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High Retention in Care Among HIV-Infected Patients Entering Care With CD4 Levels >350 cells/μL Under Routine Program Conditions in Uganda

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Background. In Africa, human immunodeficiency virus (HIV)–infected patients who present to care with CD4 levels >350 cells/μL (ie, current antiretroviral treatment thresholds) are often thought to be poorly retained in care, but most estimates do not account for outcomes among patients lost to follow-up.

Methods. We evaluated HIV-infected adults who had made a visit in the last 2.5 years in a program in Uganda. We identified a random sample of patients lost to follow-up (9 months without a visit). Ascertainers sought patients in the community in this sample and outcomes were incorporated into revised survival estimates of mortality and retention for the clinic population using a probability weight.

Results. Of 6473 patients, (29% male, median age 29 years, median CD4 count 550 cells/μL), 1294 (20%) became lost to follow-up over 2.5 years. Two hundred seven (16%) randomly selected lost patients were sought, and in 175 (85%) vital status was ascertained. In 19 of 175 (11%), the patient had died. Of the 156 (89%) alive, 74 (47%) were interviewed in person, and 38 of 74 (51%) reported HIV care elsewhere, whereas 36 of 74 (49%) were not in care. Application of weights derived from sampling found that at 2.5 years, retention among patients who enrolled with CD4 levels >350 cells/μL was 88.2% and mortality was 2.5%. Lower income, unemployment, and rural residence were associated with failure to be retained.

Conclusions. Retention in patients entering care with high CD4 counts under routine program conditions in Africa is high in a Ugandan care program and may be systematically underestimated in many other settings.

Keywords. HIV; Africa; retention; CD4.

Although the public health response to the human immunodeficiency virus (HIV) epidemic in Africa initially focused on starting emergency antiretroviral therapy (ART) for patients with overt immunosuppression, attention is now turning toward sustaining treatment benefits over time and preventing new infections. Retaining patients who enter care with CD4 levels above the treatment threshold of 350 cells/μL—many of whom are without overt symptoms—is critical to achieving these long-term goals. Care continuity in this population allows prompt ART initiation when the CD4 levels do reach 350 cells/μL, thus applying ART services to maintain rather than restore health—a less costly and less complex task [1]. Furthermore, ART initiation at CD4 thresholds >350 cells/μL—recently recommended for resource-limited settings by the World Health Organization—can mitigate long-term renal, liver, and cardiovascular disease and therefore long-term benefits of therapy [2–4]. In addition, recent trials

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show that treatment for persons with CD4 levels up to 550 cells/μL can dramatically reduce HIV transmission to stable seronegative partners [5]. Expanding treatment will only yield improved public health outcomes if patients who are healthy will remain in care. Using ART as prevention also depends on retaining persons with high CD4 levels in care.

At present, retention in care among patients who enroll with CD4 counts above the 350 cells/μL treatment threshold in Africa is thought to be poor. In Malawi, a report found that >90% of patients with World Health Organization stage I or II disease were not in care 1 year later [6]. In an Ethiopian hospital-based care center, the rate of loss to follow-up was 1.9-fold higher among patients with stage I or II disease compared to those with a stage III or IV condition [7]. In KwaZulu Natal, a study using a repeat CD4 test as a sign of retention found that only 45% of patients without indications for ART returned for a 1-year monitoring CD4 count [8], and a study in Cape Town found the same figure to be 46% [9]. A systematic review summarizing these findings suggested that overall, 55% of patients who enroll with CD4 levels above treatment thresholds remain in care until ART eligibility and initiation [10]. These figures, at first glance, suggest that practices such as timely ART initiation following eligibility, reducing long-term morbidity and mortality with treatment at higher CD4 treatment thresholds, and "treatment as prevention" are unlikely to yield population-level health benefits in the real world.

To further characterize retention and outcomes in patient populations who enter care with CD4 levels above the treatment threshold at the time of the study (ie, 350 cells/μL), we studied 2 prototypical scale-up HIV/AIDS care clinics, 1 rural and 1 urban, in Uganda. Whereas existing studies considered all patients who were lost to follow-up (LTFU) as no longer retained in care, we hypothesized that many of these patients would be healthy and working, and therefore may have relocated for work, marriage, or other reasons and continued to access care at other sites (ie, as "silent transfers"). At the same time, mortality among those lost is also likely to be hidden by losses to follow-up. To assess retention in care and mortality, we used a sampling-based approach to reassign outcomes among those LTFU through seeking updated vital status and healthcare utilization information in a numerically small but random sample of lost patients [11–13]. By using the outcomes in the sample to reclassify outcomes in all patients LTFU and therefore "fill in the blanks," we sought to obtain a more complete understanding of retention in care for HIV-infected patients who enter care with CD4 levels above treatment thresholds in Africa.

METHODS

Patients

We evaluated all ART-naive, HIV-infected adults who enrolled in care with a CD4 level >350 cells/μL between 1 October 2008 and 30 April 2011 at 2 "prototypical" scale-up HIV clinics in Uganda. The first clinic is the Mbarara Municipal Clinic, which is located at a level 4 health center located in the semirural Mbarara District in southwestern Uganda. The second clinic is the Immune Suppression Syndrome Clinic at the national referral center of Mulago Hospital in the city of Kampala. The Makerere Joint AIDS Program (funded by the President's Emergency Plan for AIDS Relief [PEPFAR]) complements the Ugandan Ministry of Health efforts at both sites. Observation for this analysis began at clinic enrollment and ended at death, known transfer out, loss to follow-up (defined as 6 months late for an appointment) or database closure on 30 April 2011. In a random sample of the lost patients, observation was extended by 2 "ascertainers" who had worked as peer educators to ascertain vital status and current care status in the community. Supplemental information obtained from tracking was recorded on a standardized form after verbal consent in the field was obtained. The size of the sample was determined by anticipated operational capacity.

Measurements

Sociodemographic and clinical data were derived from routine clinical care and stored in a Microsoft Access database maintained by the clinic. The "ascertainer" used locator information in the patient charts to try and find lost patients in the community. Locator information included telephone numbers, when recorded, and/or residence information. Vital status was ascertained through interview of the patient or of a close informant. Patients interviewed in person were also asked to provide updated information about HIV care including whether they had seen a doctor or a nurse for HIV care in the last 6 months and also whether they had started ART elsewhere. Patients were considered "disengaged" if they had not seen a provider for HIV in the previous 6 months before the interview with the ascertainer. The ascertainer also solicited reasons for disengagement from care (for patients who were no longer in care) or transfers of care (for patients who reported seeking care at another clinic) using a standardized form.

Analyses

In the original underlying clinic population and using only outcomes known to the clinic before any supplemental tracking was conducted, we estimated the incidence of loss to follow-up using the cumulative incidence approach where deaths known to the clinic population were treated as a competing risk [14–16]. We then incorporated the vital status outcomes among the sample of lost patients back into the underlying clinic cohort to obtain corrected estimates of survival and mortality in the entire clinic population [12, 17, 18]. For the specific outcome of retention in care, we assumed that being in care among those interviewed in person represented being in care among all lost patients who

were alive. Therefore, patients who were lost and interviewed in person were additionally weighted in inverse proportion to the probability that a living patient was interviewed in person. Because this assumption is open to question, we explored possible implications with a sensitivity analysis where we carry out the sample-corrected estimate retention under 2 additional assumptions: (1) the "optimistic" assumption is that all patients who were tracked and found alive—but not interviewed in person—are in care; and (2) the "pessimistic" assumption is that all patients in the sample who were tracked and deemed to be alive—but not interviewed in person—are not in care. These results provide information about the extent of potential bias in the estimate of retention in care. We also calculated the cumulative incidence of ART initiation among those patients who remained in their original clinics as well as those who were lost from their original clinic before initiating ART elsewhere. Confidence intervals for weighted descriptive estimates were obtained through bootstrapping. Weights were derived separately for each clinic. For mortality and retention in care, we used weighted Cox proportional hazards models to identify factors associated with the failures of retention in care (which we called "disengagement from care") and death. For the outcome of disengagement, we entered all variables into the final multivariable model because the larger number of events obviated the need for data reduction. Factors associated with loss to follow-up were also calculated to as a point of comparison and to illustrate that predictors of this misclassified outcome may be biased. For mortality, we carried out multivariable analysis using age and sex (variables with a priori predictive value) as well as other variables identified in single predictor analyses to be associated with mortality at a P value of $\leq .1$. All analyses were conducted using Stata software, version 11 (StataCorp, College Station, Texas). This study received ethical approval from the University of California, San Francisco Committee for Human Research, the Makerere School of Medicine Research and Ethics Committee, and the Uganda National Council of Science and Technology.

RESULTS

Over the course of 2.5 years, 6473 patients entered care in Mbarara Municipal Clinic and the Kampala Immune Suppression Syndrome Clinic with a CD4 level >350 cells/μL and were not immediately offered antiretroviral therapy: 4145 in Kampala (64%) and 2328 (36%) in Mbarara (Figure 1). The median age was 29 years (interquartile range [IQR], 25–35 years), men comprised 29% of the patients, and the median CD4 count at presentation was 550 cells/μL (IQR, 436–721 cells/μL) (Table 1). Characteristics of patients who were lost, sampled, and successfully sought were similar. Over 2.5 years, 1294 (20%), patients were LTFU, 207 (16%) were randomly selected for additional outcome ascertainment, and in 175 (85%), updated outcome information was ascertained. In 101 cases (58%) a proxy was interviewed, and in 74 (42%) the patient him or herself was interviewed. Of those directly interviewed, 38 (51%) were seeing a provider at a new clinic, whereas 36 (49%) reported no longer seeing an HIV provider, with most patients visiting a new clinic within 6 months of their last visit (Supplementary Figure). Overall, 19 (11%) of the 175 lost patients in whom updated information was obtained had died.

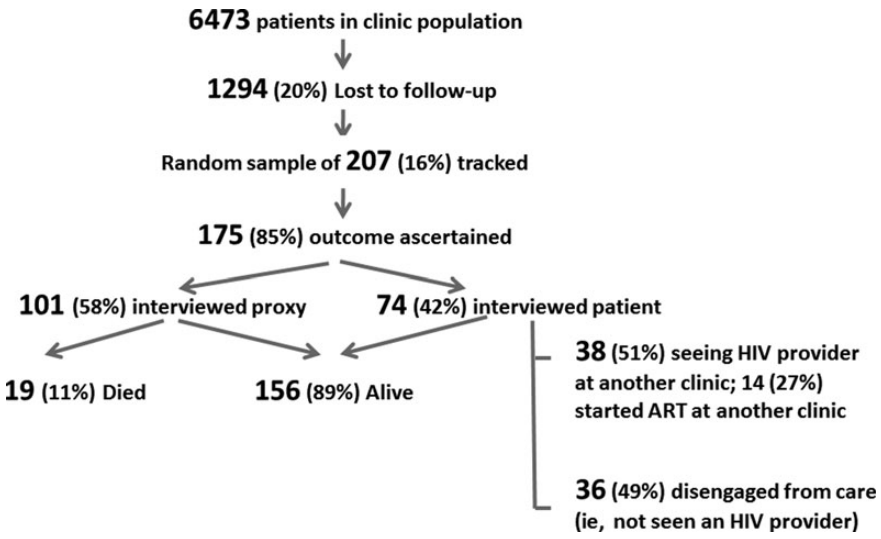

Figure 1. Flow chart depicting patients who presented to care with a CD4 level >350 cells/μL and who were not immediately eligible for antiretroviral therapy. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Table 1. Patient Characteristics

Characteristic	All Patients in Clinic With a CD4 >350 Cells/μL (N = 6473)	Patients Who Were Lost to Follow-up (n = 1294)	Random Sample of Lost Patients (n = 207)	Outcome Ascertained Through Tracking (n = 175)
Kampala clinic site	4145 (64)	759 (59)	113 (55)	95 (54)
Age at enrollment, y, median (IQR)	29 (25–35)	28 (24–34)	28 (24–34)	29 (24–34)
Male, No. (%)	1863 (29)	444 (34)	77 (37)	70 (40)
Pregnant at enrollment (among 4778 women), No. (%)	340 (7)	79 (9)	7 (5)	5 (5)
Enrollment $CD4^+$ T-cells/μL, median (IQR)	550 (436–721)	549 (439–712)	562 (437–711)	553 (435–712)
Weight at enrollment, kg, median (IQR)[a]	56 (50–63)	55 (50–62)	55 (50–62)	55 (50–62)
Enrollment date, median (IQR)	8 August 2008 (20 August 2007 to 8 June 2009)	29 May 2008 (5 July 2007 to 6 February 2009)	2 July 2008 (19 July 2007 to 24 February 2009)	12 June 2008 (18 July 2007 to 19 February 2009)
Monthly income, Ugandan shillings, No. (%)[b]				
No income	1435 (24)	309 (25)	55 (28)	42 (25)
1–50 000	1649 (28)	313 (25)	42 (22)	35 (21)
50 000–100 000	1022 (17)	199 (16)	36 (18)	34 (20)
>100 000	1814 (31)	436 (35)	62 (32)	55 (33)
Unemployed, No. (%)	1195 (18)	276 (21)	39 (19)	35 (20)
Educational attainment, No. (%)[c]				
No education	569 (10)	152 (12)	21 (11)	17 (10)
Primary	3067 (51)	657 (52)	108 (55)	93 (56)
Secondary	1920 (32)	385 (30)	54 (28)	46 (28)
Tertiary	405 (7)	76 (6)	13 (7)	11 (7)
Marital status, No. (%)[d]				
Never married	3421 (57)	658 (52)	115 (59)	97 (58)
Married	1414 (24)	334 (26)	47 (24)	39 (23)
Separated/divorced	556 (9)	168 (13)	22 (11)	20 (12)
Widowed	571 (10)	110 (9)	12 (6)	11 (7)

Abbreviation: IQR, interquartile range.

[a] Weight at enrollment was missing in 730 of 6473 (11.2%) patients.

[b] Income at enrollment was missing in 553 of 6473 (8.5%) patients.

[c] Educational attainment at enrollment was missing in 512 of 6473 (7.9%) patients.

[d] Marital status was missing in missing in 511 of 6473 (7.8%) patients.

At 2.5 years, the combined retention within the 2 clinics was 69.5% (95% confidence interval [CI], 66.1%–72.9%). When outcomes among the LTFU patients were incorporated, retention in care rose to 88.2% (95% CI, 84.2%–92.1%; Figure 2). A sensitivity analysis where we assumed that all patients LTFU and alive but not interviewed in person were no longer in care yielded an estimate of retention of 80% at 2.5 years (95% CI, 76%–84%). Under the optimistic assumption that all patients alive but not interviewed in person were indeed in care, the 2.5-year estimate of retention was 95% (95% CI, 91%–98%).

Among patients not LTFU, the cumulative incidence of ART initiation after 2.5 years was 35.4% (95% CI, 29.6%–41.3%). After accounting for the outcomes among patients initially LTFU at the original clinic, overall incidence of ART initiation at 2.5 years among the cohort of 6473 patients who enrolled in

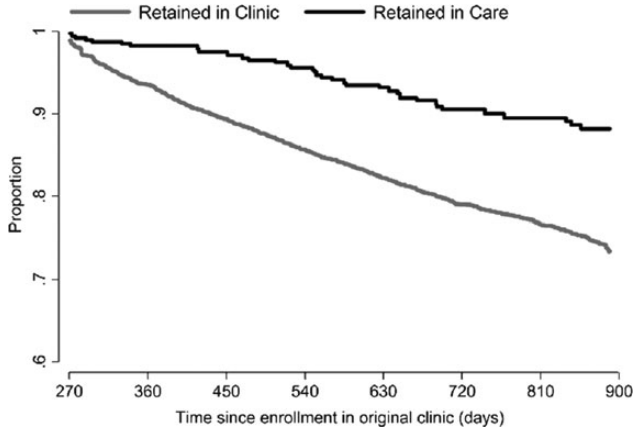

Figure 2. Proportion of patients retained in care (black line) and retained in clinic (gray line). Considering all lost patients to be out of care underestimates retention.

care with CD4 levels above treatment thresholds was 27.0% (95% CI, 24.7%–29.3%).

In multivariable analysis, we estimated the factors associated with "disengagement from care" (the complement of retention in care) (Table 2). Factors associated with loss to follow-up as the outcome are also shown to illustrate that epidemiologic analysis of predictors of this misclassified outcome may differ from disengagement from care, and that analyses using loss to follow-up as an outcome are likely biased and potentially misleading.

Before incorporating outcomes from the patients LTFU, 1 death was known to the clinic and the cause of death for that patient was unknown. Among the 19 patients whose deaths were ascertained through tracking, 17 died of illness, 1 of accident/injury, and 1 during childbirth. After incorporating the deaths discovered through tracking, we estimated the cumulative incidence of mortality in the entire population of patients at 1, 2, and 2.5 years to be 0.6%, 1.6%, and 2.5%, respectively (Figure 3*A*). The rate of death increased over time; in the first year after enrollment there were 0.6 deaths per 100 person-years (95% CI, .3–2.8), in the second year there were 1.0 deaths per 100 person-years (95% CI, .5–2.5), and between 2 and 2.5 years there were 2.8 deaths per 100 person-years (95% CI, 1.4–6.7) (Figure 3*B*). A multivariable proportional hazards regression using age and sex (prespecified variables of interest) as well as weight at clinic entry (the only other factor with $P < .1$ in univariate analysis) found significant associations between age (hazard ratio [HR] = 1.81 per 10 years [95% CI, 1.3–2.6]), weight at clinic entry (HR = 0.43 per 10 kg [95% CI, .25–.75]), and mortality.

Table 2. Factors Associated With Disengagement From Care or Loss to Follow-up From Original Clinic Site

	Disengagement From Care		Lost to Follow-up	
Characteristic	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Clinic site				
Mbarara	Ref	.04	Ref	<.01
Mulago	0.51 (.27–.95)		0.62 (.54–.71)	
Age at enrollment, per 10 y	0.78 (.50–1.20)	.26	0.86 (.79–.93)	<.01
Sex				
Female	Ref		Ref	
Male	2.03 (.78–5.26)	.15	1.67 (1.45–1.93)	<.01
Enrollment CD4 level, per 50 cells	0.98 (.90–1.07)	.71	0.99 (.98–1.00)	.14
Monthly income, Ugandan shillings				
No income	Ref	.04	Ref	.05
1–50 000	0.46 (.17–.23)		0.99 (.84–1.18)	
50 001–100 000	0.69 (.28–1.71)		0.99 (.81–1.23)	
>100 000	0.27 (.10–.74)		1.28 (1.05–.56)	
Employment status				
Employed	Ref		Ref	
Unemployed	3.65 (1.28–10.38)	.02	1.10 (.89–1.35)	.38
Education level		.78		.14
No education	Ref		Ref	
Primary	1.61 (.44–5.82)		0.83 (.68–.10)	
Secondary	1.85 (.48–7.10)		0.81 (.66–.99)	
Tertiary	1.23 (.20–7.63)		0.74 (.55–.99)	
Weight at enrollment, kg, per 10 kg	0.73 (.53–1.01)	.05	0.95 (.90–1.01)	.13
Marital status		.92		<.01
Never married	Ref		Ref	
Married	0.86 (.36–2.04)		1.40 (1.22–1.62)	
Separated/divorced	1.02 (.34–3.02)		1.51 (1.26–1.82)	
Widowed	0.61 (.13–2.78)		1.27 (1.02–1.58)	
Calendar date of enrollment, per 6 mo	1.02 (.85–1.22)	.84	1.08 (1.05–1.12)	<.01

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Defined as no visit to an HIV provider in the past 6 months using supplemental data from a random sample of patients lost to follow-up who were tracked and had outcomes ascertained.

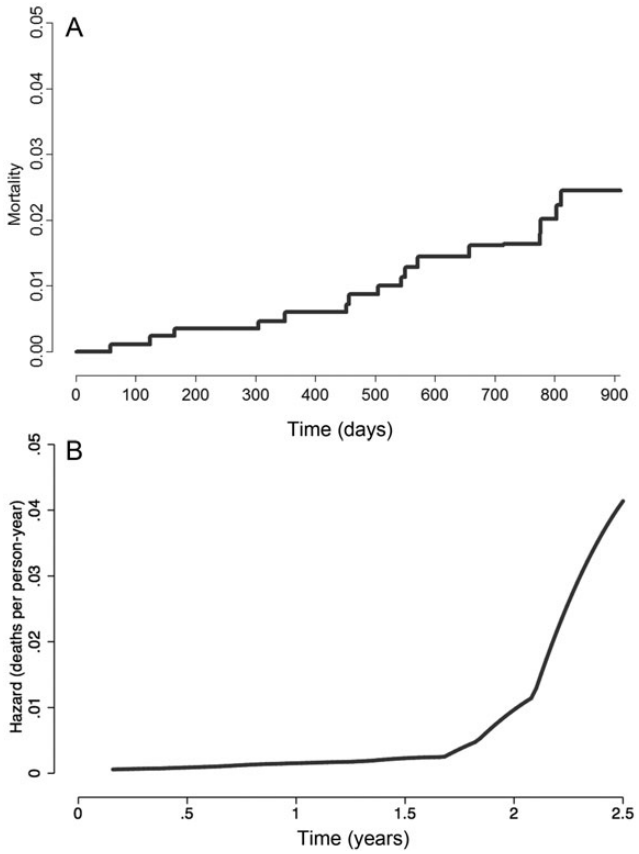

Figure 3. Sample-weighted cumulative incidence (*A*) and hazard of mortality (*B*) among patients who present to care with a CD4 level >350 cells/μL.

Table 3. Patient-Reported Reasons for Disengagement From Care or "Silent" Transfer (n = 74)[a]

Reason Reported by Patient	Disengaged From Care, No. (%) (n = 36)	Silent Transfer, No. (%) (n = 38)
Socioeconomic		
Had to work	10 (28)	9 (24)
Didn't have enough money	4 (11)	3 (8)
No transportation to the clinic	1 (3)	5 (13)
The clinic was too far away	0 (0)	5 (13)
Had to take care of children	1 (3)	1 (3)
Knowledge, beliefs, attitudes		
Felt well	9 (25)	0 (0)
Because of religious beliefs or traditional healing	4 (11)	NA
Denied HIV status	1 (3)	NA
A family member told you not to come	0 (0)	0 (0)
Felt too sick	0 (0)	0
Health care delivery/operations		
Work or lives closer to new clinic	NA	10 (26)
Preferred another clinic	1 (3)	11 (29)
Conflict with staff	5 (14)	8 (21)
The clinic was not helping you feel better	0 (0)	0 (0)
Moved where there was no access to care	7 (20)	NA

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

[a] "Disengaged from care" was defined as not seeing any HIV provider; "silent transfer" was defined as seeing a provider at a new clinic without having a documented transfer.

For the 36 patients who were found through tracking and no longer seeking care, the most common patient-reported reasons were that work responsibilities kept them from seeking care or that they moved to an area not serviced by an HIV treatment facility. A substantial proportion of 25%, however, reported they felt well (Table 3). Among the "silent transfers" (the patients lost from clinic but who reported seeking HIV at another site), the most common reasons for transfer were that the new clinic was closer to their work or home (26%), a generic statement that they preferred the new clinic (24%), or that they had had a conflict with staff at the existing clinic (21%).

DISCUSSION

For HIV-infected persons with CD4 levels >350 cells/μL in a rural and an urban clinic in Uganda, a sampling-based approach to reclassify outcomes among those LTFU found that retention in care—defined as retention within the system of care rather than at a particular clinic—to be nearly 90% even 2.5 years after enrollment in care. Addressing loss to follow-up also yielded identified deaths that were unknown to the clinic and yielded an overall cumulative incidence of estimate of mortality at 2.5 years of 2.5%. Socioeconomic factors—specifically unemployment and lower income—were associated with poorer retention in epidemiologic analyses. Structural barriers (transportation and work responsibilities) were the most commonly cited reasons for both disengagement altogether and transfer to another clinic. A substantial minority, however, reported reasons due to inadequate knowledge (eg, "felt well") or problems with the care delivery at the initial site of care (eg, conflict with staff).

Our estimates contrast with previous literature that suggests that <50% of patients who present with CD4 levels above treatment thresholds are retained [6], with high retention in

pre-ART patients in Rwanda as a rare counterexample in which retention was high [19]. Our results differ from previous estimates in which retention is low in part because we calculated retention differently: whereas previous researchers considered all patients LTFU to be not retained in care, we believed that outcomes among lost patients would include retention within the greater system of care. We therefore used supplemental data from a random sample of lost patients to reclassify outcomes among all patients with unknown outcomes. With this adjustment, the proportion of patients retained rose from 70% to almost 90% at 2.5 years. Different methods, however, do not account for all the observed differences; the uncorrected estimate of retention in our clinic sites was still 70% at 2.5 years, a figure also higher than in most previous reports. We believe this may be a result of support at these clinics provided by the Makerere Joint AIDS Program—a public health implementer linked to an academic medical center that is relatively well-resourced and has strong human resources.

These findings imply that retaining largely asymptomatic patients in care, even in Africa where barriers to care are common, is possible and that public health strategies that depend on retention of persons with high CD4 levels are feasible. These strategies include starting ART at higher CD4 levels as observational studies have shown that initiation between 350 cells/μL and 500 cells/μL [20–22]—and in one study >500 cells/μL [23]—reduces AIDS progression and mortality. Furthermore, treating the infected individual in serodiscordant heterosexual partnerships with ART at a CD4 level between 350 cells/μL and 550 cells/μL reduced transmission dramatically in a randomized trial and therefore public health planners are seeking ways to use treatment as prevention under program conditions [5]. Our findings suggest that real-world patient populations, at least in some settings, may be receptive and ready for these interventions [24].

Despite high overall retention, we did find lapses in retention in a notable fraction of patients. Lower income and unemployment predicted failure to be retained. Patient-reported reasons among those disengaged from care and recorded by the "ascertainers" also underscored structural barriers, with the largest categories relating to money, work, and transportation. Several found work in places without care including outside of Uganda. These barriers highlight the complexity of providing lifelong care for patients who must seek livelihood both near and far. Opportunity as well as transportation expenses associated with clinic visits may mean that many patients cannot afford "free" care [25]. Care coordination—the ability to navigate a complex healthcare environment within priorities in a patient's life—is a major topic in primary care in the United States [26] and may have lessons for global HIV care. A number of patients reported feeling well and conflict with staff as reasons for disengagement.

This study offers the first estimate of mortality among patients who enter care with CD4 levels above the treatment threshold of 350 cells/μL in a real-world public health setting. The estimate of 2.5% at 2.5 years is not insubstantial and may suggest a need to initiate ART at even higher levels than the current threshold of 350 cells/μL. We believe that the deaths we observed are likely due to HIV because the instantaneous rate of mortality (Figure 3) rose over observation time. Because the hazard of death due to other common reasons such as accidents, childbirth, or even other illnesses should be constant over time, the rising hazard of death after enrollment points to HIV disease progression as the culprit. Epidemiologic analyses in observational studies employing strategies to address time-dependent confounding and lead-time bias have consistently suggested that ART between 350 cells/μL and 500 cells/μL can reduce AIDS and deaths [22, 23, 27]. We believe ART initiation at higher thresholds in this patient population may well have reduced deaths substantially within this real-world context.

There are a number of limitations in this study. First, we did not ascertain outcomes in all patients LTFU and, therefore, residual bias in our estimates may persist. The possibility of bias in the revised estimate of retention is greater than for the estimate of mortality as the fraction with updated care status was lower than the fraction with updated vital status ascertainment. We conducted, however, a sensitivity analysis which suggested that even under extreme assumptions, the inference that retention in care is higher than retention in clinic is unchanged. In addition, the reasons for failure to continue care were taken from patients who were alive and found in person, and therefore may also not be representative of all patients who were alive and not in care. Furthermore, data were derived from a clinic database and contained missing data. Third, social desirability bias or recall bias might have led to overreporting of care among the lost who were found and interviewed in person.

In summary, we found retention in care among patients who enter care with a CD4 level >350 cells/μL and therefore ineligible for ART to be higher than previous estimates. Retention was worse for patients with sociostructural barriers to care and those with lower income. Mortality was not unsubstantial, and the increasing hazard of death suggested HIV to be the cause of death. Interventions that depend on retaining patients with high CD4 counts at enrollment, and who therefore largely do not have histories of severe illness, are feasible in Africa.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http:/cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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