MTN Delivers: 14 Years of Pushing for HIV Prevention Research with Pregnant and Breastfeeding Populations

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2006: A bit of a black box
We were a new network with questions!

Will products be safe for mothers and babies in pregnancy?

Will products be safe for mothers and babies during breastfeeding (BF)?

Will a chemoprevention pregnancy registry be feasible?

Will mothers use HIV prevention products during pregnancy and BF?

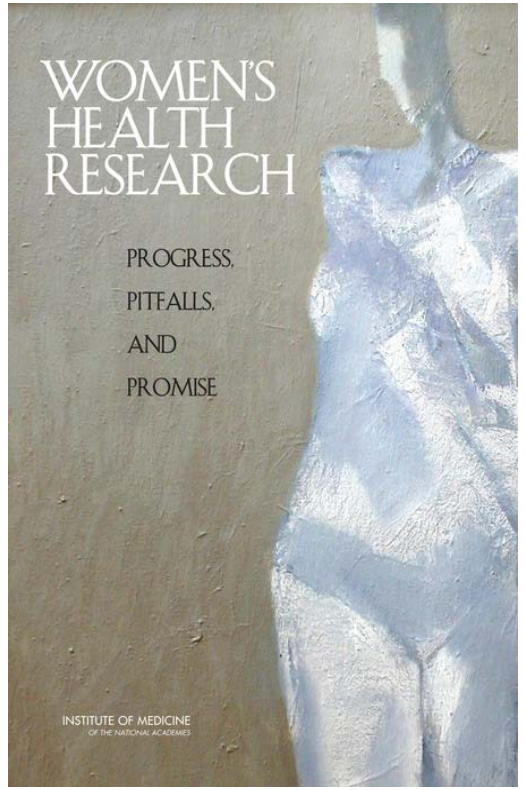
Will topically administered ARVs cross the placental barrier?

Will topically administered ARVs pass into human breast milk?

Will we even be able to understand product safety when background rates of safety events are challenging to capture in local context?

This research is challenging! Why did we bother?

- Pregnant and BF populations largely excluded from trial participation and its associated "evidence benefits"
- Clinical practice without evidence base
- Ethical obligations
  - Pregnant and BF women need safe, effective therapies
  - Untested therapies jeopardize safety
  - Justice
- <10% medications approved by FDA since 1980 have enough data to determine risk for birth defects



Prevention can't exclude pregnant and breastfeeding women, especially given higher risk for HIV acquisition

	Total Fertility Rate (births/woman)	% infants ever breastfed
Malawi	5.1	97.7
RSA	2.4	87.4
Uganda	5.8	98.2
Zimbabwe	3.9	98.1

- HIV transmission probability
  - 1.05/1,000 sex acts (non-pregnant)
  - 2.19 in early pregnancy
  - 2.97 in late pregnancy
  - 4.18 in postpartum women
- Thus, risk higher vs. non-pregnant time
  - Late pregnancy (aRR 2.82, p=0.01)
  - Postpartum (aRR 3.97, p=0.01)

TFR, World Bank, 2014; Malawi, 2015-6 DHS; South Africa, 1998 DHS; Uganda, 2011 DHS; Zimbabwe, 2015 DHS

Thomson KA, et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. *J Infect Dis*. 2018;218(1):16–25.

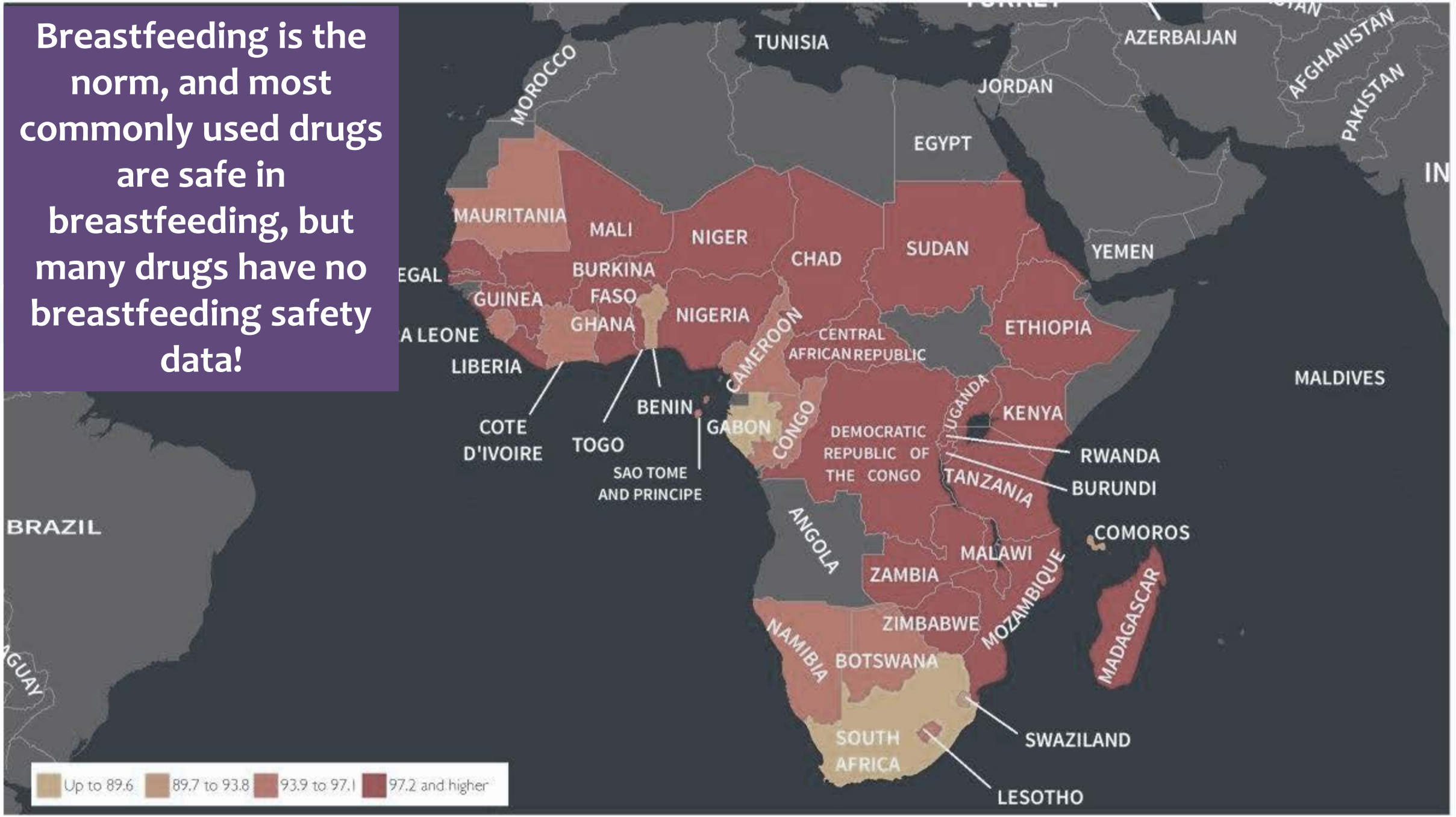
Breastfeeding data are critical

- Many safety/pharmacokinetic (PK) studies exclude breastfeeding (BF)
- WHO recommends exclusive BF 6 months, then 2+ years
- Possible ↑ risk HIV acquisition
- High total fertility rates and long BF in areas with ↑HIV incidence
- FDA recommends BF studies

http://www.who.int/topics/breastfeeding/en/.

De Schacht, C. et al. High HIV incidence in the postpartum period sustains vertical transmission in settings with generalized epidemics: a cohort study in Southern Mozambique. JIAS. 2014; 17:18808.

https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf.


Children ever breastfed
Breastfeeding is the norm, and most commonly used drugs are safe in breastfeeding, but many drugs have no breastfeeding safety data!
TUNISIA
MOROCCO
AZERBAIJAN
AFGHANISTAN
PAKISTAN
JORDAN
EGYPT
MAURITANIA
MALI
NIGER
CHAD
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BOTSWANA
SOUTH AFRICA
SWAZILAND
LESOTHO
Up to 89.6
89.7 to 93.8
93.9 to 97.1
97.2 and higher

The MTN approach, including for studies in pregnant and breastfeeding populations

Design studies to support licensure and regulatory approval of HIV prevention products for populations most vulnerable to HIV

Collaborate with clinical sites across the world on clinical trials

International investigators, community partners, industry

Work together to evaluate promising products

Stakeholder/community engagement

Key civil society groups and stakeholders

MTN-002: Phase 1 single-dose TFV 1% gel

- Pharmacokinetics and placental transfer of TFV 1% vaginal gel among healthy term gravidas
- N=16, scheduled for elective cesarean
  - Pittsburgh, PA, USA
- 1st study of candidate microbicide in pregnancy
  - Platform for conducting additional studies of safety in pregnancy
- Documented drug transfer, no safety concerns
  - Median maternal peak concentration and cord blood TFV concentrations 4.3 and 1.9 ng/mL, respectively
- Presented at Microbicides 2010 and IDSOG

Beigi et al. PK and Placental Transfer of Single-Dose TFV 1% Vaginal Gel in Term Pregnancy, *JID*, 204, Issue 10, 2011.

Meeting to drive proactive engagement and planning

- 2010: *Next Steps for Microbicide and PrEP Research in Pregnancy*
- US NIH, Bethesda, MD, USA
- Included clinical (infectious disease and maternal-newborn health), ethical, research, regulatory perspectives
- Set the stage for continued study of candidate HIV prevention products in pregnancy and BF

NIH National Institute of Allergy and Infectious Diseases

MTN microbicide trials network

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

MTN-008: Phase 1 safety and drug absorption with daily use TFV gel

- Two cohorts, 7 days exposure
  - Third trimester pregnancy (at 37 weeks and 34 weeks gestation)
  - Breastfeeding (n=16) – 1st study of topical ARV in BF mother-infant pairs
- Design incorporated a safety review between term and late preterm cohorts
- Recent evidence supported prospect of benefit
- Daily TFV gel use safe, well tolerated
- No significant accumulation of TFV in milk
- Absorption low in breastfeeding infants

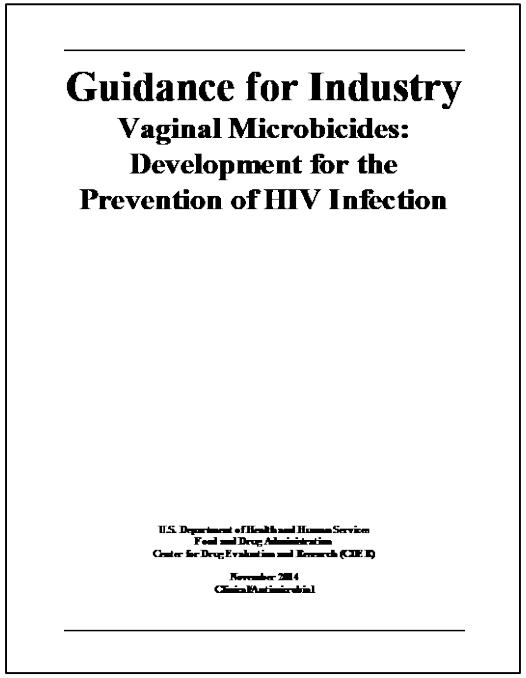
Beigi et al. J Int AIDS Soc 2016 Sep 21;19(1):20990.

Noguchi et al. AAC 2016 Aug 22;60(9):5616-9.

Montgomery et al. AIDS Behav 2018 Feb;22(2):402-411.

MTN-016: EMBRACE

- Prevention Agent Pregnancy Exposure Registry
  - EMBRACE: Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure (2008)
- Prospective observational cohort study
  - Fell pregnant during trials, or planned exposures in safety studies
- 460 women and 413 infants enrolled across 17 sites


Guidance for Industry

Vaginal Microbicides: Development for the Prevention of HIV Infection

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2014
Clinical/Medical

"Women who become pregnant during the trial should be followed in a pregnancy exposure registry such as the Microbicide Trials Network Registry MTN-016."
– 2014 Guidance for Industry

MTN-016: what were we trying to learn?

- Adverse pregnancy outcomes
- Growth parameters of infants during first year of life
- Prevalence of major malformations in infants during first year of life
- Prevalence and persistence of HIV drug resistance mutations in plasma among HIV-infected infants

- *MTN-016 unique design allows for capture of outcomes among those randomized to placebo as well*

MTN-016 (ASPIRE DATA)

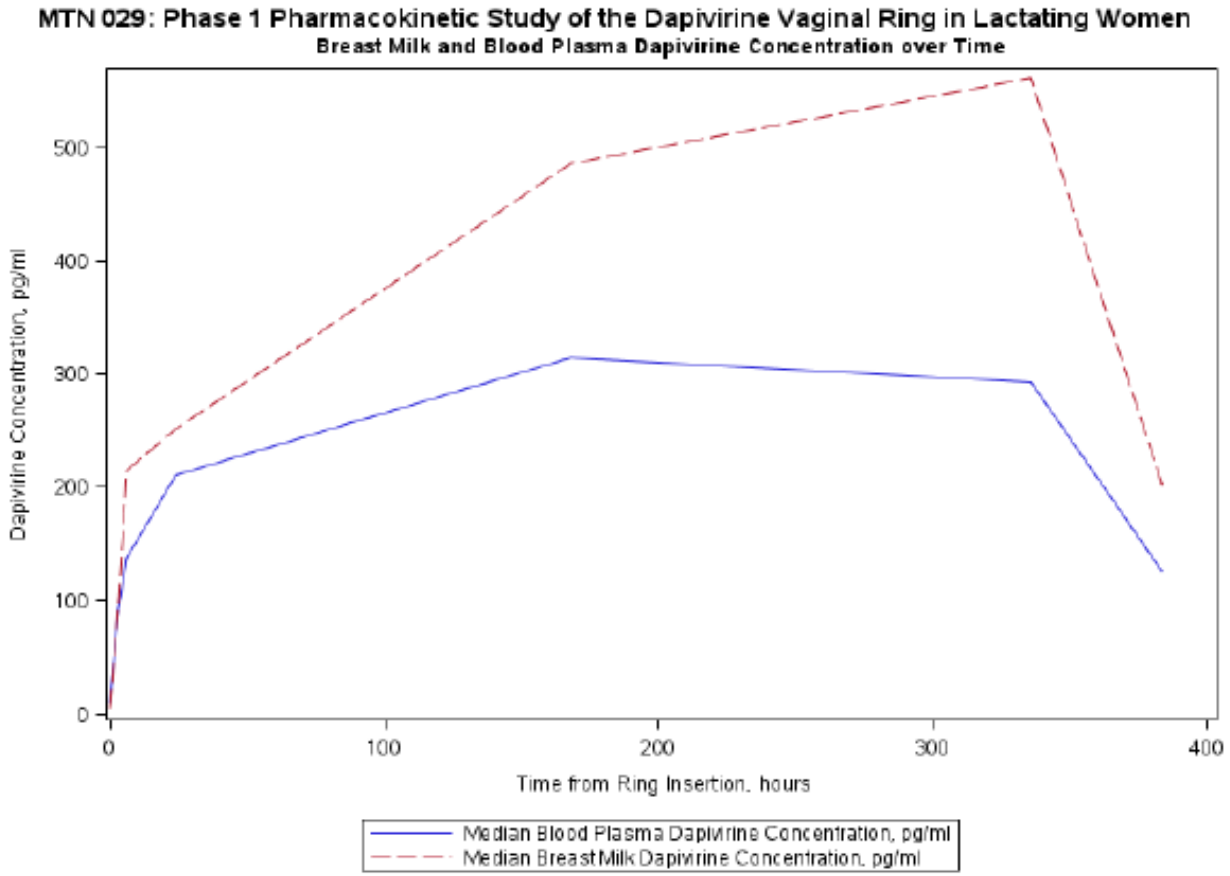
- 2,629 women enrolled
- 169 women pregnant during follow up
- 179 incident pregnancies and 181 pregnancy outcomes

Makanani B, Balkus et al. **Pregnancy and Infant Outcomes Among Women Using the Dapivirine Vaginal Ring in Early Pregnancy.** J Acquir Immune Defic Syndr 2018 Dec 15;79(5):566-572

- **Dapivirine use in periconception period does not appear to be associated with adverse effects on pregnancy or infant outcomes**
- Still more to learn after MTN-016…

MTN-029/IPM 039

- Same 25 mg DPV VR used in Phase 3 studies x 14 days of use
- 16 women at sites in Birmingham and Pittsburgh
  - 18+ years old, HIV-, >6 weeks post-del.
  - Lactating but **weaning completed**
- PK – (plasma, milk, CVL)
- Results
  - 100% retention
  - Safe – very few adverse events
  - Extremely low drug transfer to milk



Noguchi et al. Antimicrob Agents Chemother 2019 Feb 26;63(3).

HIV-1 Prevention During Pregnancy and Breastfeeding: A Portfolio of MTN Studies

MTN-016 MTN-002 MTN-008 MTN-029

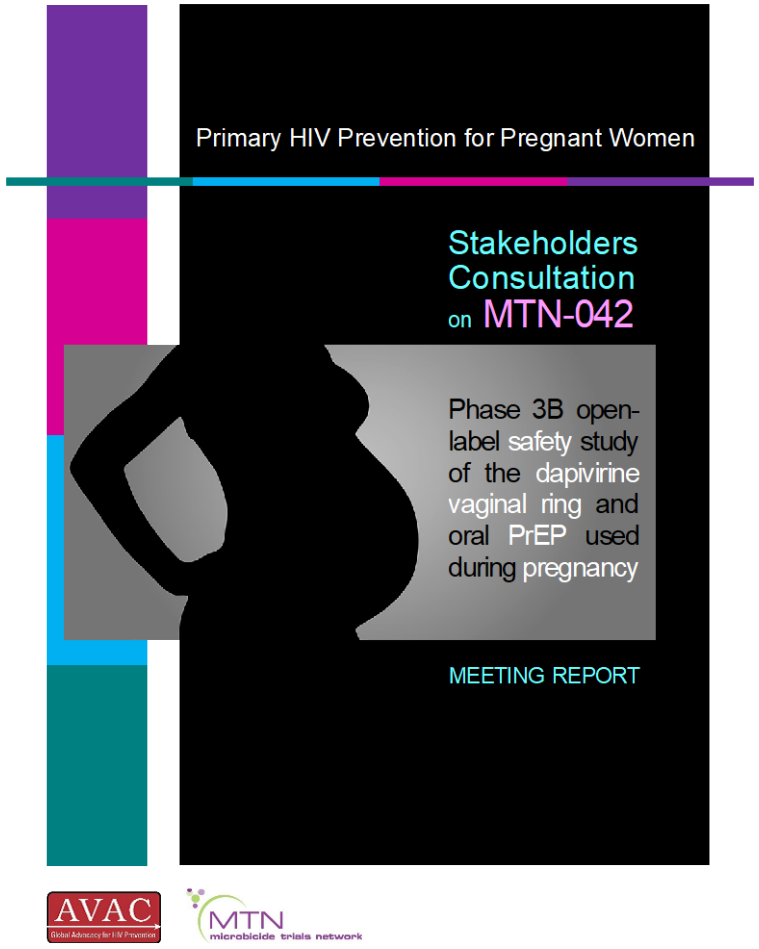
MTN-041
MAMMA

MTN-042B &
Systematic
Literature Review

MTN-042
Deliver

MTN-043
B-PROTECTED

Consultation with key stakeholders in Johannesburg, South Africa, 5-6 April 2018



- Timing of the consultation so that stakeholder feedback could be considered by study team at protocol development meeting a few days later
- Experts in bioethics, maternal and fetal health, HIV prevention clinical trial design, regulatory affairs, health policy, as well as civil society and community representatives
- Most from countries with MTN-042 sites
- Stakeholders very supportive of study and design incorporating interim reviews
- Unanimous in view that time is right to move forward with this agenda

MTN-041: Microbicide/PrEP Acceptability among Mothers and Male Partners in Africa (MAMMA)

- Primary Objectives
  - Attitudes about vaginal ring (VR) or oral PrEP during pregnancy (P) and breastfeeding (BF), incl. willingness to use
- Secondary Objectives
  - Potential preference for VR or oral PrEP during P/BF
  - Attitudes and perceptions re sexual activity during P/BF
  - Perceptions of HIV risk, community beliefs and practices
- Study completed – findings used to Inform study tools, recruitment, retention and community activities, counseling, and participant engagement plans

Systematic Literature Review: Objectives

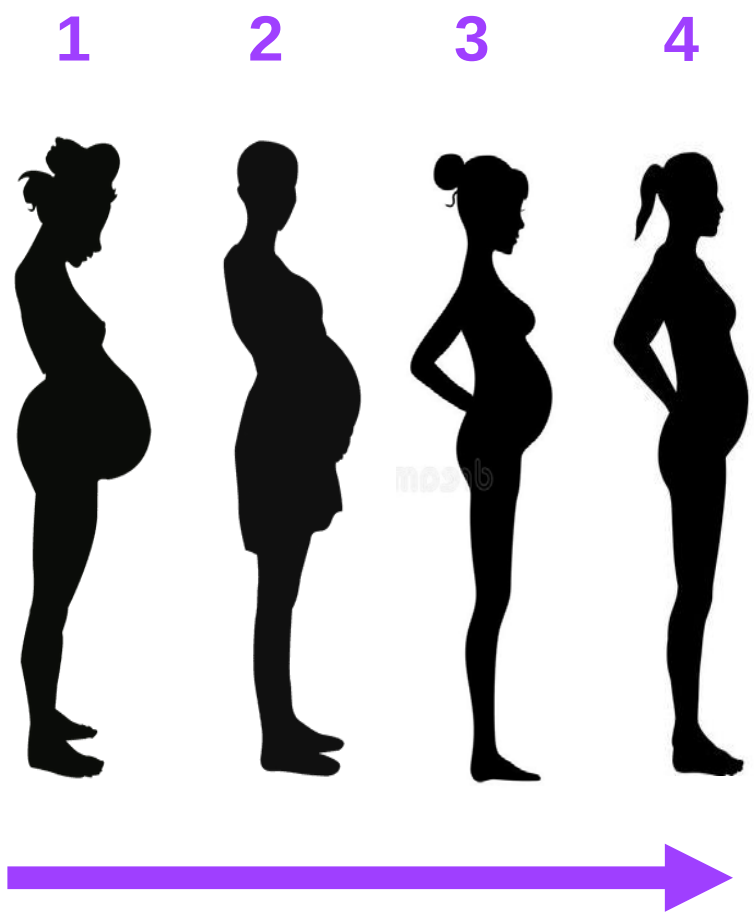
Provide estimates of the frequency of adverse pregnancy outcomes conducted in the countries of participating in MTN-042

Compare theses estimates with the frequency of adverse pregnancy outcomes observed among women who became pregnant in MTN trials (MTN-003, MTN-020, MTN-025)

MTN-042/MTN-043: Assessing safety of dapivirine VR and oral PrEP in pregnancy and beyond

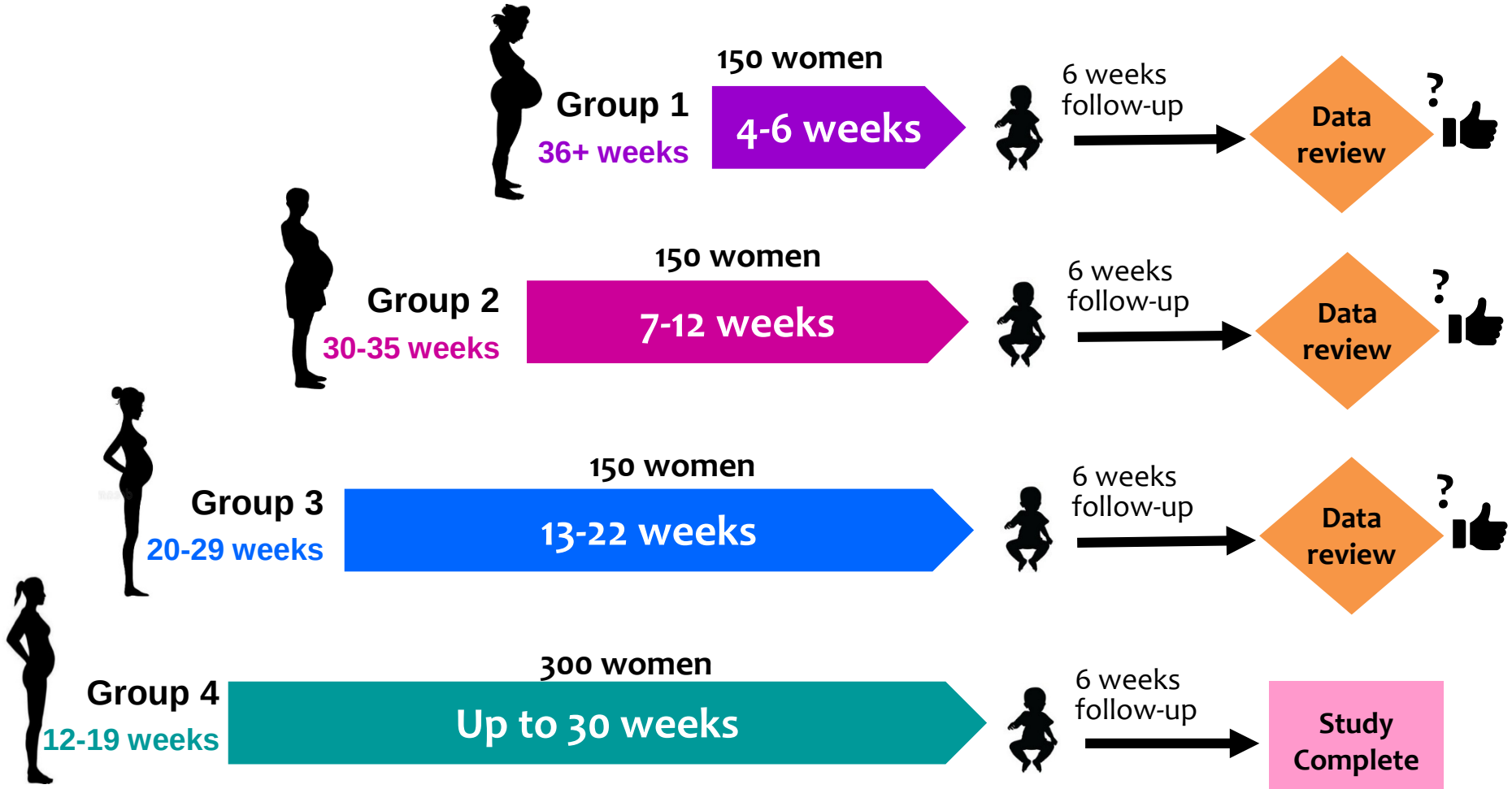
~6 weeks	12 weeks – delivery	6 weeks pp	>6 weeks pp
Data from ASPIRE/MTN-016 showed no differences in maternal or infant outcomes[1]	MTN-042 will assess the safety of DPV ring and PrEP at different time points in pregnancy	Time period not currently being assessed	MTN-043 will assess the safety of DPV ring and PrEP at different time points in postpartum women and breastfeeding infants

MTN-042/Deliver study design



- Women randomly assigned to use either monthly ring or daily PrEP until delivery
  - For every one woman assigned to use PrEP, two will use the ring
- Will be conducted in a stepwise fashion starting with women late in pregnancy
- Interim reviews will be conducted before deciding to enroll the next group of women

A stepwise approach with interim reviews



MTN-042B: Assessing baseline pregnancy outcomes in sub-Saharan Africa

- **Study Design**: Multi-site, chart review, cross sectional study
- **Study Population**: All women delivering or receiving immediate postpartum care (within one week of delivery) at one or two facilities affiliated with each of the 4 sites, a primary care facility and a referral facility
- **Sample Size:** Approximately 11,000 (8 weeks of deliveries at 4 sites)
- **Objectives**
  - Primary: To determine frequency of key pregnancy outcomes
  - Secondary: To determine frequency of pregnancy and infant complications, method of delivery, birth weight, and proportion of low birth weight (<2500g)

MTN-043/B-PROTECTED

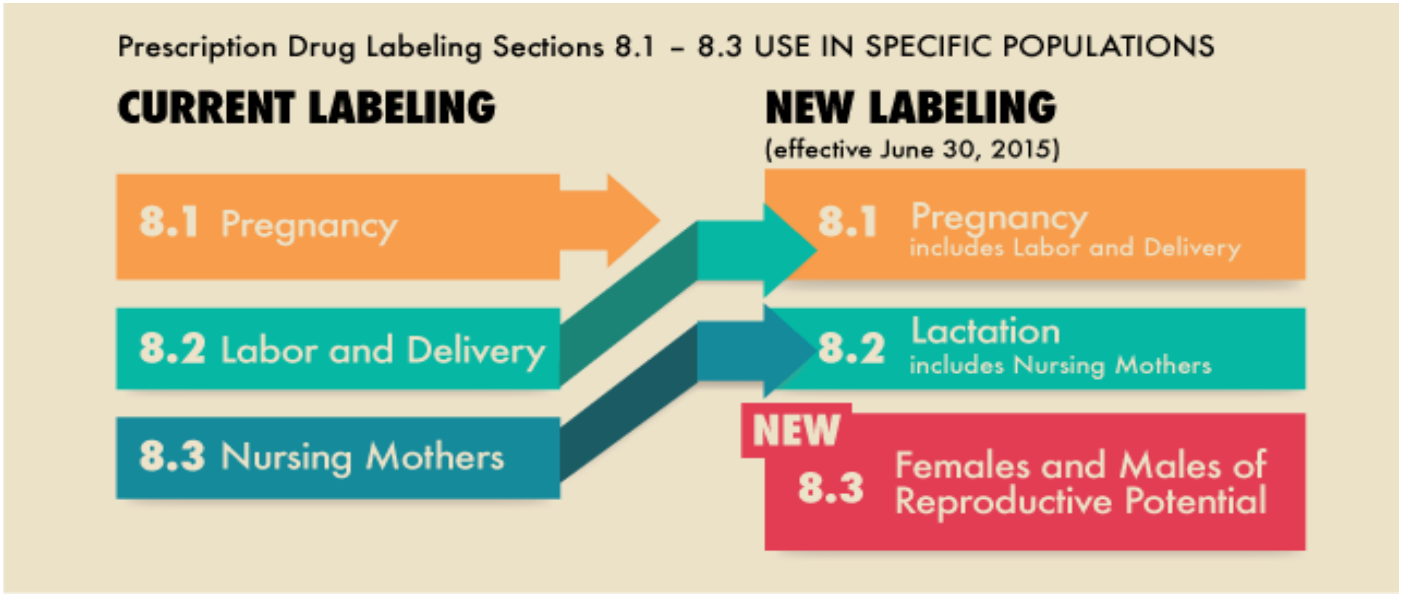
Study Design: Phase 3B, randomized, open-label, multi-site, mother-infant pair safety and drug detection study, 12 weeks of study product exposure to DPV VR or oral Truvada® tablet

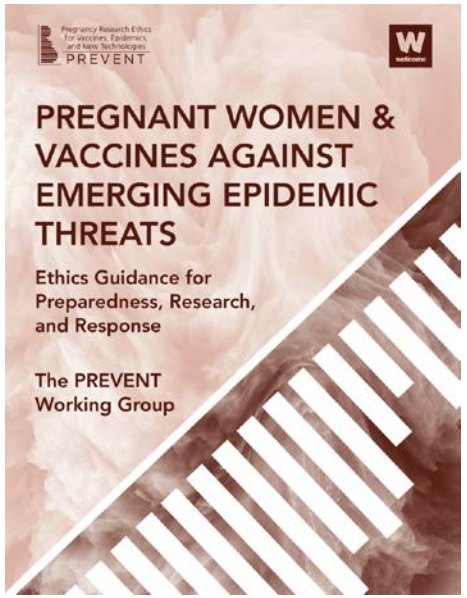
Study Population: Healthy, HIV-uninfected breastfeeding women and their healthy infants between 6 and 12 weeks old

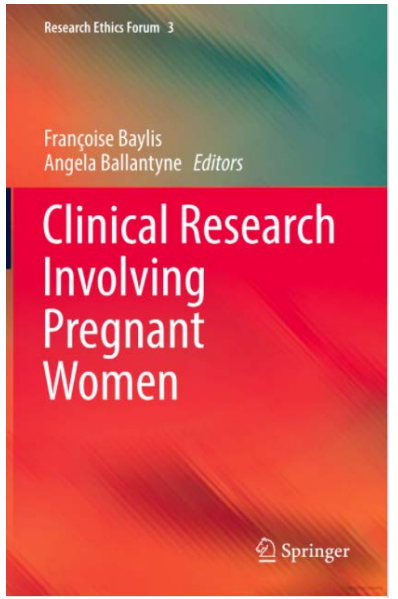
Sample size: Approximately 200 mother-infant pairs

The landscape has changed and momentum is still building…

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)







2006: We had questions…

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Will products be safe for mothers and babies during breastfeeding?

Will a chemoprevention pregnancy registry be feasible?

Will mothers use HIV prevention products during pregnancy and breastfeeding?

Will topically administered ARVs cross the placental barrier?

Will topically administered ARVs pass into human breast milk?

Will we even be able to understand product safety when background rates of safety events are challenging to capture in local context?

2020: We have many key answers!

All products MTN studied appear safe for mothers and babies in pregnancy.

All products MTN studied appear safe for mothers and babies during breastfeeding.

MTN-016 not only feasible but acknowledged as a model for other registries.

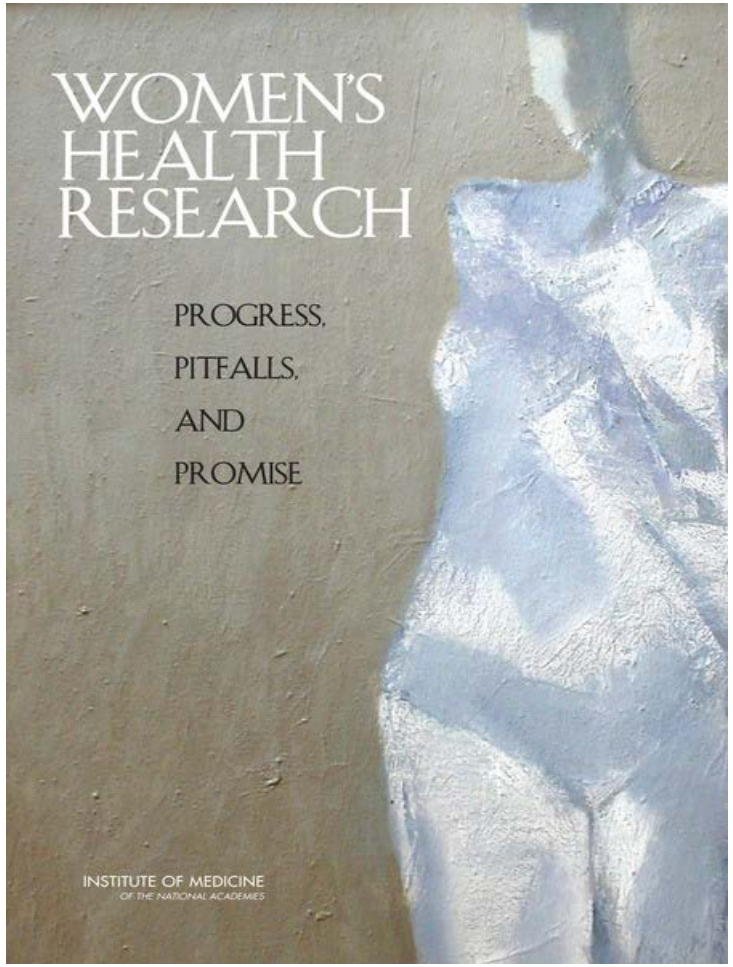
ARVs were detectable in blood of those who used active products in pregnancy.

Topically administered ARVs can cross the placental barrier.

Topically administered ARVs can pass into breast milk, but so far at very low levels.

MTN-042B is capturing maternal newborn health outcomes in unexposed populations in the same contexts as MTN-042 and MTN-043.

We have addressed calls to action…



Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact the Division of Pediatric and Maternal Health (CDER) at (301) 796-2200 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Clinical/Medical
Revision 1

…and together, we have fueled science dissemination here…

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21-25 OCTOBER 2018
MADRID

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9TH IAS CONFERENCE ON HIV SCIENCE
PARIS, FRANCE – 23-26 JULY 2017

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SEEKING EQUITABLE STUDY

HIV RESEARCH FOR PREVENTION
HIVR4P
Satellite

PrEPWatch

CROI
Conference on Retroviruses and Opportunistic Infections

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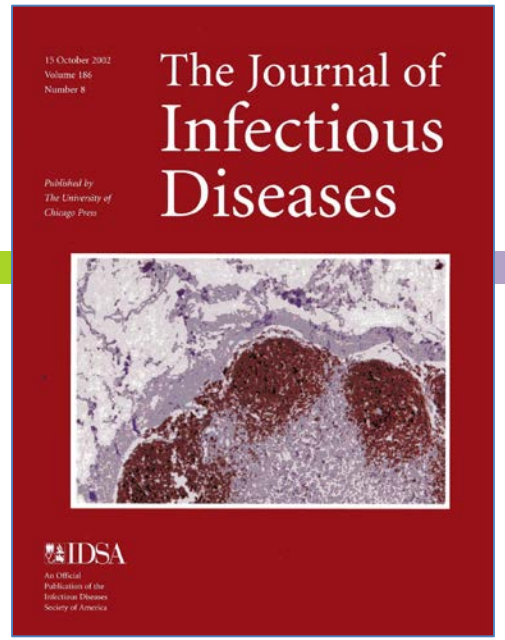
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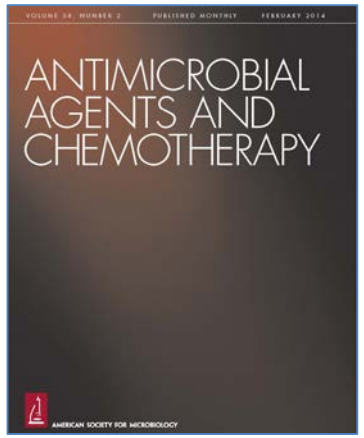
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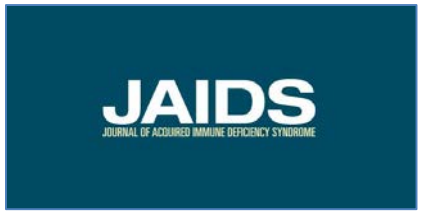
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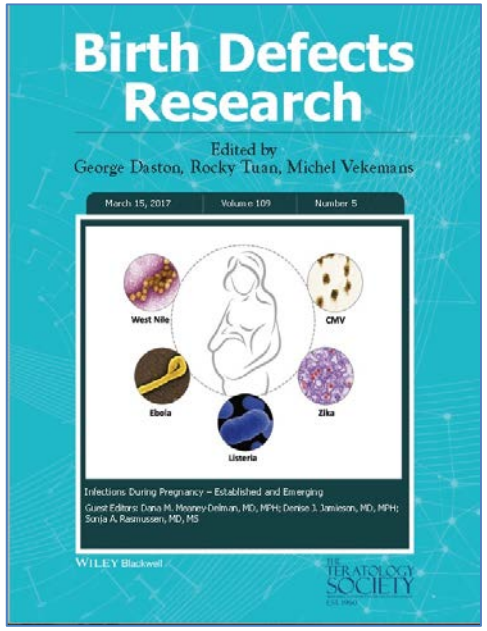
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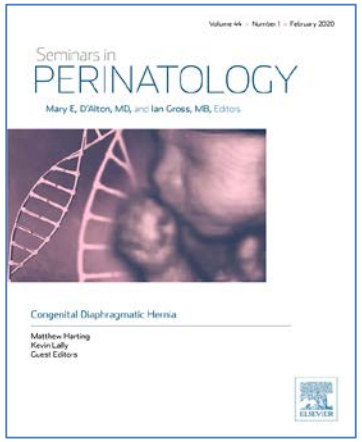
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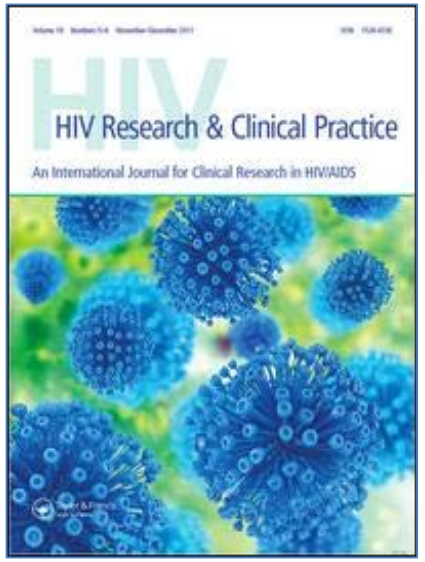
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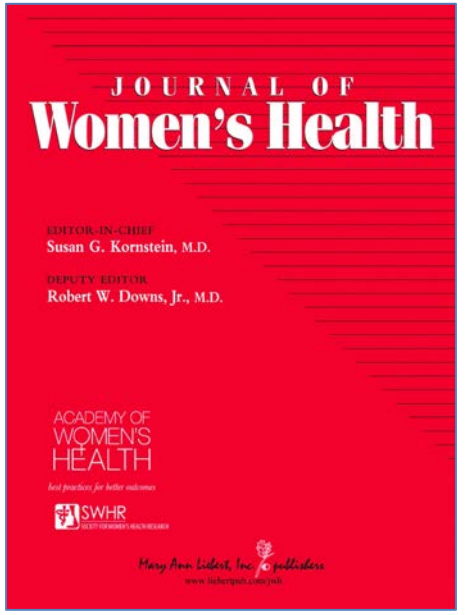
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