Treatment and resistance outcomes of Asian children on second-line antiretroviral therapy

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On behalf of the TASER-Pediatrics Study

Background

- Life-long therapy is a particular challenge for perinatally infected children
  - Impact of PMTCT interventions
  - Adherence challenges during adolescence
- Although second-line ARVs are largely accessible in Asia, there are few third-line options
- Data on second-line durability, risk of failure, and resistance patterns are needed to guide future regimen sequencing

Study Objectives

TREAT Asia Studies to Evaluate Resistance (TASER)-Pediatrics

- Evaluate immunologic response, virologic suppression, adherence, and HIV drug resistance in children and adolescents on second-line ART
- Characterize resistance mutations after second-line failure
  - Susceptibility to third-line ARVs

Study Methods

Inclusion criteria

- Infected perinatally or in early childhood
- Being switched to or already on second-line ART regimens
  - A major ARV class switch due to treatment failure, according to local definitions

Exclusion criteria

- Prior mono/dual-NRTI
- First failure to a triple-NRTI regimen
- Switch due to toxicity
- Non-standard ART
  - Once-daily LPV/r; mono-therapy with a PI; dual-therapy with two PIs

Study Methods

- Clinical assessments and laboratory testing performed every 6 months up to 120 weeks
- Genotyping and therapeutic drug monitoring done at virologic failure (VF)
  - VF ≥1000 copies/ml
  - Viral suppression by lower threshold of local assay
- Adherence evaluated using pill count and visual analogue scale
- Cox proportional hazards regression for predictors of VF when P <0.10 in univariate

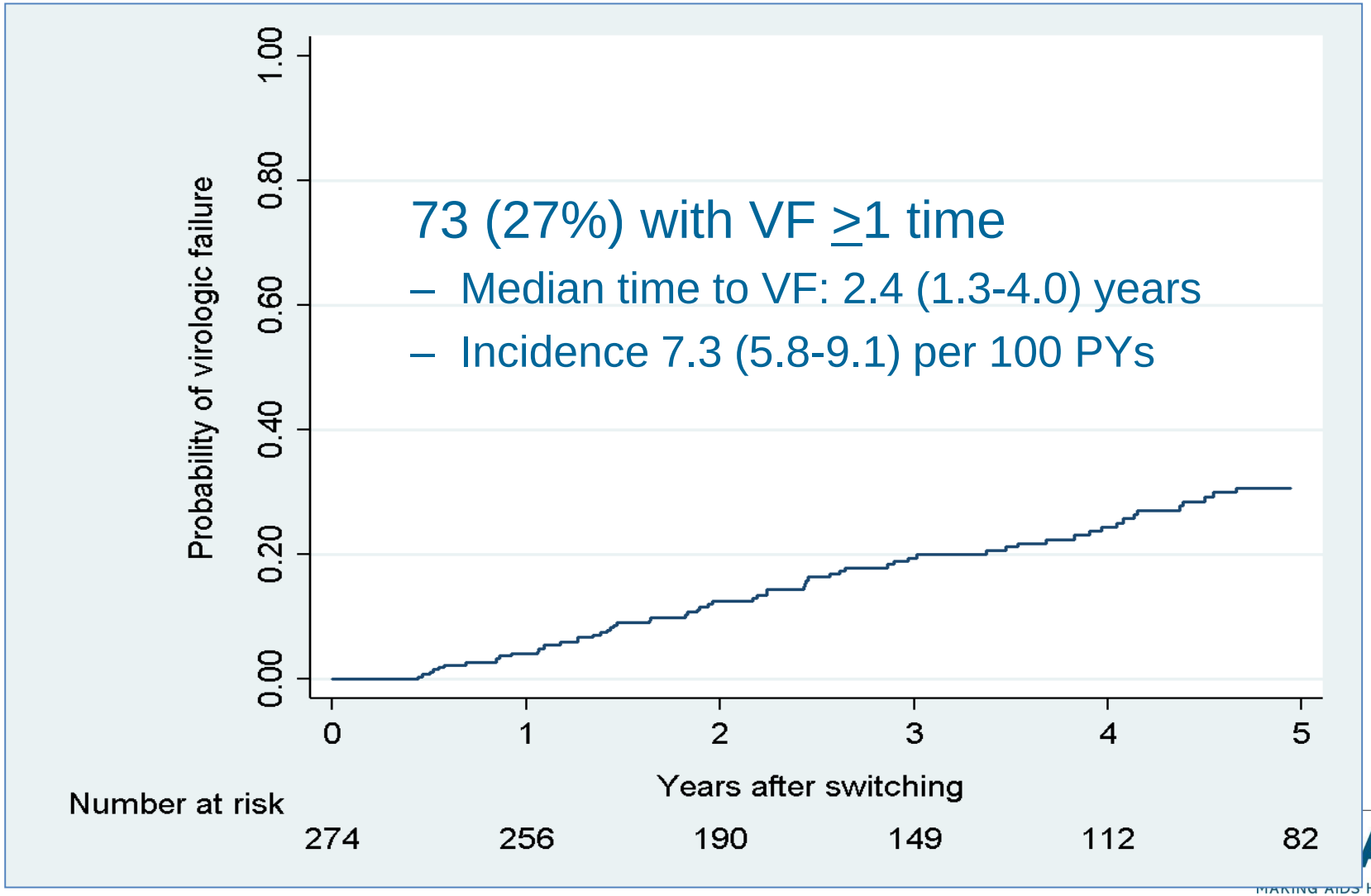
Results

- Mar 2011 to Dec 2012: 277 children enrolled
- 8 sites: 1 Indonesia, 4 Thailand, 3 Vietnam
  - 34 (12%) switched to second-line at enrollment
  - 243 (88%) on second-line before enrollment
  - 274 with ≥6 months of follow-up

Patient Characteristics

Characteristics	At second-line switch (N=277)	At last visit or VF (N=274)	P-value
Female	113 (40.8)	112 (40.9)	
Age, years	7.5 (5.3-10.3)		
WHO stage 3 or 4	117 (42.2)		
LPV/r-based 2nd-line	271 (98)	254 (93)	
Median years on ART	2.7 (1.7-4.2)	3.6 (2.0-5.4)	
Median CD4, cells/mm^3	300 (146-562)	763 (556-1060)	<0.001
Median CD4, percentage	13.4 (7-20)	26.0 (20.4-30.9)	<0.001
Median HIV-RNA, $\log_{10}$	5 (4.4-5.5)	2.4 (1.53-3.1)	<0.001

Probability of VF after Second-line Switch

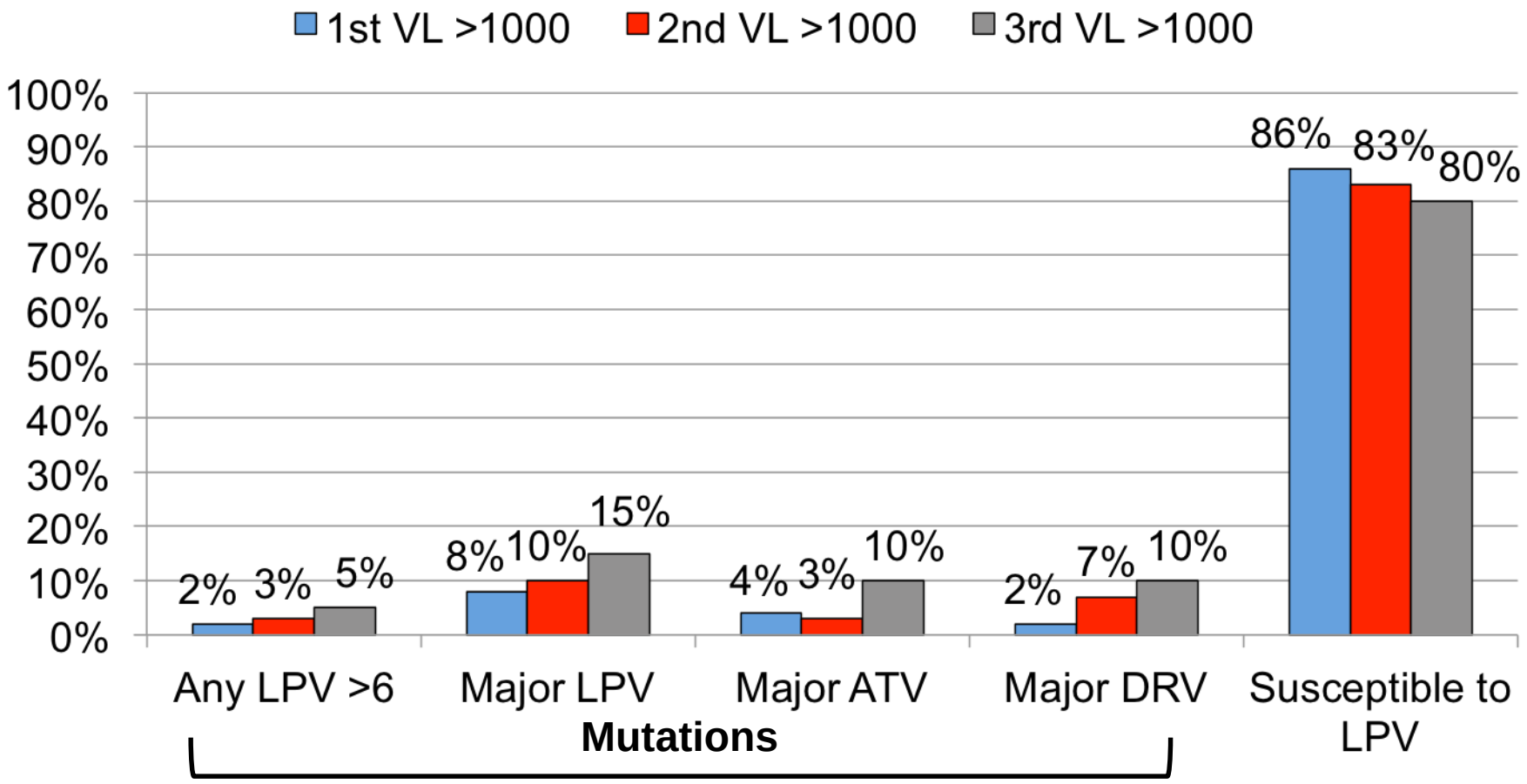


Initial and Repeat VF on Same Regimen

Variables	1st VL ≥1000	2nd VL ≥1000	3rd VL ≥1000
Total	**73**	**40**	**23**
Female, N (%)	28 (38)	15 (38)	9 (39)
Median (IQR) age, years	11 (8-14)	11 (7-15)	10 (7-16)
Median (IQR) CD4%	22 (16-27)	15 (10-21)	16 (6-23)
Median (IQR) VL Log10	3.9 (3.4-4.8)	4.4 (3.7-5.1)	4.5 (4-4.9)
Years on second-line	2.4 (1.3-4)	2.6 (1.5-3.9)	3.1 (1.8-4.1)
Pill Count ≥95%, N (%)	52 (71)	26 (65)	13 (57)
VAS ≥95%, N (%)	53 (73)	27 (68)	12 (52)
TDM available, N (%)	51 (70)	38 (95)	22 (96)
TDM <LLOQ, N (%)	12 (16)	20 (50)	13 (57)
Genotype available, N (%)	50 (68)	30 (75)	20 (87)

VAS-visual analogue scale; TDM-therapeutic drug monitoring; LLOQ-lower limit of quantification

PI Resistance and Susceptibility after Second-line VF



LPV-lopinavir; ATV-atazanavir; DRV-darunavir.
Susceptibility by Stanford interpretation.

Independent Risk Factors for Second-line VF

- Age at second-line initiation >11 years
  - Hazard ratio 4.1 (95%CI 2.2-7.7), p <0.01
- VL at second-line initiation >5.0 $\log_{10}$
  - Hazard ratio 2.4 (95%CI 1.3-4.6), p <0.01

- Not associated: sex, duration on 1st-line, weight- or height-for-age, WHO stage, CD4

Summary

- 70% of patients on second-line PI-based ART had virologic suppression over >3 years
- Of those with VF, ≤15% developed major mutations to second-line PIs
  - Half of those with repeated VF had unquantifiable PIs
  - VAS and pill count not reliable in those with VF
  - Those with a single elevated VL were able to re-suppress
- Adolescents need better adherence support to prevent VF and further resistance

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Proportions with Undetectable VL and VF, by Study Week