PURPOSE

Prevention with PURPOSE

IAS 2023

HIV recency assays: lessons learned and challenges presented

Moupali Das, MD, MPH

Executive Director, HIV Clinical Development, Gilead Sciences

www.purposestudies.com

Forum for Collaborative Research, AVAC, Berkeley Satellite Symposium

Tuesday July 25th, 2023

More PrEP options urgently needed

Innovation required in *both SCIENCE* and *HEALTH EQUITY*

Trial design

Investigational drug

Partnerships

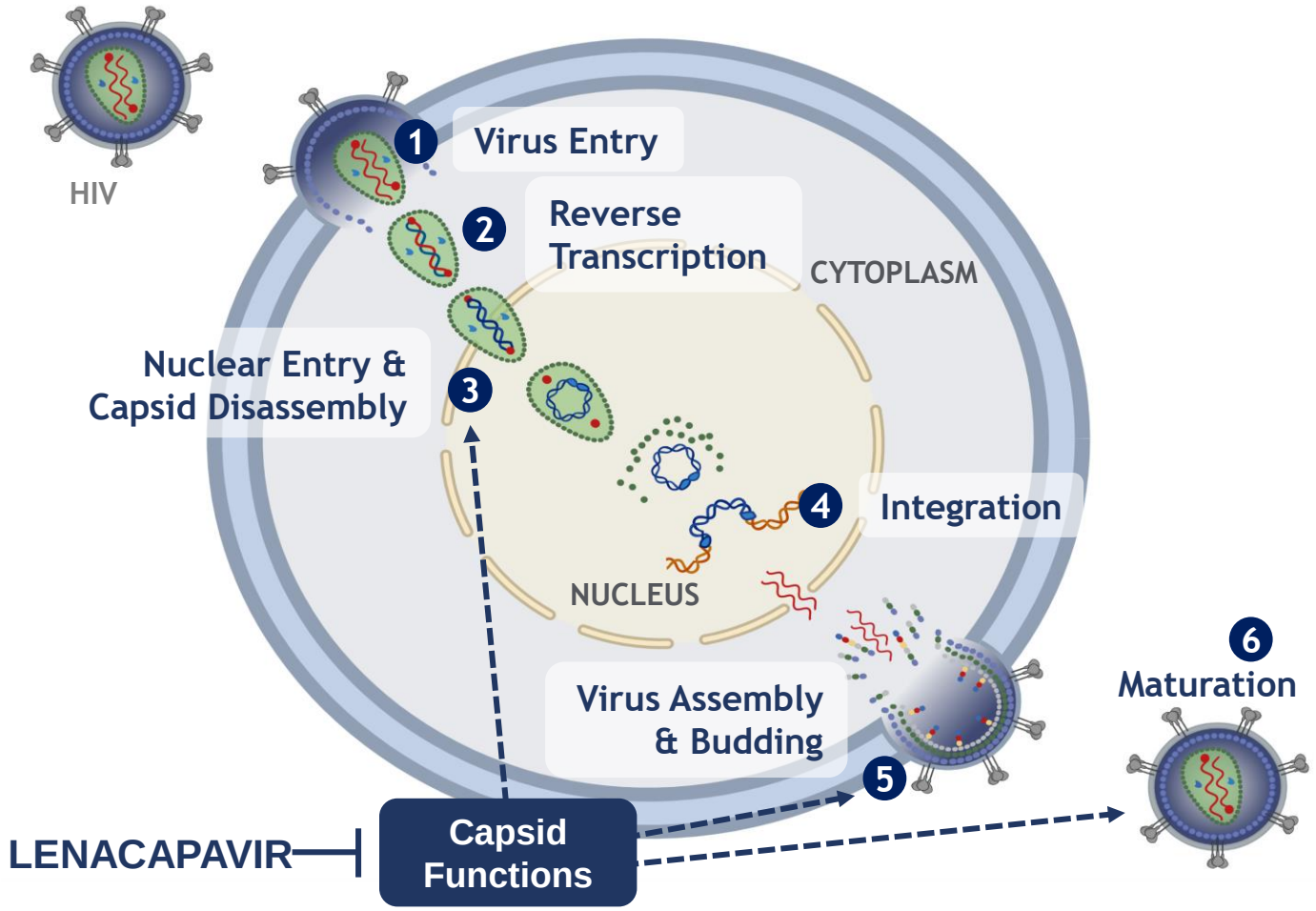
Voice of PWBP and community (G-CAGs)

Person-centric design

Diversity, equity, inclusion

G-CAG, Global Community Advisory Groups; PrEP, pre-exposure prophylaxis; PWBP, people who would benefit from PrEP.

Lenacapavir: A first-in-class multistage HIV capsid inhibitor



LEN is a small molecule capsid inhibitor:

- High potency (EC_{50} = 100 pM)
- Well-characterized PK including a long half-life
- Potential for a flexible dosing profile (oral or injectable)
- Approved in combination with an optimized background regimen for HIV treatment in persons with multidrug-resistant HIV-1 infection in Australia, Canada, Europe, Israel, Switzerland, The United Arab Emirates, United Kingdom and United States

LEN (twice yearly, subcutaneous, single agent) is being studied for HIV prevention (PrEP)

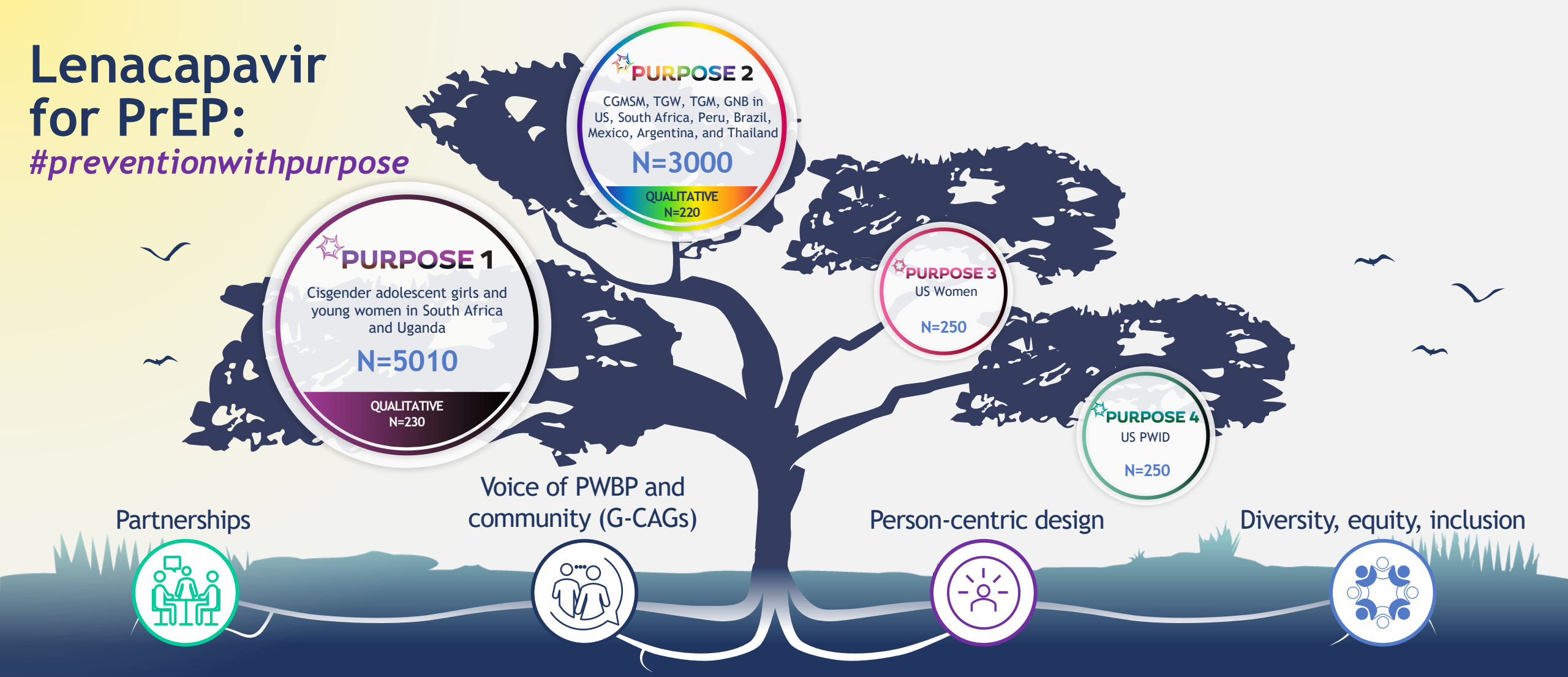
EC_{50}, half maximal effective concentration; HIV, human immunodeficiency virus; LEN, lenacapavir; PK, pharmacokinetics; pM, picomolar; PrEP, pre-exposure prophylaxis.

Scan QR code for MOA video

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

Lenacapavir for PrEP:

#preventionwithpurpose



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

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

PURPOSE 1 NCT identifier: NCT04994509; PURPOSE 2 NCT identifier: NCT04925752
CGMSM, cisgender men who have sex with men; G-CAG, Global Community Advisory Groups; GNB, gender nonbinary individuals;
LEN, lenacapavir; MDR, multi-drug resistant; 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; US, United States.

Purpose Studies. Available at: https://www.purposestudies.com/. Accessed July 2023.

Challenges facing HIV prevention clinical trial design

Superiority to placebo

Unethical in most situations given safe, efficacious PrEP options[1]

Superiority to active comparator

Requires nonadherence to the active comparator
May not be reasonable to assume superiority to active comparator[2]

Noninferiority to active comparator

Large cohort sizes with long-duration[3]
Infeasible in populations where the active comparator's efficacy has been variable in clinical trials (e.g., cisgender women)[1]

HIV, human immunodeficiency virus; F/TDF, emtricitabine/tenofovir disoproxil fumarate; PrEP, pre-exposure prophylaxis.

1. Janes H, et al. *Lancet HIV*. 2019;6:e475-82; 2. Cutrell A, et al. *HIV Clin Trials*. 2017;18:177-88; 3. Grobler AC and Karim Abdool SS *AIDS*. 2012;26:529-532.

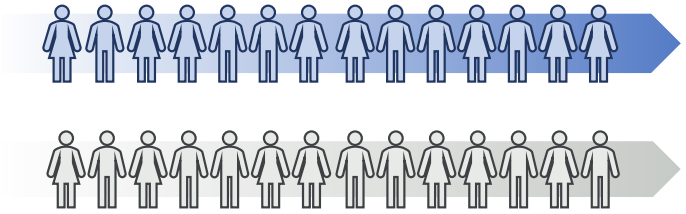
What is a counterfactual?

coun·ter·fac·tu·al: relating to or expressing what has not happened, or is not the case

Counterfactual trial design

\+ Intervention
factual

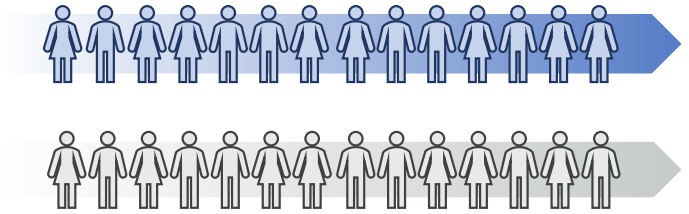
\- Intervention
counterfactual estimate



Randomized controlled trial

\+ Intervention
factual
Placebo

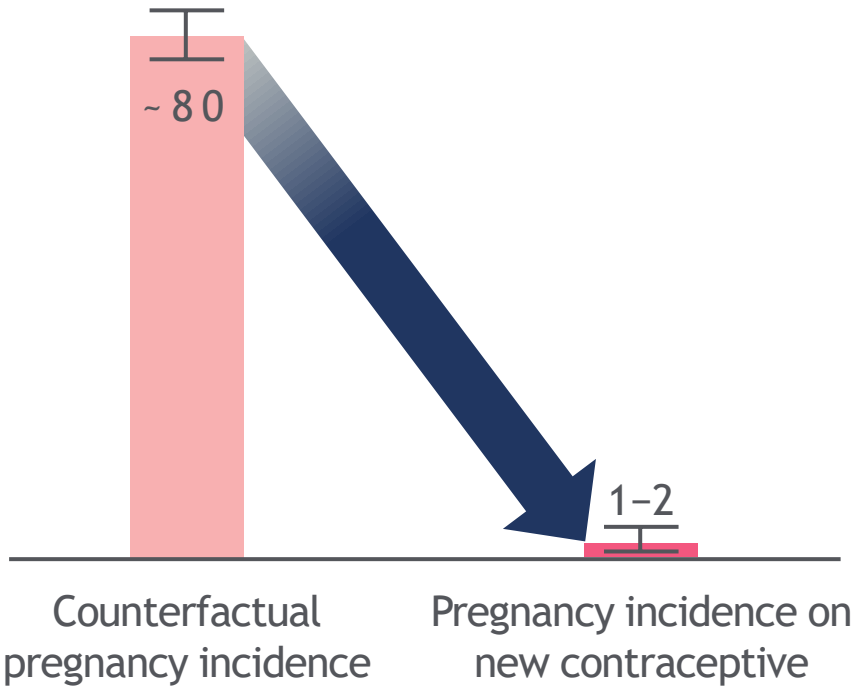
\- Intervention
counterfactual estimate

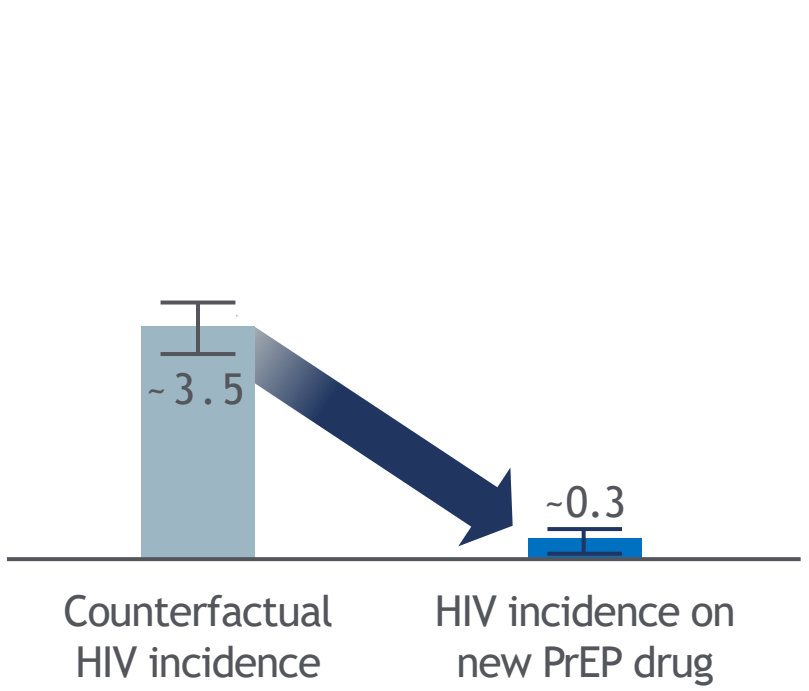


The randomized placebo-controlled trial is a specific type of **counterfactual design**

1. Eichler H-G, et al. *Clin Pharmacol Ther*. 2016;100:699-712; 2. Goring S, et al. *BMJ Open*. 2019;9:e024895.

Counterfactual incidence designs for pregnancy and HIV





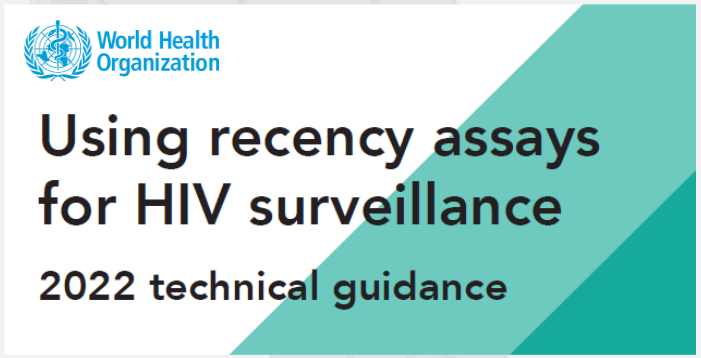
bHIV, background HIV; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; PY, person years.

Adapted from Murray, F (Presented at IAS, 2019).

Recent Infection Testing Algorithms (RITAs) have been used to estimate HIV incidence for public health

1 Collect specimens from population/ geography of interest > 2 Conduct standard HIV testing > 3 Conduct recency assay for HIV positive samples > 4 Estimate HIV incidence

$$\text{HIV incidence rate}^{1} = \frac{\left(\frac{\text{Recent infections}}{\text{Persons without HIV}}\right)}{\text{Recency lookback period}}$$



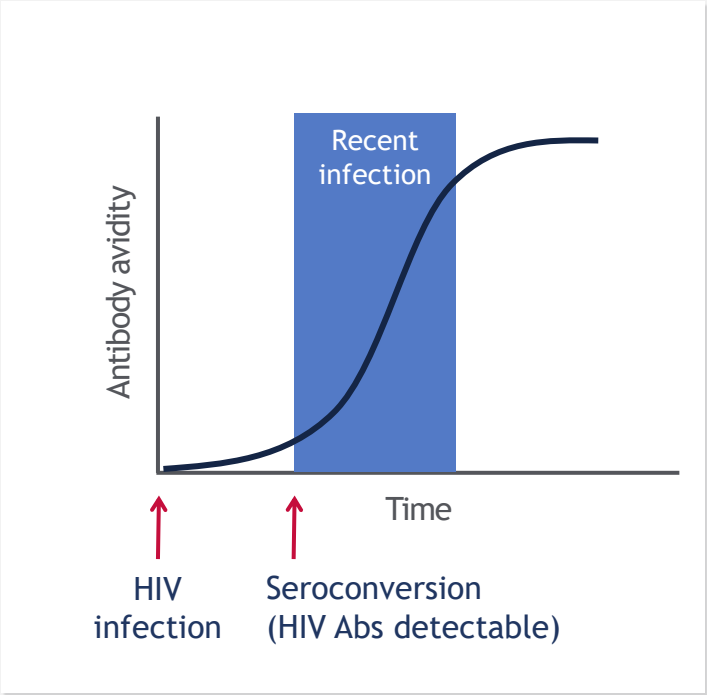
RITAs are used to **understand HIV incidence trends** at the population level

HIV, human immunodeficiency virus; RITA, recent infection testing algorithm.

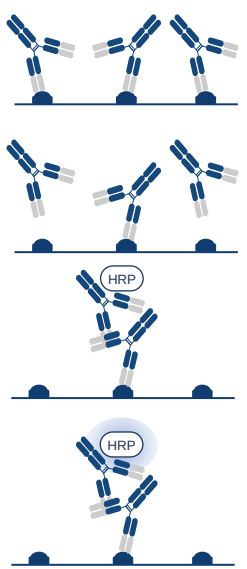
1. Kassanjee R, et al. *Epidemiology*. 2012;23:721-8; 2. Parkin N, et al. *Clin Pharmacol Ther*. 2022;15:3083-94.

What is a recency assay?

Recency assays measure HIV antibody avidity through limiting-antigen (LAg) avidity testing and normalized optical density values recent HIV infection (ODn ≤ 1.5)[1]



LAg-avidity assays[2]:



High and low avidity HIV-1 antibody binds to HIV-1 antigen on the microplate

Dissociation Buffer preferentially removes low avidity IgG

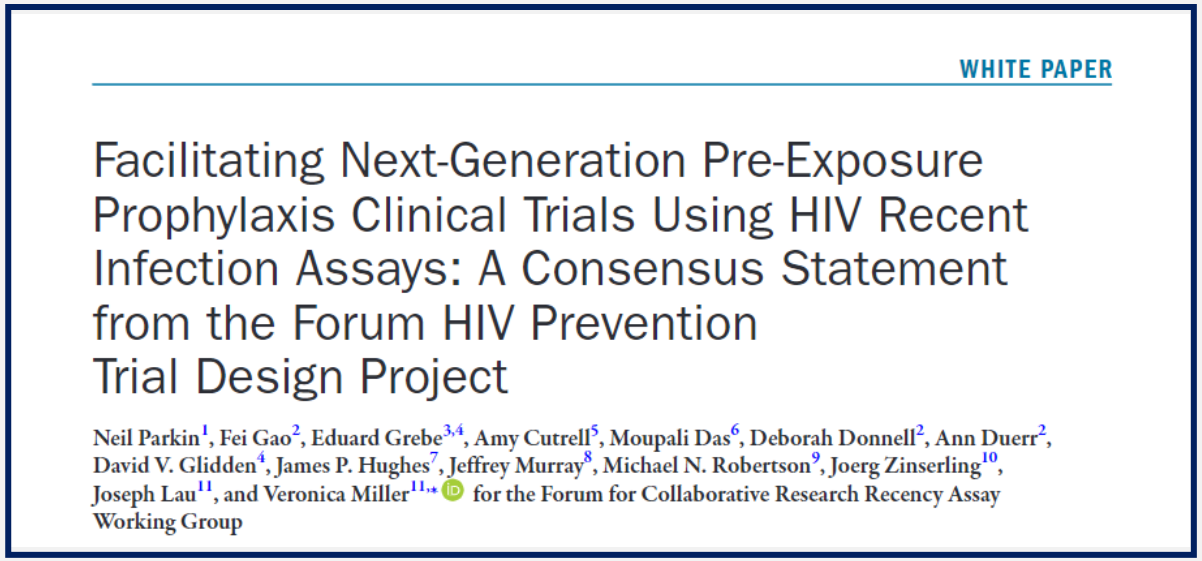
Goat anti-human IgG-HRP binds to bound IgG

TMB color is proportional to the amount of HRP

Abs, antibodies; Ag, antigen; HIV, human immunodeficiency virus; HRP, horseradish peroxidase; IgG, immunoglobin G; LAg, limiting Ag; ODn, normalized optical density; TMB, 3,3',5,5'-tetramethylbenzidine.

1. Parkin N, et al. *Clin Pharmacol Ther*. 2022;15:3083-94;
2. Moyo S, et al. *Viruses*. 2015;7:5508-24.

Consensus reached on how to use the RITA to estimate counterfactual bHIV incidence in the new PrEP trials



Regulatory agencies

FDA

European Medicines Agency
Science Medicines Health

SAHPRA
South African Health Products Regulatory Authority

Federal Institute for Drugs and Medical Devices

THE FORUM
For Collaborative Research℠

Drug developers

MERCK

ViiV Healthcare

Academic / non-profit

University of Washington

London School of Hygiene & Tropical Medicine

WVCTSI

LSTM Liverpool School of Tropical Medicine

vitalant

HPTN HIV Prevention Trials Network

Columbia University

MeSH Consortium
Measurement & Surveillance of HIV Epidemics

UCSF

Bill & Melinda Gates foundation

fhi 360
The Science of Improving Lives

Data First Consulting, Inc.

Stellenbosch University
iYunivesithi
Universiteit

Johns Hopkins University

Fred Hutch Cancer Center

Intergovernmental / governmental agencies

UNAIDS

CDC

World Health Organization

Diagnostics

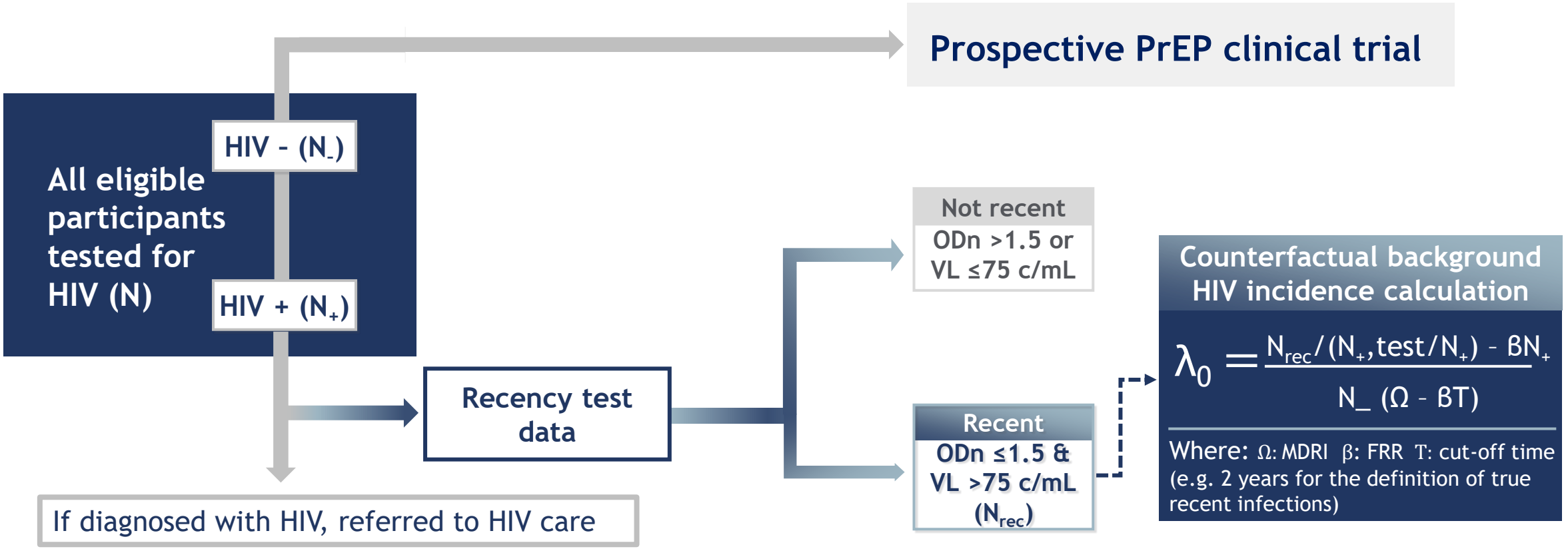
SEDIA Biosciences Corporation

MaximBio

bHIV, background HIV; HIV, human immunodeficiency virus; RITA, recent infection testing algorithm.

Parkin N, et al. *Clin Pharmacol Ther*. 2022;15:3083-94.

Applying the RITA to estimate bHIV incidence in a PrEP clinical trial[1,2]

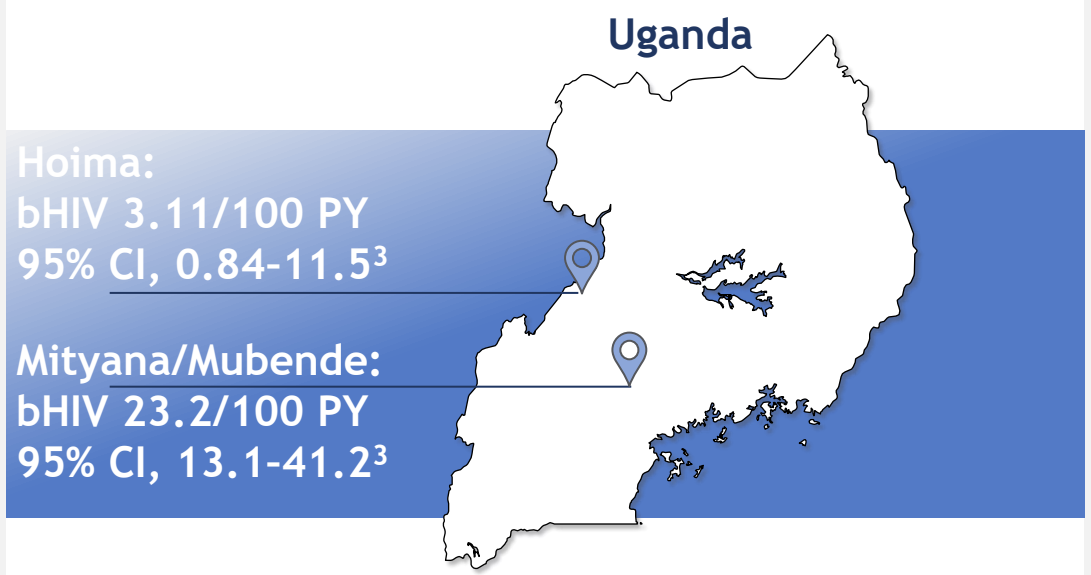


bHIV, background HIV; c/mL, copies per mL; FRR, false-recent rate; HIV, human immunodeficiency virus; MDRI, mean duration of recent infection; ODn, normalised optical density; RITA, recent-infection testing algorithm; VL, viral load.

1. Kassanjee R, et al. *Epidemiology*. 2012;23:721-8;
2. Gao F, et al. *Stat Commun Infect Dis*. 2021;13:20200009.

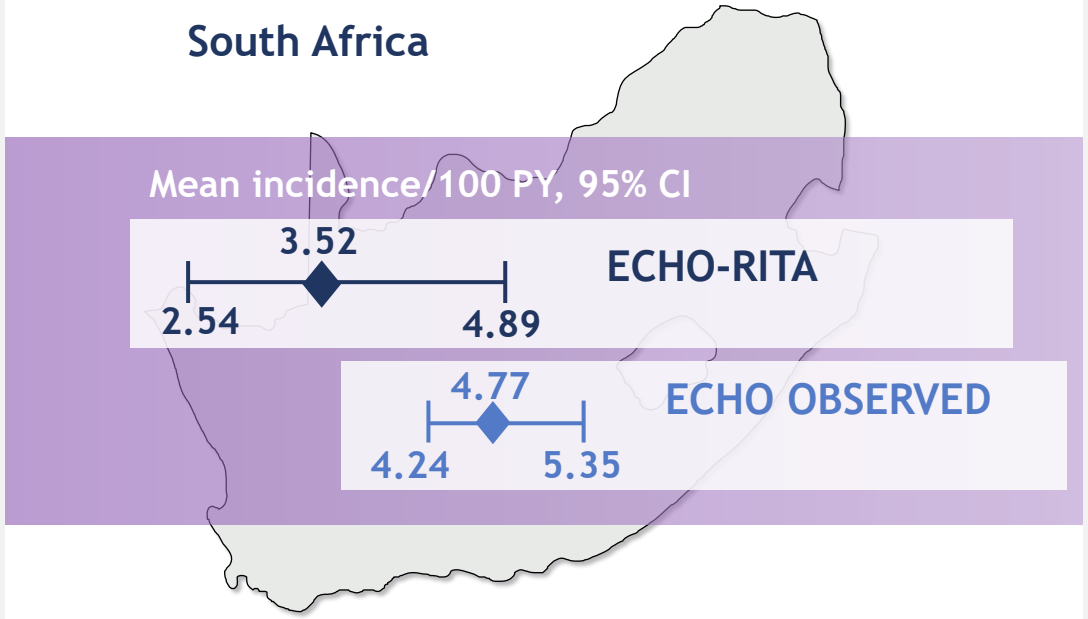
SIENA & ECHO-RITA results support use of Sedia LAg-EIA and RITA to estimate bHIV in Uganda and South Africa

SIENA[1,2]



Data from SIENA confirmed Sedia LAg-EIA performance with A/E clades, estimated bHIV incidence in unknown suspected hyperendemic sites, and supported site selection for the PURPOSE 1 trial

ECHO-RITA



Data from ECHO-RITA demonstrated that RITA-estimated bHIV incidence (by Sedia LAg-EIA) was similar to the observed incidence in ECHO, a contraceptive trial with AGYW in South Africa

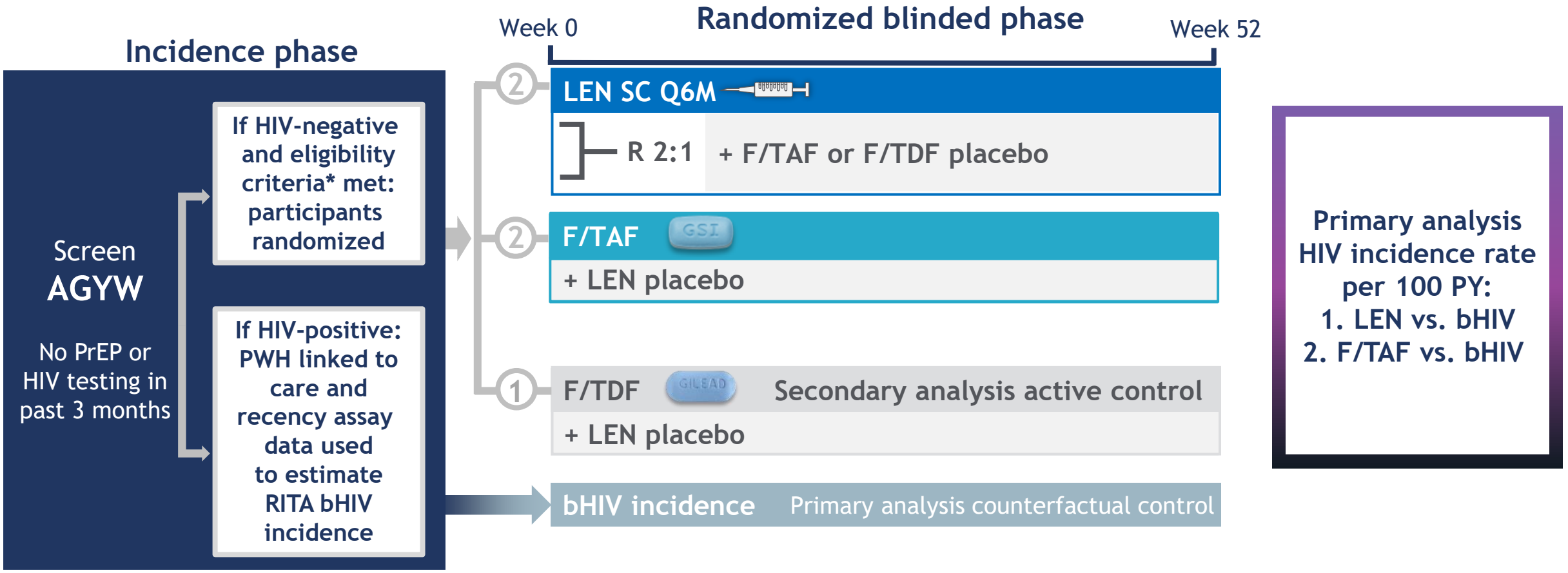
AGYW, adolescent girls and young women; bHIV, background HIV; CI, confidence interval; ECHO, The Evidence for Contraceptive Options and HIV Outcomes; EIA, enzyme immunoassay; HIV, human immunodeficiency virus; LAg, limiting antigen avidity; PY, person years; RITA, recent infection testing algorithm; SIENA, eStimating hIv incidEnce amoNg Agyw.

Cox S, et al. IAS 2023 (Presentation EPC0319)

1. Cox S, et al. Presented at HIV Glasgow 2022. Poster P003;
2. Cox S, et al. Presented at IDWeek 2022. Poster 2079;
3. Kiweewa FM, et al. Presented at AIDS 2022. Poster EPC114.

PURPOSE 1 design: randomized blinded phase

LEN for PrEP, prevention of vaginal HIV acquisition



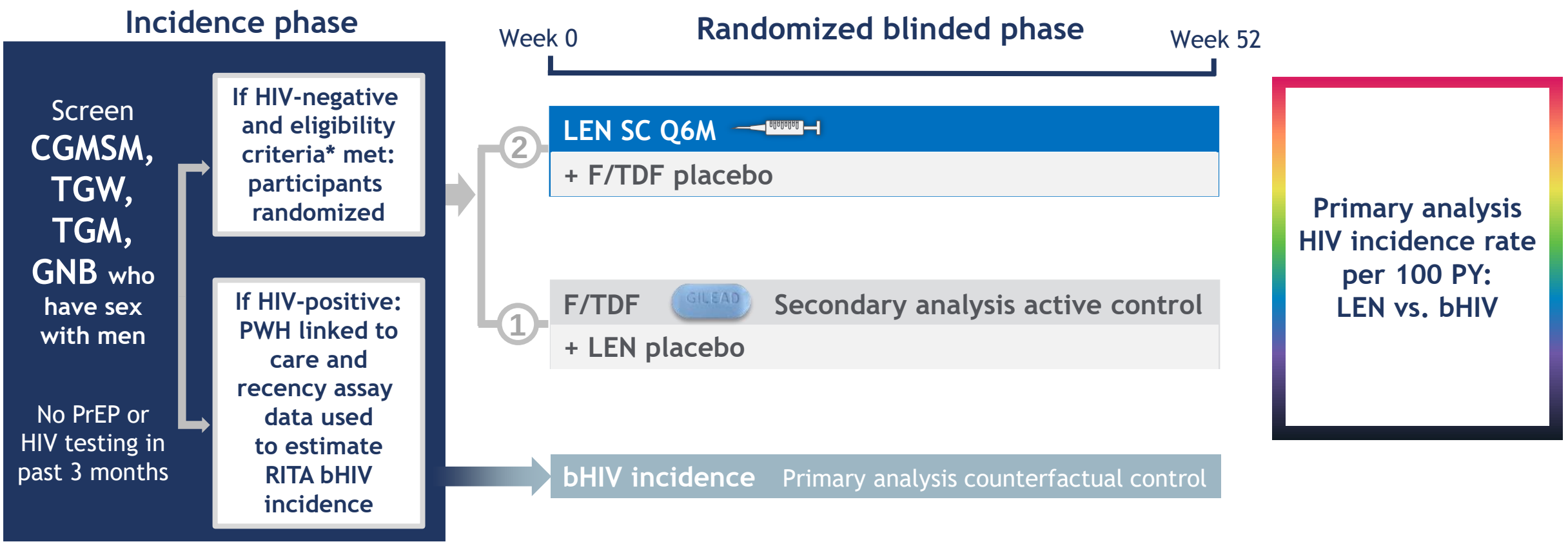
*High-level eligibility criteria: eGFR=> 60 ml/min, >=35 kg

AGYW, adolescent girls and young women; bHIV, background HIV; eGFR, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; PWH, people with HIV; PY, person years; Q6M, every six months; RITA, recent-infection testing algorithm; SC, subcutaneous.

ClinicalTrials.gov identifier: NCT04994509

PURPOSE 2 design: randomized blinded phase

LEN for PrEP, prevention of rectal HIV acquisition



*High-level eligibility criteria: eGFR=> 60 ml/min, >=35 kg

bHIV, background HIV; CGMSM, cisgender men who have sex with men; eGFR, estimated glomerular filtration rate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; GNB, gender nonbinary individuals; HIV, human immunodeficiency virus; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; PY, person years; Q6M, every six months; RITA, recent-infection testing algorithm; SC, subcutaneous; TGM, transgender men, TGW, transgender women.

ClinicalTrials.gov identifier: NCT04925752

Operational considerations for implementation of recency assays and RITAs in new PrEP clinical trials

Clinical trial design considerations

- **Who** do you screen? PrEP, recent HIV
- **Where** do you screen? High bHIV required for trials
- **How** do you balance the needs of bHIV incidence vs recruitment for randomized clinical trials?
- **How** does the above affect clinical trial site selection?

Recency assay and RITA considerations

- **How** do you account for false-recency rates, ART users, elite controllers, and variable look-back periods?
- MDRI, FRR, and other RITA considerations
- **How** do you address ethical issues? Recency assay are for research use only, not for individual use

ART, antiretroviral therapy; bHIV, background HIV;
G-CAG, Global Community Advisory Groups; FRR, false-recent rate; HIV, human immunodeficiency virus;
MDRI, mean duration of recent infection; PrEP, pre-exposure prophylaxis; PWBP, people who would benefit from PrEP; RCT, randomized controlled trial; RITA, recent infection testing algorithm.

Early, committed, and consistent community and stakeholder engagement for the PURPOSE program

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*)
- Established meeting frequency every other month video conference and annually F2F
- Established subcommittee to review study documents
- Includes individuals from South Africa, Brazil, Peru, Uganda, and the United States – will expand as countries expand
- G-CAG members have led presentations on PURPOSE studies including DEI, inclusion of PLP, adolescents, etc.

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
September 2022

AGYW, adolescent girls and young women; DEI, diversity, equity, and inclusion; F2F, face-to-face; G-CAG, Global Community Advisory Groups; MSM, men who have sex with men; US, United States.

Foundational Pillars of PURPOSE: Health Equity

Partnerships

- Engagement with stakeholders including PIs
- Public-private partnerships with government, civil society, and academic institutions

Voice of PWBP and community (G-CAGs)

- Establish global community advisory group for each study with robust representation of historically under-represented and disproportionately affected populations
- Broader community engagement

Person-centric design

- Provide support to reduce barriers to enrollment and retention including food, transportation, educational/vocational and empowerment initiatives
- Choose sites with expertise with vulnerable populations
- Require anti-racism, gender-diversity trainings

Diversity, equity, inclusion

- Site PI and staff representative of participants
- Specific enrollment goals for race, ethnicity, and gender
- Include PLP, adolescents and PWIDs
- Evaluate LEN & HC / GAHT and in pregnant, PLP, breast milk, infants

Ensuring we are intentional in our innovation to build towards health equity

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; PWID, people who inject drugs.

PURPOSE 1

First to intentionally include pregnant and lactating people in Phase 3 clinical trials

PURPOSE 2

First to intentionally include transgender men and gender nonbinary individuals

PURPOSE 1 and 2: First to include adolescents in Phase 3 clinical trials

Partnerships

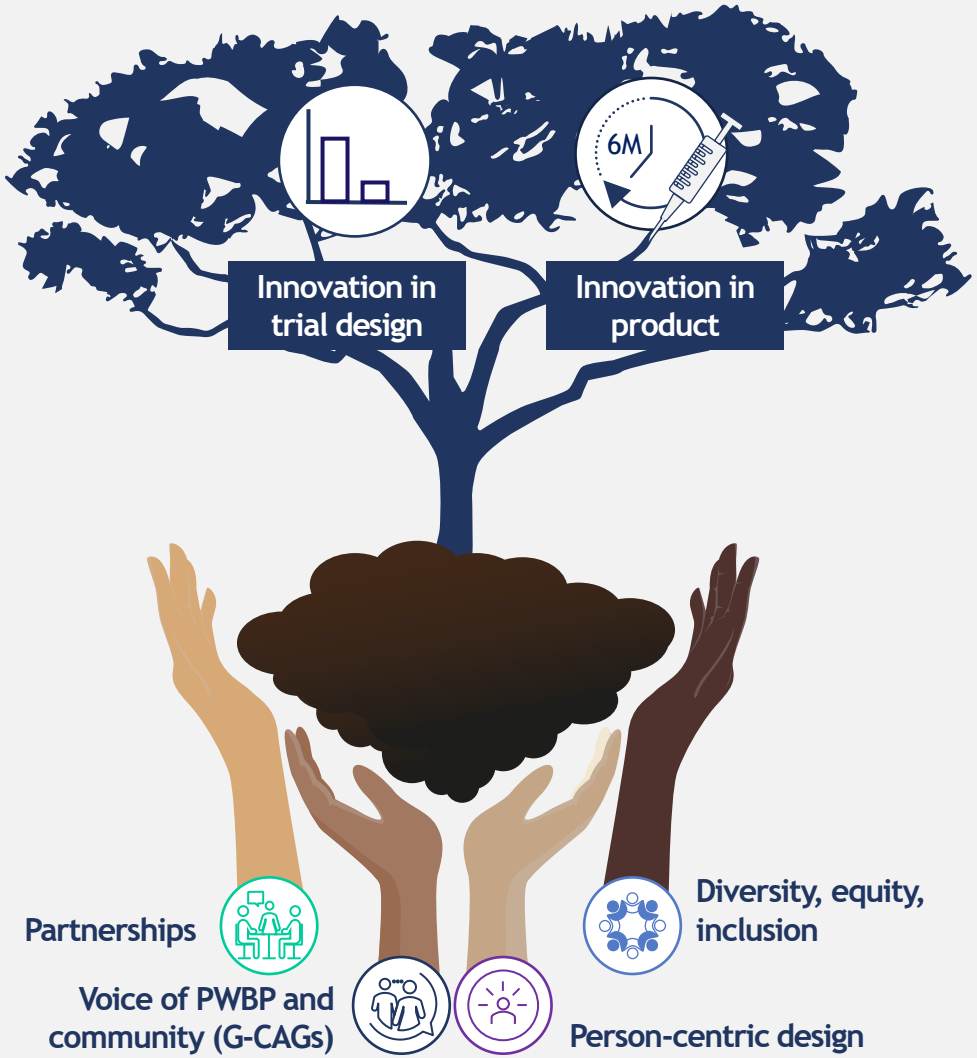
Voice of the PWBP and Community (G-CAGs)

Person-Centric Design

Diversity, Equity, and Inclusion

Changing where, with whom, and how we work so we can end the HIV epidemic for everyone, everywhere

To summarize…



G-CAGs, Global Community Advisory Groups; LEN, lenacapavir; PWBP, people who would benefit from PrEP; MoA, mechanism of action.

We would like to extend our thanks to all the participants, their partners and families, global community advisors, our investigators and site staff, and all our partners for their support of the PURPOSE program

Moupali Das, MD, MPH

linkedin.com/in/moupali-das-9b8b245

@drmoupali

Cox S, et al. IAS 2023 (Presentation EPC0319)

LEN MoA animation