# 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

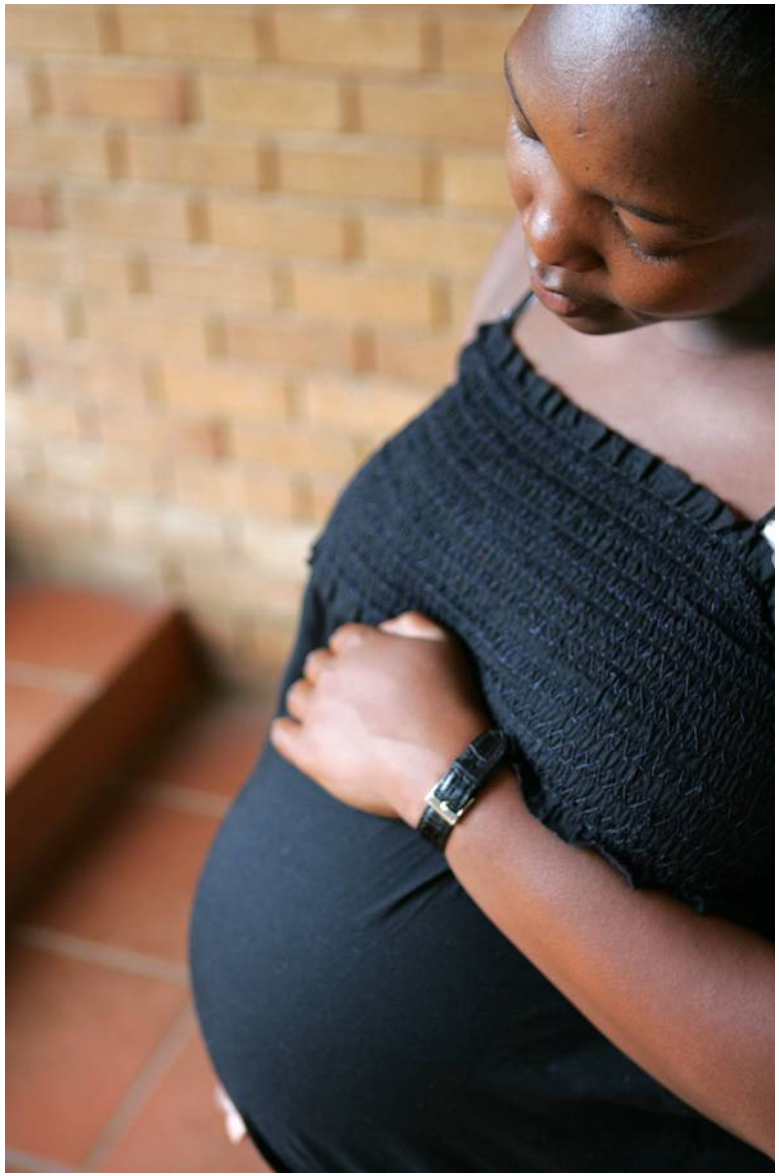
Remember the PMTCT cascade!

*Pre-conception*

*Pregnancy and Labour*

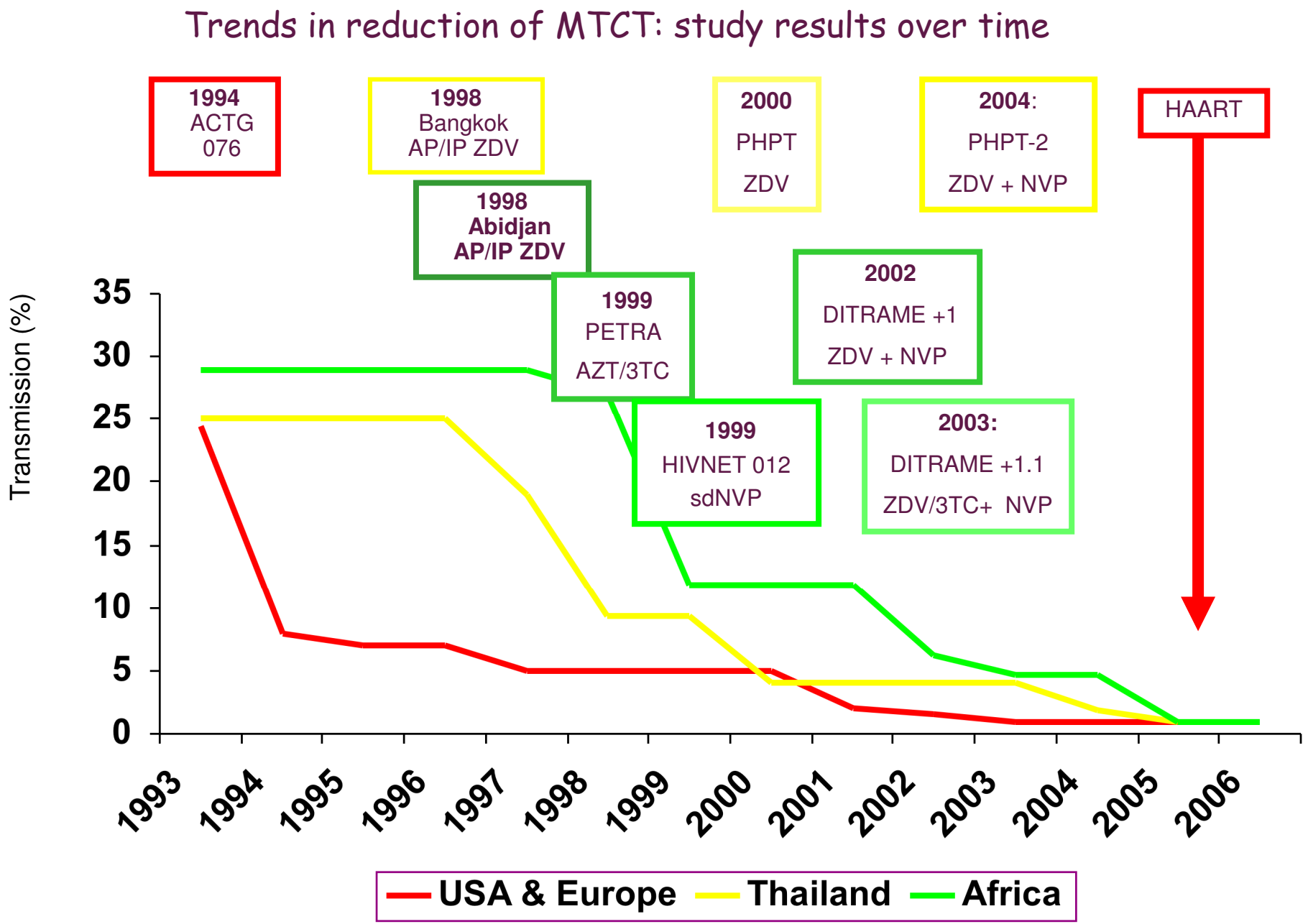
*Post-natal*

Every non-infertile couple whether both infected or discordant, should be asked what their reproductive intentions are at every clinic contact.

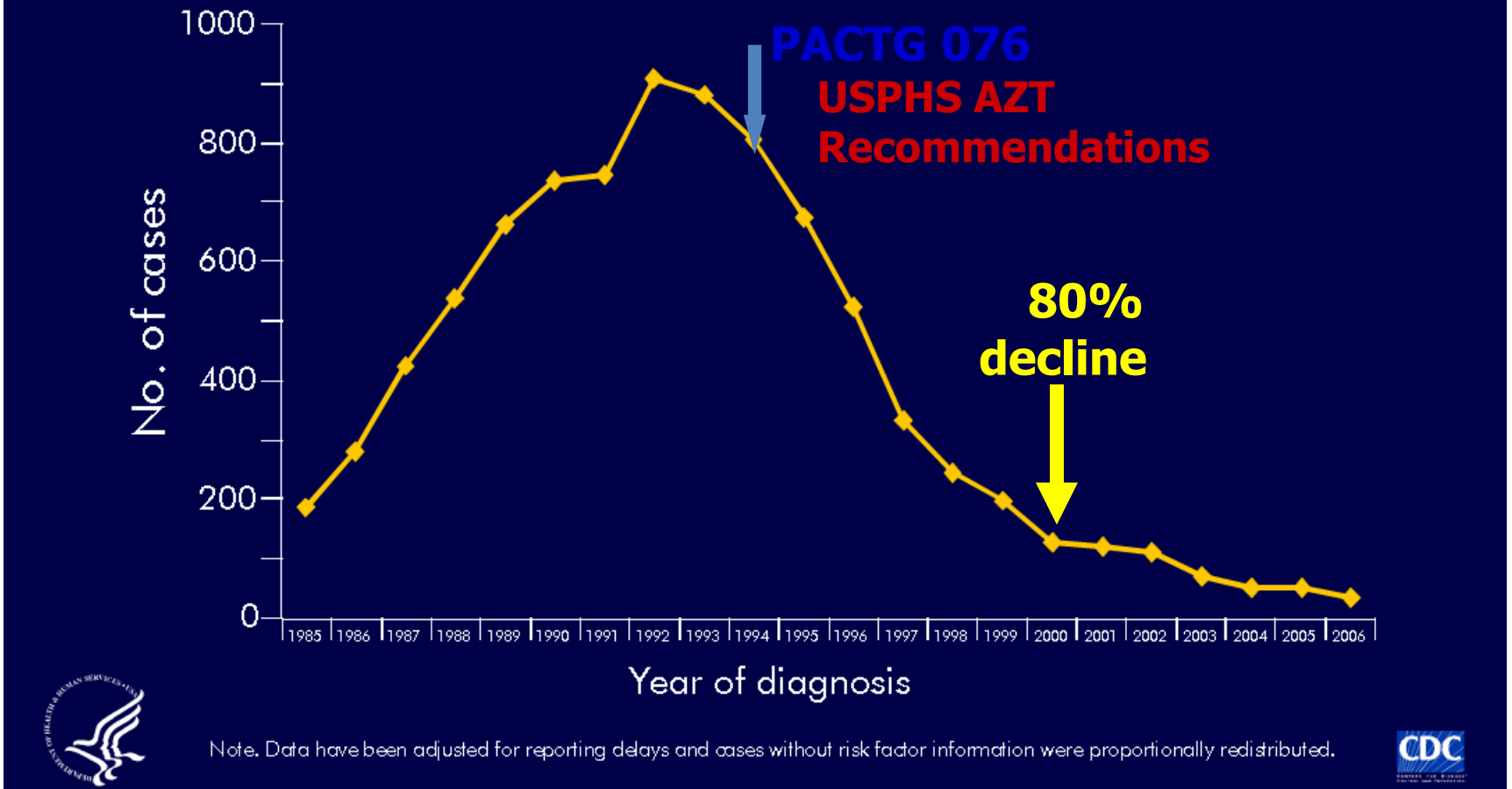


# % Risk of transmission without intervention

| Transmission time | No BF | BF 6/12 | BF 24/12 | |
|---|---|---|---|---|
| During Pregnancy | 5-10 | 5-10 | 5-10 | |
| During labour | 10-15 | 10-15 | 10-15 | |
| During BF | 0 | 5-10 | 15-20 | |
| OVERALL | 15-25 | 20-35 | 30-45 | |


Trends in reduction of MTCT: study results over time
1994
ACTG
076
1998
Bangkok
AP/IP ZDV
1998
Abidjan
AP/IP ZDV
2000
PHPT
ZDV
2004:
PHPT-2
ZDV + NVP
HAART
1999
PETRA
AZT/3TC
2002
DITRAME +1
ZDV + NVP
1999
HIVNET 012
sdNVP
2003:
DITRAME +1.1
ZDV/3TC+ NVP
Transmission (%)
35
30
25
20
15
10
5
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
USA & Europe
Thailand
Africa

# Estimated Number of Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985–2006—United States and Dependent Areas




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

# Outline

How do we protect

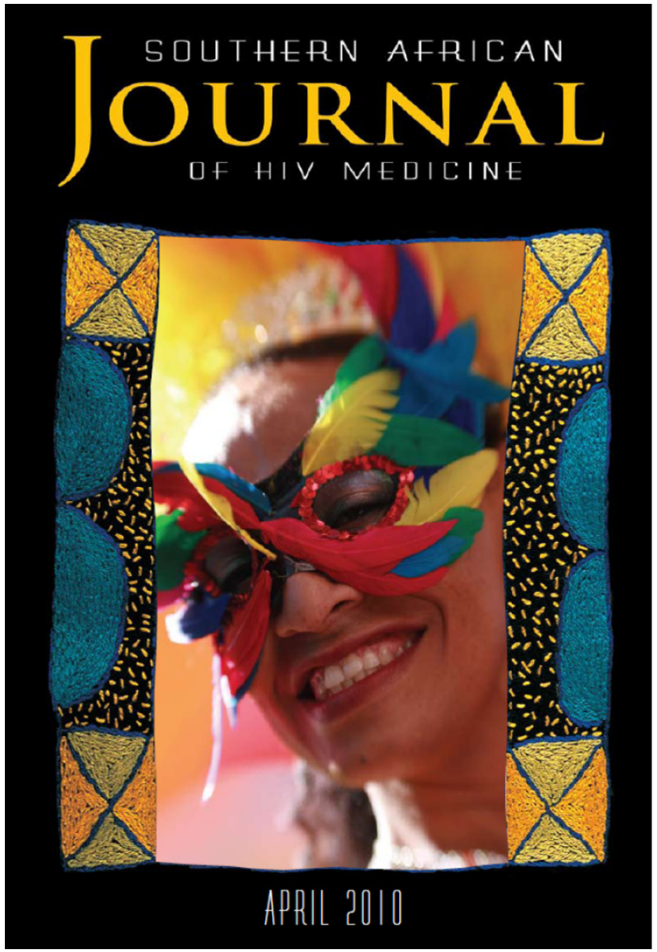
- Our fertile women
- Our women that are pregnant
- Our newborn babies

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**

Auvert B, PloS Med 2005
Gray R, Lancet 2007
Bailey R, Lancet 2007

**Treatment of STIs**

Grosskurth H, Lancet 2000

**Treatment for prevention**

Donnell D, Lancet 2010
Cohen M, NEJM 2011

**Female Condoms**

**Male Condoms**

**Behavioural positive prevention**

Fisher J, JAIDS 2004

**Oral pre-exposure prophylaxis**

Grant R, NEJM 2010 (MSM)
Baeten J , 2011 (Couples)
Paxton L, 2011 (Heterosexuals)

**HIV Counselling and Testing**

Coates T, Lancet 2000

**Behavioural Intervention**

- Abstinence
- Be Faithful


**Post Exposure prophylaxis (PEP)**

Scheckter M, 2002

**Vaccines**

Rerks-Ngarm S, NEJM 2009

*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

| Study, population | PrEP agent | # of HIV infections | | PrEP efficacy (95% CI) publication |
|---|---|---|---|---|
| | | PrEP | placebo | |
| Partners PrEP Study<br>Heterosexual couples<br>Kenya, Uganda (n=4758) | TDF/FTC | 13 | 52 | 75%<br>(55-87%) |
| | TDF | 17 | | 67%<br>(44-81%)<br>Baeten et al. N Engl J Med 2012 |
| TDF2 Study<br>Heterosexuals<br>Botswana (n=1219) | TDF/FTC | 10 | 26 | 62%<br>(16-83%)<br>Thigpen et al. N Engl J Med 2012 |
| Bangkok Tenofovir Study (BTS)<br>IDUs<br>Thailand (n=2413) | TDF | 17 | 33 | 49%<br>(10-72%)<br>Choopanya et al. Lancet 2013 |
| iPrEx<br>MSM<br>Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499) | TDF/FTC | 36 | 64 | 44%<br>(15-63%)<br>Grant et al. N Engl J Med 2010 |

# 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:

| | HIV risk reduction |
|---|---|
| Partners PrEP | |
| any tenofovir | 90% |
| iPrEx / iPrEx OLE | |
| any tenofovir | 92% |
| 4-6 doses/week | 96 - 100% |
| 7 doses/week | 99 - 100% |

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

Baeten et al. NEJM 2012; Grant et al. NEJM 2010; Anderson et al. Science Transl Med 2012; Grant et al. Lancet ID 2014

# Public sector: Key Populations

First population targeted: Sex workers

Next Key population

*Young women aged 16-24 years old*

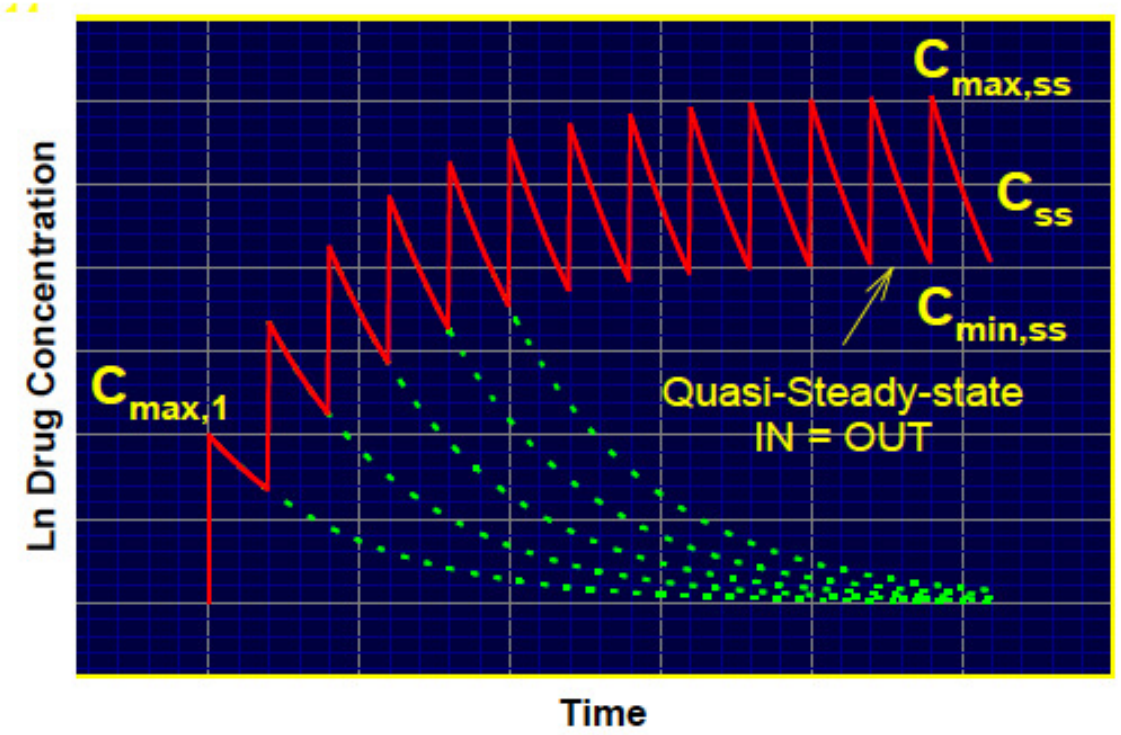
# PrEP

**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

World Health Organization

# Concentration – Time Principles




- Repeat dosing gradually raises peaks ($C_{max}$) & troughs ($C_{min}$)
- *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

- PrEP may be discontinued 28 days after the last potential exposure to HIV-infected fluids
  - .....if no continuing substantial risk for acquiring HIV infection

World Health Organization

# 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


- Moodley D, et al. Incident HIV infection in pregnant and lactating women and its effect on mother-to-child transmission in South Africa. J Infect Dis. 2011 May 1;203(9):1231-4.
- Moodley D, at al. High HIV incidence during pregnancy: compelling reason for repeat HIV testing. AIDS. 2009 Jun 19;23(10):1255-9.

# 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)


- Johnson LF, et al. The contribution of maternal HIV seroconversion during late pregnancy and breastfeeding to mother-to-child transmission of HIV. J Acquir Immune Defic Syndr. 2012 Apr 1;59(4):417-25.
- Goga AE, et al; South Africa PMTCT Evaluation (SAPMCTE) Team.. Population-level effectiveness of PMTCT Option A on early mother-to-child (MTCT) transmission of HIV in South Africa: implications for eliminating MTCT. J Glob Health. 2016 Dec;6(2)
- Drake AL, et al. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. 2014 Feb 25;11(2):e1001608.

# PrEP in pregnancy

Southern African Journal of HIV Medicine
ISSN: (Online) 2078-6751, (Print) 1608-9693



# 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

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

National Policy on HIV Pre-exposure Prophylaxis (PrEP)
and Test and Treat (T&T)

FINAL DRAFT - 5 MAY 2016

**No mention of pregnancy**

Seidman DL et al. *Journal of the International AIDS Society* 2017, **20(Suppl 1)**:21295
http://www.jiasociety.org/index.php/jias/article/view/21295 | http://dx.doi.org/10.7448/IAS.20.2.21295

Commentary

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

Dominika L Seidman[1§], Shannon Weber[2] and Deborah Cohan[1,2]

[§]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

World Health Organization

**2015**

## Recommendation

NEW

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

| | |
|---|---|
| Pregnant/Breastfeeding women (to detect HIV sero-conversion) | » Every 3 months throughout pregnancy<br>» At labour/delivery<br>» At the 6 week EPI visit<br>» Every 3 months throughout breastfeeding |

Clinical Infectious Diseases Advance Access published August 18, 2015

MAJOR ARTICLE HIV/AIDS

# No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception

Laurent Mandelbrot,[1,2,5,8] Roland Tubiana,[9,10] Jerome Le Chenadec,[2] Catherine Dollfus,[11] Albert Faye,[5,12] Emmanuelle Pannier,[8,13] Sophie Matheron,[5,14] Marie-Aude Khuong,[17] Valerie Garrait,[18] Veronique Reliquet,[19] Alain Devidas,[20] Alain Berrebi,[21] Christine Allisy,[22] Christophe Elleau,[23] Cedric Arvieux,[24] Christine Rouzioux,[6,15] Josiane Warszawski,[2,3,4] and Stéphane Blanche[7,16]; for the ANRS-EPF Study Group[a]

# 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:

| Timing of ART | % with VL<50 c/ml |
|---|---|
| Preconception | **75.4** |
| 1st T | **74.2** |
| 2nd T | 64.8 |
| 3rd T | 44.1 |

(P <0.001)

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

# Perinatal transmission

| Maternal VL | Timing of ART Initiation: Before Conception[a] PT, % (95% CI) | Before Conception[a] No. With PT/Total No. | 1st Trimester (<14 wk) PT, % (95% CI) | 1st Trimester (<14 wk) No. With PT/Total No. | 2nd Trimester (14–27 wk) PT, % (95% CI) | 2nd Trimester (14–27 wk) No. With PT/Total No. | 3rd Trimester (≥28 wk) PT, % (95% CI) | 3rd Trimester (≥28 wk) No. With PT/Total No. | *P* Value |
|---|---|---|---|---|---|---|---|---|---|
| Maternal VL nearest delivery, copies/mL | | | | | | | | | |
| ≥400 | 2.2 (.7–5.0) | 5/230 | 1.5 (.04–7.8) | 1/69 | 2.4 (1.0–4.9) | 7/291 | 4.4 (2.1–7.9) | 10/228 | .37 |
| 50–400 | 0.3 (.01–1.8) | 1/301 | 1.6 (.04–8.8) | 1/61 | 1.4 (.5–2.8) | 7/515 | 3.0 (1.4–5.7) | 9/297 | .06 |
| Undetectable, threshold >50 | 0.0 (0–1.7) | 0/212 | 0.0 (0–6.8) | 0/52 | 0.6 (<.01 to 3.3) | 1/169 | 0.0 (0–8.6) | 0/41 | .5 |
| <50 | 0.0 (0–.1) | 0/2651 | 0.2 (<.01 to 1.1) | 1/507 | 0.5 (.2–1.0) | 9/1735 | 0.9 (.2–2.3) | 4/452 | .002 |
| Missing VL | . . . | 0/111 | . . . | 0/20 | | 0/100 | . . . | 0/33 | . . . |
| Undetermined child HIV status | . . . | . . ./287 | . . . | . . ./55 | . . . | . . ./184 | . . . | . . ./77 | . . . |

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

[a] 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

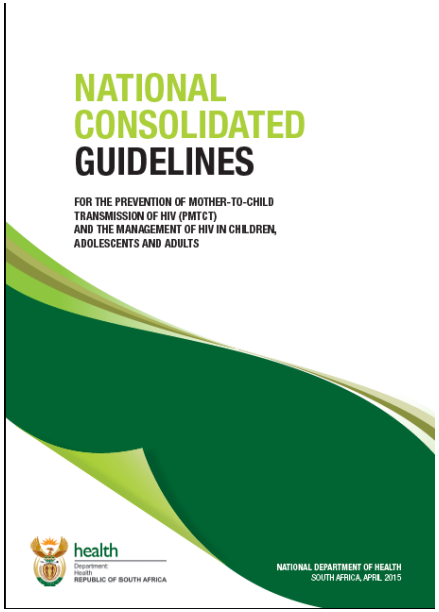
Few cases of transmission with VL <50 c/mL at delivery occurred

- when ART was started beyond the 1st T or interrupted during the pregnancy

- ART initiated in the 1st 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

WHO B+ PROGRAM

# 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 2nd line drugs

- 2nd VL undetectable or reduction in VL ≥1 log (10-fold), continue existing regimen

- VL unchanged or increased, switch to 2nd line therapy

# Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis

**Nathan Ford[a], Lynne Mofenson[b], Zara Shubber[c], Alexandra Calmy[d,e], Isabelle Andrieux-Meyer[e], Marco Vitoria[a], Nathan Shaffer[a] and Françoise Renaud[a]**

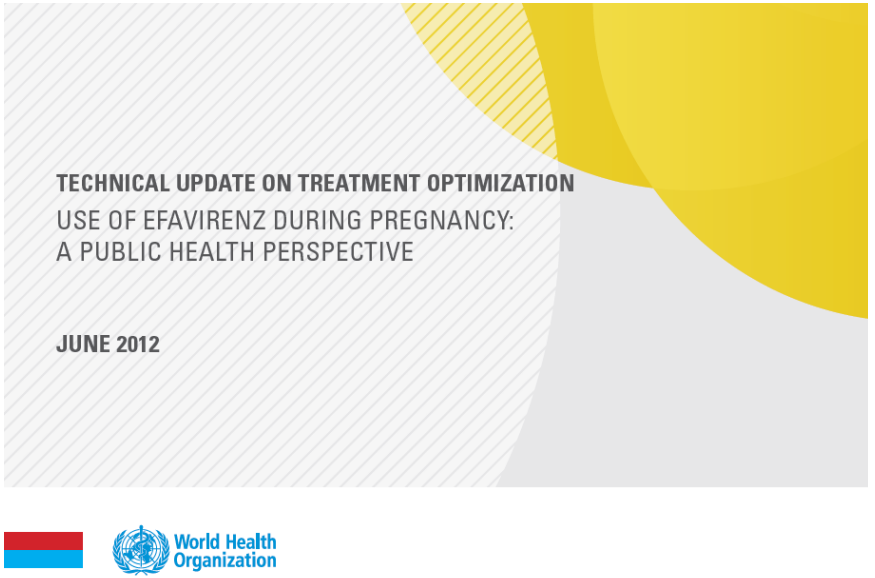
*AIDS* 2014, **28** (Suppl 2):S123–S131

**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

J Acquir Immune Defic Syndr. 2017 Mar 10. doi: 10.1097/QAI.0000000000001359. [Epub ahead of pr

# Safety of Tenofovir Disoproxil Fumarate-Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their Infants: A Systematic Review and Meta-Analysis.

Nachega JB[1], Uthman OA, Mofenson LM, Anderson JR, Kanters S, Renaud F, Ford N, Essajee S, Doherty MC, Mills EJ.

**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

*Olalekan A Uthman, Jean B Nachega, Jean Anderson, Steve Kanters, Edward J Mills, Françoise Renaud, Shaffiq Essajee, Meg C Doherty, Lynne M Mofenson*

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

Lancet HIV 2017; 4: e21–30

# 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

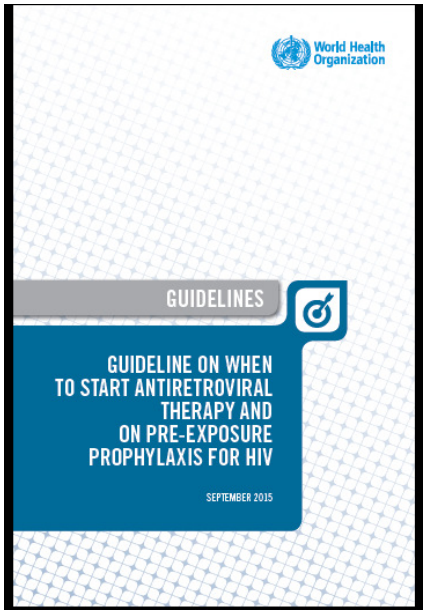
Lancet HIV 2017; 4: e21–30

# 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

*Lancet HIV* 2017; 4: e21–30

# WHO guidelines 2015



# WHO guidelines 2015

NEW

## 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/mm$^3$ *(strong recommendation, moderate-quality evidence)*.

World Health Organization

# 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

World Health Organization

ORIGINAL ARTICLE

# 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)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

N Engl J Med 2015;373:808-22.

# 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**,[2] MB ChB, FC Rad Diag (SA); **E Nicolaou**,[1,3] MD, FCOG (SA), Dip Fet Med

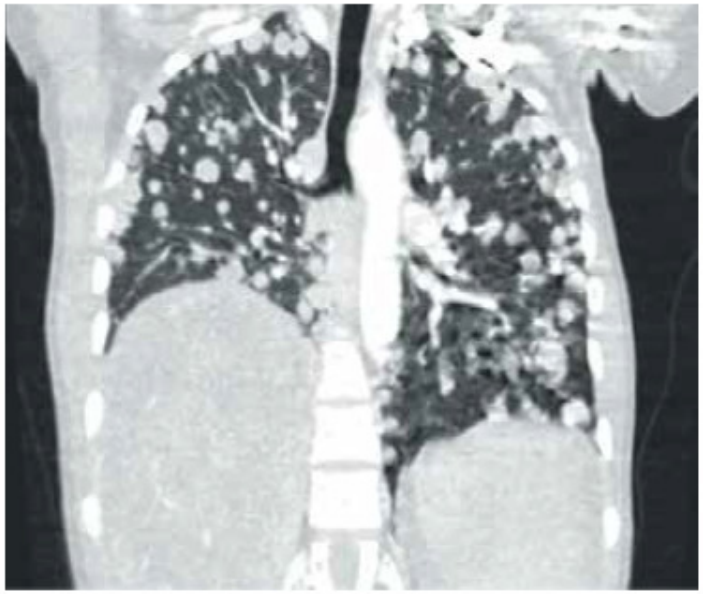


*Fig. 1. A CT scan of the chest (coronal view), showing bilateral cannon ball lesions (white lesions) in the lung fields (CT = computed tomography).*

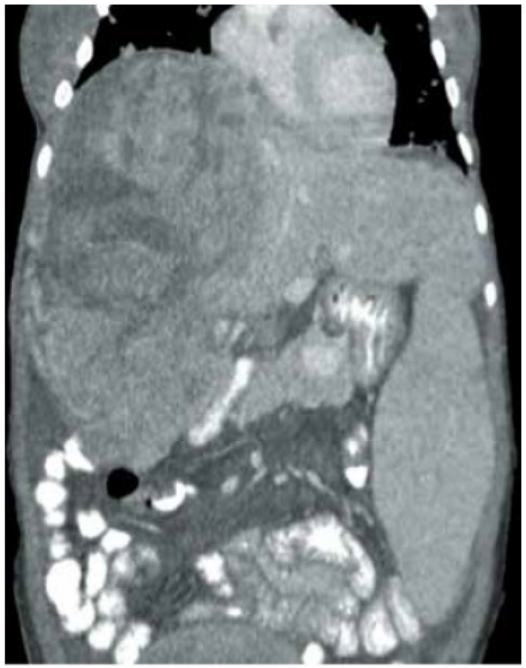


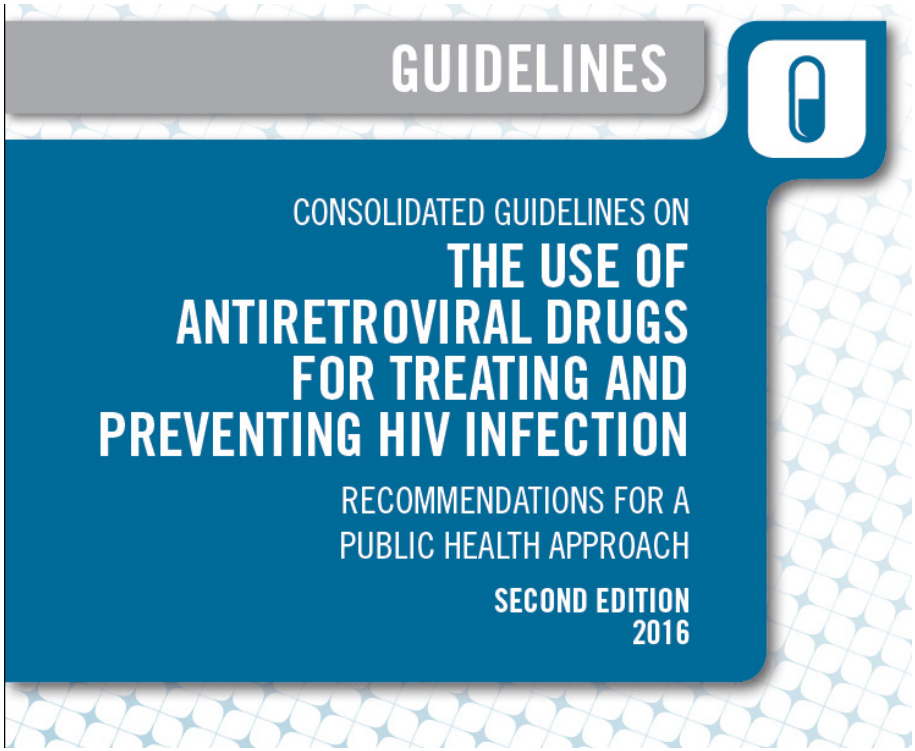
*Fig. 2. A CT scan of the abdomen (coronal view), showing a large mass in the right hepatic lobe and splenomegaly. The vascular mass occupies the whole of the right lobe, where dense and hypodense areas are seen within the liver.*

# 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.

World Health Organization

# WHO guidelines 2016



# WHO guidelines 2016

NEW

## 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).

*Source*: HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

# 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'*

World Health Organization

# WHO guidelines 2016

Pregnant or breastfeeding women

**Preferred 1st line regimen**

- TDF + 3TC (or FTC) + EFV

**Alternative 1st 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 2nd line regimen**

- 2 NRTIs + ATV/r or LPV/r

**Alternative 2nd 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:
  - AZT+3TC
  - TDF+FTC
  - 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

Developed by the HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

**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…

World Health Organization

# 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

World Health Organization

# 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."

World Health Organization

# Dolutagravir: 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.

OBSTETRICS

# Integrase inhibitors in late pregnancy and rapid HIV viral load reduction

Lisa Rahangdale, MD, MPH; Jordan Cates, MSPH; JoNell Potter, PhD; Martina L. Badell, MD; Dominika Seidman, MD; Emilly S. Miller, MD, MPH; Jenell S. Coleman, MD, MPH; Gweneth 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

MARCH 2016 American Journal of Obstetrics & Gynecology

# 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

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

    - 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 breast feeding 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.

*AIDS* 2013, **27** (Suppl 2):S187–S195

# 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

(Sugandhi N, et al. *AIDS* 2013, 27 (Suppl 2):S187–S195)

# HEU children

(Mofenson LM. 2015 *CID*)

- Limited data, 1º 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

# SA Journal HIV Medicine

## Antiretroviral therapy during the neonatal period

**Author:**
James J.C. Nuttall[1,2]

**Affiliations:**
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[2]Department of Paediatrics and Child Health, University of Cape Town, South Africa

**Correspondence to:**

### Rationale for initiating combination antiretroviral therapy during the neonatal period

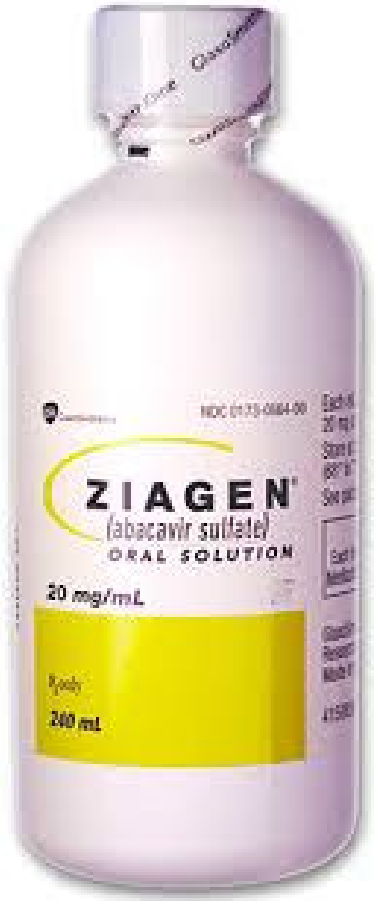
Initiation of combination antiretroviral therapy (cART) at 6–9 weeks of age has been shown to reduce early infant mortality by 76% and HIV progression by 75% compared with cART deferred until clinical or CD4 criteria were met.[1] In the landmark Children with HIV Early Antiretroviral Therapy (CHER) trial, 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/mm$^3$ or World Health Organization [WHO] Stage 3 or 4) at initiation.[2]

http://www.sajhivmed.org.za doi:10.4102/sajhivmed.v16i1.361

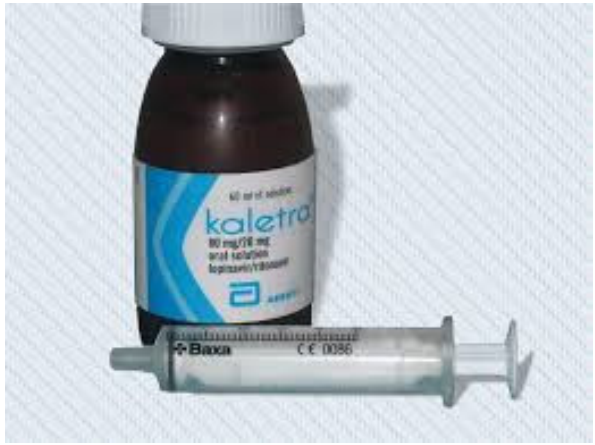
# ABACAVIR

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)

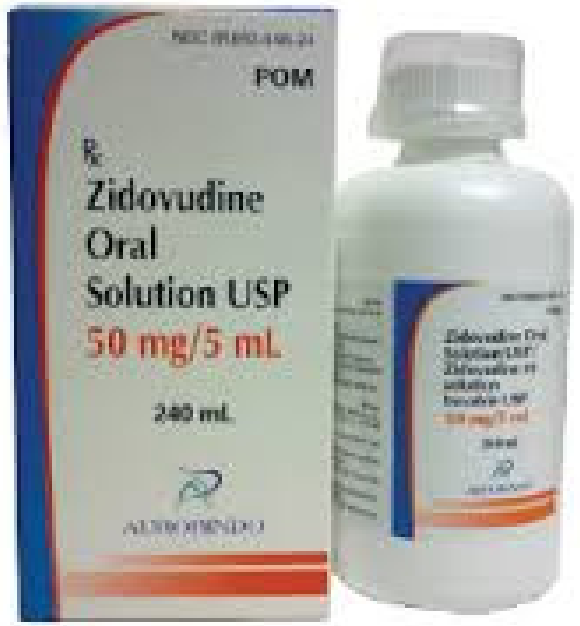
- 4 mg/kg/dose

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

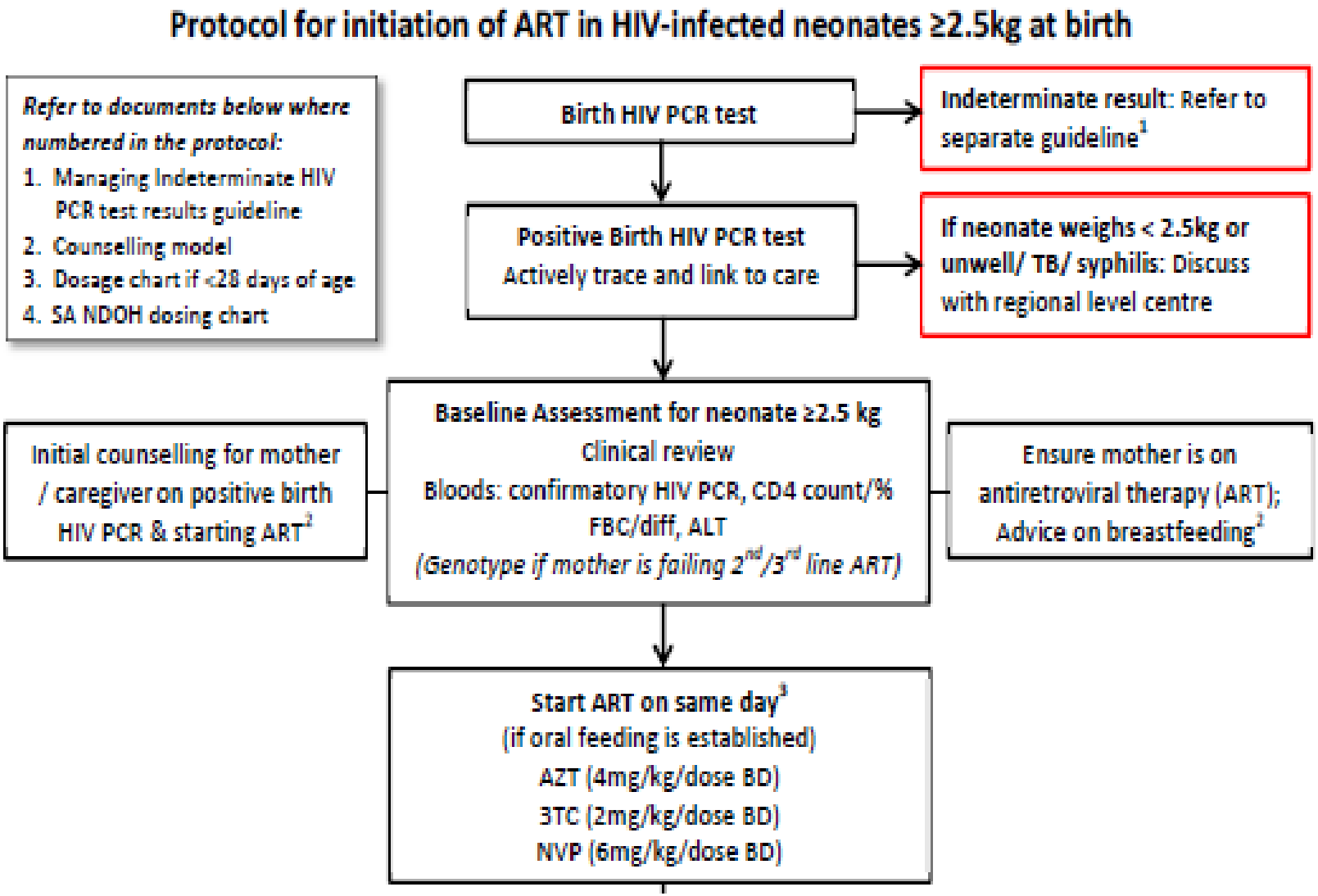
After 6 weeks of age the SA ARV drug dosing chart can be used.

# Nevirapine

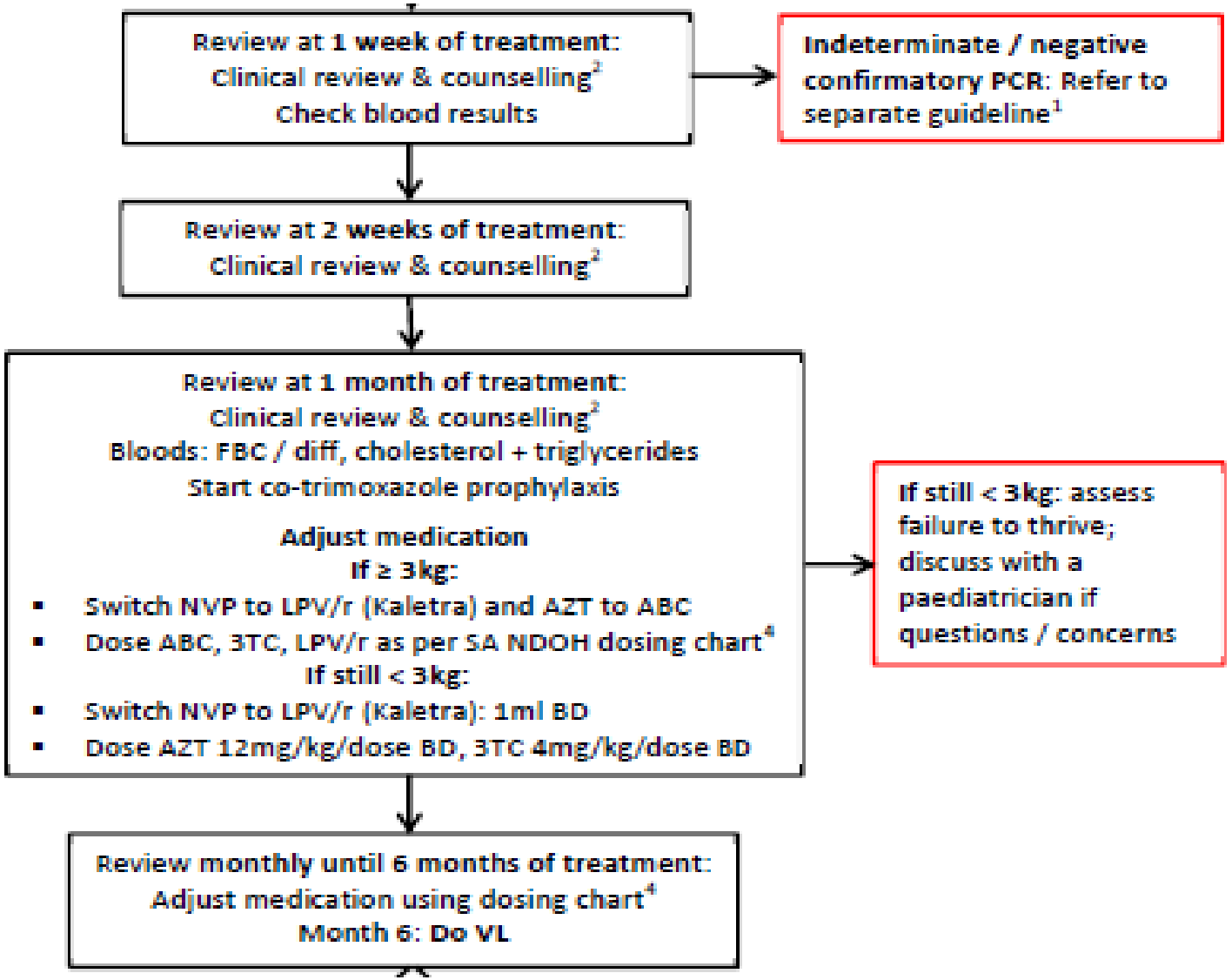

Use neonatal dosing chart to avoid under or overdosing

No lead-in dose over a14 day period  required.

# Neonatal Management: Steps 1 - 3



# Neonatal Management: Steps 4-8



# Neonatal ART Dosage Chart

## Only if <28 days AND >2.5kg

| | Lamivudine (3TC) | | Zidovudine (AZT) | | Nevirapine (NVP) | |
|---|---|---|---|---|---|---|
| **Target dose** | 2mg/kg/dose TWICE daily (BD) | | 4mg/kg/dose TWICE daily (BD) | | 6mg/kg/dose TWICE daily (BD) | |
| **Available formulation** | 10mg/ml | | 10mg/ml | | 10mg/ml | |
| **Weight (kg)** | **Dose in ml** | **Dose in mg** | **Dose in ml** | **Dose in mg** | **Dose in ml** | **Dose in mg** |
| **≥2.5-<3.0** | 0.6 ml BD | 6 mg BD | 1.2 ml BD | 12 mg BD | 1.8 ml BD | 18 mg BD |
| **≥3.0-<3.5** | 0.7 ml BD | 7 mg BD | 1.4 ml BD | 14 mg BD | 2.1 ml BD | 21 mg BD |
| **≥3.5-<4.0** | 0.8 ml BD | 8 mg BD | 1.6 ml BD | 16 mg BD | 2.4 ml BD | 24 mg BD |
| **≥4.0-<4.5** | 0.9 ml BD | 9 mg BD | 1.8 ml BD | 18 mg BD | 2.7 ml BD | 27 mg BD |
| **≥4.5-<5.5** | 1.0 ml BD | 10 mg BD | 2.0 ml BD | 20 mg BD | 3.0 ml BD | 30 mg BD |
| **≥5.5-<6.5** | 1.2ml BD | 12 mg BD | 2.4 ml BD | 24 mg BD | 3.6 ml BD | 36 mg BD |

CF16

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

# 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**

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

| | Abacavir (ABC) | Lamivudine (3TC) | Efavirenz (EFV) | Lopinavir/ritonavir (LPV/rtv) | Ritonavir boosting (RTV) | Stavudine (d4T) | Didanosine (ddI) | Nevirapine (NVP) | Zidovudine (AZT) | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Target Dose** | 8mg/kg TWICE daily OR ≥10kg: 16mg/kg ONCE daily | 4mg/kg TWICE daily OR ≥10kg: 8mg/kg ONCE daily | By weight band ONCE daily | 300/75mg/m²/dose LPV/rtv TWICE daily | ONLY as booster for LPV/rtv when on Rifampicin TWICE daily (0.75ml LPV dose bd) | 1mg/kg/dose TWICE daily | 180-240mg/m²/dose ONCE daily | 160-200 mg/m²/dose TWICE daily (after once daily lead in x 2 wks) | 180-240mg/m²/dose TWICE daily | **Target Dose** |
| **Available Formulations** | Sol 20mg/ml Tabs 60mg (scored dispersible), 300mg (not scored), ABC/3TC 600/300mg | Sol. 10mg/ml Tabs 150mg (scored), 300mg, ABC/3TC 600/300mg | Caps 50,200mg Tabs 50,200, 600mg (not scored) | Sol. 80/20mg/ml Adult Tabs 200/50mg, Paeds Tabs 100/25mg | Sol. 80mg/ml | Sol. 1mg/ml Caps 15,20,30mg | Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC | Sol. 10mg/ml Tabs 200mg (scored) | Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored), AZT/3TC 300/150mg | **Available Formulations** |
| **Wt. (kg)** | Currently available tablet formulations of abacavir (except 60mg), efavirenz, LPV/rtv and AZT must be swallowed whole and NOT chewed, divided or crushed | | | | | | | | | **Wt. (kg)** |
| **<3** | Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg | | | | | | | | | **<3** |
| **3-3.9** | 2ml bd | 2ml bd | Avoid using when <10kg or <3 years: dosing not established | *1ml bd | 1ml bd | 6ml | Avoid | 5ml bd | 6ml bd | **3-3.9** |
| **4-4.9** | | | | | | | 100mg od: (2x50mg tabs) | | | **4-4.9** |
| **5-5.9** | 3ml bd | 3ml bd | | *1.5ml bd | 1.5ml bd | 7.5mg bd: open 15mg capsule into 5ml water: give 2.5ml | | | 9ml bd | **5-5.9** |
| **6-6.9** | | | | | | | 125mg od: (1x100mg + 1x25mg tabs) | 8ml bd | | **6-6.9** |
| **7-7.9** | 4ml bd | 4ml bd | | | | 10mg bd: open 20mg capsule into 5ml water: give 2.5ml | | | | **7-7.9** |
| **8-8.9** | | | | | | | | | 1 cap bd OR 12ml bd | **8-8.9** |
| **9-9.9** | | | | | | | | | | **9-9.9** |
| **10-10.9** | Choose only one option: 6ml bd OR 2x60mg tabs bd / 12ml od OR 4x60mg tabs od | Choose only one option: 6ml bd / 12ml od | 200mg nocte (1x200mg cap/tab) | 2ml bd | 1.5ml bd | 15mg bd: open 15mg capsule into 5ml water | 150mg od: (1x100mg + 1x50mg tabs) | 10ml bd | | **10-10.9** |
| **11-13.9** | | | | | | | | | | **11-13.9** |
| **14-16.9** | 8ml bd OR 2.5x60mg tabs bd / 5x60mg tabs od OR 1x300mg tab od OR 15ml od | ½ x150mg tab bd OR 8ml bd / 1x150mg tab od OR 15ml od | 300mg nocte: (200mg cap/tab + 2x50mg cap/tab) | Choose one option: -2.5ml bd -100/25mg paeds tabs: 2 bd -200/50mg adult tabs: 1 bd | 2ml bd | 20mg bd: open 20mg capsule into 5ml water (if the child is unable to swallow a capsule) | 175mg od: (1x100mg + 1x50mg + 1x25mg) | 1 tab am ½ tab pm OR 15ml bd | 2 caps am 1 cap pm OR 15ml bd | **14-16.9** |
| **17-19.9** | | | | | | | | | | **17-19.9** |
| **20-22.9** | 10ml bd OR 3x60mg tabs bd / 1x300mg tab + 1x60mg tab od | 1x150mg tab bd OR 15ml bd / 2x150mg tab od OR 1x300mg tab od OR 30ml od | | Choose one option: -3ml bd - 100/25mg paeds tabs: 2 bd - 200/50mg adult tabs: 1 bd | 2.5ml bd | | 200mg od: (2x100mg tabs) | | 2 caps bd OR 20ml bd | **20-22.9** |
| **23-24.9** | 1x300mg tab + 2x60mg tabs od | | | | | | | | | **23-24.9** |
| **25-29.9** | 1x300mg tab bd / 2x300mg tabs od OR 1xABC/3TC 600/300mg tab od | 1x150mg tab bd / 2x150mg tabs od OR 1x300mg tab od OR 1xABC/3TC 600/300mg tab od | 400mg nocte: (2x200mg caps/tabs) | Choose one option: - 3.5ml bd - 100/25mg paeds tabs: 3 bd - #200/50mg adult tabs: 1 bd + 100/25mg paeds tabs: 1 bd | 3ml bd | 30mg bd | 250mg od: (2x100mg + 1x50mg tab) OR 1x250mg EC cap od | 1 tab bd | 1x300mg tab bd OR 1xAZT/3TC 300/150mg tab bd | **25-29.9** |
| **30-34.9** | | | | Choose one option: - 4ml bd - 100/25mg paeds tabs: 3 bd - #200/50mg adult tabs: 1 bd + 100/25mg paeds tabs: 1 bd | | | | | | **30-34.9** |
| **35-39.9** | | | | Choose one option: - 5ml bd - 200/50mg adult tabs: 2 bd | 4ml bd | | | | | **35-39.9** |
| **>40** | | | 600mg tab nocte | | | | | | | **>40** |

od = once a day (usually at night)
bd = twice a day

* 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 (40 weeks post conception) or obtain expert advice.
# Children 25-34.9kg may also be dosed with LPV/rtv 200/50mg adult tabs: 2 tabs am; 1 tab pm

| Weight (kg) | 3-4.9 | 5-9.9 | 10-13.9 | 14-29.9 | ≥30 |
|---|---|---|---|---|---|
| Cotrimoxazole Dose | 2.5ml od | 5ml od | 5ml od | 10ml or 1 tab od | 2 tabs od |
| Multivitamin Dose | 2.5ml od | 2.5ml od | 5ml od | 5ml od | 10ml or 1 tab od |

**CF16** LEE: Update to 2013

Candice Fick, 2015/05/17

# Monitoring

(DOH Guidelines 2014)

| Test | Timing |
|---|---|
| **CD4 count and percentage** | **At initiation**<br>**Then every 12 months** |
| **VL** | **At initiation**<br>**After 6 months then 1yr of into ART, then annually** |
| **FBC** | **ALL children as baseline**<br>**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
  - Raltagravir?
- Cover Breastfeeding

Thanks to

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