Incorporating Loss to Follow-up in Estimates of Survival Among HIV-Infected Individuals in Sub-Saharan Africa Enrolled in Antiretroviral Therapy Programs

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(See the editorial commentary by Hirschhorn and Pagano, on pages 4–5.)

Background. Measuring the survival of human immunodeficiency virus–infected adult patients enrolled in antiretroviral therapy (ART) programs is complicated by short observation periods and loss to follow-up. We synthesized data from treatment cohorts in sub-Saharan Africa to estimate survival over 5 years after initiation of ART.

Methods. We used data on retention, mortality, and loss to follow-up from 34 cohorts, including a total of 102,306 adult patients from 18 sub-Saharan African countries. These data were augmented by data from 13 sub-Saharan African studies tracking death rates among adult patients who were lost to follow-up (LTFU). We used a Poisson regression model to estimate survival over time, incorporating predicted mortality among LTFU patients.

Results. Across studies, the median CD4+ cell count at ART initiation was 104 cells/mm3, 65% of patients were female, and the median age was 37 years. Survival at 1 year and 5 years were estimated to be 0.87 (95% confidence interval [CI], 0.72–0.94) and 0.70 (95% CI, 0.36–0.86), respectively, after adjustment for loss to follow-up. The life-years gained by a patient during the 5-year period after starting ART were estimated at 2.1 (95% CI, 1.6–2.3) in the adjusted model, compared with 1.7 (95% CI, 1.1–2.0) if there was 100% mortality among LTFU patients and with 2.4 (1.7–2.7) if there was 0% mortality among LTFU patients.

Conclusions. Accounting for loss to follow-up produces substantial changes in the estimated life-years gained during the first 5 years of ART receipt.

Keywords. HIV treatment; antiretroviral therapy; survival; loss to follow-up; retention; cost-effectiveness; sub-Saharan Africa.

In the last decade, under the leadership of the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the United States President’s Emergency Plan for AIDS Relief (PEPFAR), substantial scale-up of antiretroviral therapy (ART) coverage has been achieved. An estimated 300,000 human immunodeficiency virus (HIV)–infected people in low- and middle-income countries were receiving ART in 2002, when the “3 by 5” initiative was launched, which aimed to have 3 million people receiving ART by 2005. The number of people receiving ART rose to approximately 6.7 million by the end of 2010 [1]. In sub-Saharan Africa, an estimated 5.1 million people were receiving ART in 2010, which represented 49% coverage among those in need of treatment in the region, according to World Health Organization (WHO) eligibility criteria [1].

The monitoring of ART programs at the national and regional level and the comparative evaluation of performance across programs are essential activities...
for determining how to maximize the population health impact of programs run under severely constrained resources. The survival of patients receiving ART is often reported in the literature in a way that accounts only for "known mortality" (ie, deaths among patients who remained in treatment) [2, 3]. This measure can be an overestimate of survival, as it does not account for mortality among patients who are lost to follow-up (LTFU), which can be substantial [4]. Several prior studies have identified this critical issue of loss to follow-up among ART recipients [5, 6]. In particular, a meta-analysis of 16 sub-Saharan African studies and 1 Indian study found that mortality among LTFU patients could be as high as 40% (95% confidence interval [CI], 33%-48%) [7].

Patient retention is a key monitoring measure of ART performance. For a cohort of ART recipients, retention is understood as the proportion of patients known to be still receiving ART (ie, the proportion who have not died nor been LTFU) at a given time after ART initiation [1]. Data are routinely collected at the national level to assess the retention of patients receiving ART 12–48 months after enrollment in an ART program [1, 8]. Of 47 sub-Saharan African countries, 22, 13, 10, and 5 countries reported retention rates at 12, 24, 36, and 48 months, respectively, after ART initiation [8]. In 2008, the retention rates in sub-Saharan Africa were 75% and 67% at 12 and 24 months, respectively [8]. These figures were consistent with data from published systematic reviews [9, 10]. Retention is often used as a proxy for quality of care but may be a conservative quality measure if death rates among LTFU patients are relatively low.

In health impact measurement and cost-effectiveness analysis of antiretroviral therapy, usually, the 2 extreme metrics described above are used to estimate survival. The former metric takes into account only observed deaths within the patient cohort [2, 3]; the latter metric assumes that LTFU patients do not survive [11]. Survival estimates in fact need to be adjusted by incorporating loss to follow-up. Only a few studies to date have accounted for LTFU patients in their mortality outcomes and adjusted survival curves accordingly. A notable example is the work by Egger and colleagues [12], who developed a weighted average method to adjust mortality for the first year of ART receipt.

In this study, we adapt the method from Egger et al and apply it to sub-Saharan Africa cohort data. We estimate survival among ART recipients 6, 12, 24, 36, 48, and 60 months after ART initiation, accounting for imputed mortality among LTFU patients and including quantification of uncertainty around these survival outcomes. These survival estimates are then used to derive a measure of population-level ART impact that is expressed as life-years gained. In addition to overall survival, we also present estimates stratified by CD4⁺ cell count at ART initiation.

**METHODS**

**Data Sources**

**Retention and Loss to Follow-up Data**

We used retention data indicating the proportion of ART recipients still in care up to 60 months after starting therapy. Data were extracted from a systematic review [10] that built on earlier work [9] by compiling results from 33 studies reporting on 39 cohorts, including a total of 226 307 patients in 18 countries. The review estimated attrition (defined as the number of patients who died plus the number of LTFU patients) after

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Table 1. Data Sources for the Analysis

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Studies</th>
<th>Total Sample Size</th>
<th>Dates of Cohort Observation</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congo</td>
<td>1</td>
<td>222</td>
<td>Mar 2005–Dec 2007</td>
<td>[31]</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>1</td>
<td>10 211</td>
<td>May 2004–Feb 2007</td>
<td>[20]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1</td>
<td>321</td>
<td>Sep 2005–Sept 2006a</td>
<td>[33]</td>
</tr>
<tr>
<td>Kenya</td>
<td>1</td>
<td>830</td>
<td>Jan 2005–Sept 2007a</td>
<td>[34]</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1</td>
<td>2596</td>
<td>2004–2007a</td>
<td>[35]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1</td>
<td>1552</td>
<td>Jan 2005–Dec 2006</td>
<td>[36]</td>
</tr>
<tr>
<td>Rwanda</td>
<td>1</td>
<td>3194</td>
<td>Jan 2004–Dec 2005</td>
<td>[37]</td>
</tr>
<tr>
<td>Uganda</td>
<td>3</td>
<td>2206</td>
<td>Sep 2003–May 2006</td>
<td>[14, 47, 48]</td>
</tr>
<tr>
<td>Zambia</td>
<td>1</td>
<td>37 039</td>
<td>Apr 2004–Nov 2008</td>
<td>[49]</td>
</tr>
<tr>
<td>Multiple 1(Mozambique, Tanzania, Malawi)</td>
<td>1</td>
<td>3456</td>
<td>Jan 2003–Jun 2006</td>
<td>[50]</td>
</tr>
<tr>
<td>Multiple 2(Mozambique, Malawi, Guinea)</td>
<td>1</td>
<td>3749</td>
<td>Feb 2002–Jun 2007</td>
<td>[18]</td>
</tr>
</tbody>
</table>

* Period during which patients started antiretroviral therapy; patient follow-up extends beyond dates shown.
ART initiation for each of the studies included. The review did not report on deaths among LTFU patients. For our analysis, we retained 29 data sources describing 34 cohorts, which are summarized in Table 1 (further details are provided in the Supplementary Data). Four studies involving 5 cohorts were excluded, as they did not present specific estimates of loss to follow-up. The selected data included a total of 102,306 patients in 18 countries. Across studies, the median CD4+ cell count at ART initiation was 104 cells/mm³, 65% of the patients were female, and the median age at ART initiation was 37 years.

**Mortality Among Patients LTFU**

To estimate mortality among LTFU patients, we followed the approach of Egger et al [12], which used results from a meta-analysis of death rates among LTFU adults from 17 studies [7]. Of these studies, 16 were from sub-Saharan Africa and 1 was from India, with a total of 6420 patients. We excluded the Indian study from our analysis. An additional study, from South Africa, was also excluded because it did not report on the percentage of LTFU patients in the patient cohort [7]. The 15 studies from sub-Saharan Africa that remained were extracted from 14 publications [7] and included 9 countries: 4 studies were from South Africa, 3 were from Malawi, 2 were from Uganda, and 1 each was from Zambia, Botswana, Ethiopia, Kenya, Tanzania, and Mali. Nine studies were from urban or semiurban settings, and 5 were from rural settings [7]. Although the definition of loss to follow-up varied across studies, 5 studies and 4 studies considered patients to be LTFU if the patients missed appointments over intervals of >1 month and >3 months, respectively. LTFU patients were traced using telephone calls, by home visits, or through social networks. The median duration of follow-up after the start of ART was not reported in 11 studies. The 15 studies reported on the status of LTFU patients by means of 3 distinct categories: unknown, alive, and dead [7].

**Analysis**

**Overall Adjusted Survival**

We estimated overall adjusted survival in 4 steps. First, we collected data on retention of ART patients from the 29 studies retained (Table 1). Each site in a study contributed observations from multiple times, for a total of 55 “site-time” observations.

Second, for each site-time observation, we followed the methods of Egger et al [12] to compute an adjusted survival estimate, which incorporated estimated mortality among LTFU patients. The adjusted survival of ART recipients at time $t$, $S(t)$, is given by

$$S(t) = 1 - [M_{NL}(t) + L(t)M_{L}(t)],$$

where $M_{NL}(t)$ is the proportion of the initial cohort of ART recipients that was known to have died by time $t$, $L(t)$ is the proportion of the cohort that was LTFU by $t$, $M_{L}(t)$ is the fraction of LTFU patients who had died by $t$, and $R(t) = 1 - [M_{NL}(t) + L(t)]$ is the retention proportion at time $t$ of the initial cohort of ART recipients. $R(t)$, $M_{NL}(t)$, and $L(t)$ were observed, whereas $M_{L}(t)$ was unknown.

$M_{L}(t)$ may be expressed as a function of $L(t)$ [7]. Our estimate of a linear regression relating $M_{L}(t)$ to $L(t)$ started with the 15 studies of mortality among LTFU patients [7]. Two of the 15 studies [4, 7, 13] appeared to be outliers from this linear relationship, so we excluded them in our base-case analysis (Supplementary Data). We used the estimated coefficients from the regression to predict $M_{L}(t)$ for each of the 55 site-time points. Combination of these predictions with the empirical estimates of $R(t)$, $M_{NL}(t)$, and $L(t)$ yielded adjusted survival estimates of $S(t)$, based on equation 1.

Third, to produce an estimated survival curve among ART recipients, we converted the adjusted survival estimates from step 2 into estimated counts of deaths. We estimated a Poisson count model in which the expected number of deaths occurring within $t$ months since ART initiation in cohort $i$, $D_{ti}$, is characterized as follows:

$$\ln(D_{ti}) = \beta_0 + \beta_1 t + \ln(N_i) + u_i,$$

where $N_i$ is the cohort size, and $u_i$ is a random effect for study $i$, which accounts for heterogeneity across cohorts and clustering of errors within multiple observations from the same cohort. Estimates of survival were computed on the basis of deaths predicted in equation 2 by assuming an initial cohort, $N_0$, of 1000 and setting $u_i$ equal to 0 in equation 2.

Fourth, we conducted Monte Carlo simulations to estimate uncertainty intervals around our survival estimates. These intervals reflected the multiple sources of uncertainty, including sampling uncertainty in the data inputs and estimation uncertainty in the intermediate and final regression analyses. Technical details are provided in the Supplementary Data.

**Adjusted Survival Stratified by CD4+ Cell Count**

We conducted a parallel set of survival analyses, stratified by CD4+ cell count at treatment initiation. The analyses were limited to the studies reporting the median CD4+ cell count at cohort initiation (38 site-time observations). It followed the same procedures described above, except that the model specification in equation 2 added an indicator variable for a CD4+ cell count of <100 cells/mm³ at initiation and another term making this indicator variable interact with the variable $t$.

**Adjusted Life-Years Gained**

From the estimates $S(t_k)$ ($t_1 = 1/2$, …, $t_5 = 5$ years), we derived the number of life-years gained during the first 5 years of ART, $LY_{Gr}$, compared with the counterfactual condition of no
where $LY_0$ corresponds to the number of life-years lived for a person eligible for ART who does not receive ART. We assumed that $LY_0$ is equal to 2 years, following Stover and colleagues [11].

**Comparison With Overall Unadjusted Survival**

We compared our results to estimates of overall survival and life-years gained through ART that did not adjust for mortality among LTFU patients. These estimates were computed from the same 55 site-time observations. Two different extreme scenarios were considered: one assumed no mortality among LTFU patients, and the other assumed 100% mortality among LTFU patients.

All analyses were conducted using R software (http://www.r-project.org).

**RESULTS**

The results of the linear regression analysis on the fraction of LTFU patients who had died, $M_t$, as a function of the proportion of the cohort that was LTFU, $L$, are given in Table 2. The base-case analysis, which excluded 2 outliers, had an $R^2$ of 0.84 and a root-mean-square error (RMSE) of 0.062. An alternative regression that included all 15 studies had a substantially lower goodness of fit, with an $R^2$ of 0.39 and a RMSE of 0.142. The adjusted predictions for overall survival estimates and corresponding uncertainty estimates changed only slightly when the analysis included all 15 studies (Supplementary Data).

The adjusted and unadjusted survival estimates for each of the 55 site-time points used are plotted in Figure 1. Results from the Poisson regression model for overall survival and for survival stratified by CD4+ cell count at initiation are provided in Table 2. We considered alternative functional forms for this model, including Weibull and linear rate models. In each case, the goodness of fit, based on $R^2$ and RMSE values, was worse than for the Poisson model. Details of the comparison are provided in the Supplementary Data. In the analysis of survival stratified by CD4+ cell count at ART initiation, the intercept but not the time coefficient was significantly different for those with a CD4+ cell count of <100 cells/mm³, suggesting that there are differences in early survival but that subsequent mortality risks are similar.

Adjusted predictions for overall survival estimates and their corresponding uncertainty intervals are provided in Table 3 and Figure 2. We observed a sharp survival decline of about 2 years for patients lost to follow-up compared to those who remained enrolled in care.
12% (95% CI, 6%–26%) during the first 6 months after ART initiation. This sharp decline was followed by a more modest decline of 18% between 6 months (88% [95% CI, 74%–94%]) and 5 years (70% [95% CI, 36%–86%]) after initiation. These survival estimates, in keeping with the design of the study, fall between the 2 extreme scenarios described above that involve implicit assumptions of either 100% or 0% mortality among LTFU patients (Table 3 and Figure 3). For example, survival estimates at 6 months and 5 years are 0.84 (95% CI, .70–.92) and 0.54 (95% CI, .12–.76), respectively, if we assume that all LTFU patients have died; survival estimates at 6 months and 5 years are 0.94 (95% CI, .75–.99) and 0.79 (95% CI, .12–.95), respectively, if we account only for known mortality (ie, if we assume 0% mortality among LTFU patients).

If we stratify by initial CD4+ cell count, we find that, for CD4+ cell counts of >100 cells/mm³ at initiation, survival estimates at 6 months and 1, 3, and 5 years are 0.89 (95% CI, .77–.94), 0.88 (95% CI, .76–.94), 0.85 (95% CI, .69–.92), and 0.81 (95% CI, .59–.90), respectively. For CD4+ cell counts of <100 cells/mm³ at ART initiation, survival estimates at 6 months and 1, 3, and 5 years are 0.83 (95% CI, .65–.92), 0.82 (95% CI, .61–.91), 0.78 (95% CI, .54–.89), 0.75 (95% CI, .46–.87), and 0.70 (95% CI, .36–.85), respectively (Table 3 and Figure 4).

One way to summarize the impact of accounting for predicted mortality among LTFU patients is to quantify the difference the adjustment makes in terms of the number of life-years gained over the first 5 years of ART. Adjusted life-years gained for 1 patient receiving ART are 2.1 (95% CI, 1.6–2.3), compared

### Table 3. Estimated Survival Among Antiretroviral Therapy (ART) Recipients, With or Without Adjustment for Mortality Among Recipients Lost to Follow-up (LTFU), by Time After ART Initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival (95% CI), by Time Since ART Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 mo</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.88 (.74–.94)</td>
</tr>
<tr>
<td>By CD4+ cell count at ART initiation</td>
<td></td>
</tr>
<tr>
<td>&lt;100 cells/mm³</td>
<td>0.83 (.65–.92)</td>
</tr>
<tr>
<td>&gt;100 cells/mm³</td>
<td>0.89 (.77–.94)</td>
</tr>
<tr>
<td>Not adjusted, by assumed mortality for LTFU recipients</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>0.84 (.70–.92)</td>
</tr>
<tr>
<td>0%</td>
<td>0.94 (.75–.99)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
with 1.7 (95% CI, 1.1–2.0), if we assumed that all LTFU patients had died, or with 2.4 (95% CI, 1.7–2.7), if we assumed that all LTFU patients were still alive. In other words, for the first 5 years of ART, consideration only of observed deaths in the cohort leads to an overestimate of around 0.3 life-years gained per ART recipient, which is an error of approximately 14%; on the other hand, assumption of 100% mortality among LTFU patients leads to an underestimate of around 0.4 life-years gained per ART recipient, or an error of approximately 19%.

**DISCUSSION**

In this article, we estimated survival for 6 months to 5 years after ART initiation among people in sub-Saharan Africa, after accounting for predicted mortality among LTFU patients. We found relatively high mortality in the first 6 months after ART initiation, followed by a more gradual decline in survival through 5 years after ART initiation. Overall, 70% of patients were predicted to be alive 5 years after starting treatment. Our survival estimates fall between the retention estimates of treatment cohorts [2, 3], on the upper end. Similarly, we determined adjusted survival for patients with different CD4+ cell counts at initiation. As the CD4+ cell count at initiation went from >100 to <100 cells/mm$^3$, the death rate increased both during the initial 6 months of ART and during the subsequent period of more gradually declining survival. A total of 81% versus 64% of patients were still alive after 5 years of treatment completed if they had a CD4+ cell count at initiation of >100 cells/mm$^3$ versus one of <100 cells/mm$^3$.

Further analysis of survival stratified by age, sex, and treatment program characteristics would be useful, but such analyses have not been possible because of data limitations. Similar limitations hinder efforts to understand mortality among patients who are receiving second-line therapy because of virological failure or drug regimen substitutions. Only a few studies have reported on these topics, and sample sizes and detailed information on patients are relatively limited [14–20]. In this respect, the information collected by the International Epidemiological Databases to Evaluate AIDS (IeDEA) (http://www.iedea-hiv.org) shows great promise. The IeDEA network in sub-Saharan Africa includes a large number of sites and patients, which will potentially allow for the identification of the determinants of treatment outcomes at the program or even individual level. The data are gathered across a wide variety of settings (eg, urban and rural clinics and government-led or nongovernmental organization–led programs) [21], and the participating sites often have good clinical capacity, which can yield key information on CD4+ cell count and second-line therapy [21].

Our methods and estimates present some limitations. There is uncertainty around the estimates reported by the programs themselves, but this uncertainty is often omitted from reports on results from ART programs. In addition to reflecting the effectiveness of treatment programs, estimates also reflect the programs’ capacity in data management and patient follow-up and programs with higher capacity may have stronger ability to conduct and publish research [8, 10]. Hence, our data may represent better-resourced programs of sub-Saharan Africa and may therefore lack generalizability to all national or local programs within sub-Saharan Africa. Another potential source of selection bias is that programs with stronger performance may be those that are most likely to report results to ministries of health, as funding may be dependent on performance. In addition, the studies retained in this analysis did not equally report at all time points of interest: most time points were from <12 months after initiation (Figure 1 and Supplementary Data), when attrition rates are the highest [1, 8, 10]. Although a single set of survival estimates may not generalize to all sub-Saharan African ART programs, our CIs capture the substantial heterogeneity among programs associated with our data: over the first 5 years of ART, the life-years gained range from 1.6 to 2.3 years, a 0.7-year span across programs (which represents one-third of the central estimate of 2.1 years).

Future survival models should include, when data permit, additional determinants of mortality during ART, including age, sex, tuberculosis status, hemoglobin level, and CD4+ cell count at initiation. For example, LTFU patients with a history of tuberculosis, CD4+ cell count of <100 cells/mm$^3$, hemoglobin level of <10g/dL, and ART receipt for <6 months have been observed to have the highest risk of death [22]. Incorporation of these predictors, which can vary with time since...
initiation and within each cohort, and the use of a consistent definition for LTFU patients across sites [23], can bring substantial improvement to correction models, producing changes in the survival estimates [24]. In particular, some correction models may be able to estimate the effects of predictors of mortality, such as severe tuberculosis [24]. Our model did not incorporate the potential change in mortality among LTFU patients over time, because of a lack of data. However, the proportion of deaths among LTFU patients and the factors associated with LTFU patients’ mortality are likely to change with time. For instance, one study showed that the probability of survival among LTFU patients was 0.69, 0.64, and 0.59 at 1, 2, and 3 years [22]. In the long-term, there may be fewer LTFU patients and lower mortality if, as the availability of ART programs broadens, patients transfer to other facilities instead of ceasing treatment.

The approach we have presented can be applied to ART programs in other settings and geographical areas and to situations in which a proportion of LTFU patients have been traced. If the status of some LTFU patients is known through tracing, the imputation of outcomes can be restricted to untraced patients, who may be at a higher risk of death than traced ones. The imputation of outcomes can be further refined with the use of specific weights to account for the fact that only traced patients have known status, for example [24]. Our approach is one of several approaches [12, 22, 24–27] that can be used to adjust mortality estimates among ART programs. For example, Egger et al [12] estimated an adjusted 1-year survival of 0.87 (average weighted by cohort size), using some cohort data that likely overlapped with ours [7, 15, 20]; An et al [25] estimated an adjusted 1-year survival of 0.90 for a selected PEPFAR program. Henriques et al [24] used 6 alternative imputation methods to estimate a range of 0.77 to 0.89 in adjusted 1-year survival on the basis of routine program data from Malawi.

The survival estimates we provide augment the information currently used to assess the quality of ART programs in sub-Saharan Africa. By accounting for predicted mortality among people who withdraw from ART programs, we provide a more complete assessment of survival during therapy. In terms of metrics such as the number of life-years added through ART, we show that adjustment for loss to follow-up can produce substantial change, on the order of ≥15%, in the estimated population-level impact of treatment. Such a metric can be a useful addition to evaluations of the population health benefits and cost-effectiveness of ART programs. Our work underlines the urgent need for more data on both retention and the outcomes of LTFU patients after ART initiation, with a particular emphasis on the major determinants of retention in care [28]. Research on interventions to improve patient follow-up and retention, strengthened by incorporating analytical methods such as the one presented here, is needed for the design of cost-effective strategies to prevent loss to follow-up [28, 29]. As momentum gathers to scale-up HIV treatment-as-prevention programs, improved referral to care for HIV-infected individuals and improved outreach to LTFU patients are essential for optimizing the effectiveness of these programs.

### Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copiededit. 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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### References