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


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

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

- 73 (27%) with VF ≥1 time
- Median time to VF: 2.4 (1.3-4.0) years
- Incidence 7.3 (5.8-9.1) per 100 PYs
## Initial and Repeat VF on Same Regimen

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

VAS-visual analogue scale; TDM-therapeutic drug monitoring; LLOQ-lower limit of quantification
PI Resistance and Susceptibility after Second-line VF

Susceptibility by Stanford interpretation.

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
Acknowledgements

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Proportions with Undetectable VL and VF, by Study Week

- Week 0: 58% Undetectable, 25% Viral failure
- Week 24: 75% Undetectable, 14% Viral failure
- Week 48: 74% Undetectable, 16% Viral failure
- Week 72: 77% Undetectable, 15% Viral failure
- Week 96: 76% Undetectable, 13% Viral failure