Estimating the Benefits of Antiretroviral Therapy Programs: How Certain Can We Get?

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(See the major article by Verguet et al, on pages 72–9.)

Measuring the effectiveness of programs in ensuring success with human immunodeficiency (HIV) care and treatment and lives saved is critical to identifying areas for improvement and the most effective models for scale-up as countries work toward the goal of universal coverage for antiretroviral therapy (ART) [1]. The survival rate is one critical metric to measure the effectiveness of ART programs in resource-limited and resource-richer settings, but measuring these rates has been a challenge because of the uncertainty of outcomes among patients no longer in care. This loss to follow-up has been identified as a challenge regardless of setting [2]. Although there has been increased focus on reducing rates of loss to follow-up, through improved outreach and by addressing barriers to retention, nonadherence to care remains a challenge for many ART programs.

The variability in the definition of “lost to follow-up” (LTFU) and in how LTFU patients are included in measuring program success have made it challenging to understanding the effectiveness of different models [3]. When programs and decision makers cannot determine whether patients classified as LTFU have had a bad outcome (eg, they are no longer in care or they died) or whether they have simply transferred care either to a more accessible site in the setting for scale-up or because of migration out of the area, measuring the effectiveness of a model becomes a significant challenge. Given limited resources, determining the outcome of all LTFU patients is often not feasible and may have limited clinical benefit particularly for those who have been lost from care for an extended period [4]. As governments and policy makers work to determine the most effective models of care for decreasing HIV-related mortality, identification of methods that use routinely available data to determine the survival outcomes of LTFU patients and that can either define or decrease the level of uncertainty in the results is critical to ensuring that decisions about which programs can scale-up are based on evidence. Statistically, there are a number of challenges to incorporating loss to follow-up into estimates of program success. These challenges are even greater if there are different reasons beyond mere randomness about why patients are LTFU, because a bias then enters into the evaluations.

In this issue, Verguet and colleagues [5] expand on a relatively simple approach initially developed by Egger et al [6] to provide policy makers and implementers with better estimates of the survival benefits related to ART programs. Verguet et al use ART cohort data from published studies to impute mortality rates among LTFU patients on the basis of retention rates and to calculate an adjusted survival estimate at multiple time points after ART initiation. They compare the adjusted estimates with unadjusted estimates that assume the worst-case scenario (ie, all LTFU patients die) and the best-case scenario (ie, all LTFU patients survive). These 2 extremes provide brackets between which the true, full information estimate must lie. The authors then use the adjusted rates to estimate the number of life-years gained during the initial first 5 years of ART receipt, compared with no ART receipt.

By use of these methods, the adjusted survival rates drop early after treatment initiation, reflecting the pattern seen across many other studies, which used a range of approaches to define mortality among LTFU patients [7]. Similar to other studies, higher mortality is also seen among patients initiating ART at more advanced stages of HIV disease, with the difference persisting to 5 years: 81% of patients survived to this time point if ART was started at a CD4+ cell count of >100 cell/mm3, compared with 64% who had more-advanced disease at treatment initiation. The survival rates,
as expected, fall between the estimates calculated using the worst-case scenario and the best-case scenario. Inclusion of these 2 extremes as an additional measure of uncertainty around estimates of survival benefits is another useful tool to help decision makers understand the limitations of the data available.

Use of these brackets (ie, all LTFU patients die, and all LTFU patients survive) is a respectable technique dating back to the evaluation of the Kinsey report by Cochran and colleagues in 1953 [8]. The bounds are sometimes quite wide, which may explain why the technique is not more popular than it is, but these bounds typically more properly reflect the uncertainty in the data. An alternative approach is to ignore LTFU patients, but this would be statistically acceptable only if their becoming LTFU is “completely random,” such that their outcomes are the same as those of patients who remain in care, a circumstance that is known to false in resource-limited and less constrained settings. Another possible approach, which has its own problems, is to assume that LTFU patients are missing at random and then impute the missing values.

There are a number of challenges to incorporating imputed data into decisions about the effectiveness of models, largely because of the limitations of available data, including whether the relationship between the mortality and LTFU rates used to impute mortality are constant regardless of initial CD4+ cell count. If, after ART is stopped, LTFU patients who start ART at lower CD4+ cell counts are more likely to die than those who start ART at higher CD4+ cell counts, the estimated survival benefit may differ. We are also not able to determine whether this relationship is constant across different patient characteristics (eg, sex, age, and urban vs rural residence), which would also be critical because the effectiveness of models is compared on the basis of adjusted mortality. For example, if LTFU women are more or less likely than LTFU men to transfer care to another facility, there would be a sex-based difference in mortality among LTFU patients. Similar questions need to be answered for urban versus rural settings, where accessibility to alternate care sites are significantly different. More research is needed to understand this potential for heterogeneity across or even within a clinic and how statistical methods may need to be refined to identify more effective models for improving life-years gained in different settings. New data are also needed to understand the current relationship between LTFU and mortality: increased access to ART sites may increase the proportion of LTFU patients who have simply transferred care, as well as the proportion who have been in care for ≥5 years. Regardless, the methods and explicit calculation of the range of survival benefits on the basis of different assumptions are important additions to help program and national decision makers understand the successes and limitations of the current models of care.

The article by Verguet et al also serves as a reminder that, although statistical methods can help adjust for the uncertainty of outcomes related to loss to follow-up and give us a more accurate assessment, the method is far from perfect. This further emphasizes the importance of strengthening systems of care and follow-up as means to decrease loss to follow-up and the proportion of patients whose outcomes are unknown. Work is ongoing to achieve these goals, both through active efforts to prevent loss to follow-up by addressing barriers and providing rapid outreach for patients who have missed visits, as well as by strengthening health information and referral systems to ensure that programs are able to document and facilitate successful transfer of patients who are moving to other sites [9]. Modeling of data from Cote d’Ivoire found that efforts to prevent loss to follow-up would improve survival and are cost-effective [4]. A number of programs have already shown the potential to decrease rates of loss to follow-up to close to 0 [10], a critical goal on the path to ensuring that universal access to HIV care and treatment has a universal benefit.

**Note**

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