Paediatric HIV treatment update

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Red Cross War Memorial Children’s Hospital & University of Cape Town

ART Resistance & New Treatment Options
6th FIDSSA Conference, 5-7 November 2015
# ART Eligibility

<table>
<thead>
<tr>
<th>Age group</th>
<th>SA April 2015</th>
<th>WHO Sept 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (&lt;1 yr)</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Child (1-5 yrs)</td>
<td>All</td>
<td>All Priority: Children &lt;2 yrs, clinical stage 3 or 4, CD4 &lt;25% (if &lt;5 yrs) or ≤350 (if ≥5 yrs)</td>
</tr>
<tr>
<td>Child (5-10 yrs)</td>
<td>Clinical stage 3 or 4, or CD4 ≤500</td>
<td>All Priority: CD4 ≤350 or advanced HIV disease</td>
</tr>
<tr>
<td>Adolescent (10-19 yrs)</td>
<td>Clinical stage 3 or 4, or CD4 ≤500</td>
<td>All Priority: CD4 ≤350 or advanced HIV disease</td>
</tr>
<tr>
<td>Adult (&gt;19 yrs)</td>
<td>Clinical stage 3 or 4, or CD4 ≤500, Active TB, Pregnancy &amp; breastfeeding, Hepatitis B co-infection Priority: CD4 ≤350 or advanced HIV disease</td>
<td>All Priority: CD4 ≤350 or advanced HIV disease</td>
</tr>
<tr>
<td>Age group</td>
<td>SA 2015</td>
<td>WHO 2013</td>
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<tr>
<td>-----------------------------------</td>
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</tr>
<tr>
<td>Neonate (&lt;1 mth)</td>
<td>Separate guideline</td>
<td>Not included</td>
</tr>
<tr>
<td>Infant (1-12 mths) &amp; Child (1-3 yrs)</td>
<td>ABC/3TC/LPV/r</td>
<td>ABC/3TC/LPV/r</td>
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<tr>
<td>Child (&gt;3-10 yrs)</td>
<td>ABC/3TC/EFV</td>
<td>ABC/3TC/EFV</td>
</tr>
<tr>
<td>Early adolescent (10-15 yrs)</td>
<td>ABC/3TC/EFV</td>
<td></td>
</tr>
<tr>
<td>Late adolescent (15-19 yrs)</td>
<td>TDF/FTC (or 3TC)/EFV</td>
<td>TDF/FTC (or 3TC)/EFV</td>
</tr>
<tr>
<td>Adult (&gt;19 yrs)</td>
<td>TDF/FTC (or 3TC)/EFV</td>
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</table>
# Preferred 2\textsuperscript{nd} line ART regimens

<table>
<thead>
<tr>
<th>Failed 1\textsuperscript{st} line ART regimen</th>
<th>2\textsuperscript{nd} line ART regimen</th>
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<tbody>
<tr>
<td></td>
<td>SA 2015</td>
</tr>
<tr>
<td>1\textsuperscript{st} line PI-based regimen</td>
<td>Consult with expert for advice</td>
</tr>
<tr>
<td></td>
<td>WHO 2013</td>
</tr>
<tr>
<td>• &lt;3 yrs: remain on PI-based regimen, improve adherence</td>
<td></td>
</tr>
<tr>
<td>• ≥3 yrs: switch to NNRTI (EFV) + 2 NRTIs</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>1\textsuperscript{st} line NNRTI-based regimen:</td>
<td></td>
</tr>
<tr>
<td>• ABC (or TDF) + 3TC (or FTC) + EFV (or NVP)</td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>• d4T (or AZT) + 3TC + EFV (or NVP)</td>
<td>ABC (or TDF) + 3TC (or FTC) + LPV/r</td>
</tr>
<tr>
<td></td>
<td>ABC (or TDF) + 3TC (or FTC) + LPV/r</td>
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</tbody>
</table>
Outline

• Neonatal ART

• Protease-inhibitor resistance in children

• Treatment of HIV/TB co-infection
Neonatal ART

Rationale

• Early morbidity & mortality
  – Children with HIV Early Antiretroviral (CHER) (2008)
    • Median age at ART start in early arm was 7.4 wks
    • 33% (10/30) deaths occurred in early ART arm
  
  – Innes et al (2014)
    • Median age at ART start 8.4 wks
    • 62% (250/403) had advanced HIV disease at starting ART

• HIV PCR testing at birth

• Limiting HIV reservoirs in body
Neonatal ART
Concerns

- Safety / toxicity
  - Lopinavir/ritonavir LPV/r (Kaletra), zidovudine (AZT) / lamivudine (3TC)

- Very limited pharmacokinetic data to guide dosing
  - AZT, 3TC, LPV/r
  - ABC, NVP

- Efficacy
  - NNRTI vs PI regimen
  - No appropriate regimen currently available for children <3yrs of age with LPV-resistance
    - Darunavir approved from 3yrs of age (Raltegravir from 4 wks of age)

- Premature neonates
Neonatal ART

Specific safety / toxicity concerns

- Lopinavir/ritonavir (LPV/r, co-formulated as Kaletra oral solution)
  - Approved for use in children ≥14 days old in 2008
  - 2011, FDA advisory: 10 reported cases of toxicity in neonates, (8/10 premature), 1 death
  - Cardiac toxicity (bradycardia, heart block, cardiomyopathy, cardiac failure), neuromuscular toxicity (hypotonia, altered LOC, abN EEG), acute renal failure, respiratory & GIT complications
  - 8/10 neonates received Kaletra within 2 days of birth, toxicity developed within 1-6 days
  - Doses administered not provided in report
  - Following discontinuation of Kaletra, 6 neonates recovered within 5 days

- Infants <6 wks of age & premature neonates, doses >300mg/m2/dose 12hrly may be required to achieve plasma LPV trough levels (correlated with efficacy) within the recommended range (1-4mcg/ml)

FDA, 2011
Chadwick, 2009, 2011
Holgate, 2012
Neonatal ART
Specific safety / toxicity concerns

• Zidovudine (AZT) / lamivudine (3TC)
  – Haematological toxicity (anaemia, neutropenia, thrombocytopenia)
  
  – Dose-related: reduced dosing for premature neonates

  – Haematological toxicity increased when AZT + 3TC used for prophylaxis compared with AZT alone
Neonatal ART

Dosing issues

• Zidovudine
  – 4 mg/kg/dose bd (>35 wks gestation) <4 wks of age thereafter 12 mg/kg/dose bd
  – Separate dosing for gestational age <35 wks

• Lamivudine
  – 2mg/kg/dose bd <4 wks of age, thereafter 4 mg/kg/dose bd

• Nevirapine
  – Investigational treatment dose of 6 mg/kg/dose bd (term infants from 2 weeks of age) with no lead-in dose (IMPAACT study)

• Lopinavir/ritonavir
  – 300 mg/m2/dose 12 hrly < 4 wks of age
  – Monitor LPV levels if possible & adjust doses

• Abacavir
  – Dosing data lacking <3 mths of age
Protocol for initiation of ART in HIV-infected neonates ≥2.5kg at birth

Refer to documents below where numbered in the protocol:
1. Managing Indeterminate HIV PCR test results guideline
2. Counselling model
3. Dosage chart if <28 days of age
4. SA NDOH dosing chart

Birth HIV PCR test

Indeterminate result: Refer to separate guideline

Positive Birth HIV PCR test
Actively trace and link to care

If neonate weighs < 2.5kg or unwell/ TB/ Syphilis: Discuss with Regional level centre

Baseline Assessment for neonate ≥2.5 kg
Clinical review
Bloods: confirmatory HIV PCR, CD4 count/%
FBC/diff, ALT
(Genotype if mother on failing 2nd/3rd line ART)

Ensure mother is in a treatment pathway;
Advice on breastfeeding

Post-test and initial adherence counselling for mother / caregiver

Start ART on same day
(if oral feeding is established)
AZT (4mg/kg/dose BD)
3TC (2mg/kg/dose BD)
NVP (6mg/kg/dose BD)
Review at 1 week of treatment:
Clinical review & counselling
Check blood results

Review at 2 weeks of treatment:
Clinical review & counselling

Review at 1 month of treatment:
Clinical review & counselling
Bloods: FBC / diff
Start co-trimoxazole prophylaxis
Adjust medication
If ≥ 3kg:
- Switch NVP to LPV/r (Kaletra) and AZT to ABC
- Dose ABC, 3TC, LPV/r as per SA NDOH dosing chart
If still < 3kg:
- Switch NVP to LPV/r (Kaletra): 1ml BD
- Dose AZT 12mg/kg/dose BD, 3TC 4mg/kg/dose BD

If still < 3kg: assess failure to thrive; discuss with Paediatrician if questions / concerns

Review monthly until 6 months of treatment:
Adjust medication using dosing chart
Month 6: Do VL, CD4
ARV drug dosing chart for children <28 days of age and weighing ≥2.5 kg at birth

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.5-&lt;3.0</td>
<td>0.6 ml BD 6 mg BD</td>
<td>1.2 ml BD 12 mg BD</td>
<td>1.8 ml BD 18 mg BD</td>
</tr>
<tr>
<td>≥3.0-&lt;3.5</td>
<td>0.7 ml BD 7 mg BD</td>
<td>1.4 ml BD 14 mg BD</td>
<td>2.1 ml BD 21 mg BD</td>
</tr>
<tr>
<td>≥3.5-&lt;4.0</td>
<td>0.8 ml BD 8 mg BD</td>
<td>1.6 ml BD 16 mg BD</td>
<td>2.4 ml BD 24 mg BD</td>
</tr>
<tr>
<td>≥4.0-&lt;4.5</td>
<td>0.9 ml BD 9 mg BD</td>
<td>1.8 ml BD 18 mg BD</td>
<td>2.7 ml BD 27 mg BD</td>
</tr>
<tr>
<td>≥4.5-&lt;5.5</td>
<td>1.0 ml BD 10 mg BD</td>
<td>2.0 ml BD 20 mg BD</td>
<td>3.0 ml BD 30 mg BD</td>
</tr>
<tr>
<td>≥5.5-&lt;6.5</td>
<td>1.2 ml BD 12 mg BD</td>
<td>2.4 ml BD 24 mg BD</td>
<td>3.6 ml BD 36 mg BD</td>
</tr>
</tbody>
</table>

Caregivers who will be administering ARV medication to the child must be supplied with a syringe (1ml or 2ml) for each of the 3 ARVs and shown how to prepare and administer the correct dose. If possible, bottles and syringes should be colour coded with stickers and a sticker of the relevant colour used to mark the correct dose on the syringe.
Neonatal ART

• In utero transmission associated with early morbidity & mortality

• Impact of co-infections (TB exposure, congenital syphilis)

• Concerns about adherence and follow-up
  – Many mothers of birth PCR have not accessed adequate antenatal care or ART themselves
  – Additional adherence support required
HIV resistance in children

• Transmitted (primary)
  – Mother failing 1\(^{st}\) / 2\(^{nd}\) / 3\(^{rd}\) line ART
    • Antenatally
    • During breastfeeding

• Acquired
  – During PMTCT (NVP ± AZT for 6-12wks)
  – During ART (child failing 1\(^{st}\) / 2\(^{nd}\) / 3\(^{rd}\) line ART)

• NRTI/NNRTI/PI/II
Resistance in newly diagnosed children (Kuhn, 2014)

- Genotypic resistance testing in 230 newly diagnosed HIV-infected children <2 yrs of age during 2011 in Jhb
- 67.4% exposed to maternal ± infant PMTCT intervention

- Among PMTCT-exposed children, 56.8% had NNRTI, 14.8% had NRTI, and 1.3% PI mutations
- In children with no recorded PMTCT exposure, 24% had NNRTI, 10% NRTI, and 1.3% PI resistance mutations

- Findings support 1st line PI-based ART in newly diagnosed infants & young children regardless of PMTCT history
Resistance in children with virologic failure on LPV/r-based ART (Meyers 2015)

- Genotypic resistance testing in 75/152 children in Soweto with virologic failure on 1st line LPV/r-based ART (92% d4T-containing NRTI backbone) between 2000-2011

- 10.7% (8/75) had significant LPV resistance, including 2 with intermediate Darunavir resistance

- M184V (3TC mutation) occurred in 59%, Thymidine analogue mutations in 8%, NNRTI mutations in 12%
Resistance in children with virologic failure on LPV/r-based ART (Meyers 2015)

- 12/152 (8%) of children in cohort switched to 2nd line NNRTI-based ART, and only 4/12 (33%) re-suppressed

- 84% (63/75) of children remained on LPV/r-based ART, and 51% (32/63) of these achieved viral suppression (including 2 children with LPV resistance)
Resistance in children with virologic failure on Protease inhibitor-based ART (Rossouw 2015)

• Children who initiated PI-based ART in Tshwane district and had subsequent virologic failure

• Virologic failure: confirmed VL >40 >6mths post ART initiation

• Genotypic resistance testing in 65 children with virologic failure in whom adherence interventions failed to result in viral suppression (2008-2012)

• 44/65 children were still on PI-based ART at time of genotyping, 19 had been switched to NNRTI-based ART (off PI for median 25.5mths)

• PI use with rifampicin-based TB Rx: transition from RTV (2004-2008) to double-dose LPV/r to super-boosted LPV (LPV/r + additional RTV)
Resistance in 65 children with virologic failure on Protease inhibitor-based ART (Rossouw, 2015)

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Median value (IQR)</th>
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<tbody>
<tr>
<td>Age at ART initiation</td>
<td>16.8mths (7.8-23.3)</td>
</tr>
<tr>
<td>Duration of PI exposure</td>
<td>25.5mths (15.7-40.4)</td>
</tr>
<tr>
<td>Duration of virological failure</td>
<td>38.0mths (19.1-51.0)</td>
</tr>
<tr>
<td>Wt-for-age Z score</td>
<td>-2.4</td>
</tr>
<tr>
<td>Ht-for-age Z score</td>
<td>-3.1</td>
</tr>
<tr>
<td>Baseline CD4&lt;15%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Baseline WHO stage 4</td>
<td>54.1%</td>
</tr>
<tr>
<td>ART initiation regimen:</td>
<td></td>
</tr>
<tr>
<td>d4T/3TC/LPV/r</td>
<td>64.6%</td>
</tr>
<tr>
<td>d4T/3TC/RTV</td>
<td>24.6%</td>
</tr>
<tr>
<td>d4T/3TC/LPV/r + r</td>
<td>4.6%</td>
</tr>
<tr>
<td>ABC/3TC/LPV/r</td>
<td>3.1%</td>
</tr>
<tr>
<td>AZT/3TC/LPV/r</td>
<td>1.6%</td>
</tr>
<tr>
<td>AZT/3TC/RTV</td>
<td>1.6%</td>
</tr>
<tr>
<td>Ever on TB Rx</td>
<td>(47/61), 77%</td>
</tr>
<tr>
<td>On TB Rx at or after ART initiation</td>
<td>(43/47), 91.5%</td>
</tr>
</tbody>
</table>
Resistance in children with virologic failure on Protease inhibitor-based ART (Rossouw 2015)

- Major PI resistance mutations were detected in 49% of children (V82A, I54V, M46I, L76V)
- NRTI mutations in 97% (Thymidine analogue mutations in 25% (50% ≥3), K65R in 3%, NNRTI mutations in 45%)

<table>
<thead>
<tr>
<th>Significant risk factor for developing major PI mutations</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low wt. &amp; ht.-for-age Z scores</td>
<td>Duration of RTV use as single unboosted PI</td>
<td></td>
</tr>
<tr>
<td>Longer duration on ART or PI</td>
<td>Duration of PI exposure</td>
<td></td>
</tr>
<tr>
<td>Duration of virologic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased time to first suppressed VL or failure to suppress VL by 12 months on ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB Rx at time of ART initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTV use as single unboosted PI during TB Rx</td>
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</tbody>
</table>
Resistance in children with virologic failure on Protease inhibitor-based ART (Rossouw 2015)

• Children starting ART while on TB Rx were 4.6 times more likely to develop major PI resistance than those not on TB Rx

• Children with major PI mutations
  – 100% intermediate/high level resistance to Lopinavir
  – 31.2% intermediate resistance to Darunavir

  – 48.4% intermediate/high level resistance to Efavirenz

  – 71% susceptible to Tenofovir
HIV/TB co-infection & treatment

• Very common problem
  – 29-66% of children on TB Rx at time of starting ART in SA studies (Meyers 2011, Rossouw 2015)

• First line ART regimen for children <3 yrs of age is LPV/r-based

• Rifampicin dramatically reduces plasma LPV concentrations predisposing patients on rifampicin-based TB treatment & LPV/r to treatment failure & LPV resistance

• For adult patients on a PI regimen, options include:
  – Boosting with additional ritonavir
  – Double-dose Aluvia
  – Rifabutin instead of rifampicin
HIV/TB co-infection
Treatment in children

• For young children (7mths-<4yrs) on LPV/r & rifampicin only current option is boosting with additional ritonavir (Ren, 2008)
  • But poor palatability, short supply, short expiry period

• Double-dose LPV/r failed to maintain adequate lopinavir exposure in children aged 6mths-2.5yrs (McIlneron, 2011)

• Rifabutin dosed at 5mg/kg 3 x/wk in 6 children <5yrs of age on LPV/r
  • failed to achieve PK targets equivalent to current adult dosing recommendations (150mg daily)
  • resulted in high rates of severe transient neutropenia (Moultrie, 2015)
Eligibility for genotypic resistance testing (SA NDOH, 2015)

• Failure on 2\textsuperscript{nd} line ART regimen
  – HIV RNA >1000 copies/ml on 2\textsuperscript{nd} line ART for >12-18 mths despite adherence interventions

• Failure on 1\textsuperscript{st} line PI-based ART regimen (children)
  – HIV RNA >1000 (if previous unboosted PI or rifampicin-based TB treatment) or 30000 copies/ml on 1\textsuperscript{st} line PI-based regimen despite adherence interventions
Eligibility for genotypic resistance testing (W Cape, 2015)

• Infants <2yrs of age who are newly diagnosed as HIV-positive if their mothers were exposed to PI-based ART during pregnancy or breastfeeding

• Patients on a PI regimen with ≥3 viral loads of ≥1000 at east 8-12 weeks apart after adherence has been addressed
  – Children (<15yrs) on PI regimen for ≥1 year
  – Adults on PI regimen for ≥2 yrs

• Requires motivation (incl. adherence assessment) & approval by committee
3rd line ART

Expert review committee manages access to 3rd line ART

– National / Provincial

– Genotype-proven PI resistance is pre-requisite for 3rd line ART

– 3rd line regimen based on genotype result, expert opinion and supervised care

– Darunavir/ritonavir, Raltegravir, Etravirine
3rd line ART
ARVs & formulations

• Darunavir (DRV)
  – Tablets: 75mg, 150mg, 600mg
  – Oral suspension (100mg/ml): unregistered, Sec 21/compassionate use access
  – DRV not approved for use <3yrs of age/<10kg

• Raltegravir
  – Tablets: 25mg/100mg (chewable), 400mg (film-coated), not interchangeable
  – Oral suspension (100mg powder for suspension): unregistered, Sec 21/compassionate use access
  – Not approved for children <4 weeks of age/<3kg

• Etravirine
  – Tablets: 100mg (registered), 25mg: unregistered, Sec 21/compassionate use access
  – ETR not approved for children <6yrs of age
New ARVs & new uses for current ARVs

• Raltegravir
  – Role in PMTCT (maternal use during pregnancy)
  – Approved from 4 wks of age but consider use only in exceptional circumstances (risk of resistance)
  – Role in 3rd line ART in combination with DRV/r

• Dolutegravir is awaited (currently approved for use in children >12 yrs of age)
  – Safety, pharmacokinetics & efficacy of dolutegravir in treatment-experienced HIV-infected adolescents (IMPAACT P1093)*
  – Investigational dose in clinical trial in ART-experienced children <12yrs of age

• Atazanavir/r powder formulation approved from 3 mths/10kg, no approved dose of powder formulation for children >25kg unable to swallow tablets

*Viani, 2015
Concluding comments

• Neonatal initiation of ART is increasingly common despite limited dosing safety & efficacy data

• Treatment of HIV/TB co-infection remains a major challenge in paediatrics

• Protease inhibitor resistance & the need for 3\textsuperscript{rd} line ART regimens is here