PURPOSE

Prevention with PURPOSE

Lenacapavir Update in Pregnancy

Christoph Carter, MD, PhD

www.purposestudies.com

IMAACT Annual Meeting

Tuesday, 24 September 2024

Significant Unmet Need for New PrEP Options in Pregnant and Lactating People

Requires innovation in *both SCIENCE* and *HEALTH EQUITY*

Science

Trial design

Investigational drug

Health Equity

Partnerships

Voice of PWBP and community (G-CAGs)

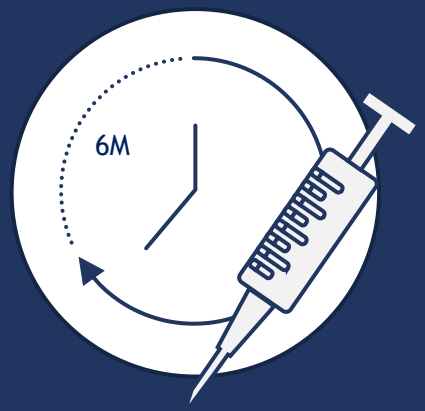
Person-centric design

Diversity, equity, inclusion

Innovation without intention could exacerbate inequality

G-CAG, Global Community Advisory Groups; PrEP, pre-exposure prophylaxis.

Product

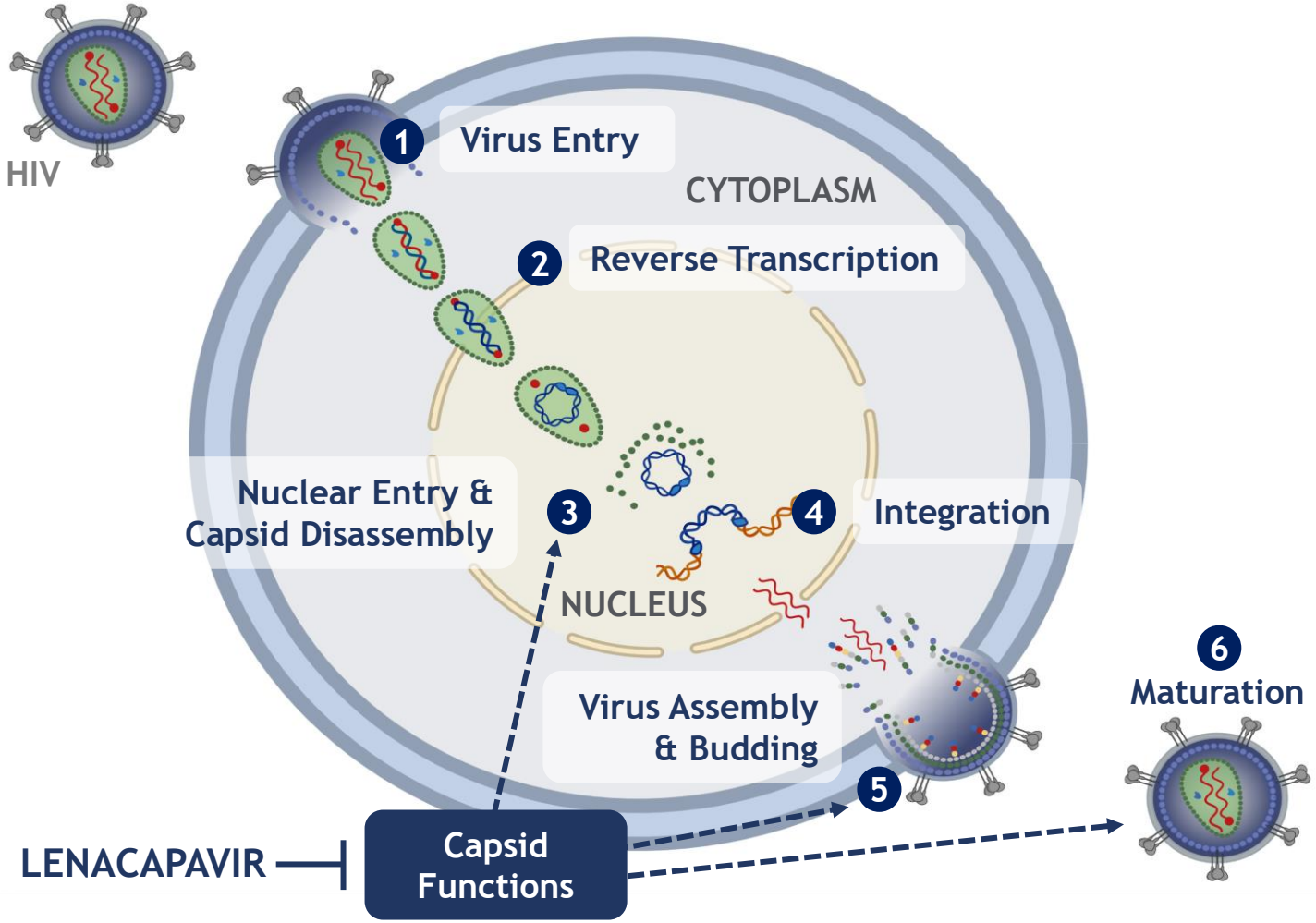


Study Design

Innovation in the Science

Developing a long-acting antiretroviral for HIV prevention

Lenacapavir: A First-in-Class Multistage HIV Capsid Inhibitor



LEN is a small-molecule capsid inhibitor:

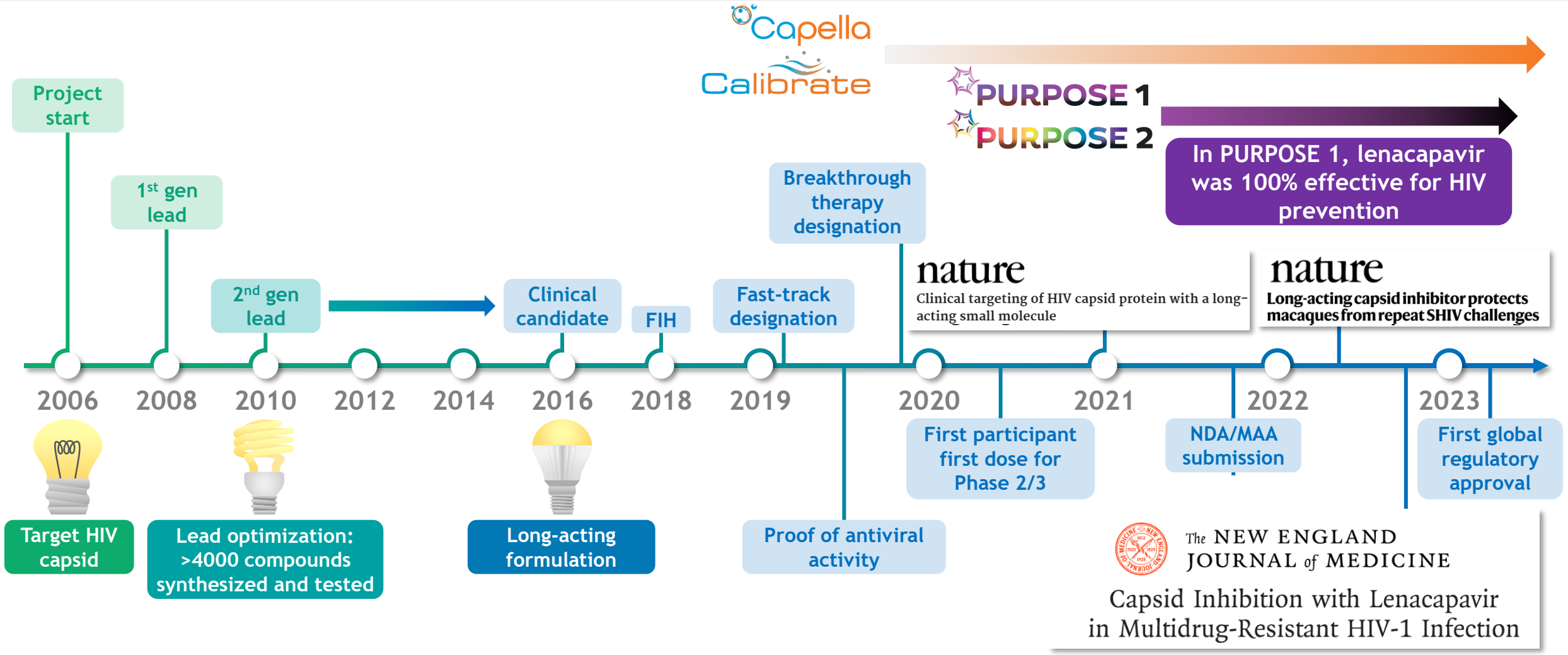
- High potency (EC_{50} = 100 pM)
- Multistage, selective inhibitor of HIV capsid mechanism
  - Pre- and post-integration
- Well-characterized PK with long half-life
- Extensive safety database in PWH and Phase 1
- Proof of concept for prevention of vaginal and rectal acquisition in non-human primates

- **Approved** in combination with an optimized background regimen for **HIV treatment** in persons with multidrug-resistant HIV-1 infection in the US, EU, and several other countries globally
- **LEN (twice yearly, subcutaneous, single agent) is being studied for HIV PrEP in the PURPOSE Program**

EC_{50}, half maximal effective concentration; EU, Europe; HIV, human immunodeficiency virus; LEN, lenacapavir; PK, pharmacokinetics; pM, picomolar; PrEP, pre-exposure prophylaxis; PWH, people with HIV; US, United States.

Dvory-Sobol H, et al. Curr Opin HIV AIDS. 2022;17:15-21.

Gilead's Commitment to Long-Acting Innovation



FIH, first-in-human; gen, generation; HIV, human immunodeficiency virus; MAA, marketing authorization application; NDA, new drug application.

Lenacapavir for PrEP:

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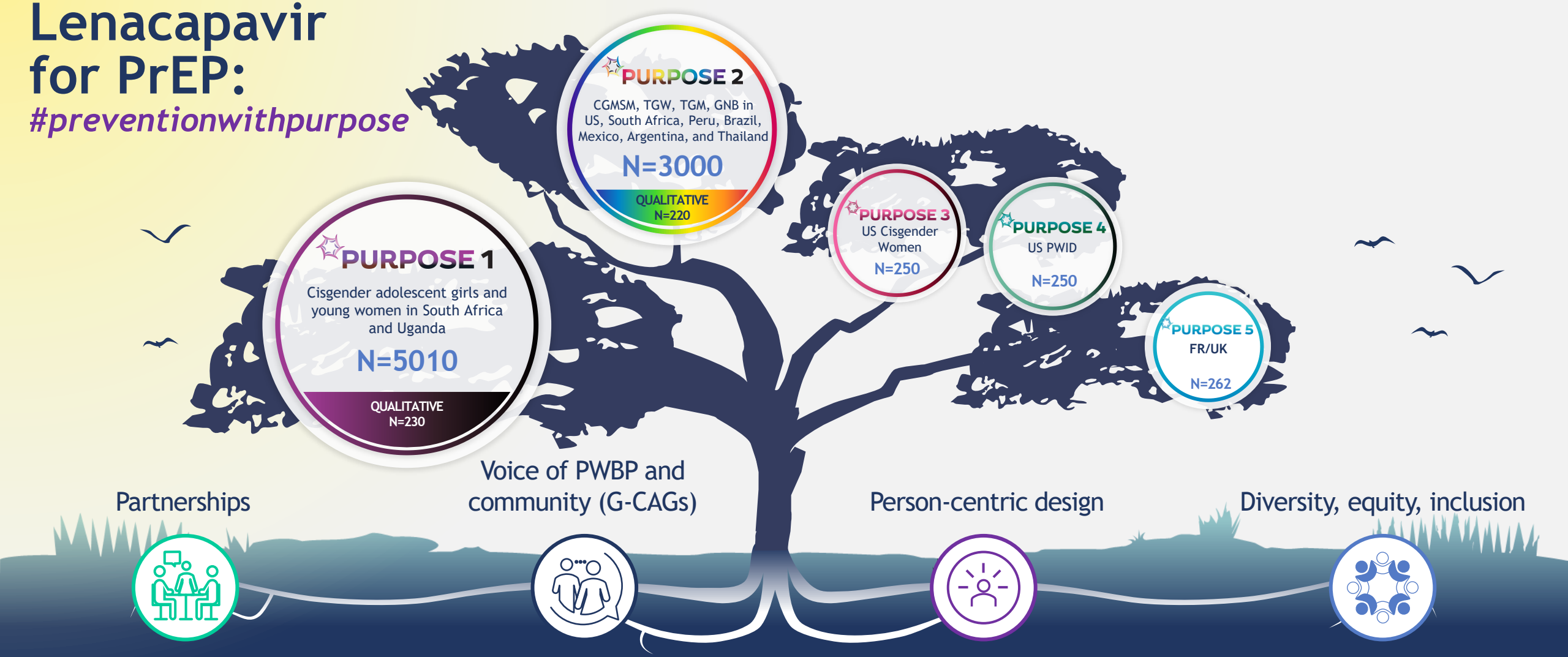
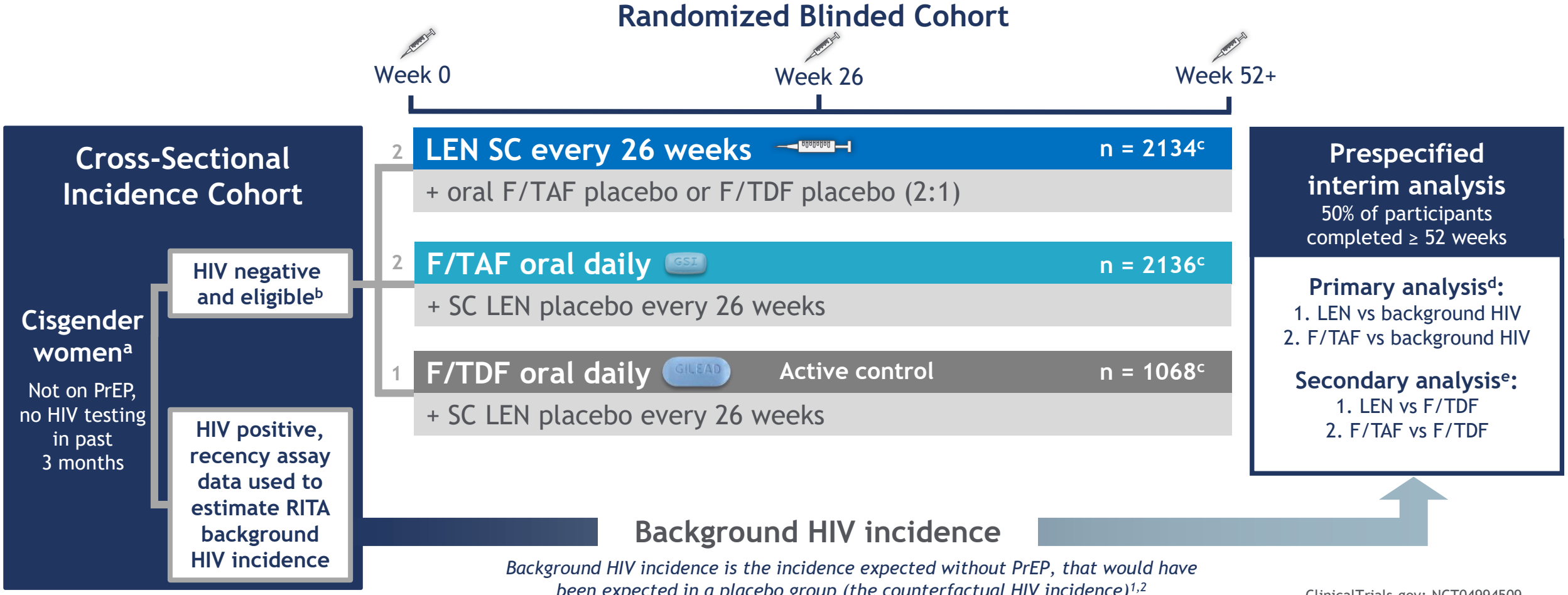


Proof of concept that capsid inhibitors prevent SHIV in non-human primates;
Robust PK and safety database in persons with and without HIV

Capella **LEN for HIV Tx in MDR HIV**

CGMSM, cisgender men who have sex with men; FR, France; G-CAG, Global Community Advisory Groups; GNB, gender nonbinary individuals; MDR, multi-drug resistant; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; PWBP, people who would benefit from PrEP; PWID, people who inject drugs; SHIV, simian-human immunodeficiency virus; TGM, transgender men; TGW, transgender women; Tx, treatment; UK, United Kingdom; US, United States.
PURPOSE 1 ClinicalTrials.gov identifier: NCT04994509; PURPOSE 2 ClinicalTrials.gov identifier: NCT04925752; Purpose Studies. Available at: https://www.purposestudies.com/. Accessed July 2023.

PURPOSE 1 Study Design



ClinicalTrials.gov: NCT04994509

[a]The first participant was screened in August 2021, the 50th percentile participant was randomized in May 2023, and the last participant was randomized in September 2023. [b]Eligibility criteria included: weight ≥35 kg, eGFR ≥60 ml/min, not pregnant. [c]n numbers represent the full analysis set for efficacy analyses. [d]IRR was assessed using a Wald test or likelihood ratio test if there were zero infections.[1,2] [e]IRR was assessed using Poisson regression or an exact conditional Poisson regression model in case of zero infections. eGFR, estimated glomerular filtration rate; IRR, Incidence rate ratio; RITA, recent-infection testing algorithm.

1. Gao F, et al. *Stat Commun Infect Dis.* 2021;13(1):20200009. **2.** Shao Y, Gao F. *Stat Commun Infect Dis.* 2024;16(1):20230004.

Primary, Secondary, and Exploratory Outcomes

PURPOSE 1

Incidence phase	1º EP	bHIV incidence rate in the screened population
Randomized phase Primary and secondary outcomes	1º EP	1. LEN efficacy vs bHIV 2. F/TAF efficacy vs bHIV
	2º EP	LEN efficacy vs F/TDF F/TAF efficacy vs F/TDF LEN and F/TAF efficacy in adherent participants LEN and F/TDF safety and tolerability LEN and F/TAF safety and tolerability in adolescents

Randomized phase Exploratory outcomes	LEN adherence by on-time injection LEN plasma levels
	F/TAF and F/TDF adherence by TFV-DP in DBS
	LEN acceptability
	LEN PK in pregnant and postpartum AGYW, in breast milk, and in infants
	LEN and long-acting hormonal contraceptive PK in AGYW

LEN PK during pregnancy is a PURPOSE 1 exploratory objective

bHIV, background HIV; EP, endpoint; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; LEN, lenacapavir.
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Lenacapavir for PrEP:

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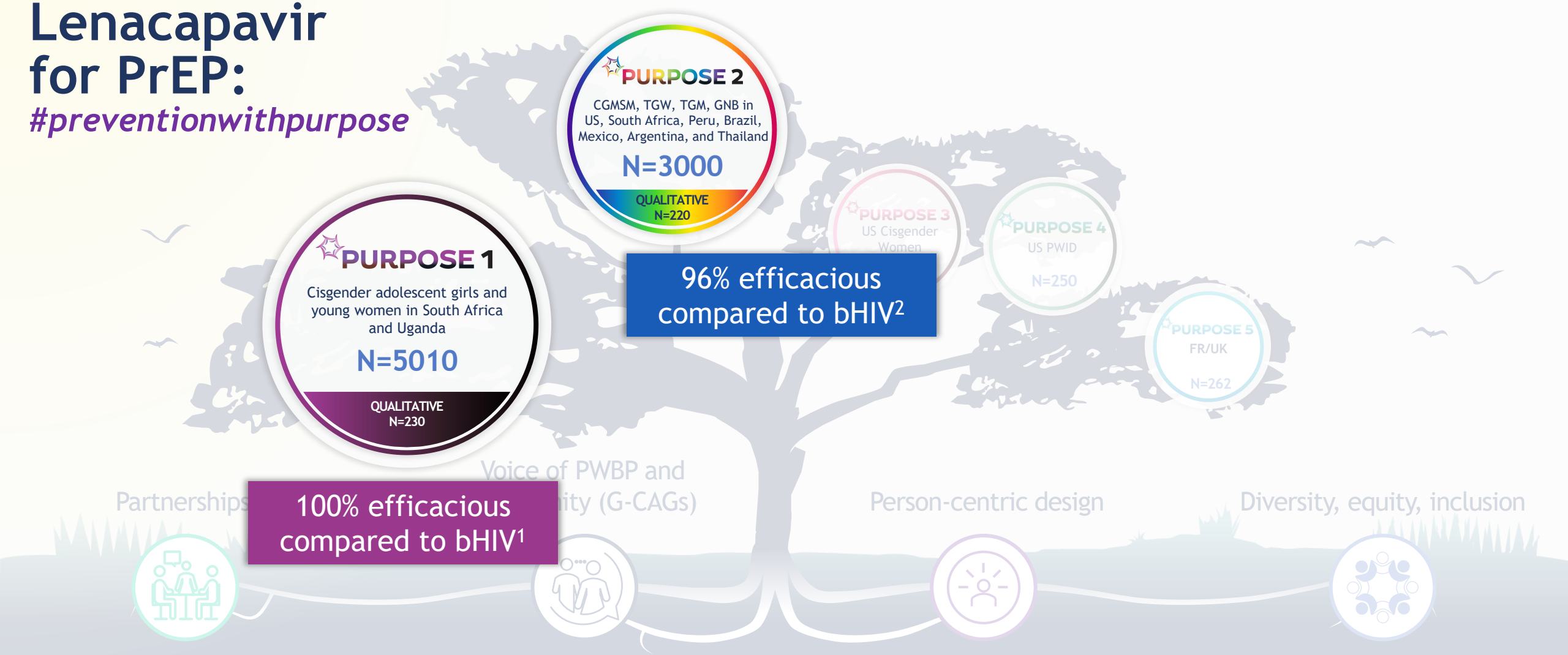

Proof of concept that capsid inhibitors prevent SHIV in non-human primates;
Robust PK and safety database in persons with and without HIV

Capella **LEN for HIV Tx in MDR HIV**

1. Bekker et al. N Engl J Med. 2024 Jul 24. 2. https://www.gilead.com/news-and-press/press-room/press-releases/2024/9/gileads-twiceyearly-lenacapavir-for-hiv-prevention-reduced-hiv-infections-by-96-and-demonstrated-superiority-to-daily-truvada-in-second-pivotal-ph

CGMSM, cisgender men who have sex with men; FR, France; G-CAG, Global Community Advisory Groups; GNB, gender nonbinary individuals; MDR, multi-drug resistant; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; PWBP, people who would benefit from PrEP; PWID, people who inject drugs; SHIV, simian-human immunodeficiency virus; TGM, transgender men; TGW, transgender women; Tx, treatment; UK, United Kingdom; US, United States.

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Partnerships

Voice of PWBP and community (G-CAGs)

Person-centric design

Diversity, equity, inclusion

Innovation in Health Equity

Facilitating the inclusion of pregnant and lactating people in PURPOSE 1

Keys to Including PLP in PURPOSE 1

Preclinical science

Thorough understanding of study drug effects on fertility, fetal development, and postnatal development

The voice of the people

Engagement with key community stakeholders, such as our Global Community Advisory and Accountability Group, including pregnant and lactating women

Winning over hearts and minds

Engagement (and sometimes debate) with regulatory agencies, ethics committees and institutional review boards

Study design

Sites and PIs with experience caring for pregnant women in a research setting

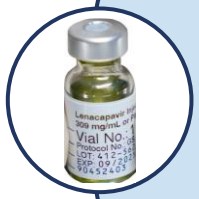
Collect key pregnancy data without creating undue burden or excessive complexity

G-CAGs, Global Community Advisory Groups; GAHT, gender-affirming hormone therapy; HC, hormone control; HIV, human immunodeficiency virus; LEN, lenacapavir; PI, principal investigator; PLP, pregnant and lactating people; PrEP, pre-exposure prophylaxis; PWBP, people who would benefit from PrEP.

Preclinical science: F/TDF, F/TAF, and Lenacapavir in Pregnant and Lactating People

- The safety of F/TDF in PLP has been established[1]

- The safety of F/TAF during pregnancy has been established[2,3]
- Currently available data on F/TAF use lactating people have not revealed safety concerns
  - PK studies have shown low TAF levels in breast milk and cord blood[4]



- Preclinical studies do not indicate harmful effects of LEN on fertility, pregnancy, fetal development, postnatal development, or juvenile development

F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; PK, pharmacokinetics; PLP, pregnant and lactating people; TAF, tenofovir alafenamide.

1. World Health Organization. (2017). WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection: module 1: clinical. World Health Organization; 2. Zhang, et al. AIDS. 2024 Jan 1;38(1); 3. Lockman et al. Lancet. 2021 Apr 3;397(10281):1276-1292. 4. Bojun L, et al. 29th Annual Conference of the APASL 2020, Abstract 1444.

Listening to the Voice of the People

Stakeholder Consultation
Kigali, Rwanda

Stakeholder Consultation
Durban, South Africa

Ugandan Stakeholder Meeting

US Women's Study Consultation

PURPOSE G-CAGs

Every ~2 months

- Empaneled the PURPOSE 1 and PURPOSE 2 G-CAGs (*early 2021*)
- G-CAG members advised on study design and conduct, and have led presentations on PURPOSE studies, including on inclusion of PLP

2019 | 2020 | 2021 | 2022 | 2023 | Ongoing collaboration

AVAC-Sponsored Meeting
New York, USA

South African & Ugandan Advocates

US MSM and Trans Stakeholder Meeting

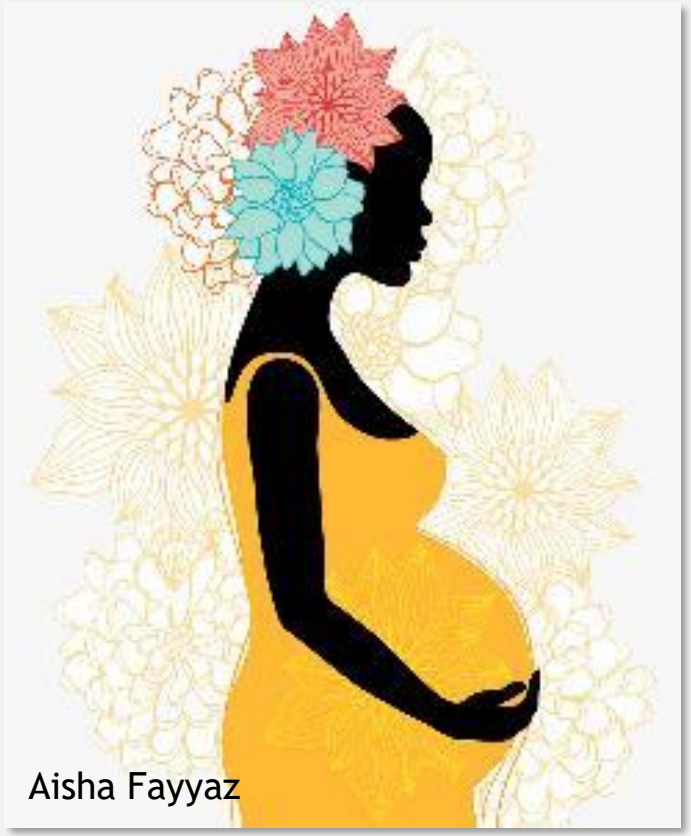
South African Stakeholder Meeting

F2F Meeting
Johannesburg and site visits in Durban and Cape Town
June 2022

F2F Meeting
Foster City, California, USA
September 2022

AVAC, AIDS Vaccine Advocacy Coalition; DEI, diversity, equity, and inclusion; F2F, face-to-face; G-CAG, Global Community Advisory Groups; MSM, men who have sex with men; PLP, pregnant and lactating people; US(A), United States (of America).

PURPOSE 1 The Voice of the People



Nothing about us without US

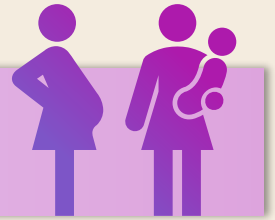
"Without the complete and explicit inclusion of adolescents and pregnant people in every aspect of HIV prevention research like PURPOSE 1, especially that which expands options and respects body autonomy, there is no end to the HIV epidemic. Period."

Kigali, Rwanda, December 2019

HIV, human immunodeficiency virus.

Winning Over Hearts and Minds: Key Paradigm Shifts Driven by IMPAACT, PHASES, and WHO

	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.[1]

Guidance published by experts in the field were key to convincing stakeholders to support PLP inclusion in PURPOSE 1[1-5]

PLP, pregnant and lactating people.

1. The PHASES Working Group. Ending the evidence gap for pregnant women around HIV and co-infections: A call to action. Jul 2020; 2. Committee on Ethics. Obstet Gynecol. 2015;126:e100-7; 3. US Food and Drug Administration. Enhancing the diversity of clinical trial populations—eligibility criteria, enrollment practices, and trial designs: guidance for industry; Nov 2020; 4. US Food and Drug Administration. Pregnant women: scientific and ethical considerations for inclusion in clinical trials: guidance for industry; Apr 2018; 5. 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.

Study Design: Inclusion of PLP in PURPOSE 1 and Beyond

PURPOSE 1

- Participants may choose whether to receive contraception
- Participants who become pregnant while on study **are able to continue on study** after reconsent

PURPOSE 2

- Contraception required for those AFAB of childbearing potential
- Participants who become pregnant while on study **are able to continue on study** after reconsent[a]

HPTN 102 PURPOSE 3

- Participants may choose whether to receive contraception
- Participants who become pregnant while on study **are be able to continue on study** after reconsent

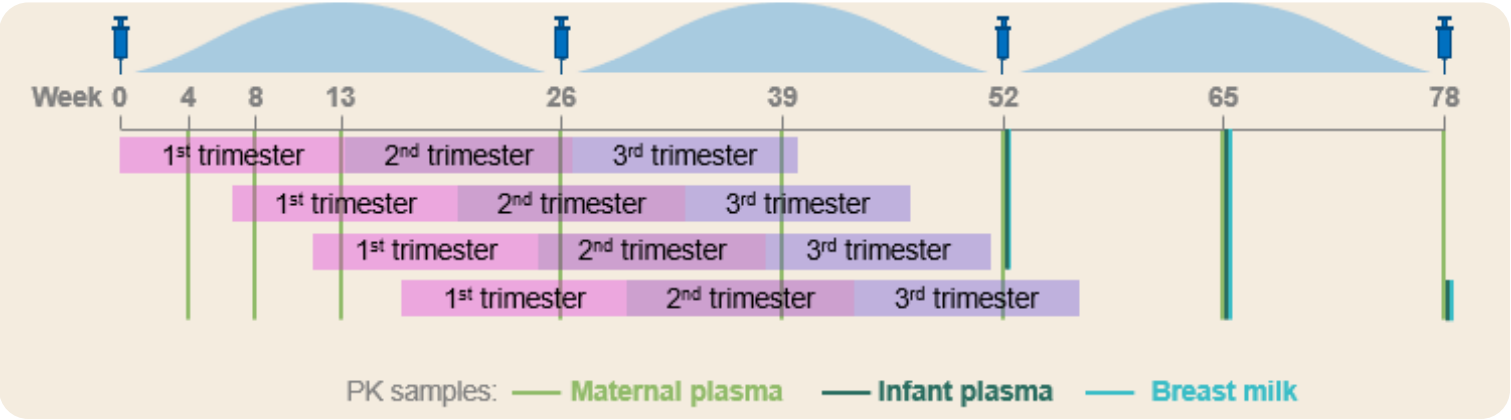
HPTN 103 PURPOSE 4

- Participants may choose whether to receive contraception
- Participants who become pregnant while on study **are able to continue on study** after reconsent

[a]If taking testosterone, they must discontinue testosterone if continuing the pregnancy and wish to continue study drug.
AFAB, assigned female at birth; HPTN, HIV Prevention Trials Network; PLP, pregnant and lactating people.
PURPOSE studies. Available at: https://www.purposestudies.com/. Accessed July 2024.

Study Design: Collection of Key Pregnancy Data in PURPOSE 1

Pregnancy, Breast Milk, and Infant Substudy



- Participants who become pregnant can continue study drug after reconsent
- Data will include maternal, infant and breast milk PK

Objectives	• Describe maternal systemic drug concentrations during pregnancy and postpartum period • Assess ratios of drug concentrations between maternal plasma and breast milk or paired infant plasma
Limit burden	• No additional samples for maternal PK • Breast milk and infant samples collected at 2 scheduled visits post delivery • Participants can opt out of breast milk and infant PK sampling

We worked with investigators and sites experienced in caring for complex pregnant and lactating people

G-CAG, Global Community Advisory Group; HIV, human immunodeficiency virus; PK, pharmacokinetics; PLP, pregnant and lactating people.

Results

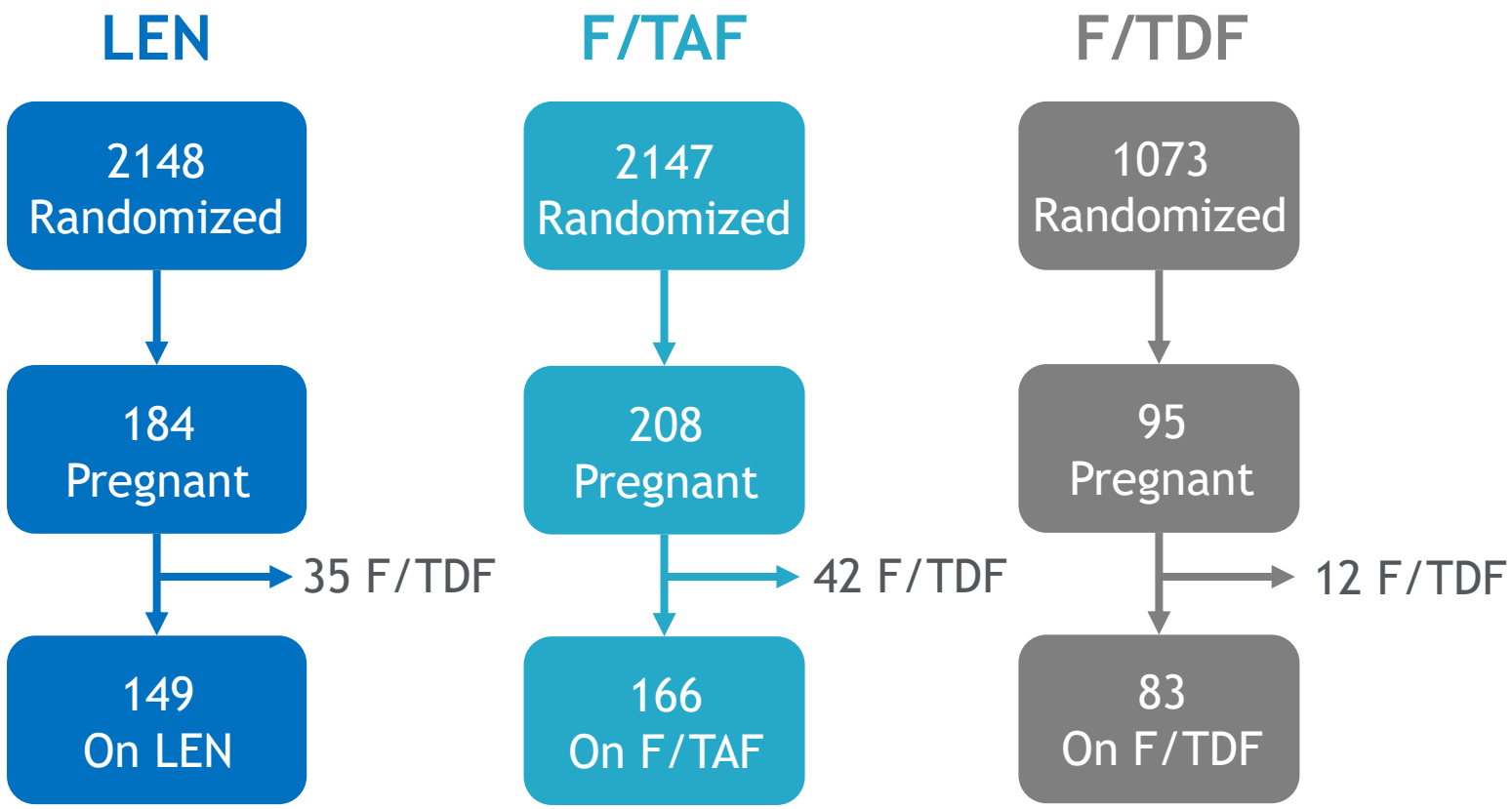
Innovation in the Science

Pregnancy Disposition

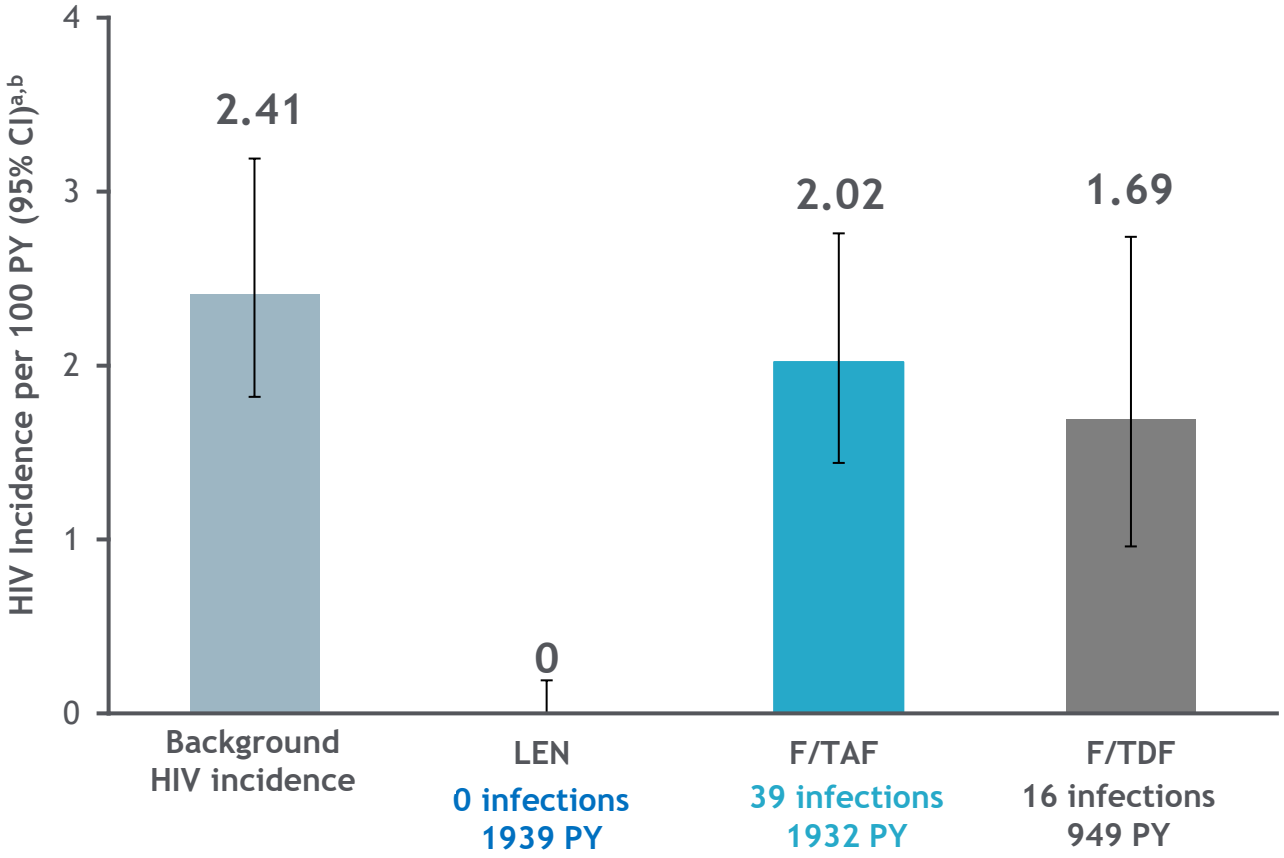
510 pregnancies among 487 participants

Participants who became pregnant could opt to reconsent and remain on randomized study drug or receive open-label F/TDF

Most pregnant participants opted to continue randomized study drug



Efficacy: Zero HIV Infections in Pregnant Women receiving LEN



5 Incident HIV infections among pregnant women:

- 0 in the LEN group
- 4 in the F/TAF group
- 1 in the F/TDF group

No cases of vertical transmission

[a]Overall n: background HIV incidence group 8094; LEN, 2134; F/TAF, 2136; F/TDF, 1068. [b]95% CIs: background HIV incidence group 1.82, 3.19, LEN 0, 0.19, F/TAF 1.44, 2.76. F/TDF 0.96, 2.74.
CI, confidence interval; PY, person-years.

Safety: Pregnancy Outcomes

Participants and Pregnancies, n (%)	LEN n = 2138	F/TAF n = 2137	F/TDF n = 1070
Participants with confirmed pregnancies	184	208	95
Confirmed pregnancies	193	219	98
Completed pregnancies	105 (54.4)	119 (54.3)	53 (54.1)
Ongoing pregnancies	88 (45.6)	100 (45.7)	45 (45.9)
Births[a]	55 (28.5)	45 (20.5)	21 (21.4)
Interrupted pregnancies	50 (25.9)	74 (33.8)	32 (32.7)
Induced abortion	30 (15.5)	40 (18.3)	20 (20.4)
Spontaneous miscarriage[b]	20 (10.4)	34 (15.5)	12 (12.2)

One congenital abnormality: polydactyly in a participant with strong family history (LEN group)

Safey: Pregnancy-Related Adverse Events

Occurring in >1 participant, excluding spontaneous abortions

Participants and Pregnancies, n (%)	LEN n = 193	F/TAF n = 219	F/TDF n = 98
Pregnancy, puerperium and perinatal conditions	30	37	17
Cephalo-pelvic disproportion	2	1	1
Gestational hypertension	2	1	1
Fetal death	3	0	0
Ruptured ectopic pregnancy	1	2	0
Anembryonic gestation	0	2	0
Fetal distress syndrome	1	0	1
Obstructed labor	0	0	2
Stillbirth	0	1	1

Next steps

- Follow all 510 pregnancies to completion
- Characterize observed LEN PK
  - Pregnant participants by trimester
  - Plasma-breastmilk ratios
  - Maternal-infant ratios
- Population PK modeling of maternal LEN concentrations

Questions?