Current challenges of paediatric HIV care – Experiences in Sub-Saharan Africa

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Current Challenges of Paediatric HIV Care – What is Happening in the Countries?

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## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tbody>
<tr>
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<td>Employee</td>
<td>University of Nairobi</td>
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<td>Consultant</td>
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<tr>
<td>Major Stockholder</td>
<td>Nil</td>
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**Presentation includes discussion of the off-label use of a drug or drugs**
Outline

- Linkage of newly diagnosed HIV+ children to long-term HIV care
- Late presentation of most children in advanced HIV disease
- Late detection of ART failure using current monitoring approaches
- High TB – HIV co-infection and drug interaction challenges for children < 3yr.
- Limited paediatric ARV formulations, and limited options for children failing PI regimens
LINKAGE OF NEWLY DIAGNOSED HIV INFECTED CHILDREN TO CARE
Children (0–14 yr old) eligible for ART (2005–2011) and receiving it (2005–2012)
Sub Saharan Africa Gap in ART for Children

Why are 72% of eligible African HIV infected children not on ART?

- They do not yet know their diagnosis
- When diagnosed, poor linkage to long-term care
- Even after starting ART, high drop off due various factors
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Kenya Natl. Survey</th>
<th>S. African 5 sites 4 countries*</th>
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</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>7,332</td>
<td>8,225</td>
</tr>
<tr>
<td>Female %</td>
<td>51.2%</td>
<td>49.4%</td>
</tr>
<tr>
<td>Median age, years (IQR)</td>
<td>2.6 (1.1-6.4)</td>
<td>4.0 (1.5-7.7)yr</td>
</tr>
<tr>
<td>HIV WHO Stage III/IV</td>
<td>45.6%</td>
<td>78.4%</td>
</tr>
<tr>
<td>Median baseline CD4% (IQR)</td>
<td>16 (10-24)%</td>
<td>11.6 (7-17)%</td>
</tr>
<tr>
<td>Median follow-up time, yrs (IQR)</td>
<td>2.4 (0.6, 4.2)</td>
<td>1.4 (0.6-2.5)yr</td>
</tr>
<tr>
<td>Proportion Deaths</td>
<td>7.3%</td>
<td>4.5%**</td>
</tr>
<tr>
<td>Died in 1st 3 mth ART</td>
<td>-</td>
<td>273/391 (70%)</td>
</tr>
</tbody>
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* Malawi, Cape Town, Johannesburg, Zimbabwe, Mozambique
** Unadjusted
LATE DETECTION OF ART FAILURE USING CURRENT MONITORING APPROACHES
Clinical/Immunologic Criteria Inadequate for Detecting & Confirming ART failure

<table>
<thead>
<tr>
<th>Country</th>
<th>Cohort size</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rakai, Uganda&lt;sup&gt;a&lt;/sup&gt; 2009</td>
<td>1133</td>
<td>28</td>
<td>90</td>
<td>8</td>
<td>97</td>
</tr>
<tr>
<td>Nigeria (4 sites)&lt;sup&gt;b&lt;/sup&gt; 2011</td>
<td>9690</td>
<td>58</td>
<td>75</td>
<td>39</td>
<td>87</td>
</tr>
</tbody>
</table>

- CD4 has low sensitivity and positive predictive value (PPV) to detect virologic ART failure
- Targeted VL in children with WHO defined clinical/immunologic failure increased the PPV of WHO criteria from **49% to 82%** (South Africa)<sup>c</sup>.
- WHO 2013 guideline now recommends routine VL monitoring
- But: access extremely limited in SS Africa due to cost.

<sup>a</sup>HE Rawizza et al, CID 2011.  
<sup>b</sup>SJ Reynolds et al, AIDS 2009.  
<sup>c</sup>ieDEA-SA, Mary-Ann Davies, Trop Med Int Health 2012
Long-term Virologic Response and Genotypic Resistance Mutations in HIV-1 Infected Kenyan Children on Combination Antiretroviral Therapy

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The implications of delay in detecting virologic failure are illustrated in this cohort
High TB – HIV co-infection and drug interaction challenges for children < 3yr.
High TB – HIV Co-infection in SS Africa

HIV Prevalence in All TB cases (WHO 2007)
- Southern Africa: > 50%
- Eastern Africa: 20 – 49%
- Central Africa: 5 – 19%
- West Africa: 5 – 49%
- SS Africa: 43%
  (UNAIDS 2013)

In Children, HIV prevalence
- Kenya National 2007: 38%
- S. Africa (CT, 2007): 32%
- Ethiopia 2009: 5%
Autopsies on 264 children who died from respiratory disease.
Age 0 – 15yr, median age 8mth. **Top causes of pneumonia death:**
HIV positive: Pyogenic pneumonia, PCP, **TB**, CMV
HIV negative: Pyogenic pneumonia, TB, viral (interstitial pneumonitis)
ART reduces incidence of TB 5 fold in HIV infected Children (DR Congo)

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Concurrent ART with Anti-TB Treatment Poses Many Challenges In Children

Rifampicin – Backbone of TB Rx – induces metabolism of several key ARV drugs:

• Reduces NVP levels by 10-68%
  – Minimal effect on EFV
• Reduces Lopinavir levels by 80%
  – Double dosing LPV/r does not fix this
  – Super-boosting with Ritonavir fixes it, but unpalatable unstable liquid formulations limit feasibility in SSA
• Limited options for Rx child < 3yr
  – Triple NRTI (efficacy?) versus EFV (dose uncertain)
  – Then revert to 2 class drug regimen after TB Rx

LIMITED PAEDIATRIC ARV FORMULATIONS
LIMITED OPTIONS FOR CHILDREN FAILING PROTEASE INHIBITOR BASED REGIMENS
Limited Paediatric FDC Formulations

Shows all WHO Paed ARV approvals over period 2002 – 2009

- Notable few FDCs formulations
- Most FDCs are solid
- Few dispersible
- Most FDCs have single company manufacturer

Implication:
- Young children receive 3 separate ARV drugs
- Complex for parent to measure
- High pill/volume burden

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Waning et al. BMC Pediatrics 2010
Current need for Paediatric HIV Care

- New guidelines for paediatric HIV care issued by the World Health Organization in June 2013
- Important special formulations for children living with HIV identified
- Simpler treatment options, if possible in fixed-dose combinations needed

✧ Paediatric market is small
✧ Unattractive for companies to invest in new formulations
✧ This can compromise access

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## WHO Mid and Long-term Priorities

### Formulations
- ABC/3TC/EFV
- ABC or AZT/3TC/LPVr
- RTV granules
- DRV/r co-formulated
- ATV/r in co-formulated

### New Agents
- Dolutegravir
- TAF
- Cobicistat

### Table: Treatment Strategies

<table>
<thead>
<tr>
<th></th>
<th>Age 0–3 years</th>
<th>Age 3–10 years</th>
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<tbody>
<tr>
<td></td>
<td>Option 1</td>
<td>Option 2</td>
</tr>
<tr>
<td><strong>Medium-term</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>ABC + 3TC + LPV/r</td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>Second line</td>
<td>AZT + 3TC + DRV/r</td>
<td>ABC + 3TC + RAL&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Third line</td>
<td>Optimized background regimen + RAL</td>
<td>Optimized background regimen + DRV/r</td>
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<tr>
<td><strong>Long-term</strong></td>
<td></td>
<td></td>
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<tr>
<td>First line</td>
<td>TAF + 3TC + DTG or ABC + 3TC + DTG</td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>AZT + 3TC + LPV/r or ATV/r&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Third line</td>
<td>DRV/r&lt;sup&gt;c&lt;/sup&gt; + ETR or EFV</td>
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Adapted from the recommendations of the Paediatric ARV Drug Optimization Conference, Dakar, Senegal, 22–23 October 2013.
Summary – Africa Challenges

- Children present with advanced HIV
- Challenges in linking all newly diagnosed children to long-term care
- Current monitoring approaches detect ART failure late
- TB – HIV co-infection is common and drug interaction challenges for children < 3yr.
- Limited paediatric ARV formulations, and limited options for children failing PI regimens