Multicenter Analysis of Second-line Antiretroviral Treatment in HIV-infected Children: Adolescents at High Risk of Failure

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Background: Almost 50% of children and adolescents living with HIV worldwide currently have access to antiretroviral treatment (ART). With increasing ART coverage, the number of HIV-infected children and adolescents who fail first-line and will require second-line ART in low- and middle-income countries (LMICs) is rising as well. Data on pediatric second-line ART outcomes in LMIC and potential risk factors for virologic failure are essential to improve HIV care in LMIC, as pediatric third-line ART is not routinely available.

Methods: Multicenter analysis
Virologic failure rates and predictors of virologic failure among children and adolescents on second-line ART in LMIC
Systematic review to identify eligible cohorts
Patient-level data
Kaplan-Meier survival estimates and Cox proportional hazard models to describe cumulative rates and predictors of failure
Virologic failure: 2 consecutive viral load measurements >1000 copies/ml or death, after at least 6 months of treatment

Results:
12 cohorts representing 928 children on second-line protease inhibitor (PI)-based ART in 14 countries in Asia and sub-Saharan Africa.
Most common second-line regimen: AZT/3TC/LPV/r in 194 children (21.3%).
Data on second-line ART after failure of a first-line PI-based regimen (as per 2016 World Health Organization guidelines) were too limited (n=30 children) to include in our analysis.
After 24 months, 9.1% (95%CI 6.6-12.4) of children (3-9 years) and 26.3% (95%CI 21.7-31.8) of adolescents (10-18 years) experienced virologic failure, <0.001 (figure).
Failure rates: 4.5% (95%CI 3.4-5.8) for children and adolescents (9-17.6) per 100 person-years for adolescents.
Risk factors for virologic failure: adolescence and short duration of first-line ART before switch second-line ART (table).

Conclusions:
In LMIC, PI-based second-line ART is associated with relatively low virologic failure rates in children. However, adolescents show exceptionally poor virologic outcomes in LMIC. Optimizing their HIV care requires urgent attention. Children and adolescents who fail PI-based treatment must have access to salvage regimens, particularly integrase inhibitor-based ART.

Table: factors associated with second-line virologic failure

<table>
<thead>
<tr>
<th>Age group</th>
<th>Virologic failure rate per 100 person-years (95%CI)</th>
<th>Adjusted hazard ratio (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>In multivariable model: 15.0 (10.0-21.9)</td>
<td>2.19 (1.12-4.26)</td>
<td>0.022</td>
</tr>
<tr>
<td>Adolescents</td>
<td>In multivariable model: 17.5 (12.9-23.6)</td>
<td>2.19 (1.12-4.26)</td>
<td>0.022</td>
</tr>
<tr>
<td>Male</td>
<td>In multivariable model: 17.5 (12.9-23.6)</td>
<td>2.19 (1.12-4.26)</td>
<td>0.022</td>
</tr>
<tr>
<td>Female</td>
<td>In multivariable model: 17.5 (12.9-23.6)</td>
<td>2.19 (1.12-4.26)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Figure: Cumulative incidence of virologic failure among children and adolescents on second-line treatment.
Virologic failure is defined as two consecutive >1000 copies/ml or death after at least 6 months of second-line treatment. Y axis is set at 5 months after treatment switch, total follow-up time is 60 months.