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Prognostic significance of the intervals between the initiation of antiretroviral therapy and anti-tuberculosis treatment in HIV-tuberculosis co-infected patients: Results from the TREAT Asia HIV Observational Database

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Abstract

Objectives—We evaluated the effect of time intervals between the initiation of antiretroviral therapy (ART) and tuberculosis (TB) treatment on clinical outcomes in HIV-TB co-infected patients in an Asian regional cohort.

Methods—Adult HIV-TB co-infected patients in an observational HIV cohort database who had a known date of ART initiation and history of TB treatment were eligible for study inclusion. The time intervals between the initiation of ART and TB treatment were categorized as follows: TB diagnosed while on ART, early ART (<90 days after TB treatment), delayed ART (>90 days after TB treatment), and ART not started. Outcomes were assessed using survival analyses.

Results—A total of 768 HIV-TB co-infected patients were included in this study. Median CD4 T-cell count at TB diagnosis was 100 (IQR 40–208) cells/μL. The treatment outcomes between early ART and delayed ART initiation were not significantly different. Kaplan-Meier analysis indicated that mortality was highest for those diagnosed with TB while on ART (3.77 deaths per

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100 person-years), and the prognoses of other groups were not different (in deaths per 100 person-years: 2.12 early ART, 1.46 delayed ART, and 2.94 ART not started). In a multivariate model, the interval between ART initiation and TB therapy did not significantly impact all-cause mortality.

Conclusions—The negative impact of delayed ART in patients co-infected with TB was not observed in this observational cohort of moderately to severely immunosuppressed patients. The broader impact of earlier ART in actual clinical practice should be monitored more closely.

Keywords

HIV; tuberculosis; antiretroviral therapy; antitubercular agents

Introduction

Tuberculosis (TB) is the most common opportunistic disease and cause of death in patients with HIV infection in developing countries (1). The two diseases are closely intertwined, and the number of co-infected patients continues to rapidly grow (2). The optimal time to begin antiretroviral therapy (ART) in patients with both TB and HIV has been carefully studied. Immune reconstitution inflammatory syndrome (IRIS), pharmacological interactions, and high pill burden have previously argued against a simultaneous therapy for both HIV and TB (3–6). In contrast, a delay in starting ART, specifically in severely immunosuppressed patients, is associated with disease progression and higher mortality (7, 8).

Previous World Health Organization (WHO) guidelines recommended that ART should be started between two and eight weeks after the start of TB therapy in persons with CD4 T-cell counts below 200 cells/μL, but the commencement of ART may be delayed for patients with CD4 T-cell counts above 200 cells/μL (9). Prospective studies have evaluated the optimal time for initiating ART in HIV/TB-coinfected persons (4), including randomized clinical trials in South Africa (SAPiT), Cambodia (CAMELIA), and global regions (STRIDE) (4, 10, 11). Both studies demonstrated a mortality reduction among those starting ART during the early part of TB therapy compared to those who started later or after completion of TB therapy. Current WHO guidelines now recommend that ART be initiated as soon as TB therapy is tolerated, ideally as early as two weeks and not later than eight weeks, regardless of CD4 T-cell counts (9). However, it is not clear how ART timing in TB co-infected patients impacts clinical outcomes in “real-life,” non-trial settings. Another issue is the risk of starting ART in a patient with underlying but quiescent TB, which may lead to unmasking of TB disease and IRIS in the absence of anti-TB treatment.

The objective of this analysis was to evaluate the effects of the time interval between the initiation of ART and TB treatment on clinical outcomes in a regional observational cohort of HIV-TB co-infected Asian patients.

Methods

Study population

We analysed data from the TREAT Asia HIV Observational Database (TAHOD), a prospective, observational cohort study of adults with HIV from 18 sites in the Asia-Pacific region (12). The structure of the database and standardized mechanisms for data collection and quality control have previously been described (12). Additional TB-related variables, such as diagnostic site of TB, diagnostic methods, TB treatment, mycobacterial resistance, and treatment outcomes were retrospectively collected for this analysis using a standardized form. All co-infected patients in TAHOD whose dates of TB diagnosis, TB therapy

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initiation, and ART initiation were known, and were aged 18 years or older at TB diagnosis were eligible for inclusion in this analysis.

Variables and definitions

The following variables were assessed: age at TB diagnosis; sex; reported route of HIV infection; prior AIDS diagnoses before TB; hepatitis B or C co-infection; HIV and TB treatment regimens, dates of starting and stopping, adverse events, and outcomes; CD4 T-cell count (cells/μL) and HIV viral load (copies/mL); development of IRIS. The most advanced US Centers for Disease Control and Prevention (CDC) clinical category recorded was used as the clinical status for the analysis (13). TB treatment outcomes were defined according to WHO TB reporting forms (14). A patient who was initially culture- or smear microscopy-positive at the beginning of TB treatment but who was smear-negative in the last month of treatment and on at least one previous occasion was considered as 'cured.' 'Treatment failure' was defined as i) a patient who is culture- or smear-positive at five months or later during initial TB treatment, or who is switched to a regimen including second-line TB drugs because of culture results showing multidrug-resistant (MDR)-TB, or ii) a previously-treated patient who is culture- or smear-positive at the end of a re-treatment regimen or who is switched to a regimen including second-line TB drugs because of culture results showing MDR-TB. A patient who completed treatment but did not meet criteria to be classified as 'cured' or a 'treatment failure' was considered as 'treatment completed.' 'Died' meant a patient who died from any cause during the course of TB treatment. A patient was considered as having 'defauIted' if TB treatment was interrupted for two or more consecutive months. A patient was considered as 'transferred out' if transferred to another health facility and the TB treatment outcome was not known. Immunological response (IR) at 12 months after ART initiation was defined as a rise in CD4 T-cell count of at least 100 cells/μL. The severity of adverse events of TB therapy was determined by a modified WHO toxicity grading scale (15). IRIS was diagnosed by the consensus case definitions of the International Network for the Study of HIV-associated IRIS (16). The exposures of interest were the time intervals between TB therapy and ART initiation, categorized into four groups according to the date of TB therapy and ART initiation, including: TB diagnosed while on ART, early ART (ART initiated within 90 days after TB therapy), delayed ART (ART initiated later than 90 days after TB therapy), and ART not started. Death was confirmed by local medical staff and reported using standardized Cause of Death (CoDe) forms. AIDS-defining illnesses were defined according to the modified 1993 CDC definitions (13).

Data analysis

Demographic and clinical characteristics were compared between patients in the four groups. All-cause mortality following TB diagnosis was examined using survival analysis methods. The survivor function for death of each group was compared using the Kaplan-Meier curve and the Cox proportional hazards model. For overall survival, time was calculated from the initiation of TB diagnosis and ended at the time of death, or the last follow-up visit. The final multivariate model included all covariates that remained significant at the 0.10 level (2-sided). All analyses were performed using SAS (version 9.1, SAS Institute Inc., Cary, North Carolina, USA) and STATA (version 10.1, StataCorp, College Station, Texas, USA).

Results

Demographic and clinical characteristics of subjects

A total of 768 HIV-TB co-infected patients were included in the analysis, including those diagnosed with TB while on ART (N=191), early ART (N=238), delayed ART (N=280), and not started on ART during the scope of the data collection (N=59). Durations between

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the initiation of ART and TB therapy varied (Table 1). Overall, 609 (79%) were male, with a median age of 34 years [interquartile range (IQR) 29–39], a median CD4 T-cell count at TB diagnosis of 100 (IQR 40–208) cells/μL, and a median HIV viral load of 81,650 (IQR 499–330,000) copies/mL (Table 2). The most common HIV exposure category was heterosexual contact (69%), followed by injection drug use (16%). The majority of patients had no prior AIDS-related illness reported (86%). NNRTI-based first-line regimens were prescribed to 615 (80%) patients and PI-based regimens to 39 (5%) patients. TB cases included pulmonary (42%), extrapulmonary (23%), and both (10%). In 25% of cases, the site of TB infection could not be identified. Age, sex, and reported route of infection were not different among the four groups (Table 2). The rate of prior AIDS diagnosis at TB diagnosis was highest in the group diagnosed while already on ART (29%), followed by the early ART group (13%). The CD4 T cell counts at TB diagnosis were highest in the group that had not yet started ART, followed by the group with TB diagnosed while on ART, the delayed ART group, and the early ART group.

TB treatment outcomes

Within the TB treatment outcomes categories, 240 (31%) individuals were considered cured, 435 (57%) completed treatment, 3 (0.4%) were treatment failures, 21 (3%) died, 29 (4%) defaulted, and 9 (1%) transferred out (Table 3). Overall survival was 91% during the follow-up period, with the highest death rate per 100 person-years in the group diagnosed with TB while on ART (3.77/100 person-years), followed by the group not started on ART (2.94/100 person-years), the early ART group (2.12/100 person-years), and then the delayed ART group (1.46/100 person-years). The incidence of new AIDS-defining illnesses excluding TB was highest in the group not started on ART (13.66/100 person-years), followed by the group diagnosed with TB while on ART (5.06/100 person-years), the early ART group (4.24/100 person-years), and then the delayed ART group (2.91/100 person-years). The rate of favorable outcomes (i.e., cured or treatment completed) was lowest in the group not started on ART. IRIS was most common in the early ART group.

Effects of time intervals between the initiation of ART and TB treatment on overall survival

We evaluated the prognostic significance of the time intervals between the initiation of ART and TB therapy in Cox proportional hazards analysis of all-cause mortality (Table 4). There were 70 deaths reported during 2973 person-years of follow-up [an incidence of 2.35 per 100 person-years, 95% confidence interval (CI) 1.86–2.98]. Patients with early ART or delayed ART had a lower risk of mortality than those in the group with TB diagnosed while on ART ($p<0.01$). However, the difference between early ART and delayed ART was not significantly different ($p=0.46$). In the multivariate model, injection drug users were at significantly higher risk of death compared with other HIV exposure risks (adjusted hazard ratio=1.96, 95% CI 1.05–3.66, $p=0.035$). The interval between the initiation of ART and TB therapy did not have a significant impact on all-cause mortality in the multivariate model. The Kaplan-Meier curve summarizing time to death indicated that mortality was highest for the group diagnosed with TB while on ART; the prognoses of other groups were not significantly different (Fig. 1).

Discussion

TB is highly prevalent in Asia, accounting for 55% of all global cases in 2008 (16). Our group previously reported TB to be the most common AIDS-defining diagnosis (45%) in TAHOD patients, and that survival after TB was 50% lower than that of patients without an AIDS-defining illness (17). Clinical trial data have shown that the optimal time to begin ART in HIV-TB co-infected patients is earlier than has previously been recommended (10, 18). The CAMELIA trial in Cambodia showed that early ART (within two weeks) improved

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survival in patients with CD4 T-cell counts lower than 50 cells/μL (18). These results were confirmed by two additional trials: the global STRIDE study and the South African SAPiT trial (11, 19). In these trials, early or immediate ART was also associated with an increased risk of IRIS, but did not result in poorer overall survival. Although the risk-benefit balance of earlier initiation of ART after initiation of TB treatment is not clear for patients with higher CD4 T-cell counts, WHO changed TB-HIV management guidelines on the basis of these robust results.

Our observational study showed that the treatment outcomes and overall mortality of patients with TB initiated on early ART did not significantly differ from those with delayed ART. The lower overall mortality rate in our cohort of 2.35 per 100 person-years and different end points may be possible reasons why we could not see a difference between the groups. Specifically, the rates of death in the CAMELIA trial were 8.28 per 100 person-years in the early ART group, and 13.77 per 100 person-years in the delayed ART group (18). The primary composite end point of the global STRIDE study was new AIDS-defining illness or death, and they proved the benefit of early ART group among patients with CD4 T-cell counts less than 50 cells/μL (11). Due to the small numbers of cases in our cohort within the multiple treatment categories and CD4 strata, we did not perform subgroup analyses breaking down the CD4 T-cell count categories.

Patient data for our study were collected before regional HIV-TB treatment recommendations were changed and reflect how TB management was practically implemented for patients with moderate to severely suppressed immune systems. To our knowledge, this study is the first in our region to compare clinical outcomes of non-trial patients who were diagnosed with TB after ART initiation to those who had TB prior to ART initiation. Interestingly, our data showed that those diagnosed with TB while on ART may have a poorer prognosis than those who had TB prior to ART initiation. High incidence rates of TB have been reported shortly after ART initiation both in developed countries and in resource-limited settings (20). Among 191 individuals who developed TB while on ART in our cohort, 108 (56%) had TB treatment within one year after initiating ART. Incident TB during ART can arise because of residual immunodeficiency, and some cases of previously subclinical disease may manifest because of restoration of TB antigen-specific immune responses. A subset of these cases may have inflammatory symptoms consistent with IRIS (21). While the use of ART decreases the risk of developing TB by 70–90% (22–24), our data reinforce the importance of latent TB screening and treatment and the recommendation to carefully exclude TB prior to ART initiation to avoid unmasking TB and its associated morbidity and mortality (25–27).

It is unclear why patients diagnosed with TB while on ART had a poorer prognosis compared to the other groups with ART after TB treatment. The patients who started ART before TB diagnosis were more likely to have prior AIDS diagnoses, suggesting that they could have had a history of greater immunodeficiency compared to those who started ART after TB diagnosis. Some of those who had previously initiated ART also had first-line ART failure at the time of TB diagnosis, which could result in poorer outcomes than ART-naïve patients starting on a suppressive antiretroviral regimen. TB as unmasking IRIS may have worse prognosis than TB without IRIS or TB with paradoxical IRIS.

The study's limitations include the observational nature of the data, and the retrospective collection of some of the TB-related variables. Another issue is generalizability to other clinical centers in the region. TAHOD participating sites are generally urban referral centers, and patients are enrolled who are considered likely to remain in long-term follow-up. The site and patient selection criteria consequently prevent broad generalizations, but also offer the opportunity to gather reliable longitudinal data in a non-trial setting. Furthermore, only

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40% of TB cases were microbiologically diagnosed, and testing for TB drug susceptibility was not a consistent practice. We arbitrarily defined early ART with a cut-off of 90 days, although previous reports have used different cut-offs such as 14 or 60 days. However, when we compared the outcomes between 60 days and 90 days, the results were similar with regards to the hazard ratios for death (data not shown).

In summary, our data demonstrate that treatment outcomes and overall mortality of HIV-TB co-infected patients who started ART within 90 days of TB treatment did not differ from those of started ART later in this observational cohort of moderately to severely immunosuppressed patients. In addition, overall mortality was highest among patients who were diagnosed with TB while on ART. TB screening efforts prior to ART initiation should be reinforced in HIV care settings in the region. As revised guidelines to initiate ART earlier for co-infected patients are more widely implemented, further studies will be needed to evaluate the broader clinical impact of early ART initiation for patients with TB in Asia.

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Appendix 1

The TREAT Asia HIV Observational Database (TAHOD)

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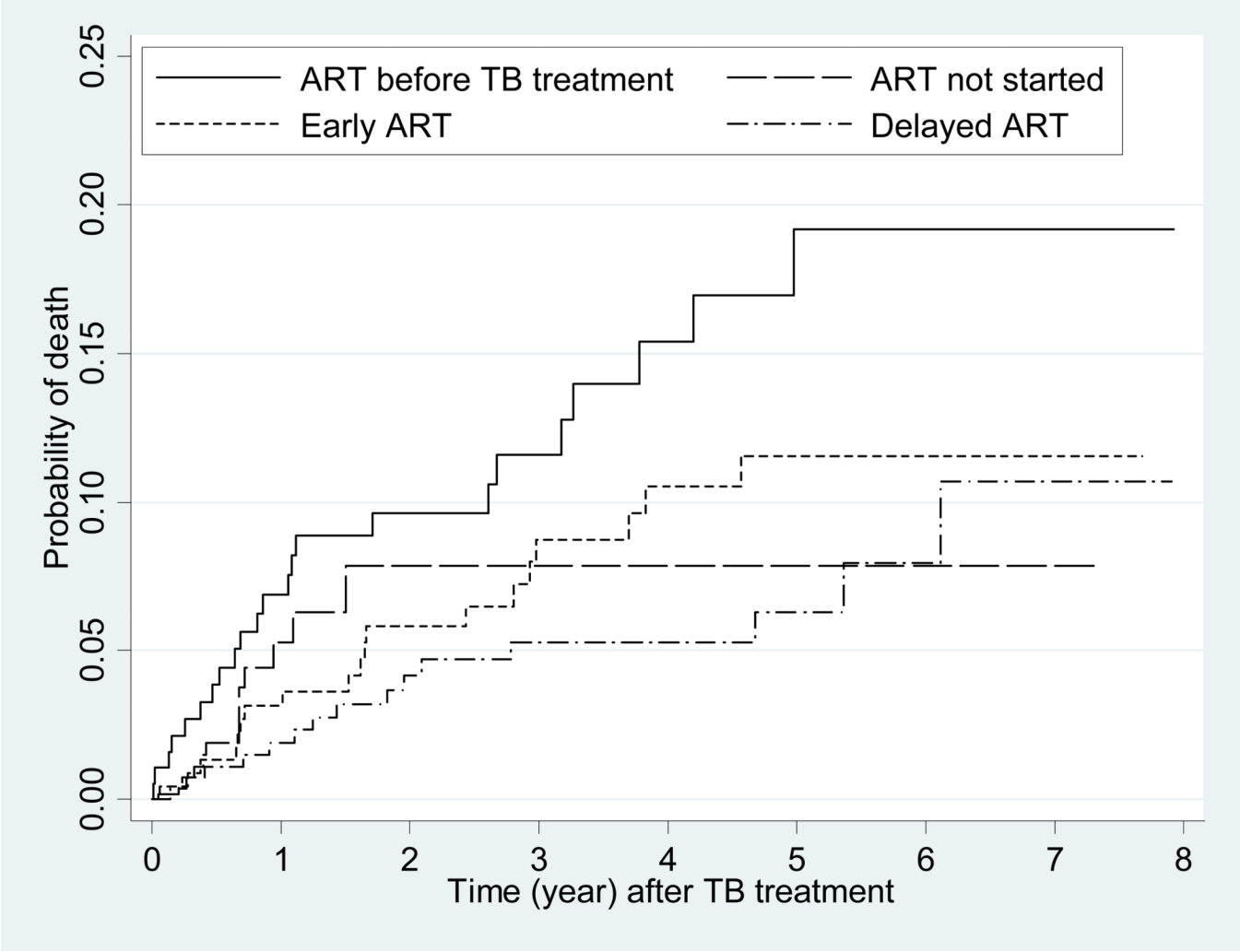

Fig. 1.
Time to death based on intervals between the initiation of antiretroviral therapy (ART) and tuberculosis (TB) treatment.

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Table 1

Time intervals between the initiation of ART and TB treatment among HIV-TB co-infected patients (N=768)

Duration between the initiation of ART and TB treatment (days)	N (%)
ART after TB treatment	518 (67%)
>365	79 (10%)
181–365	90 (12%)
91–180	110 (14%)
61–90	71 (9%)
31–60	76 (10%)
15–30	41 (5%)
0–14	51 (7%)
ART before TB treatment	191 (25%)
>365	83 (11%)
181–365	17 (2%)
91–180	24 (3%)
61–90	14 (2%)
31–60	20 (3%)
15–30	11 (1%)
0–14	21 (3%)
ART was not started	59 (8%)

ART, antiretroviral therapy; TB, tuberculosis

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Table 2

Characteristics of patients with HIV-TB co-infection, by ART initiation category

Characteristic	Total N=768	TB diagnosed while on ART N=191	Early ART N=238	Delayed ART N=280	ART not started N=59
Age at TB diagnosis, median years (IQR)	34 (29, 39)	35 (30, 41)	33.5 (29, 39)	33 (29, 38.5)	32 (30, 37)
Sex, male	609 (79%)	149 (78%)	206 (86%)	207 (74%)	47 (80%)
Reported exposure route of HIV infection					
Heterosexual contact	530 (69%)	129 (68%)	163 (68%)	197 (70%)	41 (69%)
Homosexual contact	67 (9%)	27 (14%)	18 (8%)	18 (7%)	4 (7%)
Injecting drug use	128 (16%)	24 (12%)	43 (18%)	51 (18%)	10 (17%)
Other/unknown	43 (6%)	11 (6%)	14 (6%)	14 (5%)	4 (7%)
Prior AIDS-defining diagnosis at TB diagnosis					
No	662 (86%)	136 (71%)	208 (87%)	263 (94%)	55 (93%)
Yes	106 (14%)	55 (29%)	30 (13%)	17 (6%)	4 (7%)
Hepatitis B co-infection					
No	465 (61%)	106 (56%)	136 (57%)	188 (67%)	35 (59%)
Yes	46 (6%)	10 (5%)	15 (6%)	20 (7%)	1 (2%)
Not tested	257 (33%)	75 (39%)	87 (37%)	72 (26%)	23 (39%)
Hepatitis C co-infection					
No	303 (39%)	72 (38%)	92 (39%)	123 (44%)	16 (27%)
Yes	116 (15%)	27 (14%)	32 (13%)	51 (18%)	6 (10%)
Not tested	349 (46%)	92 (48%)	114 (48%)	106 (38%)	37 (63%)
CD4 T-cell count at TB diagnosis, median cells/μL (IQR)	100 (40, 208)	151 (50, 243)	66 (28, 142)	119 (48, 238)	357 (125, 505)
HIV viral load at TB diagnosis, median copies/mL (IQR)	81650 (499, 330000)	707.5 (<400, 80027)	206902 (42400, 4880000)	170000 (11104, 552216)	132518 (41135, 466718)
Initial ART					
NRTI+NNRTI	615 (80%)	145 (76%)	213 (90%)	257 (92%)	---
NRTI+PI	39 (5%)	19 (10%)	5 (2%)	15 (5%)	---
Other combination	114 (15%)	27 (14%)	20 (8%)	8 (3%)	---
Type of TB					

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Characteristic	Total N=768	TB diagnosed while on ART N=191	Early ART N=238	Delayed ART N=280	ART not started N=59
Pulmonary	321 (42%)	84 (44%)	91 (38%)	125 (45%)	21 (36%)
Extrapulmonary	178 (23%)	57 (30%)	50 (21%)	58 (21%)	13 (22%)
Both	74 (10%)	15 (8%)	25 (11%)	30 (11%)	4 (6%)
Unknown	195 (25%)	35 (18%)	72 (30%)	67 (24%)	21 (36%)
Median days of total TB therapy (IQR)	275 (186,427)	256 (183, 379.5)	275.5 (185, 411)	303.5 (214, 534)	190 (111, 281)
Median days between TB therapy and ART initiation (IQR)	---	Before TB therapy: 223 (51, 790)	After TB therapy: 42 (17, 64)	After TB therapy: 212 (137.5, 407.5)	---

Data are frequencies and percentages in parentheses, unless otherwise indicated. TB, tuberculosis; ART, antiretroviral therapy; IQR, interquartile range; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

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Table 3

Clinical outcomes of patients with HIV-TB co-infection, by ART initiation category

Outcome	Total N=768	TB diagnosed while on ART N=191	Early ART N=238	Delayed ART N=280	ART not started N=59
TB treatment outcomes, N (%)					
Cured	240 (31%)	61 (32%)	79 (33%)	92 (33%)	8 (14%)
Treatment completed	435 (57%)	99 (52%)	137 (58%)	171 (61%)	28 (47%)
Treatment failure	3 (0%)	0 (0%)	0 (0%)	1 (0%)	2 (3%)
Died during TB treatment	21 (3%)	10 (5%)	3 (1%)	1 (0%)	7 (12%)
Defaulted	29 (4%)	8 (4%)	7 (3%)	6 (2%)	8 (14%)
Transferred out	9 (1%)	4 (2%)	2 (1%)	2 (1%)	1 (2%)
Current treatment without failure	20 (3%)	6 (3%)	7 (3%)	5 (2%)	2 (3%)
Missing	11 (1%)	3 (2%)	3 (1%)	2 (1%)	3 (5%)
Mortality					
Follow-up, person-years	2973	611	896	1025	441
Deaths	70	23	19	15	13
Rate per 100 person-years, 95% CI	2.35 (1.86, 2.98)	3.77 (2.50, 5.67)	2.12 (1.35, 3.32)	1.46 (0.88, 2.43)	2.94 (1.71, 5.07)
New AIDS-defining illness, excluding TB					
Follow-up, person years	2531	533	777	824	395
New AIDS cases	138	27	33	24	54
Rate per 100 person-years, 95% CI	5.45 (4.62, 6.44)	5.06 (3.47, 7.38)	4.24 (3.02, 5.97)	2.91 (1.95, 4.34)	13.66 (10.46, 17.83)
AIDS-defining illness (excluding TB) or death					
Follow-up, person-years	2531	533	777	824	395
New AIDS cases or death	189	46	48	32	63
Rate per 100 person-years, 95% CI	7.47 (6.48, 8.61)	8.62 (6.46, 11.51)	6.17 (4.65, 8.19)	3.88 (2.75, 5.49)	15.93 (12.45, 20.40)
IRIS, N (%)	34 (4%)	8 (4%)	14 (6%)	11 (4%)	1 (2%)
Immunological response at 12 months after ART initiation*					

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Outcome	Total N=768	TB diagnosed while on ART N=191	Early ART N=238	Delayed ART N=280	ART not started N=59
No	167 (33%)	52 (40%)	49 (30%)	66 (31%)	---
Yes	338 (67%)	77 (60%)	115 (70%)	146 (69%)	---
Incomplete information	204	62	74	68	---
Virological response at 12 months after ART initiation **					
Yes	38 (18%)	13 (25%)	7 (12%)	18 (17%)	---
No	178 (82%)	40 (75%)	50 (88%)	88 (83%)	---
Test not done	493	138	181	174	---
Toxicities of TB therapy greater than grade 3	22 (3%)	4 (2%)	3 (1%)	13 (5%)	2 (3%)

Data are frequencies and percentages in parentheses, unless otherwise indicated.

* CD4 T-cell counts increase of 100 cells/μL from ART initiation up to 12 month visit (testing range: 6–18 months)

** HIV viral load <500 copies/mL (6–18 months)

ART, antiretroviral therapy; TB, tuberculosis; IRIS, immune reconstitution inflammatory syndrome.

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Table 4

Cox proportional hazards analysis of all-cause mortality for HIV-TB co-infected patients (N=768)

Variable	Follow up in person-years	Deaths	Unadjusted HR	P-value	Adjusted HR	95 % CI	P-value
Age at ART initiation, years							
≤30	854	19	1		1		
30–41	1463	31	0.96	0.886	1.14	(0.63, 2.04)	0.667
>41	657	20	1.38	0.311	1.62	(0.84, 3.15)	0.151
Sex							
Male	2332	61	1		1		
Female	641	9	0.53	0.075	0.52	(0.25, 1.06)	0.072
Reported exposure route of HIV infection							
Heterosexual contact	2235	44	1		1		
Homosexual contact	290	4	0.70	0.503	0.55	(0.19, 1.53)	0.252
Injecting drug use	311	17	2.27	0.005	**1.96**	**(1.05, 3.66)**	**0.035**
Other/unknown	136	5	1.72	0.252	1.42	(0.56, 3.61)	0.464
Prior AIDS diagnosis at ART initiation							
No	2547	57	1		1		
Yes	426	13	1.39	0.284	1.68	(0.90, 3.12)	0.102
Hepatitis B co-infection							
No	1804	30	1		1		
Yes	187	5	1.64	0.306	1.47	(0.57, 3.83)	0.425
Not tested	982	35	2.17	0.002	**2.60**	**(1.58, 4.28)**	**<0.001**
Hepatitis C co-infection							
No	1304	23	1		1		

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Variable	Follow up in person-years	Deaths	Unadjusted HR	P-value	Adjusted HR	95 % CI	P-value
Yes	320	10	1.47	0.310	0.70	(0.28, 1.71)	0.431
Not tested	1349	37	1.51	0.118	1.05	(0.47, 2.38)	0.902
CD4 T-cell count (cells/μL) at TB diagnosis							
≤100	716	22	1		1		
>101	893	15	0.55	0.076	0.69	(0.35, 1.36)	0.282
Missing	1364	33	0.89	0.679	0.96	(0.55, 1.67)	0.890
HIV viral load (copies/ml) at TB diagnosis							
<500	113	4	1		1		
≥500	26	1	1.17	0.886	1.52	(0.17, 13.74)	0.707
Missing	2833	65	0.74	0.552	0.84	(0.30, 2.32)	0.733
Type of TB							
Pulmonary	1116	36	1		1		
Extrapulmonary	730	21	0.94	0.825	1.02	(0.57, 1.84)	0.937
Both	255	5	0.59	0.269	0.65	(0.25, 1.65)	0.360
Not tested or reported	871	8	0.32	0.003	**0.31**	**(0.14, 0.70)**	**0.005**
Time intervals between initiation of TB therapy and ART initiation							
TB diagnosed while on ART	611	23	1		1.00		
ART not yet started	441	13	0.63	0.197	0.80	(0.39, 1.66)	0.551
Early ART after TB therapy	896	19	0.61	0.114	0.69	(0.37, 1.28)	0.239
Delayed ART after TB therapy	1025	15	0.51	0.050	0.57	(0.29, 1.12)	0.101

TB, tuberculosis; ART, antiretroviral therapy.

Bold text denotes adjusted hazard ratios with significant p values; TB, tuberculosis; ART, antiretroviral therapy.