Treatment needs and strategies for young children

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Pediatric HIV could be quasi eliminated

- HIV diagnosis and prophylaxis/treatment initiation of all pregnant women
- Full implementation of option A (ZDV during pregnancy, continuous NVP during breastfeeding) and option B (HAART during pregnancy and breastfeeding) of equivalent efficacy
  - NVP syrup stock out and dispersible formulation tablets not available
- Under the best circumstances the risk of transmission is less than 1%
  - Point of care HIV tests for early diagnosis still needed
But the reality is that

- Women may not know that they are infected
  - Primary infection during pregnancy, or in the postpartum
  - Unavailability of antiretrovirals or late presentation
- Need to treat an increasing number of perinatally infected infants/children
  - Half a million infants newly infected every year
  - Less than half a million of all ages currently treated
- What comes next partly depends on what was done/not done to prevent and diagnose perinatal HIV
  - Presence of primary resistance to antiretrovirals, age at diagnosis and co-infections/morbidities at treatment initiation
## Drugs available for children at different ages

<table>
<thead>
<tr>
<th>Drug</th>
<th>1y</th>
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<tbody>
<tr>
<td>ZDV</td>
<td>10 mg/mL; 100 mg; 300 mg</td>
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<td>ABC</td>
<td>20 mg/mL; 300 mg</td>
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<tr>
<td>ddI</td>
<td>20 mg/mL; 125/200/250/400 mg enteric-coated; 200/250/400 delayed released</td>
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<td>TDF Gilead filing for children 2-12yo</td>
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<td>3TC/FTC</td>
<td>5/10 mg/mL; 100/150/200 mg</td>
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<td>NVP P1103 PK of full dosing at treatment initiation</td>
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<td>EFV</td>
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<td>EFV P1070 PK in HIV and HIV/TB 3months-3 years</td>
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<td>ETR</td>
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<td>ETV in ARV experienced children</td>
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<td>RPV</td>
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<td>RPV in ARV in adolescents</td>
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<td>LPV/r</td>
<td>80/20 mg/mL; 100/25 mg; 200/50 mg</td>
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<td>ATV</td>
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<td>ATV Prince 1 &amp; 2 oral powder + ritonavir liquid</td>
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<td>FPV</td>
<td>50 mg/mL; 700 mg unboosted/ boosted or unboosted</td>
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<td>DRV Tibotec safety/PK study 3-6 years completed</td>
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<tr>
<td>TPV</td>
<td>100 mg/mL; 250 mg</td>
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<td>Dolutegravir P1066 PK/safety granules/susp. chewable tablets for 2-12 yrs</td>
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</tbody>
</table>

Dolutegravir P1093 planned in experienced children 6 wks to 18 yrs
Different strategies to address different needs

Children are likely to be treated for decades; use of efficacious, safe, well tolerated, child friendly regimen

As immediate needs and treatment options differ according to age, strategies are likely to differ

- Newly infected adolescents (once a day FDCs)
- Perinatally infected adolescents need more complex second or third line regimen
- Children have fewer options. Naïve long term survivors
  - often severely immunosuppressed at therapy initiation,
  - acute context of opportunistic infection/malnutrition, and co-infections
- Infants and young children: what options?
# FDA Approved ARVs (as of July 2011)

## Limited choices for **neonates and infants**

<table>
<thead>
<tr>
<th>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</th>
<th>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</th>
<th>Protease Inhibitors (PIs)</th>
<th>Integrase Inhibitor</th>
<th>Fusion Inhibitor</th>
<th>CCR5 Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir (ABC)/ Ziagen</strong></td>
<td>Delavirdine (DLV)/ Rescriptor</td>
<td>Atazanavir (ATV)/ Reyataz</td>
<td>Raltegravir (RAL)/ Isentress</td>
<td>Enfuvirtide (T20)/ Fuzeon</td>
<td>Maraviroc (MVC)/ Selzentry</td>
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<tr>
<td><strong>Didanosine (ddI)/ Videx EC</strong></td>
<td>Efavirenz (EFV)/ Sustiva</td>
<td>Darunavir (DRV)/ Prezista</td>
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<tr>
<td><strong>Emtricitabine (FTC)/ Emtriva</strong></td>
<td>Etravirine (ETR)/ Intelence</td>
<td>Fosamprenavir (FPV)/ Lexiva **</td>
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<tr>
<td><strong>Lamivudine (3TC)/ Epivir</strong></td>
<td>Nevirapine (NVP)/ Viramune</td>
<td>Indinavir (IDV)/ Crixivan</td>
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<tr>
<td>Stavudine (d4T)/ Zerit</td>
<td>Etravirine (ETR)/ Intelence</td>
<td>Lopinavir/Ritonavir (LPV/r)/ Kaletra</td>
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<tr>
<td>Tenofovir Disoproxil Fumarate (TDF)/ Viread</td>
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<td>Nelfinavir (NFV)/ Viracept</td>
<td>Ritonavir (RTV)/ Norvir</td>
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<tr>
<td><strong>Zidovudine (ZDV, AZT)/ Retrovir</strong></td>
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<td>Saquinavir (SQV)/ Invirase</td>
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<td></td>
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<td></td>
<td>Tipranavir (TPV)/ Aptivus</td>
<td></td>
<td>Not approved in neonates and infants</td>
</tr>
</tbody>
</table>

**Notes:**
- Ritonavir (RTV)/ Norvir
- Saquinavir (SQV)/ Invirase
- Tipranavir (TPV)/ Aptivus
- Not approved in neonates and infants
Starting life long therapy

• Without treatment, half of the children die before reaching their second birthday.

• WHO now recommends (2010)
  – Early diagnosis and immediate triple therapy initiation

• But infants/young children have
  – HIV concentration 10 to 100 times higher than in adults
  – Viruses often resistant to some antiretroviral drugs
    • Late initiation of prophylaxis/HAART
    • Option A: long term exposure to NVP
    • Option B: failing HAART and drug exposure through breast milk

Start with the

- most efficacious and safe drugs,
- compatible treatment of childhood diseases: malaria, tuberculosis, diarrhea, malnutrition...
HIV in infants and young children: Overlapping epidemics
Options for infants and young children are few and not adapted

- For infants with high viral loads and often partly resistant viruses, the recommended option is to start with lopinavir/r (+ 2 NRTIs)
  - Horrible taste solution containing over 40% alcohol
  - Unstable in tropical climates
- Nevirapine based alternative is not as potent and marginally better adapted
- In some settings, up to 50% of the children will need an anti-TB therapy with major negative interactions with lopinavir/r
DNDi pediatric HIV program

- Develop improved PI based first-line combination treatments for infants and children less than 3 years

**Target Produce Profile (April 2011 Expert meeting)**

<table>
<thead>
<tr>
<th>Profile</th>
<th>Ideal</th>
<th>Acceptable</th>
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</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>NVP-exposed and non-exposed HIV+ children under 3 year old</td>
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<tr>
<td><strong>Dosing frequency</strong></td>
<td>QD</td>
<td>BID</td>
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<tr>
<td><strong>Formulation</strong></td>
<td>Water-soluble, dispersible tablet</td>
<td>Sprinkles dosage form may work</td>
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<td>Same dosage form that can be used for 2 to 36 months old.</td>
<td>Crushable pill that can be used in “food” may be acceptable.</td>
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<tr>
<td><strong>Pill burden</strong></td>
<td>1 (scored) pill - usable across broad weight bands (WHO table)</td>
<td>If 2 pills, must be same tablet count (or same fraction) for both</td>
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<tr>
<td><strong>Durability</strong></td>
<td>High genetic barrier (PI-like). Long plasma half-life.</td>
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<tr>
<td><strong>Efficacy</strong></td>
<td>Same as for adults</td>
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<tr>
<td><strong>Safety/tolerability</strong></td>
<td>Well tolerated and no laboratory monitoring needed</td>
<td>No laboratory monitoring needed</td>
</tr>
<tr>
<td><strong>Palatability (taste)</strong></td>
<td>No taste or nice taste for children</td>
<td>Palatable</td>
</tr>
<tr>
<td><strong>Drug-drug interaction (TB Rx)</strong></td>
<td>No drug-drug interaction with TB medicines</td>
<td>Some drug-drug interaction with TB medicines, dose adjustments</td>
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<tr>
<td><strong>Stability</strong></td>
<td>No cold chain, minimum 2 years shelf life at room temperature</td>
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<tr>
<td><strong>Cost</strong></td>
<td>≤ 50 USD/patient/year (adult)</td>
<td>To be investigated</td>
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</table>
1 - Development of an improved PI formulation that ideally can be incorporated in a dispersible fixed dose combination tablet

• Lopinavir (LPV) and ritonavir (RTV) (as booster) most preferred
  – Approved for infants/young children, lots of experience
  – But unfavourable lipid profile
  – Cipla sprinkles evaluated; Abbott pediatric formulation?

• ATV/r as a secondary option
  – Not yet approved for infants/young children (Prince 1 and 2 on-going trials)
  – Potential for once a day dosing
  – One of the preferred PIs in adults
  – Elevated bilirubin (no liver damage)

✓ Taste ... may be a deciding factor
New formulations for PIs
nanoparticles, nanodispersion, prodrugs

• Nano dispersion & nanoparticles, chemistry and PK studies on-going short term (not NCE)

• Pro-drug approach, chemistry studies on-going, longer term (NCE)
2 - Evaluate different NRTI backbone options for use in 1st-line

- TDF – [TDF+3TC].
  - FDA submitted for > 2 years old;
  - <2 years old ?? Taste ?
  - Altered bone metabolism & renal toxicity

- ABC – [ABC+3TC], first-line in South Africa
  - Hypersensitivity (low risk in Africa)
  - Favourable resistance profile
  - Fixed dose combinations

- AZT – [AZT+3TC]
  - Anemia
  - Lots of experience; fixed dose combination in infants
3 - Help resolve the incompatibility between antiretrovirals and TB medicines due to drug-drug interaction

- Adapting TB therapy
  - replacing rifampicin by rifabutin (TB-Alliance)

Vital need for correctly dosed paediatric FDCs for susceptible TB and adapted formulations for resistant TB treatments

- Adapting ART
  - super-boosting PI-based first-line ARV with an improved/additional dose of RTV (pro-drug or new formulation) or cobicistat (Gilead)?
  - EFV? Unstable levels in < 3 years old
  - Integrase Inhibitors e.g. raltegravir to replace PIs? (ANRS RAL adult study on-going, IMPAACT study planned)
Stand alone dispersible tablet for super-boosting

- Concomitant rifampicin decreases LPV/r or ATV/r exposure by > 90%
- Super-boosting PK studies 3 month – 3 years children
- Development of a pro-drug or new ritonavir or atazanavir formulation? Cobicistat?

TB/HIV coinfected children receiving LPV/r with additional ritonavir (LPV/r ratio of 1:1)

Ren et al J Acquir Immune Defic Syndr Vol 47, Number 5, April 15, 2008
4 - Investigate an “Induction-Maintenance” scheme for ‘under-3’ (longer term objective)

Overcoming initially high viral load, primary resistance & minimizing long term toxicities

• Using drugs ~ available for older children

• Role for Integrase Inhibitors?
  – Raltegravir
  – Dolutegravir

• Role for second generation NNRTIs?
  – Etravirine
  – Rilpivirine
Thank you

Brooklyn Chest Hospital – Cape Town

Photo: Anne Detjen