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Optimal Timing of Antiretroviral Therapy Initiation in Children and Adolescents With Human Immunodeficiency Virus-Associated Pulmonary Tuberculosis

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Background. There is insufficient evidence in children and adolescents with human immunodeficiency virus (CAHIV) to guide the timing of antiretroviral treatment (ART) initiation after starting treatment for pulmonary tuberculosis (pTB). To address this knowledge gap, we evaluated the risk of mortality associated with timing of ART initiation in ART-naive CAHIV treated for pTB.

Methods. Data were extracted from electronic medical records of ART-naive patients, aged 0–19 years, who were treated for HIV-associated pTB at Baylor Centers of Excellence in Botswana, Eswatini, Malawi, Lesotho, Tanzania, or Uganda between 2013 and 2020. Data were analyzed against a primary outcome of all-cause mortality with unadjusted Kaplan-Meier curves and Cox proportional hazard models.

Results. The study population included 774 CAHIV with variable intervals to ART initiation after starting TB treatment: <2 weeks (n = 266), 2 weeks to 2 months (n = 398), >2 months (n = 66), and no ART initiated (n = 44). Adjusted Cox proportional hazards models demonstrated increased mortality 1 year from TB treatment initiation in children never starting ART (adjusted HR [aHR]: 2.67; 95% CI: 1.03, 6.94) versus children initiating ART between 2 weeks and 2 months from TB treatment initiation. Mortality risk did not differ for the <2-weeks group (aHR: 1.02; 95% CI: .55, 1.89) versus the group initiating ART between 2 weeks and 2 months.

Conclusions. This retrospective study demonstrated no increase in mortality among CAHIV initiating ART <2 weeks from TB treatment initiation. Given the broad health benefits of ART, this evidence supports the recent WHO recommendation for CAHIV to initiate ART within 2 weeks of initiating TB treatment.

Keywords. tuberculosis; HIV; children; ART.

People with human immunodeficiency virus (PHIV) are 18 times (uncertainty interval: 15 to 21 times) more likely than human immunodeficiency virus (HIV)–negative people to develop tuberculosis (TB) [1]. Children and adolescents with HIV (CAHIV) also experience increased risk of TB following TB exposure, with increased risk in infancy and adolescence [2–5]. Antiretroviral therapy (ART) reduces TB incidence in CAHIV, but the risk remains elevated above that of HIV-negative children [5, 6].

Children and adolescents with HIV also have a higher risk of death due to TB than their HIV-negative peers. Recent programmatic data from cohorts in Kenya and South Africa suggest that the adjusted hazard ratio (aHR) for mortality ranges from 4.84 to 7.99 in ART-naive CAHIV and 3.69 to 5.11 in CAHIV treated with ART [7, 8]. Children and adolescents with HIV with preserved immune function are at reduced risk of mortality secondary to HIV-associated TB as compared with children with advanced HIV [5].

Universal and rapid initiation of ART in CAHIV has clear benefits for mortality reduction and improved quality of life [9]; however, concerns about immune reconstitution syndrome (IRIS) and

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drug interactions have led to uncertainty about the timing of ART initiation relative to TB treatment initiation in CAHIV who are ART naive.

A systematic review of studies in adults was conducted to inform the 2021 World Health Organization (WHO) HIV Guidelines and found that ART initiation within 2 weeks of TB treatment as compared with within 8 weeks resulted in no increase in mortality regardless of CD4 count, and with no difference in viral suppression or AIDS defining events [10]. These data led to a WHO recommendation to initiate ART as soon as possible and within 2 weeks of TB treatment initiation in all PHIV, including CAHIV, given the other known benefits of rapid ART initiation.

There is a scarcity of evidence in CAHIV to guide the timing of ART initiation from within 2 weeks compared with within 8 weeks of initiating TB treatment. Further, only limited data suggest that ART initiation within 8 weeks of TB treatment improves HIV-associated TB treatment outcomes [11]. To address this knowledge gap, we evaluated the risk of mortality associated with the timing of ART initiation in ART-naive CAHIV treated for pulmonary TB (pTB) in a large, multinational retrospective cohort from TB/HIV high-burden settings throughout sub-Saharan Africa.

METHODS

STROBE Statement

Study implementation was aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. The primary objective was to evaluate if the interval from initiation of treatment for pTB to ART initiation is associated with the risk of mortality in CAHIV.

Participants

The study population included CAHIV initiating treatment for pTB and HIV at 7 Centers of Excellence (COEs) within the Baylor International Pediatric AIDS Initiative (BIPAI) network across 6 countries, including Botswana, Eswatini, Lesotho, Malawi, Tanzania (Mbeya and Mwanza), and Uganda. To reduce bias, all ART-naive CAHIV who were aged 0 to 19 years at treatment initiation for pTB were included in the analysis.

Outcomes of Interest

Mortality was the primary outcome. However, considering the high risk of death among CAHIV who are lost to follow-up (LTFU) [13, 14], a planned sensitivity analysis was performed, assuming death as the outcome among those LTFU. Children and adolescents with HIV who transferred out were censored at the time of transfer.

Data Extraction

Patient data were extracted and analyzed from the electronic medical record (EMR) as previously reported [5]. In brief, the database allows extraction of patient-level data, supporting longitudinal individual patient-level analysis. The period of analysis differed among the COEs based on the timing of the introduction of standardized TB-specific EMR fields to optimize data validity and homogeneity. All COEs introduced TB-specific EMR fields in 2013, except for Malawi, which began in 2016, and data were extracted through September of 2020. Covariates, thought to be potential confounders, were identified a priori, including sex, age, COE location, body mass index (BMI) z score (defined by WHO growth charts), TB confirmation status (confirmed by a positive acid-fast smear, Xpert [MTB/RIF or Ultra] test (Cepheid, Sunnyvale, California), or *Mycobacterium tuberculosis* culture vs unconfirmed), CD4 percent, and a composite variable categorizing immunosuppression as preserved (CD4 of >350 cells/μL in children aged ≥5 years or >25% in children <5 years) or suppressed (defined as the inverse of the definition for preserved). Time period for anti-tuberculosis therapy (ATT) initiation was stratified by into 3 periods—2013–2015, 2016–2017, and 2018–2020—to evaluate changes in the cohort composition over time.

Statistical Approach

Descriptive statistics were performed on the cohort, stratified by the primary exposure. Chi-square tests were performed for categorical covariates and analysis of variance for continuous variables. Kaplan–Meier curves were developed, with time to ART initiation as a fixed variable, with death and death or LTFU as the outcome (R package "survival"; R Foundation for Statistical Computing). Unadjusted and adjusted Cox regression models, with timing of ART initiation as a time-dependent variable, were developed and adjusted for covariates found to vary by the primary exposure ($P < .2$). For the regression models, all patients were classified as untreated until ART initiation to limit immortal time bias [15]. The adjusted models included age, BMI z score, time period of TB treatment initiation, TB certainty, and immune status as defined by CD4 category. Models were developed for the primary outcome of mortality and a composite outcome of death and LTFU. The duration of follow-up was evaluated at 2-year intervals (1 year, 3 years, 5 years, and current). All statistical analysis was performed in R (version 1.3.959) using the packages described above for each analysis. An adjusted complete case analysis was performed for the primary analysis. To assess whether the data supporting the complete case analysis were representative of the full cohort, an unadjusted complete case analysis was compared with the unadjusted analysis in the full dataset. Further, imputation of missing data was performed using multiple imputation by chained equations (MICE) with polytomous regression for categorical variables and predictive mean matching for continuous variables (R package: Mice) [16].

All clinical investigation supporting the data handling, analysis, and reporting of these findings was conducted according to the principles of the Declaration of Helsinki. Approval was obtained from the national ethical bodies in each country and the Baylor College of Medicine Institutional Review Board.

RESULTS

The analytic study population included all 774 CAHIV who were ART naive at the time of pTB treatment initiation. This cohort was divided across 4 exposure categories: those who (1) never initiated ART (no ART, n = 44), (2) started ART within 2 weeks of TB treatment (<2 weeks, n = 266), (3) started ART at least 2 weeks after but less than 2 months from TB treatment (2 weeks–2 months, n = 398), and (4) started ART more than 2 months after TB treatment (>2 months, n = 66).

Patient characteristics were compared across the different ART initiation timing groups (Table 1). Sex proportions were balanced across the 4 groups ($P = .516$). Although the no-ART group had the lowest median age (2.76 years) at ATT initiation, the confidence intervals (CIs) for all groups were overlapping ($P = .072$), suggesting no difference in age composition. The proportion of patients within the ART initiation groups varied by study sites (COEs) ($P < .001$); however, at all sites, the greatest proportion of patients initiated ART in the less-than-2-week or 2-week to 2-month time period.

Although BMI *z* score medians were broadly similar across groups, the no-ART group had the lowest *z* score (−1.99; 95% CI: −3.2 to −.6) compared with the other 3 groups, which had *z* score values approximating −1.6 ($P = .206$). The no-ART group was also quite different with respect to TB certainty; most patients had unconfirmed TB (82%). In contrast, 34% of the less-than-2-week group had confirmed TB ($P = .006$). Baseline CD4 percentage was lowest in the no-ART group (11%; 95% CI: 8.3–20.3%) but was not different from the other groups ($P = .970$). The more-than-2-month group had the highest CD4 percentage (16%; 95% CI: 8.0–19.0%) and also the highest rate of preserved immune function (53%).

Table 1. Baseline Characteristics Per Exposure Category

	ATT to ART Interval: Exposure Categories				
	No ART (n = 44)	<2 Weeks (n = 266)	2 Weeks–2 Months (n = 398)	>2 Months (n = 66)	*P*
Gender (female)	19 (43%)	140 (53%)	198 (50%)	37 (56%)	.516
Age in years	2.76 (1.10, 7.30)	3.16 (1.40, 8.55)	4.71 (1.37, 10.36)	4.59 (1.32, 9.14)	.072
Age category					.398
<1 year	9 (20%)	45 (17%)	61 (15%)	11 (17%)	
1–4 years	20 (45%)	108 (41%)	143 (36%)	23 (35%)	
5–9 years	10 (23%)	61 (23%)	87`` (22%)	17 (26%)	
10–19 years	5 (11%)	52 (20%)	107 (27%)	15 (23%)	
COE					<.001
Botswana	0	20 (8%)	7 (2%)	2 (3%)	
Eswatini	5 (11%)	18 (7%)	70 (18%)	27 (41%)	
Lesotho	4 (9%)	34 (13%)	127 (32%)	22 (33%)	
Malawi	0	13 (5%)	3 (1%)	1 (2%)	
Mbeya	4 (9%)	37 (14%)	27 (7%)	2 (3%)	
Mwanza	15 (34%)	84 (32%)	73 (18%)	6 (9%)	
Uganda	16 (36%)	60 (23%)	91 (23%)	6 (9%)	
BMI *z* score	−1.99 (−3.2, −0.6)	−1.75 (−3.1, −0.6)	−1.62 (−2.8, −0.3)	−1.45 (−2.7, −0.3)	.206
Missing	8 (18%)	23 (9%)	39 (10%)	16 (24%)	
TB certainty					.006
Confirmed	3 (7%)	90 (34%)	110 (28%)	19 (29%)	
Unconfirmed	36 (82%)	172 (65%)	288 (72%)	46 (70%)	
Missing	5 (11%)	4 (2%)	0	1 (2%)	
CD4 percent	11 (8.3, 20.3)	14 (7, 21.3)	13.8 (6.9, 21)	16 (8, 19)	.970
Missing	13 (30%)	52 (20%)	74 (19%)	18 (27%)	
CD4 category					.130
Preserved	18 (41%)	120 (45%)	190 (48%)	35 (53%)	
Suppressed	14 (32%)	107 (40%)	149 (37%)	14 (21%)	
Missing	12 (27%)	39 (15%)	59 (15%)	17 (26%)	
Year of ATT start					<.001
2013–2015	12 (27%)	89 (33%)	206 (52%)	47 (71%)	
2016–2017	17 (39%)	88 (33%)	124 (31%)	14 (21%)	
2018–2020	15 (34%)	89 (33%)	68 (17%)	5 (8%)	

Continuous variables are summarized with median and IQR, while categorical variables are summarized with counts and percentages. Statistical differences among exposure groups were assessed with ANOVA for continuous variables and chi-square for categorical variables.

Abbreviations: ANOVA, analysis of variance; ART, antiretroviral therapy; ATT, anti-tuberculosis therapy; BMI, body mass index; COE, Center of Excellence; IQR, interquartile range; TB, tuberculosis.

Overall, the other groups were evenly split by categorical immune status, with just over half the cohort being defined as having preserved immune function. The interval from ATT to ART initiation was also associated with the time period of ART initiation. Given the prolonged analytic period and the association with the ATT to ART interval, we evaluated the cohort by time period (Table 2). While largely similar over time, children initiated on ATT in later time periods were slightly younger ($P = .026$) and had increased rates of immune preservation ($P < .001$) and malnutrition ($P = .008$). Children in later time periods were also more likely to be initiated on ART less than 2 weeks from ATT initiation ($P < .001$).

Kaplan–Meier curves demonstrate survival after initiation of ART or TB treatment in the case of the no-ART group (Figure 1*A*) and survival and retention in care (Figure 1*B*). The no-ART group experienced high rates of early mortality, with just under 70% of the population surviving to 100 days post–ATT initiation. This group continued to experience higher rates of LTFU throughout the year following ATT initiation, and less than half of patients remained active in care at the end of 1 year. The unadjusted mortality and mortality and retention in care were broadly similar in the remaining groups. Analysis was repeated in the cohort stratified by age (<1 year, 1–4 years, and ≥ 5 years) (Supplementary Figure 1). The Kaplan–Meier curves demonstrated overall higher rates of mortality in the younger populations, but the relationship between the ATT to ART initiation interval groups remained similar.

Cox proportional hazards models were generated to control for potential confounders and covariates that were included in the model based on evidence of differences between ART initiation groups (Table 3). The complete case analysis, controlling for age, BMI *z* score, COE location, TB certainty, and immune

Table 2. Baseline Characteristics by Time Period of Tuberculosis Treatment Initiation

	ATT to ART Interval: TB Treatment Initiation Time Period			
	2013–2015 (n = 354)	2016–2017 (n = 243)	2018–2020 (n = 177)	*P*
Gender (female)	192 (54%)	125 (51%)	77 (44%)	.065
Age in years	5.06 (1.53, 10.18)	2.95 (1.31, 8.72)	3.92 (1.23, 8.12)	.026
Age category				.084
<1 year	124 (35%)	104 (43%)	66 (37%)	
1–4 years	52 (15%)	40 (16%)	34 (19%)	
5–9 years	85 (24%)	44 (18%)	46 (26%)	
10–19 years	93 (26%)	55 (23%)	31 (18%)	
COE				.172
Botswana	10 (3%)	15 (6%)	4 (2%)	
Eswatini	89 (25%)	23 (9%)	8 (5%)	
Lesotho	111 (31%)	57 (23%)	19 (11%)	
Malawi	1 (0.3%)	10 (4%)	6 (3%)	
Mbeya	22 (6%)	28 (12%)	20 (11%)	
Mwanza	75 (21%)	55 (23%)	48 (27%)	
Uganda	46 (13%)	55 (23%)	72 (41%)	
BMI *z* score	−1.47 (−2.6, 0.3)	−1.81 (−3.3, −0.5)	−1.91 (−3.2, −0.7)	.005
Missing	49 (14%)	11 (4.5%)	26 (15%)	
TB certainty				.275
Confirmed	93 (26%)	76 (31%)	53 (30%)	
Unconfirmed	261 (74%)	161 (66%)	120 (68%)	
Missing	0	6 (2%)	4 (2%)	
CD4 percent	14 (6, 20)	13 (8, 21)	14.3 (8, 22.6)	.227
Missing	37 (10%)	61 (25%)	59 (33%)	
CD4 category				<.001
Preserved	204 (58%)	104 (43%)	55 (31%)	
Suppressed	123 (35%)	86 (35%)	75 (42%)	
Missing	27 (8%)	53 (22%)	47 (27%)	
ART timing				<.001
No ART	12 (3%)	17 (7%)	15 (8%)	
<2 weeks	89 (25%)	88 (36%)	89 (50%)	
2 weeks to 2 months	206 (58%)	124 (51%)	68 (38%)	
>2 months	47 (13%)	14 (6%)	5 (3%)	

Continuous variables are summarized with median and IQR, while categorical variables are summarized with counts and percentages. Statistical differences among exposure groups were assessed with ANOVA for continuous variables and chi-square for categorical variables.

Abbreviations: ANOVA, analysis of variance; ART, antiretroviral therapy; ATT, anti-tuberculosis therapy; BMI, body mass index; COE, Center of Excellence; IQR, interquartile range; TB, tuberculosis.

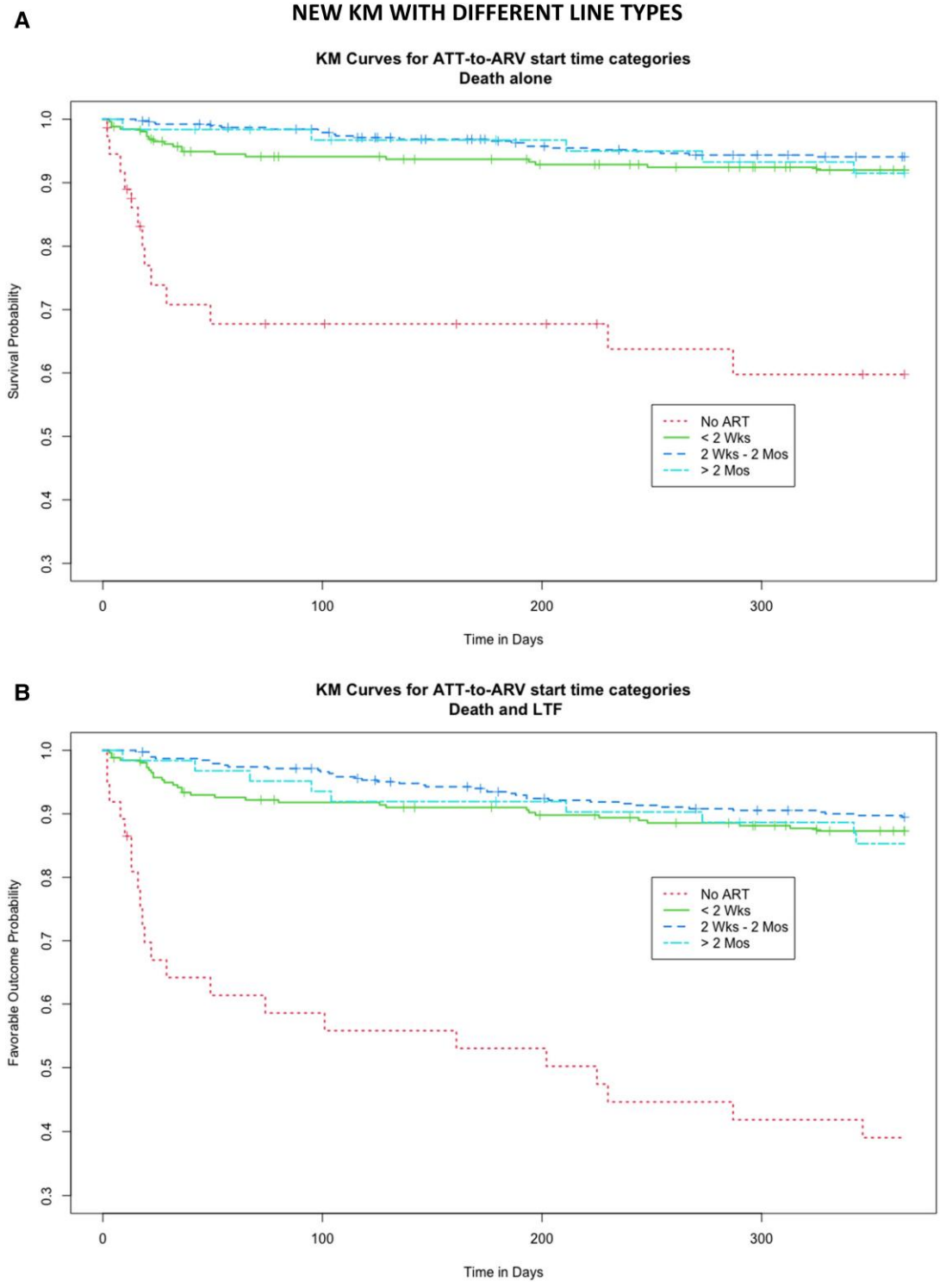

Figure 1. Kaplan–Meier curves demonstrating the unadjusted risk of survival (*A*) and a favorable outcome as evidenced by retention in care without death or lost to follow up (*B*). Timing of ART initiation is defined by line pattern in the figure legend. Abbreviations: ART, antiretroviral therapy; ATT, anti–tuberculosis treatment; Mos, months; TB, tuberculosis; Wks, weeks.

status, included 71% of the total cohort and 2178 years of patient follow-up time. At 1-year follow-up, the no-ART group had an increased risk of mortality in the adjusted analysis (aHR: 2.67; 95% CI: 1.03–6.94) and death and LTFU (aHR: 3.29; 95% CI: 1.49–7.25) compared with the reference group of ART initiation at 2 weeks to 2 months. There were no differences in the aHR for

death or death and LTFU for the other ART initiation groups. To evaluate the effect of the primary exposure (timing of ART initiation) on death at defined intervals, this analysis was repeated with an endpoint of 3 years, 5 years, and indefinite from treatment initiation; results of this analysis were similar to those of analysis with unlimited follow-up time (Supplementary Table 1). The Cox regression model was also performed on the imputed dataset, which did not reveal any differences in survival between groups (Supplementary Table 2).

DISCUSSION

In this multinational observational cohort of 774 CAHIV treated for TB prior to ART initiation, over 2632 person-years of follow-up we found no increase in death or death and LTFU in patients initiating ART in the first 2 weeks following TB treatment initiation compared with patients initiating ART later (up to 2 months following TB treatment initiation). These data are derived from 7 clinics across 6 high-burden TB/HIV countries in sub-Saharan Africa and are among the most generalizable data available for CAHIV in the region.

These data provide evidence that rapid initiation of ART, both in children who are being evaluated for presumptive pTB and in children diagnosed with HIV-associated TB, will not increase the risk of death. These data provide evidence to support the recommendation from the WHO to initiate ART as soon as possible and within 2 weeks of pTB treatment initiation in CAHIV, which was informed purely from adult data. This evidence in adults suggests that initiation of ART within 2 weeks of TB treatment initiation as compared with 2 to 8 weeks does not increase mortality (risk difference= −0.01; 95% CI: −.06 to .04) or result in differences in viral load suppression or AIDS defining events [10, 17].

A randomized controlled trial of hospitalized CAHIV [18], 15% of whom were admitted with TB, demonstrated no difference in survival between children randomized to urgent initiation of ART within 48 hours of admission or 7 to 14 days following admission (HR: 1.26; 95% CI: .67–2.37). Further, there was no increase in the risk of IRIS in the urgent-initiation group (HR: .96; 95% CI: .41–2.23) [18]. While this was a very specific population of very ill CAHIV, with an overall mortality of 22%, it provides reassurance that rapid initiation of ART in medically unstable children does not result in harm. Another study among CAHIV with severe malnutrition, a large proportion of whom had TB, also suggested that early compared with deferred initiation of ART resulted in similar outcomes. These data among extremely ill cohorts of CAHIV with a high TB prevalence also suggest that early ART is unlikely to cause harm but may not result in dramatic reductions in mortality.

Our study, and others in children less acutely ill, also suggests that mortality is predominantly attributable to whether ART is initiated at all [19] or initiated within 2 months of TB treatment in children with severe immunocompromise [20], rather than the rapidity of ART initiation in all children with HIV-associated TB. While a benefit of initiation of ART within 2 weeks has not been shown in any study of HIV-associated TB in CAHIV, a large, prospective, observational cohort of ART-naive children, 59% of whom had TB, suggested that initiation of ART within 1 month of follow-up reduced mortality (aHR: .08; 95% CI: .01–.67) [21]. Collectively, these data suggest that initiation of ART within 1 to 2 months of TB treatment initiation is likely to be beneficial. Importantly, our data demonstrate that initiation of ART within 2 weeks of TB treatment initiation is unlikely to be harmful in CAHIV, a population at high risk of death and with much to gain from ART initiation.

Even without dramatic mortality reductions, rapid initiation of ART is important for PHIV of all ages but may be most critical in CAHIV [9]. In infants and young children diagnosed with HIV, rapid initiation of ART improves immune recovery [22] and neurocognitive development and growth [23, 24] and reduces HIV reservoirs and immune activation [25]. In older children and in adolescents, rapid initiation of ART enhances immune recovery [22, 24], normalizes pubertal development

Table 3. Survival Analysis 1 Year From Tuberculosis Treatment Initiation Expressed With Unadjusted and Adjusted Hazard Ratios and 95% Confidence Intervals

Outcome and Model	No ART	<2 Weeks	2 Weeks–2 Months	>2 Months
Death and LTFU				
Unadjusted (n = 743[a])	2.09 (1.17, 3.74)	1.11 (.69, 1.79)	1	.95 (.29, 3.11)
Unadjusted CCA (n = 552)	3.11 (1.42, 6.78)	1.13 (.62, 2.07)	1	1.88 (.56, 6.31)
Adjusted[b] (n = 552)	3.29 (1.49, 7.25)	.85 (.44, 1.64)	1	2.70 (.77, 9.54)
Death alone				
Unadjusted (n = 743[a])	1.76 (0.90, 3.46)	1.21 (.76, 1.93)	1	.48 (.11, 1.98)
Unadjusted CCA (n = 552)	2.82 (1.07, 7.38)	1.25 (.70, 2.23)	1	.46 (.06, 3.39)
Adjusted[b] (n = 552)	2.67 (1.03, 6.94)	1.02 (.55, 1.89)	1	.81 (.10, 6.31)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CCA, complete case analysis; COE, Center of Excellence; LTFU, lost to follow-up; TB, tuberculosis.

[a]Reduced from total cohort due to poorly defined outcomes (n = 31).

[b]Models adjusted for the following covariates: age, BMI *z* score, COE, TB certainty, CD4 category, and year of TB treatment initiation.

[26], and reduces HIV-related cardiac and pulmonary complications [27, 28]. Therefore, in the absence of harm related to rapid ART initiation following a diagnosis of HIV-associated pTB, it is imperative that CAHIV experience the other benefits of rapid ART initiation.

This study is subject to limitations. Most notably, the data were derived from routine sources and, therefore, the analysis was complicated by missing data. We addressed this both through careful comparison of the complete case cohort and the full cohort, as well as through imputation. Results were consistent across all methods. However, routine viral load and CD4 data had too much missingness to be evaluated as outcomes following ART initiation. Observational studies evaluating treatment initiation strategies are also subject to immortal time bias, which we addressed through statistical methods, but we cannot exclude residual confounding. Certainly, the high rates of mortality observed in the Kaplan–Meier curves are not attributable solely to the absence of ART initiation. The reduction in the unadjusted and adjusted HRs in the Cox models using a time-dependent variable for timing of ART initiation suggests that we effectively addressed this bias. The clinical settings described in this study, while established as public–private partnerships, are each part of and predominantly supported by the Ministry of Health in each country. The settings are representative of care provided nationally, but with the benefit of caring for a higher volume of CAHIV due to referrals. The CAHIV described may also have more advanced disease due to referral bias but, in general, had immune status that aligned with CAHIV in other studies in other high-burden settings [29]. Due to the prolonged analytic period, there were changes in health policy, and in general, children were initiated on ART after a shorter interval during the most recent study period. This was adjusted for through inclusion of treatment time period in the model. The decreased age, increased malnutrition, and immune suppression among children treated during the most recent time period may reflect a survival bias present among the children treated between 2013 and 2015 but also indicates the ongoing need for improved case finding of CAHIV. Finally, with observational retrospective studies, it is difficult to exclude misattribution errors through inaccurate data entry, although steps were taken to limit this risk through manual data checks. Further, prospective randomized studies are unlikely to be performed to address this question in CAHIV.

The age of initiation and the low rate of disease confirmation highlight the ongoing challenge with TB diagnosis in children and indicate that infants with HIV-associated TB continue to go undiagnosed. These diagnostic challenges speak to the importance of data-driven clinical diagnostic algorithms in CAHIV [30], particularly in the absence of large immunologic or microbiologic diagnostic advances. It is also possible that benefits of early ART were not fully realized due to the limited ART options available for infants and children with HIV-associated TB. Triple nucleoside reverse transcriptase inhibitors, nevirapine, and lopinavir-ritonavir all had limitations. The introduction of pediatric dolutegravir marks the first time that many CAHIV less than 3 years of age have had access to effective and child-friendly ART regimens while receiving TB treatment. This treatment option, when dosed twice daily, is likely to be more effective than the previously available ART treatment regimens and has a lower risk of toxicity. With reduced concerns about drug interactions and toxicity, clinicians may now also feel more comfortable rapidly initiating ART in children with TB.

CONCLUSIONS

This study provides critical data indicating that rapid initiation of ART, within 2 weeks following initiation of TB treatment, is not associated with an increased risk of death or death and LTFU. The data support existing recommendations from the WHO to initiate ART within 2 weeks in CAHIV who are being evaluated for presumptive TB or who are being treated for HIV-associated TB.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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