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Treatment outcomes and resistance patterns of children and adolescents on second-line antiretroviral therapy in Asia

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Abstract

Background—Data on pediatric treatment outcomes and drug resistance while on second-line antiretroviral therapy (ART) are needed to guide HIV care in resource-limited countries.

Methods—HIV-infected children <18 years old who were switched or switching to second-line ART after first-line failure were enrolled from eight sites in Indonesia, Thailand, and Vietnam. Genotyping was performed at virologic failure (VF; HIV-RNA >1000copies/mL). Cox proportional hazards regression was used to evaluate factors predicting VF.

Results—Of 277 children, 41% were female. At second-line switch, age was 7.5 (5.3–10.3) years, CD4 count was 300 (146–562) cells/mm³ and percentage was 13 (7–20)%; HIV-RNA was

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5.0 (4.4–5.5) log₁₀ copies/mL. Second-line regimens contained lamivudine (90%), tenofovir (43%), zidovudine or abacavir (30%), lopinavir (LPV/r; 91%), and atazanavir (ATV; 7%). After 3.3 (1.8–5.3) years on second-line ART, CD4 was 763 (556–1060) cells/mm³ and 26 (20–31)%. VF occurred in 73 (27%), with an incidence of 7.25 per 100 person-years (95% confidence interval [CI] 5.77–9.12). Resistance mutations in 50 of 73 children with available genotyping at first VF included M184V (56%), 1 thymidine analogue mutation (TAM; 40%), >4 TAMs (10%), Q151M (4%), any major LPV mutation (8%), >6 LPV mutations (2%), and any major ATV mutation (4%). Associations with VF included age >11 years (hazard ratio [HR] 4.06; 95% CI 2.15–7.66) and HIV-RNA >5.0 log₁₀ copies/mL (HR 2.42; 95% CI 1.27–4.59) at switch, and was seen more commonly in children from Vietnam (HR 2.79; 95% CI 1.55 – 5.02).

Conclusions—One-fourth of children developed VF while on second-line ART. However, few developed major mutations to protease inhibitors.

Keywords

Second-line antiretroviral therapy; children; adolescents; Asia; outcomes; resistance

Introduction

The number of HIV-infected children accessing HIV care and treatment has been increasing worldwide. Triple-drug combinations consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) are the most commonly used first-line antiretroviral therapy (ART) regimens in Asia¹. Data from cohorts in resource-limited settings have shown that up to 80% of children receiving first-line ART achieved viral suppression after the first year of treatment.^{2–4} However, increasing numbers of children are developing first-line treatment failure.

Studies in Thai and Ugandan cohorts found that one-third of children receiving NNRTI-based first-line ART experienced virologic failure (VF), with the majority detected within the first year of treatment.^{5,6} A history of adherence problems during first-line treatment is associated with subsequent second-line treatment failure.⁷ Therefore, long-term adherence and regimen durability are particular challenges for perinatally infected children, given the potential for pre-ART drug resistance associated with prevention of mother-to-child HIV interventions and the need for life-long therapy.^{6,8–10}

Although second-line boosted protease inhibitors (PIs) are largely accessible for children and adolescents in the region, the availability of alternative antiretrovirals beyond these drugs is limited. As clinicians and policy makers consider how to prepare for procuring third-line drug options, data on second-line treatment effectiveness, risk of failure, and resistance patterns are critically needed to guide prevention interventions, management decisions, and treatment guidelines.

Methods

Study design and enrollment

The Prospective Monitoring of Second-line Antiretroviral Therapy Failure and Resistance in Children (TASER-P) study is a longitudinal observational cohort study to monitor for treatment failure on second-line ART in Asian children. We included HIV-infected children <18 years old who failed first-line ART and were switched to second-line ART prior to the enrollment and currently taking their second-line ART or about to switch to second-line ART at the enrollment from eight sites in Indonesia (1 site), Thailand (4 sites) and Vietnam (3 sites). Second-line ART was defined as the second-regimen with an antiretroviral class switch from an NNRTI to a PI. Children who were exposed to mono/dual NRTI therapy prior to a triple-drug regimen, were switched to second-line ART without failure of first-line therapy (e.g., for toxicity), and those on non-standard treatment regimens including once-daily boosted lopinavir (LPV/r) or mono boosted PI without any NRTI or double boosted PI were not eligible for the study. Criteria to switch to second-line ART and ART regimens were determined by the treating physicians and the patients based on previous treatment history, viral resistance results, current clinical staging, other medical considerations, local ARV drug availability and local pediatric guidelines at each site.

Data collection and monitoring

Patients were evaluated at study entry and every six months thereafter. Clinical assessments and laboratory testing including HIV-RNA were conducted every six months and up to week 168 of the study. Adherence was evaluated using pill counts and the WHO's adherence visual analogue scale.^{11,12} All patients were co-enrolled in a parallel cohort study (TREAT Asia Pediatric HIV Observational Database; TApHOD¹³). Clinical data prior to TASER-P enrolment were collected through that study.

Patients with HIV-RNA >1000 copies/mL (virologic failure; VF) had resistance testing on the same blood sample. Genotyping was done at each study site. Local laboratories participated in an external HIV drug resistance quality assurance program for the duration of the study¹⁴. Resistance testing was interpreted using the Stanford University HIV Drug Resistance Database.^{15,16}

Statistical analysis

Patients with study follow-up for at least six months were included in the analysis. The primary endpoint was VF. Secondary endpoints were resistance by drug mutation development, adherence, and predictors of VF. Demographic and clinical characteristics were summarized in terms of medians (interquartile range, IQR) and proportions, as appropriate. Baseline was at the time of switching to second-line ART, and the last clinic visit was the most recent visit with an available viral load test. Virologic suppression was defined as having HIV-RNA levels <400 copies/ml throughout the study period. Persistent VF was when repeated, consecutive viral load tests were >1000 copies/ml. VF rates were calculated and Cox proportional hazards regression analysis was used to determine predictors of VF as a first event. For children not experiencing VF, data were censored at the last clinic visit. The linearity of continuous covariates was assessed against the hazard

function, and where these assumptions were not met, covariates were modeled as quartiles. Adjacent categories were collapsed together if the hazard ratio (HR) and size of the 95% confidence interval (CI) were similar.

Univariate risk factor analysis for VF included age, weight for age z score, height for age z score, sex, WHO clinical disease stage, CD4, and HIV-RNA at baseline, and duration of first-line ART. All covariates with p-value <0.10 were adjusted for in multivariate analyses. Resistance patterns were reported as proportions of children with VF. Statistical significance was based on a two-sided p-value of 0.05. Analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA) and Stata version 12 (Statacorp, College Station, TX, USA).

Ethical considerations

All participating study sites and coordinating centers obtained local Institutional Review Board approvals for study participation. Informed consent was provided by primary caregivers; children over the age of seven years who were aware of their own HIV status through previous disclosure were asked to provide assent when this was required by the local review board.

Results

Characteristics at switching to second-line ART

A total of 277 children were enrolled in the TASER-P study between February 2011 and December 2012. At enrollment, 41% were female and 134 (48%) were Vietnamese, 115 (42%) were Thai and 28 (10%) were Indonesian (Table 1). Of these, they were experienced the WHO clinical stage 1 (41; 15%), stage 2 (91; 33%), stage 3 (87; 31%) and stage 4 (31; 11%). The median (IQR) age at the enrollment was 9.9 (7.3 to 12.9) years. The median age at first-line ART initiation was 4.1 (2.6 to 6.7) years, and the median weight for age z score was -0.64 (-1.44 to 0.21). Most patients (243; 88%) were switched to second-line ART prior to study enrollment. At second-line switch, the median age was 7.5 (5.3 to 10.3) years, the median prior duration on first-line ART was 2.7 (1.7 – 4.2) years, the median weight for age z score was -1.27 (-2.06 to -0.35), the median CD4 count was 300 (146–562) cells/mm³, the median CD4 percentage was 13 (7–20) %, and the median HIV-RNA was 5.0 (4.4–5.5) log₁₀ copies/mL. All children had been on NNRTI-based first-line regimens.

Second-line regimens contained lamivudine (3TC; 90%), tenofovir (TDF; 43%), and zidovudine (ZDV) or abacavir (ABC) (30%). Most of the children were on LPV/r-based regimens (91%), 7% were on boosted atazanavir (ATV/r) and 2% were on boosted indinavir (IDV/r). Of the 156 (56%) children who had available resistance testing at the time of first-line failure, mutations included M184V (82%), 1 thymidine analog mutation (TAM; 64%), 4 TAMs (18%), T215Y/F (43%), K65R (10%), 1 NNRTI mutation (92%), Y181I/C (44%), G190A (33%), K103N/S (27%), and V108I (15%); 30 (19%) children had DUET weighted scores 4 (Table 2).

Second-line outcomes

A total of 274 of 277 children were followed for at least six months after study enrollment and included in the study analyses; 112 (41%) were female. At the last follow-up visit or upon censoring at VF, the median duration on second-line ART was 3.3 (1.8–5.3) years, median CD4 count was 763 (556–1060) cells/mm³ and median CD4 percentage was 26 (20–31)%, and 192 (70%) had HIV-RNA <400 copies/ml; 18 (6%) had WHO clinical stage 3 or 4 events during the follow-up period. There were five (2%) deaths from HIV-related illnesses; three occurred during the first six months after enrollment.

At one year of second-line ART, 5% of children had VF, and this increased to 20% within three years after switch (Figure 1). The median duration after second-line switch to the first documented VF was 2.4 (1.3–4.0) years, 2.6 (1.5–3.9) years to the second documented VF, and 3.1 (1.8–4.1) years to the third documented VF.

During the study monitoring period, 73 (27%) children developed VF, representing an incidence of 7.25 per 100 person-years (95% CI 5.77–9.12). Forty of 73 (55%) children had persistent VF for 24 weeks and 23 (32%) children had persistent VF for 48 weeks of follow-up, while remaining on second-line regimens. At the time of the first documented VF during the study monitoring period, >95% adherence was reported among 52 (71%) by pill count and 53 (73%) by visual analogue scale. In those with persistent VF, adherence decreased to 65% by pill count and 68% by visual analogue scale at the second documented VF, and to 57% by pill count and 52% by visual analogue scale at the third documented VF. Patients who developed VF during the study period were counseled and managed according to the local/nation treatment guidelines which were determined by their physicians and patients based on their decision. None of the patients switched from second- to third-line regimens during the study monitoring period.

Multivariate analysis showed that VF was associated with starting second-line ART at age >11 years (HR 4.06; 95% CI 2.15–7.66) and having an HIV-RNA >5.0 log₁₀ copies/mL (HR 2.42; 95% CI 1.27–4.59) at the time of second-line ART switch, and was seen more commonly in children enrolled in sites in Vietnam (HR 2.79; 95% CI 1.55 – 5.02) (Table 3). However, sex, prior duration on first-line ART, WHO stage, CD4, and weight or height for age z score at initiation of second-line ART were not significantly associated with VF.

Resistance mutations after virologic failure

At the first documented VF while on second-line ART, HIV drug resistance genotypes were available for 48 (66%) children. NRTI mutations included 1 TAM (40%), 4 TAMs (10%), T215Y/F (23%), Q151M (4%), M184V (56%), K65R (2%). Data on PI resistance mutations were available among 50 (68%) children, and included any major LPV mutation (L76V, V82A, V82S; 8%), 6 LPV mutations (2%), any major darunavir (DRV) mutation (I84V, L76V; 2%), and any major ATV mutation (I84V, N88S; 4%) (Table 2).

At the first documented VF during the study monitoring period. There was high-level resistance to 3TC (56%), AZT (25%), and TDF (10%). Most patients remained susceptible to LPV (86%) and ATV (84%). Among children who had persistent VF, 30/40 (75%) had genotypes available at the second VF and 20/23 (87%) at the third VF. Percentages of NRTI

and PI resistance mutations were the same or decreased with successive viral load testing. However, overall susceptibility to LPV decreased from 86% to 83% to 80% with each subsequent viral load >1000 copies/ml.

Discussions

This is the first prospective, regional observational cohort study of Asian HIV-infected children receiving second-line ART. We identified generally high rates of virologic suppression during the study period. Our data are consistent with suppression rates in Thai¹⁷ (79%) and Ugandan¹⁸ (84.5%) cohorts of children on PI-based second-line regimens. Higher virologic suppression rates have been reported while on second-line PI regimens compared to second-line NNRTI regimens (80% vs. 25%; $p=0.009$),¹⁹ reflecting the potency of boosted PI regimens and the reduced risk of archived mutations compared to NNRTIs.^{20,21} Although the majority of our patients remained virologically suppressed throughout the study period, 27% developed at least one episode of VF during the study monitoring period. We observed that 55% of those with an initial elevated viral load had persistent VF for 24 weeks (two consecutive measurements) and 32% had persistent VF for 48 weeks (three consecutive measurements). Of note is that 45% were able to achieve virologic suppression after the first documented VF without switching to third-line or intensification of their regimen.

Even among those with persistently elevated viral load, only a small percentage acquired major PI resistance mutations, with most patients remaining susceptible to second-line PIs throughout the follow-up period, representing a median time on second-line of 3.3 years. At second-line switch, about half or more of the patients already had high-level resistance to 3TC (87%), d4T (52%), and AZT (50%). At the first documented VF during the study, the percentage of children with high-level NRTI resistance decreased (e.g., 3TC 87 to 56%, AZT 50 to 24%). Although we observed a decrease over time in adherence in children with persistent VF, overall adherence levels by self-report and pill count were still higher than expected in comparison to HIV-RNA results. It is likely that the low levels of resistance were related in part to reversion to wild-type virus due to low drug exposure.^{22,23}

Significant risk factors for VF identified in this study were older age (age >11 years; HR 4.06), higher HIV-RNA level (>5.0 log₁₀ copies/mL; HR 2.4) at second-line ART switch, and being enrolled at sites in Vietnam. The challenges associated with transitioning into adolescence are exacerbated by HIV infection, and can result in poor adherence, mental health conditions (e.g., depression), and high rates of loss to follow-up.^{24–26} Unfortunately, we were not able to include adherence in the statistical models because we were missing adherence data from the time period immediately following second-line switch and before study enrolment. Interventions to ensure adherence and prevent treatment failure during adolescence are critical to prevent treatment failure, particularly when third-line options are limited. It is unclear why children from Vietnam were at higher risk of VF, and may be related to variations in adherence support, clinic volumes, and healthcare provider staffing levels.

Poor adherence is a major risk factor for treatment failure. Although adherence monitoring is a critical tool to promote ART success,^{1,27} different adherence assessment methods may not be sensitive enough to identify patients at risk of VF.²⁸ Providing effective adherence support is more challenging with children and adolescents because of issues such as limited drug formulations, reliance on caretakers to supervise taking medicines, and pill fatigue associated with life-long therapy. High pill burden and increased medicine frequency are known barriers to adherence,²⁹ and second-line regimens often require more pills more often than first-line ART.

Our study also identified low levels of PI resistance after VF. Susceptibility to LPV only decreased from 86% to 80% at 48 weeks of persistently elevated viral load. These data are consistent with reports in adults which observed limited PI resistance after PI regimen failure, where adherence strengthening helped improve virologic responses.^{30,31} In our study, 45% were able to re-suppress their virus after the initial VF and an additional 23% were able to re-suppress within 48 weeks after counseling, but without major changes to their regimens. The viral re-suppression after VF in this study may be related to better adherence and improved understanding of treatment outcomes after counseling following VF. It is notable that none of the children and adolescents were switched to third-line during the study monitoring period, reflecting concerns for making switches because of poor adherence and the lack of accessible third-line options in our region. Although serious triple-class failure is rare (e.g., DRV resistance was 10%), additional research is needed to determine optimal second-line failure management strategies to maximize future therapeutic options.

A key limitation of this study is that the majority of the participants were switched to second-line ART prior to study enrollment, and unlike clinical and treatment data, adherence data was not recorded prior to the study enrollment. In addition, 10% had VF before the study enrollment, resulting in incomplete adherence and resistance data. Moreover, although we were able to combine retrospective and prospective HIV-RNA data to improve our assessment of VF (e.g., reflected in Figure 1), adherence was not evaluable in our risk factor analysis. Study sites are all tertiary-care referral centers in largely urban areas, which limit the generalizability of our results to centers with fewer sub-specialty resources and in rural settings.

In summary, we observed high rates of extended virologic suppression among a cohort of Asian children and adolescents on second-line ART. One-fourth developed VF within a few years after second-line ART initiation. However, only few acquired major PI resistance mutations and most remained susceptible to their regimens, which likely reflects poor adherence. Older age and high HIV-RNA level at the start of second-line ART were significant risk factors, and emphasize the importance of providing additional adherence support for adolescents on second-line to maximize treatment effectiveness over time and prevent treatment failure.

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Appendix

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Figure 1.
The probability of virologic failure after second-line antiretroviral therapy initiation

Table 1

Characteristics of HIV-infected children at switching to second-line ART and at the last visit or virologic failure

Characteristics	At switching to second-line ART (n=277)	At last visit or virologic failure (n=274)	P-value
Median (IQR) duration on ART, year	2.7 (1.7 – 4.2)	3.3 (1.8–5.3)	
Median (IQR) CD4 cell count, cells/mm ³	300 (146 – 562), n=235	763 (556 – 1060), n=252	<0.001
Median (IQR) CD4 percentage	13.4 (7 – 20), n=216	26 (20 – 31), n=220	<0.001
Median (IQR) HIV-RNA, log 10	5.0 (4.4 – 5.5), n=212	2.4 (1.5 – 3.1), n=274	<0.001
Viral load 1000 copies/ml	205 (97)	73 (27)	<0.001
Viral load <400 copies/ml	1 (1)	192 (70)	<0.001

ART: antiretroviral therapy; IQR: interquartile range

Table 2

Resistance mutations at first-line ART failure (baseline) and at second-line virologic failure* during the study monitoring period

Resistance mutations	Baseline (n=156)		First virologic failure (n=48)		Second virologic failure (n=30)		Tthird virologic failure (n=20)	
	n	percentage	n	percentage	n	percentage	n	percentage
NRTI mutations								
M41L	47	30%	7	15%	2	7%	1	5%
D67N	40	26%	6	13%	4	13%	2	10%
K70R	48	31%	11	23%	6	20%	2	10%
L210W	32	21%	4	8%	1	3%	1	5%
T215Y/F	67	43%	11	23%	5	17%	4	20%
K219Q/E	31	20%	6	13%	4	13%	2	10%
K65R	15	10%	1	2%	0	0%	0	0%
Q151M	12	8%	2	4%	0	0%	0	0%
M184V	128	82%	27	56%	10	33%	7	35%
1 TAMs	100	64%	19	40%	9	30%	5	25%
4 TAMs	28	18%	5	10%	2	7%	1	5%
PI mutations								
	n=50		n=30		n=23			
	n	percentage	n	percentage	n	percentage	n	percentage
6 of any LP mutation	1	2%	1	3%	1	5%		
Any major LPV mutation	4	8%	3	10%	3	15%		
I47V	0	0%	1	3%	0	0%		
L76V	1	2%	1	3%	1	5%		
V82A	3	6%	1	3%	2	10%		
V82S	1	2%	1	3%	1	5%		

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	1	2%	2	7%	2	10%
Any major DRV mutation	1					
I50V	0	0%	0	0%	1	5%
I47V	0	0%	1	3%	0	0%
I84V	1	2%	0	0%	1	5%
L76V	1	2%	1	3%	1	5%
Any major ATV mutation	2	4%	1	3%	2	10%
I84V	1	2%	0	0%	1	5%
N88S	1	2%	1	3%	1	5%

* Virologic failure was defined as an HIV-RNA of >1000 copies/mL.

NRTI: nucleoside reverse transcriptase inhibitor; ART: antiretroviral therapy; PI: protease inhibitor; LPV: lopinavir; DRV: darunavir; ATV: atazanavir

Table 3

Risk factors for first virologic failure during the study monitoring period

Characteristics	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Male	1.14 (0.71 – 1.83)	0.59		
Country		0.002		
Thailand	Ref		Ref	0.002
Vietnam	2.45 (1.48 – 4.05)		2.79 (1.55 – 5.02)	
Indonesia	1.53 (0.52 – 4.5)		1.80 (0.57 – 5.62)	
Age at second-line ART initiation		0.031		<0.0001
11 years	Ref		Ref	
>11 years	1.84 (1.09 – 3.12)		4.06 (2.15 – 7.66)	
Duration on first-line ART		0.17		
5 years	1.72 (0.75 – 3.97)			
>5 years	Ref			
Baseline WHO stage		0.66		
Stage 1 and 2	1.11 (0.69 – 1.8)			
Stage 3 and 4	Ref			
Weight for age at baseline		0.12		
–1.25	1.39 (0.73 – 2.65)			
< –1.25 to –0.5	1.10 (0.48 – 2.51)			
> –0.5	Ref			
Height for age at baseline		0.12		
–2.5	Ref			
< –2.5 to –0.5	1.02 (0.54 – 1.92)			
> –0.5	1.45 (0.67 – 3.10)			
Baseline CD4 15%	1.77 (1 – 3.14)	0.091	1.21 (0.66 – 2.21)	0.81
Baseline HIV-RNA 5.0 log ₁₀ copies/ml	2.39 (1.38 – 4.14)	0.004	2.42 (1.27 – 4.59)	0.009

ART: antiretroviral therapy; HR: Hazard ratio; 95% CI: 95% confidence interval; Ref: reference