Duration of first line antiretroviral therapy (ART) in children in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

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Background

- Limited data on durability of first line ART in children in routine care settings across regions
- Estimated rates of switch vary
  - Clinical trials: 23% in PENPACT-1, ~5% in ARROW and 2% in CHER at 5 years of ART
  - Observational cohorts: 17% in EPPICC infants, 21% in Thailand at 5 years and 6.2% at 3 years in South Africa.
- Studies used different definitions of ‘switch’ and regimens varied
- Need data to inform:
  - programme planning & forecasts for paediatric formulations
  - treatment guidelines

18 cohorts from 17 countries including Thailand.

All cohorts have at least 6-monthly VL and CD4 measurements.
Methods

• Inclusion criteria: age<18 years at initiation of a ‘standard’ ART regimen: NNRTI or boosted PI + ≥2NRTI.

• Switch to second line defined as:
  (i) change across drug class (PI to NNRTI or vice versa) and ≥1 NRTI;
  (ii) change within PI-class plus ≥1 NRTI;
  (iii) single to dual PI; or
  (iv) an addition of a new drug class (eg. PI to an NNRTI-based regimen)

• Ignored switches with reason due to simplification, TB or pregnancy

• Competing risk model with death as competing risk to switch
Results

- 3,696 children included: 48% male, 90% perinatally infected. Median duration of follow up: 5.6 years [2.9-8.7].

<table>
<thead>
<tr>
<th>Characteristics at ART initiation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median [IQR]</td>
<td>6.0 [1.7-10.4]</td>
</tr>
<tr>
<td>CD4% if &lt;5 yrs ; CD4 cell count if ≥5 yrs</td>
<td>20% [14-31%]; 215 cells [60-376]</td>
</tr>
<tr>
<td>Viral load, log_{10} copies/mL</td>
<td>5.0 [4.4-5.6]</td>
</tr>
<tr>
<td>CDC stage C</td>
<td>431 (12%)</td>
</tr>
<tr>
<td><strong>Initial regimen</strong>: EFV-based</td>
<td>1193 (32%)</td>
</tr>
<tr>
<td>NVP based</td>
<td>1123 (30%)</td>
</tr>
<tr>
<td>PI-based</td>
<td>1214 (33%)</td>
</tr>
<tr>
<td>NNRTI+3NRTI</td>
<td>166 (4)</td>
</tr>
<tr>
<td><strong>Region</strong>: UK/Ireland</td>
<td>1077 (29%)</td>
</tr>
<tr>
<td>Thailand</td>
<td>695 (19%)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>510 (14%)</td>
</tr>
<tr>
<td>Russia</td>
<td>137 (4%)</td>
</tr>
<tr>
<td>Rest of Europe</td>
<td>1277 (35%)</td>
</tr>
</tbody>
</table>
Results

• Overall, 107 (3%) children died, 514 (14%) lost to follow up and 829 (22%) met the definition of switch.

• Cumulative proportion of switch:
  • 14% (95% CI, 13-15) at 3 years
  • 21% (95% CI, 20-23) at 5 years

• Median time to switch: 30 months [IQR, 15-58]

• Reasons for switch were reported in 654/829 (79%):
  • 63% were for failure
  • 12% toxicity
  • 25% other reasons.

• Assessing failure in the 6 months prior to switch:
  • 587/829 (71%) had VL>1000 copies or a new/recurrent CDC B/C event or no CD4 gain from baseline.

• Time to switch was similar in those with/without reason for switch
## Predictors of switch

### Multivariable model

<table>
<thead>
<tr>
<th>Region</th>
<th>SHR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK/Ireland</td>
<td>1</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rest of Europe</td>
<td>0.90</td>
<td>(0.76-1.07)</td>
<td></td>
</tr>
<tr>
<td>Russia/Ukraine</td>
<td>0.65</td>
<td>(0.47-0.88)</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>0.52</td>
<td>(0.42-0.64)</td>
<td></td>
</tr>
</tbody>
</table>

### Age at ART initiation, years

<table>
<thead>
<tr>
<th>Age at ART initiation, years</th>
<th>SHR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>1</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2-4</td>
<td>0.95</td>
<td>(0.75-1.20)</td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>1.27</td>
<td>(1.03-1.58)</td>
<td></td>
</tr>
<tr>
<td>10+</td>
<td>1.54</td>
<td>(1.24-1.92)</td>
<td></td>
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### First-line regimen

<table>
<thead>
<tr>
<th>First-line regimen</th>
<th>SHR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV + 2NRTI</td>
<td>1</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NVP + 2NRTI</td>
<td>1.38</td>
<td>(1.16-1.65)</td>
<td></td>
</tr>
<tr>
<td>NNRTI+3NRTI</td>
<td>0.89</td>
<td>(0.62-1.27)</td>
<td></td>
</tr>
<tr>
<td>bPI + 2 NRTI</td>
<td>0.62</td>
<td>(0.49-0.78)</td>
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</table>

### VL at ART initiation, c/ml

<table>
<thead>
<tr>
<th>VL at ART initiation, c/ml</th>
<th>SHR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100,000</td>
<td>1</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>≥100,000</td>
<td>1.37</td>
<td>(1.14-1.64)</td>
<td></td>
</tr>
</tbody>
</table>
Cumulative incidence of switch to second-line ART
By age at ART initiation

Age ≥10 yrs

Years since ART initiation

Cumulative Incidence

0 1 2 3 4 5

By age at ART initiation

Cumulative incidence of switch to second-line ART

Age ≥10 yrs
Initial regimen

Cumulative incidence of switch to second-line ART

By initial ART regimen

- PI-based
- NVP-based
- EFV-based
- NNRTI+3NRTI

Cumulative incidence of switch to second-line ART

Years since ART initiation

0 1 2 3 4 5

Initial regimen

- Boosted PI + 2NRTI
- EFV + 2NRTI
- NVP + 2NRTI
- NNRTI + 3NRTI
Cumulative incidence of switch to second-line ART

By region

- High income countries
- Middle income countries

Cohort Region

Years since ART initiation

0 1 2 3 4 5

Cumulative Incidence

UK/Ireland Thailand Eastern Europe Western Europe

Cohort Region

Clinical Trials Unit

UCL
Sensitivity Analyses

- Including switches across class or within PI class with no change in NRTI
  - 112 additional people switched
  - 91% NNRTI -> PI with no change to NRTI; 46% Thailand, 26% UK/Ireland
  - Cumulative proportion of switch: **23% (95% CI, 22-25) at 5 years**
  - Thailand becomes more similar to Russia/Ukraine; other risk factors unchanged.

- Ignoring switches in first 6 months:
  - 67 switches: 19% bPI, 33% EFV, 36% NVP, 12% 3NNRTI
  - Cumulative proportion of switch: **19% (95% CI, 17-21) at 5 years**
  - No change in factors associated with switch

- Treating LTFU as a competing risk: No change in risk factors
Conclusion

- 21% of children in EPPICC, with access to VL and CD4 monitoring, switched to second line ART by 5 years of therapy
- Two-thirds of switches were failure related
- Older age, higher viral load at ART initiation, and NVP based regimen associated with more rapid time to switch
- Children in Thailand, Russia and Ukraine switched later compared to those in Western Europe, possibly due to lack of available second-line regimen
Acknowledgements

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Participating cohorts:

- **Europe-wide**: PENTA trials long-term follow-up (Prof Carlo Giaquinto, Prof Di Gibb)
- **Europe-wide**: European Collaborative Study (Dr Claire Thorne)
- **Belgium**: Hospital St Pierre Cohort, Brussels (Dr Tessa Goetghebuer)
- **France**: French Perinatal Cohort Study / Enquête Périnatale Français (Dr Josiane Warszawski)
- **Germany**: Competence Network (Dr Chris Koenigs)
- **Greece**: Greek cohort (Dr Vana Spoulou)
- **Italy**: Italian Register for HIV infection in children (Prof Maurizio de Martino, Prof Luisa Galli)
- **Netherlands**: ATHENA paediatric cohort (Peter Reiss, Henriette Scherpbier, Colette Smit)
- **Poland**: Polish paediatric cohort (Magda Marczynska)
- **Portugal**: Centro Hospitalar do Porto (Laura Marques)
- **Portugal**: Lisbon paediatric cohort (Filipa Prata)
- **Romania**: "Victor Babes" Hospital Cohort, Bucharest (Dr Luminita Ene)
- **Russia**: Republican Hospital of Infectious Diseases, St Petersburg (Prof E Voronin, Dr Inga Latysheva)
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- **Spain**: Co-RISPE-1, rest of Spain (Dr Pablo Rojo Conejo)
- **Sweden**: Swedish Cohort Study (Lars Naver)
- **Switzerland**: Swiss Mother and Child HIV Cohort Study (Dr Christoph Rudin)
- **Thailand**: Perinatal HIV Prevention Trials cohort (Dr Gonzague Jourdain)
- **Ukraine**: Paediatric HIV Cohort (Dr Ruslan Malyuta, Dr Galena Kiseleva)
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- **UK & Ireland**: Collaborative HIV Paediatric Study (Dr Ali Judd, Prof Di Gibb)