2003; Catz et al., 2000; Do et al., 2010; Malcolm et al., 2003; Maskew et al., 2007; Murphy et al., 2000; Nam et al., 2008; Ncama et al., 2008; Richard et al., 2009; Weiser et al., 2003). Non-disclosure can lead to circumstances and situations in which taking the prescribed antiretrovirals or attending clinic visits is difficult. Patients may need to avoid taking medications in public spaces – including communal areas of the home or workplace – in order to avoid inadvertent exposure (Abel & Painter, 2003; Maskew et al., 2007; Murphy et al., 2000; Weiser et al., 2003); where avoidance is impossible, doses may be missed or delayed. Patients may also feel uncomfortable going to HIV clinic visits due to confidentiality concerns (Weiser at al., 2003). Nondisclosure not only leads directly to avoidance of medication-taking or clinic attendance in certain circumstances, but prevents patients from accessing social support. Barriers to disclosure tend to include fear of stigmatization and social rejection (Do et al., 2010). Despite the country's high HIV prevalence rates and efforts to destigmatize the disease, stigma and discrimination surrounding HIV is sadly still rife in South Africa (Ncama et al., 2008). Stigma continues to result in rejection by family and partners, ostracism from community and even loss of employment. To avoid such unwanted consequences, patients may avoid disclosure, thereby impacting their ability to adhere. Using a checklist to elicit barriers to treatment adherence in HAART patients, Catz et al. (2000) found that 71% of their sample cited not wanting other people to know their HIV status as a barrier to

medication adherence. A patient in Murphy et al.'s (2000, p.53) focus group discussions on barriers to ART adherence in a United States sample, a patient explained, 'During May and June and July, I may go home to Memphis and stay anywhere from two to four months. So, the biggest problem I was having there was ducking and dodging my nieces and nephews and sister-in-law, in taking my medication.' Other investigations into the impact of disclosure on adherence behaviour have found that disclosure has no bearing on adherence rates (Spire et al., 2002).

Patients may be more likely to miss ART doses if they do not have sufficient social support (Carrieri et al., 2006; Catz et al., 2000; Gardenier et al., 2010; Gordillo et al., 1999; Spire et al., 2002). Gardenier et al. (2010) conducted a recent study that addressed social support and adherence in a sample of HAART patients with comorbid medical or psychiatric conditions, and found significant differences between levels of social support reported by adherent versus nonadherent patients. These differences were observed on the overall social support score of the social support scale used, both of its two indices (emotional support and instrumental support), and four of its six component subscales (guidance, attachment, social integration and reassurance of worth). In Gordillo et al.'s (1999) earlier cross-sectional study of HAART patients assessing the role of various socio-demographic and psychosocial variables on self-reported and pill count adherence, having good self-perceived social support meant the likelihood of achieving adherence success doubled.

Qualitative data on patient-reported adherence barriers concurs (Malcolm et al., 2003; Murphy et al., 2000; Nam et al., 2008). Participants in Nam et al.'s (2008) one-to-one in-depth interviews examining barriers to and facilitators of antiretroviral adherence explained that finding a confidante who could both share their disease burden and encourage hope and a will to live positively for the future was beneficial. One participant explained, 'She told me you have to… "eat well, sleep well. You are going to live a normal life better than somebody who is negative if you just take care of yourself and you just take the medicines"' (p.305). Significant others may even take on the role of reminding the patient to take the medication (Malcolm et al., 2003; Murphy et al., 2000). A patient in Murphy et al.'s (2000, p.53) analysis of facilitators of and barriers to HAART adherence said, 'My wife keeps me on schedule… Regardless of what I'm doing, if I'm awake, if I'm sick over the toilet or something like that [laughs], she gives them to me.'

The social support may be further strengthened if the supportive other is also HIV-positive or even on antiretrovirals themselves, facilitating the development of informal 'buddy systems'. Another of Murphy et al's participants explained, 'We call each other… "Take the pills and have you taken yours?" If you have somebody who's on the same schedule as you, it's easier because then you can… keep up with each other. It helps.' Beneficial and supportive social networks may be informal as just described, but do include formal structures such as church networks, sports clubs and support groups (Malcolm et al., 2003; Nam et al., 2008). Other assessments of the relationship between levels of social support and ART adherence have noted no relationship (Golin et al., 2002; Kerr et al., 2005; Ncama et al., 2008).

Household size and composition has also been studied for its impact on ART patient adherence (Do et al., 2010; Gebo et al.,2003; Wagner, 2002). Living with more people may lead to more possibilities for social support, or greater risk of exposure if no disclosure has taken place. Larger household size may also be a marker of low socio-economic status. In an assessment of 180 patients who had been on HAART for one month or more, Wagner (2002) observed that living alone was associated with greater adherence as measured by both electronic monitoring and self-report, and a large household with lower adherence as measured by self-report and medication diaries. Some studies have seen no relationship between number of people sleeping in the home and adherence (Do et al., 2010; Gebo et al., 2003).

Studies assessing patients on ARV's indicate the importance of the patient-health care provider relationship in determining a patient's adherence rates (Abel & Painter, 2003; Gardenier et al., 2010; Golin et al., 2002; Malcolm et al., 2003; Murphy et al., 2000; Nam et al., 2008; Roberson et al., 2009; Spire et al., 2002). Poor communication quality and clarity (Murphy et al., 2000; Roberson et al., 2009; Spire et al., 2002), difficult interactions, breaches in confidentiality and lack of provider respect for patients (Roberson et al., 2009) and low patient trust in provider competence (Malcolm et al., 2003; Spire et al., 2002) have all been observed or reported to negatively impact adherence behaviour. One ART patient in Roberson et al.'s (2009) exploration of female prison inmates' facilitators of and barriers to adherence explained, 'It hurts [being treated like you] don't matter' (p.56), and another from Malcolm et al.'s (2003) qualitative

assessment said, 'All [the doctor's] going to do is what a drug company tells him' (p.257).

Conversely, a positive relationship and supportive health care provider can enhance patients' adherence (Abel & Painter, 2003; Gardenier et al., 2010; Golin et al., 2002; Malcolm et al., 2003; Nam et al., 2008; Roberson et al., 2009). A qualitative study of 32 adults on ART aimed to deepen understanding of the predictors of adherent behaviour (Nam et al., 2008) and found that some patients considered clinicians confidantes in their disease process ('like a sister or mother', p.304) and transmitters or messages of hope, which they said contributed to their self-respect, sense of hope and good adherence. In Golin et al.'s (2002) cohort of HAART patients, while the number of specific provider counseling behaviours (things the provider had done to increase adherence), overall patient satisfaction with the health care at the clinic, and the extent of the continuity of care (whether or not they saw the same doctor at each visit) were not predictive of adherence, patients who reported high levels of trust in their health care providers were significantly more likely to adhere well subsequently (p=.03). Results from other investigations show no relationship between patient-provider relationship and medication adherence (Gordillo et al., 1999).

Factor	Significant result	Non-significant result
Relationship status	Parruti et al., 2006 Spire et al., 2002 Wagner, 2002	Golin et al., 2002 Weiser et al., 2003 Zachariah et al., 2008
Disclosure	Abel & Painter, 2003 Catz et al., 2000 Do et al., 2010 Malcolm et al., 2003 Maskew et al., 2007 Murphy et al., 2000 Nam et al., 2008 Ncama et al., 2008 Richard et al., 2009 Weiser et al., 2003	Spire et al., 2002
Social support	Carrieri et al., 2006 Catz et al., 2000 Gardenier et al., 2010 Gordillo et al., 1999 Malcolm et al., 2003 Murphy et al., 2000 Nam et al., 2008 Spire et al., 2002	Golin et al., 2002 Kerr et al., 2005 Ncama et al., 2008
Household size and composition	Wagner, 2002	Do et al., 2010 Gebo et al., 2003

Patient-provider relationship	Abel & Painter, 2003 Gardenier et al., 2010 Golin et al., 2002 Malcolm et al., 2003 Murphy et al., 2000 Nam et al., 2008 Roberson et al., 2009 Spire et al., 2002	Gordillo et al., 1999

Table 4. Social factors assessed for impact on adherence behaviour in literature.

Miscellaneous predictors

Making use of certain reminder tools has been reported to enhance ART adherence (Abel & Painter, 2003; Golin et al., 2002). After a follow-up of 12 months, Golin et al. (2002) showed that ART patients who used the most (upper quartile) adherence aids took on average 76% of their ARV doses, while patient who used no adherence aids took 68%. In a pilot study exploring factors that influence adherence among women in the United States, participants explained that using strategies like alarm clocks, having family members remind them and writing reminder notes were central maintaining their adherence (Abel & Painter, 2003).

Research has also highlighted the importance of costs and time associated with clinic visits for HAART adherence. In developing countries, the economic burden of HIV/AIDS on households has been shown to be cumulative and catastrophic. Studies have consistently shown that patients who are required to pay for their antiretroviral drugs adhere more poorly (Bisson et al., 2006; Braitstein et al., 2006; Ivers, Kendrick & Doucette, 2005; Laniece et al., 2003; Weiser et al., 2003; Zachariah et al., 2008). Although the costs of antiretrovirals and medical care are oftentimes covered by universal healthcare systems, and this is true of the South African situation, indirect user-end costs, including cost of travel and loss of casual labour work due to clinic appointments, can pose significant barriers to treatment success. Studies have shown that ART patients experience difficulty leaving work to make clinic appointments (Maskew et al., 2007; Weiser et al., 2003), sometimes risking exposure and job loss, and for the contract worker, missing a day's wages (Maskew et al., 2007). Those who live far from ARV facilities struggle to travel long distances to ART clinics (Catz et al., 2000; Morse et al., 1995; Weiser et al., 2003) and incur the associated travel costs (Lubega et al., 2010; Maskew et al., 2007).

One recent study described the results of interviews and focus groups with clinic managers, patients currently in pre-ARV care, patients who had dropped out of pre-ARV care and families and friends of people living with HIV/AIDS on the reasons for drop-out from pre-ARV care in eastern Uganda (Lubega et al., 2010). The study found that difficulty affording transport costs was mentioned often as a barrier to clinic attendance. Catz et al. (2000) found that difficulty traveling to clinic appointments was a barrier to medication adherence significantly more often cited by nonadherent patients than adherent patients. Patients also mentioned long waiting lines as a deterrent. One female who had dropped out of pre-ARV care remarked: 'Why should I waste money on transport to get nothing I rather spend it on food and fees for my children.' (p.156). In Morse et al.'s (1995) series of interviews conducted with 18 clinicians at various community centers conducting ARV trials, one of the most frequently mentioned patient barriers to recruitment, retention and adherence was transportation (endorsed by 21% of clinicians). There are exceptions however. Some observational studies have however found no association between travel time from home to ART clinic and medication adherence (Do et al., 2010), virological failure (van Oosterhout et al., 2005) or adherence to care (Karcher et al., 2007).

Factor	Significant result	Non-significant result
Use of reminder tools	Abel & Painter, 2003 Golin et al., 2002	-
Costs and time associated with medication-taking and clinic visits	Bisson et al., 2006 Braistein et al., 2006 Catz et al., 2000 Ivers et al., 2005 Laniece et al., 2003 Lubega et al., 2010 Maskew et al., 2007 Morse et al., 1995 Weiser et al., 2003 Zachariah et al., 2008	Do et al., 2010 Karcher et al., 2007 van Oosterhout et al., 2007

Table 5. Miscellaneous factors assessed for impact on adherence behaviour in literature.

Summation and next steps

The above review has shown that the literature suggests a diverse array of demographic, biomedical, psychological and social factors that may impact ART adherence and/ or adherence to HIV care. The studies outlined have been conducted

using various methodologies, many of which – likely due to resource constraints – have been less than ideal. Most studies have used self-report as a means of assessing adherence, rather than objective measures like pill count, HIV RNA level tests, electronic monitoring devices, pharmacy records or therapeutic drug monitoring. Almost all have been conducted with participants already on ART, meaning we have little knowledge of baseline predictive factors. Most studies are cross-sectional, limiting our understanding of causality. Few have included psychological or social assessments, and even fewer neuropsychological testing. Most literature stems from developed settings, oftentimes IDU, MSM or prison populations, and it is not known how applicable these results are to the general South African ART-initiating population.

Partly due to conflicting methodologies and partly due to differing patient populations, results across most constructs have been inconsistent and are in need of further investigation. There is an urgent need to conduct methodologically-sound population-specific research in a low-resource sub-Saharan African population to investigate the predictors of adherence behaviour in this context. This study sets out to do that, using an objective measure of adherence, assessing psychological, social and neuropsychological assessments, within an ART-initiating population, using a longitudinal study design.

CHAPTER 3

Methods

Design

Longitudinal cohort study.

Although much of the previously work in this area has been conducted using cross-sectional designs, it was determined that a longitudinal cohort study would be the most effective design to evaluate the causative role that demographic and biopsychosocial factors have on adherence outcomes.

Population and sampling

Study setting

The study was conducted in the Nyanga district, a peri-urban settlement close to Cape Town (geographical location in Figure 2a), South Africa. The district has an estimated population of 350,000 (City of Cape Town, 2003) and an HIV prevalence of 29% (Western Cape Provincial Department of Health, 2007). According to the last census, the population of the suburb of Guguletu within the Nyanga district was 99% Black African and 95% Xhosa-speaking. Thirty-nine percent of the population live in shacks/ informal dwellings, 71% of adults age 20 years and over have not completed Grade 12, and 51% of the 'economically-active' population (age 15–65 years) is unemployed. Sixty-seven percent of earners receive less than R1,600 per month (Statistics South Africa, 2001). The geographical location of the district is shown in Figure 2b.

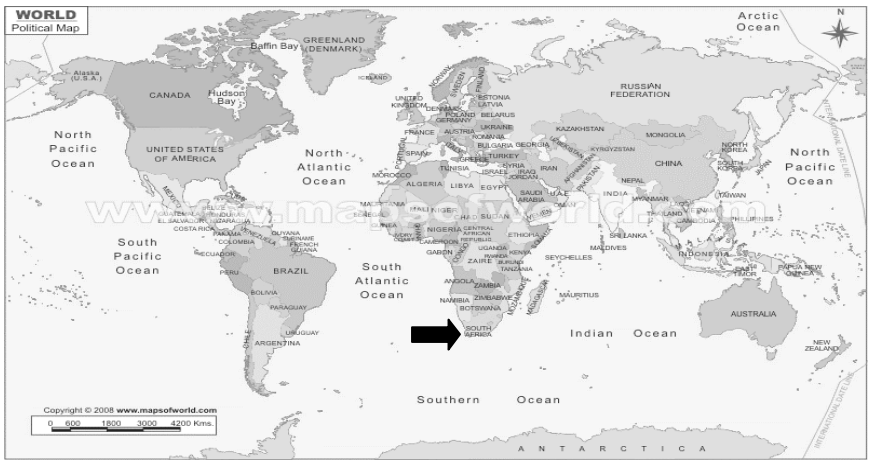

Figure 2a. Geographical location of Cape Town, South Africa (©2009 Google – Map data).

Figure 2b. Geographical location of Nyanga district, Western Cape (©2009 Google – Map data).

Patients were recruited from the well-established Hannan Crusaid Treatment Centre (HCTC). The clinic was set up in 2002 as a result of a pilot programme predating the national roll-out of ART, by the Desmond Tutu HIV Centre (DTHC) – a not-for-profit HIV research and academic centre affiliated with the University of Cape Town – and a UK-based charity fund, Crusaid. The clinic is one of the longest-running public-sector community-based ART programmes in sub-Saharan Africa (Bekker et al., 2006). It has subsequently been integrated into the Provincial Administration Western Cape's (PAWC) ART roll-out programme. Today, the clinic is managed as a public sector facility offering comprehensive outpatient primary HIV/AIDS care by PAWC in collaboration with the DTHC. The clinic is a free-standing structure within the grounds of the local PHC clinic, the Guguletu Community Health Centre. A secure supply of drug is maintained at all times, and as part of the national Department of Health programme, there are no direct

user fees incurred for patients accessing any of the medications or clinical services. Patients enter the clinic through voluntary counseling and testing (VCT), inpatient and outpatient referrals. Patients requiring inpatient care are referred on to a nearby 200-bed secondary hospital, GF Jooste Hospital. The clinic had initiated 3,162 HIV-infected patients on antiretroviral therapy between 2002 and the start of the study, primarily drawn from the local community.

Patients' first clinic visit (–4 weeks) is followed by a screening visit two weeks later (–2 weeks), where CD4 + cell count, viral load, liver function test (LFT) and full blood count (FBC) are performed, followed by a treatment initiation visit (0 weeks). This pre-treatment visit schedule is truncated for women presenting in the later stages of pregnancy. After ART initiation, standard medical follow-up occurs at +4, +8 and +16 weeks, and at 16-week intervals thereafter (those initiated on nevirapine [NVP] are seen at +2 weeks as well in order to assess for potential hepatoxicity). Pharmacy visits – where a supply of medications is provided and pill counts are performed – are conducted at the standard medical follow-ups as just described, as well as at +12 weeks and at the midpoint between the 16-week intervals between medical follow-ups (i.e. 8-weekly after the first 16 weeks). Viral load, CD4+ cell count, LFT and FBC measurements are performed at 16-week intervals during treatment. Patients may visit the clinic outside of the visit schedule for medical problems that arise. Duration of visits excluding waiting time varies between 15 and 45 minutes, with highest durations at early ART initiation. Patients are asked to bring their pill bottles to each clinic visit, where pill counts are routinely performed. Virological failure is defined as two consecutive viral load levels above 1,000 copies/mL, and an indication for initiating second line therapy.

Antiretroviral treatment was available at the time of the study according to the Department of Health (2004) guidelines, in accordance with the WHO's 2002 recommendations for scaling up ART in resource-limited settings. Patients were medically eligible for HAART if they had a CD4+ cell count of less than 200 cells/μL or a WHO stage IV disease condition. (The national guidelines have since been updated to include pregnant women at CD4+ cell counts of less than 350 cells/μL and all patients co-infected with TB, regardless of CD4+ cell count [Department of Health, 2010b]). Treatment was also prescribed according to Department of Health (2004) guidelines and WHO (2002) recommendations, with first-line triple therapy combinations of two NRTI's

(stavudine [d4T] and lamivudine [3TC]) combined with an NNRTI (either efavirenz [EFV] or NVP, with NVP substituted for EFV in women of child-bearing potential, and EFV preferred in those with TB co-infection). (The updated national guidelines reduce the use of d4T due to associated peripheral neuropathy, lipodystrophy and hyperlactataemia, replacing it with tenofovir [TDF], Department of Health, 2010b). If patients failed first-line therapy, they moved on to a PI-based second-line treatment including combinations of lopinavir/ritonavir (LPV/r), AZT and ddI (see Table 6). Individual drugs were substituted in the event of severe toxicity. All medications were registered with the Medicines Control Council of South Africa, and sourced from a single pharmaceutical supplier.

Medication	Type	Dosing	Possible side effects
First-line ART			
d4T (stavudine)	NRTI	1 x 30mg (<60kg); 1 x 40mg (>60kg) 12-hourly	Peripheral neuropathy, gastrointestinal, headache, elevated AST and ALT levels
3TC (lamivudine)	NRTI	1 x 150mg 12-hourly	Nausea, headache, fatigue, insomnia
EFV (efavirenz)	NNRTI	2 x 200mg (<40kg) 1 x 600mg (>40kg) once daily at night	CNS effects, rash, elevated AST and ALT levels, contraindicated in pregnancy
NVP (nevirapine)	NNRTI	1 x 200mg once daily for 14 days, thereafter 1 x 200mg 12-hourly	Rash, Stevens-Johnson syndrome, fever, elevated AST and ALT levels, nausea, headache
Second-line ART			
LPV/r (lopinovir/ritonavir)	PI	3 x 133/33mg 12-hourly [refrigerated]	Nausea, diarrhea, taste perversion, elevated AST and ALT levels, asthenia, headache, vomiting, anorexia, perioral dysesthesia, hypertriglyceridemia, hypercholesterolemia
AZT (zidovudine)	NRTI	1 x 300mg 12-hourly	Headache, fatigue, neutropenia, nausea, anemia, insomnia, vomiting, myalgia, myopathy
ddI (didanosine)	NRTI	4 x 100mg (>60kg) 2 x 100mg + 1 x 50mg (<60kg) once daily [on empty stomach; dissolved in water]	Pancreatitis, diarrhea, peripheral neuropathy, elevated AST and ALT levels

Table 6. ART drugs available at Hannan Crusaid Treatment Centre (Department of Health, 2004; Max & Sherer, 2000; WHO, 2002). NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; AST, aspartate amino transferase; ALT, amino alanine transferase; CNS, central nervous system.

The clinic's adherence model consists of a treatment readiness programme prior to ARV initiation and a system of both in-clinic and outreach counseling once treatment begins. Both the treatment readiness programme and the on-treatment counseling are administered by a team of approximately thirty counselors. The counselors are lay persons who have been trained in HIV/AIDS and ART and who themselves are HIV-infected. Many of them are on ART. At the first clinic visit (–4 weeks), each new patient is assigned to a particular counselor for ongoing counseling support for the duration of his or her retention in care at the clinic. The assignment is based in part on geographical location; patients are matched with counselors who live in close proximity to them in order to facilitate home visits. The treatment readiness programme is compulsory, and comprises three education sessions and a home visit every two weeks pre-treatment. The education sessions are run by the lay counselors and administered to a group of patients at the HCTC. The treatment readiness decision is made at –1 week at a weekly interdisciplinary case review team meeting, attended by clinic doctors, nurses and adherence counselors, and is based on –2-week blood results and psychosocial treatment readiness (as determined by attendance at the three treatment readiness sessions, and the counselor's impressions of the home visits). Despite the advantages of this facility – extensive experience, academic expertise and additional donor support – the strain of rapid programme expansion is evident. Since 2006, the number of employed lay counselors has remained constant at 30, despite the significant increase in patient numbers from 2,503 to 3,162. The ratio of patients to counselor has increased from 13:1 in 2002/2003 to 98:1 in 2007/2008.

Once patients are on treatment, the generalized adherence programme involves a home visit each month until viral suppression is achieved, and every three to four months thereafter. Where the attending clinician identifies an adherence concern (a pill count adherence of less than 85% or a viral load greater than 1,000 copies/mL at any follow-up visit during ART), the patient is moved to the clinic's 'Red Alert' group, and a targeted adherence intervention is commenced. Patients who move onto Red Alert are required to re-attend the three treatment readiness education sessions, and are issued with a pill box and a dosing diary. From that point on until their adherence increases to over 85% and/ or their HIV RNA load becomes undetectable again (<50 copies/mL) (a repeat viral load measurement is taken six to eight weeks after identification as Red Alert), patients

are marked for attention with a red sticker on their clinic folder, the frequency of their clinic visits (and the associated pill counts) increases to monthly, and the frequency of their home visits increases to weekly. A second viral load measurement >1,000 copies/mL is defined as virological failure and triggers a switch to second-line therapy.

The HCTC facility was chosen as an ideal setting for this research for a number of reasons. First, the study set out to enroll patients at HAART initiation so as to ensure that any biopsychosocial differences between adherent and nonadherent patients were pre-existing, as opposed to a consequence of adherent or nonadherent behaviour; in the 12 months preceding the data collection period of this study, 685 patients initiated treatment at the center, suggesting a large potential participant base for the upcoming 12 months. Second, in order to assess medication adherence in a methodologically-rigorous way (see review of various adherence methodologies later in this chapter), a combination of two objective measures of adherence behaviour was chosen: pill counts and viral load tests. Pill counts are performed routinely at HCTC at each pharmacy visit, despite the fact that they are not mandated in the national (Department of Health, 2004; 2010b) or provincial (PAWC, 2004) protocols and rarely occur in the public sector, likely because they are particularly labour-intensive. HIV viral load measurement is also performed routinely at HCTC at 16-week intervals on treatment, even though it is only recommended in the national and provincial protocols to be performed 6-monthly, due to high cost and insufficient laboratory facilities. Finally, the allocation of each patient to a lay counselor is not just an effective adherence intervention, but a valuable means of determining true patient outcomes; those patients who fail to attend scheduled clinic visits are traced, and so the determination of patients as LTFU in the programme is likely to be true LTFU, as opposed to hidden mortality or clinic transfer.

Eligibility and recruitment

Patients initiating HAART between April 2007 and January 2008 were invited to participate. Participation in the study was voluntary. For the purpose of the study, HAART was defined as any combination of three or more ARV agents that included at least one NNRTI or PI. Inclusion criteria for the study were: adults aged 18 years and older, scheduled for self-administered HAART, and able and willing to provide informed consent. Inclusion criteria were deliberately broad as the study intended to enroll the

wide range of patients presenting to the clinic, so that any results, outcomes and conclusions were applicable to the heterogeneous patient base.

A total of 150 patients initiating treatment were recruited via staff referrals and assessed for eligibility.

Procedures

Data collection

Across the study, five types of data were collected:

1. Psychological and social information was elicited through face-to-face interviews conducted within seven days of HAART initiation (Week 0)
2. Demographic and clinical data were extracted from clinic files at the time of the interview (Week 0)
3. Pill count adherence was measured across the first 16 weeks of HAART through routine pill counts at the clinic and subsequent calculations by the researcher (Week 16)
4. Virological suppression was measured at the 96-week visit through routine viral load monitoring at the clinic (Week 96)
5. LTFU was assessed at 96 weeks through assessment of clinic files and discussions with the lay counselor to whom the patient had been assigned (Week 96)

See Figure 3 for the data collection timeline.

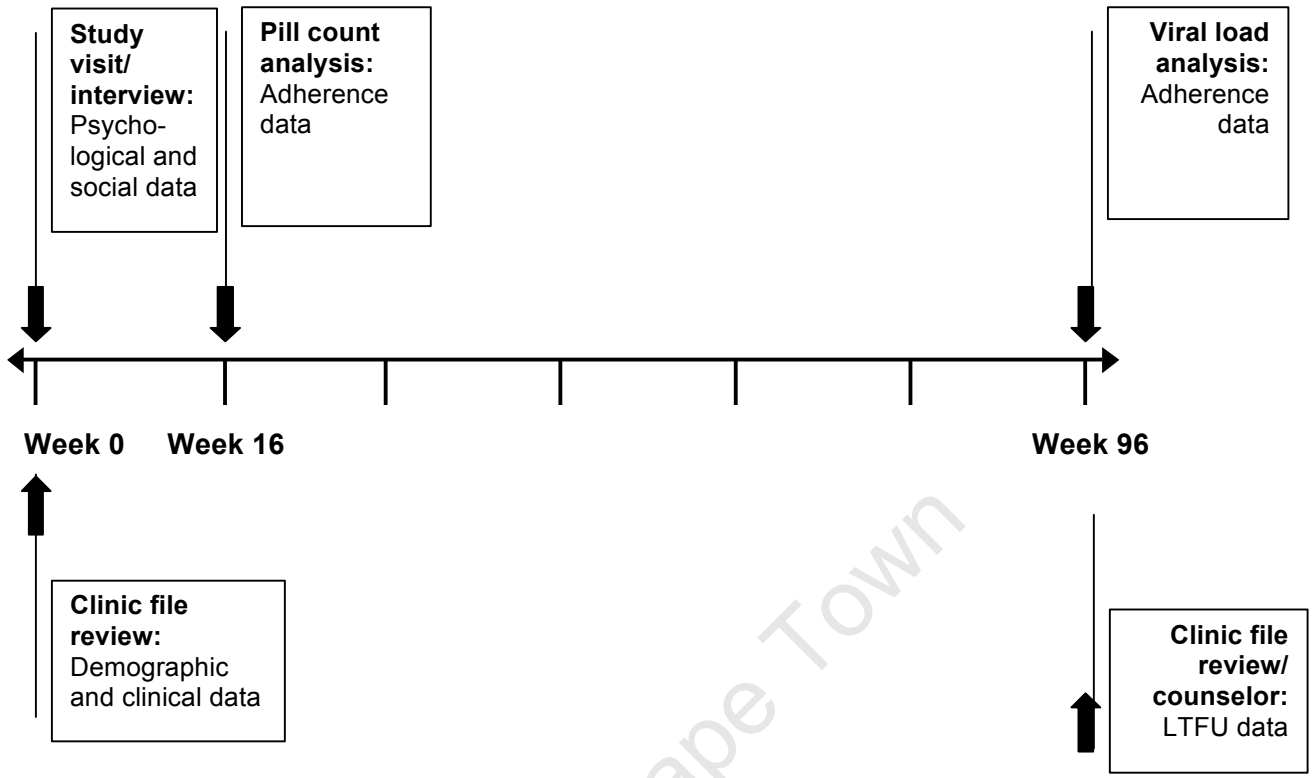

Figure 3. Data collection timeline.

Study visit

The study visit took place in a private room in an outbuilding of the HCTC, on its premises. This outbuilding was chosen in order to facilitate ease of participation due to proximity to the clinic, whilst also presenting the interview as separate from standard clinical care, and therefore decrease the likelihood of participants responding according to perceived social desirability. The visit lasted approximately two hours. A short break was offered to participants between the first and second hours. In a few cases, participants completed the second hour the following day. At the study visit, each participant was evaluated in a face-to-face interview, using a structured Biopsychosocial Questionnaire (Appendix A), a validated depression scale (Appendix B), a validated alcohol abuse scale (Appendix C), and a validated neuropsychological test battery (list of tests to follow in chapter). A translator was available to assist where necessary, and was used in 49 (33%) of the interviews. The study visit was scheduled to take place as close as possible to, but a maximum of seven days from, the clinic visit at which patients were initiated on ART. Twenty-one (14%) of the interviews were conducted on the day of the clinic visit, and a further 53 (35%) on the day before or the day after the visit. One

hundred and thirteen (75%) of the interviews took place within three days of the clinic visit. Participants received a R50 stipend for study participation and attendance at the study visit, and signed a Receipt of Reimbursement Form (Appendix D).

For components of the interview that may have elicited social desirability bias or performance anxiety – specifically, the alcohol abuse scale, depression scale, and neuropsychological test battery – an introductory statement was used that normalized the 'undesirable' behaviour or poor performance, and acknowledged the associated challenges.

Clinic file review

At the time of the study visit, patient clinic files were reviewed, and relevant medical information extracted, including retrospective data about the patient's history: date of testing HIV positive and reason for test, previous prescriptions of antiretroviral regimens and clinical episodes, history of mental illness, history of neurological deficits, and comorbid and chronic health conditions. Standardized clinical and biomedical data was also extracted, including: WHO HIV disease stage, most recent HIV-1 RNA level, most recent CD4+ cell count and prescribed ARV schedule.

Measures

Biopsychosocial Questionnaire

The Biopsychosocial Questionnaire was developed for the purposes of the present study, based on the literature outlined in the previous chapter which links certain demographic, biomedical, psychological and social constructs with antiretroviral medication adherence and retention to care, and after consultation with several experts in the field of antiretroviral treatment and adherence. The questionnaire was informed by cognitive theories like the Health Belief Model (Rosenstock, 1974) and the Theory of Reasoned Action (Terry, Gallois & McCamish, 1993) in their recognition of 'subjective' factors like perceived disease severity and self-efficacy for adherence to the regimen. The questionnaire was piloted with five HAART-initiating patients from a similar population prior to data collection and modified accordingly.

The questionnaire comprised 40 primary and 12 supplementary questions and explored 10 domains: demographics (7 items); perceived HIV symtomatology (2 items),

understanding of HIV illness, information about own biomedical status, such awareness of latest CD4+ cell count and viral load test results, the implications of nonadherence, understanding of resistance and the names of each medication in the prescribed ART regimen (6 items), attitudes towards and concerns about HIV and ART, including belief in ART efficacy and concern about anticipated side effects (7 items), confidence in own ability to adhere to ARV regimen (adherence self-efficacy) (1 item), illicit drug use (2 items), perceived social support and disclosure (15 items); perceived quality of relationship with health care provider, including level of trust and the extent to which able to communicate problems and challenges to the provider during the consultations (6 items), planned use of adherence aids (1 item), and proximity to clinic and associated time and travel costs (5 items). The Biopsychosocial Questionnaire is reproduced in the appendix (Appendix A).

Depression scale

Depressive symptomatology was assessed with the Centre for Epidemiological Studies in Depression Scale (CES-D) (Radloff, 1977). The CES-D is a 20-item self-rating scale that assesses symptoms associated with depression. Respondents report on a 4-point scale, using response anchors ranging from 0 (*rarely or none of the time*) to 3 (*most or all of the time*) for how often during the past week they had experienced each symptom. Sample items include 'I was bothered by things that usually don't bother me' and 'I had crying spells'. A higher score indicates greater levels of depressive symtomatology. Standard clinical cut-offs were used to define severity of depressive symptoms: a score of 15 or below indicated none or low depressive symptomatology, a score in the range of 16–21 indicated symptoms associated with mild to moderate depression, and a cut-off point of 22 or higher indicated symptoms associated with a major depressive episode. This measure has been validated for use in community settings to detect the presence of depressive symptoms (Boyd, Weissman, Thompson & Meyers, 1982; Meyers & Weissman, 1980; Roberts & Vernon, 1983; Weissman, Sholomskas, Pottenger, Prusoff & Locke, 1977) and has been validated in many cross-cultural samples (Ghubash, Daradkeh, Al Naseri, Al Bloushi & Al Daheri, 2000; Iwata & Buka, 2002; Munet-Villaro, Folkman & Gregorich, 1999), ethnic groups (Guarnaccia, Angel & Worobey, 1989; Roberts, 1980; Roberts, Rhoades & Vernon, 1990) and used extensively in persons with HIV infection (Burrack et al., 1993; Catz et al., 2000; Cook et al., 2004; Duran et al., 2001; Himelhoch, Medloff & Oyeniyi, 2007; Ickovics et al., 2001; Lyketsos et al., 1996;

McClure, Catz, Prejean, Brantley & Jones, 1996). It has also previously been used in South Africa with sufficient reliability and validity (Jewkes et al., 2006; Simbayi et al., 2007). The CES-D is reproduced in the appendix (Appendix B).

Alcohol abuse scale

Alcohol abuse was measured with the Alcohol Use Disorders Identification Test (AUDIT) (WHO, 1992). The AUDIT is a 10-item self-rating scale that assesses hazardous drinking. Most of its items are scored on a 5-point scale, ranging from 0 (*never*) to 4 (*daily or almost daily*) and a summary score of 8 or more indicates a presence of hazardous or harmful drinking. Sample items include 'How often do you have six or more drinks on one occasion?' and 'How often during the last year have you had a feeling of guilt or remorse after drinking?' The AUDIT was developed and validated by the WHO in a cross-national study that included six different countries (Saunders, Aasland, Babor, de la Fuente, & Grant, 1988). It has been validated in a variety of community and primary health care settings (Bohn, Babor & Kranzler, 1995; Cherpitel & Borges, 2000; Cherpitel & Clark, 1995) and cultures, including Mexico (Medina-Mora, Carreno & de la Fuente, 1998), Venezuala (Seale, Seale, Alvarado, Vogel & Terry, 2002), Hong Kong (Leung & Arthur, 2000) and Zimbabwe (Chinyadza et al., 1993). In all of these studies it outperformed other self-report measures in the identification of hazardous drinking. The scale has been used extensively in South Africa (Dunkle, 2006; Jewkes et al., 2006; Kalichman et al., 2007; Myer et al., 2008; Peltzer, 2006; Simbayi et al., 2004), and among persons with HIV infection (Conigliaro, Gordon, McGinnis, Rabeneck & Justice, 2003; Cook et al., 2001; Justice, 2004; Palepu et al., 2003; Shaffer, Njeri, Justice, Odero & Tierney, 2004). The AUDIT is reproduced in the appendix (Appendix C).

Neuropsychological assessment

A battery of neuropsychological tests was administered by the researcher, a trained neuropsychologist. The neuropsychological assessment was designed to focus on the areas of cognition sensitive to HIV-associated cognitive dysfunction: attention, motivation, speed of mental processing and executive functions. Verbal memory tests were also conducted due to their relevance to adherence behaviour. The Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan & Kramer, 2001) and the Wechsler Memory Scale – Third Edition (WMS-III) (Wechsler, 1997) served as comprehensive standardized executive functions and memory batteries, from which individual subtests

were selected. The batteries are the gold standards of executive functions and memory testing for both neuropsychological research and clinical utility. Both have been established as reliable and valid in the United States, and the WMS-III in the United Kingdom as well. Because the present study's sample does not match the populations in which the batteries have been validated, two precautions were taken. The first was to adapt the administration to the local population, and the second was to adapt the scoring to the local population. For the first, all of the stimulus information was thoroughly reviewed for applicability to the South African culture. This was approached conservatively so as to make only minor, necessary word substitutions so as to increase applicability of the items without compromising their level of difficulty. Of the six tests used across the two batteries, only one test – WMS-III Logical Memory – required word substitutions. Table 7 lists the four word substitutions applied to this test. For the second precaution, participant test results were not converted into scaled scores or percentile ranks based upon United States or United Kingdom norms. Instead, raw test scores were used for the statistical analyses.

Original wording on US/ UK versions	SA modifications
Story A	
South Boston/ South London	East London
the High Street	the Main Road
dollars/ pounds	Rand
Story B	
San Francisco/ Liverpool	Durban

Table 7. Word substitutions applied to WMS-III Logical Memory test.

The D-KEFS is a set of nine standardized tests focusing on higher order cognitive functions or *executive functions*. The tests measure functioning in either verbal or non-verbal domains. Each test is designed to function as either a stand-alone instrument or to be utilized in conjunction with the rest of the battery, depending on the pathology and the context. Several of the tests are comprised of multiple conditions, with earlier conditions measuring fundamental cognitive skills upon which the higher executive functions measured in the later conditions depend. Earlier conditions may be administered individually without moving on to administration of the later conditions, but the reverse is not true. The tests generally have high ceilings and low floors, meaning that they can detect both subtle cognitive deficits in those with high baseline functioning and distinctions in performance between those with severe functional impairment. The

administration manual provides detailed and clear instructions on test administration and scoring. Each test has standardized discontinue rules and time-limits to minimize examinee and examiner burden. Instructions and prompts are also prescribed and standardized. Each test has a primary score to characterize overall performance on the test (e.g. time taken to complete the task), as well as various process scores which characterize performance on key components or specific aspects of the task. The D-KEFS standardization sample consisted of 1750 individuals age 8–89 years, and stratification of age, gender, race, ethnicity was matched to the latest United States census data. Because of the variability of tests within the battery, each D-KEFS test has separately calculated internal consistency and test-retest reliability. With just a few exceptions, the tests show moderately good internal consistency coefficients and good test-retest reliability (Swanson, 2005).

The following D-KEFS subtests were administered:

- D-KEFS Verbal Fluency Test – verbal domain (Condition 1 – Letter Fluency; Condition 2 – Category Fluency; Condition 3 – Category Switching):

In the first condition, the examinee is required to generate as many words as possible that begin with a series of designated letters (F, A, S) in three trials of 60 seconds each. In the second condition, the examinee is required to generate as many words as possible that belong to designated semantic categories (‘animals’ and ‘boy’s names’), in two trials of 60 seconds each. The third condition requires participants to use designated semantic categories again (‘fruit’ and ‘furniture’), this time alternating between them, in one trial of 60 seconds. For this test, four types of process measures are recorded: 1) number of correct responses in each of the three conditions, and the number of correct switches in the third condition, 2) contrast in performance between generating words in the first and second conditions, and contrast in performance between the second and third conditions, 3) errors of repetition (same response generated more than once within a trial) and errors of set-loss (response generated that does not follow the phonemic or semantic rule of the trial), and 4) time-interval analyses (i.e. the number of correct words generated during each of the four 15-second intervals making up a trial). The test provides a measure of the examinee’s ability to generate words fluently in both a restricted phonemic format (letter fluency) and a restricted semantic format (category fluency), providing a good indication of generativity, motivation and spontaneity. The

switching condition requires rapid shifting from one cognitive set to another, assessing cognitive flexibility and the ability to undertake and manage conflicting demands.

- D-KEFS Design Fluency Test – nonverbal domain (Condition 1 – Filled Dots; Condition 2 – Empty Dots Only; Condition 3 – Switching):

This test is a non-verbal variation of the D-KEFS Verbal Fluency test. In the first condition, the examinee is required to generate as many designs as possible by connecting filled circles in a single trial of 60 seconds. In the second condition, the examinee is required to do the same, this time with empty circles. For the third condition, the examinee is again required to produce as many designs as possible, this time shifting between connecting filled and open circles. For this test, four types of measures are recorded: 1) number of correct responses in each of the three conditions, across the first two conditions and across all three conditions, 2) total number of designs attempted across all three conditions, 3) contrast in performance between the first and second conditions compared with the third condition, and 4) errors of repetition and errors of set-loss. Like the D-KEFS Letter Fluency Test, the test provides a measure of generativity, motivation, spontaneity and cognitive flexibility, this time in the non-verbal domain.

- D-KEFS Colour-Word Interference Test – verbal domain (Condition 1 – Colour Naming; Condition 2 – Word Reading; Condition 3 – Inhibition):

The first condition requires examinees to name coloured patches and the second condition requires examinees to read colour-words (e.g. 'red') printed in black ink. The third condition requires examinees to name the ink colour of colour-words where the ink colour differs from the colour-word (e.g. the word 'blue' printed in red ink). For these conditions, three types of measures are recorded: 1) number of seconds the examinee takes to complete each condition, and the combined number of seconds the examinee takes to complete the first two conditions, 2) contrast in performance between seconds to complete the third condition versus the first condition, and 3) self-corrected errors and uncorrected errors. The test assesses the examinee's ability to inhibit a learned response (e.g. reading printed words) in order to generate a required and conflicting response (e.g. naming the dissonant ink colour in which the words are printed).

- D-KEFS Tower Test – nonverbal domain (single condition):

This test requires the examinee to move discs varying in size across three pegs, in the fewest number of moves possible within set time limits, to build a series of nine towers that match the target pictures shown by the examiner. In constructing the towers, the examinee is required to move only a single disc at a time and never place a larger disc

over a smaller disc. For this test, two types of measures were recorded: 1) number of moves used to build a correct tower within the time limit, and 2) mean number of rule violations made across the nine trials. The test evaluates the examinee's ability to initiate and maintain planning and problem-solving behaviour, as well as follow rules and inhibit unplanned, impulsive responses in the pursuit of an established goal.

The WMS-III comprises eleven standardized tests which assess learning, memory and working memory. Like the D-KEFS, WMS-III tests measure functioning in either verbal or non-verbal domains. Many of the tests are separated into two conditions: an immediate condition, and a delayed condition which is administered 25–35 minutes after the immediate condition. The administration manual provides instructions on administration and scoring, and there are standardized discontinue rules but no time-limits. Each test has a primary score to characterize overall test performance, and several tests have supplemental scores as well which document performance on specific aspects of performance. The WMS-III was developed using a stratified standardization sample of 1,250 adults in the United States and was adapted for use in the United Kingdom in a sample of 332 adults.

The following WMS-III subtests were utilized:

- WMS Logical Memory – verbal domain (Condition 1 – Immediate; Condition 2 – Delayed)

In the first condition, two short stories are presented orally to the examinee; the first story is presented once and the second story twice. The examinee is then required to retell the stories from memory. In the second condition, after a 25–35 minute delay, the examinee is required to retell both stories. Then, the examinee is required to answer a series of 30 yes/ no questions, 15 about each story. For this test, four types of measures are recorded: 1) number of correctly recalled story units for each of the two stories and across both stories, and for each of the conditions and across both conditions, 2) the number of correctly recalled story themes from each story and across both stories, and for each of the conditions and across both conditions, 3) the improvement in recall after the second presentation of the second story (learning slope), and 4) number of correct responses to yes/ no questions. The test assesses auditory immediate and auditory delayed recall as well as auditory delayed recognition.

- WMS Digit Span – verbal domain (Condition 1 – Digit Span Forwards; Condition 2 – Digit Span Backwards)

This test requires the examinee to recall a series of digits, increasing in length, and to repeat them back to the examiner. The test consists of 30 items, starting at two digits in the series for both conditions, and increasing up to nine digits in the first condition, and eight digits in the second condition. In the first condition, examinees are required to repeat each series as it was presented (forwards); in the second condition, examinees are required to repeat each series in the reverse order (backwards). For this test, two measures were recorded: 1) number of correctly recalled items in each condition and across both conditions, and 2) number of correctly recalled digits in each condition. The test evaluates auditory working memory.

Adherence and LTFU monitoring

Methods of assessing adherence and their challenges

Diverse strategies have been used to measure and document adherence in antiretroviral research. These methods differ in meaningful ways; each has theoretical, empirical and practical advantages and disadvantages and a certain level of systematic measurement error. Utilization of these different methods within adherence research is likely to account for some of the variations in findings in the predictor literature described in the previous chapter. Assessment of adherence remains an imperfect science and no universally accepted method exists (Berg & Arnsten, 2006; Chesney et al., 2000; Wutoh et al., 2003). The methods may reasonably be divided into subjective (recall survey and visual analogue scale, pill identification test, medication diary, and clinician estimate) and objective (pharmacy records, electronic monitoring devices, therapeutic drug monitoring, directly observed therapy, pill counts and HIV RNA level tests).

The most widely used (Chesney, 2000) measure of adherence is the self-report recall survey. These assessments are based on patients' retrospective recall of past adherence, ranging in the literature from three days (Wagner, 2002) to one year (Weiser et al., 2003). Its widespread use is a function of its many administrative advantages: it is inexpensive, easily implemented and has a low patient burden (Chesney et al., 2000; Chesney, 2000). One common permutation of the recall survey is the Visual Analogue Scale (VAS), that positions a line with one end representing the minimum possible

adherence (e.g. 0%) or the lowest possible adherence score (e.g. 0), and the other end representing the maximum possible adherence or the highest possible adherence score. Patients are asked to position their adherence somewhere along the line.

Subjective recall does have several distinct disadvantages and was therefore not selected as an adherence measurement methodology for the present study. First, in order to minimize recall errors, self-report usually examines the shortest time period of all the adherence measures, making the data less representative (Chesney, 2000; Wutoh et al., 2003). Second, self-report is known to over-estimate adherence, probably because of social desirability bias, wherein patients misrepresent the degree of their compliance in order to avoid judgment on the part of the clinician or researcher (Chesney, 2000; Chesney et al., 2000; Wagner, 2002). Because of this tendency for self-report data to be positively skewed, it is predisposed to the 'ceiling effect' and its associated analytic challenges (Wagner, 2002). Third, the recall survey relies heavily on cognitive functions such as attention, motivation, insight and memory (Chesney, 2000). As discussed in the previous chapter, these are the very functions associated with HIV-associated cognitive dysfunction, making self-report an unlikely choice for this patient group with high rates of cognitive compromise. Fourth, the significant variability in survey types and characteristics – time-frame monitored, Likert versus visual analogue scale, closed- versus open-ended questions, single-item versus scale – has led to poor agreement between different self-report adherence measurements (Berg & Arnsten, 2006), which decreases comparability between studies.

Other subjective methods of assessing adherence include the medication diary, the Pill Identification Test (PIT), and the clinician estimate. Medication diaries require patients to complete a diary form each day, indicating the time they took each ARV medication and how many pills they took at each dose time. Because the medication diary is also a self-report measure, adherence rates reported in medication diaries are often biased upwards, once again likely because of perceived desirability of responses (Wagner, 2002), and the diary also relies heavily on cognitive functions such as attention, motivation and memory. It is also important to consider that patients who complete diaries are also likely by definition to be adherent (Matsui et al., 1994). It is for these reasons that the diary was also not selected for use in this study. In the PIT, the clinician asks the patient to inspect each medication container and its contents, or a photograph

thereof, and then name the medication, outline the number of pills per dose, dosing frequency, and any additional administration instructions. Although used as a measure of adherence, the PIT is a knowledge index rather than a marker of behaviour, and as presented in the previous chapter, knowledge levels are not necessarily associated with adherence behaviour (Gordillo et al., 1999; Weiser et al., 2003). The clinician estimate measure asks health care providers to assign each patient an adherence score, based upon the provider's subjective impression of the patient's conduct. However, as described in the first chapter, research shows that clinicians are poor predictors of patient adherence (Gerbert et al., 2000; Miller et al., 2002; Paterson et al., 2000; Weiser et al., 2003) tending to overestimate medication adherence and insufficiently detect poor adherence. Miller et al. (2002) analyzed the accuracy of clinician estimates by calculating the difference between estimated adherence and measured adherence for the same period, and found mean clinician estimated adherence to be 86.2% compared with a mean measured adherence of 77.3%, a 9% difference. The sensitivity of clinician estimates to detect nonadherent patients was poor (24% to 62%), and the difference between clinician estimate and measured adherence was between +5% and –5% in 36% of cases.

Pharmacy records have been used as an objective measure of adherence, the premise being that patients who do not collect their refills timeously are missing doses, to the extent of the time lag between expected collection and actual collection. There are two major limitations to this measure. First, pharmacy records provide a crude score compared with pill counts and are therefore less amenable to statistical analysis. Second, pharmacy records provide only an approximation of adherence, since what they measure is a step removed from the action of pill-taking itself. Using pharmacy refill data assumes that patients who collect their medication on time ingest all of it correctly and timeously, which is logically not the case.

Electronic monitoring devices (EMD) such as the Medication Events Monitoring System (MEMS) are relatively new to adherence research as compared with other measures (Wagner, 2002). One such EMD, The MEMS, developed by the Aardex Company in 2005, employs a pressure-activated microprocessor in the medication bottle cap that records the date, time and duration of each bottle opening. At the clinic visit, patients are required to return the bottle cap, which is then scanned for retrieval of adherence data,

and the information transferred to a MEMS database. While MEMS adherence data is closely correlated with HIV RNA levels (Liu et al., 2001; Arnsten et al., 2001) and is able to detect more detailed aspects of pill-taking behaviour like dosing intervals (McNabb, Nicolau, Stoner & Ross, 2003), it does have several significant limitations. The first is the expense (Chesney et al., 2000) and therefore inaccessibility of MEMS technology (in terms of the computerized medication bottles, the computer software to scan and analyze the caps, and the specialized staff to manage it). This is obviously pertinent in resource-poor settings like South Africa, and all but prohibitive for local research. Even in those developed settings where electronic drug monitoring technology has been afforded, usually only one of the three or more antiretroviral medications is fitted with a MEMS cap due to cost constraints (Bova et al., 2005; Hinkin et al., 2004; Wagner, 2002) so the data is less representative of the complete regimen. Second, although the MEMS technology is seen as an objective measure, the objective record is of bottle opening (each cap opening is assumed to reflect a single medication-taking event) rather than pill-taking behaviour itself, and these are not always indistinguishable. For instance, some patients tend to remove more than one dose at a time (for example, taking out an extra 'pocket dose' in the morning for later ingestion before going out for the day), which leads to underestimates of adherence (Bova et al., 2005; Bangsberg et al., 2000; Chesney, 2000; Chesney et al., 2000; Hinkin et al., 2004), while others may open the device to show it to friends or check medication supply without actually ingesting medication. In an exploratory study of EMD use among HIV-infected adults enrolled in a randomized clinical trial, Bova et al. (2005) found that 41% of the sample reported having taken out more than one dose at a time (pocket dosing), and 26% reported having opened the device without taking out a dose of medication. So, while EMD data tends to reflect lower adherence levels than self-report measures or pill count, it is not clear whether EMD data are really more accurate or simply provide an inaccurately lower estimate of adherence.

Third, assigning patients to MEMS cap monitoring might actually act as an adherence-improving intervention (Wagner & Ghosh-Dastidar, 2002), in accordance with the 'Hawthorne effect', rendering MEMS data incomparable to retrospective adherence evaluations like self-report. Finally, MEMS caps are large and bulky; they tend not to fit commercially available bottles, meaning clinics or patients need to transfer and re-label their medications; they are not conducive to travel (Bova et al., 2005), and their uptake

precludes the use of medication organizers like pill boxes (Golin et al., 2002; Wagner, 2002), a cheap and common method many patients use as an adherence aid. These features have lead to high refusal rates (Turner & Hecht, 2003), possibly introducing a selection bias, and may in themselves adversely affect adherence rates.

Therapeutic drug monitoring (TDM), wherein serum drug levels are assessed, has also been used as an objective adherence measure. However, TDM relies on laboratory use, and the expense related to performing therapeutic drug measurements is prohibitive (Chesney, 2000). It is also the most invasive of all the adherence measures. Also, serum drug levels only reflect adherence over the past 24 hours, just a recent snapshot of a chronic behaviour (Chesney, 2000). Finally, serum drug levels are affected by factors other than adherence, including diet and drug interactions, and also individual pharmacokinetic variation.

The directly observed therapy (DOT) method, wherein patients are required to visit the clinic for each pill ingestion for observation by the health care provider, has been used extensively in chronic diseases like tuberculosis. While DOT is the only adherence assessment that assesses the behaviour itself rather than a proxy (e.g. number of times the medication container was opened), several major criticisms of the method exist. First, DOT requires extensive operational costs, which makes its use as both a research methodology and adherence intervention impractical in resource-constrained settings. Second, DOT has been labeled paternalistic, and threatening to the clinician-patient relationship, the bedrock upon which successful research and retention in clinical care are founded. Finally, the assessment itself is the most obviously impactful as an intervention, and so not an ideal observational research methodology.

The most widely-used (Golin et al., 2002; Gordillo et al., 1999; Laniece et al., 2003; Weidle et al., 2006) objective measure of patient adherence is the pill count, whereby patients are asked to return their medication bottles to clinic visits for the clinician to empty and count. While pill counts are time-consuming and computationally complex for resource-limited clinics, the HCTC includes routine pill counts at every pharmacy visit, which was one of the primary reasons that the center was chosen as the research setting. The concept of measuring returned medicine as a proxy for consumed medicine does pose a particular challenge through the phenomenon of ‘pill dumping’, where

patients dispose of surplus medication without ingesting the medication before the clinic visit (Chesney, 2000). While this phenomenon cannot be excluded, the significant association between pill count adherence and EDM and virological suppression (Liu et al., 2001; Bangsberg et al., 2000) suggests that pill count correlates well with actual adherence. For this study in particular, because it was conducted in a clinical setting with a high emphasis on adherence at treatment readiness sessions, on-treatment lay counseling, and routine pill counts, it was especially important to utilize an objective measure of adherence because of the potential for social desirability bias. Also, because one of the premises of the study is that HIV-associated cognitive dysfunction impacts behavioural ability, self-report measures of adherence such as the recall survey, which rely heavily on memory, motivation, attention and executive functions, were not used. For these reasons, pill counts were chosen as an objective behavioural marker of medication adherence for the present study.

Biological endpoint measures like HIV RNA level have also been used as objective measures of adherence (Bisson et al., 2006; Roco et al., 1999; van Oosterhout et al., 2005; Weidle et al., 2006). Although factors like viral resistance and fitness, drug pharmacokinetics, and cellular metabolism may also come into play (Brigado et al., 2001), adherence plays a central role in determining clinical outcome, especially in patients naïve to previous ART early on treatment, which is the case in the present study. For this study, viral load level was used as an objective clinical marker of medication adherence.

Finally, some studies have used a combination of some or all of the above approaches, either replacing one measure with another if the first was missing or unavailable or setting out to formulate a composite adherence score (Golin et al., 2002; Gordillo et al., 1999; Laniece et al., 2003; Parruti et al., 2006; Roco et al., 1999; van Oosterhout et al., 2005; Wagner, 2002). In an editorial on measuring adherence, Turner and Hecht (2003) concluded that while self-report is likely the most practical approach for clinical patient care, a combination of measures is best for research purposes. Similarly, after reviews of the literature on predictors of adherence, Chesney (2000) and Wutoh et al. (2003) both advocated the use of simultaneous multiple methods to assess adherence adequately.

Adherence outcome variables in the present study

In order to best capture the complex variations in adherence from different angles, and in accordance with the recommendations to use a combination of adherence measures for research purposes (Chesney, 2000; Turner & Hecht, 2001; Wutoh et al., 2003), medication adherence was measured and evaluated according to four indices: i) early behavioural marker of medication adherence ('early pill count adherence'), ii) late clinical marker of medication adherence ('late virological suppression'), iii) late behavioural marker of clinical care adherence ('retention to care'), and iv) a composite measure of all three ('composite adherence success').

i) *Early behavioural marker of medication adherence – 'early pill count adherence'*

As discussed earlier, although pill counts are not mandated in either the national (Department of Health, 2004; 2010b) or provincial (PAWC, 2004) protocols and rarely occur in the public health sector, likely because they are time-consuming and computationally complex, they are performed routinely at HCTC at each pharmacy visit. Pharmacy visits occur at standard medical follow-up (+4, +8 and +16 weeks, and at 16-week intervals thereafter, with those initiated on NVP also are seen at +2 weeks) and at +12 weeks and at the midpoint between the 16-week intervals between medical follow-up. This means that pill count data is available in 4-week intervals for the first 16 weeks of treatment, and 8-week intervals thereafter. Patients are asked to bring their pill bottles to each clinic visit, where a lay counselor performs the pill count. The counselor counts and records the number of pills remaining in the bottle and subtracts those numbers from the pharmacy record of the number of pills dispensed, in order to determine the number of pills consumed. This number is then divided by a multiplication of the required daily consumption and the number of days since the last pharmacy visit. The adherence computation is presented in Figure 4. This calculation is performed for each prescribed ARV medication.

Metric	Derivation
Percent adherence	$\frac{\text{DISPENSED – RETURNED}}{\text{REQUIRED DAILY CONSUMPTION X NUMBER OF DAYS}}$ **X 100**

Figure 4. Pill count computation.

Although these computations are completed at the clinic by the lay counselor, for the purposes of this study, these calculations were re-performed by the researcher to ensure accuracy and completeness. The pharmacy record of the number of pills dispensed and the counselor's documentation of the number of pills remaining in the bottle were drawn from the clinic folder and entered into a Microsoft Excel database for calculations.

Pill count data was extracted and computed for each of the four 4-week time intervals in the first 16 weeks after HAART initiation. The choice of four months to define 'early' treatment has been used elsewhere (Carrieri et al., 2006; Cornell, Myer, Kaplan, Bekker & Wood, 2009; Lawn et al., 2006), with this period previously shown to require the highest adherence rates in order to achieve long-term immuno-virological success (Carrieri et al., 2003). For the purposes of this study, and in line with the WHO's recommended strategy for prevention and assessment of HIVDR in resource-limited countries (Bennet et al., 2008), and Harries, Nyangulu, Hargreaves, Kaluwa and Salaniponi's (2001) recommended framework for an effective antiretroviral programme in sub-Saharan Africa, patients were defined as adherent if they had taken 90% or more of their prescribed drugs across the 16 weeks. This is also in accordance with many other studies which have also used the 90% cut-off for good adherence (Arnsten et al., 2007; Gebo et al., 2003; Gordillo et al., 1999; Murphy et al., 2010; Parruti et al., 2006). Pill count calculations were performed for each medication in the prescribed regimen as opposed to just one. Selective adherence to certain but not all medications prescribed in combination therapy would mean that the anticipated benefits of combination therapy (pharmacological synergy) would not be realized. Thus, for each participant, either eight or twelve pill count calculations were performed: one calculation for each of the four time-intervals per ARV medication.

ii) *Late clinical marker of medication adherence – 'late virological suppression'*
As outlined earlier, while viral load measurement is only recommended in the national (Department of Health, 2004; 2010b) and provincial (PAWC, 2004) protocols to be performed 6-monthly due to high cost and insufficient laboratory facilities, viral load testing is performed routinely at HCTC at 16-week intervals on treatment. Laboratory work is performed on site in a stand-alone laboratory (a modified shipping container) on the premises. Viral load is measured with the Versant HIV-1 RNA 3.0 assay performed

on a 340 bDNA analyzer (Bayer Diagnostics, Tarrytown, NY, USA), which is sensitive for detecting 50 copies or more of HIV-1 RNA per milliliter of blood plasma. Internal and interlab quality assurance (QA) is performed routinely for viral load measurements. HIV RNA levels are expressed in log10 and reported in copies/mL.

For the purposes of this study, viral load levels were accordingly classified as either detectable ≥50 copies/mL (log<1.49) or undetectable <50 copies/mL at the 96 week clinic visit as a clinical marker of medication adherence. This assay-detection threshold is lower than the commonly-used 500 copies/mL or 400 copies/mL marks of some years ago, and has been used by many studies as the cut-off point for suppression of viraemia in recent years (Cooper et al., 2008; Lehrman et al., 2005; Steigbigel et al., 2008; Trkola et al., 2005; van Oosterhout et al., 2005). Individuals who achieved an HIV RNA level of less than 50 copies/mL were classified as achieving virological suppression according to this clinical marker.

The use of a single elevated viral load result was necessary because while the assay used had a detection threshold of 50 copies/mL, allowing for increased sensitivity in a population with proven high suppression rates (Bekker et al., 2003; Bekker et al., 2006; Orrell et al., 2007), the clinic's targeted adherence intervention (with increased viral load monitoring) was only triggered at the 1,000 copies/mL threshold, meaning that for all patients with viral load's between 50 copies/mL and 1,000 copies/mL, the follow-up viral load measurement occurred only 16 weeks later. The use of a single elevated viral load result is however justified because studies have shown that a single elevated viral load is associated with a higher risk of subsequent virological failure (Easterbrook et al., 2002; Masquelier et al., 2005; Moore et al., 2002). Moreover, studies have also shown that one elevated viral load result (termed 'initial' or 'primary' virological failure [Orrell et al, 2007]) is more suggestive of lack of adherence than viral resistance at the time of the single elevated viral load (Masquelier et al., 2005), and therefore most closely represented the study's focus on adherence.

iii) *Late behavioural marker of clinical care attendance – 'retention to care'*
Patients are lost to care due to death, transfer to an alternate service or loss to follow-up. As discussed, the HCTC has 30 lay counsellors on staff, with each new patient allocated to one of these counsellors based on geographic location to facilitate home

visits. This allocation is intended as an adherence/ retention intervention, but also facilitates the determination of true patient outcomes; patients who fail to attend their scheduled clinic visits are traced through home visits by the counselors, and so the identification of patients as LTFU in the programme is an indication of true LTFU, as opposed to hidden mortality or clinic transfer. All participant clinic files were reviewed at 96 weeks to evaluate loss to follow-up and possible causes thereof. For the purposes of this study, and in accordance with the WHO's recommended strategy for prevention and assessment of HIVDR in resource-limited countries (Bennet et al., 2008), patients were defined as lost to follow-up if at the end of the monitoring period (in this study, 96 weeks post treatment initiation), they had not returned to the clinic for 90 days or more since their last appointment and were not known to have died or transferred out to another treatment facility. This is in accordance with the 90-day definition used in other retention studies (Cornell et al., 2009; Laurent et al., 2005; Lawn et al., 2006; van Oosterhout et al., 2005). Patients who did not return to the clinic for 90 days or more after a clinic appointment but subsequently returned to the clinic during the 96-week monitoring period were not defined as LTFU. The date of LTFU was recorded as the date of the last visit to the clinic.

iv) *Composite measure – 'composite adherence success'*

Development of a composite measure is in accordance with several adherence reviews (Chesney, 2000; Turner & Hecht, 2001; Wutoh et al., 2003) that have advocated for a combination of measures to properly assess adherence in a research context. A composite measure of overall adherence success was developed, comprising the three adherence indicators just described: i) early behavioural marker of medication adherence ('early pill count adherence'), ii) late clinical marker of medication adherence ('late virological suppression'), and iii) late behavioural marker of clinical care adherence ('retention to care'). Patients were defined as achieving adherence success if their mean pill count adherence across the first 16 weeks of treatment was greater than or equal to 90%, they achieved an HIV RNA level of less than 50 copies/mL at the 96 week visit, and they were retained in care at 96 weeks. A similar method of adherence appraisal (utilizing medication adherence, viral load suppression and adherence to care) has been utilized previously (Roco et al., 1999).

Data management

Raw data – including all psychological and social information, demographic and clinical data, pill count records, viral load results and retention data – were captured using Microsoft Excel. Data cleaning was performed by running all frequencies, identifying missing records and entering or replacing them.

A set of principles to guide interpretation of missing and inconsistent data was established in advance and used throughout. Pill count adherence was calculated using an intention-to-treat analysis: patients who were LTFU during the 16-week pill count monitoring period were included in the pill count analysis and assigned an adherence value of 0% from the date of their first missed scheduled pharmacy visit, at which point they would have run out of drug. This principle has been used in other cohort studies (Karcher et al., 2007). Similarly, patients who interrupted treatment (did not return to the clinic for >1 day after a scheduled pharmacy visit, but returned before the end of the 16-week monitoring period) were also assigned an adherence value of 0% from the date of their missed scheduled pharmacy visit until the date of their return, i.e. for the period that they were without drug.

Patients who died on treatment during the early pill count adherence monitoring period were included in the analysis so as not to positively bias the adherence outcomes. In this case however, rather than being assigned an adherence value of 0% for the remainder of the 16-week monitoring period, they were considered only until their death. This is because there are a number of potential causes of early mortality in ART programmes other than nonadherence, including: delayed initial presentation for treatment and therefore advanced HIV disease, opportunistic infections, and severe HIV-related complications such as bacteraemia and tuberculosis (Antiretroviral Therapy in Lower Income Countries [ART-LINC] Collaboration & ART Cohort Collaboration [ART-CC] Groups, 2006). Importantly also, death records include death for any reason while on ART, including reasons unrelated to HIV. Patients who notified the clinic that they were transferring to another HIV treatment facility to continue ART during the pill count monitoring period were classified as transferred out (TFO) and only considered until the time of their transfer.

Periods of missing pill count data due to prescribed non-use (such as doctor-initiated treatment gaps due to side effects), hospitalizations and incarcerations were distinguished from poor adherence through extensive file reviews and the preceding 4-week interval's pill count adherence value was brought forward. In those cases where medication was dispensed from a different facility (e.g. an unplanned trip) without the patient transferring out and that facility also performed routine pill counts, efforts were made to obtain pharmacy record and pill count data from the facility. Where this was impossible, the preceding 4-week interval's pill count adherence value was brought forward. If patients notified the clinic at a scheduled pharmacy visit that they would be unavailable to attend the following scheduled pharmacy visit and were thus dispensed medications for eight weeks of use, pill count adherence was calculated for the 8-week interval and applied to each of the two 4-week intervals. Where patients visited the clinic between scheduled pharmacy visits (i.e. within a 4-week interval) to report lost medication and request a new pill set, pill count adherence was calculated based only on the remaining time between the new pill set and the next scheduled pharmacy visit and applied to the entire 4-week interval. If patients failed to bring their pill bottles to a certain pharmacy visit so that remaining pills could not be counted, the preceding 4-week interval's pill count adherence value was brought forward. In those cases where medication changes (such as a switch from NVP to EFV due to side effects) were made between scheduled pharmacy visits, the pill count calculation was performed for each of the two periods, weighted according to time on each regime and applied to the entire 4-week period.

Pill count adherence scores greater than 100% reflected consumption of more than the prescribed dose during the measurement period. So as not to reward patients for over-consumption in calculations of mean scores across multiple time periods or drugs (for instance, if a patient took 120% of prescribed dose for 8 weeks and 80% of prescribed doses for the remaining 8 weeks, or 120% of certain drug and 80% of another drug), and because – unlike poor adherence – data on the clinical implications of over-consumption are limited, pill count adherence scores greater than 100% were truncated at 100%.

Patients who died on treatment and TFO before the 96 week visit were excluded from the late virological suppression analysis. As in pill count analysis, patients who were LTFU before the 96 week visit were included in the virological suppression analysis, and

assigned as unsuppressed. For those patients who had not died on treatment, TFO or LTFU, where a viral load test result was unavailable for the 96 week visit, the closest preceding viral load measurement by date was used.

Statistical analysis

All statistical analyses were carried out using the SAS package (SAS Institute, Inc., Cary, North Carolina). Conventional significance levels were adopted for all tests ($p \leq 0.05$) and 95% confidence intervals used throughout.

Baseline predictor and follow-up outcome variables were described using means and standard deviations for normally distributed continuous variables, medians and interquartile ranges (IQR's) for continuous variables that were not normally distributed, and counts and percentages for categorical data.

Within the interview data, a composite knowledge score was developed, and calculated as the number of correct answers to the six items pertaining to basic HIV illness, own biomedical status, implications of nonadherence, understanding of resistance and the names of each medication in the prescribed ART regimen; a higher knowledge score indicated greater knowledge levels. For all knowledge questions, participants who answered 'unsure' were grouped with those who answered incorrectly for that item. For the single open-ended knowledge question (understanding of resistance), participants were graded as 0 (*no/ poor understanding*) or 1 (*good understanding*) according to the a priori scoring system. A score of 1 was recorded if the participant mentioned that incomplete adherence may lead to medication not working/ not working as well. A composite antiretroviral therapy attitude score was also developed, calculated as the number of positive responses to the five items pertaining to the efficacy, benefits and drawbacks of the medication; a higher score indicated a more positive attitude. Finally, a composite patient-clinic relationship score was developed, calculated as the number of positive responses to the four items pertaining to communication, trust, respect and satisfaction with clinic staff; a higher score indicated a greater level of satisfaction with the relationship.

Pill count adherence was analyzed as a continuous measure to determine mean, median and range during the monitoring period and for other descriptive purposes, and as a dichotomous measure (<90% versus ≥90%) for bivariate analyses and the statistical model. Pill count adherence rates were calculated for each 4-week time interval first, to facilitate comparisons between adherence rates across time. Thereafter, mean adherence across the full 16-week measurement period was computed by weighting each between-visit measurement period (usually four weeks, but variable due to patient, clinic and environmental factors) appropriately. Similarly, adherence for each antiretroviral drug was calculated first, to facilitate comparisons between drug-specific adherence rates. Thereafter, mean adherence across all prescribed antiretroviral drugs was computed by averaging drug-specific adherence values. Pill count adherence scores ranged from 0% to 100%, with 0% indicating complete nonadherence and 100% indicating perfect adherence.

Bivariate analyses were used to investigate the association of each demographic, biomedical, psychological and social factor with the four adherence outcomes: early pill count adherence (mean ≥90% across first 16 weeks of treatment), late viral load adherence (<50 copies/mL at the 96 week visit), late adherence to clinical care (retained in care at the 96 week visit) and the combined adherence success measure (mean pill count adherence ≥90% across first 16 weeks of treatment, viral load <50 copies/mL at the 96 week visit, and retained in care at the 96 week visit). Differences in the prevalence of each adherence outcome according to each potential predictor were examined using chi-square tests with 95% confidence intervals (95% CI).

Finally, multiple logistic regression analysis was performed, with the combined adherence success measure as the dependent variable. This analysis allows each predictor variable to be assessed for its capacity to enhance the prediction of the outcomes variable over and above all of the other predictor variables.

For those baseline predictor variables that contained one response set that made up 95% or more of responses, only counts and percentages are presented descriptively; bivariate analyses were unable to be performed and they were excluded from the statistical model. Variables that were highly correlated with other variables (meaning that they provide the same information as another variable) were excluded from the model so

that the model was not influenced by the effect of multicolinearity. Because of the large number of bivariate analyses undertaken, all significant associations were assessed for plausibility and discarded from the regression model where appropriate. All variables excluded from the model and the reasons for exclusion are listed in Appendix E. For risk factors identified in the multivariate analysis, odds ratios (OR) are presented.

Supplementary exploratory analyses were performed where appropriate to investigate alternative interpretations of primary results.

Ethical considerations

Approval

The study protocol was approved by the University of Cape Town's Research Ethics Committee, the Institute of Infectious Disease and Molecular Medicine's Internal Review, and the University of Cape Town's Department of Psychology's Ethical Review.

Consent process

Informed consent was obtained prior to conducting any study procedures. Prior to consenting, written information in the form of an information sheet with attached consent form, available in both English (Appendix F) and Xhosa (Appendix G), was given to the patient to read. The researcher went through each paragraph of the information sheet with the patient and answered any questions as they arose. If the patient decided to participate, he or she signed two copies of the consent form, witnessed by the researcher. The participant kept one copy, and the other was kept secure by the researcher. If the participant elected not to keep a copy (e.g. for confidentiality reasons, in the case of non-disclosure), the researcher documented this and kept both copies.

Participant withdrawal

Patients were informed prior to consenting and in the information sheet that they were free to withdraw from the study at any time without any penalty or loss of benefits that they would otherwise have been entitled to receive. This included, but was not limited to, social and medical benefits, and future care at the study site or clinic.

Privacy and confidentiality protection

Confidentiality was strictly maintained. All study procedures were conducted in private, to the extent possible. A unique participant identity number was allocated to each participant and it is this number that was recorded on all study records – such as the questionnaire, administrative forms and other study-related reports and databases – in order to maintain participant confidentiality. All records that contained names or other personal identifiers, such as the participant log and the informed consent documents, were stored separately from the study records identified by the unique participant identity number. Hard copies of the records that contained names were stored in a separate, locked cabinet with limited access. Electronic copies of the records that contained names were secured with password-protected access systems.

CHAPTER 4

Biomedical, psychological and social characteristics of the sample

This chapter sets out to describe, in detail, the demographic, biomedical, psychological and social characteristics of the sample. The reason for the allocation of an entire chapter to this description is that, as will be outlined in this and the following chapters, the sample is broadly demographically and clinically representative of patients initiating ART at this particular clinic (Chapters 4 and 5) as well as broadly demographically and clinically representative of public-sector patients accessing ART in South Africa (Cornell et al., 2010) and even public-sector patients accessing ART in sub-Saharan Africa (Rosen et al., 2007) (Chapter 6). The psychological and social characteristics of ART patients seen in routine clinical practice are largely unknown in this under-researched population. The extensiveness and diversity of material covered in the interviews provided a unique opportunity for the detailed description of a demographically and clinically representative ARV patient base, which may be of use to public health professionals and clinicians in policy, planning and approaches to patient interactions. After this description, Chapter 5 will go on to explore the implications of the demographic, biomedical, psychological and social characteristics described in this chapter on treatment outcomes.

Demographic characteristics of the sample

A total of 150 patients initiating treatment were recruited into the study. Participants were predominantly female (n=95, 63%). The median age of the sample at enrolment was 34 years (IQR, 29–40 years). Ninety-seven percent (n=145) spoke Xhosa as their home language. Only 32 (21%) had completed school; across the sample, the median level of education attained was Grade 10 (IQR, Grades 8–11). The mean number of years of education was 9.47 years (SD 2.22). Just 17 (11%) had post-school education; of these, the median length of post-school education was one year (IQR, 0.35–2 years).

Employment status and categories are presented in Figures 5 and 6. Most (n=110, 73%) were unemployed, and a further 19 (13%) were self-employed or engaged in casual work. Only 15 (10%) were employed in full-time positions; the remaining 6 (4%) were

employed part-time. According to Annexure 3 of the Employment Equity Act 55 of 1998 (see Appendix H), of those who were employed (full-time, part-time or self-employed/ engaged in casual work), 17 (49%) would be classified as Category 9 (Elementary Occupations), a grouping defined as those occupations which require relatively low/ elementary levels of knowledge and experience. Examples of Category 9 occupations within this sample include 'domestic worker' (n=4) and 'fruit and vegetable seller' (n=3). The remaining participants fell into the following categories: Category 6 (Service and Sales Workers), 26%; Category 7 (Craft and Related Trades), 17%; Category 4 (Clerks), 6%; Category 3 (Technicians and Associated Professionals), 2%.

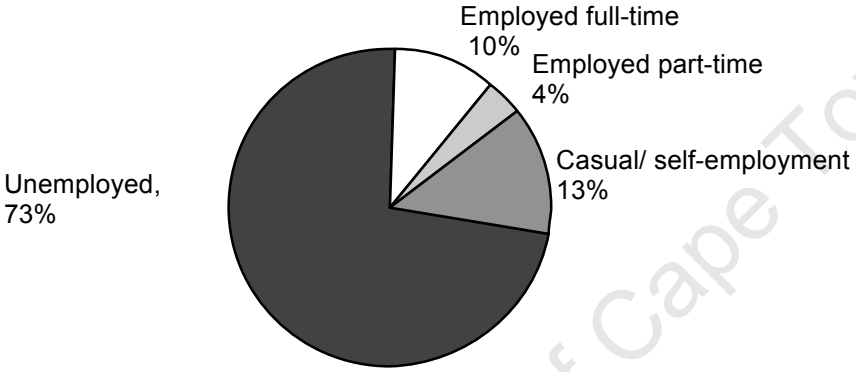

Figure 5. Employment status.

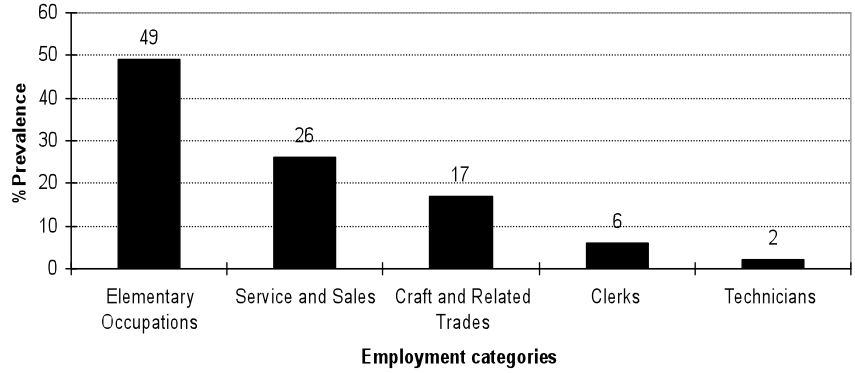

Figure 6. Employment categories.

Twenty (13%) had a disability grant (DG), and a further 68 (45%) had applied for a DG, and were awaiting approval[1]. The mean monthly income of the sample, including all current and expected wages and grants for the follow-up period, was R968.63 per month (range 0–6,000 ZAR [South African Rands]). Twenty-four patients (16%) had no current or expected monthly income from any source.

The demographic characteristics of the sample are presented in Table 8.

Characteristic	N or mean/ median
Gender	
Female	95 (63%)
Age	
Median (years)	34 (IQR, 29–40)
Home language	
English	1 (0.67%)
Southern Sotho	1 (0.67%)
Shona	1 (0.67%)
Sothu	2 (1.33%)
Xhosa	145 (96.67%)
Education	
Completed school	32 (21%)
Median highest grade	Grade 10 (IQR, 8–11)
Mean education (years)	9.47 (SD, 2.22)
Employment	
Full-time	15 (10%)
Part-time	6 (4%)
Self-employed/ casual	19 (13%)
Unemployed	110 (73%)
Disability grant	
Yes	20 (13%)
Applied	68 (46%)
No	62 (41%)
Expected monthly income*	
Mean (ZAR)	968.63

Table 8. Demographic profile of the sample (n=150). * Includes all current and expected wages and grants for the follow-up period. IQR, interquartile range; ZAR, South African Rands.

The study sample represented 4% of the clinic's ever-treated population (those patients who had ever initiated HAART treatment at the HCTC since its inception in 2002 until the end of the study's monitoring period, n=4,302), and 29% of patients who initiated treatment during the study enrolment period (April 2007 – January 2008, n=521). The sample was very similar to both populations (demographic characteristics are presented

[1] A disability grant is a government grant provided to patients with temporary or permanent disability, generally available to patients with a CD4+ cell count below 200 cells/μ or WHO stage IV disease. At the time of the study, disability grants provided approximately R700 support per month (Cornell et al., 2009)

in Table 9 and biomedical characteristics in Table 12 to follow), and when the study sample was compared with the total who initiated treatment during the study enrolment period, there were no significant differences observed with regard to gender (*p*=.26) or age (*p*=.98).

Demographic characteristic	Sample (n=150)	HCTC ever-treated population (n=4,302)	HCTC initiated during study enrolment period (n=521)
Gender	63% female	67% female	68% female
Age (mean)	34.31 years	34.52 years	34.33 years

Table 9. Comparison of study sample gender and age composition with HCTC ever-treated and initiated during study enrolment populations. HCTC, Hannan Crusaid Treatment Centre.

Biomedical characteristics of the sample

Participants' median CD4+ cell count at the start of the study was 117 cells/μL (IQR, 54–172 cells/μL). Thirty-two (21%) had a CD4+ cell count below 50 cells/μL, 67 (45%) below 100 cells/μL, and 134 (89%) below 200 cells/μL. The median plasma viral load level was 4.98 $\log_{10}$ RNA copies/mL (IQR, 4.62–5.46 $\log_{10}$ copies/mL). Seventeen (11%) patients had HIV RNA levels greater than 500,000 copies/mL. The staging of infection across the sample, according to the WHO classification, was distributed as follows: WHO stage I (asymptomatic and including acute HIV infection), 12%; WHO stage II (early disease), 12%; WHO stage III (late disease), 44%; WHO stage IV (AIDS), 32%.

Most patients had tested HIV-positive relatively recently: 85 (57%) had tested within the last 12 months. The median time since diagnosis was eight months (IQR, 3–42 months).

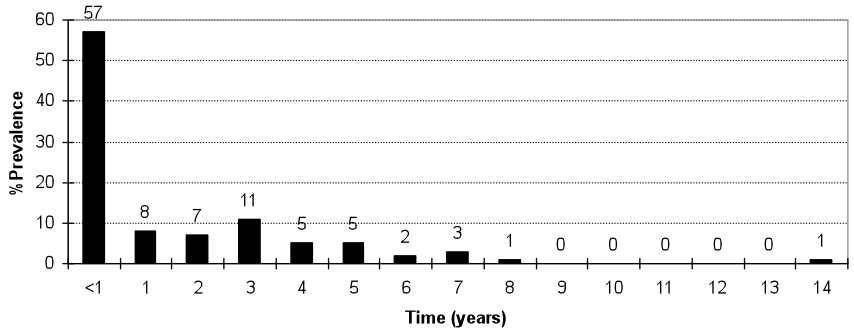

Figure 7. Length of time since HIV-positive diagnosis.

Most had tested because of medical advice to do so: 81% versus the 19% who had tested through VCT. The reasons for medical advice to test were: personal illness other than TB (44%), TB (20%), pregnancy (16%), and child's illness (1%), reflecting the known major entry points to care.

Sixty-nine percent of patients reported currently experiencing or having experienced one or more physical symptoms that they ascribed to HIV. The most frequently reported symptoms were dermatological (n=50, 33%), followed by neurological (n=43, 29%), gastrointestinal (n=32, 21%) and constitutional (n=31, 21%) symptoms. Thereafter, the following symptoms were reported at 10% or less frequency: cardiopulmonary, ear, nose and throat (ENT), haematological, lymphatic, musculoskeletal, ophthalmic, psychiatric, respiratory and urogenital. (See Appendix I for symptom categorizations.) The most frequently reported individual complaint was 'rash' (n=22, 15%). The most frequently reported neurological symptom was 'headache' (n=15, 10%), and no cognitive symptoms were reported. The most frequently reported psychiatric symptom was 'insomnia' (n= 2, 1%). Of those who reported one or more symptoms, 55 (53%) considered these symptoms severe, 29 (28%) mild and 20 (19%) moderate.

Twelve (13%) of the women were pregnant. Almost half of the sample (49%) was on TB therapy.

Four patients had a documented history of mental illness prior to initiating treatment: two had been treated for depression, and two for acute psychosis. Thirty-five patients (23%) had a documented neurological history prior to initiating treatment. Nine had had motor vehicle accidents with associated loss of consciousness (LOC), and a further nine various closed-head trauma (defined as a significant blow to the head resulting in loss of consciousness). Seven had had tuberculosis meningitis (TBM), two Cryptococcus meningitis, and one undifferentiated meningitis. Five had epilepsy or a history of single seizures.

One hundred and thirty-six patients (91%) were naïve to previous ART. Of the 14 who had been exposed to previous therapy, ten had received single-dose nevirapine (sd-NVP) as prevention of mother-to-child transmission (PMTCT), two had participated in

previous ART drug trials, and two had defaulted treatment and presented during the study period for re-initiation.

On initiation, 99% of patients were placed on first-line therapy including one NNRTI (EFV or NVP) boosted by two NRTI's (d4T, 3TC or AZT): 81% were on either EFV plus d4T and 3TC (45%) or NVP plus d4T and 3TC (36%). Eighteen percent were started on EFV plus AZT and 3TC (7%) or NVP plus AZT and 3TC (11%). One patient was started on the second-line EFV (replacing LPV/r due to resistance on genotyping) plus AZT and ddI (see Table 10).

Antiretroviral regimen	Number	Percentage
NNRTI + NRTI		
EFV + d4T + 3TC	68	45%
NVP + d4T + 3TC	54	36%
EFV + AZT + 3TC	11	7%
NVP + AZT + 3TC	16	11%
EFV + AZT + ddI	1	1%

Table 10. ART drugs prescribed to sample. NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; EFV, efavirenz; d4T, stavudine; 3TC, lamivudine; NVP, nevirapine; AZT, zidovudine; ddI, didanosine.

Table 11 summarizes the biomedical characteristics of the sample.

Characteristic	N or median
CD4+ cell count at initiation	
Median (cells/μL)	117 (IQR, 54–172)
CD4+ cell count	
<50 cells/μL	32 (21%)
<100 cells/μL	67 (45%)
<200 cells/μL	134 (89%)
Log HIV RNA level at initiation	
Median (copies/mL)	4.98 (IQR, 4.62–5.46)
HIV RNA level	
> 500,000 copies/mL	17 (11%)
< 500,000 copies/mL	133 (89%)
WHO stage	
I	18 (12%)
II	18 (12%)
III	66 (44%)
IV	48 (32%)
Time since diagnosis*	
Median (years)	0.66 (IQR, 0.24–3.45)

Reason for HIV test*	
VCT	26 (19%)
TB	27 (20%)
Personal illness other than TB	61 (44%)
Pregnancy	22 (16%)
Child's illness	2 (1%)
HIV symptoms	
Yes	103 (69%)
No	47 (31%)
Pregnant**	
Yes	12 (13%)
No	83 (87%)
Current TB therapy	
Yes	73 (49%)
No	77 (51%)
Psychiatric history	
Yes	4 (3%)
No	146 (97%)
Neurological history	
Yes	35 (23%)
No	115 (77%)
Naïve to previous ART	
Yes	136 (91%)
No	14 (9%)
NNRTI + NRTI	
Yes	149 (99%)
No	1 (1%)

Table 11. Biomedical profile of the sample (n = 150). *Data not available for 12/150 participants. **Percentage given of total women (n = 95) in sample. IQR, interquartile range; WHO, World Health Organisation; VCT, voluntary counselling and testing; TB, tuberculosis; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

The study sample was similar to HCTC's ever-treated population and to those patients who initiated treatment during the study enrolment period (Table 12), and when the study sample was compared with the total who initiated treatment during the study enrolment period, there were no significant differences observed with regard to mean CD4+ cell count (*p*=.86), CD4+ cell count <200 cells/μL (*p*=.51), HIV RNA level >500,000 copies/mL (*p*=.90), percentage WHO stage III or IV (*p*=.52) and pregnancy (*p*=.86).

Biomedical characteristic	**Sample (n=150)**	**HCTC ever-treated population (n=4,302)**	**HCTC initiated during study enrolment period (n=521)**
CD4+ cell count (mean)	119 cells/μL	115 cells/μL	121 cells/μL
CD4+ cell count <200	89%	87%	88%

cells//μL			
HIV RNA level >500,000 copies/mL	11%	10%	11%
WHO stage III or IV	76%	74%	69%
Pregnant*	13%	15%	14%

Table 12. Comparison of study sample CD4+ cell count, HIV RNA level, WHO stage and pregnancy rates with HCTC ever-treated and initiated during study enrolment populations. *Percentage given of total women. HCTC, Hannan Crusaid Treatment Centre; WHO, World Health Organisation.

Psychological characteristics of the sample

Sixty-four patients (43%) knew their latest CD4+ cell count test result. Only one patient knew their latest HIV RNA test result. While 130 patients (87%) were able to accurately identify the names of at least one medication of their prescribed ARV regimen, less than half (n=71, 47%) knew the names of all (two or three) medications in their regimen. When asked to list all possible consequences of nonadherence to ARV's, almost all patients (n=141, 94%) spontaneously mentioned poor clinical or laboratory outcomes, but only 11% referred to resistance, and only 5% mentioned that resistant virus could be transmitted to others. Only 21 patients (14%) were able to define resistance, according to the a priori scoring system. One hundred and twenty-five patients (89%) knew that they needed to take 'all or almost all' (defined in the questionnaire as 95% or more) of their ARV regimen in order to achieve best clinical and laboratory outcomes. The remaining 11% thought they had to take 'most' (defined as 60% to 94%) (7%), 'about half' (40% to 59%) (1%), or 'some' (less than 40%) of their medication (1%), or didn't know how much they needed to take (2%).

A composite knowledge score, comprising the six knowledge questions described above (awareness of latest CD4+ cell count and HIV RNA test results, able to identify the names of their prescribed ARV's, knew possible implications of poor adherence, understood meaning of resistance, and knew they needed to take all of their ARV regimen) was calculated. The mean score across the sample was 2.4/6, or 40% (SD 1.03). 73% of the sample scored below 50%.

One hundred and five patients (70%) considered HIV a serious disease. Twelve (8%) thought they could fight off the disease without ARV's. One hundred and thirty-one patients (87%) believed that ARV's were going to improve their health. Sixty-four patients (43%) were concerned about possible side-effects of their prescribed regimen.

Nine (6%) said they did not like to think about ARV's because the medications were a reminder of their HIV-positive status. One hundred and thirty-nine patients (93%) felt that the good things about ARV's outweighed the bad. Eighty-nine patients (59%) endorsed the statement 'I know better than my doctor when to when to take my medications because only I know how I am feeling'.

A composite ARV attitudes score, comprising five of the attitudes questions described above (whether they thought they could fight off the disease without ARV's, whether they believed ARV's were going to improve their health, if they were concerned about possible side-effects of their prescribed regimen, if they didn't like to think about ARV's because the medications were a reminder of their HIV-positive status, and whether they felt the good things about ARV's outweighed the bad) was calculated. A higher score indicated a more positive attitude. The median score across the sample was 4.25/5 (IQR, 4–5). 84% of the sample scored 4 or 5.

Almost all patients felt 'very confident' (n=129, 86%) or 'quite confident' (n=17, 11%) that they would be able to take their ARV medications as directed.

According to the CES-D, more than a third of the sample (n=58, 39%) had symptoms associated with depression. Of these, 23 patients (15%) had symptoms associated with mild to moderate depression, and 35 patients (23%) had symptoms associated with a major depressive episode. The following statements were true for more than 20% of patients three or more days a week: 'I felt fearful' (26%), 'I have been bothered by things that don't usually bother me' (25%), 'I could not get going during the day' (25%), 'I did not feel like eating, my appetite was poor' (23%), 'I felt depressed and sad' (23%) and 'I felt lonely' (22%). The following statements were true for more than 20% of patients two days or less a week: 'I enjoyed life' (28%) and 'I felt that I was just as good as other people' (24%). All items from the CES-D are presented in Table 13.

Symptom	**Frequency (percentage)**			
	Rarely/ none of the time <1 day	**Some of the time 1–2 days**	**Occasionally/ moderately 3–4 days**	**Most/ all of the time 5–7 days**
1. I was bothered by things that usually don't bother me	75 (50%)	37 (25%)	20 (13%)	18 (12%)

2. I did not feel like eating; my appetite was poor	92 (62%)	23 (15%)	18 (12%)	17 (11%)
3. I felt that I could not shake off the blues (sadness) even with help from my family or friends	93 (62%)	33 (22%)	13 (9%)	11 (7%)
4. I felt that I was just as good as other people	23 (15%)	13 (9%)	6 (4%)	108 (72%)
5. I had trouble keeping my mind on what I was doing	90 (60%)	30 (20%)	17 (11%)	13 (9%)
6. I felt depressed	65 (43%)	51 (34%)	19 (13%)	15 (10%)
7. I felt that everything I did was an effort	76 (51%)	46 (31%)	14 (9%)	14 (9%)
8. I felt hopeful about the future	11 (7%)	14 (9%)	20 (14%)	105 (70%)
9. I thought my life had been a failure	92 (61%)	31 (21%)	8 (5%)	19 (13%)
10. I felt fearful	78 (52%)	33 (22%)	24 (16%)	15 (10%)
11. My sleep was restless	79 (53%)	25 (17%)	20 (13%)	26 (17%)
12. I was happy	2 (1%)	24 (16%)	44 (29%)	80 (54%)
13. I talked less than usual	96 (64%)	28 (19%)	23 (15%)	3 (2%)
14. I felt lonely	87 (58%)	30 (20%)	21 (14%)	12 (8%)
15. People were unfriendly	110 (73%)	19 (13%)	12 (8%)	9 (6%)
16. I enjoyed life	16 (11%)	26 (17%)	26 (17%)	82 (55%)
17. I had crying spells	92 (61%)	40 (27%)	15 (10%)	3 (2%)
18. I felt sad	65 (43%)	55 (37%)	18 (12%)	12 (8%)
19. I felt that people disliked me	109 (73%)	16 (11%)	17 (11%)	8 (5%)
20. I could not get 'going'	79 (53%)	33 (22%)	21 (14%)	17 (11%)

Table 13. CES-D individual item frequencies and percentages.

In Radloff's (1977) original publication of the CES-D, 16 of the 20 items were presented as contributing to four factors: Depressed affect (items 3, 6, 14, 17 and 18), Positive Affect (4, 8, 12 and 16), Somatic and Retarded Activity (1, 2, 7, 11, 20), and Interpersonal (15 and 19). For this analysis, Item 1 ('I was bothered by things that usually don't bother me') was shifted from Somatic and Retarded Activity to Depressed Affect, Item 14 ('I felt lonely') was shifted from Depressed Affect to Interpersonal, and an additional factor – Cognitive – was added, comprising one item (item 5). Figure 8 compares the percentage prevalence of the sample experiencing each of the five factors more than 1 day per week (prevalence for the Positive Affect factor is presented as the absence of the positive symptom).

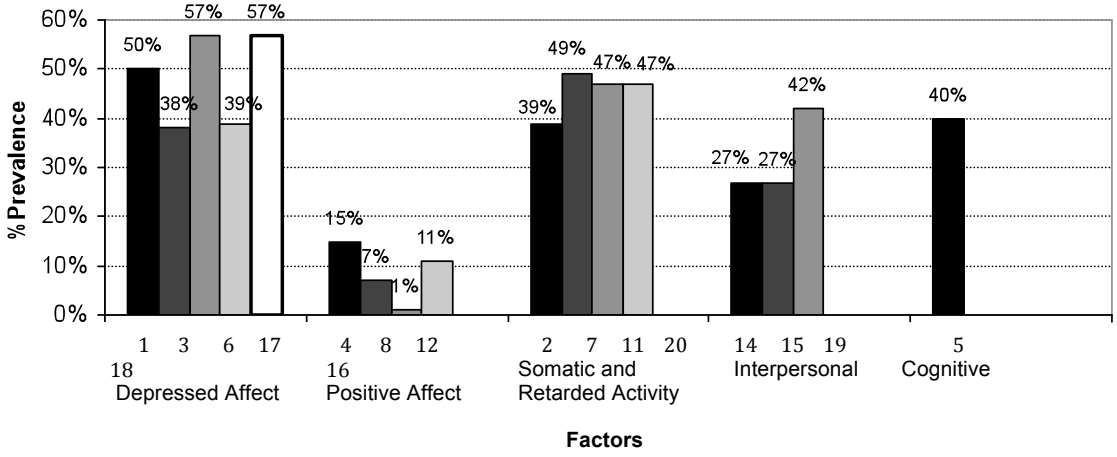

Figure 8. Comparison of depressive symptoms by factor.

According to the AUDIT's cut-off point of 8, 61 participants (41%) were classified as engaging in alcohol consumption that was hazardous or harmful. Just under one quarter of the sample (24%) drank seven or more drinks containing alcohol on a typical day when they were drinking. Nineteen percent of patients failed, at least weekly, to do what was normally expected of them because of drinking. Nine percent of patients needed a first drink in the morning, at least weekly. Nineteen percent had injured themselves or someone else because of their drinking. More than a third of participants (35%) had had a relative, friend, doctor or other health care worker concerned about their drinking, almost all of these (92%) within the last year. The following statements were true for more than 20% of patients at least weekly: 'A feeling of guilt or remorse after drinking' (29%) and 'six or more drinks on one occasion' (28%). All items from the AUDIT are presented in Table 14.

Symptom	Frequency (percentage)				
	Never	**Monthly or less**	**2–4 times per month**	**2–3 times per week**	**4 or more times per week**
1. How often do you have a drink containing alcohol?	79 (53%)	6 (4%)	21 (14%)	37 (25%)	7 (4%)

	1 or 2	3 or 4	5 or 6	7–9	10 or more
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	85 (57%)	16 (11%)	12 (8%)	13 (8%)	24 (16%)
	Never	**Less than monthly**	**Monthly**	**Weekly**	**Daily or almost daily**
3. How often do you have six or more drinks on one occasion?	100 (67%)	1 (1%)	7 (4%)	36 (24%)	6 (4%)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	120 (80%)	2 (1%)	7 (5%)	14 (9%)	7 (5%)
5. How often during the last year have you failed to do what was normally expected from you because you had been drinking?	110 (73%)	2 (1%)	10 (7%)	25 (17%)	3 (2%)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	135 (90%)	0 (0%)	1 (1%)	11 (7%)	3 (2%)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	89 (59%)	5 (3%)	13 (9%)	32 (22%)	11 (7%)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	120 (80%)	2 (1%)	9 (6%)	16 (11%)	3 (2%)
	No	**Yes, but not in the last year**		**Yes, during the last year**	
9. Have you or someone else been injured as a result of your drinking?	121 (81%)	19 (13%)		10 (6%)	
10. Has a relative or friend or a doctor been concerned about your drinking or suggested you cut down?	98 (65%)	4 (3%)		48 (32%)	

Table 14. AUDIT individual item frequencies and percentages.

The AUDIT's first three items assess the amount and frequency of alcohol consumption (hazardous alcohol use), items 4–6 assess alcohol dependence, and items 7–10 assess

the problems caused by alcohol (harmful alcohol use). Figure 9 compares the percentage prevalence of the sample experiencing each of the three areas of alcohol-related problems (prevalence of each symptom was considered if the response was not 'never', '1 or 2' or 'no').

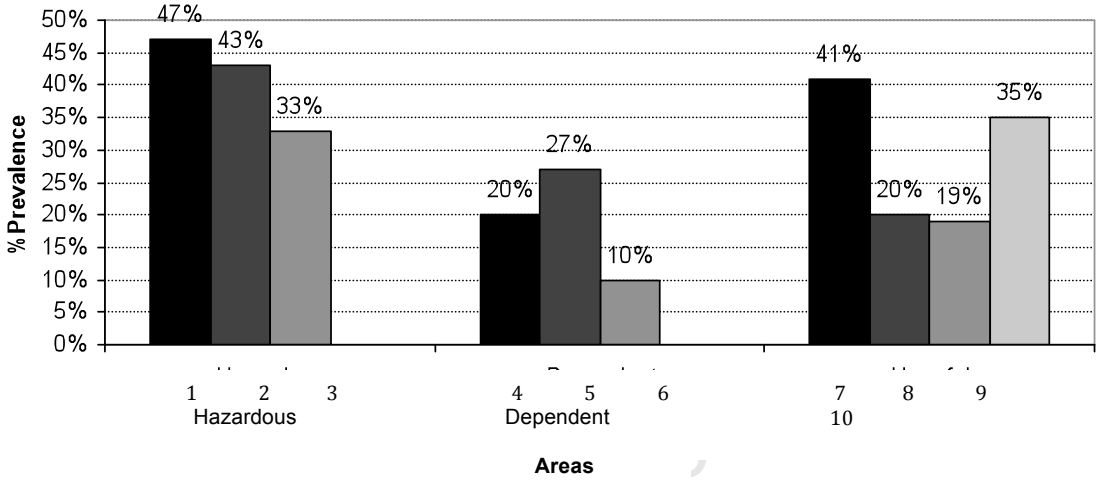

Figure 9. Comparison of alcohol abuse symptoms by area.

Ten participants (7%) had used recreational drugs in the last 12 months, all of whom had taken marijuana, and two of whom had taken mandrax.

Neuropsychological test scores consist of primary scores which summarise overall performance on the task (e.g. number of correct responses or time to complete) as well as various process scores which characterise performance on key components or specific aspects of the task (e.g. contrast in performance across different trials or number of errors made). Mean neuropsychological test scores and standard deviations are reported in Appendix J.

There were several relationships observed between neurolopsychological test scores and various disease indicators (HIV RNA level, CD4+ cell count and WHO stage). Unsurprisingly, in most cases (14/18), poor cognitive performance was related to advanced disease. All 14 of these cases were scores of production or accuracy (producing words or designs in the D-KEFS Verbal Fluency and Design Fluency subtests or remembering story units in the WMS Logical Memory subtest), meaning that healthier patients were able to produce more words and designs and remember more of

the stories read to them. All 4 of the remaining cases were error scores (repetition or set loss errors made in the course of producing words or designs); given healthier patients' higher productivity rate, it is understandable that they would have made more errors. WHO was the disease indicator most frequently related to cognitive functioning, accounting for 15 of the 18 relationships observed. These chi-square results are presented in Appendix K.

Table 15 summarizes the key psychological characteristics of the sample.

Characteristic	N
Knowledge	
Knew latest CD4+ cell count	
Yes	64 (43%)
No	86 (57%)
Knew latest HIV RNA test result	
Yes	1 (1%)
No	149 (99%)
Knew names of ≥1 ARV medication	
Yes	130 (87%)
No	20 (13%)
Knew names of all ARV medications	
Yes	71 (47%)
No	79 (53%)
Knew implications of nonadherence	
Clinical/ laboratory outcomes	141 (94%)
Resistance	16 (11%)
Transmitted resistance	7 (5%)
Able to define 'resistance'*	
Yes	21 (14%)
No	129 (86%)
Reported required adherence**	
All (≥95%)	125 (89%)
Most (60%–94%)	10 (7%)
Half (40%–59%)	1 (1%)
Some (<40%)	1 (1%)
Unsure	3 (2%)
Attitudes	
Considered HIV a serious disease	
Yes	105 (70%)
No	45 (30%)
Believed could fight off HIV without ART	
Yes	12 (8%)
No	138 (92%)
Believed ART would improve health	
Yes	139 (87%)
No	19 (13%)
Concerned about side effects	
Yes	64 (43%)
No	86 (57%)

Preferred not to think about ART	
Yes	9 (6%)
No	141 (94%)
Believed good things about ART outweighed bad	
Yes	139 (93%)
No	11 (7%)
Believed knew better than doctor when to take medications	
Yes	89 (59%)
No	61 (41%)
ART self-efficacy	
Very confident	129 (86%)
Quite confident	17 (11%)
Quite unconfident	3 (2%)
Very unconfident	1 (1%)
CES-D score	
Mild to moderate depression	23 (15%)
Major depressive episode	35 (23%)
Total with depressive symptoms	58 (39%)
AUDIT score	
Hazardous or harmful alcohol consumption	61 (41%)
Illicit drug use in last 12 months	
Yes	10 (7%)
No	140 (93%)

Table 15. Psychological profile of the sample (n=150). *According to the a priori scoring system. ** Data available for 140/150 participants. CES-D, Centre for Epidemiological Studies on Depression Scale; AUDIT, Alcohol Use Disorders Identification Test.

Social characteristics of the sample

Forty-nine (33%) were single, 28 (19%) married, 27 (18%) cohabiting but not married, 44 (29%) in a relationship but not cohabiting or married, one widowed and one separated. The median household size was 4 (IQR, 3–6). Nine participants (6%) lived alone. Forty (27%) lived in a household of six or more people. Fifty-three (35%) lived with a partner, 67 (45%) with their child(ren), 43 (29%) with a parent, and 100 (67%) with other family. Four were living with a friend or border. Almost all patients (96%) felt they had a strong emotional bond with at least one other person.

One hundred and twenty-seven participants (85%) knew someone else who was HIV-positive. The mean number of HIV-positive people that participants knew was two (IQR, 1–4.25). Forty-five (30%) had an HIV-positive spouse or partner. Of the patients who were in a relationship (married, cohabiting or in a relationship but not cohabiting or married), 46% had an HIV-positive partner. Nine (6%) had an HIV-positive child, five

(3%) a positive parent, and 55 (37%) a positive family member (other than spouse, child or parent). Sixty-nine (46%) had a positive friend and 49 (33%) a positive neighbour.

Ninety-nine patients (66%) knew someone else who was on ART. The mean number of people on ART that participants knew was 1 (IQR, 0–2). Fourteen (9%) of sample, 14% of those in a relationship) had a spouse or partner on ART. Five (3%) had a child on ART, four (3%) a parent on ART, and 28 (19%) a family member (other than spouse, child or parent) on ART. Forty (27%) had a friend on ART, and 34 (23%) a neighbour on ART. Twenty-seven participants (18%) were living with someone who was on ART.

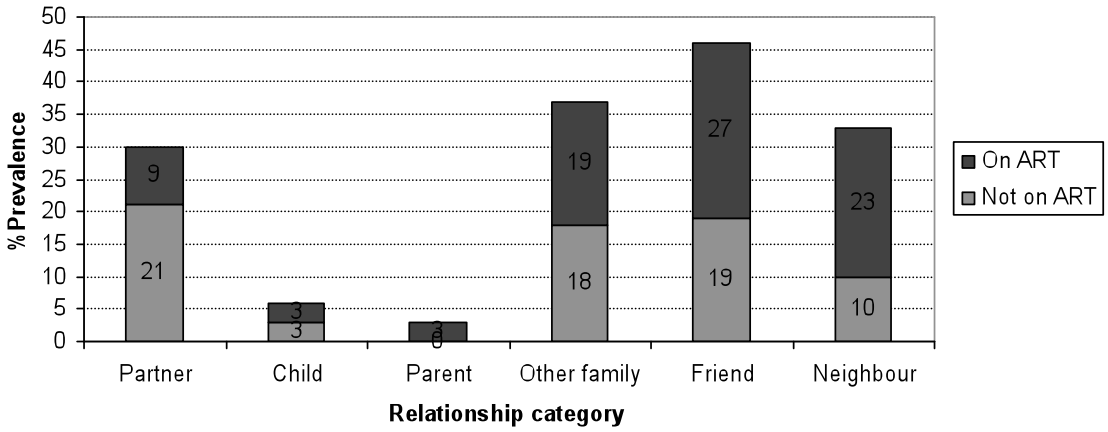

Figure 10. HIV-positive others known to sample.

Almost all participants (97%) had disclosed their HIV-positive status to at least one other person. The mean number of people disclosed to was 3 (IQR, 2–7.25). Of the patients who were in a relationship (married, cohabiting or in a relationship but not cohabiting or married), 88% had disclosed to their partner. Of the patients who lived with their child(ren), 69% had disclosed to their child(ren). Sixty-five (43%) had disclosed to a parent, 122 (81%) a family member (other than spouse, child(ren) or parent), 57 (38%) a friend, and 24 (16%) a neighbour. One hundred and twenty-nine patients (86%) were living with someone they had disclosed to, and 99 patients (66%) had disclosed to everyone in their household. One hundred and fifteen patients (77%) had disclosed to someone who would remind them to take their ART. Seventeen patients (11%) were living with someone they had disclosed to and who would remind them to take their ART. Only seven patients had disclosed to someone who felt they should not start ART.

Twenty-three patients (15%) said they 'always' saw the same doctor at their clinic visits, 12 (8%) 'rarely' and 115 (77%) 'never'. Patients said the doctors and nurses at the clinic spoke to them in their home language 'always' (n=9, 6%), 'sometimes' (n=43, 29%) and 'never' (n=98, 65%). One hundred and thirty-one patients (87%) felt they could talk to the doctors and nurses at the clinic about any problems they were having. One hundred and thirty-six patients (91%) said they trusted the doctors and nurses. One hundred and forty-five patients (97%) felt the doctors and nurses at the clinic respected them. One hundred and forty-five patients (97%) were satisfied with their relationship with the doctors and nurses at the clinic.

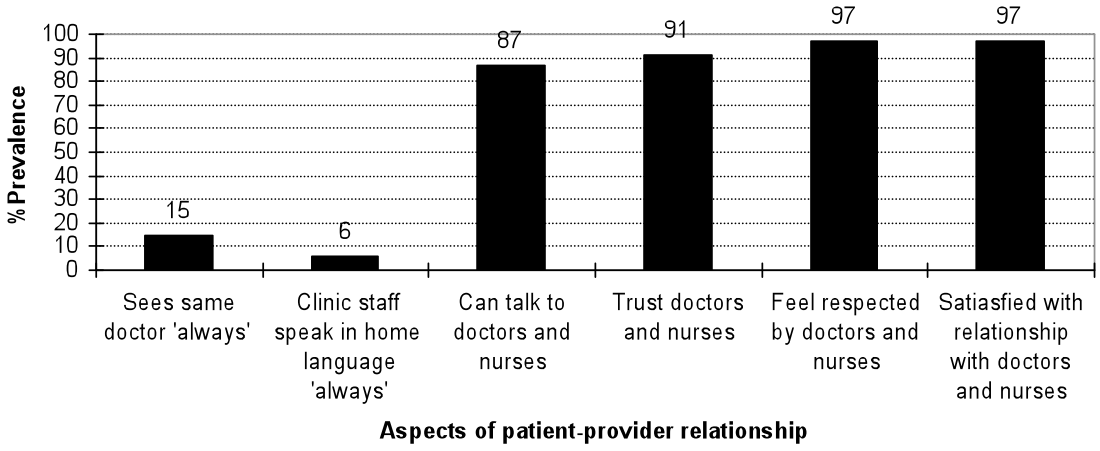

Figure 11. Self-reported relationship with health care provider.

A composite patient-clinic relationship score, comprising four of the questions described above (whether patients felt they could talk to doctors and nurses at the clinic about any problems they were having, whether they trust the doctors and nurses, whether they felt the doctors and nurses at the clinic respect them, and whether they are satisfied with their relationship with the doctors/ nurses at the clinic) was calculated. The median score across the sample was four. Seventy-eight percent of the sample scored a full four.

Key social characteristics of the study participants are presented in Table 16.

Characteristic	N or median
Relationship status	
Single	49 (32%)
Married	28 (19%)
Relationship – cohabiting	27 (18%)
Relationship – non-cohabiting	44 (29%)
Widowed	1 (1%)
Separated	1 (1%)
Household size	
Median	4 (IQR, 3–6)
Living alone	9 (6%)
Household ≥6 people	40 (27%)
Reported emotional bond with another	144 (96%)
HIV-positive others	
Knew HIV-positive other	127 (85%)
Number of HIV-positive others know (median)	2 (IQR, 1–4.25)
Knew other on ART	99 (66%)
Number of others on ART known (median)	1 (IQR, 0–2)
Disclosure	
Disclosed to at least one person	145 (97%)
Number of people disclosed to (median)	3 (IQR, 2–7.25)
Living with someone disclosed to	129 (86%)
Disclosed to everyone in household	99 (66%)
Support	
Someone will assist with ART adherence	115 (77%)
Living with someone who will assist	17 (11%)
≥1 person against patient taking ART	7 (5%)
Patient-provider relationship	
Always sees same doctor at clinic	23 (15%)
Provider speaks in home language	9 (6%)
Can talk to provider about problems	131 (87%)
Trusts provider	136 (91%)
Feels provider respects him/ her	145 (97%)
Satisfied with relationship with provider	145 (97%)

Table 16. Social characteristics of the sample (n = 150). IQR, interquartile range.

Miscellaneous characteristics of the sample

The adherence aid most planned for use by patients initiating treatment was a pillbox (n=141, 94%). Thereafter, in descending order of planned use, were: alarm clock on cellular telephone (n=63, 42%), television or radio programme (n=16, 11%), alarm clock on wrist watch (n=9, 6%), free-standing alarm clock (n=7, 5%), diary (n=7, 5%) and calendar (n=5, 3%).

Almost all patients traveled to the clinic by taxi (n=80; 53%) or on foot (n=69; 46%). Only one traveled by car. The median length of time patients spent traveling to the clinic was

25 minutes each way (IQR, 15–30 minutes). Of the 80 (53%) patients paying for transportation to the clinic, 80% paid R8 for return transportation (range 7–26 ZAR). Fifty-nine (77%) considered this quite unaffordable or very unaffordable. When asked to consider both time and cost, 99 (66%) thought clinic visits were very convenient or quite convenient, and 51 (34%) very inconvenient or quite inconvenient.

Miscellaneous characteristics of the sample are presented in Table 17.

Characteristic	N or mean/ median
Planned adherence aids	
Pillbox	141 (94%)
Alarm clock on cellular telephone	63 (42%)
Television or radio programme	16 (11%)
Alarm clock on wrist watch	9 (6%)
Free-standing alarm clock	7 (5%)
Diary	7 (5%)
Calendar	5 (3%)
Transport type to clinic	
Taxi	80 (53%)
On foot	69 (46%)
Car	1 (1%)
Transport cost to clinic*	
Mean (ZAR)	8 (range 7–26)
Considered transport cost unaffordable	59 (77%)
Time to clinic**	
Median	25 minutes each way (IQR, 15–30 min)
Clinic visits convenient	
Yes	99 (66%)
No	51 (34%)

Table 17. Miscellaneous characteristics of the sample (n=150). *Transport cost and attitudes provided for those patients paying for transportation to the clinic (n=80, 53%). **Time to clinic data not available for 2/150 participants. ZAR, South African Rands; IQR, interquartile range.

CHAPTER 5

Outcomes at 16 and 96 weeks: Medication adherence, virological suppression and retention to care

As outlined in Chapter 3, medication adherence was measured and evaluated according to four indices: 1) early behavioural marker of medication adherence ('early pill count adherence'), 2) late clinical marker of medication adherence ('late virological suppression'), 3) late behavioural marker of clinical care adherence ('retention to care') and 4) a composite measure of all three ('composite adherence success').

Patients enrolling in the study were followed for 96 weeks: their early pill count adherence was assessed over the first 16 weeks (weeks 0–16), and their late virological suppression and retention to care assessed at 96-weeks (Week 96). A study timeline of the measurement of the adherence indices is presented in Figure 12 and their definitions, measurement periods and exclusions in Table 18.

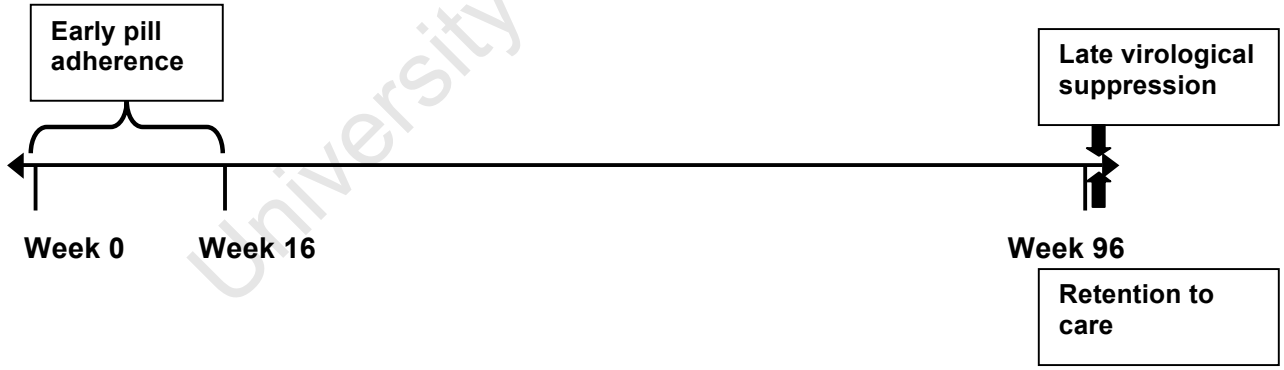

Figure 12. Adherence indices and timeline.

	Adherence indices			
	Early pill count adherence	**Late virological suppression**	**Retention to care**	**Composite adherence success**
Definition	≥90% of prescribed medications	HIV RNA level <50 copies/mL	<90 days since last clinic appointment	≥90% of prescribed medications, HIV RNA level <50 copies/mL, and <90 days since last clinic appointment

Measure	Pill count	HIV RNA test	File review, counselor consult	Pill count, HIV RNA test, file review and counselor consult
Measurement period	Week 0 – 16	Week 96	Week 96	Week 0 – 96
Excluded status	None*	Died, TFO	Died, TFO	None*
Final n	n=149	n=133	n=133	n=149

Table 18. Definitions, measurement periods and exclusions of adherence indices. *1 patient who died on treatment between Week 0 and Week 4 excluded as no data available. TFO, transferred out.

Early pill count adherence (Week 0 – Week 16)

Early pill count adherence was assessed over the initial 16-week period following the first prescription visit (Week 0–Week 16). During the early pill count adherence monitoring period, 3 patients died on treatment, 5 TFO to other facilities and 15 were LTFU. For 7 of the 8 patients who died on treatment or TFO, the sub-period for which they had been monitored (4, 8 or 12 weeks) was used in the analyses. Pill count data was unavailable for one patient who died on treatment between Week 0 and Week 4 – after study enrolment and treatment initiation but before the first pill count – so was excluded from the early pill count adherence and subsequent analyses. The 15 patients who were LTFU were considered throughout the 16-week monitoring period and assigned a value of 0% adherence from the date of their first missed scheduled pharmacy visit. (See Chapter 3 for definitions of death on treatment, TFO and LTFU and justifications for their inclusion/ exclusion and data management).

Patients were defined as adherent if they had taken 90% or more of their prescribed drugs across the 16 weeks. According to the definition, 112 patients (75%) were defined as adherent and 37 patients as nonadherent. Patient outcomes from the early pill count adherence analysis are presented in Figure 13.

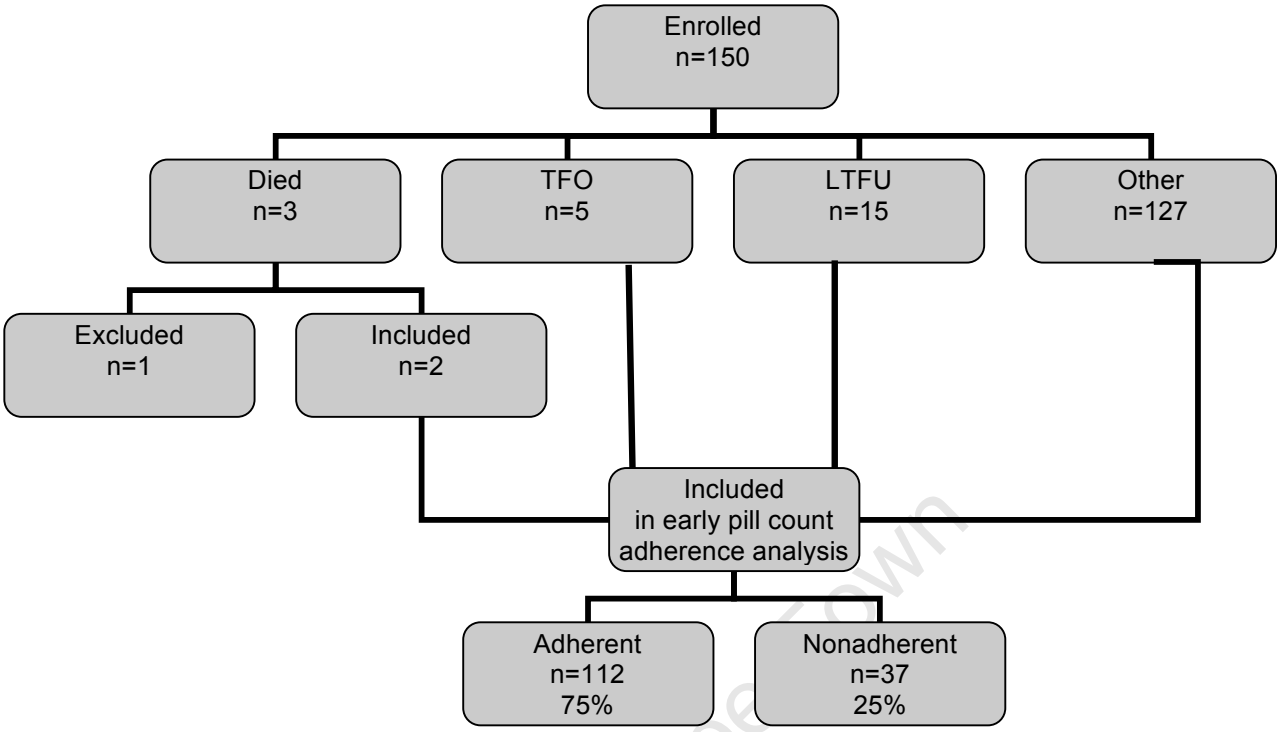

Figure 13. Patient outcomes in early pill count analysis (Weeks 0–16).

The sample's mean pill count adherence across the 16 weeks was 87%. The number of patients whose mean adherence across the 16-week monitoring period fell into each 10% adherence band is presented in Figure 14.

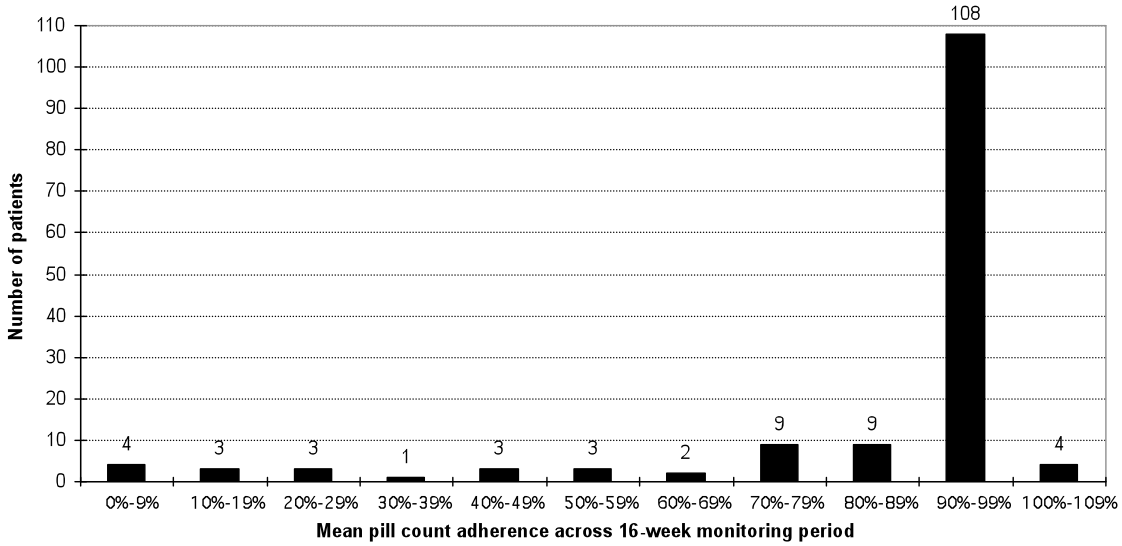

Figure 14. Number of patients falling into 10% mean adherence bands across the early pill count analysis (Weeks 0–16).

Although 37 patients (25%) had a mean adherence across the 16-week monitoring period of less than 90%, 56 patients (38%) had a single adherence measurement of less than 90% during at least one of the 4-week time periods comprising the 16-week monitoring period. The number of patients whose lowest recorded adherence during any 4-week time period comprising the 16-week monitoring period fell into each 10% adherence band is presented in Figure 15.

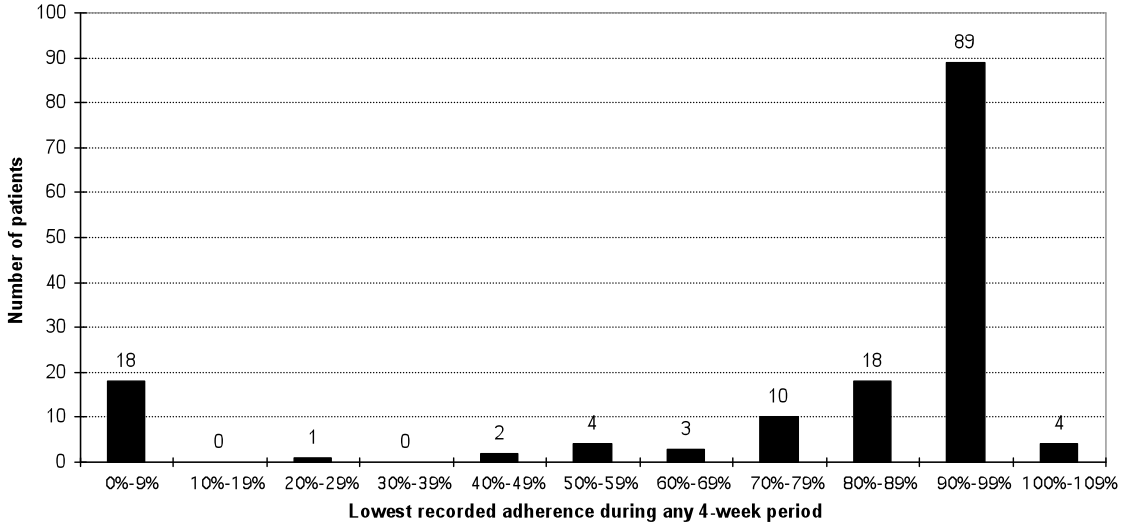

Figure 15. Number of patients whose lowest recorded adherence during any 4-week time period fell into each 10% adherence band.

When comparing the sample's mean pill count adherence across each of the 4-week intervals within the 16-week monitoring period, results showed a consistent decrease in adherence with time. The sample's mean adherence was 93%, 88%, 84% and 83% for each of the 4-week time intervals taken chronologically, and the difference was significant (F (4) = 3.29, p=.01). Comparisons of the 4-week time intervals within the 16-week monitoring period are presented in Table 19 and Figure 16.

	Week 0 – Week 4	Week 4 – Week 8	Week 8 – Week 12	Week 12 – Week 16
Mean	93%	88%	84%	83%
SD (range)	18% (0% - 100%)	26% (0% - 100%)	31% (0% - 100%)	33% (0% - 100%)
Number (percentage) of sample with mean adherence ≥90%	n=125 (84%*)	n=116 (80%**)	n=111 (77%***)	n=106 (75%****)

Table 19. Comparison of pill count adherence across 4-week time intervals within 16-week monitoring period. *1 excluded due to death. **4 excluded due to death/ TFO. ***5 excluded due to death/TFO. ****8 excluded due to death/TFO. SD, standard deviation.

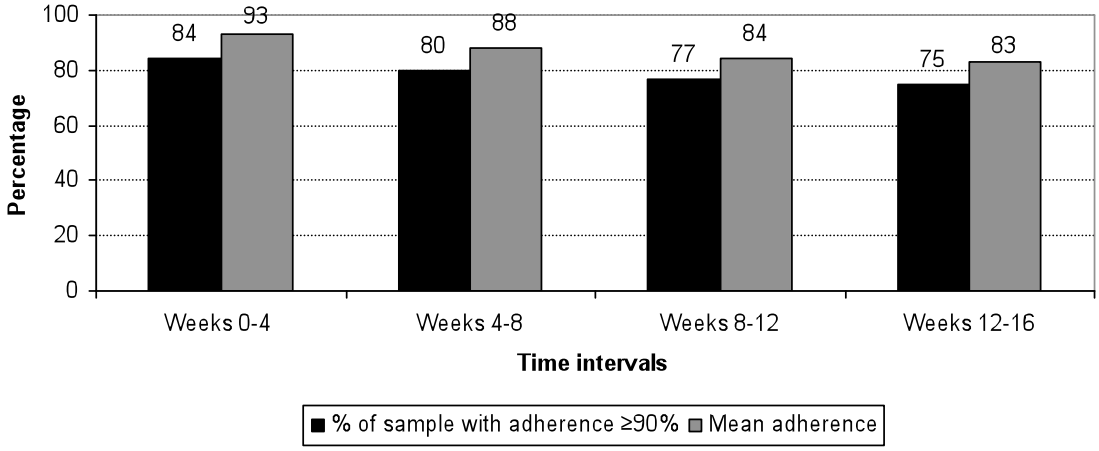

Figure 16. Comparison of pill count adherence across 4-week time intervals within 16-week monitoring period. Note: Mean adherence not cumulative.

When comparing the sample's pill count adherence to each of the five drug regimens across the 16-week monitoring period, results showed variations in adherence by regimen. The sample's mean pill count adherence across 16 weeks to d4T/3TC/EFV was 88%, d4T/3TC/NVP 83%, AZT/3TC/EFV 92% and AZT/3TC/NVP 91%, and the single patient on AZT/ddI/EFV had an adherence of 99% and the difference between them was significant (F (4) = 2.47, p=.04). Comparisons of the sample's mean pill count adherence to each of the five drug regimens are presented in Table 20 and Figure 17.

	d4T/3TC/EFV	**D4T/3TC/NVP**	**AZT/3TC/EFV**	**AZT/3TC/NVP**
Mean	88%	83%	92%	91%
SD (range)	25% (0% - 100%)	32% (0% - 100%)	21% (0% - 100%)	20% (0% - 100%)
Number (percentage) on regimens with mean adherence ≥90%	n=51 (79%*)	n=40 (74%**)	n=8 (73%***)	n=12 (75%****)

Table 20. Comparison of the sample's pill count adherence to each of the 4 drug regimens (excluding the single patient on AZT/ddI/EFV). *Includes 68 patients. **Includes 54 patients. ***Includes 11 patients. ****Includes 16 patients. SD, standard deviation.

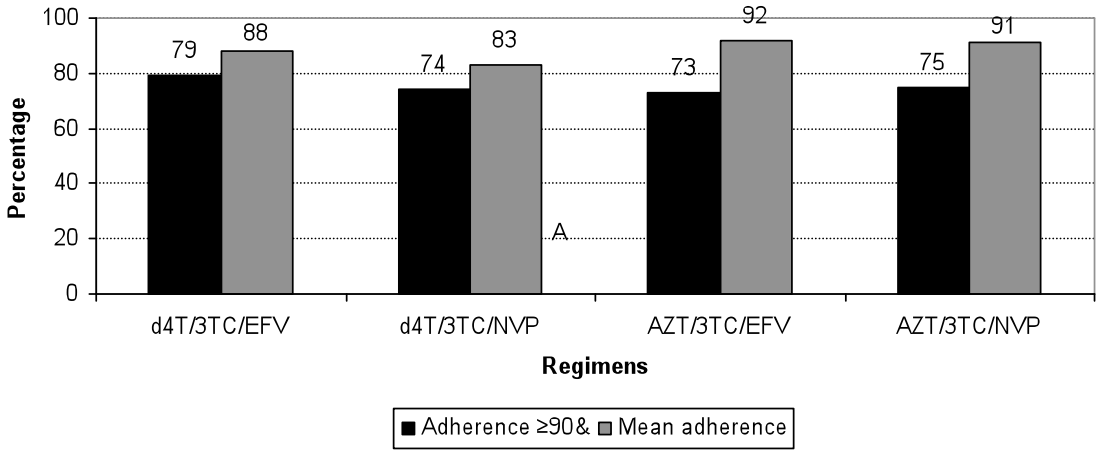

Figure 17. Comparison of the sample's pill count adherence to each of the 4 drug regimens (excluding the single patient on AZT/ddI/EFV).

Late virological suppression (Week 96)

Late virological suppression was assessed at the 96-week visit. During the study's 96-week monitoring period, 7 patients died on treatment, 10 TFO to other facilities and 38 were LTFU. Patients who died on treatment and TFO before the 96 week visit were excluded from the late virological suppression analysis. Patients who were LTFU before the 96 week visit were included in the virological suppression analysis and assigned as unsuppressed with a maximum value of >500,000 copies/mL. For patients who had not died, been TFO or LTFU, where a viral load test result was unavailable for the 96 week visit, the closest preceding viral load measurement by date was used. Due to the exclusions mentioned above, 133 patients were included in the late virological suppression analysis. (See Chapter 3 for definitions of death on treatment, TFO and LTFU and justifications for their inclusion/ exclusion and data management).

Patients were defined as achieving virological suppression if their viral load levels were undetectable (<50 copies/mL) at the 96 week clinic visit. According to the definition and death, TFO and LTFU inclusions/ exclusions outlined in the previous paragraph, 73 patients (55%) were defined as achieving virological suppression and 60 patients as not achieving virological suppression. It should be considered that 38 of the 60 unsuppressed patients were in fact LTFU at 96 weeks; excluding these patients would

lift the sample's suppression rate from 55% to 77%. Patient outcomes from the late virological suppression analysis are presented in Figure 18.

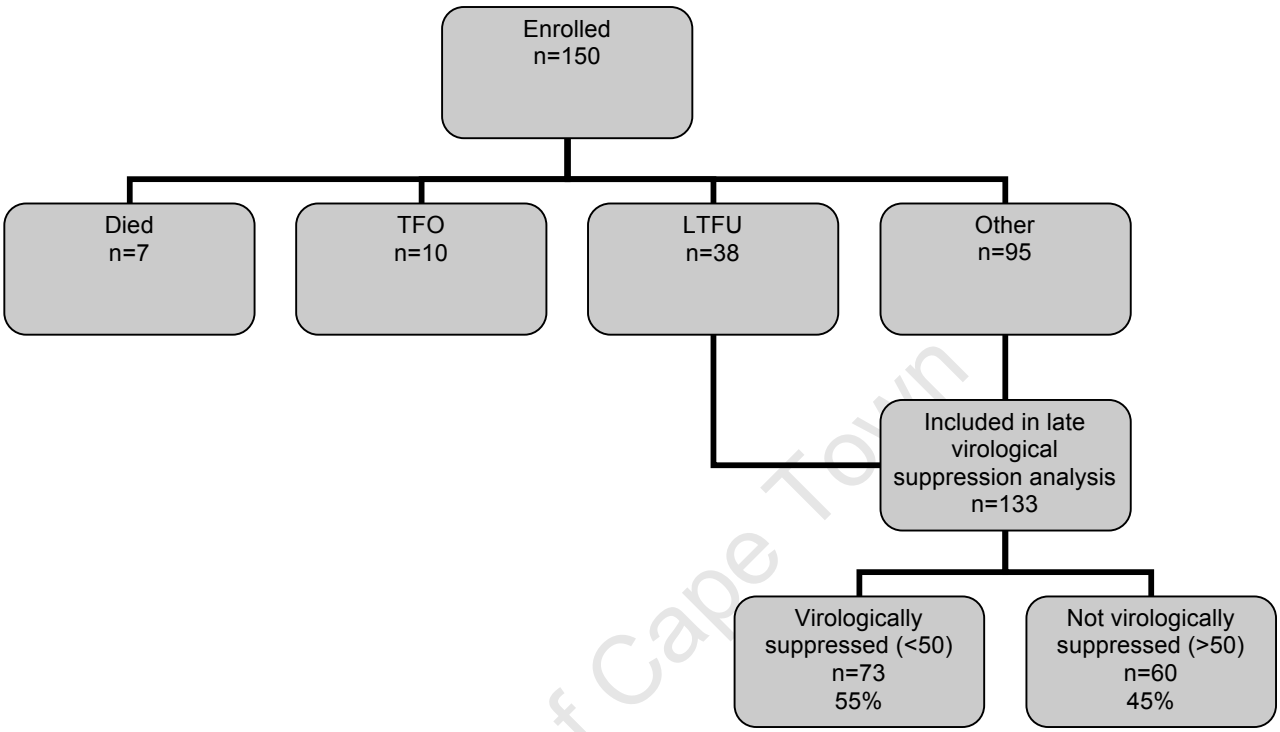

Figure 18. Patient outcomes in late virological suppression analysis (Week 96).

HIV RNA level across the sample at 96 weeks ranged from undetectable (<50 copies/mL) to greater than the assay's ability to quantify (>500,000 copies/mL), with a median of <50 copies/mL (IQR, <50 – >500,000 copies/mL). The number of patients whose viral load at the 96-week visit fell into each viral load band is presented in Figure 19.

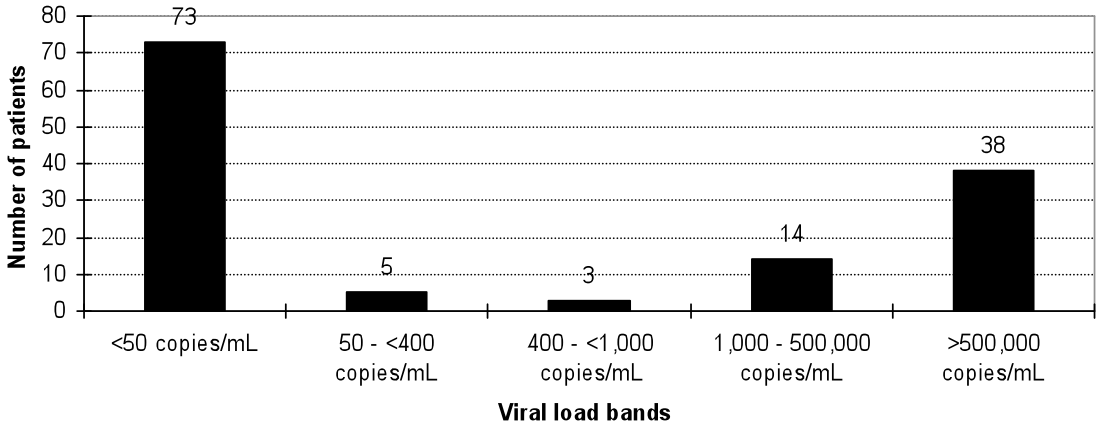

Figure 19. Number of patients falling into each viral load band at the 96-week visit.

Achieving a mean pill count of ≥90% across the first 16 weeks of treatment was significantly associated with achieving virological suppression (<50 copies/mL) at 96 weeks (p<.0001). Sixty-nine percent (n=70) of those who showed good adherence were virologically suppressed at 96 weeks, compared with only 10% (n=3) of those with poor initial adherence (see Figure 20). Similarly, 96% (n=70) of the patients who had undetectable viral loads at 96 weeks showed good adherence initially, compared with just 53% (n=32) of those with viral loads >50 copies/mL.

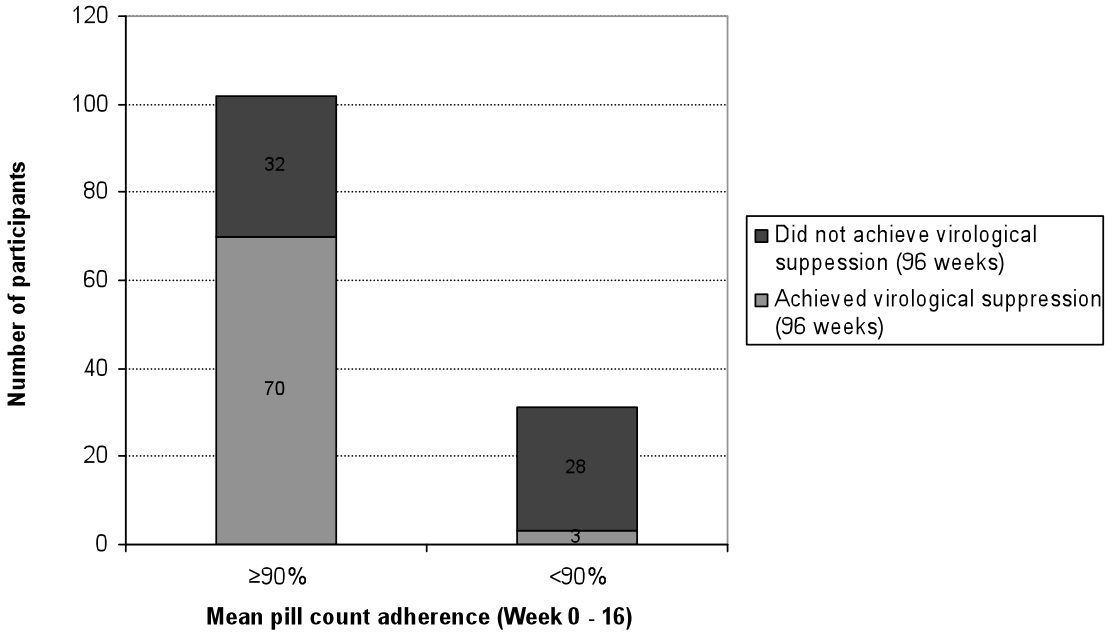

Figure 20. Comparison of number of patients achieving virological suppression to mean pill count adherence.

Table 21 compares mean pill count adherence across the first 16 weeks of treatment to virological outcomes at 96 weeks.

Mean pill count adherence (Week 0 – 16)	Percent virologically suppressed (<50 copies/mL) at 96 weeks
0 – 9% (n=3)	0%
10 – 19% (n=3)	0%
20 – 29% (n=3)	0%
30 – 39% (n=1)	0%
40 – 49% (n=3)	0%
50 – 59% (n=2)	0%
60 – 69% (n=1)	0%
70 – 79% (n=7)	14%
80 – 89% (n=8)	25%
90 – 100% (n=102)	69%

Table 21. Associations between mean pill count adherence across the first 16 weeks of treatment and virological outcomes at 96 weeks.

There was a negative correlation between lowest recorded pill count adherence during any 4-week interval within the first 16 weeks of treatment and HIV RNA level at 96 weeks (r=-0.56). Only 25% of those with a lowest recorded pill count adherence during any 4-week interval within the first 16 weeks of treatment of <90% were suppressed at 96 weeks.

Retention to care

Retention to care was assessed at the 96-week visit. As outlined earlier, 7 patients died on treatment and 10 TFO to other facilities. Patients who died and TFO before the 96 week visit were excluded from the retention to care analysis. (See Chapter 3 for definitions of deaths on treatment and TFO and justifications for their inclusion/ exclusion and data management).

Patients were defined as LTFU if they had not returned to the clinic for 90 days or more since their last appointment. Patients who did not return to the clinic for 90 days or more after a clinic appointment but subsequently returned to the clinic during the 96-week monitoring period were not defined as LTFU. According to the definition, 95 patients (71%) were defined as retained in care ad 38 patients as LTFU. Patient outcomes from the retention to care analysis are presented in Figure 21.

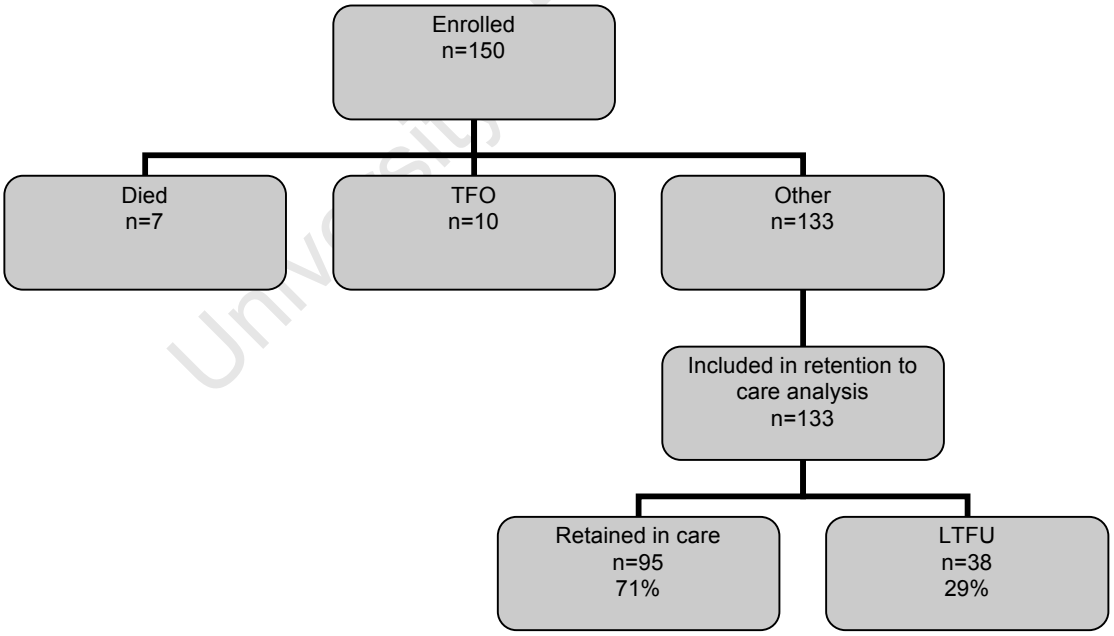

Figure 21. Patient outcomes in retention to care analysis (Week 96).

Achieving a mean pill count of ≥90% across the first 16 weeks of treatment was significantly associated with retention to care at 96 weeks ($[chi]^2(1) = 30.39$, $p<.0001$). Eighty-three percent (n=85) of those who showed good adherence were retained in care at 96 weeks, compared with only 32% (n=10) of those with poor initial adherence (see Figure 22). Similarly, 90% (n=85) of the patients who were retained in care at 96 weeks showed good adherence initially, compared with just 45% (n=17) of those who were LTFU.

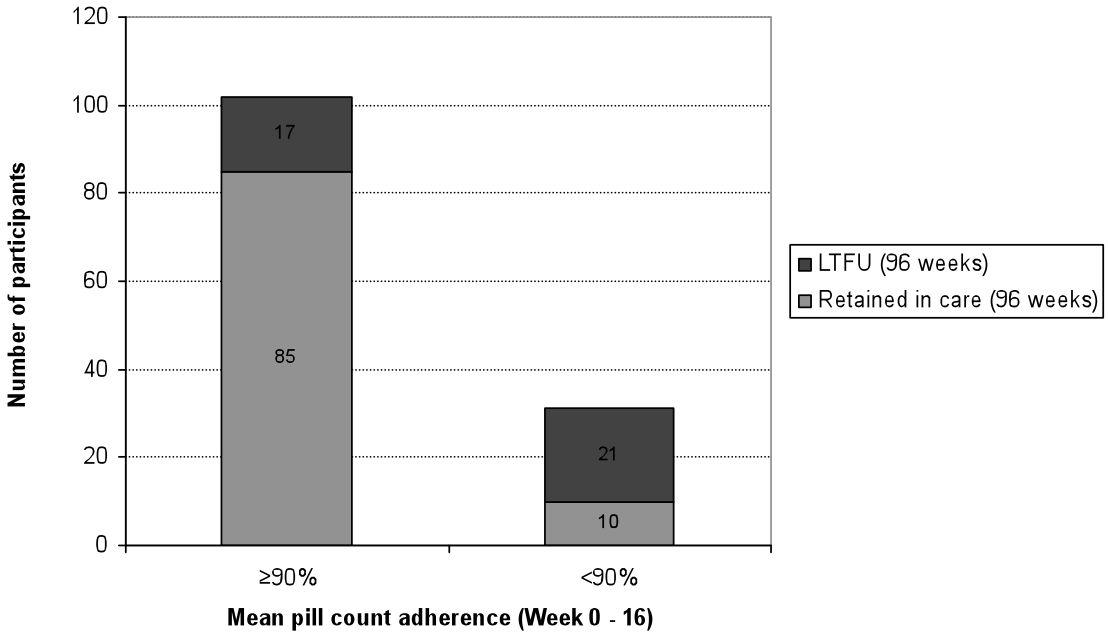

Figure 22. Comparison of number of patients retained in care by mean pill count adherence.

Table 22 compares mean pill count adherence across the first 16 weeks of treatment with retention outcomes at 96 weeks.

Mean pill count adherence (Week 0 – 16)	Percent retained in care at 96 weeks
0 – 9% (n=3)	0%
10 – 19% (n=3)	0%
20 – 29% (n=3)	0%
30 – 39% (n=1)	100%
40 – 49% (n=3)	0%
50 – 59% (n=2)	50%
60 – 69% (n=1)	0%
70 – 79% (n=7)	57%
80 – 89% (n=8)	50%
90 – 100% (n=102)	83%

Table 22. Associations between mean pill count adherence across the first 16 weeks of treatment and retention outcomes at 96 weeks.

Similarly, the mean pill count adherence across the first 16 weeks of treatment amongst those retained in care at 96 weeks was 93%, compared with the mean pill count adherence of those LTFU at 96 weeks which was 57%, a difference that was highly significant (p<.0001).

There was also a relationship between lowest recorded pill count adherence during any 4-week interval within the first 16 weeks of treatment and retention in care at 96 weeks (p<.0001). Just 48% of those with a lowest recorded pill count adherence during any 4-week interval within the first 16 weeks of treatment of <90% were retained in care at 96 weeks, compared with 85% of those whose lowest recorded pill count adherence never fell below 90%.

Composite adherence success

The composite adherence success measure comprised the three adherence indices described above: early pill count adherence, late virological suppression and retention to care. At the end of the study's 96-week monitoring period, patients were defined as achieving composite adherence success if they had achieved ≥90% mean adherence across the first 16 weeks of treatment, achieved virological suppression at 96 weeks and it was <90 days since their last clinic visit. Patients were included in the analysis if there was any pill count, HIV RNA test or retention data recorded for them. For all patients who had TFO or been LTFU, and all but one of those who had died on treatment before the end of the 96 week follow-up period, pill count data from their first 16 week follow-up period was available. The single patient who had died just after Week 0 and before the next clinic visit had no pill count, HIV RNA test or retention data available and was excluded from the composite adherence success analysis, meaning that 149 patients were analysed.

According to the above definition of composite adherence success, 80 patients (54%) achieved adherence success and 69 patients (46%) did not. Patient outcomes from the composite adherence success analysis are presented in Figure 23.

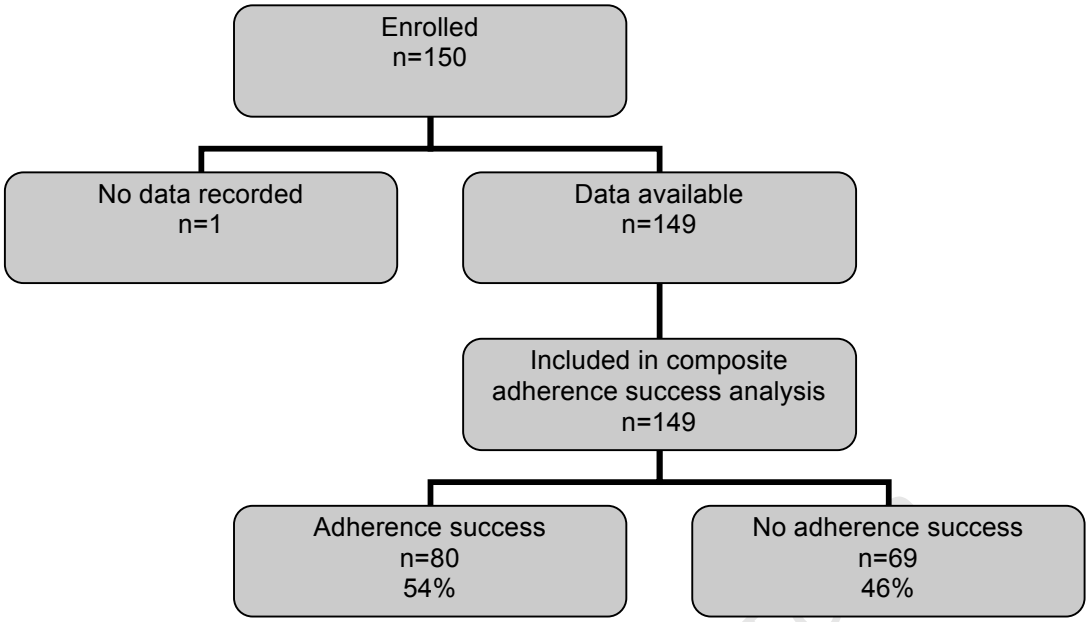

Figure 23. Patient outcomes in composite adherence success analysis (Week 0 – Week 96).

Of the 69 patients who did not achieve adherence success, nine (13%) were assigned to the unsuccessful group because they had not achieved ≥90% mean pill count adherence during the first 16 weeks of treatment, twelve (18%) because they were LTFU at 96 weeks, fifteen (22%) because they did not achieve virological suppression at the 96-week visit, three (4%) because they had not achieved ≥90% mean pill count adherence during the first 16 weeks of treatment and were LTFU at 96 weeks, seven (10%) because they had not achieved ≥90% mean pill count adherence during the first 16 weeks of treatment and did not achieve virological suppression at the 96-week visit, five (7%) because they were LTFU and did not achieve virological suppression at 96 weeks, and eighteen (26%) because they had not achieved ≥90% mean pill count adherence during the first 16 weeks of treatment and were LTFU and did not achieve virological suppression at 96 weeks. Figure 24 depicts the reasons for patients' failure to achieve composite adherence success.

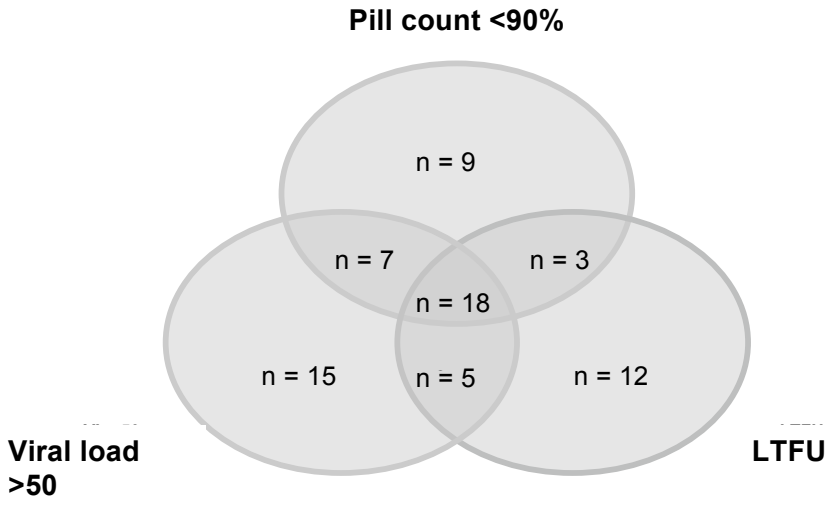

Figure 24. Reasons for failure to achieve adherence success.

As discussed in Chapter 4, the study sample represented 29% of patients who initiated treatment during the study enrolment period (April 2007 – January 2008, n=521). Although pill count calculations are routinely performed at HCTC at each pharmacy visit, these data are only recorded in patient clinic files and so was unavailable for comparison. However, HIV RNA test and LTFU data are recorded on a well-maintained clinic database, as are death and TFO data. When the study sample was compared with the total who initiated treatment during the study enrolment period, there were no significant differences observed in regard to rates of death on treatment (*p*=.08), TFO (*p*=.09), virological suppression (*p*=.12) and retention to care (*p*=.08) (see Table 23).

Outcome	Sample (n = 150)	HCTC initiated during study enrolment period (n = 521)
Died on treatment	7 (5%)	38 (7%)
TFO	10 (7%)	55 (11%)
% Virologically suppressed at 96 weeks	88 (66%)	364 (70%)
% Retained in care at 96 weeks	95 (71%)	408 (78%)

Table 23. Comparison of study sample outcomes at 96 weeks with those of all patients initiating treatment at HCTC during the enrolment period. HCTC, Hannan Crusaid Treatment Centre; TFO, transferred out.

Factors associated with early pill count adherence

Table 24 displays the factors significantly associated with early pill count adherence in chi-square analyses.

Demographic
Employed, *p*=.04
Biomedical
Report never having experienced haematological symptoms as a result of HIV, *p*=.01
Report ever having experienced dermatological symptoms as a result of HIV, *p*=.01
Psychological
No presence of alcohol abuse on AUDIT scale, *p*=.0004
Drinking alcohol less frequently, *p*=.0003
Drinking fewer alcoholic drinks on a typical day of drinking, *p*=.008
Drinking 6 or more drinks on one occasion no more than monthly, *p*=.0009
Never being unable to remember what happened the night before because of drinking, *p*=.03
Experiencing feelings of guilt or remorse after drinking less than monthly, *p*=.01
Never failing to do what is expected because of drinking, *p*<.0001
Score of ≥20 on Verbal Fluency Category Fluency: Total Correct, *p*=.04
No set loss errors on the 'animals' semantic condition of Verbal Fluency, *p*<.0001
No repetition errors or 5 or more repetition errors across Verbal Fluency and Design Fluency, *p*=.04
Social
Knowing 3 or 4 people also on ART, *p*=.03
Miscellaneous
None

Table 24. Factors significantly associated with achieving ≥90% mean early pill count adherence. AUDIT, Alcohol Use Disorders Identification Test.

Demographic factors

In bivariate analyses, employment status was the only demographic factor that was independently associated with achieving a mean pill count adherence of 90% or more during the first 16 weeks of treatment (see Figure 25). While 87% of patients who were employed (formally employed full-time or part-time or engaged in casual labour) at treatment initiation achieved a mean pill count adherence of 90% or more, only 71% of unemployed patients were able to do so, a difference that was statistically significant [[chi]^2(1) = 4.08, *p*=.04].

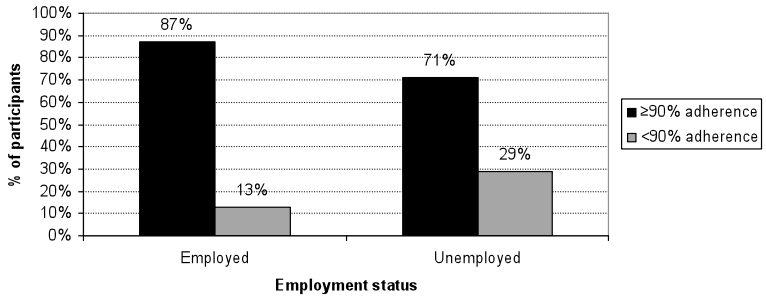

Figure 25. Percentage of participants achieving mean pill count ≥90% by employment status.

Patient gender (*p*=.31), age (*p*=.84*)*, education (grade completed, *p*=.31; years of education, *p*=.86), disability grant status (*p*=.29) and income (*p*=.77) were not associated with early pill count adherence.

Biomedical factors

While ever having experienced one or more symptoms as a result of HIV, and the severity of these symptoms when they were reported, were not associated with early pill count adherence (*p*=.86 and *p*=.85), patients who reported ever having experienced haematological symptoms specifically (such as a 'nodule in the neck' or 'swollen glands') were significantly less likely to achieve a mean pill count adherence of 90% or more during the first 16 weeks of treatment: while only 46% of those who had experienced haematological symptoms were able to achieve early pill count adherence, 78% of those who had not experienced such symptoms managed to do so [[chi]^2(1) = 6.42, *p*=.01] (see Figure 26). The relationship was confirmed in a corresponding t-test which showed a significant difference between the mean pill count adherence of those who had experienced haematological symptoms (mean pill count adherence, 73%) and the mean pill count adherence of those who had never experienced haematological symptoms (mean pill count adherence, 88%), *p*=.02. Conversely, patients who reported ever having experienced dermatological symptoms (such as 'dandruff' or 'dry skin') were significantly more likely to achieve ≥90% mean pill count adherence, with 88% of these patients achieving ≥90% adherence compared with 69% of patients not reporting dermatological symptoms [[chi]^2(1) = 6.20, *p*=.01] (see Figure 27). Other reported symptoms were not significantly related to early pill count adherence, including respiratory (*p*=.86), urogenital (*p*=.85), cardiopulmonary (*p*=.80), ophthalmic (*p*=.15), psychiatric (*p*=.99), lymphatic

(*p*=.43), musculoskeletal (*p*=.73), neurological (*p*=.31), constitutional (*p*=.12) and gastrointestinal (*p*=.34) symptoms. (See Appendix I for symptom categorisations.)

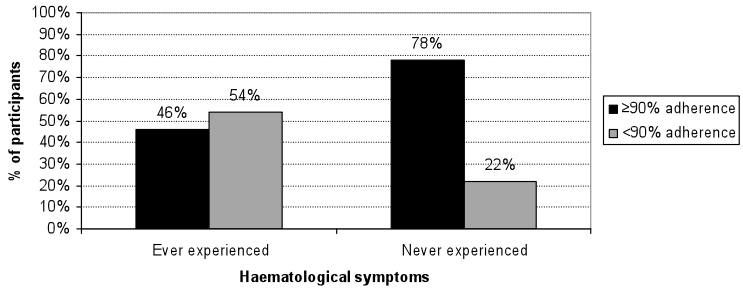

Figure 26. Percentage of participants with haematological symptoms achieving mean pill count ≥90%.

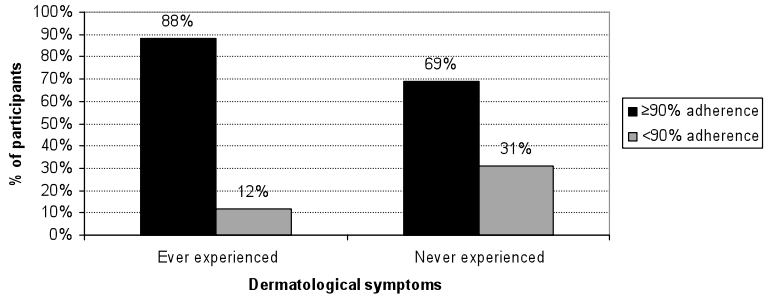

Figure 27. Percentage of participants with dermatological symptoms achieving mean pill count ≥90%.

No other investigated biomedical factors were associated with early pill count adherence, including CD4+ cell count at treatment initiation (*p*=.25), HIV RNA level at treatment initiation (*p*=.54), WHO stage (*p*=.74), time between positive HIV diagnosis and HAART initiation (*p*=.76), reason for HIV test (*p*=.16), pregnancy at treatment initiation (*p*=.37), TB therapy at treatment initiation (*p*=.74), neurological history (*p*=.80), having previously been exposed to ART (*p*=.10) and prescribed ARV regimen (*p*=.96).

Psychological factors

Scores on each of the individual knowledge questions as well as the composite knowledge score (*p*=.15) were not predictive of likelihood of achieving ≥90% mean pill count adherence across the first 16 weeks of treatment. This included awareness of latest CD4+ cell count result (*p*=.73), understanding the consequences of non-adherence (*p*=.39), understanding the concept of resistance (*p*=.51) and knowing the required level of adherence (*p*=16). There was a trend towards a relationship between ability to name each of the ARV's in the prescribed regimen and achieving ≥90% pill

count adherence, with 83% of those who could do so most likely to achieve ≥90% adherence, but this did not reach statistical significance (*p*=.06).

Similarly, neither the attitudes towards or concerns about HIV and ART assessed at treatment initiation, nor the composite ARV attitudes score (*p*=.72) had any bearing on the likelihood of achieving mean pill count adherence of ≥90% across the first 16 weeks of treatment. Patients who thought HIV was not a 'serious disease' (*p*=.37), said they could 'fight off HIV' without HAART (*p*=.23), doubted the efficacy of the medication (*p*=.20), were concerned about ARV side-effects (*p*=.27), feared taking daily ARV's would be an unwanted reminder of their HIV status (*p*=.85), and were unconvinced that the benefits of HAART would outweigh the drawbacks (*p*=.85) were equally likely to achieve ≥90% adherence as those with more positive attitudes. Patients' degree of self-efficacy (whether or not they believed they would be able to adhere to the extent required) (*p*=.13) and whether they ascribed primary responsibility for medication decision-making to themselves or to their health care provider (*p*=.14) were also not determinants of early pill count adherence.

Neither the CES-D depression score (*p*=.14) nor any of its 20 individual questions was associated with early pill count adherence.

Results showed strong associations between alcohol abuse at treatment initiation according to the AUDIT and early pill count adherence. While 87% of patients who scored seven or lower on the scale (indicating no presence of alcohol abuse) were able to achieve ≥90% mean pill count adherence across the first 16 weeks of treatment, just 64% of patients who scored 8–15 and 57% of patients who scored 16 or higher managed to do so, a difference that was statistically significant [[chi]^2(2) = 15.60, *p*=.0004] (see Figure 28). The relationship between AUDIT score and pill count adherence was confirmed in corresponding t-tests which showed significant differences between the mean pill count adherence of those who scored seven or lower (mean pill count adherence, 94%), the mean pill count adherence of those who scored 16 or higher (mean pill count adherence, 77%), *p*=.0001, the mean pill count adherence of those who scored 8–15 (mean pill count adherence, 71%) and the mean pill count adherence of those who scored 16 or higher (mean pill count adherence, 77%), *p*=.001.

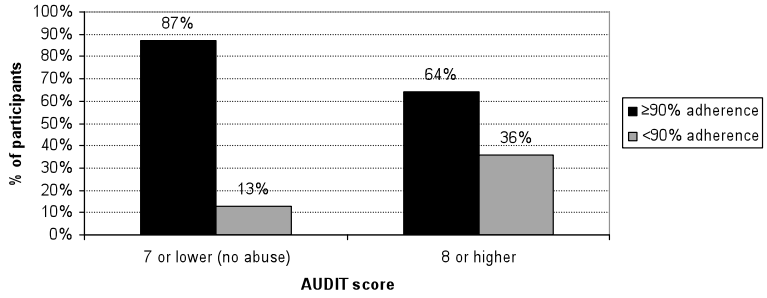

Figure 28. Percentage of participants achieving mean pill count ≥90% by AUDIT score.

Six of the AUDIT's 10 individual items independently predicted likelihood of achieving ≥90% mean pill count adherence across the first 16 weeks of treatment, including:

1) How often an alcoholic drink is consumed (86% of those drinking monthly or less achieved ≥90% adherence compared with 76% of those drinking 2–4 times monthly, and 54% of those drinking twice or more weekly, *p*=.0003)
2) The average number of alcoholic drinks consumed on a typical day of drinking (85% of those drinking one or two drinks achieved ≥90% adherence, compared with 71% of those drinking 3–6 drinks, and 56% of those drinking 7 or more drinks, *p*=.008)
3) How often six or more drinks is consumed on one occasion (82% of those who did so monthly or less achieved ≥90% adherence, compared with just 56% of those who did so weekly or daily, *p*=.0009)
4) How often they are unable to remember what happened the night before because of drinking (79% of those to whom this never happened achieved ≥90% adherence, compared with 73% of those to whom this happened monthly or less, and 50% of those to whom this happened weekly or daily, *p*=.03)
5) How often they experience feelings of guilt or remorse after drinking (82% of those who did so less than monthly achieved ≥90% adherence, compared with 64% of those that did so monthly, weekly or daily, *p*=.01)
6) And a particularly strong association with how often they fail to do what is expected of them because of drinking (85% of those who never failed achieved ≥90% adherence, compared with 49% of those that did, *p*<.0001).

Two other items (whether a friend, relative, doctor or other health care worker had been concerned about their drinking, and how often they could not stop drinking once they

had started) showed a trend towards a relationship with pill count adherence, but did not reach statistical significance (p=.08 and p=.09). Only two items on the AUDIT appeared unrelated to early pill count adherence: how often a drink was needed first thing in the morning after a heavy drinking session (p=.32) and whether they or someone else had been injured as a result of their drinking (p=.60).

Marijuana use did not increase the likelihood of not achieving mean early pill count adherence ≥90% (p=.70).

Three neuropsychological test scores predicted the likelihood of achieving mean pill count adherence ≥90% across the first 16 weeks of treatment. Two of these three scores were derived from the Verbal Fluency subtest of the D-KEFS, and one from both the Verbal Fluency and Design Fluency subtests. Patients who scored higher on the *Category Fluency: Total Correct* score (a combined measure of correctly generated animals and boys' names within the Verbal Fluency subtest) were significantly more likely to achieve ≥90% early pill count adherence (p=.04). Specifically, 82% of those who could generate 20 or more correct (no set loss or repetitions) animals and boys' names within the 120 seconds across the two conditions were later classified as good adherers according to pill count, compared with only 60% of those who could not. There was a particularly strong relationship between set loss (classification errors) on the animals semantic condition of the Verbal Fluency subtest and likelihood of achieving ≥90% early pill count adherence [[chi]^2(1) = 17.79, p<.0001]. While 79% of patients who made no set loss errors managed to achieve ≥90% early pill count adherence, only 13% of those who made one or more set loss errors did the same. Finally, patients who made either no repetition errors or many (5 or more) repetition errors across the Verbal Fluency and Design Fluency subtests were more often (83% versus 63%) adherent on early treatment, than those who made some (1–4) errors (p=.04).

Three other neuropsychological test scores from the Verbal Fluency subtest (set loss within the 'A' letter fluency trial, set loss across the two semantic fluency trials [animals and boys' names], and all responses [including repetition and set loss errors] generated within the semantic switching trial) showed a trend towards a relationship with early pill count adherence, with patients who generated more responses and made less errors more likely to achieve ≥90% adherence, but did not reach statistical significance (77%

versus 50%, *p*=.06; 77% versus 56%, *p*=.06; and 61% versus 70%, 81% and 94%, *p*=.08 respectively).

Three test scores from the D-KEFS Colour-Word Interference subtest also bordered on significance (self-corrected errors in the naming condition, all errors in the inhibition condition, and all errors across the subtest [82% versus 71% and 62%, *p*=.08; 94% versus 76% and 67%, *p*=.07; and 82% versus 69%, *p*=.08 respectively]), with patients who showed more errors less likely to achieve ≥90% adherence. One test score from the WMS Logical Memory subtest (combined measure of delayed recall of both units and themes from the second story) did the same (65% versus 77% and 86%, *p*=06), with patients who were able to recall more story units and themes more likely to achieve ≥90% adherence.

No neuropsychological test scores from the D-KEFS Tower subtest or WMS Digit Span subtest predicted early pill count adherence.

Social factors

Only one social factor was a significant predictor of likelihood of achieving ≥90% adherence across the first 16 weeks of treatment. While knowing anyone else on ART (binary response) was not predictive of achieving ≥90% adherence (*p*=.57), the number of people patients knew who were also on ART was predictive (*p*=.03). Patients who knew three people on ART, and patients who knew four or more people on ART were most likely to achieve ≥90% adherence (100% of the first group and 92% of the second group managed to adhere), while patients who knew no-one, one person or two people were less like to achieve ≥90% adherence (77%, 72% and 57% from each group respectively managed to adhere) (see Figure 29). Patients' relationships with those they knew on ART was not predictive however, with patients who had a partner or spouse on ART (*p*=.13), other family on ART (*p*=.64), a friend on ART (*p*=.38) or lived with someone on ART (*p*=.73) equally likely to achieve ≥90% adherence as those who did not.

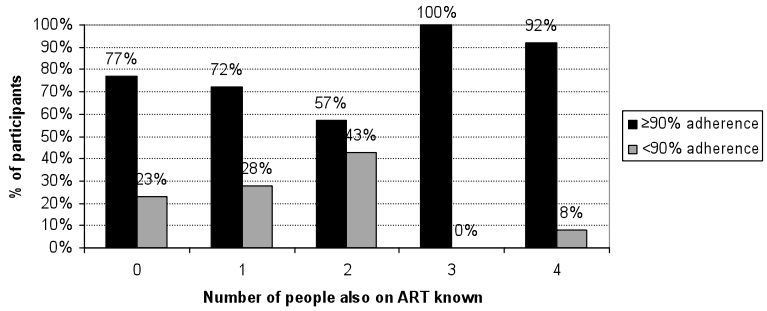

Figure 29. Percentage of participants achieving mean pill count ≥90% by number of people also on ART known.

Three other social factors approached significance as predictors of achieving ≥90% early pill count adherence. While 84% of patients who were not in a relationship achieved ≥90% adherence, 76% of those who were married or cohabiting, and 64% of those who were married but separated or in a non-cohabiting relationship managed to do so, although these associations did not reach significance (*p*=.09). For those with a partner, living with that partner increased the likelihood of adherence (77% compared 63% achieved ≥90% adherence, *p*=.05). For those with a partner, if that partner was HIV-positive, the patient was more likely to adhere (78%) than if the partner was HIV-negative (64%) (*p*=.05).

No other social variables were predictive of early pill count adherence. Aside from the benefit just mentioned for those with a partner of living with that partner, no other household-related social variables influenced early pill count adherence, including household size (*p*=.83), and living with one's child(ren) (*p*=.20), parent(s) (*p*=.86) or other family members (*p*=.17). Again, aside from the other benefit just mentioned of increased likelihood of achieving ≥90% adherence for those with a partner if that partner was HIV-positive, no other variables related to knowing HIV-positive others impacted on adherence, including knowing anyone (binary response) HIV-positive (*p*=.71), having an HIV-positive child (*p*=.16), family member (*p*=.52) or friend (*p*=.67), or the total number of HIV-positive people known (*p*=.41).

Disclosure did not seem to affect patients' ability to adhere. This included having disclosed to a partner (for those who had a partner) (*p*=.10), children (*p*=.62), parents (*p*=.14), other family members (*p*=.64) or friends (*p*=.27). Living with someone disclosed to (*p*=.16), disclosing to everyone in household (*p*=.81), living with someone disclosed to

who was also on ART and would remind them to take the ART (*p*=.19), attitudes towards ART of those disclosed to (*p*=.79) and the total number of people disclosed to (*p*=.18) did not affect early pill count adherence.

No factors relating to the patient's relationship with the health care provider impacted patients' likelihood of achieving ≥90% early pill count adherence, including whether they saw the same doctor at clinic visits (*p*=.48), whether the doctors and nurses at the clinic spoke to them in their home language (*p*=.17), if they felt they could talk to the doctors and nurses at the clinic about any problems they were having (*p*=.20) and whether they felt they could trust the doctors and nurses at the clinic (*p*=.32). The composite patient-clinic relationship score (*p*=.26) was not of predictive value either.

Miscellaneous factors

Use of material aids such as pill boxes (*p*=.33), cell phone alarms (*p*=.36) and wrist watch alarms (*p*=.85) did not impact ability to achieve ≥90% mean pill count adherence across the first 16 weeks of treatment.

The mode of transport patients used to get to clinic visits (*p*=.14), how long it took them to travel to the clinic (*p*=.31), how much this transport cost them (*p*=.39) and whether or not they felt this cost was affordable (*p*=.24) did not influence the likelihood of achieving ≥90% mean pill count adherence. When asked to take both time and costs associated with clinic visits into account, patients who considered clinic visits convenient were no more likely to achieve ≥90% mean pill count adherence than those who did not (*p*=.12).

In sum, several demographic, biomedical, psychological and social factors at treatment initiation were significantly associated with likelihood of achieving early pill count adherence ≥90% over the first 16 weeks of treatment. Patients who were employed were more likely to adhere (*p*=.04) as were patients who had never experienced haematological symptoms as a result of HIV (*p*=.01) and patients who had ever experienced dermatological symptoms as a result of HIV (*p*=.01). Patients who showed no presence of alcohol abuse on the AUDIT scale (*p*=.0004) and who reported drinking less frequently (*p*=.0003), drinking fewer alcoholic drinks on a typical day of drinking (*p*=.008), drinking six or more drinks on one occasion no more than monthly (*p*=.0009), never being unable to remember what happened the night before because of drinking

(*p*=.03), experiencing feelings of guilt or remorse after drinking less than monthly (*p*=.01) and never failing to do what is expected because of drinking (*p*<.0001) were most likely to adhere. Patients who scored ≥20 on the Verbal Fluency: Total Correct (*p*=.04), made no set loss errors on the 'animals' semantic condition of Verbal Fluency (*p*<.0001) and no repetition errors or five or more repetition errors across Verbal Fluency and Design Fluency (*p*=.04) did best. Finally, patients who knew three or four people also on ART (*p*=.03) were most likely to adhere.

Factors associated with late virological suppression

Table 25 displays the factors significantly associated with late virological suppression in chi-square analyses.

Demographic
Employed, *p*=.04
No disability grant, *p*=.006
Biomedical
Reported ever having experienced urogenital symptoms as a result of HIV, *p*=.04
Psychological
No presence of alcohol abuse on AUDIT scale, *p*=.0001
Drinking alcohol less frequently, *p*<.0001
Drinking fewer alcoholic drinks on a typical day of drinking, *p*=.0005
Drinking 6 or more drinks on one occasion no more than monthly, *p*=.0004
Never being unable to remember what happened the night before because of drinking, *p*=.007
Experiencing feelings of guilt or remorse after drinking less than monthly, *p*=.02
Never failing to do what is expected because of drinking, *p*<.0001
Never having had a friend, relative, doctor or health care worker concerned about their drinking, *p*=.007
Never being unable to stop drinking once they had started, *p*=.003
6 or fewer errors on Colour-Word Interference, *p*=.003
2 or fewer self-corrected errors on Colour-Word Interference, *p*=.002
Improving by 1-2, 3 or 4-5 points after second exposure in Logical Memory, *p*=.03
Inability to recall longer number series in Digit Span, *p*=.04
Social
Living alone or with one other person, *p*=.007
Miscellaneous
Planning to use cell phone alarm as reminder, *p*=.0003

Table 25. Factors significantly associated with achieving virological suppression. AUDIT, Alcohol Use Disorders Identification Test.

Demographic factors

In the bivariate analyses examining the relationships between demographic factors and the likelihood of achieving HIV RNA suppression (<50 copies/mL) at the 96 week visit, employment status at treatment initiation was again independently associated with

outcome. While 80% of patients who were employed achieved late virological suppression, just 61% of unemployed patients were able to do so, a difference that was statistically significant [[chi]^2(1) = 4.06, *p*=.04] (see Figure 30).

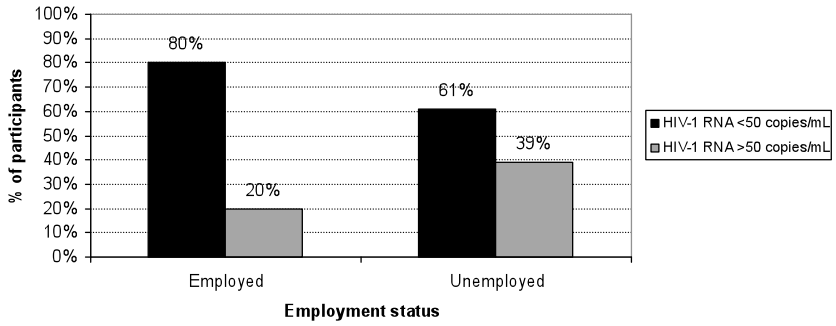

Figure 30. Percentage of participants achieving virological suppression by employment status.

In addition, while disability grant status at treatment initiation had not been associated with early pill count adherence, it was independently associated with late virological suppression [[chi]^2(2) = 10.31, *p*=.006]. Patients without a disability grant were most likely to achieve late virological suppression (82%); patients who already held a disability grant or had applied for one pending approval were less likely to be suppressed (65% and 53% respectively) (see Figure 31).

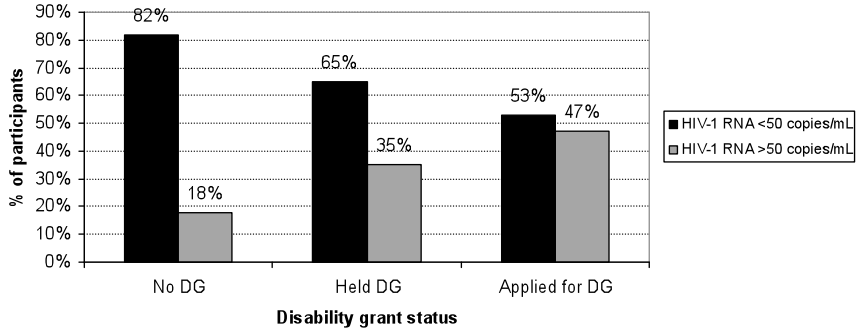

Figure 31. Percentage of participants achieving virological suppression by disability grant status. DG, disability grant.

Patient gender (*p*=.42), age (*p*=.17*)*, education (grade completed, *p*=.31; years of education, *p*=.51) and income (*p*=.18) were not associated with late virological suppression.

Biomedical factors

As with the early pill count adherence analyses, ever having experienced one or more symptoms as a result of HIV, and the severity of these symptoms when they were reported, were not associated with late virological suppression (p=.57 and p=.73). However, the reporting of specific symptoms was again predictive; in this analysis, having experienced urogenital symptoms (such as 'discharge' or 'genital ulcers') emerged as significantly associated with virological suppression at 96 weeks, with 100% of patients who reported ever having experienced urogenital symptoms suppressed compared with 64% of those who did not report urogenital symptoms [[chi]^2(1) = 4.35, p=.04] (see Figure 32).

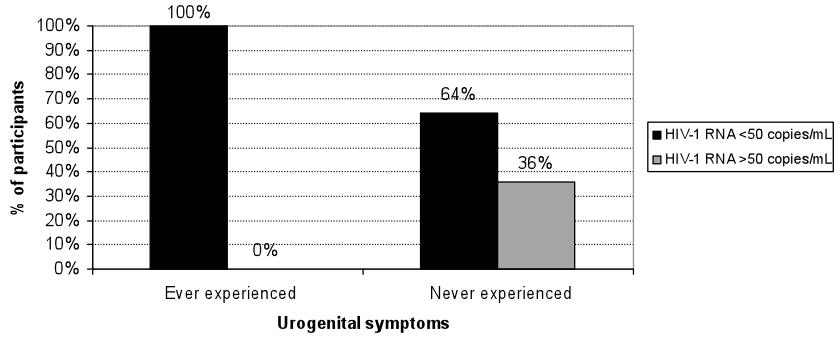

Figure 32. Percentage of participants achieving virological suppression by urogenital symptoms.

Ophthalmic symptoms (such as 'visual disturbances') also approached significance [[chi]^2(1) = 3.03, p=.08], in this case as a deterrent to achieving virological suppression, with only 33% of those who had experienced ophthalmic symptoms suppressed compared with 68% of those who had not. Other reported symptoms were not related to late virological suppression, including dermatological (p=.93), haematological (p=.67), respiratory (p=.97), cardiopulmonary (p=.71), psychiatric (p=.71), lymphatic (p=.49), musculoskeletal (p=.50), neurological (p=.30), constitutional (p=.69) and gastrointestinal (p=.61) symptoms.

Although a trend towards a relationship between CD4+ cell count at treatment initiation and late virological suppression was clear, with patients who had lower CD4+ cell counts (<100 cells/μL and 100–199 cells/μL) less likely to achieve virological suppression at 96 weeks than those with CD4+ cell count at treatment initiation >200 cells/μL (56%, 74%

and 75% respectively), this did not reach significance (*p*=.08). Another trend that also did not reach significance (*p*=.06) was seen in the relationship between having previously been exposed to ART and failure to virologically suppress at 96 weeks, with only 42% of the ART-exposed achieving suppression compared with 69% of the ART-naïve.

No other biomedical variables were predictive of late virological suppression, including HIV RNA level at treatment initiation (*p*=.44), WHO stage (*p*=.82), time between positive HIV diagnosis and HAART initiation (*p*=.39), reason for HIV test (*p*=.21), pregnancy at treatment initiation (*p*=.60), TB therapy at treatment initiation (*p*=.99), neurological history (*p*=.94) and prescribed ARV regimen (*p*=.93).

Psychological factors

As with the early pill count adherence analyses, scores on each of the individual knowledge questions as well as the composite knowledge score (*p*=.52) were not predictive of likelihood of achieving virological suppression at 96 weeks. This included awareness of latest CD4+ cell count result (*p*=.11), understanding the consequences of non-adherence (*p*=.43), understanding the concept of resistance (*p*=.77) and knowing the required level of adherence (*p*=14). In this analysis, there was no trend towards a relationship between ability to name each of the ARV's in the prescribed regimen and achieving ≥90% mean pill count adherence (*p*=.46).

Similarly, and as with the early pill count analysis, none of the attitudes towards or concerns about HIV and ART assessed at treatment initiation or the composite ARV attitudes score (*p*=.58) influenced late virological suppression. Patients who thought HIV was not a 'serious disease' (*p*=.31), said they could 'fight off HIV' without HAART (*p*=.79), doubted the efficacy of the medication (*p*=.63), were concerned about ARV side-effects (*p*=.61), feared taking daily ARV's would be an unwanted reminder of their HIV status (*p*=.59), and were unconvinced that the benefits of HAART would outweigh the drawbacks (*p*=.45) were equally likely to achieve virological suppression as those with more positive attitudes. And, as with the early pill count analysis, whether patients ascribed primary responsibility for medication decision-making to themselves or their health care provider (*p*=.33) did not determine their likelihood of achieving virological suppression. While in the early pill count adherence analysis patients' degree of self-

efficacy for treatment adherence did not predict ≥90% adherence, in the late virological suppression analysis there was a trend towards a relationship between self-efficacy and likelihood of achieving virological suppression, with 69% of those who were very confident that they could take their ART regimen as prescribed, virologically suppressed at the 96 week visit, compared to just 47% of those who were quite confident, quite unconfident or very unconfident) (p=.06).

As with the early pill count analysis, neither the overall CES-D depression score (p=.23) nor any of its 20 individual questions was associated with late virological suppression.

Results examining the relationship between alcohol abuse at treatment initiation and late virological suppression at 96 weeks showed even stronger associations than those between alcohol abuse at treatment initiation and early pill count adherence across the first 16 weeks of treatment. This was true of the overall alcohol abuse score on the AUDIT (p=.0001 versus p=.0004), with 80% of patients who scored seven or lower achieving undetectable viral loads and just 47% of patients who scored eight or higher managing to do so (see Figure 33), and five of the AUDIT's six items that had been significantly associated with early pill count adherence:

1) How often an alcoholic drink is consumed (81% of those drinking monthly or less achieved virological suppression, compared with 67% of those drinking 2–4 times monthly, and 40% of those drinking twice or more weekly, p<.0001)
2) The average number of alcoholic drinks consumed on a typical day of drinking (80% of those drinking one or two drinks achieved undetectable viraemia, compared with 61% of those drinking 3–6 drinks, 54% of those drinking 7–9 drinks, and 33% of those drinking 10 or more drinks, p=.0005)
3) How often six or more drinks is consumed on one occasion (76% of those who did so monthly or less achieved suppression compared with just 44% of those who did so weekly or daily, p=.0004)
4) How often they were unable to remember what happened the night before because of drinking (73% of those who to whom this never happened achieved suppression, compared with 46% of those to whom this happened monthly or less, and 38% of those to whom this happened weekly or daily, p=.007)

5) How often they fail to do what is expected of them because of drinking (79% of those who never failed achieved suppression, compared with 34% of those that did, *p*<.0001).

The other item that had been a significant predictor of early pill count adherence was also a predictor of late virological suppression: how often they experience feelings of guilt or remorse after drinking, with 74% of patients who did so less often than monthly achieving suppression, compared with 54% of those that did so monthly, weekly or daily (*p*=.02).

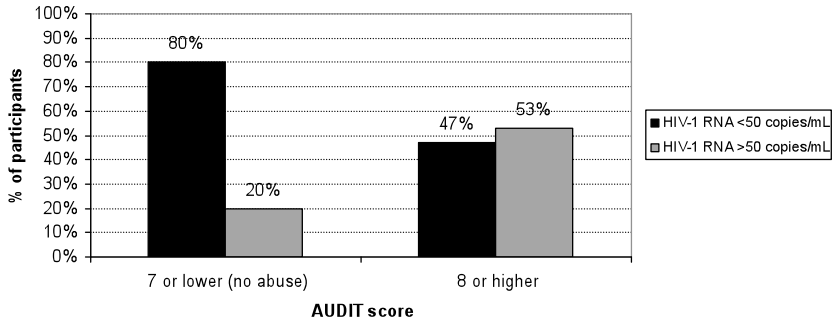

Figure 33. Percentage of participants achieving virological suppression by AUDIT score.

Furthermore, the two items that had been close to significance in the pill count adherence analyses (whether a friend, relative, doctor or other health care worker had been concerned about their drinking and how often they could not stop drinking once they had started) emerged as significant in this analysis, with 74% of those who had never had someone concerned achieving viral loads <50 copies/mL, compared with 51% of those who had, *p*=.007 and 74% of those who were never unable to stop drinking achieving suppression, compared with 44% of those who were unable to stop drinking monthly or less, and 38% of those who were unable to stop drinking weekly or daily, *p*=.003. One of the two items that had been unrelated to early pill count adherence (how often a drink was needed first thing in the morning after a heavy drinking session) approached significance in this analysis (*p*=.05), and the other remained insignificant (whether they or someone else had been injured as a result of their drinking, *p*=.13).

As with the early pill count analysis, marijuana use did not increase the likelihood of having a detectable viral load at 96 weeks (*p*=.32).

Four neuropsychological test scores predicted the likelihood of achieving virological suppression at the 96 week visit. One of these four (all errors across the D-KEFS Colour-Word Interference subtest) had bordered on significance in the early pill count adherence analysis (p=.08), but reached significance in this analysis (p=.04), with 75% of those who made six or fewer errors achieving virological suppression, compared with 58% of those who made seven or more errors. The other three neuropsychological test scores that were predictive of virological suppression at the 96 week visit had not been predictive of achieving ≥90% early pill count adherence. The first, also a marker of errors made across the D-KEFS Colour-Word Interference subtest but this time including only self-corrected errors, was highly significant (p=.002), with 83% of those who made two or fewer errors achieving virological suppression, compared with 61% of those who made three to six errors, and 49% of those who made seven or more errors. The second, from the WMS Logical Memory subtest, a marker of improved recall of a story after a second exposure to it, showed that those patients who did not improve at all, and those patients who improved dramatically were less likely to achieve viral suppression than those who improved by one–two, three, or four–five points, 66% and 50%, compared with 69%, 74% and 82% respectively (p=.03). The fourth and final significant neuropsychological test score predictor of virological suppression at the 96 week visit was a marker of ability to accurately recall a series of numbers and repeat them back to the examiner both forwards and backwards from the Digit Span test. Here, the longer the series that the patient was able to recall, the less likely he or she was to achieve virological suppression (p=.04).

One of the other two D-KEFS Colour-Word Interference subtests that had bordered on significance in the early pill count adherence analysis (self-corrected errors in the naming condition) continued to approach significance in this analysis (p=.09) while the other (all errors in the inhibition condition) did not show a trend towards significance in this analysis (p=.24). Another neuropsychological test score from the D-KEFS Colour-Word Interference subtest (self-corrected errors in the inhibition condition) was close to significance in the late virological suppression analysis, with those patients who made more errors less likely to achieve virological suppression below 50 copies/mL at 96 weeks (p=.08). Another neuropsychological test score from the WMS Logical Memory subtest, a combined measure of delayed recall of both units and themes from the

second story that had bordered on significance in the pill count analyses (*p*=.06), was not significant in this analysis (*p*=.61).

None of the scores from the Verbal Fluency or Design Fluency subtests of the D-KEFS significantly predicted ability to achieve late virological suppression, including the two scores from the Verbal Fluency subtest that were predictive of early pill count adherence (a combined measure of correctly generated 'animals' and 'names', and set loss errors on the 'animals' semantic condition), the one score derived from the Verbal Fluency and Design Fluency subtests that was predictive of early pill count adherence (repetition errors) and the three scores from the Verbal Fluency subtest that showed a trend towards a relationship with early pill count adherence (set loss within the 'A' letter fluency trial, set loss across the two 'animals' and 'boys' names' semantic fluency trials, and all responses generated within the semantic switching trial).

As with the early pill count analyses, no neuropsychological test scores from the D-KEFS Tower subtest predicted virological suppression at the 96 week visit.

Social factors

Only one social variable at treatment initiation was a significant predictor of virological suppression at 96 weeks. Patients who lived in smaller households (either alone or with one other person) were significantly more likely to achieve undetectable viral loads at 96 weeks than those living in households of three or more people (89% versus 61%, *p*=.007) (see Figure 34). There was a trend towards a relationship between living with a parent and failure to achieve virological suppression, with just 55% of those living with a parent achieving suppression, compared to 71% of those who did not (*p*=.09). Although in the early pill count adherence analysis, for those who were in a relationship, living with that partner had been predictive of adherence, this was not a significant factor in the virological suppression analysis (*p*=.30). As with the early pill count analysis, living with one's child(ren) (*p*=.70) or other family members (*p*=.21) did not impact virological suppression.

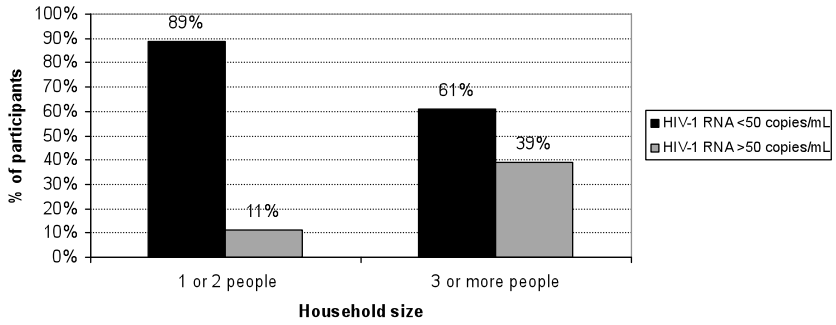

Figure 34. Percentage of participants achieving virological suppression against household size.

While a significant predictive relationship had been observed between having an HIV-positive partner and achieving ≥90% mean early pill count adherence (amongst those who had a partner), this relationship was not evident in the virological suppression analysis (p=.40). As with the early pill count adherence analyses, no other variables related to knowing HIV-positive others impacted virological suppression, including knowing anyone HIV-positive (p=.48), having an HIV-positive child (p=.15), family member (p=.73) or friend (p=.39), or the total number of HIV-positive people known (p=.71).

While a significant predictive relationship had been observed between the number of people patients knew who were also on ART and their likelihood of achieving ≥90% mean early pill count adherence, this relationship was not evident in the virological suppression analysis (p=.13). As with the early pill count adherence analysis, no other variables related to knowing others on treatment impacted likelihood of achieving virological suppression, including knowing anyone on ART (p=.13), knowing other family on ART (p=.83), knowing a friend on ART (p=.14) and living with someone on ART (p=.49).

As with the early pill count adherence analysis, disclosure did not seem to affect patients' likelihood of suppression. This includes having disclosed to a partner (for those who had a partner) (p=.13), children (p=.45), parents (p=.37), other family members (p=.61), total number of people disclosed to (p=.11), disclosing to everyone in household (p=.69), and attitudes towards ART of those disclosed to (p=.83). There was however a trend towards a predictive relationship between disclosing to a friend and failure to achieve virological suppression at 96 weeks (p=.09), and a predictive relationship

between living with someone disclosed to who was also on ART and had agreed to remind them to take the ART and success in achieving virological suppression 96 weeks (p=.08), with 87% of those to whom this applied achieving suppression compared with 64% to whom this did not.

Like with the early pill count adherence analysis, no factors related to the patient's relationship with the health care provider impacted likelihood of achieving HIV RNA suppression, including whether they saw the same doctor at clinic visits (p=.62), whether the doctors and nurses at the clinic spoke to them in their home language (p=.35), if they felt they could talk to the doctors and nurses at the clinic about any problems they were having (p=.89) and whether they felt they could trust the doctors and nurses at the clinic (p=.81). The composite patient-clinic relationship score (p=.63) was again not of predictive value either.

Miscellaneous factors

Unlike the early pill count adherence analysis, use of a material aid was predictive of likelihood of achieving virological suppression. Specifically, 84% of patients who planned to use cell phone alarms were virologically suppressed at the 96 week visit, compared with 54% of those not planning to use them (p=.0003) (see Figure 35). Other material aids such as pill boxes (p=.82) and wrist watch alarms (p=.76) did not impact likelihood of achieving virological suppression.

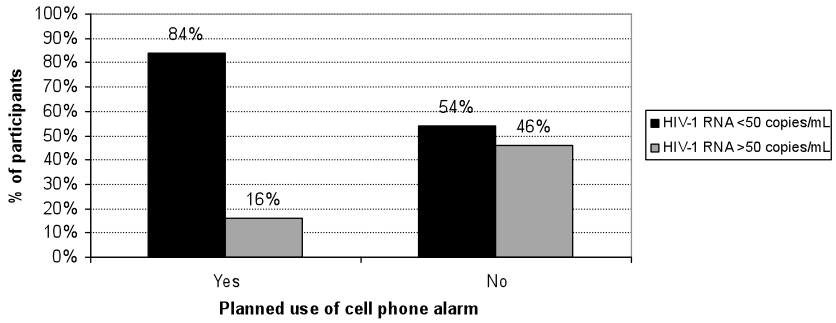

Figure 35. Percentage of participants achieving virological suppression against planned use of cell phone alarm as adherence reminder.

As with the early pill count adherence analysis, the mode of transport patients used to get to clinic visits (p=.18), how long it took them to travel to the clinic (p=.65), how much

this transport cost them (p=.47) and whether or not they felt this was affordable (p=.11) did not influence the likelihood of achieving late virological suppression. And again, when asked to take both time and costs associated with clinic visits into account, patients who considered clinic visits convenient were no more likely to achieve HIV RNA suppression than those who did not (p=.32).

In sum, several demographic, biomedical, psychological, social and miscellaneous factors at treatment initiation were significantly associated with likelihood of achieving late virological suppression at 96 weeks. Patients who were employed were more likely to adhere (p=.04) as were patients who did not hold and had not applied for a disability grant (p=.006) and patients who had ever experienced urogenital symptoms as a result of HIV (p=.04). Patients who showed no presence of alcohol abuse on the AUDIT scale (p=.0001) and who reported drinking less frequently (p<.0001), drinking fewer alcoholic drinks on a typical day of drinking (p=.0005), drinking six or more drinks on one occasion no more than monthly (p=.0004), never being unable to remember what happened the night before because of drinking (p=.007), experiencing feelings of guilt or remorse after drinking less often than monthly (p=.02), never failing to do what is expected because of drinking (p<.0001), never having had a friend, relative, doctor or health care worker concerned about their drinking (p=.007) and never being unable to stop drinking once they had started (p=.003) were most likely to be suppressed. Patients who made six or fewer total errors or two or fewer self-corrected errors on the Colour-Word Interference Test (p=.003 and p=.002), patients who improved by 1–2, 3 or 4–5 points after the second exposure in the Logical Memory Test (p=.03) and who could not recall a longer number series in the Digit Span test (p=.04) did best. Patients who lived alone or with one other person (p=.007) were most likely to achieve suppression. Finally, patients who planned to use a cell phone alarm as an adherence reminder (p=.0003) were most likely to be suppressed.

Factors associated with retention to care

Table 26 displays the factors significantly associated with retention to care at 96 weeks in chi-square analyses.

Demographic
Employed, *p*=.009
Biomedical
Never having experienced ophthalmic symptoms as a result of HIV, *p*=.04
Psychological
No presence of alcohol abuse on AUDIT scale, *p*=.02
Drinking alcohol less frequently, *p*=.02
Drinking 6 or more drinks on one occasion no more than monthly, *p*=.01
Experiencing feelings of guilt or remorse after drinking less often than monthly, *p*=.04
Never failing to do what is expected because of drinking, *p*=.002
Generating 7 or more words on the letter 'A' fluency trial of Verbal Fluency, *p*=.02
Generating 16 or more words across all 3 letter fluency trials of Verbal Fluency, *p*=.03
Generating 16 or more correct words across all 3 letter fluency trials of Verbal Fluency, *p*=.02
Any repetition errors in the 'animals' semantic category of Verbal Fluency, *p*=.002
More repetition errors across Verbal Fluency and Design Fluency, *p*=.04
Higher proportion of original recall remembered in delayed recall in Logical Memory, *p*=.04
Social
Not living with family other than spouse, child, or parent, *p*=.02
Not disclosing to family other than spouse, child, or parent, *p*=.03
Not disclosing to a friend, *p*=.03
Miscellaneous
None

Table 26. Factors significantly associated with retention to care at 96 weeks. AUDIT, Alcohol Use Disorders Identification Test.

Demographic factors

In the bivariate analyses examining the relationships between demographic factors and the likelihood of remaining in care at 96 weeks (consistent with earlier definition, patients not remaining in care had not returned to the clinic for 90 days or more since their last appointment and were not known to have transferred out to another treatment facility or died), employment status was once again associated with outcome, with 89% of patients who were employed at treatment initiation retained in care at 96 weeks compared with 65% of unemployed patients [[chi]^2(1) = 6.84, *p*=.009] (see Figure 36). Disability grant status had been significantly associated with late virological suppression but was not related to retention to care (*p*=.18).

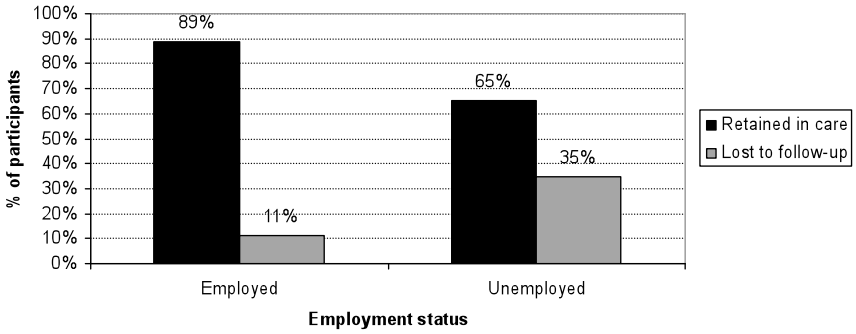

Figure 36. Percentage of participants retained in care by employment status.

As with the early pill count and late virological suppression analyses, patient gender (p=.33), age (p=.86), education (grade completed, p=.35; years of education, p=.70), and income (p=.22) were not associated with retention to care.

Biomedical factors

As with the early pill count and late virological suppression analyses, ever having experienced one or more symptoms as a result of HIV, and the severity of these symptoms when they were reported, were not associated with retention to care (p=.77 and p=.77). However, the reporting of a specific symptom was again predictive; in this analysis, having experienced ophthalmic symptoms (such as 'visual disturbances') (which had approached significance in the virological suppression analysis at p=.08) emerged as a significant barrier to retention to care, with only 33% of those who had experienced ophthalmic symptoms retained in care compared with 73% of those who had not [$[chi]^2(1) = 4.47$, p=.04] (see Figure 37). Other reported symptoms were not related to retention to care, including dermatological (p=.12), haematological (p=.41), respiratory (p=.34), cardiopulmonary (p=.87), psychiatric (p=.87), lymphatic (p=.34), musculoskeletal (p=.77), neurological (p=.27), constitutional (p=.89), urogenital (p=.82) and gastrointestinal (p=.41) symptoms.

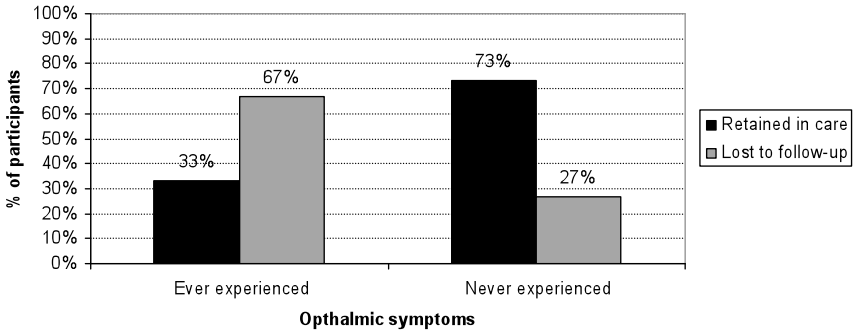

Figure 37. Percentage of participants retained in care against ophthalmic symptoms.

A trend towards a relationship between CD4+ cell count at treatment initiation and retention to care was seen (as had been the trend towards a relationship between CD4+ cell count at treatment initiation and late virological suppression), with patients who had the lowest CD4+ cell counts (<100 cells/μL) less likely to remain in care at 96 weeks than those with CD4+ cell count 100–199 cells/μL and >200 cells/μL (61%, 81% and 75% respectively), although this did not reach significance (*p*=.06).

No other investigated biomedical variables were predictive of retention to care, including HIV RNA level at treatment initiation (*p*=.91), WHO stage (*p*=.24), time between positive HIV diagnosis and HAART initiation (*p*=.59), reason for HIV test (*p*=.17), pregnancy at treatment initiation (*p*=.62), TB therapy at treatment initiation (*p*=.91), neurological history (*p*=.95), having previously been exposed to ART (*p*=.77) and prescribed ARV regimen (*p*=.94).

Psychological factors

As with the early pill count adherence and late virological suppression analyses, scores on each of the individual knowledge questions as well as the composite knowledge score (*p*=.20) were not predictive of likelihood of remaining in care at 96 weeks. This included awareness of latest CD4+ cell count result (*p*=.87), understanding the consequences of non-adherence (*p*=.80), understanding the concept of resistance (*p*=.75), ability to name each of the ARV's in the prescribed regimen (*p*=.97) and knowing the required level of adherence (*p*=82).

As with the early pill count and late virological suppression analyses, none of the attitudes towards or concerns about HIV and ART assessed at treatment initiation or the composite ARV attitudes score (*p*=.35) influenced retention to care. Patients who thought HIV was not a 'serious disease' (*p*=.31), said they could 'fight off HIV' without HAART (*p*=.41), doubted the efficacy of the medication (*p*=.52), were concerned about ARV side-effects (*p*=.17), feared taking daily ARV's would be an unwanted reminder of their HIV status (*p*=.30), and were unconvinced that the benefits of HAART would outweigh the drawbacks (*p*=.23) were equally likely to remain in care as those with more positive attitudes. Patients' degree of self-efficacy for treatment adherence (*p*=.81) and whether they ascribed primary responsibility for medication decision-making to themselves or their health care provider (*p*=.47) were also not determinants of retention to care.

As with the early pill count and virological suppression analyses, neither the overall CES-D depression score (*p*=.49) nor any of its 20 individual questions was associated with retention to care.

Results showed associations between alcohol abuse at treatment initiation according to the AUDIT and retention to care, as they had with the previous outcomes. While 80% of patients who scored seven or lower on the scale remained in care, just 60% of patients who scored 8 or higher did so, a difference that was statistically significant (*p*=.02) (see Figure 38).

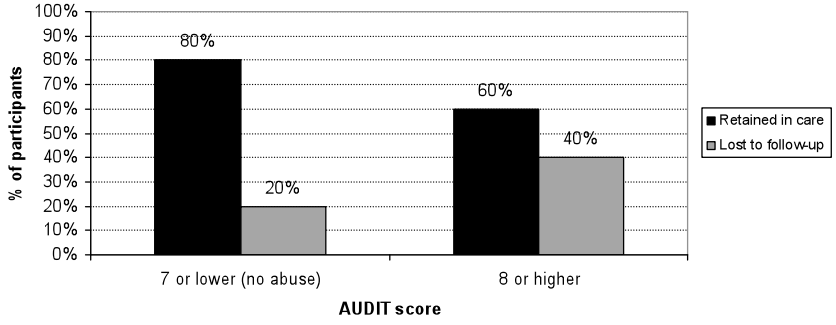

Figure 38. Percentage of participants retained in care against AUDIT score.

Four of the AUDIT's 10 individual items independently predicted likelihood of remaining in care, including:

1) How often an alcoholic drink is consumed (79% of those drinking monthly or less remained in care, compared with 76% of those drinking 2–4 times monthly, and 55% of those drinking twice or more weekly, *p*=.02)
2) How often six or more drinks is consumed on one occasion (78% of those who did so monthly or less often remained in care, compared with just 56% of those who did so weekly or daily, *p*=.01)
3) How often they experience feelings of guilt or remorse after drinking (78% of those who did so less often than monthly remained in care, compared with 62% of those that did so monthly, weekly or daily, *p*=.04)
4) How often they fail to do what is expected of them because of drinking (79% of those who never failed remained in care, compared with 53% of those that did, *p*=.002).

There was a trend towards a significant association between the average number of alcoholic drinks consumed on a typical day of drinking (*p*=.09), although this did not reach significance. The other five items appeared unrelated to retention to care: how often they are unable to remember what happened the night before because of drinking (*p*=.29), whether a friend, relative, doctor or other health care worker had been concerned about their drinking (*p*=.30), how often they could not stop drinking once they had started (*p*=.52), how often a drink was needed first thing in the morning after a heavy drinking session (*p*=.53) and whether they or someone else had been injured as a result of their drinking (*p*=.25).

Marijuana use, as with early pill count and late virological suppression, did not increase the likelihood of not remaining in care at 96 weeks (*p*=.56).

Six neuropsychological test scores predicted the likelihood of remaining in care at 96 weeks. Four of these six scores derived from the Verbal Fluency subtest of the D-KEFS, one from both the Verbal Fluency and Design Fluency subtests, and one from the Logical Memory subtest of the WMS. Patients who were able to generate more words (including errors) in the 'A' letter fluency trial were more likely to remain in care, with 83% of those who generated seven or more words remaining in care, compared with 64% of those who generated six or less words [[chi]^2(1) = 5.80, *p*=.02]. Patients who were able to generate more words (including errors) across the three letter fluency trials

were more likely to remain in care, with 81% of those who generated 16 or more words remaining in care, compared with 57% of those who generated 15 or less words (*p*=.03). This was also true of correctly generated words (excluding errors) across the three letter fluency trials, with 76% of those who generated 16 or more words remaining in care, compared with 59% of those who generated 15 or less words (*p*=.02). Patients who made any repetition on the 'animals' semantic category trial and patients who made more repetition errors across the Verbal Fluency and Design Fluency subtests were likely (100% versus 66% and 85% versus 62% respectively) to remain in care at 96 weeks than those who made no or fewer errors (*p*=.002 and *p*=.04). Finally, patients who were able to recall, after a delay, a greater proportion of the units and themes from the second story that they had originally recalled were more likely to remain in care, with 88% of those who could recall all units and themes that they had originally recalled remaining in care, compared with 66% of those who remembered only some of the units and themes that they had originally recalled (*p*=.04). One other neuropsychological test score bordered on significance as a predictor of retention to care (correctly generated words in the 'A' letter fluency trial) (*p*=.08).

No neuropsychological test scores from the D-KEFS Colour-Word Interference subtest, D-KEFS Tower subtest or WMS Digit Span subtest predicted retention to care.

Social factors

Three social factors were significant predictors of likelihood of remaining in care at 96 weeks. Living with family members other than spouse, child(ren) or parent(s) was predictive of failure to remain in care, with 65% of those who did so remaining in care, compared with 84% of those who did not (*p*=.02) (see Figure 39). Disclosing to family members other than spouse, child(ren) or parent(s) was predictive of failure to remain in care, with 67% of those who had done so remaining in care, compared with 89% of those who had not (*p*=.03) (see Figure 40). Similarly, disclosing to friends was predictive of failure to remain in care, with 59% of those who had done so remaining in care, compared with 79% of those who had not (*p*=.03) (see Figure 41).The total number of people disclosed to approached significance as a predictor of retention to care (*p*=.06), with patients who disclosed to the smallest number of people more likely to be retained (87% of those who disclosed to no-one or one person, 74% of those who disclosed to 2–

5 people, 73% of those who disclosed to 6–7 people and 55% of those who disclosed to 8 or more people).

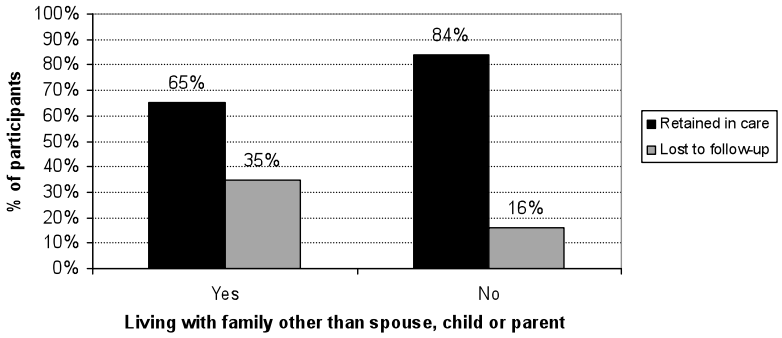

Figure 39. Percentage of participants retained in care by household composition.

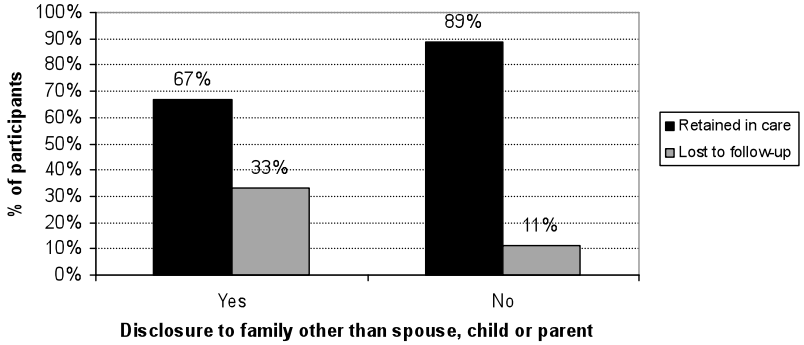

Figure 40. Percentage of participants retained in care by disclosure to family.

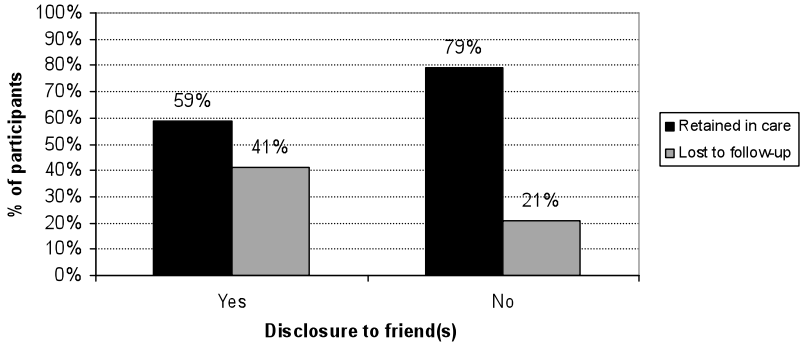

Figure 41. Percentage of participants retained in care by disclosure to friend(s).

While knowing anyone else on ART (*p*=.29), the number of people patients known on ART (*p*=.44), having a partner or spouse (*p*=.27) or friend on ART (*p*=.32), and living with someone on ART (*p*=.36) were not predictive of retention to care at 96 weeks, knowing family members other than spouse, child(ren) or parent(s) on ART approached significance (*p*=.06) as a predictor of loss to follow-up, with 56% of those who knew family members on ART remaining in care, compared with 75% of those who did not.

Having disclosed to a partner (for those who had a partner) (*p*=.95), child(ren) (*p*=.81), or parent(s) (*p*=.91), living with someone disclosed to (*p*=.63), disclosing to everyone in household (*p*=.08), living with someone disclosed to who was also on ART and would remind them to take the ART (*p*=.86) and attitudes towards ART of those disclosed to (*p*=.91) were not predictive of retention to care.

No factors related to the patient's relationship with the health care provider impacted patients' likelihood of remaining in care at 96 weeks, including whether they saw the same doctor at clinic visits (*p*=.45), whether the doctors and nurses at the clinic spoke to them in their home language (*p*=.33), if they felt they could talk to the doctors and nurses at the clinic about any problems they were having (*p*=.94) and whether or not they felt they could trust the doctors and nurses at the clinic (*p*=.64). The composite patient-clinic relationship score (*p*=.94) was not of predictive value either.

Aside from the relationship between living with family other than spouse, child(ren) and parent(s) and loss to follow-up mentioned earlier, no other household-related social variables influenced retention to care, including household size (*p*=.10), and living with one's partner or spouse (*p*=23), child(ren) (*p*=.27), or parent(s) (*p*=.95). Again, aside from the relationship between knowing family other than spouse, child(ren) and parent(s) on ART and loss to follow-up mentioned earlier, no other variables related to knowing HIV-positive others impacted adherence, including knowing anyone (binary response) HIV-positive (*p*=.51), having an HIV-positive partner (*p*=.75), child (*p*=.28), other family member (*p*=.14), or friend (*p*=.32), or the total number of HIV-positive people known (*p*=.72).

Miscellaneous factors

Use of material aids such as pill boxes (p=.82), cell phone alarms (p=.91) and wrist watch alarms (p=.39) did not impact retention to care at 96 weeks.

As with the early pill count and virological suppression analyses, the mode of transport patients used to get to clinic visits (p=.70), how long it took them to travel to the clinic (p=.77), how much this transport cost them (p=.72) and whether or not they felt this was affordable (p=.66) did not influence the likelihood of remaining in care at 96 weeks. And again, when asked to take both time and costs associated with clinic visits into account, patients who considered clinic visits convenient were no more likely to remain in care than those who did not (p=.55).

In sum, several demographic, biomedical, psychological and social factors at treatment initiation were significantly associated with likelihood of being retained in care at 96 weeks. Patients who were employed were more likely to be retained (p=.009) as were patients who never reported having experienced ophthalmic symptoms as a result of HIV (p=.04). Patients who showed no presence of alcohol abuse on the AUDIT scale (p=.02) and who reported drinking less frequently (p=.02), drinking six or more drinks on one occasion no more than monthly (p=.01), experiencing feelings of guilt or remorse after drinking less often than monthly (p=.04) and never failing to do what is expected because of drinking (p=.002) were most likely to be retained. Patients who generated seven or more words on the letter 'A' fluency trial, 16 or more words across all three letter fluency trials or 16 or more correct words across all three letter fluency trials of the Verbal Fluency Test (p=.02, p=.03 and p=.02), made any repetition errors in the 'animals' semantic category of the Verbal Fluency Test (p=.002), made more repetition errors across the Verbal Fluency and Design Fluency Tests (p=.04) and who remembered, after a delay, a higher proportion of their original recall in the Logical Memory Test (p=.04) were more likely to remain in care. Finally, patients who did not live with family other than spouse, child or parent (p=.02), had not disclosed to family other than spouse, child or parent (p=.03) and patients who had not disclosed to a friend (p=.03) were most likely to be retained.

Factors associated with combined adherence success

Table 27 displays the factors significantly associated with combined adherence success in chi-square analyses.

Demographic
Employed, *p*=.01
Biomedical
None
Psychological
Knowing none or all of the names of prescribed ARV's in regimen, *p*=.04
No presence of alcohol abuse on AUDIT scale, *p*=.02
Drinking alcohol less frequently, *p*=.006
Never failing to do what is expected because of drinking, *p*=.003
No set loss errors on the 'animals' semantic condition of Verbal Fluency, *p*=.003
Score of 20-29 on combined immediate recall of both stories on Logical Memory, *p*=.04
Social
Living with spouse or partner, *p*=.03
Miscellaneous
None

Table 27. Factors significantly associated with achieving combined adherence success. AUDIT, Alcohol Use Disorders Identification Test.

Demographic factors

In the bivariate analyses examining the relationships between demographic factors and the likelihood of achieving combined adherence success over the 96-week study monitoring period (consistent with earlier definition, patients achieving combined adherence success had achieved success in each of the three adherence indices: mean pill count adherence of 90% or more across the first 16 weeks of treatment, retention to care and virological suppression at 96 weeks), employment status was once again associated with outcome, with 74% of patients who were employed at treatment initiation achieving combined adherence success compared with 46% of unemployed patients (*p*=.01) (see Figure 42). Disability grant status had been significantly associated with late virological suppression and bordered on significance in the combined adherence success analyses (*p*=.05), with patients without a disability grant most likely to achieve combined adherence success (66%); patients who already held a disability grant or had applied for one pending approval were less likely to achieve combined adherence success (50% and 44% respectively).

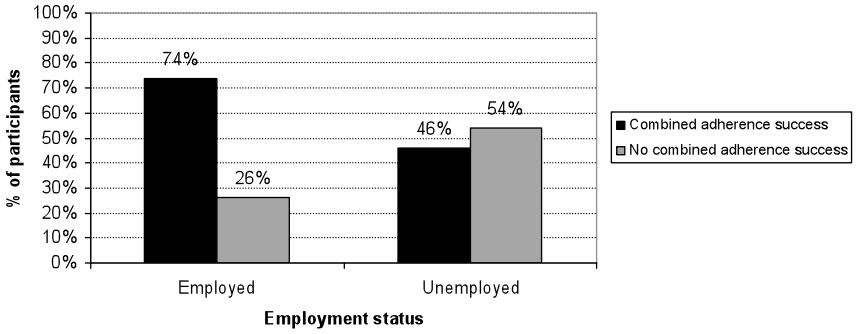

Figure 42. Percentage of participants achieving combined adherence success against employment status.

As with the early pill count, late virological suppression and retention to care analyses, patient gender (*p*=.73), age (*p*=.53*)*, education (grade completed, *p*=.34; years of education, *p*=.50) and income (*p*=.24) were not associated with combined adherence success.

Biomedical factors

As in the individual outcome analyses, ever having experienced one or more symptoms as a result of HIV, and the severity of these symptoms when they were reported, were not associated with the combined adherence success measure (*p*=.80 and *p*=.53). None of the specific symptoms were associated with the combined adherence success measure either, although there was a trend towards a relationship between having experienced ophthalmic symptoms (which had approached significance in the virological suppression analysis at *p*=.08 and emerged as a significant barrier in the retention to care analyses at *p*=.04), with 17% of those who had experienced ophthalmic symptoms achieving combined adherence success compared with 55% of those who had not [[chi]^2(1) = 3.45, *p*=.06]. Other reported symptoms were not related to combined adherence success, including dermatological (*p*=.10), haematological (*p*=.25), respiratory (*p*=.61), cardiopulmonary (*p*=.23), psychiatric (*p*=.88), lymphatic (*p*=.77), musculoskeletal (*p*=.79), neurological (*p*=.21), constitutional (*p*=.79), urogenital (*p*=.91) and gastrointestinal (*p*=.74) symptoms.

Although a trend towards a relationship between having previously been exposed to ART and failure to achieve combined adherence success was seen, with only 29% of

the ART-exposed achieving combined adherence success compared with 56% of the ART-naïve, this did not reach significance (*p*=.05).

No other biomedical variables were predictive of combined adherence success, including CD4+ cell count at treatment initiation (*p*=.62), HIV RNA level at treatment initiation (*p*=.47), WHO stage (*p*=.23), time between positive HIV diagnosis and HAART initiation (*p*=.53), reason for HIV test (*p*=.52), pregnancy at treatment initiation (*p*=.89), TB therapy at treatment initiation (*p*=.38), neurological history (*p*=.92) and prescribed ARV regimen (*p*=.73).

Psychological factors

As in the individual outcome analyses, scores on most of the individual knowledge questions as well as the composite knowledge score (*p*=.15) were not predictive of likelihood of achieving combined adherence success. This included awareness of latest CD4+ cell count result (*p*=.26), understanding the consequences of non-adherence (*p*=.14), understanding the concept of resistance (*p*=.73) and knowing the required level of adherence (*p*=.99). In this analysis however, there was a significant relationship between ability to name each of the ARV's in the prescribed regimen and likelihood of achieving combined adherence success (*p*=.04), with patients who knew none or all of the names most likely to achieve success (65% and 62%) and patients who knew one or two names least likely to do so (44% and 38%) (see Figure 43).

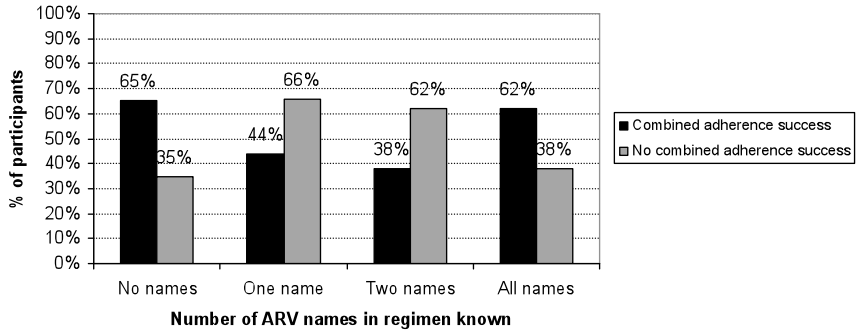

Figure 43. Percentage of participants achieving combined adherence success against number of ARV names in regimen known.

As with the other outcome analyses, none of the attitudes towards or concerns about HIV and ART assessed at treatment initiation or the composite ARV attitudes score

(*p*=.22) influenced combined adherence success. Patients who said they could fight off HIV without HAART (*p*=.53), doubted the efficacy of the medication (*p*=.55), were concerned about ARV side-effects (*p*=.55), feared taking daily ARV's would be an unwanted reminder of their HIV status (*p*=.42) and were unconvinced that the benefits of HAART would outweigh the drawbacks (*p*=.67) were equally likely to achieve combined adherence success as those with more positive attitudes. Patients' degree of self-efficacy for treatment adherence (*p*=.38) and whether they ascribed primary responsibility for medication decision-making to themselves or their health care provider (*p*=.80) were also not determinants of achieving combined adherence success. There was a trend towards a relationship between believing HIV was not a serious disease and achieving combined adherence success, with 64% of those who believed it was not a serious disease achieving combined adherence success across the study's 96-week monitoring period, compared with 49% of those who believed it was a serious disease, although this did not reach significance (*p*=.08).

As with the outcomes analyses, neither the overall CES-D depression score (*p*=.82) nor any of its 20 individual questions was significantly associated with combined adherence success. However, in this analysis, two of the individual items approached significance: the item measuring frequency of feelings of loneliness (*p*=.08) and the item measuring frequency of feelings of hope for the future (*p*=.05). In the negative item measuring loneliness, patients on both extremes (less than 3 days per week or more than 5 days per week) did best (58% as opposed to 37%), and in the positive item measuring hope, patients on both extremes did worst (52% as opposed to 63%).

Results showed associations between alcohol abuse at treatment initiation according to the AUDIT and combined adherence success, as they had with each of the three individual outcomes. While 64% of patients who scored seven or lower on the scale achieved combined adherence success, just 38% of patients who scored 8 or higher did so, a difference that was statistically significant (*p*=.02) (see Figure 44).

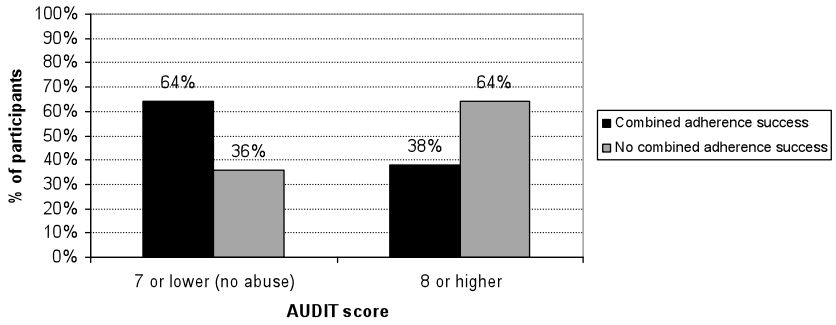

Figure 44. Percentage of participants achieving combined adherence success by AUDIT score.

Two of the AUDIT's 10 individual items independently predicted likelihood of achieving combined adherence success: how often an alcoholic drink is consumed (64% of those drinking monthly or less frequently achieved combined adherence success, compared with 62% of those drinking 2–4 times monthly, and 30% of those drinking twice or more weekly, *p*=.006) and how often they fail to do what is expected of them because of drinking (63% of those who never failed, achieved success, compared with 53% of those that did, *p*=003). There were trends between three other items and combined adherence success, including: the average number of alcoholic drinks consumed on a typical day of drinking (*p*=.05), how often six or more drinks is consumed on one occasion (*p*=.05), and how often they experience feelings of guilt or remorse after drinking (*p*=.09). The other five items were not associated with combined adherence success: how often they are unable to remember what happened the night before because of drinking (*p*=.40), whether a friend, relative, doctor or other health care worker had been concerned about their drinking (*p*=.50), how often they could not stop drinking once they had started (*p*=.55), how often a drink was needed first thing in the morning after a heavy drinking session (*p*=.54) and whether they or someone else had been injured as a result of their drinking (*p*=.68).

Marijuana use once again did not increase the likelihood of not achieving combined adherence success over the 96 weeks (*p*=.12).

Two neuropsychological test scores predicted the likelihood of achieving combined adherence success across the 96-week study monitoring period. Set loss (classification errors) on the 'animals' semantic condition of the Verbal Fluency subtest was predictive (as it had been in the early pill count adherence analysis) [[chi]^2(2) = 9.80, *p*=.007]. The

number of units and thematic units immediately recalled across both stories in the WMS Logical Memory subtest was also predictive [[chi]^2(36) = 51.86, *p*=.04].

No neuropsychological test scores from the D-KEFS Design Fluency subtest, D-KEFS Colour-Word Interference subtest, D-KEFS Tower subtest or WMS Digit Span subtest predicted combined adherence success.

Social factors

Only one social factor was predictive of combined adherence success. While 65% of patients who had a partner and who lived with that partner achieved combined adherence success across the study's 96-week monitoring period, just 39% of patients who had a partner but did not live with that partner managed to do so (*p*=.03) (see Figure 45). Living with family other than spouse, child(ren) or parent(s) approached significance (*p*=.07), with 49% of those who lived with other family achieving combined adherence success, compared with 64% of those who did not. Relationship status also approached significance (*p*=.05), with 56% of patients who were not in a relationship, 65% of those who were married or cohabiting, and 38% of those who were married but separated or in a non-cohabiting relationship achieving combined adherence success.

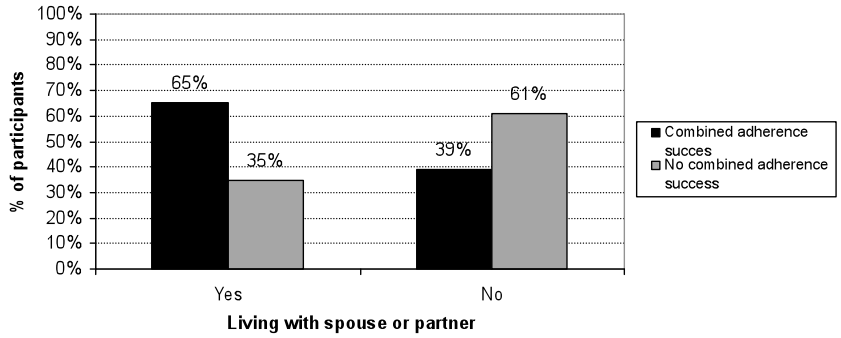

Figure 45. Percentage of participants achieving combined adherence success against living with partner. Note: only participants who reported being in a relationship included in this analysis.

No other social variables predicted combined adherence success, including all other household-related variables (household size, *p*=.60; living with child(ren), *p*=.40; living with parent(s), *p*=.10), variables related to knowing HIV-positive others (knowing anyone HIV-positive, *p*=.45; total number of HIV-positive others known, *p*=.25; having an HIV-positive spouse or partner, child, other family or friend, *p*=.44, *p*=.21, *p*=.87 and *p*=.73),

variables related to knowing others on ART (knowing anyone on ART, *p*=.27; living with someone on ART, *p*=.83; total number of others on ART known, *p*=.29; having a spouse or partner, family member other than child or parent, or friend on ART, *p*=.12, *p*=.99 and *p*=.36), variables related to disclosure (total number disclosed to, *p*=.26; disclosure to partner, child)ren, parent(s), other family members, or friends, *p*=.59, *p*=.62, *p*=.20, *p*=.41 and *p*=.12; living with someone disclosed to, *p*=.10; disclosed to everyone in household, *p*=.33; living with someone disclosed to who was also on ART and would remind them to take ART, *p*=.14; attitudes towards ART of those disclosed to, *p*=.44) and variables related to the patient-health care provider relationship (whether they saw the same doctor at clinic visits, *p*=.93; whether the doctors and nurses at the clinic spoke to them in their home language, *p*=.41; if they felt they could talk to the doctors and nurses at the clinic about any problems they were having, *p*=.83; whether they felt they could trust the doctors and nurses at the clinic, *p*=.95; composite patient-clinic relationship score, *p*=.46).

Miscellaneous factors

Use of material aids such as pill boxes (*p*=.91), cell phone alarms (*p*=.12) and wrist watch alarms (*p*=.42) did not impact ability to achieve combined adherence success across the study's 96-week monitoring period.

The mode of transport patients used to get to clinic visits (*p*=.42), how much this transport cost them (*p*=.47) and whether or not they felt this was affordable (*p*=.34) did not influence the likelihood of achieving combined adherence success. When asked to take both time and costs associated with clinic visits into account, patients who considered clinic visits convenient were no more likely to achieve combined adherence success than those who did not (*p*=.33).

In sum, several demographic, psychological and social factors at treatment initiation were significantly associated with likelihood of achieving combined adherence success across the first 96 weeks of treatment. Patients who were employed were more likely to achieve success (*p*=.01) as were patients who could name none or all of the names of the ARV medication in their regimen (*p*=.04). Patients who showed no presence of alcohol abuse on the AUDIT scale (*p*=.02) and who reported drinking less frequently (*p*=.006) and never failing to do what is expected because of drinking (*p*=.003) were

most likely to succeed. Patients who made no set loss errors in the 'animals' semantic condition of the Verbal Fluency Test (*p*=.003) and scored 20–29 on combined immediate recall of both stories on the Logical Memory Test (*p*=.04) were more likely to achieve success. Finally, patients who lived with a spouse or partner (*p*=.03) were most likely to succeed.

Multivariate analysis

Logistic regression analysis was performed, with the combined adherence success measure as the dependent variable. As with the bivariate combined adherence success analyses, patients were included in the logistic regression analysis if there was any pill count, HIV RNA test or retention data recorded for them. For all patients who had TFO or been LTFU, and all but one of those who had died on treatment before the end of the 96 week follow-up period, pill count data from their first 16 week follow-up period were available. The single patient who had died just after Week 0 and before the next clinic visit had no pill count, HIV RNA test or retention data available and was excluded from the regression analysis, meaning that 149 patients were analyzed.

When the logistic regression analysis was performed, the following variables entered the model to predict the combined adherence success measure: number of alcoholic drinks consumed on a typical day of drinking (*p*=.002), CD4+ cell count (*p*=.004), relationship status (*p*=.009), proportion of original recall remembered in delayed recall of Logical Memory (*p*=.04), number of words generated on the letter 'F' fluency trial of Verbal Fluency (*p*=.06), planned use of cell phone alarm as reminder (*p*=.06), time taken to travel to clinic (*p*=.06) and age (*p*=.07) (see Table 28). The overall multivariate model had a Gini coefficient of .58 (58%).

Predictor	OR (95% CI)	*p*-value
Number of alcoholic drinks consumed on a typical day of drinking	0.58 (0.41–0.82)	*p*=.002
CD4+ cell count	0.61 (0.43–0.87)	*p*=.004
Relationship status	0.64 (0.44–0.92)	*p*=.009
Proportion of original recall remembered in delayed recall of Logical Memory	0.61 (0.38–0.99)	*p*=.04
Number of words generated	0.48 (0.24–0.95)	*p*=.06

on the letter 'F' fluency trial of Verbal Fluency		
Planned use of cell phone alarm as reminder	0.56 (0.31–1.02)	*p*=.06
Time taken to travel to clinic	0.41 (0.18–0.94)	*p*=.06
Age	0.60 (0.38–0.94)	*p*=.07

Table 28. Predictors of combined adherence success measure in logistic regression analysis.

RAT scorecard

Based on the prediction model, a RAT and associated scorecard was developed for use in routine PHC ART clinics. The RAT was designed for use at first clinic presentation, in order to screen and accurately identify patients at highest risk for non-adherence and LTFU, so that targeted adherence support measures could be initiated.

The tool consists of eight items, corresponding to the eight variables that entered the model to predict the combined adherence success measure. Two items are completed through clinic file review, four are asked directly of the patient, and two are completed through neuropsychological tests. Depending on the response to each item, a score is allocated. See Table 29 for items and associated scores.

Question	Score
Clinic file review	
Age	<27 years – 4 27 – 37 years – 14 38 – 40 years – 32 41 or older – 41
Most recent CD4+ cell count result	<100 cells/μL – 5 100 – 199 cells/μL – 34 ≥200 cells/μL – 44
Interview	
How long does it take you to travel to the clinic (one-way)?	<15 minutes – 34 ≥15 minutes – 5
What is your relationship status?	Single – 28 Widowed – 28 Separated – 5 In relationship, but not cohabiting – 5 In a relationship and cohabiting – 40 Married – 40
How many drinks containing alcohol do you have on a typical day when you are drinking?	0 drinks – 56 1 – 3 drinks – 29 4 or more drinks – 5
Do you plan to use an alarm clock on your cell phone to help you to remember to take your	Yes – 27 No – 5

antiretrovirals?	
Neuropsychological assessment	
Administer Logical Memory subtest from Wechsler Memory Scale (WMS): Percent retention score	Score <85% – 5 Score 85% – 99% – 14 Score 100% - 35
Administer Verbal Fluency subtest from Delis-Kaplan Executive Functions System (D-KEFS): F Total Responses	<7 responses – 5 7 – 10 responses – 27 11 or more responses – 34

Table 29. RAT questions and associated scores.

The lowest possible achievable score is 39, and highest 311; lowest scores indicate highest likelihood of failing to achieve ≥90% mean pill count adherence across the first 16 weeks of treatment, virological suppression and retention to care at 96 weeks.

Score distributions for the sample are presented in Table 30. In order for the RAT to be utilised as a profiling tool and trigger for increased support, individual programmes may use the score distribution table to select the cut-off for advanced or diminished support based on resources and funding. Using the 'Cumulative % of total' column, an estimated proportion of the patient base may be selected for additional support. For instance, if the programme chose to offer increased support to the 25% of the overall population that is most likely to not achieve adherence success, a score of 146 would be selected as the cut-off. Selecting this cut-off would mean offering additional support to an estimated five patients per 150 patients who are likely to achieve adherence success (6.3% of the patient base who are likely to achieve adherence success) and an estimated 32 patients per 150 patients who are not likely to achieve adherence success (46.4% of the patient base who are not likely to achieve adherence success).

Alternatively, using the 'Cumulative % of those not achieving adherence success' column, an estimated proportion of the patient base who are not likely to achieve adherence success may be selected for additional support. For instance, if the programme chose to offer increased support to 50% of the population that is most likely to not achieve adherence success, a score of 151 would be selected as the cut-off. Selecting this cut-off would mean offering additional support to an estimated seven patients per 150 patients who are likely to achieve adherence success (8.8% of the patient base who are likely to achieve adherence success) and an estimated 35 patients per 150 patients who are not likely to achieve adherence success (50.7% of the patient

base who are not likely to achieve adherence success).

Score	Cumulative no. of those achieving adherence success	Cumulative % of those achieving adherence success	Cumulative no. of those not achieving adherence success	Cumulative % of those not achieving adherence success	Cumulative % of total	Cumulative default rate
61	0	0	1	1.4	0.7	100
70	0	0	2	2.9	1.3	100
71	0	0	3	4.3	2	100
82	0	0	4	5.8	2.7	100
95	0	0	5	7.2	3.4	100
97	0	0	6	8.7	4	100
102	0	0	8	11.6	5.4	100
107	0	0	9	13	6	100
110	0	0	10	14.5	6.7	100
112	0	0	12	17.4	8.1	100
114	0	0	13	18.8	8.7	100
116	1	1.3	13	18.8	9.4	92.9
117	1	1.3	14	20.3	10.1	93.8
118	1	1.3	15	21.7	10.7	93.8
121	1	1.3	16	23.2	11.4	94.1
123	1	1.3	17	24.6	12.1	94.4
125	2	2.5	17	24.6	12.8	89.5
128	2	2.5	18	26.1	13.4	90
130	3	3.8	19	27.5	14.8	86.4
131	4	5	21	30.4	16.8	84
132	4	5	22	31.9	17.4	84.6
133	4	5	23	33.3	18.1	85.2
134	4	5	24	34.8	18.8	85.7
135	4	5	26	37.7	20.1	86.7
142	4	5	28	40.6	21.5	87.5
143	5	6.3	29	42	22.8	85.3
144	5	6.3	30	43.5	23.5	85.7
145	5	6.3	31	44.9	24.2	86.1
146	5	6.3	32	46.4	24.8	86.5
150	5	6.3	33	47.8	25.5	86.8
151	7	8.8	35	50.7	28.2	83.3
152	9	11.3	37	53.6	30.9	80.4
153	9	11.3	38	55.1	31.5	80.9
154	9	11.3	40	58	32.9	81.6
156	10	12.5	40	58	33.6	80
157	12	15	40	58	34.9	76.9
160	13	16.3	40	58	35.6	75.5
161	14	17.5	42	60.9	37.6	75
163	15	18.8	42	60.9	38.3	73.7
164	16	20	44	63.8	40.3	73.3
165	18	22.5	45	65.2	42.3	71.4
169	18	22.5	46	66.7	43	71.9
170	19	23.8	47	68.1	44.3	71.2
171	19	23.8	48	69.6	45	71.6
172	20	25	50	72.5	47	71.4

173	21	26.3	50	72.5	47.7	70.4
174	23	28.8	52	75.4	50.3	69.3
175	24	30	52	75.4	51	68.4
176	25	31.3	52	75.4	51.7	67.5
177	25	31.3	53	76.8	52.3	67.9
179	27	31.8	53	76.8	53.7	66.3
180	28	35	53	76.8	54.4	65.4
181	30	37.5	53	76.8	55.7	63.9
182	33	41.3	53	76.8	57.7	61.6
183	34	42.5	54	78.3	59.1	61.4
184	35	43.8	55	79.7	60.4	61.1
185	36	45	55	79.7	61.1	60.4
186	39	48.8	55	79.7	63.1	58.5
187	39	48.8	56	81.2	63.8	58.9
188	40	50	57	82.6	65.1	58.8
189	40	50	58	84.1	65.8	59.2
191	41	51.3	58	84.1	66.4	58.6
192	42	52.5	58	84.1	67.1	58
194	43	53.8	58	84.1	67.8	57.4
195	47	58.8	61	88.4	72.5	56.5
196	48	60	61	88.4	73.2	56
197	50	62.5	61	88.4	74.5	55
199	50	62.5	62	89.9	75.2	54.4
203	50	62.5	63	91.3	75.8	55.8
204	51	63.8	64	92.8	77.2	55.7
205	52	65	64	92.8	77.9	55.2
207	54	67.5	64	92.8	79.2	54.2
208	55	68.8	64	92.8	79.9	53.8
209	57	71.3	64	92.8	81.2	52.9
210	58	72.5	65	94.2	82.6	52.8
211	59	73.8	66	95.7	83.9	52.8
213	59	73.8	67	97.1	84.6	53.2
214	60	75	67	97.1	85.2	52.8
215	62	77.5	68	98.6	87.2	52.3
216	64	80	68	98.6	88.6	51.5
217	68	85	68	98.6	91.3	50
220	69	87.3	68	98.6	91.9	49.6
221	71	88.8	68	98.6	93.3	48.9
222	72	90	68	98.6	94	48.6
224	73	91.3	68	98.6	94.6	48.2
226	75	93.8	68	98.6	96	47.6
228	76	95	68	98.6	96.6	47.2
230	77	96.3	68	98.6	97.3	46.9
235	78	97.5	68	98.6	98	46.6
239	79	98.8	68	98.6	98.7	46.3
241	79	98.8	69	100	99.3	46.6
245	80	100	69	100	100	46.3

Table 30. Sample's RAT score distributions

CHAPTER 6

Interpretations and implications

New HAART regimens for the treatment of HIV disease can dramatically reduce HIV-related morbidity and mortality and improve patients' clinical and immunological health where they are available. However, the regimens are chronic and unforgiving of even modest or occasional treatment lapses, which can lead to HIV viral load rebound and ultimately antiretroviral resistance (Catz et al., 2000). In resource-constrained, high prevalence settings like South Africa, transmissible drug resistant strains are a real fear and the consequences profound, both for individual and public health. Retention in ART programmes is a precursor to medication adherence and is as essential for programme success. Promotion of good antiretroviral adherence and retention to care is imperative.

The aim of this study was to look at the role played by various demographic, biomedical, psychological and social factors in determining HIV outcomes in a resource-limited setting in Southern Africa. The study extended the research in this area by conducting bivariate and logistical regression analyses to determine which factors were associated with adherence outcomes.

One of the key strengths of this study was that it captured longitudinal rather than cross-sectional data, allowing for the determination of causal inferences rather than just associations. Of those studies that have included longitudinal data, most are measured over short periods; some only days (Spire et al., 2002; Tesoriero et al., 2003; Wagner, 2002; Wagner et al., 2002). Because HAART requires life-long adherence to be beneficial, research was needed to examine predictors of long-term adherence. Another strength was the sample composition of mostly treatment-naïve patients (91% had never been exposed to previous therapy; of the 14 who had, 10 had received sd-NVP as PMTCT, two had participated in previous ART drug trials, and two had defaulted treatment and presented during the study period for re-initiation). This eliminated uncertainty as to the direction of the relationships found (for instance, studies showing relationships between depression and ART adherence in non-naïve patients cannot determine whether poor adherence led to depression or depression led to poor

adherence), and further bolstered the capacity of the study to determine causal inferences. Another was the choice of four different complementary methods of assessing, evaluating and classifying adherence: early pill count adherence, late virological suppression, retention to care and a composite measure of all three. The two medication adherence indicators (pill count and viral load) have both been repeatedly validated in HIV-positive populations (Bisson et al., 2006; Golin et al., 2002; Gordillo et al., 1999; Laniece et al., 2003; Roco et al., 1999; van Oosterhout et al., 2005; Weidle et al., 2006). This intensive measurement approach was designed to capture the complex variations in adherence from different angles and was in accordance with adherence editorials and reviews advocating a multi-component approach to adherence measurement (Chesney, 2000; Turner & Hecht, 2001; Wutoh et al., 2003). Finally, the study included testing of neurocognitive functioning, a factor which, although repeatedly identified in numerous studies investigating reported barriers to adherence (Brigado et al., 2001; Chesney et al., 2000; Golin et al., 2002; Murphy et al., 2000; Pienaar et al., 2006; Roberts, 2000; Spire et al., 2002; Weidle et al., 2006), has rarely been objectively assessed in observational adherence research, likely due to the skill-set and associated expense involved in such testing. The study design and methodology allowed the researcher to determine valid and reliable predictors of ARV nonadherence and LTFU to follow-up in the South African context, and represented a significant methodological improvement over past studies in the field.

The demographic and clinical distributions of participants enrolled in the study (n=150) largely reflected those of the total clinic population (n=4,302) and the population initiating treatment during the study enrolment period (n=521). In the sample, total clinic population and the population initiating treatment during the study enrolment period, women predominate (63%, 67% and 68% respectively) and mean age (34 years, 35 years and 34 years), mean CD4+ cell count (119 cells/μL, 115 cells/μL and 121 cells/μL), proportion of patients with viral loads >500,000 copies/mL (11%, 10% and 11%), proportion of patients classified as WHO stage III/IV (76%, 74% and 69%), and proportion of women pregnant (13%, 15% and 14%) were very similar.

The demographic and clinical characteristics of the study sample are also broadly representative of public-sector patients accessing ART in South Africa and even public-sector patients accessing ART in sub-Saharan Africa. In the study sample, women

predominate (63%), which is also characteristic of a recent cohort analysis of 44,177 ART patients from eight public sector programmes across South Africa (Cornell et al., 2010) (68%), and a meta-analysis of 74,289 ART patients across 33 cohorts in 13 sub-Saharan countries (Rosen et al., 2007) (54%). The sample's mean age of 34 years is just slightly younger than the median age of the recent South African cohort analysis (35 years), and the weighted mean age of the sub-Saharan meta-analysis at (35.5 years). The mean starting CD4+ cell count of 119 cells/μL is slightly higher than the median starting CD4+ cell count of the recent South African cohort analysis (103 cells/μL), and lower than the weighted mean starting CD4+ cell count of the sub-Saharan meta-analysis (132 cells/μL). The median plasma starting viral load level of 4.98 $\log_{10}$ RNA copies/mL is slightly higher than the recent South African cohort analysis (4.9 copies/mL). Seventy-six percent of the sample were classified as WHO stage III/IV, slightly less than the recent South African cohort analysis (80%). Starting viral load and WHO stage data was not presented for the sub-Saharan meta-analysis.

The findings confirm the presence of symptoms associated with depression according to the CES-D in a substantial proportion of patients. Thirty-nine percent showed prominent depressive symtomatology: 15% had symptoms associated with mild to moderate depression and 23% displayed symptoms associated with a major depressive episode. There is a dearth of epidemiological data on the prevalence of psychiatric disorders in South Africa; until 2008 there had been no nationally representative data. In that year, Stein et al. (2008) reported results from a national household survey conducted with over 4,000 adult South Africans and found a lifetime prevalence of major depression of 9.8%. This study's sample presented with current symptomatology associated with a major depressive episode at more than double the lifetime prevalence of the national sample.

HIV infection has long been identified as a risk factor for major depressive disorder globally (Bing et al., 2001); a systematic review and meta-analysis showed that HIV-positive individuals have nearly double the rate of major depression as HIV-negative individuals (Ciesla & Roberts, 2001). Prevalence rates range widely, from 0% (Fukunishi et al., 1997) to 49% (Dew et al., 1997), with differences across studies likely a function of both methodological variations (e.g. use of structured psychiatric interviews versus self-report symptom checklists) and differences in study populations (e.g. injection drug

users versus general adult populations) (Rabkin, 2008). Considering the previously reported association between depressive symptoms and higher mortality rates (Ickovics et al., 2001; Wilkie et al., 1998), these results call for early identification and treatment of depression in this population for the sake of both mental health and survival time. The latest South African Department of Health clinical guidelines for HIV/AIDS management (Department of Health, 2010a) do stipulate the conduct of 'a basic psychological assessment to document social issues and current psychological state' before treatment initiation (p.12) and that clinicians 'treat depression and substance abuse' (p.17). However there is a chronic lack of mental health human resources at PHC level. This is evidenced in the study's sample: while 39% of the sample showed prominent depressive symptomatology, just two patients (1%) had a documented history of depression in their clinic files.

Alcohol abuse rates were also high in this sample with 41% classified according to the AUDIT as engaging in alcohol consumption that was hazardous or harmful. Stein et al.'s (2008) national survey found a lifetime prevalence of alcohol abuse of 11.4% in the general population. The comparatively high rate in this sample is a strong call to prioritise the identification and treatment (either pharmacologically or behaviourally) of substance abuse in ART-initiating populations in South Africa. Previous international literature has already shown that a disproportionate number of HIV-infected individuals exhibit substance use disorders relative to the general adult population (Chander, Himelhoch & Moore, 2006), with prevalence rates ranging from 8% (Galvan et al., 2002) to 41% (Lefevre et al., 1995). This may in part be explained by the role played by premorbid alcohol abuse in increasing sexual risk behaviour and HIV acquisition (Fisher, Bang, & Kapiga, 2007; Simbayi et al., 2006), but is also likely a function of alcohol abuse as a behaviour adopted in dealing with HIV disease and its associated challenges.

Optimal medication adherence (≥90%) was achieved by 112 participants (75%) across the first 16 weeks of treatment, and the sample's mean pill count adherence across the period was 87%. As outlined in Chapter 1, ART outcomes literature reports highly variable adherence rates across programmes, with mean adherence levels ranging from 71% to 100% (Lima et al., 2009; Weidle et al., 2006). For instance, a Ugandan study reported 99% of patients to be adherent (Weidle et al., 2006), contrasted with a Canadian study in which only 129 of the 278 patients participating in the study (46%)

were adherent (Palepu et al., 2006). The WHO's recommended strategy for prevention and assessment of HIVDR in resource-limited countries suggests a target of >90% of ART patients taking >90% of each of their prescribed drugs at each clinic visit. In this representative sample of 150 newly-initiated HAART patients, the finding that this target is far from being reached, with one quarter of the cohort unable to adhere to the regimen, is of concern. Given the importance of ARV adherence for optimal clinical response and the associated nonadherence risks of patient illness and death, HIV transmission, and single- and multi-drug resistance, it is critical that programmes be adapted to increase this level.

In the sample, excluding deaths and TFO, 38 patients (29%) were LTFU at 96 weeks. As discussed, LTFU rates, like adherence levels, vary widely across reports, programmes and study populations. Studies in Uganda (Kabugo et al., 2005) and Cameroon (Guiard-Schmid et al., 2004) have reported LTFU rates as high as 39.3% and 38.5%, while a study from Khayelitsha, South Africa (Coetzee et al., 2004) reported the extremely low rate of 0.3%. In the systematic review of 33 patient cohorts from sub-Saharan Africa, LTFU was highly variable, ranging from 15% to 54%, with a weighted mean of 40% at 24 months, also largely due to LTFU (figure not given) (Rosen et al., 2007). In the recent cohort analysis of patients across 8 public sector programmes across South Africa, the LTFU rate was 22% at 24 months, a level that, although lower than that of this sample, the authors considered to be a 'major threat' to the national programme (Cornell et al., 2010, p.2266). The WHO's recommended strategy for prevention and assessment of HIVDR in resource-limited countries suggests a target of <20% LTFU in first year of ART (Bennet et al., 2008). With a LTFU rate of 29% at 96 weeks, this sample has far from met that target. Since retention to clinical care is a precursor to medication adherence, attrition from ART programmes raises many of the same issues as described with regard to ART adherence. Reaching and maintaining low LTFU rates in ART programmes is key to ensuring continuity of treatment so that patients reap the survival benefits of ART, halt disease transmission and minimise both their own and society-wide resistance.

The results of this study show that when deaths (n = 7), TFO (n = 10) and LTFU (n = 38) are excluded, 73 patients (77% of the 95 patients retained in care) were virologically suppressed (<50 copies/mL) at 96 weeks. This outcome compares favourably with international benchmarks. A meta-analysis of ART programmes in resource-poor

settings which included 10 observational cohorts found the weighted mean proportion of patients with undetectable viral loads at 24 months to be .496, although this 24-month estimate only included data from the 3 studies which provided long-term data - South Africa (Coetzee et al., 2004), Cote D'Ivoire (Seyler et al., 2003) and Kenya (Macharia et al., 2003) (Ivers et al., 2005). The WHO's recommended strategy for prevention and assessment of HIVDR in resource-limited countries suggests a target of >70% of patients, who, at 12 months, had an HIV RNA level of less than the detection limit of the test used (Bennet et al., 2008), a target that was met in this cohort at the 96 week assessment.

The significant association between achieving a mean pill count of ≥90% across the first 16 weeks of treatment and achieving virological suppression (<50 copies/mL) at 96 weeks (p<.0001) suggests that pill count correlates well with actual adherence in this study, and confirms the choice to use pill counts as a proxy measure of pill-taking behaviour. That finding, along with the association between achieving a mean pill count of ≥90% across the first 16 weeks of treatment and retention to care at 96 weeks (p<.0001), shows that patients who are unlikely to achieve optimal treatment outcomes and/ or leave care may be identified early on in the treatment process. The increases in percentage of patients who were virologically suppressed by 10% mean pill count band confirms that even modest deviations in pill-taking can dramatically alter long-term treatment outcomes.

The sample's mean pill count adherence changed significantly during the 16-week monitoring period, decreasing with each 4-week interval (p = .01). The percentage of patients achieving a mean pill count adherence of ≥90% also decreased appreciably with time. This finding is consistent with several other observational cohorts also reporting decreases in adherence rates with time (Carrieri et al., 2003; Liu et al., 2001; Parruti et al., 2006; Roco et al., 1999). These results suggest that adherence interventions are needed throughout the treatment course rather than just treatment readiness preparations at the onset.

This study identified unemployed patients as being more likely to be nonadherent according to all four indices of adherence behaviour measured: early pill count adherence, late virological suppression, retention to care and the composite adherence

success measure. The finding is supported by two previous studies; one, a cross-sectional study of 366 HAART patients in Spain wherein having a job was associated with better adherence (Gordillo et al., 1999), the other a qualitative series of interviews conducted with 18 clinicians at various community centers conducting ARV trials, where the most frequently mentioned barrier to patient recruitment, retention and adherence was unemployment (endorsed by 45% of clinicians) (Morse et al., 1995).

Since neither education nor income was related to any of these four indices in this sample, it seems that the relationship was not mediated by either of these factors. Similarly none of the disease markers assessed in the study (CD4+ cell count, viral load and WHO stage) were significantly associated with any of these four indices, ruling severity of illness out as an explanation for both unemployment status and poor adherence. Other explanations could be that patients who are without employment might also consume more alcohol or be more cognitively impaired. It is possible that patients who are unemployed lead less structured lifestyles than their employed counterparts, with routine and schedule fluctuations that do not lend themselves to adherence to a daily medication regimen. It is perhaps surprising that these patients were also less likely to be retained in care at 96 weeks, since clinic visits should have been less challenging, as missing work, a factor found in previous studies (Do et al., 2010; Maskew et al., 2007; Weiser et al., 2003) to be a barrier to clinic attendance, would not have been a difficulty. It may be the case then that unemployed patients were lost to follow-up from the clinic, not because clinic visits themselves were difficult, but because they had struggled with medication adherence, and were thus less motivated to attend further visits, of which two of the primary focuses are dispensing of medication and adherence assessments. Further research is needed to clarify the exact mechanisms determining the association between unemployment and nonadherence and loss to follow-up. In the interim, special attention to this patient group in ART counseling and possible coordination of medical treatment with social services could increase adherence and facilitate retention to care in ART programmes.

In this study, those patients who had already obtained or applied for a disability grant at initiation of HAART were less likely to be virologically suppressed at 96 weeks than those who did not hold a disability grant and did not plan to apply for one. Disability grants are awarded based upon a number of criteria, most notably a confirmation from a

medical practitioner that the patient is unfit (physically or mentally) to work, and bank records indicating that the set asset and income thresholds were not exceeded in each case (South African Social Security Agency [SASSA], 2010).

While age was not found to be an independent predictor of pill-taking behaviour, virological suppression or retention to care, it did enter the multivariate model to predict the combined adherence success measure, with a p-value of .07 and an OR of .60 (.38–.94), with older patients most likely to achieve overall adherence success. This is in line with findings by others (Carrieri et al., 2006; Caluwaerts et al., 2009; Cornell et al., 2010; Golin et al., 2002; Gordillo et al., 1999; Hill et al., 2010; Hinkin et al., 2002; Hinkin et al., 2004; Karcher et al., 2007; Kerr et al., 2005; Mocroft et al., 2008; Spire et al., 2002; Wagner, 2002) that younger patients are those with the highest risk of poor adherence and loss to follow-up. Possible explanations include the fact that younger patients would have less prior experience with medication-taking and that their lifestyles are more prone to fluctuations which would make a high-burden medication regime more challenging (Hinkin et al., 2002). In this case age-specific interventions may be necessary.

In this study, as in others (Caluwaerts et al., 2009; Catz et al., 2000; Dalal et al., 2008; Do et al., 2010; Gebo et al., 2003; Karcher et al., 2007; Spire et al., 2002), other demographic factors like gender and education were not associated with any of the four adherence indices. As outlined in Chapter 2, some research has linked these demographic factors with various adherence behaviours (Gordillo et al, 1999.; Maskew et al, 2007.; Mocroft et al., 2008; Turner et al., 2003; Wagner, 2002; Wools-Kaloustian et al., 2006; Zachariah et al., 2008). But the data has been highly inconsistent across studies, which, given the relative lack of methodological challenge associated with assessing demographic profile and therefore unlikelihood of methodologically-determined findings, points to the differential impact demographics may have in different countries, cultures and contexts on health-seeking behaviour.

In bivariate analyses, patients with more advanced disease at treatment onset (higher CD4+ cell count and HIV RNA level, more advanced WHO stage) did not differ significantly in their adherence, virological suppression or retention to care rates compared with healthier patients. There was a trend towards a relationship between lower CD4+ cell count and less likelihood of both retention to care and achieving

virological suppression at 96 weeks, although neither relationship reached significance (*p*=.06 in both cases). CD4+ cell count did enter the multivariate model to predict the combined adherence success measure, with a p-value of .004 and an OR of .61 (.43–.87), with patients with lower CD4+ cell counts least likely to achieve overall adherence success. As the national ART programme continues to expand and individuals begin to access HIV care earlier in their disease process (both as a result of the decreasing backlog of supremely ill patients and new national clinical guidelines stipulating treatment initiation at a CD4+ cell count of 350 cells/μL for pregnant women and patients with TB co-infection), the country's treatment initiation base is expected to present with higher CD4+ cell counts, limiting the possible impact of severe disease on adherence and retention rates. Others have observed both decreased adherence (Ammassari et al., 2004; Gordillo et al., 1999; Weidle et al., 2006) and higher LTFU (Caluwaerts et al., 2009; Lanoy et al., 2006; Mocroft et al., 2008; Zachariah et al., 2008) in sicker patients, ascribing the finding to either decreased efficacy of treatment in those already very ill at treatment initiation, the impact of ill health on ability to attend visits and adhere to complex regimens or hidden mortality.

The study found that the reporting of one or more symptoms the patient ascribed to HIV and the severity of the symptoms when they were reported, was not associated with any of the four adherence indices. Of note, however, the reporting of certain specific symptoms was predictive of either superior or inferior adherence and retention rates. In the case of haematological symptoms (such as 'nodule in neck') and ophthalmic symptoms (such as 'visual disturbances'), patients who reported experiencing them were significantly less likely to succeed - those with haematological symptoms to achieve a mean pill count adherence of ≥90%, and those with ophthalmic symptoms to be retained in care at 96 weeks. Conversely, patients who reported ever having experienced dermatological symptoms (such as 'dandruff' or 'dry skin') or urological symptoms (such as 'discharge' or 'genital ulcers') were likely to fare better, in the case of dermatological symptoms to achieve ≥90% mean pill count adherence and in the case of urogenital symptoms to be virologically suppressed at 96 weeks. It is possible that certain symptoms, if bothersome but not significantly debilitating (such as 'dandruff' within the dermatological symptoms category), may motivate patients to attend visits and adhere to their medication in the hope of alleviating such symptoms, whilst haematological symptoms for instance, may be more likely to impact overall functioning and indicative of

more severe pathologies, might impact ability to adhere and attend visits. These results argue for 1) HIV symptomatology to be clearly assessed at clinic visits and symptoms treated aggressively in order to facilitate capacity to adhere to medication routines and clinic visits, and 2) patient education to focus on the critical need to take medications in order to minimise symptoms, using any symptoms the patient is experiencing as a motivator of adherence behaviour. HIV symptom status instruments like the Sign and Symptom Checklist for persons living with HIV disease-revised (SSC-HIV-rev) are available for ease of assessment (Holzemer et al., 1999).

All other biomedical factors that were assessed were not predictive of adherence to ARV therapy, virological suppression or retention to care, including time between positive HIV diagnosis and HAART initiation, reason for HIV test, pregnancy at treatment initiation, TB therapy at treatment initiation, neurological history, having been previously exposed to ART and prescribed ARV regimen.

Bivariate analyses demonstrated that 24 of the psychological variables and 7 of the social variables assessed were linked with adherence and retention outcomes. What is particularly noteworthy about this finding is that these data, unlike the demographic, laboratory and clinical data types outlined above, are not routinely collected at clinic visits and are therefore unlikely to be detected by health care workers like doctors and nurses, and therefore cannot be impacted or compensated for. Van Servellen, Johiro and Thichacek (2002) performed a medical record review of 146 HAART patients in four community-based clinics in the United States, checking for completeness of adherence and adherence predictor documentation, and reported that adherence issues, in both frequency and type, were inadequately documented, with the absence or presence of mental health and substance abuse problems clearly noted in just 25% and 17% of charts respectively. Several of these factors are potentially modifiable and highlight the role that psychosocial interventions may play in improving treatment adherence, retention to medical care and biomedical outcomes.

An unexpected finding was that measures of knowledge, attitudes and beliefs related to HIV and ART were largely unrelated to adherence. With the exception of being able to correctly name the medications in one's prescribed regimen – which bordered on significance as a predictor of early pill count adherence (p=.06) and was significantly

related to the combined adherence success measure (p=.04), interestingly with patients who could either name none or all of their medications faring best – none of the knowledge variables were significantly related to early pill count adherence, late virological suppression or long-term retention to care. This is an important finding as much of the focus of the latest Department of Health clinical guidelines for HIV/AIDS management (Department of Health, 2010a, p.12) is on knowledge transfer as the means to prepare patients for treatment and facilitate adherence once they are on treatment. As outlined in Chapter 1, the guidelines recommend the conduct of an 'information and education session' pre-treatment and that at the treatment commencement visit 'the multidisciplinary team should reassess ART readiness criteria', including 'patient's understanding of their HIV status, the need for ART, importance of adherence and the link to treatment outcomes, specifically virological suppression, and commitment to scheduled visits.' The guidelines also propose 'explaining the link between virological suppression and clinical outcome and adherence', 'provide ongoing education to patients on their disease, including any new diagnoses, unexplained symptoms or opportunistic infections', and 'spend(ing) time with the patient and explain(ing) the disease, the goals of therapy and why the need for adherence' as longer-term adherence support strategies (p.17).

The previous finding that depressed mood, as measured by self-report rating scales, may play a significant role in adherence behaviour (Ammassari et al., 2004; Arnsten et al., 2007; Carrieri et al., 2006; Catz et al., 2000; Do et al., 2010; Gardenier et al., 2010; Gordillo et al., 1999; Malcolm et al., 2003; Murphy et al., 2000) was not confirmed in this setting. In each of the three adherence outcomes analyses as well as the combined adherence success analysis, neither the overall CES-D depression score nor any of its 20 individual questions was significantly associated with adherence success. This is not the first study to find no association between depressed mood and adherence (Spire et al., 2002), reflecting a differential impact of mental illness in different contexts. However, as outlined earlier, the high level of depressive symptomatology in the sample (with 39% of participants reporting prominent depressive symptomatology) suggests that integration of clinical and mental health services would be beneficial to ART initiators.

Clearly, one of the most significant and consistent barriers to medication adherence, virological suppression and retention to care was alcohol abuse. These results are

consistent with numerous studies that have found a strong correlation between adherence to HAART and alcohol abuse (Chesney et al., 2000; Do et al., 2010; Golin et al., 2002; Spire et al., 2002). Patients who scored seven or lower on the AUDIT scale (indicating no presence of alcohol abuse) were more likely to achieve ≥90% mean pill count adherence across the first 16 weeks of treatment, remain in care at 96 weeks, achieve virological suppression at 96 weeks and achieve combined adherence success. Eight of the AUDIT's ten individual items independently predicted at least one of the adherence outcomes: two items (how often an alcoholic drink is consumed and how often they fail to do what is expected of them) predicted all three outcomes and the combined adherence success measure, two items (how often six or more drinks is consumed on one occasion and how often they experience feelings of guilt or remorse after drinking) predicted the three outcomes and showed a trend towards a relationship with the combined adherence success measure, one item (the average number of alcoholic drinks consumed on a typical day of drinking) predicted both likelihood of achieving ≥90% mean pill count adherence and virological suppression, showed a trend towards a relationship with retention to care and the combined adherence success measure and entered the multivariate model to predict the combined adherence success measure, with a p-value of .002 and an OR of .58 (.41–.82), one item (how often they were unable to remember what happened the night before because of drinking) predicted both likelihood of achieving ≥90% mean pill count adherence and virological suppression and two items (how often they could not stop drinking once they had started and whether a friend, relative, doctor or other health care worker had been concerned about their drinking) predicted virological suppression and showed a trend towards a relationship with early pill count adherence.

A probable explanation for this finding is that alcohol abuse acutely produces situations in which it is difficult to prioritise medication taking and more generally leads to a chaotic lifestyle that is adversative to the structure needed to adhere to a regular and complex medication regimen. The implications are dramatic – with such high alcohol abuse rates in treatment initiators and the observed relationship between alcohol abuse and adherence behaviour, this is of major concern for the country's HIV treatment programme. Since alcohol use has also been repeatedly associated with increased sexual risk behaviour (Castilla et al., 1999; Shillington et al., 1995; Stein et al., 2005; Stueve & O'Donnell, 2005), patients who abuse alcohol are more likely to adhere poorly,

develop resistance and practice unsafe sex, transmitting drug-resistant HIV strains to others. Alcohol abuse is, however, potentially modifiable, with several studies showing successful alcohol abuse interventions in primary care settings (Cordoba et al., 1998; Israel et al., 1996; Maisto et al., 2001; Ockene, Adams, Jurley, Wheeler & Hebert, 1999). The implementation of routine alcohol abuse screening and associated interventions should be implemented alongside the national ARV treatment programme as a matter of urgency in order to facilitate successful individual clinical outcomes and manage public health risk.

Drug use has been associated with decreased adherence to ART (Ammassari et al., 2004; Gebo et al., 2003; Golin et al., 2002; Hinkin et al., 2004; Lanoy et al., 2006; Lima et al., 2009; Lima et al., 2009; Malcolm et al., 2003; Roco et al., 1999; Turner et al, 2003); however this was not the case in this study. In this sample, adherence, virological suppression, retention and combined adherence success rates of patients who had used recreational drugs in the past 12 months were as good as the rates of patients who had not. This finding is perhaps attributable to the fact that just ten participants (7%) were categorised as drug users (having used recreational drugs in the previous 12 months), possibly leading to insufficient statistical power to detect a significant relationship. An alternative explanation is that the primary drug used was marijuana (all ten participants), with just two having used mandrax, reflecting a lower impact of a less psychoactive substance.

This work has provided evidence that patients who perform poorly on certain neurocognitive measures are more likely to adhere poorly, be LTFU or be virologically unsuppressed. Overall, across the four sets of bivariate analyses and the multivariate analysis, 14 of the neuropsychological test scores were related to the adherence indices. The neuropsychological test with the most associations with adherence outcomes was the Verbal Fluency subtest of the D-KEFS. As outlined in Chapter 3, the test consists of three conditions: in the first, the examinee is required to generate as many words as possible that begin with a series of designated letters (‘F’, ‘A’, ‘S’) in three trials of 60 seconds each; in the second, the examinee is required to generate as many words as possible that belong to designated semantic categories (‘animals’ and ‘boys’ names’) in two trials of 60 seconds each; and in the third, the examinee is required to use designated semantic categories again (‘fruit’ and ‘furniture’), this time alternating

between them, in one trial of 60 seconds. For this test, four types of process measures are recorded: 1) number of correct responses in each of the three conditions and the number of correct switches in the third condition, 2) contrast in performance between generating words in the first and second conditions and contrast in performance between the second and third conditions, 3) errors of repetition (same response generated more than once within a trial) and errors of set-loss (response generated that does not follow the phonemic or semantic rule of the trial) and 4) time-interval analyses (i.e. the number of correct words generated during each of the four 15-second intervals making up a trial). The test provides a measure of the examinee's ability to generate words fluently in both a restricted phonemic format (letter fluency) and a restricted semantic format (category fluency), providing both a good indication of organised thinking and volitional capacity. The switching condition requires rapid shifting from one cognitive set to another, assessing cognitive flexibility and the ability to undertake and manage conflicting demands.

Patients who were able to generate more words (including errors) in the letter 'F' fluency trial, the letter 'A' fluency trial and across all three letter fluency trials ('F', 'A' and 'S') were more likely to succeed, in the case of the letter 'F' fluency trial to achieve combined adherence success (according to the multivariate model), and in the case of the letter 'A' fluency trial and across all three letter fluency trials to be retained in care (according to the bivariate analyses). Further, patients who generated more correct words (excluding errors) across all three letter fluency trials and across both semantic categories ('animals' and 'boys' names') were more likely to be retained in care and to achieve mean early pill count adherence ≥90% respectively. These results suggest first that patients who are able to develop effective cognitive strategies that organise their thinking and thereby generate more words (for instance, using the same initial consonant, variations on a word or theme or developing sub-categories) (Lezak, 1995) are also more likely to be able to organise their thinking about, and planning for, medication adherence and clinic attendance and second that patients who show intact motivation, volition and the initiation and maintenance of intentional behaviour without prompting, resulting in superior word output, are also more likely to exhibit more volitional capacity in the context of their health behaviour.

Further, patients who made any set loss (classification) errors on the 'animals' semantic condition trial (i.e. generating a word that could not be classified as an animal) were both more unlikely to achieve mean early pill count adherence ≥90% and combined adherence success. This is logical and even expected as patients who struggle to engage in rule-following and self-regulation are unlikely to be able to comply with complex pharmacologic regimens and a demanding long-term clinic attendance schedule.

Surprisingly, at first glance, patients who made any repetition errors on the 'animals' semantic condition trial (i.e. generated the same word more than once within the trial) or more repetition errors across the Verbal Fluency and Design Fluency subtests of the D-KEFS (i.e. generated the same word or design more than once within a trial) were more likely to be retained in care at 96 weeks (in both cases) and achieve mean early pill count adherence ≥90% (in the case of repetition errors across the Verbal Fluency and Design Fluency subtests only). This unexpected outcome may be explained by taking into account the fact that those examinees that generate more words have a greater base of words from which it is possible to repeat. While the relationship between increased errors and better adherence outcomes is worthy of further study, for the purposes of this study, the finding is therefore interpreted as a consequence of increased word generation in those with intact cognitive strategizing and volition.

Two test scores from the Colour-Word Interference subtest of the D-KEFS were predictive of likelihood of virological suppression at 96 weeks. The test's first condition requires examinees to name coloured patches, the second to read colour-words (e.g. 'red') printed in black ink, and the third to name the ink colour of colour-words where the ink colour differs from the colour-word (e.g. the word 'blue' printed in red ink). For these conditions three types of measures are recorded: 1) number of seconds the examinee takes to complete each condition and the combined number of seconds the examinee takes to complete the first two conditions, 2) contrast in performance between seconds to complete the third condition versus the first condition and 3) self-corrected errors and uncorrected errors. The test assesses the examinee's ability to inhibit a learned response (e.g. reading printed words) in order to generate a required and conflicting response (e.g. naming the dissonant ink colour in which the words are printed). Patients who made fewer total errors across the subtest and patients who made fewer self-

corrected errors across the subtest were more likely to be virologically suppressed at 96 weeks - again highlighting the role that rule-following and self-regulation play in adherence behaviour.

Memory was also implicated in adherence outcomes through the Logical Memory subtest of the WMS. In the first condition, two short stories are presented orally to the examinee; the first story is presented once and the second story twice. The examinee is then required to retell the stories from memory. In the second condition, after a 25–35 minute delay, the examinee is required to retell both stories. Then the examinee is required to answer a series of 30 yes/ no questions, 15 about each story. For this test four types of measures are recorded: 1) number of correctly recalled story units for each of the two stories and across both stories, and for each of the conditions and across both conditions, 2) the number of correctly recalled story themes from each story and across both stories, and for each of the conditions and across both conditions, 3) the improvement in recall after the second presentation of the second story (learning slope) and 4) number of correct responses to yes/ no questions. Patients who were able to recall a greater number of units and themes immediately across both stories were more likely to achieve combined adherence success. Similarly patients who were able to recall, after a delay, a greater proportion of the units and themes from the second story that they had originally recalled were both more likely to be retained in care (according to the bivariate analyses) and to achieve combined adherence success (according to the multivariate model). Finally, patients who somewhat improved (improved by between one and five points) their recall of a story after a second exposure to it, were more likely to achieve virological suppression than those who did not improve at all or those who improved dramatically. This finding is understandable as those patients who improved by six or more points would have had to have a low initial score in order for such improvement to take place. These results implicate both auditory immediate and auditory delayed recall in adherence processes. Patients who are able to store and retain a greater amount of information and instruction will be more likely to remember to take their medications as required and attend their clinic appointments as scheduled; story recall omissions (both individual story units and larger story themes) will mean medication-taking omissions and missed clinic visits.

Finally, one measure from the Digit Span subtest of the WMS emerged as a significant predictor of virological suppression. This test requires the examinee to recall a series of digits, increasing in length, and to repeat them back to the examiner. The test consists of 30 items, starting at two digits in the series for both conditions, and increasing up to nine digits in the first condition and eight digits in the second condition. In the first condition, examinees are required to repeat each series as it was presented (forwards); in the second condition, examinees are required to repeat each series in the reverse order (backwards). For this test, two measures were recorded: 1) number of correctly recalled items in each condition and across both conditions, and 2) number of correctly recalled digits in each condition. Contrary to what would be reasonably expected, patients who were able to recall a longer series of numbers were less likely to achieve virological suppression. Further research is needed to clarify the relationship between this measure and adherence behaviour.

The latest South African Department of Health guidelines (Department of Health, 2010b) restrict treatment in the general adult population to patients with WHO stage IV disease or CD4+ cell counts <200 cells/μL, based on the outdated WHO 2002 guidelines (WHO, 2002), although pregnant women with CD4+ cell counts of less than 350 cells/μL and all patients co-infected with TB, regardless of CD4+ cell count, are also eligible. The guidelines, in addition to the late stage at which many patients in South Africa present for treatment (Bekker et al., 2006; Cornell et al., 2010; Lawn et al., 2006) due to poor VCT access, infrequent measurement of CD4+ cell counts and referral delays (Dalal et al., 2008; Lawn et al., 2006), means that the time of HAART initiation in South Africa is when patients are most likely to exhibit neuropsychological deficits. The WHO 2003 revised guidelines (WHO, 2003; WHO 2006; WHO, 2009) recommend earlier treatment, as does the Southern African HIV Clinicians Society. Less stringent guidelines and earlier treatment initiation would help patients to initiate treatment when they are less likely to be cognitively impacted by the disease, and thereby lower the risk of nonadherence and loss to follow-up due to cognitive dysfunction. In the meantime, health-care providers may work with the patient to incorporate the regimen and its associated instructions into the patient's daily schedule, for instance by linking it with certain everyday behaviours or occurrences. Mechanical reminders such as the use of cell phone alarms have proven successful in this sample and may be especially beneficial for those with disease-associated cognitive dysfunction. Finally, facilitating

social support in the form of an on-treatment buddy or significant other who can assist with medication reminders may be useful here.

While studies have almost uniformly shown that increased social support (Carrieri et al., 2006; Catz et al., 2000; Gardenier et al., 2010; Gordillo et al., 1999; Nam et al., 2008; Parruti et al., 2006) and disclosure (Abel & Painter, 2003; Catz et al., 2000; Do et al., 2010; Malcolm et al., 2003; Maskew et al., 2007; Murphy et al., 2000; Nam et al., 2008; Ncama et al., 2008; Richard et al., 2009) positively impact adherence levels, with just a few exceptions (Golin et al., 2002; Wagner, 2002; Weiser et al., 2003; Zacariah et al., 2008), the results of this study indicate a more complex picture.

In terms of relationship status, it appears that single and married/ cohabiting couples achieve similar good levels of adherence success, whilst those patients who are married but separated or in a non-cohabiting couple fare worst. It seems there is little difference between being single or in a 'stable' (married or cohabiting) relationship, but that if in a relationship, it is better to be in a stable one. This was evidenced by the trends towards predictive relationships between relationship status and adherence outcomes in the bivariate analyses. In both the early pill count adherence and combined adherence success analyses, patients who were married but separated or in non-cohabiting relationships fared worst; in the case of the early pill count adherence analyses, those who were single did best, with those married or in cohabiting relationships a close second, while in the case of combined adherence success, those who were married or in cohabiting relationships did best, with those who were single a close second. In the multivariate model, relationship status emerged as predictive of adherence success, again with those who were married but separated or in non-cohabiting relationships least likely to succeed, and mirroring the combined adherence success bivariate analysis with those who were married or in cohabiting relationship faring best and those who were single a close second.

Two additional analyses conducted within the in-relationship group showed similar results. In the first, for those patients who did have a partner, living with that partner increased their likelihood of achieving combined adherence success (there was also a trend towards a relationship between this factor and early pill count adherence). A possible explanation is that a live-in partner may be a more constant and reliable source

of support, which studies have shown to be an important correlate of adherence (Carrieri et al., 2006; Catz et al., 2000; Gardenier et al., 2010; Nam et al., 2008; Spire et al., 2002). A component of such support may include assistance with medication management such as personal reminders to take the antiretroviral agents, another social factor that has been presented in the literature as facilitating patient adherence behaviour (Abel & Painter, 2003; Murphy et al., 2000). In the second, a trend towards a relationship between (for those patients with partners) being in a seroconcordant rather than serodiscordant couple and achieving good (≥90%) mean early pill count adherence was observed. Being in a seroconcordant relationship may facilitate shared disease and side effect burden, both factors which may negatively impact adherence motivation (Abel & Painter, 2003; Catz et al., 2000; Gardenier et al., 2010; Parruti et al., 2006; Spire et al., 2002) and decrease the likelihood of stigma, which is sadly still common in South Africa (Ncama et al., 2008).

Perhaps surprisingly, this study found that increased levels of disclosure did not predict improved medication adherence or adherence to care. In fact there were four negative associations between level of disclosure and adherence success. There was a trend towards a relationship between the number of people disclosed to and likelihood of remaining in care at 96 weeks, with patients who had disclosed to the smallest number of people more likely to be retained. Similarly, disclosing to family members other than spouse/ partner, child(ren) or parent(s) was predictive of failure to remain in care, as was disclosing to friends (there was also a trend towards a relationship between disclosing to friends and less likelihood of achieving virological suppression).

One possibility that might explain these findings is that disclosure to more people, especially those not in direct familial relationships with the patient, may lead to higher levels of stigmatisation and social rejection, making medication-taking and clinic attendance difficult. It may be that certain types of disclosure are in fact beneficial, but that those types were not directly assessed in this study. In Nam et al.'s (2008) one-to-one interviews assessing reasons for nonadherence among on-treatment HAART patients, the concept of an encouraging confidante emerged strongly as a facilitator of medication adherence. The descriptions for such a person included someone to share the burden of their HIV status and promote messages of hope (hope for a relationship, having children and hope for a cure were mentioned). Patients initiating HAART might

disclose to a large number of people of varying relationship type, but if they do not have a particular person in whom to confide, they will not be able to access the kind of individualised, non-judgmental emotional support to which Nam et al.'s participants were referring. The present study did not directly examine this sub-concept. The items in the present study that most closely approximated this were the combined item for living with someone who is also on antiretrovirals to whom the patient has disclosed and who has committed to reminding him or her to adhere (there was a trend towards a relationship between this item and virological suppression) and number of people known who were also on antiretroviral therapy (there was a relationship between greater number of people known and greater likelihood of achieving early pill count adherence success). These findings should be used to strengthen existing disclosure messages administered by health care practitioners and counselors at patient preparedness visits, in particular about choosing appropriate confidantes in whom to confide and gain in-depth support. Furthermore, HIV programmes may need to allocate resources to enhance true and worthwhile social support. For instance, involvement of a close and potentially supportive other in clinic visits and patient education may be beneficial, as well as the establishment of regular support groups for patients on ART.

The results of this study indicate that patients who live in households of three or more people (i.e. with more than one person) are less likely to achieve undetectable viral loads at 96 weeks than those who live alone or with one other person, and that patients who live with family other than spouse, parent or child are less likely to be retained in care at 96 weeks. Several factors related to such living conditions may be at play here; these include crowded living environments and lack of privacy (impacting ability to adhere when disclosure has not taken place) as well as lower socio-economic status and food insecurity (perhaps decreasing the priority status of health behaviour as compared with more immediate drivers). Further investigation into these relationships would certainly be worthwhile in future research.

In contrast to earlier reports (Abel & Painter, 2003; Gardenier et al., 2010; Golin et al., 2002; Murphy et al., 2000; Nam et al., 2008; Roberson et al., 2009; Spire et al., 2002), this study did not find a relationship between patient-provider relationship and medication adherence or retention to care. This may be because each of the relationship indicators was so positively skewed – 87% of patients felt they could talk to the doctors

and nurses at the clinic about any problems they were having, 91% said they trusted the doctors and nurses, 97% felt the doctors and nurses at the clinic respected them and 97% were satisfied with their relationship with the doctors and nurses – making associations unlikely to be detected in this sample size. As such, the result that patient-provider relationship does not impact adherence behaviour should be interpreted with caution. It may be pertinent to consider more deeply the patient-provider relationships in this clinic in future research as a model for successful therapeutic partnerships. Previous research has indicated that factors such as seeing the clinician as a confidante (Nam et al., 2008) and high levels of trust in the provider (Golin et al., 2002) are important to patients and may facilitate adherence. After a series of focus groups focusing on barriers to ARV adherence and strategies to overcome them, Murphy et al. (2000) advocated for health care providers to promote trust in their relationships with patients by encouraging questions, involving patients in medical decision-making, and suggesting that patients contact them if side effects or other problems arise.

Planned use of a cell phone alarm as an adherence aid was associated with increased likelihood of virological suppression at 96 weeks and entered the multivariate model to predict the combined adherence success measure, with a p-value of .06 and an OR of .56 (.31–1.02), with patients planning to use cell phone alarms most likely to achieve combined adherence success. This finding is certainly of practical use in a clinical setting and advice to use this material aid should be incorporated into treatment preparedness. Interestingly, planned use of pill boxes, a commonly-provided tool in public health settings, was not related to improved adherence, although the small prevalence of non-users in this sample (just 6%) may have limited its ability to detect a relationship in this sample.

Although not a significant predictor of any of the four adherence indices in bivariate analyses, length of time spent traveling to the clinic did enter the multivariate model to predict the combined adherence success measure, with a p-value of .06 and an OR of .41 (.18–.94), with patients who spent the least time most likely to achieve overall adherence success. Conducting more home visits (Mehta et al., 1997), offering flexible clinic hours (for instance, remaining open on certain evenings or weekends), providing free or discounted transportation and offering child care services during clinic visits (Battaglioli-DeNero, 2007) are possible solutions to removing this barrier.

In sum, this work has provided evidence that both short- and long-term adherence can be reliably predicted based on patient characteristics at treatment initiation, and therefore that assessing patients' *a priori* biopsychosocial status would be beneficial in identifying patients at risk of poor adherence and defaulting. Reasons for nonadherence are multifactorial, requiring targeted interventions. Factors associated with nonadherence, nonsuppression and/ or loss to follow-up were younger age, unemployment, holding/ having applied for a disability grant, lower CD4+ cell count, haematological or ophthalmic but not dermatological or urological symptoms, ability to name just some of the medications in the prescribed regimen, alcohol abuse, poor neurocognitive performance, unmarried or in non-cohabiting relationship, disclosure to broader family or friends, less people known on antiretrovirals, living in households of three or more, no planned use of cell phone alarm as adherence aid and greater length of time spent traveling to the clinic. High depression and alcohol abuse rates call for early identification and treatment of mental health disorders in this population. Special attention should be paid to younger and unemployed patient groups in adherence counseling. HIV symtomatology should be assessed and symptoms managed aggressively. Adaptation of treatment guidelines for earlier treatment initiation would minimise cognitive compromise in initiating populations. Mechanical reminders like cell phone alarms have proven successful in this sample and may be especially beneficial to those with cognitive dysfunction. Patients should be counseled to choose appropriate confidantes for disclosure and supportive relationships should be encouraged. Clinic visit burden should be minimised through home visits, flexible clinic hours and discounted transportation.

Limitations

Certain limitations of this study deserve mention and should be considered in interpreting the study results. Although the sample is broadly demographically and clinically representative of adult ART patients in this setting, and as part of the government ART roll-out programme, likely to be demographically and clinically generalisable to other ART programmes in South Africa (since 80% of the population rely on the public sector for health services [Barron & Roma-Reardon, 2008]), the true generalisability of these results is unclear due to the fact that the sample was a single-

center cohort and also in part to the specific center chosen. While the sample may have been demographically and clinically similar to broader populations, since psychological and social data is not routinely collected in public-sector biomedical settings (as evidenced in this study by the disparity between a 39% prevalence of prominent depressive symptomatology on investigation versus a 1% documentation of depression in clinic files), it is not known how concordant the sample's psychological and social profiles are with other South African settings or even the total clinic population at this center. Although referrals for participation included all patients initiating treatment during the study enrolment period whose clinic visits fell within the times when the interviewer was present at the clinic, patients who agreed to participate were ultimately volunteers who self-selected to take part. We have little information on those patients who refused to participate; we do know that gender, age, starting CD4+ cell count, starting HIV RNA level, WHO stage and pregnancy rates did not differ between the study sample and the total who initiated treatment during the study enrolment period. However, these patients may have differed in meaningful psychological or social ways from those that did not agree to take part, ways that were unable to be assessed as it was not available for comparison. For instance, study participants may conceivably have been more or less satisfied with their relationship with the clinic (more willing to spend extra time at the clinic, or wanting a space to air complaints) or more or less depressed (drawn to a private session where psychological issues would be discussed, or more motivated to engage in a new task like study participation). It is also unknown whether they differed behaviourally in terms of pill count adherence, as this data – unlike the virological suppression and adherence to care data – was unavailable for all patients. For instance, patients who are able to set and keep a study appointment visit may be more motivated or able to adhere to an antiretroviral regimen than the average patient.

Moreover, although the clinic is part of the government ARV programme, it works in partnership with an NGO linked to a major academic institution and thus may have impacted patient outcomes in positive ways unavailable to clinics without such support. However, in a comprehensive comparative analysis of five diverse ART clinics in the Western Cape that included the Hannan Crusaid Treatment Centre among them, Pienaar et al. (2006) found that despite different settings, support networks, staff profiles, patient education programmes, adherence systems and opening hours, there were no significant differences in the proportion of patients retained in care at six months

or rates of virological suppression. That said, the findings in this study require further investigation in other settings.

Partly due to the necessarily labour-intensive interview schedule and its associated running time of three hours, which is unlike the larger observational cohorts described in Chapter 2, an appropriate but modest sample size of 150 was chosen. Because of this sample size the study may not have detected some weaker associations between certain factors and outcomes owing to insufficient statistical power. It is for this reason that relationship trends were also presented in Chapter 5. Contrarily, because this study set out to undertake a comprehensive assessment of demographic, biomedical, psychological and social factors, a large number of bivariate analyses were carried out, wherein some significant ($p \leq .05$) relationships could have occurred due to chance alone. To address this issue, all significant associations were assessed for plausibility and discarded from the regression model where necessary.

Although almost all participants were Xhosa-speaking, the D-KEFS and WMS are only available in English and were administered by a tester who spoke English to the participant. Although reliable translators were available, and utilized in 33% of cases, with translation, the reliability and validity of tests may have been weakened. Further, although precautions were taken to adapt the neuropsychological administration to a local population, including the use of adapted measures (see Chapter 3 for wording modifications), translators where necessary, and raw scores rather than developed-world norms, the administration may have been challenging for participants with a low educational background (only 21% of the sample had completed high school) and neither the D-KEFS not the WMS allow for factors like educational background or social circumstances to be taken into consideration when scoring.

The depression survey instrument used in this study, the CES-D, provides an assessment of symptoms associated with depression. Unlike a full psychiatric assessment, it cannot be utilised as a diagnostic tool, but rather a screening instrument to identify individuals with depressive symptoms. As such, this study is limited in its ability to make conclusions about the prevalence of verified mood disorders. Given the study aims (to formulate a screening assessment for adherence risk to be administered at lay counselor level) and context (a naturalistic study carried out in a busy primary

health care clinic), such rating scales are appropriate, and have been utilised in similar work in almost all cases (Ammassari et al., 2004; Arnsten et al., 2007; Carrieri et al., 2006; Catz et al., 2000; Do et al., 2010; Gordillo et al., 1999; Spire et al., 2002).

Furthermore, although the interview was conducted by a researcher unknown to the patient base, in an outbuilding separate from the clinic building, and confidentiality of responses was assured during the consent process, it cannot be excluded that answers might have been biased by social desirability. With the emphasis on things like decreased alcohol intake and disclosure at this relatively-resourced clinic, visible to patients in treatment readiness sessions and on-treatment adherence, participants may have under-reported alcohol use and over-reported disclosure.

In addition, pill counts, while widely used and repeatedly validated (Golin et al., 2002; Gordillo et al., 1999; Laniece et al., 2003; Weidle et al., 2006), have well-known limitations. The concept of measuring returned medicine as a proxy for consumed medicine poses particular challenges - the phenomenon of 'pill dumping', where patients dispose of surplus medications, has been reported. In order to mitigate this problem all adherence scores of greater than 100% were capped at 100%; however, this did not deal with those cases of non-adherence which were increased up to 100% due to pill-dumping. Nevertheless, the significant association between pill count adherence and virological suppression in the present study and in others (Bangsberg et al., 2000; Liu et al., 2001) suggests that pill count correlates well with actual adherence and confirms the choice to use pill counts as a proxy measure of pill-taking behaviour. Moreover, even if an overestimate of pill-taking behaviour did occur through reliance on pill counts as the index, this is not likely to have impacted the observed associations between medication adherence and the predictors examined.

Since this study set out to observe and statistically assess predictors of adherence behaviour, quantitative methodology was used. Because of this, a structured interview schedule was utilised. As such, the depth of insight and thorough exploration of relationships between various predictors gained through qualitative methodologies like in-depth interviews or focus groups could not be gained.

One of the strengths of this study was in its assessment at HAART initiation, rather than when patients were already on treatment. However this meant that other factors (factors that by definition could only have occurred once treatment had begun – for instance real or perceived rather than anticipated side effects) were unable to be assessed. In the same way, many of the factors that were assessed at treatment initiation in this study are not static, but adapt and transition due to changing external (e.g. new disclosures) and internal (e.g. negative ART experiences) circumstances throughout the course of treatment. Conducting a baseline assessment only meant that these changes were not picked up and their impact not assessed.

The above-mentioned potential limitations may impact the interpretation of the results. Notwithstanding the interpretive cautions noted above, the findings from this study showing significant relationships between certain demographic, biomedical, psychological and social factors and various adherence behaviours remain important, given the significance of medication adherence and retention to care for individual clinical outcomes and public health.

CHAPTER 7

The final word: Conclusions, recommendations and next steps

The results of this study have profound implications for the practical delivery of comprehensive HIV/AIDS care services in under-resourced settings. It is important to note that the intention of this research has not been to provide justifications or rationalisations for delaying or denying HAART provision to at-risk patients. Predictions about specific risk profiles do not apply to all persons fitting such profiles. Instead and as initially described, this work sets out to inform the delivery of targeted treatment readiness and on-treatment support programmes. The results of this study have clearly shown that no 'silver bullet' treatment readiness or adherence support intervention will be possible; there are too many and too varied a group of factors associated with adherence behaviour. Instead, what will be necessary is a multidimensional, interdisciplinary approach, applying several methods of promoting adherence simultaneously.

This study identified younger, unemployed and disability grant-holding patients as more likely to be nonadherent or LTFU; accordingly, special attention should be paid to these patient groups in adherence counseling. Patients with lower starting CD4+ cell counts also fared poorly, likely because of the impact of poor health on their ability to attend clinic visits and adhere to complex regimens. Relaxing treatment guidelines to include patients with higher CD4+ cell counts and encouraging earlier patient presentation will reduce the impact of severe illness on adherence and retention rates. Patients reporting haematological or ophthalmic symptoms were less likely to adhere (in the case of haematological symptoms) and remain in care (in the case of ophthalmic symptoms), while patients with dermatological or urogenital symptoms did better than others. It seems that certain symptoms may motivate patients to adhere and attend visits in the hope of alleviating them, while others are actually prohibitive. In this case, HIV symtomatology should be assessed at each clinic visit, so that symptoms may be managed and also used as a stimulus for adherence behaviour. With the exception of being able to name some of the medications in the prescribed regimen, none of the measures of knowledge levels, attitudes or beliefs related to HIV and ART were related

to adherence behaviour, which is a noteworthy finding given the focus of many treatment readiness and on-treatment adherence programmes on knowledge transfer.

Alcohol abuse was a significant and consistent barrier to each of the adherence outcomes, and especially important given the high prevalence rate in the sample. Initiating routine alcohol abuse screening and targeted interventions should be prioritised. Support may be offered directly through multi-disciplinary clinics or health care workers who develop skills in both HIV care and psychosocial interventions. Alternatively, substance abuse issues may be identified at primary health care level for referral to other professionals for case management (e.g. psychologists or social workers).

The relationships found between executive functioning and adherence behaviour points to the need for interventions that assist patients in setting and organising their medication-taking routines at the outset, planning and problem-solving how they will manage medication-taking in the context of other competing life circumstances. The associations between memory performance and adherence emphasise the need for interventions that help patients to make complex regimens easier to recall. Neuropsychological dysfunction should be compensated for through adaptation of national treatment guidelines for earlier treatment initiation and advising patients to use mechanical reminders like cell phone alarms.

The finding that unmarried patients, patients in non-cohabiting relationships, patients who had disclosed to broader family or friends and patients who lived in households of three or more were least likely to succeed argues against the uniform giving of advice to disclose as widely as possible. Instead, patients should be encouraged to identify appropriate confidantes within their environments and develop supportive relationships as far as possible. Finally, greater length of time spent traveling to the clinic was a barrier to achieving combined adherence success and could be mediated through home visits, longer refill periods, flexible clinic hours and free or discounted clinic transportation.

Some of these results also have implications for the structure of treatment readiness and on-treatment adherence programmes. For instance, the fact that mean pill count

adherence and percentage of patients achieving a mean pill count adherence of ≥90% decreased with each 4-week interval suggests that adherence is not static, but a 'moving target'. Patients who adhere well initially may not maintain high levels of adherence due to treatment fatigue, the emergence of side effects, and other setbacks. This means that ongoing programmes are needed throughout the treatment course, rather than just at initiation, in order to facilitate durable adherence. Further, the finding that greater length of time traveling to the clinic was a barrier to achieving combined adherence success implies that interventions should either be home-based or integrated as far as possible into existing clinic visits, rather than requiring additional clinic attendance. Lastly, the significant relationship between patients knowing more people also on ART and the greater likelihood of achieving early pill count adherence success suggests that group, rather than one-on-one programmes, should be the chosen modality for message delivery.

This study set out to develop a RAT to predict treatment success, suitable for routine clinical use by lay counselors in resource-limited settings, in order to facilitate the detection of those patients at high risk for nonadherence and LTFU and in need of increased adherence support. The tool was successfully developed and should now be pilot-tested for its feasibility, acceptability and efficacy in a community clinic setting and in a more diverse set of environments. It is expected that data obtained from this pilot will provide sufficient evidence for wider implementation. The feasibility analysis should include the following: assessment of lay counselors' ability to administer the tool, integration of its administration within routine clinical activities and the time and costs associated with its administration. The time and costs involved in effecting the intervention should be weighed against the gains of preserving first-line regimens, decreasing hospitalisations and health care system burden, decreasing LTFU and therefore LTFU tracing. The acceptability analysis should be conducted with both clinic staff and patients, and examine ease of use (usability) and perceived effectiveness (utility). Finally, the efficacy analysis should include sufficient orientation and training with lay community counselors on tool administration and subsequent administration to a powered sample of patients presenting for ART initiation. The tool should be validated through comparisons with pill count, virological suppression and LTFU data as proxy objective measures. Interim analysis of the data should be performed with final analysis at the end of the pilot. To establish the tool's usefulness in other settings (for instance,

its usefulness in other groups with HIV such as those with higher education levels or higher CD4+ counts), samples from various primary health care settings should be used, focusing on a comparison of feasibility, acceptability and efficacy outcomes. Finally, changes resulting from the implementation of this tool should be evaluated and reported.

The above-mentioned steps are necessary to validate the tool before it may function as an important component of effective HIV care delivery to the growing millions who need it in resource-limited settings. The tool, if implemented, could make possible stratified retention and adherence support, so that rather than all patients receiving modest levels of support, those patients who would gain the most from increased and directed support would receive it. This implementation would make the best use of our health system's limited resources and human capital, and in so doing, minimize the risk of society-wide resistance associated with this growing pandemic.

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APPENDIX A

Biopsychosocial Questionnaire

Biopsychosocial Questionnaire Version 1.1, July 2007 Participant Number Date / /	
DEMOGRAPHICS	
1. What is your gender?	Male Female
2. What is your date of birth?	/ /
3. What language do you speak at home?	Xhosa English Afrikaans Other: _____
4. What is the highest level of education you have completed?	Grade: _____ If participant has completed Grade 12, ask: 4a. Have you completed any tertiary education? Yes. Number of years: _____ No
5. How would you describe the work that you do?	Permanent part- or full-time Self-employed or engaged in casual work. If so, nature of work: _____ Unemployed with disability grant Unemployed without disability grant Applied for disability grant Other: _____
6. What is your total monthly income (including all wages and grants)?	R _____

PERCEIVED HIV SYMPTOMATOLOGY	
7. Have you experienced any symptoms from HIV?	Yes: _____ _____ No If participant has experienced symptoms, ask: 7a. How would you describe these symptoms? Mild Moderate Severe
KNOWLEDGE	
8. What is your most recent CD4+ cell count?	CD4+ cell count according to patient: _____ Unsure *Check clinic file for patient's degree of accuracy.* *CD4+ cell count in file: _____* *Patient correct/ incorrect/1*
9. What is your most recent viral load test result?	Viral load according to patient: _____ Unsure *Check clinic file for patient's degree of accuracy.* *Viral load in file: _____* *Patient correct/ incorrect/1*
10. What are the names of the antiretroviral medications that have been prescribed for you?	Medications according to patient: 1. _____ 2. _____ 3. _____ Unsure *Check clinic file for patient's degree of accuracy.* *Medications according to file:* *1.* _____ *2.* _____ *3.* _____ *Patient correct/ incorrect/3*
11. If patients do not take all of their prescribed antiretroviral medications, what are all of the possible consequences? *No prompt.* *Tick all that apply.*	The virus may not be adequately suppressed/ their viral load test result will be above the limits of detection Their immune functions may not improve/ their CD4+ cell count will remain high Their HIV may become 'resistant' to antiretrovirals This resistant HIV may be passed on to others Unsure
12. In HIV medicine, when we talk about 'resistance' what do we mean? *No prompt.*	_____ _____ *A score of 1 is recorded if the participant mentions that incomplete adherence may lead to medication not working/ not working as well.*

	Patient correct/ incorrect/1
13. How much of your antiretroviral medications do you need to take correctly in order for them to be most effective?	All or almost all (95% or greater) Most (60 - 94%) About half (40 – 59%) Some (less than 40%) Unsure
ATTITUDES, SEFL-EFFICACY	
Please indicate whether or not you agree with the statements below. 14. HIV is a serious disease. Agree Disagree 15. I can fight off HIV without the antiretrovirals. Agree Disagree 16. Antiretrovirals will improve my health. Agree Disagree 17. I am concerned about the possible side effects of my prescribed regimen. Agree Disagree 18. I don't like to think about antiretrovirals because they remind me that I have HIV. Agree Disagree 19. The good things about antiretrovirals outweigh the bad. Agree Disagree 20. I know better than my doctor when I know better than my doctor when to take my medications because only I know how I am feeling. Agree Disagree	
21. How confident do you feel that you will be able to take your antiretroviral medications as directed?	Very confident Quite confident Quite unconfident Very unconfident
DRUG USE	
22. Have you used any illicit drugs in the past 12 months?	Yes No If participant has used illicit drugs, ask: 22a. Please specify which drug(s) you have taken. *Tick all that apply.*

	Marijuana (intsango, weed, dope, ganja) Cocaine (crack, speedball) Inhalants (glue, poppers, laughing gas) Narcotics (heroin, morphine, opium) Stimulants (speed, rush, ecstasy) Other: _____
SUPPORT SYSTEMS AND DISCLOSURE	
23. What is your relationship status?	Single In a relationship, but not cohabiting or married In a relationship, cohabiting Married Divorced Widowed Separated
24. How many people (adults and children, including you) live in your household?	Number: _____
25. With whom do you live? *Tick all that apply.*	Spouse or partner Child(ren) Parent(s) Other family member(s) Other: _____
26. Do you feel a strong emotional bond with at least one other person?	Yes No
27. Do you know anyone else who has HIV?	Yes No If participant does know anyone, ask: 27a. Who is this person? *Tick all that apply.* Spouse or partner Child(ren) Parent(s) Other family member(s) Friend(s) Colleague(s) Other: _____ 27b. Total number of people known: _____
28. Do you know anyone else who is also on antiretrovirals?	Yes No If participant does know anyone, ask: 28a. Who is this person? *Tick all that apply.* Spouse or partner Child(ren) Parent(s) Other family member(s)

	Friend(s) Colleague(s) Other: _____ 28b. Total number of people known: _____
29. Have you told anyone you are HIV-positive?	Yes No If participant has told anyone, ask: 29a. Who have you disclosed to? List: _____ _____ 29b. Total number of people disclosed to: _____ 29c. How do you think this person/ these people feel about you starting antiretrovirals? They feel I should take antiretrovirals They feel I should not take antiretrovirals They do not know I am scheduled to start antiretrovirals Other: _____ 29d. Do you think this person/ these people will help you to take your antiretrovirals (e.g. remind you at dosing times or come with you to the clinic)? Yes No
RELATIONSHIP WITH HEALTH CARE PROVIDER	
30. How often do you see the same doctor at your clinic visits?	Always Usually Rarely Never
31. Do the doctors and nurses at your clinic speak with you in your home language?	Always Usually Rarely Never
32. Are you able to talk to the doctors and nurses at your clinic about any problems you are having?	Yes No
33. Do you trust the doctors and nurses at your clinic?	Yes No
34. Do you feel the doctors and nurses at your clinic respect you?	Yes No
35. Are you satisfied with your relationship with the doctors and nurses at your clinic?	Yes No

ADHERENCE AIDS	
36. Do you plan to use any of the following to help you to take your antiretrovirals? *Tick all that apply.*	Pill box Free-standing alarm clock Alarm clock on wrist watch Alarm clock on cell phone Diary Calendar Other: _____
CLINIC VISITS	
37. How do you travel to the clinic?	Taxi Bus Train Car Foot
38. How long does it take you to get to the clinic?	Hours: _____ Minutes: _____
39. How much does it cost you to come to the clinic?	Nothing R _____ If participant spends R1 or more, ask: 69a. How affordable is this for you? Very affordable Quite affordable Quite unaffordable Very unaffordable
40. Considering both time and costs, how convenient are clinic visits for you?	Very convenient Quite convenient Quite inconvenient Very inconvenient

Thank you for your time.

APPENDIX B

Centre for Epidemiological Studies in Depression Scale (CES-D)

CENTRE FOR EPIDEMIOLOGICAL STUDIES IN DEPRESSION SCALE (CES-D) (Radloff, 1977) *Circle the number for each statement that best describes how often the participant felt or behaved in this way during the past week.*				
1. I was bothered by things that usually don't bother me	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
2. I did not feel like eating; my appetite was poor	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
3. I felt that I could not shake off the blues (sadness) even with help from my family or friends	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
4. I felt that I was just as good as other people	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
5. I had trouble keeping my mind on what I was doing	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
6. I felt depressed	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
7. I felt that everything I did was an effort	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
8. I felt hopeful about the future	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
9. I thought my life had been a failure	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
10. I felt fearful	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
11. My sleep was restless	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
12. I was happy	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
13. I talked less than usual	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days

14. I felt lonely	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
15. People were unfriendly	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
16. I enjoyed life	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
17. I had crying spells	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
18. I felt sad	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
19. I felt that people disliked me	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days
20. I could not get 'going'	Rarely/ none of the time <1 day	Some of the time 1–2 days	Occasionally/ moderately 3–4 days	Most/ all of the time 5–7 days

APPENDIX C

Alcohol Use Disorders Identification Test (AUDIT)

ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT) (WHO, 1992) *Choose the answer that best fits your behaviour or experiences over the past year.*					
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2–4 times per month	2–3 times per week	4 or more times per week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7–9	10 or more
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected from you because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative or friend or a doctor been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

APPENDIX D

Receipt of Travel Reimbursement Form

RECEIPT OF TRAVEL REIMBURSEMENT FORM

STUDY: Predicting adherence to antiretroviral therapy and retention to HIV care: Effects of baseline biopsychosocial status and neuropsychological functioning

Participant Number

I, (name and surname of participant) _____ have received R50 travel reimbursement for participation in this study.

Signature: _____

Date: / /

APPENDIX E

Variables excluded

Variables excluded from bivariate analyses and regression model as one response set ≥90%

- Home language
- Psychiatric history
- Knowing own HIV RNA test result
- Knowing that resistant virus can be transmitted to others
- Not liking to think about ARV's because the medications are a reminder of HIV-positive status
- Use of cocaine, inhalants, narcotics or stimulants
- Having a strong emotional bond with at least one other person
- Having an HIV-positive child, parent or colleague
- Having a child, parent or colleague on ART
- Having disclosed to at least one other person
- Having disclosed to a colleague
- Feeling the doctors and nurses at the clinic respect them
- Planned use of wrist watch alarm, free-standing alarm, diary or calendar as reminder aid

Variables excluded from regression model due high correlations

- Employment status
- Disability grant status
- AUDIT total score
- Having failed to do what was expected because of drinking
- Having had a relative, friend or doctor concerned about their drinking
- Disclosed to partner, child, parent, extended family or friend
- Disclosed to everyone in the home
- Whether someone disclosed to would assist with adherence
- Convenience of clinic visits

APPENDIX F

Information sheet and consent form (English)

INFORMATION SHEET

STUDY: PREDICTING ADHERENCE TO ANTIRETROVIRAL THERAPY AND RETENTION TO HIV CARE: EFFECTS OF BASELINE BIOPSYCHOSOCIAL STATUS AND NEUROPSYCHOLOGICAL FUNCTIONING

Why are we doing this study?

Antiretroviral medications have helped people with HIV to live longer healthier lives. But in order for these medications to work well, the people taking them need to take them almost 100% correctly and come to all their clinic visits. We want to find out what makes people take antiretrovirals correctly and come to their clinic visits and what stops them from being able to do so. This will help us in the future to find ways of supporting people before they start treatment and while they are on treatment.

Who will be in this study?

This study will invite people who are 18 years or older, who have HIV, who are soon going to start antiretroviral treatment, who are not inpatients in a hospital, and who are able to agree to take part in this study. By the end of the study, we will have 150 people like this in the study.

How will you consent to take part in this study?

This information sheet explaining the study will be given to you to read, or read to you if you are

If you choose to take part in the study, you will sign your name on two copies of the consent form at the back of this information sheet. One copy is for you to keep and the other will be kept by the researcher in a secure place. If you do not want to keep your copy, the researcher will keep it in a secure place for you. If you would like the researcher to, she will give information about the study to your family and/ or partner(s).

It is important that you know the following:

- Your participation is voluntary. You do not have to take part in this study.
- You can decide to stop participating in this study at any time.
- If you do not take part, or if you decide to stop taking part, none of your rights will be compromised, and you will not lose any benefits to which you would otherwise be entitled.

How long is your participation in this study?

Taking part in this study will involve a two-hour assessment. This assessment will take place at your clinic before or after the clinic appointment at which you are first prescribed antiretrovirals or within a few days of that appointment. The researcher will examine your clinic file for relevant information at the time of the assessment. Then, four to six months after the assessment, the researcher will look at your clinic file again to see if you have managed to take the medications correctly. Then, 24 to 26 months after the assessment, the researcher will look in your clinic file a final time to see your latest viral load test result and to see if you managed to stay at the clinic. If necessary, the researcher might also talk to your counselor at this time to see if you stayed at the clinic, and if not, what the reason was.

What will happen at the study visit?

First, the researcher will ask you some questions about: who you are, what HIV symptoms you have, what you know about HIV and antiretrovirals, what you believe about antiretrovirals, how confident you feel about taking antiretrovirals, whether you have people to support you, whether you have told anyone you are HIV-positive, how you feel about your doctors and nurses, how easy it is for you to attend the clinic, whether you have any symptoms of depression and how much alcohol you drink. Then, the researcher will ask you to perform a few small tasks. These tasks involve reading, writing and speaking. The questions and tasks will each take about two hours.

What are the risks of taking part in this study?

We will not be giving you any extra medications in this study or taking any extra blood from you. When you are answering questions in the study, such as those about whether you have told anyone you are HIV-positive, whether you have any symptoms of depression or how much alcohol you drink, you might become sad, afraid or embarrassed. The researcher will do her best to help you if you feel this way. If necessary, she will refer you to a social worker.

What are the benefits of taking part in this study?

While you will not benefit directly from this study in terms of health benefits, you or others may benefit in the future from facts learned in this study. The facts that we gain from this study may help with HIV research, treatment and support.

Can you withdraw from this study?

You can withdraw from the study at any time. You do not have to give a reason for withdrawing. If you choose to withdraw, you will not suffer any penalty or loss of benefits that you would otherwise have been entitled to receive. Withdrawing from the study will not affect any current or future medical care you may need. You may be removed from the study without your consent if the study is stopped or cancelled, or for other administrative reasons.

Are your results confidential?

All facts collected about you - including your medical information, the answers you give to the questions, and your performance on the small tasks - will be private and not available to anyone other than the study staff. None of these facts will be passed on without your permission. Except for your consent form (which will be kept secure) you will be identified only by your special study number, which will be known only to you and the researcher. Your identity will not be disclosed in any publication or presentation of this study.

Whom can you contact about the study?

If you have a problem related to being in the study, please call Daniella Mark at (021) 650 6987 or 083 462 9542.

If you have any questions about your rights as a research participant, please call Dr Blockman, the Chair of the University of Cape Town's Research Ethics Committee at (021) 406 6492.

CONSENT FORM

STUDY: PREDICTING ADHERENCE TO ANTIRETROVIRAL THERAPY AND RETENTION TO HIV CARE: EFFECTS OF BASELINE BIOPSYCHOSOCIAL STATUS AND NEUROPSYCHOLOGICAL FUNCTIONING

Participant

I, _____ (name of participant), agree to participate in the research study entitled: Predicting adherence to antiretroviral therapy and retention to HIV care: Effects of baseline biopsychosocial status and neuropsychological functioning.

I give permission for the researcher to access my clinic file for the next 24 months and to talk to my counselor during this time. I have been told in detail about the study and read the information sheet (or had it read to me) and know what participation will involve. I understand that my consent is entirely voluntary and that I may withdraw from the study at any time and for any reason and this will not affect the rights I may otherwise have.

Signature: _____

Date: |__|__|/|__|__|__|/|__|__|__|__|

Researcher:

I have explained the nature, demands and foreseeable risks of this study to the above participant.

Print Name: _____

Signature: _____

Date: | | |/| | | |/| | | | |

APPENDIX G

Information sheet and consent form (Xhosa)

INCWADANA YENKCAZELO

PHANDO: UQIKELELO LOKULANDELA UNYANGO LWA MACHIZA ATHOMALALISA INTHSOLONGWANE KAGAWULAYO: UBUNJANI BENTSHOLONGWANE KAGAWULAYO OKUNXULUMENE NOKUNGASEBENZI KOBUME BOMZIMBA NEMPILO

(Predicting adherence to antiretroviral therapy and retention to HIV care: Effects of baseline biopsychosocial status and neuropsychological functioning)

Kutheni sisenza olu phando?

Amachiza athomalalisa intsholongwane kagawulayo (HIV) ancede abantu abane ntsholongwane kagawulayo (HIV) ukuba baphile ubomi obude nobunempilo. Kodwa ke ukuze lamachiza asebenze kakuhle, abantu abawasebenzisayo kufuneka bawasebenzise kakuhle. Sifuna ukwazi ukuba yintoni ebangela abantu ukuba bawathathe kakuhle lamachiza athomalalisa intsholongwane kagawulayo kwaye iyintoni ebangela ukuba bawayeke ukuwathatha. Oku kuza kusinceda kwixa elizayo ukuba sigqibe ekubeni ngubani okulungeleyo ukuthatha lamachiza kwanokufumana iindlela zokuxhasa abantu xa bethe baqalisa ukuba kolu nyango.

Ngubani oza kuba kolu phando?

Olu phando lumema abantu abane 18 yeminyaka nangaphezulu, abane HIV, kwanabaza kuqalisa unyango lwamachiza athomalalisa iHIV, kwaye abangazange balufumane ngaphambili, abangezozigulana zesibhedlele, abakwaziyo ukuthetha isingesi, abangazanga baba naso isigulo sengqondo esinxulumene neHIV kwaye abathi bakuvume ukuthatha inxaxheba kolu phando. Ekupheleni kolu phando, siza kuba nabantu abayi 150 abanjengaba kolu phando.

Uza kuvuma njani ukuthatha inxaxheba kolu phando?

Le ncwadana yenkcazelo echaza uphando uza kuyinikwa ukuba uyifune. Nceda ukhululeke ukubuza nayi phina imibuzo onayo malunga nolu phando.

Ukuba ufuna ukuthatha inxaxheba kolu phando, uza kusayina igama lakho kumaphepha amabini afanayo ale ncwadana yesivumelwano kwiphepha elingemva lale ncwadana. Enye ikopi uza kuyigcina kuwe, kwaye enye iza kugcinwa sithi kwindawo ekhuselekileyo. Ukuba awufuni ukuyigcina le kopi yakho, siza kukugcinela kwindawo ekhuselekileyo. Ukuba uyathanda, singathi sinike inkcazelo yolu phando kusapho okanye amaqabane akho.

Kubalulekile ukuba wazi oku kulandelayo:

- Ukuthatha inxaxheba kolu phando kungokuzithandela. Awunyanzelekanga ukuba uthathe inxaxheba kolu phando.
- Ungathi ugqibe ukuba ufuna ukuyeka kuthatha inxaxheba kolu phando nangaliphi na ixesha
- Ukuba awuthathi nxaxheba, okanye ugqiba ekubeni uyeke ukuthatha inxaxheba, amalungelo akho awasayi kuchaphazeleka, kwaye awuyi kulahlekelwa nazo naziphina iinzuzo obe kufanele uzifumane

Luza kuba kangakani ixesha lam lokuthatha inxaxheba kolu phando?

Ukuthatha inxaxheba kolu phando kuza kuquka iyure yokuhlalutywa. Olu hlalutyo luza kwenzeka kwiklinikhi yakho ngaphambi okanye emva kolunye lotyelelo lwakho eklinikhi. Umntu omela iqela lophando uza kujonga ingxelo yakho yase klinikhi ukukhangela iinkcukacha ezingqamene nolu phando. Kwiinyanga ezine ukuya kwezi ntandathu emva koku jongwa kwale ngxelo, umntu osuka kuphando lwethu uza kujonga ingxelo yakho yase klinikhi ukuza ajonge ukuba uwathatha ngendlela eyiyo na amachiza akho.

Kuza kwenzeka ntoni kutyelelo lo phando?

Okokuqala siza kukubuza imibuzo emalunga: nokuba ungubani, zeziphi iimpawu ze HIV onazo, kulula kangakanani ukuba ukuba ufikelele eklinikhi, oko ukwaziyo nge HIV kwakunye namachiza athomalalisa iHIV, oko ukukholelwayo malunga nalamachiza athomalalisa iHIV, uzithembe kangakanani ekuthatheni la machiza, ukuba ukhe waxelela nabani na ukuba uneHIV, ukuba unabo na abantu abakuxhasayo, uvakalelwa njani na ngoogqirha kwanoonesi bakho, kuba unazo na iimpawu zokuxinzeleleka kwanokuba bungakanani na utywala obuselayo. Siza kuthi futhi sikucele ukuba wenze nje izinto ezimbalwa. Ezi zinto ziquka ukufunda, ukubhala kwanokuthetha. Imibuzo kwanezi zinto ziza kuthatha malunga nesiqingatha seyure.

Yeyiphi imingcipheko ngokuthatha inxaxheba kolu phando?

Asizokukunika mayeza kwaye asizokukutsala gazi kolu phando. Xa uphendula imibuzo kolu phando emalunga nokuba ukhona na umntu omxeleleyo ukuba uneHIV, okanye zikhona na iimpawo zoxinzeleleko onazo okanye bungakanani na utywala obuselayo, ungathi ube neetlloni okanye udakumbe. Siza kwenza kangangoko sinakho ukuba sikuncede xa uthi uvakalelwe ngolu hlobo. Ukuba kuthu kube yimfuneko, siza kuthi sikugqithisele kunontlalo-ntle.

Zeziphi iinzuzo ngokuthatha inxaxheba kolu phando?

Ngoxa ungazokuthi uzuze ngokungqalileyo kolu phando ngokwasempilweni, wena okanye abanye ningathi nizuze kwixa elizayo ngolwazi oluzakube lufumaneke kolu phando. Oko sikuzuzayo kolu phando kungathi kuncede uphando lweHIV, unyango kwanenkxaso.

Ingaba ungayeka ukuthatha inxaxheba kolu phando?

Ungathi uyeke ukuthatha inxaxheba kolu phando nangaliphi na ixesha. Awunyanzelekanga ukuba unike isizathu sokurhoxa kwakho. Ukuba ukhetha ukurhoxa, awuzokuthi uchaphazeleke okanye ulahlekelwe nazizo naziphi na iingenelo obunokuba kanti uyazifumana. Ukurhoxa kolu phando akusayi kuchaphazela naluphi uncedo lezonyago olufumanayo okanye onokuthi ulufune kwixa elizayo.

Ungathi ukhutshwe kolu phando ngaphandle kwemvume yakho ukhuba luthi olu phando luyekwe okhanye lurho xiswe, okanye nangaso nasiphina esinye isizathu.

Iingaba iingxelo zakho zikhuselekile?

Zonke iinkcukacha eziqokelelweyo malunga nawe, kuquka iingxelo zonyango, iimpendulo ozinikileyo kwimibuzo yethu, kwakunye nendlela owenze ngayo kwezinye izinto ezimbalwa obucelwe ukuba uzenze, ziza kuba yimfihlo kwaye azisayi kufumaneka nakubani na ngaphandle kwabasebenzi bophando. Akukho nanye kwezingxelo eya kwaziswa ngaphandle kwemvume yakho. Ngaphandle kwencadwana yesivumelwano (eyakuthi igcinwe kwindawo ekhuselekileyo) uza kwaziswa kuphela ngenombolo ekhethekileyo, eyakuthi yaziwe kuphela nguwe kwakunye nabasebenzi bophando. Ubuwena bakho abusayi kwaziswa kuyo nayiphina ingxelo okanye impapasho yolu phando.

Ungaqhagamshelana nabani malunga nolu phando?

Ukuba unengxaki enxulumene nokuba kolu phando, nceda utsalele uDaniella Mark kwa (021) 650 6987 okanye 083 462 9542.

Ukuba unemibuzo malunga namalungelo akho njengomntu othatha inxaxheba kuphando, tsalela uDr Blockman, usihlalo wekomiti yamalungelo ezophando kwa (021) 406 6338.

IFOMU YESIVUMELWANO

PHANDO: UQIKELELO LOKULANDELA UNYANGO LWA MACHIZA ATHOMALALISA INTHSOLONGWANE KAGAWULAYO: UBUNJANI BENTSHOLONGWANE KAGAWULAYO OKUNXULUMENE NOKUNGASEBENZI KOBUME BOMZIMBA NEMPILO

Umthathi-nxaxheba

Mna, _____ (igama lomthathi-nxaxheba), Ndiyavuma ukuthatha inxaxheba kuphando olu sisihloko: PHANDO: UQIKELELO LOKULANDELA UNYANGO LWA MACHIZA ATHOMALALISA INTHSOLONGWANE KAGAWULAYO: UBUNJANI BENTSHOLONGWANE KAGAWULAYO OKUNXULUMENE NOKUNGASEBENZI KOBUME BOMZIMBA NEMPILO.

Ndinika imvume kubasebenzi bophando ukuba bajonge ingxelo yam ngoxa ndifumana unyango kangangee nyanga ezintandathu. Ndiye ndaxelelwa ngokuzeleyo malunga nolu phando kwaye ndiyazi ukuba ukuthatha inxaxheba kuza kuquka ntoni. Ndiyaqonda ukuba ukuthatha kwam inxaxheba kungokuzithandela ngokupheleleyo kwaye ndingathi ndirhoxe kolu phando nangaliphi na ixesha kwaye nangasiphina isizathu kwaye oku akusayi kuwachaphazela amalungelo am asemthethweni endingathi ndibe nawo.

Umsayino: _____

Umhla: |__|__|/|__|__|__|/|__|__|__|__|

Umntu ofumana isivumelwano:

Ndilucacisile uhlobo lolu phando, oko kufunekayo kwanemingcipheko enokuthi ibe khona kolu phando kweli volontiya lingentla.

Igama ngokucacileyo: _____

Umsayino: _____

Umhla: |__|__|/|__|__|__|/|__|__|__|__|

APPENDIX H

Annexure 3 of the Regulations to the Employment Equity Act

Annexure 3 of the Regulations to the Employment Equity Act **EEA 10**

ANNEXURE 3: Occupational Categories

Employment Equity Act 55 of 1998

WHAT IS THE PURPOSE OF THIS ANNEXURE?

This annexure provides a summary of definitions for occupational categories which may be used by employers when completing forms EEA 2 and EEA 4.

INSTRUCTIONS

Each occupational category contains a description and illustrative list of occupations that may be included in that category. The complete guideline to occupational categories may be obtained from Statistics SA.

1. Legislators, Senior Officials and managers

This group includes occupations whose main tasks consist of determining and formulating policy and strategic planning, or planning, directing and co-ordinating the policies and activities of the organisation in the private and public sectors, determining and formulating laws and for directing and controlling the functions of the organisation. Includes: chief executive officer; president; vice president; chief operating officers; general managers and divisional heads, managers who provide the direction of a critical technical function; postmaster; superintendent; dean and school principal etc.

2. Professionals

This group includes occupations whose main tasks require a high level of professional knowledge and experience in the fields of physical and life sciences, or social sciences and humanities. The main tasks consist of increasing the existing stock of knowledge, applying scientific and artistic concepts and theories to the solution of problems, and teaching about the foregoing in a systematic manner. Includes: engineers (civil, mechanical, chemical, electrical, petroleum, nuclear, aerospace, etc.); architects; lawyers; biologists; geologists; psychologists; accountants; physicists, system analysts; assayers; valuators; town and traffic planners etc.

3. Technicians and Associate Professionals

This group includes occupations whose main tasks require technical knowledge and experience in one or more fields of the physical and life sciences, or the social sciences and humanities. The main tasks consist of carrying out technical work connected with the application of concepts and operational methods in the abovementioned fields and in teaching at certain educational levels. Includes: computer programmers; nurses; physio-and-occupational therapists; draftsmen/women; musicians; actors; photographers; illustrating artists; product designers; radio and television announcers; translators and interpreters; writers and editors; specialised inspectors and testers of electronic, electrical, mechanical, etc. products; vocational instructors; technicians (medical, engineering, architectural, dental, physical science, life science, library, etc.); pilot; broker; designer; quality inspector etc.

4. Clerks
This group includes occupations whose main tasks require the knowledge and experience necessary to organise, store, compute and retrieve information. The main tasks consist of performing secretarial duties, operating word processors and other office machines, recording and computing numerical data, and performing a number of customer orientated clerical duties, mostly in connection with mail services, money-handling operations and appointments. Includes all clerical work, regardless of difficulty, in which the activities are predominantly non-manual. Includes: bookkeepers; tellers; cashiers; collectors (bills and accounts); messengers and office helpers; office machine operators; mail clerks; typists; telephone operators; electronic data processing equipment operators; clerks (production, shipping and receiving, stock, scheduling, ticket, freight, library, reception, travel, hotel, personnel, statistical, general office); secretaries etc.

5. Service and Sales Workers
This group includes occupations whose main tasks require the knowledge and experience necessary to provide personal and protective services and to sell goods in shops or markets. The main tasks consist of providing services related to travel, housekeeping, catering, personal care, protection of individuals and property, and maintaining law and order, or selling goods in shops or markets. Includes: attendants (hospital and other institutions, including nurses' aides and orderlies); barbers; bartenders; guides; food and beverage serving occupations; housekeepers; childcare occupations;
conductors; fire-fighters; police offices; advertising agents; real estate agents; sales workers and sales clerks; shop attendants; stock brokers; insurance brokers; travel agents; sales people of technical and business services; etc.

6. Skilled Agricultural and Fishery Workers
This group includes occupations whose main tasks require the knowledge and experience necessary to produce farm, forestry and fishery products. The main tasks consist of growing crops, breeding or hunting animals, catching or cultivating fish, conserving and working forests, and selling agricultural and fishery products to purchasers. Includes: farmers; growers; planter; viticulturists; winemakers; skilled horticultural workers; greenkeepers; skilled fishermen/women etc.

7. Craft and Related Trades
This group includes occupations whose main tasks require the knowledge and experience of skilled trades and handicrafts which, among other things, involve an understanding of materials and tools to be used, as well as all stages of the production process, including the characteristics and the intended use of the final product. They are frequently journeymen/women who have received an extensive period of training The main tasks consist of extracting raw materials, constructing buildings and other structures and making various products, as well as handicraft goods. Includes: miners; quarriers; stoneworkers; bricklayers; stonemasons; carpenters; shopfitters; plasterers; plumbers; electricians; painters; mechanics; glass-makers; locksmiths; sheet metal workers; etc.

8. Plant and Machine Operators and Assemblers
This group includes occupations whose main tasks require the knowledge and experience necessary to operate and monitor large-scale and often highly automated industrial machinery and equipment. The main tasks consist of operating and monitoring of mining, processing, and production machinery and equipment, as well as driving vehicles and driving and operating mobile plant, or assembling products from components. Includes: truck and tractor drivers; bus drivers; paving, surfacing and related occupations; roofers; photographic processors; sound and video recording equipment operators; those in apprenticeship training; textile workers; production machine workers etc.

EEA 10

9. Elementary Occupations

This group covers occupations which require relatively low/elementary levels of knowledge and experience necessary to perform mostly simple and routine tasks, involving the use of hand held tools and in some cases considerable physical effort, and, with few exceptions, limited personal initiative and judgement. The main tasks consist of selling goods in streets, door-keeping and property watching, as well as cleaning, washing, pressing, and working as labourers in the fields of mining, agriculture and fishing, construction and manufacturing. Includes: news and other vendors; garage attendants; car washers and greasers; gardeners; farm labourers; unskilled railway track workers; labourers performing lifting, digging, mixing, loading, and pulling operations; garbage collectors; stevedores; sweepers; charworkers etc.

APPENDIX I

Symptom and system characterizations

SYMPTOM	SYSTEM
Abscess in perineum	Urogenital
Arm pain	Musculoskeletal
Arthralgia	Musculoskeletal
Back pain	Musculoskeletal
Bad dreams	Psychiatric
Chest pain	Musculoskeletal; Cardiopulmonary
Cough	Respiratory
Cramps in fingers and feet	Musculoskeletal; Constitutional
Dandruff	Dermatological
Depression	Psychiatric
Diarrhea	Gastrointestinal; Constitutional
Discharge	Urogenital
Dizzy	Neurological; Constitutional
Dry eyes	Ophthalmic
Dry skin	Dermatological
Ears 'leaking'	ENT
Eczema	Dermatological
Eye pain	Ophthalmic
Fatigue	Constitutional; Heamatological
Feeling cold	Constitutional
Feeling hot	Constitutional
Feet burning	Neurological
Fever	Constitutional
Flu	Constitutional
Foot pain	Musculoskeletal; Neurological
General pain	Musculoskeletal; Constitutional
Genital ulcers	Urogenital
Gets sick often	Constitutional
Headache	Neurological
Heart pain	Musculoskeletal; Cardiopulmonary
Heart palpitations	Cardiopulmonary
Herpes	Urogenital
Insomnia	Psychiatric; Constitutional
Itchy	Dermatological
Itchy eyes	Ophthalmic; Dermatological
Itchy tongue	ENT; Dermatological
Itchy vagina	Urogenital; Dermatological
Knee pain	Musculoskeletal
Leg pain	Musculoskeletal
Lip sores	Dermatological

Loss of appetite	Constitutional; Gastrointestinal
Loss of weight	Constitutional; Gastrointestinal
Meningitis	Neurological
Mouth sores	Gastrointestinal; Constitutional
Mouth ulcers	Gastrointestinal; Constitutional
Neck pain	Musculoskeletal; Neurological
Night sweats	Constitutional
No interest in sex	Psychiatric
Nodule in neck	Haematological; Lymphatic
Noise in ears	ENT
Oral thrush	Gastrointestinal; Dermatological
Pain in kidneys	Urogenital; Musculoskeletal
Pain in lungs	Cardiopulmonary; Musculoskeletal
Pain on sides	Musculoskeletal
Painful urination	Urogenital
PCP	Cardiopulmonary
Photophobia	Neurological; Ophthalmic
Pimples	Dermatological
Pins and needles	Neurological; Musculoskeletal
Problem balancing on feet	Neurological; Musculoskeletal
Rash	Dermatological
Rash - PPE	Dermatological
Rash in vagina	Urogenital
Red eyes	Ophthalmic
Ringworm	Dermatological; Gastrointestinal
Rotten nails	Dermatological
Shakiness	Constitutional; Neurological
Shingles	Dermatological
Shortness of breath	Cardiopulmonary
Sores	Dermatological
Stomach pain	Gastrointestinal
Sweating	Constitutional
Swollen glands	Constitutional; Haematological; Lymphatic
Swollen gums	Gastrointestinal
Swollen legs/ feet/ ankles	Lymphatic; Cardiopulmonary; Musculoskeletal; Haematological
TB	Respiratory; Gastrointestinal; Neurological; Respiratory
Thrush	Gastrointestinal; Urogenital; Constitutional
Vaginal sores	Urogenital
Visual disturbances	Ophthalmic; Neurological
Vomiting	Gastrointestinal
Weakness	Constitutional; Neurological; Musculoskeletal; Haematological
White tongue	Gastrointestinal

APPENDIX J

Test	Score Name	Score Type	Mean	Standard Deviation
	D-KEFS			
Verbal Fluency Test	*F Total Correct Responses*	Accuracy	8.20	3.59
	F Total Set-Loss Errors	Error	0.27	0.69
	F Total Repetition Errors	Error	0.25	0.56
	A Total Correct Responses	Accuracy	5.60	3.25
	A Total Set-Loss Errors	Error	0.40	0.82
	A Total Repetition Errors	Error	0.10	0.32
	S Total Correct Responses	Accuracy	8.22	3.92
	S Total Set-Loss Errors	Error	0.20	0.51
	S Total Repetition Errors	Error	0.15	0.45
	Letter Fluency: Total Correct	Accuracy	22.01	9.58
	Letter Fluency: Total Responses	Attempt	23.26	9.54
	Animals Total Correct Responses	Accuracy	9.81	3.13
	Animals Total Set-Loss Errors	Error	0.06	0.27
	Animals Total Repetition Errors	Error	0.19	0.48
	Boys' Names Total Correct Responses	Accuracy	13.58	4.46
	Boys' Names Total Set-Loss Errors	Error	0.08	0.38
	Boys' Names Total Repetition Errors	Error	0.19	0.58
	Category Fluency: Total Correct	Accuracy	23.39	6.40
	Category Fluency: Total Responses	Attempt	23.9	6.4
	Category Switching: Total Correct Responses	Accuracy	9.32	2.58
	Category Switching: Total Switching Accuracy	Accuracy	8.42	2.59
	Category Switching: Total Set-Loss Errors	Error	0.62	1.10
	Category Switching: Total Repetition Errors	Error	0.49	1.57
	Category Switching: Total Responses	Attempt	10.15	2.18
	Conditions 1–3 Combined Set-Loss Errors	Error	1.60	1.96
	Conditions 1–3 Combined Repetition Errors	Error	1.35	2.15
	Conditions 1–3 Combined Total Responses	Attempt	57.38	15.28
D-KEFS Design Fluency Test	*Filled Dots: Attempted Designs*	Attempt	6.47	2.64
	Filled Dots: Total Correct	Accuracy	5.54	2.18
	Filled Dots: Set-Loss Designs	Error	0.13	0.66
	Filled Dots: Repeated Designs	Error	0.79	1.16
	Empty Dots Only: Attempted Designs	Attempt	7.39	2.89
	Empty Dots Only: Total Correct	Accuracy	5.80	2.13
	Empty Dots Only: Set-Loss Designs	Error	0.14	0.42
	Empty Dots Only: Repeated Designs	Error	1.45	1.83
	Combined Filled + Empty Dots: Total Correct	Accuracy	11.34	3.90
	Switching: Attempted Designs	Attempt	7.30	2.79
	Switching: Total Correct	Accuracy	5.30	2.30
	Switching: Set-Loss Designs	Error	0.64	0.99
	Switching: Repeated Designs	Error	1.43	1.87
	Category Fluency: Attempted Designs	Attempt	21.77	10.73
	Design Fluency: Total Correct	Accuracy	17.27	9.53
	Total Set-Loss Designs	Error	0.91	1.35
	Total Repeated Designs	Error	4.33	8.92
D-KEFS Colour-Word	*Colour Naming Completion-Time*	Time	45.92	89.66
	Uncorrected Colour Naming Errors	Error	1.37	2.69

D-KEFS Colour-Word Interference Test	*Colour Naming Completion-Time*	Time	45.92	89.66
	Uncorrected Colour Naming Errors	Error	1.37	2.69
	Corrected Colour Naming Errors	Error	1.46	1.47
	Total Colour Naming Errors	Error	2.76	3.01
	Word Reading Completion-Time	Time	33.87	11.81
	Uncorrected Word Reading Errors	Error	0.38	0.91
	Corrected Word Reading Errors	Error	0.48	0.91
	Total Word Reading Errors	Error	0.86	1.45
	Combined Naming+Reading Completion-Time	Time	85.05	26.00
	Inhibition Completion-Time	Time	95.15	36.35
	Uncorrected Inhibition Errors	Error	2.97	5.42
	Corrected Inhibition Errors	Error	2.68	2.29
	Total Inhibition Errors	Error	6.96	16.94
	Inhibition Real Errors	Error	3.40	16.97
D-KEFS Tower Test	*Total Achievement Score*	Accuracy	11.38	4.13
	Rule-Violations-Per-Item Ratio	Error	0.69	0.75
	WMS			
WMS Logical Memory	*LMI Story A Recall Unit Score*	Accuracy	11.52	4.16
	LMI Story B 1st Recall Unit Score	Accuracy	7.07	3.31
	1st Recall Total Score	Accuracy	18.59	6.72
	LM Story B 2nd Recall Unit Score	Accuracy	9.28	3.90
	Learning Slope	Accuracy	2.16	2.62
	Recall Total Score	Accuracy	28.02	9.99
	LMII Story A Recall Unit Score	Accuracy	9.71	4.58
	LMII Story B Recall Unit Score	Accuracy	7.95	3.70
	LMII Recall Total Score	Accuracy	17.67	7.56
	Percent Retention	Accuracy	83.20	22.24
	Recognition Total Score	Accuracy	22.64	3.42
WMS Digit Span	*Digits Forward*	Accuracy	6.83	2.02

Appendix J. Neuropsychological test score means and standard deviations. D-KEFS, Delis-Kaplan Executive Functions System; WMS, Wechsler Memory Scale.

APPENDIX K

Test and score types	Viral load	CD4+ cell count	WHO stage
D-KEFS			
D-KEFS Verbal Fluency Test			
F Total Correct Responses	0.79	0.46	*0.04
F Total Set-Loss Errors	0.29	0.33	0.74
F Total Repetition Errors	0.85	0.54	0.15
A Total Correct Responses	0.45	0.13	0.24
A Total Set-Loss Errors	0.24	0.26	0.28
A Total Repetition Errors	0.16	0.17	0.81
S Total Correct Responses	0.17	0.36	0.25
S Total Set-Loss Errors	0.25	0.62	0.42
S Total Repetition Errors	0.11	0.95	0.69
Letter Fluency: Total Correct	0.31	0.55	0.25
Letter Fluency: Total Responses	0.39	0.64	0.33
Animals Total Correct Responses	0.95	0.28	0.14
Animals Total Set-Loss Errors	0.92	0.32	0.95
Animals Total Repetition Errors	0.78	0.26	0.18
Boy's Names Total Correct Responses	0.54	0.85	0.05
Boy's Names Total Set-Loss Errors	0.30	0.32	0.95
Boy's Names Total Repetition Errors	0.58	*0.03	0.22
Category Fluency: Total Correct	0.45	0.66	*0.0009
Category Fluency: Total Responses	0.40	0.09	*0.0008
Category Switching: Total Correct Responses	0.77	0.28	*0.002
Category Switching: Total Switching Accuracy	0.84	0.14	*0.0009
Category Switching: Total Set-Loss Errors	0.06	0.69	0.54
Category Switching: Total Repetition Errors	0.75	0.95	0.46
Category Switching: Total Responses	0.82	0.32	*0.009
Conditions 1–3 Combined Set-Loss Errors	0.48	0.93	0.46
Conditions 1–3 Combined Repetition Errors	0.62	0.56	0.96
Conditions 1–3 Combined Total Responses	0.98	0.65	*0.009
D-KEFS Design Fluency Test			
Filled Dots: Attempted Designs	0.33	0.79	*0.01
Filled Dots: Total Correct	*0.02	0.36	0.41
Filled Dots: Repeated Designs	0.62	0.30	0.25
Empty Dots Only: Attempted Designs	0.15	0.48	0.05
Empty Dots Only: Total Correct	0.47	*0.02	0.07
Empty Dots Only: Repeated Designs	0.32	0.63	0.57
Combined Filled + Empty Dots: Total Correct	0.57	0.43	0.33
Switching: Attempted Designs	0.22	0.85	0.27
Switching: Total Correct	0.77	0.67	0.47
Switching: Set-Loss Designs	0.44	0.24	0.05
Category Fluency: Attempted Designs	0.19	0.65	0.60
Design Fluency: Total Correct	0.56	0.43	0.38
Total Set-Loss Designs	0.50	0.56	*0.03
Total Repeated Designs	0.16	0.50	*0.04
D-KEFS Colour-Word Interference Test			
Colour Naming Completion-Time	0.70	0.29	0.19
Uncorrected Colour Naming Errors	0.13	0.17	*0.03
Corrected Colour Naming Errors	0.52	0.63	0.13

Total Colour Naming Errors	0.99	0.71	0.64
Uncorrected Word Reading Errors	0.37	0.61	0.75
Corrected Word Reading Errors	0.58	0.46	0.08
Total Word Reading Errors	0.96	0.63	0.40
Combined Naming + Reading Completion-Time	0.16	0.78	0.15
Inhibition Completion-Time	0.15	0.74	0.82
Uncorrected Inhibition Errors	0.32	0.23	0.74
Corrected Inhibition Errors	0.10	0.89	0.33
Total Inhibition Errors	0.48	0.94	0.56
Inhibition Real Errors	0.32	0.72	0.71
D-KEFS Tower Test			
Total Achievement Score	0.53	0.95	0.07
Rule-Violations-Per-Item Ratio	0.65	0.86	0.98
WMS			
WMS Logical Memory			
LMI Story A Recall Unit Score	0.61	0.29	*0.006
LMI Story B 1st Recall Unit Score	0.70	0.16	0.28
1st Recall Total Score	0.15	0.92	*0.004
LM Story B 2nd Recall Unit Score	0.18	0.42	0.06
Learning Slope	0.12	0.58	0.15
Recall Total Score	0.25	0.21	0.19
LMII Story A Recall Unit Score	0.43	0.71	*0.03
LMII Story B Recall Unit Score	0.78	0.67	0.23
LMII Recall Total Score	0.34	0.65	0.10
Percent Retention	0.95	0.35	*0.04
Recognition Total Score	0.07	0.25	0.07
WMS Digit Span			
Digits Forward	0.18	0.51	0.70
Digits Backward	0.21	0.10	0.36
Total Score	0.30	0.81	0.50

Appendix K. Neuropsychological test score relationships with disease markers. * Indicates significant relationships. WHO; World Health Organisation; D-KEFS, Delis-Kaplan Executive Functions System; WMS, Wechsler Memory Scale.