

Initial Response to Protease-Inhibitor-Based Antiretroviral Therapy among Children Less than 2 Years of Age in South Africa: Effect of Cotreatment for Tuberculosis

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(See the editorial commentary by Cotton et al, on pages 1113–1114.)

Background. South African guidelines recommend protease-inhibitor-based antiretroviral therapy (ART) with lopinavir-ritonavir for human immunodeficiency virus (HIV)–infected children <36 months of age. We investigated factors associated with viral suppression and mortality among young children initiating ART.

Methods. Treatment-naïve, ART-eligible, HIV-infected children (aged 6–104 weeks) were enrolled in an ART strategies trial in South Africa and initiated protease-inhibitor-based ART. Mortality and the probability of viral suppression (defined as HIV RNA load of <400 copies/mL) by 39 weeks after ART initiation were investigated.

Results. Of 254 children who initiated ART, 99 (39%) were cotreated for tuberculosis during follow-up. The mortality rate was 14%. Factors predicting mortality were lower pre-ART weight-for-age z score and higher HIV RNA load. By 39 weeks, 84% of surviving children achieved viral suppression. Children who were not cotreated for tuberculosis were more likely to achieve viral suppression (94.8%) than were children who were receiving cotreatment at ART initiation (74.2%) or who started tuberculosis cotreatment after ART initiation (51.6%; $P < .001$). Other factors predicting lower probability of viral suppression were lower pre-ART weight- and length-for-age z score, higher HIV RNA load, and World Health Organization disease stage.

Conclusion. High rates of viral suppression can be achieved among infants and young children who initiate protease-inhibitor-based ART. Cotreatment for tuberculosis reduced viral suppression. How best to treat HIV-infected children who require tuberculosis treatment warrants urgent investigation.

In 2007 an estimated 33.2 million people had human immunodeficiency virus (HIV) infection, including 2.5

million children <15 years of age [1]. In infants and young children, immune system immaturity and high viral loads lead to a high risk of rapid disease progression [2, 3], and in sub-Saharan Africa, without access to treatment, ~53% of infected children die by 2 years of age [4]. In past years, increased availability of highly active antiretroviral therapy (ART) has resulted in substantial health improvements for HIV-infected children in high-prevalence, resource-constrained settings [5].

Recently, a ground-breaking trial demonstrated a statistically significant reduction in mortality among infants in whom ART was initiated during the first months of life [6]. Accordingly, the World Health Organization (WHO) revised pediatric treatment guidelines to recommend ART initiation for all infected in-

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fants <12 months of age, regardless of clinical or immunological status [7]. Guidelines also advise that infants previously exposed to nevirapine for prevention of mother-to-child transmission receive ART with 2 nucleoside reverse-transcriptase inhibitors and a boosted protease inhibitor [7]. Although good viral responses have been reported among older children receiving protease-inhibitor-based ART [8, 9], data are limited among infants and young children.

In this study, we examined the mortality and viral response to protease-inhibitor-based ART in a cohort of children <2 years of age who were enrolled in the prerandomization phase of an ART strategies trial in Johannesburg, South Africa. Specifically, we evaluated the effectiveness of protease-inhibitor-based treatment by adherence, tuberculosis cotreatment, age, and pretreatment characteristics, including CD4 cell count and viral load.

METHODS

Study design. We report results from the prerandomization phase of an ART strategies trial [10]. HIV-infected children (aged 6–104 weeks) who were exposed to nevirapine for prevention of mother-to-child transmission and eligible for ART on the basis of immunological or clinical criteria but who were otherwise treatment-naïve were enrolled between April 2005 and July 2007 at 1 site in Johannesburg, South Africa. All children were treated with protease-inhibitor-based ART until they became eligible for randomization or until 52 weeks. The study was approved by the institutional review boards of Columbia University and the University of the Witwatersrand, and each child's guardian signed an informed consent form. For this analysis, we included only follow-up time accrued prior to randomization.

Drug regimens. All children who were ≥ 6 months of age were treated with lopinavir-ritonavir (250 mg/m²), stavudine (1 mg/kg), and lamivudine (4 mg/kg) every 12 h, following South African guidelines [11]. Children who were <6 months of age or those receiving tuberculosis treatment received ritonavir (400–450 mg/m²), stavudine (1 mg/kg), and lamivudine (4 mg/kg) every 12 h. When children passed age 6 months, or after they completed tuberculosis treatment, ritonavir was switched to lopinavir-ritonavir. At the time of the study, “super-ritonavir-boosted” lopinavir or doubling of the lopinavir-ritonavir dose had not yet been included in South African guidelines; ritonavir was the protease inhibitor recommended for young (<6 months old) and tuberculosis cotreated children [11]. Because of poor pharmacokinetic results, double-dose lopinavir-ritonavir is no longer recommended [12]. At each visit, doses were adjusted according to body surface area. All medications were administered as syrups.

Tuberculosis diagnosis was made on the basis of clinical factors; diagnostic tests were performed when available. Data on

the diagnostic tests were not systematically collected. If clinicians felt that tuberculosis treatment was indicated, it was initiated and the children's ART regimens were changed accordingly. Tuberculosis treatment was prescribed according to South African guidelines [13]: rifampin and isoniazid for 6 months, with pyrazinamide during the initial 2 months. For cases of concomitant BCG disease, ethionamide was added to the regimen, and the treatment duration was extended to 9 months. Tuberculosis treatment was also prescribed for some children with BCG disease only; treatment consisted of rifampin, isoniazid, and ethionamide for 9 months. BCG vaccination is routinely given at birth in South Africa.

Study measurements. Blood samples drawn prior to ART initiation were tested for CD4 cell count and HIV RNA quantity, using the standard assay (quantification range, 400–750,000 copies/mL; Roche Amplicor). Blood sampling was repeated at weeks 4, 8, 16, 24, 36, and 52 after ART initiation (the latter 2 time points only if the patient was not yet randomized) and tested for HIV RNA load. The ultrasensitive test (quantification range, 50–150,000 copies/mL; Roche) was usually used, but occasionally, the standard test was used instead because of errors or clinical expectations that the HIV RNA load may be high. CD4 cell counts were measured at 4, 16, 24, 36, and 52 weeks after ART initiation. At each visit, the child's weight and length were measured, and concomitant medications were recorded. Children were examined by a physician monthly and whenever medically warranted. Counseling in regard to medication administration, social needs, and adherence was provided for the children's caretakers.

Adherence assessments. At each visit, caretakers were asked to return all medication bottles and were queried about adherence. The pharmacists weighed the bottles and reconciled the contents with the expected usage of each drug since the previous visit. Caretakers' reports included missed doses for the following time intervals: 1–2 weeks, 2–4 weeks, 5–12 weeks, and >12 weeks prior to the visit. For this analysis, we used the data from weeks 4, 12, 24, and 39.

Statistical methods. We compared the demographic and clinical variables between the different subgroups before treatment by use of the Wilcoxon rank sum test for continuous variables and the χ^2 or Fisher exact test for categorical variables. The main outcome measures were mortality and viral suppression. We defined viral suppression as <400 copies/mL because this measurement was available for all children. The independent variables were age, weight-for-age *z* score, height-for-age *z* score, CD4 cell percentage, CD4 cell count, WHO disease stage, adherence level, and tuberculosis treatment. Weight-for-age *z* scores and height-for-age *z* scores were calculated using Anthro software (version 2; WHO). We used Kaplan-Meier methods to calculate for each independent variable the probability of death and the probability of viral sup-

Table 1. Characteristics of Human Immunodeficiency Virus (HIV)-Infected Infants and Young Children at Initiation of Protease-Inhibitor-Based Antiretroviral Therapy

Variable	All patients	Patients receiving ritonavir	Patients receiving lopinavir-ritonavir	<i>P</i>
No. of patients	254	116	138	...
Male sex, no. (%)	132 (52)	56 (48)	76 (55)	...
Median age, months (IQR)	8.75 (5.2–13.8)	5.65 (4.1–13.4)	9.44 (6.9–14.2)	<.001
Median HIV RNA load, 10 ³ copies/mL (IQR)	750 (642–750)	750 (668–750)	750 (442–750)	.133
Median CD4 cell count, cells/ μ L (IQR)	869.0 (466–1392)	868 (446–1404)	870.5 (473–1390)	.781
Median CD4 cell percentage (IQR)	18.95 (12.8–24.5)	17.9 (12.8–25.6)	19.2 (13.1–24.1)	.973
Mean weight-for-age z score (SD)	–2.38 (1.72)	–2.49 (1.71)	–2.29 (1.72)	.293
Mean height-for-age z score (SD)	–3.45 (1.72)	–3.53 (1.83)	–3.38 (1.61)	.558
WHO disease stage, no. (%)				
I	39 (15.4)	16 (13.8)	23 (16.7)	
II	11 (4.3)	1 (0.9)	10 (7.3)	
III	130 (51.2)	62 (53.5)	68 (49.3)	
IV	74 (29.1)	37 (31.9)	37 (26.8)	.071

NOTE. The infants and young children were 6–104 weeks of age. *P* values are for comparison between ritonavir and lopinavir-ritonavir regimens. IQR, interquartile range; SD, standard deviation; WHO, World Health Organization.

pression by 39 weeks after ART initiation. Follow-up time was censored at randomization or at time of last study assessment and was truncated at 39 weeks after ART initiation. Cox proportional hazards regression was used for multivariate analyses. Tuberculosis cotreatment was investigated as a time-dependent variable and as a fixed covariate. Variables were retained in the final models if they were statistically significantly associated with the main outcome ($P < .05$) or if their inclusion led to changes in the estimated hazard ratio (HR) of other covariates by $>10\%$.

To categorize adherence, assessed on the basis of unused medication, we assigned the child to 1 of 4 categories at each visit: (a) returning 10% more than the expected drug volume, (b) returning 10% less than the expected drug volume, (c) returning the anticipated drug volume to within 10%, and (d) not returning the bottle. The level of adherence over the entire follow-up period was defined hierarchically ($a > b > c > d$), meaning that once a child was classified as “returning more,” he or she stayed in this category throughout the remaining follow-up period. This classification was used for each drug independently and for all drugs combined. On the basis of the observed relationship between viral suppression and these categories, we combined *b* and *c* into an “adherent” category and combined *a* and *d* into a “nonadherent” category, in terms of medication return. For caretaker reports, patients were classified as nonadherent if the caregiver ever reported ≥ 1 missed dose at any visit. All analyses were performed using SAS software (version 9.1.3; SAS Institute).

RESULTS

Study population. Of 272 treatment-naive children enrolled, 9 (3.3%) died and 9 (3.3%) withdrew before ART initiation.

Characteristics of the 254 children who initiated ART are shown in Table 1. A ritonavir-based regimen was initiated because of young age in 54 (21.3%) of 254 children and because of tuberculosis cotreatment in 62 (24.4%) of 254 children. By 39 weeks, 27 (10.6%) of 254 children were lost to follow-up and 32 (14%) of 254 children had died. The median duration of follow-up while receiving therapy was 36 weeks (interquartile range [IQR], 26–47 weeks).

Tuberculosis treatment. At ART initiation, 62 (24.4%) of 254 children were receiving tuberculosis treatment, and by 39 weeks an additional 37 (14.6%) of 254 children had started tuberculosis cotreatment. Children who initiated tuberculosis treatment before they initiated ART had lower median pre-treatment CD4 cell percentage, were more wasted and growth retarded, and were older than children who were never cotreated (Table 2). For children who were receiving tuberculosis treatment at ART initiation, tuberculosis treatment continued for 30 weeks on average (IQR, 25–37 weeks). Children cotreated for tuberculosis after ART initiation had higher HIV RNA viral loads than those of children never cotreated (Table 2). For children who initiated tuberculosis cotreatment after ART initiation, the median time between ART start and tuberculosis cotreatment initiation was 4 weeks (IQR, 3–9 weeks), and the median duration of tuberculosis treatment was 24 weeks (IQR, 13–29 weeks).

Mortality. Mortality within the first 39 weeks of ART was associated with a lower weight-for-age z score and a higher HIV RNA viral load at initiation of treatment (Table 3). The mortality rate was 31% among children with a weight-for-age z score of < -4 and was 8% among those with a weight-for-age z score of > -2 (HR, 1.6 [95% confidence interval {CI}, 1.2–2.2]; $P = .002$). Children with HIV RNA loads of $\geq 750,000$

Table 2. Characteristics of Human Immunodeficiency Virus (HIV)-Infected Infants and Young Children at Initiation of Protease-Inhibitor-Based Antiretroviral Therapy (ART), Stratified by Tuberculosis Cotreatment Status

Variable	Never received tuberculosis cotreatment	Received tuberculosis treatment before ART initiation	Received tuberculosis cotreatment after ART initiation	P	
				Before vs never	After vs never
No. of patients (N = 254 total)	155	62	37
Median age, months (IQR)	7.8 (4.8–12.6)	13.2 (9.1–17.7)	6.84 (4.7–8.8)	<.001	.111
Median HIV RNA load, 10 ³ copies/mL (IQR)	750 (593–750)	750 (367–750)	750 (750–750)	.526	.039
Median CD4 cell percentage (IQR)	20.7 (13.7–26.9)	13.9 (9.9–19.7)	17.2 (13.4–25.5)	<.001	.110
Mean weight-for-age z score (SD)	–2.23 (1.8)	–2.67 (1.7)	–2.55 (1.6)	.024	.116
Mean height-for-age z score (SD)	–3.28 (1.7)	–3.90 (1.6)	–3.44 (2.0)	.019	.642
WHO disease stage, no. (%)					
I	30 (19.4)	3 (4.8)	6 (16.2)		
II	9 (5.8)	1 (1.6)	1 (2.7)		
III	79 (51.0)	33 (53.2)	18 (48.7)		
IV	37 (23.9)	25 (40.3)	12 (32.4)	.007	.660
Starting regimen, no. (%)					
Includes lopinavir-ritonavir	112 (72.3)	0 (0.0)	26 (70.3)		
Includes ritonavir	43 (27.7)	62 (100.0)	11 (29.7)	<.001	.840

NOTE. The infants and young children were 6–104 weeks of age. IQR, interquartile range; SD, standard deviation; WHO, World Health Organization.

copies/mL had a 19% probability of dying, compared with 4% among those with lower viral loads. The association between death and HIV RNA load was slightly attenuated after adjustment for pretreatment CD4 cell percentage, weight-for-age z score, and age at ART initiation (HR, 3.2 [95% CI, 0.970–10.8]; $P = .06$). Children who initiated tuberculosis cotreatment after ART initiation had a 22% probability of dying by the end of 39 weeks, compared with 11% among those who were never treated for tuberculosis and 14% among those who initiated tuberculosis cotreatment before ART start, but these differences were not statistically significant. If tuberculosis cotreatment was included as a time-dependent variable, there was still no statistically significant association between tuberculosis cotreatment and mortality (HR, 1.65 [95% CI, 0.80–3.42]).

Virological, clinical, and immunological response. Initiation of ART was associated with improvements in clinical, immunological, and virological characteristics. The probability of viral suppression was 45.6% by the end of 12 weeks, 70.8% by the end of 26 weeks, and 83.7% by the end of 39 weeks after ART initiation (Figure 1). Among the 179 children who achieved viral suppression, 170 (95%) had an ultrasensitive assay, of whom 87 (51.2%) and 111 (65.3%) had ≥ 1 measurement of <50 copies/mL by 24 and 39 weeks, respectively. The weight-for-age z score increased from -2.38 ± 1.8 at ART initiation to 0.82 ± 1.3 at 39 weeks after ART initiation, and the median increase in CD4 cell percentage was 9.4 (IQR, 4.3–15.7). Changes in CD4 cell percentage were similar regardless of tuberculosis cotreatment. The median increase in CD4 cell percentage during the first 39 weeks of ART was 10.4% (IQR, 4.3–17.5) among children never cotreated, compared with 8.3%

(IQR, 5.2–11.4; $P = .16$) among those with tuberculosis treatment at ART initiation and 9.4% (IQR, 3.1–13.4; $P = .24$) among children cotreated for tuberculosis after ART initiation.

Predictors of viral suppression. In univariate analysis, pretreatment WHO disease stage, CD4 cell percentage, height-for-age z score, weight-for-age z score, HIV RNA load, and tuberculosis cotreatment were associated with viral suppression (Table 4 and Figure 2). In multivariate analysis, pretreatment weight-for-age z score, HIV RNA quantity, and tuberculosis cotreatment remained associated with viral suppression after adjustment (Table 4). If tuberculosis cotreatment was entered as a time-dependent covariate, then the association with viral suppression was similar (HR, 0.54 [95% CI, 0.37–0.79]; $P = .002$) after adjusting for weight-for-age z score and viral load. There were no differences in suppression probabilities among children never cotreated for tuberculosis whether they initiated ritonavir-based ART (91% probability of suppression) or lopinavir-ritonavir-based ART (96.3% probability of suppression; $P = .19$ [log-rank test]).

Of 41 children who started tuberculosis treatment before ART initiation and achieved viral suppression, 22 (53.6%) achieved viral suppression while being cotreated and 19 (46.4%) achieved viral suppression after completing tuberculosis therapy. The median time to suppression was 14 weeks (IQR, 12–24 weeks), which did not differ from the time to suppression among 123 children never cotreated (median, 13 weeks [IQR, 12–24 weeks]; $P = .47$). Among 15 children who started tuberculosis cotreatment after ART initiation who achieved viral suppression, 1 (6.7%) achieved viral suppression before tuberculosis cotreatment initiation, 12 (80%) achieved viral sup-

Table 3. Factors at Time of Antiretroviral Therapy (ART) Initiation Associated with Mortality during the First 39 Weeks of Treatment

Variable	No. of patients		Kaplan-Meier results		Cox proportional hazards results			
	who died	who survived	No. of patients who survived	Probability of dying	P ^a	Crude HR (95% CI)	Adjusted HR (95% CI)	P
Total	32	222	222	14.0				
Sex								
Male	18	114	114	14.7		Ref.	...	
Female	14	108	108	13.2	.547	0.81 (0.40–1.62)	...	
Age, months								
<12	27	148	148	17.6		2.54 (0.98–6.61)	2.44 (0.92–6.45)	.073
≥12	5	74	74	6.4	.047	Ref.	Ref.	
Weight-for-age z score ^b								
>–2	8	103	103	8.1				
>–3 to –2	3	53	53	6.5				
>–4 to –3	8	34	34	20.3				
≤–4	13	32	32	30.8	.001	1.75 (1.30–2.36)	1.61 (1.19–2.19)	.002
HIV RNA load, copies/mL ^c								
<750,000	3	76	76	3.8		Ref.	Ref.	
≥750,000	29	137	137	19.3	.005	4.71 (1.44–15.48)	3.22 (0.97–10.78)	.057
Pretreatment CD4 cell percentage								
<15	17	78	78	19.1		1.97 (0.99–3.95)	1.72 (0.84–3.50)	.136
≥15	15	144	144	11.1	.051	Ref.	Ref.	
Tuberculosis treatment								
Never	16	139	139	11.2		Ref.	...	
Started before ART initiation	8	54	54	13.9		1.10 (0.47–2.56)	...	
Started after ART initiation	8	29	29	22.4	.321	1.88 (0.80–4.41)	...	

NOTE. CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; ref., reference value.

^a Log-rank test.

^b Included in Cox proportional hazard analyses as continuous variable.

^c Pretreatment viral load was unavailable for 9 children.

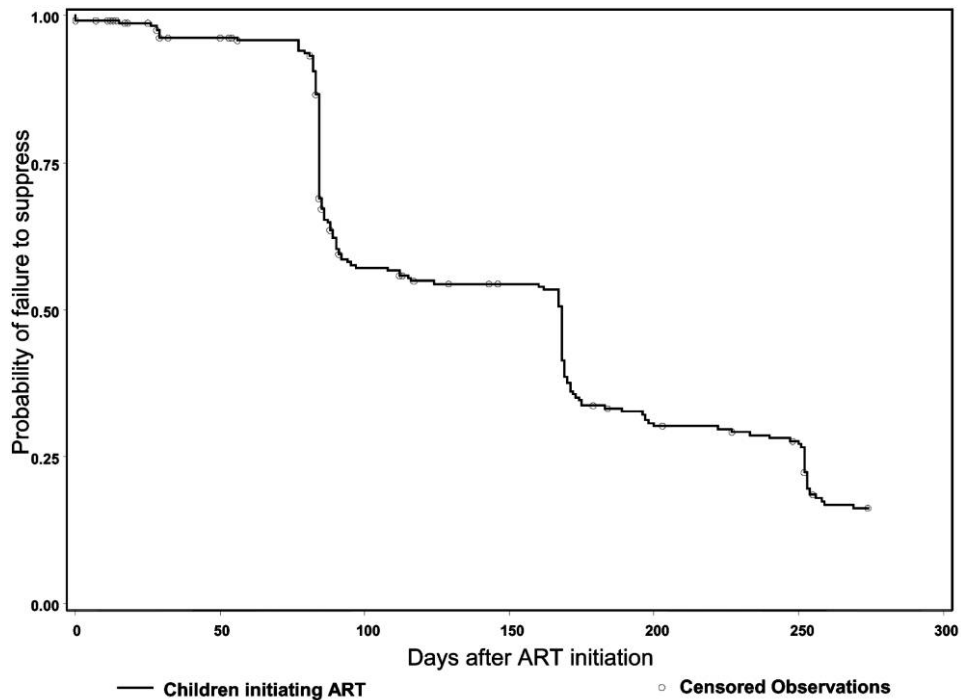


Figure 1. Kaplan-Meier analysis of human immunodeficiency virus suppression (defined as a viral load of <400 copies/mL) in children initiating protease-inhibitor-based antiretroviral therapy (ART).

pression while being cotreated, and 2 (13.3%) achieved viral suppression after completing tuberculosis therapy. The average time from ART initiation until the first viral load measurement of <400 copies/mL was 24 weeks (IQR, 12–29 weeks), which did not differ from those of children never cotreated ($P = .21$).

Viral rebound. The probability of viral rebound (viral load, >400 copies/mL) within 16 weeks after viral suppression was 17.6%. Among all factors investigated, only tuberculosis cotreatment was associated with the risk of viral rebound. Of 15 children who initiated tuberculosis cotreatment after ART initiation and achieved viral suppression, 8 (53.3%) experienced viral rebound (viral load, >400 copies/mL), compared with 12% among those without tuberculosis and 2.8% among those who started tuberculosis cotreatment before ART initiation (HR, 5.2 [95% CI, 2.1–12.9]; $P < .001$).

Adherence. There was no association between caretakers' reports of adherence and viral suppression. Cumulatively, by the end of 39 weeks, the caretakers of 42 (23.5%) of 179 children who achieved viral suppression and those of 14 (21.2%) of 66 children who did not achieve viral suppression reported ever having missed a drug dose ($P = .80$; information was missing for 9 children). In contrast, nonadherence based on medication return was statistically significantly associated with less viral suppression. Among the children classified as nonadherent on the basis of medication return ($n = 91$), 78.3%

achieved viral suppression after 39 weeks of ART, compared with 86.5% among those classified as adherent ($n = 154$; HR, 0.66 [95% CI, 0.47–0.93]; $P = .02$).

There was a statistically insignificant trend toward worse adherence (based on medication reconciliations) with tuberculosis cotreatment status: 25 (40.3%) of 62 children were classified as nonadherent among those receiving tuberculosis cotreatment at ART initiation, 16 (43.2%) of 37 children were classified as nonadherent among those cotreated for tuberculosis after ART initiation, and 50 (34.3%) of 146 children were classified as nonadherent among those never treated for tuberculosis (information was missing for 9 children). Among children who were never treated for tuberculosis ($n = 155$), the probability of viral suppression was high regardless of adherence level as determined by the amount of medication returned (92.1% of nonadherent children achieved viral suppression, and 96.1% of adherent children achieved viral suppression; $P = .14$). The association between adherence and suppression in the subgroup of children who never received tuberculosis cotreatment became statistically significant in the multivariate analysis after adjusting for pretreatment viral load and weight-for-age z score (HR, 0.64 [95% CI, 0.42–0.98]; $P = .04$). Among children ever receiving tuberculosis treatment ($n = 99$), viral suppression occurred among 58.9% of nonadherent children, compared with 70.5% of adherent children (crude HR, 0.81 [95% CI, 0.47–1.4]; $P = .44$; adjusted HR, 0.77 [95% CI, 0.43–1.4]; $P = .38$).

Table 4. Factors Associated with Human Immunodeficiency Virus (HIV) Suppression to RNA Load of <400 Copies/mL

Variable	No. of patients		Kaplan-Meier results		Cox proportional hazards results		
	with suppression	No. of patients without suppression	Probability of suppression	P ^a	Crude HR (95% CI)	P	Adjusted HR (95% CI)
Total	179	75	83.7				
Sex							
Male	91	41	82.6		Ref.		...
Female	88	34	85.1	.860	0.98 (0.73–1.31)	.870	...
Age, months							
<6	52	27	84.6		Ref.		...
6–12	67	29	84.0		1.0 (0.71–1.47)	.910	...
12–24	60	19	83.3	.990	1.0 (0.71–1.50)	.872	...
WHO disease stage							
I and II	44	6	94.9		Ref.		...
III and IV	135	69	80.8	.006	0.63 (0.45–0.89)	.008	...
Weight-for-age z score ^b							
>–2	93	18	95				
>–3 to –2	39	17	76.7				
>–4 to –3	25	17	78.7				
≤–4	22	23	67.7	.001	0.77 (0.66–0.88)	<.001	0.78 (0.68–0.91)
Height-for-age z score ^b							
>–2	39	6	93.4				
>–3 to –2	45	12	88.9				
>–4 to –3	44	21	84.7				
≤–4	51	36	73.3	.019	0.82 (0.72–0.93)	.003	...
CD4 cell percentage							
<15	59	36	77.9		0.67 (0.50–0.92)	.013	...
≥15	120	39	87	.009	Ref.		...
HIV RNA load, copies/mL ^c							
<750,000	68	11	93.1		Ref.		Ref.
≥750,000	103	63	78.4	<.001	0.47 (0.35–0.64)	<.001	0.52 (0.38–0.71)
Tuberculosis treatment							
Never	123	32	94.8		Ref.		Ref.
Started before ART initiation	41	21	74.2		0.55 (0.38–0.78)	<.001	0.54 (0.37–0.79)
Started after ART initiation	15	22	51.6	<.001	0.30 (0.17–0.51)	<.001	0.36 (0.21–0.61)

NOTE. ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; ref., reference value; WHO, World Health Organization.

^a Log-rank test.

^b Included in Cox proportional hazard analyses as continuous variable.

^c Treatment-naïve viral load was unavailable for 9 children.

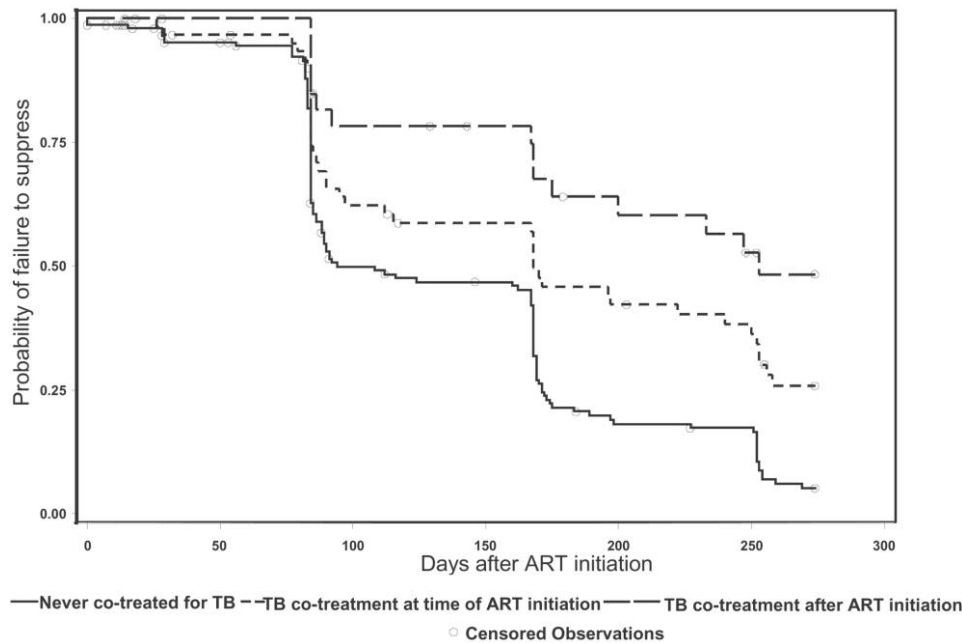


Figure 2. Kaplan-Meier analysis of human immunodeficiency virus suppression (defined as a viral load of <400 copies/mL) stratified for tuberculosis (TB) cotreatment. ART, antiretroviral therapy.

After adjusting for adherence level, the association between tuberculosis cotreatment and viral suppression remained statistically significant (HR among children cotreated for tuberculosis at ART initiation, 0.54 [95% CI, 0.37–0.78]; HR among children cotreated for tuberculosis after ART initiation, 0.36 [95% CI, 0.21–0.62]).

DISCUSSION

In this study of infants and young children with advanced HIV disease, high rates of viral suppression were achieved with protease-inhibitor-based ART. Overall, 83.7% of the patients achieved a viral load of <400 copies/mL by 39 weeks. Of those who achieved viral suppression, 17.6% experienced viral rebound within 16 weeks after suppression. These high rates of viral suppression are comparable to the rates seen in studies of other cohorts of children who received protease-inhibitor-based ART [8, 9, 14]. A multicenter study that included data from the United States, Canada, Argentina, the Bahamas, Panama, and South Africa [9] reported good clinical response, with robust weight gain and immunological improvements, which is consistent with the findings in other studies that evaluated immunological response [5, 8, 15]. At the same time, although virological response was excellent, mortality rates in our cohort were high in the first weeks of treatment, most likely because of advanced disease at ART initiation [16].

Children with higher pretreatment viral loads and lower weight-for-age *z* scores were less likely to achieve viral suppression, which is consistent with the findings in previous stud-

ies [17–20]. However, children who received tuberculosis cotreatment at the time of ART initiation and, in particular, children who initiated tuberculosis cotreatment after ART initiation were less likely to achieve viral suppression and more likely to experience viral rebound than were children who did not receive tuberculosis cotreatment. Because of the relatively short follow-up time, it is possible that this rebound rate is a minimum estimate. This finding is important given the magnitude of the tuberculosis epidemic in countries with a high burden of HIV infection. A study from the Western Cape estimated 23.4 cases of active tuberculosis per 100 HIV-infected children per year [21], and tuberculosis is the most common HIV-associated infection [22]. In sub-Saharan Africa, the high rate of concomitant tuberculosis [23] and BCG-related disease after ART initiation [10, 24] further complicate antiretroviral treatment in children.

Rifampin is part of standard tuberculosis treatment in South Africa and is also used as part of treatment of BCG disease. Rifampin, along with the nucleoside reverse-transcriptase inhibitors and protease inhibitors, is a strong inducer of cytochrome P450 enzymes. Drug-drug interactions may result in subtherapeutic plasma concentrations of antiretroviral drugs [25, 26]. In adults, coadministration of rifampin with ritonavir-boosted lopinavir and ritonavir-boosted atazanavir regimens results in subtherapeutic protease inhibitor concentrations [25, 26]. A recent pediatric pharmacokinetic study reported decreased lopinavir plasma concentrations in children receiving tuberculosis cotreatment who received lopinavir-ritonavir at

double the current therapeutic dose [12]. Such interactions may account partially for our findings of lower rates of viral suppression with tuberculosis cotreatment.

Studies among adults have shown complex associations between tuberculosis cotreatment and ART [27–32]. Those studies reporting no associations between suppression rates and tuberculosis cotreatment [28–32] for the most part did not distinguish between different ART regimens, and in 1 study, rifabutin was used [28]. Drug-drug interactions may also result in inadequate levels of tuberculosis medications, particularly rifampicin, and possible undertreatment of tuberculosis. Two recent pediatric studies reported serum values for tuberculosis drugs that were considerably lower than the suggested lower limits in adults [33, 34].

Ritonavir was recommended for children receiving ART who required tuberculosis treatment at the time this study was initiated. Ritonavir is no longer recommended, but optimal ART regimens for children who require tuberculosis cotreatment are still a controversial matter. In contrast to the findings of studies with standard protease inhibitor regimens and the pediatric study of double-dose lopinavir-ritonavir [12], the findings of 2 recent studies suggest that “superboosted” lopinavir treatment (ie, lopinavir-ritonavir with additional ritonavir) provides adequate lopinavir plasma concentrations when administered in combination with rifampin [12, 26]. However, superboosted dosing has been associated with high rates of hepatotoxicity in adults [26], raising challenges for appropriate treatment recommendations.

Another possible explanation for our findings might be differences in the level of adherence between tuberculosis cotreated and untreated groups due to the poor palatability of ritonavir [35] or the increased medication burdens associated with treating 2 diseases. There was a suggestion in our data that the high burden of multiple medications influenced adherence: patients who were cotreated for tuberculosis were slightly less likely to be adherent. These results are difficult to interpret because caretakers’ reports may be biased toward socially acceptable responses and because medicine reconciliations are difficult to interpret, given the necessity of repeat dosing in young children through spitting, etc.

Ritonavir may be less potent than ritonavir-boosted lopinavir, and in adults, protease inhibitor resistance occurs more often with unboosted protease-inhibitor-based therapy than with boosted protease-inhibitor-based therapy [36]. Chadwick and colleagues [14] reported good virological response at 36 weeks in children who received ritonavir-based treatment, but at 104 weeks only 36% of children had viral loads of <400 copies/mL. Children in our study who received ritonavir because of their young age, and not because of tuberculosis cotreatment, had outcomes similar to those of children who started with a lopinavir-ritonavir-based regimen. However, chil-

dren were switched to lopinavir-ritonavir once they reached 6 months of age, which may have masked differences.

Rather than direct effects, the observed association may be due to confounding by the severity of disease between those who did and those who did not receive tuberculosis cotreatment. Children who initiated tuberculosis treatment before ART initiation had lower pretreatment CD4 cell percentages than those of children who never received cotreatment, and children cotreated for tuberculosis after ART initiation had higher pretreatment viral loads than those of children never cotreated. Such children may also have had advanced and rapidly progressing HIV disease, which might explain the lower suppression probabilities. We adjusted for these baseline factors, but we may not have been able to fully account for all differences.

Another possible mechanism to explain differences in suppression probabilities relates to interindividual differences in immunological and viral responses to therapy. An insufficient immunological response after ART initiation might lead to a higher risk of developing tuberculosis, or conditions that might be confused with tuberculosis, and these processes, rather than exposure to the drugs, could be related to failure to achieve suppression, resulting in reverse causality. A study among South African adults [31] observed a smaller median increase in CD4 cell count after ART initiation among those who developed tuberculosis, compared with those without tuberculosis. As a consequence, the researchers concluded an association between suboptimal immunological response to ART and development of tuberculosis. However, in our study, there was no difference in the median change in CD4 cell percentage between children in the different tuberculosis treatment exposure categories. Overall, the median increase in CD4 cell percentage in our study was comparable with those in other pediatric studies [8, 9, 15, 37]. Immune reconstitution inflammatory syndrome might be another explanation. Many of the children who initiate tuberculosis cotreatment after ART initiation meet criteria for immune reconstitution inflammatory syndrome. We have previously observed BCG- and tuberculosis-related immune reconstitution inflammatory syndrome to be common (21%) and to adversely affect viral suppression rates [10]. However, this would not explain the poor virological response among children who initiated tuberculosis treatment before initiating ART.

There are several limitations to our study. We stratified the patients into tuberculosis cotreatment groups rather than tuberculosis disease groups, because of the difficulties of diagnosing tuberculosis in young children. The diagnosis of tuberculosis was made on the basis of clinical findings, chest X-ray radiographs, and exposure history. Sputum cultures were rarely performed, and interferon γ release assays were not used. Therefore, it is possible that some children who received tuberculosis treatment did not have tuberculosis. Our findings

highlight the urgent need to improve tuberculosis diagnostics for children, because tuberculosis cotreatment in the ART-treated child may have adverse consequences. Another limitation of our study is that no further viral load quantification was performed for pretreatment loads of $\geq 750,000$ copies/mL, which limited our ability to adjust for pretreatment viral load and potentially contributed to residual confounding.

In conclusion, high rates of viral suppression can be achieved among infants and young children who initiate protease-inhibitor-based ART. Our findings suggest that ritonavir-based ART in children <2 years of age who are cotreated for tuberculosis is associated with lower rates of viral suppression. How best to diagnose tuberculosis in infants and young children remains an ongoing challenge. The ideal treatment strategy for young children who require cotreatment with antiretroviral and antituberculosis therapy remains elusive. Given that many children will be cotreated for tuberculosis, there is an urgent need to determine optimal drug regimens and dosing to ensure successful outcomes for HIV-infected children initiating ART.

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