



ART during pregnancy – programmatic issues

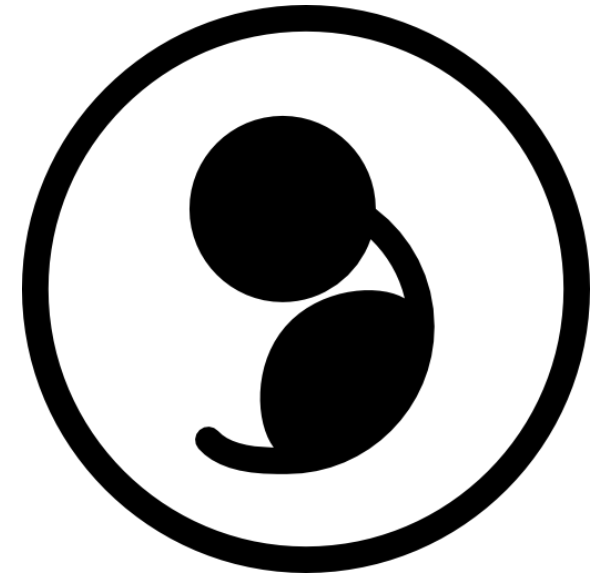
Coceka Nandipha Mnyani

26 October 2018



Outline

- Engagement and retention in care
- The 'forgotten' psychosocial aspect of care
- Routine maternal monitoring
- Fetal surveillance
 - The outliers...



Access to care

Indicator	FY 2014/15	FY 2015/16	FY 2016/17*	FY 2016/17 Target
Antenatal 1st visit before 20 weeks:				
Numerator: Antenatal 1st visit before 20 weeks	53.8%	61.2%	65.5%	60%
Denominator: Antenatal 1st visits, total				

SAHR 2017

DHIS data

Retention in HIV Care During Pregnancy and the Postpartum Period in the Option B+ Era: Systematic Review and Meta-Analysis of Studies in Africa

Brandon A. Knettel, PhD, Cody Cichowitz, BS,*† James Samwel Ngocho, MD,§
Elizabeth T. Knippler, BA,* Lilian N. Chumba, MD,* Blandina T. Mmbaga, MD, PhD,*†§ and
Melissa H. Watt, PhD**

(J Acquir Immune Defic Syndr 2018;77:427–438)

Conclusions: Retention rates in prevention of mother-to-child transmission under option B+ were below those of the general adult population, necessitating interventions targeting the complex circumstances of women initiating care under option B+. Improved and standardized procedures to track and report retention are needed to

Retention in care

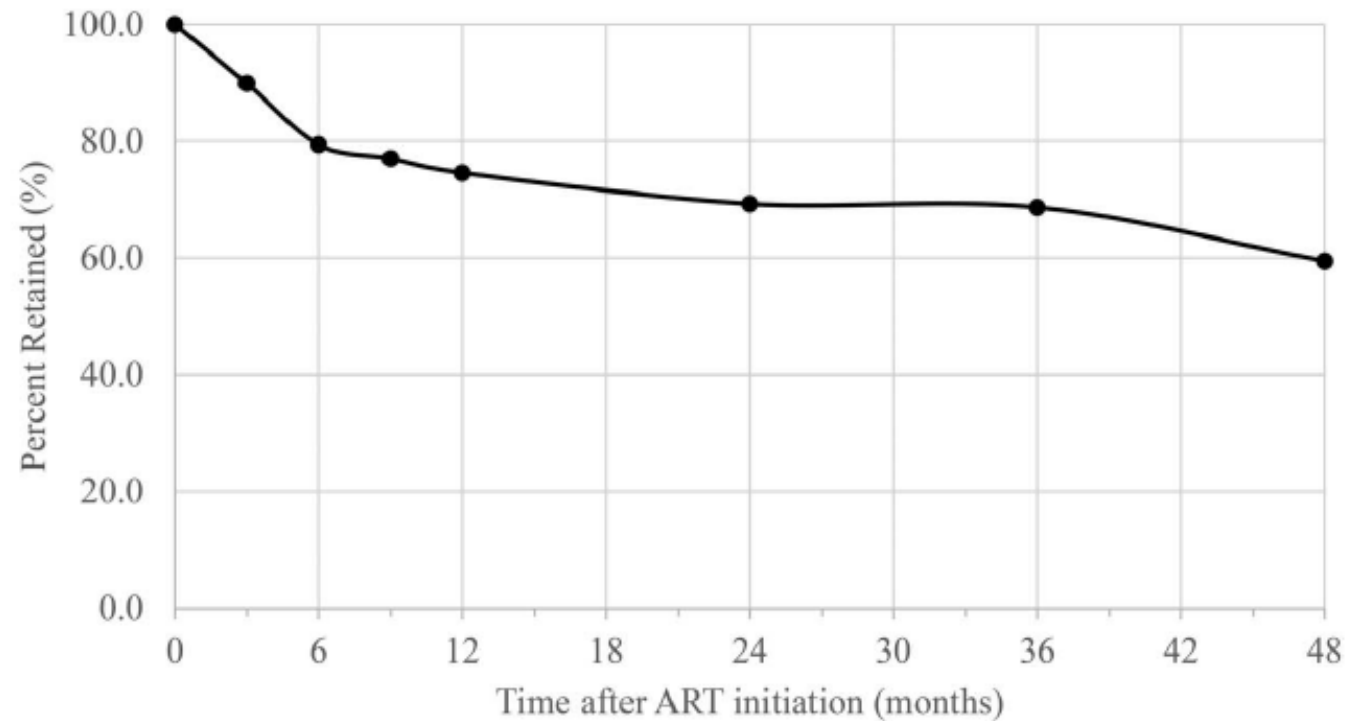


FIGURE 3. Cumulative probability of retention in care.

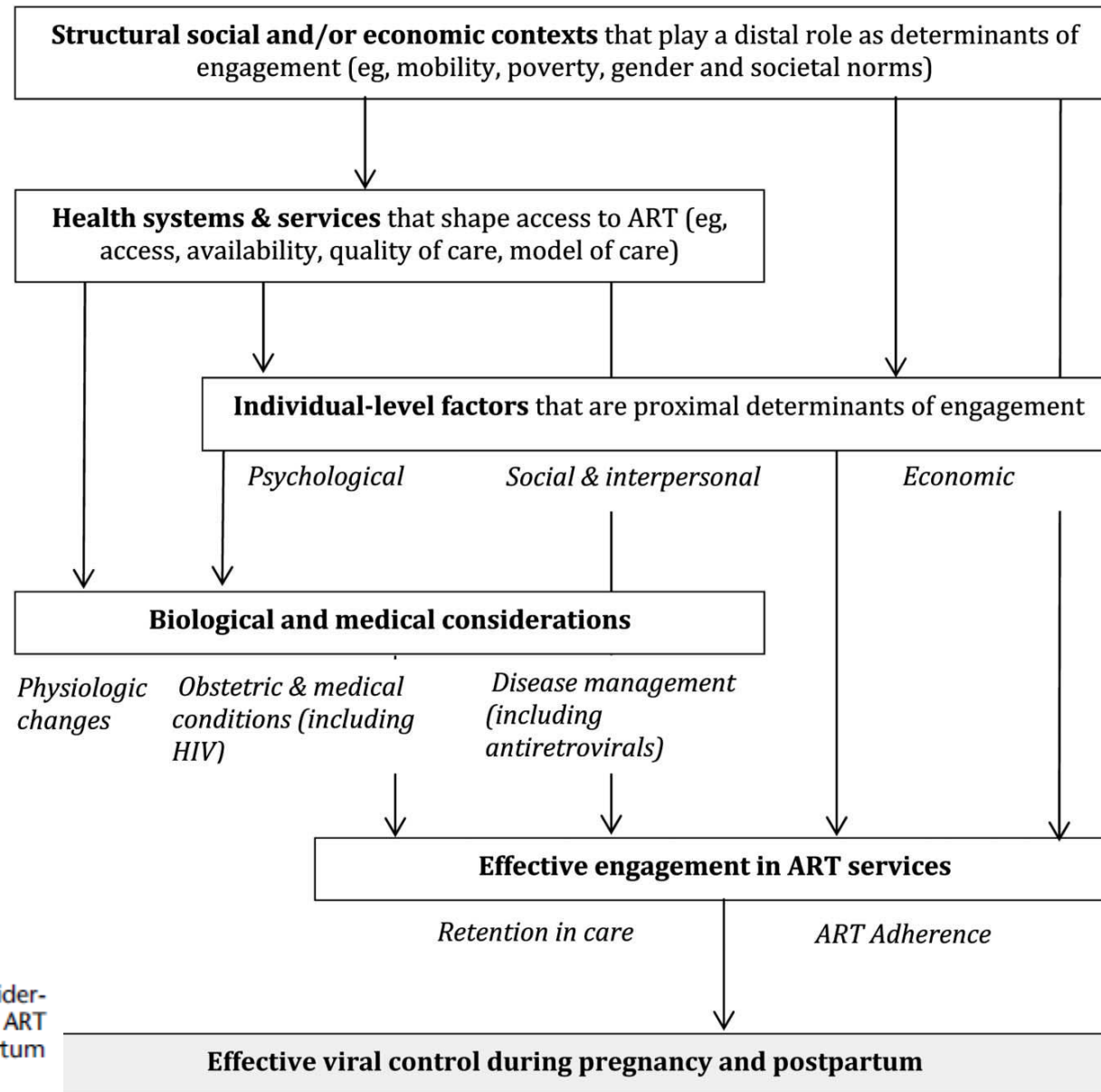


FIGURE 3. Conceptual model for considering determinants of engagement in ART services in pregnant and postpartum women.

TABLE 1. Examples of Intervention Strategies Proposed, Developed, or Evaluated to Enhance Engagement in ART Services by Pregnant and/or Postpartum Women Receiving ART

Enhanced patient education and counseling
Integration of ART and MCH services: antenatal and/or postnatal
Peer support programs and patient navigators
Community health worker/home-based care programs
Family-focused ART services
Male partner involvement
Text reminders and mHealth interventions
Directly observed therapy
Community-based ART delivery and “adherence clubs”
Health systems quality improvement
Conditional cash transfers
Intensive case managers

The 'forgotten' psychosocial aspect of care

- Depression, HIV-related stigma and low levels of social support prevalent
- May adversely affect health and treatment outcomes among HIV-infected pregnant women

(Brittain et al. *AIDS and Behavior* 2017;21(1):274–282)

- Also affect infant treatment outcomes in cases of MTCT

(Mvo et al. *S Afr Med J* 2018;108(8):609-610)

The 'forgotten' psychosocial aspect of care

Unmet needs of high-risk mothers reduce success of antiretroviral treatment in HIV-infected infants

S Afr Med J 2018;108(8):609-610.

Key factors:

- Non-disclosure of HIV status
- Dependence on partners for basic needs
- Lack of support
- Domestic violence

Medication adherence in pregnant women with human immunodeficiency virus receiving antiretroviral therapy in sub-Saharan Africa: a systematic review

Olumuyiwa Omonaiye^{1*}, Snezana Kusljic², Pat Nicholson¹ and Elizabeth Manias¹

Omonaiye et al. *BMC Public Health* (2018) 18:805

<https://doi.org/10.1186/s12889-018-5651-y>

Conclusion: This review revealed several barriers and enablers of adherence among pregnant women taking ART in sub-Saharan Africa. Major barriers included the fear of HIV infection status disclosure to partners and family members, stigma and discrimination. A major enabler of adherence in women taking ART was women's knowledge of their HIV status prior to becoming pregnant. Enhanced effort is needed to facilitate women's knowledge of their HIV status before pregnancy to enable disease acceptance and management, and to support pregnant women and her partner and family in dealing with fear, stigma and discrimination about HIV.

[Opinion / Columnists](#)

HIV/AIDS

JONNY STEINBERG: Despair multiplies when we are silenced by secrecy

The fear and silence surrounding the HIV/AIDS epidemic compounds the crisis

BL PREMIUM

16 February 2018 - 05:38 Jonny Steinberg



Routine maternal monitoring

- Drug toxicity
- Viral suppression
- TB screening
 - ☐ IPT initiation

Viral suppression

- During pregnancy
 - Intrapartum
 - Postpartum during breastfeeding
 - Lifelong...

Viraemia before, during and after pregnancy in HIV-infected women on antiretroviral therapy in rural KwaZulu-Natal, South Africa, 2010–2015

Terusha Chetty^{1,2}, Marie-Louise Newell³, Claire Thorne⁴ and Anna Coutsooudis⁵

Tropical Medicine and International Health

VOLUME 23 NO 1 PP 79–91 JANUARY 2018

Overall (*N* = 1425)

Viral load (copies/ml)	Before pregnancy <i>n</i> = 988 (%)	Pregnancy <i>n</i> = 854 (%)	Post-partum		
			6 months <i>n</i> = 527 (%)	12 months <i>n</i> = 437 (%)	24 months <i>n</i> = 656 (%)
<50	810 (82.0)	657 (76.9)	406 (77.0)	330 (75.5)	497 (75.8)
50–999	67 (6.8)	67 (7.8)	38 (7.2)	29 (6.6)	50 (7.6)
≥1000	111 (11.2)	130 (15.2)	83 (15.7)	78 (17.8)	109 (16.6)

Frequency of Viremic Episodes in HIV-Infected Women Initiating Antiretroviral Therapy During Pregnancy: A Cohort Study

Landon Myer,^{1,2} Lorna Dunning,¹ Maia Lesosky,¹ Nei-Yuan Hsiao,³ Tamsin Phillips,^{1,2} Greg Petro,⁴ Allison Zerbe,⁵ James A. McIntyre,^{1,6} and Elaine J. Abrams^{5,7}

Clinical Infectious Diseases® 2017;64(4):422–7

Cohort of 523 women initiating ART during pregnancy, and followed up for 12 months postpartum

Analyses described the incidence of **major (>1000 copies/mL) and minor (50–1000 copies/mL) viraemic episodes**, and factors associated with major viraemic episodes

Results

- 70% maintained viral suppression throughout follow-up
- 8% experienced minor viraemic episodes only
- At least 1 major viraemic episode documented in 22% of women
- Major viraemic episodes after initial viral suppression associated with:
 - younger age, ART initiation during the 3rd trimester, previous defaulting on ART, and postpartum follow-up

TB screening and IPT

TB screening

Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis

Yohhei Hamada, Johnny Lujan, Karl Schenkel, Nathan Ford, Haileyesus Getahun



Lancet HIV 2018; 5: e515–23

Published Online

August 20, 2018

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S2352-3018(18)30137-1)

[S2352-3018\(18\)30137-1](http://dx.doi.org/10.1016/S2352-3018(18)30137-1)

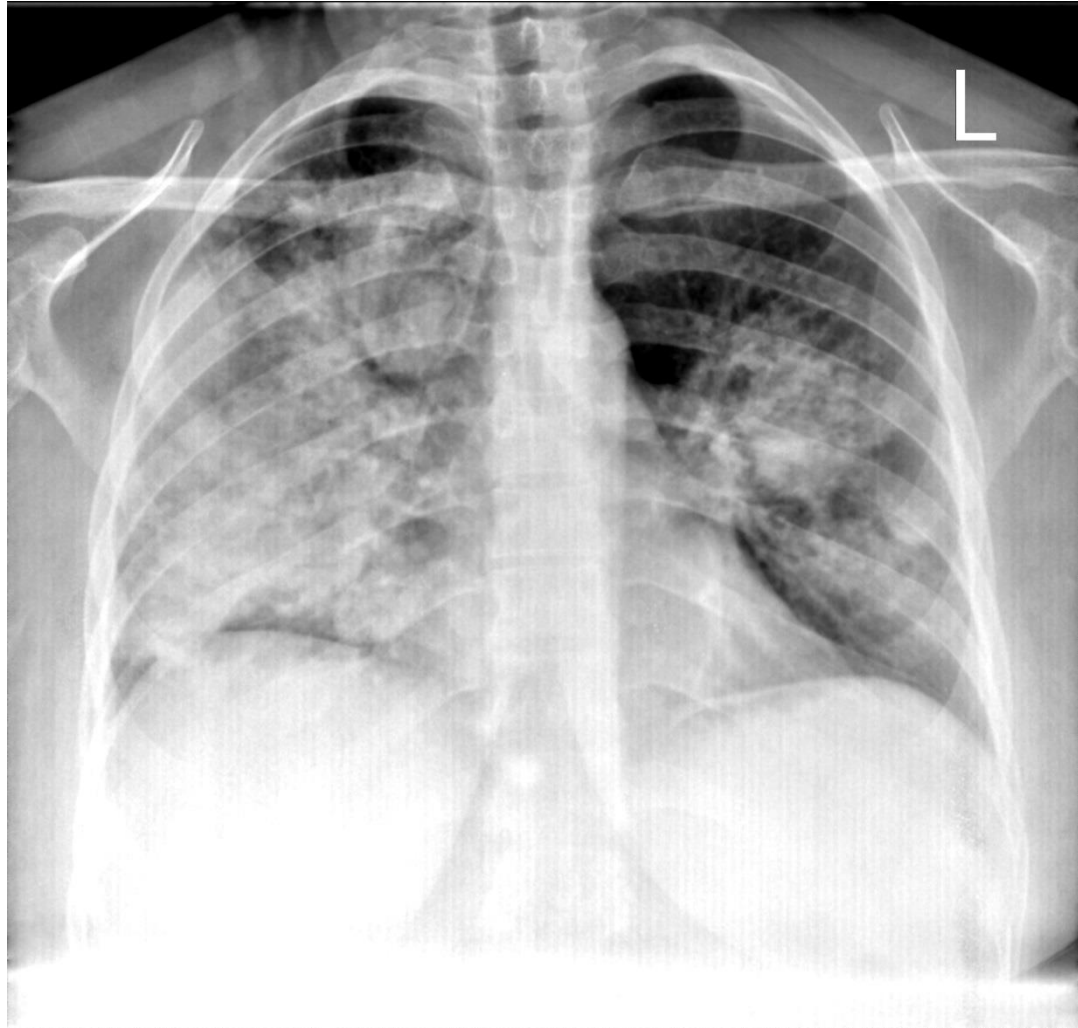
Interpretation Our review suggested a lower sensitivity of the WHO four-symptom screening rule among people with HIV who are on ART than in those who are ART naive. The addition of chest radiography could improve the screening rule in people living with HIV who are on ART, provided it does not pose a barrier to preventive treatment.

Delayed diagnosis

- 34 yo P2, no previous TB
- Booked at 15 weeks; TB screening not documented
- Known HIV+ on ART since 2011 – CD4 466; VL LDL
- Seen 5 weeks later – dry cough and fever
- No TB contact, no constitutional symptoms
- Discharged on oral antibiotics

Follow-up two weeks later

- Night sweats and LOW
- Xpert® - TB confirmed
- IUFD



BUT...

...not all lung infiltrates are TB

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,^{1,2} MD, FCOG (SA), Dip Fet Med

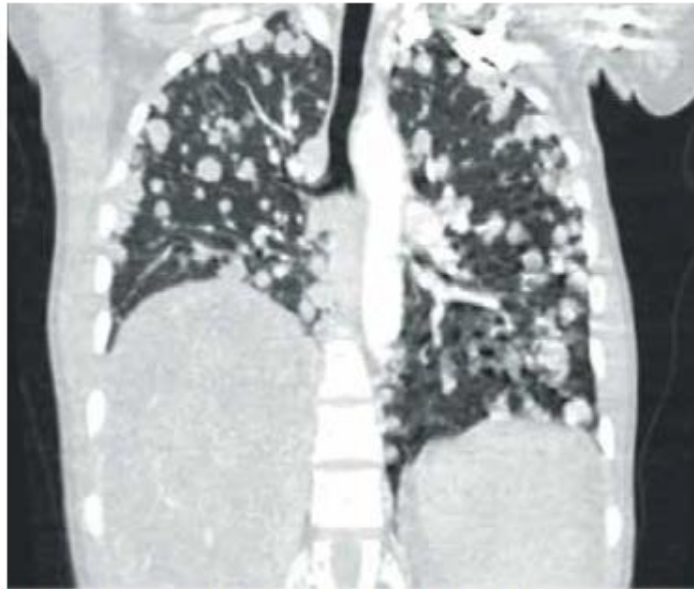


Fig. 1. A CT scan of the chest (coronal view), showing bilateral cannon ball lesions (white lesions) in the lung fields (CT = computed tomography).

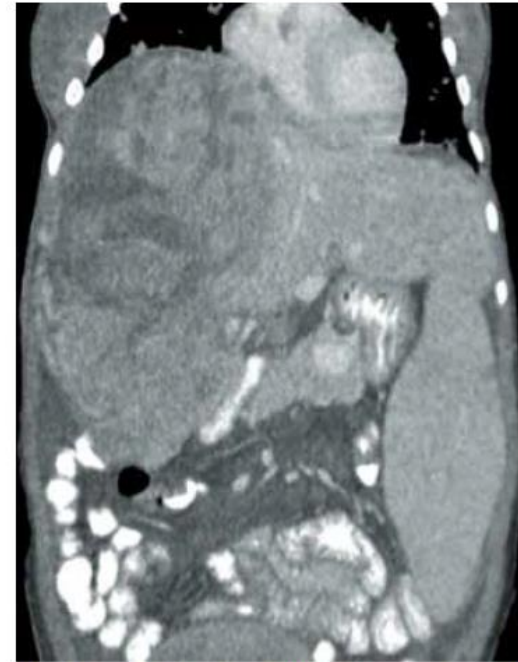
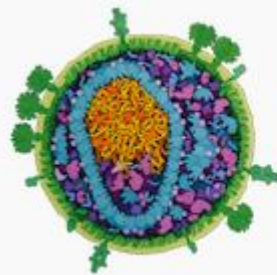


Fig. 2. A CT scan of the abdomen (coronal view), showing a large mass in the right hepatic lobe and splenomegaly. The vascular mass occupies the whole of the right lobe, where dense and hypodense areas are seen within the liver.

RANDOMIZED TRIAL OF SAFETY OF ISONIAZID PREVENTIVE THERAPY DURING OR AFTER PREGNANCY

Author(s):

Amita Gupta¹, Grace Montepiedra², Lisa Aaron², Gerhard Theron³, Katie McCarthy⁴, Carolyne Onyango-Makumbi⁵, Tsungai Chipato⁶, Gaerolwe Masheto⁷, Katherine Shin⁸, Bonnie Zimmer⁹, Timothy R. Sterling¹⁰, Nahida Chakhtoura¹¹, Patrick Jean-Philippe⁸, Adriana Weinberg¹²



CROI

Conference on Retroviruses
and Opportunistic Infections

Boston, Massachusetts
March 4-7, 2018

Safety of IPT

- Double-blind, placebo-controlled trial – TB-endemic areas in Africa, Asia, and Haiti
- Compared initiation of 28 weeks of IPT
 - 6 Arm A: antepartum – 14-≤24 weeks (1/3) or 24-34 weeks (2/3)
 - 6 Arm B: 12 weeks postpartum
- Mother-infant pairs followed to week 48 PP

Safety of IPT

- 956 enrolled; median CD4 count 493
- 955 on ART – 85% EFV-based; 63% VL LDL
- ~30% had all-cause \geq grade 3 maternal adverse events, 145 in arm A and 136 in arm B
- No significant differences by treatment arm

Safety of IPT

- 6 maternal deaths – 2 in the AP arm, 4 in the PP IPT arm
 - all occurred postpartum
- 4 due to liver failure (3 treatment related)
- Age: 24 – 38; CD4 402 – 609
- All on EFV/TDF/FTC started before IPT



Perspective

Protecting Mothers and Babies — A Delicate Balancing Act

Sonja A. Rasmussen, M.D., Wanda Barfield, M.D., M.P.H., and Margaret A. Honein, Ph.D., M.P.H.

September 6, 2018

N Engl J Med 2018; 379:907-909

A delicate balancing act...

NB factors when considering choice of ARVs:

- Risk of teratogenicity
- Risk of MTCT
- Extent and timing of viral suppression
- Likelihood of developing resistance
- Side effects that may impact treatment compliance
- Cost

A delicate balancing act...

Treatment of HIV-infected pregnant women complicated:

- PMTCT AND treatment of maternal disease
- Most clinical trials on safety and efficacy of new drugs exclude pregnant women
- If women do become pregnant, drugs often discontinued

Sobering fact

* ‘A review of drugs approved by the FDA between 2000 and 2010 revealed that the teratogenic risk in human pregnancy was **“undetermined” for more than 97% of these drugs.**’

* include different types of drugs, not just ARVs



Statement on DTG – Geneva 18 May 2018

Potential safety issue affecting women living with HIV using dolutegravir at the time of conception



The United States President's Emergency Plan for AIDS Relief

15 YEARS OF SAVING LIVES THROUGH AMERICAN GENEROSITY AND PARTNERSHIPS
PEPFAR Statement on Potential Safety Issue Affecting Women Living with HIV Using Dolutegravir at the Time of Conception
May 18, 2018



[BHIVA statement on Potential Safety Signal in Infants Born to Women Conceiving on Dolutegravir \(on behalf of the BHIVA HIV in Pregnancy Guidelines Committee\)](#)

Tuesday 22nd May 2018

FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

[05-18-2018]



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir

While EMA review is ongoing, dolutegravir should not be used in women seeking to become pregnant



<https://blogs.jwatch.org/hiv-id-observations/index.php/dolutegravir-pregnancy-warning-important-now/2018/05/20/>

**Why the Dolutegravir Pregnancy Warning is Important
— and What We Should Do Now**

10/10/2018

https://www.medscape.com/viewarticle/903041_print

www.medscape.com

Efavirenz in Pregnancy Tied to Neurologic Risk in Children

Marcia Frellick

October 05, 2018

EFV and neurological disorders

- 3 747 HIV-exposed uninfected children enrolled in the SMARTT study
- Average age of D_x with a neurologic condition was 2 years (n=237)
- Children more likely to be diagnosed with a neurologic condition
 - such as microcephaly, seizures, or eye abnormalities, when maternal ART regimen included EFV

EFV and neurological disorders

- Association between neurologic conditions and EFV was statistically significant when sensitivity analyses were:
 - limited to children enrolled before or shortly after birth (aRR 1.80; 95% CI, 1.06 - 3.05)
 - when children with confirmed congenital anomalies were excluded (aRR, 1.66; 95% CI, 1.02 - 2.64)

EFV and neurological disorders

- ‘A single study, and more will be needed to better guide clinicians’
- Investigator Claudia Crowell, from Seattle Children's Hospital and the University of Washington, cautioned. ID Week 2018

Adverse pregnancy outcomes

- Fetal surveillance
- Neonatal services



Adverse pregnancy outcomes

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

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 Kanfers, Edward J Mills, Françoise Renaud, Shaffiq Essajee, Meg C Doherty, Lynne M Mofenson

Lancet HIV 2017; 4: e21–30



PLOS ONE | <https://doi.org/10.1371/journal.pone.0191389> January 19, 2018

RESEARCH ARTICLE

Preconception use of cART by HIV-positive pregnant women increases the risk of infants being born small for gestational age

Ingrid J. M. Snijdwind¹, Colette Smit², Mieke H. Godfried³, Rachel Bakker⁴, Jeannine F. J. B. Nellen³, Vincent W. V. Jaddoe^{4,5}, Elisabeth van Leeuwen⁶, Peter Reiss^{2,3,7}, Eric A. P. Steegers^{4,8}, Marchina E. van der Ende^{1*}

Results

Lancet HIV 2017; 4: e21–30

- 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

- Pre-conception cART: SGA (BW <10th centile) was 27.3% vs 21.5% in women who started cART after conception
- Risk of SGA higher with pre-conception PI-based cART (28.6%) compared to PI-based regimen started after conception (20.9%, $p = 0.01$)
- No difference seen with NNRTI-based ART



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

FREE PREVIEW

Birth Outcomes for Pregnant Women with HIV Using Tenofovir–Emtricitabine

Kathryn Rough, Sc.D., George R. Seage, III, D.Sc., M.P.H., Paige L. Williams, Ph.D., Sonia Hernandez-Diaz, M.D., Dr.P.H., Yanling Huo, M.S., Ellen G. Chadwick, M.D., Judith S. Currier, M.D., Risa M. Hoffman, M.D., Emily Barr, C.P.N.P., C.N.M., M.S.N., David E. Shapiro, Ph.D., and Kunjal Patel, D.Sc., M.P.H.et al., for the PHACS and the IMPAACT P1025 Study Teams

April 26, 2018

N Engl J Med 2018; 378:1593-1603

Birth outcomes with TDF/FTC

- Data from two US-based cohort studies

Compared risk of adverse birth outcomes among infants with in utero exposure to:

- ☐ ZDV–3TC–LPV/r,
- ☐ TDF–FTC–LPV/r,
- ☐ or TDF–FTC with ritonavir-boosted atazanavir (ATV/r)

Birth outcomes with TDF/FTC

- Evaluated risk of PTB (<37w), very PTB(<34w)
- LBW (<2500g), very LBW (<1500g)

CONCLUSIONS The risk of adverse birth outcomes was not higher with TDF–FTC–LPV/r than with ZDV–3TC–LPV/r or TDF–FTC–ATV/r among HIV-infected women and their infants in the United States, although power was limited for some comparisons. (Funded by the National Institutes of Health and others.)



Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study



Rebecca Zash, Denise L Jacobson, Modiegi Diseko, Gloria Mayondi, Mompoti Mmalane, Max Essex, Tendani Gaolethe, Chipso Petlo, Shahin Lockman, Lewis B Holmes, Joseph Makhema, Roger L Shapiro



**Lancet Glob Health 2018;
6: e804-10**

The 1° outcomes were the combined endpoints of any adverse outcome – stillbirth, preterm birth, SGA, neonatal death

Severe adverse outcomes – stillbirth, neonatal death, very preterm birth, very SGA

Safety of DTG-based vs. EFV-based ART

- 1 729 pregnant women on DTG-based ART and 4 593 on EFV-based ART
- Risk for any adverse birth outcome among women on DTG vs. EFV was similar:
 - 33.2% vs 35.0%; aRR 0.95, 95% CI 0.88–1.03
- as was the risk of any severe birth outcome
 - 10.7% vs 11.3%; 0.94, 0.81–1.11

20 OCTOBER 2018

Shocking prevalence of pregnancies, HIV infections in 9-19 year olds in Limpopo village

Newly released statistics from rural clinics outside of Thohoyandou show that children as young as nine are falling pregnant or acquiring HIV infections.



36 pupils pregnant, 31 infected with HIV in Mulenzhe – health dept

2018-10-17 19:49

Canny Maphanga

news24

"Look, these are not the most shocking numbers, three months ago we saw higher numbers in another area," he said.



Thank you...

