

Impact of TB-HIV Co-infection on Viral Suppression Rates in HIV-infected Children



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Abstract

Background: The dual HIV and TB pandemics in Southern Africa have led to a dramatic increase in co-infected children. Treatment of HIV-TB co-infection is complicated by metabolic drug interactions and overlapping toxicities, particularly in children, for whom treatment options are limited. Current South African guidelines advocate Lopinavir/Ritonavir-based HAART for children less than 3 years old, and Efavirenz-based HAART for older children. We hypothesized that interactions between Lopinavir/Ritonavir and anti-tuberculosis therapy may decrease viral suppression rates among co-infected children.

Results: A total of 1029 patients initiated Antiretroviral therapy (ART) in two centers in KwaZulu Natal, South Africa. Of these, 373 children (36.2%) received simultaneous HIV and TB treatment. The overall rate of viral suppression to < 400 copies/ml was 84.8% at 6 months and 87.2% at 12 months. Among subjects who received concurrent treatment for HIV and TB, viral suppression rates were lower 79.4% at 6 months and 85.6% at 12 months than among those without TB 87.9% at 6 months (p=0.003) and 89.9% at 12 months p=0.16. When stratified by initial ARV regimen, subjects who received NNRTI-based HAART had similar rates of viral suppression whether they received concurrent TB therapy (88.2% and 87.1% at 6 and 12 months) or not (92.3% and 89.9%; p=0.14 and p=0.4 respectively). In contrast, children who received PI-based first line therapy had significantly lower viral suppression rates with TB co-treatment (63.2% and 77.8% at 6 and 12 months) than without (78.4% and 90.6%; p=0.02 and 0.03).

Conclusion: In South Africa, concurrent treatment for TB is associated with lower rates of viral suppression among children on HAART, but this impact is limited to those receiving PI-based antiviral regimens.

Introduction

In 2008, sub-Saharan Africa accounted for 91% of new HIV infections among children. [1] South Africa alone had over 280,000 HIV infected children. [1] Without the use of antiretroviral therapy (ART), half of these HIV-infected children will die before their second birthday. [2]

Over the past 5 years there has been a dramatic rise in the number of children on ART with over 275,700 children on ART in Sub-Saharan Africa in 2008. [1] Despite this rapid expansion of pediatric ART there is a lack of evidence based ART guidelines for resource limited settings.

TB remains a diagnostic challenge for children in South Africa. Although it appears that HAART decreases the incidence of TB, the burden in children not yet receiving ART remains high. [3] Under the current South African ART Treatment Guidelines the large number of HIV-TB co-infected children could potentially lead to poor virologic outcomes.

Rifampin, which is essential to all anti-TB therapy regimens in South Africa, induces hepatic CYP3A4 enzymes that can accelerate metabolism of protease inhibitors (PIs) and some non-nucleoside reverse transcriptase inhibitors (NNRTIs) [4]. Drug-drug interactions between Rifampin and certain PIs or NNRTIs can lead to inadequate serum concentrations of antiretroviral medications and thus potentially result in virologic failure [5].

Methods

We describe a retrospective cohort study utilizing electronic medical records from HIV positive pediatric patients, less than 18 years, enrolled on antiretroviral therapy (ART) at two medical centers in KwaZulu Natal, South Africa. Viral suppression rates were analyzed in patients taking ART and TB treatment concurrently compared to those only taking ART.

A total of 1029 children initiated ART from McCord Hospital and St. Mary's Hospital in KwaZulu Natal, South Africa from May 2004 until December 2008. Of these children, 719 had at least 6 months of follow up with complete baseline CD4, TB status documentation, and viral load results after 6 months of ART. CD4, Viral load, and weight were obtained at 6 month intervals according to South African National ART guidelines.

Two-group comparisons for categorical variables were performed using Fisher's Exact Test. Statistical analysis was performed using Stata Statistical Software: Release 8.0. Multivariate logistic regression was performed to identify predictors of virologic failure at 6 and 12 months.

Results

A total of 1029 children < 18 years old initiated ART at McCord Hospital and St. Mary's Hospital in KwaZulu Natal, South Africa between May 2004 and December 2008. Their baseline characteristics can be seen in Table 1. Of these children, 609 (59.4%) had a history of TB and 373 (36.2%) were co-treated for TB-HIV. A total of 719 had at least 6 months of follow up with complete baseline CD4, TB status documentation, and viral load results after 6 months of ART and 555 had complete data at 12 months.

Baseline Characteristics	Number (%)
Female	501/1029 (49%)
Age at ART initiation	
Median age at initiation	5.1 years IQR (1.7 – 8.2)
<1 year	182/1029 (18%)
1-4 years	266/1029 (26%)
5-10 years	366/1029 (36%)
10-18 years	151/1029 (15%)
Median CD4 absolute	283 IQR (104-568)
Median CD4 percent	11.7% IQR (6%-16%)
TB	
Prior history of TB	609/1026 (59%)
TB at initiation of ART	278/1026 (27%)
Developed TB while taking ART	95/1026 (9%)
Documented opportunistic infection at baseline	361/1029 (35%)
Chronic diarrhea	159/1029 (16%)
Mean hemoglobin	9.4 mg/dL
Initial ART regimen:	
NNRTI based regimen	694/1029 (67%)
Efavirenz, Lamivudine, Stavudine	671/1029 (65%)
PI based regimen	319/1029 (31%)
Lopinavir/ritonavir, Stavudine, Lamivudine	289/1029 (28%)

Table 1

The overall rate of suppression in the cohort at 6 months was 84.8% and 87.2% at 12 months. The median age at initiation was 5.1 years with 67.4% initiating a NNRTI based regimen and 31% receiving a PI based regimen. Among the NNRTI treated children 91% had viral suppression at 6 months and 88.9% had viral suppression at 12 months. The rates for children treated with a PI as first line treatment had lower viral suppression rates with 71.1% at 6 months (p<0.0001) and 81.3% at 12 months (p=0.38) as indicated in Table 2.

NNRTI Regimen	Suppressed (%)	P- value (NNRTI vs. PI)
6 Months	445/490 (91%)	
12 Months	363/408 (88%)	
PI Regimen		
6 Months	160/219 (73%)	<0.0001
12 Months	138/160 (81%)	0.38

Table 2: Overall viral suppression rates based on 1st line ART regimen

Among subjects who received concurrent treatment for HIV and TB, viral suppression rates were lower (79.4% at 6 months and 85.6% at 12 months) than among those without TB (87.9% at 6 months p=0.003 and 89.9% at 12 months p=0.16). (Table 3 and Figure 1) When stratified by initial ARV regimen, subjects who received NNRTI-based HAART had similar rates of viral suppression whether they received concurrent TB therapy (88.2% and 87.1% at 6 and 12 months) or not (92.3% and 89.9%; p=0.14 and p=0.4 respectively). (Table 4 Figure 2) In contrast, children who received PI-based first line therapy had significantly lower viral suppression rates with TB co-treatment (63.2% and 77.8% at 6 and 12 months) than without (78.4% and 90.6%; p=0.02 and 0.03). (Table 4 Figure 2)

Among children co-treated for TB-HIV there is a significant difference in viral suppression rates between NNRTI, 88.2%, and PI, 63.2%, at 6 months (p<0.0001) while at 12 months the rates were 87.1% for NNRTI and 77.8% for PI (p=0.12). There was not a significant difference among the differing PI treatment regimens including standard dosed Lopinavir/Ritonavir, double dosed Lopinavir/Ritonavir, unboosted Nelfinavir, unboosted Ritonavir; however, the number of subjects in these subsets were small.

Results

TB Stratification	6 Months		12 Months	
	Suppressed (%)	P-Value	Suppressed (%)	P-Value
Not Co-treated	400/455 (88%)		347/386 (90%)	
Co-treated	200/252 (79%)	0.003	154/180 (86%)	0.16
TB at Initiation of ARV's	177/219 (81%)	0.019	129/151 (85%)	0.17

Table 3: Viral suppression rates stratified for TB history

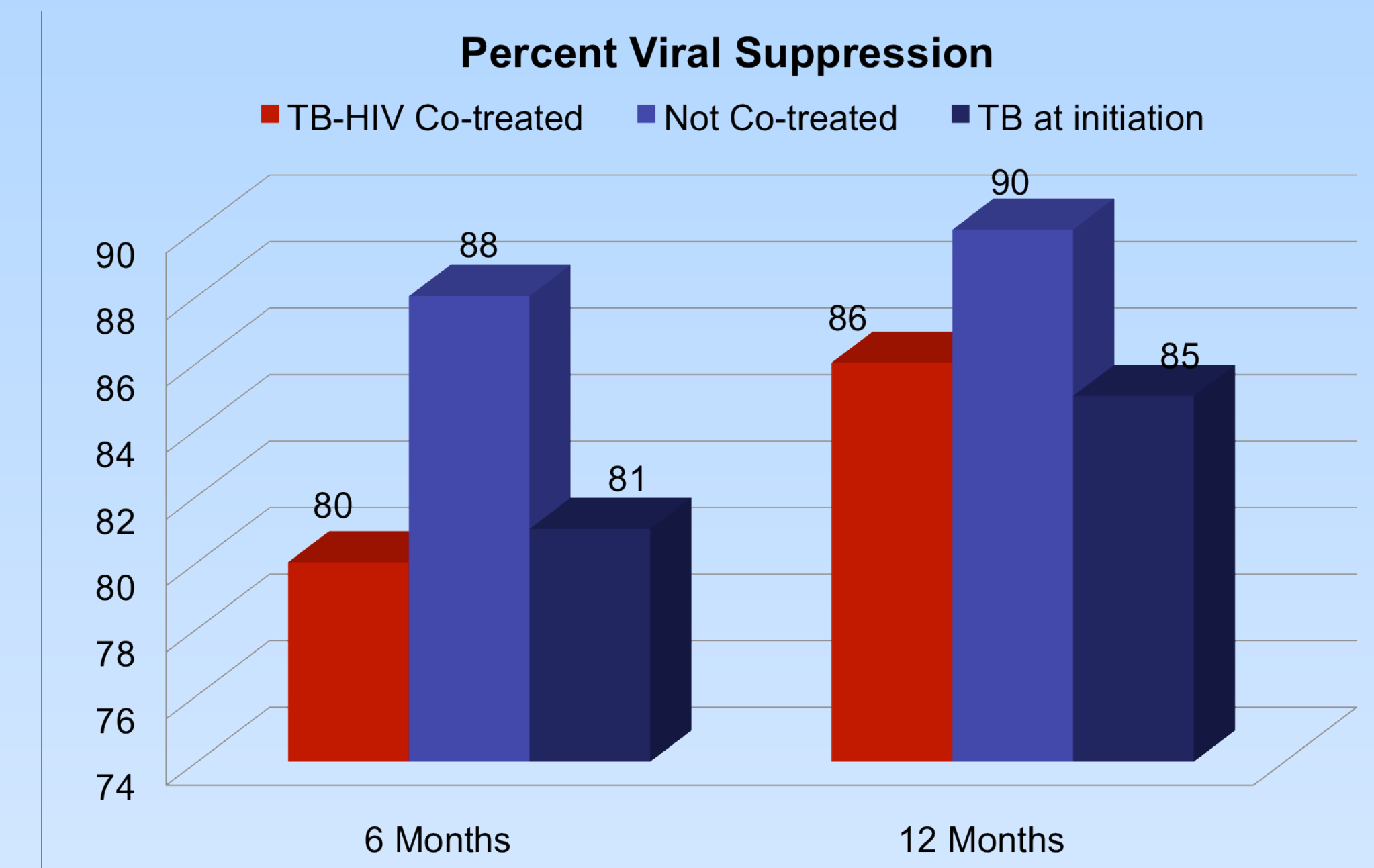


Figure 1: Viral suppression rates stratified for TB history

NNRTI	6 Months		12 Months	
	Suppressed (%)	P-Value	Suppressed (%)	P-Value
Not Co-treated	288/312 (92%)		248/276 (90%)	
Co-treated	157/178 (88%)	0.14	115/132 (87%)	0.4
Protease Inhibitor				
Not Co-treated	105/134 (78%)		96/106 (91%)	
Co-treated	55/87 (63%)	0.02	42/54 (78%)	0.03

Table 4: Viral suppression rates stratified for 1st line ART regimen and TB history

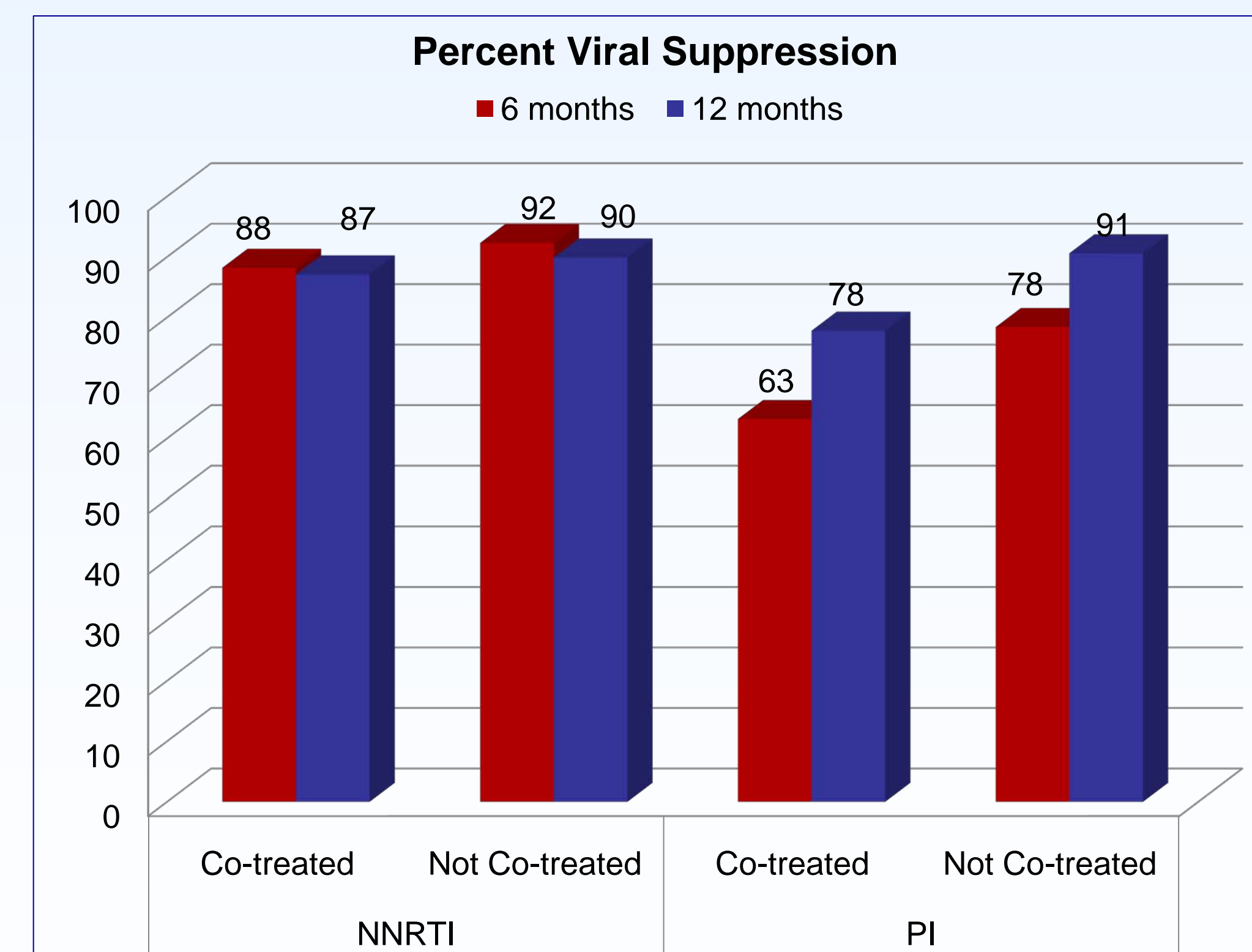


Figure 2: Viral suppression rates stratified for 1st line ART regimen and TB history

Results

Univariate logistic regression analysis found younger age, PI as 1st line ART regimen, TB co-infection and low CD4 and CD4% all associated with failure of viral suppression at 6 months. (Table 5). In our multivariate logistic regression model, PI based regimen, and TB co-infection were all independently associated with virologic failure at 6 months. (Table 6). None of these variables predicted virologic failure at 12 months, although there was a trend toward lower rates of virologic suppression among children co-infected with TB (OR 1.62 [0.97-2.72]; p=0.066).

Risk Factor	6 Months		12 Months	
	Odds Ratio [95% CI]	P-Value	Odds Ratio [95% CI]	P-Value
Age	0.84 [0.78-0.89]	<0.001	0.96 [0.90-1.03]	0.24
1 st line regimen	0.27 [0.18-0.41]	<0.001	0.83 [0.48-1.44]	0.52
TB	1.84 [1.22-2.78]	0.003	1.62 [0.97-2.72]	0.066
CD4	1.0005 [1.0001 -1.0009]	0.009	1.00 [0.99 -1.00]	0.13
CD4%	1.031 [1.004-1.058]	0.022	1.02 [0.99-1.06]	0.18

Table 5: Univariate analysis at 6 and 12 months

Risk Factor	6 Months	
	Odds Ratio [95% CI]	P-Value
Age	0.90 [0.82-0.99]	0.027
1 st line regimen	0.48 [0.25-0.92]	0.026
TB	1.85 [1.21-2.84]	0.004

Table 6: Multivariate analysis at 6 months

Conclusion

Concurrent treatment for TB is associated with lower rates of viral suppression among children on HAART, but this impact is limited to those receiving PI-based antiviral regimens (in South Africa, generally infants and children less than 3 years old. This may be due to pharmacologic interactions (CYP450 induction), decreased adherence due to overlapping toxicities or high pill burden, or biologic interactions. Although several dosing options for use of Protease Inhibitors have been proposed for TB-HIV co-infected children none have been extensively studied. Guidelines for the care of young HIV-TB co-infected infants should be continually evaluated, as PI-based ARV may not provide optimal sustained viral suppression in this population

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