Short Communication: Impact of Viral Load Use on Treatment Switch in Perinatally HIV-Infected Children in Asia

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Abstract

We sought to assess the impact of routine HIV viral load (VL) monitoring on the incidence of switching from a first- to a second-line antiretroviral therapy (ART) regimen, and to describe factors associated with switch. Data from a regional cohort of 16 clinical programs in six Asian countries were analyzed. Second-line switch was defined as a change from a non-nucleoside reverse transcriptase inhibitor (NNRTI) to a protease inhibitor (PI) or vice versa, and ≥ 1 of the following: (1) reported treatment failure by local criteria, (2) switch of ≥ 1 additional drug, or (3) a preceding HIV VL $\geq 1,000$ copies/ml. Routine VL was having ≥ 1 test after ≥ 24 weeks of ART and ≥ 1 time/year thereafter. Factors associated with time to switch were evaluated with death and loss to follow-up as competing risks. A total of 2,398 children were included in this analysis. At ART initiation, the median (interquartile range) age was 6.0 (3.3–8.9) years, more than half had WHO stage 3 or 4, the median CD4 was 189 (47–456) cells/mm³, 93% were on NNRTI-based first-line ART, and 34% had routine VL monitoring. Treatment switch occurred in 17.6% of patients, at a median of 35 (22–49) months. After adjusting for country, sex, first ART regimen, and CD4% at ART initiation, children with routine VL monitoring were 1.46 (95% confidence interval 1.11–1.93) times more likely to be switched ($p = .007$). Scale-up of VL testing will lead to earlier identification of treatment failure, and it can help guide earlier switches to prevent resistance.

Keywords: antiretroviral therapy, HIV, molecular virology

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THE VALUE OF VIRAL LOAD (VL) monitoring for routine clinical management and to determine when to switch regimens in low- and middle-income countries (LMICs) has become increasingly recognized.^{1–3} Because VL is less accessible due to cost and technologic requirements, some programs in LMICs have implemented VL testing in targeted situations to guide switch decisions when treatment failure is suspected on the basis of clinical or immunological criteria.⁴ Routine VL monitoring may be more valuable in a pediatric population that requires life-long therapy from infancy to optimize timing of regimen switching to avoid accumulation of HIV drug mutations, so that future treatment options may be better preserved.

We sought to assess the impact of routine VL monitoring on the incidence of switching from a first- to a second-line antiretroviral therapy (ART) regimen, and to describe factors associated with switch in a regional cohort of HIV-infected children and adolescents in Asia.

Children included in this analysis were from 16 contributing clinical programs in the TREAT Asia Pediatric HIV Observational Database (TApHOD), a member cohort of the International Epidemiology Databases to Evaluate AIDS (IeDEA). Details on the cohort's data collection methods have been previously reported.⁵ Each participating site, the data management and biostatistical analysis center (Kirby Institute, UNSW Australia), and the coordinating center (TREAT Asia/amfAR, Bangkok) have institutional review board (IRB) approval to conduct the study. As data are collected during routine clinical care and anonymized, consent is waived unless required by a local IRB.

All children starting on WHO-recommended first-line, triple-drug cART regimens with at least 6 months of follow-up while on ART were eligible for inclusion. Children switching to second-line regimens due to toxicity or drug stock-outs, after initial exposure to mono- or dual-nucleoside reverse transcriptase inhibitors (NRTIs), or after treatment with three NRTIs or dual-protease inhibitor (PI)-based regimens were excluded.

Second-line switch was defined as a single drug class switch from a non-nucleoside reverse transcriptase inhibitor (NNRTI) to a PI or vice versa maintained for ≥ 24 weeks or the total duration of follow-up if this was < 24 weeks, and at least one of the following: (1) clinician-reported treatment failure as the reason for switching, (2) simultaneous switch of at least one additional drug in the regimen, or (3) a preceding VL of $\geq 1,000$ copies/ml. Routine VL monitoring was defined as having at least one VL test after ≥ 24 weeks of cART and ≥ 1 time/year thereafter during the follow-up period. A patient was designated as lost to follow-up (LTFU) if there was no reported clinical contact for ≥ 12 months in the absence of other outcomes (e.g., transfer to another site, death).

Eligible HIV-infected children who had initiated ART from 2001 to September 2012 were included in the analysis. Baseline CD4 counts and percentages were the closest measurements to the ART start date, with a window of 180 days before to 14 days after. Baseline VL was the result taken closest to the ART start date, within a window period of 365 days before to 14 days after. Participant characteristics were summarized as medians with interquartile ranges (IQR) or frequencies, as appropriate.

Predictor covariates included whether sites used routine VL monitoring and other potential confounding covariates,

such as age, sex, WHO clinical stage, baseline CD4%, height for age Z score, and weight for age Z score. The cumulative incidence, and sub-hazard ratios (HRs) for switch were determined with death and LTFU modeled as a competing risk.⁶ Linearity of continuous covariates was checked against the hazard function, and in the case of nonlinearity covariates were modeled as quartiles. Adjacent quartiles were collapsed if the HR and 95% confidence interval (CI) were similar. Multivariate models were developed by adjusting for all other variables that were significant at $p < .10$ in univariate screening. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Inc, Cary, NC) and Stata version 12 (Statacorp, College Station, TX).

A total of 2,398 children fulfilled criteria for the analysis; 95% were perinatally infected. Countries contributing the highest frequencies of children were Thailand (46%), Vietnam (21%), and Cambodia (14%). At ART initiation, the median age was 6.0 (IQR 3.3–8.9) years and 1,184 (49%) of children were female; weight for age z score was -2.0 (-2.8 to -1.1), and height for age z score was -2.1 (-3.1 to -1.1); and 1,223 (51%) had WHO stage 3 or 4 disease. The median baseline CD4 count was 189 (IQR 47–456) cells/mm³, and the median CD4% was 8.6% (IQR 3–15). Most were on NNRTI-based regimens (97% vs. 3% for PIs). A total of 1,863 had at least one VL during follow-up, 823 of whom had routine VL monitoring. The median (IQR) period of follow-up on ART was 4.9 (2.7–6.69) years. Over 11,651 person-years of follow-up, 390 (16%) children were LTFU and 77 (3.2%) children died; 74% of deaths were HIV related, and the reasons for 14% of deaths were unknown.

For 421 (17.6%) children who switched their regimens, the median duration on first-line therapy before switch was 35 (IQR 22–49) months. Across nonmutually exclusive categories, a total of 362 met switch criteria by having a drug class switch from NNRTIs to PIs or vice versa, with the reason for changing the regimen being treatment failure; 365 children had a drug class switch and a second drug change for at least 24 weeks; 311 children had a drug class switch with a VL $\geq 1,000$ copies/ml; and 244 children met all switch criteria. For those with VL testing, the median (IQR) time from the first VL $\geq 1,000$ copies/ml to switch was 10 (4–20) months. Two hundred and forty-nine children (10.4%) with VL $\geq 1,000$ copies/ml at least once during follow-up did not switch during the follow-up period.

In multivariate analyses adjusted for country and sex, an NNRTI-based first regimen (HR 5.05, 95% CI 1.24–20.55), pre-ART CD4 $< 15\%$ (HR 1.64, 95% CI 1.17–2.28), and routine VL monitoring (HR 1.46, 95% CI 1.11–1.92) were associated with increased likelihood of switch to a second-line regimen (Table 1). The cumulative 5-year incidence of treatment switch was $\sim 17\%$ in children without routine VL monitoring and 23% in children with routine VL monitoring.

Based on the adjusted model, our results show that routinely monitoring VL was associated with a 46% increase in the relative risk of switching to second-line ART after treatment failure, and it concurs with previous studies conducted in children and adults in resource-limited settings.^{2,4,7,8} When ART options are limited, preserving future regimen potency by avoiding accumulation of resistance mutations is of greater importance.

An additional benefit of VL is to identify those at a higher risk of poor adherence, a major challenge in adolescent

TABLE 1. UNIVARIATE AND MULTIVARIATE ANALYSES FOR FACTORS ASSOCIATED WITH TIME TO SECOND-LINE SWITCH USING COMPETING RISK REGRESSION (N=2,398)

Characteristic	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	P
Male	1.23 (1.01–1.48)	.04	1.24 (0.99–1.56)	.06
Age at ART initiation (years)		.45		
<5	Ref			
5–9	0.88 (0.71–1.1)			
≥10	1.02 (0.79–1.33)			
Country		<.0001		<.0001
Thailand	Ref		Ref	
Malaysia	1.42 (1.02–1.96)		1.49 (0.93–2.37)	
India	1.03 (0.64–1.65)		1.43 (0.83–2.45)	
Indonesia	1.38 (0.97–1.98)		1.90 (1.25–2.88)	
Cambodia	0.50 (0.35–0.69)		0.51 (0.35–0.74)	
Vietnam	0.83 (0.62–1.11)		0.96 (0.65–1.43)	
Single/double orphan vs. neither	1.18 (0.96–1.44)	.11		
Weight for age z score ≤−1.5	1.08 (0.82–1.42)	.59		
Height for age z score ≤−1.5	1.13 (0.86–1.5)	.37		
First cART regimen				
Initial NNRTI (vs. PI)	6.26 (1.56–25.08)	.01	5.05 (1.24–20.55)	.02
WHO stage 3, 4 vs. stage 1, 2	0.93 (0.74–1.17)	.52		
CD4 <15% (vs. ≥15%)	1.58 (1.14–2.19)	.006	1.64 (1.17–2.28)	.004
Routine viral load (vs. targeted)	1.29 (1.06–1.57)	.01	1.46 (1.11–1.93)	.007

ART, antiretroviral therapy; cART, triple-drug combination regimen; CI, confidence interval; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

populations.^{9,10} In our cohort, some sites were able to monitor VL on a regular basis, whereas others used VL to evaluate treatment failure and the need to switch. Although routine VL monitoring may be challenging to implement in a public health approach, alternative cost-saving approaches, such as dried blood spot sampling and the emergence of newer testing platforms, will eventually allow for broader scale-up of VL monitoring as a replacement for CD4 testing in LMICs.¹¹ Concerns over the potential of switching too soon need to be weighed against the risk of accumulating drug resistance mutations, particularly in light of NNRTI-based first-line regimens with low genetic barriers to resistance.

Study limitations are primarily related to its observational nature and incompleteness of data collection. As this is a regional observational cohort, sites have differing laboratory monitoring capacity. Only Thailand and Malaysia provide free, routine VL monitoring between 1 and 2 times/year. Importantly, the cohort study does not collect resistance testing that would have demonstrated the impact of prolonged failure versus switch.

Given the short list of available second- and third-line options available in LMICs, utilizing VL testing as an adherence tool and preserving susceptibility to as many antiretrovirals as possible should be key priorities.

Acknowledgments

The TREAT Asia Pediatric HIV Observational Database is an initiative of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and Na-

tional Cancer Institute as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA; U01AI069907), and the AIDS Life Association. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and it is affiliated with the Faculty of Medicine, The University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned earlier.

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Author Disclosure Statement

No competing financial interests exist.

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