Switch to second-line ART in HIV-infected children: a Collaborative Initiative for Paediatric HIV Education & Research (CIPHER) Global Cohort Collaboration analysis

Intira Jeannie Collins, Ruth Goodall, Colette Smith and Kara Wools-Kaloustian for the CIPHER Duration of First-Line Project Team
Background

• WHO guidelines (2015) recommend universal ART in all children and adolescents (<19 years), irrespective of clinical stage or CD4.

• Estimates of need for second-line ART in perinatally infected children/adolescents is critical to informing clinical care and programme planning.

• Clinical trials report proportion of switch at 5 years of ART ranging from: 2% in CHER\(^1\), 6% in ARROW\(^2\) to 21% in PENPACT-1\(^3\).

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2. Arrow Trial; Lancet 2013
3. PENPACT-1 Lancet ID 2011
CIPHER network

- Individual-level data pooled from 12 paediatric HIV cohort networks

 Participating Cohort Networks
- **BIPAI**: Baylor International Pediatric AIDS Initiative
- **EPPICC**: European Pregnancy and Paediatric HIV Cohort Collaboration
- **IeDEA**: International Epidemiologic Databases to Evaluate AIDS (Asia-Pacific, CCASAnet, Central, East, West & Southern Africa)
- **IMPAACT P1074**: International Maternal Pediatric Adolescent AIDS Clinical Trials
- **MSF**: Médecins Sans Frontières
- **Optimal Models**: ICAP at Columbia University
- **PHACS**: Pediatric HIV/AIDS Cohort Study
Regions of CIPHER

Leading data centres: **UCT** (IeDEA Southern Africa), **UCL** (EPPICC), **Harvard** (PHACS)

Data merger
Jun 2015
Methods (1)

Inclusion criteria:

• <10 years at enrollment into cohort
• <18 years at ART initiation
• Initiated ART with ≥3 drugs (boosted PI or NNRTI-based)

Exclusion criteria:

• No follow-up after ART start
• Enrolled in trial of treatment monitoring, switch or interruption strategies
Methods (2)

Switch to second-line was defined as:

• A change in drug class and a change in ≥1 NRTI; or
• A change within PI drug class (ie. LPV/r to DRV) and a change in ≥1 NRTI; or
• Change from single PI to dual PI (ignoring ritonavir boosting); or
• Addition of new drug class

Time to switch: cumulative incidence accounting for the competing risks of death or loss to follow-up (LTFU)
## Results

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total children in dataset</td>
<td>(N=182,747)</td>
</tr>
<tr>
<td>Perinatally infected &amp; ever started ART</td>
<td>(N=106,529)</td>
</tr>
<tr>
<td>Started (\geq 3) ARVs</td>
<td>(N=97,606)</td>
</tr>
<tr>
<td>NNRTI / boosted PI-based ART</td>
<td>(N=94,055)</td>
</tr>
<tr>
<td>(\geq 1) day follow-up after ART start</td>
<td>(N=93,213)</td>
</tr>
</tbody>
</table>
Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>192</td>
<td>0.2%</td>
</tr>
<tr>
<td>South America &amp; Caribbean</td>
<td>926</td>
<td>1.0%</td>
</tr>
<tr>
<td>Europe</td>
<td>2,142</td>
<td>2.3%</td>
</tr>
<tr>
<td>Asia</td>
<td>6,107</td>
<td>6.6%</td>
</tr>
<tr>
<td>Rest of Sub-Saharan Africa</td>
<td>66,789</td>
<td>71.7%</td>
</tr>
</tbody>
</table>

Total: N = 93,213
### Demographics (1)

<table>
<thead>
<tr>
<th>Characteristics at start of ART</th>
<th>Total (n=93,213)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male sex</strong></td>
<td>46,983 (50%)</td>
</tr>
<tr>
<td><strong>Age group (years)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>39,357 (42%)</td>
</tr>
<tr>
<td>3-5</td>
<td>23,749 (26%)</td>
</tr>
<tr>
<td>6-9</td>
<td>26,550 (28%)</td>
</tr>
<tr>
<td>≥10</td>
<td>3,557 (4%)</td>
</tr>
<tr>
<td><strong>CD4 (n=50,011); Median (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>CD4 Percentage (&lt;5 yrs)</td>
<td>16 (11-23)</td>
</tr>
<tr>
<td>CD4 cell count/mm³ (≥5 yrs)</td>
<td>296 (148-506)</td>
</tr>
<tr>
<td><strong>Reported AIDS event</strong></td>
<td>40,217 (43%)</td>
</tr>
<tr>
<td><strong>Weight-for-age z-score (n=88,130)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;-2</td>
<td>30,340 (34%)</td>
</tr>
<tr>
<td>-2 to 0</td>
<td>27,756 (32%)</td>
</tr>
<tr>
<td>&gt;0</td>
<td>30,034 (34%)</td>
</tr>
</tbody>
</table>
## Demographics (2)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=93,213)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calendar year at start of ART</strong></td>
<td></td>
</tr>
<tr>
<td>≤2004</td>
<td>4,694 (5%)</td>
</tr>
<tr>
<td>2005-2007</td>
<td>23,186 (25%)</td>
</tr>
<tr>
<td>2008-2010</td>
<td>36,573 (39%)</td>
</tr>
<tr>
<td>≥2011</td>
<td>28,760 (31%)</td>
</tr>
<tr>
<td><strong>Cohort monitoring strategy</strong></td>
<td></td>
</tr>
<tr>
<td>Routine viral load &amp; CD4</td>
<td>25,984 (28%)</td>
</tr>
<tr>
<td>Targeted viral load, routine CD4</td>
<td>16,585 (18%)</td>
</tr>
<tr>
<td>No viral load, routine CD4</td>
<td>36,515 (39%)</td>
</tr>
<tr>
<td>Clinical monitoring only</td>
<td>14,129 (15%)</td>
</tr>
<tr>
<td><strong>World Bank Income Group</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>40,234 (43%)</td>
</tr>
<tr>
<td>Low middle</td>
<td>30,290 (33%)</td>
</tr>
<tr>
<td>Upper middle</td>
<td>20,773 (22%)</td>
</tr>
<tr>
<td>High</td>
<td>1916 (2%)</td>
</tr>
</tbody>
</table>

*Monitoring strategy based on proportion with CD4/ VL measurements and frequency of measurements, within cohort.*
Initial regimen by region

- **Rest of SSA**: n=66,789
- **South Africa**: n=17,057
- **Asia**: n=6,107
- **South America & Caribbean**: n=926
- **Europe**: n=2,142
- **USA**: n=194
- **Total**: n=93,213

**Initial regimen by region summary**: 89%
Follow-up

- Median follow-up from ART start: 27 mo (IQR 9, 54)
- 1% death, 25% LTFU, 20% transfer out
- LTFU range: 10% in USA to 27% in SSA

- 3,979 switches in 265,190 person-years
- Crude rate: 15.0 per 1,000 person-years
  - Median time to switch: 35 mo (IQR 19, 57)
  - 86% of switches were NNRTI → PI
Cumulative incidence of switch by region

Cumulative incidence (\%) vs Years since ART initiation

- USA
- Europe
- Asia
- S. America
- South Africa
- Rest of SSA
Overall cumulative incidence of switch at 3 years after ART initiation: 3.1% (95% CI 3.0% to 3.2%).

Range from 1.5% (1.4-1.6) in Rest of SSA to 26.1% (20.0-32.7) in USA.
• Overall cumulative incidence of switch at 3 years after ART initiation: 3.1% (95% CI 3.0% to 3.2%).
• Range from 1.5% (1.4-1.6) in Rest of SSA to 26.1% (20.0-32.7) in USA
Cumulative incidence of switch at 3 years, by region
Cumulative incidence of switch at 3 years, by initial regimen

- NNRTI based
- PI based

- SSA
- South Africa
- Asia
- S America
- Europe
- USA
Cumulative incidence of switch at 3 years, by age at ART start
Cumulative incidence of switch at 3 years, by monitoring strategy

- Routine VL & CD4
- Targeted VL
- CD4 only
- Clinical only

- SSA
- South Africa
- Asia
- S America
- Caribbean
- Europe
- USA
Cumulative incidence of switch by monitoring strategy in SSA

- Routine VL & CD4
- Targeted VL
- CD4 only
- Clinical only

Years since ART initiation

Cumulative Incidence (%)
Discussion

- Overall, switch rates were low but with substantial regional variations
- Higher incidence of switch among children:
  - initiating NNRTI-based regimens except in SSA
  - older age at ART start
  - routine viral load and CD4 monitoring
- Limitations: lower bound of true need for switch
  - varying availability of second-line ART
  - high rates of LTFU and transferred out
- Further work includes multivariable modelling to adjust for confounding and outcomes on second-line
Acknowledgements

Co-chairs: Jeannie Collins (EPPICC) and Kara Wools-Kaloustian (IeDEA East-Africa)
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