



Pregnant Woman by Cuth

IMPAACT 2009

Different Pieces of the Puzzle

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for the protocol team
25 September 2018, Cape Town



HIV Prevention Puzzle –

How to prevent new HIV infections?

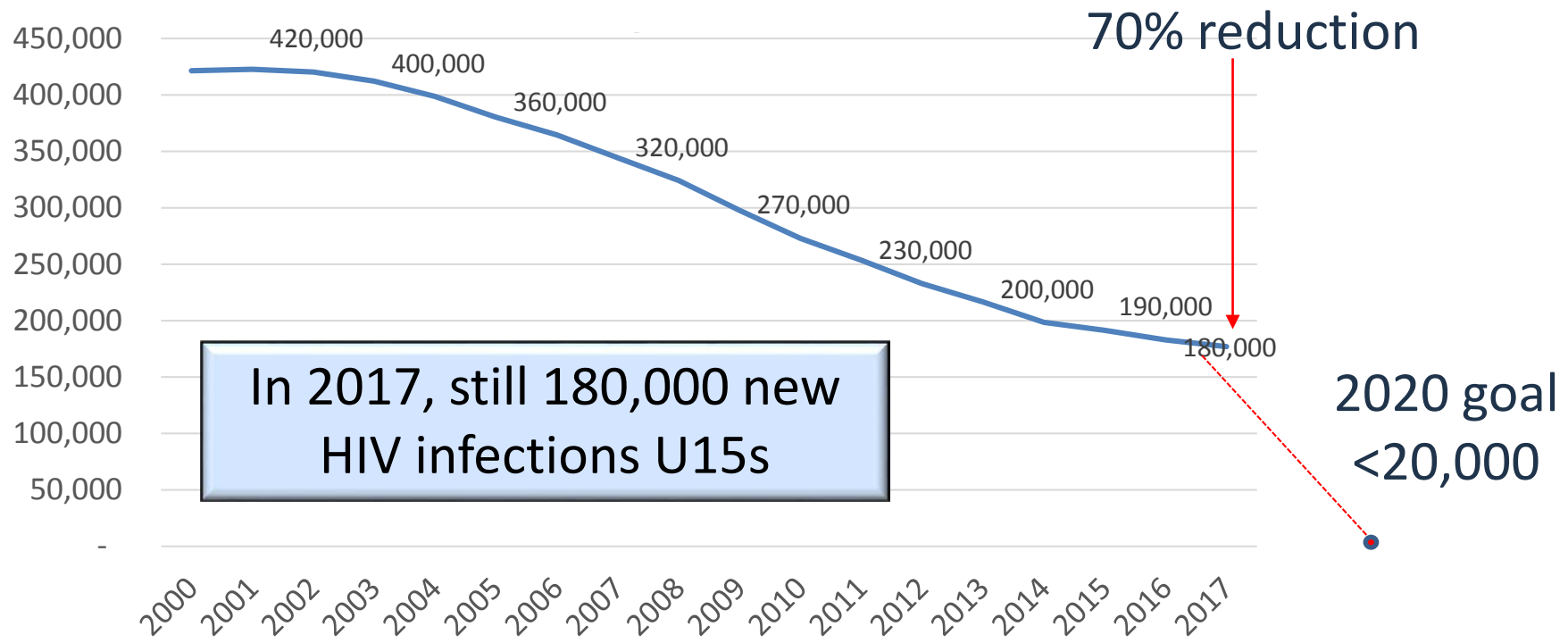


Prevention Scientific Committee

- HIV prevention strategies that are
 - Effective
 - Safe
 - Throughout the life-course
 - Don't jeopardise treatment
 - Global scale
 - Variety of health settings
- We don't have all the pieces

Many pieces in place for infants

- 70% reduction in new child infections since 2000 due to life-long ART for women



Many pieces in place for infants



1^o prevention in pregnancy





The pieces we *do* have

- 6-29% reproductive years spent pregnant and breastfeeding
- Substantial risk of new HIV infection
 - Incidence 5.37 / 100py
- Peaks in late pregnancy
- Increased risk per act vs. non-pregnant state
 - 4.97 (95%CI 2.95, 8.38)

Acquisition of HIV Among 2751 African Women With HIV-Infected Male Partners, by Reproductive Stage

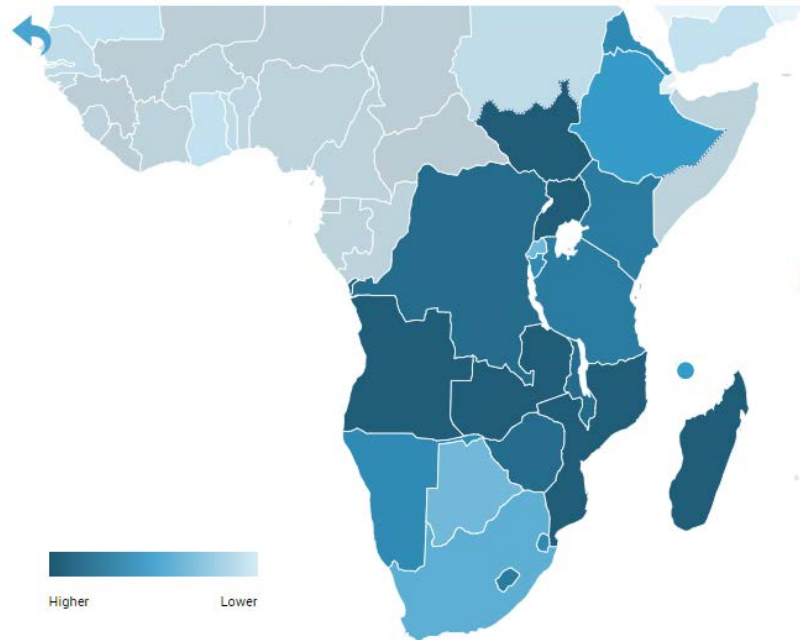
Reproductive Stage	HIV Seroconversion, Cases/Person-Years	HIV Incidence, Cases/100 Person-Years (95% CI)
Overall	82/5069	1.62 (1.29, 2.01)
Nonpregnant/postpartum periods	58/4622	1.25 (0.95, 1.62)
Early pregnancy through postpartum period	24/447	5.37 (3.44, 7.99)
Early pregnancy	5/133	3.75 (1.22, 8.75)
Late pregnancy	13/185	7.02 (3.74, 12.01)
Postpartum period	6/128	4.68 (1.72, 10.18)



The pieces we *do* have

- Mothers are young
 - Adolescent birth rate 109/1000 women aged 15-19yrs

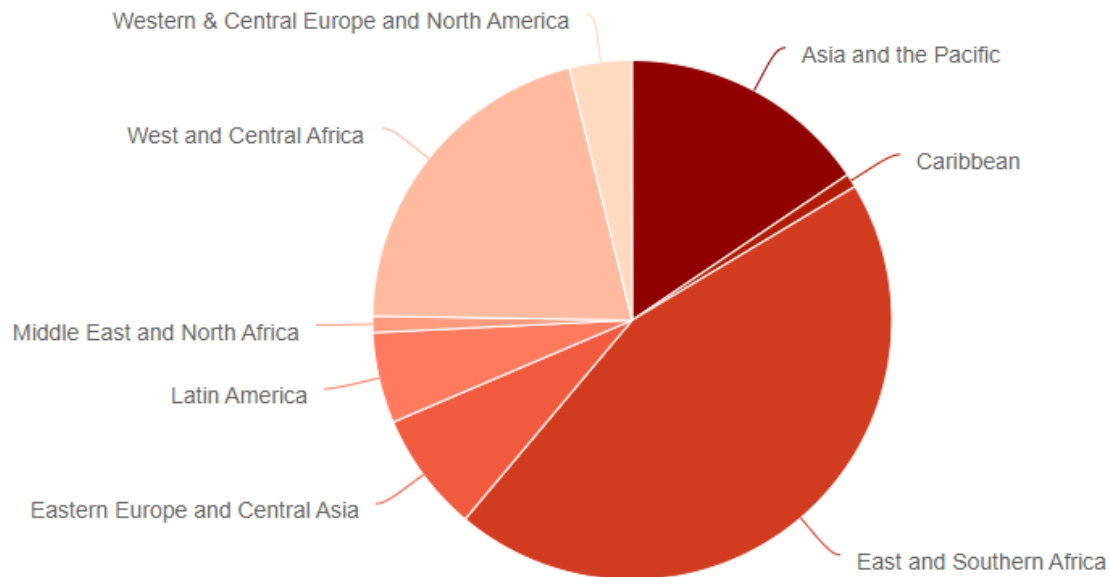
Adolescent birth rate per 1,000 girls aged 15-19, 2006-2015





The pieces we *do* have

- Women aged 15-24 years make up 19% of new HIV infections
 - Sub Saharan Africa bears the greatest burden





The pieces we *do* have

- Adolescent and young women face particular challenges
 - Accessing health care
 - HIV services
 - Sexual reproductive health services
 - Gender based violence
 - Unplanned pregnancy
 - Pregnancy complications



The pieces we *do* have

- PrEP is effective in this population
- May need specific support to adhere to medication

- PrEP
- ART
- Oral tablets
- Other product formulations

AIDS Behav (2013) 17:2143–2155
DOI 10.1007/s10461-013-0429-9

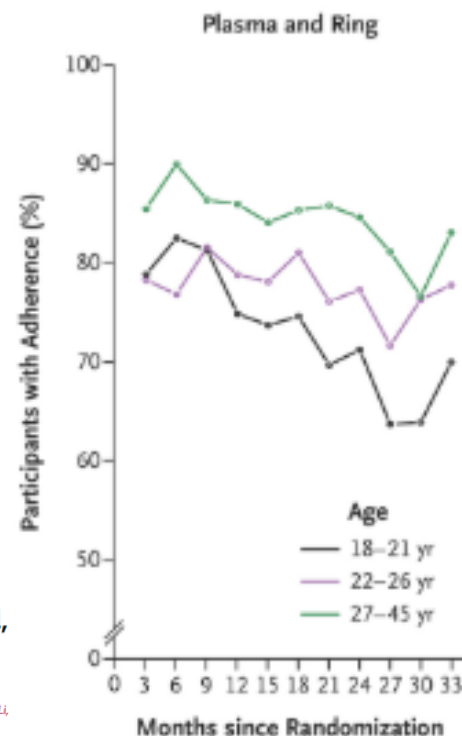
SUBSTANTIVE REVIEW

Adherence Support Approaches in Biomedical HIV Prevention Trials: Experiences, Insights and Future Directions from Four Multisite Prevention Trials

K. Rivet Amico · Leila E. Mansoor · Amy Corneli · Kristine Torjesen · Ariane van der Straten

Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial

Linda-Gail Bekker, Surita Roux, Elaine Sebastien, Ntando Yola, K Rivet Amico, James P Hughes, Mark A Marzinko, Craig W Hendrix, Peter L Anderson, Vanessa Elharrar, Michael Stirratt, James F Rooney, Estelle Piwowar-Manning, Susan H Eshleman, Laura McKinstry, Maoji Li, Bonnie J Dye, Robert M Grant, on behalf of the HPTN 067 (ADAPT) study team





The pieces we *do* have

- Tenofovir/Emtricitabine safety profile in pregnancy established
 - HIV
 - Hepatitis B
- Pharmacology studied
 - HIV-infected women (pregnant and non-pregnant)
 - HIV-exposed infants
 - HIV-uninfected men
 - HIV-uninfected non-pregnant women in the US



The pieces we *do* have

POLICY BRIEF

PREVENTING HIV DURING PREGNANCY AND BREASTFEEDING IN THE CONTEXT OF PREP

JULY 2017

Based on the available safety data, WHO considers that PrEP should not be discontinued during pregnancy and breastfeeding for women who continue to be at substantial risk of HIV infection. PrEP can also be considered as an additional prevention choice for HIV-negative pregnant women who are at substantial of HIV infection, as part of a comprehensive PMTCT package.

More safety data needed

- Adverse pregnancy outcomes
- Effects of *in utero* and breastmilk ARV exposure on infant bone development and growth
- Effects of TDF use on maternal bone mineral density
- Adolescents will require more adherence support and enhanced comprehensive SRH information

Now to put them all together for pregnant women



IMPAACT 2009

**Pharmacokinetics, Feasibility,
Acceptability, and Safety of Oral Pre-
Exposure Prophylaxis for Primary HIV
Prevention during Pregnancy and
Breast Feeding in Adolescents and
Young Women**

<https://clinicaltrials.gov/ct2/show/NCT03386578?term=2009+impaact&rank=3>





Acknowledgements

Protocol Team

Co-Chairs: **Benjamin Chi** & Lynda Stranix-Chibanda

Vice Chair: **Sybil Hosek**

Geri Donenberg, Rivet Amico, Deborah Kacanek, Sharon Huang, Lisa Hightow-Weidman, John Shepard, Nicole Tobin, Savita Pahwa, Lisa Frenkel, Jennifer Kiser, Pete Anderson, Hans Speigel, Nahida Chakhtoura, Susannah Allison, Kate Lypen, Kathy George, Emily Brown, Dina Chinichian, James Rooney, Nayri Khairalla, Laura Smith, Benjamin Johnston, Katelyn Hergott, Carolyn Yanavich, Cheryl Jennings, Dean Soko, Cheryl Cokley, Monnie Lubega, Study Site teams

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

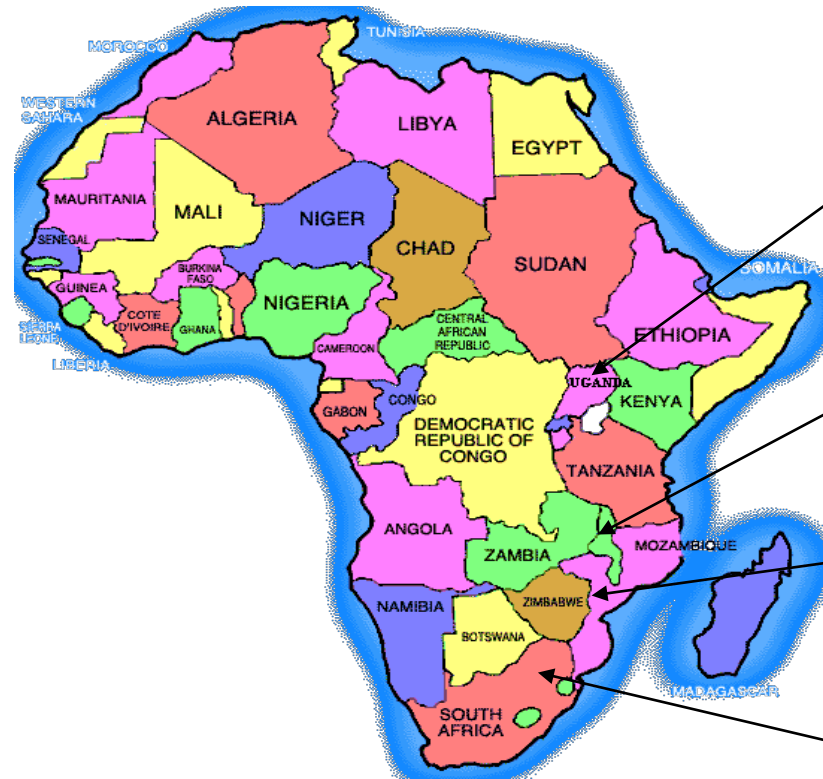
What will 2009 add to current knowledge?



- At this time of particular risk for new HIV infection in young women
 - PK in pregnancy
 - Deeper understanding of adherence
 - Safety information to inform the risk:benefit ratio



IMPAACT 2009 Study Sites



Kampala, Uganda:
Baylor CRS &
Makerere
University - JHU
CRS

Blantyre, Malawi
(JHU)

Harare, Zimbabwe:
Harare Family Care
Center, Saint Mary's &
Seke North

Johannesburg, South Africa:
Shandukani WRHI



Mother and Child by
Colleen Madamombe



Pregnant Woman
by Cuth

Pharmacokinetic (PK) Component



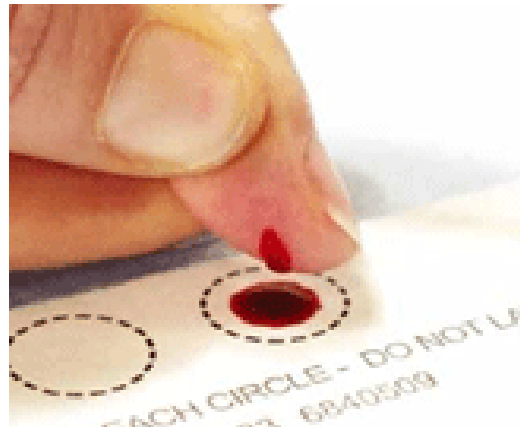
PK Component Procedures

- 12 weeks of PK monitoring, with weekly DBS specimens for drug levels
 - Followed by an observational period to 6 weeks postpartum
- Intensive monitoring of drug adherence
 - This may include
 - directly observed therapy (DOT) at the clinic,
 - DOT at the home, via community health workers, or
 - “real-time” video-based monitoring via smartphone, tablet, or computer.



PK Component Outcome

- Concentration of tenofovir diphosphate (TFV-DP) associated with adequate adherence to TDF/FTC among women observed ingesting daily oral PrEP during pregnancy and postpartum.
- Compare TFV-DP concentrations pre- and post-delivery





PrEP Comparison Component



Study Design

- Observational cohort study for HIV-uninfected healthy pregnant women aged 16-24 years with EGA <32 weeks
 - 200 pregnant women who choose PrEP
 - 100 pregnant women who decline PrEP
- Followed ~monthly in pregnancy, at L&D, then weeks 6, 14 and 26 postdelivery
 - Acceptability
 - Adherence
 - Safety

Adherence Intervention

- *integrated Next Step Counseling (iNSC).*
 - All maternal participants in both cohorts.
- *Drug level monitoring with feedback.*
 - Starting at Week 4 visit
- *SMS Adherence Support.*
 - 1-way personalized stage-based messages to support maternal and child healthcare (e.g. MAMA platform); also receive weekly 2-way text messages that provide general adherence support (i.e., “are you doing OK?”).






Primary Objectives

- To characterize PrEP adherence among HIV-uninfected women aged 16-24 years who initiate once-daily TDF/FTC in pregnancy
- To compare maternal and infant adverse events (including pregnancy outcomes) between women who initiate PrEP and those who decline PrEP

Secondary Objectives

- To identify individual, social, and structural barriers and facilitators to PrEP uptake during pregnancy
- To compare between the PrEP and non-PrEP cohorts:
 - Reported sexual risk behavior and incidence of STIs
 - HIV incidence
 - HIV drug resistance among HIV-infected mothers and infants

Outcome measures

Primary Outcome Measures – PrEP Comparison Component	
Objective	Outcome Measures
2.3.1	PrEP adherence: TFV-DP drug concentration level in Dried Blood Spots (DBS)
2.3.2 	<p>Maternal Adverse Events:</p> <ul style="list-style-type: none"> • Maternal Grade 3 or higher adverse events (signs, symptoms, labs, and diagnoses) • Maternal Grade 2 or higher chemistry abnormalities
2.3.2  	<p>Adverse Pregnancy Outcomes: Composite outcome of</p> <ul style="list-style-type: none"> • Spontaneous abortion (occurring at <20 weeks gestation) • Stillbirth (occurring at ≥ 20 weeks gestation) • Preterm delivery (<37 completed weeks' gestation) • Small for gestational age (<10th percentile using WHO norms for weight-for-age and ultrasound derived gestational age at delivery) <p>Infant Safety:</p> <ul style="list-style-type: none"> • Infant death within the first 26 weeks of life • Infant Grade 3 or higher adverse events (signs, symptoms, labs, diagnoses) reported between birth and exit • Infant bone mineral content based on DXA scan of the whole body (WB-BMC) at birth and lumbar spine (LS-BMC) at birth and 26 weeks postpartum • Infant creatinine and CrCl rate at birth and 26 weeks postpartum • Infant length for age z-score at birth and exit



MTN – 042 vs IMPAACT 2009

- Similar overarching goal to prevent HIV acquisition among pregnant and breastfeeding women in SSA
- Different agents being evaluated
- Slightly different approach and focus
- Opportunity to exchange ideas and experience





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BENHURA

Thank you Tatenda

