Using new ARVs in pregnancy

Linda-Gail Bekker
With thanks to CN Mnyani

SA HIV Clinician’s Society Meeting
3 June 2017
“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.”
In an ideal world-

This relationship will start
PRE-CONCEPTION

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

It is our ethical obligation then to guide them through the safest conception, delivery and postnatal period available in our context.
Needing updating??

- Safer conception guidelines for the non-infertile HIV infected couple.
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-2 ZDV + NVP
2002: DITRAME +1 ZDV + NVP
2003: DITRAME +1.1 ZDV/3TC+ NVP
2004: PHPT-2 ZDV + NVP
2006: HAART

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.
<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>OVERALL</td>
<td>15-25</td>
<td>20-35</td>
<td>30-45</td>
</tr>
</tbody>
</table>
Outline

• Current guidelines

• ‘The old...’
  o EFV
  o TDF

• The new...
  o ‘Newer’ ARV agents

• And the unknown...
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

• Dyslipidaemia or diarrhoea associated with LPV/r switch LPV/r to ATV/r
SA guidelines

Threshold for treatment failure:

• $\text{VL} > 1000$, adherence counselling, repeat VL in 1 month

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

• VL unchanged or increased, switch to $2^{\text{nd}}$ line therapy
**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>
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*

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*

CASE REPORT

Delayed presentation and diagnosis of metastatic hepatocellular carcinoma in pregnancy

C N Mnyani, BA, MB ChB, FCOG (SA); J C Hull, MB BCH, MRCOG, FCOG (SA), DTM & H; M B Mbakaza, MB ChB, FC Rad Diag (SA); A O A Krim, MB ChB. FC Rad Diag (SA); E Nicolaou, 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.
Metastatic HCC in pregnancy

- 30 yo 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
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
WHO guidelines 2016

Pregnant or breastfeeding women

Preferred 1\textsuperscript{st} line regimen

\begin{itemize}
  \item TDF + 3TC (or FTC) + EFV
\end{itemize}

Alternative 1\textsuperscript{st} line regimens

\begin{itemize}
  \item AZT + 3TC + EFV (or NVP) \xmark
  \item TDF + 3TC (or FTC) + NVP
\end{itemize}
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:
  - AZT+3TC
  - TDF+FTC
  - ABC+3TC
British guidelines

- Recommended 3\textsuperscript{rd} agent:
  - EFV, NVP (CD4 <250) or a boosted PI

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

- Consider 3\textsuperscript{rd} 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

Untreated presenting intrapartum:

• Stat dose of NVP; commence FDC containing raltegravir

• IV AZT during labour and delivery
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 old...’
Safety of EFV in pregnancy

- Previous concerns about risk of teratogenicity with use in the 1\textsuperscript{st} trimester (T)

- Evidence was based on animal studies and retrospective case reports of neural tube defects in infants exposed to EFV in utero.

  - Data from large observational studies don’t show an increased risk of neural tube defects with EFV use in all trimesters of pregnancy.
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 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 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
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.”
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; Emily 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 Ciaramello, 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 $\geq 100,000$
      or CD4 $< 200$ at baseline

• Insufficient data to recommend dolutegravir and elvitegravir
  (once-daily dosing) use in pregnancy
PrEP use during pregnancy
Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection


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
• 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.

**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).
HIV in pregnancy

- HIV acquisition during pregnancy and immediately following pregnancy remains high despite increased access to and initiation of antiretroviral therapy (ART).
- In South Africa (SA), the maternal HIV incidence rate was 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

Data from pharmacokinetic studies:

- up to 20 days of PrEP needed before achieving full protection for vaginal intercourse?

lead-time required to achieve steady state levels of TDF in blood and tissues
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
Compare 2 Regimens, 2 Infection Sites

- More frequent dosing, higher concentration, same time to Steady-state
- Time to Steady-State may (FGT) or may not (GI) equal Time to Protection
- Time to Protection varies with risk site & regimen
  - Ignore numbers, order of time and direction of magnitude very roughly true
Summary

- FGT protection requires 6-7 doses per week
- Time to Protection must nearly equal $T_{ss}$ (Steady-state)

- CD4+ cell most relevant cell even if site uncertain
- CD4+ TFV-DP $t_{1/2}$
  - FGT 139 hrs
  - PBMC 112 hrs
  - Colon 60 hrs

- Time to Protection
  - FGT 20 days
  - PBMC 16 days
  - Colon 9 days
PBMC ~SS 7 days

Tenofovir-diphosphate

Emtricitabine-triphosphate

Rectal mononuclear cells

TFV-DP

Css: 1450 (95% CI: 898 - 2340)

FTC-TP

Css: 0.8 (95% CI: 0.6 - 1.1)

Cervical brush cells, viable and total

- \( N=13 \)
Summary

• PBMC SS ~ day 7

• Rectal cells SS ~ day 5-7

• Cervical cells less conclusive. Under powered. Epithelial cells with low viability. Concentrations from days 1-7 overlapped with SS predictions.
Discussion points

- Parent TFV/FTC appears rapidly in CVF. Despite limited data in cervical epithelial cells, concentrations within first week overlapped with SS. Systemic drug reached SS at ~7 days.

- Relevance of male genital tract? We have no data in male genital tract tissue (eg foreskin)...possible PK similarities to female genital tract? Its relevant that we see high efficacy in MSM, presumably including insertive exposures.

- Relevance of PEP/animal models? Drug started within 36 hours after vaginal exposure effective in macaques (HIV-2). Event-driven oral dosing effective for vaginal exposures in macaques (SHIV).

PMID: 23226529, 25202923, 11000253
Predicting Efficacy in the Population
Reduced Frequency Dosing

Lower FGT Tissue

<table>
<thead>
<tr>
<th>Doses/Week</th>
<th>% Population Achieving EC90 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>4</td>
<td></td>
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<tr>
<td>5</td>
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<td>6</td>
<td></td>
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<tr>
<td>7</td>
<td></td>
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</tbody>
</table>

Rectal Tissue

<table>
<thead>
<tr>
<th>Doses/Week</th>
<th>% Population Achieving EC90 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>5</td>
<td></td>
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<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>100%</td>
</tr>
</tbody>
</table>

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
Commentary

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

Dominika L Seidman\textsuperscript{1,3}, Shannon Weber\textsuperscript{2} and Deborah Cohan\textsuperscript{1,2}

\textsuperscript{3}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
Perinatal transmission
No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception
Background

- The French Perinatal Cohort: 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>1&lt;sup&gt;st&lt;/sup&gt; T</td>
<td>74.2</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; T</td>
<td>64.8</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; T</td>
<td>44.1</td>
</tr>
</tbody>
</table>

(P <0.001)

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

<table>
<thead>
<tr>
<th>Maternal VL</th>
<th>Timing of ART Initiation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Conception⁸</td>
<td>1st Trimester (&lt;14 wk)</td>
</tr>
<tr>
<td>Maternal VL nearest delivery, copies/mL</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>
</tr>
<tr>
<td>50–400</td>
<td>0.3 (.01–1.8)</td>
<td>1/301</td>
</tr>
<tr>
<td>Undetectable, threshold &gt;50</td>
<td>0.0 (0–1.7)</td>
<td>0/212</td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.0 (.0–1)</td>
<td>0/2651</td>
</tr>
<tr>
<td>Missing VL</td>
<td>. . .</td>
<td>0/111</td>
</tr>
<tr>
<td>Undetermined child HIV status</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.

⁸ 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)
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)
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)
The HIV–exposed uninfected infant
Issues of concern

• Risk of congenital abnormalities

• Pregnancy outcomes

• Cognitive and neurodevelopmental outcomes

• Altered immune activation
Issues of concern

- Impact of HIV infection vs. ART exposure
  - In utero environment in a HIV-infected woman
  - Long-term exposure to ART in utero and during breastfeeding

- Transient vs. lifelong effects
  - Clinical significance of findings

- **Purpose** – to detect any *major teratogenic effects of ARVs*
- **Information** voluntary and provided by healthcare providers
- **Prospective** before pregnancy outcome is known
- **Updated** after delivery
Data source:

- Enrolls every year ~1300 pregnant women exposed to ARVs, in the US
- Additional 200 from other countries
- Other data from retrospective reports and clinical trials
In reviewing all reported defects... the Registry finds no apparent increases in frequency of specific defects with 1st T exposures and no pattern to suggest a common cause
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

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
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
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° 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
Implications for practice…
Implications for practice

- EFV-based ART recommended for 1st line Rx

- Reassuring data on congenital abnormalities and ART exposure in early pregnancy

  - ...but there’s still a need for continued surveillance
Implications for practice

- Jury still out on adverse pregnancy outcomes
  - Concerns about PTD, LBW and SGA
Implications for practice

• Limited data on long-term outcomes
  – morbidity and mortality
  – neurodevelopmental outcomes

• Limited data on ‘newer ARVs’
Thanks to

Dr. Mnyani
Dr. Hendrix
Dr. Anderson
Dr. Cottrill
Dr. Johnson