Published in final edited form as:

AIDS. 2010 November 13; 24(17): 2717–2725. doi:10.1097/QAD.0b013e32833fb71f.

Outcomes in Patients Waiting for Antiretroviral Treatment in the Free State Province, South Africa: Prospective Linkage Study

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Abstract

Objective—In South Africa, many HIV-infected patients experience delays in accessing antiretroviral therapy (ART). We examined pre-treatment mortality and access to treatment in patients waiting for ART.

Design—Cohort of HIV-infected patients assessed for ART eligibility at 36 facilities participating in the Comprehensive HIV and AIDS Management (CHAM) program in the Free State Province.

Methods—Proportion of patients initiating ART, pre-ART mortality and risk factors associated with these outcomes were estimated using competing risks survival analysis.

Results—44,844 patients enrolled in CHAM between May 2004 and December 2007, of whom 22,083 (49.2%) were eligible for ART; pre-ART mortality was 53.2 per 100 person-years (95% CI 51.8–54.7). Median CD4 count at eligibility increased from 87 cells/mm³ in 2004 to 101 cells/mm³ in 2007. Two years after eligibility an estimated 67.7% (67.1% – 68.4%) of patients had started ART, and 26.2% (25.6% – 26.9%) died before starting ART. Among patients with CD4 counts <25 cells/mm³ at eligibility, 48% died before ART and 51% initiated ART. Men were less likely to start treatment and more likely to die than women. Patients in rural clinics or clinics with low staffing levels had lower rates of starting treatment and higher mortality compared with patients in urban/ peri-urban clinics, or better staffed clinics.

Conclusions—Mortality is high in eligible patients waiting for ART in the Free State Province. The most immunocompromised patients had the lowest probability of starting ART and the highest risk of pre-ART death. Prioritization of these patients should reduce waiting times and pre-ART mortality.

Keywords

HIV; ART; South Africa; waiting times; mortality; treatment access

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Conflict of interest The authors declare that they have no conflict of interest.

Introduction

HIV-infected patients in South Africa may experience delays in accessing antiretroviral therapy (ART). Until recently, South African Department of Health guidelines recommended ART when the CD4 count drops below 200 cells/mm³ or if WHO stage IV illness develops. Despite this low threshold, many eligible patients do not receive treatment. A recent study reported that in 2008, only 40.2% of eligible patients in South Africa were receiving ART (1).

Pre-treatment mortality rates in HIV-infected individuals are high (2;3). Such in-program mortality has been termed “unseen”, because many studies and evaluations report only on outcomes in treated patients (4): few programs in resource limited settings have good data prior to treatment. A study from the Free State Province in South Africa suggested that 87% of all deaths were in patients who had not started ART (2). Starting eligible patients on treatment as quickly as possible is therefore a priority (3), but resource limitations mean that patients often have to wait for treatment (5;6).

This study reports on outcomes in HIV-infected patients from the time they were enrolled in the Comprehensive HIV and AIDS Management (CHAM) program in the Free State Province, South Africa. The Free State has the 3rd highest HIV prevalence of all nine South African provinces, and a population based survey in 2008 reported a prevalence of 12.6% (7). The CHAM program began enrolments in May 2004, initially in 3 assessment sites and 1 treatment site, expanding to a total of 20 sites by the end of 2004 (8). By July 2010 the Free State was providing ART at 47 nurse-led assessment and combined sites and 11 doctor-led treatment sites and planned to provide ART in all 220 nurse run primary care facilities over the next three years.

We investigated times to treatment and pre-ART death, and analyzed CD4 count changes patients who were not yet eligible for treatment. We ascertained deaths by linking the clinical database with the national death register, and used a competing risks framework to jointly model access to treatment and pre-treatment mortality, and their determinants.

Methods

Setting and patients

All patients aged ≥ 15 years enrolled in 36 facilities in the Free State public-sector treatment program from May 2004 through December 2007 were followed until December 2008. Patients were followed from their first point of contact with the program. All care, including ART and co-trimoxazole prophylaxis, was provided free of charge. Approximately 50% of documented eligible patients received co-trimoxazole but almost none received isoniazid to prevent tuberculosis. In 2005, just over 50% of patients presenting to the program had a prior positive HIV test and around 45% had voluntary counselling and testing (VCT) for the first time (9). Of those undergoing VCT at ART facilities, 95% were HIV-positive. After testing HIV-positive in any Free State clinic, patients were referred to nurse-run assessment sites for assessment of treatment eligibility, including CD4 count measurements. According to protocol (10) patients with CD4 counts between 200 and 500 cells/mm³ were asked to return for another assessment after six months and patients with CD4 counts > 500 cells/mm³ were asked to return after twelve months. Patients with CD4 counts ≤ 200 cells/mm³, or with WHO disease stage IV (AIDS) were enrolled in a three week Drug Readiness Training (DRT) program and referred for initiation of ART. Patients starting ART obtain monthly supplies of medication from their assessment site and return to treatment sites every six months, for repeat prescriptions.

By December 2007, 28 clinics and 8 hospital sites were participating in the program. Seventeen clinics were assessment-only and 11 combined assessment and treatment. Seven hospital sites provided treatment for patients referred from assessment clinics: the eighth functions as a specialist referral facility for the province.

Data Sources, Outcomes and Definitions

Clinical data from standardized forms were entered into the province's Electronic Medical Records System by trained data capturers (11). Data were downloaded weekly to the Free State Department of Health (FSDOH) Data Warehouse. Unique patient identifiers allowed tracking of patients across facilities. Program staff provided information on type of facility (assessment-only, treatment-only or combined assessment and treatment clinic), location of facility (rural/peri-urban/urban) and, if applicable, distance between assessment and ART initiation sites (kilometers). Patient load, numbers of staff and staff vacancies were obtained from the Human Resources Data Mart, part of the Data Warehouse (12). The number of patients enrolled per year was the total number enrolled throughout follow up divided by the total time that the clinic had been part of the CHAM program. The mean number of staff in each clinic from April 2005 to September 2008 was divided by the number of patients enrolled in that clinic per year in the program to obtain the number of staff per 1000 patients per year. Patients became eligible for ART as soon as a CD4 count ≤ 200 cells/mm³ was measured. WHO disease staging was not used to assess eligibility, as it was not routinely recorded. Deaths were ascertained by linking the database with the National Death Register (estimated to capture >90% of adult deaths in South Africa (13)) each month, using the National Identity Number. Patients without an ID number may belong to more marginalized populations, although we cannot infer whether they have higher mortality rates. The Data Warehouse was also linked with the National Health Laboratory Services (NHLS) Database, to obtain all measured CD4 counts (not all CD4 counts were recorded in medical records due to constraints on data entry). CD4 results were reported by the laboratory and added to medical records after the clinic visit when blood was drawn. The visit schedule was used to define whether patients were considered to be in care at the end of December 2008. Patients not seen by six months after an expected visit were defined as not in care (the six-month threshold allowed for patients who arrived late and also for visits to be recorded in the database). Untreated patients were defined as not in care according to CD4 count: ≤ 200 cells/mm³ and not seen in the last 6 months; 201-500 cells/mm³ and not seen in the last year; or >500 cells/mm³ and not seen in the last 18 months. Untreated patients with no recorded CD4 count were defined as not in care if not seen in the last 6 months.

Statistical analysis

Patients were included in survival models from the time they were eligible for treatment (first CD4 ≤ 200 cells/mm³, baseline) to the earlier of ART initiation or death. Patients not in care were censored at the date they were last seen in the program. We estimated the cumulative incidence of starting ART (overall and stratified by CD4) while accounting for censoring due to the competing risk of death, and the cumulative incidence of pre-ART death accounting for the competing risk of starting ART. We also estimated the cumulative incidence of starting ART and pre-ART death from the time of enrolment, among patients with no recorded pre-treatment CD4 count.

Competing risks proportional hazards regression models (14) were used to estimate adjusted associations of patient and facility characteristics with rates of starting ART and pre-ART death. We controlled for sex, age, weight, CD4 count, year of enrolment, staffing levels per 1000 patients per year, facility location and distance to site for ART initiation. We estimated subdistribution hazard ratios (SHRs) for these competing events: SHRs can be interpreted similarly to hazard ratios estimated in standard Cox models, but they account for the hazard

of the competing event (see Appendix 1 for further details). Data on weight were missing for 6012 of 22083 (27.2%) eligible patients and were assumed missing at random (MAR) (15). We used multiple imputation using chained equations (16) to derive 25 imputed datasets. Results from models fitted on each dataset were combined using Rubin's rules (15). Analyses restricted to individuals with complete data were also conducted (17), and in sensitivity analyses we first excluded patients without a valid ID and second assumed that patients without an ID and lost to follow up were dead. Complete case analyses were also done within CD4 strata. All analyses used Stata version 11 statistical software (18).

The FSDOH gave permission for the data to be analyzed for this study and the Human Research Ethics Committee of the University of Cape Town approved the protocol. No individual patient consent was deemed necessary as data were collected routinely for the CHAM program, and patient identifiers were removed from data extracts used for analyses.

Results

Table 1 shows characteristics of the 44,844 treatment naïve patients enrolled in CHAM between May 2004 and December 2007. Those without an ID number were younger, had a higher median pre-treatment CD4 count and were more likely to be enrolled in a site which could provide ART initiation. New enrolments to the program substantially increased with each calendar year.

Figure 1 shows the flow of patients through the program. A total of 33,182 patients (74%) had at least one pre-treatment CD4 count. For the remaining 26% of patients, CD4 either could not be linked from the NHLS, or pre-treatment CD4 was never measured. Of those patients with a pre-treatment CD4 count, 22,083 (67%) were eligible for ART before December 2008. The percentage of patients eligible at their first CD4 count was 57% in 2004; decreasing to 54% in 2005 and 2006 and increasing to 65% in 2007. There was a corresponding large increase in the number of facilities in 2007, resulting in more people presenting for HIV care with advanced disease. Of those eligible, 19,089 (86%) were eligible at their first CD4 measurement. Of the 11,662 patients with no recorded pre-treatment CD4 count, 3,528 (30%) subsequently started ART. Patients in this group may have had a $CD4 \leq 200$ which was not recorded, or have qualified for treatment on the basis of a Stage IV illness. Patients with no recorded pre-treatment CD4 were more likely to be male and to have enrolled in 2007 and less likely to have a National Identity Number.

Among all 44,844 patients enrolled in CHAM, 9,232 died before starting ART (pre-treatment mortality rate 32.4 per 100 person-years; 95% CI 31.7-33.0). Among the 22,083 patients eligible for treatment, 5,125 (23%) died before starting ART, (pre-treatment mortality rate 53.2 per 100 person-years; 95% CI 51.8-54.7). In eligible patients the median time to death was 92 (IQR 33-216) days. Among 12,963 patients who were eligible and started ART the median wait (time from eligibility to initiation) was 95 (53-170) days. Waiting times decreased from median 122 (67-200) in 2004 to 78 (45-128) days in 2007. A total of 2148 eligible patients died on ART (mortality rate 10.1 per 100 person-years; 95% CI 9.7-10.6).

The median CD4 count at eligibility moderately increased from 87 (37-142) in 2004 to 101 (48-154) cells/mm³ in 2007. However, in the 20 sites that opened at the start of the program in 2004, median CD4 decreased from 102 to 97 cells/mm³ over the same period. This is surprising as we expected initial CD4s to increase as the sites became more established in the local area, and this suggests the backlog of eligible patients remains for a number of years after a site has opened. This may be consistent with other evidence of barriers to care previously noted (1). Among 2,990 eligible patients with a previous CD4 count >200 cells/

mm³, the median of this count was 260 (227-318) cells/mm³, and was measured a median 183 (105-309) days previously. Their median CD4 count at eligibility was 160 (124-183) cells/mm³.

Figure 2 a) shows cumulative percentages of patients starting ART, and pre-ART mortality, up to 2 years after eligibility. At 2 years, 68% (67% – 68%) of eligible patients had started ART, 26% (26% - 27%) had died before starting ART: thus 6% were alive and untreated. Figure 2 b) shows cumulative percentages for starting ART and pre-ART mortality by CD4 count at eligibility. Among patients with CD4 count ≤ 25 cells/mm³ at eligibility, 48% died before starting ART and 51% initiated ART. Corresponding percentages in patients with 101-200 cells/mm³ were 20% and 78%. In patients without CD4 counts, 42% died by 2 years and 53% started ART. In a sensitivity analysis, follow-up time was extended to the database close date for those patients defined as not in care as the percentage alive and untreated at 2 years may be underestimated. This showed that by 2 years, 60% of patients were estimated to have started ART, 23% died pre-ART and 17% remained alive and untreated. Risk factor associations with both outcomes were similar to those in the main analysis.

Table 2 shows adjusted SHRs for the association of facility and patient level characteristics with 1) time to starting ART and 2) time to pre-ART death, accounting for the other (competing) event. Compared with women, men were less likely to start treatment (SHR 0.81, 95% CI 0.78-0.84) and more likely to die (SHR 1.36, 95% CI 1.28-1.44). Higher weight and CD4 counts increased the probability of starting treatment. The risk of death before starting ART decreased with higher weight and CD4 count. Mortality declined and access to treatment increased over calendar time. After accounting for the competing risk of starting treatment, the cumulative incidence function estimates that 13% of patients without an ID died before starting ART, compared to 31% of patients with an ID. However, sensitivity analyses restricted to patients who had a valid ID and one year of follow up showed the same pattern of declining mortality over calendar time, although estimates were attenuated. Enrolment in a clinic with low staffing levels was associated with a decreased probability of starting treatment, compared with better staffed clinics. Enrolment in a rural facility was associated with lower rates of starting treatment and higher mortality rates compared with those enrolled in urban or peri-urban facilities. Increasing distance from the initiation site was associated with a decreased probability of treatment and increased probability of death.

Complete case analyses (Appendix 2) showed a stronger effect of year of enrolment, staffing levels and location on the probability of starting ART, and a stronger effect of weight, year of enrolment and location on the probability of pre-ART death. The effect of distance to the initiation site on the probability of starting treatment and pre-ART death were somewhat attenuated. Sensitivity analyses that assumed patients without a valid ID and were lost to follow up were dead suggested that higher staffing levels were associated with lower mortality, but other results were similar to the main analysis. Associations estimated within CD4 strata were consistent with those shown in Table 2 (available from the authors on request).

Discussion

We found that the most immunocompromised patients had the lowest probability of starting treatment of all patients eligible for ART after accounting for the competing risk of death. This was clearly demonstrated by the graphs of the cumulative incidence of starting treatment and of pre-treatment mortality stratified by CD4 count, and was confirmed by the findings of the multivariable adjusted competing risks regression. Time to ART and death

were both strongly associated with clinic-level factors, including location, distance to ART initiation site and staffing of health facilities (19). The distance between assessment and initiation site was a proxy measure of the distance from place of residence to initiation site, and therefore can represent the potential inconvenience to the patient of attending for ART initiation. Patients also had variable distances from home to assessment clinics, but these were not recorded.

The program shows improvements in increasing access to treatment and decreasing mortality over the period 2004-2007, this reflects increasing numbers of facilities participating in the ART scale-up and increasing experience with the program. However, these data do not include patients who enrolled during the Free State drugs moratorium, when new initiations onto ART were suspended for three months over the New Year period of 2008/09 (20). Not surprisingly, the patterns of associations of covariates with mortality were the inverse of those with the outcome starting treatment.

A number of patients were followed up in the clinic before they became eligible. These patients waited a median of approximately six months for their next CD4 count to be taken, in line with national guidelines. However, CD4 counts had often dropped significantly below the threshold of 200 cells/mm³ before patients were seen again. Patients who are initially ineligible for treatment should therefore be monitored more frequently to ensure timely initiation, and should be encouraged to return promptly for their repeat CD4 count, as has also been reported in a recent study on pre-ART care from Johannesburg (21).

Our study has several strengths. We were able to follow patients from their first point of contact with the program, and patient records were linked to the National Death Register and the NHLS laboratory database. This ensured that information on deaths and CD4 counts in our data are accurate and relatively complete. Although CD4 measurements were routinely taken on almost all patients, only half of the patients had these recorded in the clinical database. Completeness of CD4 recording was improved to 74% by linkage with the NHLS using deterministic matching of records. Another strength is the use of a competing risks framework which appropriately adjusts probabilities of starting ART for the probability of death pre-ART, and vice versa. As shown in the appendix, standard methods such as Kaplan-Meier survival estimates may give a misleading impression of pre-treatment mortality in the presence of competing risks.

The amount of missing data is nevertheless a weakness of our study. Weight data were missing on a large proportion of patients and these had to be imputed based on measured patient characteristics. Results from complete case analyses and analyses based on imputed data were relatively consistent. Over a quarter of enrolled patients did not have a pre-treatment CD4 and so were not included in our analysis. These patients were more likely to be men and it may be that they did not return for follow-up. It is well documented that HIV-infected men have different health-seeking behaviours to women (22-24). These patients also had increased rates of pre-ART death, implying that many of these patients were ill and did need treatment urgently. Either CD4 counts were not measured in these patients, the counts could not be identified in the NHLS database due to variation in names, or they were considered eligible for treatment based on unrecorded criteria. A large number of patients were not in care at the database close date. These patients may have transferred out of the province to receive their care in another facility, or they may re-enter the CHAM at a later date. Improved surveillance of patients has been achieved in CHAM by monthly linkage to the death register and the NHLS database, as well as concerted efforts to collect ID numbers. Reasons for missing ID numbers included patients not knowing them or, if not legal residents, not having them. Few other provincial programs have electronic surveillance data comparable to this program. Improved monitoring of pre-ART patients with CD4 counts

close to the treatment initiation threshold might reduce pre-ART deaths. Data are not collected on WHO disease stage at enrolment. Inclusion of these data would have helped identify patients eligible to start treatment.

Previous studies have shown that patients in a wide variety of resource-limited settings including sub-Saharan Africa, Asia and Latin America, are starting ART well below the recommended treatment thresholds (25;26). However, to our knowledge, only three other studies have assessed waiting times for ART. A study based on the first five years of ART scale-up in Cambodia reported median waiting times for ART of 11.3 months in 2003, which were drastically reduced to 1.3 months in 2007 (27). A study from Cape Town found that patients waited a median of 34 days from enrolment to treatment initiation (28). This is considerably quicker than we have seen in the Free State program. However, the Cape Town program only included patients who were known to be eligible at enrolment and so waiting time did not include the time spent assessing patients for eligibility. A study at a fee-paying clinic in Durban reported a mean waiting time of 3.6 months from first CD4 count to first ART training session (29), similar to that in the publicly funded Free State program. However, the Durban study found that waiting time to first ART training session decreased with decreasing CD4 count, indicating that sicker patients were fast-tracked, which was not the case in the Free State program.

A number of studies have reported on pre-treatment mortality in HIV-infected patients. A study in Uganda reported 35 deaths per 100 person-years in the first month of screening patients for ART eligibility (30). Similar, in Cape Town, a study found pre-treatment mortality rates of 33.3 deaths per 100 person-years (28). A study of the DART trial comparison cohort in Entebbe, Uganda, reported a mortality rate of 57.7 per 100 patient years for those with CD4<200 (31), which is comparable with the rate of 53.2 per 100 patient years reported for eligible patients in the Free State cohort. Thai et al (27) reported on pre-ART mortality using standard survival analysis and conducting sensitivity analyses making different assumptions about outcomes in patients lost to follow up. In their worst- and best-case scenarios (assuming respectively that patients lost to follow up had all died or were all alive), one-year mortality among patients eligible for treatment was estimated at 49% and 20% respectively. However these authors but did not specifically allow for the competing risk of starting ART.

Many of the most immunocompromised patients will not survive drug readiness training, which is required before initiating ART. Although such training may improve patient adherence and reduce the emergence of drug resistance, it also increases waiting time for treatment. Our study shows high early mortality which suggests that severely immunosuppressed patients cannot afford the luxury of extended pre-ART education. Improved ways of delivering DRT are required, but there have been no formal evaluations of alternative modes of delivery in low-income settings. Assessment of patient readiness for treatment through DRT should not be used to ration treatment (32). New South African treatment guidelines for 2010 state that those who urgently need ART, i.e. CD4<100 or are pregnant or Stage IV or co-infected with MDR or XDR TB, should be initiated within 2 weeks (33). DRT would then have to be shortened or occur at the same time as the patient is starting ART. In general, delayed initiation was due to inadequate resources, and the shortage of doctors to assess patients and to initiate ART also contributes to the long waiting times. Prioritization of ART to those with the lowest CD4 counts, the ability to initiate ART in as many facilities as possible, earlier diagnoses and closer monitoring of ineligible patients may all contribute to reduce waiting times and pre-treatment mortality. Increased provision of co-trimoxazole could also improve outcomes for patients not yet on ART, as it has been seen to have an independent effect on mortality (2). All these strategies require more human resources, which are severely lacking in South Africa. Task-shifting may prove

to be the way forward and is a recent addition to the South African HIV/AIDS National Strategic Plan. Trials of this are currently underway and there have been promising results so far (34-37).

As most patients start treatment well below the current initiation threshold of 200 cells/mm³, increasing this may help to increase the likelihood of patients initiating at around 200 cells/mm³. On 1st December 2009, the South African government announced that the treatment threshold would be raised to 350 cells/mm³ for pregnant women and those co-infected with TB. Although this is a step in the right direction, it must be noted that raising the treatment threshold will add to the already overwhelming burden of maintaining patients on ART, as discussed in a recent commentary in *The Lancet* (6), and could lead to more delays for many other patients. To combat this, the South African government announced that ART would be available in all health care sites, not only specialist HIV clinics, a decision with implications for training and staffing levels in all facilities.

Appendix 1

Analyses accounting for competing risks

Independence assumption

Standard techniques for analysing survival data include Kaplan-Meier estimation of cumulative incidence and Cox regression models. These techniques assume that the distribution of censoring times and the time-to-event distribution are independent of each other. Often, this assumption is taken to be valid without further checks. If patients are censored administratively, then this assumption may be reasonable. However, if patients are censored through becoming lost to follow up or through experiencing another event, then censoring may be related to the time to the event of interest and the independence assumption is violated. This leads to biased estimates of survival times and overestimates of percentages experiencing the event of interest.

Competing events

In our data, this assumption is violated. For example, our event of interest is starting ART. If a patient dies before starting ART, then standard techniques would result in this patient being censored. However, this patient cannot then experience the event of interest and is not representative of those remaining in follow-up. Therefore, censoring is not appropriate. In this case, the event pre-ART death precludes the event of interest from happening and is called a competing risk.

Appendix Figure 1. Kaplan-Meier estimates of the cumulative probabilities of starting ART and death

As seen above, if competing events are present, the Kaplan-Meier curves will overestimate the percentage experiencing the event of interest within each CD4 strata. In the group with CD4 counts <25 cells/mm³, the Kaplan-Meier estimates that 87% initiate ARVs and 91% die first. The Kaplan-Meier method also estimates that over all eligible patients and all follow up time, 92% will start ARVs but that also, that 100% will die first. This is of course impossible and methods are needed to correct for this.

Cumulative Incidence Functions

Cumulative Incidence Functions (CIFs) provide an unbiased method of reporting the percentage of patients experiencing an event of interest in the presence of competing events. The CIF, $I_k(t)$, is defined as the probability of failing from cause k by time t . It is different from the Kaplan-Meier estimate as it does not simply treat failures from causes other than k as censored. The CIF estimates the probability of failing from cause k , in the presence of all other causes.

$$\widehat{I}_k(t) = \sum_{t_i \leq t} \widehat{p}_k(t_i)$$

$$\widehat{p}_k(t_i) = \widehat{\lambda}_k(t_i) \widehat{S}(t_i - 1), \quad \widehat{\lambda}_k(t_i) = \frac{d_{ki}}{n_i}$$

where $\widehat{S}(t_i)$ represents the estimate of the overall survivor function at time t_i .

In the main text of the paper we calculate CIFs for both events within CD4 strata. We report that for patients with CD4 counts <25 cells/mm³, 51% start ART and 48% die first. These estimates now make sense.

Risk Factor Associations

Cox Regression

When assessing associations of risk factors with event times, the standard technique is to use Cox regression modeling. Again, when using this technique, it is assumed that patients who are censored can be thought to be representative of the patients who remain in follow up. As this is not true in our data, Cox regression was not appropriate. However, we present the results from Cox regression as a comparison (Appendix Table 1).

With Cox regression we saw no effect of CD4 on the hazard of starting treatment, except in the group with CD4 counts <25 cells/mm³. Patients with CD4 counts <25 cells/mm³ appeared to have an increased hazard of starting treatment compared to those with CD4 counts of 100-200 cells/mm³. However, these patients also have a much greater risk of mortality. In the Cox regression, patients who die before starting ART are censored and the patients who remain in follow up are assumed to be representative of the censored patients. This leads to the hazard of starting treatment being overestimated for this group, as patients who are not able to experience the event are treated as though they could experience the event.

To properly account for the risk of dying before treatment in our estimates of associations between risk factors and hazard of starting treatment, we used competing risks regression models as defined by Fine and Gray (14) and implemented in Stata v.11 (18). These model estimate the hazard of the subdistribution (the hazard function as would be derived from the CIF), which appropriately accounts for competing risks.

By using competing risks regression models, we see that there is an association between CD4 and the hazard of starting treatment. Patients with CD4 counts <25 cells/mm³ have a lower hazard of starting treatment compared to those with CD4 counts of 100-200 cells/mm³, and this is due to the fact that they are more immunosuppressed and therefore, more likely to die before initiating ART.

Appendix Table 1

Adjusted associations of facility and patient level characteristics with time to a) starting treatment and b) pre-ART death, using 25 imputed datasets and standard Cox regression *, not taking into account competing risks.

	N (%)	HR(95% CI) for starting ART ^s	HR(95% CI) for pre-ART death ^s
Patient characteristics			
Sex			
Female	14261 (64.6)	1 (baseline)	1 (baseline)
Male	7822 (35.4)	0.85 (0.82,0.88)	1.22 (1.15,1.30)
Age at eligibility (year)			
15-29	4928 (22.3)	0.95 (0.91,1.00)	0.89 (0.83,0.96)
30-39	9474 (42.9)	1 (baseline)	1 (baseline)
40-49	5654 (25.6)	1.01 (0.97,1.06)	1.02 (0.95,1.10)

	N (%)	HR(95% CI) for starting ART [§]	HR(95% CI) for pre-ART death [§]
>=50	2027 (9.2)	1.04 (0.98,1.11)	1.27 (1.15,1.40)
Weight at eligibility (kg)			
<40	1609 (7.3)	0.75 (0.68,0.83)	1.94 (1.73,2.18)
40-49	5554 (25.2)	0.92 (0.87,0.97)	1.36 (1.26,1.46)
50-59	7620 (34.5)	1 (baseline)	1 (baseline)
60-79	6400 (29.0)	1.03 (0.98,1.08)	0.74 (0.68,0.81)
>=80	900 (4.1)	1.17 (1.07,1.29)	0.48 (0.37,0.62)
CD4 value at eligibility date (cells/mm ³)			
<=25	3207 (14.5)	1.09 (1.03,1.15)	3.69 (3.42,3.98)
25-50	2698 (12.2)	1.04 (0.99,1.11)	2.39 (2.19,2.60)
50-100	5102 (23.1)	1.03 (0.99,1.08)	1.85 (1.72,2.00)
100-200	11076 (50.2)	1 (baseline)	1 (baseline)
Year of enrolment			
2004	3997 (18.1)	1 (baseline)	1 (baseline)
2005	5340 (24.2)	1.16 (1.10,1.23)	1.10 (1.01,1.19)
2006	6192 (28.0)	1.37 (1.30,1.45)	1.10 (1.02,1.20)
2007	6554 (29.7)	1.70 (1.61,1.79)	1.03 (0.94,1.13)
Facility characteristics			
Filled posts per 1000 enrolled patients per year			
<5	6805 (30.8)	0.62 (0.59,0.65)	0.98 (0.91,1.06)
5-7.5	8116 (36.8)	1 (baseline)	1 (baseline)
>7.5	7162 (32.4)	1.01 (0.96,1.07)	1.16 (1.06,1.27)
Location			
Urban/peri-urban	16970 (76.8)	1 (baseline)	1 (baseline)
Rural	5113 (23.2)	0.92 (0.86,0.99)	1.29 (1.12,1.49)
Distance to treatment site (km)			
Same site	5698 (25.8)	1 (baseline)	1 (baseline)
<8	6923 (31.3)	0.94 (0.88,0.99)	2.02 (1.80,2.26)
8-15	6563 (29.7)	0.84 (0.79,0.90)	2.11 (1.88,2.36)
>15	2899 (13.1)	0.81 (0.75,0.87)	1.52 (1.33,1.73)

* Model for starting ART: pre-ART deaths are censored. Model for pre-ART deaths: patients starting ART are censored

[§] Mutually adjusted for all characteristics in the table

Appendix 2

Adjusted sub hazard ratios (SHR) of the associations of facility and patient level characteristics with time to a) starting treatment and b) pre-ART death, using complete case data N=16,071

	N (%)	SHR(95% CI) for starting ART [§]	SHR(95% CI) for pre-ART death [§]
Patient characteristics			
Sex			

	N (%)	SHR(95% CI) for starting ART [§]	SHR(95% CI) for pre-ART death [§]
Female	10461 (65.1)	1 (baseline)	1 (baseline)
Male	5610 (34.9)	0.82 (0.78 to 0.85)	1.39 (1.30 to 1.49)
Age at eligibility (year)			
15-29	3533 (22.0)	0.99 (0.94 to 1.05)	0.92 (0.85 to 1.01)
30-39	6895 (42.9)	1 (baseline)	1 (baseline)
40-49	4188 (26.1)	0.98 (0.94 to 1.03)	0.99 (0.91 to 1.07)
>=50	1455 (9.1)	0.95 (0.89 to 1.03)	1.20 (1.07 to 1.34)
Weight at eligibility (kg)			
<40	968 (6.0)	0.58 (0.52 to 0.65)	2.41 (2.14 to 2.71)
40-49	4229 (26.3)	0.81 (0.77 to 0.86)	1.45 (1.34 to 1.57)
50-59	5757 (35.8)	1 (baseline)	1 (baseline)
60-79	4375 (27.2)	1.16 (1.10 to 1.21)	0.72 (0.65 to 0.79)
>=80	742 (4.6)	1.26 (1.15 to 1.39)	0.46 (0.35 to 0.60)
CD4 value at eligibility date (cells/mm ³)			
<=25	2263 (14.1)	0.67 (0.62 to 0.72)	2.98 (2.73 to 3.26)
25-50	1916 (11.9)	0.79 (0.73 to 0.84)	2.07 (1.87 to 2.29)
50-100	3635 (22.6)	0.86 (0.81 to 0.90)	1.75 (1.61 to 1.90)
100-200	8257 (51.4)	1 (baseline)	1 (baseline)
Year of enrolment			
2004	3687 (22.9)	1 (baseline)	1 (baseline)
2005	4574 (28.5)	1.16 (1.10 to 1.23)	0.94 (0.87 to 1.03)
2006	4506 (28.0)	1.41 (1.33 to 1.49)	0.80 (0.73 to 0.87)
2007	3304 (20.6)	2.05 (1.92 to 2.18)	0.55 (0.49 to 0.61)
Facility characteristics			
Filled posts per 1000 enrolled patients per year			
<5	4992 (31.1)	0.65 (0.62 to 0.69)	1.34 (1.23 to 1.45)
5-7.5	6233 (38.8)	1 (baseline)	1 (baseline)
>7.5	4846 (30.2)	1.12 (1.04 to 1.21)	1.02 (0.90 to 1.14)
Location			
Urban/peri-urban	12010 (74.7)	1 (baseline)	1 (baseline)
Rural	4061 (25.3)	0.74 (0.67 to 0.80)	1.50 (1.27 to 1.78)
Distance to treatment site (km)			
Same site	3703 (23.0)	1 (baseline)	1 (baseline)
<8	4911 (30.6)	0.80 (0.74 to 0.87)	1.76 (1.53 to 2.02)
8-15	5061 (31.5)	0.72 (0.66 to 0.77)	1.97 (1.71 to 2.27)
>15	2396 (14.9)	0.75 (0.68 to 0.82)	1.54 (1.32 to 1.79)

[§]Mutually adjusted for all characteristics in the table

Acknowledgments

This study was funded by the National Institute of Allergy and Infectious Diseases (NIAID grant 1 U01 AI069924-01 to IeDEA Southern Africa). Suzanne Ingle was funded by a UK Medical Research Council PhD Studentship. Margaret May and Jonathan Sterne were supported by UK Medical Research Council grant G0700820. The Free State ART data warehouse was developed with the help of a research grant from the International Development Research Centre, Canada (IDRC-102411). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We also gratefully acknowledge the data capturers, nurses, doctors and managers of the Free State program, in particular Ronald Chapman, Cloete van Vuuren and Dewald Steyn, MediTech for assisting with data downloads to the warehouse, Krista Dong for critical input into designing the structured clinical records, Terry Marshall and Sue Candy for assisting with the preparation of NHLS data, and Adrian Spoerri who helped with data linkage. Suzanne Ingle and Lara Fairall had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We acknowledge all those who died without access to ART.

EK, VT and LF established the cohort database. KU, VT, EK were involved in data acquisition. ME, LF, MM and JS were responsible for study design. SI, MM, JS were responsible for statistical analysis and had full access to the data. SI, MM, JS and ME wrote the first draft of the manuscript. All authors helped in interpreting data, contributed to writing and approved the final version.

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Figure 1.
Flow of patients through ART program

Figure 2.
Cumulative percentages of patients starting treatment, experiencing pretreatment death and remaining untreated in the Free State Province ART program, Republic of South Africa 2004-2008

- a) Shows estimates for all eligible patients
b) Shows estimates for all eligible patients, split by CD4 count at eligibility

Table 1

Patient characteristics at enrolment into the Free State ART program

	Total (%)	With recorded pre-treatment CD4 (%)	Without recorded pre-treatment CD4 (%)
Patient characteristics (categorical)			
Total	44844 (100)	33182 (100)	11662 (100)
Sex			
Female	29898 (66.7)	22433 (67.6)	7465 (64.0)
Male	14946 (33.3)	10749 (32.4)	4197 (36.0)
Year of enrolment			
2004	6567 (14.6)	5741 (17.3)	826 (7.1)
2005	10860 (24.2)	8316 (25.1)	2544 (21.8)
2006	12872 (28.7)	9824 (29.6)	3048 (26.1)
2007	14545 (32.4)	9301 (28.0)	5244 (45.0)
Valid ID			
Yes	35288 (78.7)	27050 (81.5)	8238 (70.6)
No	9556 (21.3)	6132 (18.5)	3424 (29.4)
Facility location			
Urban	3391 (7.6)	1947 (5.9)	1444 (12.4)
Peri-urban	31465 (70.2)	23221 (70.0)	8244 (70.7)
Rural	9988 (22.3)	8014 (24.2)	1974 (16.9)
Facility type			
Assessment only	31897 (71.1)	24728 (74.5)	7169 (61.5)
Treatment only	3933 (8.8)	2218 (6.7)	1715 (14.7)
Combined	9014 (20.1)	6236 (18.8)	2778 (23.8)
Filled posts per 1000 enrolled patients per year			
<5	16468 (36.7)	11377 (34.3)	5091 (43.7)
5-7.5	14269 (31.8)	11743 (35.4)	2526 (21.7)
>7.5	14107 (31.5)	10062 (30.3)	4045 (34.7)
Distance to treatment site			
Same site	12947 (28.9)	8454 (25.5)	4493 (38.5)
<8km	12652 (28.2)	10060 (30.3)	2592 (22.2)
8-15km	13553 (30.2)	10146 (30.6)	3407 (29.2)

	Total (%)		With recorded pre-treatment CD4 (%)		Without recorded pre-treatment CD4 (%)	
>15km		5692 (12.7)		4522 (13.6)		1170 (10.0)
Patient characteristics (continuous)						
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Age (years)	44844	35 (29 - 42)	33182	35 (29 - 42)	11662	35 (29 - 42)
Weight (kg)	29352	55 (49 - 64)	24497	56 (49 - 64)	4855	55 (48 - 64)
CD4 (cells/mm ³)	33182	170 (76 - 318)	33182	170 (76 - 318)	NA	NA

Table 2

Subdistribution hazard ratios (SHR) of the associations of facility and patient level characteristics with time to a) starting treatment and b) pre-ART death

	N (%)	SHR(95% CI) for starting ART [§]	SHR(95% CI) for pre-ART death [§]
Patient characteristics			
Sex			
Female	14261 (64.6)	1 (baseline)	1 (baseline)
Male	7822 (35.4)	0.81 (0.78,0.84)	1.36 (1.28,1.44)
Age at eligibility (year)			
15-29	4928 (22.3)	0.99 (0.94,1.03)	0.94 (0.87,1.01)
30-39	9474 (42.9)	1 (baseline)	1 (baseline)
40-49	5654 (25.6)	1.01 (0.96,1.05)	1.00 (0.94,1.08)
≥50	2027 (9.2)	0.98 (0.92,1.04)	1.19 (1.08,1.32)
Weight at eligibility (kg)			
<40	1609 (7.3)	0.59 (0.53,0.65)	2.15 (1.91,2.41)
40-49	5554 (25.2)	0.83 (0.79,0.88)	1.39 (1.29,1.50)
50-59	7620 (34.5)	1 (baseline)	1 (baseline)
60-79	6400 (29.0)	1.10 (1.05,1.15)	0.74 (0.68,0.81)
≥80	900 (4.1)	1.30 (1.19,1.42)	0.44 (0.34,0.57)
CD4 value at eligibility date (cells/mm ³)			
≤25	3207 (14.5)	0.65 (0.61,0.69)	3.00 (2.78,3.24)
25-50	2698 (12.2)	0.78 (0.74,0.83)	2.08 (1.91,2.26)
50-100	5102 (23.1)	0.86 (0.82,0.90)	1.74 (1.62,1.87)
100-200	11076 (50.2)	1 (baseline)	1 (baseline)
Year of enrolment			
2004	3997 (18.1)	1 (baseline)	1 (baseline)
2005	5340 (24.2)	1.10 (1.05,1.17)	0.97 (0.90,1.05)
2006	6192 (28.0)	1.25 (1.18,1.31)	0.87 (0.80,0.94)
2007	6554 (29.7)	1.49 (1.42,1.58)	0.66 (0.61,0.72)
Facility characteristics			
Filled posts per 1000 enrolled patients per year			
<5	6805 (30.8)	0.64 (0.61,0.67)	1.35 (1.26,1.45)
5-7.5	8116 (36.8)	1 (baseline)	1 (baseline)
>7.5	7162 (32.4)	0.97 (0.92,1.03)	1.16 (1.06,1.27)
Location			
Urban/peri-urban	16970 (76.8)	1 (baseline)	1 (baseline)
Rural	5113 (23.2)	0.89 (0.83,0.96)	1.42 (1.23,1.64)
Distance to treatment site (km)			
Same site	5698 (25.8)	1 (baseline)	1 (baseline)
<8	6923 (31.3)	0.80 (0.75,0.85)	2.04 (1.82,2.28)
8-15	6563 (29.7)	0.72 (0.68,0.77)	2.29 (2.05,2.56)

	N (%)	SHR(95% CI) for starting ART [§]	SHR(95% CI) for pre-ART death [§]
>15	2899 (13.1)	0.72 (0.66,0.78)	1.65 (1.45,1.88)

*Analyses based on 25 datasets in which weight was imputed.

[§]Mutually adjusted for all characteristics in the table