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Predictors of patient attrition according to different definitions for loss to follow-up: a comparative analysis from Lusaka, Zambia

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Patient retention is critical to the long-term success of antiretroviral therapy (ART) programs worldwide. Continued follow-up in HIV care is important to ensure drug adherence, to evaluate the emergence of toxicities, to monitor treatment response, and to provide entry into other healthcare services.[1] However, many have reported substantial losses to follow-up (LTFU) longitudinally. A systematic review of 39 cohorts in sub-Saharan Africa estimated program attrition (deaths and LTFU) to be 22.6% at 12 months, 25.0% at 24 months, and 29.5% at 36 months.[2]

A challenge to ongoing research around program attrition has been the lack of standardized definitions for LTFU. Numerous metrics have been proposed in the medical literature, including time late for one's last scheduled appointment and time elapsed since last clinical or pharmacy contact. Time thresholds have also varied.[2] Efforts to establish universal LTFU definitions are important for the monitoring and evaluation of programs, particularly when comparing performance between facilities.[3,4] From a clinical perspective, however, it is possible that characteristics among lost patients may not differ substantially from definition to definition. In this analysis, we compared patient-level predictors for program attrition across a range of LTFU definitions to determine whether characteristics associated with LTFU differed according to the criteria used.

We analyzed data from a well-characterized cohort of adults initiating ART in Lusaka, Zambia. Clinical care and program characteristics have been previously described.[5] Briefly, HIV-infected patients are enrolled and screened for ART eligibility on the basis of $CD4^+$

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cell count and World Health Organization (WHO) clinical staging. ART is initiated according to Zambian national guidelines for HIV care and treatment,[6] which closely follow WHO recommendations.[7] Antiretroviral drugs are provided free of charge. Patient level data, including medical history, pharmacy dispensations, and appointment information are captured in an electronic medical record system.[8]

Our analysis cohort comprised treatment-naïve HIV-infected adults (> 15 years old) initiating ART across 18 sites. Patients who had formally withdrawn from the program or who had a documented death before the freeze date were excluded. Because their dispositions were known, in a programmatic setting they would not be considered LTFU. We used a universal freeze date of February 1, 2011 for all patients. We categorized patients as LTFU based on the following definitions: late for scheduled clinic encounter (≥30, ≥60, ≥90, ≥180, and ≥365 days) and time since last clinic encounter (≥90 and ≥180 days). Censor dates for each definition was calculated based on the time threshold since a patient's last encounter or last scheduled appointment.

In separate models for each LTFU definition, we used multivariate Cox proportional hazards regressions to identify independent predictors. We adjusted for potential confounders previously shown in the literature to be associated with follow-up losses, including age at ART initiation, sex, and baseline $CD4^+$ cell count, body mass index (BMI), hemoglobin, WHO staging, and active tuberculosis at enrollment.[9–11] Robust standard error estimates were used to account for clustering at the site level. All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC). Use of these programmatic data was approved by the University of Zambia Biomedical Research Ethics Committee (Lusaka, Zambia) and University of North Carolina at Chapel Hill Institutional Review Board (Chapel Hill, NC, USA).

The analysis cohort included 72,642 adults who initiated ART between May 1, 2004 and January 31, 2010. Over this time, 7889 (10.9%) died and 7164 (9.9%) were known to have formally withdrawn from the program; all were excluded from the analysis. The majority of the cohort was female (62.6%). Median age was 34 years (IQR: 29–40); median CD4 count at ART initiation was 146 cells/uL (IQR: 79–214); and median time of follow-up was 889 days (IQR: 466–1456).

The proportion categorized as LTFU varied according to the definition used. When we considered thresholds according to "days late" since last appointment, LTFU was 36.3% (95%CI:35.9%–36.7%) at ≥30 days late; 33.7% (95%CI:33.3%–34.1%) at ≥60 days late; 32.1% (95%CI:31.7%–32.5%) at ≥90 days late, 29.9% (95%CI:29.5%–30.3%) at ≥180 days late, and 25.8% (95%CI:25.4%–26.1%) at ≥365 days late. When we considered time since last encounter, LTFU was 36.4% (95%CI:36.0%–36.8%) at ≥90 days and 31.0% (95%CI: 30.7%–31.4%) at ≥180 days. The LTFU rate per 100 person-years ranged from 8.7 to 13.6 (see Supplemental Table I).

Patient characteristics associated with LTFU were consistent across definitions. Younger age, males, lower BMI, higher CD4 count, and lower hemoglobin were significantly associated with LTFU across all definitions. The magnitude of association appeared similar across thresholds (Figure 1). For example, adjusted hazard ratios (aHR) for sex varied by less than 2% when compared to the lowest one observed; none of the aHRs for CD4 count >350 versus 0–49 varied by more than 8%.

In this analysis, the factors associated with LTFU remained consistent across a number of different thresholds and definitions. While a standard definition for LTFU would enhance global monitoring and evaluation efforts from the clinical care perspective,[4] our results

suggest that characteristics of high-risk populations may be similar irrespective of the LTFU definition used.

Questions remain about how to improve retention in long-term HIV care. Interventions that target patients after they miss visits can be costly and labor-intensive, particularly given their incremental benefit. In Lusaka, for example, where community health workers are dispatched following missed appointments, 41% of patients could not be located. Of those successfully traced, only 30% returned to care. [12] Measures that keep patients in care – before they default – are likely to be more efficient. Work by Losina and colleagues demonstrated that an intervention of modest efficacy can be cost-effective and would substantially lower mortality.[13] "Two-way" mobile SMS reminders, specialized patient support, and monetary supplements have shown promise for improving clinical outcomes and lowering program attrition.[14–18]

For most programs, however, a "one-size-fits-all" approach to addressing the problem may be inefficient, impractical, and unaffordable. While program attrition remains a serious threat to HIV treatment programs, it is important to note that the majority of patients remain alive and active in care. Under these circumstances, the capacity to identify patients at highest risk for LTFU would have great value to front-line health providers and program managers, particularly as ART services expand. We identified several consistent risk factors for LTFU that could inform future interventions. Targeted interventions such as structural services (e.g. food rations) and rapid point-of-care assessments could improve retention amongst patients who initiate ART with poor health indicators (e.g. low BMI and low hemoglobin). Alternatively, scheduling less frequent clinical visits or active outreach activities may be beneficial for young people and males, who may be more mobile and experience greater opportunity costs when visiting a clinic.[19]

The prevalence of LTFU ranged 26% to 36% across commonly used definitions included in our analysis, figures similar to other published reports from sub-Saharan African settings.[20–23] Our cross-sectional approach may explain the low variability seen from definition to definition. A patient who has not been seen in the clinic in over a year, for example, would be considered LTFU according to all definitions. At the time of data freeze, the Lusaka ART program had been in place for more than six years; patients who initiated HIV treatment earlier had a longer follow-up window and are likely to have more time elapsed since their missed visit or last visit.

Although this study is among the first to compare predictors for LTFU across different definitions, we also recognize several limitations. First, unreported deaths and transfers out of the program were not accounted for and, as a result, these individuals may be misclassified as LTFU. While statistical methods that have been developed to correct for such biases, they do so only at the population (and not the individual) level.[24–26] Second, the external validity of our results is uncertain. However, although LTFU patients may vary from setting to setting, the characteristics that predict LTFU are unlikely to differ between definitions. Third, this analysis does not take into account patients who are lost prior to ART initiation, a period of high attrition.[27] Predictors and definitions for the pre-ART period may differ compared to those who have already initiated ART. Fourth, recent literature has proposed alternate definitions that assess different aspects of engagement in care over time, including measures of visit constancy or gaps in care.[28] These definitions may have yielded different estimates of rates and predictors of LTFU. Finally, while this analysis has shown that predictors for LTFU are relatively consistent across thresholds, a standard definition would greatly enhance comparability across programs and cohorts. We previously reported a methodology to empirically determine the optimal definition for LTFU [3,4] and continue to advocate for such standardized approaches for global monitoring and evaluation.

In summary, where there are limited resources, there is need to identify ART patients at highest risk for LTFU, so that tailored interventions can be deployed to improve their engagement in care. Although many definitions for LTFU have been proposed, our analysis suggests that characteristics associated with program attrition did not differ significantly between them. This finding has important implications for programs seeking to improve patient retention within HIV treatment programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Geng EH, Nash D, Kambugu A, et al. Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions. Current HIV/AIDS reports. Nov; 2010 7(4): 234–244. [PubMed: 20820972]
2. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Tropical medicine & international health: TM & IH. Jun; 2010 15(Suppl 1):1–15.
3. Chi BH, Cantrell RA, Mwango A, et al. An empirical approach to defining loss to follow-up among patients enrolled in antiretroviral treatment programs. Am J Epidemiol. Apr 15; 2010 171(8):924–931. [PubMed: 20219765]
4. Chi BH, Yiannoutsos CT, 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 medicine. Oct.2011 8(10):e1001111. [PubMed: 22039357]
5. Stringer JS, Zulu I, Levy J, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. JAMA: the journal of the American Medical Association. Aug 16; 2006 296(7):782–793. [PubMed: 16905784]
6. Zambia Ministry of Health. Adult and Adolescent Antiretrovial Therapy Protocols 2010. Lusaka; Zambia: 2010.
7. World Health Organization. Report of the Consensus Meeting on WHO Antiretroviral Therapy Guidelines for Adults and Adolescents. Geneva: World Health Organizaion; 2009.
8. Fusco, H.; Hubschman, T.; Mbweeta, V., et al. Electronic Patient Tracking Supports Rapid Expansion of HIV Care and Treatment in Resource-Constrained Settings [Abstract MoPe11.2C37]; 3rd IAS Conference on HIV Pathogenesis and Treatment; Rio de Janiero, Brazil. 2005.
9. Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PloS one. 2011; 6(5):e19201. [PubMed: 21559280]
10. 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. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. Jan 1; 2009 48(1):115–122. [PubMed: 20380075]
11. Wandeler G, Keiser O, Pfeiffer K, et al. Outcomes of antiretroviral treatment programs in rural Southern Africa. Journal of acquired immune deficiency syndromes (1999). Feb 1; 2012 59(2):e9–16. [PubMed: 22067665]

12. Krebs DW, Chi BH, Mulenga Y, et al. Community-based follow-up for late patients enrolled in a district-wide programme for antiretroviral therapy in Lusaka, Zambia. AIDS care. Mar; 2008 20(3):311–317. [PubMed: 18351478]

13. Losina E, Toure H, Uhler LM, et al. Cost-effectiveness of preventing loss to follow-up in HIV treatment programs: a Cote d'Ivoire appraisal. PLoS medicine. Oct.2009 6(10):e1000173. [PubMed: 19859538]

14. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. Nov 27; 2010 376(9755):1838–1845. [PubMed: 21071074]

15. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS (London, England). Mar 27; 2011 25(6):825–834.

16. Braitstein P, Siika A, Hogan J, et al. A clinician-nurse model to reduce early mortality and increase clinic retention among high-risk HIV-infected patients initiating combination antiretroviral treatment. Journal of the International AIDS Society. 2012; 15:7. [PubMed: 22340703]

17. Emenyonu, NI.; Muyindike, W.; Habyarimana, J., et al. Cash transfers to cover clinic transportation costs improve adherence and retention in care in a HIV treatment program in Rural Uganda; Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; 2010; San Francisco, CA.

18. Etienne M, Burrows L, Osotimehin B, et al. Situational analysis of varying models of adherence support and loss to follow up rates; findings from 27 treatment facilities in eight resource limited countries. Tropical medicine & international health: TM & IH. Jun; 2010 15(Suppl 1):76–81.

19. Lamb MR, El-Sadr WM, Geng E, Nash D. Association of adherence support and outreach services with total attrition, loss to follow-up, and death among ART patients in sub-Saharan Africa. PloS one. 2012; 7(6):e38443. [PubMed: 22685569]

20. Assefa Y, Kiflie A, Tesfaye D, et al. Outcomes of antiretroviral treatment program in Ethiopia: retention of patients in care is a major challenge and varies across health facilities. BMC health services research. 2011; 11:81. [PubMed: 21501509]

21. Boulle A, Bock P, Osler M, et al. Antiretroviral therapy and early mortality in South Africa. Bulletin of the World Health Organization. Sep; 2008 86(9):678–687. [PubMed: 18797643]

22. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. Mar 11; 2006 367(9513):817–824. [PubMed: 16530575]

23. Charurat M, Oyegunle M, Benjamin R, et al. Patient retention and adherence to antiretrovirals in a large antiretroviral therapy program in Nigeria: a longitudinal analysis for risk factors. PloS one. 2010; 5(5):e10584. [PubMed: 20485670]

24. Brinkhof MW, Spycher BD, Yiannoutsos C, et al. Adjusting mortality for loss to follow-up: analysis of five ART programmes in sub-Saharan Africa. PloS one. 2010; 5(11):e14149. [PubMed: 21152392]

25. 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 medicine. 2011; 8(1):e1000390. [PubMed: 21267057]

26. Yiannoutsos CT, An MW, 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(12):e3843. [PubMed: 19048109]

27. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS medicine. Jul.2011 8(7):e1001056. [PubMed: 21811403]

28. Mugavero MJ, Davila JA, Nevin CR, Giordano TP. From access to engagement: measuring retention in outpatient HIV clinical care. AIDS patient care and STDs. Oct; 2010 24(10):607–613. [PubMed: 20858055]

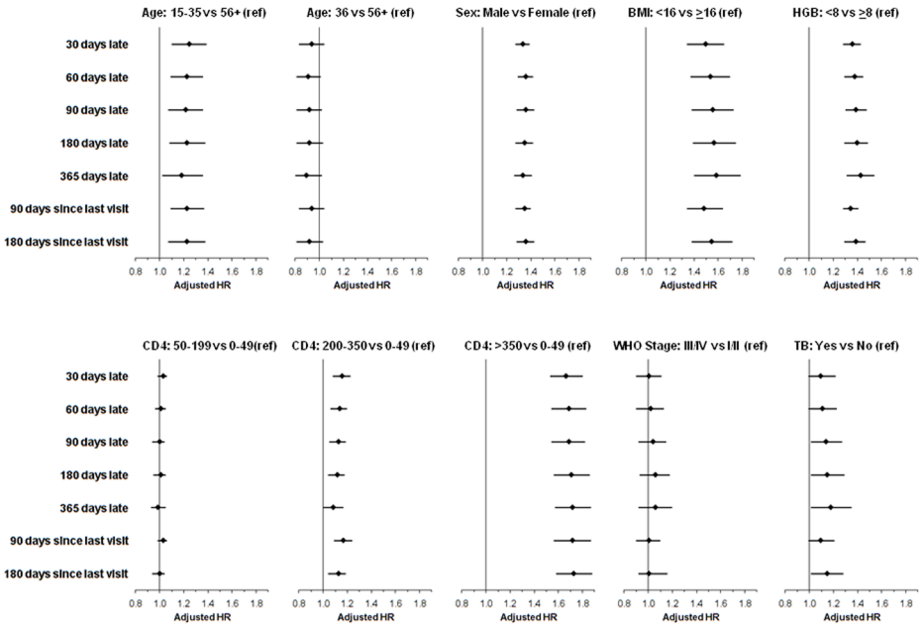

Figure 1.

Adjusted hazard ratios and 95% confidence intervals for factors associated with LTFU, according to different definitions

BMI, body mass index (kg/m^2); HGB, hemoglobin (g/dL); CD4, CD4+ cell count (cells/μL); WHO, World Health Organization; TB, tuberculosis