Virologic Outcomes of HIV-Infected Children Undergoing a Single-Class Drug Substitution from LPV/r- to EFV-Based cART: A retrospective cohort study.


\textsuperscript{1}University of Cape Town, School of Public Health and Family Medicine, Cape Town, South Africa.

For the IeDEA-SA collaboration
Background

Early cART

Durable 1st line

Accessible 2nd line

PMTCT

Early cART
Background

LPV-r
- Better virologic suppression than NVP-based cART
- Tablet size
- Palatability
- Twice-daily dosing
- Storage requirements
- Drug-drug interactions
- Long term side-effects

EFV
- Effective
- Relatively cheap
- Easy to administer
- Daily dosing
- Reasonable long term side-effect profile
- Use in <36mo old not recommended
- High-level class resistance
2013:
WHO added the option to substitute LPV/r with an NNRTI in children with sustained virologic suppression

Main evidence:
NEVEREST 2 and 3
To compare outcomes of children commencing cART with LPV/r and substituting LPV/r with efavirenz once virologically suppressed and ≥36 months old (substitution group) with those remaining on LPV/r (stay group) in a routine clinical setting
Method

Retrospective cohort

Starting cART between 2003-2010

8 South African sites

SA NDOH guidelines
  - PI recommended 1st line <36mo irrespective of PMTCT

Clinician discretion to substitute LPV/r with EFV
Method

Substitution group

Stay group

First VL>400
Median follow-up time: **25.8mo** (15.1 – 34.2)

Median follow-up time: **24.4mo** (18.1 – 31.7)
Method

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substitution group</td>
<td>36</td>
</tr>
<tr>
<td>Stay group</td>
<td>42</td>
</tr>
<tr>
<td>Exclusions</td>
<td>654</td>
</tr>
</tbody>
</table>

N = 1084

First VL >400

n = 59

n = 1025

n = 654
## Results

### Comparison of groups at *initiation* of cART

<table>
<thead>
<tr>
<th></th>
<th>Stay</th>
<th>Substitution</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (months)</td>
<td>17.6</td>
<td>15.3</td>
<td>0.381</td>
</tr>
<tr>
<td>Median pre-cART CD4 %</td>
<td>13.9</td>
<td>13.0</td>
<td>0.571</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td>-2.34</td>
<td>-2.56</td>
<td>0.130</td>
</tr>
<tr>
<td>WHO stage 3 or 4</td>
<td>89.9 %</td>
<td>80.8 %</td>
<td>0.157</td>
</tr>
<tr>
<td>HIV VL (log_{10} copies/ml)</td>
<td>5.69</td>
<td>5.51</td>
<td>0.708</td>
</tr>
</tbody>
</table>

### Comparison of groups at *36 months of age*

<table>
<thead>
<tr>
<th></th>
<th>Stay</th>
<th>Substitution</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD4 %</td>
<td>28.9</td>
<td>29.4</td>
<td>0.751</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td>-0.86</td>
<td>-0.32</td>
<td>0.074</td>
</tr>
<tr>
<td>HIV VL &lt;400 copies/ml</td>
<td>all</td>
<td>all</td>
<td></td>
</tr>
</tbody>
</table>
Results

Comparison of groups at 42 months of age or date of substitution

<table>
<thead>
<tr>
<th></th>
<th>Stay</th>
<th>Substitution</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD4 %</td>
<td>29.6</td>
<td>28.5</td>
<td>0.562</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td>-0.83</td>
<td>-0.58</td>
<td>0.420</td>
</tr>
<tr>
<td>≥ Viral blip</td>
<td>318 (48.6%)</td>
<td>10 (27.8%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Viral blip

an isolated VL >1000 copies/ml which subsequently returned to <400 copies/ml at the next measurement (conducted within 24 months) with no change in cART regimen
Factors associated with single-drug substitution

- **Favourable clinical response to cART**
  - adjusted OR 1.34 per 1 weight-for-age z-score increase, 95% CI 0.96 - 1.80
  - associated with undergoing a single-drug substitution

- **Viral blips**
  - adjusted OR 0.34, 95% CI 0.15 - 0.79
  - associated with **not** undergoing a single-drug substitution

- Immune recovery

- PMTCT exposure
Results

Primary outcomes after substitution

Incidence rate ratio of time to first VL >400 copies/ml:

1.03 (95% CI 0.43 to 2.08) in the substitution relative to the stay group

Cox regression model HR

Adjusted HR=1.43 (95% CI 0.62 - 3.32, p=0.401)
adjusted for other predictors of non-suppression
- WAZ at initiation of cART
- Duration on cART
- VL blip(s) prior to 36 months
in the substitution relative to the stay group
## Secondary outcomes after substitution

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stay (n=654)</th>
<th>Substitution (n=36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>3 (0.43)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TFO</td>
<td>278 (42.5)</td>
<td>9 (25.0)</td>
<td>0.039</td>
</tr>
<tr>
<td>LTFU</td>
<td>35 (5.4)</td>
<td>4 (11.1)</td>
<td>0.139</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>64 (9.8)</td>
<td>2 (5.6)</td>
<td>0.565</td>
</tr>
<tr>
<td>Changed back to LPV/r</td>
<td>-</td>
<td>7 (19.4)</td>
<td>-</td>
</tr>
</tbody>
</table>
In this cohort, virologic outcomes of children suppressed on LPV/r-based cART and subsequently changed to EFV were no worse than of those remaining on LPV/r.

However, this cohort was not exposed to more than a single postpartum dose of NVP as infant prophylaxis.

Thus, in carefully selected children who have had no or only a sdNVP as PMTCT, this may be a virologically safe regimen-sparing and side-effect limiting simplification strategy.
Thanks to
All the children who participated as well as their caregivers
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NIAID

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  Desmond Tutu HIV Centre and Guguletu ART Program
  University of Stellenbosch Department of Paediatrics
  Tygerberg Academic Hospital

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  Rahima Moosa Mother and Child Hospital

○ In Durban, South Africa:
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  McCord Hospital

○ In Hlabisa, South Africa:
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  ○ M, Maternal and Pediatric Infectious Disease Branch

○ In Bern, Switzerland:
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  Institute of Social and Preventive Medicine