Using new ARVs in pregnancy

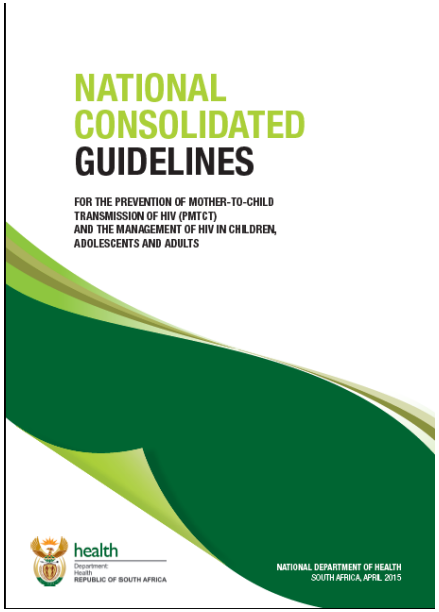
CN Mnyani

SA HIV Clinician's Society Meeting
8 April 2017

Outline

- Current guidelines
- ‘The old…’
  - EFV
  - TDF
- The new…
  - ‘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

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:

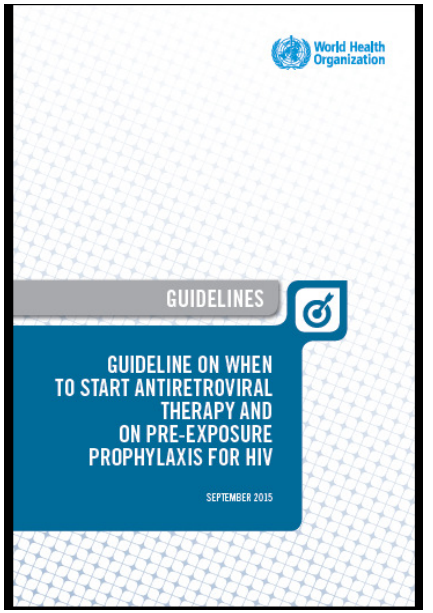
- VL>1000, adherence counselling, repeat VL in 1 month
- 2nd VL undetectable or reduction in VL ≥1 log (10–fold), continue existing regimen
- VL unchanged or increased, switch to 2nd line therapy

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 » At labour/delivery » At the 6 week EPI visit » Every 3 months throughout breastfeeding

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.

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

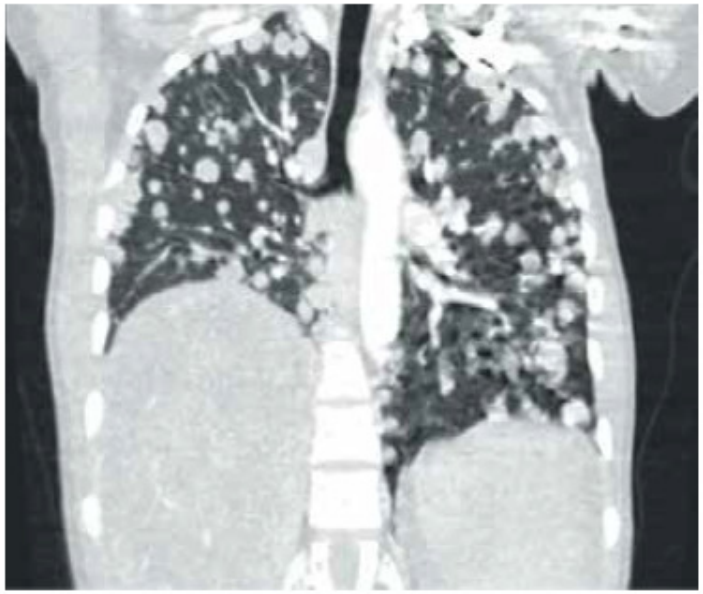


Fig. 1. A CT scan of the chest (coronal view), showing bilateral cannon ball lesions (white lesions) in the lung fields (CT = computed tomography).

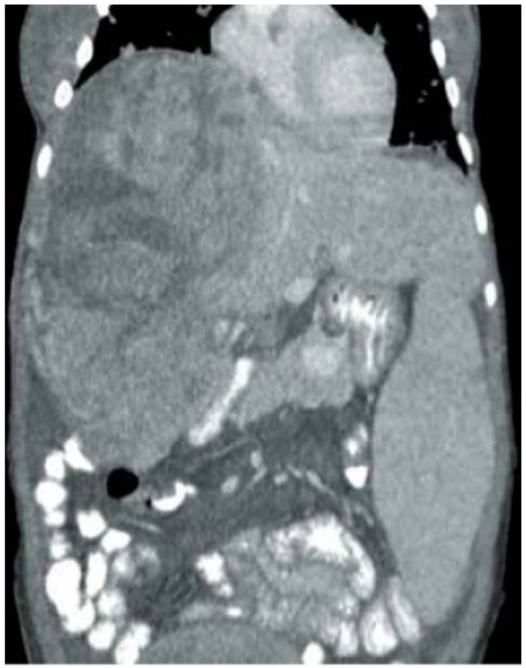


Fig. 2. A CT scan of the abdomen (coronal view), showing a large mass in the right hepatic lobe and splenomegaly. The vascular mass occupies the whole of the right lobe, where dense and hypodense areas are seen within the liver.

Metastatic HCC in pregnancy

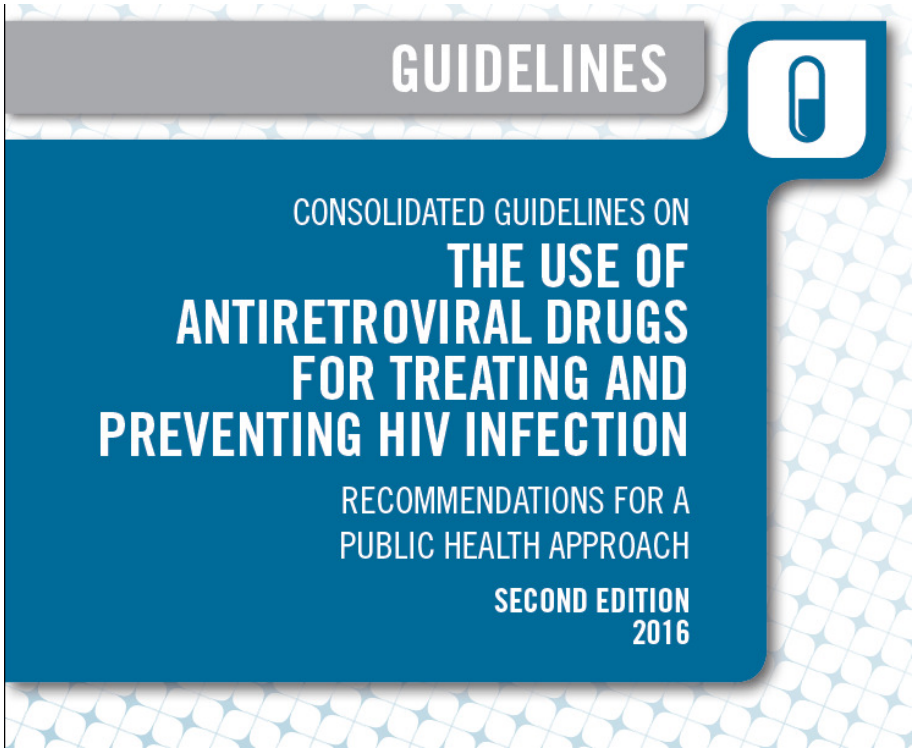
- 30 yo P1G2
- CD4 183; FDC initiated at 23 weeks
- Presented at 32 weeks with preeclampsia, and respiratory symptoms
- Initial D_x of PTB
- Further investigations – metastatic HCC

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.

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

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

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 1st T

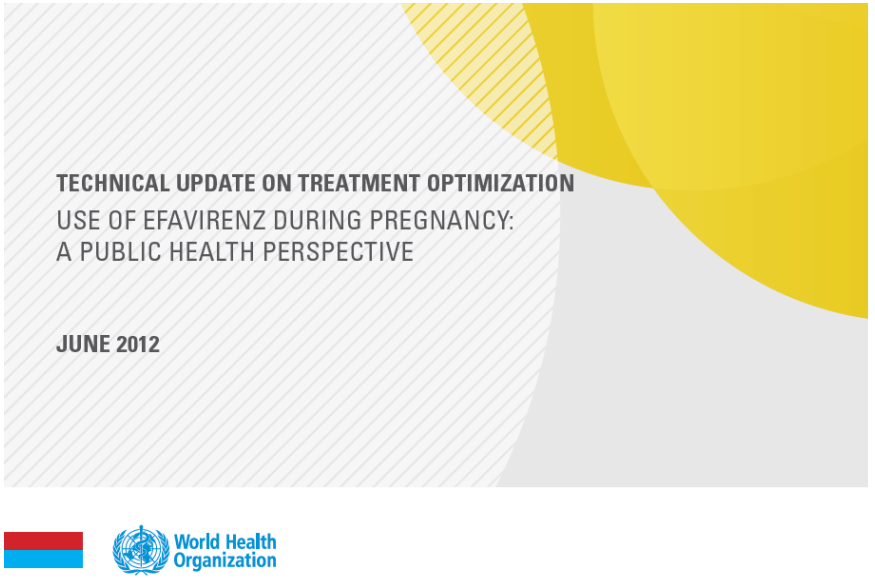
- Evidence was based on animal studies and retrospective case reports of neural tube defects in infants exposed to EFV in utero

❁ … 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[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 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

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

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

PrEP use during 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

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

PrEP

- **Data from pharmacokinetic studies:**

  - ~ 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

World Health Organization

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

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

Perinatal transmission

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: 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*)

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

Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 July 2016*

- 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

APR

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

APR

ADVISORY COMMITTEE CONSENSUS

- 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

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

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, 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’

Case study

- 37yo P3G4, 8 weeks pregnant, HIV+ and not on ART
- Prior ART use in previous pregnancy
- Creatinine 95; CD4 600
- Antenatal, intrapartum, postpartum management