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Changes in the Timing of Antiretroviral Therapy Initiation in HIV-Infected Patients With Tuberculosis in Uganda: A Study of the Diffusion of Evidence Into Practice in the Global Response to HIV/AIDS

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Background.   We aimed to determine the extent to which emerging evidence and changing guidelines regarding timing of antiretroviral therapy (ART) among human immunodeficiency virus (HIV)–infected patients with tuberculosis influenced "real-world" clinical practice in Uganda.

Methods.   We evaluated ART-naive, HIV-infected adults starting tuberculosis therapy at 2 HIV clinics in Uganda between 26 August 2006 and 29 September 2012. We used multivariate regression to calculate associations between 4 calendar periods reflecting publication of seminal clinical studies or changes in guidelines and timing of ART after tuberculosis therapy initiation.

Results.   For patients with CD4 counts <50 cells/μL, the fraction starting ART within 14 and 30 days of initiating tuberculosis therapy increased from 7% to 14% and from 14% to 86% over the period of observation. The fraction of patients with CD4 counts >50 cells/μL starting ART within 60 days increased from 16% to 28%. After adjustment for sociodemographic factors, when comparing the most recent with the earliest calendar period, the rate of ART initiation increased by 4.57-fold (95% confidence interval [CI], 1.76-fold to 11.86-fold) among patients with baseline CD4 counts ≤ 50 cells/μL and by 5.43-fold (95% CI, 3.16- fold to 9.31-fold) among those with baseline CD4 counts >50 cells/μL.

Conclusions.   We observed large changes in clinical practice during a period of emerging data and changing guidelines among HIV-infected patients with tuberculosis. Nonetheless, a significant proportion of individuals with higher CD4 cell counts do not start ART within recommended time frames. Targeted dissemination and implementation efforts are still needed to achieve target levels in practice.

Keywords.   tuberculosis; HIV; antiretroviral therapy; implementation; diffusion.

Over the last decade, several clinical studies, including randomized trials, have shown that starting antiretroviral therapy (ART) early after the initiation of tuberculosis treatment can significantly reduce AIDS progression and mortality among patients with human immunodeficiency virus (HIV)–associated tuberculosis [1–5]. However, the extent to which these emerging data and the changing clinical guidelines based on these data are routinely implemented in Africa—where the burden of tuberculosis/HIV coinfection is the highest—remains incompletely understood. Some experts have suggested that it takes up to 17 years for 14% of evidence to make its way into clinical practice [6]. Given the high mortality of patients with HIV-associated tuberculosis, this rate of change would be unacceptable. Understanding the diffusion of clinical evidence into practice for patients in

Africa is urgently needed to quantify gaps in implementing the global response to the burden of tuberculosis among patients with HIV/AIDS.

Prior studies have documented suboptimal ART initiation after tuberculosis therapy initiation in Africa [7–10], but to date no studies have explicitly sought to identify an association between emerging scientific evidence and changing clinical practice. In South Africa, an integrated tuberculosis/HIV treatment center documented only 66% ART uptake after the initiation of tuberculosis therapy, but this study sought to identify sociodemographic and clinical predictors of ART initiation, and did not evalute the relationship between changes in evidence over time and changes in practice [9]. Another study found that the median time from tuberculosis therapy initiation to ART initiation was >2.5 months [8]. However, the study does not capture the effects of important data from 3 recent randomized trials [1, 4, 5]. Finally, a study in Malawi evaluated changes in rates of ART initiation after a specific initiative to shorten timing of ART after tuberculosis diagnosis (ie, dissemination), and found that the rate of ART initiation did in fact increase [10] but remained far from optimal at only 24% 3 months after tuberculosis therapy initiation.

In 2006, the World Health Organization (WHO) guidelines for ART initiation in resource-limited settings recommended starting ART within 2–8 weeks after initiating tuberculosis therapy for patients with a CD4 level <200 cells/μL, 8–24 weeks for patients with a CD4 level of 201–350 cells/μL, and after tuberculosis therapy for patients with a CD4 count >350 cells/μL [11, 12]. In 2010, WHO recommended that individuals start ART within 8 weeks of initiating tuberculosis therapy in all patients irrespective of CD4 levels [2, 3, 13]. In October 2011, 3 randomized trials were published which suggested that for patients with a CD4 level ≤50 cells/μL in particular, initiation of ART within 2 weeks of starting tuberculosis therapy reduced mortality and AIDS progression [1, 4, 5], and this in turn led to updated guidelines from WHO in 2012 [14].

In this analysis, we assessed whether changes in evidence and guidelines over a 6-year observation period were associated with changes in the rate of ART initiation among individuals with HIV-associated tuberculosis in 2 clinics operated by a large Ugandan nongovernmental organization. Our primary aim was to describe the extent to which current practices with respect to ART initiation in patients with HIV-associated tuberculosis in a low-income country were associated with these discrete changes in guidelines as well as emerging scientific evidence.

METHODS

Study Design and Patient Population
We evaluated HIV-infected adult patients with a bacteriological or clinical diagnosis of tuberculosis and who were initiated on tuberculosis treatment in 2 HIV clinics in Uganda supported by the Makerere University Joint AIDS Program (MJAP) between 26 August 2006 and 29 September 2012. The first clinic site was the Mulago Immune Suppression Syndrome (ISS) clinic in Kampala, the capital city of Uganda. Patients diagnosed with tuberculosis at the ISS clinic are given their first prescription for tuberculosis treatment and then are transferred to a separate specialized clinic that provides HIV and tuberculosis care within 300 meters from the HIV clinic. The second clinic site was the Mbarara Municipal Clinic (MMC) in Mbarara, a semirural district in Uganda. MMC provides tuberculosis and HIV services for all of their HIV-infected patients at the same facility. The study population consisted of all adult patients ≥18 years of age diagnosed with and receiving treatment for tuberculosis who had not previously started ART. This study was approved by the institutional review boards of the University of California, San Francisco and Makerere University as well as the Uganda National Council for Science and Technology.

Measurements
We obtained sociodemographic and clinical data from the clinic databases. Clinical information is recorded on standardized forms provided by the Ugandan Ministry of Health (MOH) and subsequently entered into a database. Dates of tuberculosis treatment initiation were recorded in the MJAP clinical database regardless of where tuberculosis treatment was initiated. In this region, a diagnosis of tuberculosis is most commonly diagnosed using the WHO 4-point clinical symptom scoring system followed by sputum smear positivity (via the Ziehl-Neelsen staining method or fluorescent microscopy with an auramine-rhodamine stain) and/or a suggestive chest radiograph. Additional diagnostic methods include abdominal ultrasound or fine needle aspiration of lymph nodes. Our primary predictor variable was calendar time, divided into 4 intervals representing changes in evidence and guidance from WHO. Our framework was based on the observation that WHO guidelines informed Ugandan MOH guidelines during this observation period and independently may have affected changes in clinical practice [11, 15]. From August 2006 until December 2009, WHO recommended starting ART 2–8 weeks after tuberculosis therapy initiation for patients with a CD4 count <200 cells/μL, 8–24 weeks for patients with a CD4 count of 201–350 cells/μL, and after tuberculosis therapy initiation in patients with a CD4 count >350 cells/μL [12]. We divided this period into 2 intervals (before and after 1 January 2008, which marked the changes in MOH guidelines to reflect 2006 WHO guidelines) to identify whether underlying temporal trends in time to ART initiation were occurring in the absence of specific changes in evidence and guidance. The third interval began 1 January 2010, after WHO issued rapid guidance that ART

should start immediately after initiation tuberculosis therapy for all patients irrespective of CD4 levels [2]. The fourth period in the analysis started 1 October 2011, when 3 trials showing that ART initiation within 2 weeks for patients with a CD4 count <50 cells/μL reduces mortality and AIDS progression were published [1, 4, 5]. During the interval of evaluation, there was no managed practice change regarding the timing of ART initiation among tuberculosis patients in the clinics included in this study.

Analysis

We compared baseline characteristics between the 2 sites using Wilcoxon rank-sum and χ^2 tests for continuous and categorical variables, respectively. We described the cumulative incidence of ART initiation after tuberculosis therapy initiation in the presence of competing risks of loss to follow-up and deaths [16, 17]. In this analysis, observation begins on the date tuberculosis therapy is initiated, and ART initiation is considered the event of interest. In Kaplan-Meier estimates, loss to follow-up or deaths before ART initiation would be censored, but this assumes that the occurrence of the outcome is unchanged by censoring events. This assumption is unlikely for those lost to follow-up and conceptually meaningless for the outcome of death. We therefore treated loss to follow-up and deaths before ART initiation as a competing risk event. We defined individuals who were lost to follow-up as not having a follow-up visit within 90 days of their last visit and not having started ART by the time of database closure. The primary predictor variable was the calendar period of initiation of tuberculosis treatment, which was specified as 4 categories to capture changes in practice associated with changes in guidance and emergence of new scientific evidence as described above. To evaluate the association of specific factors and timing of ART initiation, we used 2 analytic approaches. First, we used survival analysis and Cox proportional hazards models to estimate changes in time to an event, which is more "sensitive" to changes in practice. Second, we analyzed the outcome as a binary variable of having initiated ART or not within a certain recommended time frame. We used log-link Poisson models with robust standard error estimation instead of logistic regression to provide more interpretable risk ratios instead of odds ratios. Given the fact that the evidence for timing of ART in tuberculosis patients differed with respect to the CD4 level of patients at tuberculosis initiation, we included an interaction term between CD4 cell count (stratified as ≤50 cells/μL or >50 cells/μL) and calendar time of tuberculosis therapy initiation. For both models, variables were chosen for the multivariate analysis based on a significance level of $P < .10$ in the univariate analysis. All analyses were conducted using Stata software, version 11.2 (StataCorp, College Station, Texas).

RESULTS

We evaluated 882 ART-naive individuals who were treated for tuberculosis: 575 were from the Mulago ISS clinic and 307 were from MMC (Table 1). Among patients with a CD4 count ≤50 cells/μL at the time of tuberculosis therapy initiation, the fraction initiating ART initiation within 2 weeks was 6.9%, 15.1%, 8.8%, and 14.3% in the 4 calendar periods (Figure 1). When analyzed as the fractions starting within 4 weeks, the figures rose to 13.7%, 27.3%, 24.4%, and 85.7% (Figure 1). Among those with a CD4 count >50 cells/μL, the fraction initiating by 8 weeks was 16.4%, 12.1%, 19.7%, and 28.2% in the 4 calendar periods (Figure 1). Compared with the earliest time period, the adjusted risk ratios for starting ART among those with CD4

Table 1. Baseline Characteristics of Cohort, Stratified by Site and Combined

Demographic Variable	Mulago (n = 575)	Mbarara (n = 307)	Combined (N = 882)
Female sex, %	45.0%	38.6%	42.7%
Age at time of tuberculosis treatment initiation, median (IQR)	33 (28–39)	31 (28–38)	32 (28–39)
Baseline CD4 count at time of tuberculosis treatment initiation, cells/μL, median (IQR)	134 (46–314)	180 (56–357)	145 (50–332)
Baseline weight at time of tuberculosis treatment initiation, kg, median (IQR)	50* (45–56)	54* (49–60)	52 (46–58)
Calendar time			
Tuberculosis treatment initiation dates			
No. of individuals (%)			
Before 1 January 2008	82 (14.3)*	97 (31.6)*	179 (20.3)
1 January 2008–31 December 2009	267 (46.4)*	29 (9.5)*	296 (33.6)
1 January 2010–30 September 2011	121 (21.0)*	126 (41.0)*	247 (28.0)
On or after 1 October 2011	105 (18.3)*	55 (17.9)*	160 (18.1)

Abbreviation: IQR, interquartile range.

*P < .05.
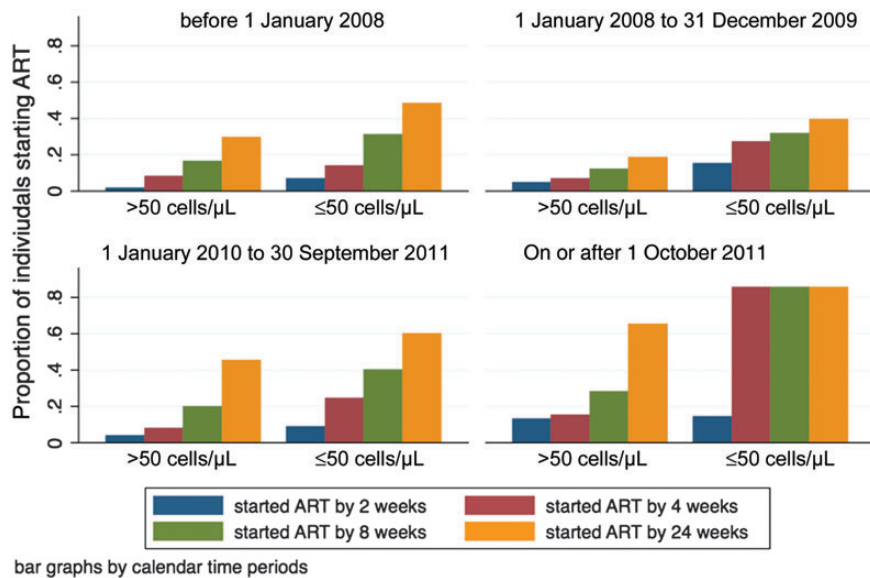
Figure 1. Bar graph depicting proportion of individuals starting antiretroviral therapy (ART) at 2, 4, 8, and 24 weeks after initiation of tuberculosis therapy.

cell counts ≤50 cells/μL in the most recent calendar period were only significant at 4 weeks (12.86 [95% confidence interval [CI], 4.27–38.7]) and 8 weeks (2.71 [95% CI, 1.43–5.14], but not at 2 weeks (3.86 [95% CI, .34–44.17]). In contrast, the adjusted risk ratio for starting ART within 8 weeks for those with CD4 cell counts >50 cells/μL was not significant (1.83 [95% CI, .93–3.60]). The only time-independent variable that was associated with a higher likelihood of starting ART at all benchmarks was baseline CD4 cell count (P < .05).

The cumulative incidence of loss to follow-up by 6 months was 28% (95% CI, 24%–31%). When stratified by calendar time periods, the rates of loss to follow-up did not differ measurably. Among patients with CD4 cell counts ≤50 cells/μL, only those in the most recent calendar period of later than 1 October 2011 had a significantly greater hazard of starting ART than the baseline calendar period, with a hazard ratio of 4.57 in the multivariate analysis (Table 2). Among those with CD4 counts >50 cells/μL, individuals had a 1.90 and 5.43 greater hazard of starting ART in the 2 most recent calendar periods compared with the baseline calendar period (Table 2 and Figure 2). Both low baseline weight and CD4 cell count were associated with earlier ART initiation (Table 2).

DISCUSSION

In our study, we assessed the diffusion of new scientific evidence and changing guidelines regarding the timing of ART initiation in patients with tuberculosis into practice in Uganda. Notably, whereas there were no differences in the uptake of
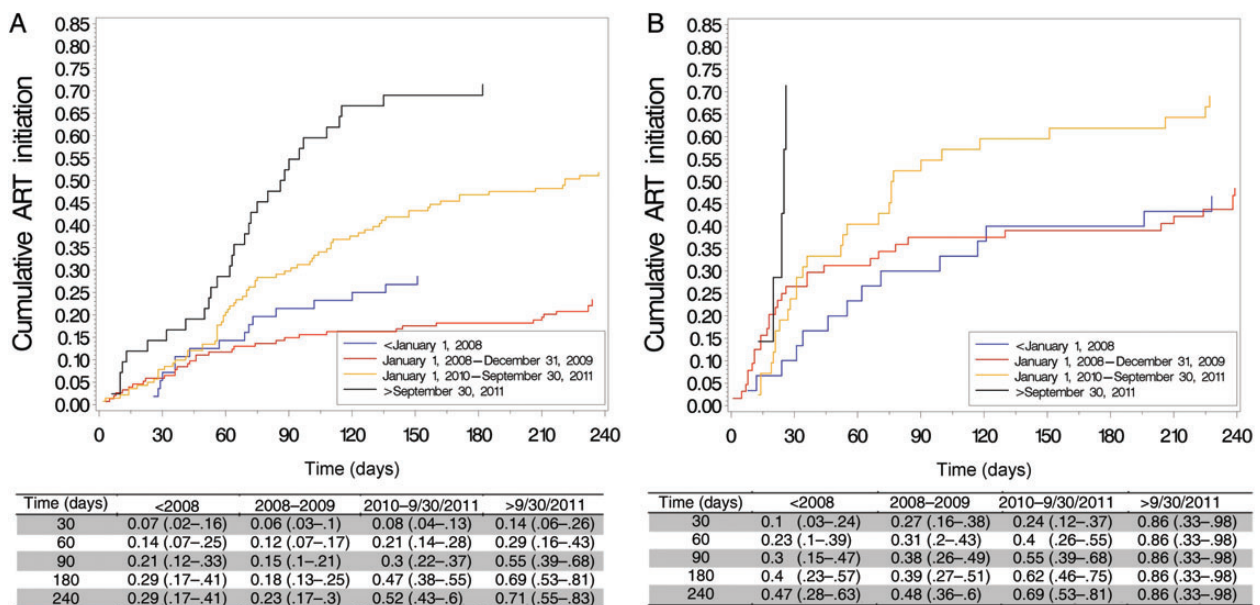
ART initiation among individuals with CD4 counts ≤50 cells/μL in the first 2 calendar periods when evidence and guidelines did not change (before 2008 and between January 2008 and January 2010), there was a marked change in the rate of ART initiation in the most recent calendar period after the publication of scientific evidence that highlighted the important of rapid ART among patients with low CD4 levels. Similarly, among patients with CD4 cell counts >50 cells/μL, ART initiation rates rose dramatically in the 2 most recent calendar time periods when changes in guidance from WHO were published. We note that during this time interval, Uganda issued guidelines in 2008 to reflect the WHO 2006 guidelines and again in 2011 to reflect the WHO 2010 guidelines. Remarkably, there were no significant changes in rates of ART uptake between the first 2 calendar intervals, which would have marked the issuance of the 2006 WHO and 2008 MOH guidelines, respectively. In addition, although there was no difference in the rate of ART change by 60 days among those with higher CD4 cell counts after 2010 (which reflects the MOH recommendations at the time), there was a significant change by 180 days (Figure 2), suggesting that both Ugandan and WHO guidelines had some influence on clinical practice. Overall, these findings suggest that the translation of evidence into practice at the front lines of the response to HIV/AIDS occurred in this program at an impressive rate through diffusion (ie, the passive changes through existing modes of communication and influence) without a specific initiative of managed practice change.

This study challenges prevailing assumption that the diffusion of changes in clinical practice in resource-limited settings

Table 2. Univariate and Multivariate Cox Proportional Hazard Models Describing Factors Associated With Rate of Antiretroviral Therapy Initiation

Factor	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age, per 10 y	1.03 (.94–1.14)	NA
Sex		
Female	Reference	
Male	1.18 (.99–1.40)	1.08 (.86–1.36)
Baseline weight, per 5 kg	0.92 (.88–.91)	0.94 (.89–1.00)
Baseline CD4 count, per 50 cells/μL	0.88 (.85–.91)	0.86 (.82–.89)
Site		
Mbarara	Reference	
Mulago	0.98 (.82–1.18)	NA
Calendar time if CD4 count >50 cells/μL		
Before 1 January 2008	Reference	Reference
1 January 2008–31 December 2009	1.11 (.81–1.51)	0.84 (.55–1.28)
1 January 2010–30 September 2011	2.21 (1.64–2.98)	1.90 (1.25–2.89)
On or after 1 October 2011	8.17 (5.88–11.36)	5.43 (3.16–9.31)
Calendar time if CD4 count ≤50 cells/μL		
Before 1 January 2008	Reference	Reference
1 January 2008–31 December 2009	0.97 (.58–1.63)	0.94 (.56–1.56)
1 January 2010–30 September 2011	1.22 (.71–2.11)	1.24 (.72–2.16)
On or after 1 October 2011	4.91 (1.90–12.70)	4.57 (1.76–11.86)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.

Time (days)	<2008	2008–2009	2010–9/30/2011	>9/30/2011
30	0.07 (.02–.16)	0.06 (.03–.1)	0.08 (.04–.13)	0.14 (.06–.26)
60	0.14 (.07–.25)	0.12 (.07–.17)	0.21 (.14–.28)	0.29 (.16–.43)
90	0.21 (.12–.33)	0.15 (.1–.21)	0.3 (.22–.37)	0.55 (.39–.68)
180	0.29 (.17–.41)	0.18 (.13–.25)	0.47 (.38–.55)	0.69 (.53–.81)
240	0.29 (.17–.41)	0.23 (.17–.3)	0.52 (.43–.6)	0.71 (.55–.83)

Time (days)	<2008	2008–2009	2010–9/30/2011	>9/30/2011
30	0.1 (.03–.24)	0.27 (.16–.38)	0.24 (.12–.37)	0.86 (.33–.98)
60	0.23 (.1–.39)	0.31 (.2–.43)	0.4 (.26–.55)	0.86 (.33–.98)
90	0.3 (.15–.47)	0.38 (.26–.49)	0.55 (.39–.68)	0.86 (.33–.98)
180	0.4 (.23–.57)	0.39 (.27–.51)	0.62 (.46–.75)	0.86 (.33–.98)
240	0.47 (.28–.63)	0.48 (.36–.6)	0.69 (.53–.81)	0.86 (.33–.98)

Figure 2. Kaplan-Meier curves depicting cumulative incidence of antiretroviral therapy initiation after initiation of therapy for tuberculosis stratified by calendar time. *A*, Individuals with CD4 counts >50 cells/μL at the time of tuberculosis therapy initiation. *B*, Individuals with CD4 counts ≤50 cells/μL at the time of tuberculosis therapy initiation. Data are shown as cumulative incidence (95% confidence interval). Abbreviation: ART, antiretroviral therapy.

is, as a rule, slower than in resource-rich settings. This may in part be explained by the simple fact that starting early ART is a relatively concrete and easy policy to adopt (in contrast to switching drug regimens in cases of treatment failure, for example). Additionally, despite the fact that most front-line health providers in Africa do not regularly attend international conferences where new data are presented and do not have easy access to journals, there may be specific features of healthcare systems in Africa that may facilitate change rapidly. First, social network scientists believe that a "radial" topology of social relationships and influence (where relationships cascade outward from several central "opinion leaders") are more conducive to change than "clustered" social networks where small groups of practitioners influence each other but in which influence across these clusters is limited [18, 19]. Studies have suggested that physicians in North America tend to form clustered cliques [20], and, anecdotally, we believe that providers in Uganda have a more radial network. In addition, regions of the world where healthcare is delivered largely by midlevel providers where practice is more standardized may accept evidence more easily than in high-resource settings where individual practitioners feel entitled to evaluate evidence—whether they do so rightly or wrongly—for themselves. Finally, Uganda has been noted to have a greater diversity of implementing partners and a heterogeneous delivery infrastructure. Whereas some speculate that this diversity leads to greater costs, it may also allow the implementing landscape to include "early adopters" of innovations.

Despite these increased rates in ART initiation, limitations remain, and this study does give credence to the emerging consensus that even in settings where diffusion is evident, dissemination (targeted and strategic knowledge transfer) and implementation (active, managed adoption into local settings) are needed for uptake to achieve acceptable levels. Specifically, in our study, the absolute fraction of patients with a CD4 level ≤50 cells/μL initiating ART within 1 month did change dramatically, but the fraction reaching the 2-week benchmark defined in some of the randomized trials did not change measurably. Also, we note that only 28% of those with CD4 cell counts >50 cells/μL started ART within the recommended time frame of 2–8 weeks in the most recent calendar period. Identifying and systematically addressing the remaining barriers is needed to complete the translation of evidence into practice. These barriers may include fears of developing immune reconstitution inflammatory syndrome; increased drug toxicity from combined tuberculosis and HIV treatment; increased pill burden, which could adversely affect adherence; and reduced efficacy of ART because of drug interactions [21, 22]. In addition, logistical challenges to rapid initiation may also be at play: patients often must return at a second visit for CD4 results, and the return visit is often 2 weeks from the first visit. At that return visit, even if ART is started immediately, the 2-week benchmark will have been missed. Additional systems-level changes, such as the implementation of point-of-care CD4 cell count testing, may enable earlier ART initiation in this subpopulation.

Our study has limitations. Given that we only focused on 1 region of the world and in a particular organization with academic affiliations and with several medical doctors on staff, our study may not be generalizable to all HIV service programs in Africa. However, by looking at both an urban and a more rural health facility, we provide a unique opportunity to see the spectrum of the management of HIV/tuberculosis coinfection in Uganda. Second, the cumulative incidence of individuals who were defined as lost to follow-up by 6 months was 28%. Our use of the competing risk models, however, is tantamount to assuming that both patients who have died and those who are lost to follow-up fail to start ART, and is therefore conservative. Third, we note that there may be other secular trends that might account for these changes in the rates of ART initiation, including greater patient acceptability, availability of ART, and overall comfort of the clinic staff in starting ART. However, given that there were no significant changes in the rate in the first 4 years of observation (2006–2010), we speculate that by and large, changes in recommendations and emerging data played a far more central role. Finally, the use of a clinic-based database also prevented us from inferring possible explanations for delayed ART initiation. Further research is needed to identify whether delays in the recent era were due to patient, context, or facility. Examples include personal health beliefs about starting ART, food insecurity and poverty, transportation difficulties, stigma, lack of service integration, or lack of social support [7–9, 23, 24].

In summary, we found that at 2 ART delivery clinics in Uganda, rapid diffusion of scientific evidence into clinical practice is occurring at the front lines of the response to HIV/AIDS. Although change was rapid, the fraction of patients who start within benchmarks defined by randomized trials of within 2 weeks of tuberculosis therapy initiation for patients with a CD4 count ≤50 cells/μL and within 8 weeks for all other patients remains suboptimal. Additional studies using quantitative and qualitative methods must be done to specifically address the specific provider, patient, and structural barriers to ART initiation among individuals with HIV-associated tuberculosis, in an effort to develop novel strategies to further close this gap between evidence, policy, and clinical practice.

Notes

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