MAJOR ARTICLE

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

Stéphane Verguet,[1] Stephen S. Lim,[1] Christopher J. L. Murray,[1] Emmanuela Gakidou,[1] and Joshua A. Salomon[2]

[1]Institute for Health Metrics and Evaluation, University of Washington, Seattle; and [2]Department of Global Health and Population, Harvard School of Public Health, Cambridge, Massachusetts

(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/mm^3, 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

Received 31 January 2012; accepted 10 July 2012; electronically published 24 October 2012.

Correspondence: Stéphane Verguet, PhD, Department of Global Health, University of Washington, 325 9th Ave, Box 359931, Seattle, WA 98104 (verguet@uw.edu).

The Journal of Infectious Diseases 2013;207:72–9

DOI: 10.1093/infdis/jis635

Table 1. Data Sources for the Analysis

Country	No. of Studies	Total Sample Size	Dates of Cohort Observation	Reference(s)
Botswana	2	1043	Jan 2002–Apr 2007	[4, 30]
Cameroon	1	1187	Jul 2001–Jun 2007	[19]
Congo	1	222	Mar 2005–Dec 2007	[31]
Côte d'Ivoire	1	10 211	May 2004–Feb 2007	[20]
Democratic Republic of the Congo	1	494	Oct 2003–Jan 2006[a]	[32]
Ethiopia	1	321	Sep 2005–Sep 2006[a]	[33]
Ghana	1	237	Jan 2004–Jan 2007	[16]
Kenya	1	830	Jan 2005–Sep 2007[a]	[34]
Mozambique	1	2596	2004–2007[a]	[35]
Nigeria	1	1552	Jan 2005–Dec 2006	[36]
Rwanda	1	3194	Jan 2004–Dec 2005	[37]
South Africa	9	26 756	Jan 1998–Dec 2007[a]	[15, 17, 38–44]
Tanzania	2	7213	Oct 2003–May 2007	[45, 46]
Uganda	3	2206	Sep 2003–May 2006	[14, 47, 48]
Zambia	1	37 039	Apr 2004–Nov 2008	[49]
Multiple 1 (Mozambique, Tanzania, Malawi)	1	3456	Jan 2003–Jun 2006	[50]
Multiple 2 (Mozambique, Malawi, Guinea)	1	3749	Feb 2002–Jun 2007	[18]

[a] Period during which patients started antiretroviral therapy; patient follow-up extends beyond dates shown.

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

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/mm^3, 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

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

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, $D_{t,i}$, is characterized as follows:

$$\ln(D_{t,i}) = \beta_0 + \beta_1 t + \ln(N_i) + u_i, \quad (2)$$

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_i, 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/mm^3 at initiation and another term making this indicator variable interact with the variable t.

Adjusted Life-Years Gained

From the estimates $S(t_k)$ ($t_1 = 1/2, \ldots, t_6 = 5$ years), we derived the number of life-years gained during the first 5 years of ART, LY_G, compared with the counterfactual condition of no

ART receipt:

$$LY_G = \sum_{k=3}^{6} \frac{1}{2}(S(t_{k-1}) + S(t_k)) + \frac{1}{4}(1 + 2S(t_1) + S(t_2)) - LY_0, \quad (3)$$

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_L, 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/mm^3, 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

Table 2. Regression Results for Linear Regression of Mortality Among Patients Lost to Follow-up (LTFU) and Poisson Regression of Deaths Over Time

Coefficient	Estimate	Standard Error	*P*
Mortality among LTFU patients (n = 13)			
β_0 (intercept)	66.816	3.874	< .001
β_1 (LTFU)	−1.347	0.180	< .001
R^2	0.84	NA	
RMSE	0.062	NA	
Deaths over time (n = 55)			
β_0 (intercept)	−2.228	0.0738	< .001
β_1 (time)	0.0171	0.0005	< .001
$Var(u_i)$ (random effect)	0.1474	NA	
R^{2a}	0.86	NA	
RMSE[a]	0.025	NA	
Deaths over time, stratified by CD4 (n = 38)			
β_0 (intercept)	−2.275	0.0799	< .001
β_1 (time)	0.0105	0.0011	< .001
β_2 (CD4[b])	0.4021	0.1099	< .001
β_3 (CD4*time)	0.0036	0.0022	.10
$Var(u_i)$ (random effect)	0.1208	NA	
R^{2a}	0.88	NA	
RMSE[a]	0.024	NA	

Abbreviations: CD4, $CD4^+$ cell count; NA, not applicable; RMSE, root-mean-square error.

[a] R^2 and RMSE are computed on the basis of the survival estimate, where $S = 1 - D/N$, as the dependent variable.

[b] The indicator variable for $CD4^+$ cell count is 1 when the $CD4^+$ cell count at initiation is <100 cells/mm^3; the variable is otherwise 0.

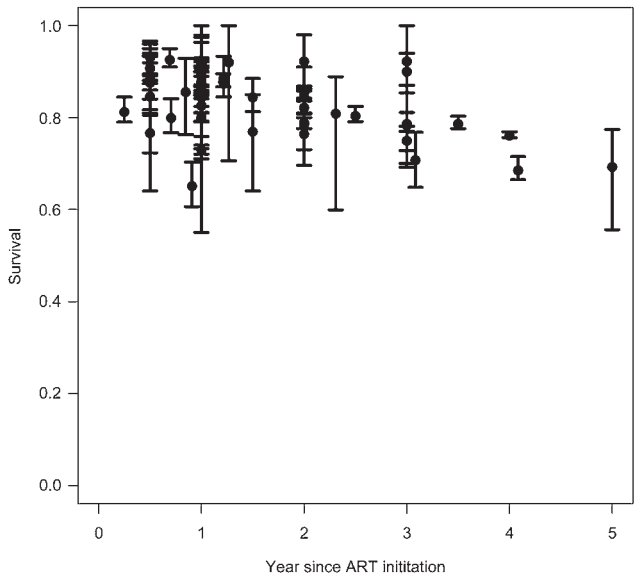

Figure 1. Overall survival adjusted for mortality among patients lost to follow-up (black dot) and unadjusted overall survival (bar bounds) corresponding to the 2 extreme scenarios of either 0% or 100% mortality among patients lost to follow-up for 29 studies in sub-Saharan Africa.

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

Variable	Survival (95% CI), by Time Since ART Initiation					
	6 mo	1 y	2 y	3 y	4 y	5 y
Adjusted						
Overall	0.88 (.74–.94)	0.87 (.72–.94)	0.84 (.65–.92)	0.80 (.57–.91)	0.76 (.48–.89)	0.70 (.36–.86)
By $CD4^+$ cell count at ART initiation						
<100 cells/mm^3	0.83 (.65–.92)	0.82 (.61–.91)	0.78 (.54–.89)	0.75 (.46–.87)	0.70 (.36–.85)	0.64 (.23–.82)
>100 cells/mm^3	0.89 (.77–.94)	0.88 (.76–.94)	0.87 (.73–.93)	0.85 (.69–.92)	0.83 (.64–.92)	0.81 (.59–.90)
Not adjusted, by assumed mortality for LTFU recipients						
100%	0.84 (.70–.92)	0.82 (.66–.91)	0.77 (.57–.88)	0.71 (.46–.85)	0.63 (.32–.80)	0.54 (.12–.76)
0%	0.94 (.75–.99)	0.93 (.71–.98)	0.91 (.60–.98)	0.88 (.50–.97)	0.84 (.29–.96)	0.79 (.12–.95)

Abbreviation: CI, confidence interval.

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/mm^3 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/mm^3 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), 0.75 (95% CI, .46–.87), and 0.64 (95% CI, .23–.82), 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

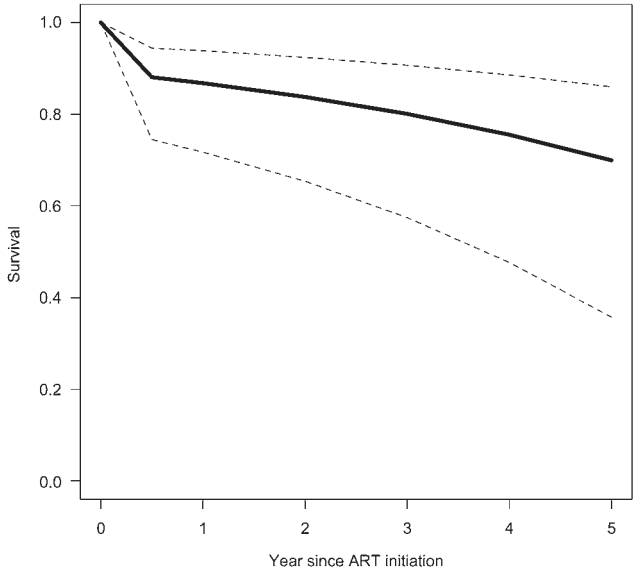

Figure 2. Estimated survival (thick line) and 95% confidence intervals (dashed lines), adjusted for mortality among patients lost to follow-up.

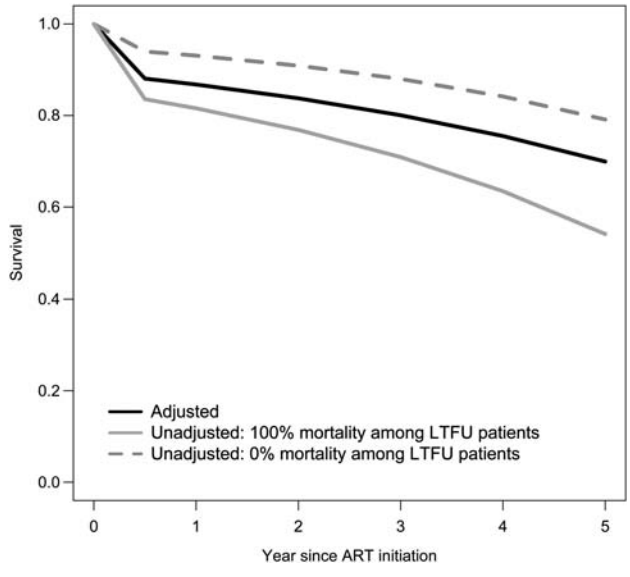

Figure 3. Estimated survival, unadjusted or adjusted for mortality among patients lost to follow-up (LTFU).

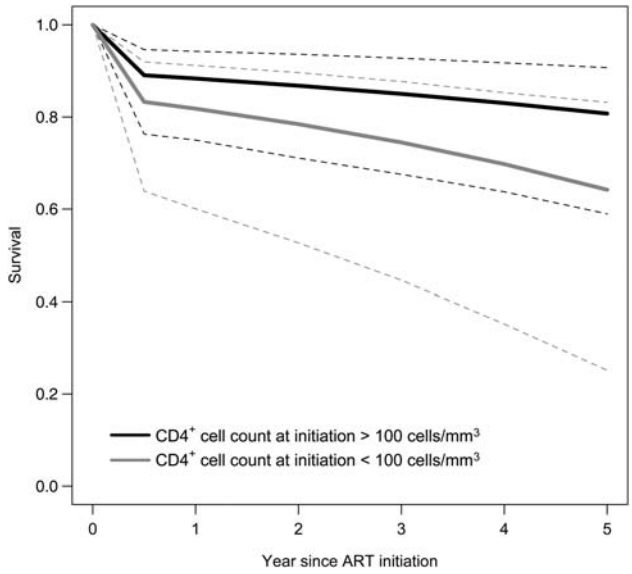

Figure 4. Survival curves (thick line) and 95% confidence intervals (dashed lines) by $CD4^+$ cell count at antiretroviral therapy initiation, adjusted for mortality among patients lost to follow-up.

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 provided by the WHO [1, 8], on the lower end, and the survival 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 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

Acknowledgments. We thank 2 anonymous reviewers for providing very valuable comments on the manuscript.

Financial support. This work was supported by the Bill & Melinda Gates Foundation.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization, UNAIDS, UNICEF. Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011. Geneva: World Health Organization, **2011**.
2. Braitstein P, Brinkhof MWG, Dabis F, et al. for the ART-LINC Collaboration. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet **2006**; 367:817–24.
3. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS **2008**; 22:1897–908.
4. Bisson GP, Gaolathe T, Gross R, et al. Overestimates of survival after HAART: implications for global scale-up efforts. PLoS ONE **2008**; 3: e1725.
5. Brinkhof MWG, Dabis F, Myer L, et al. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bull World Health Organ **2008**; 86:559–67.
6. Yu JK-L, Chen SC-C, Wang K-Y, et al. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. Bull World Health Organ **2007**; 85:550–4.
7. Brinkhof MWG, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS ONE **2009**; 4:e5790.
8. Tassié JM, Baijal P, Vitoria MA, et al. Trends in retention on antiretroviral therapy in national programs in low-income and middle-income countries. J Acquir Immune Defic Syndr **2010**; 54:437.
9. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Med **2007**; 4:e298.
10. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Trop Med Int Health **2010**; 15(Suppl 1):1.
11. Stover J, Korenromp EL, Blakley M, et al. Long-term costs and health impact of continued global fund support for antiretroviral therapy. PLoS ONE **2011**; 6:e21048.
12. Egger M, Spycher BD, Sidle J, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. PLoS Med **2011**; 8:e1000390.

13. Hochgesang M, Kuyenda A, Hosseinipour M, et al. Active tracing of ART patients lost to follow-up at Lighthouse shows that few 'stopped' treatment for their own reasons, but many have died [abstract TUPE0119]. In: 16th International AIDS Conference, Toronto, Canada, August 13–18, 2006.
14. Ahoua L, Guenther G, Pinoges L, et al. Risk factors for virological failure and subtherapeutic antiretroviral drug concentrations in HIV-positive adults treated in rural northwestern Uganda. BMC Infect Dis **2009**; 9:81.
15. Boulle A, Bock P, Osler M, et al. Antiretroviral therapy and early mortality in South Africa. Bull World Health Organ **2008**; 86:678–87.
16. Collini P, Schwab U, Sarfo S, et al. Sustained immunological responses to highly active antiretroviral therapy at 36 months in a Ghanaian HIV cohort. Clin Infect Dis **2009**; 48:988–91.
17. Nachega JB, Hislop M, Dowdy DW, et al. Efavirenz versus nevirapine-based initial treatment of HIV infection: clinical and virological outcomes of Southern African adults. AIDS **2008**; 22:2117–25.
18. Palombi L, Marazzi MC, Guidotti G, et al. Incidence and predictors of death, retention, and switch to second-line regimens in antiretroviral-treated patients in sub-Saharan African sites with comprehensive monitoring availability. Clin Infect Dis **2009**; 48:115–22.
19. Sieleunou I, Souleymanou M, Schonenberger AM, Menten J, Boelaert M. Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North Province, Cameroon. Trop Med Int Health **2009**; 14:36–43.
20. Toure S, Kouadiou B, Seyler C, et al. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Côte d'Ivoire: 2-year outcomes and determinants. AIDS **2008**; 22:873–82.
21. Egger M, Ekouevi DK, Williams C, et al. Cohort profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol **2011**; 40:1–9.
22. Fox MP, Brennan A, Maskew M, MacPhail P, Sanne I. Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa. Trop Med Int Health **2010**; 4:405–11.
23. Chi BH, Yiannoutsos CE, Westfall AO, et al. Universal definition of loss to follow-up in HIV treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America. PLoS Med **2011**; 8:e1001111.
24. Henriques J, Pujades-Rodriguez M, McGuire M, et al. Comparison of methods to correct survival estimates and survival regression on a large HIV African cohort. PLoS ONE **2012**; 7:e31706.
25. An M-W, Frangakis CE, Musick BS, Yiannoutsos CT. The need for double-sampling designs in survival studies: an application to monitor PEPFAR. Biometrics **2009**; 65:301–6.
26. Geng EH, Emenyonou N, Bwana MB, et al. Sampling-based approach to determine outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. JAMA **2008**; 300:506–7.
27. Yiannoutsos CT, An M-W, Frangakis CE, et al. Sampling-based approaches to improve estimation of mortality among patient dropouts: experience from a large PEPFAR-funded program in Western Kenya. PLoS ONE **2008**; 3:e3843.
28. Geng EH, Nash D, Kambugu A, et al. Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions. Curr HIV/AIDS Rep **2010**; 7:234–44.
29. Losina E, Touré H, Uhler LM, et al. Cost-effectiveness of preventing loss to follow-up in HIV treatment programs: a Côte d'Ivoire appraisal. PLoS Med **2009**; 6:e1000173.
30. Bussman H, Wester CW, Ndwapi N, et al. Five-year outcomes of initial patients treated in Botswana's national antiretroviral treatment program. AIDS **2008**; 22:2303–11.
31. O'Brien DP, Mills C, Hamel C, Ford N, Pottie K. Universal access: the benefits and challenges in bringing integrated HIV care to isolated and conflict affected populations in the Republic of Congo. Confl Health **2009**; 3:1.
32. Culbert H, Tu D, O'Brien DP, et al. HIV treatment in a conflict setting: outcomes and experiences from Bukavu, Democratic Republic of the Congo. PLoS Med **2007**; 4:e129.
33. Gugsa S, O'Malley G, John Stewart G. Determinants of retention and mortality during 6-month follow-up after initiation of HAART in an Ethiopian public HIV treatment program [abstract CDB0246]. In: 17th International AIDS Conference, Mexico City, Mexico, August 3–8, 2008.
34. Unge C, Sodergard B, Ekstrom AM, et al. Challenges for scaling up ART in a resource-limited setting: a retrospective study in Kibera, Kenya. J Acquir Immune Defic Syndr **2009**; 50:397–402.
35. Auld A, Mobofana F, Sanchez M, et al. Treatment outcomes of HIV-infected adults enrolled in the national antiretroviral therapy program – Mozambique, 2004–2007 [abstract 1608]. In: Program and abstracts of the HIV/AIDS Implementers' Meeting, Windhoek, Namibia, June 10–14, 2009.
36. DeSilva MB, Merry SP, Fischer PR, et al. Youth, unemployment, and male gender predict mortality in AIDS patients started on HAART in Nigeria. AIDS Care **2009**; 21:70–7.
37. Lowrance DW, Ndamage F, Kayirangwa E, et al. Adult clinical and immunologic outcome of the national antiretroviral treatment program in Rwanda during 2004–2005. J Acquir Immune Defic Syndr **2009**; 52:49–55.
38. Dahab M, Charalambous S, Karstaedt A, et al. Off the radar screen: comparing reasons for treatment default in a workplace ART programme and a public sector clinic in South Africa [abstract THPE0123]. In: 17th International AIDS Conference, Mexico City, Mexico, August 3–8, 2008.
39. Barth RE, Tempelman HA, Hoepelman AIM. Long-term follow-up of HIV-infected adults in rural South Africa; good virological results in spite of early mortality [abstract CDB084]. In: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, July 19–22, 2009.
40. Kahn MSH. Retention and attrition of patients commenced on HAART at Ladysmith Provincial Hospital in South Africa [abstract MO-PEB045]. In: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, July 19–22, 2009.
41. MacPherson P, Moshabela M, Martinson N, Pronyk P. Mortality and loss to follow-up among HAART initiators in rural South Africa. Trans R Soc Trop Med Hyg **2009**; 103:588–93.
42. Ojikutu BO, Zheng H, Walensky RP, et al. Predictors of mortality in patients initiating antiretroviral therapy in Durban, South Africa. S Afr Med J **2008**; 98:204–8.
43. Rosen S, Long L, Sanne I. The outcomes and outpatient costs of different models of antiretroviral treatment delivery in South Africa. Trop Med Int Health **2008**; 13:1005–15.
44. Grimwood A, Magege A, Scheepers E, et al. Public-private partnership achieves long-term ARV adherence in South Africa [abstract CDB0221]. In: 17th International AIDS Conference, Mexico City, Mexico, August 3–8, 2008.
45. Chalamilla G, Mwanyika-Sando M, Hawkins C, et al. Predictors of clinical and immunological outcomes among HIV-infected subjects on ART in Tanzania [abstract 824]. In: 15th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 3–6, 2008.
46. Johannesen A, Naman E, Ngowi BJ, Sandvik L, Matee MI, Aglen HI. Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC Infect Dis **2008**; 8:52.
47. Chang LVW, Alamo S, Guma S, et al. Two-year virologic outcomes of an alternative AIDS care model: evaluation of a peer health worker and nurse-staffed community-based program in Uganda. J Acquir Immune Defic Syndr **2009**; 50:276–82.
48. Martin J. Initial treatment outcomes from a rural-based ART scale-up program in East Africa: The UARTO Cohort [abstract 816]. In: 15th Conference on Retroviruses and Opportunistic Infections, Boston, MA, **2008**. February 3–6, 2008.
49. Chi B, Cantrell RA, Zulu I, et al. Adherence to first-line antiretroviral therapy affects non-virologic outcomes among patients on treatment for more than 12 months in Lusaka, Zambia. International Journal of Epidemiology **2009**; 38:746–56.
50. Marazzi MC, Liotta G, Germano P, et al. Excessive early mortality in the first year of treatment in HIV type 1-infected patients initiating antiretroviral therapy in resource-limited settings. AIDS Res Hum Retrovirus **2008**; 24:555–60.