

Virologic Response to Protease-Inhibitor-Based Antiretroviral Therapy among Children less than 2 Years of Age Co-treated for Tuberculosis in South Africa

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Abstract

Background: South African guidelines recommend protease-inhibitor (PI)-based antiretroviral therapy (ART) with lopinavir/ritonavir (LPV/r) for HIV-infected children < 36 months (mos) of age. We describe factors associated with viral suppression among young children initiating ART.

Methods: Treatment-naïve ART eligible HIV-infected children, ages 6 weeks-24 mos were enrolled into an ART strategies trial in Johannesburg, South Africa. Children < 6 mos of age received LPV/r, stavudine (d4T) and lamivudine (3TC). Children < 6 mos or receiving TB treatment (rifampin, isoniazid, pyrazinamide, and ethambutol if necessary) received ritonavir (RTV)+d4T+3TC. The probability of achieving a HIV RNA < 400 copies/ml at 9 mos was calculated by Kaplan Meier methods.

Results: 254 children (median age 9 mos, 80% WHO stage III/IV, median CD4 19%) initiated ART. At ART initiation, 24% were receiving TB treatment, during follow-up, another 15% began TB treatment. At 9 mos mortality was 14% and 84% of surviving children achieved HIV RNA < 400 copies/ml. While 84.8% of children never co-treated for TB suppressed, only 74.2% of those on TB treatment at ART initiation and 51.6% of those starting TB treatment after ART initiation suppressed. Pre-ART low weight- and height- for- age z-scores, WHO-stage and higher viral load were each associated with significantly reduced likelihood of suppression. Younger age was associated with increased mortality but not with likelihood of viral suppression.

Conclusions: High rates of viral suppression can be achieved among infants and young children initiating PI-based ART. Co-treatment for TB adversely influences suppression rates. How best to treat HIV-infected children who require TB treatment needs urgent investigation.

Background

In the last decade the introduction of highly activated ART has led to significant improvements in mortality and morbidity of HIV-infected children. The first-line regimen recommended for nevirapine-exposed infants is two nucleoside reverse transcriptase inhibitors (NRTI) combined with the boosted protease inhibitor (PI) lopinavir/ritonavir (LPV/r-Kaletra)[®]. In older children, good virological response to ART has been reported, not only in children and infants experience, particularly with boosted TB-based therapy is still limited. In sub-Saharan Africa, pediatric ART is complicated by the high rate of concomitant tuberculosis (TB) and Bacillus Calmette-Guérin (BCG) related complications after ART initiation, requiring co-treatment for these diseases. Both TB/BCG-disease and HIV necessitate multiple drugs for effective treatment. This raises concerns about possible drug-drug interactions resulting in decreased drug concentrations, increased hepatic toxicity, and altered drug-absorption.

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Methods

Study design: The NEVEREST study, a randomized ART strategies trial, took place in Johannesburg, Gauteng, South Africa. HIV-infected children aged 6 weeks to 24 months who were perinatally nevirapine-exposed and eligible for ART, were enrolled. Children > 6 months of age were started on LPV/r, d4T and 3TC. Children under 6 months of age or children receiving co-treatment for TB were started on ritonavir (RTV), d4T and 3TC and were switched to a LPV/r based regimen when 6 months old or after finishing TB co-treatment respectively. TB treatment consisted of rifampin and isoniazid for 6 months with pyrazinamide added during the initial 2 months. In case of concomitant BCG-disease, ethambutol was added to the treatment and therapy was expanded to 9 months.

Before ART initiation and during follow up HIV RNA viral load (Roche Diagnostics, Branchburg, NJ, USA) and CD4 count were measured. For this analysis viral suppression was defined as HIV RNA < 400 copies/ml and viral rebound was defined as HIV RNA > 400 copies/ml after being initially suppressed. If viral suppression was achieved for at least 3 months, children were randomized to one of two different ART regimens of the NEVEREST study.

Statistical analysis: For this analysis follow up was censored at time of randomization. Main outcome measures are viral suppression and mortality. Wilcoxon signed-rank-test was used for continuous variables and Chi-square test or Fisher's exact test for categorical variables. We calculated for each independent variable (a) the probability to achieve a HIV RNA < 400 copies/ml by 9 month post-ART initiation and b) the probability of death, using Kaplan-Meier methods. Finally we performed Cox proportional hazards regression analyses relating immunological and clinical characteristics at ART initiation with viral suppression or death, adjusting all models for potential confounders.

Results

Study population: 254 children with a median age of 9 months initiated ART and are included in this analysis. 191(75.2%) had a CD4 percentage below 25%, 167(67.7%) children had an HIV RNA > 750,000 copies/ml and 204 (80.2%) children were classified as WHO-stage III or IV at ART initiation.

Drug regimen
Of those 254 children newly initiating ART 136 (54.3%) started a LPV/r-based regimen and 116 (45.7%) patients started a RTV-based regimen. This was due to age < 6 mos in 54 (46.6%) children and lo co-treatment for TB in 62 (53.4%) children. By the end of 9 months an additional 37(14.6%) children started TB treatment.

Characteristics of study population at time of ART initiation	
Total	254
Median age in months (IQR)	8.75 (5.18-13.8)
Median viral load in copies/ml (IQR)	750,000 (642,000-750,000)
CD4% median (IQR)	18.95% (12.8-24.5)
Mean weight-for-age z-score (WAZ) (std. dev.)	-2.38 (1.7)
Mean height-for-age z-score (HAZ) (std. dev.)	-3.41 (1.7)
WHO stage (% of total)	
I	39 (15.4)
II	11 (4.3)
III	130 (51.2)
IV	74 (29.1)

Characteristics of children in subgroups of TB co-treatment

Children who started TB treatment before ART treatment were older than those never treated for TB/BCG-disease, had lower CD4% and had higher HAZ-scores. 94% were classified as WHO stage III or IV.

Children who started TB treatment after ART treatment initiation had a higher median viral load (p=0.04) compared to those never treated for TB. There were no differences in age, CD4%, WHO-stage, WAZ-scores and HAZ-scores.

	"Never TB"	"TB at" ART start	"TB at" vs. "never TB"	"TB after" ART start	"TB after" vs. "never TB"
Total	155	62		37	
Median age in months (IQR)	7.8(4.8-12.6)	13.2(9.1-17.7)	<0.001	6.8(4.7-8.8)	0.1
Median viral load in copies/ml (IQR)	750,000 (593,000-750,000)	750,000 (367,000-750,000)	0.5	750,000 (750,000-750,000)	0.04
Median CD4% (IQR)	20.7(13.7-26.9)	13.9(9.9-18.7)	<0.001	17.2 (13.4-25.5)	0.1
Mean WAZ (std.dev.)	-2.23 (1.8)	-2.67(1.7)	0.01	-2.56(1.6)	0.3
Mean HAZ (std.dev.)	-3.28(1.7)	-3.90(1.6)	0.01	-3.44(2.0)	0.7
WHO stage					
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)	0.007	12(32.4)	0.7

Follow up and Mortality

During follow-up 63 (24.8%) children were randomized, 27(10.6%) did not continue with the study and 32 died (mortality rate 14%). Children who did not continue in the study were significantly younger than children remaining in the study (6.0 mos vs. 9.3 mos (p=0.028)). In the Kaplan Meier analysis, higher mortality was significantly associated with younger age, lower WAZ-score and higher pretreatment viral load. The association between viral load and mortality was attenuated after adjusting for age, CD4% and WAZ-score. Neither CD4% nor TB co-treatment at or after ART initiation were associated with mortality (p= 0.10 and p=0.32).

	Kaplan Meier				Cox regression analyses			
	Dead	Alive	Prob. dying	Log rank	Crude HR	95% CI	Adj. HR	95%CI
Total	32	132	14.0					
Age (months)								
≤12	5	86	17.6	0.04	2.6	1.0-6.8	2.9	1.1-7.8
>12	5	46	6.4		Ref	Ref	Ref	Ref
Pretreatment WAZ (SD)								
>=2	8	52	8.1	0.0004	Ref	Ref	Ref	Ref
>-3 to -2	3	33	6.5		0.71	0.2-2.7	0.5	0.1-2.1
>-4 to -3	8	23	20.3		2.7	1.0-7.6	2.0	0.7-5.6
≤-4	13	24	30.8		4.6	2.0-11.2	3.3	1.4-8.2
Pretreatment HIV RNA (copies/ml)								
≥ 750,000	29	89	19.3	0.04	5.4	0.7-39.4	3.1	0.4-23.5
100 000-<750,000	2	27	3.5		0.98	0.1-10.9	0.7	0.1-8.2
≤100 000	1	6	7.1		Ref	Ref	Ref	Ref

Clinical, immunological and viral response.

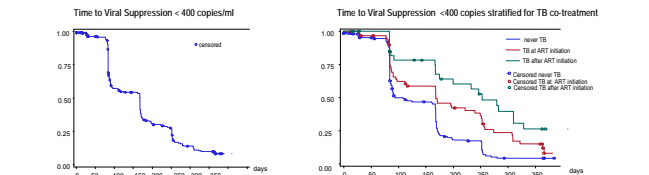
By the end of 9 months the mean WAZ-score had increased from -2.38SD (std.dev.1.8) to 0.82SD (std.dev.1.3) and there was on average a 9.5% increase in the median CD4%. In Kaplan-Meier analyses, the probability of viral suppression was 45.6% at 3 months, 70.8% at 6 months and 83.7% at 9 months after ART initiation

Viral suppression and factors associated with viral suppression

In univariable Kaplan-Meier analyses, WHO stage and HAZ-score, WAZ-score, pre-treatment viral load and TB treatment were each related to the probability of achieving viral suppression.

In multivariable Cox proportional hazards analyses only pre-treatment WAZ-score, pre-treatment viral load and TB treatment were associated with viral suppression after adjusting for each other. Neither CD4% nor age at time of ART initiation were associated with viral suppression.

	Kaplan Meier			Log rank	Cox regression analyses			
	Suppressed	Not suppressed	Prob. of suppressing		Crude HR	95%CI	Adj. HR	95%CI
Total	179	29	63.7					
Pretreatment WAZ (SD)								
>=2	93	4	95.0	0.0005	Ref	Ref	Ref	Ref
>-3 to -2	39	11	76.7		0.6	0.4-0.9	0.7	0.5-1.0
>-4 to -3	25	6	78.7		0.6	0.4-0.9	0.6	0.4-1.0
≤-4	22	8	67.7		0.5	0.3-0.7	0.5	0.3-0.8
Pretreatment HIV RNA (copies/ml)								
≥750,000	103	23	78.4	<0.0001	0.1	0.1-0.3	0.1	0.1-0.3
>100 000-<750,000	51	4	92.7		0.3	0.1-0.6	0.2	0.1-0.5
10,000-<100,000	11	1	91.2		0.3	0.1-0.7	0.3	0.1-0.8
≤10,000	6	0	100.0		Ref	Ref	Ref	Ref
TB treatment								
Never	123	6	94.8	<0.0001	Ref	Ref	Ref	Ref
at start of ART	41	12	74.2		0.6	0.4-0.8	0.6	0.4-0.8
after ART start	15	11	51.6		0.4	0.2-0.6	0.4	0.2-0.6



Viral rebound.

In the group overall, the probability of viral rebound within 4 months of being suppressed was 17.6%. Among all factors investigated, only TB co-treatment was associated with the probability of viral rebound. Of 15 children who initiated TB treatment after ART and suppressed, 8 had a follow-up HIV RNA > 400 copies/ml with a 53.3% probability of rebound compared to 12% among those without TB and 2.8% probability among those who started TB treatment before ART initiation (p<0.0001; adj. HR=5.2 (95%CI 2.1-12.9)).

Conclusion

High rates of viral suppression can be achieved among children < 2 years of age initiating PI-based ART. Our study shows that in children < 2 years TB co-treatment is associated with a lower probability of viral suppression and a higher probability of viral rebound. How best to treat HIV-infected children co-infected with TB remains an unsolved problem. There is an urgent need to further evaluate the pharmacokinetics and clinical outcomes in children co-treated for these two diseases so that evidence-based recommendations can be made.