Updates on Paediatric HIV & TB
DCH 2016

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### Global summary of the AIDS epidemic | 2014

#### Number of people living with HIV

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>36.9 million</td>
<td>[34.3 million – 41.4 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>34.3 million</td>
<td>[31.8 million – 38.5 million]</td>
</tr>
<tr>
<td>Women</td>
<td>17.4 million</td>
<td>[16.1 million – 20.0 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>2.6 million</td>
<td>[2.4 million – 2.8 million]</td>
</tr>
</tbody>
</table>

#### People newly infected with HIV in 2014

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2.0 million</td>
<td>[1.9 million – 2.2 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>1.8 million</td>
<td>[1.7 million – 2.0 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>220 000</td>
<td>[190 000 – 260 000]</td>
</tr>
</tbody>
</table>

#### AIDS deaths in 2014

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.2 million</td>
<td>[980 000 – 1.6 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>1.0 million</td>
<td>[760 000 – 1.8 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>150 000</td>
<td>[140 000 – 170 000]</td>
</tr>
</tbody>
</table>

UNAIDS, 2015.  
HIV epidemic in South Africa

- Number of adults and children living with HIV: 6.8 million, 95%CI: 6.5 – 7.5 [2014]
- Children aged 0 – 14 years living with HIV: 340,000, 95%CI: 310,000 – 370,000 [2014]
- Orphans due to AIDS aged 0 – 17 years: 2.3 million, 95%CI: 1.1 – 2.9 [2014]
- 16,000 new paediatric infections & 1,094,000 live births [2013]
HIV prevalence among antenatal women, South Africa, 1990-2012

WHO 4 pronged PMTCT strategy

• Primary Prevention of HIV infection

• Prevention of unintended pregnancies in HIV infected women

• Prevention of HIV transmission from HIV infected women to their infants

• Provision of treatment, care and support of HIV infected women, their infants and their families
Efficacy of ARVs in breastfeeding African populations

1994 2010

Transmission Rate (%)

20-40
13
12
9.3
6.5
4.7
1.5

none  SD ZDV  SD NVP  ZDV+3TC sc  Sc ZDV + NVPsd  Sc ZDV+3TC + NVPsd  HAART

Source: C Luo, UNICEF
How effective is PMTCT in South Africa?
(SAPMTCTCTE cross-sectional surveys)

- **National infant HIV-exposure prevalence (weighted)**
  - 2012-2013: 33.1% (95% CI: 31.8 – 34.4)
  - 2011-2012: 32.2% (95% CI: 30.7 – 33.6)
  - 2010: 32.0% (95% CI: 30.7 – 33.3)

- **National early MTCT aged 4 – 8 weeks (weighted)**
  - 2012-2013: 2.6% (95% CI: 2.0 – 3.2)
  - 2011-2012: 2.7% (95% CI: 2.1 – 3.2)
  - 2010: 3.5% (95% CI: 2.9 – 4.1%)

Source: Ameena Goga, 28 July 2015
Antiretroviral therapy coverage in adults and children, 2000-2014

Estimated coverage among children in South Africa: 63% (2012)

Estimated number of children on ART, 2014

<table>
<thead>
<tr>
<th>Region</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia &amp; the Pacific</td>
<td>72,297 (8.8)</td>
</tr>
<tr>
<td>Caribbean</td>
<td>4,573 (0.56)</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>13,602 (1.7)</td>
</tr>
<tr>
<td>Latin America</td>
<td>17,994 (2.2)</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>1,965 (0.24)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>691,482 (84.0)</td>
</tr>
<tr>
<td>Western &amp; Central Europe and North America</td>
<td>............</td>
</tr>
</tbody>
</table>
Under-five mortality estimates (with 90% uncertainty bounds) together with respective MDG4 target levels for 2015 (two-thirds reduction from 1990)
## Change in cause of U5 mortality

<table>
<thead>
<tr>
<th>Cause</th>
<th>2008</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal death</td>
<td>29%</td>
<td>27%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>HIV infection</strong></td>
<td><strong>46%</strong></td>
<td><strong>8%</strong></td>
</tr>
<tr>
<td>Injuries</td>
<td>2%</td>
<td>9%</td>
</tr>
<tr>
<td>Other causes</td>
<td>9%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Reference: Countdown to 2015: Maternal, newborn & child survival
Paediatric HIV infection

• Dynamic, rapidly evolving field: research, policy, practice
  
  – Prevention of mother to child transmission (PMTCT)
    • Pregnancy: less complexity: universal cART before/during pregnancy, breastfeeding (but adherence, treatment failure etc)
    • HIV-exposed infant: increasing complexity: intensified testing & prophylaxis in high-risk transmission scenarios
  
  – Diagnosis of HIV infection
    • timing, technologies, linkage to treatment
  
  – Combination antiretroviral therapy (cART)
    • Timing of initiation (neonates, CD4 thresholds), regimens, adherence, drug resistance testing, new drugs, drug interactions, HIV/TB co-infection
HIV exposure & infection

• HIV exposure
  – An infant born to a mother with HIV infection and indicated by the presence of HIV antibodies in blood of a child <18 months of age
  – Ingestion of breastmilk from a woman with HIV infection (HIV antibodies in blood of infant may be absent)
  – Exposure to certain other body fluids of an HIV-infected person (e.g. following sexual abuse)

• “Seroreversion”
  – Absence of HIV antibodies in a child known to be HIV exposed

• HIV infection
  – <18 months of age: PCR or viral load (x2)
  – ≥18 months of age: antibody tests (rapid tests, x2)

• HIV exposed uninfected (HEU)
  – PCR negative HIV exposed child
  – Seroreversion
Suspect HIV infection in the presence of:

- Two or more of:
  - Generalised lymphadenopathy
  - Hepatomegaly
  - Splenomegaly
  - Dermatitis
  - Parotid enlargement
  - Persistent candidiasis
  - Recurrent or persistent upper respiratory infection or otitis media

- Other marker conditions include:
  - Repeated or chronic diarrhoea
  - Bacterial infection – single or multiple episodes
  - Tuberculosis
  - Persistent wasting
  - Chronic lung disease
  - Persistent anaemia, neutropenia or thrombocytopenia
  - Atypical infection incl. Pneumocystis jiroveci pneumonitis, salmonella septicaemia, severe or disseminated chickenpox, shingles, recurrent herpes stomatitis, neurodevelopmental delay, progressive encephalopathy, malignancy & low birth weight

Bottom line: HIV status of all infants and children should be established, testing should not just be on “clinical suspicion”
Natural history of HIV infection: adolescents & adults

• Acute (primary) infection
• Window period (HIV ELISA negative, PCR positive)
• Seroconversion (HIV ELISA becomes positive)
• Asymptomatic phase (1-10 years)
• Clinical symptoms & signs of disease (staging)
• AIDS-defining illness / severe immunosuppression (CD4 <200)
• Progression to death or antiretroviral treatment
Natural history of HIV infection: infants & children

• Vertical transmission rate 10-40% (without PMTCT)

• HIV-infected children have more frequent and more severe episodes of common childhood illnesses such as pneumonia & gastroenteritis

• Frequent infections further weaken the immature immune system

• Frequent co-morbidity of HIV infection with TB & malnutrition

• The CD4 count is less predictive of immunity during the first 2 years

• Without antiretroviral therapy, median survival in symptomatic infants <1 year of age in Cape Town was about 34 months
WHO Clinical Staging for Paediatric HIV Infection

Stage One

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)
WHO Clinical Staging for Paediatric HIV Infection

Stage Two

• Unexplained persistent hepatosplenomegaly
• Papular pruritic eruptions
• Extensive wart virus infection
• Extensive molluscum contagiosum
• Recurrent oral ulcerations
• Unexplained persistent parotid enlargement
• Lineal gingival erythema
• Herpes zoster
• Recurrent / chronic URTI (otitis media, sinusitis, otorrhoea)
• Fungal nail infections
WHO Clinical Stage 2 conditions
WHO Clinical Staging for Paediatric HIV Infection

Stage Three

- Unexplained moderate malnutrition (60 - 80% EWFA) not responding adequately to standard therapy
- Unexplained persistent diarrhoea (≥14 days)
- Unexplained persistent fever (>1 month)
- Persistent oral candidiasis (after first 6 weeks of life)
- Oral hairy leukoplakia

- Acute necrotizing ulcerative gingivitis / periodontitis
- Lymph node TB
- Pulmonary TB
- Severe recurrent presumed bacterial pneumonia (≥2 episodes in 6 months)
- Symptomatic lymphoid interstitial pneumonitis (LIP)
- Chronic HIV-associated lung disease incl. bronchiectasis
- Unexplained anaemia (<8g/dl), neutropaenia (<500/mm3) or thrombocytopenia (<50,000/mm3) for > 1 month
WHO Clinical Stage 3 conditions
WHO Clinical Staging for Paediatric HIV Infection

Stage four

- Unexplained severe malnutrition (< 60% EWFA)
- Pneumocystis pneumonia
- Recurrent severe presumed bacterial infections (excl. pneumonia)
- Chronic herpes simplex infection (>1 month duration)
- Extrapulmonary TB
- Kaposi's sarcoma
- Oesophageal candidiasis
- CNS toxoplasmosis outside neonatal period
- HIV encephalopathy
- CMV infection (retinitis or another organ outside neonatal period)

- Extrapulmonary cryptococcosis incl. meningitis
- Any disseminated endemic mycosis
- Chronic cryptosporidiosis or Isosporiasis (with diarrhoea > 1 month)
- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- HIV-associated cardiomyopathy or nephropathy
- Acquired HIV-associated rectovaginal fistula
WHO Clinical Stage 4 conditions
CD4 Count monitoring

• The total (absolute) number of CD4 cells is age-dependent and decreases over the first few years of life (in all children)

• The CD4 percentage (% of lymphocytes which are CD4+ cells) is less variable with age

• HIV infection results in destruction of CD4 lymphocytes over time

• Both the CD4 percentage and the total CD4 count are used to monitor the degree of immunosuppression in young HIV-infected children

• A patient with a ‘low’ CD4 count is at risk of acquiring other infections which may be life-threatening

• CD4 count & clinical stage of disease are currently used to decide when to start ART in children over 5 years of age
Antiretrovirals

• Entry and Fusion inhibitors
  
  • Nucleoside (NRTI) & nucleotide (NtRTI) reverse transcriptase inhibitors
    – Stavudine, lamivudine, zidovudine, didanosine, abacavir, tenofovir
  
  • Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
    – Efavirenz, nevirapine, etravirine
  
• Integrase inhibitors
  – Raltegravir

• Protease inhibitors (PIs)
  – Lopinavir/ritonavir, ritonavir, atazanavir, darunavir
1. Free virus

2. Binding and Fusion: Virus binds to cell at two receptor sites.

3. Infection: Virus penetrates cell. Contents emptied into cell.

4. Reverse Transcription: Single strands of viral RNA are converted into double-stranded DNA by the reverse transcriptase enzyme.

5. Integration: Viral DNA is combined with the cell's own DNA by the integrase enzyme.

6. Transcription: When the infected cell divides, the viral DNA is "read" and long chains of proteins are made.


8. Budding: Immature virus pushes out of the cell, taking some cell membrane with it.

9. Immature virus breaks free of the infected cell.

10. Maturation: The protein chains in the new viral particle are cut by the protease enzyme into individual proteins that combine to make a working virus.
# 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>
</tbody>
</table>
| Adult (>19 yrs)      | Clinical stage 3 or 4, or CD4 ≤500
Active TB
Pregnancy & breastfeeding
Hepatitis B co-infection
Priority: CD4 ≤350 or advanced HIV disease | All Priority: CD4 ≤350 or advanced HIV disease |
National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults

24 December 2014

What’s new in the paediatric guidelines
http://orient8.co/SAHIV/Paeds/

What’s new in PMTCT guidelines
http://orient8.co/SAHIV/EMTCT/
1.2 WHAT IS NEW IN THESE GUIDELINES

The main changes for pregnant/breastfeeding women, paediatrics, adolescents and adults are summarised in Boxes 1-3 below.

**Box 1: Changes specific to pregnant/breastfeeding women**

- Immediate initiation of lifelong ART for all HIV-positive women who are pregnant, breastfeeding or within 1 year post-partum, regardless of CD4 cell count
- Use of EFV as part of the first-line regimen, regardless of the gestation of the pregnancy
- Use of maternal lifelong ART throughout pregnancy and breastfeeding to reduce MTCT
- Viral load testing for women on ART ≥3 months at confirmation of pregnancy to direct management
- Repeat HIV testing for HIV-negative women 3-monthly during pregnancy, at labour/delivery, at the 6 week Expanded Programme on Immunisation (EPI) visit and 3-monthly throughout breastfeeding. This should be done during routine antenatal care, postnatal care and EPI/child health follow-up visits
- Women with contraindications to FDC should be considered high-risk pregnancies. They should be initiated on AZT immediately and referred urgently for initiation on to three single ART drugs
- Provision of birth HIV PCR for all HIV exposed neonates
- Use of extended 12 weeks NVP or dual post-exposure prophylaxis with NVP and AZT for infants where maternal viral load suppression may be inadequate
Box 2: Changes specific to infants and early adolescents

» Provision of ART for all children under 5 years, regardless of their CD4 cell count or clinical staging

» ART initiation for children ≥5 years now starts at CD4 count ≤500 cells/μl regardless of clinical staging

» Immediate initiation of infant ART with first positive HIV PCR, whilst waiting for confirmatory test results

» Use of second HIV PCR test as a confirmatory for positive HIV PCR test

» No longer use viral load as part of baseline assessment for ART initiation in children

» Birth PCR HIV testing of all HIV-exposed neonates, repeated at 10 weeks and Rapid HIV test at 18 months. For those on extended 12 week NVP, the PCR will be repeated at 18 weeks and a Rapid HIV test at 18 months.
Box 3: Changes specific to late adolescents and adults

- Earlier initiation of ART at CD4 count ≤500 cells/μl
- Provision of ART for those with Hepatitis B (HBV) co-infection, regardless of CD4 count or clinical staging
- Harmonised ART regimen across populations, mainly pregnant and breastfeeding women, adolescents and adults
- Initiation of ART for all HIV/TB coinfected patients
- Inclusion of guidance on HIV for key populations
- Use of simplified fixed-dose combinations for ART
- Use of viral load for monitoring treatment success and early identification of treatment failure
- Routine cryptococcal infection screening for all HIV-infected patients with CD4 <100 cells/μl
- Use of Tuberculin Sensitivity Test (TST) as part of screening for IPT
- Use of third-line drugs for patients failing second-line regimens
Paediatric Antiretroviral Therapy (ART)
SA NDOH 2015

• Eligibility
  – Children less than 5 years of age:
    • All
  – Children ≥5 years to 15 years:
    • Clinical Stage 3 or 4 OR CD4 <500 cells/µl

• Fast-track initiation (within 1-2 weeks of eligibility)
  – Children <1 year of age
  – Stage 4 HIV disease
  – MDR or XDR – TB
  – CD4 <15% OR <200 cells/µl
Steps to starting ART in Children

- Confirm HIV diagnosis & provide counseling
- Assess and manage opportunistic illnesses & malnutrition if present
- Clinical & immunological staging: criteria for starting ART (>5yrs of age)
- Social criteria for starting ART: identification of reliable caregiver
- Further counseling: treatment literacy & treatment readiness
- Baseline investigations
- Appropriate drug regimen (protocols)
Social requirements for ART

**Mandatory:**
- a reliable, responsible adult to at least administer medication

**Desirable:**
- Treatment “ready” i.e. clinic attendance, adequate counselling and demonstration of medication.
- Able to travel to and attend ARV centre monthly and without difficulty
- Disclosure to household or friend

**Certainly advisable...**
- “Assistant caregiver” identified and included in work-up
- “Back-up” plan in case of crisis
- Know maternal CD4 count and assess general health. Refer or treat if indicated
# Preferred 1\textsuperscript{st} line ART regimens

<table>
<thead>
<tr>
<th>Age group</th>
<th>SA 2015</th>
<th>WHO 2013</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<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></td>
<td></td>
</tr>
</tbody>
</table>
1st line ART regimens for children & adolescents (SA NDOH 2015)

- **Infants and children <3yrs or <10kg:**
  - Abacavir (ABC) + Lamivudine (3TC) + Lopinavir/ritonavir (LPV/r, Kaletra)
    - Neonates (<4 weeks of age): avoid LPV/r (Kaletra)

- **Children ≥3yrs (& ≥10kg) & early adolescents (<15yrs & <40kg):**
  - Abacavir (ABC) + Lamivudine (3TC) + Efavirenz (EFV)
    - Children ≥3 years and exposed to Nevirapine (NVP) for 6 weeks or longer (PMTCT) should be initiated on ABC + 3TC + LPV/r

- **Late adolescents (≥15yrs & ≥40kg):**
  - Tenofovir (TDF) + Emticitabine (FTC) (or Lamivudine (3TC)) + Efavirenz (EFV)
## Baseline investigations at HIV diagnosis & before starting ART (Infants, children, early adolescents)

<table>
<thead>
<tr>
<th>At initial diagnosis of HIV</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm HIV status</td>
<td>Requires 2 x HIV PCR tests in children &lt;18 months of age and 2 x HIV rapid tests or ELISA tests in children &gt;18 months of age</td>
</tr>
<tr>
<td>Document weight, height, head circumference (&lt;2 yrs) &amp; development</td>
<td>To monitor growth &amp; development &amp; identify eligibility for ART</td>
</tr>
<tr>
<td>Screen for TB symptoms</td>
<td>To identify HIV/TB co-infection</td>
</tr>
<tr>
<td>WHO clinical staging (≥5 yrs)</td>
<td>To determine if patient is eligible for ART</td>
</tr>
<tr>
<td>CD4 count</td>
<td>Baseline assessment</td>
</tr>
<tr>
<td>FBC &amp; differential white cell count</td>
<td>To detect anaemia, neutropaenia, thrombocytopenia</td>
</tr>
<tr>
<td>Neurocognitive developmental assessment</td>
<td>With appropriate available tool</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior to initiation of ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>If &lt;8 g/dl start ART &amp; discuss with specialist</td>
</tr>
<tr>
<td>CD4 count (if not done in last 6 mths)</td>
<td>Baseline assessment</td>
</tr>
<tr>
<td>Cholesterol &amp; triglycerides if on PI regimen</td>
<td>Baseline assessment</td>
</tr>
<tr>
<td>ALT (if jaundiced or on TB Rx)</td>
<td>To assess for liver dysfunction</td>
</tr>
<tr>
<td>Neurocognitive developmental assessment</td>
<td>With appropriate available tool</td>
</tr>
</tbody>
</table>
# Baseline investigations at HIV diagnosis (Late adolescents 15-19 yrs)

<table>
<thead>
<tr>
<th>At initial diagnosis of HIV</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm HIV status</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count &amp; WHO clinical staging</td>
<td>To assess eligibility for ART (CD4&lt;500), fast-tracking (CD4&lt;200 / stage 4), prioritisation (CD4 &lt;350), Co-trimoxazole prophylaxis (CD4&lt;200), CrAg/CLAT testing (CD4&lt;100)</td>
</tr>
<tr>
<td>Screen for pregnancy</td>
<td>Pregnant women eligible for ART. Conception counselling</td>
</tr>
<tr>
<td>Screen for TB symptoms</td>
<td>To identify HIV/TB co-infection</td>
</tr>
<tr>
<td>Mantoux test</td>
<td>Assess need for IPT</td>
</tr>
<tr>
<td>Screen for STIs &amp; syphilis</td>
<td>For treatment &amp; counselling</td>
</tr>
<tr>
<td>Assessment of major non-communicable diseases</td>
<td>To identify concomitant chronic disease</td>
</tr>
<tr>
<td>Screen for hepatitis B</td>
<td>To identify HIV/HBV co-infection &amp; eligibility for ART</td>
</tr>
<tr>
<td>Weight and height in adolescents</td>
<td>To determine appropriate ART regimen</td>
</tr>
</tbody>
</table>
Baseline investigations before starting ART  
(Late adolescents 15-19 yrs)

<table>
<thead>
<tr>
<th>Prior to initiation of ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrAg / CLAT if baseline CD4 &lt;100</td>
<td>To identify patients who require treatment or prophylaxis for cryptococcal meningitis</td>
</tr>
<tr>
<td>Serum creatinine for clients starting on Tenofovir</td>
<td>To detect renal insufficiency (calculate creatinine clearance)</td>
</tr>
<tr>
<td>Hb &amp; differential white cell count for clients starting on Zidovudine</td>
<td>To detect anaemia / neutropaenia: do not use AZT if Hb ≤8)</td>
</tr>
<tr>
<td>Cholesterol &amp; triglycerides if on PI regimen</td>
<td>Baseline assessment</td>
</tr>
<tr>
<td>ALT if client starting on Nevirapine</td>
<td>To assess for liver dysfunction</td>
</tr>
<tr>
<td>Fasting cholesterol and triglycerides for clients starting on Lopinavir/ritonavir</td>
<td>To identify clients with contraindications to LPV/r or at risk of LPV/r related hyperlipidaemia. If total cholesterol &gt;6 mmol/l or triglycerides &gt;5 mmol/l, consider using Atazanvir/r instead of LPV/r</td>
</tr>
</tbody>
</table>
# Antiretroviral Drug Dosing Chart for Children 2013

Compiled by the Child and Adolescent Committee of the SA HIV Clinicians Society in collaboration with the Department of Health

## Target Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>8mg/kg TWICE daily OR 16mg/kg ONCE daily</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>4mg/kg TWICE daily OR 8mg/kg ONCE daily</td>
</tr>
<tr>
<td>Efavirenz (EVF)</td>
<td>600mg capsule into 5ml water given 2.5ml</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/RTV)</td>
<td>300/75mg PO/dose LPV/rtv TWICE daily</td>
</tr>
<tr>
<td>Ritonavir boosting (RTV)</td>
<td>50mg/50mg adult tabs 100/100mg Paed Tabs 100/50mg</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>1mg/kg/dose twice daily</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>180-2400 mg/m two doses TWICE daily after once daily load-in x 2 wks</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>160-200 mg/m two doses TWICE daily</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>180-2400 mg/m two doses TWICE daily</td>
</tr>
</tbody>
</table>

## Available Formulations

<table>
<thead>
<tr>
<th>Available Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sol 20mg/ml Tabs 60mg scored dispencables, ABC/3TC 600/300mg combination</td>
</tr>
<tr>
<td>Sol 10mg/ml Tabs 150mg scored dispencables, ABC/3TC 600/300mg combination</td>
</tr>
<tr>
<td>Caps 50,200mg Tabs 50,200mg</td>
</tr>
<tr>
<td>Sol 80/20mg/ml Adult Tabs 200/50mg Paed Tabs 100/25mg</td>
</tr>
<tr>
<td>Sol 80mg/ml</td>
</tr>
<tr>
<td>Sol 1mg/ml Caps 15,20,30mg</td>
</tr>
<tr>
<td>Tabs 250,100mg (dispensable in 30mg water) Caps 250mg EC</td>
</tr>
<tr>
<td>Sol 10mg/ml Caps 100mg</td>
</tr>
<tr>
<td>Sol 10mg/ml Tabs 300mg (not scored)</td>
</tr>
</tbody>
</table>

## Available Formulations

<table>
<thead>
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<td>Sol 20mg/ml Tabs 60mg scored dispencables, ABC/3TC 600/300mg combination</td>
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<td>Sol 80/20mg/ml Adult Tabs 200/50mg Paed Tabs 100/25mg</td>
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<tr>
<td>Sol 10mg/ml Caps 100mg</td>
</tr>
<tr>
<td>Sol 10mg/ml Tabs 300mg (not scored)</td>
</tr>
</tbody>
</table>

## Currently available tablet formulations of abacavir (except 60mg), efavirenz, LPV/rtv and AZT must be swallowed whole and NOT chewed, divided or crushed

- <3
  - Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg

## Dosing Schedule

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>3.4-9</th>
<th>5-9.9</th>
<th>10-13.9</th>
<th>14-25.9</th>
<th>≥20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole Dose</td>
<td>2.5ml od</td>
<td>5ml od</td>
<td>10ml or 1 tab od</td>
<td>2 tabs od</td>
<td></td>
</tr>
<tr>
<td>Multivitamin Dose</td>
<td>2.5ml od</td>
<td>5ml od</td>
<td>10ml or 1 tab od</td>
<td>2 tabs od</td>
<td></td>
</tr>
</tbody>
</table>

* Avoid LPV/rtv solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (60 weeks post conception) or obtain expert advice.

# Notes

- od – once a day
- bd – twice a day
Staying on ART

Four main aspects requiring on-going monitoring are:

– Adherence & support
– Treatment efficacy: clinical, CD4, viral load
– Drug toxicity and adverse events
– Developmental and psychosocial progress
Assessment & support of caregivers

- **Pre-ART**
  - Screening form
  - 3 counselling sessions
  - Home visit if necessary
  - Child support grants
  - Secondary caregiver (treatment partner)
  - Practical demonstration of ARV drug regimen

- **On ART**
  - Interview with caregivers
  - Return of medications / pill counts & demonstration
  - Support groups
  - Assistance with disclosure
  - **Referral of mother / father / siblings for HIV testing / care / ART**
  - Referral to community-based services where possible
Return of medication at each clinic visit

- Provides a focus for the consultation (doctor, nurse, counsellor)
- Demonstrate dosing procedures
- Pill counts
- Problems
- Drug side-effects
- Avoids wastage and accumulation of half-used bottles at home (re-issue)
ART demonstration kit to teach caregivers
Pillbox & pill counter
## Monitoring treatment efficacy on ART
(Infants, children, early adolescents, late adolescents)

<table>
<thead>
<tr>
<th>On ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, weight, head circumference (&lt;2 years) and development</td>
<td>To monitor growth and developmental stage</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>To monitor response to ART, and exclude adverse effects</td>
</tr>
<tr>
<td>CD4: ALL at mth 12, then 1-5 years: 6 mthly &gt; 5 years: If CD4 &lt; 200 cells/mm3 repeat 6 mthly until two consecutive CD4’s &gt; 200 cells/mm3</td>
<td>To monitor response to ART, stop co-trimoxazole prophylaxis as per national guidelines</td>
</tr>
<tr>
<td>VL: All: at mth 4 and 12, then - children &lt;5 years: 6 mthly - children 5 years to 15 years: 12 mthly</td>
<td>To monitor viral suppression response to ART To identify treatment failure and problems with adherence</td>
</tr>
<tr>
<td>Neurocognitive developmental assessments</td>
<td>With appropriate available tool</td>
</tr>
</tbody>
</table>
## Monitoring toxicity on ART (Infants, children, early adolescents)

<table>
<thead>
<tr>
<th>On ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb and differential white cell count at month 1, 2, 3 and 6 months if on AZT</td>
<td>To identify Zidovudine-related haematological toxicity</td>
</tr>
<tr>
<td>Cholesterol &amp; triglycerides at 1 year &amp; then every 12 months if on PI-based regimen</td>
<td>To monitor for PI-related metabolic side-effects. Advise dietary modification &amp; refer for appropriate management if hyperlipidaemia present</td>
</tr>
</tbody>
</table>
## Monitoring toxicity on ART (Late adolescents)

<table>
<thead>
<tr>
<th>On ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine: at month 1, 4, 12 and then annually if on Tenofovir</td>
<td>To identify TDF toxicity, calculate creatinine clearance</td>
</tr>
<tr>
<td>ALT:</td>
<td></td>
</tr>
<tr>
<td>• If on Nevirapine or Efavirenz and develops rash or symptoms suggestive of hepatitis</td>
<td></td>
</tr>
<tr>
<td>• If on TB treatment &amp; LPV/r</td>
<td>To detect NVP or EFV toxicity</td>
</tr>
<tr>
<td></td>
<td>Weekly while while increasing from standard dose to double dose LPV/r, then monthly for duration of TB treatment</td>
</tr>
<tr>
<td>Hb and differential white cell count at month 1, 2, 3 and 6 months if on AZT</td>
<td>To identify Zidovudine-related haematological toxicity</td>
</tr>
<tr>
<td>Fasting cholesterol &amp; triglycerides at month 3 on Lopinavir/ritonavir. Repeat annually if clinically indicated</td>
<td>To detect clients LPV/r toxicity. If total cholesterol &gt;6 mmol/l or triglycerides &gt;5 mmol/l, consider switch to Atazanvir/r. Management of hyperlipidaemia should include dietary modification and statins if indicated.</td>
</tr>
<tr>
<td>Hep B sAg</td>
<td>To identify HBV co-infection in pts on TDF switching to 2nd line regimens so that TDF can be retained in the 2nd line regimen</td>
</tr>
</tbody>
</table>
Drug toxicity in children on ART

- Drug toxicity much less of a problem than complications of HIV disease
- Drug tolerance may be a problem
- Toxicity according to ARV drug classes
- Abacavir hypersensitivity

<table>
<thead>
<tr>
<th>NRTI’s</th>
<th>Stavudine (d4T), Lamivudine (3TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zidovudine (AZT), Didanosine (ddI)</td>
</tr>
<tr>
<td></td>
<td>Abacavir (ABC)</td>
</tr>
<tr>
<td>NNRTI’s</td>
<td>Efavirenz (EFV), Nevirapine (NVP)</td>
</tr>
<tr>
<td>PI’s</td>
<td>Lopinavir/ritonavir (Kaletra), Ritonavir</td>
</tr>
</tbody>
</table>
Major adverse drug events

1. Mitochondrial dysfunction (NRTIs)
   - lactic acidosis; hepatic toxicity/steatosis;
   - pancreatitis; peripheral neuropathy

2. Metabolic abnormalities (PIs)
   - fat maldistribution and body habitus change
   - hyperlipidaemia; hyperglycaemia and insulin resistance

3. Haematological (AZT, 3TC)
   - bone marrow suppression: anaemia, neutropaenia, thrombocytopenia

4. Allergic reactions (NNRTIs, ABC)
   - skin rashes; hypersensitivity responses e.g. Stevens Johnson syndrome
ADVERSE REACTIONS TO ART

• Abacavir hypersensitivity reaction
  – ≥2 of:
    • fever
    • rash
    • gastrointestinal symptoms (e.g. D+V, abdominal pain)
    • constitutional symptoms (e.g. fatigue, myalgia)
    • respiratory symptoms (e.g. dyspnoea, cough, pharyngitis)
  – Symptoms worsen immediately after dose
  – Early consultation with health care provider
  – Avoid stopping therapy without consultation if possible. Also avoid ongoing use / re-challenge as risk of mortality

• Lipodystrophy syndrome
  – Electively switch from stavudine or zidovudine to abacavir (or tenofovir in older children/adolescents) in patients who are virally suppressed
# 2nd-line ART regimens

## Infants & children

<table>
<thead>
<tr>
<th>1st line regimen</th>
<th>2nd line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI-based</strong></td>
<td><strong>Consult with expert for advice</strong></td>
</tr>
<tr>
<td>ABC + 3TC + LPV/r</td>
<td>d4T + 3TC + LPV/r</td>
</tr>
<tr>
<td>d4T + 3TC + LPV/r</td>
<td>Unboosted PI-based regimen</td>
</tr>
<tr>
<td></td>
<td>Rifampicin while on LPV/r</td>
</tr>
<tr>
<td><strong>NNRTI-based</strong></td>
<td></td>
</tr>
<tr>
<td>ABC + 3TC + EFV</td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>or NVP</td>
<td>AZT + ABC + LPV/r</td>
</tr>
<tr>
<td>d4T + 3TC + EFV</td>
<td></td>
</tr>
<tr>
<td>or NVP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Adolescents & adults

<table>
<thead>
<tr>
<th>1st line regimen</th>
<th>2nd line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF-based regimen</td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>d4T-based regimen</td>
<td>TDF + 3TC (or FTC) + LPV/r</td>
</tr>
</tbody>
</table>
# 2nd line ART after PI-based 1st line

<table>
<thead>
<tr>
<th>1st line “3rd drug”</th>
<th>2nd line “3rd drug”</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/rtv</td>
<td>“Refer” No standard recommendation</td>
<td>Seek expert advice and genotyping to inform choice of regimen. Avoid empirical use of NNRTI + 2 NRTIs as may lead to rapid virological failure. Consider new generation boosted PI (DRV) +/or NNRTI (e.g. etravirine) +/or integrase inhibitor (e.g. raltegravir)</td>
</tr>
</tbody>
</table>

- If LPV/r is 1st PI, virus *usually* remains susceptible to LPV even in setting of treatment failure. Exceptions include co-treatment with rifampicin, breaking/crushing of Aluvia tablets.

- NRTI cross-resistance, 3TC resistance, and archived NNRTI resistance following NVP exposure in PMTCT programme may impact on potency of 2nd line regimen

Taylor BS et al. *AIDS Res Hum Retroviruses* 2011;27:945-56
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)
HIV resistance in children

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

• Acquired
  – During PMTCT (NVP ± AZT for 6-12wks)
  – During ART (child failing 1\textsuperscript{st} / 2\textsuperscript{nd} / 3\textsuperscript{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 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>
</tr>
</thead>
<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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
</tr>
<tr>
<td>Low wt. &amp; ht.-for-age Z scores</td>
</tr>
<tr>
<td>Longer duration on ART or PI</td>
</tr>
<tr>
<td>Duration of virologic failure</td>
</tr>
<tr>
<td>Increased time to first suppressed VL or failure to suppress VL by 12 months on ART</td>
</tr>
<tr>
<td>TB Rx at time of ART initiation</td>
</tr>
<tr>
<td>RTV use as single unboosted PI during TB Rx</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
</tr>
<tr>
<td>Duration of RTV use as single unboosted PI</td>
</tr>
<tr>
<td>Duration of PI exposure</td>
</tr>
<tr>
<td>Duration of PI exposure</td>
</tr>
<tr>
<td>Duration of PI exposure</td>
</tr>
</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
Genotypic resistance testing: Important principles

• Only useful for detecting resistance to drugs currently being taken by patient (or within 4 weeks of stopping them)

• Helps to exclude drugs from a future regimen, may not indicate which drugs will work

• Viral load must be >1000 copies/ml & won’t detect resistance in minor variants (<20% of viral population)

• Interpretation may be difficult and requires expertise

• Expensive (±R2000): few guidelines on optimal use of resistance testing in large treatment programmes
Eligibility for genotypic resistance testing (SA NDOH, 2015)

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

• Failure on 1\text{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\text{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
Neonatal ART
Rationale

• Can we reduce both the early and late HIV-associated morbidity & mortality by starting ART during the neonatal period?

• Identification of HIV infection by PCR testing at birth rather than at 6 weeks of age

• Preservation of capacity to respond to routine infant vaccines (Penisieroso, PNAS 2009)
• Rapid control of HIV viraemia in infants can reduce size of HIV reservoir (Persaud, 2012)
• Possibility of later structured ART interruption following very early ART initiation (CHER study)?
• (HIV cure agenda...)

Neonatal ART
Rationale
Early HIV-associated morbidity & mortality

- Children with HIV Early Antiretroviral Therapy Study (CHER), (Violari, NEJM, 2008)
  - HIV PCR testing at 4 weeks of age
  - Randomised to early or deferred ART
  - Median age at ART start in early arm was 7.4 wks
  - Early ART reduced early infant mortality by 76% and HIV progression by 75% compared to ART deferred until clinical or CD4 criteria were met
  - 33% (10/30) deaths occurred in early ART arm

- Early severe HIV disease precedes early antiretroviral therapy in infants: Are we too late? (Innes, JIAS 2014)
  - Cohort of infants from Soweto & Cape Town
  - Median age at ART start 8.4 wks (IQR 7.2-9.7)
  - 62% (250/403) had advanced HIV disease at time of starting ART
  - Each month increase in age at ART initiation increased the odds of advanced HIV disease at ART initiation (OR: 1.69, CI: 1.05-2.71)
HIV PCR testing at birth

• Detection of intrauterine HIV transmission to infant
  – Associated with rapid HIV disease progression
  – Very early (neonatal) ART initiation offers a window of opportunity to prevent or reduce rapid disease progression

• ARV prophylaxis for HIV-exposed neonates
  – Single (NVP) or dual (AZT+NVP) ARV prophylaxis
  – Transition from ARV prophylaxis to ART (SA & US)
  – ART as prophylaxis and treatment if HIV-infected (UK)
Neonatal ART
What are the risks?

• Safety & efficacy of ART in neonatal population
  – PI vs NNRTI-based regimens
  – Uncertain dosing

• Neonatal pharmacokinetics & pharmacodynamics: immature physiological systems (renal, hepatic, GIT)
  – Premature neonates

• Co-morbidities in neonatal period
  – Congenital syphilis, TB, CMV

• Optimal transition from neonatal ARV prophylaxis to neonatal ART?
  – Maternal ART & neonatal ARV prophylaxis also complicates HIV diagnosis in neonate
Are we able to recommend a safe and effective neonatal ART regimen...

• “For neonates and for premature infants (until 42 weeks corrected gestational age), PK data are currently inadequate to formulate an effective complete ART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of ART.

• Providers considering treatment of infants <2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what to use will involve weighing the risks and benefits of using unapproved ART dosing, and incorporating case-specific factors such as exposure to ARV prophylaxis.”

# Neonatal ART Regimen considerations

## ABC/3TC/LPV/r
- **Safety / toxicity**
  - **Abacavir**
    - Dosing data lacking <3 mths of age
    - Toxicity not dose-dependent in older infants
  - **3TC**
    - Dosing data is available
    - Haematological toxicity
  - **LPV/r (Kaletra®)**
    - Dosing data is available
    - Serious toxicity reports

- **Efficacy**
  - Unknown in neonatal/early infancy period
  - Superior to NVP-based regimens in older children regardless of perinatal NVP exposure (P1060 study)

## AZT/3TC/NVP
- **Safety / toxicity**
  - **AZT**
    - Dosing guidelines are available
    - Haematological toxicity
  - **3TC**
  - **NVP**
    - Lack of dosing data for treatment
    - Potential hepatotoxicity

- **Efficacy**
  - NVP-based regimen may be inferior to PI-based regimen particularly in NNRTI-exposed neonates
  - Transitional regimen
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

Positive Birth HIV PCR test
Actively trace and link to care

Indeterminate result: Refer to separate guideline

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

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

Indeterminate / negative confirmatory PCR: Refer to separate guideline
### ARV drug dosing chart for children <28 days of age and weighing ≥2.5 kg at birth

<table>
<thead>
<tr>
<th>Target dose</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWICE daily (BD)</td>
<td>2mg/kg/dose</td>
<td>4mg/kg/dose</td>
<td>6mg/kg/dose</td>
</tr>
<tr>
<td>Available formulation</td>
<td>10mg/ml</td>
<td>10mg/ml</td>
<td>10mg/ml</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Dose in ml</td>
<td>Dose in mg</td>
<td>Dose in ml</td>
</tr>
<tr>
<td>≥2.5-&lt;3.0</td>
<td>0.6 ml BD</td>
<td>6 mg BD</td>
<td>1.2 ml BD</td>
</tr>
<tr>
<td>≥3.0-&lt;3.5</td>
<td>0.7 ml BD</td>
<td>7 mg BD</td>
<td>1.4 ml BD</td>
</tr>
<tr>
<td>≥3.5-&lt;4.0</td>
<td>0.8 ml BD</td>
<td>8 mg BD</td>
<td>1.6 ml BD</td>
</tr>
<tr>
<td>≥4.0-&lt;4.5</td>
<td>0.9 ml BD</td>
<td>9 mg BD</td>
<td>1.8 ml BD</td>
</tr>
<tr>
<td>≥4.5-&lt;5.5</td>
<td>1.0 ml BD</td>
<td>10 mg BD</td>
<td>2.0 ml BD</td>
</tr>
<tr>
<td>≥5.5-&lt;6.5</td>
<td>1.2 ml BD</td>
<td>12 mg BD</td>
<td>2.4 ml 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

Gaps

• Safety / toxicity
  – Choice of drugs to include in ART regimen?
    • Term & preterm neonates

• Efficacy (short & longer term)
  – NNRTI vs PI regimen?
  – Role of integrase inhibitors (prophylaxis & treatment)?
  – Neonates with LPV-resistant HIV?
    • Darunavir only approved from ≥3 yrs of age
    • Raltegravir only approved from ≥4 wks of age