

# Outcomes of Children on Non-Nucleoside Reverse Transcriptase Inhibitor versus Protease Inhibitor HAART Regimens in Resource-limited Settings

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## Introduction

Few data exist as to the most effective regimens for children with vertically acquired HIV infection. Many underdeveloped countries have limited regimens based on Nucleoside Analog Reverse Transcriptase Inhibitor (NRTI) backbones combined with either a Non-NRTI or a Protease inhibitor (PI). Often nevirapine (NVP) is used for vertical transmission prevention (pMTCT) in these settings. This study describes the outcomes of a cohort of 389 children on highly active antiretroviral therapy (HAART), and determinants thereof.

## Objectives

1. To evaluate the outcomes of children on HAART in a resource-limited setting.
2. To compare laboratory and clinical outcomes of children on PI versus nNRTI-containing regimens.
3. To determine the correlates of virologic suppression (VS).

## Methods

Data were collected prospectively on all children receiving HAART through the infectious diseases clinic of a public hospital. Children were started HAART that included an NRTI backbone, and either an nNRTI (nevirapine or efavirenz) or a PI (lopinavir/ritonavir or ritonavir) as their third drug. Viral load (VL) and CD4% were collected six-monthly, and weight and height at every visit. Weight for Age Z score (WAZ) was calculated using WHO standard curves. Data were analysed using Stata 9. Endpoints were compared between the regimens. A generalized estimating equation population-averaged model was used to identify associations with virological suppression and a log rank test explored associations with survival.

## Results

389 children were included in the analysis. Approximately 50% of the patients were on PI versus nNRTI regimens. Baseline data are shown in Table 1. Few children were exposed to Nevirapine for PMTCT. There was no significant difference in the baseline characteristics of patients on the different regimens with regard to VL, CD%, WAZ or HAZ, however the age for those started on nNRTIs was significantly higher.

**Table 1: Baseline characteristics of the cohort overall and by regimen.**

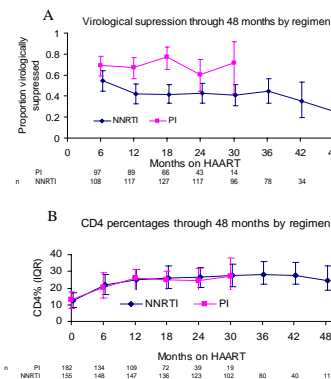
Variable	N	n (%)	95% CI	P value
<b>NNRTI regimens</b>	389	189 (48.6%)		
d4T, 3TC, EFV	189	19 (4.9%)		
ZDV, 3TC, EFV	189	3 (0.8%)		
d4T, 3TC, NVP	189	6 (1.5%)		
ZDV, 3TC, NVP	189	161 (41.4%)		
<b>PI regimens</b>	389	200 (51.4%)		
d4T, 3TC, LPV/r	200	124 (31.9%)		
ZDV, 3TC, LPV/r	200	29 (7.5%)		
d4T, 3TC, RTV	200	34 (8.7%)		
ZDV, 3TC, RTV	200	13 (3.3%)		
<b>Female gender</b>	388	183 (47%)	42 - 52%	
NNRTI	199	105 (41%)	34 - 49%	
PI	189	78 (53%)	46 - 60%	0.02
<b>N</b>		<b>Median</b>	<b>IQR</b>	
<b>Age (months)</b>	387	26.3	12.4 - 53.8	
NNRTI	188	34.3	16.5 - 60.4	
PI	199	21.8	9.1 - 34.9	<0.01
<b>CD4 percent</b>	337	13.0	8.0 - 17.6	
NNRTI	155	12.4	8.0 - 17.0	
PI	182	13.2	8.0 - 17.6	0.43
<b>Log viral load</b>	139	5.5	4.8 - 6.0	
NNRTI	67	5.4	4.8 - 6.0	
PI	66	5.6	4.6 - 6.0	0.97
<b>WAZ</b>	272	-2.5	-4.0 - 1.2	
NNRTI	146	-2.4	-3.6 - -1.1	
PI	126	-2.8	-4.4 - -1.4	0.09
<b>Duration on HAART (years)</b>	386	1.9	0.7 - 3.0	
NNRTI	188	3	1.7 - 3.4	
PI	198	1.2	0.4 - 2.0	<0.001

All parameters improved after the initiation of HAART (Table 2). VS was greater for those receiving PIs at all time points through 48 months. This difference was not apparent in CD4 % or WAZ scores (Figure 1).

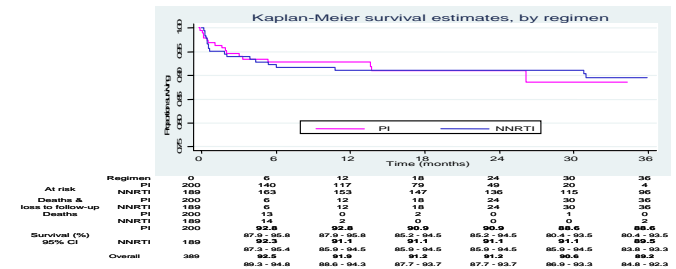
**Table 2: Outcomes at 24 months overall and by regimen**

Variable	N	Median	IQR	P value
<b>CD4 percent</b>	162	26.3	19.4 - 32.2	
NNRTI	123	26.4	20.4 - 32.2	
PI	39	24.6	18.4 - 31.8	0.33
<b>Log viral load</b>	161	2.9	2.6 - 4.5	
NNRTI	117	3.8	2.6 - 4.6	
PI	43	2.6	2.6 - 3.5	0.05
<b>Proportion suppressed</b>	160	61	54 - 68%	
NNRTI	117	43%	34 - 52%	
PI	43	60%	44 - 75%	0.05
<b>WAZ</b>	133	-0.7	-1.8 - -0.1	
NNRTI	117	-0.9	-1.9 - -0.2	
PI	21	-0.5	-1.8 - 0.1	0.43

**Figure 1: Virological (A) and immunological (B) outcomes by regimens through month 48**



**Figure 2: Kaplan Meier plots of survival by regimen**



In a multivariate analysis predicting VS, PI containing regimens were strongly associated with VS, as was WAZ and age (Table 3).

**Table 3: Generalized Estimating Equation population-averaged model predicting virological suppression up to 24 months**

Variable	Adjusted OR	95% CI	P value
CD4 %	1.04	1.02 - 1.06	0.001
WAZ	1.23	1.07 - 1.42	0.004
NNRTI regimen	0.26	0.13 - 0.53	<0.001
Age (years)	1.34	1.2 - 1.5	<0.001
Year of HAART start	1.02	0.69 - 1.53	0.90
HAART > 6 months	0.05	0.37 - 0.70	<0.001

## Conclusions

Despite profound improvements in outcomes for all children on HAART, an unexpected finding in this study was the inferiority of nNRTI-based regimens in achieving and maintaining virological suppression. The implications of detectable viremia in children are that resistance may develop and switches to second line regimens may therefore occur sooner. In developing country settings where regimens are limited, the goal of HAART should be to reach and maintain undetectable viral loads.

The effectiveness of regimens containing nNRTIs may be decreased in this setting due less than optimal dosing, drug-drug interactions (such as TB therapy), or to pMTCT programs.

There is an urgent need to further explore optimal regimens, dosing, and pharmacokinetic interaction studies for children on HAART in these settings.

References available upon request

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