Time to First-line ART Failure and Switch to Second-line ART in the IeDEA Pediatric Cohort


HIV Pediatrics Workshop - Melbourne
July 2014
ART in Children

• Initiation: 2013 WHO guidelines recommend all <5 years
• Duration: Once initiated, ART is lifelong
• Viral suppression first-line: 53% at 12 mo (95% CI, 50-55%)\(^1\)
• Durability of first-line
  - Cross-sectional survey (2008-2009)\(^2\)
    - Southern Africa IeDEA sites: 3%
    - Asia IeDEA sites: 10%
  - Rates of switch at 5 years of ART
    - Europe (EPICC)\(^3\) cohort: 16.7%
    - Thailand\(^4\) cohort: 21%
    - Europe, North and South America (PENPACT)\(^5\) trial: 29%

\(^1\) Ciaranello, Clin infect Dis 2009; \(^2\) TApHOD and IeDEA South Africa, JIAS 2011; \(^3\) Judd, AIDS 2011;
Objectives

• To determine the time from first-line ART initiation to treatment failure in children

• To assess the time from failure to initiation of second-line ART in children
IeDEA Global Consortium

• Established in 2005
• Funded by: NIAID, NCI, NICHD
• Seven geographic regions addressing high priority questions about HIV care
• Core functions:
  - Collect/define key variables
  - Harmonize data
  - Apply new analytic methods to HIV epi research
Methods

Population:
• Eligibility: Age 2-13 years at ART initiation

Outcomes:
• Failure after 24 weeks on ART as defined by the site
  - Clinical: appearance or reappearance of WHO 3 or 4 disease; increase in WHO stage
  - Immunologic: develop/return to thresholds
    ▪ CD4 <200 cells/µl or CD4% <10 for a child between 2-5 years
    ▪ CD4 <100 cells/µl for a child >5 years
  - Virologic: >5000 copies/µl
• Change to second-line ART
  - Class change (e.g., NNRTI to PI) + ≥1 NRTI
Methods

Data Sources:
- Patient level data pooled from 5 IeDEA Regions
- Site-level survey
  - Standard first- and second-line regimens
  - Method(s) for assessing failure

Analysis:
- Cumulative incidence computed:
  - For first-line failure and second-line switch
  - Death and LTFU treated as a competing event
- Cause-specific proportional hazards model
  - To identify factors associated with each outcome
Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=16,183</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>1883</td>
<td>(11.6)</td>
</tr>
<tr>
<td>Central Africa</td>
<td>49</td>
<td>(0.3)</td>
</tr>
<tr>
<td>East Africa</td>
<td>7101</td>
<td>(43.9)</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>5823</td>
<td>(36.0)</td>
</tr>
<tr>
<td>West Africa</td>
<td>1327</td>
<td>(8.2)</td>
</tr>
<tr>
<td>Female</td>
<td>7964</td>
<td>(49.2)</td>
</tr>
<tr>
<td>Deceased</td>
<td>775</td>
<td>(4.8)</td>
</tr>
<tr>
<td>Lost to follow-up¹</td>
<td>2877</td>
<td>(17.8)</td>
</tr>
<tr>
<td>Initial regimen type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI-based</td>
<td>15818</td>
<td>(97.7)</td>
</tr>
<tr>
<td>NRTI-based</td>
<td>54</td>
<td>(0.3)</td>
</tr>
<tr>
<td>PI-based</td>
<td>311</td>
<td>(1.9)</td>
</tr>
</tbody>
</table>

- [1] >6 months without a visit and no documentation of transfer
- [2] Within 90 days prior and 7 days post ART initiation
- [3] Patients ≥5 years
- [4] Patients <5 years

| Age at first visit | 5.8 (3.5-8.7) |
| Age at ART start   | 6.7 (4.4-9.4) |
| CD4 cells/µl at ART start² | 231 (73-423)³ |
| CD4% at ART start²  | 13 (8.0-18)⁴ |
Results
Probability of Failure or Death/LTFU

- **Total: 16,183**
  - Failure: 4,032
  - Death/LTFU: 2,837

- **1 year after ART**
  - Failure: 12.0% (95%CI: 11.5-12.6)
  - Death/LTFU: 11.6% (95%CI: 11.2-12.2)

- **5 years after ART**
  - Failure: 35.0% (95%CI: 34.3-36.2)
  - Death/LTFU: 22.1% (95%CI: 21.4-23.1)
## Results

### FACTORS ASSOCIATED WITH FAILURE AND DEATH/LTFU

<table>
<thead>
<tr>
<th>Factor</th>
<th>Failure</th>
<th>Death/LTFU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male (Ref: female)</td>
<td>1.06</td>
<td>1.0 - 1.13</td>
</tr>
<tr>
<td>Age ART initiation (per year increase)</td>
<td>1.03</td>
<td>1.02 - 1.04</td>
</tr>
<tr>
<td>Regimen (Ref: NNRTI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• NRTI</td>
<td>1.18</td>
<td>0.70 - 2.0</td>
</tr>
<tr>
<td>• PI</td>
<td>0.54</td>
<td>0.40 - 0.72</td>
</tr>
<tr>
<td>Confirmatory VL (Ref: routine VL)</td>
<td>1.36</td>
<td>1.28 – 1.45</td>
</tr>
<tr>
<td>No access to VL* (Ref: routine VL)</td>
<td>0.73</td>
<td>0.62 – 0.87</td>
</tr>
</tbody>
</table>

*final 2 rows reflect corrected text following the presentation.*
Results
Probability of Change after Failure

- **Total: 4032**

1 year after failure
- Death/LTFU: 9.6%
  
  (95% CI: 8.7 – 10.7)
- Second-line: 11.3%
  
  (95% CI: 10.4 – 12.5)

5 years after failure
- Death/LTFU: 22.3%
  
  (95% CI: 21.0 – 24.6)
- Second-line: 29.3%
  
  (95% CI: 27.9 – 32.0)
### FACTORS ASSOCIATED WITH CHANGE TO SECOND-LINE AND DEATH/LTFU

<table>
<thead>
<tr>
<th>Factor</th>
<th>Change to Second-Line</th>
<th>Death/LTFU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male (Ref: female)</td>
<td>1.33</td>
<td>1.15 - 1.53</td>
</tr>
<tr>
<td>Age ART initiation (per year increase)</td>
<td>1.09</td>
<td>1.07 – 1.12</td>
</tr>
<tr>
<td>Regimen (Ref: NNRTI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• NRTI</td>
<td>0.44</td>
<td>0.06 - 3.11</td>
</tr>
<tr>
<td>• PI</td>
<td>0.85</td>
<td>0.38 - 1.90</td>
</tr>
<tr>
<td>Confirmatory VL (Ref: routine VL)</td>
<td>0.54</td>
<td>0.46 - 0.62</td>
</tr>
<tr>
<td>No access to VL (Ref: routine VL)</td>
<td>0.52</td>
<td>0.31 – 0.85</td>
</tr>
</tbody>
</table>
Conclusions

- High rates of death/LTFU and first-line failure were identified in children within 5 years after ART initiation.
- Children in facilities without routine VL were less likely to be identified as failing but more likely to be LTFU or dead.
- Children without access to any VL were less likely to switch.
- Associations with VL access may be related to other site-level factors, including background mortality.
- Of children meeting failure criteria, only a third were changed to second-line ART by 5 years while about a quarter had died.
- Efforts need to be made to determine the reasons for delays in switching of antiretroviral regimens in children who have been identified as failing first-line.
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