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Global Consultation to Plan for Inclusion of Pregnant and Lactating Populations in a Phase 3 PrEP Clinical Trial

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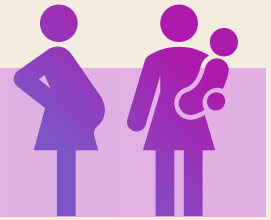
Introduction

- HIV acquisition risk increases during pregnancy and postpartum periods[1,2]
  - Implications for both the pregnant individual and child
  - The World Health Organization and Centers for Disease Control and Prevention both recommend using pre-exposure prophylaxis (PrEP) during these times for those who would benefit from its use[3,4]
- Pregnant and lactating populations (PLP) are often excluded from clinical trials, thus limiting safety and pharmacokinetic (PK) data for these populations[5]
  - Median time from regulatory approval of an antiretroviral (ARV) to first PK data in PLP is **6 years**
- It is important to understand PrEP safety and efficacy in PLP[6]
  - Safety for both PLP and child
  - Impact of physiologic changes on PrEP PK and efficacy
- Lenacapavir (LEN) is an HIV capsid inhibitor being studied for PrEP
  - Preclinical studies do not indicate harmful effects of LEN on fertility, pregnancy, fetal development, or postnatal development

1. Thomson KA. *J Infect Dis*. 2018;218(1):16-25; **2.** Vazquez L. *AIDS Patient Care STDs.* 2019;33:2149; **3.** CDC US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update Clinical Practice Guideline. 2021; **4.** WHO. Preventing HIV during Pregnancy and Breastfeeding in the Context of PrEP. 2017 July; **5.** Colbers A. *Clin Infect Dis.* 2019;69:1254-1258; **6.** The PHASES Working Group. Ending the evidence gap for pregnant women around HIV and co-infections: A call to action. 2020 July.

Recent Conceptual Shifts For Research in Pregnancy

	Shift from...	...To
Population Definition	**Vulnerable** population • Suggests unable to give valid consent • Subject to exploitation	**Complex** population • Describes physiologic changes in pregnancy and ethical considerations
Research Approaches	Protection **from** research • Risks of drug in pregnancy not observed until drug is in clinical setting	Protection **through** research • Allowing PLP access to studies that may offer benefit • Data collection in a controlled research setting to minimize potential population risks
Eligibility	Presumptive **exclusion** • General exclusion from clinical trials • Need justification for inclusion	Equitable **inclusion** • Evaluating potential risks to PLP and their children • Need justification for exclusion



Adapted from Pregnancy and HIV/AIDS Seeking Equitable Study (PHASES) Working Group.[6]

- Regulatory authorities and experts in the field published guidance documents advocating for PLP inclusion in clinical trials of novel antiretrovirals[7-10]

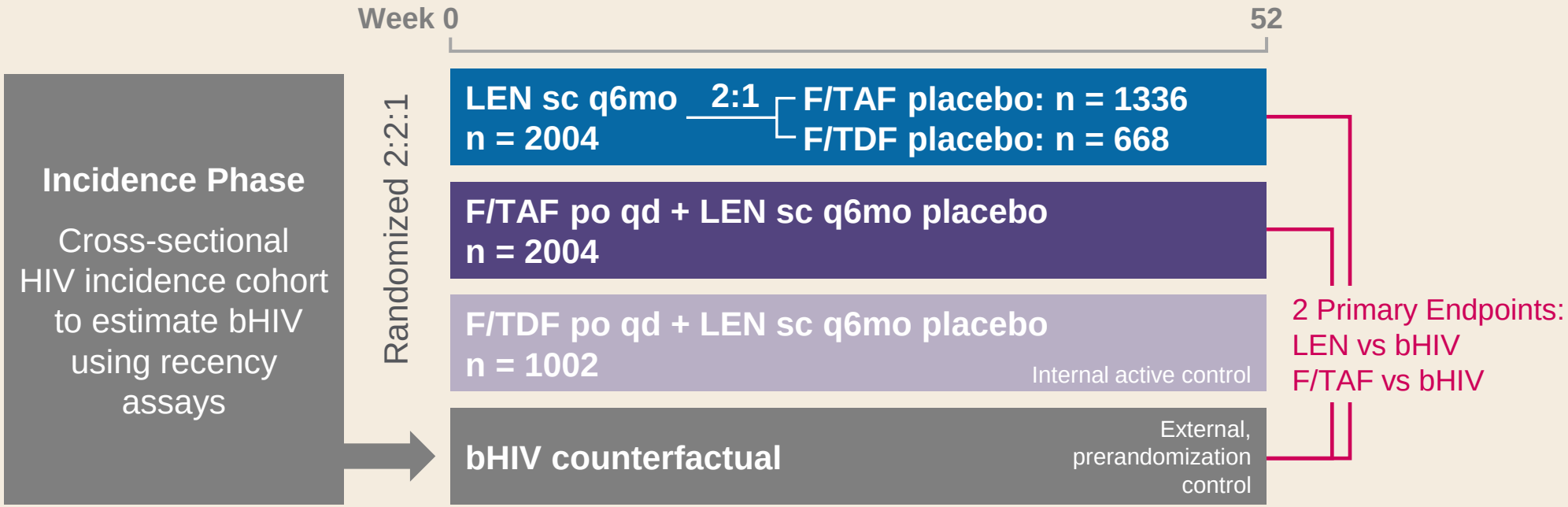
7. Committee on Ethics. Obstet Gynecol. 2015;126:e100-7; **8.** Food and Drug Administration. Enhancing the diversity of clinical trial populations—eligibility criteria, enrollment practices, and trial designs: guidance for industry; Nov 2020; **9.** Food and Drug Administration. Pregnant women: scientific and ethical considerations for inclusion in clinical trials: guidance for industry; Apr 2018; **10.** WHO, IMPAACT, and CIPHER. Research for informed choices: accelerating the study of new drugs for HIV in pregnant and breastfeeding women: a call to action.

Description

Study Design

PURPOSE 1

Cisgender Women: N = 5010

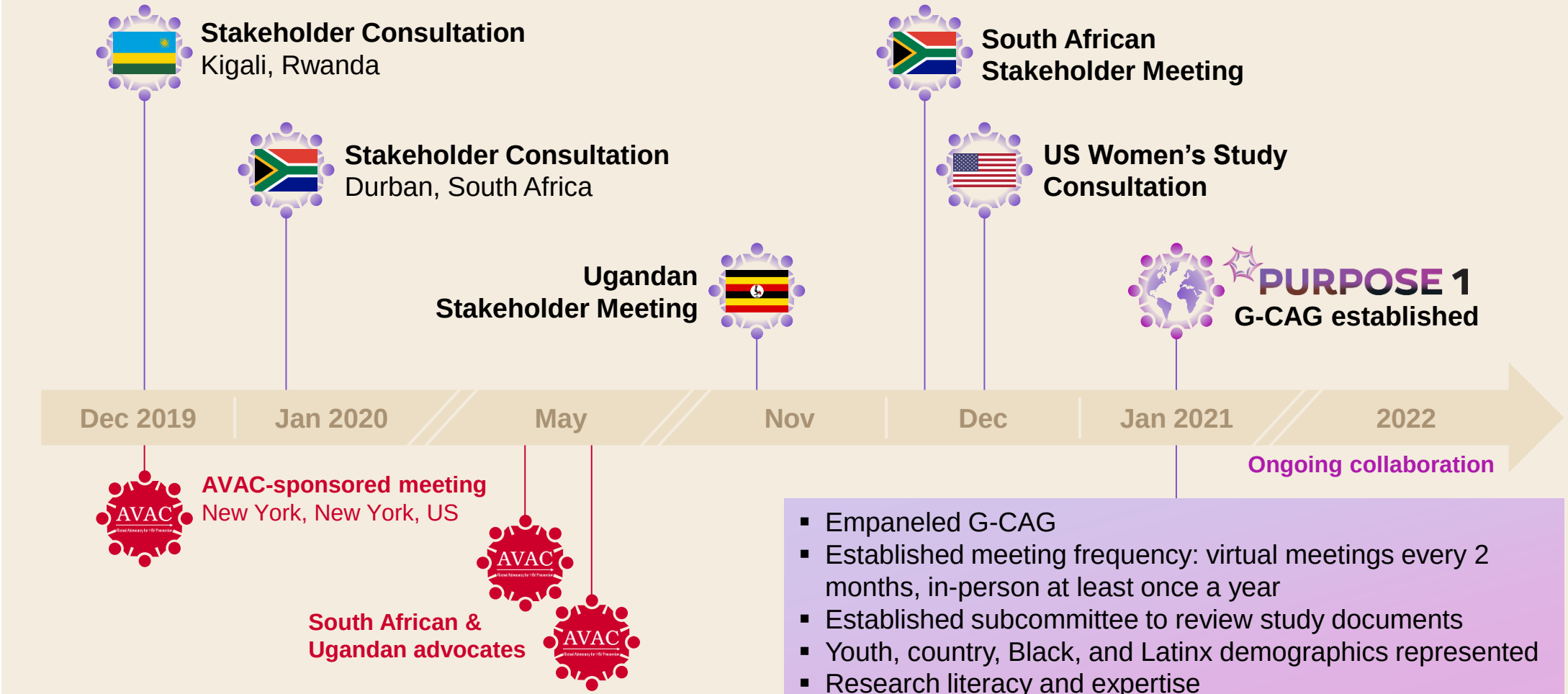


ClinicalTrials.gov NCT04994509.
bHIV = background HIV incidence; F/TAF = emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate.

- Phase 3 study with sites in South Africa and Uganda with high HIV incidence (> 3.5/100 person-years)

Description

Continuous Community Engagement



G-CAG = global community advisory/accountability group.

PLP Inclusion Identified as a Priority

- Include PLP and study PK in pregnancy, breast milk, and infant plasma
- Collect pregnancy, maternal, and infant outcomes

- Assess intimate partner violence and social harms, and provide counseling and social work support for participants and families

- Provide contraception (optional), HBV vaccines, and STI treatments
- Drug-drug interaction studies with LEN and long-acting contraceptives

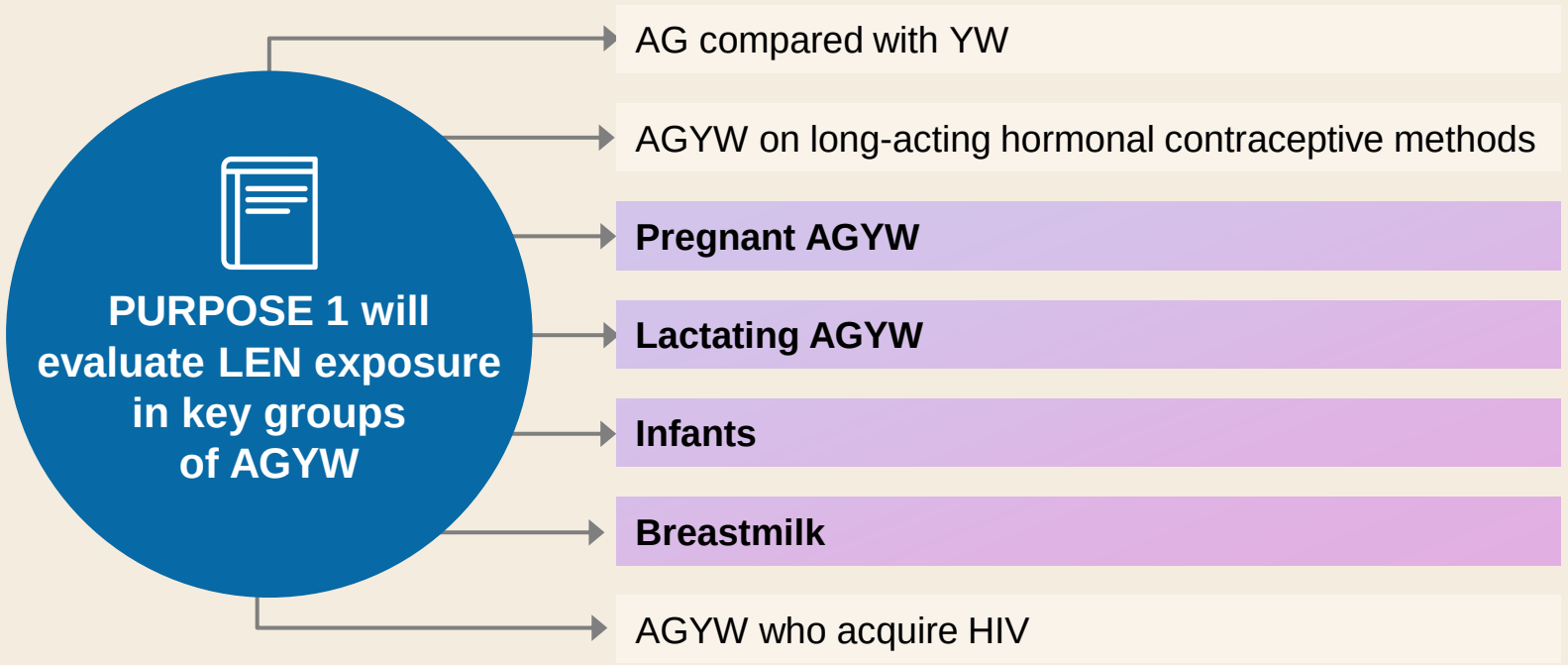
HBV = hepatitis B virus; STI = sexually transmitted infections.

- Meetings with stakeholders (community advocates, trial investigators, scientists not involved in the trial, ethics review committee members, and regulators) and the PURPOSE 1 G-CAG during trial design identified priorities:
  - PLP inclusion
  - Ensure trial sites had experience in caring for the complex PLP

Inclusion of PLP

- PURPOSE 1 is the first Phase 3 PrEP clinical trial to include PLP
  - All participants assigned female at birth are supported in their reproductive choices
- The PURPOSE 1 protocol intentionally addresses stakeholder priorities and evidence gaps by allowing:
  - Individuals not on contraception to make an informed decision to participate in the trial
  - Individuals who become pregnant to make an informed decision to continue study drug through pregnancy and lactation
- Inclusion of PLP and supporting participants' reproductive choices will contribute to safety, efficacy, and adherence data for LEN and F/TAF as potential HIV prevention agents, thereby affording more PrEP options for PLP

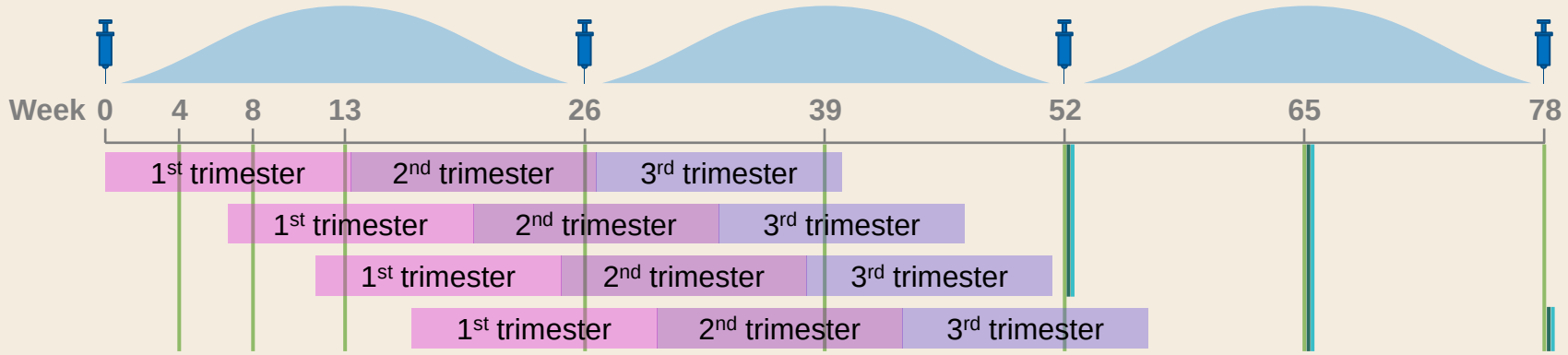
Pharmacokinetic Substudy Among PLP



AG = adolescent girls; YW = young women.

- A dedicated substudy with qualitative PK assessments in PLP and infants was defined as a protocol objective

Pregnancy, Breast Milk, and Infant PK Substudies



- Substudy objectives:
  - To describe maternal systemic drug concentrations during pregnancy and postpartum period
  - To qualitatively assess drug concentrations in maternal breast milk and paired infants
- Approach:
  - No additional visits needed
  - Drug concentration sampling covered in main consent—no additional samples for maternal systemic PK
  - Breast milk and infant samples collected at 2 scheduled visits postdelivery
    - Participants can opt out of breast milk and infant PK sampling
- Compared with studies of prior HIV drugs, the pregnancy, lactation, and breast milk substudy in PURPOSE 1 will provide data on these key populations at the time of approval instead of years later

Importance of Dedicated Dialogue

- Dedicated dialogue with stakeholders across countries where the study is conducted results in:
  - Understanding diverse perspectives:
    - One study site was reluctant to allow PLP to remain on study drug, potentially because the site was not up to date with new guidance
    - Some sites made provisions to involve fathers (if available) in consent for infant sample collection
  - Discussing study design to ensure feasibility:
    - Frequency of monitoring
    - Ease of parental consent
    - Balancing concern for infant sampling with need for the data
    - Use of breast pumps vs manual expression for breast milk collection

Recommendations

- Strong stakeholder engagement supports the inclusion of complex populations in clinical trials
- Inclusion of PLP in HIV prevention trials will inform safety and proper dosing, potentially accelerating safe access

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Disclosures

DD Diallo, Y Raphael, N Yola, B Jjuuko, M Happy, E Spooner, D Moodley, F Matovu-Kiweewa: members of the PURPOSE 1 G-CAG; **M Das, J Yager, A Kintu, C Carter, P Arora, J Baeten:** Gilead.