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Effect on mortality and virological response of delaying antiretroviral therapy initiation in children receiving tuberculosis treatment

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Abstract

Objective—To estimate the effect of delaying antiretroviral treatment (ART) for 15, 30, or 60 days after tuberculosis (TB) treatment initiation on mortality and virological suppression.

Design—Cohort of 573 ART-naive HIV-infected children initiated on TB treatment at an outpatient clinic in South Africa between April 2004 and March 2008.

Methods—Hazard ratios for mortality and viral suppression were estimated using marginal structural models and multivariate Cox models, respectively.

Results—During follow-up (median 9.64 months), 37 HIV-infected children died after a median of 62 days of TB treatment. ART was initiated in 461 children at a median of 17 days after TB treatment initiation, 415 (90%) achieved viral suppression. The hazard ratios of death for initiating ART more than 15, more than 30, or more than 60 days of TB treatment compared with initiating within 15, 30 and 60 days, respectively, were 0.82 (95% CI: 0.48, 1.41), 0.86 (95% CI: 0.46, 1.60), and 1.32 (95% CI: 0.55, 3.16). Hazard ratios for analysis restricted to severely immunosuppressed children were: 0.92 (95% CI: 0.51, 1.63), 1.08 (95% CI: 0.56, 2.08), and 2.23 (95% CI: 0.85, 5.80), respectively. Hazard ratios for viral suppression were 0.98 (95% CI: 0.76, 1.26), 0.95, (95% CI: 0.73, 1.23), 0.84 (95% CI: 0.61, 1.15), respectively and did not change with restriction to children severely immunosuppressed.

Conclusion—In this observational study, we found that delaying ART for 2 months or more in children diagnosed with TB may be associated with poorer virological response and increased mortality, particularly in children with severe immunosuppression. These findings should be confirmed in a randomized controlled trial.

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Keywords

ART initiation; children; HIV; South Africa; tuberculosis

Introduction

Worldwide, about 1200 new pediatric HIV infections occur daily and more than 90% of new infections happen in sub-Saharan Africa [1]. Children who are infected early in life progress more rapidly to AIDS and death. Tuberculosis (TB) is a major cause of morbidity and mortality among HIV-infected children in Africa [2]. Following TB infection, children (particularly young infants), have a higher risk of progression to disease (extrapulmonary and pulmonary) and death irrespective of their HIV status [3]. However, HIV is also a major risk factor for childhood TB [4]. The burden of TB in HIV-infected children is not well known because of the difficulties in diagnosing TB in this population [5]. Though it might be greatly influenced by selection bias, reported prevalence of HIVamong TB-infected children range from less than 5% in industrialized settings to over 50% in some African settings [6–8]. In HIV/TB coinfected children, diminished cell-mediated immunity increases the risk for disseminated TB disease, especially in advanced stages of HIV infection, resulting in high mortality [9,10]. Restoration of cellular immunity with antiretroviral therapy (ART) reduces the susceptibility to TB [11].

The WHO recommends initiation of TB treatment as soon as the diagnosis of TB is suspected in an HIV-infected child. The management of HIV-infected children with TB is complicated as rifampicin, the backbone of any TB treatment regimen, has been shown in adults to reduce the serum concentrations of most protease inhibitors by about 80% or more, and that of nonnuclease reverse transcriptase inhibitors by 20–60% [12]. In addition, TB drugs and ART have overlapping toxicities. To avoid drug interactions and to differentiate side effects for TB drugs and ART, WHO advises that initiation of ART be delayed for at least 2–8 weeks after TB treatment initiation [12,13]. In South Africa, national guidelines recommend completion of TB therapy before starting ART in children not severely immunosupressed [CD4 percentage (CD4%) ≥25% in children, ≤11 months, ≥20% for children aged 12–35 months, or ≥15% for older children], or delay of ART for 4–8 weeks in children with severe immunosuppression [14]. The potential effects of delaying ARTon survival or virological response to ART are unknown.

In this study, we aimed to estimate the effect of delaying ART initiation for at least 15, 30, or 60 days in children initiating TB treatment on virological suppression and survival. We hypothesized that children in whom ART is delayed will be at higher hazard of death but will be more likely to achieve viral suppression once they are initiated on ART.

Methods

Data

We used routinely collected data from an observational cohort of HIV-infected children, who sought care at the Harriet Shezi Children's Clinic, an outpatient pediatric HIV clinic at Chris

Hanni Baragwanath Hospital in Soweto, South Africa, during the first 4 years (April 2004 to March 2008) of the government ART program [15]. TB was routinely diagnosed on clinical grounds including severe failure to thrive, prolonged (more than 2 weeks) cough, suspicious chest radiograph with or without a positive contact history. Bacteriological confirmation was attempted in older children who can produce a sputum sample. Children were treated according to national guidelines with a combination of rifampicin, isoniazid, and pyrazinamide for the initial 2 months followed by rifampicin + isoniazid for the remaining 4 months [16].

According to the South Africa National Guidelines [17], all HIV-infected children diagnosed with TB are eligible for ART. The first line ART regimen for children receiving TB treatment consists of stavudine, lamivudine, and ritonavir-boosted lopinavir (LPV/*r*) for children 3 years or younger; or stavudine, lamivudine and efavirenz for those over 3 years and over 10 kg of weight. Double doses of ritonavir dose were given during antitubercular treatment [18,19].

Children initiated on ART were clinically assessed at 1 month, at 3 months, and every 3 months thereafter or as needed clinically. Laboratory investigations (i.e., viral load and CD4 cell count) were done at baseline and every 6 months or whenever indicated. Clinical and laboratory information were entered in an electronic database.

Children were included in this analysis if their first visit in the clinic occurred between 1 April, 2004 and 31 March, 2008; they were initiated on TB treatment prior to ART initiation; and were 15 years or younger at the time of TB treatment initiation. Children who were already on TB treatment at first visit in the clinic were excluded. For analysis of time to viral suppression, eligible children had to also have at least one viral load measurement post-ART initiation.

Two main outcomes were considered. Survival was defined as time from TB treatment initiation to death. For six children whose exact date of death was unknown, the last clinic visit date was used. Time to viral suppression was defined as time from ART initiation to the date of first viral load measure below 400 HIV RNA copies/ml.

For presentation of results, time from TB treatment initiation to ART initiation was categorized as more than 15, more than 30, or more than 60 days. The 15, 30, and 60 days cut-offs were chosen to correspond to the minimum 2–8 weeks delay between TB treatment and ART initiation recommended by the WHO [12].

Additional covariables considered were level of immunosuppression, viral load (dichotomized at about the median of 5 $\log_{10}$ copies/ml), age at TB initiation (<18 months, 18–35 months, 36–59 months, 60 months or older), and weight-for-age Z score (WAZ) (greater than –2SD (no undernutrition), –2SD to –3SD (undernutrition), and less than – 3SD (severe undernutrition) [20,21].

Statistical analysis

Baseline characteristics (at time of TB treatment initiation) were compared using Wilcoxon Rank-Sum test for continuous variables and Pearson chi squared for categorical variables.

For the analysis of mortality, inverse probability-of-treatment-and censoring (IPTC) weighting of marginal structural models was used to adjust for time-dependent confounding [22,23]. Time-dependent confounding could occur because, even though per guidelines all children with TB were eligible for ART, the decision to initiate or delay ART for a given child was likely to be influenced by clinical and immunological characteristics, with children with advanced disease being more likely to be initiated on ART earlier. Stabilized weights for treatment and censoring were estimated as described in reference [22]. Time from TB treatment to ART initiation or to the end of follow-up due to administrative censoring (at 36 months of follow-up or at last visit before 31 March, 2008 whichever came first) or informative censoring (loss of follow-up defined as no clinic visit for at least 6 months and unsuccessful contact tracing by phone and/or home visit) were treated as failure times. Using pooled logistic models, we estimated the probabilities of initiating ART (treatment weights) or remaining in care (censoring weights) at each visit with baseline level of immunosuppression, log viral load, WAZ, age at TB treatment initiation, and the interaction term between WAZ and level of immunosuppression as fixed covariates for the numerators of weights. For the denominators, time-dependent level of immunosuppression, log viral load, WAZ, and ART initiation were added as covariates in the models. Restricted cubic spline terms for time from TB treatment (with 5 knots at 5th, 25th, 50th, 75th, and 95th percentile of its distribution) were also included in these models. The stabilized weights for ART initiation, administrative censoring, and informative censoring were multiplied together to obtain the final IPTC weights. Assuming no misspecification of the models for IPTC weight estimation, and provided that data are available on all important time-dependent and baseline predictors of ART initiation, drop out and mortality, then IPTC weighted estimation of a marginal structural model provides a valid method to account for confounding and selection bias [22–24]. A necessary condition for correct model specification is that the stabilized weights have a mean of one [25]. The mean of the IPTC weights was 1.01 and its values ranged from 0.24 to 5.60. Both unweighted and IPTC-weighted (trimmed at the first and 99th percentiles) Cox proportional models for mortality were fit for each of the three categories of time between initiation of TB treatment and ART.

To assess hazards of viral suppression children had to be on ART. Hence, there were no time-dependent confounders and the only potential source of confounding that had to be adjusted for in the estimation of the effect of timing of ART initiation on viral suppression were the fixed baseline characteristics. Cox proportional models were used to obtain the crude and adjusted effect of the timing of ART initiation on virological suppression. All covariates included in the models were formally assessed for the proportional hazard assumption using the Kolmogorov-type supremum test [26].

To assess if the effects of delaying ART on mortality or viral suppression vary by the level of immunosupression at baseline, each analysis was repeated for each stratum of level of immunosuppression when there were sufficient data. All analyses were conducted using SAS 9.1 (SAS Institute, Cary, North Carolina, USA) and all tests were conducted using a two-sided 0.05 significance level, without correction for multiple comparisons. All confidence intervals (CI) were estimated using robust variances [27].

Results

Between April 2004 and March 2008, 3187 HIV-infected children initiated care in the clinic. In 909 children, TB treatment was initiated after their initial visit in the clinic. Of those 909, 336 were excluded from this analysis eight were older than 15 years and 328 were on ARTat the time of TB treatment. The 573 children included in the analysis were followed for a median time of 9.6 [interquartile range (IQR): 1.9 to 23.1] months, 75 (13%) were lost to follow up: 38 prior to ART initiation and 37 while on ART. Children lost to follow-up did not differ from those still in care by any of the baseline characteristics or timing of ART initiation.

The median age of the 573 children included in this analysis, was 3.5 (IQR: 1.4 to 6.8) years (Table 1). At baseline, the median CD4% was 11.9% (IQR: 6.6–18.3%), and the majority (75.2%) were severely immunosuppressed (CD4% below 25% for children younger than 1, or below 20% for children 1 to 2 years, or below 15% for children 3–15 years [12]); the median viral load was 5.2 (IQR 4.5–5.9) log copies/ml; and the median WAZ was−2.3 (IQR: −3.6—1.3) with 34.7% of children severely under-weight-for-age.

Most children (461/573 80.5%) were initiated on ART. ARTwas started at a median time of 17 (IQR 0–49) days after TB treatment initiation. Time between the start of TB treatment and initiation of ART was more than 15 days in 55% (275/501) of children, more than 30 days in 42% (206/498), and more than 60 days 23% (111/494) (denominator decreases with increased duration of follow-up time due to censoring). Thirty one percentage (141/461) were started on ART the same day TB treatment was initiated and 6% (27/461) were initiated on ART 6 months after TB treatment initiation and 13 of the 112 children (12%) who were never initiated on ART have longer that 6-months of follow-up. Children who were initiated on ARTearlier (within 1 month of starting TB treatment) had lower CD4 cell count, and lower WAZ, than those in whom ART was delayed for more than 1 month (Table 1).

Mortality

Seven (1.2%) children died before ART initiation (3 within 30 days of TB treatment and 4 after 60 days) and 30 died after ART initiation (22 in the first 2 weeks of TB treatment, 25 in the first 30 days, and 26 in the first 60 days of TB treatment. Children who died were more likely at baseline to be younger (median age 1.4 vs. 3.7 years, $P<0.01$), to be severely underweight for age (median WAZ −3.8 vs. −2.2, $P<0.01$), to have higher viral load (median 5.9 vs. 5.2, $P<0.01$), and to have severe immunosuppression (8.7% vs. 3.2, $P=0.04$)) (Table 2). Kaplan–Meier survival cures show that while the survival probability curve of children in whom ART was delayed was initially slightly higher, it declined continuously and eventually past below that of those initiated on ART immediately, particularly in severely immunosuppressed children (Fig. 1).

Adjusted hazard ratios (aHR) for the effect on mortality of delaying ART for more than 15, more than 30, or more than 60 were 0.82 (95% CI 0.48, 1.63), 0.86 (95% CI 0.46, 1.60), and 1.32 (95% CI 0.55, 3.16), respectively. All aHRs account for the time-varying level of immunosuppression, log viral load, WAZ, and censoring prior to ART, and time fixed age at

TB treatment initiation (Table 3). Analysis with IPCTweights trimmed at the first and 99th percentiles produced results with similar aHR for the first two estimates: [0.76 (95% CI 0.43, 1.34), 0.72 (95% CI 0.37, 1.38)], but a different estimate for the aHR for delay of at least 60 days [0.86 (95% CI 0.36, 2.09)].

Full stratification of the analysis of mortality by level of immunosuppression was not possible because only four deaths occurred among the 125 children not severely immunosuppressed at baseline (one immediately after TB treatment initiation and before ARTand three after ART initiation). Restriction of the analysis to children with severe immunosuppression resulted in stronger effects for delaying ART initiation for more than 60 days, with an aHRs of 2.23 (95% CI 0.85, 5.80) (Table 3). Analysis with the IPCTweights trimmed at the first and 99th percentiles did not change these results.

Virological suppression

Of the 461 children initiated on ART, 324 (70%) had at least one viral load measurement post-ART initiation (after a median time of 5.51 months of ART initiation) of whom 291 (90%) ever achieved viral load below 400 copies/ml. Children who achieved virologic suppression were more likely at the time of TB treatment initiation to be older (median age 4.0 vs. 1.6 years, $P<0.01$), to have higher weight-for-age (median WAZ −2.2 vs. −3.1, $P<0.02$), and to have lower viral load (median log 5.2 vs. 5.8, $P=0.01$).

Delaying ART for more than 15 or more than 30 days had no effect on viral suppression [aHRs=0.98 (95% CI 0.76, 1.26) and 0.95 (95% CI 0.73, 1.23), respectively], but delaying more than 60 days after TB treatment initiation tended towards lower hazards of achieving virological suppression [aHR 0.84 (95% CI 0.54, 1.10)]. All hazard ratios were adjusted for level of immunosuppression, log viral load, WAZ, and age at TB treatment initiation (Table 3).

Full stratification of the analysis of viral suppression by level of immunosuppression was again not possible because only 63 of the 324 children with a viral load measurement on ART were not severely immunosuppressed at baseline and only six of them had not yet achieved virological suppression at the time of analysis. Restricting the analysis to only severely immunosuppressed children did not change the results substantially the [aHRs 0.96 (95% CI: 0.73, 1.26), 0.91 (95% CI: 0.67, 1.24), and 0.77 (95% CI: 0.50, 1.18) for delay of at least 15, at least 30 or at least 60 days, respectively].

Discussion

We sought to estimate the effect of delaying ART initiation in children receiving TB treatment on mortality and virologic response to ART. The analysis of a cohort of 573 South African children showed that a delay of 30 days or less between TB treatment and ART initiation had no effect on mortality or viral response to ART. Although not statistically significant, the effect of delaying ART for more than 60 days tended towards higher hazards of death and lower hazards of viral suppression. Severely immunosuppressed children at time of TB treatment initiation in whom ART was delayed for more than 60 days were twice as likely to die (aHR 2.23, 95CI 0.85, 5.80).

This is the first report on the effect of timing of ART initiation in children diagnosed with TB. In a recent analysis of a cohort of HIV/TB coinfected adults in Spain, simultaneous ART and TB treatment (ART initiated within ±2 months of TB treatment) was associated with improved survival [28]. In a randomized trial of early (within 14 days) versus deferred ART initiation in adults with opportunistic infections other than TB, early ART resulted in less AIDS progression or death with no increase in adverse events including the immune reconstitution inflammatory syndrome (IRIS) [29]. In young infants, it has been shown that, independent of TB status; early initiation of ART even in asymptomatic infants is associated with improved survival [30].

The principal justifications for the current recommendation to delay ART in children initiating TB treatment is to allow differentiation between side effects from ART and TB drugs, to avoid occurrence of IRIS [31,32], and to improve the viral response to ART by avoiding drug interactions [13]. The observation in this cohort that the hazard of viral suppression among children for whom ART was delayed did not differ from those with early initiation suggests that delaying ART in children initiating TB treatment has little or no effect on virological response to ART. Similarly, in a randomized controlled trial of immediate versus delayed ART initiation in adults with TB meningitis, the proportions with viral suppression in the two arms did not differ by 9 months of ART even though the median time to virological suppression was significantly longer in the deferred arm [33].

Our analysis had several strengths. First, we used data from one of the largest pediatric HIV clinics in sub-Saharan Africa, resulting in a large sample size of 573 HIV-infected children with TB of whom 461 initiated ART. Second, we used appropriate methods to measure the effect of delaying ART on mortality in an observational study, by controlling for a bias due to confounding by indication and selective drop out using a marginal structure model. We acknowledge that even the most appropriate statistical method may not adequately control for such confounding, especially in the routine clinic setting where initiation of ART is most likely closely linked to severity of disease. Third, by considering different cut-offs for the definition of delay, we were able to elicit a ‘dose–response’relationship, with a tendency of increasing negative effect on both mortality and viral response to ART with increasing length of delay. Fourth all children in our cohort came from a single clinic. This is important as initiation of TB treatment and assessment of ART involves some subjectivity; having the same set of clinicians making those decisions, limits the variability. Fifth, only 8% of children were lost to follow-up after they were initiated on ART, and loss to follow-up was not associated with timing to ART initiation or the baseline covariates.

Our study also suffered from limitations. First, this is a retrospective analysis of data from an observational clinical cohort. As result, we do not have data on side effects, drug interactions, or IRIS, individual reasons for initiation or delay of ART and adherence to TB treatment or ART. Compared with asymptomatic children, children in more advanced stage of HIV disease at ART initiation have been shown to be more likely to be adherent to treatment [34]. In our cohort, children with more advanced HIV disease at TB initiation were more likely to be initiated earlier on ART than those with less advanced disease. Differential adherence between children with less and those with more advanced HIV disease could therefore underlay some of our findings on hazard ratio for virological

suppression [35]. Second, children receiving rifampin were treated with efavirenz (if older than 3 years) or ritonavir-boosted lopinavir (if 3 years or younger) to achieve optimal virological outcomes [18,19]. These regimens are often not available in resource-poor countries, limiting the generalizability of our results. Third, due to the small number of children not severely immunosuppressed at baseline and particularly the limited number of events among them, it was not possible to fully assess effect of delaying ART on mortality or viral suppression among those children. It is possible that the effect of delaying ART on mortality differs by the level of immunosuppression.

In conclusion, results suggest that delaying ART initiation in children with TB for up to 30 days is not associated with increased mortality, while delaying for more than 60 days might decrease survival, especially in severely immunosuppressed children. Given the burden of TB in HIV-infected children, it is important that these results be confirmed in a randomized controlled trial.

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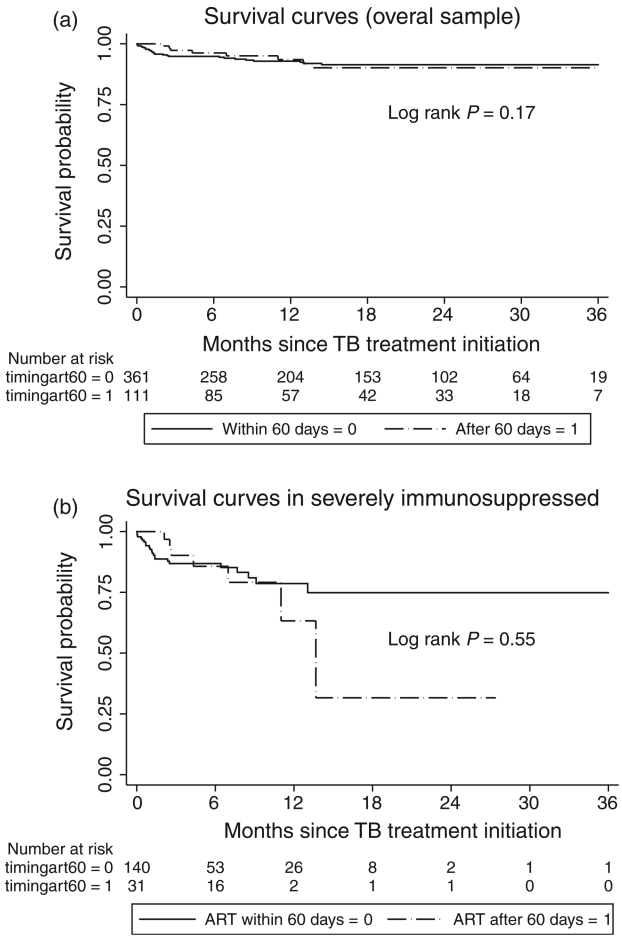

Fig. 1.

Kaplan–Meier plot of survival by timing of antiretroviral therapy (within or >60 days from TB treatment initiation) for the whole sample (a) and among severely immunosuppressed (CD4 percentage (CD4%) ≥25% in children, ≤ 11 months, ≥20% for children aged 12–35 months, or ≥15% for older children) children (b).

Table 1

Characteristics of 573 HIV-infected, antiretroviral-naive children, 15 years or younger, initiated on TB treatment at Harriet Shezi Children Clinic in Soweto, South Africa between April 2004 and March 2008.

		Initiation of ART			Timing of ART initiation‡		
Baseline characteristics	**Overall (573)**	**No (112)**	**Yes (461)**	***P*-value***	**<1month (288)**	**≥1 month (206)**	***P*-value***
CD4 cell count/μl: median (IQR)	392 (165–773)	745 (436–1211)	327 (137–701)	<0.01	273 (98–604)	533 (238–868)	<0.01
CD4 cell percentage: Median (IQR)	11.9 (6.6–18.3)	19.5 (12.1–25.9)	10.1 (6.0–16.5)	<0.01	8.0 (4.6–13.6)	15.0 (9.8–21.2)	<0.01
Level of immunosuppression							
Mild/not significant/advanced: *n* (%)	125 (24.8)	45 (53.6)	80 (19.0)		25 (9.6)	74 (38.7)	
Severe†: *n* (%)	379 (75.2)	39 (46.4)	340 (80.9)	<0.01	235 (90.4)	117 (61.2)	<0.01
Log viral load: median (IQR)	5.2 (4.5–5.9)	4.9 (4.3–5.9)	5.3 (4.6–5.9)	0.02	5.3 (4.6–6.0)	5.2 (4.5–5.8)	0.24
> 5: *n* (%)	284 (58.6)	33 (44.6)	251 (61.1)		154 (60.9)	108 (57.8)	
0–5: *n* (%)	201 (41.4)	41 (55.4)	160 (38.9)	0.01	99 (39.1)	79 (42.3)	0.53
Weight-for-age z score: median (IQR)	−2.28 (−3.58–−1.26)	−1.63 (−3.09–−0.84)	−2.38 (−3.81–−1.36)	<0.01	−2.71 (−4.11–−1.60)	−1.92 (−2.92–−0.83)	<0.01
≥−2SD: *n* (%)	241 (42.7)	63 (56.2)	178 (39.29)		96 (34.3)	106 (51.5)	
−2 to −3SD: *n* (%)	127 (22.5)	19 (17.0)	108 (23.84)		62 (22.1)	53 (25.7)	
<−3SD: *n* (%)	196 (34.8)	30 (26.8)	167 (36.87)	<0.01	122 (43.6)	47 (22.8)	<0.01
Age at TB treatment initiation: median (IQE) years	3.5 (1.4–6.8)	2.5 (1.3–5.5)	3.7 (1.4–7.0)	0.20	3.5 (1.4–7.1)	3.5 (1.4–6.7)	0.45
0.0–1.4: *n* (%)	158 (27.6)	36 (32.1)	122 (26.5)		78 (27.1)	54 (26.21)	
1.5–2.9: *n* (%)	107 (18.7)	26 (23.2)	81 (17.6)		52 (18.1)	37 (17.7)	
3.0–4.9: *n* (%)	96 (16.7)	17 (15.2)	79 (17.1)		44 (15.3)	41 (19.9)	
5.0–15.0: *n* (%)	212 (37.0)	33 (29.5)	179 (38.8)	0.31	114 (39.6)	74 (35.9)	0.12
Time from TB to ART initiation: median (IQR) days (*n* = 461)	17 (0–49)		17 (0–49)		4 (0–14)	59 (42–130)	<0.01
Survival time after TB treatment initiation: median (IQR) months	9.6 (1.9–23.0)	0.0 (0.0–2.0)	14.2 (5.1–26.1)	<0.01	14.0 (2.9–26.4)	12.7 (5.7–24.2)	0.33

IQR, Interquartile range; SD, standard deviation.

†CD4 percentage below 25% for children younger than 1, or below 20% for children 1–2 years, or below 15% for children 3–15 years.

*From Wilcoxon Rank sum test for continuous variables and Pearson chi squared test for categorical variables.

‡Only results with cut-off at 30 days from TB treatment initiation are presented here; distribution of baseline characteristics was similar for 15 and 60 days cut-offs.

Table 2

Characteristics associated with mortality and virologic response of 573 HIV-infected, ART-naive children, 15 years or younger, initiated on TB treatment at Harriet Shezi children's clinic, Soweto, South Africa (April 2004, March 2008).

	Mortality			Virological suppression*		
Baseline characteristics	**Total eligible**	**Number of events *n* (%)**	**Hazard ratio (95% CI)**	**Total eligible‡**	**Number of events *n* (%)**	**Hazard ratio (95% CI)**
Severe immunosuppression						
No	125	4 (3.20)	1	63	57 (90.48)	1
Yes†	379	33 (8.71)	2.38 (0.85, 6.68)	250	226 (90.40)	0.89 (0.68, 1.16)
Viral load (log copies/ml)						
> 5	284	28 (9.86)	1	186	165 (88.71)	1
0–5	201	8 (3.98)	0.42 (0.19, 0.93)	118	112 (94.92)	1.11 (0.87, 1.42)
Weight-for-age z score						
≥−2SD	241	5 (2.07)	1	133	125 (93.98)	1
−2 to −3SD	127	7 (5.51)	2.50 (0.74, 8.36)	75	68 (90.67)	0.70 (0.52, 0.93)
<−3SD	196	24 (12.24)	6.22 (2.21, 17.54)	112	95 (84.82)	0.79 (0.58, 1.06)
Age at TB treatment initiation: years						
0.0–1.4	158	21 (13.29)	1	78	62 (79.49)	1
1.5–2.9	107	5 (4.67)	0.32 (0.12, 0.88)	61	56 (91.80)	1.12 (0.76, 1.65)
3.0–4.9	96	4 (4.17)	0.28 (0.09, 0.83)	58	54 (93.10)	1.42 (0.93, 2.16)
5.0–15.0	212	7 (3.30)	0.22 (0.09, 0.51)	127	119 (93.70)	1.41 (1.00, 1.98)

CI, confidence interval: estimated using robust variance;SD, standard deviation.

*First viral load measure below 400 HIV RNA copies/ml.

‡The total eligible for viral suppression dropped to 324 because of the need for having at least one follow-up viral load post-ART initiation (for all but 17 children this means having at least 6 months of follow-up).

†CD4 cell count percentage below 25% for children younger than 1, or below 20% for children 1–2 years, or below 15% for children 3–15 years. All estimates were obtained the weighted Cox proportional hazard.

Table 3

Effect of delaying ART initiation on mortality and virologic response among a cohort of 573 HIV infected, ART-naive children, 15 years or younger, initiated on TB treatment at Harriet Shezi children's clinic, Soweto, South Africa (April 2004, March 2008).

Model & cut-off used for exposure	Total eligible[‡†]	Number of events[‡†] *n* (%)	Hazard ratio (95%CI)		
			Crude	Adjusted for baseline characteristics[‡]	Weighted[**]
Mortality[†]					
Overall					
≤15 days	226	22 (9.73)	1	1	1
>15 days	275	13 (4.73)	0.44 (0.22, 0.88)	0.73 (0.34, 1.55)	0.82 (0.48, 1.41)
≤30 days	288	25 (8.68)	1	1	1
>30 days	206	9 (4.37)	0.46 (0.22, 0.98)	0.72 (0.32, 1.61)	0.86 (0.46, 1.60)
≤60 days	378	26 (6.88)	1	1	
>60 days	111	8 (7.21)	0.96 (0.44, 2.12)	1.76 (0.71, 4.40)	1.32 (0.55, 3.16)
Restricted to severely immunosuppressed children at baseline					
≤15 days	184	21 (11.41)	1	1	1
>15 days	170	11 (6.47)	0.53 (0.26, 1.09)	0.71 (0.32, 1.59)	0.92 (0.51,1.63)
≤30 days	235	24 (10.21)	1	1	1
>30 days	117	7 (5.98)	0.56 (0.24, 1.28)	0.68 (0.27, 1.71)	1.08 (0.56, 2.08)
≤60 days	298	24 (8.05)	1	1	
>60 days	54	7 (12.96)	1.61 (0.71, 3.67)	2.04 (0.77, 5.44)	2.23 (0.85, 5.80)
Virological suppression[*]					
Overall					
≤15 days	152	136 (89.47)	1	1	
>15 days	172	155 (90.12)	1.07 (0.86, 1.35)	0.98 (0.76, 1.26)	–
≤30 days	197	179 (90.86)	1	1	
>30 days	127	112 (88.19)	1.03 (0.81, 1.30)	0.95 (0.73, 1.23)	–
≤60 days	265	238 (89.81)	1	1	
>60 days	59	53 (89.83)	0.96 (0.72, 1.27)	0.84 (0.61, 1.15)	–
Restricted to severely immunosuppressed children at baseline					
≤15 days	133	120 (90.23)	1	1	
>15 days	117	106 (90.60)	1.06 (0.82, 1.37)	0.96 (0.73, 1.26)	–
≤30 days	173	158 (91.33)	1		
>30 days	77	68 (88.31)	0.96 (0.72, 1.28)	0.91 (0.67, 1.24)	–
≤60 days	222	201 (90.54)	1		
>60 days	28	25 (89.29)	0.84 (0.57, 1.23)	0.77 (0.50, 1.18)	–

CI, Confidence interval: estimated using robust variance.

[*] First viral load measure below 400 HIV RNA copies/ml.

[**] Crude and baseline adjusted estimates were obtained using Cox proportional models. Weighted estimates were obtained using pooled logistic regression and accounted for time-dependent level of immuno-suppression, viral load, Weight-for-age Z score and age at TB treatment initiation.

‡†The total eligible varies with each cut-off due to censoring (for example, a child whose follow-up ended 25 days after TB initiation and prior to ART could be classified for the 15 days cut-off but not the 2 other).

†The total eligible for viral suppression dropped to 324 because of the need for having at least one follow-up viral load post-ART initiation (for all but 17 children this means having at least 6 months of follow-up).