Time to Initiation of Antiretroviral Therapy Among Patients With HIV-Associated Tuberculosis in Cape Town, South Africa

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Abstract: We studied the time interval between starting tuberculosis treatment and commencing antiretroviral treatment (ART) in HIV-infected patients (n = 1433; median CD4 count 71 cells per microliter, interquartile range: 32–132) attending 3 South African township ART services between 2002 and 2008. The overall median delay was 2.66 months (interquartile range: 1.58–4.17). In adjusted analyses, delays varied between treatment sites but were shorter for patients with lower CD4 counts and those treated in more recent calendar years. During the most recent period (2007–2008), 4.7%, 19.7%, and 51.1% of patients started ART within 2, 4, and 8 weeks of tuberculosis treatment, respectively. Operational barriers must be tackled to permit further acceleration of ART initiation as recommended by 2010 WHO ART guidelines.

Key Words: Africa, antiretroviral, delay, timing, tuberculosis

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INTRODUCTION

The high mortality risk of patients with HIV-associated tuberculosis (TB) is reduced by 64%–95% by antiretroviral therapy (ART).[1] However, the optimal time to start ART during TB treatment has for a long time remained unclear. Findings from observational studies and recent randomized controlled trials have demonstrated that delayed ART initiation is associated with increased mortality risk across a wide spectrum of baseline CD4 cell counts.[2–6] The World Health Organization (WHO) has updated ART guidelines on several occasions between 2002 and 2010, recommending progressively higher CD4 cell count thresholds for ART eligibility and more rapid initiation of ART during TB treatment.[7] Guidelines published in 2010 recommend ART be given to all patients with HIV-associated TB regardless of CD4 cell count and that this be started as soon as possible after TB treatment is tolerated and not later than 8 weeks.[7]

The operational feasibility of early initiation of ART in TB patients under routine program conditions in resource-limited settings is not known, however. The timing of ART may be influenced by many factors, including delays associated with HIV testing and CD4 cell count measurement, constraints within the health system that contribute to delays in referral and access to ART clinics, and changes in programmatic efficiency and clinical expertise over time. In this study, we quantified and explored factors associated with delays between starting TB treatment and starting ART among TB patients enrolling in 3 large community-based ART services in townships in South Africa.

METHODS

Antiretroviral Treatment Cohorts

Provision of ART within 3 primary care clinics in the townships of Khayelitsha, Gugulethu, and Masiphumelele in Cape Town, South Africa, started between 2001 and 2003.[8–13] ART was provided free of charge under the South African national guidelines for patients with WHO stage 4 disease and all those with blood CD4 cell counts <200 cells per microliter.[14] The huge burden and complications of TB in these services has been previously reported.[9,15–17] TB treatment and ART in South Africa are typically delivered by

separate primary care clinics.[16] TB was treated using standardized rifampicin-based regimens of 6 months duration for new TB cases and 8 months for retreatment cases. The total treatment period, however, was longer for those with treatment interruptions or drug-resistant disease.

Data Sources

Each of the clinics participates in the International epidemiological Databases to Evaluate AIDS in Southern Africa network (www.iedea-sa.org). Prospective clinical databases have been maintained for all patients enrolling in these services.[9,11,12] All sites obtained ethical approval from relevant local institutions before contributing anonymized patient data collected between 2002 and 2008 to this collaborative analysis. Data were included from patients aged older than 18 years who had a notified diagnosis of TB, initiated ART for the first time during the course of TB treatment, and were followed up for a minimum period of 10 months from TB diagnosis during which ART could be started. For each patient, demographic details, TB classification, WHO clinical stage, blood CD4 cell counts, and dates of TB diagnosis and ART initiation were recorded. Where details of TB diagnoses were missing, these were sought from clinic TB registers and the Cape Town electronic TB register.

Statistical Analyses

Patient characteristics were summarized by calendar period of starting TB treatment. Data were aggregated into 4 sequential calendar periods, 2002–2004, 2005, 2006, and 2007–2008, such that there were at least 200 patients represented in each period. The time from start of TB treatment to start of ART was the outcome of primary interest.

Accelerated failure time (AFT) models were used to determine crude and adjusted associations between hypothesized risk factors and time to initiation of ART. The AFT metric was chosen because of its specific reference to time and impact on time and because the proportional hazards assumption was not satisfied by the data. The Weibull, generalized gamma, log-logistic, lognormal, and exponential AFT models were each considered. The gamma model had the lowest values for the Akaike Information Criteria and Bayesian Information Criteria. The Wald test on the 2-shape parameters confirmed that none of the simpler distributions were appropriate. The gamma model had the best model fit based on a graph plotting the Cox-Snell residuals against the cumulative hazard of time. The coefficients of the generalized gamma AFT model were transformed to acceleration coefficients by taking the exponent of the negative coefficient. These acceleration coefficients measure the relative acceleration (and associated shortening of time) to ART initiation.

RESULTS

Patient Characteristics

During the analysis period, 1433 patients who started ART during TB treatment were eligible for inclusion. Patients were adults with a median age of 33 years [interquartile range (IQR): 29–39] and 60% were women. Sixty one per cent were recorded as having pulmonary disease alone, and 39% had extrapulmonary disease with or without concomitant pulmonary involvement. Treatment for recurrent TB was received by 29% of patients. CD4 counts were available for 1152 (80.4%) patients with a median of 71 cells per microliter (IQR: 32–132). When stratified by calendar period, patient characteristics did not vary substantially (see **Table, Supplemental Digital Content 1,** http://links.lww.com/QAI/A157) although the proportion of patients who were male tended to increase over time and the proportion of patients receiving a retreatment TB regimen decreased over time.

Time to Initiation of ART

The time between starting TB treatment and starting ART was highly variable with a median of 2.66 months (IQR: 1.58–4.17). Using AFT models (Table 1), crude analyses showed that delays were shorter among younger patients, those with a first episode of TB, sputum smear-positive disease, lower CD4 cell counts, and treatment in later calendar periods. However, in fully adjusted models, only 3 variables remained significantly associated with time to ART as follows: the blood CD4 cell count, calendar year, and the treatment site (Table 1).

The longest predicted delays between start of TB treatment and ART initiation were among those with blood CD4 cell counts of ≥200 cells per microliter who started TB treatment during the calendar period 2002–2004 at site 2; the average time was 4.73 months (95% confidence interval: 4.12 to 5.33). Time to ART initiation was significantly accelerated among those with lower CD4 counts (Fig. 1A). In patients with CD4 counts of 100–199, 50–99, and <50 cells per microliter, time to starting ART was accelerated by 20%, 34%, and 75%, respectively (Table 1), giving mean times of 3.95, 3.53, and 2.77 months. Similarly, mean times were accelerated among patients treated in calendar periods 2005, 2006, and 2007–2008 by 8%, 22%, and 39%, respectively, giving mean times of 4.36, 3.87, and 3.41 months (Fig. 1B). Considerable heterogeneity in time to ART start was also observed between the 3 different treatment sites (Fig. 1C), although the associations with CD4 cell count and calendar period were observed at all 3 sites. The shortest predicted delays between start of TB treatment and ART initiation were among those with a blood CD4 cell count of <50 cells per microliter who started TB treatment during the calendar period 2007–2008 at site 3; the average time was 1.28 months (95% confidence interval: 1.15 to 1.42).

Comparison With 2010 WHO Guidelines

WHO ART guidelines (2010 revision) recommend that ART should be started as soon as possible within 2–8 weeks of starting TB treatment, regardless of CD4 cell count. We examined the timing of ART among patients treated in the most recent calendar period, 2007–2008. The proportions starting ART within 2, 4, 6, and 8 weeks of TB treatment were 4.7% (n = 11), 19.7% (n = 46), 35.6% (n = 83), and 51.1% (n = 119), respectively. For those with the most advanced immunodeficiency (CD4 count less than 50 cells/μL) treated in this period, the corresponding percentages were 6.2% (n = 5), 33.3% (n = 27), 61.7% (n = 50), and 77.8% (n = 63).

TABLE 1. Crude and Adjusted Analyses Showing Factors Associated With Time to Starting Antiretroviral Therapy (ART) Among Patients With HIV-associated Tuberculosis (TB).

	Crude Accelerators	95% CI	*P**	Adjusted Accelerators	95% CI	*P**
Age category at start of TB treatment			0.008			
≥40 (baseline)	1	—	—	—	—	—
25–39	1.12	1.04 to 1.21	0.003	—	—	—
18–24	1.15	1.02 to 1.30	0.022	—	—	—
Gender						
Male	1	—	—	—	—	—
Female (baseline)	1.01	0.94 to 1.07	0.879	—	—	—
Clinic			<0.001			<0.001
2 (baseline)	1	—	—	1	—	—
1	1.08	1.00 to 1.15	0.046	1.39	1.29 to 1.48	<0.001
3	1.34	1.21 to 1.48	<0.001	1.56	1.42 to 1.71	<0.001
Year started TB treatment			<0.001			<0.001
2002–2004 (baseline)	1	—	—	1	—	—
2005	1.08	0.98 to 1.18	0.111	1.08	0.99 to 1.19	0.079
2006	1.34	1.23 to 1.46	<0.001	1.22	1.12 to 1.33	<0.001
2007–008	1.83	1.65 to 2.03	<0.001	1.39	1.25 to 1.54	<0.001
CD4 count categories (cells/μL)†			<0.001			<0.001
≥200 (baseline)	1	—	—	1	—	—
100–199	1.16	1.03 to 1.32	0.017	1.20	1.07 to 1.34	0.002
50–99	1.29	1.14 to 1.47	<0.001	1.34	1.19 to 1.50	<0.001
0–49	1.70	1.49 to 1.94	<0.001	1.75	1.55 to 1.98	<0.001
Classification of TB						
Retreatment (baseline)	1	—	—	—	—	—
New TB case	1.11	1.03 to 1.19	0.004	—	—	—
Type of TB			0.018			
Smear-negative pulmonary TB (baseline)	1	—	—	—	—	—
Extrapulmonary TB	1.05	0.97 to 1.13	0.262	—	—	—
Smear-positive pulmonary TB	1.12	1.04 to 1.22	0.005	—	—	—

Shape parameters of multivariate gamma model: kappa = 0.7 (95% CI: 0.57 to 0.84); sigma = 0.42 (95% CI: 0.39 to 0.45) for all strata other than CD4 count less than 50 cells per microliter (sigma = 0.59, 95% CI:0.50 to 0.69) and clinic 1 (sigma = 0.51, 95% CI: 0.44 to 0.60).

*The *P* value in line with the heading of each variable with more than 2 categories was calculated using the Wald Test.

†CD4 count taken closest start of TB treatment that satisfied criteria of being taken not earlier than 183 days before or 91 days after start of TB treatment and not more than 7 days after start of ART.

CI, confidence interval.

DISCUSSION

The use of ART must be carefully optimized to maximize the benefit for patients with HIV-associated TB. This study found that the time interval between starting TB treatment and starting ART among patients treated under routine program conditions was prolonged but highly variable and strongly associated with 3 key factors. Delays varied between different clinics but were shorter for those with lower CD4 counts and for those treated in more recent calendar periods. However, delays must be reduced much further as recommended by current WHO guidelines.

The numbers of patients referred to ART clinics with a TB diagnosis has increased over time such that these comprised over one-third of all referrals to ART services in Cape Town by 2008.[9,16] In addition, intensive TB screening just before ART initiation has found that up to 25% of other referrals also have sputum culture-positive TB.[18,19] These patients typically have low CD4 counts and high mortality risk. Data from a randomized controlled trial conducted in Cambodia (the CAMELIA trial)[5] found that TB patients with advanced immunodeficiency (median CD4 cell count, 25 cells per microliter) had 34% higher greater mortality if they received ART after 2 months of TB treatment rather than starting ART within the first 2 weeks, showing the need for rapid initiation in this group.[5]

Overall, we found a strong graded relationship between CD4 count and timing of ART with progressively more rapid ART initiation among those in lower CD4 count strata. These data may reflect growing clinical expertise and recognition of the need for greater rapidity of ART among those with advanced immunodeficiency.[10,15] However, despite local and international guidelines, only one-third of patients with CD4 counts of <50 cells per microliter treated in 2007–2008 received ART within the first 1 month of TB treatment, which may suggest the existence of constraints within the care pathway (such as referral delays between TB and ART clinics)[16] to achieving more rapid ART initiation.

Delays in initiation of ART diminished substantially between sequential calendar periods and this may reflect growing awareness over time of the high mortality risk associated with

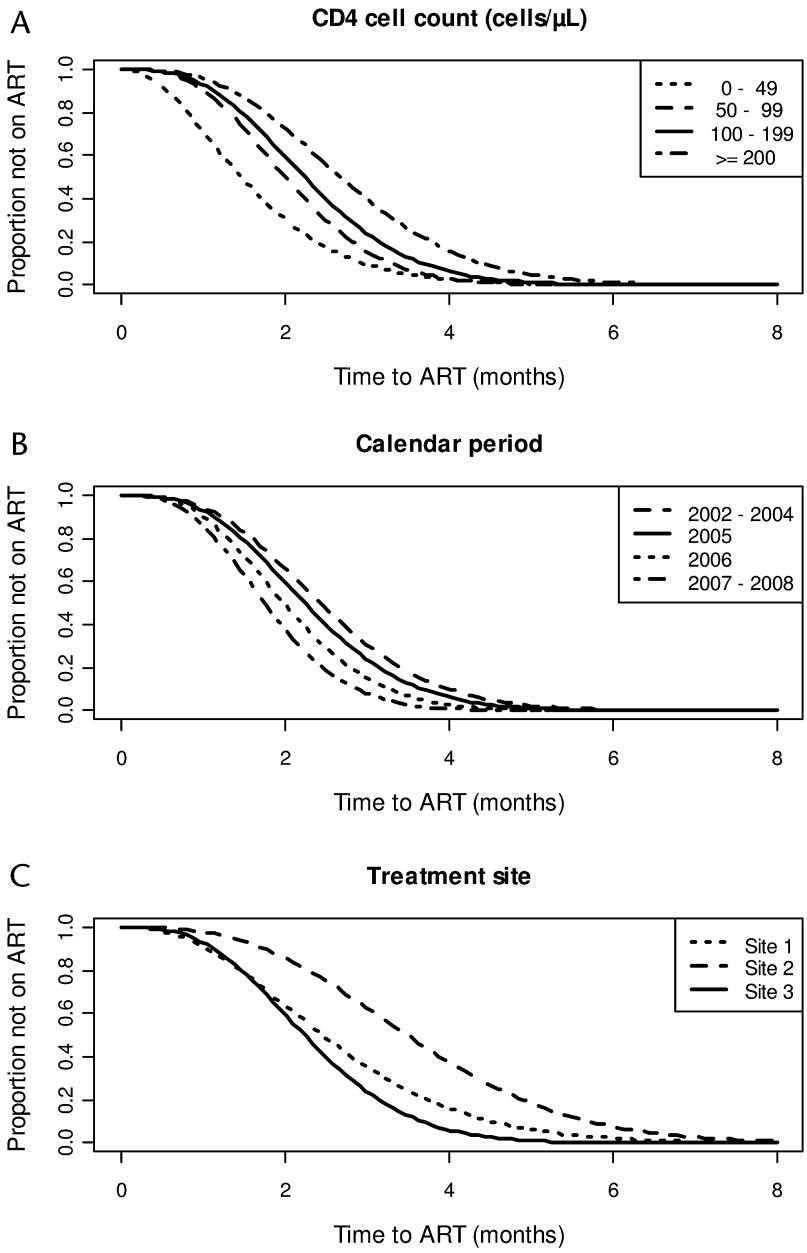

FIGURE 1. Gamma survival curves showing the proportion of patients who have yet to start ART (survival) with increasing duration of TB treatment (analysis time in months). Data are adjusted for other covariates shown in Table 1 with the reference group in each plot representing patients with CD4 cell counts in the range 100–199 cells per microliter cared for at treatment site 3 in 2005. Data are shown stratified by the following: A, blood CD4 cell count; B, calendar year of starting treatment; and C, treatment site.

delays in ART[10] and more efficient HIV testing procedures. After 2005, a traditional model of voluntary counselling and testing for HIV with very poor uptake was replaced by a model of provider-initiated testing and counselling, which has achieved testing rates of more than 90% in local TB clinics.[16] Provider-initiated testing and counselling is likely to have resulted in increases in the numbers of TB patients referred for ART and the rapidity with which this is done.

There were differences in the timing of ART among patients attending the three separate treatment sites that were independent of other variables. This may reflect differences in referral processes and patient accessibility to ART services or differences in the clinical decision making process. Further operational research studies are needed to better characterize the various component delays associated with different models of care. In particular, as individual sites move toward integration of TB treatment and provision of ART, the impact on timing of ART should be investigated and timing might be used as an indicator the quality of care.

The 2010 WHO ART guidelines and South African national ART guidelines recommend ART be started as soon as TB treatment is tolerated and not later than after 8 weeks.[20] However, in the most recent calendar period (2007–2008), only 1 half of patients started ART within an 8-week time frame. Much progress now needs to be made in identifying the operational barriers to more rapid ART initiation. Integration of TB care and ART in the same clinic would be likely to decrease these delays. However, this may also be associated

with increased risks of TB immune reconstitution disease,[5,17,21] which will require appropriate management, and nosocomial TB transmission,[22] which require improved infection control measures.

Strengths of this study include the large number of patients analyzed; the patient populations attending primary care ART cohorts were typical of public sector ART clinics in the southern African region; careful prospective recording of patient data, and inclusion of patients enrolled over a 7-year period permitting analysis of temporal trends. Weaknesses of the study include the retrospective study design and lack of identification of the constituent delays contributing to the overall delay in starting ART. The clinical consequences of delays in ART initiation have not been demonstrated and patients who died or were lost to follow-up before initiating ART have not been quantified. Further operational research is needed to study the impact of interventions to accelerate ART access and the time to starting ART should be prospectively monitored within programs.

In conclusion, the timing of ART among TB patients attending 3 large ART services in townships around Cape Town was very heterogeneous. However, delays decreased substantially over a 7-year period and those with lower CD4 cell counts received ART more rapidly. New WHO ART guidelines and national ART guidelines now recommend much greater acceleration of ART initiation among all TB patients, which is likely to require models of care with much better integration of TB and ART treatment.

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