Practice of Epidemiology

Do Increasing Rates of Loss to Follow-up in Antiretroviral Treatment Programs Imply Deteriorating Patient Retention?

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In several studies of antiretroviral treatment (ART) programs for persons with human immunodeficiency virus infection, investigators have reported that there has been a higher rate of loss to follow-up (LTFU) among patients initiating ART in recent years than among patients who initiated ART during earlier time periods. This finding is frequently interpreted as reflecting deterioration of patient retention in the face of increasing patient loads. However, in this paper we demonstrate by simulation that transient gaps in follow-up could lead to bias when standard survival analysis techniques are applied. We created a simulated cohort of patients with different dates of ART initiation. Rates of ART interruption, ART resumption, and mortality were assumed to remain constant over time, but when we applied a standard definition of LTFU, the simulated probability of being classified LTFU at a particular ART duration was substantially higher in recently enrolled cohorts. This suggests that much of the apparent trend towards increased LTFU may be attributed to bias caused by transient interruptions in care. Alternative statistical techniques need to be used when analyzing predictors of LTFU—for example, using "prospective" definitions of LTFU in place of "retrospective" definitions. Similar considerations may apply when analyzing predictors of LTFU from treatment programs for other chronic diseases.

acquired immunodeficiency syndrome; antiretroviral treatment; HIV; loss to follow-up; survival analysis

Abbreviations: ART, antiretroviral treatment; HIV, human immunodeficiency virus; LTFU, loss to follow-up.

Loss to follow-up (LTFU) can substantially bias estimates of event rates in cohort studies (1). Thus, in cohort studies of persons with human immunodeficiency virus (HIV) infection, LTFU has come to be regarded as an event in its own right (2, 3). In several studies of antiretroviral treatment (ART) programs in developing countries, investigators have reported that there has been a higher rate of LTFU among patients initiating ART in recent years than among patients who initiated ART during earlier time periods (4–10). This is often interpreted as reflecting deterioration of patient retention in the face of increasing patient loads (8–10), prompting concern about the long-term sustainability of ART programs in developing countries and the ultimate impact of ART on mortality. However, the apparent increases in rates of LTFU in recent years have not led to increases in mortality in analyses that have linked patient records to national vital registration

systems (6, 11). It is also difficult to reconcile the apparently increasing rates of LTFU with the findings of a recent systematic review, in which Fox and Rosen (12) found mean rates of retention in ART programs in developing countries to be higher than those estimated in an earlier systematic review (13).

In light of these inconsistencies, it is appropriate to question whether increases in rates of LTFU do indeed imply deterioration in patient retention. Some authors have noted that undocumented transfers may provide an alternative explanation for the increasing rates of LTFU, particularly as ART programs have expanded and become more decentralized (7). Alternatively, rising LTFU rates may reflect challenges in data management for increasingly large programs (5, 14). Another explanation, which has been largely overlooked, is that persons with HIV intermittently drop out of care and/or

interrupt treatment (15–18), and the effect of these interruptions on LTFU rates is not the same in patients who have recently started ART as in patients who started ART during earlier periods. Among the latter patients, many of those currently in care may have interrupted care during previous periods, but in most standard statistical analyses they are treated as having been retained in care for the entire duration of follow-up, leading to a bias when these patients are compared with those who started ART more recently. In this paper, we illustrate this bias through a simulation example and evaluate implications for analyses of trends in patient retention.

METHODS

We simulated a population of 20,000 HIV-positive adults starting ART. We randomly assigned each individual an ART starting date, by sampling from a uniform distribution spanning the interval from January 1, 2003, to December 31, 2012. In our simulation, persons on ART are assumed to interrupt ART at an annual rate equal to

$$\theta a^T,$$

where T is time (in years) since the individual first started ART and the parameters θ and a have been set to 0.13 and 0.75, respectively, consistent with South African data (19). Persons who have interrupted ART are assumed to resume therapy at a rate of 0.6 treatment resumptions per year, consistent with the same South African data (19). Patients can interrupt and resume treatment multiple times. In treated individuals, the annual mortality rate is assumed to be

$$Bc^s d^t,$$

where s is the cumulative time (in years) spent on ART prior to the most recent resumption (0 if the patient has not previously interrupted ART) and t is the time (in years) spent on ART since the most recent ART resumption. Parameter B has been set to 0.28, consistent with the high rates of mortality observed in the first month of ART (20). Parameter c has been set to 0.75, reflecting residual benefit from previous ART exposure, and parameter d has been set to 0.05, consistent with South African mortality data (21). The same formula is used to determine mortality in persons who have interrupted ART, but with t set to 0. A more detailed description of the model is provided in Web Appendices 1 and 2 (available at http://aje.oxfordjournals.org/).

For each individual, a sequence of treatment interruptions and resumptions was simulated until the person either died or survived to mid-2013. LTFU was defined retrospectively, that is, based on whether the individual was considered to have been in care at the analysis closure date. LTFU was defined using a 6-month window (22): Patients were considered LTFU if they were not receiving any ART during the period from January 1, 2013, to mid-2013 and had not died while on ART (deaths occurring while off ART were included in the LTFU definition, as these deaths would not usually be reported to the ART program). For persons designated LTFU, the LTFU date was defined as the most recent date of ART interruption prior to the start of 2013. Patients were coded

as deceased if they had died while on ART prior to January 1, 2013. All other individuals were censored at January 1, 2013 (the analysis closure date).

All patient outcomes were simulated in Excel and Visual Basic (Microsoft Corporation, Redmond, Washington), while survival analyses were performed using STATA 12.0 (StataCorp LP, College Station, Texas). The probability of being classified as LTFU was calculated using the cumulative incidence command, and in a sensitivity analysis the competing risk-adjusted estimate of the probability of LTFU was calculated (23). In an additional sensitivity analysis, a "prospective" definition of LTFU was considered, classifying individuals as LTFU at the time they *first* interrupted ART for more than 6 months (2). All software code used to simulate the patient data and perform the statistical analyses is available in the Web material.

RESULTS

Simulated probabilities of being classified as LTFU are shown in Figure 1A for patients enrolled during different time periods. Although the model assumes rates of ART interruption and mortality to be constant over time, the simulations show a trend towards increasing LTFU in more recently enrolled cohorts.

Differences between cohorts enrolled during different periods remained significant in sensitivity analyses that considered alternative definitions of LTFU (3 months with no visit instead of 6 months), alternative assumptions about rates of ART interruption and ART resumption (including constant rates of interruption), and alternative assumptions about mortality, as well as in competing-risks analyses (Web Appendix 3). However, differences between cohorts enrolled in different periods became less pronounced when lower rates of ART resumption were assumed, and in the extreme case in which rates of restarting ART were set to zero, differences between cohorts ceased to be significant (Figure 1B). Similar results were obtained when using the prospective LTFU definition (Figure 1C). In Web Appendix 4, we provide a mathematical proof of the dependence of the retrospective LTFU definition on the time to analysis closure and demonstrate that the prospective LTFU definition is independent of the time to analysis closure.

DISCUSSION

These results suggest that much of the apparent increase in rates of LTFU among recently enrolled ART cohorts can be attributed to a bias caused by transient gaps in follow-up, which differentially affects patients enrolled during different time periods. In recently enrolled cohorts, there has been less time to come back into care, following an interruption at a specific ART duration, than there has been in earlier cohorts, and hence recently enrolled individuals who temporarily interrupt care are more likely to be classified as lost. Transitions into and out of ART care are very common; in a recent systematic review, the median proportion of patients interrupting treatment was approximately 23%, and the median duration of interruption was estimated at 150 days (15). Interruptions are particularly common among women who start ART during pregnancy (24), younger patients, patients with higher viral loads, and patients using drugs or alcohol (15); bias in the
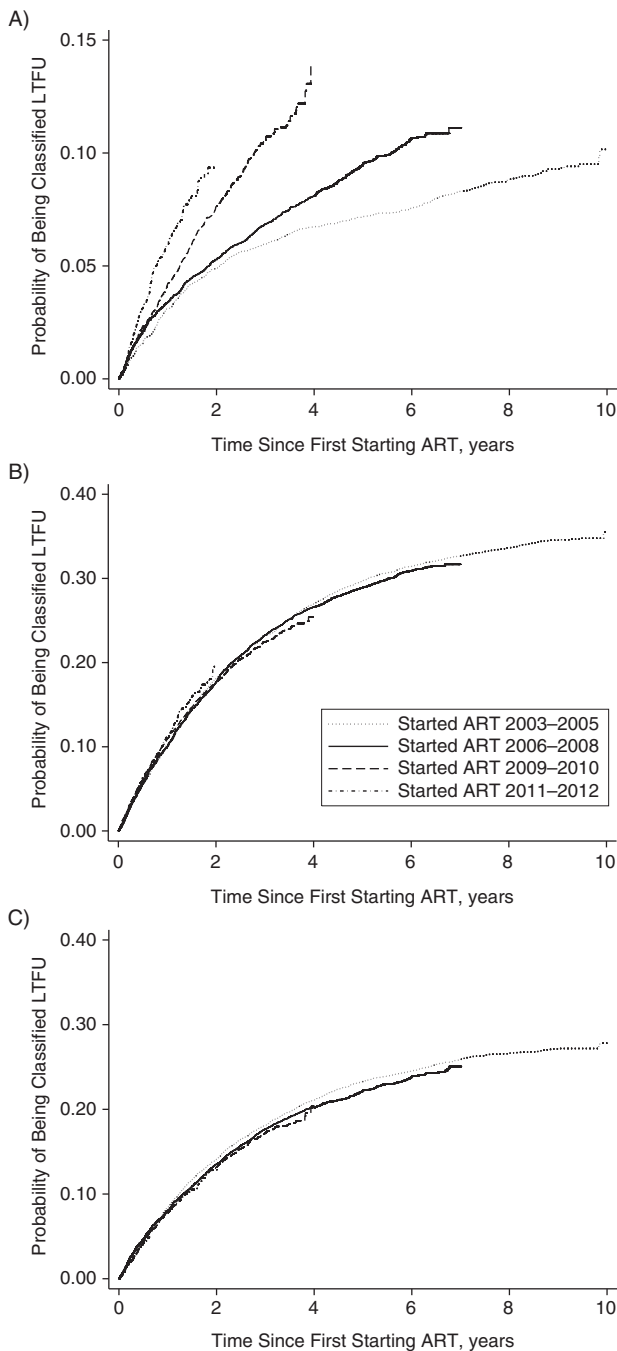
A)

B)

Started ART 2003–2005
Started ART 2006–2008
Started ART 2009–2010
Started ART 2011–2012

C)

Figure 1.   Association between period of enrollment in antiretroviral treatment (ART) and probability of being classified as lost to follow-up (LTFU). In part A, the probability of LTFU is calculated using standard assumptions (persons who return to care after an interruption are treated as if they have remained in care for the duration of the interruption). In part B, the probability of LTFU is calculated on the basis of the assumption of no return to care after an interruption. In part C, patients are classified as LTFU when they first interrupt ART for more than 6 months (prospective LTFU definition).

estimation of LTFU is therefore likely to be particularly substantial in these groups.

The model considered here does not make any allowance for changes over time in rates of ART interruption, rates of mortality, or accuracy of outcome ascertainment. In addition, the model does not consider transfer between ART services (documented or undocumented). Thus, the substantial differences shown in Figure 1A are due only to the phenomenon of transient ART interruptions; if it is instead assumed that all persons who stop ART do so permanently (and do not resume treatment), differences between cohorts disappear (Figure 1B). Therefore, observed increases in rates of LTFU in recently enrolled cohorts should not be interpreted as evidence of a deterioration in patient retention when using standard retrospective LTFU definitions. A strength of this analysis is that we have shown the conclusions to be robust across a range of assumptions and have provided a mathematical proof that this conclusion will generally hold when retrospective LTFU definitions are used.

These results have important implications for analyses that aim to compare rates of LTFU or retention associated with different ART initiation criteria or different patient management approaches, particularly when the patient groups being compared were enrolled during different periods and analyses do not control for the period of enrollment. For example, HIV patients who initiate ART according to newer ART eligibility criteria (starting with CD4 cell counts above 200 cells/µL or starting in pregnancy) may appear to have higher rates of LTFU than patients who started ART under previous eligibility criteria because they started ART in more recent periods, not necessarily because the new eligibility criteria are associated with poorer retention. Similar considerations may apply when analyzing predictors of LTFU from treatment programs for other chronic diseases.

More generally, this analysis points to problems with the use of standard survival analysis techniques in modeling LTFU as an outcome, if LTFU is the outcome of primary interest. Various alternative statistical approaches can be considered, depending on the specific research question. One approach might be to employ a prospective definition of LTFU—that is, to classify all persons as LTFU at the time they first meet the LTFU definition and not readmit them into the analysis if they subsequently return to care. This would avoid inconsistencies that arise when some patients are reclassified as having been continuously in care when they subsequently return to care. However, using a prospective definition will lead to a substantially higher rate of LTFU (2), and it may be less confusing to describe this as a cumulative probability of a gap in care of at least 6 months rather than a probability of LTFU. Alternatively, multiple-failure models could be used (25). For analyses comparing patients starting ART according to different eligibility criteria, it may suffice to control for the calendar year of ART initiation. The most useful statistical approach may be a multistate modeling approach, in which movements into and out of care are modeled explicitly (26). Examples illustrating the application of these alternative methods to our simulated data are included in Web Appendices 5 and 6.

Although these findings point to problems with the traditionally used retrospective definition of LTFU when the outcome of interest is LTFU, the retrospective definition of LTFU may still be appropriate when other outcomes are being assessed.

In our simulations, for example, estimates of the cumulative probability of death were similar when retrospective and prospective definitions of LTFU were used and were not sensitive to the year of ART initiation (results not shown). In the case of mortality outcomes, the retrospective LTFU definition might be considered preferable, as it allows for the inclusion of more follow-up time than the prospective method. The choice of LTFU definition should therefore depend on the outcome of interest and the research question (2).

LTFU in ART programs remains a poorly understood phenomenon. Although LTFU is often assumed to be synonymous with stopping ART, as we have assumed in this analysis, other causes of LTFU also need to be considered, such as unrecorded mortality, undocumented transfers to other ART programs, and administrative lapses in updating patient records (27, 28). Because the model presented here does not consider these alternative causes of LTFU, it may underestimate overall rates of LTFU, and to the extent that people can return to care following these other events, the model may underestimate the extent of the bias. Despite these limitations, the model demonstrates clearly that the traditional "retrospective" definition of LTFU can be problematic when analyzing predictors of LTFU and that it can lead to incorrect conclusions regarding trends in retention in care.

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