

Determinants of Mortality and Nondeath Losses from an Antiretroviral Treatment Service in South Africa: Implications for Program Evaluation

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(See the editorial commentary by Weller on pages 777–8)

Background. The scale-up of antiretroviral treatment (ART) services in resource-limited settings requires a programmatic model to deliver care to large numbers of people. Understanding the determinants of key outcome measures—including death and nondeath losses—would assist in program evaluation and development.

Methods. Between September 2002 and August 2005, all in-program (pretreatment and on-treatment) deaths and nondeath losses were prospectively ascertained among treatment-naïve adults ($n = 1235$) who were enrolled in a community-based ART program in South Africa.

Results. At study censorship, 927 patients had initiated ART after a median of 34 days after enrollment in the program. One hundred twenty-one (9.8%) patients died. Mortality rates were 33.3 (95% CI, 25.5–43.0), 19.1 (95% CI, 14.4–25.2), and 2.9 (95% CI, 1.8–4.8) deaths/100 person-years in the pretreatment interval, during the first 4 months of ART (early deaths), and after 4 months of ART (late deaths), respectively. Pretreatment and early treatment deaths together accounted for 87% of deaths, and were independently associated with advanced immunodeficiency at enrollment. Late deaths were comparatively few and were only associated with the response to ART at 4 months. Nondeath program losses (loss to follow-up, 2.3%; transfer-out, 1.9%; relocation, 0.7%) were not associated with immune status and were evenly distributed during the study period.

Conclusions. Loss to follow-up and late mortality rates were low, reflecting good cohort retention and treatment response. However, the extremely high pretreatment and early mortality rates indicate that patients are enrolling in ART programs with far too advanced immunodeficiency. Causes of late access to the ART program, such as delays in health care access, health system delays, or inappropriate treatment criteria, need to be addressed.

Although sub-Saharan Africa is home to just 10% of the world's population, more than 60% of the world's HIV-infected people live there; in 2005 alone, an estimated 2.4 million people in the region died of HIV/AIDS [1]. As one component of a strategy to address this devastating epidemic, access to antiretroviral treatment (ART) is now being rapidly expanded within the

region. In June 2005, it was estimated that 6.5 million people urgently required treatment in resource-limited settings. In view of the enormous scale of this intervention, a simplified programmatic approach has been adopted to facilitate delivery of treatment [2–4]. The efficacy of ART, as reflected by virological and immunological responses, is similar among patients treated in high-income countries and patients treated in resource-limited countries [5, 6]. The impact of ART programs in low-income countries is, therefore, unlikely to be related to questions of drug efficacy, but rather to health system issues and program effectiveness [7]. Parameters with which to evaluate the effectiveness of programs need to be identified. Tuberculosis treatment programs provide a useful model of how evaluation of carefully defined outcome measures permits

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longitudinal program assessments and comparisons [8]. Similar principals might usefully be applied to ART programs.

Two key goals of ART programs are to prevent mortality and to retain people within the program, receiving treatment in the long term. In this study, we describe mortality occurring (1) in the short interval between program enrollment and initiation of ART (the pretreatment interval), (2) during early ART (0–4 months), and (3) during late ART (4 months to 3 years). We also characterized nondeath losses. We have accurately quantified these different losses during the first 3 years of a community-based ART program in South Africa. We identified the temporal distribution and determinants of these different outcomes, which have thereby provided important insights into program performance.

SUBJECTS AND METHODS

ART. The ART service described here is based at the Gugulethu Community Health Centre in Cape Town and has previously been described in detail [9–11]. This district has a predominantly African population of >300,000, the vast majority of whom live in conditions of low socioeconomic status. In 2003, the antenatal HIV seroprevalence was 28%. Patients are referred to the ART program from primary care HIV clinics. Treatment criteria are based on the World Health Organization's (WHO's) 2002 recommendations [3], which include a prior AIDS diagnosis (WHO stage 4 disease) or a blood CD4 cell count <200 cells/ μ L.

The time between enrollment of a patient in the service and initiation of ART is ~1 month, to permit thorough evaluation of patients and preparation for treatment as described previously [9–11]. Assignment of each patient to a community-based therapeutic counselor facilitates this preparation and provides an efficient system for determining outcomes for all patients, including tracing those who do not attend follow-up appointments. A proportion of patients do not initiate treatment in this service for a variety of reasons other than death; such individuals are deferred from the program, and follow-up is censored at this time-point. However, all individuals contributed to the pretreatment person-time of observation, regardless of whether they subsequently received ART.

First-line ART consisted of stavudine and lamivudine plus a nonnucleoside reverse transcriptase inhibitor (efavirenz or nevirapine). The second-line regimen for those for whom first-line treatment failed was composed of lopinavir/ritonavir, zidovudine, and didanosine. All treatment was provided free of charge. Treatment adherence and viral load suppression at a level of <400 copies/mL in this cohort both exceeded 90% at 1 year [10–12]. All patients with CD4 counts <200 cells/ μ L received prophylaxis with daily trimethoprim-sulfamethoxazole or dapsones as an alternative. In addition to scheduled clinic

appointments at 4, 8, and 16 weeks and once every 16 weeks thereafter, patients had open access to the clinic for medical problems.

Definitions. "Permanent deferrals" were patients who did not receive ART for a reason other than pretreatment death and who were subsequently excluded from the program. "Pretreatment deaths" were those that occurred among patients who had enrolled into the program but who had not yet initiated ART. "Early on-treatment deaths" were those that occurred during the first 4 months of ART, and "late on-treatment deaths" were those that occurred after 4 months of ART. "Transfers-out" were patients whose care was transferred to another ART program. "Relocations" were patients who moved to another location but who were not referred to an ART service in the new area. "Losses to follow-up" were patients receiving ART who were >4 weeks late for a scheduled clinic or pharmacy visit and who were neither transfers-out nor relocations. "Non-death losses" were the sum total of transfers-out, relocations, and losses to follow-up.

Data sources. Structured clinical records were maintained for all patients screened on entry to the ART program. This information was transferred to a computer database on a weekly basis. Data were analyzed from the start of the program in September 2002 until data censorship in August 2005. This study was approved by the Research Ethics Committee of the University of Cape Town, and all patients who were enrolled gave written, informed consent.

Data analysis. Data were analysed using Stata, version 9.0 (StataCorp). Wilcoxon rank-sum and Fisher's exact tests were used to compare medians and proportions, respectively. In separate analyses, we calculated rates of mortality and other outcomes from either program enrollment (the date of initial screening by the service) or from ART initiation. Person-time was censored at the end of August 2005 for individuals who were alive and who had been retained by the service. Product-limit analyses were used to calculate the instantaneous hazard of death or other losses through time among individuals receiving ART; we plotted smoothed hazard-function estimators using weighted kernel-density estimates based on an Epanechnikov function [13]. In other product-limit analyses, log-rank tests were used to examine the effect of baseline WHO clinical stage and category of CD4 cell count on survival probabilities. All statistical tests are 2-sided at $\alpha = .05$.

Multivariate analysis employed proportional hazard models to examine determinants of mortality among individuals receiving ART. Separate models were developed to examine factors associated with early mortality, late mortality, and all deaths. In separate models, baseline CD4 cell count was modeled as both a continuous variable (per 50-cell/ μ L change in the CD4 cell count) and a categorical variable, to demonstrate

threshold effects. Covariates were included in the model if they demonstrated an appreciable association with the relative hazard of mortality, or if their removal affected associations involving other covariates. Model diagnostics and the proportional hazards assumption were examined using Schoenfeld and scaled Schoenfeld residuals [14].

RESULTS

Cohort and follow-up. During the period of September 2002 through August 2005, 1340 patients enrolled in the program. Those who were not naive to ART ($n = 53$) and those <15 years of age at enrollment ($n = 52$) were excluded. Among 1235 patients who remained in the analysis, the median age was 33 years (interquartile range [IQR], 28–38 years), and 882 patients (71%) were female. Baseline plasma viral load and blood CD4 cell counts were available for 1086 and 1120 patients, respectively. The median plasma viral load was 4.81 \log_{10} copies/mL (IQR, 4.42–5.23 \log_{10} copies/mL), and the median blood CD4 cell count was 100 cells/ μ L (IQR, 47–160 cells/ μ L). Most patients (79%) had symptomatic disease, and 644 (52%) and 332 (27%) had WHO stage 3 and 4 disease, respectively.

Nine hundred twenty-seven patients (75%) received ART during the study period, and 117 (9.5%) were preparing for treatment at the time the study was censored (figure 1). The median time between enrollment in the program and initiation of treatment was 34 days (IQR, 28–50 days). Over the course of the study, 170 person-years of observation were accrued in the pretreatment interval, and 808 person-years were accrued during treatment.

Numbers and characteristics of deaths and nondeath losses.

One hundred thirty-five (9.5%) patients were deferred from the service before initiation of ART (figure 1) for a variety of reasons, including decision to access treatment elsewhere, failure to attend follow-up clinic appointments, movement out of the area, or for psychosocial reasons. Among total deaths ($n = 121$), 56 (46%) occurred in the pretreatment interval, 49 (40%) were early on-treatment deaths, and 16 (13%) were late on-treatment deaths. The death rate was high in the pretreatment interval (33.3 deaths/100 person-years; 95% CI, 25.5–43.0 deaths/100 person-years) but decreased during the first 4 months of ART (19.1 deaths/100 person-years; 95% CI, 14.4–25.2 deaths/100 person-years), and was lower still beyond 4 months ART (2.9 deaths/100 person-years; 95% CI, 1.8–4.8 deaths/100 person-years). After 1 year of ART, the mortality rate was just 1.3 deaths/100 person-years (95% CI 0.4–3.9 deaths/100 person-years).

Among those who initiated ART ($n = 927$), 110 patients (11.9%) were lost from the program (figure 1). Among these, death was the most common reason, accounting for 65 (7.0%) of losses, whereas 45 (4.9%) were due to other causes. These

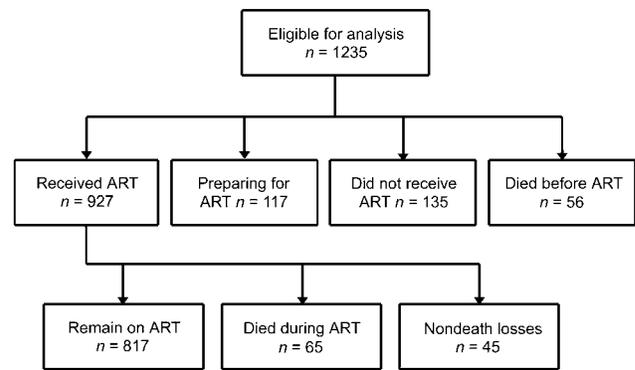


Figure 1. Flow diagram showing the outcomes of patients included in the analysis ($n = 1235$) at the time that data were censored. ART, antiretroviral therapy.

nondeath losses were due to transfer-out (18 [1.9%]), relocation (6 [0.7%]), and loss to follow-up (21 [2.3%]).

We compared the characteristics of patients who were lost from the program due to death with those who were lost due to other reasons or who continued to receive treatment when the data was censored (table 1). In univariate analyses, those who died in the pretreatment interval or during early ART were more likely to have a prior AIDS diagnosis, a baseline CD4 cell count <100 cells/ μ L, and a baseline plasma viral load $>10^5$ copies/mL, compared with those who remained in the program. Those who died after 4 months of ART (late deaths) were also more likely to have a baseline CD4 cell count <100 cells/ μ L, although this association did not persist in the multivariate analysis (see below). In contrast, nondeath losses were not associated with baseline immunodeficiency. Kaplan-Meier analyses confirmed that the probability of in-program death was strongly associated with WHO stage of disease and baseline CD4 cell count (figure 2).

Temporal distribution of program losses. The risk of loss from the program changed markedly during follow-up of patients receiving ART (figure 3A). Risk of death had 3 distinct phases: an initially high—but steeply decreasing—risk during the initial months of ART, followed by a moderate risk of death up to ~ 1 year, and a very low risk of death after 1 year (figure 3B). In contrast, the risk of program loss due to other causes was relatively constant (figure 3C). After ~ 1 year of ART, risk of nondeath losses to the program exceeded losses due to death.

Multivariate analysis for risk of death during ART. In multivariate analysis to predict the relative hazards of death during ART, death was significantly associated with baseline CD4 cell count and WHO clinical stage, but not with age, sex, or baseline viral load. However, risk factors for early deaths versus late deaths differed markedly (table 2). Early on-treatment deaths were associated with advanced WHO clinical stage, lower baseline blood CD4 cell counts, and male sex (table 2).

In contrast, late on-treatment deaths were only independently associated with the response to ART at 4 months, as reflected by blood CD4 cell count and viral load. Although the number of late deaths was small (data were available for 12 of 16 deaths), this association with CD4 cell count was statistically highly significant, and the trend towards an association with viral load approached statistical significance.

CD4 cell count increases and risk of loss to program.

We examined how on-treatment program losses (death and nondeath) were associated with CD4 cell counts at baseline and after 4 months of ART. Although the median CD4 cell increases among patients retained in the cohort (99 cells/ μ L; IQR, 49–162 cells/ μ L) were similar to those among nondeath losses (83 cells/ μ L; IQR, 49–133 cells/ μ L), those who subsequently died had much smaller CD4 cell count increases (44 cells/ μ L; IQR, 5–83 cells/ μ L). The vast majority of deaths occurred among individuals who had a baseline CD4 cell count <100 cells/ μ L and a CD4 cell count <200 cells/ μ L at 4 months (figure 4A). In contrast, nondeath losses were not associated with the CD4 cell count distribution (figure 4B).

DISCUSSION

In this study we carefully quantified mortality and nondeath losses in a community-based ART program in South Africa and identified the temporal distribution and risk factors associated with these losses. We defined pretreatment, early and late ART mortality, and nondeath losses as useful outcome measures of ART programs. Loss to follow-up and late mortality rates were low, reflecting excellent cohort retention and treatment response in this program. In contrast, however, pretreatment and early mortality rates were very high: this finding very strongly suggests that patients were enrolling with far too advanced immunodeficiency. To reduce in-program mortality, the causes of late program entry need to be addressed.

On-treatment mortality rates were similar to or better than

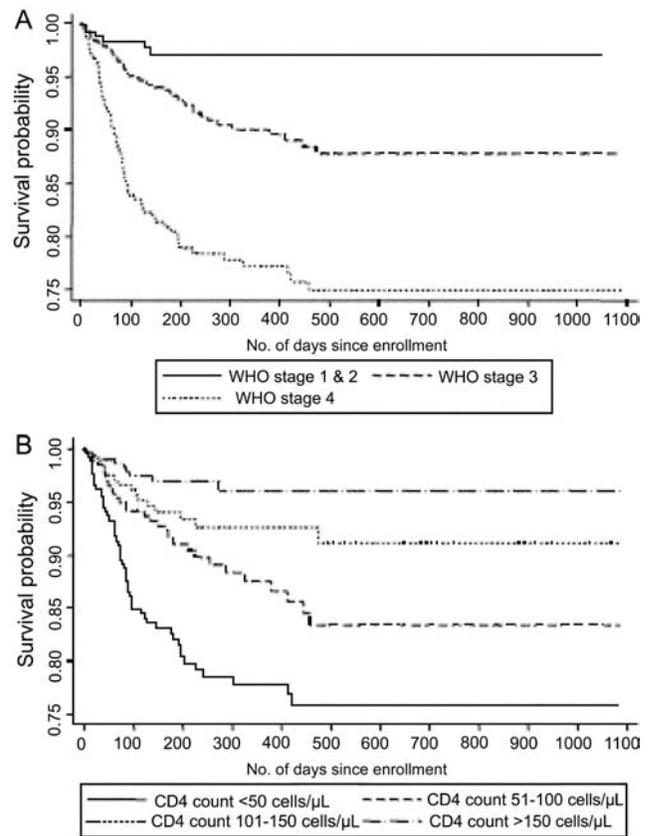


Figure 2. Kaplan-Meier plots showing survival of patients from entry into the program stratified by World Health Organization (WHO) clinical stage (A) and baseline blood CD4 cell count (B). These reveal that risk of death early in the program was strongly associated with the baseline degree of immunodeficiency at enrollment.

those previously reported from resource-limited settings [15–19]. Although previous studies have not reported mortality occurring within the program prior to actual initiation of ART, we demonstrated that a large proportion of early program

Table 1. Baseline characteristics of patients who either remained in the program, died, or were lost from the program for other reasons (transfer-out, relocation, or loss to follow-up).

Characteristic	Remained in program	Death			Other program losses
		Pretreatment	Early	Late	
No. of patients	817	56	49	16	45
Female sex	601 (74)	37 (66)	25 (49)	12 (75)	32 (71)
Age, median years (IQR)	33 (28–38)	32 (28–40)	34 (28–39)	35 (32–41)	31 (27–35)
Prior AIDS diagnosis	207 (25)	30 (54) ^a	29 (59) ^a	7 (44)	12 (27)
CD4 count <100 cells/ μ L	410 (50)	35 (63) ^a	40 (82) ^a	13 (81) ^b	27 (60)
Viral load >10 ⁵ copies/mL	301 (37)	19 (59) ^b	26 (54) ^b	9 (56)	21 (47)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Statistical comparisons were made between characteristics of those who were retained in the program, compared with the characteristics of those who were lost to the program. IQR, interquartile range.

^a $P < .05$.
^b $P < .001$.

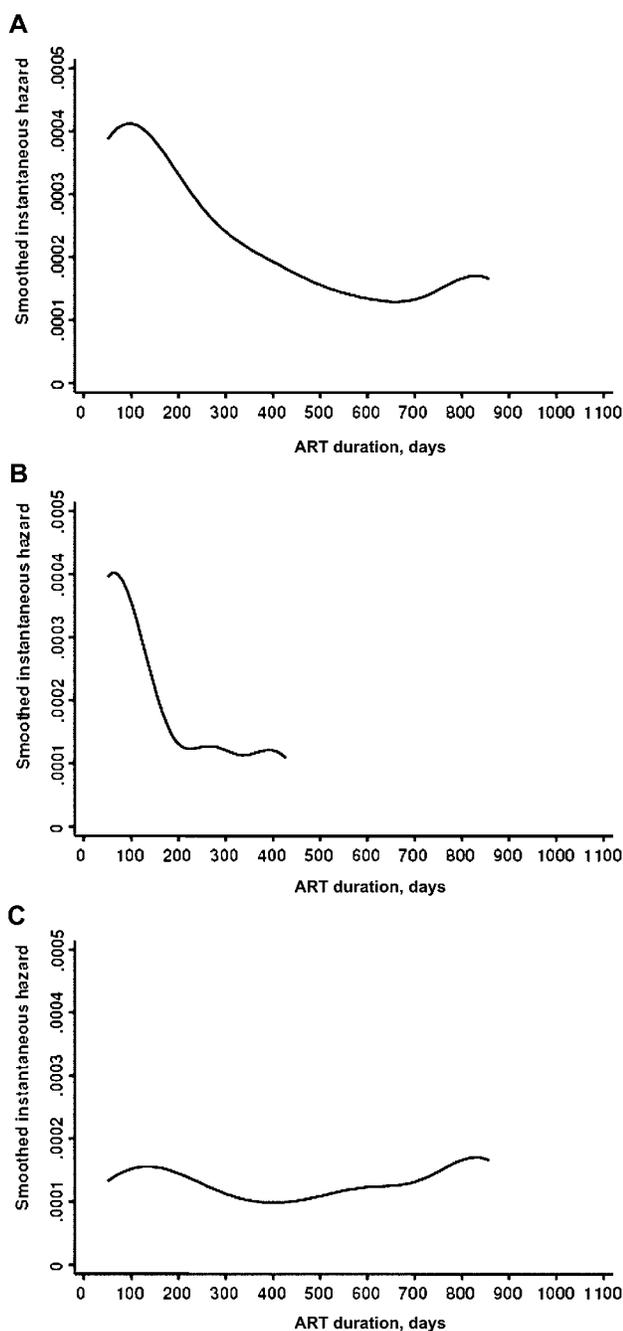


Figure 3. Smoothed hazard estimates for total losses to program (A), death (B), and nondeath losses to program (C; i.e., transfers-out, relocations, and losses to follow-up). Risk of mortality was initially high but decreased steeply, and there were very few deaths after 400 days of ART. Risk of nondeath losses was relatively consistent during follow-up. ART, antiretroviral therapy

deaths occur during this pretreatment interval [9]. The pretreatment interval in the present analysis (median, 34 days) is shorter than reported elsewhere [15] but permitted careful evaluation, investigation, and treatment of opportunistic infections, as well as thorough preparation of patients for ART. We believe

this preparation is key to the very high adherence rates and excellent virological and immunological outcomes observed in this program [10, 11]. Within this service, clinicians were able to “fast-track” patients who had the most advanced immunodeficiency; however, shortening the pretreatment interval for all patients may not necessarily reduce early mortality and may actually compromise long-term outcomes.

The present analysis shows that, after 3 years of this program, deaths in the pretreatment interval contributed >46% of total program mortality and therefore represent a very important outcome measure. This mortality is likely to reflect a far greater burden of mortality that is actually occurring prior to program entry. Those who died in the first 4 months of treatment (early deaths) shared the same baseline characteristics and risk factors as those who died in the pretreatment interval (tables 1 and 2); together, deaths in these 2 intervals constituted 87% of total program mortality. The strong association of these deaths of patients who had advanced immunodeficiency at baseline clearly indicates that many of these patients had advanced disease that could not be salvaged by ART, despite the active management in many patients of concurrent infections. One-half of the patients enrolling into this program had a baseline CD4 cell count <100 cells/ μ L. Kaplan-Meier survival analyses revealed that early mortality was high among patients with WHO stage 3 and stage 4 disease (i.e., symptomatic disease) and patients with baseline CD4 cell counts <100 cells/ μ L (figure 2).

The reasons why patients typically enter this and other programs in resource-limited settings with such advanced disease

Table 2. Results of separate Cox’s models predicting relative hazards of early deaths ($n = 49$) and late deaths ($n = 12$) after initiation of antiretroviral therapy (ART).

Variable	Early deaths	Late deaths ^a
Age ^b	1.01 (0.97–1.05)	1.07 (0.99–1.14)
Sex		
Female	1.00	1.00
Male	2.00 (1.10–3.62)	0.58 (0.16–2.03)
WHO stage		
1, 2, or 3	1.00	1.00
4	2.78 (1.52–5.09)	1.71 (0.50–5.82)
Baseline CD4 count ^c	0.62 (0.47–0.83)	0.98 (0.58–1.65)
CD4 count at 4 months	...	0.42 (0.25–0.73)
Baseline viral load		
$\leq 10^5$ log ₁₀ copies/mL	1.00	1.00
$> 10^5$ log ₁₀ copies/mL	1.37 (0.77–4.44)	1.24 (0.36–4.28)
Viral load at 4 months		
<50 copies/mL	...	1.00
≥ 50 copies/mL	...	3.17 (0.94–10.71)

NOTE. Data are hazard ratio (95% CI). WHO, World Health Organization.

^a Complete data available for 12 of 16 patients.

^b Analyzed as a continuous variable.

^c Analyzed in 50-cell/ μ L increments.

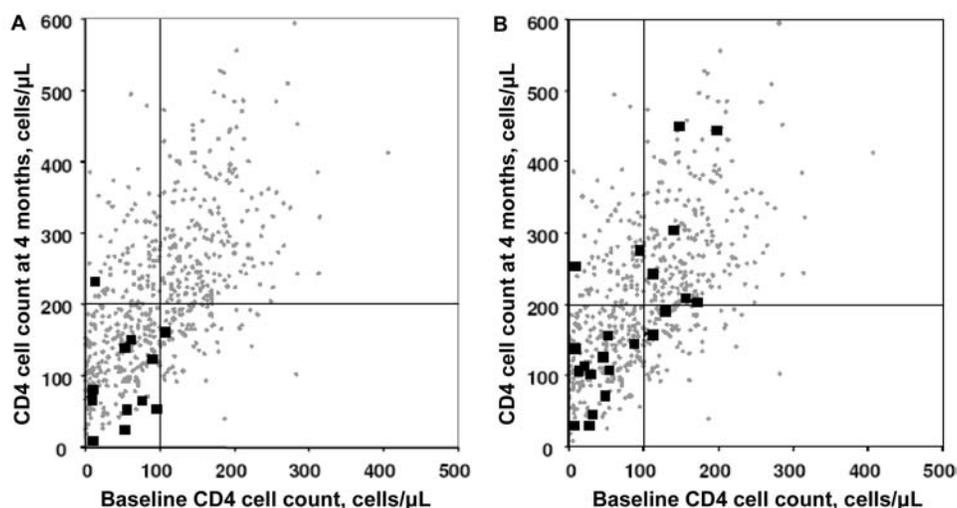


Figure 4. Scatter plots of baseline CD4 cell count against CD4 cell count at the 16-week follow-up time-point. On these plots, individual patients (dark squares) who either died (A; data available for 12 of 16 patients) or were lost to the program for other reasons (B; $n = 22$) after 4 months of antiretroviral therapy (ART) are indicated. Deaths—but not nondeath losses—occurred among individuals with advanced baseline immunodeficiency and persisting immunodeficiency after 16 weeks of ART.

need to be identified. Possible reasons include (1) barriers to voluntary counseling and testing and to access to health care, (2) lack of routine blood CD4 cell count testing for patients with new HIV diagnoses, (3) health system delays in referral patients to ART clinics, (4) waiting times to enter programs, and (5) criteria for initiation of ART that only include patients with advanced disease. How to best promote early access of ART-eligible patients to treatment programs is a central challenge facing the scale-up of these programs in resource-limited settings [20]. Moreover, the South African national ART program uses the WHO 2002 ART guidelines, which restricts treatment to patients with stage 4 disease or CD4 cell counts < 200 cells/ μ L [3]. The revised WHO 2003 guidelines for resource-limited settings recommend earlier treatment [4], and the use of these may help to lower mortality. Moves to earlier initiation of treatment are supported by a collaborative analysis of datasets that reveal that mortality rates in ART programs in resource-limited settings are higher than those in high-income countries [5].

In contrast to early deaths, mortality after 4 months of ART (late death) was independent of baseline immune status but was strongly associated with the response to ART, as reflected by the absolute blood CD4 cell count and viral load at 4 months. As such, the late mortality rate reflected therapeutic success, including drug regimen efficacy and tolerability as well as patient adherence to treatment. After the first year of ART, mortality rate was very low—approaching 1% per year—and the risk of loss to program due to nondeath causes exceeded those due to death (figure 3). Thus, the effectiveness of programs beyond 1 year is likely to relate to issues of long-term patient retention rather than death. As patients remain healthy on long-

term medication, their motivation to continue treatment in the longer term may diminish [21]. It remains unknown whether an increasing rate of treatment failure and a secondary increase in the death rate may occur with longer follow-up.

Among ART programs in sub-Saharan Africa, rates of non-death program losses range from $< 5\%$ [15, 17] to $> 50\%$ [22]. When patients are termed “lost to follow-up” simply on the basis of persistent failure to attend clinic appointments, it is possible that some may in fact have died without detection by the ART program. The true mortality rate among patients receiving ART may, therefore, often be underestimated. However, in this analysis, the use of community-based therapeutic counselors that were allocated to each patient enhanced the data completeness and assessment of outcomes for patients who failed to attend follow-up appointments.

Nondeath program losses in this setting were heterogeneous in nature. Patients who moved out of the area accounted for 22% of total on-treatment program losses. As opposed to those transferred to another ART program, the care of some patients (here termed “relocations”) was not transferred, often because of lack of provision of ART services in other areas. Because the number of patients who are physically well and who are receiving long-term medication is increasing, the number of patients moving out of an area for social or economic reasons may continue to increase. This finding emphasizes the importance of systems within national ART programs that can ensure continuity of care for highly mobile populations of young adults. Losses to follow-up in this treatment service were low, likely as a result of dedicated community-based counsellors allocated to each patient and thorough preparation of patients for ART.

In summary, high pretreatment and early on-treatment mortality rates in this program reflected very advanced immunodeficiency. The reasons for patients' late access to the program urgently need to be identified. It is likely that these early in-program deaths reflect a far greater burden of mortality within the health system and in the community that is occurring "up stream" of the ART program. However, this study found that, once patients have initiated ART and survived the initial few months of treatment, the risk of death or loss to the program thereafter was very low. Evaluation of these various outcome measures provides important means of assessment for ART programs, which thereby facilitates development of optimum models of care in resource-limited settings.

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