GENDER DIFFERENCES IN PRESENTATION AND EARLY SURVIVAL IN AN ANTIRETROVIRAL THERAPY PROGRAMME IN GUGULETHU, SOUTH AFRICA, 2002-2007

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ABSTRACT

By 2005, an estimated 500 000 people with HIV had initiated highly active antiretroviral therapy (HAART) in sub-Saharan Africa. However, disproportionately more women than men have accessed HAART in most developing countries including South Africa. While there has been considerable recent interest in the determinants of mortality among patients receiving HAART in developing countries, there is conflicting evidence about gender differences and survival in HAART programmes.

This study explored whether there were gender differences in early mortality among 2 843 treatment-naïve men and women entering care in a large South African HAART programme. The study was a secondary analysis of patient records covering three time periods: person-time from programme entry to the initiation of HAART; person-time from HAART initiation to one year on treatment; and the total person-time from programme entry to one year on HAART. Cox's proportional hazards regression was used to investigate crude and adjusted associations between baseline characteristics and mortality as well as loss-to-follow-up (LTFU). Using the Sobel test, the study explored whether the degree of disease (according to CD4 count and WHO stage) played a mediating role in any association between gender and mortality.

In all three time periods, the analysis found a strong crude association between male gender and mortality. Prior to HAART-initiation, there was a 31% increase in the risk of mortality (crude Hazard Ratio (HR) 1.31, 95% CI, 0.93-1.86; p=0.131). In the period on HAART, this association strengthened (crude HR 1.57, 95% CI, 1.14-2.16; p=0.005). Overall, male gender increased the risk of mortality in the total cohort by 49% (crude HR, 1.49, 95% CI, 1.17-1.88; p=001).

Adjustment for baseline characteristics, including CD4 count and WHO stage, attenuated these crude associations. After adjustment, there was no increase in risk associated with male gender in the period pre-HAART (HR 1.01, 95% CI, 0.67-1.51). On HAART, there was a 19% increase in risk (HR 1.19, 95% CI, 0.88-1.67). In the total cohort, this was slightly attenuated (HR 1.15, 95% CI,

0.93-1.50). There was evidence of mediation by degree of disease. In the pre-HAART period, the Sobel test found significant associations between mortality and CD4 count ($p=0.044$) as well as WHO stage ($p=0.003$). On HAART, too, CD4 count ($p=0.045$) and WHO stage ($p<0.001$) appeared to mediate the effect of gender on death. Similarly, in the total cohort, there was evidence to support mediation by CD4 count ($p=0.035$) and WHO stage ($p<0.001$).

There was a crude association between male gender and the risk of being LTFU (HR for LTFU during the total study period comparing males to females, 1.26, 95% CI, 0.89-1.78; $p=0.194$). This was strengthened by adjustment for age and monthly income (HR,1.35, 95% CI, 0.92-1.97).

In this cohort, men appeared to have worse survival prospects than women due to more advanced HIV disease on programme entry. Previous studies have attributed the disproportionate access of women to HAART to gender differences in health seeking behaviour. This study argues that the prime obstacle might be the existing orientation of primary health care systems in developing countries towards the needs of women more than those of men. It suggests that women have better access to primary health services through the existing focus on maternal and child health. Women who are diagnosed and referred for HAART through these services are generally younger and healthier than men, who are diagnosed through services for tuberculosis (TB) and sexually transmitted infections (STIs). This might explain why fewer men than women access HAART, and why they are diagnosed at later stages of disease progression. As a result, men may be disadvantaged in access to HAART in South Africa.

The study suggests a number of short- and long-term solutions including: further research on obstacles to male access to HAART; changes in national policy; and the establishment of male-friendly services as an entry point for men into broader health services. Such approaches might facilitate the earlier diagnosis and treatment of men and improve their survival in HAART programmes.

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ABBREVIATIONS

CI	Confidence interval
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ART-CC	ART Cohort Collaboration
ART-LINC	Antiretroviral Treatment in Lower Income Countries Collaboration
ARV	Antiretroviral
CHC	Community health centre
HIV	Human Immunodeficiency Virus
HAART	Highly active antiretroviral therapy
HCTC	Hannan Crusaid Treatment Centre
HR	Hazard ratio
LTFU	Loss-to-follow-up/lost-to-follow-up
NGO	Non-government organisation
NSP	National Strategic Plan 2007-2011
OR	Odds ratio
PHC	Primary health care
RNA	Ribonucleic acid
SANAC	South African National AIDS Council
STI	Sexually transmitted infection
TB	Tuberculosis
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organisation

1 INTRODUCTION

The HIV/AIDS pandemic continues to grow. A recent report from UNAIDS and the World Health Organisation estimates that there are over 33 million people worldwide living with HIV (UNAIDS/WHO, 2007). Sub-Saharan Africa is the worst-hit region with 22.5 million adults and children living with HIV and an estimated 1.6 million adult and child deaths due to AIDS (UNAIDS/WHO, 2007). Women are disproportionately affected by HIV infection, both in living with infection and in acting as caregivers for infected family members. In sub-Saharan Africa, the majority of people living with HIV infection are women, and the figure has risen steadily since 1990.

Southern Africa remains at the centre of the pandemic: 35% of all people infected with HIV live, and 32% of AIDS deaths worldwide occur, in the region (UNAIDS/WHO, 2007). South Africa has one of the world's worst epidemics. In 1995, national HIV prevalence was estimated at 4.5%, increasing to 9.9% by 1998. By 2006, the country had the largest number of people living with HIV infection in the world. National prevalence was estimated at 11.8%. Prevalence among women was higher than among men (12.7% vs 10.2%), amounting to nearly 5.4 million South African adults and children infected with HIV (Harris et al., 2007). The scale of the HIV/AIDS epidemic in South Africa has a massive impact on both individual and population health. The burden of opportunistic infections is growing, mortality is increasing, and life expectancy is dropping. By 2010, it is estimated that life expectancy may fall below 40 years of age (Anderson and Van Rensburg, 2006).

The advent of highly active antiretroviral therapy (HAART) in 1996 transformed the prognosis for people living with HIV/AIDS. Until then, only single or dual therapy was available, and drug resistance developed fairly quickly. With HAART, HIV became a chronic managed disease for those who could afford the treatment. Until fairly recently, HAART was unaffordable to most people living with HIV in developing countries. Over the past few years, however, access to HAART has been expanded dramatically. In 2005, there were an

estimated 500 000 people on HAART in sub-Saharan Africa (Bekker et al., 2006), the majority of whom were women (UNAIDS/WHO, 2007). Prior to the widespread availability of HAART, the median survival in Africa after an AIDS diagnosis was less than one year (Rosen et al., 2007). As treatment is only initiated after an AIDS diagnosis for most Africans living with HIV, most of those who started treatment would have died within a year without treatment. The individual and public health benefits of this reduced morbidity and delayed mortality are enormous.

In developing countries there are now large cohorts of people on HAART, with high-quality data on clinical and immunological outcomes. Several studies (Lawn et al., 2006a, Bekker et al., 2006, Etard et al., 2006, Stringer et al., 2006) have found an increased risk of mortality within the first 4-6 months of entering HAART programmes in developing countries. From six months, however, clinical, virological and immunological responses to HAART in developing countries compare favourably with those in developed countries (Coetzee et al., 2004, Braitstein et al., 2006, Bekker et al., 2006, Stringer et al., 2006, Ferradini et al., 2006). This provides a valuable opportunity to explore differences within fairly homogeneous and representative populations. However, there has been little analysis of the impact of gender on mortality in HAART programmes.

At first, research on these programmes focused largely on comparing outcomes in developing and developed countries. As the HAART programmes matured, issues of sustainability and patient retention came to the fore. This shifted the focus of research to issues such as: how effective are the services, how can they be rolled out to reach the largest numbers, how to cope with co-infections such as TB, and what are the gaps in service delivery.

One such gap appears to be the late diagnosis and initiation of treatment for men. HIV/AIDS is commonly known as a gendered epidemic because of the perceived triple burden borne by women: in addition to living with HIV infection, women also care for sick family members and are often the primary breadwinners in households (National Department of Health, 2004a). In South Africa, women

account for 55% of the HIV-positive adults overall, and in certain age groups, the proportion is even greater (National Department of Health, 2004a). The prevalence in young adults (15-24 years) is 3.7% for males and 16.9% for females (Harris et al., 2007). Among those aged 25-29 years, the prevalence is 33.3% among women and 12.1% for men. However, uptake of HAART in three South African provinces has been 75% female and 25% male (Schneider et al., 2007). At the Johannesburg General Hospital, twice as many women as men accessed HAART (Hudspeth, 2004). The situation appears to be the same in the private sector. In one large workplace programme, for example, 60.5% of those accessing HAART were female although women only comprise 33% of the formal workforce (Nachega J, 2006).

Reasons for the low uptake of HAART services by men have not been fully explored, and the evidence is mixed. It seems likely that gender differences in health seeking behaviour play a part. However, there appears to be a broader issue: men's limited access to general health services. The 1998 Demographic and Health Survey (Department of Health and Medical Research Council, 1998) reported that across all race groups and geographic areas, significantly more women than men accessed public health services.

In view of the massive scale-up of HAART, it is important to understand potential gender differences in the progression of HIV and in access and responses to HAART. This dissertation uses the term 'gender' to include both sex and gender differences between men and women. Historically, sex was regarded as the biology of being male or female, while gender described socially constructed roles for men and women in a given society. Towards the end of the 20th century, feminist theory developed terminology for gender issues. By 1980, there was consensus among most feminist writers that 'gender' would only be used for traits that were socioculturally adapted and would not include biological differences (Phillips, 2005). However, some writers (Phillips, 2005, Diamond, 1995) argue that it is not possible to assess the impact of sex or gender on health independently of each other. They note the strong interaction between gender and biology in

every setting. Phillips (Phillips, 2005), for example, argues for a broader use of gender 'as the composite of both social and biological health effects associated with being either male or female'. She suggests that by doing this, researchers may be able to study the true effects without 'getting stuck at enumerating sex differences'. In this dissertation, the term 'gender' has been used to describe issues of both sex and gender.

This analysis explores one aspect of the gendered epidemic: the comparative survival of men and women in a South African HAART programme. HAART was initially only available to patients in the public sector through research sites and a pilot project run by Médecins sans Frontières from 2001. In 2004, government reluctantly began offering HAART through the public health system. Due to resource constraints, treatment was only available to individuals with advanced disease. By April 2007, the International Treatment Preparedness Coalition (ITPC) estimated that about 260 000 people were receiving HAART in the public sector and an estimated 31 000 were on official waiting lists (International Treatment Preparedness Coalition, 2006). However, ITPC estimated that over 625 000 people in South Africa still urgently required HAART.

In the early days of HAART, there was concern that men would have better access to HAART due to existing gender imbalances (Nattrass, 2006). In fact, it appears that women have better access to HAART in many developing countries (Muula et al., 2007). In addition, there is some evidence to suggest that women may survive better than men in HAART programmes (Ferradini et al., 2006). However, few analyses from developing countries have examined the potential role of gender in influencing outcomes on HAART.

If it is true that women have better comparative survival rates, this may be due to biological, social and/or structural factors, or due to degree of disease at initiation of HAART. The possibility of mediation by degree of disease is especially plausible, as numerous studies have found CD4 cell count at baseline to be a risk factor for mortality on HAART. In Zambia, for example, a study of over

16 0000 individuals found a strong association between mortality and advanced disease stage at baseline (Stringer et al., 2006).

It is possible that women may do better on HAART simply because they are diagnosed and initiate HAART earlier in the course of disease. Certainly, public health services in much of sub-Saharan Africa, and particularly South Africa, are oriented more towards the health needs of women than men, with a strong focus on maternal and child health. As a result, more women use the public health services, more women access voluntary counselling and HIV testing, often during pregnancy (Lawn et al., 2006a), and more women than men are on HAART (Bekker et al., 2006). If men are being diagnosed and started on treatment at a later stage of disease, it is possible that degree of disease is mediating the apparent association between gender and the risk of mortality in a HAART programme.

This analysis explores whether there is a difference in the survival of men and women in a large South African HAART programme. If such a difference is present, the analysis will assess whether this association is explained by degree of disease. If mediation is found, the study will explore reasons why men are accessing HAART later than women, and suggest some possible solutions to address any gender disparities in access to HAART.

2 AIM

The aim of this analysis is to explore the association between gender and death from programme entry to a year on HAART, among treatment-naïve individuals entering a government antiretroviral therapy programme. To achieve this, the study objectives are:

2.1 To describe the demographic and clinical characteristics of the study cohort;

2.2 To examine overall survival and loss-to-follow-up (LTFU) in the programme, making distinctions between person-time pre-HAART, person-time on-HAART and total person-time;

2.3 To identify crude associations between gender, other baseline participant characteristics and the occurrence of death in each time period. Of the characteristics of interest include age, viral load, CD4 cell count, WHO stage, haemoglobin and income;

2.4 To investigate how the association between gender and mortality during each of the three time periods changes after adjustment for other participant characteristics;

2.5 To assess whether degree of disease (as measured by viral load, CD4 cell count and/or WHO stage) mediates any association between gender and death;

2.6 To identify crude associations between gender, other baseline participant characteristics and the occurrence of LTFU in the time period on HAART and the total time period;

2.7 To identify how the association between gender and LTFU changes in the time period on HAART and the total time period after adjustment for other participant characteristics.

3 LITERATURE REVIEW

A search of the electronic database Medline using the PubMed interface (National Library of Medicine, Bethesda, MD) was conducted to review the literature on HIV/AIDS, sex/gender and HAART, and access to HAART. Search terms included: 'gender and HIV/AIDS', 'sex natural progression HIV', 'HAART', 'biologic differences and HAART', 'mortality pre-HAART and on-HAART', 'gender and health seeking behaviour', 'gender and access to health services', 'barriers to health care', 'utilisation of health services in South Africa'. The search reviewed studies in developed as well as developing countries, but only included publications in English. The literature review included studies on mortality among HIV-infected individuals immediately prior to, and/or during, HAART.

3.1 HIV epidemiology

It is estimated that there are over 33 million people worldwide living with HIV (UNAIDS/WHO, 2007). Nearly two-thirds of these people (22.5 million adults and children) live in sub-Saharan Africa, where the epidemics are different in scale and trends. Southern Africa is the most seriously affected region, home to over one-third of all people living with HIV. South Africa is the epicentre of HIV, with the highest prevalence in the world (UNAIDS/WHO, 2007). It appears that the rapid spread of HIV in the country has been fuelled by a legacy of social inequality, poverty, mobile populations, high levels of sexual violence, disrupted family structures and weak leadership (National Department of Health, 2004a).

In South Africa, as in many other developing countries, women are disproportionately affected by HIV/AIDS. In 2006, national prevalence was estimated at 11.4%: among women, prevalence was 12.7% compared with 10.2% among men (Harris et al., 2007). Nearly 55% of HIV-positive adults are female (National Department of Health, 2004a, SANAC, 2007) and within certain age groups, there is a startling gender disparity. In young adults, an overall prevalence

(15-24 years) of 10.4% masks the difference between 3.7% for males and 16.9% for females (Harris et al., 2007). This disparity persists at older ages. In the age group 20-24 years, there is 23.9% prevalence among women and 6.0% among men. Similarly, among those aged 25-29 years, the prevalence is 33.3% among women and 12.1% for men. Women in the age group 25-29 are the worst affected with prevalence rates of up to 40% (Harris et al., 2007).

Women appear to be at higher risk of HIV acquisition than men due to biological and social reasons. Possible biological mechanisms include: immature genital tracts in young women, increased area for surface contact in the vagina, high rates of undetected sexually transmitted infections (STIs), and the fact that the vagina retains fluids for a comparatively long time (National Department of Health, 2004a). Social reasons include the often marginalised status of women and constraints on their participation in the economic, social, and political life of a country. Generally, women experience discrimination on the basis of class, race and gender (National Department of Health, 2004a, SANAC, 2007). Economic dependence on men can restrict women's ability to protect themselves from HIV infection. High levels of violence against, and abuse of, women also contribute to their vulnerability.

3.2 Natural history of HIV

HIV (the human immunodeficiency virus) is a retrovirus that infects the human immune system and undermines its functioning. Initially there is a brief period of sub-clinical infection, often unnoticed by the infected individual. Thereafter, HIV can remain latent and asymptomatic for up to 10 years. Over time the immune system weakens, causing increased susceptibility to opportunistic infections. Symptoms of early symptomatic disease include fever, diarrhoea, recurrent herpes simplex infections and unexplained weight loss. An AIDS diagnosis is made once the CD4 cell count drops below 200 cells/μL and/or the individual has one or more AIDS-defining illnesses (National Department of Health, 2004a).

Before the advent of HAART, there were high levels of morbidity and mortality once individuals had progressed to AIDS. This pattern was found in both developed and developing countries. Pre-HAART, median survival from seroconversion to death in Africa was approximately 10 years. This was about a year less than the median survival time to death in developed countries pre-HAART (Morgan et al., 2002).

3.3 HIV/AIDS & HAART

The advent of highly active antiretroviral therapy (HAART) in 1996 transformed the prognosis for people living with HIV/AIDS. Previously the only treatment was single or dual therapy for a limited period, after which drug resistance would develop. For individuals who could afford the prohibitively expensive triple therapy, HIV/AIDS became a chronic managed disease. Egger (Egger et al., 1997) prospectively followed 5176 Swiss patients with HIV who started HAART. Depending on the year of enrolment into the cohort, the risk of mortality was reduced by 19% - 62% and the risk of progression to AIDS was reduced by 18% - 73%. More recently, the CASCADE collaboration pooled data from 22 European cohorts and confirmed that HAART decreased overall and cause-specific mortality (Smit et al., 2006).

In developing countries, too, there are now large cohorts of people on HAART with good quality data. After six months on treatment, clinical, virological and immunological responses in developing countries compare favourably with those in developed countries (Marins et al., 2003, Coetzee et al., 2004, Braitstein et al., 2006, Bekker et al., 2006, Stringer et al., 2006, Zachariah et al., 2006). Ferradini (Ferradini et al., 2006) found that even in a large-scale programme in Malawi with simplified HAART regimens and few medical and monitoring resources, outcomes were comparable with those in developed countries.

Although the overall outcomes are good, numerous studies report high early mortality rates among patients entering HAART programmes in developing countries (Etard et al., 2006, Bekker et al., 2006, Stringer et al., 2006, Braitstein et al., 2006). A comprehensive review of mortality rates in adults on HAART in sub-Saharan Africa found that 9% - 26% of patients die within their first year on HAART, the majority in the first few months (Lawn et al., 2006a). A comparison of mortality rates in the first year on HAART in high- and low-income countries found that the adjusted hazard ratio of mortality (low-income vs high-income settings) dropped from 4.31 (95% CI, 1.57-11.81) during the first month to 1.5 (0.70-3.01) in the last 5 months of the analysis (Braitstein et al., 2006).

These extremely high rates of early mortality appear to be largely due to delays in diagnosis and initiation of HAART (Lawn et al., 2006a). In a recent study, Fairall and colleagues followed 4 570 patients in a South African public sector HAART programme (Fairall et al., 2008). After a year, more than half (53.2%) had died. Of those patients who had died, 87% had not received HAART. This is probably due to strict criteria for initiating therapy in resource-constrained settings. As a result, many patients starting HAART in poorer countries have advanced disease, and are suffering from co-infections including tuberculosis and invasive infections (Braitstein et al., 2006). These patients have limited - if any - access to comprehensive HIV management and care, and it is highly likely that they would be sicker than patients starting HAART in richer countries. This confirms the need to diagnose and initiate treatment at earlier stages of disease, and to understand any gender differences in access and response to HAART.

3.3.1 Gender and survival on HAART

Although it is biologically plausible that women and men may progress and survive differently on HAART, there does not appear to be any consensus on the issue. Numerous studies have confirmed low CD4 cell count at baseline as the strongest predictor of early mortality on HAART (Hogg et al., 2001, Egger et al., 2002, Lawn et al., 2006a). There is some evidence to suggest that CD4 cell counts may differ by gender, with or without HIV. For example, an early study to

establish reference ranges for CD4 cell counts in HIV-negative women and men found that the absolute CD4 cell counts were higher in women than in men (Maini et al., 1996). Some years later, Prins and colleagues (Prins et al., 1999) found that prior to the advent of HAART, women seroconverted, progressed to AIDS and died at higher CD4 cell counts than men did. Giordano (Giordano et al., 2003) found that on HAART, the CD4 cell response of women was greater than that of men, even after adjusting for baseline disease parameters. They suggested that this was probably due to pharmacokinetic differences but might also be due to women repopulating CD4 cells in response to virus suppression faster than men.

Viral loads may also differ between men and women. For example, Sterling and colleagues (Sterling et al., 2005) found that at given CD4 cell counts, average viral loads were lower in women than in men. The underlying mechanisms for differences in viral dynamics have not been established but may include hormonal influences such as sexual maturation, the menstrual cycle, hormonal contraception, hormonal replacement therapy and pregnancy.

If it is true that viral dynamics are different between men and women, their responses to treatment may also be different. On the basis of this, Finkel (Finkel et al., 2003) studied patients who had achieved sustained virological suppression on HAART. They found that women in this group had a greater immunological response to therapy than men and suggested that this may be due to significant pathological differences between men and women. Similarly, in a study of 2620 patients on HAART, Collazos (Collazos et al., 2007) found that women had better clinical and viro-immunological responses to HAART than men, even after adjusting for other variables. The authors concluded that gender played a small but significant role in clinical and laboratory outcomes of HIV infection. In contrast, a recent systematic review (Nicastri et al., 2007) found little evidence that gender influenced responses to HAART. The authors noted, however, that most of these studies may have had insufficient power to detect true gender differences.

If gender does influence responses to treatment, it is important to understand how it impacts on survival in HAART services. There are now large HAART programmes in developing countries which are being accessed predominantly by women. In the early days of HAART, there was concern that men would have better access than women due to existing gender inequities (Nattrass, 2006). In fact, women appear to have disproportionately better access than men in developing countries (Muula et al., 2007). However, there has been little in-depth analysis of the impact of gender on mortality in HAART programmes. The studies that have been undertaken have produced mixed results.

Two studies from Brazil found that women were at higher risk of mortality on HAART than men. An early study (Santoro-Lopes et al., 1998) found that after adjusting for age, AIDS-defining conditions and baseline CD4, the risk of mortality in women was more than three times the risk in men (adjusted HR 3.33; p=0.170). In a subsequent retrospective cohort study of university out-patient attendees, Braga and colleagues (Braga et al., 2007) found a slight increase in risk among women compared with men (crude HR 1.22), which strengthened when adjusted for a number of baseline factors (adjusted HR 1.86; 95% CI, 1.14-3.03; p=0.020).

Conversely, a number of African studies found that male gender was an independent predictor of death in the first six months on HAART (Ferradini et al., 2006, Lawn et al., 2006a, Stringer et al., 2006). Lawn (Lawn et al., 2006a) found that in the first four months of treatment, men had nearly double the relative hazard of death of women (HR 2.00; 95% CI, 1.10-3.62). In rural Malawi, after adjusting for numerous baseline factors, Ferradini (Ferradini et al., 2006) found that in the first six months of HAART, men had nearly twice the crude risk of death of women (HR 1.76; 95% CI, 1.29-2.39). After this period, and after adjusting for BMI and CD4 cell count at baseline, the risk for men was slightly attenuated, but still significantly higher than for women (HR 1.63, 95% CI, 1.15-2.31). The authors suggested that this could be due to confounding factors that had not been identified.

Finally, numerous studies found no evidence of gender-based differences in survival on HAART (Hacker et al., 2004, Nicastri et al., 2005, Hogg et al., 2001, Seyler et al., 2003, Weidle et al., 2002). A collaborative analysis of 13 cohort studies found that despite gender differences in responses to treatment, there was no difference in the prognosis of men and women (Egger et al., 2002). In Brazil, Hacker (Hacker et al., 2004) found that the large differences in male and female death-to-case ratios that were present pre-HAART had mostly disappeared in a few years. In a large national roll-out programme in Zambia, Stringer and associates (Stringer et al., 2006) also found that an apparent association between male gender and mortality (crude HR 1.40; 95% CI, 1.20-1.60) was attenuated after adjustment for baseline factors (HR 1.20; 95% CI, 0.90-1.50).

These conflicting results led to two reviews on the issue. One review comparing low and high-income countries found no significant association between gender and progression rates on HAART (Braitstein et al., 2006). Similarly, a systematic review of published studies on gender and HAART found little evidence of differences in the survival of women and men on HAART (Nicastri et al., 2007).

Although there is little consensus on gender differences in responses to HAART, there is more substantial evidence that gender disparities in access to HAART could impact on outcomes. This seems to be due to a range of social and structural factors, which differ depending on the context.

3.4 Gender & access to health services

Women and men appear to access health care services differently (Govender and Penn-Kekana, 2007). These disparities manifest differently in developed and developing countries, and might be a reflection of inequities in health systems rather than individual health seeking behaviour.

In developed countries, women appear to be disadvantaged in access to health care (Bhalotra et al., 2007, Gebo et al., 2005). Often poor and marginalised,

they juggle the needs of their children and other dependants with their own needs, often at the cost of their health. Obstacles to health access for women include their marginalised social status, low socio-economic status (SES) and attitudes of health care providers (Bertakis et al., 2000). For example, an American study early in the epidemic found that HIV-infected women were at increased risk of death (Melnick et al., 1994). The authors ascribed this to differential access to health services and the low socio-economic status of women. These disparities can be seen in other areas of health. Bhalotra (Bhalotra et al., 2007) describes, for instance, how gender disparities in access to health services lead to poor health outcomes in coronary heart disease (CHD) treatment. Following the natural history of CHD, the authors found gender differences at every stage: risk management, screening, diagnosis, treatment and rehabilitation. Women had more risk factors and were less likely to receive lifesaving treatment. Similarly, a recent study in Sweden found that men presenting with skin diseases at an outpatient clinic received better treatment than women (Osika et al., 2005).

These differences persist in access to HAART. Data from the first years of HAART in the United States of America showed that men were more likely to receive HAART than women (Smith and Kirking, 1999, Andersen et al., 2000). In more recent years, the situation appears unchanged. A recent study of 10 905 Americans with HIV confirmed that males were still more likely to receive HAART than women (Gebo et al., 2005).

In contrast, women in developing countries are generally reported to be better users of primary health care (PHC) services (Govender and Penn-Kekana, 2007), although there is limited and sometimes only anecdotal evidence to support this. This appears to fly in the face of explanations for women's limited access to health in richer countries. Why do women in poorer countries, despite inequities in power, social and economic status (Braitstein et al., 2008a), often have better access to health services?

The reasons do not appear to have been rigorously explored. Differences in health seeking behaviour may provide a partial explanation. On balance, however,

it seems more likely that the major obstacle is structural: an inherent orientation of the health services towards the needs of women rather than those of men.

3.4.1 Health seeking behaviour

Govender & Penn-Kekana (Govender and Penn-Kekana, 2007) recently undertook a comprehensive review of the evidence on gender and health access in developing countries. Focusing on experiences of care for TB and depression, the authors found that men and women understood and spoke about illnesses differently and had different health seeking behaviour.

One such difference may arise from prevailing beliefs about masculinity and what it means to be a man (Braitstein et al., 2008a, Govender and Penn-Kekana, 2007, Nattrass, 2006, Muula et al., 2007). Shared notions that a man should be 'strong, independent and self-reliant' (Govender and Penn-Kekana, 2007) may prevent men from accessing health care at early stages of illness, HIV-related or other. Indeed, a review of South African men's role in the response to HIV/AIDS suggests that 'illness (be it of self or one's partner) seem[s] to interfere with the script of being a "real" man' (Kometsi, 2004).

Another reason for disparities in accessing health services may be that women seek and receive treatment earlier than men due to their increased exposure to PHC services. In addition to their own clinic visits, women generally accompany sick family members to clinics (Muula et al., 2007). This increased exposure to clinics and health professionals may increase the likelihood that women are diagnosed and treated for health problems earlier than men. A study by Bertakis and colleagues (Bertakis et al., 2000) provides some evidence in support of this argument. Researchers explored why women were more likely than men to be diagnosed with depression by their primary health care giver. They found that women sought and received care at the primary care level, while men accessed more in-patient care. They reported a significant association between number of clinic visits and diagnosis of depression.

Cultural norms may also limit men's access to health care. Health care services in developing countries are run predominantly by women (Muula et al.,

2007). In patriarchal societies, men may be reluctant to consult with female providers, particularly on sensitive issues such as sexually transmitted infections (Govender and Penn-Kekana, 2007).

While these arguments may provide some explanation of gender differences in access to HAART, the evidence is not entirely convincing. In a recent paper exploring gender differences in access to HAART, Nattrass (Nattrass, 2006) concluded that gendered norms prevented men from acknowledging weakness and seeking medical attention. A review of the literature suggests that, in fact, this may not be the prime obstacle.

3.4.2 Gender orientation of health services in developing countries

A more compelling explanation for the disparities in access to health care may be that primary health care services in most developed countries focus more on the health needs of women than those of men (Braitstein et al., 2008a, Lawn and Wood, 2006). Women can access a range of reproductive and child health services targeting healthy young women of reproductive age. In contrast, men are offered few, if any, sexual and reproductive health services (Varga, 2001). Indeed, Mehta (Mehta et al., 2004), describing work with South African men in clinics and communities, suggest that 'men are generally the forgotten reproductive health care clients'. In a review of sexual and reproductive health and men in sub-Saharan Africa, Varga (Varga, 2001) called males 'the forgotten fifty per cent'. Could it be true, as Hawkes (Hawkes and Hart, 2000) argues, that women are regarded as having rights regarding reproductive health while men have responsibilities?

In South Africa, the limited primary health care services for men consist mainly of curative services for STIs and TB (Lawn and Wood, 2006). As men are not being offered services at a primary health care level, they are less likely than women to seek and receive appropriate primary health care at earlier stages of illness (Govender and Penn-Kekana, 2007). Consequently, men may be less likely to be diagnosed at an early stage of HIV due to their limited interaction with primary health care services.

In addition, men have less access than women to voluntary counselling and testing (VCT) for HIV. HIV testing is not routinely offered in all health care facilities (National Department of Health, 2004a, SANAC, 2007). Women are offered routine VCT through antenatal programmes and are also more likely to be offered VCT due to their increased exposure to clinics and health professionals. In contrast, men would be offered VCT in STI, TB or general curative services (Lawn and Wood, 2006). These men would tend to be sicker than the women being referred from reproductive health services.

The South African government has attempted to address existing gaps in access to testing (National Department of Health, 2004a). The National Strategic Plan (NSP) aims to increase provider-initiated VCT in all health settings, primarily STI, TB, antenatal, family planning and general curative services. Unfortunately VCT in these settings will not identify men requiring HAART at earlier stages of disease, as has been illustrated.

The NSP also fails to address other needs of men in the PHC services. The special needs of women and children are prioritised for treatment, care and support. There is, however, no mention of the special needs of men, other than those of men who have sex with men. In fact, there is almost no mention of men in the entire NSP. As Jordaan (Jordaan, 2006/7) argues, 'ignoring half of the population and in effect making the other half solely responsible for HIV prevention cannot be a durable strategy'.

3.5 Summary

HIV/AIDS continues to spread unabated through the world. Southern Africa is the epicentre of the HIV/AIDS epidemic, home to nearly one third of all people living HIV. South Africa has the highest prevalence of HIV in the world, with women comprising 55% of those infected. Data on the natural history of HIV suggest that there may be gender differences in progression to AIDS and death. This might be due to biological, social and/or structural factors.

Access to HAART has transformed the prospects of people living with HIV/AIDS, reducing morbidity and mortality and allowing HIV/AIDS to be treated as a chronic managed disease. For some years, there was only very limited access to HAART due to the prohibitive cost. However, international advocacy has reduced the costs substantially and many developing countries are now offering HAART. With increasing numbers of people - predominantly women - on HAART through public health systems, it is essential to understand the impact of gender on access and responses to antiretroviral therapy.

It is biologically plausible that women and men may respond differently to HAART. It is also likely that disparities in access to HAART could impact on outcomes. Numerous studies have explored these issues, with conflicting results. However, most analyses that adjust for baseline factors find no significant difference in outcomes. It is possible that apparent gender differences in survival are mediated by the degree of disease at start of treatment. Certainly, it seems that people who start HAART with more advanced disease are likely to have worse outcomes than those who are diagnosed and treated at earlier stages.

The reasons why women may be diagnosed earlier than men in developing countries are complex and difficult to quantify. They include differences in health seeking behaviour and the existing gender orientation of primary health services. Further research is needed to understand gender-based differences in access to health services in order to ensure that women and men are diagnosed and initiated on HAART as early as possible, to improve their survival in HAART programmes.

4 METHODS

4.1 Study design

This cohort study explored gender differences in the survival of HIV-infected people enrolling on a treatment programme at the Hannan Crusaid Treatment Centre (HCTC), an antiretroviral therapy (ART) clinic based in Gugulethu, Cape Town. The study was a retrospective review and secondary analysis of the patient records contained in the HCTC database. During routine assessment, demographic, clinical and other data on 2843 treatment-naïve adults were collected between September 2002 and April 2007. All patients who had started treatment in another facility were excluded as being non-naïve.

Numerous HAART service evaluations (Bekker et al., 2006, Etard et al., 2006, Stringer et al., 2006) have reported high rates of early mortality, which tend to decline after the first few months. It was anticipated that in this cohort, the major burden of mortality would fall within the first year. Most HAART cohort studies only report data from the date of initiation of HAART. However, Lawn (Lawn et al., 2006a) found that after three years of a HAART programme, deaths in the period between entry and initiation of HAART accounted for nearly half of the total mortality. Thus, this analysis followed patients from the first visit at the clinic to one year after the initiation of HAART.

4.2 Study site and population

Based in the Gugulethu Community Health Centre, the HCTC provides HAART to residents of Nyanga. Nyanga is a predominantly African township on the outskirts of Cape Town with a population estimated at 300 000. Most inhabitants are of low socio-economic status, as are the majority of black South Africans. Antenatal HIV seroprevalence in 2003 was 28%. The patient profile is representative of patients accessing HAART in South Africa. Originally established for research, the HCTC was one of the first sites in the Western Cape

to roll-out antiretrovirals in September 2002 (Bekker et al., 2003, Bekker et al., 2006, Lawn et al., 2006a).

The referral system comprises nine primary health care (PHC) clinics, two community health care centres (CHCs) and a Midwife Obstetric Unit (MOU) that provides antenatal care. The PHC clinics are run by the city health services and offer primary care for HIV, TB and sexually transmitted infections (STIs). The CHCs offer general medical services for adults, often with HIV clinics. ARV therapy is provided to patients on the basis of the 2002 guidelines of the World Health Organisation (WHO), i.e. WHO stage 4 disease or CD4 cell count below 200 cells/μL. All individuals referred to HCTC have already been identified as requiring ARV therapy. In line with provincial guidelines, the clinic offers first-line HAART and a second-line regimen for those who fail treatment. Most patients have not previously received HAART and receive standard first-line therapy (Lawn et al., 2006a). First-line treatment in South Africa for men, women of child-bearing potential and pregnant women consists of stavudine, lamivudine and nevirapine (NVP). For any conditions where NVP is contra-indicated, efavirenz is substituted (National Department of Health, 2004b).

The average time from first visit to initiation of HAART is approximately one month, during which time patients undergo clinical and psycho-social assessment. Typically, this includes clinical staging, blood tests in order to establish baseline levels of CD4 cell count and HIV viral load, and collection of demographic data.

In addition, patients undergo three group treatment-readiness sessions to ensure that they are ready to initiate and remain on long-term therapy. Patients are then assigned to a community-based therapeutic counsellor from the Sizophila programme. The counsellors provide support on site and follow up with home visits. This therapeutic support contributes to high rates of adherence and viral suppression and low rates of loss-to-follow-up (LTFU) (Lawn et al., 2006a, Orrell et al., 2003). Patients are encouraged to disclose their HIV status to a friend or family member, as additional treatment support. After enrolment, adults on first-

line HAART see a medical doctor at four, eight and 16 weeks and every four months thereafter, for clinical, immunological and virological assessment. All treatment is free of charge, and drugs are dispensed every two months. At each visit, patients see the therapeutic counsellor for psychosocial support, and to return unused pills.

This cohort has been well-studied but there has been no systematic evaluation of the impact of gender on survival and LTFU after entry into the programme. Previous studies have established that there is high early mortality in this programme (Lawn et al., 2006a). However, previous analyses have not examined whether there was a gender difference in mortality in the pre-treatment period. Over three years, only 21 individuals (2.3%) were lost-to-follow-up, but there was no analysis of gender differences within this group.

4.3 Definitions

'Deaths pre-HAART' were those patients who died after entry into the programme but before initiating HAART. 'Permanent deferrals' were those individuals who did not ever initiate HAART but did not die pre-HAART. 'Awaiting treatment' were those who had not initiated treatment at the date of censoring. 'Started treatment' were those who started HAART. 'Deaths on HAART' were patients who died while on treatment. 'Transfers out' were those individuals who were transferred to another facility, having initiated therapy. 'LTFU on HAART' were patients who started HAART and have been absent from the clinic for longer than 3 months. 'Still on treatment' were patients who were still on HAART at the date of censoring.

4.4 Measurements

Demographic and clinical data were collected via standard HCTC data collection forms (Appendix 8.4) and entered onto an MS Excel database. Variables treated as continuous in this analysis were: age (years), viral load at

baseline (log copies of HIV RNA/ml), CD4 cell count at baseline (cells per microlitre), haemoglobin (g/dL) and income (R/month). Categorical variables were: gender (1=female, 2=male), WHO stage at baseline (I & II, III or IV), CD4 cell count (<50, 51-100, 101-150 and >150 cells/μL), and income (R0/month, R1-R699/month or >=R700/month). There were data on education level (primary/secondary) for 2544 subjects. As 2303 (91%) of these had at least secondary level education, education level was excluded from the analysis. In order to assess associations with clinical outcomes at 48 weeks, two responses variables were generated: CD4 cell count at 48 weeks (continuous) and viral suppression at 48 weeks (binary).

Generally, there was a period of about four weeks between patients' first visit and the start of treatment. During this time, patients underwent screening and treatment-readiness. The first visit was known as week minus 4, or 'week -4'. The visit at which patients were started on treatment was regarded as the baseline visit or 'week 0'. However, for a few patients who were very ill, or who had previously undergone treatment-readiness sessions elsewhere, their first visit was also regarded as their baseline (visit 0), at which they started HAART. In order to include these in the analysis, the date of starting treatment was recorded as one day later than their first visit. One patient died on the day s/he started treatment. In order to include this death in the analysis, date of death was recorded as one day later than the start of treatment. The clinic defines patients as LTFU if there has been an absence of three months since their last clinic visit. As patients receive 1-2 months HAART at a visit, this means that they will have missed 1 or more months of HAART. Overall, five patients were recorded as lost-to-follow-up (LTFU) on their start dates. To include their data, the date of LTFU was estimated at three months after the start date.

The data set contained CD4 cell counts and viral load measures taken on specific visits. In instances when these were not taken at a particular visit, the data sometimes included an interim measure taken between visits. This analysis assumed that any such measure would be used to represent the CD4 or viral load

of the previous missed visit. Where, for example, the CD4 cell count from a week 4 visit was missing but there was a value for a measure taken before the week 8 visit, the measure taken between the two visits was used as the value for the week 4 visit.

WHO staging was done by medical doctors at screening visits, according to the 2002 WHO clinical guidelines. CD4 cell count and HIV RNA viral load testing were done in an on-site laboratory. CD4 cell count was done using flow cytometry (FACSCount™, Becton Dickinson, Franklin Lakes, NJ, USA). HIV RNA viral load was tested with branch DNA hybridisation technique (VersantTM HIV-1 RNA 3.0 branched chain DNA assay (Bayer Healthcare, Leverkusen, Germany).

4.5 Analysis

Cleaning, coding and analysis of data were done in Intercooled STATA 10.0 for Windows (STATA Corporation, College Station, TX). In the exploratory data analysis, the distribution of continuous variables was tested in histograms. As the variables were non-parametrically distributed, the study reported medians and inter-quartile ranges. Differences between groups were tested using the Wilcoxon sum rank test for medians and the chi-square test for proportions.

Observation time was calculated in three different ways. The first time period was the observation time from the patient's first visit to one of four outcomes: (1) death before initiating HAART; (2) permanent deferral of treatment; (3) awaiting treatment at date of censoring; or (4) initiation of treatment. The second time period was the observation time from the start of treatment to one of four possible outcomes: (1) death on HAART; (2) transfer to another facility; (3) LTFU on HAART; or (4) still on treatment at date of censoring. The third time period was the total observation time from the first visit to the closure of the database, 24 April 2007, with six possible outcomes: (1) death before or on HAART; (2) alive on treatment at censoring date; (3) awaiting

HAART at censoring date; (4) permanent deferral before initiation of HAART; (5) transferral to another facility while on HAART; (6) LTFU on HAART.

Age, viral load and CD4 cell count were modelled as continuous and categorical variables, and different cut-off points were tested. Age was retained as a continuous variable as its association with death was continuous. Although the effects of CD4 cell count and viral load were continuous, they were modelled as categorical variables in line with current practice. In testing categorical variables for significance, this analysis reported the global p-value instead of separate p-values for each level of the variable. Haemoglobin was measured at the baseline visit (week 0) and not at the first visit (week -4). However this measure was included here as a baseline characteristic in analysis, since there is likely to be minimal variability in haemoglobin over this short (2-4 week) period. Haemoglobin measurements were only available for 1853 patients, and it is included here only as a descriptive measure. As the inclusion of haemoglobin in multivariate models would have required dropping an additional 600 observations, it was not included in a final model.

The comparative survival by gender in the three observation periods was estimated and compared with Kaplan-Meier survival curves and use of the log rank test. Survivor functions were generated for each of the three observation periods, with a comparison at the same time points by gender. Cox's proportional hazards regression was used to estimate the crude impact of the variables on the hazard of death in the three groups. Cox's proportional hazards regression was also used to investigate the effect of gender on the hazard of death after adjusting for participant demographic and HIV disease-related characteristics. The best-fit model was selected on the basis of changes to the crude association between gender and mortality, as well as the number of observations being lost with the addition of each new variable.

Cox's proportional hazard regression models rely on the assumption that the effect of variables on survival time remains constant over time, i.e. the hazards are proportional. Thus, a test for proportional hazards is equivalent to testing for a

non-zero slope in a regression of Schoenfeld residuals on a function of time (Cleves et al., 2002). This analysis tested the proportional hazards assumption using Schoenfeld and scaled Schoenfeld residuals on the rank of time (Appendix 8.3.1). In addition, Cox-Snell residuals were generated to assess overall model fit (Cleves et al., 2002). If the line did not deviate much from the reference line, the models appeared to provide a good fit for the data.

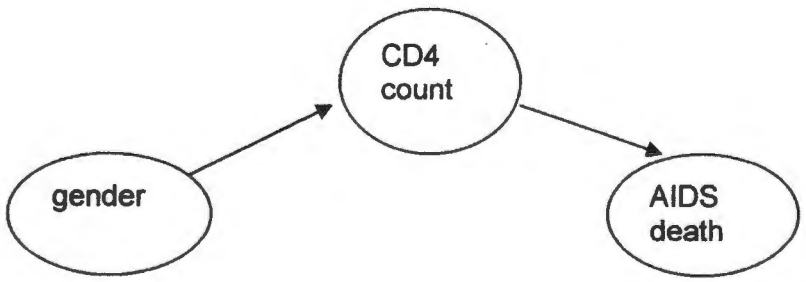
Logistic regression was used to estimate the crude impact of the variables on the binary response variable (viral suppression at 48 weeks). It was also utilised to investigate the effect of gender on viral suppression at 48 weeks, adjusted for participant demographic and HIV disease-related characteristics. The model was checked by testing the general fit and the adequacy of the linear component (Appendix 8.3.2). The goodness-of-fit statistic was generated, with a p-value >0.05 showing that the model was a fairly good fit for the data (Juul, 2006).

Multiple linear regression was used to estimate the crude impact of the variables on the continuous response variable (CD4 cell count at 48 weeks). It was also used to explore the effect of gender on CD4 cell count at 48 weeks after adjustment for baseline characteristics. The model was checked by testing the normality of residuals and by assessing whether collinearity was present (Appendix 8.3.3). Residuals were plotted in a histogram and a two-way scatter and assessed for normality. Individual and global variance inflation factors (VIFs) were calculated. An individual VIF >10 would suggest that this variable may be redundant in the model (Juul, 2006). Logistic regression was also used to estimate the crude impact of sex on the binary response variables (CD4 cell count at 48 weeks >200 vs <200; and >350 vs <350).

The study tested if degree of disease was acting as a mediator that might explain the apparent association between gender and death. As shown in Figure 1 below, for a disease parameter to act as a mediator, it must be part of the causal pathway connecting exposure (gender) to disease (AIDS death) (Susser et al., 2006). If this is the case, it is not desirable to remove its effect, as with confounding, but rather to understand how this factor acts together with gender to

cause death. It is not possible to distinguish between confounders and mediators on the basis of data alone (Susser et al., 2006), although tests can provide evidence to corroborate a biologically plausible hypothesis. It is biologically plausible that instead of gender causing AIDS mortality directly, gender may cause differences in CD4 cell counts which in turn cause AIDS deaths. Regression co-efficients from adjusted models were used to examine the potential mediating role of individual disease parameters in the association between gender and mortality using the Sobel test (Shrout and Bolger, 2002). The Sobel test tells whether the indirect effect of the independent variable on the dependent variable through the mediator variable is significant. It does this by testing the hypothesis that there is no difference between the direct effect and the total effect. The Sobel test is believed to be superior, for example, to the Baron & Kenny method, in terms of power, Type I error, suppression effects, addressing the significance of the indirect effect. It is limited by the underlying assumption that the sampling distribution is normal(Tein and MacKinnon, 2003). Throughout the analysis, 2-sided statistical tests at alpha=0.05 and 95% confidence intervals were used unless otherwise indicated.

Figure 1: CD4 cell count mediating the association between gender and AIDS mortality



4.6 Ethics

The key ethical issues that arose in undertaking this analysis involved aspects of beneficence, justice and, to some extent, autonomy.

Beneficence implies that patients are not intentionally harmed and that possible benefits to patients are maximised while possible harms are minimised (Joubert and Ehrlich, 2007). This analysis posed no risk or discomfort to the patients since it did not involve additional human subjects research and only utilised data that had already been collected as part of clinic routine. This data collection was formally approved by the UCT Research Ethics Committee (Appendix 8.1).

The concept of justice in medical research ethics is closely tied to that of beneficence. However, it raises additional questions for researchers: who should benefit from the research, and who should bear the burden of such research (Joubert and Ehrlich, 2007)? In this study, participants represent South Africans accessing HAART through the public health system. Although the analysis will not directly benefit the participants bearing the burden of the research, it could potentially offer some benefit to this broader community. It could increase existing knowledge about the impact of gender on survival of people in HAART programmes in developing countries. By analysing the comparative survival of men and women pre- and on-treatment, and by exploring whether this is mediated by degree of disease, the study could increase knowledge about gender differences in HAART programmes. It could support policy aimed at improving access to public health services and national HAART programmes. If no mediation is found, this information could guide future research into other factors impacting on survival. The requirement of justice appears to be satisfied.

With respect to autonomy, all subjects have already been provided with information about ongoing research at the HCTC. At their first visit, subjects sign an informed consent form confirming that they understand the nature of the research and agree to the collection of relevant data to this end. As the study utilises a data base which does not contain patient identifiers, patient confidentiality is ensured. A confidentiality agreement at the HCTC further protects patients' rights. Patients who choose not to sign the informed consent form still receive treatment.

5 RESULTS

5.1 Baseline characteristics

A total of 3162 adults were referred for HAART at HCTC between 2 September 2002 and 23 April 2007. Patients who had started HAART at another facility and then transferred into the programme were excluded (n=319). This analysis includes the remaining 2843 HAART-naïve individuals, 1889 (66%) of whom were female. An estimated 8% of these women were pregnant at programme entry, and may thus have initiated HAART at a higher CD4 count and/or lower WHO stage than others entering the programme. A total of 329 (12%) started with CD4 counts above 200 cells/μL, of whom 246 were female and 83 male ($p<0.001$).

As shown in Table 1, there were significant gender differences in key baseline characteristics on entry into the HAART programme. On average, women were younger than men (31 years vs 36 years, $p<0.001$) and had higher median CD4 cell counts at baseline (112 vs 89 cells/μL; $p<0.001$). Women had significantly lower haemoglobin counts than men (10.7g/dL vs 12.2 g/dL; $p<0.001$). Haemoglobin counts for women and men were lower than the bottom limit of the normal ranges[1].

More women than men (28% vs 16%) presented with early stage disease, classified as WHO stage I & II, while more men than women (29% compared with 20%) were classified as WHO stage IV at entry ($p<0.001$). The median log viral load was higher among men (4.97, IQR, 4.55-5.40) than among women (4.78, IQR, 4.30-5.20; $p<0.001$). Approximately half of all females and males earned no monthly income, and 240 (16%) of females and 49 (7%) of males earned R1-R700/month ($p<0.001$).

[1] According to the Oxford Handbook of Clinical Medicine, normal haemoglobin ranges are 11.5-16g/dL for women and 13-18g/dL for men.

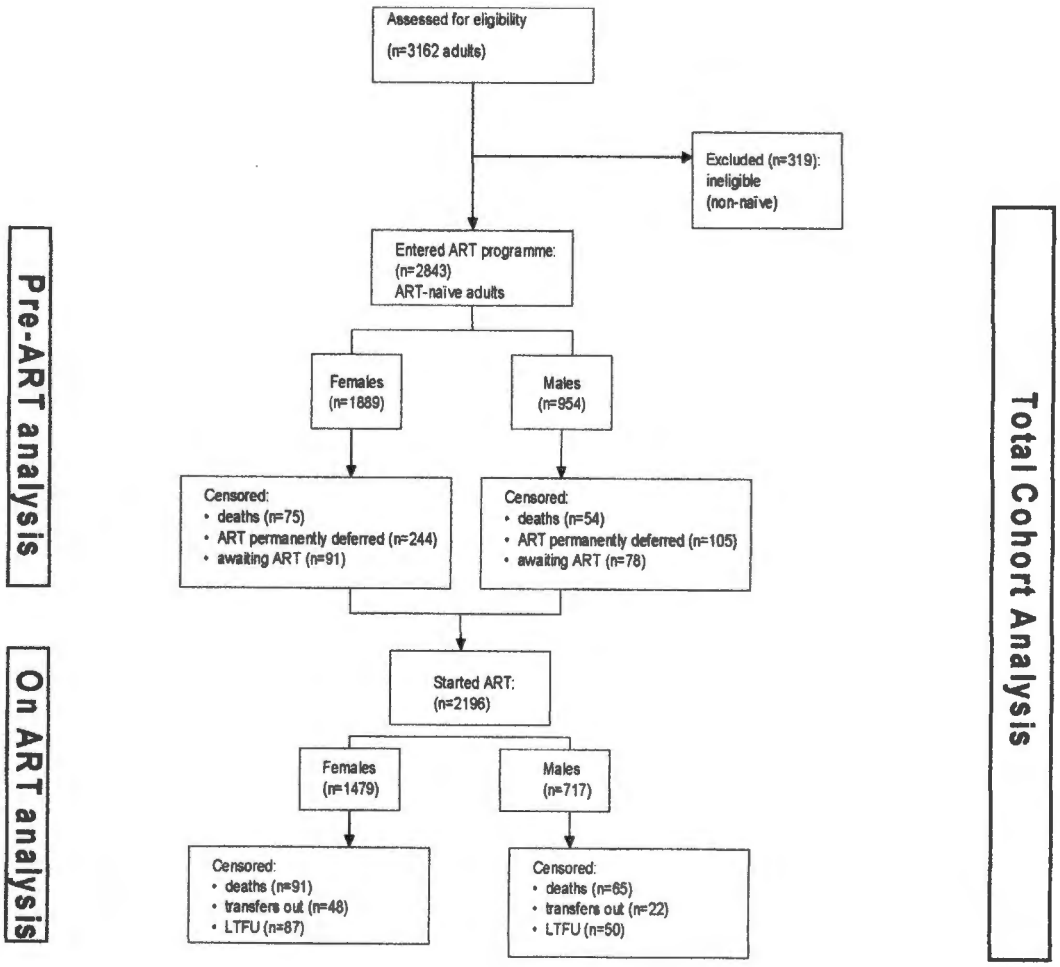
Table 1: Baseline characteristics of cohort at entry to HAART programme

Characteristic	Total cohort (n=2843)	Women (n=1889)	Men (n=954)	p-value
Age, median (y) (IQR)	33 (28-39)	31 (27-37)	36 (31-42)	p<0.001
Haemoglobin (g/dL), median (IQR)	11 (9.8-12.4)	10.7 (9.6-11.8)	12.2 (10.5-13.6)	p<0.001
CD4 cell count (cells/μL), median (IQR)	105.5 (48-164)	112 (57-169)	89 (38-154)	p<0.001
CD4 cell count (cells/μL), *n* (%)				p<0.001
<50	627 (26%)	367 (23%)	260 (33%)	
51-100	521 (22%)	338 (21%)	183 (23%)	
101–150	515 (21%)	368 (23%)	147 (18%)	
> 150	745 (31%)	541 (33%)	204 (26%)	
WHO stage at entry, *n* (%)				p<0.001
I & II	679 (24%)	528 (28%)	151 (16%)	
III	1508 (53%)	979 (52%)	529 (56%)	
IV	650 (23%)	378 (20%)	272 (29%)	
HIV RNA level (log_{10} copies/ml), median (IQR)	4.83 (4.38-5.28)	4.78 (4.3-5.2)	4.97 (4.55-5.4)	p<0.001
HIV RNA level (log_{10} copies/ml), *n* (%)				p<0.001
<= 5 log	1349 (59%)	966 (63%)	383 (52%)	
> 5 log	920 (41%)	571 (37%)	349 (48%)	
Monthly income, *n* (%)				p<0.001
No income	1196 (54%)	821 (54%)	375 (53%)	
R1–R700	289 (14%)	240 (16%)	49 (7%)	
>R700	730 (33%)	448 (39%)	282 (40%)	

5.2 Enrolment and follow-up

The data were divided into three analyses based on time spent in the programme (Figure 2). These were: pre-HAART time (from entering the programme to initiation of HAART), time on HAART (from start of therapy to the end of the period of observation) and total cohort time (pre- and on-HAART).

Figure 2: Description of an adult HAART-naïve antiretroviral therapy programme cohort, Gugulethu, South Africa (September 2002-April 2007)



The total follow-up time was 2102 person-years, 1437 person-years of which were for female patients (Table 2).

Table 2: Follow-up time

	Total	Females	Males
Total person-years	2102	1437	665
Pre-HAART person-years	451	291	160
On-HAART person-years	1651	1146	505
Deaths	285	166 (58%)	119 (42%)

During the pre-HAART period, 647 (23%) adults were censored. Of these, 129 were censored due to death. Treatment was permanently deferred for 349 individuals. The remaining 169 were still awaiting treatment at the end of the period. During the on-HAART period, 363 (17%) were censored. A total of 156 patients died, 70 were transferred to another facility and 137 were LTFU. In the total cohort, 1010 (36%) were censored. Overall, 285 patients died, 169 were awaiting treatment and 349 had HAART permanently deferred. A further 70 individuals were transferred to another facility and 137 were LTFU.

5.3 Results for pre-HAART period

5.3.1 Enrolment and follow-up: pre-HAART

The pre-HAART period included a total of 2843 HAART-naïve adults who entered the programme but had not yet initiated HAART. During the pre-HAART period, a total of 647 (23%) subjects were censored. A total of 129 (5%) adults died and 349 (12%) had HAART permanently deferred. A total of 169 (6%) were still awaiting treatment at the date of censoring. The total duration of follow-up was 451 person-years. Females were followed for a total of 291 person-years, and males for 160 person-years. The median duration of follow-up in the pre-HAART period was 35 person-days (IQR, 26-63). Among females, the median follow-up was 35 person-days (IQR, 28-62). The median follow-up among males was 35.5 person-days (IQR, 28-69).

5.3.2 *Mortality pre-HAART*

Table 3 compares baseline characteristics between those who did not start HAART and are still alive with those who started HAART.

Table 3: Baseline characteristics by mortality: pre-HAART

Characteristic	Started HAART	Did not start HAART, not dead	p-value[2]	Died before starting HAART	p-value[3]
Female, *n* (%)	1479 (67%)	335 (65%)	0.244	75 (58%)	0.041
Age, (y), median (IQR)	33 (28-39)	32 (27-39)	0.287	34 (29-40)	0.098
CD4 cell count (cells/μL), median (IQR)	102 (48-158)	164 (86-271)	<0.001	49 (22-110	<0.001
CD4 cell count (cells/μL), *n* (%)			<0.001		<0.001
<50	524 (26%)	48 (17%)		55 (53%)	
51-100	468 (23%)	34 (12%)		19 (18%)	
101-150	452 (22%)	47 (17%)		16 (15%)	
>150	576 (29%)	155 (55%)		14 (14%)	
WHO stage at entry, *n* (%)			<0.001		<0.001
I & II	495 (23%)	179 (35%)		5 (4%)	
III	1197 (56%)	248 (48%)		63 (49%)	
IV	502 (23%)	87 (17%)		61 (47%)	
HIV RNA level, $\log_{10}$ copies/ml, median (IQR)	4.84 (4.4-5.3)	4.64 (3.94-5.17)	<0.001	5.38 (4.79-5.7)	<0.001
HIV RNA level, $\log_{10}$ copies/ml, *n* (%)					
<= 5 log	1181 (60%)	145 (68%)	0.015	23 (32%)	<0.001
> 5 Log	803 (40%)	68 (32%)		49 (68%)	
Monthly income, *n* (%)			0.657		0.250
No income	1007 (54%)	124 (52%)		65 (62%)	
R1–R700	243 (13%)	36 (15%)		10 (9%)	
>R700	621 (33%)	79 (33%)		30 (29%)	

[2] p-value for comparisons between those who did not start HAART and are not dead vs those who started HAART

[3] p-value for comparisons between those who died before starting HAART and those who started HAART

Table 3 also compares characteristics of those who died before starting HAART with those who started HAART.

There was high early mortality, with 129 (45%) of the total cohort deaths occurring in this period. The incidence rate was 28.6/100 person-years of observation. The incidence rate among women was lower than among men (25.8/100 vs 33.8/100 person-years; p=0.133).

On average, those who died during the pre-HAART period had lower median CD4 cell counts than those who started treatment (49 vs 102 cells/μL; p<0.001). They also had higher log viral loads than those who started HAART (5.38 vs 4.84; p<0.001). There were differences in WHO stage at entry. Those classified as stage I & II, III or IV among the deaths and those initiating HAART were respectively 4% vs 23%, 49% vs 56%, and 47% vs 23% (p<0.001). There were no significant differences in median age and monthly income between those who died and those who started HAART.

Table 3 also compares baseline characteristics of those who started HAART with those who did not start HAART and did not die in this period. There was no significant gender difference between the proportions of men and women who did and did not start HAART (p=0.244). Those who had not started HAART and were not dead tended to have higher CD4 cell count than those who started HAART (164 vs 102 cells/μL; p<0.001). Those who started HAART had higher median log viral loads than those alive and not starting therapy (4.84 vs 4.64; p<0.001). Those classified as stage I & II, III or IV among those alive and not on HAART vs those who started HAART were respectively 35% vs 23%, 48% vs 56%, and 17% vs 23% (p<0.001). The median age was not different between these groups (p=0.287), nor was monthly income (p=0.657).

5.3.3 Crude association between baseline characteristics and mortality: pre-HAART

Table 4 shows the crude associations between baseline characteristics and the hazard of mortality.

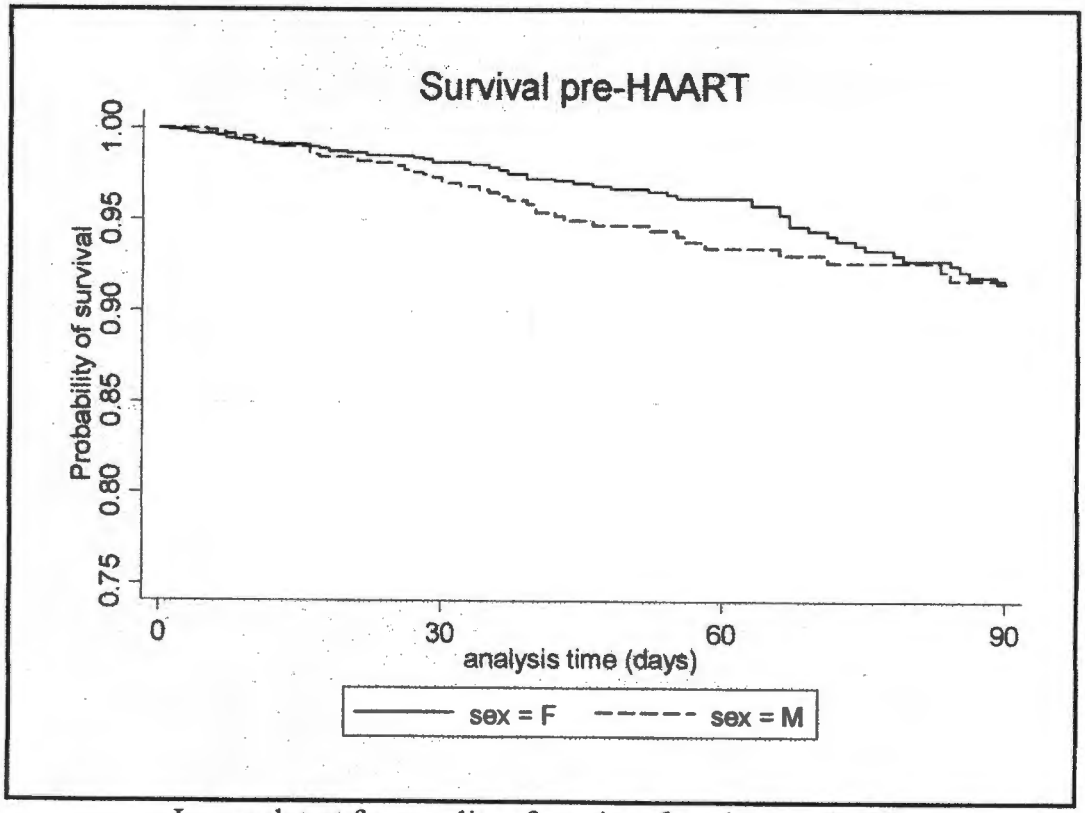
Table 4: Crude association between baseline characteristics and mortality: pre-HAART

Characteristic	HR	95% CI	p-value
Gender			
Female	1.0		
Male	1.31	(0.93-1.86)	0.131
Age	1.02	(1.00-1.04)	0.086
CD4 cell count (cells/μl)	0.99	(0.99-0.99)	<0.001
CD4 cell count (cells/μL)			<0.001
<50	1.0		
51-100	0.38	(0.23-0.64)	
101-150	0.30	(0.17-0.52)	
>150	0.15	(0.08-0.27)	
WHO stage at entry			<0.001
I & II	1.0		
III	5.91	(2.38-14.71)	
IV	13.64	(5.48-33.96)	
HIV RNA level, log_{10} copies/ml	2.92	(1.87-4.55)	<0.001
<= 5 Log	1.0		
> 5 Log	3.0	(1.83-4.94)	
Monthly income			0.089
No income	1.0		
R1-R700	0.60	(0.31-1.18)	
>R700	0.66	(0.43-1.01)	

Male gender increased the risk of mortality (HR 1.31, 95% CI, 0.93-1.86; p=0.131) as did age (HR for a one-year increase in age, 1.02, 95% CI, 1.00-1.03; p=0.086). Those presenting with higher CD4 cell counts at baseline were less likely to die in the pre-HAART period than those with lower CD4 cell counts (HR 0.99, 95% CI, 0.99-0.99; p<0.001). This benefit was most marked among those who had >150 cells/μL at baseline compared with <50 cells/μL (HR 0.15, 95% CI, 0.08-0.27; p<0.001). There was a six-fold increase in the relative hazard of mortality among those classified as WHO stage III compared with WHO stage I & II at entry (HR 5.91, 95% CI, 2.38-14.70) and a fourteen-fold increase among those classified stage IV compared with stage I & II (HR 13.64, 95% CI, 5.48-33.96; p<0.001). For every one log increase in the baseline HIV RNA level, there was a three-fold increase in hazard (HR 2.92, 95% CI, 1.87-4.55; p<0.001). Those

earning any income had a 40% reduction in risk compared with those earning nothing (HR 0.60, 95% CI, 0.31-1.18; p=0.089). The corresponding Kaplan-Meier curves (Figure 3) and survival estimates (Table 5) suggest that there was no difference in survival between women and men before starting HAART, unadjusted for baseline characteristics.

Figure 3: Kaplan-Meier survival curves: men and women: pre-HAART



Log rank test for equality of survivor functions: p=0.129

Table 5: Kaplan-Meier survival estimates: pre-HAART

Time (days)	Females	Males
0	1.000	1.000
30	0.982	0.971
60	0.962	0.935
90	0.916	0.917

5.3.4 Adjusted effect of male gender on mortality in the pre-HAART period

Proportional hazards models were used to assess the adjusted effect of male gender on the risk of mortality (Table 6). After adjustment for WHO stage at entry, the hazard ratio for male gender was reduced from 1.31 (95% CI, 0.92-1.86) to 1.10 (95% CI, 0.77-1.56). It was further reduced to 1.07 (95% CI, 0.74-1.53) after adjusting for both WHO stage and age. Adjusted for WHO stage, age and CD4 cell count at entry, male gender did not appear to be a risk factor for death (HR 1.01, 95% CI, 0.67-1.51).

Table 6: Adjusted effect of male gender on mortality: pre-HAART

Characteristic	Model 1	Model 2	Model 3	Model 4
Gender				
Female	1.0	1.0	1.0	1.0
Male	1.31 (0.92-1.86)	1.10 (0.77-1.56)	1.07 (0.74-1.53)	1.01 (0.67-1.51)
WHO stage at entry				
I & II		1.0	1.0	1.0
III		5.8 (2.30-14.5)	5.77 (2.30-14.38)	4.06 (1.45-11.36)
IV		13.4 (5.37-33.43)	13.19 (5.28-32.94)	8.49 (3.01-23.95)
Age			1.01 (0.99-1.03)	1.02 (0.99-1.04)
CD4 cell count (cells/μL)				
<50				1.0
51-100				0.46 (0.27-0.78)
101-150				0.42 (0.24-0.75)
>150				0.22 (0.12-0.40)

5.3.5 Mediation by degree of disease

In a separate analysis (not shown), there was evidence to suggest that disease parameters mediate the apparent association between gender and death pre-HAART. The Sobel test found significant associations with CD4 cell count (p=0.044) and WHO stage at entry (p=0.003). Supporting this, the mediating role can be seen plainly in Table 6 above. Comparing the crude and adjusted hazard ratios, there was a marked attenuation, amounting to a 30% reduction in the log hazard for death (comparing gender coefficients from models 1 and 4).

5.4 Results for on HAART analyses

5.4.1 Enrolment & follow-up: on HAART

The on-HAART period includes a total of 2196 HAART-naïve adults who initiated HAART after entering the programme. During this period, 363 (16%) were censored. This comprised 156 (7%) deaths, 70 (3%) transferrals to another facility and 137 (6%) who were LTFU. The total duration of follow-up was 1651 person-years, of which 1146 person-years were among female patients and 505 person-years among males (Table 2). The median duration of follow-up in the on-HAART period was 365 person-days (IQR, 183-365). Among females, the median follow-up time was 365 person-days (IQR, 202-365). The median follow-up time among males was 343 person-days (IQR, 145-365).

5.4.2 Mortality: on HAART

Table 7 compares baseline characteristics of those who died with those who did not die and were not transferred to another facility or LTFU in the on-HAART period. It also compares characteristics of those who were LTFU with those who did not die, were not LTFU and were not transferred. In this period, 55% (n=156) of the total cohort deaths occurred. The incidence rate was 9.45/100 person years of observation. More than half of those who died (58%) were female (p=0.010). The incidence rate was lower among women than men (7.9/100 person-years vs 12.9/100 person-years; p=0.003).

On average, those who died had lower haemoglobin counts at baseline than those who did not die (p<0.001). Overall, the patients who died were older (p=0.007) and had far lower median CD4 cell counts at baseline than those who survived (p<0.001). The proportions of those who died vs those who survived with CD4 cell counts <50, 51-100, 101-150 and >150 cells/μL respectively were 48% vs 25%, 22% vs 21%, 14% vs 22%, and 16% vs 32% (p<0.001). There were significant differences in WHO stage at entry. Those classified as Stage I & II, III

Table 7: Baseline characteristics by mortality and loss-to-follow-up: on HAART

Characteristic	Not died, not LTFU or transferred	Died	p-value[4]	LTFU	p-value[5]
Female, *n* (%)	1798 (67%)	91 (58%)	0.010	87 (64%)	0.240
Haemoglobin, (g/dL), median (IQR)	11.1 (9.8-12.4)	10.1 (8.9-11.3)	<0.001	11 (9.7-12.3)	0.400
Age, median (y) (IQR)	32 (28-39)	35 (29-43)	0.007	31 (26-37)	0.037
CD4 cell count (cells/μL), median (IQR)	108 (52-166)	53 (14-112)	<0.001	114 (40-170)	0.881
CD4 cell count (cells/μL), *n* (%)			<0.001		0.051
<50	555 (25%)	72 (48%)		41 (30%)	
51-100	488 (21%)	33 (22%)		24 (18%)	
101-150	494 (22%)	21 (14%)		24 (18%)	
>150	721 (32%)	24 (16%)		47 (34%)	
WHO stage at entry, *n* (%)			<0.001		0.879
I & II	667 (25%)	12 (8%)		35 (26%)	
III	1427 (53%)	81 (52%)		72 (53%)	
IV	587 (22%)	63 (40%)		30 (22%)	
HIV RNA level, $\log_{10}$ copies/ml, median (IQR)	4.82 (4.35-5.27)	5.04 (4.59-5.44)	0.001	4.84 (4.35-5.4)	0.490
HIV RNA level, $\log_{10}$ copies/ml					
<=5 Log	1279 (60%)	70 (49%)		81 (60%)	
> 5 Log	846 (40%)	74 (51%)		54 (40%)	
Monthly income, *n* (%)			0.015		0.004
No income	1104 (53%)	92 (63%)		86 (66%)	
R1–R700	270 (13%)	19 (13%)		11 (9%)	
>R700	695 (34%)	35 (24%)		32 (25%)	

[4] p-value for comparison between those who died and those who did not die, were not LTFU or transferred to another facility

[5] p-value for comparison between those who were LTFU and those who did not die, were not LTFU or transferred to another facility

or IV among the deaths and survivors in the programme were respectively 8% vs 25%, 52% vs 53%, and 40% vs 22% (p<0.001). On average, the median log viral load at baseline was significantly higher among those who died than among those still alive (5.04 vs 4.82; p=0.001). More than half of those who died (63%) and those who did not die (53%) received no monthly income (p=0.015).

5.4.3 Crude association between baseline characteristics and mortality: on HAART

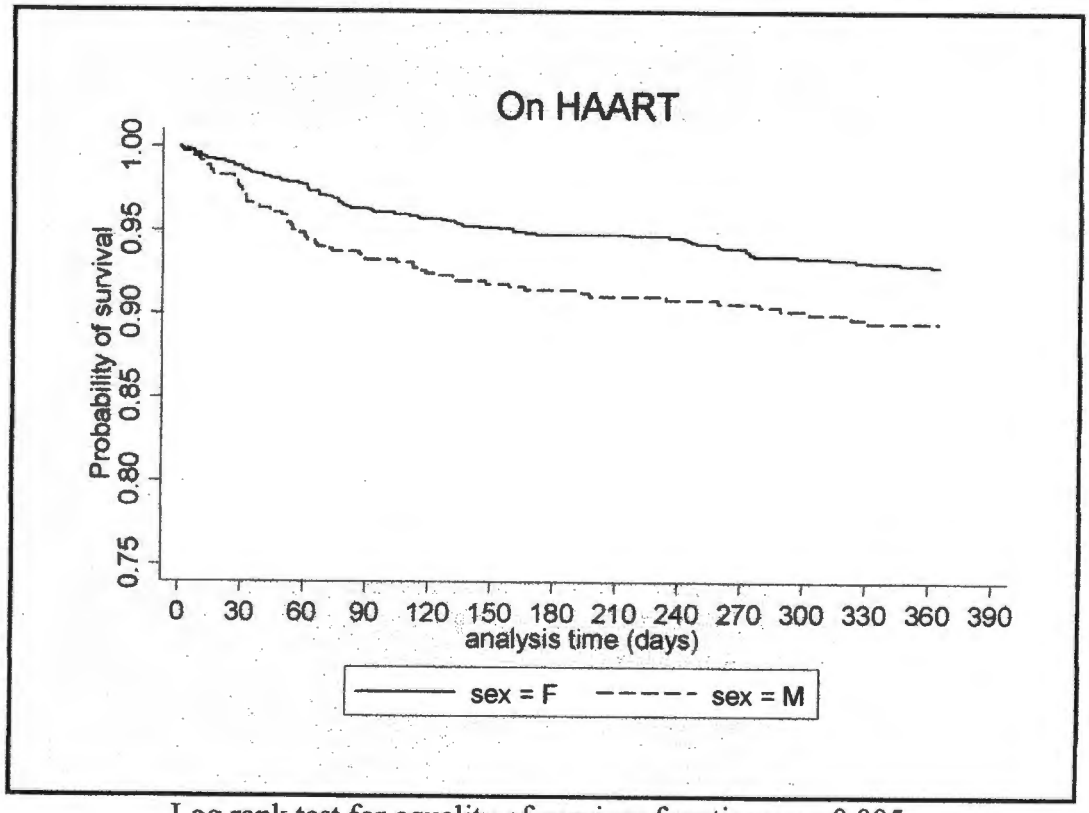
Table 8 shows the crude association between baseline characteristics and the risk of death on treatment. In this time period, male gender increased the risk by 57% (HR 1.57, 95% CI, 1.14-2.16; p=0.005). This is confirmed in the corresponding Kaplan-Meier curve (Figure 4) and survival estimates (Table 9).

Table 8: Crude association between baseline characteristics and mortality: on HAART

Characteristic	HR	95% CI	p-value
Gender			
Female	1.0		
Male	1.57	(1.14-2.16)	0.005
Haemoglobin (g/dL)	0.83	(0.76-0.91)	<0.001
Age	1.03	(1.01-1.05)	<0.001
CD4 cell count (cells/µl)	0.99	(0.99-0.99)	<0.001
CD4 cell count (cells/µl)			<0.001
<50	1.0		
51-100	0.47	(0.31-0.71)	
101-150	0.31	(0.19-0.51)	
>150	0.28	(0.18-0.45)	
WHO stage at entry			<0.001
I & II	1.0		
III	2.73	(1.49-5.00)	
IV	5.24	(2.83-9.71)	
HIV RNA level, log_{10} copies/ml	1.45	(1.13-1.88)	0.004
HIV RNA level, log_{10} copies/ml			
<= 5 Log	1.0		
> 5 Log	1.61	(1.16-2.24)	
Monthly income			0.022
No income	1.0		
R1-R700	0.80	(0.49-1.32)	
>R700	0.58	(0.39-0.86)	

A one-unit increase in haemoglobin at baseline was associated with a 17% reduction in the risk of mortality (HR 0.83, 95% CI, 0.76-0.91; p<0.001). The risk of death increased with age (HR for a one-year increase in age, 1.03, 95% CI, 1.01-1.05; p<0.001). The risk was lower for those with higher CD4 cell counts at entry than those with lower CD4 cell counts (HR 0.99, 95% CI, 0.99-0.99; p<0.001). This benefit was most marked among those with CD4 cell counts above 150 cells/μL (HR 0.28, 95% CI, 0.18-0.45; p<0.001). Compared with those classified WHO stage I & II at entry, there was a nearly three-fold increase in hazard among those classified stage III (HR 2.73, 95% CI, 1.49-5.00) and a five-fold increase among those classified stage IV (HR 5.24, 95% CI, 2.83-9.71; p<0.001). For every one-log increase in HIV RNA level, there was a 45% increase in the risk of death (HR 1.45, 95% CI, 1.13-1.88; p=0.004). Increased income was associated with a reduction in risk. Those earning above R700/month had a 42% reduction in risk compared with those earning nothing (HR 0.58, 95% CI, 0.39-0.86; p=0.022).

Figure 4: Kaplan-Meier survival curves: men and women: on HAART



Log rank test for equality of survivor functions: p=0.005

Table 9: Kaplan-Meier survival estimates: men and women: on HAART

Time (days)	Females	Males
30	0.987	0.973
60	0.978	0.946
90	0.963	0.933
120	0.958	0.925
150	0.952	0.918
180	0.948	0.914
210	0.948	0.911
240	0.946	0.909
270	0.940	0.907
300	0.934	0.902
330	0.932	0.898
360	0.930	0.895

5.4.4 Adjusted effect of male gender on mortality in the period on HAART

Proportional hazards models were used to assess the adjusted effect of male gender on the risk of death on HAART (Table 10). After adjusting for WHO stage at entry, the hazard ratio for male gender was reduced from 1.57 (95% CI, 1.14-2.16) to 1.38 (95% CI, 1.00-1.91). It was further reduced to 1.25 (95% CI, 0.90-1.74) after adjusting for both WHO stage and age. Adjusted for WHO stage, age and CD4 cell count on entry, male gender increased the risk of death by 19% (HR 1.19, 95% CI, 0.88-1.97).

Table 10: Adjusted effect of male gender on mortality: on HAART

Characteristic	Model 1	Model 2	Model 3	Model 4
Gender				
Female	1.00	1.00	1.00	1.00
Male	1.57 (1.14-2.16)	1.38 (1.00-1.91)	1.25 (0.90-1.74)	1.19 (0.88-1.97)
WHO stage at entry				
I & II		1.00	1.00	1.00
III		2.63 (1.43-4.83)	2.54 (1.39-4.67)	2.35 (1.21-4.58)
IV		4.92 (2.65-9.16)	4.76 (2.56-8.86)	3.93 (1.98-7.80)
Age			1.02 (1.01-1.04)	1.02 (1.01-1.04)
CD4 cell count (cells/μL)				
<50				1.00
51-100				0.54 (0.35-0.81)
101-150				0.40 (0.24-0.66)
>150				0.35 (0.22-0.56)

5.4.5 Mediation by degree of disease

Utilising the Sobel test, there was evidence to suggest that both CD4 ($p=0.045$) and WHO stage at entry ($p<0.001$) mediated the apparent association between gender and death on HAART. Supporting this, the mediating role can be seen plainly in Table 10 above.

There was a marked attenuation between the crude and adjusted hazard ratios, amounting to a 38% reduction in the log hazard for death (comparing gender coefficients from models 1 and 4).

5.4.6 Loss-to-follow-up on HAART

Table 7 (pg 49) also compares baseline characteristics of those LTFU with those who did not die and were not transferred or LTFU while on HAART. Of the 2196 patients who initiated HAART, 137 (6%) were LTFU within a year. Of these, 87 (64%) were female. There was no significant difference in gender distribution between those LTFU and those who were alive at one year ($p=0.240$). The median age was slightly lower among those LTFU than those who were retained on HAART (31 vs 32, $p=0.037$). Neither median CD4 cell count ($p=0.881$) nor median log viral load ($p=0.490$) differed between LTFU and those who survived. However, when comparing the number of patients with CD4 cell counts at different levels, there were significant differences between those LTFU and those retained. The proportions of those LTFU vs those who survived in the programme with CD4 cell counts <50, 51-100, 101-150 and >150 cells/μL respectively were 30% vs 25%, 18% vs 21%, 18% vs 22% and 34% vs 32% ($p=0.051$). Over half of those LTFU (66%) and those who survived (53%) earned no monthly income ($p=0.004$).

5.4.6.1 Crude association between baseline characteristics and loss-to-follow-up: on HAART

Table 11 shows the crude association between baseline characteristics and the risk of being LTFU on HAART. Males were 30% more likely to be LTFU on

HAART (HR 1.30, 95% CI, 0.92-1.84; p=0.140). A one-year increase in age was associated with a 2% reduction in the risk of LTFU (HR 0.98, 95% CI, 0.96-1.00; p=0.050). The risk of LTFU reduced with increasing CD4 cell count at entry (p=0.063). WHO stage at entry was not associated with the hazard of being LTFU on HAART (p=0.630), nor was log viral load (p=0.840). There was a highly significant dose response with monthly income (p=0.003). There was a 51% reduction in the risk of being LTFU for those earning R1-R700/month compared with those earning nothing (HR 0.49, 95% CI, 0.26-0.91). This association was attenuated when comparing those earning over R700/month with those earning nothing (HR 0.55, 95% CI, 0.37-0.83).

Table 11: Crude association between baseline characteristics and risk of loss-to follow-up: on HAART

Characteristic	HR	95% CI	p-value
Gender			
Female	1.00		
Male	1.30	0.92-1.84	0.140
Age	0.98	0.96-1.00	0.050
CD4 cell count (cells/μL)			0.063
<50	1.00		
51-100	0.59	(0.36-0.98)	
101-150	0.61	(0.37-1.02)	
>150	0.96	(0.63-1.45)	
WHO stage at entry			0.630
I & II	1.00		
III	0.82	(0.55-1.23)	
IV	0.85	(0.52-1.38)	
HIV RNA level, log_{10} copies/ml			0.840
<= 5 Log	1.00		
> 5 Log	1.04	(0.73-1.46)	
Monthly income			0.003
No income	1.00		
R1-R700	0.49	(0.26-0.91)	
>R700	0.55	(0.37-0.83)	

5.4.6.2 Adjusted effect of male gender on LTFU in the period on HAART

Proportional hazards models were used to assess the adjusted effect of male gender on the risk of being LTFU (Table 12). After adjustment for age, the hazard ratio for male gender was inflated from 1.30 (95% CI, 0.92-1.84) to 1.49 (95% CI, 1.03-2.14). After adjustment for age and monthly income, this association was reduced to 1.38 (95% CI, 0.94-2.01). Inclusion of CD4 cell count in the model reduced the association further to 1.34 (95% CI, 0.91-1.96).

Table 12: Adjusted effect of male gender on risk of loss-to-follow-up: on HAART

Variables	Model 1	Model 2	Model 3	Model 4
Gender				
Female	1.0	1.0	1.0	1.0
Male	1.30 (0.92-1.84)	1.49 (1.03-2.14)	1.38 (0.94-2.01)	1.34 (0.91-1.96)
Age		0.97 (0.95-0.99)	0.98 (0.95-1.00)	0.98 (0.96-1.00)
Monthly income				
R0			1.0	1.0
R1-R700			0.51 (0.27-0.95)	0.51 (0.27-0.96)
>R700			0.57 (0.38-0.86)	0.57 (0.38-0.87)
CD4 cell count (cells/μL)				
<50				1.0
51-100				0.62 (0.37-1.00)
101-150				0.58 (0.34-0.99)
>150				1.00 (0.65-1.54)

5.5 Results for total cohort

5.5.1 Enrolment & follow-up: total cohort

The total cohort includes 2843 HAART-naïve adults who entered the programme. At the end of one year's treatment, 1010 (36%) individuals had been censored and 1833 (64%) were still on HAART. Of those censored, 285 died and 349 had HAART permanently deferred. A total of 70 individuals were transferred to another facility and 137 were LTFU. At the time of censoring, 169 individuals were awaiting treatment. The total duration of follow-up time was 2102 person-years. Females contributed 1437 person-years to follow-up time, and males 665 person-years. The median duration of follow-up was 326 person-days (IQR, 95-

395). Among females, the median follow-up time was 358 person-days (IQR, 103-398). Among males, the median follow-up time was 267 person-days (IQR, 90-394).

5.5.2 Mortality: total cohort

Table 13 compares baseline characteristics between those who died in the total cohort and those who were alive and were not transferred or LTFU to another facility after one year on HAART. It also compares characteristics of those who were LTFU vs those still alive on HAART. Overall, 285 (10%) people died. Of these, 166 (58%) were female (p=0.001). The incidence rate was 13.6/100 person-years, with a marked gender difference. The incidence rate was lower among women than men (11.5/100 person-years vs 17.9/100 person-years, p<0.001).

On average, those who died were older than those who survived in the programme (34 vs 33, p=0.003). They had lower median CD4 cell counts than survivors (51 vs 106 cells/μL, p<0.001). Median log viral loads were higher among those who died than those who did not (5.16 vs 4.81, p<0.001). Those classified WHO stage I & II, III or IV among those who died and those who survived were respectively 6% vs 24%, 51% vs 55% and 43% vs 22 (p<0.001). Most of the individuals who died and over half of those who survived (62% vs 52%) earned no monthly income (p=0.004). Table 14 shows the comparative survival proportions of the total cohort.

Table 13: Baseline characteristics by mortality and loss-to-follow-up: total cohort

Characteristic	Alive on HAART	Deaths	p-value[6]	LTFU	p-value[7]
Female, *n* (%)	1253 (68%)	166 (58%)	0.001	87 (64%)	0.240
age, median (y) (IQR)	33 (28-38)	34 (29-41)	0.003	31 (26-37)	0.037
CD4 cell count (cells/μL), median (IQR)	106 (55-159)	51 (16-111)	<0.001	114 (39.5-170)	0.880
CD4 cell count (cells/μL), *n* (%)			<0.001		0.051
<50	388 (23%)	127 (50%)		41 (30%)	
51-100	399 (24%)	52 (20%)		24 (18%)	
101-150	393 (24%)	37 (15%)		24 (18%)	
>150	485 (29%)	38 (15%)		47 (34%)	
WHO stage at entry, *n* (%)			<0.001		0.879
I & II	436 (24%)	17 (6%)		35 (25%)	
III	999 (55%)	144 (51%)		72 (53%)	
IV	396 (22%)	124 (43%)		30 (22%)	
HIV RNA level, $\log_{10}$ copies/ml, median (IQR)	4.81 (4.39-5.24)	5.16 (4.65-5.55)	<0.001	4.84 (4.35-5.4)	0.490
HIV RNA level, $\log_{10}$ copies/ml			<0.001		0.817
<= 5 Log	1256 (61%)	93 (43%)		81 (60%)	
> 5 Log	797 (39%)	123 (57%)		54 (40%)	
Monthly income, *n* (%)			0.004		0.004
No income	788 (52%)	157 (62%)		86 (67%)	
R1–R700	205 (13%)	29 (12%)		11 (8%)	
>R700	205 (13%)	65 (26%)		32 (25%)	

[6] p-value for comparison between those who died and those alive on HAART
[7] p-value for comparison between those who were LTFU and those known to be alive on HAART

Table 14: Kaplan-Meier survival estimates: men and women: total cohort

Time (days)	Females	Males
0	1.000	1.000
30	0.981	0.970
60	0.964	0.937
90	0.945	0.915
120	0.933	0.907
150	0.925	0.887
180	0.919	0.881
210	0.915	0.875
240	0.913	0.868
270	0.908	0.863
300	0.903	0.861
330	0.899	0.855
360	0.897	0.853
390	0.893	0.853

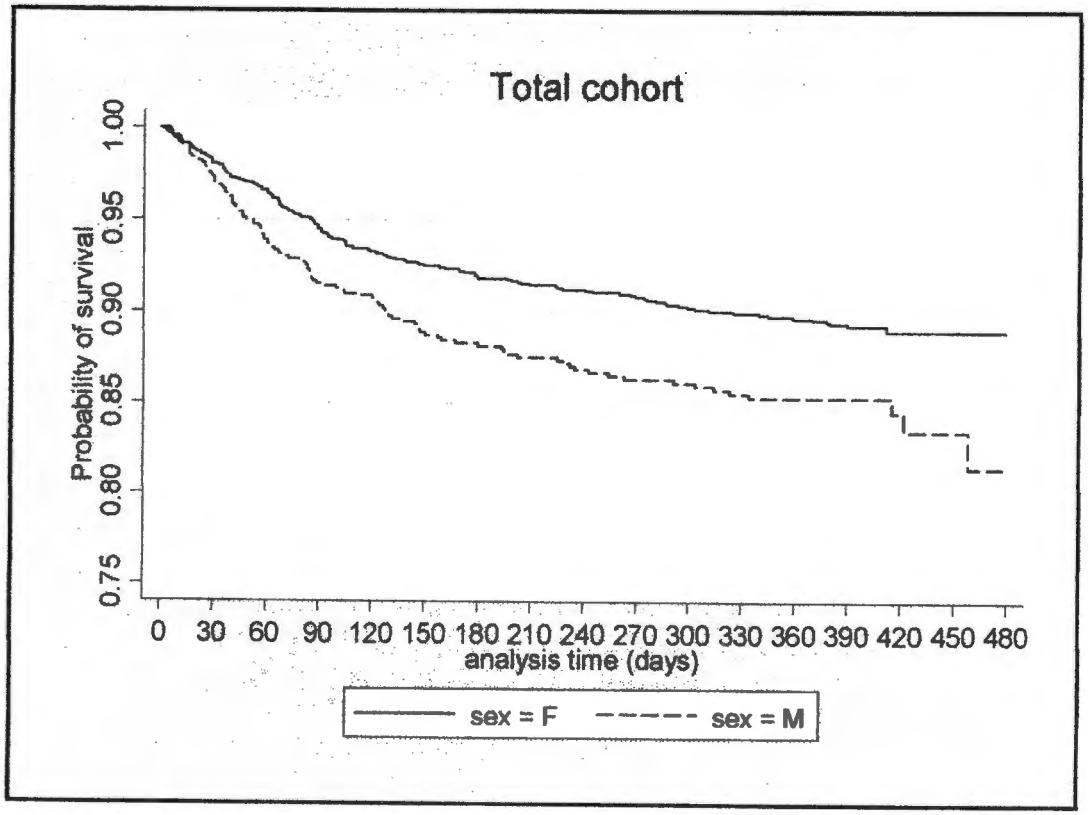
5.5.3 Crude association between baseline characteristics and mortality: total cohort

Table 15 shows the crude association between baseline characteristics and the risk of death in the total cohort. Between entry into the programme and the end of a year's therapy, male gender increased the risk of death by 49% (HR 1.49, 95% CI, 1.17-1.88; p=0.001). This is confirmed in the Kaplan-Meier survival curves (Figure 5). Older people were more at risk than younger (HR for a one-year increase in age, 1.02, 95% CI, 1.01-1.03; p<0.001). The risk of death was lower for those with higher CD4 cell counts at entry than those with lower CD4 cell counts (HR 0.99, 95% CI, 0.99-0.99; p<0.001). This benefit was most marked among those with CD4 cell counts above 150 cells/μL (HR 0.24, 95% CI, 0.17-0.34; p<0.001). Compared with those classified WHO stage I & II at entry, there was a greater than three-fold increase in risk for those in WHO stage III (HR 3.60, 95% CI, 2.18-5.96). This strengthened to a nearly eight-fold increase in risk for individuals in WHO stage IV (HR 7.60, 95% CI, 4.55-12.55; p<0.001). For every one-log increase in HIV RNA level, there was a doubling in hazard (HR 1.98, 95% CI, 1.52-2.60; p<0.001). Increased income was associated with a reduction in risk. Those earning above R700/month had a 37% reduction in risk compared with those earning nothing (HR 0.63, 95% CI, 0.47-0.85; p=0.006).

Table 15: Crude association between baseline characteristics and risk of mortality: total cohort

Characteristic	HR	95% CI	p-value
Gender			
Female	1.0		
Male	1.49	(1.17-1.88)	0.001
Age	1.02	(1.01-1.04)	<0.001
CD4 cell count (cells/μL)	0.99	(0.99-0.99)	<0.001
CD4 cell count (cells/μL)			<0.001
<50	1.0		
51-100	0.44	(0.32-0.61)	
101-150	0.32	(0.22-0.46)	
>150	0.24	(0.17-0.34)	
WHO stage at entry			<0.001
I & II	1.0		
III	3.60	(2.18-5.96)	
IV	7.56	(4.55-12.55)	
HIV RNA level, log_{10} copies/ml			<0.001
<= 5 Log	1.0		
> 5 Log	1.98	(1.52-2.60)	
Monthly income			0.006
No income	1.0		
R1-R700	0.73	(0.49-1.09)	
>R700	0.63	(0.47-0.85)	

Figure 5: Kaplan-Meier survival curves: men and women: total cohort



Log rank test for equality of survivor functions: p=0.009

5.5.4 Adjusted effect of male gender on the risk of mortality: total cohort

Proportional hazards models were used to assess the adjusted effect of male gender on the risk of mortality in the total cohort (Table 16). The hazard ratio for male gender was reduced from 1.49 (95% CI, 1.17-1.88) to 1.30 (95% CI, 1.01-1.62) after adjustment for WHO stage at entry. It was further reduced to 1.19 (95% CI, 0.93-1.50) after adjusting for WHO stage and age. Adjusted for WHO stage, age and CD4 cell count at entry, males had a 15% higher risk of death than women in the total cohort (HR 1.15, 95% CI, 0.93-1.50).

Table 16: Adjusted effect of male gender on risk of mortality: total cohort

Characteristic	Model 1	Model 2	Model 3	Model 4
Gender				
Female	1.0	1.0	1.0	1.0
Male	1.49 (1.17-1.88)	1.30 (1.01-1.62)	1.19 (0.93-1.50)	1.15 (0.89-1.49)
WHO stage at entry				
I & II		1.0	1.0	1.0
III		3.50 (2.11-5.79)	3.40 (2.06-5.64)	2.80 (1.60-4.90)
IV		7.20 (4.30-12.00)	7.02 (4.20-11.70)	5.26 (2.98-9.29)
Age			1.02 (1.00-1.03)	1.02 (1.01-1.04)
CD4 cell count (cells/μL)				
<50				1.0
51-100				0.51 (0.37-0.71)
101-150				0.43 (0.29-0.62)
>150				0.31 (0.22-0.45)

5.5.5 Mediation by degree of disease

In the total cohort, degree of disease progression appeared to mediate the association between gender and death. Utilising the Sobel test, there was evidence to suggest that both CD4 ($p=0.035$) and WHO stage at entry ($p<0.001$) independently mediated the association between gender and death in the total cohort. Table 16 shows the marked attenuation between the crude and adjusted hazard ratios, amounting to a 34% reduction in the log hazard for death (comparing gender coefficients from models 1 and 4).

5.5.6 Loss-to-follow-up: total cohort

Table 13 (pg 57) also compares baseline characteristics of those LTFU with those who were still on treatment after one year. Of the patients who entered the programme, 137 (4.8%) were LTFU one year after starting therapy. Of these, 87 (64%) were female. There was no significant difference in gender distribution between those LTFU and those who were still on HAART ($p=0.240$). The median age was slightly lower among those LTFU than those still on therapy (31 vs 33, $p=0.037$). Neither median CD4 cell count ($p=0.880$) nor median log viral load ($p=0.490$) differed significantly between those LTFU and those who were retained

on HAART. However, when comparing the numbers of patients with CD4 cell counts at different levels, there were significant differences between groups. The proportions of those LTFU vs those who survived in the programme with CD4 cell counts <50, 51-100, 101-150 and >150 cells/μL respectively were 30% vs 23%, 18% vs 24%, 18% vs 24%, and 34% vs 29% (p=0.051). Overall, 86 (67%) of those LTFU and 788 (52%) of the survivors earned no monthly income (p=0.004).

5.5.7 Crude association between baseline characteristics and loss-to-follow-up: total cohort

Table 17 shows the crude association between baseline characteristics and loss-to-follow-up in the total cohort.

Table 17: Crude association between baseline characteristics and loss-to-follow-up: total cohort

Characteristic	HR	95% CI	p-value
Gender			
Female	1.0		
Male	1.26	(0.89-1.78)	0.194
Age	0.98	(0.96-1.00)	0.056
CD4 cell count (cells/μL)	1.00	(1.00-1.00)	0.582
CD4 cell count (cells/μL)			0.101
<50	1.0		
51-100	0.60	(0.36-0.99)	
101-150	0.60	(0.37-1.00)	
>150	0.87	(0.57-1.33)	
WHO stage at entry			0.714
I & II	1.0		
III	0.85	(0.56-1.27)	
IV	0.87	(0.53-1.41)	
HIV RNA level, log_{10}			
<= 5 Log	1.0		
>5 Log	1.02	(0.72-1.44)	0.916
Monthly income			0.002
No income	1.0		
R1-R700	0.48	(0.25-0.89)	
>R700	0.54	(0.36-0.80)	

Between programme entry and the end of 48 weeks of HAART, men were at a slightly increased risk of being LTFU (HR 1.26, 95% CI, 0.89-1.78; p=0.194). There was a minimal reduction in the risk of LTFU with increasing age (HR for a one-year increase in age, 0.98, 95% CI, 0.96-1.00; p=0.056). When CD4 count was used as a continuous variable, it did not appear to impact on LTFU (p=0.101). However, when included as a categorical variable, it seemed that those who enrolled with lowest CD4 cell counts were less likely to be LTFU, but this protection was reduced for those with CD4 cell counts >150. Neither WHO stage (p=0.714) nor viral load (p=0.916) impacted on the risk of LTFU. Income had the greatest effect on the risk of LTFU (p=0.002). There was a 52% reduction in the risk of LTFU among those earning up to R700/month compared with those with no income (HR 0.48, 95% CI, 0.25-0.89).

5.5.8 Adjusted effect of male gender on risk of loss-to-follow-up: total cohort

Proportional hazards models were used to assess the adjusted effect of male gender on the risk of being LTFU in the total cohort (Table 18). Adjustment for age increased the risk for men compared with women (HR 1.43, 95% CI, 0.99-2.06). Further adjustment for monthly income reduced the effect slightly (HR 1.35, 95% CI, 0.92-1.97). Men were 35% more likely to be LTFU at 48 weeks than women.

Table 18: Adjusted effect of male gender on risk of loss-to-follow-up: total cohort

Characteristic	Model 1	Model 2	Model 3
Gender			
Female	1.0	1.0	1.0
Male	1.26 (0.89-1.78)	1.43 (0.99-2.06)	1.35 (0.92-1.97)
Age		0.97 (0.95-0.99)	0.98 (0.96-1.00)
Monthly income			
R0			1.0
R1-R700			0.49 (0.26-0.93)
>R700			0.55 (0.37-0.83)

5.6 Clinical outcomes at 48 weeks

5.6.1 Viral load at 48 weeks

Viral load <50 copies/ml was regarded as viral suppression. Viral load measurements at 48 weeks were available for a total of 1012 patients, 824 (81%) of whom were female. There was no significant gender difference between the proportions achieving undetectable viral loads at 48 weeks (p=0.913).

5.6.1.1 Crude association between baseline characteristics and viral suppression at 48 weeks

Table 19 shows the crude association between baseline characteristics and viral suppression at 48 weeks. Only age is significantly associated with the outcome (OR 1.04, 95% CI, 1.02-1.06; p=0.001).

Table 19: Crude association between baseline characteristics and viral suppression at 48 weeks

Characteristic	OR	95% CI	p-value
Gender			
Female	1.0		
Male	1.02	(0.72-1.45)	0.913
Age	1.04	(1.02-1.06)	0.001
CD4 cell count (cells/μL)			0.388
<50	1.0		
51-100	1.33	(0.84-2.10)	
101-150	0.96	(0.62-1.49)	
>150	1.27	(0.82-1.97)	
WHO stage at entry			0.243
I & II	1.0		
III	0.7	(0.46-1.06)	
IV	0.81	(0.49-1.34)	
HIV RNA level, log_{10} copies/ml			
<= 5 log	1.0		
>5 log	0.93	(0.75-1.16)	0.545
Monthly income			
No income	1.0		0.380
R1-R700	1.29	(0.85-1.98)	
>R700	1.21	(0.84-1.76)	

5.6.1.2 Adjusted effect of male gender on viral suppression at 48 weeks

Logistic regression models were used to assess the adjusted effect of male gender on viral suppression at 48 weeks (Table 20). In multivariate analysis, only age and WHO stage significantly influenced viral suppression. Adjustment for viral load at baseline and age reduced the odds ratio for male gender from 1.03 (95% CI, 0.72-1.46) to 0.85 (95% CI, 0.59-1.24). Further adjustment for WHO stage at entry did not change this association (OR 0.86; 95% CI, 0.59-1.25). Men appeared to be 14% less likely to be virally suppressed at 48 weeks than women.

Table 20: Adjusted effect of male gender on viral suppression at 48 weeks

Characteristic	Model 1	Model 2	Model 3
Gender			
Female	1.0	1.0	1.0
Male	1.03 (0.72-1.46)	0.85 (0.59-1.24)	0.86 (0.59-1.25)
HIV RNA level, log_{10} copies/ml			
<= 5 log	1.0	1.0	1.0
>5 log	0.93 (0.75-1.16)	0.91 (0.73-1.14)	0.95 (0.76-1.18)
Age		1.04 (1.02-1.07)	1.04 (1.02-1.07)
WHO stage:			
I & II			1.0
III			0.66 (0.43-1.02
IV			0.79 (0.47-1.33)

5.6.2 CD4 cell count at 48 weeks

CD4 measurements were available at 48 weeks for a total of 1 046 patients. Of these, 751 (72%) were female. The mean CD4 cell count at 48 weeks for women was 296 cells/μL (range 54-724). Among men, the mean was 266 cells/μl (range 24-654). This difference was statistically significant ($p<0.001$).

5.6.2.1 Crude association between baseline characteristics and CD4 cell count at 48 weeks

Modelling CD4 cell count at 48 weeks as a continuous variable (Table 21), on average men had 30.1 cells/μL less than women (95% CI, -48.8 - -11.5; $p=0.002$). CD4 cell count at baseline ($p<0.001$), age ($p<0.001$) and log viral load at entry ($p=0.012$) impacted on CD4 cell count at 48 weeks. Baseline

characteristics that did not significantly influence CD4 cell count at 48 weeks were WHO stage at entry (p=0.922) and monthly income (p=0.222). In addition, CD4 count at 48 weeks was modelled as two binary outcomes (CD4 cell count at 48 weeks >200 vs <200; and CD4 >350 vs <350). Using logistic regression (not shown), men were 38% less likely than women to have a CD4 cell count >200 at 48 weeks. They were 28% less likely than women to reach a CD4 cell count >350 at 48 weeks.

Table 21: Crude association between baseline characteristics and CD4 cell count at 48 weeks

Characteristic	β (co-efficient)	95% CI	SE	p-value
Male gender	-30.1	(-48.8; -11.5)	9.5	0.002
Baseline CD4 cell count (cells/μL)				<0.001
51-100	11.3	(-11.3; 33.8)	11.5	
101-150	57.4	(34.5; 80.4)	11.7	
>150	124.8	(103.1; 146.5)	11.1	
Age	-3.2	(-4.2; -2.1)	0.5	<0.001
WHO stage at entry				0.922
III	3.3	(-13.6; 20.3)	8.7	
IV	-0.8.	(-21.1; 19.5)	10.4	
HIV RNA level, log_{10} copies/ml				
Logvl>5	22.9	(4.9; 40.1)	8.9	0.012
Monthly income:				0.222
R1-R700	-4.7	(-26.9; 17.6)	11.3	
>R700	-16.9	(-36.2; 2.3)	9.8	

5.6.2.2 Adjusted effect of male gender on CD4 cell count at 48 weeks

Linear regression models were used to assess the adjusted effect of male gender on CD4 cell count at 48 weeks (Table 22). Adjusting for age and CD4 cell count at baseline, the association between male gender and CD4 cell count was weakened. After adjustment for age and CD4, WHO stage and viral load at entry, men had lower CD4 cell counts at 48 weeks than women (-15.3 cells/μL; range -33.2; 2.6).

Table 22: Adjusted effect of male gender on CD4 cell count at 48 weeks

Characteristic	Model 1	Model 2	Model 3	Model 4
Male gender	-23.4 (-40.8; -5.9)	-10.30 (-28.20; 7.7)	-12.7 (-30.7; 5.3)	-15.3 (-33.2; 2.6)
CD4 cell count (cells/μL)				
51-100	9.1 (-13.4; 31.7)	13.0 (-9.4; 35.3)	17.5 (-5.0; 39.9)	20.8 (-1.6; 43.2)
101-150	54.9 (31.9; 77.9)	57.7 (34.9; 80.4)	65.7 (42.4; 89.1)	74.8 (51.5; 98.0)
>150	122.4 (100.6; 144.1)	121.9 (100.4; 143.4)	127.2 (105.5; 148.9)	139.6 (117.6; 161.5)
Age		-2.6 (-3.6; -1.6)	-2.8 (-3.8; -1.8)	-2.9 (-3.9; -1.9)
WHO stage at entry				
III			26.8 (6.9; 46.6)	18.1 (-1.6; 37.9)
IV			34.8 (10.5; 59.0)	28.1 (4.1; 52.2)
HIV RNA level, $\log_{10}$ copies/ml				
>5 log				49.9 (33.4; 66.5)

6 DISCUSSION

This analysis explored gender differences in presentation and early survival in a South African community-based HAART programme. During the study period, 285 patients (10%) died. The pre-treatment mortality rates were high, but not different by gender (p=0.133). In contrast, the death rate was significantly lower among women than men in the period on treatment (7.9/100 person-years vs 12.9/100 person-years, p=0.003). The mortality rate in the total cohort was also significantly higher among males than females (17.9/100 vs 11.5/100 person-years, p<0.001).

Overall, these results demonstrate a strong crude association between male gender and survival that was attenuated after adjustment for baseline markers of disease severity. In the pre-HAART period, there was a strong crude association between male gender and survival (HR 1.31, 95% CI, 0.93-1.86; p=0.131), which disappeared with adjustment for baseline characteristics (HR 1.01, 95% CI, 0.67-1.51). On HAART, the strong crude association (HR 1.57, 95% CI, 1.14-2.16; p=0.005) was attenuated after adjusting for the same characteristics (HR 1.19, 95% CI, 0.88-1.97). In the total cohort, male gender increased the crude risk of death by 49% (HR 1.49, 95% CI, 1.17-1.88; p=0.001). This association was weakened after adjustment for WHO stage, age and CD4 cell count (HR 1.15, 95% CI, 0.93-1.50). Degree of disease severity at programme entry appeared to mediate the effect of gender on survival.

The analysis found that men were more likely to be LTFU on HAART in both univariate (crude HR 1.30, 95% CI, 0.92-1.84; p=0.140) and multivariate analyses (HR 1.34, 95% CI, 0.91-1.96).

In terms of virological outcomes, after adjustment for baseline characteristics, men appeared less likely than women to reach viral suppression at 48 weeks (HR 0.86, 95% CI, 0.59-1.25).

On average, women had higher CD4 cell counts at 48 weeks than men did (p<0.001). There was a crude association between male gender and lower CD4

cell count at 48 weeks. On average, men had 30.1 cells/μL less than women (95% CI, -48.8--11.5; p=0.002). After adjustment for disease parameters at baseline, men still had on average 15.3 cells/μL less than women (95% CI, -33.2 – 2.6). As women had significantly higher median CD4 cell counts at baseline than men (p=0.001), it seems likely that the association reflects disparities at baseline rather than a gender difference in clinical progression.

6.1 Strengths & limitations

The strengths of this study are a well-maintained cohort with near complete ascertainment of outcomes, low levels of LTFU, the inclusion of analysis time prior to HAART initiation, the large sample size and high quality baseline measurements. In addition, the study explores some of the underlying reasons why men are accessing HAART at later stages of disease progression than women. The major limitation of this analysis is the generalisability of results to other populations.

6.1.1 Ascertainment of outcomes

In low-income countries, ascertainment of outcomes is generally constrained by a lack of resources (Rosen et al., 2007). Failure to ascertain outcomes accurately impacts on the validity of any measure of association that is estimated from data. If, for instance, the majority of those who were recorded as LTFU had actually died, the measure of association would underestimate the true association between exposure and mortality (Joubert and Ehrlich, 2007). Any systematic difference between those who were retained in care and those who were lost to the programme might render the measure of association invalid.

In the Gugulethu cohort, the low rate of LTFU reflects the fact that ascertainment of outcomes is fairly complete, due to the Sizophila adherence counsellors. In addition to supporting patients on treatment, the counsellors also undertake home visits. They are able to ascertain outcomes more accurately than

sites which rely on passive ascertainment. This is reflected in the low rate of LTFU. These findings are comparable with those from a large Canadian study (n=1219) with excellent ascertainment of outcomes. Hogg (Hogg et al., 2001) used physician reports and record linkages with the registry of vital statistics to confirm outcomes. They found a non-significant crude association with male gender (RR 1.45, 95% CI, 0.70-3.02). After adjustment for baseline CD4, viral load and other factors, male gender did not predict survival. Good ascertainment of outcomes increases confidence in the findings of this analysis.

6.1.2 Loss-to-follow-up

A strength of this analysis is that this is a large, well-maintained cohort with low levels of LTFU. The issue of LTFU is highly topical with widescale HAART roll-out. Many developing countries are expanding their national programmes but lack resources to follow up patients who do not return once HAART is initiated. A recent systematic review of published papers on patient retention in Sub-Saharan Africa found extremely high levels of LTFU (Rosen et al., 2007). On average, the authors estimated that African HAART programmes retained about 80% of patients at six months on HAART and 60% after two years on HAART. The main causes of loss to programme were reportedly LTFU (56%) and death (40%) (Rosen et al., 2007). Although the study did not analyse the data by gender, if there were a systematic gender difference between patients retained on HAART and those LTFU, this would result in selection bias. The true association between gender and survival would be unknown as the true outcome of the men and women lost to follow up would not be known (Joubert and Ehrlich, 2007).

This is a crucial issue for programme monitoring and evaluation, as can be seen in the findings from a recent study in Malawi. The Malawian national HAART programme estimates that 9% of its patients on HAART are LTFU. In this study, researchers actively followed up a group of patients who were reportedly LTFU, to ascertain the true outcomes. They found that 50% (127) of

253 patients reported to be LTFU had actually died, most of them shortly after missing their last clinic visit (Yu et al., 2007).

Braitstein (Braitstein et al., 2006) also highlighted the importance of LTFU in treatment programmes in developing countries. They suggest that with different assumptions of outcomes for those LTFU, the true mortality in their study might have been as high as 15% and not 6.4%, as estimated. This is a critical point, as there is enormous variability in definitions of LTFU. In a review of 33 cohorts, Rosen (Rosen et al., 2007) found a wide range of definitions of LTFU including: missing two consecutive clinic visits; having no viral load results after treatment initiation; more than one month (or two months/three months/four months) late for a visit or medication pickup or no visit in past one/two/three/four months; missing two consecutive clinic visits or no visit in the past three months. Comparing data with such widely varying definitions raises many analytical problems. The low rate of LTFU within this cohort strengthens confidence in the validity of the findings reported in this dissertation.

6.1.3 Sample size

A systematic review of earlier studies found little evidence of gender-specific differences on HAART but suggested that the studies may have been underpowered to detect such differences (Nicastri et al., 2005). The large sample size is a strength of this analysis. Although the Gugulethu site has been the subject of a fair amount of research previously, none of the previous studies has included as many study subjects. The most recent survival analyses on this cohort included 1 235 adults, 927 of whom started therapy (Lawn et al., 2006b). This analysis included more than double the number of participants (n=2843), 2196 of whom started HAART.

The literature contains few other studies with comparable sample sizes, and most of these are collaborative analyses across different sites (Braitstein et al., 2006, Egger et al., 2002, Nicastri et al., 2005). Multi-site analyses face a host of

analytical problems which may undermine the validity of their findings. These include differing definitions of key variables (as with LTFU); the inclusion of different variables in crude and adjusted analyses; different time periods, drug regimens, study populations, sample sizes and study methodologies. For these reasons, inferences from well-conducted, single-site studies with large sample sizes may provide stronger evidence of association. The only other analyses with larger sample sizes from a single site are from Brazil (n=2821) and Zambia (n=16198). Both studies reported similar results to this analysis: a crude association between male gender and survival on HAART which was attenuated after adjustment for stage of disease at baseline. The large sample size in a single site allows for precise estimates of effect and increases confidence in the findings of this analysis.

6.1.4 Measurements

Initially established for research, the HCTC operates as a government HAART roll-out site as well as a research site. Clinic staff are trained and supported by staff from the Desmond Tutu HIV Centre at the University of Cape Town. The site is well-equipped. Staff have access to good laboratory services, some of them on-site, and a range of tests are performed at baseline and subsequent visits. As a result the cohort had high quality measures, which may explain some of the differences between this and previous studies.

For example, the results of this analysis differed from the findings of a large study (n=1308) in Malawi investigating the effectiveness of a large-scale, simplified HAART programme (Ferradini et al., 2006). The study population was similar to the Gugulethu cohort: poor, African and predominantly female. In this study, the association between male gender and death persisted even after adjustment for baseline factors including CD4 cell count (adjusted HR 1.63, 95% CI, 1.15-2.31). This may be partly due to the measurement of CD4 cell counts, which were initially measured manually and later semi-automatically. After a year, no systematic baseline CD4 cell count was done. In contrast, baseline CD4

cell counts were available for 85% of the Gugulethu patients and were performed at a quality-controlled laboratory on site. Without a fairly full set of valid baseline CD4 cell counts, it would be difficult to adjust adequately for the effect of CD4 on mortality. This may have resulted in an over-estimation of effect in the Malawi study.

Zachariah (Zachariah et al., 2006) provides some evidence to support this argument. Studying early deaths on HAART in the public sector, investigators had full baseline measurements for 1507 study participants, 66% of whom were female. Their estimated crude association between male gender and early death on treatment (OR 1.30) reduced when adjusted for baseline characteristics including CD4 cell count and WHO stage (adjusted OR, 1.20, 95% CI, 0.80-1.80). Similarly, the results of the Malawi study (Ferradini et al., 2006) may have been undermined by the use of WHO stage as a proxy when CD4 was not available. The two measures were used interchangeably in the multivariate analysis. This may have artificially strengthened the apparent association between gender and death.

Measurement issues may also have influenced the results of a national study of survival among adult Brazilians with AIDS (Marins et al., 2003). Researchers found that female gender predicted survival in crude (HR 1.15, p=0.022) as well as multivariate analyses (HR 1.15, p=0.053). As CD4 cell counts and viral load testing were unavailable for most of the study period, the study may not have adjusted adequately for baseline disease parameters. Instead researchers utilised a range of AIDS-defining criteria as proxies. It is possible that more adequate adjustment for stage of disease at baseline may have further weakened the estimate of the effect of gender on survival.

6.1.5 Generalisability

One major limitation of this analysis is generalisability. If one assumes that there is internal validity, and the findings reflect the true association between

gender and mortality after one year in an HAART programme, how may these findings apply to other populations?

The HCTC is a unique clinic. Unlike general HIV clinics, it does not offer general HIV management to HIV-infected individuals who are in the early stages of HIV disease. Patients have already been tested, diagnosed and identified as requiring HAART. Consequently they may not be a representative sample of the general population of people with HIV who require HAART but have not yet been diagnosed.

On the other hand, the study sample probably represents the population accessing HAART through the public health sector in South Africa as referrals in the public sector generally follow the same channels. Most women are tested and referred for treatment during pregnancy via the programme to prevent mother-to-child transmission, while men are diagnosed when presenting for TB or STI treatment. The findings may be generalisable to people accessing HAART via the public sector in South Africa and should have relevance to public health debates and decisions.

It is not clear whether the results would be generalisable to other populations. However, congruence of study findings between this analysis and large studies of public HAART programmes in other African countries suggests that this may be the case. Future research should analyse and compare gender and survival in large cohorts in different settings. If significant differences are found between the results of this analysis and others in different settings, the reasons should be explored. This may provide invaluable data to inform HAART programmes in South Africa and elsewhere. The strong association between monthly income and the risk of LTFU in a HAART programme also suggests the need for further research on the impact of socio-economic conditions in different settings.

Finally, this analysis does not speak to long-term outcomes in an HAART programme. The Gugulethu programme is still in its infancy, as are many others in developing countries. Over the next few years, South Africa and other African

countries will face a host of new challenges in retaining patients on long-term treatment. With longer periods of follow-up, systematic gender differences in adherence, patient retention/LTFU), death and/or other outcomes may emerge, especially with many such health systems in crisis.

Indeed, the strong crude association between gender and survival in this analysis suggests that over time, survival may in fact be different for men and women. While it is possible that gender disparities in survival are due to biological causes, it seems more likely that the underlying determinants may be sociological and/or structural. The crude association between male gender and the risk of being LTFU suggests that gender may impact on issues such as adherence. It will be important to undertake similar analyses over longer study periods in order to establish whether there are in fact gender differences in retention of patients on long-term treatment. If such differences are found, the reasons should be explored.

6.2 Interpretation

6.2.1 Gender & survival

With the widescale roll-out of HAART in developing countries, it is vital to understand whether and how gender affects survival. This analysis extends the findings of a recent collaborative study (Braitstein et al., 2008a). Utilising baseline measurements from 29 sites including the Gugulethu clinic, the authors also found that women were starting HAART with less advanced HIV disease than men. In addition to this, the results of this analysis confirm that apparent gender disparities in survival on HAART may be due to the fact that men are only accessing HAART at later clinical stages of HIV than women.

These findings are consistent with the results of other studies which found that after adjustment for stage of disease at programme entry, there was no significant association between gender and survival. Two other large studies in public sector HAART programmes in Malawi and Zambia provide the most

relevant comparisons (Zachariah et al., 2006, Stringer et al., 2006). Probably the largest single cohort of patients on HAART (n=16198) is the Lusaka programme (Stringer et al., 2006). The authors found that a crude association between male gender and survival (crude HR 1.40, 95% CI, 1.20-1.60) was attenuated after adjustment for baseline measures of disease progression (HR 1.20, 95% CI, 0.90-1.50). In Malawi, too, a crude association between male gender and mortality (crude OR 1.30) was weakened after adjustment for stage of disease at presentation (adjusted OR 1.20, 95% CI, 0.80-1.80, p=0.40).

In developed countries, similar results have been found. Braitstein and colleagues (Braitstein et al., 2006) undertook a large retrospective multicentre cohort study comparing patients in low- and high-income countries and found little difference between the settings. Females had less risk of death on HAART in low-income settings (crude HR 0.84, 95% CI, 0.58-1.22) and in high-income settings (crude HR 0.85, 95% CI, 0.66-1.09). The ART-CC collaboration (Egger et al., 2002) analysed data on 12574 HAART-naïve adults in 13 cohort studies in Europe and North America. The study did not report crude associations but in multivariate analysis including baseline disease parameters, female gender did not increase the hazard of death (HR 1.05, 95% CI, 0.77-1.42). Our findings provide additional evidence to support the results of these large studies from low and high-income settings.

In contrast to these findings, a large Brazilian retrospective review (Braga et al., 2007) found that women were at a higher risk of mortality on HAART than men. The study found a crude association between female gender and mortality (HR 1.22, p=0.020), which strengthened after adjustment for age at HIV diagnosis, lowest CD4 count during follow-up, highest viral load, AIDS-defining illness before admission and during follow-up, and ART at end of follow-up (adjusted HR 1.86, 95% CI, 1.14-3.03). The authors found that women were significantly more likely to be diagnosed at a younger age and to receive HAART at earlier stages of disease. If women were healthier than men at the start of HAART, it seems unlikely that their survival would have been worse. It seems

more likely that the study detected an artefactual gender difference which would have disappeared or been attenuated with adjustment for disease parameters.

There is overwhelming evidence that stage of HIV disease at programme entry is the main determinant of survival. For this reason, Lawn & Wood (Lawn and Wood, 2006) previously highlighted the need for earlier diagnosis and treatment. This dissertation confirms the finding of the recently published ART-LINC paper (Braitstein et al., 2008b) that there is a particular need for the earlier diagnosis and treatment of men in developing countries.

6.2.2 Survival pre-HAART

This is the first detailed analysis in a low-income country of survival by gender in the period before initiation of therapy. Most studies only report survival after initiation of HAART. In low-income countries, most patients presenting for treatment are already at advanced stages of disease progression due to stringent criteria for initiating HAART. Inclusion of data on patients in the period before starting HAART provides valuable insight into gender and pre-HAART mortality. It also provides some sense of the huge public health burden of HIV morbidity that remains hidden if people die before receiving treatment.

In the pre-HAART period, there was a strong crude association between male sex and survival (HR 1.31, 95% CI, 0.93-1.86, p=0.131). The association disappeared with adjustment for baseline characteristics including disease parameters (HR 1.01, 95% CI, 0.67-1.51). It is possible that due to the short period of follow-up prior to treatment (median duration 35 person-days; IQR, 26-63), there was limited statistical power to detect a gender difference. The effect of male gender might only have become discernible over a slightly longer period, and might have been detected in the early period on HAART. Results from other studies reporting male gender as a risk factor for early mortality on HAART (Ferradini et al., 2006, Zachariah et al., 2006) provide some evidence to support this.

6.3 Implications of this analysis

This analysis found that mortality during the first year on HAART in this cohort is not independently associated with gender, but is mediated by stage of disease at entry into a programme. Although men appear to have poorer survival on HAART than women, this may be due to their later diagnosis and entry into an HAART programme. At present, South African men using the primary health services seem to be disadvantaged in access to HAART. Unless this issue is resolved, men may continue to have worse survival prospects than women in HAART programmes in South Africa, and possibly in other developing countries. The following section suggests some possible interventions to address this critical issue.

6.3.1 Qualitative studies

The results of this analysis highlight complex issues surrounding gender, HIV and health. However, the literature abounds with unsupported generalisations about men's health seeking behaviour. This begs the question: would men have different health seeking behaviour if the health services were more geared to their needs? In-depth qualitative studies in different settings are urgently needed to explore the real reasons why men make less use of public health services than women.

6.3.2 Changes in national policy

In order to ensure that the primary health care services in South Africa address the health needs of men, changes in national health policy are required. In particular, the HIV/AIDS National Strategic Plan 2007-2011 should be revised urgently to address the existing gaps. In the light of these findings, the implementation plan should include a focus on how to diagnose and treat men at earlier stages of HIV disease. Men should be included in the section on

populations at higher risk. It might be appropriate to include a separate goal addressing the special needs of men, as the programme appears to have failed to do so to date.

While it is vital to redress the gender imbalance in primary health care services, and specifically in access to HAART, this should not undermine existing health services for women, or obstruct their access to early diagnosis and treatment. Fortunately, with the existing strong focus on maternal and child health, particularly in HIV/AIDS, it seems unlikely that this would happen.

6.3.3 Men-friendly services

Although policy changes create the framework for changes in health service delivery, these are long-term solutions. It is also essential to find short-term, achievable ways of increasing men's access to VCT and HAART.

One solution would be to create preventive and reproductive health services that specifically target men. This could be done in partnership with non-government organisations (NGOs), which may be better placed to initiate such projects. In Soweto, for example, the Imbizo Health Project set up two male-only health care facilities in 2005. The clinics provide health information in an environment that is supportive, confidential and private. Between November 2006 and September 2007, a total of 4 758 males were tested, close to the target of 4 950 (Whiting, 2008). The men who tested positive were referred to HAART sites, while those testing negative were referred to Imbizo post-test support services. Steven Whiting, Chief Executive Officer of HIVSA, the founding organisation, argues that if there were public services targeting issues that men regard as important such as penile dysfunction and prostate cancer, men would flood into the services (Whiting, 2008). This would increase men's exposure to broader health services. Ultimately, increased interaction with health facilities is likely to increase the chances of men being diagnosed with HIV earlier, and consequently receiving earlier treatment.

Unfortunately such initiatives are subject to the same problems facing the beleaguered health services: a crisis in human resources, insufficient funding, and inexperienced management. They will require vision and commitment in order to succeed. Lessons may be learnt from the experience of a male-only clinic in Khayelitsha, Cape Town. The clinic was established recently as an entry point for men to the health services, in response to a perception that the PHC clinics were women's clinics or baby clinics which did not cater for the health needs of men (De Azevedo, 2008).[8] The clinic is run collaboratively by provincial and city health authorities, a local NGO and an international NGO (Hope Worldwide and Médecins sans Frontières). Accessibly located near the train station, the clinic is staffed by male nurses and counsellors and provides STI treatment and VCT. All patients are counselled and offered the opportunity to test for HIV. If they test positive, they are referred to local clinics for management and HAART, as needed. Evaluation of services such as those offered by this clinic could inform similar projects elsewhere.

6.3.4 Outreach programmes

In addition to finding ways of bringing men into existing health services, it may be necessary to take services to men. Engender Health, an international organisation active in international reproductive health issues, advocates reaching men in places where they congregate naturally.

Providing HIV testing facilities and equipment to measure CD4 cell counts in such venues could greatly increase men's access to diagnosis and early treatment. Imbizo Health currently offers VCT in shopping malls, one fixed site and mobile caravans. Nearly 500 men are tested a month, mostly at the mobile caravans which are situated close to where men gather socially or for work (Whiting, 2008).

[8] De Azevedo confirms that in fact, the PHC clinics only offer preventive/promotive health services for women and babies and offer no adult curative services except for TB and STIs.

With government support, such organisations could offer more accessible - possibly even mobile - health services for men including HAART. For men who are working and cannot take off time without a doctor's note, these services should be offered outside working hours. VCT could also be offered at workplaces, sporting or religious events, and social places such as shebeens (informal bars).

In view of the public health relevance of this issue, a range of pilot studies should be undertaken to experiment with different innovative models for different settings. These could include: male-run clinics; separate rooms for men and women within the same clinic; separate days for men and women; after-hours clinics; mobile clinics taking male-targeted services to men where they gather socially or for work; and possibly mobile clinics offering HAART. Good monitoring and evaluation systems are central to such studies. Planning should focus on flexibility and moving quickly to build on successful initiatives and drop those that are not working.

6.3.5 Changing attitudes

It appears plausible that men's delayed diagnosis and treatment is due more to structural barriers than men's health seeking behaviour. However, if it is true that prevailing beliefs about masculinity prevent men from accessing general health services, these should be addressed.

One way of changing stereotypes and behaviour is through national campaigns. The South African mass edutainment organisation Soul City utilises multimedia including print, television and radio, to promote important health messages. Such organisations could assist in formulating targeted, useful messages for men. These messages could, for example, highlight the benefits of early diagnosis and testing in terms of long-term prognosis. Similarly, instead of promoting condom use only to prevent HIV transmission, public messages could focus on the benefits of condoms for men living with HIV infection: not only in

protecting others from infection, but in preventing their own acquisition of STIs, resistant virus and re-infection. This might help to shift the emphasis from men as perpetrators to men as partners in the epidemic, and emphasise the benefits of men knowing their status earlier.

At an individual level, a number of men's organisations around the world are working to transform gender stereotypes. Most of these are small and still in their infancy, but could provide invaluable input on how to increase men's access to HAART. One such initiative, Men as Partners, works to involve men in reproductive health. MAP collaborates with organizations and industries which are male-dominated, including the armed forces, mines, long distance transport and trade unions. Another organisation in India, Men in Maternity, actively involves men in maternity care. The organisation found significant changes in the family planning knowledge and behaviour of men who accompanied their wives to the clinics and participated actively in the intervention (Varkey et al., 2004). An additional change to health care delivery in South Africa might be to create reproductive health services based on a family-focused care model, so that men could be offered HIV testing and access to treatment at the time of their partner's pregnancy.

Further qualitative research on the shared meanings of masculinity in different African settings is needed. This study's finding that men are diagnosed and treated later than women is consistent with results from other large African HAART cohorts. This appears to be due to a complex, intertwined mix of behavioural, social and structural factors. It is important to recognise that there is no such entity as a stereotypical African man. On the contrary, there is huge diversity in gender norms and stereotypes which influence how men behave and how health services are structured. Further research on different constructs of masculinity in different contexts could shed light on this vital issue.

6.4 Summary

In summary, there is mixed evidence to date on the association between gender and mortality among HIV-infected individuals starting HAART, especially in developing countries. This analysis found that in the pre-HAART period, a strong crude association between male gender and death might be explained by the stage of disease at programme entry. Thus, men are being diagnosed and initiating HAART at more advanced stages of disease progression than women, and consequently have worse survival prospects in the month between programme entry and initiation of therapy.

On HAART, and in the total cohort, the marked increase in the risk of death among males was attenuated but not entirely accounted for by controlling for markers of disease stage and severity of immune suppression. This suggests that in these time periods, other factors such as adherence may also influence survival. The fact that males are at a higher risk of being LTFU at 48 weeks provides some evidence to support this argument.

In the light of these findings, further research is needed on obstacles to male access to HAART. Changes to national policy are needed to fill existing gaps in health services. Male-friendly services including VCT and referral for HAART could become an entry point for men into the PHC system. This would facilitate the earlier diagnosis and treatment of men, and may improve their survival in a HAART programme. In addition, studies with longer follow-up periods are needed to identify other risk factors which may increase the risk of men being lost to programmes and/or being non-adherent to HAART.

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8 APPENDICES

8.1 UCT Research Ethics Committee Letter of Approval

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: preaward@curie.uct..ac.za

20 April 2007

REC REF: 174/2007

Ms Morna Cornell
c/o Dr L Myer
Public Health & Family Medicine

Dear Ms Cornell

PROJECT TITLE: PRESENTATION AND SURVIVAL OF MEN AND WOMEN WITH HIV IN AN ANTIRETROVIRAL THERAPY PROGRAMME

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

Signed by candidate

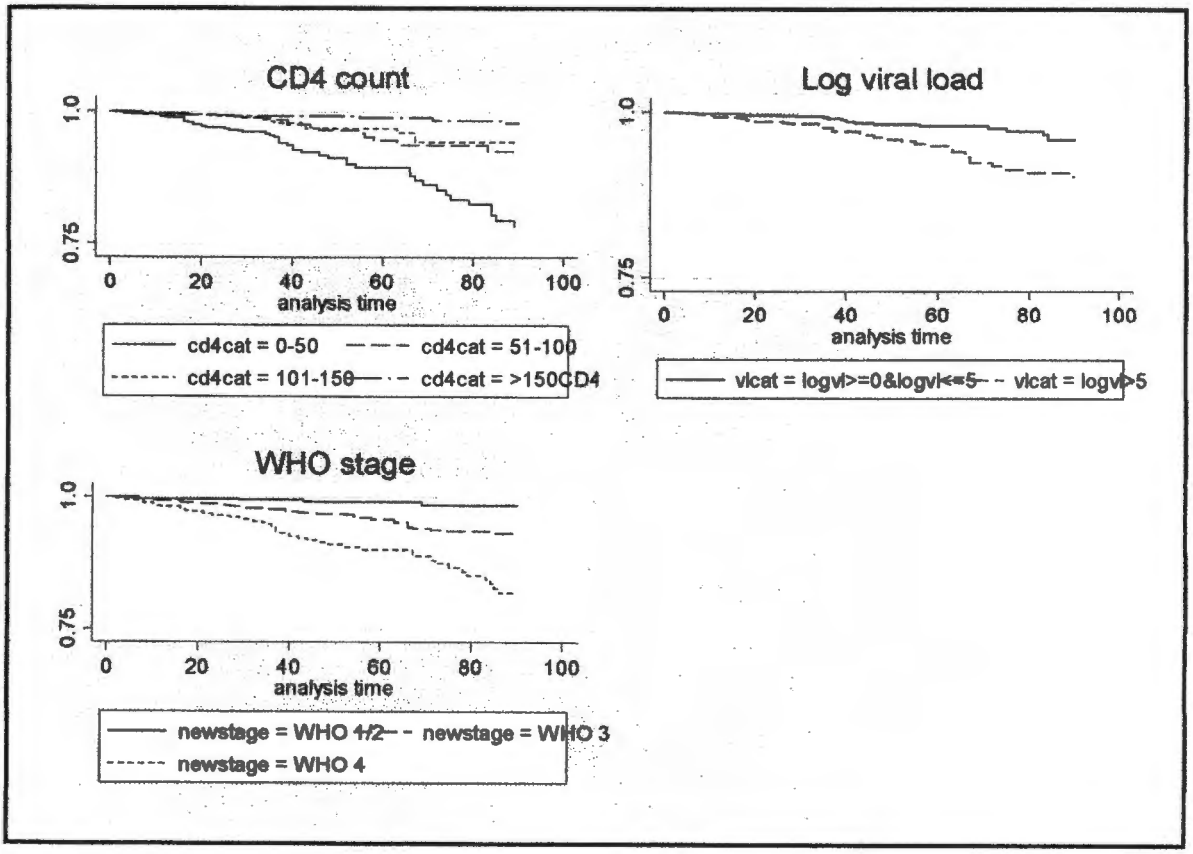
Signature Removed

pp **A/PROF. M. BLOCKMAN**
CHAIRPERSON, HSF HUMAN ETHICS

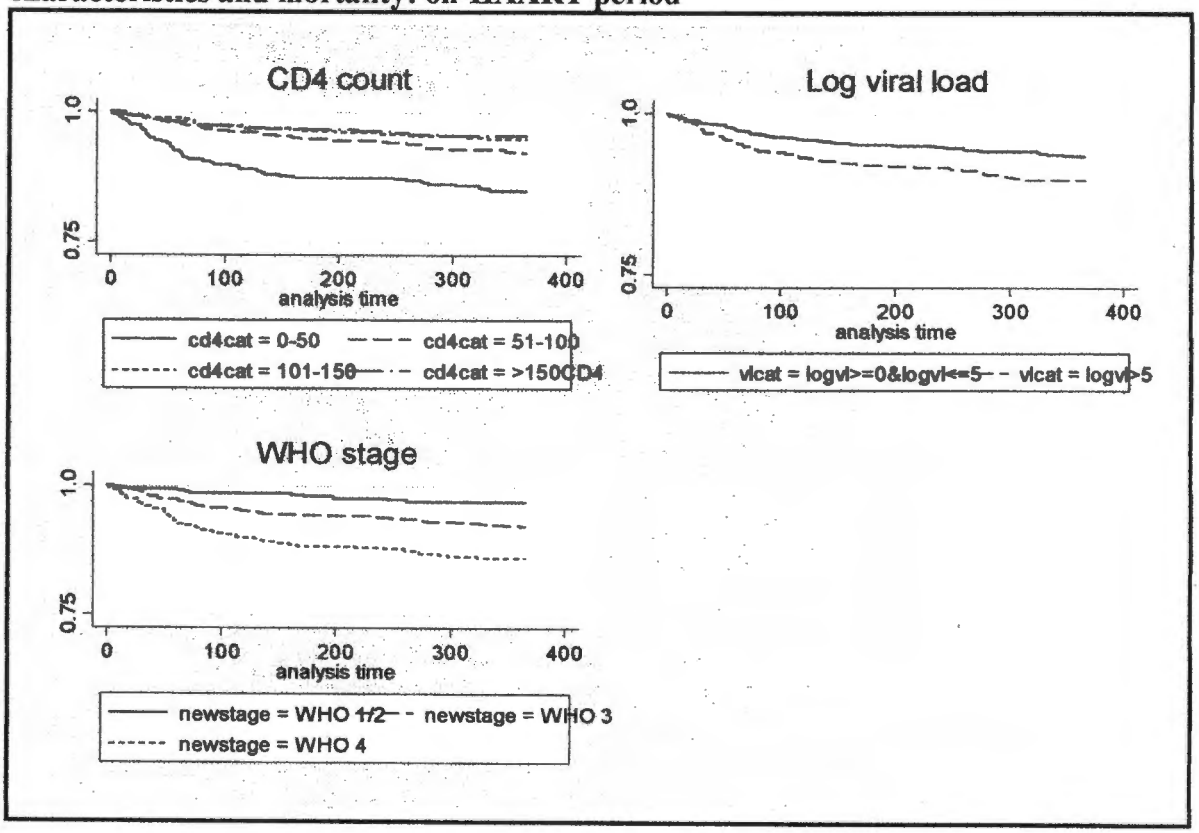
lemjedi

Appendix 8.2

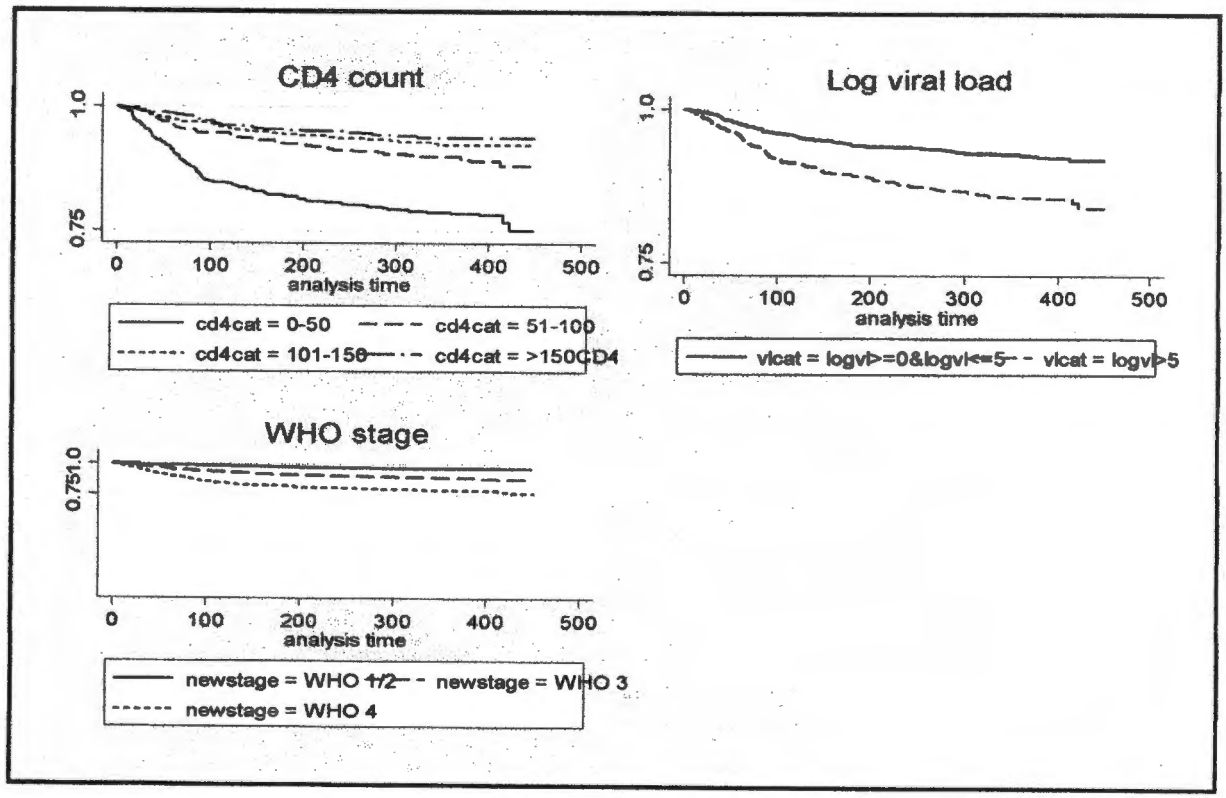
8.2.1 Kaplan-Meier graphs: crude association between baseline characteristics and mortality: pre-HAART period



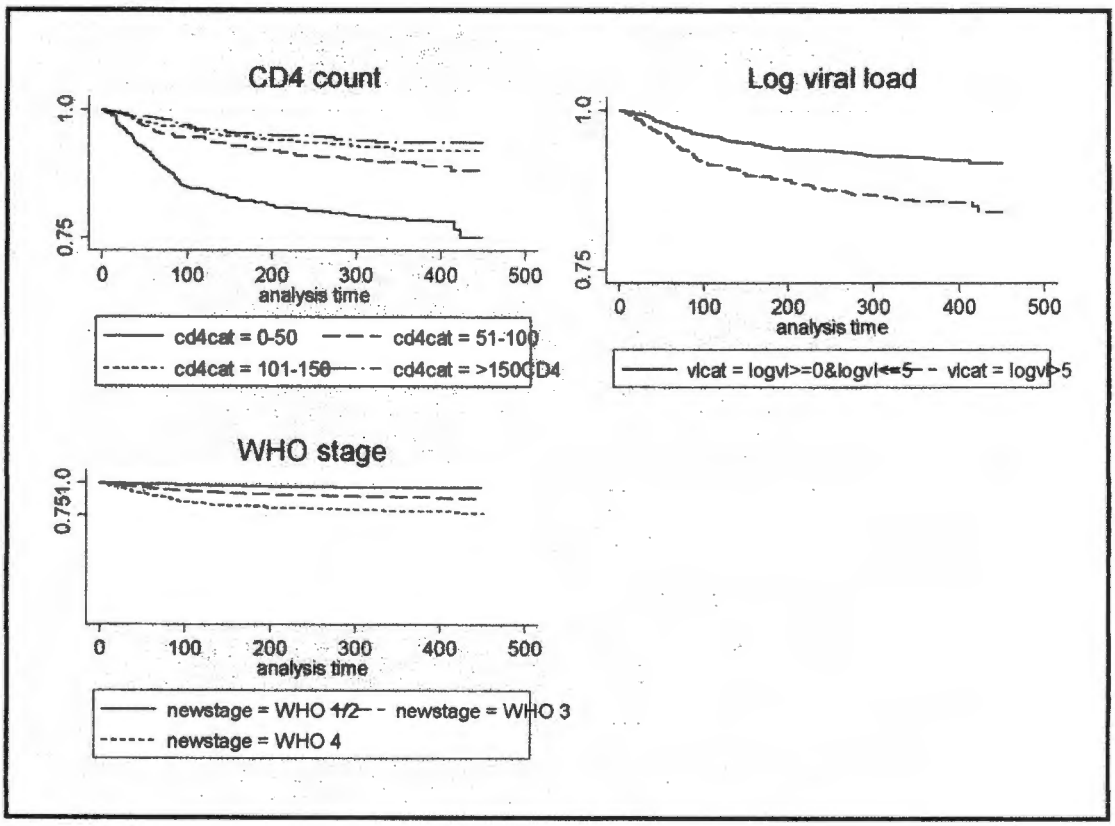
8.2.2 Kaplan-Meier graphs: crude association between baseline characteristics and mortality: on-HAART period



8.2.3 Kaplan-Meier graphs: crude association between baseline characteristics and LTFU: on-HAART period



8.2.4 Kaplan-Meier graphs: crude association between baseline characteristics and mortality: total period

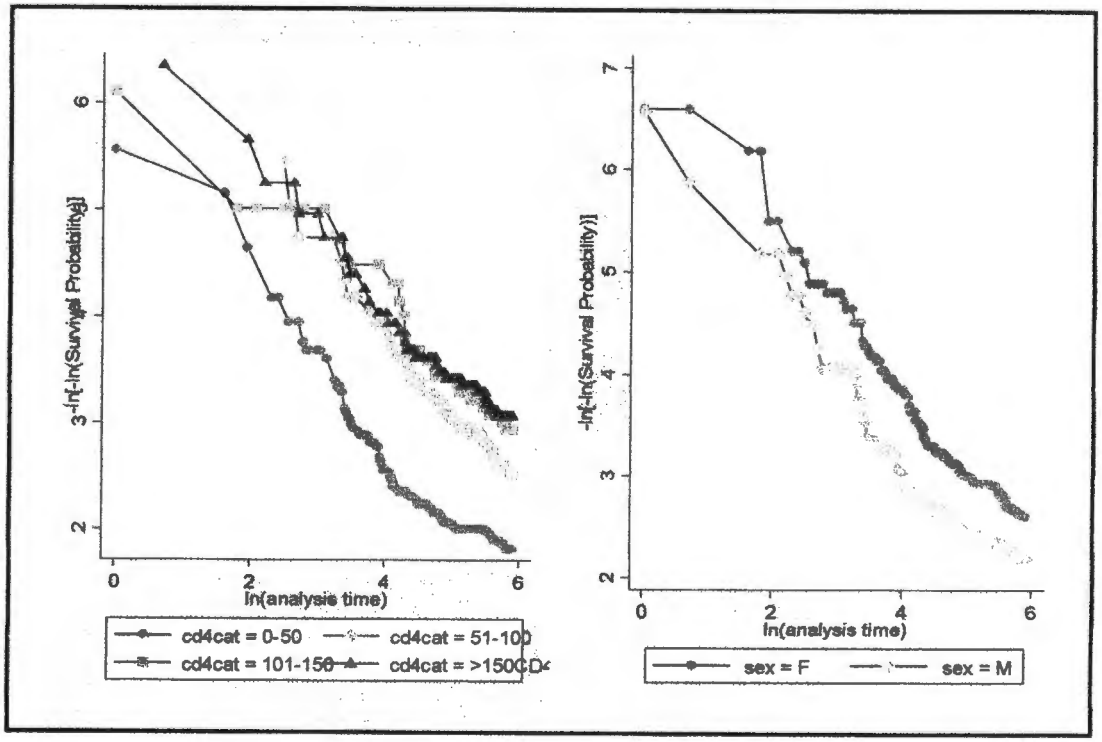


Appendix 8.3
Model diagnostics

8.3.1 Cox's proportional hazard regression models

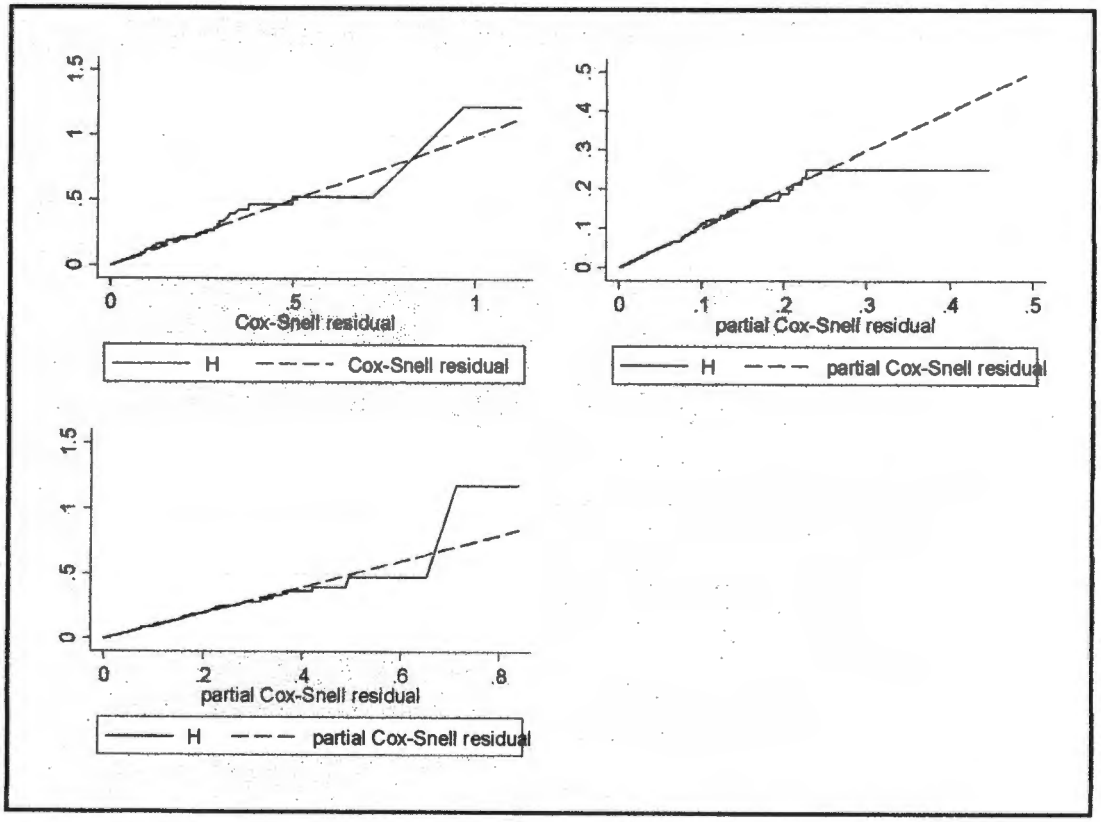
In the pre-HAART and total cohort models, overall and with respect to the individual covariates, the proportional hazards assumption was valid. In the on-HAART model, the proportional hazards assumption was valid overall (p=0.123) and for all the individual variables except CD4 category 2 vs 1 (p=0.048). Although this is a minor violation of the proportional hazards assumption, as can also be seen in Figure 6 below, this is not a major concern as the focus of this analysis was the effect of gender on mortality. In addition, it is difficult to differentiate between a CD4 cell count below 50 cells/μLand a CD4 cell count below 100 cells/μL. As a further check, the models were run including each level of CD4 cell count separately, and this did not significantly change the effect of gender on mortality. As can be seen below, the proportional hazards assumption was not violated for gender.

Figure 6: Tests of proportional hazards assumption for CD4 cell count and gender: on-HAART period



Cox-Snell residuals were generated to check overall model fit. Kaplan-Meier curves were plotted with residuals (as the time variable) against death (Figure 7). For all three time periods, the line does not deviate much from the reference line, and the models provide a reasonably good fit for the data.

Figure 7: Kaplan-Meier curves: Cox-Snell residuals vs mortality: pre-HAART, on HAART and total cohort



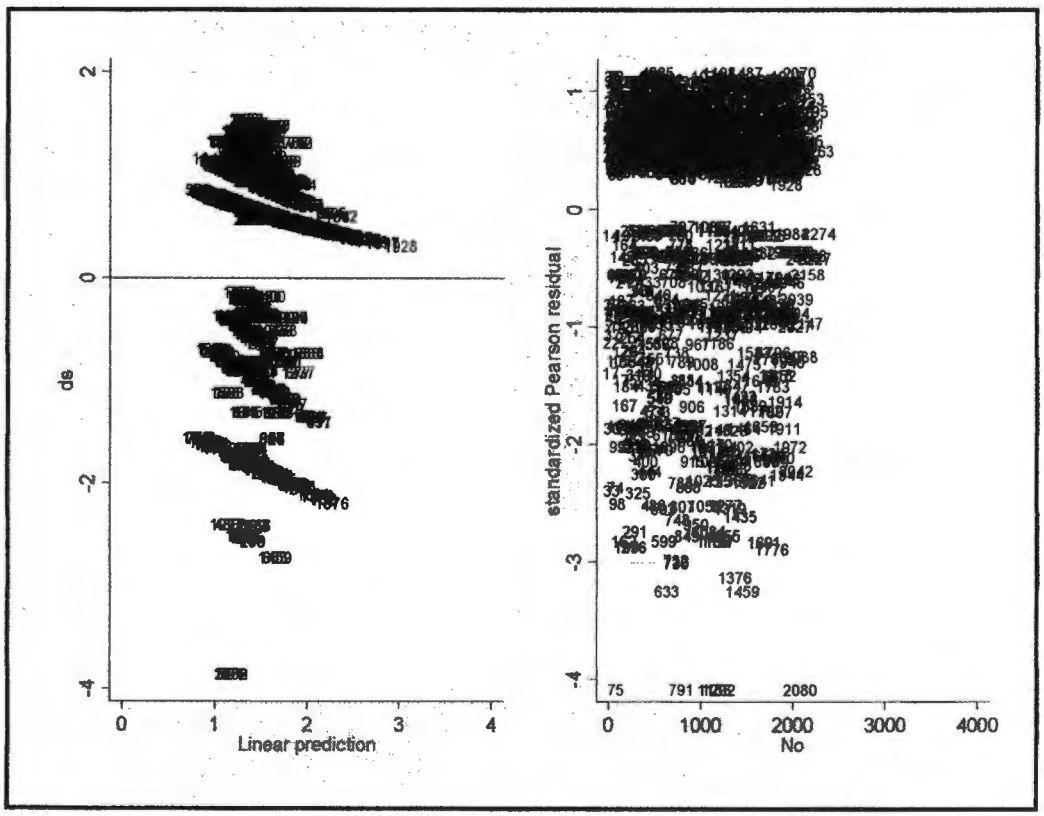
8.3.2 Logistic regression model

The following assumptions were tested:

- adequacy of the linear component
- presence of outliers

The linear predictor (Figure 8) appeared to be generally adequate. The two-way scatter (Figure 8) showed two groups fairly randomly scattered around zero. There did not appear to be any major outliers. The goodness-of-fit test produced a non-significant result (p=0.236), showing that the predicted probability of viral suppression at 48 weeks did not differ substantially from the observed probability. Thus, this appears to be an acceptable predictive model. The logit transformation is appropriate for a binary response. The model appears to be valid.

Figure 8: Diagnostics: logistic regression model



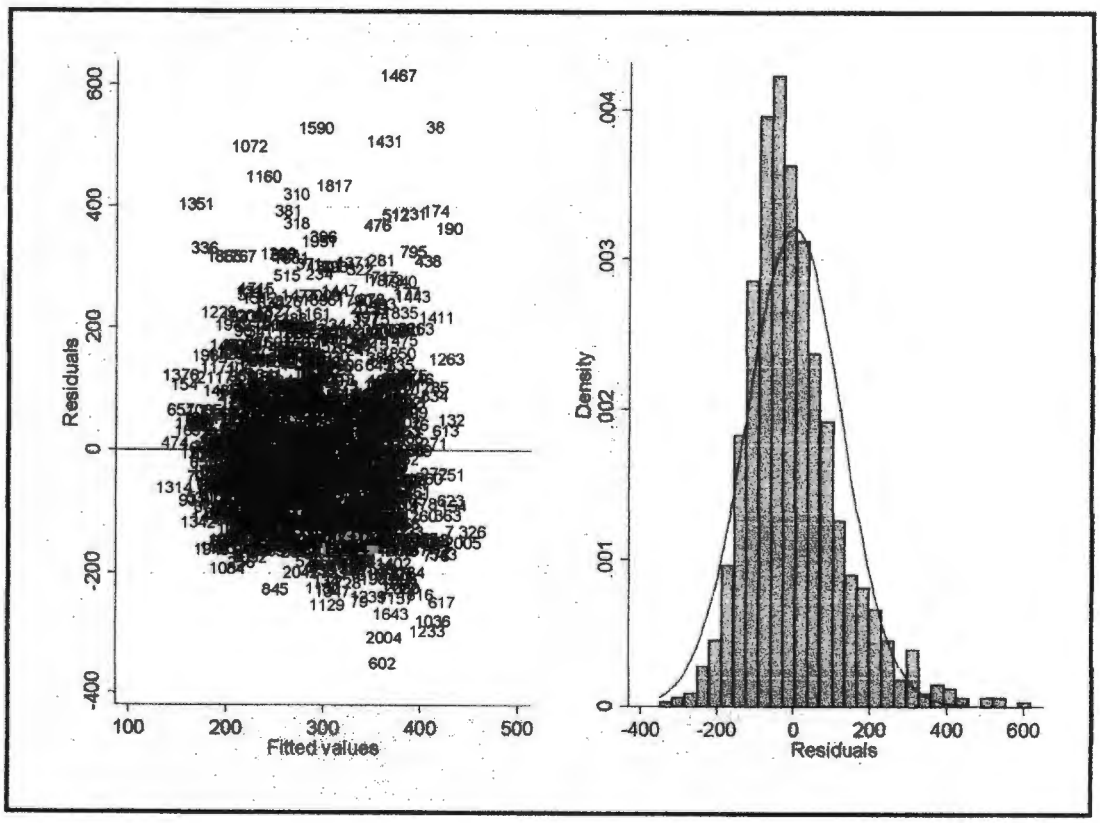
8.3.3 Linear regression model

The following assumptions were tested:

- Normality of residuals
- Collinearity

The residuals appear to be normally distributed (Figure 9). Individual and global variance inflation factors (VIFs) were calculated. The individual VIFs were all <10 and the mean VIF was 1.45. No collinearity was detected. The linear regression model appeared to be valid.

Figure 9: Linear regression model: residuals



Appendix 8.4: HCTC data collection forms

8.4.1 Gugulethu ARV site data capture: <u>week –4s</u>

Date:___________

Initials	Number	DoB	Gender	WHO stage	Date of –4 visit	Comment: (Pregnant, transfer in, non-naïve)

8.4.2 Gugulethu ARV site data capture: <u>week –2s</u>

Date of meeting:___________

Initials	Number	Outcome (order/defer)	Drug requested (E30, N40 etc)	Comment: (Pregnant, transfer in, non-naïve)

Bring back to Desmond Tutu Centre:

- All week 0 plastic folders (with carbon copies)
- All on-treatment visit forms (carbon copies)
- All change of treatment forms.

8.4.3 Hannan Treatment Centre: patient background[9]

Date:

Name:	Treatment no:

Gender: M / F	**DOB:** ...../...../.....
1) Background	**History of ARV:** Naïve / Non-Naïve / PMTCT
Has patient transferred in? Yes / No	ART start date (if already on ARVs) ...../...../.....
Language spoken at home:	**Is patient employed?** Yes / No

Level of education:			
Grade 1 / Sub A	Grade 5 / Std 3	Grade 9 / Std 7	Tertiary Education
Grade 2 / Sub B	Grade 6 / Std 4	Grade 10 / Std 8	Unknown
Grade 3 / Std 1	Grade 7 / Std 5	Grade 11 / Std 9	Other
Grade 4 / Std 2	Grade 8 / Std 6	Grade 12 / Matric	None

Date of last HIV (-) test: ...../...../.....	**Reason for test:** illness TB
Date of first HIV (+) test: ...../...../.....	MTCT VCT Other

Probable route of infection: Blood products	Homosexual
Intravenous Drug Use	MTCT
Heterosexual	Unknown

2) Disclosure of status:			
Partner or spouse	Other family member	Other household member	Friend
Employer	Community	Other	None

3) Clinical Information:		
Height:	**WHO Stage:** Stage 1	Stage 2
Weight:	Stage 3	Stage 4
Is patient pregnant: Yes / No	If yes, LMP: ...../...../.....	
Bloods: Referral CD4 count:	Date taken (CD4): ...../...../.....	

4) TB		
On TB therapy now: Yes / No	**How confirmed:**	Clinical
Retreatment: Yes / No	Smear	Chest X-Ray
Start Date: ...../...../.....	Other	Culture
TB site:		

[9] The original data collection form used at baseline visits was unavailable electronically. It has been replaced by this patient background form, which collects similar information.

5) Cotrimoxazole: Start date: ……/……/……	
6) Previous HIV related illnesses:	**Date:**
Last pap smear (for women) ……/……/……	**VDRL status:** positive negative unknown
Relationship status: Single With Partner	Partner informed of HIV status: Yes / No
Partner tested for HIV: Yes / No If yes, is partner: Positive / Negative	
Children tested for HIV: Yes / No If yes, specify age of child and status:	
Form completed by:	

8.4.4 Gugulethu ARV site data capture: <u>permanent outcomes</u>

Date:_____

Permanent defers			
Initials:	Number:	Date:	Reason
Death PRE-treatment			
Initials	Number	Date of death	Reason
Deaths ON treatment			
Initials	Number	Date of death	Reason
LTFU/Transfer out			
Initials	Number	Date	Comment
Undefers:			
Initials	Number	Date	Comment