HIV prevention options during pregnancy and breastfeeding – what's in the pipeline?

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MTN microbicide trials network

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A Study of PrEP and the Dapivirine Ring in Pregnant Women

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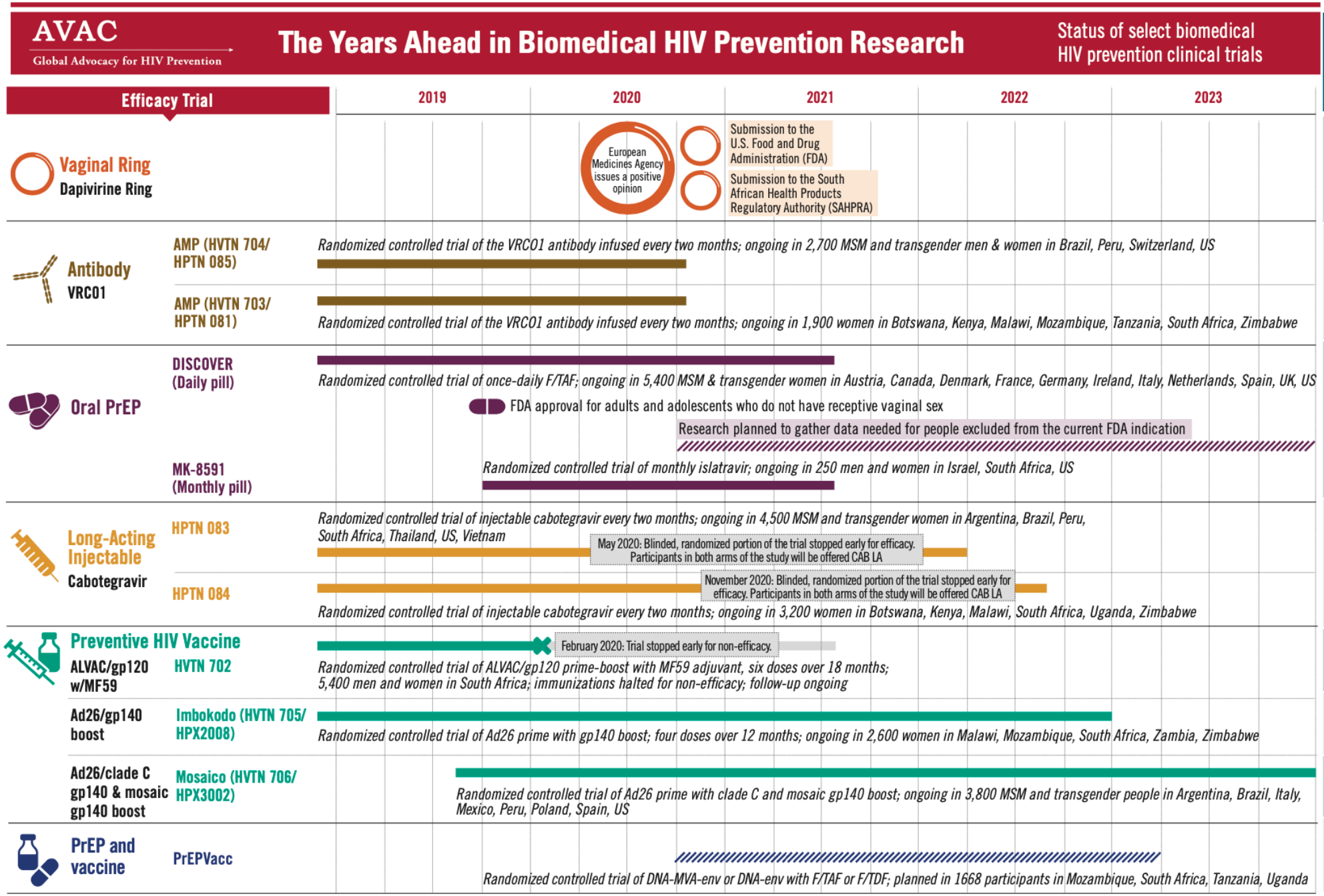
Overview

- Review current research pipeline for HIV prevention options during pregnancy and breastfeeding
- What are some key areas for future research?
- What are some key areas for engagement of advocates?



Pregnancy and Breastfeeding
Included in ongoing trials (MTN-042, MTN-043)
Excluded
Plan to collect selected data on pregnancies that occur in IMPOWER-22
Limited data on safety and pharmacokinetics in preg./BF for this product
Excluded
Excluded
Excluded
Excluded

How can you tell when pregnant and breastfeeding people are being excluded from studies?

- Look in online registers for clinical trials, like www.clinicaltrials.gov
  - Check the section called “Criteria” – Inclusion and exclusion
- Check protocols published online for the DAIDS clinical trials networks (study population, eligibility criteria)
- Look in package inserts (medicine information from industry) – sections on pregnancy and lactation
  - If they talk about inadequate data, it’s often because of exclusion
- For antiretroviral drugs, check the Antiretroviral Pregnancy Registry
  - http://www.apregistry.com/
  - Summarizes what is known about safety in pregnancy
- Often INCLUSION gets publicized more than exclusion

Oral pre-exposure prophylaxis (PrEP)

- Where we have the most safety data (among the biomedical interventions)
- Recommended by WHO, including for pregnant and breastfeeding populations
- New sample clinical guidelines from the CHOICE project are freely available and adaptable (December 2020)
  - PrEPWatch (https://www.prepwatch.org/resource/prep-for-pregnant-and-breastfeeding-women/)
  - Featured and linked within PEPFAR 2021 Country and Regional Operational Plan (COP/ROP) Guidance for all PEPFAR Countries
- Still some gaps in evidence
  - More complete evidence on safety of exposure in different trimesters, for extended periods of time
  - Implementation research on best strategies for demand generation, community-based delivery, uptake/continuation, acceptability, feasibility of integration into antenatal and postnatal care services

Dapivirine vaginal ring – WHO approval is here and we already know some important things about pregnancy and BF!

- Some pregnancy and lactation data already published
- We know that…
  - Limited exposures to the ring in early pregnancy weren't associated with safety risks
  - Drug levels in breast milk of lactating women (who were no longer breastfeeding their infants) were really, really, really low – unlikely to cause risks for infants
  - The ring doesn't disrupt the balance of normal bacteria in a non-pregnant woman's reproductive tract – this is important during pregnancy, because some disruptions may increase the chance that waters break or infants arrive too early

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More data coming soon

- More research coming (see www.mtnstopshiv.org)!
  - DELIVER (MTN-042)
  - B-PROTECTED (MTN-043)
- These studies will give us even more answers about safety, drug levels, adherence, etc.
- Data from first cohort of DELIVER (of four total) this year, as well as results from B-PROTECTED
- Additional implementation research will still be needed
- WHO statement acknowledged forthcoming data

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A Study of PrEP and the Dapivirine Ring in Pregnant Women

Breastfeeding PrEP & Ring Open-label Trial B PROTECTED

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What do we know about injectable CAB-LA?

- Long-acting (LA) HIV integrase inhibitor, given monthly or every 2 months
  - Drug can stay in the body for a year or longer following discontinuation, possibly longer on average in women than men
- What about pregnancy?
  - Studies in animals did not show any warning signs related to pregnancy
  - We have some limited data in human pregnancies but more would be better!
  - No clear safety signal for pregnancy
- Same class of drug as dolutegravir (DTG)
  - May 2018: possible association of DTG with fetal neural tube defects when taken around conception
  - BUT – more recent data showed no substantial difference in risk vs. other ARVs

CROI Conference on Retroviruses and Opportunistic Infections
CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS
Boston, Massachusetts
March 8–11, 2020

Patel et al. Abstract #775.

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Antibodies for HIV prevention?

- Antibodies can be made by immune system (to clear infections) or in a lab
- bNAbs are antibodies that can neutralize many different genetic variants of HIV
- bNAbs against HIV develop naturally in some people after a while in small amounts
- In HIV prevention studies, bNAbs can be given by intravenous infusion or injection
- Could we use antibodies for HIV prevention? Maybe!
- What did we learn from the AMP study recently?
  - People given infusions of monoclonal antibodies every 8 weeks had 75% lower risk of getting HIV—but only if they were exposed to strains of HIV that stayed susceptible to the antibody
- Any research on bNAbs in pregnancy for prevention of HIV? Not quite yet…

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What about vaccines?

- Vaccine trials have generally excluded pregnant and breastfeeding populations
- Standard approach
  - Pregnant women not currently accepted as volunteers
  - Women who plan pregnancy should postpone it until after trial participation
  - Pregnancy tests are done as part of the screening process and before each immunization
  - Women of childbearing age must agree to an adequate method of birth control prior to and during the immunization period
- However, sometimes pregnancies occur anyway…

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What can those “unintended pregnancies” from HIV-1 vaccine trials tell us about safety in pregnancy?

- Recent analysis on data from 53 Phase 1 and Phase 2a HIV-1 vaccine clinical trials conducted by HVTN
  - 2,673 women of reproductive potential identified and 193 pregnancies reported
  - 74% studies had at least one pregnancy reported, overall pregnancy rate of 3.15/100 w-yr
  - 25% studies had follow-up period during which pregnancy was no longer discouraged
  - Pregnancy rate was higher during that follow-up period
- Trials had many differences, but no signal of increased risk for pregnancy or birth
- Researchers concluded: **More complete data on pregnancy outcomes should be collected in a systematic fashion in early phase HIV-1 vaccine clinical trials**

Stranix-Chibanda et al, 2020

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AVAC
Global Advocacy for HIV Prevention

The Future of ARV-Based Prevention and More

The pipeline of non-vaccine HIV prevention products includes oral pills, vaginal rings, vaginal and rectal gels, vaginal films, long-acting injectable antiretrovirals and more. Also pictured are the range of multipurpose prevention technologies in development that aim to reduce the risk of HIV and STIs and/or provide effective contraception for women. (Visit *www.avac.org/hvad* for vaccine and broadly neutralizing antibody pipelines.)

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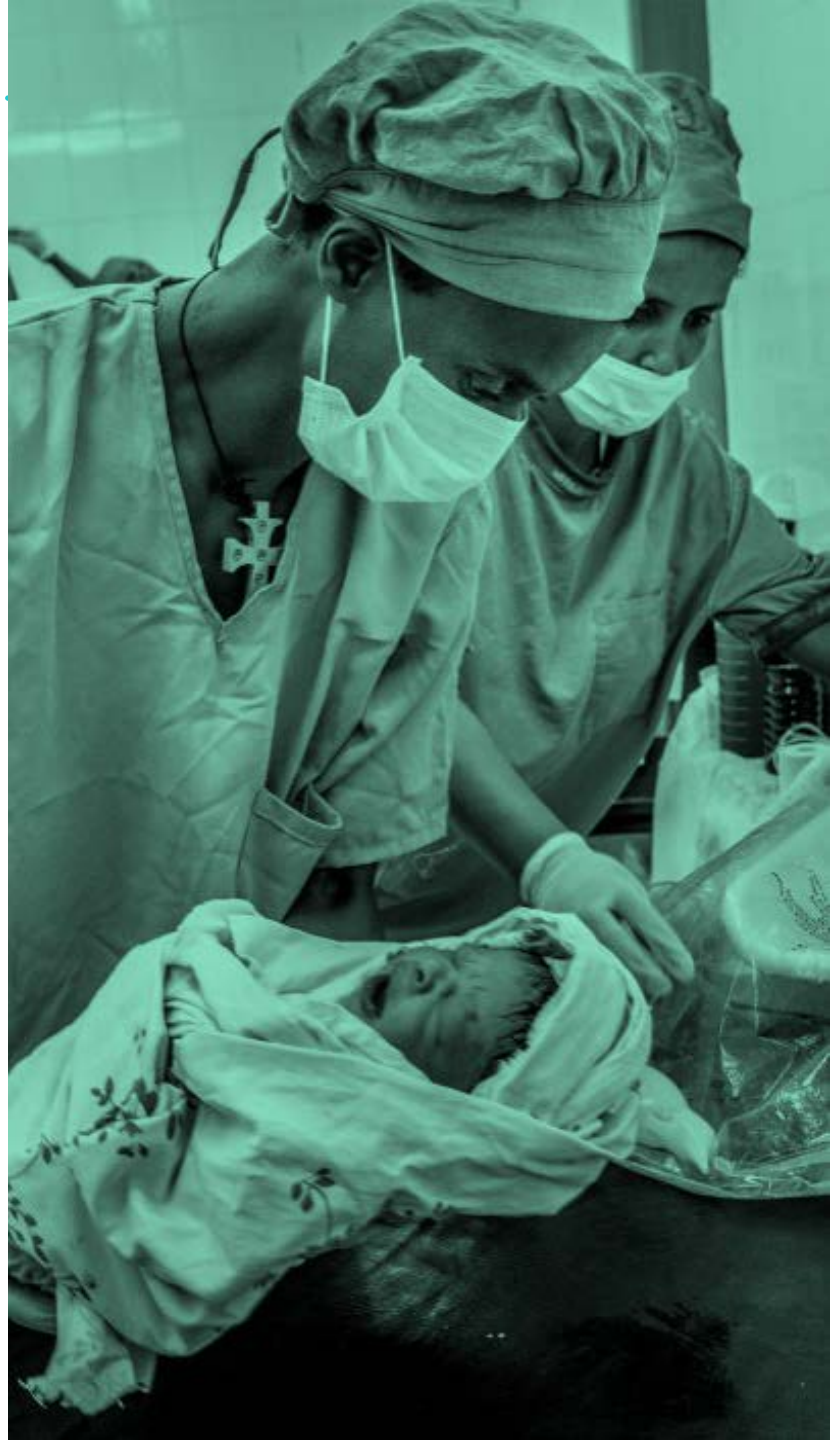
What do we need to move towards safe and ethical inclusion of pregnancy and BF for these newer products under study?

- Researchers, industry, clinicians, funders, and civil society come together to share knowledge and collaborate on a way forward – and make these paths transparent
- Many of these conversations will require specialized expertise from many different areas
  - Reproductive toxicology, obstetrics and gynecology, neonatology and pediatrics, HIV immunology, virology, infectious disease, pharmacokinetics, behavioral science
  - Regulatory pathways
  - **Community partnership and research literacy**
  - **Lived experience of these populations**



	1. Pregnancy & BF people are a critically important population for novel HIV prevention methods.	2. Research on HIV prevention options for pregnant and breastfeeding people is often too little, too late.	3. Safe and ethical inclusion of pregnant and breastfeeding people in this research must be accelerated.

Examples of supporting facts and data	• **They are at high risk**
	  • Biologic, cultural, behavioral factors contribute to higher risk during pregnancy & BF, compared to times when not pregnant or BF – as well as higher transmission risk to infants
	  • Years spent pregnant & BF are substantial in areas where epidemic is worst
	• Safe & acceptable methods during pregnancy/BF are **desired** by users!
	• **Perinatal transmission persists, despite effective drugs – the current approach to prevention clearly isn't working for all moms & babies**
		• Even in global recommendation for PrEP in pregnancy & BF, **WHO acknowledged need for more data**
		• WHO statement on encouraging results for CAB-LA noted lack of pregnancy outcome data **– pushed to post-market**!
		• **Delays** in animal reproductive toxicity studies can delay study of new biomedical prevention options in pregnant & BF people
		• **Most new trials exclude pregnancy & BF**, without giving option of informed choice for participation
		• **Products are used post-approval anyway** during pregnancy & BF without good safety data for clients or providers!
		• **Analyzing data on unintended pregnancy from Phase 3 trials has big drawbacks** (small #s of participants & important outcomes, may be first trimester only)
			• Proactive, inclusive, transparent planning takes time, resources, & commitment
			• Frameworks for safe/ethical inclusion before regulatory submissions have already been pioneered successfully
			• Multi-disciplinary collaboration is both possible and essential!
			• Research marches on for new methods of HIV prevention, but plans & timelines for inclusion of pregnant & BF people are not transparent to advocates
			• Rationales for exclusion, even if temporary, could be made available
			• **"Insufficient safety data" rationale typically has insufficient detail** –need to ask **how & why**

Some questions for consideration

Questions	What's a desirable outcome here?
Is there a possibility (or intention) that product will be used by someone at risk for pregnancy? If yes, is there a plan for understanding safety/acceptability in pregnancy and BF? What is it? If not, why not?	We have adequate range of choices for everyone at risk for HIV. People have HIV prevention choices where risk/benefit profile is well understood – including during pregnancy and BF.
Are reproductive safety studies in animals completed?	These studies are completed. If not completed, they are underway. If not underway, they are planned, budgeted, undertaken, and reported well before efficacy studies start.
When in the research timeline will pregnant and BF people be included and why?	We understand safety, pharmacokinetics (drug levels) for mothers and infants, and acceptability for mothers before products come to market.
For trials that exclude pregnancy and BF, will data be collected on key outcomes when unplanned exposures occur? If so, what, how, and when?	We have maximized opportunities to collect high quality data on key outcomes. Stakeholders are familiar with valid and feasible strategies to do this.
For approved products with inadequate data in pregnancy and BF, why was this approach taken?	We understand the who, how, and why of missed opportunities, and we hold our field accountable.
What do we still need to learn about optimizing access, feasibility for pregnant and BF populations?	We realize that the journey doesn't end with an approved product! "Rollout research" is inclusive and well-funded.

Thank you!

Extra slides

Pregnant people living with HIV also make bNAbs

- We just haven't figured out yet how to use them for prevention!
- >180,000 infants become infected every year via vertical transmission of HIV
  - Despite effective maternal antiretroviral treatment!
- Some researchers are investigating bNAbs from maternal plasma to see if they might be part of a strategy to eliminate perinatal HIV transmission
  - However, important to avoid a response that lets some viruses escape – particular the ones called T/F that start infection in infants

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Which drugs have pregnancy data in the APR?

Abacavir

Abacavir+Lamivudine

Abacavir+Lamivudine+Zidovudine

Adefovir Dipivoxil

Atazanavir

Darunavir

Didanosine

Efavirenz

Efavirenz+Lamivudine+Tenofovir Disoproxil Fumarate

Efavirenz+Emtricitabine+Tenofovir Disoproxil

Entecavir

Lamivudine

Lamivudine+Tenofovir Disoproxil Fumarate

Lamivudine+Zidovudine

Lopinavir+Ritonavir

Nevirapine/Nevirapine extended release

Ritonavir

Stavudine

Tenofovir Disoproxil

Tenofovir Disoproxil+Emtricitabine

Zidovudine (Oral)

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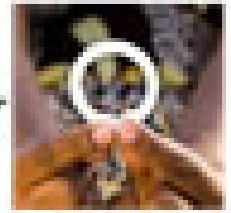
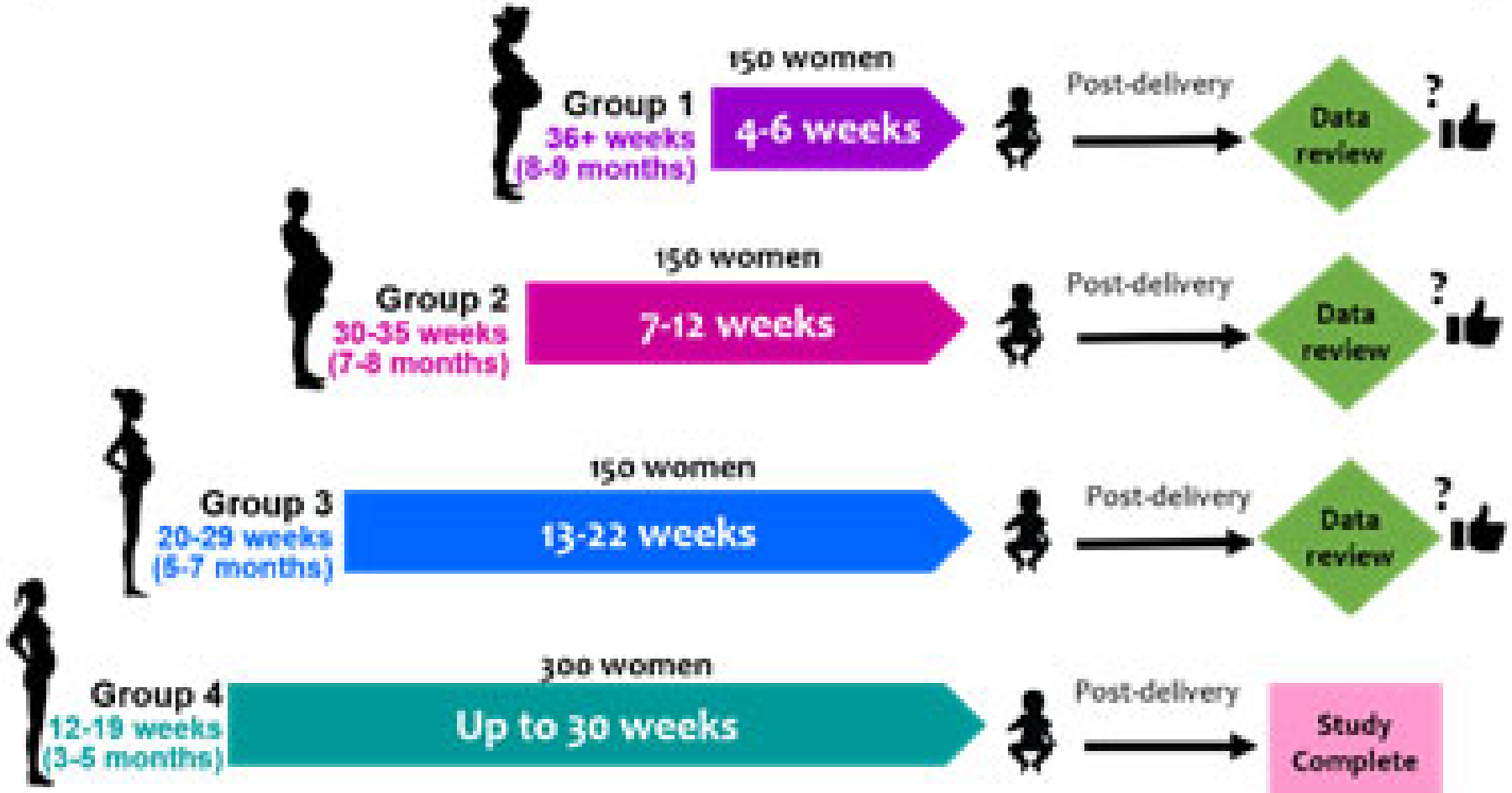
or



DELIVER will be conducted in four phases with one group enrolled at a time, beginning with women who are late into their pregnancies. Study participants will be randomly assigned to use either Truvada as daily oral PrEP or the monthly dapivirine ring until the time they deliver, with each group of women using their assigned product for longer periods of time, as depicted in the color bars below.



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Pregnancy data from Phambili study

Web appendix table 3: Pregnancies [a]

No. of women becoming pregnant (%)	35/178 (19.7%)	28/182 (15.4%) p (p=0.33) [b]
No. of pregnancies	36	30
No. occurring after the vaccination period	33 (91.7%)	26 (86.7%)
No. occurring post-unblinding	30 (88.3%)	23 (76.7%)
No. of known outcomes	36	29
Full term live birth (%)	20 (55.6%)	15 (51.7%)
Premature live birth (%)	7 (19.4%)	4 (13.8%)
Elective/therapeutic abortion (%)	7 (19.4%)	6 (20.7%)
Spontaneous abortion (%)	1 (2.8%)	3 (10.3%)
Spontaneous fetal deaths/still birth (%)	0 (0%)	1 (3.4%)

[a] Pregnancy data are for pregnancies reported as of August 31, 2009 (event cutoff date), with follow-up for outcomes through January 15, 2010.

[b] P-values are from Fisher exact tests comparing none vs any severity of the symptom. P-values are not adjusted for multiple comparisons

Supplement to: Gray GE, Allen M, Moodie Z, et al on behalf of the HVTN 503/Phambili study team. Safety and efficacy of the HVTN 503/Phambili Study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis 2011; published online May 12. DOI:10.1016/S1473-3099(11)70098-6.

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