Using new ARVs in pregnancy

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Slides courtesy of Linda-Gail Bekker
With thanks to CN Mnyani
SA HIV Clinician's Society Meeting
5 August 2017

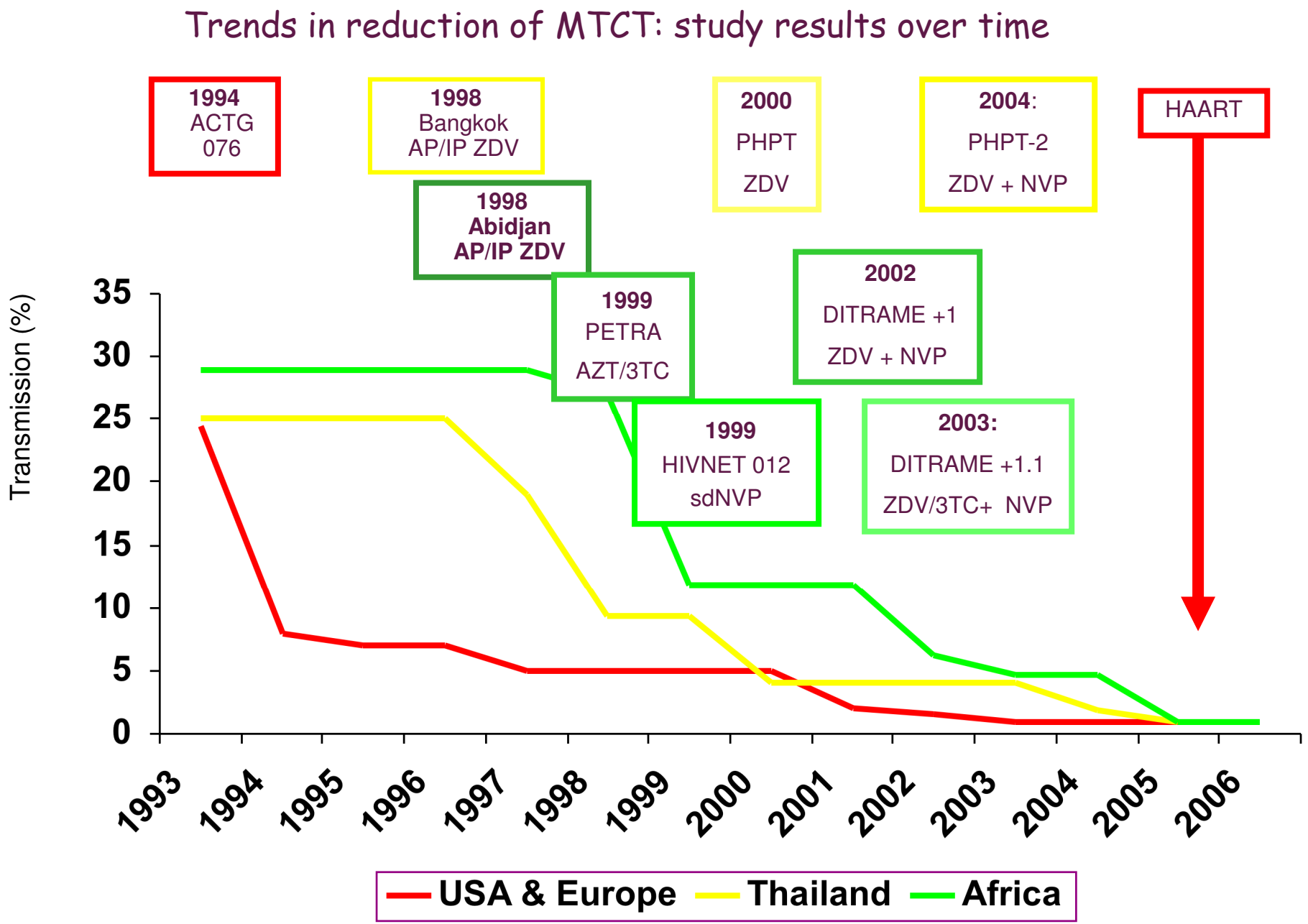
“We have effective drugs.

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.”

Ban Ki Moon
NY, September 2009


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

% Risk of transmission without intervention

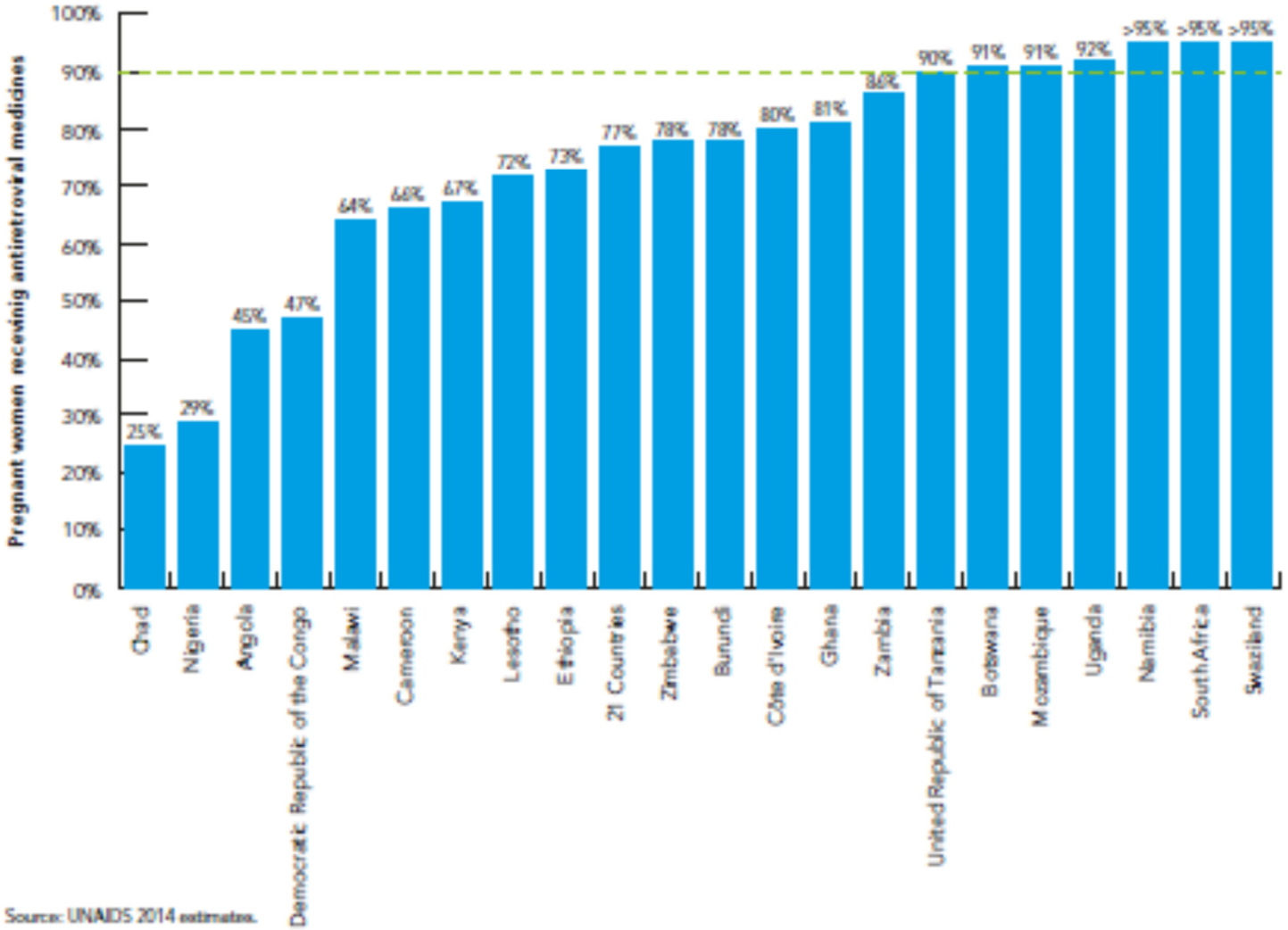
Transmission time	No BF	BF 6/12	BF 24/12	
During Pregnancy	5-10	5-10	5-10	
During labour	10-15	10-15	10-15	
During BF	0	5-10	15-20	
OVERALL	15-25	20-35	30-45	

2015 UNAIDS Progress report

- 21 high HIV burden countries in 2014
- 3 countries have achieved >95% PMTCT coverage
  - South Africa, Namibia, Swaziland
- SA and Botswana have lowest estimated transmission rates of 4% (includes breastfeeding transmission)
- Before the new National PMTCT policy adopting B+ option
- Transmission rates should now be much lower in SA as we are covering breastfeeding

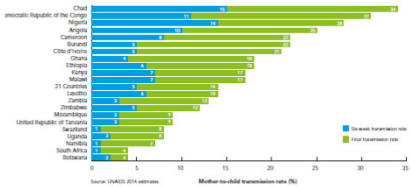
Figure 4

Percentage of pregnant women living with HIV receiving antiretroviral medicines to prevent mother-to-child transmission in 21 Global Plan priority countries, 2014



Source: UNAIDS 2014 estimates.

Figure 5
Six-week and final mother-to-child transmission rates in 21 Global Plan priority countries, 2014



How do we get to Zero?

<u>Need to address high risk mother baby pairs</u>

- HIV pos woman on ARVs but failing and not monitored with VL or not changed to new regimen
- Untested/ Unbooked mother
- HIV negative pregnant/breastfeeding woman who seroconverts with high risk of acute transmission of HIV

SA national guidelines

- All pregnant women to be tested for HIV at booking
- All HIV positive pregnant and breastfeeding women to be initiated Day 1 and have first VL in 3 months
- All HIV pos pregnant and breastfeeding women on ARVs at booking to have VL taken immediately
- All women on regimen 1 and not suppressing despite adherence support for one month are to be changed to regimen 2
- All tested, treated and monitored and suppressed!

SA guidelines

- From January 2015, all HIV-infected pregnant and breastfeeding women initiated on an EFV-based FDC
- TDF/FTC/EFV fixed dose combination tablet
- 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/3TC + TDF + LPV/r (4 drugs if HBV co-infected)
- *In practice just use TDF FTC LPV/r as individual TDF hard to access!!*

Failing on a d4T or AZT-based 1st line regimen

- TDF /FTC + LPV/r

- Dyslipidaemia or diarrhoea associated with LPV/r switch 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
- Easy way to assess 1 log drop is to divide 1st VL by 10 and the second VL must be lower than that….

- 2nd VL less than 1 log drop……. switch to 2nd line therapy

SA guidelines

Unbooked HIV pos mother presenting in labour

Start FDC immediately

If for emergency C/S TDF FTC 1 tab stat
NVP stat dose

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

Other guidelines

- WHO British and USA guidelines all recommend:
- TDF/FTC/EFV as regimen 1 throughout pregnancy
- WHO suggests 2 NRTIs plus either Atazanavir/rit or LPV/r as second line

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

Safety and effectiveness of current and new ARVs in pregnancy

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 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

- No evidence of teratogenic effects of EFV in women who used EFV in all 3 trimesters

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.

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 infants

Conclusions

- TDF containing ART in pregnancy appears to be generally safe for women and their infants

Future possibilities for optimisation of ARV using new drugs

- Some studies on adding integrase inhibitors to a new regimen in patients with uncontrolled VL after 20 weeks gestation
- Some evidence of rapid virological suppression
- Very limited data on safety of raltegravir
- No data on the safety of Dolutegravir in pregnant women

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

Possible new ARVs in pregnant women in SA?

- No recommendations as yet for using
  - Raltegravir as 3rd or 4th drug in optimised regimen? difficult to access in public sector as it is restricted to Regimen 3
  - Dolutegravir no evidence on safety and effectiveness in pregnancy
  - EFV 400mg no evidence on efficacy in pregnancy
  - Tenofovir alfenamide TAF 50mg still no evidence in pregnancy of effectiveness

Practical implications in SA

- Monitor VLs in HIV pos pregnant women on ARVs
- Reg 1 with TDF FTC EFV is a very good and safe regimen with good suppression of VL if taken correctly
- If VL not suppressing with regimen 1
- Change immediately to Regimen 2 with either AZT 3TC OR TDF FTC Plus Lpv/rit
- Safe very effective regimen
- Raltegravir not easily available
- PI based regimens are very effective n reducing VL
- Every reduction in VL reduces chance of transmission!

Practical implications in SA

- Pregnant or breastfeeding women who are not suppressed on Regimen 2 with Lopinavir/r or Atazanavir/ritonavir
- This is an emergency!
- Check for intolerance to LPV? If so change immediately to Atazanavir/rit
- Refer urgently to ARV specialist
- Urgent genotyping to exclude resistance to LPV

PrEP use during pregnancy

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
    - 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.

WHO recommendations

- PrEP appears to be safe in pregnancy and breastfeeding
  - Extrapolation from studies on the use of TDF and FTC as part of ART in HIV pos pregnant women
- Women who are at substantial risk of HIV transmission during pregnancy or breastfeeding should be offered PrEP
- Risk assessment and other prevention interventions extremely important

PrEP

- PrEP regimen TDF/FTC 1 tab daily
- Ongoing monitoring
  - 3 monthly Creatinine and HIV test
- Should be considered in high risk situations
- Part of other prevention interventions
  - Partner testing
  - ARVs and VL monitoring for infected partners
  - Decreasing risky behaviour (needle exchanges, decreasing number of partners)

Risk assessments for PrEP in pregnant women

- Number of present and previous sexual partners
- Presence of vaginal infections
- Positive VDRL
- Domestic violence

All these factors increase risk of HIV acquisition

SA NDOH 2016 policy on PrEP

- PrEP recommended ONLY for certain at high risk populations
  - MSM with multiple partners
  - Sex workers
- No mention of PrEP in pregnancy
- No policy to offer PrEP to HIV neg pregnant women
- Individual decision based on risk assessment

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*)

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*)

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*)

Conclusions

- GOOD news!
- We can abolish perinatal transmission if we can get women on ARVS early in the pregnancy and VL LDL before delivery
- ??BAD News
- What is the evidence around adverse effect of ARVs on pregnancy outcomes, fetal abnormalities and neonatal and other infant outcomes

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

- 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, 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
- Role of underlying HIV chronic immune activation uncertain

Conclusions?

- ARVs can abolish MTCT
- ARVs *may* cause slight increase in LBW and Pre term deliveries
- HIV exposed but noninfected children *may* have increased illnesses and mortality
- Is this the effect of
  - ARVs?
  - Ongoing HIV inflammation?
  - Socioeconomic factors?

Summary

- Regimen 1 TDF FTC EFV good evidence, safe
- Prompt change to Regimen 2 AZT 3TC LPV/r (or ATZ/r) if mother failing to suppress on Reg 1
- If ARVs started early and VL LDL can *abolish transmission*
- Uncertain evidence of poorer pregnancy and neonatal outcomes due to ARVs
- No good evidence on new drugs like Dolutegravir, Tenofovir alafenamide in pregnant women

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