Treatment Optimization for EMTCT

Dr Madeleine Muller
With thanks to CN Mnyani and Linda-Gail Bekker

SA HIV Clinician’s Society Meeting
25 Nov 2017
Having children is one of the greatest joys and privileges of being human

The double tragedy of HIV for the mom-to-be
“We have effective drugs. There is no reason why any mother should die of AIDS. There is no cause for any child to be born with HIV. If we work hard enough we can virtually eliminate mother-to-child transmission.”

Ban Ki Moon
NY, September 2009
To Eliminate MTCT
Remember the PMTCT cascade!

Pre-conception

Pregnancy and Labour

Post-natal

Every non-infertile couple whether both infected or discordant, should be asked what their reproductive intentions are at every clinic contact.
% Risk of transmission without intervention

<table>
<thead>
<tr>
<th>Transmission time</th>
<th>No BF</th>
<th>BF 6/12</th>
<th>BF 24/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>During Pregnancy</td>
<td>5-10</td>
<td>5-10</td>
<td>5-10</td>
</tr>
<tr>
<td>During labour</td>
<td>10-15</td>
<td>10-15</td>
<td>10-15</td>
</tr>
<tr>
<td>During BF</td>
<td>0</td>
<td>5-10</td>
<td>15-20</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>15-25</td>
<td>20-35</td>
<td>30-45</td>
</tr>
</tbody>
</table>
Trends in reduction of MTCT: study results over time

- 1994: ACTG 076
- 1998: Bangkok AP/IP ZDV
- 1998: Abidjan AP/IP ZDV
- 1999: PETRA AZT/3TC
- 1999: HIVNET 012 sdNVP
- 2000: PHPT ZDV
- 2000: PHPT ZDV + NVP
- 2002: DITRAME +1 ZDV + NVP
- 2003: DITRAME +1.1 ZDV/3TC+ NVP
- 2004: PHPT-2 ZDV + NVP
- 2004: PHPT-2 ZDV + NVP

- USA & Europe
- Thailand
- Africa
Estimated Number of Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985–2006—United States and Dependent Areas

PACTG 076
USPHS AZT Recommendations

80% decline

Note: Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.
Outline

How do we protect

Our fertile women

Our women that are pregnant

Our newborn babies
Protecting our moms

SAFER CONCEPTION
PLANNED PREGNANCY AND HIV PREVENTION
Needing updating??

- Safer conception guidelines for the non-infertile HIV infected couple.
HIV PREVENTION TOOL-KIT

- Microbicides for women
  - Abdool Karim Q, Science 2010

- Male circumcision
  - Gray R, Lancet 2007

- Treatment of STIs
  - Grosskurth H, Lancet 2000

- Female Condoms

- Male Condoms

- Oral pre-exposure prophylaxis (PEP)
  - Grant R, NEJM 2010 (MSM)
  - Baeten J, 2011 (Couples)
  - Paxton L, 2011 (Heterosexuals)

- Post Exposure prophylaxis (PEP)
  - Scheckter M, 2002

- Vaccines
  - Rerks-Ngarm S, NEJM 2009

- Treatment for prevention
  - Donnell D, Lancet 2010
  - Cohen M, NEJM 2011

- Behavioural positive prevention
  - Fisher J, JAIDS 2004

- HIV Counselling and Testing
  - Coates T, Lancet 2000

- Behavioural Intervention
  - Abstinence
  - Be Faithful

Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission.
Some Key tools

HIV +ve partner: Suppress the VL!

Minimise condom free sex

MMC!

PrEP for HIV negative partner
The New wave in Prevention
Partner 1 Study

• Partner 1: studied heterosexual discordant couples
• By 2016: 58213 condomless sex acts
  – NO transmissions if VL <200copies /ml

VL <200 - Maximum possible likelihood of transmission of HIV to HIV negative partner is zero

\[ U = U \]
Minimise Condomless sex
When shall we go for it doc?

• Help patients identify their most fertile time every month
  – VL can be affected by illness, STIs, drug interactions etc.

• 20 /10 Rule
  – Take average cycle length: subtract 20 / subtract 10
  – E.g. if you have a 33 day cycle
    • You are fertile from day 13 to day 23
Don’t forget MMC
PrEP
PrEP 101

For the HIV Negative Partner

Who is unsure of sexual partner’s status

Truvada Once A day
### Evidence for oral PrEP efficacy – reducing susceptibility

<table>
<thead>
<tr>
<th>Study, population</th>
<th>PrEP agent</th>
<th># of HIV infections</th>
<th>PrEP efficacy (95% CI) publication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PrEP Study</strong></td>
<td>TDF/FTC</td>
<td>13</td>
<td>75% (55-87%)</td>
</tr>
<tr>
<td>Heterosexual couples</td>
<td>TDF</td>
<td>17</td>
<td>67% (44-81%)</td>
</tr>
<tr>
<td><strong>TDF2 Study</strong></td>
<td>TDF/FTC</td>
<td>10</td>
<td>62% (16-83%)</td>
</tr>
<tr>
<td>Heterosexuals</td>
<td>TDF</td>
<td>17</td>
<td>49% (10-72%)</td>
</tr>
<tr>
<td><strong>Bangkok Tenofovir Study (BTS)</strong></td>
<td>TDF</td>
<td>17</td>
<td>44% (15-63%)</td>
</tr>
<tr>
<td>IDUs</td>
<td>TDF/FTC</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Thailand (n=2413)</td>
<td></td>
<td></td>
<td>Grant et al. N Engl J Med 2010</td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>TDF/FTC</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td></td>
<td></td>
<td>Grant et al. N Engl J Med 2010</td>
</tr>
<tr>
<td>Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When taken, PrEP is estimated to be 90-100% protective against HIV

For those with tenofovir detected in blood samples* HIV protection from PrEP was extremely high:

<table>
<thead>
<tr>
<th>PrEP Type</th>
<th>HIV risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP</td>
<td></td>
</tr>
<tr>
<td>any tenofovir</td>
<td>90%</td>
</tr>
<tr>
<td>iPrEx / iPrEx OLE</td>
<td></td>
</tr>
<tr>
<td>any tenofovir</td>
<td>92%</td>
</tr>
<tr>
<td>4-6 doses/week</td>
<td>96 - 100%</td>
</tr>
<tr>
<td>7 doses/week</td>
<td>99 - 100%</td>
</tr>
</tbody>
</table>

* compared to tenofovir not detected (restricted to active PrEP arm)

Public sector: Key Populations

First population targeted: Sex workers

Next Key population

Young women aged 16-24 years old
PrEP

Data from pharmacokinetic studies:

- up to 20 days of PrEP needed before achieving full protection for vaginal intercourse (vs 7 days for rectal tissue)

- lead-time required to achieve steady state levels of TDF in blood and tissues
Concentration – Time Principles

- Repeat dosing gradually raises peaks ($C_{\text{max}}$) & troughs ($C_{\text{min}}$)
- Steady-state occurs when peaks and troughs no longer change
- Time to Steady-state varies w/ half-life ($t_{1/2}$), independent of dose
- Time to Protection determined by dose, frequency, PK
PrEP may be discontinued 28 days after the last potential exposure to HIV-infected fluids if no continuing substantial risk for acquiring HIV infection
Steps to PrEP Script

• Check eligibility and motivation
• Screen for HIV, Hep B, creatinine, pregnancy, (Hep B vaccination if HepB neg)
• Start on Truvada and counsel on lead in time:
  – 7 days for men
  – 20 days for women
• Give condoms
• Regular follow up: HIV testing, creatinine, STI screening
• If no longer at risk: continue for 28 days
PMTXT cascade phase 2

THE MOM-TO-BE
HIV in pregnancy

HIV acquisition during pregnancy and immediately following pregnancy remains high despite increased access to and initiation of antiretroviral therapy (ART).

- In SA: maternal HIV incidence rate
  - 10.7 per 100 person years (PY), and 12.4 per 100 PY in urban health facilities in 2013

Acute infection and transmission....

In a recent meta-analysis, MTCT risk was significantly higher among women with incident vs. chronic HIV infection in the postpartum period

- (odds ratio [OR] 2.9, 95% confidence interval [CI] 2.2-3.9) or in pregnancy/postpartum periods combined (OR 2.3, 95% CI 1.2-4.4)

PrEP in pregnancy
Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection

S Afr J HIV Med. 2016;17(1),

Data on safety of PrEP during pregnancy limited... clinician to discuss potential risks and benefits of PrEP initiation or maintenance during pregnancy
National Policy on HIV Pre-exposure Prophylaxis (PrEP) and Test and Treat (T&T)

Final Draft - 5 May 2016

No mention of pregnancy
Commentary

Offering pre-exposure prophylaxis for HIV prevention to pregnant and postpartum women: a clinical approach

Dominika L Seidman\textsuperscript{1,}\textsuperscript{5}, Shannon Weber\textsuperscript{2} and Deborah Cohan\textsuperscript{1,}\textsuperscript{2}

\textsuperscript{5}Corresponding author: Dominika L. Seidman, Obstetrics, Gynecology & Reproductive Sciences, University of California San Francisco, 1001 Potrero Ave, Ward 6D, 94110, San Francisco, CA, USA, 011.415.206.3030, Dominika.seidman@ucsf.edu
Recommendation

Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).

- Risks, benefits and alternatives of continuing PrEP during pregnancy and breastfeeding should be discussed

- **Further research is needed** to fully evaluate PrEP use during pregnancy and breastfeeding
Preventing HIV transmission in pregnancy
**SA guidelines**

Retesting of pregnant and postpartum women who initially test HIV negative

<table>
<thead>
<tr>
<th>Pregnant/Breastfeeding women (to detect HIV sero-conversion)</th>
<th>Every 3 months throughout pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At labour/delivery</td>
</tr>
<tr>
<td></td>
<td>At the 6 week EPI visit</td>
</tr>
<tr>
<td></td>
<td>Every 3 months throughout breastfeeding</td>
</tr>
</tbody>
</table>
No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception

Laurent Mandelbrot,1,2,5,6 Roland Tubiana,1,6 Jerome Le Chenadec,1 Catherine Dollfus,11 Albert Faye,5,12 Emmanuelle Pannier,1,13 Sophie Matheron,5,14 Marie-Aude Khuong,15 Valerie Garrait,13 Véronique Reliquet,19 Alain Devidas,19 Alain Berrebi,19 Christine Allisy,22 Christophe Elleau,23 Cédric Arvieux,26 Christine Rouzioux,6,15 Josiane Warszawski,2,3,4 and Stéphane Blanché2,16, for the ANRS-EPF Study Group9
Background

- **The French Perinatal Cohort study**: an ongoing, prospective, observational study involving 90 perinatal centres in France

- 8075 HIV-infected mother/infant pairs included from 2000 to 2011

- Perinatal transmission analysed according to maternal VL at delivery and timing of ART initiation

(Mandelbrot L, et al. 2015 *CID*)
Results

- 80.4% had prenatal HIV diagnosis

VL <50 copies/ml at delivery:

<table>
<thead>
<tr>
<th>Timing of ART</th>
<th>% with VL&lt;50 c/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception</td>
<td>75.4</td>
</tr>
<tr>
<td>1st T</td>
<td>74.2</td>
</tr>
<tr>
<td>2nd T</td>
<td>64.8</td>
</tr>
<tr>
<td>3rd T</td>
<td>44.1</td>
</tr>
</tbody>
</table>

(P <0.001)

(Mandelbrot L, et al. 2015 CID)
## Perinatal transmission

### Timing of ART Initiation

<table>
<thead>
<tr>
<th>Maternal VL</th>
<th>Before Conception&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1st Trimester (&lt;14 wk)</th>
<th>2nd Trimester (14–27 wk)</th>
<th>3rd Trimester (≥28 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT, % (95% CI)</td>
<td>No. With PT/Total No.</td>
<td>PT, % (95% CI)</td>
<td>No. With PT/Total No.</td>
</tr>
<tr>
<td>≥400</td>
<td>2.2 (.7–5.0)</td>
<td>5/230</td>
<td>1.5 (.04–7.8)</td>
<td>1/69</td>
</tr>
<tr>
<td>50–400</td>
<td>0.3 (.01–1.8)</td>
<td>1/301</td>
<td>1.6 (.04–8.8)</td>
<td>1/61</td>
</tr>
<tr>
<td>Undetectable,</td>
<td>0.0 (0–1.7)</td>
<td>0/212</td>
<td>0.0 (0–6.8)</td>
<td>0/52</td>
</tr>
<tr>
<td>threshold &gt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.0 (0–1)</td>
<td>0/2651</td>
<td>0.2 (&lt;.01 to 1.1)</td>
<td>1/507</td>
</tr>
<tr>
<td>Missing VL</td>
<td>..</td>
<td>0/111</td>
<td>..</td>
<td>0/20</td>
</tr>
<tr>
<td>Undetermined</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>child HIV</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; PT, perinatal transmission; VL, viral load.

<sup>a</sup> In case of treatment interruption of the first ART regimen for >2 weeks in the first trimester, the date of treatment initiation was defined as the time when ART was reintroduced.

(Mandelbrot L, et al. 2015 *CID*)
French Perinatal Cohort study Results

Few cases of transmission with VL <50 c/mL at delivery occurred

☐ when ART was started beyond the 1\textsuperscript{st} T or interrupted during the pregnancy

☐ ART initiated in the 1\textsuperscript{st} T, nearly as effective as preconception ART

(Mandelbrot L, et al. 2015 *CID*)
SA guidelines 2015
SA guidelines

• From January 2015, all HIV-infected pregnant and breastfeeding women initiated on an EFV-based FDC

TDF+3TC (FTC)+EFV

• Regardless of CD4 count, WHO stage or infant feeding practice

• FDC continued for life once started
SA guidelines

Second-line regimen

Failing on a TDF-based 1st line regimen
• AZT + 3TC + LPV/r
• AZT + TDF + 3TC + LPV/r (4 drugs if HBV co-infected)

Failing on a d4T or AZT-based 1st line regimen
• TDF + 3TC (or FTC) + LPV/r

Diarrhoea associated with LPV/r switch LPV/r to ATV/r
SA guidelines

Threshold for treatment failure:

- VL$>1000$, 
  - A adherence counselling,
  - B Bugs
  - C Correct drugs
  - D Drug interactions
  Repeat VL in 1 month with your 2\textsuperscript{nd} line drugs

- 2\textsuperscript{nd} VL undetectable or reduction in VL $\geq 1$ log (10-fold), continue existing regimen

- VL unchanged or increased, switch to 2\textsuperscript{nd} line therapy
Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis

Nathan Ford\textsuperscript{a}, Lynne Mofenson\textsuperscript{b}, Zara Shubber\textsuperscript{c}, Alexandra Calmy\textsuperscript{d,e}, Isabelle Andrieux-Meyer\textsuperscript{c}, Marco Vitoria\textsuperscript{a}, Nathan Shaffer\textsuperscript{a} and Françoise Renaud\textsuperscript{a}

\textit{AIDS} 2014, \textbf{28} (Suppl 2):S123–S131

\textbf{Discussion:} This updated analysis found no evidence of an increased risk of overall or central nervous system congenital anomalies associated with first-trimester exposure to efavirenz, similar to previous systematic reviews. This review contributed to the evidence base for the revised 2013 WHO guidelines on antiretroviral therapy, which
Safety of EFV in pregnancy

WHO guidance based on available data and programmatic experience:

• EFV use in early pregnancy not associated with increased birth defects or other significant toxicities
Safety of TDF in pregnancy

Concerns about...

- Congenital abnormalities
- Growth restriction
- Loss of bone mineral density (maternal and fetal)
- Low birth weight
- Preterm delivery
- Pregnancy losses
Safety of Tenofovir Disoproxil Fumarate-Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their Infants: A Systematic Review and Meta-Analysis.

METHODS: We conducted a systematic review of studies published between January 1980 and January 2017 that compared adverse outcomes in HIV-infected women receiving TDF- vs. non-TDF-based ART during pregnancy. The relative risk for associations was pooled using a fixed-effects model.

CONCLUSIONS: TDF-based ART in pregnancy appears generally safe for women and their infants. However, data remain limited and further studies are needed, particularly to assess neonatal mortality and infant growth/bone effects.
Conclusions – TDF-based ART in pregnancy

No evidence of increased risk of:

- Congenital anomalies
- Maternal and infant adverse outcomes
- Pregnancy loss or miscarriage
- Small for gestational age
- Low birth weight
- Infant mortality at age >14 days
Conclusions – TDF-based ART in pregnancy

Data limited and inconclusive evidence on:

• Effects of in utero TDF exposure on bone and long-term growth

• Neonatal deaths <14 days in very preterm (<14 weeks) infants
Adverse pregnancy outcomes
Adverse pregnancy outcomes

Suggestion that cART is responsible for increased risk of adverse pregnancy outcomes

Conflicting results from different studies:

- Different populations studied
- Available obstetric care
- Adjustment for confounders; selection of exposure categories
- Inflammatory effect of HIV infection

(Li N, et al. *JID* 2015)
Discussion

Potential mechanisms for ART and adverse pregnancy outcomes:

- **Immune reconstitution** – reverses pregnancy-associated cytokine changes

- Disruption of physiological angiogenesis in the **placenta**
  - lower placental weight, placental abnormalities, and placental insufficiency

(Li N, et al. *JID* 2015)
Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis


Lancet HIV 2017; 4: e21-30
Background

• Systematic review of studies from low-, middle- and high-income countries

• Studies done between January 1980 and June 2016

• 1° measure: to assess association between selected pregnancy outcomes and ART initiation pre-conception vs. after conception
Results

• 11 studies with 19,189 mother–infant pairs

• Women who started ART before conception significantly more likely to:
  - deliver preterm (RR 1·20, 95% CI 1·01–1·44)
  - very preterm (1·53, 1·22–1·92)
  - have LBW infants (1·30, 1·04–1·62)

• …than were those who began ART after conception

*Lancet HIV 2017; 4: e21–30*
Results

• Associations highest in studies done in low- and middle-income countries

• …where background rates of PTD and LBW are higher than in high-income countries

• Association with PI-use often reported

• …background risk factors for these pregnancy outcomes not always controlled for
Results

• Few data exist for neonatal mortality

• No significant difference in risk of very LBW, SGA, severe SGA, and stillbirths

• …data for the extent and severity of these risks are scarce and of low quality
WHO guidelines 2015
WHO guidelines 2015

**Recommendation**

- ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count (*strong recommendation, moderate-quality evidence*).
  - As a priority, ART should be initiated among all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤350 cells/mm³ (*strong recommendation, moderate-quality evidence*).
Rationale

• Increasing evidence that untreated HIV infection may be associated with:

  – …development of several non-AIDS-defining conditions (CVD, kidney and liver disease, several types of cancer and neurocognitive disorders)

  – …initiating ART earlier reduces such events and improves survival
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

The NEW ENGLAND JOURNAL OF MEDICINE

This article was published on July 20, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1506816

(START: Strategic Timing of Antiretroviral Treatment)
A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group

Interesting case

- 30 yr P1G2
- CD4 183; FDC initiated at 23 weeks
- Presented at 32 weeks with preeclampsia, and respiratory symptoms
- Initial $D_x$ of PTB
- Further investigations – metastatic HCC
CASE REPORT

Delayed presentation and diagnosis of metastatic hepatocellular carcinoma in pregnancy

C N Mnyani,1 BA, MB ChB, FCOG (SA); J C Hull,1 MB BCH, MRCOG, FCOG (SA), DTM&H; M B Mbakaza,2 MB ChB, FC Rad Diag (SA); A O A Krim,3 MB ChB, FC Rad Diag (SA); E Nicolaou,1,4 MD, FCOG (SA), Dip Fet Med

Fig. 1. A CT scan of the chest (coronal view), showing bilateral cannon ball lesions (white lesions) in the lung fields (CT = computed tomography).

Fig. 2. A CT scan of the abdomen (coronal view), showing a large mass in the right hepatic lobe and splenomegaly. The vascular mass occupies the whole of the right lobe, where dense and hypodense areas are seen within the liver.
WHO guidelines 2015

Increasing evidence to support earlier ART initiation among all adults as described in the previous section, as well as widespread uptake of option B+ and emerging programme data on the success of option B+ in practice, all support a revised recommendation in 2015 that all pregnant and breastfeeding women living with HIV should initiate ART and remain on lifelong treatment regardless of clinical or CD4 stage of disease. As a result, option B is no longer relevant.
WHO guidelines 2016

CONSOLIDATED GUIDELINES ON
THE USE OF
ANTIRETROVIRAL DRUGS
FOR TREATING AND
PREVENTING HIV INFECTION

RECOMMENDATIONS FOR A
PUBLIC HEALTH APPROACH
SECOND EDITION
2016
WHO guidelines 2016

**Recommendation**

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).

WHO guidelines 2016

• Recommendation applies to breastfeeding and non-breastfeeding populations
• Health benefits of universal ART for pregnant and breastfeeding women outweigh potential harm
• Health benefits – immunological and clinical

‘the decision to initiate treatment remains a personal one that must be made on the basis of informed consent’
WHO guidelines 2016

Pregnant or breastfeeding women

Preferred 1\textsuperscript{st} line regimen
- TDF + 3TC (or FTC) + EFV

Alternative 1\textsuperscript{st} line regimens
- AZT + 3TC + EFV (or NVP)
- TDF + 3TC (or FTC) + NVP
WHO guidelines 2016

- ABC or boosted PIs (ATV/r, DRV/r, LPV/r) in special circumstances

- Safety and efficacy data on use of dolutegravir (DTG) and EFV_{400} in pregnant women not yet available
WHO guidelines 2016

Pregnant or breastfeeding women

**Preferred 2\textsuperscript{nd} line regimen**
- 2 NRTIs + ATV/r or LPV/r

**Alternative 2\textsuperscript{nd} line regimen**
- 2 NRTIs + DRV/r

(similar to adults and adolescents)
British HIV Association guidelines for the management of HIV infection in pregnant women 2012
(2014 interim review)

_HIV Medicine_ (2014), 15 (Suppl. 4), 1–77

To be updated in 2017
British guidelines

• Women conceiving on an effective cART – continue regimen even if it contains EFV or does not contain AZT

Treatment naïve

• Acceptable backbones:
  o AZT+3TC
  o TDF+FTC
  o ABC+3TC
British guidelines

• Recommended 3rd agent:
  • EFV, NVP (CD4 <250) or a boosted PI

• No routine dose alterations recommended during pregnancy if ARVs used at adult licensed doses

• Consider 3rd T therapeutic dose monitoring if combining TDF and ATV/r
British guidelines

Treatment naïve presenting after 28 weeks

• If VL unknown or > 100 000, a 3 or 4 drug regimen that includes raltegravir is suggested
British guidelines

• **VL monitoring** during pregnancy, **at 36 weeks** and at delivery

• **If not suppressed at 36 weeks,**
  - Adherence counselling
  - Resistance test if appropriate
  - Consider therapeutic drug monitoring
  - Optimize to best regimen
  - Consider intensification
Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

2016 update
US guidelines

• ART should be initiated as early in pregnancy as possible

• ART during pregnancy generally does not increase the risk of birth defects

• No restriction on EFV use before 8 weeks’ gestation
US guidelines

• Women who become pregnant on suppressive EFV-containing regimens should continue their current regimens

• Safety and PK data on tenofovir alafenamide use in pregnancy insufficient to recommend for ARV-naïve women

• AZT monotherapy during pregnancy no longer recommended
The new...
Safety of integrase inhibitors

- Lack of safety data on integrase inhibitor (raltegravir and dolutegravir) use during pregnancy and breastfeeding

- Some experience with raltegravir

- Very limited with dolutegravir...
Safety of integrase inhibitors

• No published safety or efficacy data on outcomes of dolutegravir use during pregnancy

• Calcium or iron supplements (commonly used in pregnancy) could significantly reduce dolutegravir drug levels

• Transaminases need to be monitored
Safety of integrase inhibitors

“In the absence of well-controlled studies in pregnant women, dolutegravir and raltegravir should be used only if the perceived benefits outweigh the risk.”
Dolutegravir: current evidence

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (aids.info)

*Preliminary human data suggest that use of dolutegravir during pregnancy is not associated with an increased risk of birth defects and miscarriage.*

But more data are needed, particularly with dolutegravir exposure before conception, to reach definitive conclusions, according to analyses presented at IAS 2017.

Evidence limited to 2 studies and case reports. *(small numbers 133 / 42 / 116):*

High placental transfer
Darunavir/ ritonavir

FDA recommendation Darunavir/r:

- Give twice daily during pregnancy
- Unless already suppressed on Darunavir/r and twice daily dosing will compromise adherence
Rilpivirine / Etravirine

- Pregnancy Category B

- No change in dosage needed.
Integrase inhibitors in late pregnancy and rapid HIV viral load reduction

Lisa Rahangdale, MD, MPH; Jordan Gates, MSPH; JoNell Potter, PhD; Martina L. Badell, MD; Dominika Seidman, MD; Emily S. Miller, MD, MPH; Jenell S. Coleman, MD, MPH; Gweneith B. Lazenby, MD, MSCR; Judy Levison, MD; William R. Short, MD, MPH; Sigal Yawetz, MD; Andrea Ciaranello, MD, MPH; Elizabeth Livingston, MD; Lunthita Duthely, EdD, MS; Bassam H. Rimawi, MD; Jean R. Anderson, MD; Elizabeth M. Stringer, MD, HOPES (HIV OB Pregnancy Education Study) Group

MARCH 2016 American Journal of Obstetrics & Gynecology
Study design

- Retrospective cohort study of pregnant HIV-infected women in 11 centres in the US
- Study period: 2009 – 2015
- Included 101 women who initiated ART, intensified their regimen, or switched to a new regimen due to detectable viraemia (HIV RNA >40 copies/ml) at ≥ 20 weeks gestation
Results and conclusion

• Median VL at time of ART intervention was 16,030 copies/ml (IQR: 3,370 – 46,271)

• Found rapid viral load reduction with integrase inhibitor-containing regimen

• **Limitations:** retrospective study; small sample size
Discussion

• Raltegravir – twice-daily dosing

  o RCT (excl. pregnant women) looking at once-daily dosing (800mg)

    o Longer time to viral suppression esp. with VL > 100,000 or CD4 < 200 at baseline

• Insufficient data to recommend dolutegravir and elvitegravir (once-daily dosing) use in pregnancy
Prevention of HIV transmission during labour.

INTRAPARTUM
SA Guidelines

• Test All women in labour for HIV
  – Only need consent once during pregnancy

• HIV positive: sdNVP, Truvada STAT. AZT every 3 hours.

• Start 1TFE the next day
British guidelines

Untreated presenting intrapartum:
• Stat dose of NVP; commence AZT, 3TC and raltegravir (FDC)

• IV AZT during labour and delivery – throughout.
French Perinatal Cohort study
Discussion

• Reports that neither C/S nor intrapartum IV AZT offer additional protection against perinatal transmission if LDL VL

• Postnatal prophylaxis (AZT or NVP) for the infant:

  - Trials needed to evaluate whether still required when mother has long-term optimal VL control with no breastfeeding

(Mandelbrot L, et al. 2015 CID)
Protecting baby

POST EXPOSURE PROPHYLAXIS
Phase 1: the 28 days after labour
Three Scenarios for PEP for labour

1 The virally suppressed mom  
   6 weeks NVP

2 The mom who has just started ART (within 4 weeks prior to labour) – resistance unlikely  
   12 weeks NVP if breast feeding

3 The mom who has a VL >1000 (been on ART >3months)  
   AZT and NVP for 6 weeks. No breast feeding
Phase 2: the breast feeding mom
Breast feeding PEP/ PrEP options for baby

1 Newly diagnosed Breast feeding mom
   Mom on 1TFE
   Start baby on AZT and NVP
   if PCR negative stop AZT, continue NVP 12 weeks

2 Breastfeeding mom >6 weeks and VL >1000
   AZT is NOT a best choice for prevention
   ? Use of three drugs
   ? But what of resistance

ASK an EXPERT
Neonatal PEP

**AZT**
- Extensively studied as neonatal PEP
- Potential toxic (bone marrow suppression)
- High genetic barrier
- Reduced efficacy in preventing breastfeeding transmission
- Used in UK – twice a day for 28 days if mother VL LDL

**NVP**
- Evidence has confirmed NVP efficacy
- Very few adverse events (in neonates)
- Risk of NVP resistance
- Better choice in preventing breastfeeding transmission of HIV
- Once daily in South Africa
British Guidelines

• If mother VL LDL
  AZT for 28 days (bd dosing)

• If mother VL > 50 copies /ml
  – Use a three anti-retroviral therapy for 4 weeks.
HIV-exposed infants: rethinking care for a lifelong condition

Sugandhi N, et al.

HEU children

• Data from Botswana – both weight for age and length for age significantly lower in HEU infants exposed to ART in utero

• Long-term impact unknown

Could predispose the child to subsequent poorer health, obesity, chronic disease or cognitive dysfunction

HEU children

(Mofenson LM. 2015 CID)

- Limited data, 1\textsuperscript{o} from high-resource settings, suggest that:
  - HIV and possibly ART exposure may be associated with immunologic and biologic abnormalities that could predispose HEU children to:
    - increased risk of illness and mortality, particularly in the first few years of life
HEU children

(Mofenson LM. 2015 CID)

- Firm conclusions about potential long-term effects of prolonged exposure to ART – in utero and during breastfeeding – in the HEU child, are lacking

- Role of socioeconomic factors
The HIV infected baby

NEONATAL ART
Antiretroviral therapy during the neonatal period

Rationale for initiating combination antiretroviral therapy during the neonatal period

Initiation of combination antiretroviral therapy (cART) at 6–9 weeks of age has been shown to reduce early infant mortality by 76% and HIV progression by 75% compared with cART deferred until clinical or CD4 criteria were met.¹ In the landmark Children with HIV Early Antiretroviral Therapy (CHER) trial, although the median age of starting cART in the early treatment arm was 7.4 weeks, one-third (10/30) of the overall mortality in the trial occurred in the early treatment arm.¹ In another study, 62% of 403 infants who initiated cART at median 8.4 weeks of age already had advanced HIV disease (CD4 < 25% or < 1500 cells/mm³ or World Health Organization [WHO] Stage 3 or 4) at initiation.²

No dosing instructions for children <3kg due to lack of PK studies

Insufficient data to recommend its use in infants < 3 months old
LOPINAVIR/ritonavir

CONTRA-INDICATED in any term baby less than 2 weeks of age
AND in
Premature babies until they have reached 42 weeks gestational age (so 2 weeks corrected age)

e.g. Born prematurely at 34 weeks: NO Kaletra until 8 weeks old
Lamivudine

Paediatric dose (> 4 weeks)
  – 4 mg/kg/dose

Neonatal dose (<4 weeks)
  – 2mg/kg/dose

RISK OF OVERDOSING THE NEONATE
Zidovudine

Standard AZT paediatric dose: risk of anaemia in premature infants: use neonatal ARV chart

After 6 weeks of age the SA ARV drug dosing chart can be used.
Nevirapine

Use neonatal dosing chart to avoid under or overdosing

No lead-in dose over a 14 day period required.
Neonatal Management: Steps 1 - 3

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

If neonate weighs < 2.5kg or unwell/ TB/ syphilis: Discuss with regional level centre

Positive Birth HIV PCR test
Actively trace and link to care

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

Ensure mother is on antiretroviral therapy (ART);
Advice on breastfeeding

Initial counselling for mother / caregiver on positive birth HIV PCR & starting ART

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)
Neonatal Management: Steps 4-8

- 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, cholesterol + triglycerides
  - 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 a paediatrician if questions/concerns

- Review monthly until 6 months of treatment:
  - Adjust medication using dosing chart
  - Month 6: Do VL
# Neonatal ART Dosage Chart

Only if <28 days AND >2.5kg

<table>
<thead>
<tr>
<th>Target dose</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2mg/kg/dose</td>
<td>4mg/kg/dose</td>
<td>6mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>TWICE daily (BD)</td>
<td>TWICE daily (BD)</td>
<td>TWICE daily (BD)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Available formulation</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10mg/ml</td>
<td>10mg/ml</td>
<td>10mg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
</tr>
</thead>
<tbody>
<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>
<td>12 mg BD</td>
<td>1.8 ml BD</td>
<td>18 mg 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>
<td>14 mg BD</td>
<td>2.1 ml BD</td>
<td>21 mg 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>
<td>16 mg BD</td>
<td>2.4 ml BD</td>
<td>24 mg 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>
<td>18 mg BD</td>
<td>2.7 ml BD</td>
<td>27 mg 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>
<td>20 mg BD</td>
<td>3.0 ml BD</td>
<td>30 mg 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>
<td>24 mg BD</td>
<td>3.6 ml BD</td>
<td>36 mg BD</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

<table>
<thead>
<tr>
<th>Target Dose</th>
<th>Available Formulations</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 kg</td>
<td>2nd bd</td>
<td>3rd bd</td>
</tr>
<tr>
<td>3-4.9 kg</td>
<td>2nd bd</td>
<td>3rd bd</td>
</tr>
<tr>
<td>5-5.9 kg</td>
<td>2nd bd</td>
<td>3rd bd</td>
</tr>
<tr>
<td>6-6.9 kg</td>
<td>2nd bd</td>
<td>3rd bd</td>
</tr>
<tr>
<td>7-7.9 kg</td>
<td>4th bd</td>
<td>5th bd</td>
</tr>
<tr>
<td>8-8.9 kg</td>
<td>4th bd</td>
<td>5th bd</td>
</tr>
<tr>
<td>9-9.9 kg</td>
<td>Choose only one option</td>
<td>Choose only one option</td>
</tr>
<tr>
<td>10-10.9 kg</td>
<td>6th bd OR 2x tablets bd</td>
<td>7th bd OR 4x tablets bd</td>
</tr>
<tr>
<td>11-11.9 kg</td>
<td>6th bd OR 2x tablets bd</td>
<td>7th bd OR 4x tablets bd</td>
</tr>
<tr>
<td>12-12.9 kg</td>
<td>8th bd OR 3x tablets bd</td>
<td>9th bd OR 6x tablets bd</td>
</tr>
<tr>
<td>13-13.9 kg</td>
<td>8th bd OR 3x tablets bd</td>
<td>9th bd OR 6x tablets bd</td>
</tr>
<tr>
<td>14-14.9 kg</td>
<td>10th bd OR 5x tablets bd</td>
<td>11th bd OR 10x tablets bd</td>
</tr>
<tr>
<td>15-15.9 kg</td>
<td>10th bd OR 5x tablets bd</td>
<td>11th bd OR 10x tablets bd</td>
</tr>
<tr>
<td>16-16.9 kg</td>
<td>12th bd OR 7x tablets bd</td>
<td>13th bd OR 14x tablets bd</td>
</tr>
<tr>
<td>17-17.9 kg</td>
<td>12th bd OR 7x tablets bd</td>
<td>13th bd OR 14x tablets bd</td>
</tr>
<tr>
<td>18-18.9 kg</td>
<td>14th bd OR 9x tablets bd</td>
<td>15th bd OR 18x tablets bd</td>
</tr>
<tr>
<td>19-19.9 kg</td>
<td>14th bd OR 9x tablets bd</td>
<td>15th bd OR 18x tablets bd</td>
</tr>
<tr>
<td>20-20.9 kg</td>
<td>16th bd OR 11x tablets bd</td>
<td>17th bd OR 22x tablets bd</td>
</tr>
<tr>
<td>21-21.9 kg</td>
<td>16th bd OR 11x tablets bd</td>
<td>17th bd OR 22x tablets bd</td>
</tr>
<tr>
<td>22-22.9 kg</td>
<td>18th bd OR 13x tablets bd</td>
<td>19th bd OR 25x tablets bd</td>
</tr>
<tr>
<td>23-23.9 kg</td>
<td>18th bd OR 13x tablets bd</td>
<td>19th bd OR 25x tablets bd</td>
</tr>
<tr>
<td>24-24.9 kg</td>
<td>20th bd OR 15x tablets bd</td>
<td>21st bd OR 27x tablets bd</td>
</tr>
<tr>
<td>25-25.9 kg</td>
<td>20th bd OR 15x tablets bd</td>
<td>21st bd OR 27x tablets bd</td>
</tr>
<tr>
<td>26-26.9 kg</td>
<td>22nd bd OR 17x tablets bd</td>
<td>23rd bd OR 29x tablets bd</td>
</tr>
<tr>
<td>27-27.9 kg</td>
<td>22nd bd OR 17x tablets bd</td>
<td>23rd bd OR 29x tablets bd</td>
</tr>
<tr>
<td>28-28.9 kg</td>
<td>24th bd OR 19x tablets bd</td>
<td>25th bd OR 31x tablets bd</td>
</tr>
<tr>
<td>29-29.9 kg</td>
<td>24th bd OR 19x tablets bd</td>
<td>25th bd OR 31x tablets bd</td>
</tr>
<tr>
<td>30-30.9 kg</td>
<td>26th bd OR 21x tablets bd</td>
<td>27th bd OR 33x tablets bd</td>
</tr>
<tr>
<td>31-31.9 kg</td>
<td>26th bd OR 21x tablets bd</td>
<td>27th bd OR 33x tablets bd</td>
</tr>
<tr>
<td>32-32.9 kg</td>
<td>28th bd OR 23x tablets bd</td>
<td>29th bd OR 35x tablets bd</td>
</tr>
<tr>
<td>33-33.9 kg</td>
<td>28th bd OR 23x tablets bd</td>
<td>29th bd OR 35x tablets bd</td>
</tr>
<tr>
<td>34-34.9 kg</td>
<td>30th bd OR 25x tablets bd</td>
<td>31st bd OR 37x tablets bd</td>
</tr>
<tr>
<td>35-36.9 kg</td>
<td>30th bd OR 25x tablets bd</td>
<td>31st bd OR 37x tablets bd</td>
</tr>
<tr>
<td>≥37 kg</td>
<td>32nd bd OR 27x tablets bd</td>
<td>33rd bd OR 39x tablets bd</td>
</tr>
</tbody>
</table>

###Notes:
- * Avoid LPV/r solution to any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice.
- * Children 25-34 kg may also be dosed with LPV/r 200/50 mg adult tabs. 2 tabs are 1 tab pm.

###Weight (kg)
- 3-4.9
- 5-9.9
- 10-13.9
- 14-20.9
- ≥30

###Dosage:
- Cotrimoxazole Dose: 2.5ml od OR 3 capsule bd
- Multivitamin Dose: 2.5ml od OR 3 capsule bd
CF16  LEE: Update to 2013  
Candice Fick, 2015/05/17
Monitoring

(DoH Guidelines 2014)

<table>
<thead>
<tr>
<th>Test</th>
<th>Timing</th>
</tr>
</thead>
</table>
| CD4 count and percentage      | At initiation
Then every 12 months                                                  |
| VL                            | At initiation
After 6 months then 1yr of into ART, then annually                   |
| FBC                           | ALL children as baseline
Child on AZT – baseline, 1,2,3 monthly then annually                   |
| Cholesterol, Triglycerides    | Children on Lopinavir/ritonavir, baseline and then annually            |
| ALT                           | Child on NVP and TB treatment – baseline, repeat if child develops rash or jaundice |

It is essential to check the weight, height and development at each visit.
Implications for practice...
The EMTCT cascade: new key messages

• Prevent HIV infection
  – Remember PrEP

• Protect the mom: ARVs soon and forever

• Cover labour: intrapartum and PEP
  – Raltaggravir?

• Cover Breastfeeding
Thanks to

Dr. Mnyani
Dr. Hendrix
Dr. Anderson
Dr. Cottrill
Dr. Johnson
Dr. Lochan
Dr James Nuttall