QUALITY OF LIFE OF HIV-INFECTED INDIVIDUALS IN A COMMUNITY-BASED ANTIRETROVIRAL PROGRAMME

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DECLARATION

I, Jennifer Pitt, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background: With increasing numbers of HIV positive individuals being enrolled onto highly active antiretroviral therapy (HAART) and increasing survival among these patients, there is a growing interest in morbidity-related outcomes in HIV treatment programmes, and in particular the impact of HAART on the quality of remaining life. The impact of HAART on health related quality of life (HRQoL) has been widely researched in the developed world, however, there is limited data coming out of the developing world and in particular sub-Saharan Africa, where the vast majority of HIV-infected individuals live. This study examined HRQoL among HIV positive individuals initiating HAART at the Hannan Crusaid Treatment Centre in Gugulethu, Cape Town and explored the impact of HAART-related drug toxicities and adherence to HAART on HRQoL.

Methods: HRQoL was assessed using a standardised questionnaire, the Medical Outcomes Survey Short Form 36 (MOS SF36). The MOS SF36 was administered by trained Sizophila adherence counsellors pre-HAART and at regular intervals during the first 48 weeks of HAART. Demographic, clinical and adherence data were collected using the standard Gugulethu paperwork. Drug toxicities were detected by the medical doctor at clinical visits through clinical questioning, examination and safety blood draws. Four sets of outcome variables were used in this analysis: 1) pre-HAART physical health summary (PHS) and mental health summary (MHS) scores; 2) change in PHS and MHS scores; 3) negative PHS and negative MHS; and 4) adherence. The relationships between various socio-demographic, baseline and on treatment variables and study outcomes were assessed both in unadjusted bivariate and adjusted multivariate analyses.

Results: Quality of life data were available for 295 patients – 93 percent of patients who reached the first on treatment assessment. Complete HRQoL data – obtained pre-treatment and at every scheduled on treatment visit - were available for 147 patients only. This study reported a significant increase in HRQoL during the first 48 weeks on HAART with the bulk of this increase occurring early - during the first sixteen weeks on treatment. Although there was a general improvement in HRQoL on HAART, twenty three percent of participants reported a decline in PHS score and thirty four percent, a decline in MHS score. Average drops in median PHS and MHS scores were 8.4 units (SD 9.31) and 9.9 units (SD 11.4) respectively. Participants who experienced drug toxicity reported lower PHS scores than

participants without a drug toxicity at all time points and achieved less increase in score by week 48. The differences between scores was most significant at 48 weeks when participants with drug toxicity achieved median PHS scores that were 16 units less than participants without toxicity (p=0.0581). In contrast, drug toxicities had little impact on MHS scores. A tentative positive association between higher levels of adherence and greater gains in HRQoL was shown. Participants with median adherence >95%, had higher HRQoL scores at week 48 (median PHS score 54 versus 53, p=0.811; median MHS score 51 versus 48, p=0.243) and greater increases in PHS and MHS scores (increase in PHS score 9.79 versus 5.49, p=0.360; increase in MHS score 6.02 versus 4.69, p=0.307) than participants with lower median adherence, however these differences were not statistically significant.

Conclusions: This study confirmed the HRQoL benefits of HAART in a community ARV clinic in South Africa. While the majority of patients experienced a significant improvement in HRQoL on HAART, up to a third of patients reported declines in HRQoL. HAART-related drug toxicities (especially those secondary to the use of stavudine) had a significant negative impact on physical HRQoL highlighting the need for less toxic drug regimens in the national ARV roll-out programme.

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Dedicated to my Oupa, Professor Theunis Coetzee: 28 December 1920 – 14 April 2008.

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Abbreviations

AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
ARVs	antiretrovirals
HAART	highly active antiretroviral therapy
HCTC	Hannan Crusaid Treatment Centre
HIV	human immunodeficiency virus
HRQoL	health related quality of life
IQR	interquartile range
LTFU	loss to follow-up
MHS	mental health summary
MOS	medical outcomes survey
NRTIs	nucleoside reverse transcriptase inhibitors
NNRTIs	non-nucleoside reverse transcriptase inhibitors
OR	odds ratio
PHS	physical health summary
PIs	protease inhibitors
QoL	quality of life
SD	standard deviation
SSA	sub-Saharan Africa
WHO	world health organisation
95% CI	95% confidence interval

1 INTRODUCTION

By December 2006, an estimated 39.5 million people worldwide were living with HIV and a further 2.9 million people had died due to AIDS. The bulk of infections (63% of the global burden) occurred in Sub-Saharan Africa where 24.7 million people were reported to be HIV infected. (UNAIDS, 2006) In South Africa alone, 5.4 million people were estimated to be infected with HIV by the middle of 2006 and 600 000 were thought to have AIDS. Since the beginning of the South African epidemic, an estimated 1.5 million people have lost their lives to HIV/AIDS and 1 million children have become AIDS orphans. (Dorrington et al, 2006) Prior to 2004, people infected with HIV in South Africa who were unable to access life-saving antiretroviral therapy progressed to AIDS and died of their disease. The rollout of highly active antiretroviral therapy (HAART) through national and provincial programmes has dramatically altered this experience.

HAART is the combination of three or more antiretroviral agents chosen from at least two different drug classes. In the South African public health sector there are three classes of antiretroviral drug available for use: the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). These drugs act at different stages in the life cycle of HIV to limit replication of the virus. NRTIs (eg. stavudine and lamivudine) and NNRTIs (eg. nevirapine and efavirenz) inhibit the reverse transcriptase enzyme and PIs (eg. Kaletra®) inhibit the protease enzyme. HAART allows suppression of the virus to levels below detection (measured as a viral load <50 copies/ml). This is accompanied by an improvement in immune function (measured by a rise in CD4 cell count in cells/mm^3) and, thereby, an improvement in physical health and delay of death due to AIDS for some years.

Since the advent of HAART in the late 1990's, the primary focus of antiretroviral research has been the mortality and morbidity benefits of sustained viral suppression. These benefits are well established in both developed and developing country settings (Feinberg, 1996; Mocroft et al, 1998; Valdez et al, 2001; Texeira et al, 2004). With increased survival among HIV positive individuals, there is a growing interest in morbidity-related outcomes in HIV treatment programmes, and in particular the impact of HAART on the quality of remaining life. (Wachtel et al, 1992; Franchi and Wenzel, 1998; Wu, 2000; Casado, 2005; Clayson et al, 2006)

The World Health Organisation defines quality of life (QoL) as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". (WHO, 1997) Health-related quality of life (HRQoL) limits the concept of QoL to those aspects of life directly impacted by health. (Shumaker et al, 1997; Franchi and Wenzel, 1998) It refers to the physical, functional, mental and social domains of health and how these impact on an individual's ability to function and pursue valued life goals. (Testa et al, 1996; Shumaker et al, 1997)

HRQoL is an important outcome measure for assessing the impact of chronic diseases and their treatment and has been widely used in healthcare practice and research among patients with pulmonary, cardiac, rheumatological and oncological disease. (Guyatt et al, 1993; Sprangers and Aaronson, 1992; Testa et al, 1996; Franchi and Wenzel, 1998; Casado, 2005) In healthcare practice, HRQoL measures provide practitioners with a more comprehensive picture of a patient's health guiding how the clinician manages the patient (e.g. allowing better choices to be made in terms of treatment) and improving the doctor-patient relationship. In the research setting, HRQoL measures provide additional information on the effectiveness of a treatment and are increasingly used as outcome measures in research into new therapies. HRQoL is also used in health services evaluation and policy development to evaluate current practices and to establish clinical guidelines that achieve optimal outcomes for all. (WHO, 1997; Wachtel, 1992)

By the middle of 2006, an estimated 225 000 HIV positive individuals were receiving HAART in South Africa. According to projections of the ASSA2003 AIDS and Demographic model, the provision of HAART will reduce the number of deaths per year due to AIDS in 2010 from around 505 000 to around 388 000 – a difference of almost 120 000 deaths due to AIDS in one year. Furthermore, HAART is expected to reduce the drop in life expectancy from 19 years to less than 16 years by 2015. (Dorrington et al, 2006) With increasing numbers of HIV positive individuals being enrolled onto HAART and increasing survival among these patients, there is a growing need to understand the impact of HAART use on the quality of lives of HIV-infected individuals in South Africa. However there have been few investigations of quality of life among HIV-infected individuals living in developing countries, particularly in sub-Saharan Africa where the vast majority of HIV-infected individuals live. This thesis investigates the HRQoL of HIV-infected individuals initiating HAART in a large primary care clinic in Cape Town, South Africa.

2 STUDY AIM AND OBJECTIVES

The aim of this study was to examine the changes in health-related quality of life (HRQoL) among HIV positive individuals initiating HAART at the Hannan Crusaid Treatment Centre in Gugulethu, Cape Town. To achieve this aim, the following specific objectives were proposed:

1. To describe the study cohort.
   - To describe the demographic, baseline and on-treatment characteristics of the overall cohort and examine differences in baseline characteristics between those with and without complete HRQoL data available.

2. To describe the changes in HRQoL in subjects on HAART over 48 weeks.
   - To describe changes in the eight health concepts of HRQoL pre-HAART and at week 16, 32 and 48.
   - To compare physical health summary (PHS) and mental health summary (MHS) pre-HAART and at week 16, 32 and 48.

3. To describe the association between baseline and on-treatment factors and HRQoL.
   - To determine factors associated with pre-HAART HRQoL (including age, gender, baseline WHO stage, baseline CD4 count, baseline viral load and baseline log viral load).
   - To determine factors associated with change in HRQoL (as a continuous variable) at week 48 (including baseline factors listed above as well as change in CD4 count and change in log VL).
   - To describe negative changes in HRQoL (as a binary construct) at week 48.
   - To compare baseline and on-treatment factors between subjects experiencing negative change in HRQoL and positive change in HRQOL at week 48.

4. To describe the HRQoL in patients experiencing drug toxicity, and compare this to HRQoL in patients not experiencing toxicity.
   - To describe different categories of drug toxicity occurring in the first year of the cohort.

- To describe PHS and MHS pre-HAART and at week 16, 32 and 48 in patients experiencing drug toxicity.
- To compare the change in PHS and change in MHS of patients with and without drug toxicity.
- To describe the association between drug toxicity and changes in HRQoL.
- To describe the association between drug toxicity and negative HRQoL (as a binary construct).

5. To describe the association between HRQoL and adherence to HAART.
   - To describe mean percentage adherence, and the proportion of patients achieving >95% adherence, at week 16, 32 and 48.
   - To describe the association between change in HRQoL and adherence >95% at week 48.

3 LITERATURE REVIEW

Quality of life (QoL) is a complex, multidimensional concept - the assessment of which is difficult. (Bergner, 1989; Testa et al, 1996; Casado, 2005) Not only does debate exist around who is the most appropriate person to assess QoL – the patient or the healthcare provider - but also which instrument to use. (Slevin et al, 1988; Sprangers and Aaronson, 1992; Clayson et al, 2006)

3.1 Assessment of Health-related Quality of Life

Health-related quality of life (HRQoL) is assessed by instruments (questionnaires) that measure a number of domains or areas of health experience. (Guyatt et al, 1993) Core domains that are important in the assessment of HRQoL include physical health and functioning, mental health and functioning, social and role functioning and general health perceptions and wellbeing. (Clayson et al, 2006) Additional domains that assess more specific aspects of HRQoL are symptoms, somatic discomfort (pain), energy and vitality and cognition. (Bergner, 1989; Cleary et al, 1993)

HRQoL instruments can be generic or specific. Generic instruments attempt to provide a broad overview of an individual's health status by measuring most of the core domains of HRQoL. Generic instruments are of two types: health profiles and preference based measures. (Guyatt et al, 1993; Clayson et al, 2006) Health profiles produce a series of scores representing the individual core domains of HRQoL, whereas preference based measures produce a single overall index on a scale from 0.0 (death) to 1.0 (perfect health). (Clayson et al, 2006) As generic instruments assess HRQoL broadly, they can be used to compare the HRQoL of different patient populations as well as different diseases and treatments. (Guyatt et al, 1993; Franchi and Wenzel, 1998; Tsasis, 2000) Specific instruments include core and additional domains that focus on aspects of HRQoL (such as symptoms, pain or cognitive function) that are specific to the patient, disease or treatment of interest. These instruments are therefore more sensitive to change in HRQoL. (Guyatt et al, 1993; Shumaker et al, 1997)

It has been suggested that the ideal instrument for assessing HRQoL in people with HIV/AIDS should be generic enough to allow for comparison of HRQoL across populations but specific enough to capture the complex natural history of the disease and the effects of

treatment. (Shumaker et al, 1997) It should also have adequate psychometric properties – internal consistency, construct validity and reliability. Clayson et al (2006) conducted a "comprehensive review following pre-defined selection criteria" of all HRQoL instruments reported in the HIV/AIDS literature since 1990 to identify those "most worthy of consideration" for use in future research. The review involved three stages. All formal HRQoL instruments used for assessment of HRQoL in patients with HIV/AIDS were identified in the first stage. In the second stage, each of the identified HRQoL instruments were assessed in terms of content, practicality, psychometric properties and, for the generic instruments, the availability of normative data and/or population-based preference weights. The final stage involved the selection of those instruments deemed "most appropriate for use" in adult HIV/AIDS research.

Of the initial 34 HRQoL instruments identified, three generic and six specific instruments were selected for in-depth review. The generic instruments included the Medical Outcomes Study Short Form 36 (MOS-SF36), EQ-5D and Health Utilities Index (HUI). The MOS-SF36 is a 36-item multi-attribute scale that measures eight health domains – including physical functioning, social functioning, limitations in role function due to physical problems, limitations in role function due to emotional problems, emotional well-being, general health perception, pain and vitality. The EQ-5D instrument consists of two parts. A five-question multi-attribute component measures the following five domains: anxiety/depression, mobility, usual activities, pain/discomfort and self-care. A visual analogue scale (VAS) scores self-reported health status from 0 (worst imaginable) to 100 (best imaginable). (Wu et al, 2002) The HUI currently consists of two multi-attribute health status classification systems: HUI2 and HUI3. The HUI2 system covers seven domains - including sensation, mobility, emotion, cognition, self-care, pain and fertility - and describes 24,000 unique health states The HUI3 system covers eight domains – including vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain – and defines 972,000 unique health states. (Horsman et al, 2003)

The six specific instruments included the Medical Outcomes Study HIV Health Survey (MOS-HIV), Functional Assessment of HIV Infection (FAHI), Multidimensional Quality of Life for Persons Living with HIV/AIDS (MQoL-HIV), HIV/AIDS-Targeted QOL (HAT-QOL), Living with HIV (LWH) and General Health Self-Assessment Questionnaire (GHSA). (Table 1)

Table 1 Description of the six HIV-specific HRQoL Instruments.
(Adapted from Clayson et al, 2006)

Instrument	Items	Domains
MOS-HIV	35-item	Physical functioning, role functioning, pain, social functioning, emotional well-being, energy/fatigue, cognitive functioning, general health perceptions, health distress, overall QoL.
FAHI	38-item	Physical well-being, emotional well-being, social/family well-being, functional well-being, relationship with physician.
MQoL-HIV	40-item	Mental health, physical health, physical functioning, social functioning, social support, cognitive functioning, financial status, partner intimacy, sexual functioning, perceived access to medical care.
HAT-QOL	42-item	Overall function, sexual function, disclosure worries, health worries, financial worries, HIV mastery, life satisfaction, medication concerns, provider trust.
LWH	32-item	HIV reverence, cherishing the environment, coveting time, resolving spiritual issues, HIV struggles, avoiding the fear zone, loss, body image, juggling of treatment and adverse effects, independence, death calculations.
GHSA	49-item	General health perception, physical functioning, psychological functioning, role/social functioning, HIV-related symptoms, healthcare utilisation.

The overall finding of the study was that there is no one best HRQoL instrument. Rather, "the selection of a particular measure or combination of measures will be driven by the target population and the study end-points". While all three generic instruments were considered worthy of future use, the MOS-SF36 had "more evidence supporting its use in HIV/AIDS". Among the HIV-specific instruments, the MOS-HIV and FAHI were deemed most appropriate. (Clayson et al, 2006) The MOS surveys featured prominently among both the generic and disease specific measures.

3.1.1 The Medical Outcomes Surveys

The Medical Outcomes Study (MOS) surveys are among the leading HRQoL instruments used in HIV/AIDS research. These instruments are derived from the Medical Outcomes Study– a four-year observational study of variations in physician practice and patient outcomes in a variety of medical care settings - and exist in several forms. (Wu et al, 1997a) The MOS surveys assess two major health constructs - physical health and mental health - from five perspectives: clinical status, physical functioning, mental functioning, social functioning and general health perceptions. (Wu et al, 1997a; Tsasis, 2000) The instruments all generate a series of subscales that can be converted in two summary scales – the physical health summary and mental health summary scores. There is substantial evidence for the

reliability and validity of the surveys as measures of HRQoL in people with various stages of HIV disease and demographic characteristics. (Wu et al, 1997a) The MOS summary scales and subscales correlate well with number of symptoms and clinical stage and are able to discriminate between individuals with asymptomatic HIV infection, symptomatic HIV disease and AIDS. (Wu et al, 1991; Wachtel et al, 1992) The MOS-HIV and MOS-SF36 are the most popular of the MOS surveys to be used in HIV/AIDS research.

3.1.2 The MOS-HIV Instrument

The MOS-HIV is a specific instrument that was developed to evaluate the HRQoL of HIV-infected patients in multi-centre AIDS clinical trials. (Wu, 1997b) It uses 35-items to assess ten domains of health including physical functioning, role functioning, social functioning, cognitive functioning, mental health, general health perceptions, health distress, pain, energy/fatigue and overall quality of life. In addition two summary scores can be generated: a physical health summary (PHS) that summarizes physical function, pain, role function and social function and a mental health summary (MHS) that includes mental health, health distress, quality of life, cognitive function and energy. (Wu et al, 1997a; Wu et al, 1997b; Wu et al, 2002)

The MOS-HIV has been widely used in HIV/AIDS research and substantial evidence for its reliability, validity and responsiveness exists. (Wu et al, 1997b) The instrument has been shown to be responsive to clinical changes including opportunistic infections, adverse events, increased symptoms and AIDS-related events. (Wu et al, 1997a; Wu et al, 1997b; Clayson et al, 2006) However, there are limitations to the instrument. A decrease in the measurement precision of the physical functioning, social functioning and role functioning scales has led to problematic ceiling and floor effects for these scales in longitudinal studies of HRQoL. (Shahriar et al, 2003).

3.1.3 The MOS-SF36 Instrument

The MOS-SF36 is a generic health profile that was developed for use in clinical practice and research, health policy evaluations and general population surveys. (Clayson et al, 2006) The instrument was designed to address those aspects of HRQoL that are most influenced by a disease state and its treatment. (Wu et al, 1997a) It uses 36 items to assess eight domains of QoL: physical functioning, social functioning, limitations in role function due to physical problems, limitations in role function due to emotional problems, emotional well-being,

general health perception, pain and vitality. It can also be scored to yield two summary scales for physical and mental health.

The MOS SF36 is one of the most widely used HRQoL instruments and has been administered to hundreds of thousands of patients in diverse populations. (Clayson et al, 2006; Shahriar et al, 2003; Wu et al, 1997a) It is easy to administer, has good psychometric properties and normative values are available for the general populations in the USA, United Kingdom and numerous other countries. (Tsasis, 2000; Shariar et al, 2003; Clayson et al, 2006) Among patients with HIV/AIDS, the instrument is sensitive to clinical differences and correlates well with number of symptoms, stage of disease, change in CD4 count and viral load and commencement of HAART. (Tsasis, 2000; Clayson et al, 2006) The summary scales are responsive to disease progression (Shariar et al, 2003) and have been shown to be reliable and valid measures for demonstrating treatment impact on patient functioning and well-being. (Revicki et al, 1998) The only major drawback of the MOS-SF36 instrument is that it does not specifically assess cognitive functioning – an important domain of HRQoL in HIV/AIDS. (Wu et al, 1997a; Tsasis, 2000)

Shariar et al (2003) compared the use of the MOS-SF36 and MOS-HIV instruments in studies of individuals with HIV/AIDS and concluded that there was insufficient evidence to recommend the use of the MOS-HIV instrument over the MOS-SF36. In fact, they felt that the latter was the instrument of choice.

3.2 Assessment of HRQoL in the developed world

The impact of HIV/AIDS on HRQoL has been extensively studied in the developed world. In the early 1990's – prior to the advent of antiretroviral therapy - research focused on the change in HRQoL associated with HIV disease progression. As CD4 counts dropped and patients progressed clinically from asymptomatic HIV infection to symptomatic infection and AIDS, so health status was seen to decrease significantly. The decline was more marked for physical health than mental health. (Lubeck and Fries, 1992; Revicki, Wu and Murray, 1995; Tsevat et al, 1996; Lubeck and Fries, 1997) (Vidrine et al, 2003; Bing et al, 2000; Call et al, 2001)

With the advent of early antiretroviral therapy, the focus of research shifted to the impact of antiretrovirals on HRQoL. Early randomised controlled trials assessing nucleoside mono- and dual therapy, reported a decline in HRQoL over time associated with the use of NRTIs – although this was most likely due to the side-effects of early drug therapies. (Wu et al, 1990; Wu et al, 1993; Lenderking et al, 1994) These findings of an overall decline in HRQoL associated with antiretroviral use were not supported by a large observational study of patients on mono- and dual therapy. (Campsmith et al, 2003) As NRTI drug formulations and doses improved so too did HRQoL and baseline health status was maintained during the study period. (Scott-Lennox et al, 1998; Chatterton et al, 1999)

Early protease inhibitor (PI) therapies were also associated with small declines in HRQoL (Revicki et al, 1999; Weinfurt et al, 2000) – more notably for physical than mental health status – but as PI-based triple therapy (a PI combined with 2 NRTIs) and HAART became common practice, HRQoL stabilised and was even seen to increase. (Cohen et al, 1998; Zinkernagel et al, 1999; Nieuwkerk et al, 2000; Low-Beer et al, 2001; Nieuwkerk et al, 2001; Brechtl et al, 2001)

There is a sizeable body of research on the impact of HAART on HRQoL in the developed world. Most recent cohort studies in the USA and Europe have shown no significant change in HRQoL within the first two years of HAART (Brechtl et al, 2001; Murri et al, 2003; Burgoyne et al, 2004) although one showed an increase in mental QoL only (Carrieri et al, 2003) and two a decrease in physical QoL (Gill et al, 2002; Liu et al, 2006a). In contrast, the 2NN study, which compared the efficacy and safety of three NNRTI-containing regimens: nevirapine (NVP), efavirenz (EFV) and NVP plus EFV in combination with stavudine and lamivudine, showed an overall improvement in HRQoL over 48 weeks (van Leth et al, 2004).

The 2NN study included a high proportion of patients with advanced disease from developing countries. Seventy three percent of patients enrolled in the study came from developing countries and 36 percent came from South Africa alone. The patient population was 63 percent male with a median age of 34 years (IQR 29 - 40). The baseline CD4 count was 190 cells/mm^3 (IQR 70 - 330), baseline log viral load was 4.7 (IQR 4.4 - 5.5) and 21 percent had CDC category C disease indicating more advanced HIV disease. As the main study showed a difference in safety profiles between NVP and EFV, a sub-study was undertaken to assess whether this translated into a difference in HRQoL. The sub-study reported an increase in

both physical health summary (PHS) score and mental health summary (MHS) score across all three arms and that these changes in PHS and MHS scores occurred most predominantly in the first 12 weeks of treatment. Patients with grade 3 or 4 adverse events had slightly lower increases in PHS score (although this was not statistically significant) but significantly lower increases in MHS score than patients without grade 3 or 4 events.

There are more recent reports of improved HRQoL on HAART that have come out of the developed world. A large international cohort study (Bucciardini et al, 2007) and a national cohort study from France (Preau et al, 2007) both observed increases in physical and mental HRQoL after three plus years of HAART. Improvement in physical HRQoL was much more marked than in mental HRQoL.

Not only has the impact of HAART on HRQoL been widely researched in the developed world but also the impact of socio-demographic, psychosocial and clinical factors on HRQoL of individuals receiving HAART. (Stangl et al, 2007) Among the socio demographic factors, low level of education, low socio-economic status and unemployment are associated with lower baseline PHS scores, while low education and unemployment are associated with lower baseline MHS scores. (Murri et al, 2003) For individuals on HAART, low socio-economic status and unemployment predict lower PHS score (Liu et al, 2006b); whereas lower education predicts lower MHS score. (Murri et al, 2003) Age has been shown to be associated with both PHS and MHS with older individuals achieving lower scores. (Liu et al, 2006b; Murri et al, 2003) In terms of gender, Mrus et al (2005) reported that women have significantly lower HRQoL at baseline and on HAART than men. The only psychosocial factors shown to be associated with HRQoL in patients on HAART are social support and depression. Individuals with depression and less social support report significantly lower MHS scores than individuals without depression and better social support. (Liu et al 2006b)

Clinical factors associated with poor HRQOL at baseline include CD4 count below 200 cells/mm^3, hospitalisation within 3 months preceding HAART initiation and the presence of symptoms. (Murri et al, 2003) For individuals receiving HAART, the most significant predictors of HRQoL are the baseline PHS and MHS scores. (Carrieri et al, 2003; Murri et al, 2003; Burgoyne et al, 2004; Liu et al, 2006b) Other factors associated with improved HRQoL on HAART are an undetectable viral load (Gill et al, 2002; Burgoyne et al, 2004; Carrieri et al, 2003), increase in CD4 count (Gill et al, 2002; Burgoyne et al, 2004) and lower number of

reported symptoms (Burgoyne et al, 2004; Carrieri et al, 2003). Low baseline CD4 count (Carrieri et al, 2003; Murri et al, 2003; Liu et al, 2006b), more advanced stage of disease (Murri et al, 2003; Liu et al, 2006b) and greater number of symptoms (Murri et al, 2003; Liu et al , 2006b) are all associated with lower PHS scores on HAART; whereas greater number of symptoms (Murri et al, 2003) and HAART interruption (Liu et al, 2006b) have been associated with lower MHS scores.

3.3 Assessment of HRQoL in the developing world

There is a growing pool of data on HRQoL in the developing world and Sub-Saharan Africa in particular. Table 2 lists 12 studies from developing countries that have appeared in the recent literature. These papers describe HRQoL in HIV infected individuals attending a wide variety of HIV services including self-help groups, community HIV clinics and hospital outpatient departments. The studies are all observational and ten of them are cross-sectional in design. Various instruments – some generic and others disease-specific - have been used to assess HRQoL and include the MOS-HIV (2 studies), MOS-SF36 (2 studies), MOS-SF20 (1 study), EQ5D (4 studies), WHOQOL-Bref (2 studies) and HAT-QOL (1 study). Lau et al (2000) validated the Chinese version of the MOS-HIV in their study. In only six of the studies are participants receiving HAART.

3.3.1 HRQoL in untreated cohorts

Six studies dealt with HRQoL in untreated cohorts. Two of these studies compared the HRQoL of HIV positive patients to an HIV negative control population and showed that HIV positive patients had significantly lower levels of QoL. Four of the studies examined changes in HRQoL with HIV disease progression – as evidenced by clinical, CD4 count and / or viral load markers – and found that QoL decreased significantly as CD4 counts dropped, viral loads increased and patients progressed from asymptomatic HIV infection to symptomatic disease and AIDS. Finally, four of the studies assessed the association between various socio-demographic factors and HRQoL. All of these studies were cross-sectional in design.

Phaladze et al (2005) explored what constitutes HRQoL for people living with HIV/AIDS in sub-Saharan Africa. Study variables were arranged into 6 groups: individual characteristics, environmental characteristics, biological and physiological factors, symptom status, functional status and general health perceptions. Each of these groups of variables had a

significant impact on HRQoL. Participants with higher HRQoL scores were less educated, had disclosure and financial worries, did not have an AIDS diagnosis, did not have other co-morbidities, had lower symptom intensity, greater functioning and fewer health worries. Functional status was the most significant predictor of HRQoL. People with an impaired ability to carry out their daily activities had the lowest QoL scores.

Two studies compared the HRQoL of HIV positive patients with HIV negative controls in South Africa. O'Keefe and Wood (1996) used the MOS-SF36 instrument to compare the HRQoL of patients attending an HIV out-patient clinic to a control population of healthy non-medical hospital personnel. Among the HIV positive patients, 32 percent were black, 34 percent were female and 60 percent had WHO Stage 3&4 disease. HIV positive patients reported significantly lower HRQoL across all domains than HIV negative controls with the majority of decline occurring early during WHO Stage 1&2 disease. This impact was most pronounced for mental health domains; whereas physical health domains showed a more linear decline with disease progression. The only scale to be affected by race/gender was physical function. Hughes et al (2004) reported similar findings when comparing the HRQoL of people living with HIV/AIDS to an HIV negative reference population. Overall HRQoL (as measured by the VAS score) was significantly lower amongst people with HIV/AIDS (VAS score 60.4 versus 80.1, $p<0.001$). A higher proportion of people with HIV/AIDS experienced severe limitations in mobility (30.9% versus 14.8%, $p<0.001$), selfcare (14.8% versus 4.6%, $p=0.016$), usual activities (31.7% versus 10.2%, $p<0.001$) and pain/discomfort (33.4% versus 24.2%, $p=0.123$) than the reference population. Gender did not significantly impact on HRQoL.

Three studies assessed the determinants of HRQoL in HIV positive individuals in India. Naveet et al (2006) assessed the impact of socio-demographic and clinical factors on the HRQoL of HIV positive patients receiving care at a tertiary hospital in Northern India. Subjects were male (89%) with evidence of advanced disease – 46% diagnosed with AIDS and 46% with CD4 count <200 cells/mm^3. Using unadjusted analyses only, the study found that QoL was determined by education, income, occupation, family support and clinical stage. QoL scores decreased with clinical disease progression in both the physical domain (asymptomatic 14.65 versus symptomatic without AIDS 12.0 ($p=0.014$); versus AIDS 10.43 ($p<0.001$)) and psychological domain (asymptomatic 14.16 versus symptomatic without AIDS 12.1 ($p=0.014$); versus AIDS 12.4 ($p<0.001$)).

The studies by Kholi et al (2005) and Chandra et al (2006) addressed associations between HRQoL and clinical disease progression. Kholi et al (2005) used a modified MOS instrument to study the HRQoL of HIV infected patients enrolled in a "clinical progression of HIV" cohort in Pune, India. The patients were mostly men (66%), who tended be older and have more advanced disease than women. The study reported "low QoL scores" (actual values were not given) – most notably for the physical health, work and earnings, routine activities and appetite and food intake domains. Marital status, clinical status and CD4 count were associated with QoL in men, whereas age, marital status, education and clinical status predicted QoL in women. QoL scores decreased with both declining CD4 counts and clinical disease progression from asymptomatic infection to symptomatic disease and AIDS. Interestingly, women reported significantly lower QoL than men despite having less advanced disease.

Chandra et al (2006) assessed the HRQoL of HIV positive patients with asymptomatic infection and its association with biological markers of disease progression – namely CD4 counts and viral loads. They reported that patients with CD4 counts below 200 cells/mm^3 had lower scores across all six HRQoL domains (physical, psychological, level of independence, social relationships, environment and spirituality) however this association was only significant for the psychological ($p=0.014$) and social relationships domains. Similarly, patients with a viral load $>10 \times 10^6$ copies/ml had lower scores across all six domains although this was only significant for the physical, psychological, level of independence and environment domains.

These six studies in untreated HIV positive populations reported similar findings to those in the developed world. People living with HIV/AIDS experience lower levels of HRQoL than those who are HIV negative. Furthermore, HRQoL declines significantly with HIV disease progression - as evidenced by decreasing CD4 counts, increasing viral loads and clinical progression from asymptomatic to symptomatic HIV infection and AIDS. In terms of socio-demographic and other factors associated with HRQoL, it was generally agreed that education, employment / income, social (family) support and clinical state are associated with HRQoL although the nature of these associations differed between the various populations. In addition, Kholi et al (2005) found that in India, age and marital status are strongly associated with QoL. Although Kholi et al (2005) found a significant difference in the emotional and

sexual domains of HRQoL between genders, Hughes et al (2004) reported no difference in HRQoL between men and women.

3.3.2 HRQoL in treated cohorts

Six studies assessed HRQoL in treated cohorts but only four of these addressed the impact of HAART on HRQoL in developing countries. The most comprehensive study to date is that of Stangl et al (2007) who examined the trends and predictors of HRQoL over 12 months among HIV positive adults initiating HAART in rural Uganda. The study population was 75 percent female with a median age of 38.7 years. The mean CD4 count was 124 cells/μl and mean viral load was 5.2 $\log_{10}$ copies/ml. Male participants were more likely to have more advanced disease than female participants. The study reported a significant improvement in HRQoL across all subscales and both summary scales between baseline and 12 months of HAART. The physical health summary score increased from a mean baseline score of 39.2 (SD 9.8) to 54.2 (SD 7.3) at 12 months follow-up ($p<0.001$); whereas the mental health summary score increased from 40.0 (SD 11.2) to 54.2 (SD 6.9) ($p<0.001$). The bulk of improvement occurred by the third month of treatment.

In terms of predictors associated with HRQoL, Stangl et al found that a baseline CD4 count ≥50 cells/μl was associated with higher baseline PHS scores (*B*-coefficient 3.0; $p=0.001$); whereas a baseline viral load of ≥5 $\log_{10}$ copies/ml and WHO Stage 3 or 4 disease were associated with lower baseline PHS scores (*B*-coefficient -1.4, $p<0.001$ and *B*-coefficient -2.6, $p<0.001$ respectively). Improved MHS scores at baseline were associated with a baseline CD4 count ≥100 cells/μl (*B*-coefficient 2.5; $p=0.008$); whereas a baseline viral load of ≥5 $\log_{10}$ copies/ml was associated with lower MHS scores (*B*-coefficient -2.2; $p=0.004$). The effect of these baseline clinical variables on HRQoL diminished over time and no significant association between these and PHS or MHS score were found at 12 months. Age, sex and marital status were not significantly associated with PHS or MHS score; whereas level of education and financial dependence on others were.

Three studies examined the impact of public sector ART on the HRQoL of HIV positive individuals in South Africa. Wouters et al (2007) modelled the relationships between patient characteristics, socioeconomic position, HAART duration and physical and emotional HRQoL. Both physical and emotional HRQoL improved significantly during the first 6 months of treatment with HAART with HRQoL scores increasing as duration on HAART

increased (standardised coefficient 0.21, p<0.01 for physical QoL and standardised coefficient 0.10, p<0.01 for emotional QoL). Interestingly, the model also showed that not only did emotional HRQoL improve with duration on HAART but also with increasing physical HRQoL (standardised coefficient 0.30, p<0.01). HAART therefore has an indirect effect on emotional health via improved physical health. Other factors in the model that impacted significantly on physical HRQoL were age, gender and level of education. Women reported worse physical HRQOL than men (standardised coefficient -0.25, p<0.05), whereas older patients and those with a higher level of education reported better physical HRQoL than younger patients or those who were less educated (standardised coefficient 0.17, p<0.05 and standardised coefficient 0.20, p<0.05 respectively). No other factors were found to be associated with emotional HRQoL.

Louwagie et al (2007) compared the HRQoL of HIV positive patients receiving HAART with those awaiting HAART in the public sector ARV rollout programme in the Free State, South Africa. The study was cross-sectional in design. Sixty-five percent of the participants were female and all had WHO stage 4 disease and/or a CD4 count of <200 cells/mm^3. Participants were interviewed two months after the first patients in each district initiated HAART. Participants on HAART had significantly higher HRQoL scores than those awaiting HAART (EQ-index score 0.87 versus 0.80, p=0.004 and VAS score 66 versus 62, p=0.04) and were less likely to report problems with mobility (19% versus 29%, p=0.026), self-care (6% versus 18%, p=0.001) and pain or discomfort (39% versus 57%, p=0.022). In contrast to the findings of Wouter et al (2007), women were found to have higher HRQoL scores than men (4.7 difference in mean VAS score, 95% CI 0.79; 8.5). Employed patients also reported better HRQoL than unemployed patients (9.1 difference in mean VAS score, 95% CI 4.3; 13.7).

Jelsma et al (2005) investigated the impact of HAART use on HRQoL in a community antiretroviral programme in South Africa. The study population was largely female (74.5%) and all had advanced HIV disease (WHO stage 3 and 4). Using the EQ5D instrument, HRQoL at baseline was compared with that after 12 months of HAART and a significant improvement in self-care (9.5% reported problems at baseline versus 0% at 12 months, p=0.031), usual activities (24.2% reported problems at baseline versus 6.0% at 12 months, p=0.001), pain (70.5% reported problems at baseline versus 26.5% at 12 months, p=0.001) and anxiety/depression (31.6% reported problems at baseline versus 14.5% at 12 months, p=0.023) was reported over this period. Most of the improvement in HRQoL occurred within

the first month of HAART. Although overall HRQOL (as measured by the VAS score) increased from 61.7 to 76.1 on treatment, final scores were noted to be still lower than a reference HIV negative population.

In contrast to these findings, Bastardo and Kimberlin (2000) reported that HAART use was associated with a non-significant decrease in HRQoL when comparing the HRQoL between patients with asymptomatic HIV infection, symptomatic infection and AIDS using the MOS-SF36 instrument. The study population was largely male (87.3%), educated (49.2% had a high school education and 41.5% a college education), 65.2% were employed, 55.1% had asymptomatic HIV infection, 27.1% had AIDS and 66% were on HAART. Study results also showed that individuals with symptomatic infection and AIDS reported lower QoL scores than those with asymptomatic infection. However, this difference was not significant for the physical function, social function and mental health scales. No correlation was found between HRQoL and age, sex or income.

Lastly, Lau et al (2006) described the HRQoL of people living with HIV/AIDS attending public sector outpatient clinics in Hong Kong as part of a validation exercise of the Chinese MOS-HIV survey. The patient population were largely male (87.9%), educated (76% had received 11 years or less of formal education), 35% had asymptomatic HIV infection, 43% had AIDS and all had free access to HAART (the actual number of patients on HAART was not reported). The study demonstrated that the physical health summary scale was highly correlated with baseline clinical stage (mean PHS scores for asymptomatic infection, symptomatic disease and AIDS were 52, 49.4 and 48.7 respectively, p=0.03). There were no significant associations between any of the other scales and clinical stage or CD4 count. The study did not address the association between HRQoL and HAART use.

Of these six studies addressing HRQoL in treated cohorts, four reported a significant improvement in HRQoL on HAART. These four studies were all conducted in Africa and had study populations that were largely female and with more advanced disease. Wouters et al (2007) and Louwagie et al (2007) assessed the impact of HAART on HRQoL in cross-sectional surveys and showed a significant association between HAART and improved physical and emotional health. Unfortunately, the cross-sectional nature of these two studies and the limited time that participants were on HAART (6 months or less) restrict the inferences that can be drawn from these studies. Only the two studies by Stangl et al (2007)

and Jelsma et al (2005) assessed longitudinal changes in HRQoL associated with HAART use. Both reported a significant improvement in HRQoL over 12 months of HAART with the bulk of this improvement occurring within the first three months on treatment. In contrast to this, Bastardo and Kimberlin (2000) reported a non-significant decrease in HRQoL associated with HAART use. However, their study was cross-sectional in nature and conducted in a population that was largely male, highly educated and with earlier HIV disease.

In terms of other explanatory factors that are associated with HRQoL in a treated cohort, age (Wouters et al, 2007), gender (Louwagie et al, 2007; Wouters et al, 2007), level of education (Wouters et al, 2007) and employment (Louwagie et al, 2007) were significantly associated with HRQoL. Furthermore, Stangl et al (2007) reported that while baseline CD4 count and viral load predicted baseline physical health and mental health summary scores this effect was no longer evident at 12 months of HAART. None of these studies addressed the impact of HAART-related toxicities on HRQoL or the association between HRQoL and adherence to HAART.

3.4 HRQoL and HAART-related toxicities

Internationally, there is concern about the impact of HAART-related toxicity on HRQoL. In fact, it has been suggested that studies, which only consider mortality outcomes, ignore treatment-related morbidity and may actually overestimate the benefits of HAART. (Wu et al, 1990) These international concerns are echoed in South Africa, where there is an ongoing debate about whether or not the side-effect profile of HAART may adversely affect the HRQoL of HIV positive individuals. Boulle et al (2007) explored the patterns and reasons for ARV drug substitutions during the first three years of HAART among patients attending the Hannan Crusaid Treatment Centre and found that 28% of patients switched regimen during this period. While substitutions due to nevirapine (8% by 3 years), efavirenz (2%) and zidovudine (8%) occurred early, substitutions due to stavudine accumulated over time and reached 21% by 3 years. However, empirical data on the impact of these HAART-related toxicities on HRQoL are few. Available data are preliminary and need to be further investigated.

3.5 HRQoL and adherence to HAART

Long-term adherence to HAART is required for sustained viral suppression and ongoing mortality and morbidity benefits. (Altice and Friedland, 1998) These benefits could result in improved HRQoL. On the other hand, the optimisation of HRQoL is essential for achieving good adherence to therapy. (Mannheimer et al, 2005; Carballo et al, 2004; Wu, 2000)

The association between HRQoL and adherence to HAART has received some attention in the developed world. Carballo et al (2004) studied the impact of QoL on adherence in a Spanish HIV cohort. Using the MQOL-HIV instrument as a measure of HRQoL, they reported significant associations between the mental health, cognitive functioning, partner intimacy, financial status and medical care domains and adherence. In the multivariate analysis, high financial status score and high cognitive functioning score were both significantly associated with good adherence (adherence ≥95%); whereas low medical care score predicted poor adherence (adherence <95%).

Mannheimer et al (2005) evaluated the impact of adherence to HAART on changes in HRQoL over time in HIV-infected individuals. They found that QoL was significantly associated with self-reported adherence at 12 months of HAART. Persons reporting higher levels of adherence (adherence 100%) achieved significantly higher physical health summary and mental health summary scores than persons reporting lower levels of adherence (80 – 99% or <80% adherence) while persons with adherence <80% achieved QoL scores lower than those at baseline.

The relationship between HRQoL and adherence to HAART has not been explored in Sub-Saharan Africa. Hence it is not known if HRQoL can be further improved by good adherence or what the impact of poor HRQoL on adherence to HAART is in our population. Furthermore, the impact of HAART-related toxicities on the relationship between HRQOL and adherence is unknown. Early drug toxicities may have a lasting impact on HRQoL and thereby affect long-term adherence to therapy.

3.6 Summary

As access to HAART becomes more widely available so HIV is becoming a chronic manageable illness and the importance of quality of life as a treatment outcome is increasing. Quality of life is a complex concept and the measurement thereof is not easy. Numerous instruments have been developed to assess health related quality of life. The MOS surveys – of which the MOS-SF36 and MOS-HIV are the most popular - are some of these. The impact of HAART on HRQoL has been widely researched in the developed world, however, there is limited data coming out of the developing world. This review found only six studies that have addressed this topic and none that have assessed the impact of HAART-related toxicities on HRQoL or the association between HRQoL and adherence to HAART. These issues need to be explored in developing countries to inform program and policy decisions about HAART roll-out strategies in order to maximise the quality of life of HIV infected individuals.

Table 2 Description of studies addressing HRQoL in untreated and treated cohorts in developing countries.

Untreated Cohorts							
Author	**Year**	**Setting**	**Design**	**Population**	**Objective(s)**	**Measure**	**Key Findings**
Phaladze NA, Human S, Dlamini SB, Hulela EB, Hadebe IM, Sukati NA, Makoae LN, Seboni NM, Moleko M & Holzemer WL.	2005	Sub-Saharan Africa: Botswana, South Africa, Lesotho and Swaziland	Cross-sectional	Adults living with HIV/AIDS 61.2% female 62% AIDS	Assess impact of outcome variables on HRQoL – individual, environmental, physiological, symptom status, functional status, general health perceptions.	HAT-QOL	All variables significantly impacted on HRQoL. Higher HRQoL associated with less education, disclosure and financial worries, no AIDS diagnosis, lower symptom intensity, higher functional status and fewer health worries.
O'Keefe EA & Wood R.	1996	Hospital HIV Clinic, South Africa	Cross-sectional	HIV+ patients attending HIV clinic; HIV- non-medical hospital personnel.	1. Establish normal HRQoL values for South African population. 2. Survey of HRQoL of HIV+ patients.	MOS-SF36	1. Black females scored lower on all scales except physical function. 2.1. HIV+ patients scored significantly lower on all scales then HIV- controls. 2.2. Physical scores decreased linearly with disease progression.
Hughes J, Jelsma J, Maclean E, Darder M & Tinise X	2004	Community HIV clinic, South Africa	Cross-sectional	HIV+ patients enrolled in ARV programme but pre-HAART; HIV- people living in community - matched for age and area.	1. Comparison of HRQOL between HIV+ and HIV-. 2. Influence of gender on HRQOL	EQ-5D	1.1. Significant difference in mobility, self-care, usual activities and pain but not anxiety/depression. 1.2. VAS score: 60.4 (HIV+) versus 80.1 (HIV-) 2. No gender difference.
Naveet W, Raja L, Hemraj P, Vivek A, Mohan MC & Kumar AS.	2006	Tertiary hospital, Northern India	Cross-sectional	HIV+ patients attending HIV clinic or admitted to hospital. 89% male 46% AIDS	1. Assess impact of socio-demographic and clinical factors on HRQoL.	WHOQOL-Bref	1.1. Education, income, occupation, family support are associated with HRQoL. 1.2. QoL decreases with clinical progression.
Kholi RM, Sane S, Kumar K, Paranjape RS & Mehendale SM.	2005	HIV clinic at National AIDS Research Institute, Pune, India	Cross-sectional	HIV+ patients enrolled into a prospective longitudinal cohort study. 34% female 29% AIDS	1. Assess impact of socio-demographic and clinical factors on HRQoL. 2. Describe change in HRQoL with disease progression.	Modified MOS	1. Age, education, marital status and clinical status associated with QOL. 2. Decrease in QoL as CD4 count decreases and as progress to AIDS.

Chandra PS, Gandhi C, Satishchandra P, Kamat A, Desai A, Ravi V, Ownby RL, Subbakrishna DK & Kumar M.	2006	South India	Cross-sectional	HIV+ patients enrolled in a longitudinal study. 52% female Asymptomatic HIV infection.	1. Assess association between HRQoL and biological markers of disease progression – viral load and CD4 count.	WHOQOL-Bref	1.1 Lower CD4 counts predict low psychological and social QoL scores. 1.2. Higher viral loads predict lower physical, psychological, level of independence and environment QoL scores.

Treated Cohorts

Author	Year	Setting	Design	Population	Time Frame	Measure	Change in QOL
Stangl AL, Wamai N, Mermin J, Awor AC & Bunnell RE.	2007	Rural Uganda	Longitudinal	HIV+ people enrolling on HAART 75% female 31.3% WHO stage 3&4	0, 3, 6, 9 and 12 months	MOS-HIV	Significant improvement in HRQoL with HAART use.
Wouters E, Meulemans H, Van Rensburg HJC, Heunis JC & Mortelmans D.	2007	Public sector ARV roll-out programme, Free State, South Africa	Cross-sectional	HIV+ people awaiting HAART & on HAART	N/A	EQ5D	Significant improvements in physical and emotional HRQoL during first 6 months of HAART.
Louwagie GM, Bachmann MO, Meyer K, Booysen FR, Fairall LR & Heunis C.	2007	Public sector ARV roll-out programme, Free State, South Africa	Cross-sectional	HIV+ people awaiting HAART & on HAART 65% female 100% WHO stage 4 and/or CD4 count <200 cells/mm^3	N/A	EQ5D, EQ-index & VAS	Higher HRQoL scores for those on HAART.
Jelsma J, Maclean E, Hughes J, Tinise X & Darder M.	2005	Community ARV Clinic, Western Cape, South Africa	Longitudinal	HIV+ people enrolling on HAART 74.5% female 100% WHO stage 3&4	0, 1, 6 and 12 months	EQ5D & VAS	Significant improvement in HRQoL with HAART use.
Bastardo YM & Kimberlin CL.	2000	HIV organisations, support groups and health care institutions, Venezuela	Cross-sectional	HIV+ people in HIV services 67% on HAART 87% male 55% asymptomatic HIV	N/A	MOS SF36	Lower HRQoL scores across all domains but only significant for social functioning.
Lau JTF, Tsui HY, Patrick LCK, Rita CWY & Molassiotis A	2006	Public sector HIV clinics in Hong Kong	Cross-sectional	HIV+ with access to HAART 88% male 35% asymptomatic HIV	N/A	MOS-HIV	Impact of HAART on HRQoL not assessed.

4 METHODS

4.1 Study Design

This cohort study examined the HRQoL reported by HIV positive individuals pre-HAART and at regular intervals during their first year of receiving HAART. Quality of life data were collected as part of the routine service provided by the Hannan Crusaid Treatment Centre between September 2002 and March 2005. The collection of these data formed part of the overall assessment of one of the province's first antiretroviral rollout sites. (Bekker et al, 2006; Bekker et al, 2003; Lawn et al, 2006; Lawn et al, 2005a)

4.2 Study Site and Population

The Hannan Crusaid Treatment Centre (HCTC) is a combined antiretroviral and research clinic in Gugulethu, Nyanga. This clinic began as a joint venture between the Western Cape Department of Health, Desmond Tutu HIV Foundation and Crusaid, a UK-based NGO, which raises funds to support people living with HIV/AIDS, and was one of the first antiretroviral (ARV) rollout sites in the Western Cape Province. The HCTC is situated alongside the Gugulethu Community Health Centre and boasts a multidisciplinary team of medical doctors, clinical nurse practitioners, clinic nurses, Sizophila adherence counsellors and a pharmacist.

The HCTC was initiated in September 2002 as a community-based ARV pilot project. An easily reproducible service model was used incorporating 1 doctor, 1 nurse and a team of 8 adherence counsellors. Sizophila adherence counsellors were HIV-infected individuals from the community who had been trained in ARVs and adherence. The role of the counsellors was to provide ongoing counselling support, to reinforce the need for high levels of adherence, to maintain communication between patients and clinic staff and to visit patients at their homes. Early data from the project confirmed that an ARV programme could be successfully initiated within an existing primary care facility and highlighted ethical, medical and logistic challenges (including resource issues such as staffing) that would need to be addressed prior to scaling up ARV roll-out. (Bekker et al, 2003)

By 2005, the HCTC had grown rapidly. Not only had the number of patients accessing care increased from 150 to over 1000 but the clinic staff had also increased to 4 doctors, 3 nurses,

1 pharmacist and 28 adherence counsellors. Despite this rapid scaling up of services, data showed that programme performance had not been compromised. For the 2002, 2003 and 2004 cohorts, the proportion of patients remaining in care were 82%, 86% and 91% respectively and the proportion who were virally suppressed (viral load <400 copies/ml) were 100%, 92% and 98%. (Bekker et al, 2006)

Between September 2002 and August 2005, 9.8% of patients died and a further 4.9% were lost from the programme for reasons other than death. (Lawn et al, 2006) The high pre-treatment and early on-treatment mortality (87% of deaths occurred between enrolment onto the programme and four months on treatment) reflected the advanced degree of immunodeficiency of patients entering the programme. (Lawn et al, 2006) However, within the first month of initiating ARVs, the mortality rate decreased by 2.03 fold and after 6-9 months the mortality rate was 13.2 fold lower than the baseline rate. (Lawn et al, 2005a).

The HCTC provided anti-retroviral care for HIV positive individuals living in the Nyanga District. This district had an estimated population of 300 000, the majority of whom were socio-economically deprived with 57% of the population unemployed and 81% living in informal housing. (City of Cape Town, 2003; Statistics SA, 2001) In 2003, the antenatal HIV seroprevalence rate was 28%, making Nyanga the second highest prevalence district in the Western Cape. (Uys, 2004)

4.3 ARV Programme

The HCTC serviced the HIV population from ten primary care HIV clinics in the surrounding communities (referring women and men who tested HIV positive in routine counselling and testing services), as well as the local Midwife Obstetric Unit (referring women who were pregnant or post-partum). HIV positive individuals who met clinical and immunological criteria were able to access ARV care here. As per the national ARV guidelines, adult patients who had WHO Stage 4 disease and/or a CD4 count of < 200 cells/mm^3 were commenced on first-line ARVs. (NDOH, 2004) The majority of patients initiated on treatment were ARV naïve.

The clinic followed a programmatic approach to ARV care with a standard first- and second-line regimen. In keeping with the World Health Organisation recommendations for scaling up

antiretroviral treatment in resource-poor settings, the first-line regimen was non-nucleoside reverse transcriptase inhibitor (NNRTI) -based and the second was protease inhibitor (PI) -based. (WHO, 2000)

HIV positive individuals enrolled onto the programme were assessed at two visits prior to initiating ARVs to allow for clinical staging and baseline bloods (HIV viral load and CD4 cell count) to be drawn and for an assessment of treatment readiness to be made. Patients were required to attend three treatment readiness education sessions prior to commencing ARVs. These sessions provided information on basic HIV/AIDS, antiretroviral therapy and positive living. Patients were discussed by the multidisciplinary team at the weekly pre-treatment review meeting and those who met eligibility criteria and were deemed treatment ready were initiated on ARVs.

Not all patients enrolled into the programme initiated ARVs. For some patients, treatment was temporarily or permanently deferred and others died prior to commencing ARVs. Reasons for temporary deferral of treatment included investigation of an intercurrent opportunistic infection, lack of treatment readiness and failure to attend follow-up appointments. Reasons for permanent deferral of treatment included not being eligible for treatment, decision to access treatment elsewhere, failure to attend follow-up clinic appointments, relocation out of the area and psychosocial issues. (Lawn et al, 2005a)

Adults commenced on the first-line NNRTI-based regimen (efavirenz or nevirapine plus stavudine and lamivudine) were reviewed at 4, 8 and 16 weeks and thereafter every 4 months by a medical doctor. At these scheduled visits, patients were assessed clinically, virologically and immunologically. The medical doctor looked for any clinical and/ or laboratory evidence of drug toxicity and reviewed adherence over the past four months. If all was well, the prescription was renewed and further ARVs dispensed.

Tablets were dispensed every two-months. Patients returned to the clinic between scheduled doctor visits to have their tablet returns counted and noted in their folder by the Sizophila adherence counsellors. Prior to initiating ARVs, patients were allocated to a community based Sizophila adherence counsellor, who was responsible for treatment readiness education and ongoing counselling support to maintain high levels of treatment adherence. Any adherence issues were brought to the attention of the medical doctor.

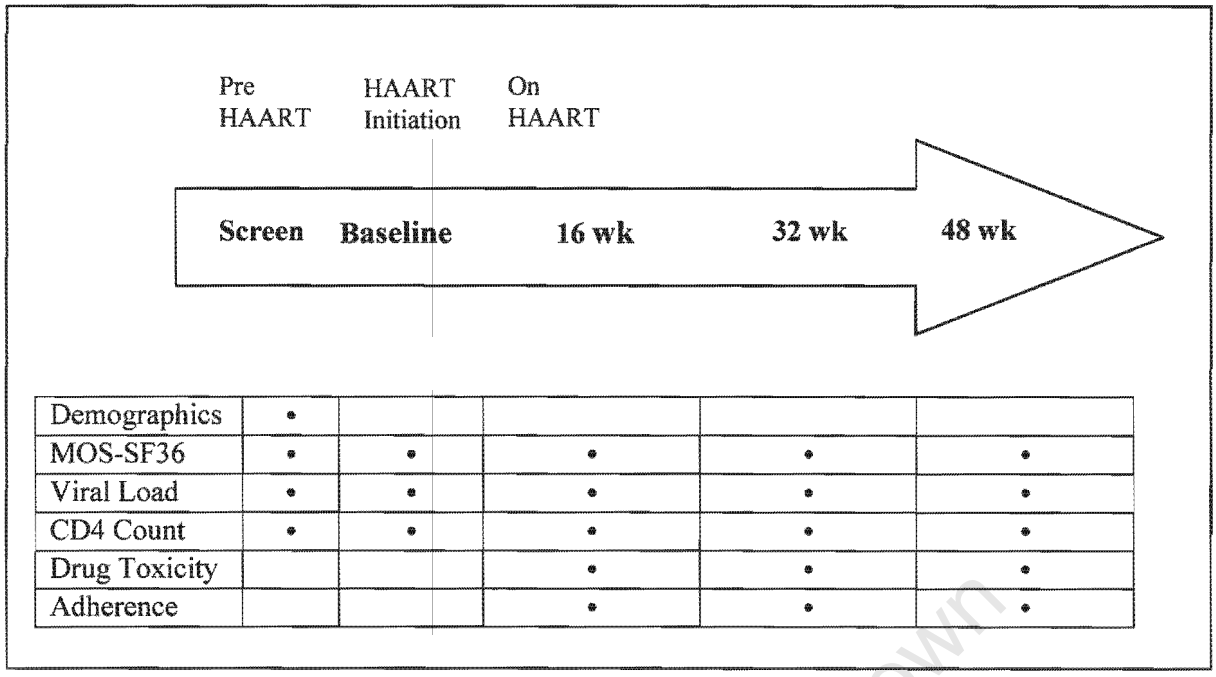
Patients who failed their first-line regimen – either virologically or for toxicity reasons - were worked up for the second-line PI-based regimen (Kaletra®, didanosine and zidovudine). Nucleoside Reverse Transcriptase Inhibitor (NRTI) substitutions were made within regimen 1 or 2 for NRTI-associated toxicities. All treatment was supplied free of charge.

4.4 Study Procedures

At the screening visit, HIV positive individuals referred to the HCTC met with one of the Sizophila adherence counsellors prior to seeing the doctor. The adherence counsellor explained to them that this was a research clinic and that above the routine information that was collected at provincial ARV clinics, they would also be asked to complete adherence and quality of life questionnaires at each of their scheduled visits. Patients were requested to sign a research consent form (Appendix 1) indicating their willingness to have additional research information collected.

Patients then met with the clinic nurse who completed a demographic information sheet. This sheet captured basic information including age, date of birth, gender, disclosure status, level of education and employment. The clinic nurse drew blood for viral load, CD4 cell count and safety blood testing at the screening visit and all subsequent scheduled visits prior to the patient seeing the doctor.

The quality of life questionnaire was administered by a trained Sizophila adherence counsellor at each of the following scheduled visits: screening, baseline, week 16, week 32, week 48 and week 64. Although HRQoL data continued to be collected at scheduled visits following week 64, this study focussed on quality of life during the first year of ARVs only.



Demographics	•				
MOS-SF36	•	•	•	•	•
Viral Load	•	•	•	•	•
CD4 Count	•	•	•	•	•
Drug Toxicity			•	•	•
Adherence			•	•	•

Figure 1 Table of events for HRQoL study.

HRQoL data were intended to be collected on all patients at all scheduled visits within the first year; however this was not always possible. Reasons for incomplete HRQoL data were death, loss to follow up, transfer out and patients leaving the clinic without the questionnaire being administered.

4.5 Study Measures

4.5.1 HRQoL Instrument – the MOS-SF36 Questionnaire

Health Related Quality of Life (HRQOL) was assessed using a standardised questionnaire, the Medical Outcomes Survey Short Form 36 (MOS SF36) (Appendix 2). The MOS SF36 instrument is derived from the pool of HRQoL-items developed as part of the Medical Outcomes Study (MOS) – a four year observational study of variations in physician healthcare practice and patient outcomes in different healthcare settings. (Wu et al, 1997) The instrument addresses those aspects of HRQoL that are most influenced by a disease state and its treatment. (Wu et al, 1997) The MOS SF36 was designed as a compromise between the lengthier, more comprehensive multi-item health measures and the brief single-item scales. This combination of brevity and comprehensiveness drives the popularity of the instrument. (Ware and Sherbourne, 1992)

The MOS SF36 uses 36 items to assess eight health concepts: (1) physical functioning, (2) role limitations because of physical health problems, (3) bodily pain, (4) social functioning, (5) general mental health, (6) role limitations because of emotional problems, (7) vitality and (8) general health perceptions. (Ware and Sherbourne, 1992) The self-reported physical functioning scale measures the ability of patients to perform different types of physical activities and captures both the presence and severity of physical limitations. The scale covers 10 items ranging from vigorous activities (such as running, lifting heavy objects or participating in strenuous sports) to basic activities (such as bathing or dressing one's self). Each item is scored from 1 (limited a lot) to 3 (not limited at all). The scores for the ten items are then summed to give an overall physical functioning scale score. A low scale score indicates that the individual is severely limited in performing all physical activities – including bathing and/or dressing. A high score indicates that the individual is able to perform even the most vigorous activities without limitations.

The physical and emotional role functioning scales assess limitations in work or other daily activities due to physical and mental health problems. The physical role functioning scale includes four items relating to the amount of time spent on work or other activities, whether or not a person has accomplished less than they would like, whether or not a person was limited in the kind of work or activities they were able to perform and whether or not a person had difficulty performing work or other activities. The emotional role functioning scale includes three items relating to the amount of time spent on work or other activities, whether or not a person has accomplished less than they would like and whether a person was able to do work or other activities as carefully as usual. For both of these scales, items are scored 1 for a positive response and 2 for a negative response. A low scale score indicates that the patient has problems with work or other daily activities due to physical and/or emotional health issues. A high score indicates that the patient has no problems with work or other daily activities.

The bodily pain scale consists of two items that assess both the frequency of pain and how this impacts on usual daily activities. The first item addresses the amount of bodily pain experienced in the past four weeks – ranging from none (scored as 1) to very severe (scored as 6). The second item assesses how much pain interfered with a person's normal work – ranging from not at all (scored as 1) to extremely (scored as 5). The item scores are inverted

and then summed as a scale score. A low scale score indicates very severe and extremely limiting pain; whereas a high score indicates no pain.

The social functioning scale measures the impact of physical health or emotional health problems on social activities. This scale includes an item that assesses the extent to which physical health or emotional problems interfered with a person's normal social activities with family, friends, neighbours or groups in the past four weeks – scored 1 (not at all) to 5 (extremely) – and an item that assesses the amount of time that these activities were interfered with – scored 1 (all of the time) to 5 (none of the time). A low scale score indicates that the person experiences extreme and frequent interference with normal social activities due to physical and emotional problems. A high score indicates that the person is able to perform normal social activities without any limitations.

The mental health scale assesses the four major dimensions of mental health: anxiety, depression, loss of behavioural or emotional control and psychological wellbeing. The scale includes five items that are assessed on a scale of 1 (all of the time) to 6 (none of the time). A low scale score indicates that the person experiences feelings of nervousness and depression all of the time; whereas a high score indicates that the person feels peaceful, happy and calm all of the time. The vitality scale consists of four items that capture differences in subjective wellbeing in terms of energy levels and fatigue. A low vitality score indicates that the person feels tired and worn out all of the time while a high score indicates that the person feels full of energy all of the time. The general health perceptions scale covers five items that capture differences in the perceived level of personal health. A low general health perceptions score indicates that the person believes that their health is poor and likely to get worse, whereas a high score indicates that the person believes that their health is excellent. The scores of the eight scales can be converted in two summary scales – the physical health summary (PHS) and mental health summary (MHS) by using standardised factor analysis-based weights.

The MOS SF36 instrument has been translated and culturally adapted into more than 30 languages thereby allowing the pooling of data collected across different languages and cultures. (Wu et al, 1997a) It has been widely used in studies of quality of life in HIV positive patients in both developed and developing countries and has performed well in all of these settings. (Liu et al, 2006a; Burgoyne et all, 2004; Carrieri et al, 2003; Bing et al, 2000; Call et al, 2000; Bastardo and Kimberlin, 2000; O'Keefe and Wood, 1996) The instrument has also

undergone validity and reliability testing in a multiracial South African population and was able to differentiate between HIV infected and non-infected individuals. (O'Keefe EA and Wood R, 1996) Population values exist for several countries including South Africa.

The MOS SF36 questionnaire was administered by the Sizophila adherence counsellors. The adherence counsellors all underwent training in the administration of the questionnaire. This training was repeated when new adherence counsellors were employed. Although we did have access to a Xhosa translation of the questionnaire, the adherence counsellors opted to use the English version of the instrument with standard Xhosa explanations given by the counsellors for difficult concepts.

4.5.2 Socio-demographic and Clinical Information

4.5.2.1 Demographic Data

Demographic information – including date of birth, age, gender, level of education, employment status and disclosure status - was collected at screening using the standard Gugulethu paperwork (Appendix 3). Patients were staged according to WHO clinical criteria by the medical doctor at their screening visit.

4.5.2.2 Viral Load and CD4 Count Data

Viral load and CD4 cell count testing were performed by the Toga Laboratory in Johannesburg. Viral load testing made use of the branch DNA hybridisation technique (Versant™ HIV-1 RNA 3.0 branched chain DNA assay (Bayer HealthCare, Leverkusen, Germany)) and CD4 cell counts were measured by flow cytometry (FACSCount™, Becton Dickinson, Franklin Lakes, NJ, USA). Viral load and CD4 cell count results were recorded on the Continuation Sheet of the standard Gugulethu paperwork (Appendix 3) at each scheduled visit.

4.5.2.3 Adherence Data

Adherence data (in the form of objective tablet return counts) were collected at each visit by the Sizophila adherence counsellors. The counsellors counted and recorded tablet returns for all three drugs on the Drug Accountability Form of the standard Gugulethu paperwork (Appendix 3). This data was then transformed into an adherence percentage using the following calculation:

(1 – (no. tablets dispensed – no. tablets returned / no. days x no. doses per day)) x 100%

Average adherence across the three drugs was calculated.

4.5.2.4 Drug Toxicity Data

Drug toxicities were detected by the medical doctor at clinical visits (both scheduled and unscheduled) through clinical questioning, examination and safety blood draws. Drug toxicities were defined as any adverse event thought by the clinician to be HAART-related and that required a change in antiretroviral therapy. They included a wide range of conditions such as peripheral neuropathy, hyperlactataemia, lactic acidosis, elevated transaminases, hepatitis, pancreatitis, anaemia, hypersensitivity reaction and psychosis. Peripheral neuropathy, hypersensitivity reaction and psychosis were all defined clinically – by suggestive signs and symptoms; whereas elevated transaminases and anaemia were defined according to laboratory criteria. Transaminases that were five times or more the upper limit of normal were considered significantly elevated and fulfilled one of the conditions to prompt a drug switch. Similarly, haemoglobin of less than 6.5 g/dL was considered a significant anaemia and a reason to switch drug. Hyperlactataemia, lactic acidosis, hepatitis and pancreatitis were defined by a combination of clinical and laboratory criteria. Drug changes could either be a NRTI substitution (for example d4T substituted by AZT due to severe peripheral neuropathy) or a change from NNRTI to PI (for example nevirapine substituted by Kaletra® for a hypersensitivity reaction).

4.6 Variables

4.6.1 Outcome variables

Four sets of outcome variables were used in this analysis: 1) pre-HAART physical health summary (PHS) and mental health summary (MHS) scores; 2) change in PHS and MHS scores; 3) negative PHS and negative MHS; and 4) adherence. Change in PHS and MHS were continuous variables and were calculated by subtracting the pre-HAART PHS and MHS scores from the 48 week PHS and MHS scores respectively. Negative PHS and negative MHS were binary constructs and were defined as a negative change in PHS score and a negative

change in MHS score respectively. Adherence was categorized into adherence percentage above and below 95% at week 48.

4.6.2 Explanatory variables

Explanatory variables were continuous (age, baseline CD4 count, baseline viral load, baseline log viral load, week 48 CD4 count, week 48 viral load, week 48 log viral load, change in CD4 count and change in log viral load) and categorical (gender, WHO stage, and drug toxicity).

Age was categorized around the median age of 34 years. Baseline CD4 count was categorized as >50 cells/mm^3 and ≤50 cells/mm^3 and baseline log viral load was categorized as >5.0 log copies/ml and ≤5.0 log copies/ml. Week 48 CD4 count was categorised as both a binary variable (≥250 cells/mm^3 versus <250 cells/mm^3) and a polychotymous variable (<50 cells/mm^3 / 50 – 199 cells/mm^3 / 200 – 349 cells/mm^3 / 350 – 499 cells/mm^3 / ≥500 cells/mm^3). Week 48 viral load was categorised as a binary variable (<50 copies/ml and ≥50 copies/ml) and a polychotymous variable (<50 copies/ml / 50 – 399 copies/ml / 400 – 4999 copies/ml / ≥5000 copies/ml) and, similarly, week 48 log viral load was categorized as a binary variable (<1.69 log copies/ml and ≥1.69 log copies/ml) and a polychotymous variable (<1.69 log copies/ml / 1.69 – <2.60 log copies/ml / 2.60 <3.69 log copies/ml / ≥3.69 log copies/ml). Change in CD4 count was calculated as week 48 CD4 count minus baseline CD4 count. Change in log viral load was calculated as week 48 log viral load minus baseline log viral load. Drug toxicity was defined as any change in drug (NRTI switch and/or switch from NNRTI to PI) due to an adverse event.

4.7 Analysis

4.7.1 Handling of data

Quality of life data were entered using a custom-designed EPI INFO template to ensure high data quality. On completion of data entry for each questionnaire, scores for the eight health components were automatically generated according to standard scoring algorithms. This algorithm computes raw scores by summing individual items within the same scale and then linearly transforms these raw scores to a 0 – 100 scale: where a higher score indicates a better state of health. Data were then transferred into a Microsoft Excel spreadsheet where health

component scores were transformed into the physical health summary (PHS) and mental health summary (MHS) scores using standardised factor analysis-based weights.

Missing questionnaire items were estimated using a standard scoring algorithm that estimates missing values. If ≤50% of the items were missing for a multi-item scale, then these were substituted using a person specific estimate – the average score across the completed items for that person. (IRCHC, 1992)

HRQoL data for participants who had completed all on treatment questionnaires were included in the analysis. Scores for screening and baseline were combined to form an average pre-HAART score. For participants where week 48 scores were not available week 64 scores were used to replace missing data. This replacement of scores was deemed acceptable as data analysis demonstrated no significant difference between overall week 48 and week 64 scores.

Demographic, clinical, laboratory, drug toxicity and adherence data were entered into a separate Microsoft Excel database. The two databases were merged using unique identifiers (other than patient name) to link participant information. All databases were anonymous.

4.7.2 Descriptive statistics

The cohort was initially described using means, medians and proportions as appropriate. Continuous data were reported using means and 95 percent confidence intervals (95% CI) or medians and interquartile ranges (IQR); whereas categorical data were reported using proportions. Changes in HRQoL pre-HAART and at week 16, 32 and 48 were compared using Wilcoxon Rank Sum Test. Crude associations were first examined using Fisher's Exact, Chi Squared and Wilcoxon Rank Sum tests as appropriate. Bivariate relationships were then explored between the various outcome variables –pre-HAART PHS, pre-HAART MHS, change in PHS, change in MHS, negative PHS and negative MHS - and each explanatory variable using linear or logistic regression.

4.7.3 Multivariate analysis

Multivariate analyses made use of linear and logistic regression models to examine the adjusted association between HRQOL and various socio-demographic, baseline and on-treatment explanatory variables as appropriate. All explanatory variables found to be associated with the outcome in the bivariate analyses were included in the multivariate

analysis. The pre-HAART models therefore included demographic characteristics and baseline factors only; whereas the change in HRQoL, negative HRQoL and adherence models included demographic and baseline variables as well as change in viral load and change in CD4 count. As the week 48 variables (viral load, log viral load and CD4 count) were not significantly associated with any of the outcomes in the bivariate analyses, they were not included in the change in HRQoL and negative HRQoL multivariate models.

Model building began with a full model for each outcome. Explanatory variables were then removed from the model based on non-significant p-values. The impact of variables on other explanatory variables in the model was examined by observing the change in B-coefficients or odds ratios as variables were removed and added. The final multivariate model was based on the best adjusted r-squared (or log likelihood) value as well as changes in the B-coefficients and odds ratios.

4.7.4 Model checking

All final linear and logistic regression models were checked against model assumptions. Outliers and potentially influential observations were identified and examined to ensure that model results were not being unduly influenced by a small number of non-representative observations. All models were rerun with selected observations excluded.

All statistical analyses were performed using Intercooled Stata Version 8.2 (Stata Corporation, College Station, Texas, USA). All statistical tests are 2-sided at alpha=0.05.

4.8 Ethics

The UCT Research Ethics Committee approved all research activities involving antiretroviral service delivery and patient outcomes at this site (Appendix 4). The key ethical principles that needed to be addressed during the conduct of this study were autonomy, beneficence and non-maleficence. All participants attending the Hannan Crusaid Treatment Centre were informed of the research activities that took place at the site. Participants were requested to sign a consent form indicating their willingness to allow additional information to be collected and used for research purposes.

There was no direct benefit for participants through the collection of quality of life and other data. However, participants may have benefited indirectly from this research as we gained insight into factors affecting HRQOL in a community ARV programme. By using quality of life as a more subtle programme outcome, we were able to assess ARV-related and other factors impacting on patients' overall well-being and could make suggestions to the Provincial Department of Health about appropriate changes to the ARV programme. Furthermore by examining the link between HRQOL and adherence, it may be possible to identify patients at risk of poor adherence allowing for adherence interventions to be initiated prior to virological failure.

The administration of the MOS SF36 questionnaire posed minimal risk to patients. The only concern was the emotional risk of disclosing sensitive information regarding perceived mental and physical health status. To reduce this risk, participants were interviewed by a trained Sizophila adherence counsellor in a private environment. Every attempt was made to maintain the confidentiality of participants throughout the conduct of this study. All staff working at the Hannan Crusaid Treatment Centre were bound by a confidentiality agreement. Furthermore, participants were ~~each assigned a unique identifier (initials plus ARV~~ treatment number) on enrolling into the ARV programme. All data were collected and entered under this unique identifier and not participant name. In addition, all databases in both Excel and STATA used the unique identifier and were password protected. Participants were not identified by name during the presentation of research findings.

5 RESULTS

Four hundred and forty adult patients were referred for antiretroviral therapy between September 2002 and September 2004. (Figure 1) Of these, 358 (81 percent) initiated antiretroviral therapy and 317 (72 percent) completed at least 16 weeks of treatment.

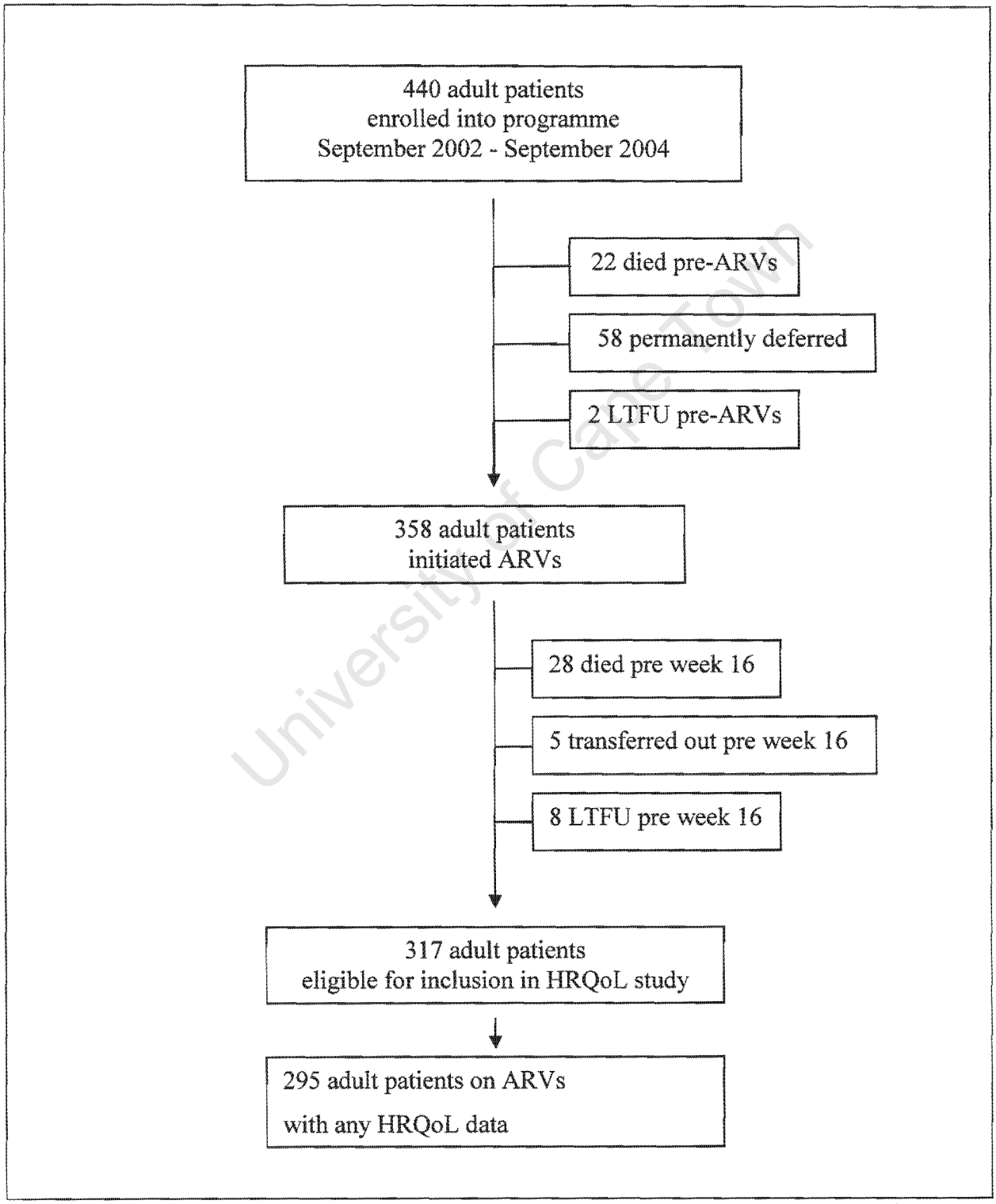


Figure 2 Adult patients who were enrolled into the ARV programme and were eligible for inclusion in the HRQoL study.

Common reasons for discontinuation were death, deferral (temporary or permanent), transfer out (patients who moved out of the treatment referral area were transferred to other clinics for ongoing care) and loss to follow up: 50 patients died (22 pre-treatment and 28 before week 16), 58 were permanently deferred pre-treatment, 5 transferred out and 10 were lost to follow-up. Quality of life data were available for 295 patients – 93 percent of patients who reached the first on treatment assessment.

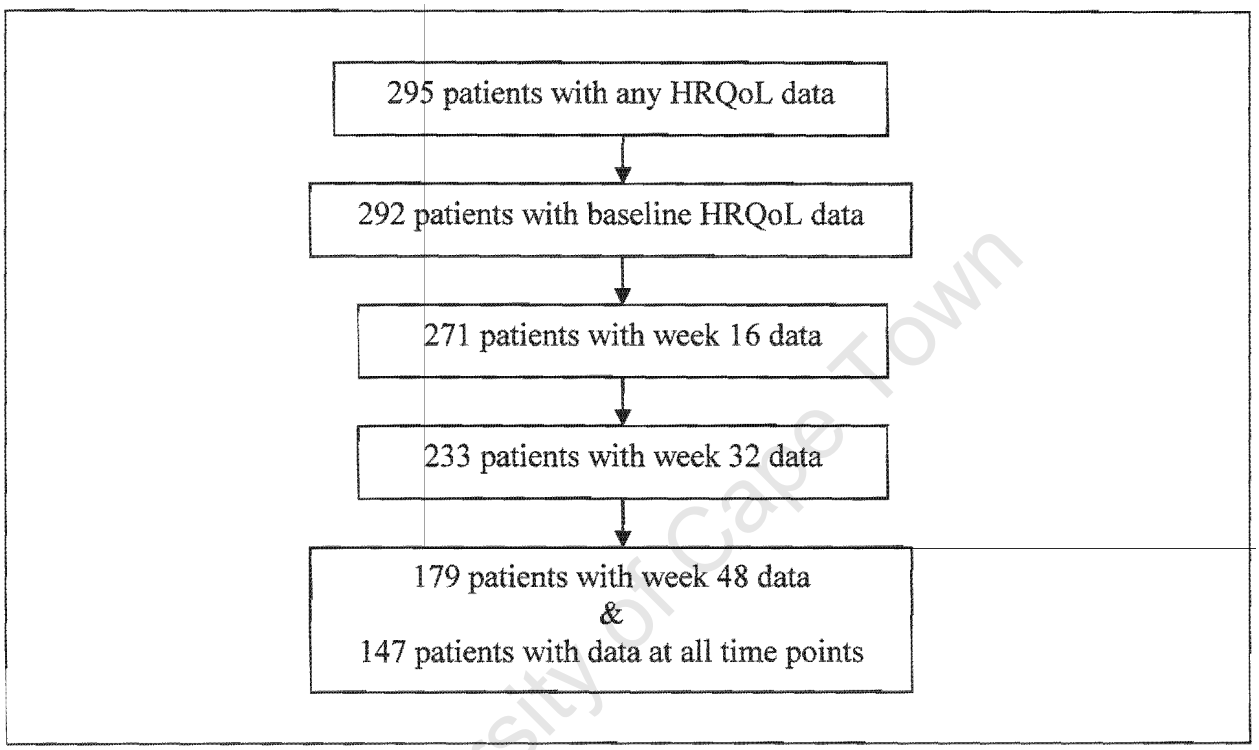


Figure 3 Patients with HRQoL data at various study time points.

Of the 295 patients with any HRQoL data, 292 (99 percent) had baseline data, 271 (92 percent) week 16 data, 233 (79 percent) week 32 data and 179 (61 percent) week 48 data. (Figure 2) Complete HRQoL data – obtained pre-treatment and at every scheduled on treatment visit - were available for 147 patients.

5.1 Demographic, baseline and on-treatment characteristics

Table 3 describes the demographic and baseline characteristics of the 440 patients referred for antiretroviral therapy. The average age of the cohort was 34 years (standard deviation (SD) 4) and 73 percent of patients were female (n=322). Eighty-four percent of patients (n=370) had WHO Stage 3 & 4 disease. The median baseline CD4 count was 88 cells/mm^3 (inter quartile range (IQR): 44, 154) and median baseline log viral load was 4.9 (IQR 4.5, 5.3). Female patients tended to be younger than their male counterparts and had earlier disease – as

evidenced by a lower percentage with WHO Stage 3 and 4 disease (81 percent versus 92 percent), higher baseline CD4 count (100 cells/mm^3 versus 71 cells/mm^3) and lower baseline viral load (74 301 copies/ml versus 81 720 copies/ml).

Table 3 Demographic and baseline characteristics of all patients (male and female) enrolled into the programme. (n= 440)

Variable	All	Male	Female	P-value
Number	440	118	322	
Age (years) (mean, (SD))	34 (7)	37 (7)	33 (7)	<0.001
Female (n,(%))	322 (73)	-	-	
WHO stage 3 & 4 (n, (%))	370 (84)	109 (92)	261 (81)	0.004
Baseline CD4 count cells/mm^3 (median, (IQR))	88 (44, 154)	71 (50, 167)	100 (30, 128)	0.015
Baseline viral load copies/ml (median, (IQR))	76 337 (32232, 191490)	81 720 (39150, 209447)	74 301 (26602, 190991)	0.136
Baseline viral load log copies/ml (median, (IQR))	4.9 (4.5, 5.3)	4.9 (4.6, 4.9)	4.7 (4.4, 5.3)	0.042

Among the 317 patients (72 percent) who reached the first on treatment assessment (and were therefore considered eligible for inclusion in the HRQoL study), there were no significant differences in demographic, baseline and on-treatment characteristics between those with any HRQoL data (n=295) and those with none (n=22). (Appendix 5 Table 1)

Similarly, there were no differences between patients with complete HRQoL data (n=147) and those with incomplete data (n=148). (Appendix 5 Table 2) Among patients with complete data (Table 4), men were older (37 (SD 6.7) years versus 34 (SD 7.3) years) and had more advanced disease than women. Male patients had lower baseline CD4 counts (69 (IQR: 26, 199) cells/mm^3 versus 103 (IQR: 57, 170) cells/mm^3), higher baseline viral loads (126 213 (IQR: 52 650, 266 669) copies/ml versus 81 325 (IQR: 32 232, 191 490) copies/ml) and a greater percentage had WHO stage 3&4 disease (90.9% versus 87.7%). Male patients achieved significantly lower week 48 CD4 counts than female patients (199 (IQR: 162, 278) cells/mm^3 versus 265 (IQR: 204, 364) cells/mm^3) despite similar changes in CD4 count between baseline and week 48. Week 48 viral load and reduction in viral load from baseline to week 48 were similar between the genders. The majority of drug toxicities (90.9%)

occurred in women with only one drug change made due to toxicity among men. Percentage adherence at week 48 was similar between male and females (98.1% versus 99.2%).

Table 4 Demographic, baseline and on-treatment characteristics of female and male patients followed to week 48. (n= 147)

Variable	Female	Male	P-value
Age (years) (mean, (SD))	34 (7.3)	37 (6.7)	0.022
WHO stage 3 & 4 (n,(%))	100 (87.7)	30 (90.9)	0.614
Baseline CD4 count cells/mm^3 (n, (IQR))	103 (57, 170)	69 (26, 119)	0.019
Baseline viral load copies/ml (n, (IQR))	81 325 (32 232, 191 490)	126 213 (52 650, 266 669)	0.042
Baseline viral load log copies/ml (n, (IQR))	4.91 (4.5, 5.3)	5.10 (4.7, 5.4)	0.042
Week 48 CD4 count cells/mm^3 (n, (IQR))	265 (204, 364)	199 (162, 278)	0.008
Week 48 viral load copies/ml (n,(IQR))	49 (49, 49)	49 (49, 55)	0.194
Week 48 viral load log copies/ml (n,(IQR))	1.69 (1.69, 1.69)	1.69 (1.69, 1.88)	0.114
Change in CD4 count cells/mm^3 (n, (SD))	175 (140)	146 (88)	0.255
Change in viral load log copies/ml (n, (SD))	-3.0 (0.89)	-3.2 (0.66)	0.143
Drug Toxicity* (n, (%))	10 (90.9)	1 (9.09)	0.145
Adherence at week 48 (%)	99.2	98.1	0.172

5.2 Health Related Quality of Life Data

The median scores for the eight health concepts pre-treatment and at regular intervals on treatment are described in Table 5. The scores all demonstrated an increase in HRQoL between pre-HAART and week 48 with the greatest increase occurring at week 16. For example, the vitality score increased from 55 units pre-HAART to 75 units at week 16 and then to 80 units at week 32 and 85 units at week 48. Similarly, the physical function score increased from 85 units pre-HAART to 95 units at week 16 and then 100 units at both weeks 32 and 48. The physical role, social function and emotional role scores also increased

* While the bulk of the analysis was based on participants with complete week 48 HRQoL data (n=147), for the drug toxicity analysis, participants with any HRQoL data (n=295) were included. The reason for this is the limited number of participants who reported drug toxicities.

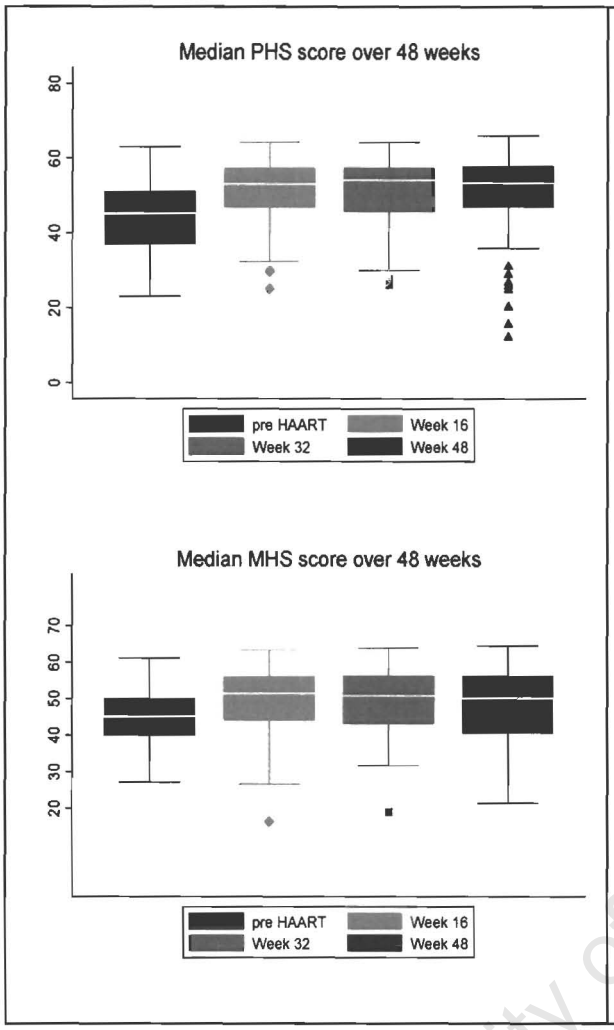
between pre-HAART and week 16 but then remained the same at week 32 and week 48. For example, the physical role score increased from 50 units pre-HAART to 100 units at week 16 and then remained at 100 units at week 32 and week 48. The general health and mental health concepts both showed an increase in score at week 16 and week 32 but then a decrease at week 48. The week 48 score for these concepts remained higher then the pre-HAART scores though. For example, the mental health score increased from 68 units pre-HAART to 72 units at week 16 and 76 units at week 32. It then decreased to 72 units at week 48.

Table 5 Median scores for the eight health concepts pre-HAART and at week 16, 32 and 48 on HAART. (n= 147)

	Pre-HAART	Week 16	Week 32	Week 48
Physical function	85	95	100	100
Physical role	50	100	100	100
Bodily pain	61	84	74	84
General health	54	77	77	72
Vitality	55	75	80	85
Social function	75	100	100	100
Emotional role	50	99	99	99
Mental health	68	72	76	72

The physical health summary (PHS) and mental health summary (MHS) scores also showed an improvement in HRQoL over time. (Figure 4a) There was a significant increase in both summary scores between pre-HAART and week 16. Median PHS score increased from 45 to 53 units and median MHS score increased from 45 to 51 units. These increases were then maintained through weeks 32 and 48. However, not all participants experienced a linear increase in HRQoL. Using a random sample of fifteen participants, it was evident that while the bulk of participants experienced a gradual improvement in HRQoL, others experienced a worsening of HRQoL. (Figure 4b)

While the average change in PHS score between pre-HAART and week 48 was an increase of 7 units (SD 11.9), 23 percent of participants experienced a decrease in PHS score during this period. The average drop in PHS score among these participants was 8.4 units (SD 9.31). Similarly, while MHS score increased by an average of 3.3 units (SD 11.4) between pre-HAART and week 48, 34 percent of participants experienced a decline in MHS score. The average drop in MHS score among these participants was 9.9 units (SD 5.92).



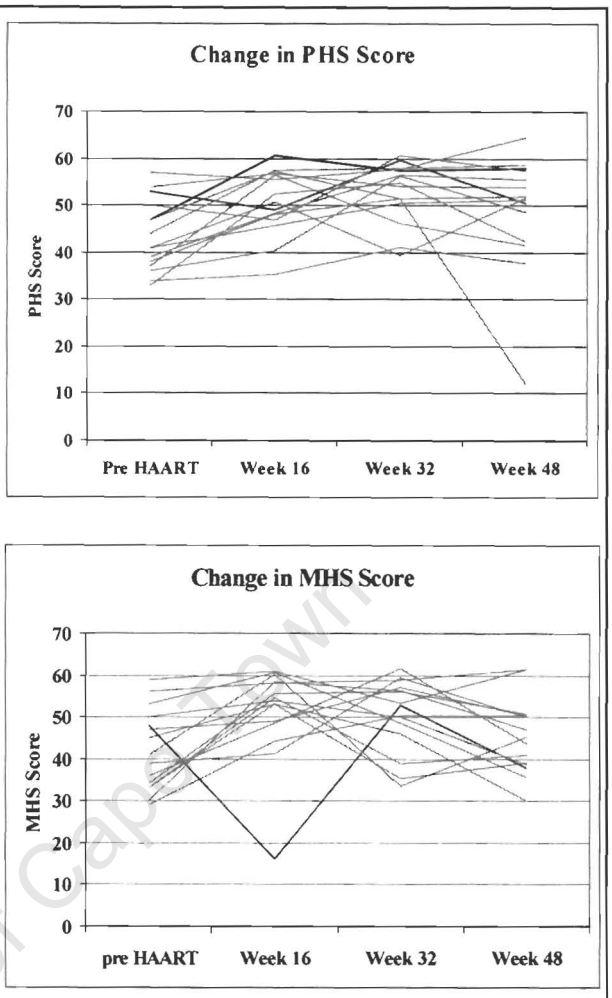


Figure 4 a: Change in median Physical Health Summary (PHS) score and median Mental Health Summary (MHS) score over the first 48 weeks of HAART.

Figure 4 b: Change in Physical Health Summary (PHS) score and Mental Health Summary (MHS) score over the first 48 weeks of HAART for 15 random participants.

Table 6 describes the physical health summary (PHS) score for different categories of participant – male versus female, median age above and below 34 years, WHO stage 1&2 versus WHO stage 3&4, baseline CD4 count above and below 50 cells/mm^3 and baseline log viral load above and below 5.0. Across all these categories, the greatest increase in PHS score occurred between pre-HAART and week 16. The magnitude of the increase ranged from 6 to 12 units. For example, male participants increased from a pre-HAART PHS score of 41 units to 53 units at week 16. These changes in score were generally maintained through weeks 32 and 48.

Within categories, males, participants over the age of 34 years and those with more advanced disease (WHO stage 3&4, baseline CD4 count $\leq$50 cells/mm^3 and/or baseline log viral load >5.0) had lower pre-HAART PHS scores than females, participants under the age of 34 years and those with less advanced disease. In most cases, this difference in PHS score disappeared by week 16. Participants over the age of 34 years and participants with a baseline CD4 count $\leq$50 cells/mm^3 however only achieved similar levels of PHS score to younger participants and those with higher baseline CD4 counts by week 32.

Table 6 Comparison of median Physical Health Summary (PHS) pre-HAART and at week 16, 32 and 48 for various categories. (n =147)

	Pre-HAART	Week 16	Week 32	Week 48
Female	45	53	53	53
Male	41	53	55	53
Age >34 years	43	50	53	53
Age $\leq$34 years	46	55	54	53
WHO Stage 1&2	49	55	56	53
WHO Stage 3&4	44	53	53	53
Baseline CD4 count >50 cells/mm^3	47	54	53	53
Baseline CD4 count $\leq$50 cells/mm^3	39	50	55	53
Baseline viral load >5.0 log copies/ml	44	53	55	54
Baseline viral load $\leq$5.0 log copies/ml	46	53	53	53

A similar picture was seen with the Mental Health Summary (MHS) scores. (Table 7) Median MHS scores increased between pre-HAART and week 48 across all the categories, with the greatest increase in MHS score occurring between baseline and week 16. The magnitude of this early increase ranged from 5 to 11 units. The largest increase in MHS score occurred among participants with baseline CD4 count $\leq$50. MHS score increased from 42 units pre-treatment to 53 units at week 16. These increases in score were then generally maintained through weeks 32 and 48.

Within categories, pre-HAART MHS scores were lower for males and participants with more advanced disease (WHO Stage 3&4 disease, baseline CD4 count $\leq$50 cells/mm^3 and baseline log viral load >5.0). These differences were less marked than for PHS scores though. Interestingly, older participants had a higher pre-treatment MHS score than younger participants (46 units versus 45 units) - although this difference was not statistically significant. Differences in pre-HAART MHS scores within categories generally disappeared by week 16 on HAART although it took older participants and those with lower baseline CD4 counts until week 32 to achieve similar MHS scores to younger participants and those with

higher baseline CD4 counts. Interestingly, by week 48, women had a significantly lower MHS scores than men and participants with higher baseline log viral loads had significantly higher scores than those with lower baseline log viral loads.

Table 7 Comparison of median Mental Health Summary (MHS) pre-HAART and at week 16, 32 and 48 for various categories. (n=147)

	Pre-HAART	Week 16	Week 32	Week 48
Female	46	51	51	48
Male	45	51	52	54
Age >34 year	46	52	50	48
Age ≤34 years	45	51	52	51
WHO Stage1&2	49	49	51	52
WHO Stage 3&4	45	51	51	49
Baseline CD4 count >50 cells/mm^3	46	49	51	48
Baseline CD4 count ≤50 cells/mm^3	42	53	52	51
Baseline viral load >5.0 log copies/ml	45	51	53	51
Baseline viral load ≤5.0 log copies/ml	46	51	50	47

5.3 Factors associated with pre-HAART quality of life

5.3.1 Factors associated with pre-HAART PHS score

In both univariate and multivariate regression models, baseline CD4 count was the strongest predictor of pre-HAART physical health. (Table 8) In the univariate model, participants with a baseline CD4 count ≤50 cells/mm^3 had significantly lower PHS scores than participants with a baseline CD4 count >50 cells/mm^3 (*B*-coefficient -5.10; 95% CI -8.39, -1.81; p= 0.003). In the multivariate model, this difference was -4.67 units (95% CI -8.01, -1.34; p= 0.006). Baseline WHO stage was also weakly associated with pre-HAART PHS score. In the univariate model, participants with WHO Stage 3&4 disease had lower PHS scores than participants with WHO Stage 1&2 disease (*B*-coefficient -4.43; 95% CI -8.87, 0.33; p= 0.068). This association was no longer significant in the multivariate model (*B*-coefficient -3.16; 95% CI -7.72, 1.40; p= 0.173). Age, gender and baseline log viral load were not significantly associated with pre-HAART physical health status.

Table 8 Factors associated with pre-HAART Physical Health Summary score (n=147).

Variable	Univariate Model	Multivariate Model 1	Multivariate Model 2	Multivariate Model 3
	B-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)
Age (continuous)	-0.09 (-0.30; 0.11) 0.380	-0.07 (-0.28; 0.13) 0.481	-0.08 (-0.28; 0.12) 0.417	-0.88 (-0.27; 0.12) 0.453
Age (≤34 =0, >34 =1)	-0.91 (-3.91; 2.08) 0.547			
Gender (male =0, female =1)	-2.14 (-5.72; 1.45) 0.240	-0.83 (-4.48; 2.83) 0.655		
WHO Stage (1&2 =0, 3&4 =1)	-4.43 (-8.87; 0.33) 0.068	-2.94 (-7.58; 1.70) 0.213	-2.92 (-7.54 1.71) 0.214	-3.16 (-7.72 1.40) 0.173
Baseline CD4 count cells/mm^3 (>50 =0, ≤50 =1)	-5.10 (-8.39; -1.81) 0.003	-4.35 (-7.79; -0.90) 0.014	-4.46 (-7.86 -1.06) 0.010	-4.67 (-8.01 -1.34) 0.006
Baseline log viral load log copies/ml (≤5 =0, >5 =1)	-2.05 (-5.01; 0.90) 0.172	-0.91 (-3.95; 2.12) 0.552	-1.01 (-4.01 1.99) 0.506	

5.3.2 Factors associated with pre-HAART MHS score

There were no associations between demographic and baseline characteristics and pre-HAART MHS score in either the univariate or multivariate regression models. (Table 9) In particular, baseline CD4 count and WHO stage did not impact on pre-HAART mental health status. Although participants with a baseline CD4 count ≤50 cells/mm^3 reported lower pre-HAART MHS scores than participants with a baseline CD4 count >50 cells/mm^3, these differences were not significant (*B*-coefficient -1.52; 95% CI -4.50, 1.47; p= 0.318). Similarly, the pre-HAART MHS score of participants with WHO stage 3&4 disease was not significantly lower than that of participants with WHO Stage 1&2 disease (*B*-coefficient -1.71; 95% CI -5.82, 2.40; p= 0.413).

Table 9 Factors associated with pre-HAART Mental Health Summary score (n = 147).

Variable	Univariate Model	Multivariate Model 1	Multivariate Model 2	Multivariate Model 3
	B-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)
Age (continuous)	-0.06 (-0.23; 0.12) 0.532	-0.07 (-0.25; 0.12) 0.470		
Age (≤34 =0, >34 =1)	-0.29, (-2.9; 2.31) 0.825			
Gender (male =0, female =1)	-0.33 (-3.46; 2.80) 0.835	0.52 (-2.74; 3.78) 0.752		
WHO Stage (1&2 =0, 3&4 =1)	-2.48 (-6.50; 1.54) 0.225	-1.64 (-5.77; 2.50) 0.435	-1.71 (-5.82; 2.40) 0.413	
Baseline CD4 count cells/mm^3 (>50 =0, ≤50 =1)	-1.95 (-4.88; 0.98) 0.191	-1.37 (-4.44; 1.70) 0.380	-1.35 (-4.37; 1.67) 0.378	-1.52 (-4.50; 1.47) 0.318
Baseline viral load log copies/ml (≤5 =0, >5 =1)	-2.10 (-4.67; 0.46) 0.107	-1.81 (-4.52; 0.89) 0.187	-1.66 (-4.32; 0.99) 0.217	-1.83 (-4.45; 0.79) 0.169

5.4 Factors associated with change in quality of life

5.4.1 Factors associated with change in PHS score†

Table 10 describes the associations between demographic, baseline and on treatment variables and change in PHS score between pre-HAART and week 48 on HAART. In the univariate models, WHO stage, baseline CD4 count, baseline log viral load, pre-HAART PHS score, change in CD4 count and change in log viral load were all significantly associated with change in PHS score.

Pre-HAART PHS score was the most significant predictor of increase in PHS score at week 48. For every 1 unit increase in pre-HAART PHS score, change in PHS score decreased by 0.82 units (*B*-coefficient -0.82; 95% CI -0.99, -0.65; p<0.001). Participants with WHO stage 3&4 disease achieved 7.09 units greater increase in PHS score than participants with WHO stage 1&2 disease (*B*-coefficient 7.09; 95% CI 1.10, 13.08; p= 0.021). Participants with a baseline CD4 count ≤50 cells/mm^3 (*B*-coefficient 4.48; 95% CI 0.08, 8.88; p= 0.046) and

† The non-normality of the residuals for the change in PHS multivariate model indicated that this outcome would have been better modeled differently (e.g. using a log transformation of the outcome variable); however this was beyond the scope of this thesis.

those with a baseline log viral load >5 (*B*-coefficient 5.38; 95% CI 1.58, 9.19; p= 0.006) also experienced greater positive change in PHS score by week 48. For every 50 unit increase in CD4 count between baseline and week 48, change in PHS score increased by 1 unit (95% CI 0.02, 1.98; p= 0.022) moreover, for every 1 log decrease in viral load between baseline and week 48, change in PHS score increased by 3.85 units (95% CI 1.61, 6.10; p= 0.001)

Pre-HAART PHS score was the strongest predictor of change in PHS score in the multivariate model. For every 1 unit increase in pre-HAART PHS score, change in PHS score decreased by 0.79 units (*B*-coefficient -0.79; 95% CI -0.95, -0.63; p<0.001). Change in log viral load was also strongly associated with change in PHS score in the multivariate model. For every 1 log decrease in viral load, change in PHS score increased by 3.52 units (95% CI 1.81, 5.24; p< 0.001). Age was weakly associated with change in PHS score. Participants over the age of 34 years had less increase in PHS score than younger participants (*B*-coefficient -0.21 ; 95% CI -0.40, -0.01; p=0.041). WHO stage, baseline CD4 count, baseline log viral load and change in CD4 count were all not associated with outcome in the multivariate model. Neither gender nor any of the week 48 variables (CD4 count, viral load and log viral load) were predictive of change in PHS score at week 48.

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Table 10 Factors associated with change in Physical Health Summary score at week 48.

Variable		Univariate Model	Multivariate Model 1	Multivariate Model 2	Multivariate Model 3
		B-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)
Age (continuous)		-0.14, (-0.41; 0.13) 0.294	-0.21, (-0.43; 0.004) 0.055	-0.21 (-0.42; 0.003) 0.054	-0.21 (-0.40; -0.01) 0.041
Gender (male =0, female =1)		0.99, (-3.73; 5.72) 0.679	-1.45, (-5.20; 2.31) 0.446	-1.42 (-5.07; 2.23) 0.444	
WHO Stage (1&2 =0, 3&4 =1)		7.09, (1.10; 13.08) 0.021	3.14, (-1.54; 7.81) 0.187	3.14 (-1.43; 7.71) 0.176	3.01, (-1.52; 7.55) 0.190
Baseline CD4 count cells/mm^3 (>50 =0, ≤50 =1)		4.48, (0.08; 8.88) 0.046	0.27, (-3.31; 3.85) 0.880		
Baseline viral load log copies/ml (≤5 =0, >5 =1)		5.38, (1.58; 9.19) 0.006	-0.21, (-3.96; 3.54) 0.912		
Pre-HAART PHS Score (continuous)		-0.82 (-0.99; -0.65) <0.001	-0.80 (-0.97; -0.63) <0.001	-0.80 (-0.97; -0.64) <0.001	-0.79 (-0.95; -0.63) <0.001
Week 48 CD4 count cells/mm^3 (<250 =0, ≥250 =1)		0.25, (-3.68; 4.18) 0.9			
Week 48 CD4 count cells/mm^3	<200	1			
	200 -350	-2.32, (-7.05; 2.40) 0.333			
	350-500	1.08, (-4.81; 6.97) 0.72			
	≥500	0.64, (-6.92; 8.19) 0.87			
Week 48 viral load copies/ml (<50 =0, ≥50 =1)		-1.14, (-5.92; 3.64) 0.638			
Week 48 viral load copies/ml	<50	1			
	50-399	1.22, (-4.62; 7.06) 0.681			
	400-4999	-0.88, (-12.88; 11.12) 0.885			
	≥5000	-6.87, (-15.49; 1.76) 0.118			
Week 48 log viral load log copies/ml (<1.69 =0, ≥1.69 =1)		-1.14, (-5.92; 3.64) 0.638			
Week 48 log viral load log copies/ml	<1.69	1			
	1.69-2.59	0.06, (-5.69; 5.81) 0.983			
	2.60-3.69	-0.88, (-12.95; 11.20) 0.886			
	≥3.69	-4.72, (-13.96; 4.52) 0.375			
Δ CD4 count cells/mm^3		0.02, (0.003; 0.03) 0.022	0.004, (-0.02; 0.01) 0.593	-0.004 (-0.02; 0.01) 0.577	
Δ log viral load log copies/ml		3.85, (1.61; 6.10) 0.001	3.82, (1.70; 5.95) 0.001	3.76 (1.93; 5.59) <0.001	3.52, (1.81; 5.24) <0.001

5.4.2 Factors associated with change in MHS score

On examining the associations between demographic, baseline and on treatment variables and change in MHS score at week 48, baseline CD4 count, baseline log viral load, pre-HAART MHS score and change in log viral load were all associated with outcome in the univariate models. (Table 11) Participants with a baseline CD4 count ≤50 cells/mm^3 (*B*-coefficient 4.61; 95% CI 0.44, 8.88; p= 0.031) and those with a baseline log viral load >5 (*B*-coefficient 6.05; 95% CI 2.47, 9.63; p= 0.001) experienced greater positive change in MHS score by week 48. For every 1 unit increase in pre-HAART MHS score, change in MHS score decreased by 0.76 units (*B*-coefficient -0.76 ; 95% CI -0.96, -0.56; p<0.001), while for every 1 log decrease in viral load between baseline and week 48, change in MHS score increased by 2.43 units (95% CI 0.23, 4.63; p= 0.031).

Pre-HAART MHS score and baseline log viral load were the most significant predictors of outcome in the multivariate model. For every 1 unit increase in pre-HAART MHS score, change in MHS score decreased by 0.73 units (*B*-coefficient -0.73; 95% CI -0.92, -0.53; p<0.001), while participants with a baseline log viral load >5.0 had a 4.07 unit (95% CI 0.95, 7.18; p=0.011) greater increase in MHS score than participants with a baseline log viral load ≤5.0. In contrast to the findings of change in PHS score, age was not associated with change in MHS score at 48 weeks (*B*-coefficient -2.23; 95% CI -5.34, 0.87; p=0.158), however gender was weakly associated with the outcome. Women reported a 3.19 unit greater increase in MHS score at week 48 than men (95% CI -0.58, 6.97; p=0.096). None of the week 48 variables (CD4 count, viral load and log viral load) predicted change in MHS score at 48 weeks.

Table 11 Factors associated with change in Mental Health Summary score at week 48.

Variable		Univariate Model	Multivariate Model 1	Multivariate Model 2	Multivariate Model 3
		B-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)	*B*-coefficient, 95% CI (P-value)
Age (≤34 =0, >34 =1)		-1.76, (-5.50; 1.97) 0.352	-2.68, (-6.11; 0.75) 0.125	-2.24, (-5.37; 0.89) 0.159	-2.23, (-5.34; 0.87) 0.158
Gender (male =0, female =1)		3.81, (-0.65; 8.27) 0.093	2.83, (-1.18; 6.84) 0.165	2.86, (-0.96; 6.68) 0.141	3.19 (-0.58; 6.97) 0.096
WHO Stage (1&2 =0, 3&4 =1)		1.60, (-4.21; 7.40) 0.587	-1.47, (-6.52; 3.58) 0.565	-1.56 (-6.49; 3.37) 0.533	
Baseline CD4 count cells/mm^3 (>50 =0, ≤50 =1)		4.61, (0.44; 8.88) 0.031	2.41, (-1.39; 6.21) 0.212	2.18, (-1.47; 5.84) 0.239	
Baseline viral load log copies/ml (≤5 =0, >5 =1)		6.05, (2.47; 9.63) 0.001	3.90, (-0.13; 7.94) 0.058	3.90, (0.70; 7.11) 0.017	4.07, (0.95; 7.18) 0.011
Pre-HAART MHS score		-0.76 (-0.96; -0.56) <0.001	-0.72 (-0.92; -0.52) <0.001	-0.72 (-0.92; -0.53) <0.001	-0.73 (-0.92; -0.53) <0.001
Week 48 CD4 count cells/mm^3 (<250 =0, ≥250 =1)		-0.74, (-4.48; 2.99) 0.695			
Week 48 CD4 count cells/mm^3	<200	1			
	200 -350	-4.82, (-9.26; -0.37) 0.034			
	350-500	-0.51, (-6.05; 5.03) 0.856			
	≥500	-1.72, (-8.82; 5.38) 0.633			
Week 48 viral load copies/ml (<50 =0, ≥50 =1)		-0.623, (-5.17; 3.93) 0.787			
Week 48 viral load copies/ml	<50	1			
	50-399	-0.72, (-6.33; 4.89) 0.801			
	400-4999	1.12, (10.40; 12.65) 0.848			
	≥5000	-1.27, (-9.55; 7.01) 0.762			
Week 48 log viral load log copies/ml (<1.69 =0, ≥1.69 =1)		-0.62, (-5.17; 3.93) 0.787			
Week 48 log viral load log copies/ml	<1.69	1			
	1.69-2.59	-0.49, (-5.98; 4.99) 0.860			
	2.60-3.69	1.12, (-10.4; 12.64) 0.848			
	≥3.69	-1.99, (-10.81; 6.82) 0.656			
Δ CD4 count cells/mm^3		0.01, (-0.003; 0.03) 0.109	0.004 (-0.02; 0.01) 0.546		
Δ log viral load log copies/ml		2.43, (0.23; 4.63) 0.031	0.57, (-1.72; 2.85) 0.626		

5.5 Factors associated with negative change in quality of life (negative HRQoL)

5.5.1 Factors associated with negative change in PHS score (negative PHS)

Similar factors that were associated with change in PHS score were associated with negative PHS in the univariate analysis. (Table 12) Baseline log viral load, pre-HAART PHS score, change in CD4 count and change in log viral load were all strongly associated with the outcome, whereas WHO stage and baseline CD4 count were weakly associated with negative PHS.

Participants with a baseline log viral load >5 were 0.24 times less likely to experience negative PHS than participants with a baseline log viral load ≤5 (OR 0.24; 95% CI 0.10, 0.59; p= 0.002). Participants with higher pre-HAART PHS scores were 1.14 times more likely to experience negative PHS than participants with lower pre-HAART PHS scores (OR 1.14; 95% CI 1.07, 1.21; p<0.001). For every 1 unit increase in CD4 count between baseline and week 48, participants were less likely to report negative PHS (OR 0.995; 95% CI 0.99, 1.0; p=0.01) while for every 1 unit greater change in log viral load, participants were 0.58 times less likely to report negative PHS score (OR 0.58; 95% CI 0.37, 0.90; p=0.015).Participants with WHO stage 3&4 disease (OR 0.38; 95% CI 0.13, 1.08; p= 0.068) and those with a baseline CD4 count ≤50 cells/mm^3 (OR 0.42 ; 95% CI 0.15, 1.17 ; p=0.098) were less likely to experience negative PHS.

In the multivariate model, pre-HAART PHS score and baseline log viral load were the strongest predictors of negative PHS at week 48. For every 1 unit increase in pre-HAART PHS score, participants were 1.15 times more likely to report negative PHS (OR1.15; 95% CI 1.08, 1.23; p<0.001). Participants with a baseline log viral load >5.0 were 0.37 times less likely to have negative PHS than participants with a baseline log viral load ≤5.0 (95% CI 0.15, 0.96; p=0.040). Age was also predictive of negative PHS. Participants above 34 years of age were 1.07 times more likely to report negative PHS than younger participants (OR 1.07; 95% CI 1.01, 1.14, 0.085; p=0.029). Neither gender nor any of the week 48 variables were associated with negative PHS.

Table 12 Factors associated with negative Physical Health Summary score at week 48.

Variable		Univariate Model	Multivariate Model 1	Multivariate Model 2
		Odds Ratio, 95% CI (P-value)	Odds Ratio, 95% CI (P-value)	Odds Ratio, 95% CI (P-value)
Age (continuous)		1.04, (0.98; 1.09) 0.184	1.08, (1.01; 1.15) 0.034	1.07 (1.01; 1.14) 0.029
Age (≤34 =0, >34 =1)		1.20, (0.56; 2.60) 0.637		
Gender (male =0, female =1)		0.55, (0.19; 1.56) 0.260	0.52, (0.14; 1.99) 0.341	
WHO Stage (1&2 =0, 3&4 =1)		0.38, (0.13; 1.08) 0.068	0.61, (0.17; 2.15) 0.441	
Baseline CD4 count cells/mm^3 (>50 =0, ≤50 =1)		0.42, (0.15; 1.17) 0.098	0.93, (0.25; 3.41) 0.910	
Baseline viral load log copies/ml (≤5 =0, >5 =1)		0.24, (0.10; 0.59) 0.002	0.48, (0.14; 1.65) 0.245	0.22, (0.08; 0.60) 0.003
Pre-HAART PHS score (continuous)		1.14 (1.07; 1.21) <0.001	1.16 (1.08; 1.24) <0.001	1.15 (1.08; 1.23) <0.001
Week 48 CD4 count cells/mm^3 (<250 =0, ≥250 =1)		0.63, (0.29; 1.37) 0.245		
Week 48 CD4 count cells/mm^3	<200	1		
	200 -350	0.62, (0.25; 1.51) 0.29		
	350-500	0.67, (0.22; 2.07) 0.483		
	≥500	0.42, (0.08; 2.21) 0.309		
Week 48 viral load copies/ml (<50 =0, ≥50 =1)		0.96, (0.37; 2.48) 0.935		
Week 48 viral load copies/ml	<50	1		
	50-399	0.39, (0.08; 1.79) 0.224		
	400-4999	1.10, (0.11; 11.00) 0.936		
	≥5000	3.30, (0.77; 14.07) 0.107		
Week 48 log viral load log copies/ml (<1.69 =0, ≥1.69 =1)		0.96, (0.37; 2.48) 0.935		
Week 48 log viral load log copies/ml	<1.69	1		
	1.69-2.59	0.58, (0.16; 2.14) 0.414		
	2.60-3.69	1.10, (0.11; 11.00) 0.936		
	≥3.69	2.47, (0.51; 11.74) 0.225		
Δ CD4 count cells/mm^3		0.995, (0.991; 0.999) 0.010	0.998, (0.993; 1.003) 0.420	
Δ log viral load log copies/ml		0.58, (0.37; 0.90) 0.015	0.66, (0.36; 1.27) 0.209	

5.5.2 Factors associated with negative change in MHS score (negative MHS)

Similar to the findings for change in MHS score, baseline CD4 count, baseline log viral load, pre-HAART MHS score and change in log viral load were all associated with negative MHS in the univariate models. (Table 13) Pre-HAART MHS score was the strongest predictor of negative MHS. For every 1 unit increase in pre-HAART MHS score, participants were 1.1

times more likely to experience negative MHS than participants with lower pre-HAART MHS scores (OR1.10; 95% CI 1.05, 1.16; p=0.001).

Table 13 Factors associated with negative Mental Health Summary score at week 48.

Variable		Univariate Model	Multivariate Model 1	Multivariate Model 2
		Odds Ratio, 95% CI (P-value)	Odds Ratio, 95% CI (P-value)	Odds Ratio, 95% CI (P-value)
Age (continuous)		1.01, (0.96; 1.06) 0.767		
Age (≤34 =0, >34 =1)		1.49, (0.75; 2.96) 0.258	2.20, (0.94; 5.15) 0.068	1.77, (0.83; 3.78) 0.142
Gender (male =0, female =1)		0.58, (0.24; 1.41) 0.227	0.65, (0.23; 1.85) 0.419	
WHO Stage (1&2 =0, 3&4 =1)		0.94, (0.33; 2.71) 0.906	1.45, (0.44; 4.83) 0.543	
Baseline CD4 count cells/mm^3 (>50 =0, ≤50 =1)		0.35, (0.14; 0.86) 0.022	0.38, (0.14; 1.07) 0.067	0.41, (0.16; 1.09) 0.075
Baseline viral load log copies/ml (≤5 =0, >5 =1)		0.41, (0.20; 0.83) 0.014	0.55, (0.20; 1.49) 0.239	0.50, (0.23; 1.09) 0.081
Pre-HAART MHS score (continuous)		1.10 (1.05; 1.16) <0.001	1.10 (1.04; 1.16) <0.001	1.09 (1.04; 1.15) 0.001
Week 48 CD4 count cells/mm^3 (<250 =0, ≥250 =1)		1.67, (0.83; 3.37) 0.151		
Week 48 CD4 count cells/mm^3	<200	1		
	200 - 350	5.18, (1.92; 13.96) 0.001		
	350-500	2.39, (0.72; 7.91) 0.155		
	≥500	2.52, (0.58; 10.88) 0.216		
Week 48 viral load copies/ml (<50 =0, ≥50 =1)		1.30, (0.57; 2.94) 0.535		
Week 48 viral load copies/ml	<50	1		
	50-399	0.95, (0.33; 2.69) 0.919		
	400-4999	2.05, (0.28; 15.14) 0.481		
	≥5000	2.05, (0.49; 8.66) 0.327		
Week 48 viral load log copies/ml (<1.69 =0, ≥1.69 =1)		1.30, (0.57; 2.94) 0.535		
Week 48 viral load log copies/ml	<1.69	1		
	1.69-2.59	0.88, (0.31; 2.47) 0.808		
	2.60-3.69	2.05, (0.28; 15.14) 0.481		
	≥3.69	2.74, (0.58; 12.85) 0.202		
Δ CD4 count cells/mm^3		0.999, (0.996; 1.002) 0.414	1.002, (0.998; 1.01) 0.389	
Δ log viral load log copies/ml		0.67, (0.44; 1.01) 0.054	0.74, (0.43; 1.28) 0.282	

Participants with a baseline CD4 count ≤50 cells/mm^3 were 0.35 (95% CI 0.14, 0.86; p=0.022) times less likely to have negative MHS than participants with a baseline CD4 count >50 cells/mm^3 and participants with a baseline log viral load >5.0 were 0.41 (95% CI 0.20, 0.83; p=0.014) times less likely to have negative MHS than participants with baseline log viral load ≤5.0. Change in log viral load was weakly associated with negative change in MHS score in the univariate model (OR 0.67; 95% CI 0.44, 1.01; p=0.054) but this association was no longer significant in the multivariate model (OR 1.3; 95% CI 0.78, 2.17; p=0.317).

Pre-HAART MHS score was once again the strongest predictor of negative MHS at 48 weeks in the multivariate model. Participants with higher pre-HAART MHS scores were 1.09 times more likely to report negative MHS than participants with lower pre-HAART MHS scores (OR 1.09; 95% CI 1.04, 1.15; p=0.001). Baseline CD4 count and baseline log viral load remained weakly associated with the outcome. Participants with a baseline CD4 count ≤50 cells/mm^3 were 0.41 times less likely to experience negative MHS than participants with a baseline CD4 count >50 cells/mm^3 (95% CI 0.16, 1.09; p=0.075); whereas participants with a baseline log viral load >5.0 were 0.5 times less likely to experience negative MHS than participants with a baseline log viral load ≤5.0 (95% CI 0.23, 1.09; p=0.081). Gender and the week 48 variables were not predictive of negative MHS at 48 weeks.

5.6 Drug toxicities and quality of life

Eleven participants experienced drug related toxicities during the first 48 weeks of HAART. Ninety-one percent (n=10) of these toxicities occurred in women. Participants experiencing drug toxicities had similar demographic and baseline characteristics to the overall cohort: 82% (n=9) had WHO stage 3&4 disease, the median baseline CD4 count was 88 cells/mm^3 (IQR: 7, 151) and the median baseline log viral load was 4.9 (IQR: 3.9, 5.3). (Appendix 5 Table 3)

Table 14 Description of drug toxicities occurring during the first year of HAART.

Description	Wk 0-16	Wk 16-32	Wk 32-48	Total
Any toxicity	2	2	7	11
EFV Hypersensitivity Reaction	2	***	1	3
Peripheral Neuropathy	***	2	***	2
Transaminitis	***	***	1	1
Hyperlactataemia/ Lactic Acidosis	***	***	5	5

Table 14 describes the types of drug toxicities that occurred during the first year of HAART. Efavirenz hypersensitivity reactions were the cause of drug toxicities within the first 16 weeks of HAART. Between weeks 16 and 32, peripheral neuropathies were the main reason for drug changes. Transaminitis and hyperlactatemia were the main causes of drug toxicities between weeks 32 and 48 of HAART. One patient experienced an efavirenz hypersensitivity reaction between weeks 32 and 48. This was due to the fact that the patient was switched to efavirenz at this point in time. The bulk (64%) of toxicities occurred during the week 32 to 48 interval.

5.6.1 Drug toxicities and median QoL scores

Participants with a drug toxicity reported lower median PHS scores at the time point immediately following the toxicity than participants without drug toxicity for all toxicity types. (Appendix 5 Table 4) The difference in median PHS scores was largest for participants with and without hyperlactataemia (or lactic acidosis). Participants with hyperlactataemia reported a median PHS score of 36 compared to a median PHS score of 53 in participants without hyperlactataemia. Similarly, participants with drug toxicities reported lower median MHS scores than participants without a drug toxicity. Participants with transaminitis reported a median MHS score of 38 compared to a median score of 48 among participants without transaminitis. However, participants with hyperlactataemia had a higher median MHS score than participants without (56 versus 48).

Looking at drug toxicities by treatment interval, participants with any drug toxicity reported lower median PHS scores at each time point than participants without drug toxicity. This difference was significant at week 48, when participants with a drug toxicity had a 17 unit lower median PHS score than participants without drug toxicity (p=0.058). (Table 15)

Table 15 Median PHS scores at week 16, 32 and 48 in patients with any drug toxicity during the preceding treatment interval compared to patients without drug toxicity during the preceding treatment interval.

	n	Week 16	n	Week 32	N	Week 48
Drug toxicity	2	46	2	45	5	36
No drug toxicity	269	52	229	53	163	53
p-value		0.306		0.355		0.058

Similarly, participants with any drug toxicity reported lower median MHS scores at each time point than participants without drug toxicity. (Table 16) However, at week 48, this was reversed and participants with toxicity had an 8 unit higher median MHS score than participants without toxicity. This difference was not statistically significant (p=0.135).

Table 16 Median MHS scores at week 16, 32 and 48 in patients with any drug toxicity during the preceding treatment interval compared to patients without drug toxicity during the preceding treatment interval.

	n	Week 16	n	Week 32	N	Week 48
Drug toxicity	2	48	2	44	5	56
No drug toxicity	269	50	229	49	163	48
p-value		0.928		0.378		0.135

The eleven participants who experienced any drug toxicity during the first 48 weeks of HAART achieved lower PHS scores at all time points than the 281 participants who did not have toxicity. While these differences were not statistically significant pre-HAART and at weeks 16 and 32, they did become significant at week 48. The median PHS score at week 48 was 50 for participants with drug toxicity compare to 53 for participants without drug toxicity (p= 0.0053). (Table 17)

Table 17 Median PHS pre-HAART and at week 16, 32 and 48 in patients with any drug toxicity at any time in the first year compared to patients without drug toxicity.

	n	Pre-HAART	Week 16	Week 32	Week 48
Drug toxicity	11	39	51	52	50
No drug toxicity	281	44	52	53	53
p-value		0.8541	0.2253	0.3903	0.0053

Drug toxicities did not appear to have a significant impact on median MHS scores over the first 48 weeks of HAART. The eleven participants with any drug toxicity had a lower median MHS score pre-HAART than the 281 participants without drug toxicity but this difference was not statistically significant (42 versus 45, p=0.1793). However, at weeks 16, 32 and 48,

participants with any drug toxicity reported higher median MHS scores than those without toxicity with the greatest difference between median MHS scores occurring at week 48. Again these differences were not statistically significant. (Table 18)

Table 18 Median MHS pre-HAART and at week 16, 32 and 48 in patients with any drug toxicity at any time in the first year compared to patients without drug toxicity.

	n	Pre-HAART	Week 16	Week 32	Week 48
Drug toxicity	11	42	51	51	52
No drug toxicity	281	45	50	49	48
p-value		0.1793	0.5394	0.3257	0.9120

Univariate regression models, demonstrated a non-significantly lower PHS score among participants experiencing drug toxicity at weeks 16 and 32. (Table 19) However, at week 48, participants experiencing drug toxicity during the preceding treatment interval had a 16 unit lower PHS score than participants who did not have drug toxicity (95% CI -24.62, -8.20; p<0.001). MHS scores were not associated with drug toxicities in the preceding time interval. Multivariate analyses were not done as toxicity data were too few.

Table 19 Univariate analysis of the association between drug toxicity and median PHS and median MHS score at the following visit.

Variable	PHS		MHS	
	Bcoeff (95% CI)	P-value	*Bcoeff (95% CI)*	P-value
Drug toxicity b/line* to 16 wks (0= no toxicity, 1= toxicity)	-3.94 (-13.18; 13.54)	0.503	0.18 (-13.18; 13.54)	0.979
Drug toxicity 16 to 32 wks (0= no toxicity, 1= toxicity	-5.54 (-18.32; 7.24)	0.394	-4.41 (-17.56; 8.74)	0.509
Drug toxicity 32 to 48 wks (0= no toxicity, 1= toxicity	-16.41 (-24.62; -8.20)	<0.001	7.01 (-1.90; 15.91)	0.122

* baseline

5.6.2 Drug toxicities and change in QoL score

For change in PHS score between pre-HAART and 48, participants with drug toxicity had less increase in score than participants without toxicity (change in PHS score: 1.4 versus 7.2). This was most noticeable during the week 32-48 treatment interval, when participants with drug toxicity reported a 7.5 unit lower increase in score compared to participants without drug toxicity. In contrast, participants with drug toxicity had greater increases in MHS score between pre-HAART and 48 than participants without drug toxicity (change in MHS score: 9.5 versus 3.4). This difference in change in MHS score was also noted at the baseline-16 weeks, 16-32 weeks and 32-48 weeks treatment intervals. (Appendix 5 Table 5)

Table 20 further describes the association between drug toxicity and change in PHS and MHS scores. Participants who had any drug toxicity during the first 48 weeks of HAART had significantly lower increases in PHS scores (-11.75 units) than participants without drug toxicity. In contrast, participants with drug toxicity during the first 48 weeks of HAART had greater increases in MHS scores (8.01 units) than those without toxicity. This difference was of borderline significance. The strongest association between drug toxicity and change in HRQoL was seen during the week 32-48 treatment interval. Participants experiencing drug toxicity between week 32 and 48 had -9.95 unit less change in PHS score (p=0.031) and 10.65 unit greater change in MHS score (p=0.025) than participants without toxicity during the same time interval. No significant association was demonstrated between drug toxicity and change in PHS score or MHS score at weeks 16 and 32 respectively. Multivariate analyses were not done as toxicity data were too few.

Table 20 Univariate analysis of association between drug toxicity and change in quality of life score at the following visit.

Variable	**Δ PHS**		**Δ MHS**	
	Bcoeff (95% CI)	P-value	*Bcoeff (95% CI)*	P-value
Drug toxicity at any time (0= no toxicity, 1= toxicity)	-11.75 (-20.81; -2.69)	0.011	8.01 (-0.38; 16.39)	0.061
Drug toxicity b/line* to 16 weeks (0= no toxicity, 1= toxicity)	2.65 (-11.21; 16.51)	0.707	4.85 (-10.83; 20.54)	0.543
Drug toxicity 16 to 32 weeks (0= no toxicity, 1= toxicity	2.91 (-16.63; 22.44)	0.77	8.01 (-15.93; 31.95)	0.51
Drug toxicity 32 to 48 weeks (0= no toxicity, 1= toxicity	-9.95 (-19.00; -0.90)	0.031	10.65 (1.36; 19.94)	0.025

* baseline

5.6.3 Drug toxicities and negative QoL

Examining the associations between drug toxicity and negative HRQoL, it was noted that 27% (3) of all drug toxicities occurred among participants who reported negative PHS while no drug toxicities occurred among participants who reported negative MHS. Drug toxicities were not reported by participants with negative PHS or negative MHS during the baseline-16 weeks and 16-32 weeks treatment intervals. However, 43% (3) of all drug toxicities reported during the 32-48 weeks treatment interval occurred among participants with negative PHS. No drug toxicities were reported during this treatment interval for participants with negative MHS.

Univariate analysis showed that participants with drug toxicity during the 32-48 weeks treatment interval were 4.16 times more likely to have negative PHS than participants without drug toxicity (95% CI 0.9, 19.23; p=0.068). (Appendix 5 Table 6) Multivariate analyses were not done as toxicity data were too few.

5.7 Adherence and quality of life

The median adherence for the cohort at weeks 16, 32 and 48 was above 98%. (Appendix 5 Table 7) Adherence at these time points did not differ between genders, age above and below 34 years or baseline log viral load above and below 5 log copies/ml. However, participants with a baseline CD4 count $\leq$ 50 cells/mm^3 had significantly lower levels of adherence at week 48 than participants with higher baseline CD4 counts (97.1% versus 99.2%, p=0.048). Comparing the proportions of participants with adherence above and below 95%, a higher proportion of women had adherence above 95% than men at all time points and a higher proportion of participants with baseline log viral load $\leq$ 5.0 copies/ml had adherence above 95% than those with higher baseline log viral loads at all time points. These differences were not statistically significant. No significant differences in proportion of participants with adherence above and below 95% were noted for age and baseline CD4 count. (Table 21)

Table 21 Comparison of proportion of participants with adherence >95% at weeks 16, 32 and 48 for various categories. (n= 147)

	Week 16	Week 32	Week 48
Female	81.7	79.1	74.8
Male	75	75	65.6
P-value	0.397	0.617	0.303
Age >34 years	85.9	78.1	76.6
Age $\leq$34 years	75.9	78.3	69.9
P-value	0.130	0.978	0.367
Baseline CD4 >50 cells/mm^3	79.8	79.8	75.2
Baseline CD4 $\leq$50 cells/mm^3	81.6	73.7	65.8
P-value	0.814	0.430	0.260
Baseline log viral load $\leq$5.0 log copies/ml	82.9	80.3	76.3
Baseline log viral load >5.0 log copies/ml	77.5	76.1	69
P-value	0.408	0.537	0.320

Median PHS and MHS scores did not differ significantly for patients with adherence above or below 95% either pre-HAART or at week 48 on HAART. (Table 22) Participants with adherence >95% did however experience greater gains in PHS score (9.79 versus 5.49, p=0.360) and MHS score (6.02 versus 4.69, p=0.307) between pre-HAART and week 48 than participants with lower levels of adherence. These differences were not statistically significant.

Table 22 Median PHS scores and median MHS scores at various time points for patients with adherence above and below 95%.

	Adherence >95%	**Adherence ≤95%**	**p-value**
Pre-HAART PHS score	44	46	0.167
Pre-HAART MHS score	45	45	0.993
PHS score at 48 weeks	54	53	0.811
MHS score at 48 weeks	51	48	0.243
Delta PHS score	9.79	5.49	0.360
Delta MHS score	6.02	4.69	0.307

Similar proportions of participants with adherence above and below 95% experienced negative change in HRQoL. While 17.5 percent of participants with adherence >95% reported negative PHS, 25.2 percent of participants with adherence below or equal to 95% reported negative PHS (p=0.322). Similarly, 30% of participants with adherence >95% reported negative MHS, while 35.5 percent of participants with adherence below or equal to 95% reported negative MHS (p=0.530). Although the proportion of participants experiencing negative HRQoL was marginally higher in the adherence ≤ 95% group, these differences were not significant.

Univariate analyses showed that neither change in PHS score (OR 0.99; 95% CI 0.95, 1.02; p=0.358) nor change in MHS score (OR 0.98; 95% CI 0.95, 1.02; p=0.305) between pre-HAART and week 48 were associated with adherence at 48 weeks. Furthermore, none of the variables included in the multivariate model were significantly associated with adherence at 48 weeks. (Appendix 5 Table 8)

6 DISCUSSION

With increased survival among HIV positive individuals accessing HAART, there is a growing interest in morbidity-related outcomes in HIV treatment programmes, and in particular the impact of HAART on the quality of remaining life. To date, research into HRQoL and HAART has largely focussed on describing the changes in HRQoL over time and assessing the associations between various socio-demographic, psychosocial and clinical factors and HRQoL.

This study not only adds to this existing literature but it also introduces two new dimensions. It is one of the first studies to explore the HRQoL among individuals who report declines in QoL on HAART. Secondly, it assesses the impact of drug toxicities on HRQoL.

6.1 Key Findings

This study reported a significant increase in HRQoL during the first 48 weeks on HAART with the bulk of this increase occurring during the first sixteen weeks on treatment. Improvement in HRQoL occurred across all core domains assessed as well as the two summary scales: physical health summary (PHS) and mental health summary (MHS).

Although there was a general improvement in HRQoL on HAART, up to a third of participants experienced a decrease in HRQoL (negative HRQoL) during the first 48 weeks of HAART. Baseline log viral load was significantly associated with negative PHS, whereas baseline log viral load and baseline CD4 count were associated with negative MHS.

Few drug toxicities were recorded during the first 48 weeks on HAART; however, there was a trend to increasing rates of drug toxicity as time on HAART increased. Drug toxicities had a major impact on physical health but less so on mental health. Participants experiencing drug toxicities reported lower PHS scores at all time points on HAART. This was most significant at 48 weeks. In contrast, drug toxicities had less of an impact on MHS score and participants with drug toxicity paradoxically reported a non-significant improvement in MHS score at 48 weeks.

6.1.1 Change in HRQoL on HAART

This study reported a significant increase in HRQoL during the first 48 weeks on HAART with the bulk of this increase occurring early - during the first sixteen weeks on treatment - thereby confirming the findings of Stangl et al (2007) and Jelsma et al (2005). Although the cohort of Stangl et al (2007) continued to show significant improvements in HRQoL up to 36 weeks of HAART and then maintained this at 48 weeks, this cohort achieved their most significant improvement in HRQoL by 16 weeks and then maintained this at weeks 32 and 48. This difference may have been the result of ceiling effects of the MOS-SF36 instrument though and not due to an actual difference in impact of HAART on HRQoL.

The dramatic increase in HRQoL during the first few weeks of HAART occurred over the time period when patients usually experience the most significant gains in health. The greatest decrease in viral load happens within the first few weeks of treatment and mortality and morbidity rates begin to fall after just a month on HAART. (Lawn et al, 2005a; Lawn et al, 2006) That the increase in physical HRQoL during the first 48 weeks of HAART is greater than that in mental HRQoL comes as no surprise as the impact of HAART on physical health is more rapidly visible. It takes much more time for patients to trust that the improvements in physical health are not temporary and to realise that they are no longer at high risk of dying.

These findings - of an improvement in both physical and mental HRQoL during the first 48 weeks on HAART - contrast with those of the developed world, where mostly declines in HRQoL on HAART have been reported. (Wu et al, 1990; Wu et al, 1993; Lenderking et al, 1994; Gill et al, 2002; Liu et al, 2006b; Carrieri et al, 2003) These differences could be explained by the earlier access to drug therapy for patients in the developed world. Patients in the USA and Europe, had access to ARVs in the pre-HAART era at a time when drug formulations were problematic, side effects were severe and pill burdens were high. These problems with early antiretroviral therapy impacted negatively on the HRQoL of patients taking them. Furthermore, patients in developed countries initiate drug therapy at an earlier stage of disease when they are usually asymptomatic. These patients then experience declines in their HRQoL when they develop HAART-related side effects. The 2NN study was one of the first studies to show a consistent improvement in HRQoL on HAART. (Van Leth et al, 2004) Not only did HRQoL increase but the bulk of change in PHS and MHS scores occurred within the first 12 weeks of treatment. It is not surprising though that the findings of this study are reflected in those of developing countries as the bulk of patients enrolled in the 2NN study came from the developing world and had advanced HIV disease.

6.1.2 Predictors of pre-HAART HRQoL

There has been much research in both developed and developing countries into the association between various socio-demographic, psychosocial and clinical factors and HRQoL pre-HAART. This study assessed the impact of two socio-demographic characteristics (age and gender) and various baseline clinical factors (WHO stage, baseline CD4 count and baseline log viral load) on HRQoL pre HAART initiation. No association was found between age or gender and pre-HAART HRQoL. Although this contrasts with the literature from developed countries where older age (Liu et al, 2006b; Murri et la, 2003) and female gender (Mrus et al, 2005) have been associated with lower HRQoL pre-HAART; this finding is similar to that of Jelsma et al (2005) and Stangl et al (2007), who reported no significant association between these variables and HRQoL pre-HAART.

Baseline CD4 count and WHO stage were both associated with pre-HAART PHS score. Participants with lower baseline CD4 counts or more advanced disease (WHO stage 3&4) had lower pre-HAART PHS scores than participants with higher baseline CD4 counts and less advanced disease (WHO Stage 1&2). These findings are similar to those of Stangl et al (2007), who found that a baseline CD4 count > 50 cells/mm^3 was the strongest predictor of better physical HRQoL pre-HAART initiation, while a baseline log viral load ≥5 copies/ml and WHO Stage 3&4 disease were strong predictors of poorer physical HRQoL pre-HAART initiation. In these two cohorts, pre-HAART physical HRQoL was most influenced by baseline clinical factors. This is to be expected as patients with more advanced stage of disease and lower CD4 counts are more symptomatic of HIV infection and more likely to suffer from concurrent opportunistic infections.

None of the socio-demographic or clinical factors that we examined were associated with pre-HAART MHS score in the multivariate analysis. This finding was somewhat surprising as the bivariate comparison of median MHS scores pre-HAART had shown that patients with WHO stage 3&4 disease, lower baseline CD4 counts and higher baseline viral loads had lower scores than patients with WHO stage 1&2 disease, higher baseline CD4 counts and lower baseline viral loads. These results were more in keeping with the findings of Stangl et al (2007), who reported that both baseline CD4 count and baseline viral load were significantly associated with MHS score pre-HAART initiation. The lack of association between these

clinical factors and pre-HAART MHS score in the multivariate model could be explained by the small number of patients included in the analysis.

6.1.3 Predictors of change in HRQoL

This study also addressed the impact of socio-demographic and clinical variables on change in HRQoL during the first 48 weeks of HAART. Pre-HAART PHS score and change in log viral load were both significantly associated with change in PHS score at 48 weeks. Participants with higher pre-HAART PHS scores reported less increase in PHS score, while participants who had a greater decrease in log viral load on HAART experienced a greater increase in PHS score. Furthermore, pre-HAART MHS score and baseline log viral load were significantly associated with change in MHS score at 48 weeks. Participants with higher pre-HAART MHS scores reported smaller increases in MHS score while participants with higher baseline log viral loads reported greater increases in MHS score.

In the developed world, the most significant predictors of change in HRQoL are the pre-HAART PHS and MHS scores. Individuals with higher HRQoL scores prior to initiating HAART are more likely to achieve higher on-treatment HRQoL scores. (Carrieri et al, 2003; Murri et al, 2003; Liu et al, 2006b) While our study confirmed that pre-HAART PHS and MHS scores were the strongest predictors of subsequent HRQoL, we found that participants with higher pre-HAART scores achieved smaller changes in HRQoL on treatment. This difference in findings could be explained by ceiling effects of the MOS-SF36 instrument in our cohort or by the fact that patients with higher pre-HAART HRQoL scores simply had less room for improvement.

The association between change in log viral load and change in PHS score reflects the finding in the developed world that undetectable viral load is associated with higher HRQoL scores on HAART. (Gill et al, 2004; Burgoyne et al, 2004; Carrieri et al, 2003) However, this study did not confirm the associations between other baseline factors – such as baseline CD4 count and WHO stage – and change in PHS score that have been shown in both developed and developing country settings (Carrieri et al, 2003; Murri et al, 2003; Liu et al, 2006b; Stangl et al, 2007). Change in viral load (a measure which is also captured by undetectable viral load on HAART) is probably the best reflection of response to treatment. Patients who are responding to HAART will have a drop in viral load from their baseline level. In contrast, patients on HAART may have a range of CD4 count changes from no change to an increase in

CD4 count while experiencing an improvement in health. So it stands that viral load may in fact be a better measure of response to treatment than CD4 count. This notion is further supported in patients who develop immune reconstitution syndrome where a reduction in viral load results in improved immune function prior to any measurable change in CD4 count. (French et al, 2004; Lawn et al, 2005b) Furthermore, the reduced impact of baseline viral load and CD4 count on subsequent mortality rates for patients on HAART has been reported. (Lawn et al, 2006; Moh et al, 2007) This could well explain the results of the multivariate model, in which change in viral load and not other baseline clinical factors was significantly associated with change in physical HRQoL.

The finding that change in MHS score is associated with baseline log viral load adds to previous reports, in which baseline CD4 count (Stangl et al, 2007), greater number of symptoms (Murri et al, 2003) and HAART interruption (Liu et al, 2006b) have been associated with lower MHS scores on HAART. Direct invasion of the central nervous system by HIV is known to result in significant neurological and neuropsychiatric disorders – including dementia, minor cognitive-motor disorder and subclinical cognitive-motor impairment. These HIV-related disorders are usually more evident in the late stages of disease when viral loads are high. (Goodkin et al, 2001; Haas et al, 1999) It therefore stands to reason that patients commencing HAART with higher baseline viral loads are at greater risk of neuropsychiatric disorders but once on HAART, they may experience greater improvements in mental health as the levels of HIV are reduced. What is difficult to explain though is why baseline log viral load impacted on change in MHS score but not baseline MHS score.

Furthermore we found that older patients had lower gains in physical HRQoL, while women had greater gains in mental HRQoL. However, the greater increase in MHS score among women was of borderline statistical significance and was not supported by week 48 data, in which women reported significantly lower median MHS scores than men. The reason for these inconsistencies could be due to the small number of men included in the multivariate analysis (n=32). Stangl et al (2007), in fact, reported no significant association between gender and change in HRQoL on HAART and a borderline negative association between age and change in HRQoL (B-coefficient -0.9; p=0.08).

6.1.4 Negative HRQoL

There have been few analyses dealing with declines in PHS and MHS scores. In fact, negative HRQoL is often overshadowed by the overwhelming positive impact of HAART on HRQoL and therefore not reported. This research showed that although there was a general improvement in HRQoL on HAART, up to a third of participants experienced a decline in HRQoL during the first 48 weeks of HAART. Twenty three percent of participants reported a drop in PHS score and thirty four percent, a drop in MHS score.

The most significant predictors of negative PHS and MHS were baseline HRQoL score, baseline log viral load and baseline CD4 count. However, as discussed before for change in HRQoL, the association between higher baseline HRQoL and negative HRQoL could have been due to the fact that patients with higher baseline scores had less room for improvement and were therefore more likely to regress. Baseline log viral load was strongly associated with negative PHS. Participants with higher baseline log viral loads were 0.22 times less likely to report negative PHS than participants with lower baseline log viral loads. Similarly, baseline log viral load and baseline CD4 count were associated with negative MHS. Participants with higher baseline log viral loads were 0.5 times less likely to report negative MHS than participants with lower baseline log viral loads and participants with lower baseline CD4 counts were 0.41 time less likely to report negative MHS than participants with higher baseline CD4 counts.

In other words, participants with more advanced disease (characterised by higher viral loads and lower CD4 counts) were less likely to report a decline in HRQoL than those with earlier disease. So, contrary to what one would expect, it is the relatively well patients entering into an ARV programme who are at greatest risk of experiencing negative HRQoL. These associations could be explained by the impact of symptoms on HRQoL. Symptoms are known to impact negatively on HRQoL. (Murri et al, 2003; Carrieri et al, 2003; Burgoyne et al, 2004) Patients with more advanced disease are more likely to have a greater number or intensity of symptoms than patients with less advanced disease pre HAART and therefore are more likely to have lower baseline HRQoL. (Murri et al, 2003) However, once on HAART, these symptoms improve and so too HRQoL. (Carrieri et al, 2003; Burgoyne et al, 2004) In contrast, patients with less advanced – and more often asymptomatic – disease may experience an increase in symptoms related to adverse effects of HAART and therefore may be more likely to experience decreases in HRQoL on treatment.

6.1.5 HRQoL and Drug Toxicity

Although there is great concern about the impact of drug toxicities on HRQoL, few studies have directly assessed this association. In the developed world, symptoms have been shown to impact negatively on both physical and mental HRQoL. (Murri et al, 2003: Liu et al, 2006b) However, the nature of the symptoms and whether they were attributed to the disease process or to HAART was not clear. In the developing world, Jelsma et al (2005) concluded that possible side effects of HAART had a negligible impact on HRQoL. This conclusion was, however, based on preliminary data – largely the fact that overall HRQoL improved on HAART.

This study assessed the impact of drug toxicities on subsequent HRQoL and found that drug toxicities had a significant negative impact on physical health but not on mental health. Participants who experienced drug toxicity reported lower PHS scores than participants without a drug toxicity at all time points and achieved less increase in score by week 48. The differences between scores was most significant at 48 weeks when participants with drug toxicity achieved median PHS scores that were 16 units less than participants without toxicity. In contrast, drug toxicities had little impact on MHS scores and participants with drug toxicity paradoxically reported a non-significant improvement in MHS score at 48 weeks. Furthermore participants with drug toxicity were more likely to report negative PHS but less likely to report negative MHS than those without toxicity.

That the impact of drug toxicities on physical HRQoL worsened over time was most likely because the rate and type of drug toxicities worsened with time on treatment. Early drug toxicities included NNRTI hypersensitivity reactions (characterised by a rash with or without constitutional symptoms) and peripheral neuropathy (characterised by a burning or tingling sensation in the soles of the feet). Both of which can be diagnosed early and settle relatively quickly on a change of therapy. The later drug toxicities – such as hyperlactataemia and lactic acidosis – can be more difficult to diagnose and symptoms (ranging from the milder spectrum of weight loss, nausea and non-specific abdominal pain to the more severe symptoms of life-threatening acidosis) may persist for some time before and after HAART is changed.

What is more difficult to explain is the apparent lack of impact of drug toxicities on mental HRQoL. Although this finding could be spurious due to the small numbers of drug toxicities (n=11) reported during the first 48 weeks, it may speak to the fact that for HIV positive patients the mental health benefit of being on HAART outweighs any negative impact of side

effects. By 48 weeks on HAART, patients have generally experienced the mortality and morbidity benefits of HAART. They have recovered from opportunistic infections and are feeling well. The trust that they have gained in antiretroviral medications allows them to divorce their physical experience of a side-effect from the mental experience as they believe that their health will once again improve.

These findings contrast with those of Van Leth et al (2004), who addressed the association between adverse events and HRQoL in the 2NN study, a randomised clinical trial of NNRTI-containing regimens. Van Leth et al reported that patients with an adverse event during the follow-up period had non-significantly smaller changes in PHS score but significantly smaller changes in MHS score. These differences in findings could be due to differences in the study populations as well as differences in how drug toxicities and/or adverse events were defined. Firstly, the cohort of Van Leth et al was multinational, predominantly male (63%) and had earlier HIV disease (21% CDC-class C, median baseline CD4 count 190 cells/mm^3 and baseline viral load 4.7 log copies/ml). In this population, their trust in HAART keeping them well may have been seriously undermined by the occurrence of an adverse event thereby negatively impacting on their mental health. Secondly, it was not clear whether the reported adverse events were largely laboratory grade 3 or 4 events (which are often asymptomatic and noted on routine blood draws) or clinical grade 3 or 4 events (with signs and symptoms). Asymptomatic laboratory adverse events may well have had less of an impact on physical health than symptomatic clinical adverse events.

6.1.6 HRQoL and Adherence

The association between HRQoL and adherence has not been widely studied in the developed or developing world. Carballo et al (2004) showed a positive association between mental health and cognitive functioning and adherence >95%, while Mannheimer et al (2005) reported on the positive impact of high levels of adherence on gains in HRQoL. The findings of this research lend support to those of Carballo and Mannheimer in that a tentative positive association between higher levels of adherence and greater gains in HRQoL was shown. Participants with median adherence >95%, had higher HRQoL scores at week 48 (median PHS score 54 versus 53, p=0.811; median MHS score 51 versus 48, p=0.243) and greater increases in PHS and MHS scores (increase in PHS score 9.79 versus 5.49, p=0.360; increase in MHS score 6.02 versus 4.69, p=0.307) than participants with lower median adherence, however these differences were not statistically significant.

Unfortunately, due to the high overall levels of adherence for the cohort (>98%), the univariate and multivariate models were unable to show any significant association between HRQoL and adherence >95% at 48 weeks. However, as time on HAART increases, the relationship between adherence and HRQoL becomes key to maintaining the long term treatment benefits for people living with HIV and therefore needs to be explored further.

6.2 Strengths & limitations of the study

The greatest strength of this study is its longitudinal design. This allowed the assessment of the associations between various socio-demographic and clinical factors and HRQoL and allowed for inferences to be made about causal relationships. Furthermore, this study was conducted in a community ARV clinic in South Africa and was one of few studies addressing the impact of HAART on HRQoL. There are, however, some limitations to this research which are discussed below.

6.2.1 Research setting and generalisability

As this study took place in a research clinic that was well-staffed, the generalisability of these results to other primary care clinic settings is not known. Furthermore, this research was conducted in the Western Cape, one of the first provinces in South Africa to commence its ARV roll-out programme. The provincial protocol, although similar to the national protocol, had subtle differences in how patients on ARVs were managed and the Hannan Crusaid Treatment Centre (HCTC) in particular followed its own protocol with visits scheduled four monthly (instead of every three months) and a wider range of safety bloods being drawn for toxicity assessments.

However, the cohort that was reported on in this study was similar to other cohorts from Africa that have appeared in the recent literature. (Stangl et al, 2007; Wouter et al, 2007; Louwagie et al, 2007; Jelsma et al, 2005) The study populations were all largely female and had advanced HIV disease as evidenced by median baseline CD4 counts of less than 200 cells/mm^3 and mean baseline log viral loads of approximately 5.0 log copies/ml. However, compared to that of Stangl et al, the population reported on in this study was younger (median age 34 years versus 39 years), had a higher proportion with WHO stage 3&4 disease (88% versus 31%) and a lower baseline CD4 count (93 cells/mm^3 versus 122 cells/mm^3). This

similarity of cohorts is favourable in terms of the generalisability of study results in an African setting.

6.2.2 Study population and selection bias

Although this study enrolled all patients initiating HAART at the HCTC, there may have been some bias in how patients were selected. Firstly, not all patients with HIV who qualified for HAART presented for therapy. Then not all patients who presented themselves were enrolled onto the programme. Some patients were lost prior to initiation of HAART and others were lost while on HAART due to reasons such as death, LTFU, and transfer out. It may well be that patients who were enrolled and continued on HAART for the full 48 weeks were different to those who were not enrolled or did not continue on HAART. These differences could have also impacted on their response to HAART and subsequently their change in HRQoL. So the study population that we assessed may well have been the sector of the population who were most likely to show the HRQoL benefits of HAART.

However, no significant differences were found in the comparison of the socio-demographic and baseline variables of patients enrolled into the programme who initiated HAART and reached 48 weeks with those who enrolled into the programme and either never initiated HAART or did not reach 48 weeks of HAART. So it seems as if selection bias would not have had an undue influence on results in this study.

Furthermore up to 50% of patients had incomplete HRQoL data (the MOS SF36 questionnaire was not completed pre-HAART and at all scheduled visits on HAART) and were not included in the final analysis. However, as there were no significant differences in demographic, baseline and on treatment characteristics between patients with incomplete and complete HRQoL data, it is unlikely that this biased the study results. This did impact on the number of patients available for analysis though and may have limited the ability of the study to detect significant associations.

6.2.3 Study measures and information bias

Information bias results from the systematic error in collecting and recording of data and, if severe, may impact on the capacity of the study to yield valid results. Information bias may have been an issue during the collection of HRQoL, drug toxicity and adherence data and is discussed below.

6.2.3.1 MOS SF36 Questionnaire

The decision to use the MOS-SF36 questionnaire was based on two main factors. Firstly, the instrument has been translated and culturally adapted into more than 30 languages, thereby allowing comparison of HRQoL among HIV populations across different languages and cultures. In this setting, it would allow the merging of this dataset with those from other SSA countries to enable HRQoL research for the region as a whole. Secondly, the instrument has undergone validity and reliability testing in South Africa and population values exist for this country. However, there were a number of limitations associated with the use of the MOS SF36 instrument, some of which could have contributed to information bias in this study.

The MOS-SF36 instrument is a generic HRQoL measure and, like all generic instruments, may not be sensitive enough to measure the more specific aspects of HRQoL related to the HIV disease process. This could lead to either an underestimation or overestimation of HRQoL scores and, more importantly, change in HRQoL scores thereby under- or over-reporting the actual impact of HAART on HRQoL. This instrument, however, has been widely used in HIV research and has been found to be sensitive to clinical differences and to correlate well with number of symptoms, stage of disease, change in CD4 count and viral load and commencement of HAART. (Tsasis, 2000; Clayson et al, 2006) Furthermore, the fact that this study reported a marked significant improvement in HRQoL yet, at the same time, was able to discriminate between patients with positive and negative change in HRQoL, demonstrates that this instrument was able to perform well in this population.

The MOS-SF36 instrument is also prone to ceiling effects – where substantial numbers of patients get the highest possible score for a domain. This would have made it difficult for the instrument to pick up changes in HRQoL at the upper end of the scale and may have been a problem with increasing time on treatment. From the results of this study, it appears that ceiling effects may have been an issue – particularly in the physical function, physical role

and social function domains. For both physical role and emotional role, patients achieved a median score of 100 at weeks 16, 32 and 48; while the median score for physical role was 100 at weeks 32 and 48. Ceiling effects would have limited the ability of the instrument to measure continuing increases in HRQoL for patients past week 16 or 32 and may be the reason for gains in HRQoL stabilising at an earlier time point in our population than that of Stangl et al (2007). Ceiling effects could therefore have lead to the underestimation of HRQoL gains – especially in the physical health domain. Floor effects – where substantial numbers of patients get the lowest possible score for a domain – are rare for the MOS-SF36 instrument even among patients with severe chronic illnesses. (IRCHC, 1992) Floor effects were not evident in the results of this study.

The English version of MOS-SF36 questionnaire was used in this study with explanations given in Xhosa given for difficult concepts. The decision to use the English version of the questionnaire was largely driven by the fact that the Sizophila adherence counsellors found the language in the Xhosa translation too complex to work with. Difficulties with Xhosa translations of questionnaires have been well described. Smit et al (2006) found that not only are there issues surrounding the appropriate form of Xhosa to use but also that there is no immediate past tense in the Xhosa language, it is difficult to distinguish between categories such as "most of the time" and "some of the time" and certain westernised emotional concepts (such as sadness and the "blues") are not familiar to the Xhosa language. Difficulties in translation occur more commonly for emotional and mental health concepts than for physical concepts and could have been the cause for the smaller gains in MHS scores reported in this study as well as the increase in MHS scores for patients experiencing drug toxicities.

Although misinterpretation of the meaning of certain items in the English MOS SF36 could have resulted in errors in assessment, the effect of this was lessened by the fact the questionnaire was administered at four consecutive visits and not just once-off. Any misinterpretation of items would have been consistent at each assessment point and the instrument would therefore have been able to pick up changes in domain scores.

The MOS-SF36 questionnaire was administered by the Sizophila adherence counsellors. This could have introduced a degree of information bias as adherence counsellors could have prompted patients to give positive responses to questions thereby overestimating the positive impact of HAART on HRQoL. It could also have been possible that adherence counsellors

would have been more likely to prompt negative responses in patients known to have a drug toxicity or poor adherence. This would have led to the overestimation of the associations between drug toxicity and poor adherence and negative HRQoL. However, not only were the adherence counsellors trained in the non-judgemental administration of the questionnaire, but they were also unaware of drug toxicity diagnoses or adherence percentages at the time of administering the MOS SF36 questionnaire. This would hopefully have limited the impact of this form of information bias on study results. Furthermore, patients themselves could have felt impelled to give falsely positive responses so as not to disappoint their healthcare providers. Again, this would have led to the overestimation of the positive effects of HAART. This bias was minimised by using the Sizophila adherence counsellors, who were themselves HIV positive individuals from the community, and not the clinicians for administration of the questionnaires.

Finally, not all items in the MOS SF36 questionnaire were completed at every visit. In a minority of patients, single items were omitted. These missing questionnaire items were then estimated using a standard scoring algorithm that calculates an average score for the item. (IRCHC, 1992) If questionnaire items were omitted at random, this would have biased study results towards the null, however, if items were omitted systematically (maybe patients struggled to understand a specific question and therefore skipped that question), this could have had a far more serious impact on the validity of study results. However, as only a small proportion of patients (<10%) had omitted items and omissions did not appear to be systematic, the impact of missed items on study results would have been minimised.

6.2.3.2 Drug toxicity assessment

Although most drug toxicities were defined and described in the national and provincial protocols, the diagnosis of some of the toxicities was based on clinical judgement. Furthermore, as in the case of hyperlactataemia and lactic acidosis, a certain degree of clinical acumen was required to even suspect the diagnosis. As this judgement was largely subjective and clinician dependant, there may have been systematic differences in the diagnosis (or non diagnosis) of drug toxicities – especially between more experienced and less experienced clinicians. However, as less experienced clinicians tended to discuss complex cases with more experienced clinicians – both at the time of consultation with the patient and during the weekly meetings - the impact of diagnostic bias on drug toxicities would have been minimised. Furthermore, this study only considered drug toxicities that were severe enough to

prompt a change in antiretroviral therapy. Less severe toxicities that may also have impacted negatively on HRQoL were not reported on. This could have led to an underestimation of the true negative impact of drug toxicities on HRQoL.

6.2.3.3 Adherence assessment

Adherence was assessed at each visit by the adherence counsellors. As the assessment took the form of an objective pill count, there was little room for the introduction of information bias by the adherence counsellors. Patients may have introduced a measure of information bias though if they did not return all their tablets at each visit thereby giving an incorrect pill count and adherence assessment. This would have been more likely to occur among patients who were less adherent to their medications and would have resulted in an over assessment of their actual adherence.

6.2.4 Analysis

There are numerous factors – both measurable and immeasurable - that impact on HRQoL. The multivariate models in this study did not include all explanatory variables and therefore were only able to explain a small percentage of variation in HRQoL. The under adjustment of the models may have led to associations being driven by factors other than those in the model and therefore an overestimation of the true associations between explanatory variables and HRQoL outcomes could have resulted. Furthermore, the change in PHS data was not modelled optimally using linear regression techniques. This may have impacted on the associations between explanatory variables and change in PHS and the associations presented are therefore tentative.

The exclusion of up to 50% of patients (due to incomplete HRQoL data) severely restricted the number of patients available for analysis. This could have impacted on the ability of the study to detect significant associations.

Finally, the analyses of the association between drug toxicities and adherence and HRQoL were severely limited by a lack of data. Only eleven drug toxicities occurred during the first 48 weeks of HAART and hence only simple bivariate analyses could be performed. Furthermore, the high levels of adherence among our patients meant that the sample size was not large enough to detect any significant associations between adherence and HRQoL.

6.3 Implications for healthcare services and future research

6.3.1 Healthcare service recommendations

The findings of this study support the ongoing provision of HAART for HIV infected people in South Africa. Not only do HIV positive individuals stand to benefit from the improved mortality and morbidity outcomes associated with HAART but also from significant improvements in HRQoL. However, up to a third of patients initiating HAART experienced declines in HRQoL and of those with declines in physical HRQoL, 6% had drug toxicities thereby emphasising the need for lower toxicity drug regimens

This need is further highlighted by the negative impact of drug toxicities on physical HRQoL. Overall, twenty-seven percent of patients with drug toxicities experienced significant declines in physical HRQoL and during the week 32-48 treatment interval (when the bulk of drug toxicities occurred), this percentage rose to 43%. Most of the toxicities reported in this study were hyperlactataemia / lactic acidosis secondary to the use of stavudine, supporting the move away from the current national first line regimen to one that has a lower toxicity potential.

6.3.2 Research recommendations

This study reported that up to a third of patients on HAART experienced declines in HRQoL. Although this study explored the associations between various socio-demographic, baseline and on treatment factors and negative HRQoL, the explanatory variables included were somewhat limited with the result that the final models only explained 25% of variation in negative PHS and 13% of variation in negative MHS. Further research - involving a bigger cohort and wider range of explanatory variables - is required to better assess the causes of negative HRQoL with the aim of minimising this event.

Furthermore as ARV roll-out enters its fifth year in South Africa, so the focus of health service delivery has shifted from how to enrol patients to how to keep patients in the programme and adherent to ARVS in order to maximise the benefits of limited treatment options. (Orrell, 2007) The link between adherence and HRQoL is bidirectional and not yet well understood. This study reported a tentative positive association between adherence and HRQoL. More research into this area is required to better understand this interaction so that not only will patients be successfully treated for longer but also achieve optimal HRQoL.

6.4 Conclusion

This study confirmed the overwhelmingly positive HRQoL benefits of HAART in a community ARV clinic in South Africa. HRQoL improved significantly during the first 48 weeks of HAART with the bulk of improvement occurring during the first 16 weeks of treatment. While the majority of patients experienced an improvement of HRQoL on HAART, up to a third of patients reported declines in HRQoL. HAART-related drug toxicities (especially those secondary to the use of stavudine) had a significant negative impact on physical HRQoL highlighting the need for less toxic drug regimens in the national ARV roll-out programme. As the roll-out of HAART moves into its fifth year in South Africa, the interplay of drug toxicities and HRQoL becomes key in maximising the quality of life of people living with HIV.

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APPENDIX 1 Research Consent Form

RESEARCH CONSENT FORM

Doctor or Sister _____ of _____ HIV clinic has explained to me that I am attending a clinic where tuberculosis and HIV are being studied. The care I will receive will be the same or better than that at any other primary care clinic in the Western Cape.

I understand that some of my personal details (including my age, sex, date of diagnosis of TB/HIV, employment and financial standing, as well as details of my illness) will be collected to increase the understanding of HIV and TB in this area. All this information will be kept CONFIDENTIAL and in a separate place from my clinic folder. Only the clinic doctors and nursing sister have access to this information. If it is used later (for further research or publication) my name will not be attached to it in any way.

I give permission for any blood or sputum samples that are sent for my health care to be kept once the test needed is completed. These samples may be used again to increase information on HIV and TB in this area. If the results of these research tests are relevant to my health care, my doctor and I will be informed of them. If the information is used more widely, my name will not be attached to it in any way.

Patient sign: _____ Date: _____
Printed name: _____

Health care worker sign: _____ Date: _____
Printed name: _____

Witness sign: _____ Date: _____
Printed name: _____
(only needed if patient is under 18 years).

APPENDIX 2 The MOS SF 36 Survey

THE HANNAN CRUSIAD TREATMENT CENTRE

THE MOS 36-ITEM SHORT-FORM HEALTH SURVEY (SF-36)

Patient ID No. _____ Treatment No. _____

Date:_____ Visit No: _____

INSTRUCTIONS This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: (circle one)

Excellent.....1

Very good.....2

Good.....3

Fair.....4

Poor.....5

2. Compared to one year ago, how would you rate your health in general now? (circle one)

Much better than one year ago.....1

Somewhat better than one year ago.....2

About the same as one year ago.....3

Somewhat better than one year ago.....4

Much worse than one year ago.....5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (circle one number on each line)

ACTIVITIES	YES, Limited a lot	YES, Limited a little	NO, not limited at all
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking **more than 1,5 kilometers**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dresses yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**
(circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities?	1	2
b. **Accomplished less** than you would like?	1	2
c. Were **limited** in the kind of work or other activities?	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5 During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities **as a result of any emotional problems** (such as feeling depressed or anxious)? (circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6 During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups ? (circle one)

Not at all 1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

7. How much **bodily pain** have you had during the **past 4 weeks**?

(circle one)

None.....1

Very mild.....2

Mild.....3

Moderate.....4

Severe.....5

Very severe.....6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (circle one)

Not at all.....1

A little bit.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:

(circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6

c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the **past 4 weeks**, how much of the time has your **physical health** or **emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time 1

Most of the time.....2

Some of the time.....3

A little of the time.....4

None of the time.....5

11. How **TRUE** or **FALSE** is **each** of the following statements for you?

(circle one number on each line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sicker a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent .	1	2	3	4	5

APPENDIX 3 Standard Gugulethu Paper Work

Paper work for Gugulethu:

Week –4:

- 3 initial forms (contact details; education and counselling flow sheet and patient page) – carbon copy
- 3 log forms (previous ARVs and chronic medication; viral load and CD4 tracking sheet; important medical events)
- Scheduled visit form (carbon copy)
- Quality of life (MOS SF36) form
- TB screen form

Week –2:

- 2 research consent forms
- 2 patient agreements
- Scheduled visit form (carbon copy)
- Treatment readiness questionnaire
- Log form update

Week 0 – baseline on drug:

- Scheduled visit form (carbon copy)
- Quality of life (MOS SF36) form
- Log form update
- Drug accountability

Weeks 4 and 8:

- Scheduled visit form (carbon copy)
- Log form update
- Drug accountability

Week 16 and 4 monthly thereafter:

- Scheduled visit form (carbon copy)
- Quality of life (MOS SF36) form
- Adherence questionnaire
- Log form update
- Drug accountability

Additional forms:

- Treatment cards (given to each patient at baseline and on change of regimen
- Unscheduled visit form
- Patient information sheets in English and Xhosa (Keeping yourself healthy; antiretroviral information.

Hannan Treatment Centre: patient background Date:

Name: | Treatment no:

low long lived in Gugulethu?

icome per month (in rands)

lo. of children:

lo. of economic dependents:

lo. of people in the household: adults / children

anguage spoken at home:

econd language?

evel of education? 1. School: standard
2. College or university
3. Other
4. None
5. Unknown

Occupation status:
1. Employed - formal
2. Employed - informal or casual
3. Unemployed
4. Pensioner
5. Home-maker
6. Disability grant
7. Student
8. Other

Date of first positive HIV test (dd/mm/yy):

Place of diagnosis:

Reason for test: (illness, TB, VCT,MTCT)

Date of last negative HIV test (dd/mm/yy): (if available)

Disclosure of status: (at first visit)
1. Nobody
2. Partner only
3. Employer
4. Family
5. Community

Relationship status: single with partner

Partner informed of HIV? y / n

Partner tested for HIV? y / n

Housing: formal informal other

GIS reference:

Serviced? yes no

Probable route of HIV infection:
1. Heterosexual
2. Homosexual
3. Vertical (MTCT)
4. Blood products
5. IV drug user
6. Unknown

Have your sexual partner/ children been tested for HIV? y / n
if yes, give relationship and result:

Clinical Information:

Height (cm):

Weight (kg)

Is patient pregnant? No Yes NA

What contraception is being used? (Men too!)

On TB therapy now? No yes - start date:

Previous tuberculosis: No yes - date:

If yes, fully treated? No yes unknown

Last pap smear (for women) (dd/mm/yy):

VDRL status: Positive negative unknown

Person completing form:

Hannan Treatment Centre: continuation sheet

Name:	Treatment no:

Programme allowing ARV access: **WHO stage:**

Drugs and dose:		
1.	**6.**	**Cotrimoxazole: y/n**
2.	**7.**	**date commenced:**
3.	**8.**	
4.	**9.**	**Mantoux:**
5.	**10.**	date and result:

please note any changes

Visit	Date	Adh. Sch.	CD4	Viral Load	Weight (kg)	Comments

Adh. Sch = adherence schedule e.g. 1A or 2B etc. See protocol.

Hannan Treatment Centre: scheduled visit form

Name:	Treatment no:

Duration of treatment: _____ Seen by: _____ Date of visit: _____
doctor/sister (circle) on time / late (circle)

Problems since last visit:

Karnofsky score:

Other medications since last visit:

Examination:

Weight:
Waist:
Hip:

Temp:
Pulse
BP:

Contraception:

Assessment

Evidence of lipodystrophy:

Plan:

Any **new chronic medication** since last visit? Yes No
(Record on log page)

Any **admissions / OIs / ongoing or severe problems / Grade 3 or 4 lab abnormalities** since last visit?
(record on log page) Yes No

Ask about adherence:
1.Any problems with taking the medication (timing, lack of food, missed doses)? Give reason, if yes.
_____ Yes No
2.Ask to describe dosing: Correct Incorrect
3. Questionnaire completed (at 4-monthly visits): Yes No
4. Adherence monitor opinion:

Routine bloods taken: (FBC, diff, LFTs) Yes No'
Extra bloods taken (e.g. lactate): Yes No
State what is requested: _____

Hannan Treatment Centre: unscheduled visit form

Name:	Treatment no:

Duration of treatment: _____ Seen by: _____ Date of visit: _____
doctor/sister (circle) on time / late (circle)

Reason for visit: Karnofsky score:

Examination: Weight:

Temp:
Pulse
BP:

Assessment:

Plan:

Any **new chronic medication** since last visit? Yes No
(Record on log page)

Any **admissions / OIs / ongoing or severe problems / Grade 3 or 4 lab abnormalities** since last visit?
(record on log page) Yes No

Adherence:
Is this unscheduled visit due to or going to lead to adherence issues?

Extra bloods taken (e.g. lactate): Yes No
State what is requested: _____

Hannan Treatment Centre: Drug accountability form

Name:	Treatment no:

	Drug 1:	Drug 2:	Drug 3:	Drug 4:
Date:				
Batch number				
Volume/number dispensed				
Date:				
Returns				
Batch number				
Volume/number dispensed				
Date:				
Returns				
Batch number				
Volume/number dispensed				
Date:				
Returns				
Batch number				
Volume/number dispensed				
Date:				
Returns				
Batch number				
Volume/number dispensed				
Record any dosing interruptions here (give interruption and recommenced dates): i.e. dd/mm/yy / dd/mm/yy				
1.	/	/	/	/
2.	/	/	/	/
3.	/	/	/	/
4.	/	/	/	/
5.	/	/	/	/
	/	/	/	/
Reason drug PERMANENTLY stopped:				
Date:				

APPENDIX 4 Ethics Correspondence and Approval

HIV Clinical Research Unit
Somerset Hospital
Waterfront 8005
Cape Town
South Africa

Professor Charles Swanepoel
Research Ethics Committee
Old main Building
University of Cape Town

09th May 2002

Diana Princess of Wales HIV Research Unit
HIV treatment programme – initial data collection.

The Diana, Princess of Wales HIV Research Unit is a non-governmental, non-profit organisation. At present we are attempting to access highly active antiretroviral therapy (HAART) for people living with HIV through investigator driven and multinational clinical drug trials. Both doctor and nursing staff at the unit are highly experienced in antiretroviral management.

Over the past year we have become involved in two communities in the Western Cape. Through overseas grant applications (pending as yet) we plan to broaden access to anti-retroviral therapy to these two sites. We will also be involved in training of staff on site in HIV and antiretroviral management.

The sites involved include:

1. Nomzamo clinic: Masiphumelele is a self-contained informal settlement of ~15 000 people, south of Noordhoek, with its own health forum that meets monthly to discuss and co-ordinate health related initiatives. Nomzamo is the only public sector primary health care clinic based in Masiphumelele. Health care is provided by state-employed clinical nurse practitioners with a twice-weekly doctor clinic. Current services include: a curative service with referral to False Bay Hospital (a secondary level hospital in the area), TB management, STD management, family planning, MTCT, a well-baby clinic and immunizations. The HIV Research Unit has close links with the clinic and provides a doctor and research nurse to run a once-weekly HIV clinic, assist nursing staff with difficult cases and train the nurses and community health workers in basic HIV care and the use of antiretrovirals.

2. The Hannan Treatment Center: This is a proposed antiretroviral treatment and training centre based on the same site as the Community Health Center (CHC) in Gugulethu. This center is a pilot project between the Diana, Princess of Wales, HIV Research Foundation and the Provincial Department of Health. Nursing and counseling staff at the treatment center would be state-employed with doctors provided by the applicant organisation. The center would accept

we will be submitting details of the therapy and the required laboratory, clinical and adherence monitoring to the Research Ethics Committee for approval.

At this point we would like to be involved in collecting demographic and epidemiological data from patients with HIV and patients with dual TB and HIV infection at both sites, particularly Masiphumelele and the Gugulethu Community Health Centre HIV clinic, in order to describe the cohorts as they appear now. The demographic and clinical data collection sheet is attached as Appendix 1. Only the clinic doctors have access to this data on-site, and the sheets are stored in a locked cupboard, separate from the patients folders.

We would also like to store the remains of both sputum and serum samples taken as part of routine clinical HIV care. No extra samples will be taken. We may have access to HIV-genotyping and TB PCR fingerprinting, that will assist us in future patient management and disease-mapping. Again, details will be submitted as these become available.

We will ask each patient for permission before collecting demographic or other information, and before allowing their specimens to be stored. We will reassure them of the confidentiality of the process. A consent form is attached as Appendix B. This will be translated into Xhosa and Afrikaans.

UNIVERSITY OF CAPE TOWN

Research Ethics Committee
Faculty of Health Sciences
OMB E46 Room 26
Queries : Xolile Fula
Tel : (021) 406-6492 Fax: 406-6411
E-mail : Xfula@curie.uct.ac.za

10 June 2002

REC REF:

Prof R Wood
Clinical Research Unit
Somerset Hospital
Greenpoint

Dear Prof Wood

DIANA PRINCESS OF WALES HIV RESEARCH UNIT
HIV TREATMENT PROGRAMME-INITIAL DATA COLLECTION

Thank you, for your letter to the Research Ethics Committee dated 09 May 2002.

- *We are impressed with your efforts to extend training, knowledge and antiretroviral treatment to two additional sites – congratulations on these efforts.*
- *Please , however, use the DNA consent form, produced by the Human Genetics Dept., for patients to sign in connection with your proposed DNA typing etc.*

The contents have been noted and added to our files.

Please quote the Reference number in all correspondence.

Yours sincerely

signature removed

A/PROF. CR SWANEPOEL
CHAIRPERSON

NEC REF 759/02 copy

Dr Catherine Orrell
Clinical Trials Manager / CIPRA investigator
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Professor Zabow
UCT Research Ethics Committee
Medical School
UCT
Observatory

02 Dec 02 cpmcu 21/12/02.

Dear Prof Zabow

HIV treatment programme: update on data collection.

In June 2002 we received permission to collect operational research data at the 2 community sites linked to our unit: Masiphumelele Clinic (previously called Nomzamo clinic) and The Hannan Crusaid Treatment Centre in Guguletu. Both sites are now recognised as Western Cape (PAWC) antiretroviral rollout sites. I enclose our original letter of application, including the patient consent and data collection forms, as well as your approval letters, as we did not receive an Ethics committee reference number.

I would like to update you on progress at the sites. Please note that our parent organisation has changed name from the Diana, Princess of Wales, HIV Research Unit to the Desmond Tutu HIV Centre (DTHC). We are now based at Medical School, UCT.

1. Masiphumelele site:

HIV clinic:

We have 780 HIV-positive people registered at the local authority HIV clinic. Doctors and nurse practitioners from the DTHC manage these patients at the weekly clinic. All clients sign the patient informed consent form (in the attached document) during their first visit to the HIV clinic. We collect demographic data from these clients as well as disease specific information (regarding TB and HIV) and monitor their CD4 counts according to the provincial protocol.

Antiretroviral (ARV) clinic:

DTHC staff manage 112 people on antiretrovirals to date, according to the PAWC ARV protocol. All these clients have passed though the HIV clinic and have signed the informed consent. Again demographic and disease related data are collected. Most of this data is now also required for the monthly and quarterly reports requested by the provincial ARV roll out programme.

This clinic will be the site for the CIPRA SA Project 1 (your ref 129/2004) and Project 3 studies (your ref 132/2004), once they receive final approvals.

2. Guguletu site (Hannan Crusaid Treatment Centre):

ARV Clinic

This clinic is purely an antiretroviral clinic and research conducted here is operational. Nursing and medical staff are PAWC employees. Counselling and pharmacy staff are employed by the DTHC and evaluation of the programme is carried out by the DTHC.

Clients are referred to the ARV clinic from a number of HIV clinics in the Nyanga district. Everyone signs a consent form prior to enrolling on antiretrovirals. Again, we collect demographic and disease-related information both for research analysis and for the PAWC ARV programme. In addition we collect data on quality of life and information of an anthropological nature, examining attitudes to antiretrovirals and acceptability of the programme. We also examine adherence data.

Information gained from the evaluation process is used to inform and advise the provincial authorities that are responsible for the PAWC ARV roll out programme.

Professor Wood has asked me to enclose a copy of a grant application to the NIH. This application "Optimising HIV care in Less Developed Countries" (revision 05/01) is an example of the type of analysis we use the data collected at these sites for. This requires no additional information to be collected from the sites, but allows key information to be collated and disseminated.

Confidentialty.

We are very careful about protecting the identity of our clients. All staff at the DTHC sign confidentiality agreements and any suspected breach of confidentially would be addressed most seriously. Most data drawn from either site is linked to a patient identity number. Only restricted staff have access to patient names: including the more senior investigators and the 1 staff member responsible for data entry. All electronic data is password protected.

Yours Sincerely

UNIVERSITY OF CAPE TOWN

Research Ethics Committee
E53 Room 44.1, Old Main Building Groote
Schuur Hospital, Observatory, 7925
Queries : Xolile Fula
Tel : (021) 406-6492 Fax: 406-6411
E-mail : Xfula@curie.uct.ac.za

15 December 2004

REC REF: 359/2002

Dr C Orrell
Desmond Tutu HIV Centre
IIDMM

Dear Dr Orrell

HIV TREATMENT PROGRAMME: UPDATE ON DATA COLLECTION

Thank you for your letter to the Research Ethics Committee

Thank you for updating us on the progress at your sites on the above mentioned study.
We note that you changed name from the Diana, Princess of Wales, HIV Research Unit to the Desmond Tutu HIV Centre (DTHC).
Your reference number from now is REC REF: 359/2002 and we are really sorry for not initially providing you with it.

Please quote the REC. REF in all your correspondence

Yours sincerely

signature removed
PROF. T. ZABOW
CHAIRPERSON

APPENDIX 5 Additional Tables

Table 1. Demographic and baseline characteristics of responders (with any HRQoL data, n = 295) and non-responders (with no HRQoL data n = 22).

Variable	Responders	Non-responders	P-value
Number	295	22	
Age (years) (mean, (SD))	34 (7.4)	34 (7.9)	0.703
Female (n,(%))	219 (74)	17 (77)	0.753
WHO stage 3 & 4 (n, (%))	254 (86)	18 (82)	0.579
Baseline CD4 count cells/mm^3 (median, (IQR))	88 (47; 148)	71 (23; 144)	0.263
Baseline viral load copies/ml (median, (IQR))	80 876 (33 194; 201 784)	72 276 (44 885; 168 503)	0.776
Baseline viral load log copies/ml (median, (IQR))	4.91 (4.52; 5.30)	4.86 (4.65; 5.23)	0.694
Week 48 CD4 count cells/mm^3 (median, (IQR))	261 (183; 340)	261 (195; 358)	0.874
Week 48 viral load copies/ml (median, (IQR))	49 (49; 49)	49 (49; 49)	0.545
Week 48 viral load log copies/ml (median, (IQR))	1.69 (1.69; 1.69)	1.69 (1.69; 1.69)	0.000
Change in CD4 cells/mm^3 (n, (SD))	178 (130)	173 (104)	0.897
Change in viral load log copies/ml (median, (IQR))	-3.3 (-3.5, -2.7)	-3.2 (-3.6, -2.6)	0.989
Drug Toxicity (n, %)	11 (4%)	0 (0%)	0.357

Table 1 shows that among the 317 patients who reached the first on treatment assessment (and were therefore considered eligible for inclusion in the HRQoL study), there were no significant differences in demographic, baseline and on-treatment characteristics between those with any HRQoL data (n=295) and those with none (n=22).

Table 2. Demographic, baseline and on-treatment characteristics of patients followed to week 48 versus not, among those with any QOL data.

Variable	Complete week 48 data	Incomplete week 48 data (Missing data, died & LTFU)	P-value
Number	147	148	
Age (years) (mean, (SD))	35 (7.3)	34 (7.4)	0.419
Female (n,(%))	115 (78)	105 (71)	0.195
WHO stage 3 & 4 (n, (%))	130 (88)	124 (84)	0.248
Baseline CD4 count cells/mm^3 (median, (IQR))	93 (49; 162)	86 (46; 145)	0.263
Baseline viral load copies/ml (median, (IQR))	92 209 (38 010; 212 637)	72 661 (32 007; 194 481)	0.221
Baseline viral load log copies/ml (median, (IQR))	5.0 (4.6; 5.3)	4.9 (4.5; 5.3)	0.123
Week 48 CD4 count cells/mm^3 (median, (IQR))	257 (189; 343)	262 (198; 363)	0.536
Week 48 viral load copies/ml (median, (IQR))	49 (49; 49)	49 (49; 49)	0.190
Week 48 viral load log copies/ml (median, (IQR))	1.69 (1.69; 1.69)	1.69 (1.69; 1.69)	0.449
Change in CD4 cells/mm^3 (n, (SD))	169 (130)	187 (129)	0.236
Change in viral load log copies/ml (median, (IQR))	-3.18 (-3.56; -2.77)	-3.11 (-3.55; -2.54)	0.311
Drug Toxicity (n, %)	7 (5%)	4 (3%)	0.351
Adherence at week 48 (%)	98.9	98.6	0.733

Table 2 shows that among the 295 patients with any HRQoL data, there were no significant differences in demographic, baseline and on-treatment characteristics between those with complete week 48 data (n=147) and those with incomplete week 48 data (n=148).

Table 3. Baseline characteristics of patients with any drug toxicity at any time during the first year of HAART.

Variable	
n	11
Age (years) (mean, (SD))	35 (7.1)
Female (n, (%))	10 (91)
WHO Stage 3&4 (n, (%))	9 (82)
Baseline CD4 count cells/mm^3 (median, (IQR))	57 (7; 151)
Baseline viral load (copies/ml) (median, (IQR))	72 972 (76 18; 218 227)
Baseline viral load (log copies/ml) (median, (IQR))	4.9 (3.9; 5.3)

Table 4. Median Physical Health Summary score (PHS) and median Mental Health Summary (MHS) score at time point immediately after drug toxicity during the first year of HAART for each toxicity type.

Description	PHS	MHS
EFV Hypersensitivity Reaction (before 16 weeks)	46	44
No toxicity by 16 weeks	52	50
Peripheral Neuropathy (between 16 and 32 weeks)	45	44
No toxicity by 32 weeks	53	49
Transaminitis (between 32 and 48 weeks)	47	38
No toxicity by 48 weeks	53	48
Hyperlactataemia / Lactic Acidosis (between 32 and 48 weeks)	36	56
No toxicity by 48 weeks	53	48

Table 4 shows that for each drug toxicity type, PHS and MHS scores are lower for patients with toxicity than without toxicity – except for hyperlactataemia / lactic acidosis, where patients with toxicity report higher MHS levels than those without toxicity.

Table 5. Change in median PHS and median MHS score for each treatment interval for patients with and without drug toxicity.

Description	n	Δ PHS	Δ MHS
Drug toxicity (any time)	7	1.44	9.51
No toxicity (at any time)	172	7.18	3.41
Drug toxicity (baseline to 16 weeks)	2	9.76	8.94
No drug toxicity (0 to 16 weeks)	267	6.05	4.29
Drug toxicity (16 to 32 weeks)	1	2.44	0.47
No drug toxicity (16 to 32 weeks)	208	0.23	7.63
Drug toxicity (32 to 48 weeks)	5	-7.50	6.59
No drug toxicity (32 to 48 weeks)	145	0.40	-0.65

Table 5 shows that overall participants with drug toxicity achieved less overall increase in PHS score than participants without toxicity; whereas participants with toxicity achieved greater increase in overall MHS score.

Table 6. Univariate analysis assessing association between drug toxicity and negative HRQoL at any time on HAART and at weeks 16, 32 and 48.

Variable	**Negative PHS**		**Negative MHS**	
	Odds Ratio (95% CI)	P-value	*Odds Ratio (95% CI)*	P-value
Drug toxicity (at any time)	2.05 (0.52; 8.01)	0.304	Predicts failure perfectly	
Drug toxicity (baseline to 16 weeks)	Predicts failure perfectly		Predicts failure perfectly	
Drug toxicity (16 to 32 weeks)	Predicts failure perfectly		Predicts failure perfectly	
Drug toxicity (32 to 48 weeks)	4.16 (0.9; 19.23)	0.068	Predicts failure perfectly	

Table 6 demonstrates that toxicity data were too few to assess the association between drug toxicity and negative HRQoL at most time points. Participants with drug toxicity during the week 32 to 48 interval were 4.16 times more likely to report negative PHS than participants without toxicity.

Table 7. Comparison of median adherence (%) at weeks 16, 32 and 48 for various categories.

	Week 16	Week 32	Week 48
	(n=146)	(n=134)	(n=131)
Total	98.8	98.9	98.7
Female	98.9	98.9	99.1
Male	98.4	98.4	98.2
P-value	0.9589	0.6215	0.3361
Age >34	99	98.5	99
Age ≤34	98.6	99.2	98.5
P-value	0.1556	0.9625	0.3556
Baseline CD4 >50 cells/mm^3	98.7	99	99.2
Baseline CD4 ≤50 cells/mm^3	98.9	98.3	97.1
P-value	0.9307	0.4996	0.048
Baseline log VL ≤5.0 copies/ml	99.4	99.3	99.2
Baseline log VL >5.0 copies/ml	98.6	98.6	98.3
P-value	0.0890	0.233	0.467

Table 7 shows median adherence at weeks 16, 32 and 48 for various categories. There were no significant differences for gender, age and baseline viral load. However, participants with a baseline CD4 count ≤ 50 cells/mm^3 had significantly lower levels of adherence at 48 weeks than participants with higher baseline CD4 counts.

Table 8. Factors associated with adherence >95% at week 48.

Variable	Univariate Model	Multivariate Model 1	Multivariate Model 2
	OR, 95% CI P-value	OR, 95% CI P-value	OR, 95% CI P-value
Age (continuous)	1.02 (0.97; 1.08) 0.443		
Age (≤34 =0, >34 =1)	1.41 (0.67; 2.96) 0.368	1.53 (0.71; 3.33) 0.278	1.58 (0.74; 3.41) 0.240
Gender (male =0, female =1)	0.64 (0.28; 1.49) 0.305	0.68 (0.28; 1.65) 0.389	0.65 (0.27; 1.55) 0.328
WHO stage (1&2 =0; 3&4 =1)	0.54 (0.15; 1.98) 0.352	0.61 (0.16; 2.37) 0.477	0.56 (0.15; 2.11) 0.388
Baseline CD4 count Cells/mm^3	1.00 (0.99; 1.01) 0.938		
Baseline CD4 count cells/mm^3 (>50 =0; ≤50 =1)	0.63 (0.29; 1.41) 0.262	0.76 (0.32; 1.80) 0.536	0.70 (0.30; 1.61) 0.398
Baseline viral load log copies/ml	0.89 (0.51; 1.57) 0.684		
Baseline viral load log copies/ml (≤5 =0; >5 =1)	0.69 (0.33; 1.43) 0.321	0.89 (0.40; 1.95) 0.763	
Δ PHS at week 48	0.99 (0.95; 1.02) 0.358	0.99 (0.96; 1.02) 0.629	
Δ MHS at week 48	0.98 (0.95; 1.02) 0.305	0.99 (0.96; 1.03) 0.624	

Table 8 shows univariate and multivariate modelling of factors associated with adherence at week 48. None of the above factors are significantly associated with adherence in either the univariate or multivariate models.

APPENDIX 6 Model Checking

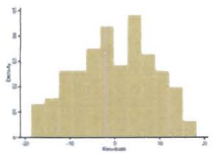
1. BASELINE PHS

1.1 Checking Model Assumptions

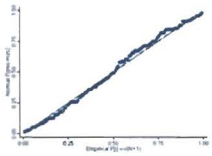
```
. reg prephs Agebin StageCat screenCD4bin
      Source |       SS       df       MS              Number of obs =     147
-------------+------------------------------           F(  3,   143) =    3.80
       Model |  889.475511     3  296.491837            Prob > F      =  0.0118
    Residual |  11169.1912   143  78.1062319           R-squared     =  0.0738
-------------+------------------------------           Adj R-squared =  0.0543
       Total |  12058.6667   146  82.5936073           Root MSE      =  8.8378
------------------------------------------------------------------------------
      prephs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      Agebin |   -.386502   1.480821    -0.26   0.794    -3.31363    2.540626
    StageCat |  -3.148808   2.320781    -1.36   0.177   -7.736277    1.438662
screenCD4bin |  -4.690782   1.691212    -2.77   0.006   -8.033787   -1.347777
       _cons |   48.21313   2.188327    22.03   0.000    43.88749    52.53878
------------------------------------------------------------------------------
```

1.1.1 Overall Plot

```
. histogram res
```



```
. pnorm res
```

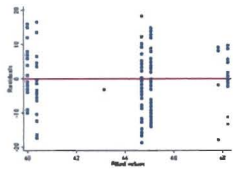


```
. swilk res
                    Shapiro-Wilk W test for normal data
    Variable |   Obs        W          V          z       Prob>z
-------------+--------------------------------------------------
         res |   147    0.98277      1.970      1.536    0.06228
```

Residuals are normally distributed.

1.1.2 Plot of residuals against fitted values

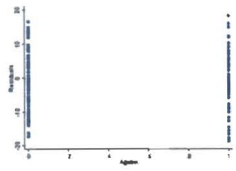
```
. rvfplot, yline(0)
```



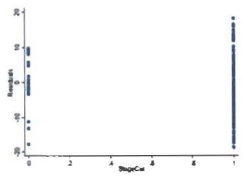
Random scatter of residuals within limited range of fitted values.

1.1.3 Plot of residuals against predictor variables

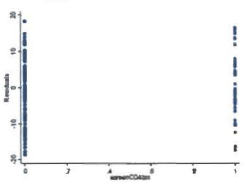
```
. rvpplot Agebin
```



```
. rvpplot StageCat
```



```
. rvpplot screenCD4bin
```



Random scatter of residuals within the binary categories.

1.2 Checking Outliers and Influential Observations

```
. list patient prephs resstu dfits cooksd
     +-------------------------------------------------+
     | patient   prephs      resstu       dfits     cooksd |
     |-------------------------------------------------|
 39. |     139        23   -2.021047   -.3762026    .034635 |
 40. |     142        63    2.119237    .2999742     .02196 |
 41. |     210        56    1.858543    .3448151   .0292228 |
 56. |      42        57    1.931802    .3595903   .0317203 |
107. |      55        26   -2.161714   -.3059867   .0228208 |
114. |      27        37   -1.312863   -.3355273   .0280029 |
128. |     136        24   -1.901662   -.3539801   .0307626 |
147. |     231        35   -1.550689   -.3963084   .0388831 |
     +-------------------------------------------------+
```

Outliers: 55, 142 Influential: 27, 231 Outlier and influential: 42, 136, 139, 210

Re-running the models with (1) outlier and influential observations 42, 136, 139 and 210 excluded and (2) influential observations 27 and 231 excluded did not significantly alter any of the associations. Hence the original model was reported in the text.

1.3 Checking for Collinearity

```
. vif
    Variable |       VIF       1/VIF
-------------+----------------------
    StageCat |      1.04    0.964589
screenCD4bin |      1.03    0.969163
      Agebin |      1.01    0.985689
-------------+----------------------
    Mean VIF |      1.03
```

No serious multi-collinearity of explanatory variables is influencing the model.

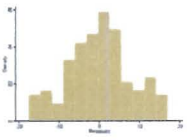
2. BASELINE MHS

2.1 Checking Assumptions

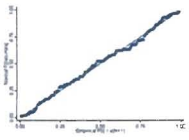
```
. reg premhs screenCD4bin logscreenvlbin
      Source |       SS       df       MS              Number of obs =     147
-------------+------------------------------           F(  2,   144) =    1.82
       Model |  224.540546     2  112.270273           Prob > F      =  0.1654
    Residual |  8872.92884   144  61.6175614           R-squared     =  0.0247
-------------+------------------------------           Adj R-squared =  0.0111
       Total |  9097.46939   146  62.3114342           Root MSE      =  7.8497

------------------------------------------------------------------------------
      premhs |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
screenCD4bin |  -1.515991   1.511415    -1.00   0.318    -4.503416    1.471433
logscreenv~n |  -1.829851   1.324197    -1.38   0.169    -4.447226    .7875242
       _cons |   46.37774   .9368009    49.51   0.000     44.52608    48.22939
------------------------------------------------------------------------------
```

2.1.1 Overall Plot

```
. histogram res
```



```
. pnorm res
```

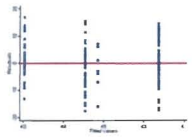


```
. swilk res
                    Shapiro-Wilk W test for normal data
    Variable |   Obs        W          V          z       Prob>z
-------------+-------------------------------------------------
         res |   147    0.98657      1.536      0.972    0.16564
```

Residuals are normally distributed.

2.1.2 Plot of residuals against fitted values

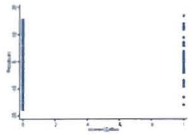
```
. rvfplot, yline(0)
```



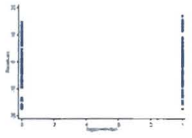
Random scatter of residuals within limited range of fitted values.

2.1.3 Plot of residuals against predictor variables

```
. rvpplot screenCD4bin
```



```
. rvpplot logscreenvlbin
```



Random scatter of residuals with binary categories indicating no abnormality.

2.2 Checking Outliers and Influential Observations

```
. list patient premhs resstu dfits cooksd
```

	patient	premhs	resstu	dfits	cooksd
7.	86	30	-1.696302	-.2964994	.0289268
16.	174	27	-2.289669	-.315913	.0323149
53.	35	29	-2.084692	-.4179042	.0568927
58.	47	60	2.224275	.3887848	.0490402
62.	23	30	-2.126997	-.2556683	.0212683
118.	10	29	-2.261374	-.2718207	.0239448
131.	22	56	1.687833	.2950192	.0286443
143.	217	30	-2.126997	-.2556683	.0212683

Outlier: 10 & 23 Influential: 22, 86 & 217 Outlier & Influential: 35, 47 & 174.

Re-running the models with (1) outlier and influential observations 35, 47 & 174 excluded and (2) influential observations 22, 86 & 217 excluded did not significantly alter any of the associations. Hence the original model was reported in the text.

2.3 Checking for Collinearity

```
. vif
    Variable |       VIF       1/VIF
-------------+----------------------
logscreenv~n |      1.04    0.957292
screenCD4bin |      1.04    0.957292
-------------+----------------------
    Mean VIF |      1.04
```

No serious multi-collinearity of explanatory variables is influencing the model.

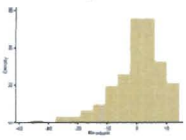
3. DELTA PHS

3.1 Checking Assumptions

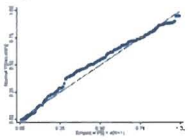
```
. reg phs048 age StageCat prephs deltalogvlrev
      Source |       SS       df       MS              Number of obs =     144
-------------+------------------------------           F(  4,   139) =   31.35
       Model |  9607.13116     4  2401.78279            Prob > F      =  0.0000
    Residual |  10650.7379   139  76.6240139            R-squared     =  0.4742
-------------+------------------------------           Adj R-squared =  0.4591
       Total |  20257.8691   143   141.66342            Root MSE      =  8.7535
------------------------------------------------------------------------------
      phs048 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |  -.2052803    .100521    -2.04   0.043    -.4040282   -.0065323
    StageCat |   2.797915   2.297854     1.22   0.225     -1.74535     7.34118
     prephs |  -.8021224   .0814813    -9.84   0.000    -.9632255   -.6410193
deltalogvl~v |    -3.4886   .8692831    -4.01   0.000    -5.207328   -1.769873
       _cons |   36.28663   6.345933     5.72   0.000      23.7396    48.83367
```

3.1.1 Overall Plot

```
. histogram res
```



```
. pnorm res
```

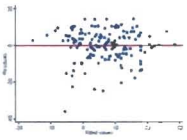


```
. swilk res
                    Shapiro-Wilk W test for normal data
    Variable |   Obs        W          V          z      Prob>z
-------------+--------------------------------------------------
         res |   144    0.93912      6.841      4.350    0.00001
```

Non-normality of residuals indicates that this outcome could be better modelled differently – for example using log transformation of the outcome variable. This was deemed beyond the scope of this thesis.

3.1.2 Plot of residuals against fitted values

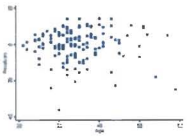
```
. rvfplot, yline(0)
```



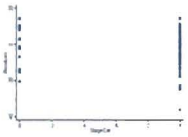
Random scatter of residuals in band around zero indicating no abnormality.

3.1.3 Plot of residuals against predictor variables

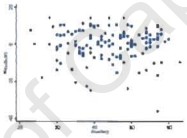
```
. rvpplot age
```



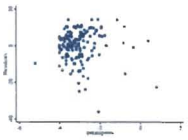
```
. rvpplot StageCat
```



```
. rvpplot prephs
```



```
. rvpplot deltalogvlrev
```



Random scatter of variables indicating no abnormality.

3.2 Checking Outliers

```
. list patient phs048 phs048hat resstu cooksd dfits
```

	patient	phs048	phs048hat	resstu	cooksd	dfits
15.	131	-20.45118	-5.21424	-1.852225	.0760866	-.6221621
56.	42	-41.53732	-5.573431	-4.457411	.1272607	-.850105
85.	71	17.98398	3.670095	1.702565	.0397266	.4487165
89.	68	16.20247	6.849583	1.133602	.0316306	.3980922
94.	265	1.394419	15.05851	-1.643528	.0507837	-.5069772
105.	138	-18.51178	6.2607	-3.045956	.1634432	-.9305286
107.	55	-1.650244	16.17971	-2.150374	.077704	-.6313874
110.	17	-25.73024	-3.219313	-2.889499	.3157365	-1.289244
111.	241	-20.26682	3.556584	-2.812385	.0260321	-.3696357
133.	110	-16.73713	-2.921825	-1.640394	.0357874	-.4255744
147.	231	-8.531676	11.90794	-2.470139	.0935389	-.6963189

Outliers: 241 Influential: 68, 71, 110, 131, 265 Outlier and influential: 17, 42, 55, 138, 231

Dropping observations that are both influential and outliers:

```
. reg phs048 age StageCat prephs deltalogvlrev
      Source |       SS       df       MS              Number of obs =     139
-------------+------------------------------           F(  4,   134) =   41.86
       Model |  8761.50089     4  2190.37522            Prob > F      =  0.0000
    Residual |  7011.16133   134  52.3220995           R-squared     =  0.5555
-------------+------------------------------           Adj R-squared =  0.5422
       Total |  15772.6622   138  114.294654           Root MSE      =  7.2334
------------------------------------------------------------------------------
      phs048 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
```

```
         age |   -.0462087   .0893969    -0.52   0.606    -.2230202    .1306027
    StageCat |    2.613025   1.967022     1.33   0.186    -1.277401    6.503451
      prephs |   -.8356221   .0693149   -12.06   0.000    -.9727149   -.6985293
deltalogvl~v |   -1.910939   .7846101    -2.44   0.016    -3.462761   -.3591166
       _cons |    38.19219   5.405927     7.06   0.000     27.50021    48.88418
------------------------------------------------------------------------------
```

Re-running the models with (1) outlier and influential observations excluded and (2) influential observations excluded did not significantly alter the associations – except that the association between age and outcome was no longer significant. The original model was reported in the text.

3.3 Checking for Collinearity

```
. vif
    Variable |       VIF       1/VIF
-------------+----------------------
    StageCat |      1.03    0.967899
      prephs |      1.03    0.970369
deltalogvl~v |      1.01    0.989650
         age |      1.01    0.991402
-------------+----------------------
    Mean VIF |      1.02
```

No serious multi-collinearity of explanatory variables is influencing the model.

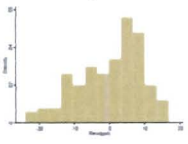
4. DELTA MHS

4.1 Checking Assumptions

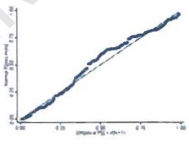
```
. reg mhs048 Agebin sex logscreenvlbin premhs
      Source |       SS       df       MS              Number of obs =     147
-------------+------------------------------           F(  4,   142) =   18.35
       Model |  6412.60729     4  1603.15182            Prob > F      =  0.0000
    Residual |   12406.758   142   87.371535            R-squared     =  0.3407
-------------+------------------------------           Adj R-squared =  0.3222
       Total |  18819.3653   146  128.899762            Root MSE      =  9.3473
------------------------------------------------------------------------------
      mhs048 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      Agebin |  -2.232389   1.571444    -1.42   0.158    -5.338837     .874059
         sex |   3.193283   1.908537     1.67   0.096    -.5795342    6.966101
logscreenv~n |   4.068832   1.576205     2.58   0.011     .9529721    7.184693
      premhs |  -.7286888   .0989126    -7.37   0.000    -.9242203   -.5331573
       _cons |   31.27024   5.188874     6.03   0.000     21.01282    41.52766
```

4.1.1 Overall Plot

```
. histogram res
```



```
. pnorm res
```

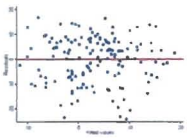


```
. swilk res
                    Shapiro-Wilk W test for normal data
    Variable |   Obs        W          V          z       Prob>z
-------------+--------------------------------------------------
         res |   147    0.96585      3.905      3.085   0.00102
```

The distribution of the residuals is approximating normal. However, these data may also have been better modelled differently.

4.1.2 Plot of residuals against fitted values

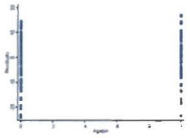
```
rvfplot, yline(0)
```



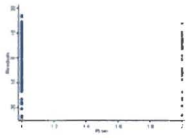
Random scatter indicating no abnormality.

4.1.3 Plot of residuals against predictor variables

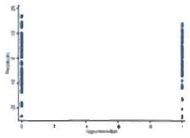
```
. rvpplot Agebin
```



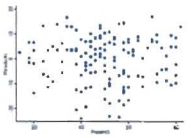
```
. rvpplot sex
```



```
. rvpplot logscreenvlbin
```



```
. rvpplot premhs
```



Random scatter (within binary categories) indicating no abnormality.

4.2 Checking Outliers

```
. list patient mhs048 resstu dfits cooksd
```

	patient	mhs048	resstu	dfits	cooksd
5.	62	-14.65497	-2.657161	-.409505	.032166
52.	214	-26.16714	-2.586836	-.4070269	.0318573
75.	81	-21.98771	-2.027398	-.3229158	.0204079
85.	71	-10.45023	-2.259076	-.3560442	.0246414
135.	157	-14.9417	-2.582709	-.5534983	.0589193
143.	217	-.243179	-1.543772	-.4414285	.0385959
147.	231	-11.55556	-2.15541	-.5212193	.0529738

Outlier: 62, 71, 81, 214 Influential: 143 Outlier and influential: 157, 231

Re-running the models with (1) outlier and influential observations 157 & 231 excluded and (2) influential observation 143 excluded did not significantly alter any of the associations. Hence the original model was reported in the text.

4.3 Checking for Collinearity

```
. vif
```

Variable	VIF	1/VIF
logscreenv~n	1.04	0.958053
sex	1.04	0.958160
Agebin	1.02	0.979110
premhs	1.02	0.981626
Mean VIF	1.03	

No serious multi-collinearity of explanatory variables is influencing the model.

5. NEGATIVE PHS

5.1 Checking Assumptions

```
. logistic negdeltaphs age logscreenvlbin prephs

Logistic regression                               Number of obs   =        147
                                                  LR chi2(3)      =      39.82
                                                  Prob > chi2     =     0.0000
Log likelihood =  -59.59284                       Pseudo R2       =     0.2504

------------------------------------------------------------------------------
 negdeltaphs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.070912   .0336728     2.18   0.029     1.006907    1.138986
logscreenv~n |   .2208711   .1118498    -2.98   0.003     .0818631    .5959226
      prephs |   1.153839   .0371298     4.45   0.000     1.083314    1.228956
------------------------------------------------------------------------------
```

```
. lfit
Logistic model for negdeltaphs, goodness-of-fit test

      number of observations =       147
 number of covariate patterns =       142
           Pearson chi2(138) =    116.39
                 Prob > chi2 =    0.9091
```

Non-significant test indicating good fit.

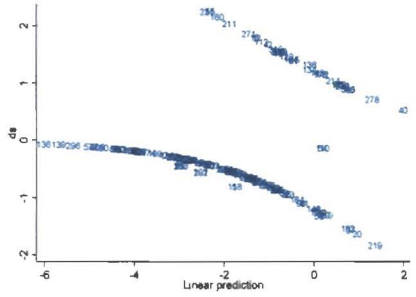
```
. twoway (scatter rs patient, msymbol (none) mlabel (patient) mlabposition(0))
```

The scatter plot of residuals plotted against patient number demonstrated random scatter.

```
. twoway (scatter ds patient, msymbol (none) mlabel (patient) mlabposition(0))
```

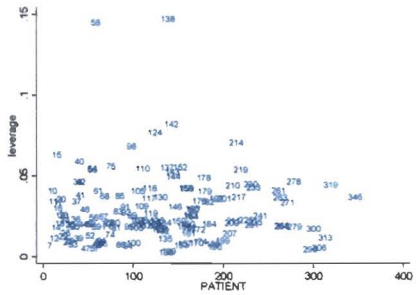
The scatter plot of deviances plotted against patient number demonstrated random scatter.

```
twoway (scatter ds xb, msymbol (none) mlabel (patient) mlabposition(0) yline(0))
```



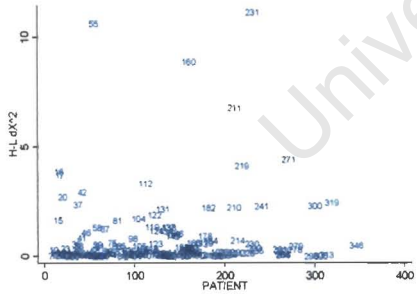
The scatter plot of deviances plotted against the linear predictor looked generally OK.

```
. twoway (scatter h patient, msymbol (none) mlabel (patient) mlabposition(0))
```



This scatter plot looked for possibly influential observations. Observations 58 and 138 were noted as being possibly influential. However, as their values fell below the cut-off leverage point of 2.1, they were deemed not influential.

```
. twoway (scatter d2 patient, msymbol (none) mlabel (patient) mlabposition(0))
```



This scatter plot looked for outlier observations. Observations 55, 160, 211 and 231 were noted as being outliers. The model was rerun with these observations excluded. As there were no significant changes to the associations in the model, the original model was reported in the text.

6. NEGATIVE MHS

6.1 Checking Assumptions

```
. logistic negdeltamhs Agebin screenCD4bin logscreenvlbin premhs

Logistic regression                             Number of obs   =        147
                                                LR chi2(4)      =      25.32
                                                Prob > chi2     =     0.0000
Log likelihood = -81.587147                     Pseudo R2       =     0.1343
------------------------------------------------------------------------------
```

```
 negdeltamhs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      Agebin |   1.766736   .6846581     1.47   0.142     .8266243    3.776029
screenCD4bin |    .414065    .205381    -1.78   0.075     .1566256    1.094648
logscreenv~n |   .5033188   .1977346    -1.75   0.081     .2330445    1.087045
      premhs |    1.09421   .0287771     3.42   0.001     1.039236    1.152091
------------------------------------------------------------------------------
```

```
. lfit
Logistic model for negdeltamhs, goodness-of-fit test

      number of observations =       147
 number of covariate patterns =       104
            Pearson chi2(99) =    103.49
                 Prob > chi2 =      0.3588
```

Non-significant test indicating good fit.

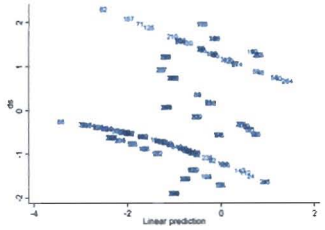
```
twoway (scatter rs patient, msymbol (none) mlabel (patient) mlabposition(0))
```

The scatter plot of residuals plotted against patient number demonstrated random scatter.

```
. twoway (scatter ds patient, msymbol (none) mlabel (patient) mlabposition(0))
```

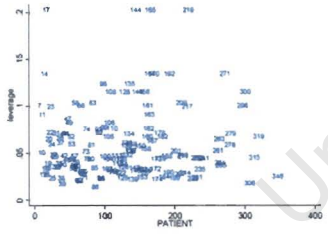
The scatter plot of deviances plotted against patient number demonstrated random scatter.

```
. twoway (scatter ds xb, msymbol (none) mlabel (patient) mlabposition(0) yline(0))
```



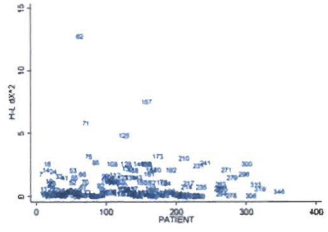
Scatter plot of deviances plotted against the linear predictor. There are an increased number of observations that are not well predicted by the model.

```
. twoway (scatter h patient, msymbol (none) mlabel (patient) mlabposition(0))
```



This scatter plot looked for possibly influential observations. Observations 17, 144, 165 and 219 were noted as being possibly influential. However, as their values fell below the cut-off leverage point of 2.8, they were deemed not influential.

```
. twoway (scatter d2 patient, msymbol (none) mlabel (patient) mlabposition(0))
```



This scatter plot looked for outlier observations. Observations 62, 71 and 157 were noted as being outliers. The model was rerun with these observations excluded and the association between age and the outcome variable became significant (OR 2.37; 95% CI 1.05, 5.36; p= 0.038). The original model was reported in the text.