Innovations in HIV Prevention Clinical Trial Designs and the Recency Assay

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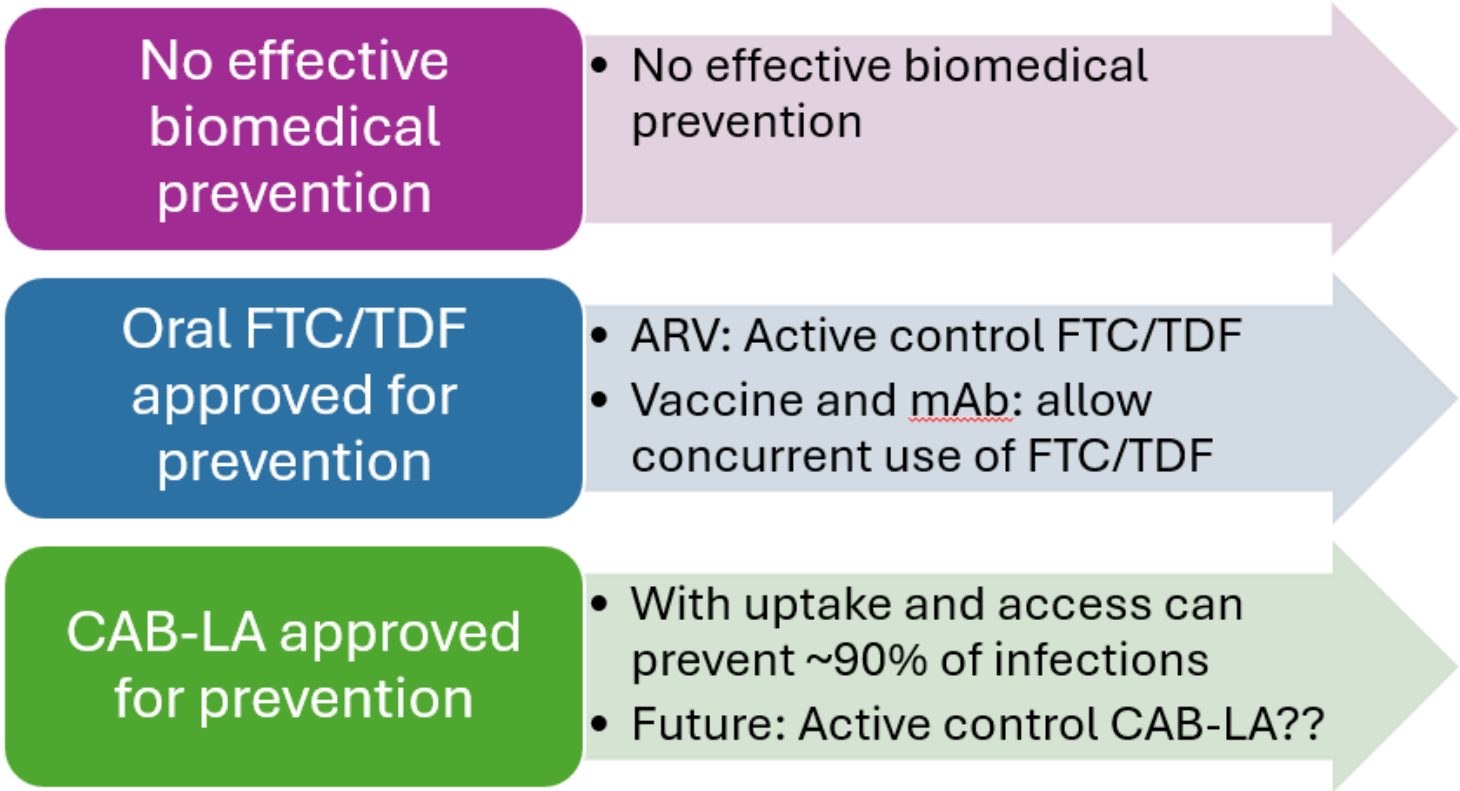
The Evolving Landscape of HIV Prevention

- HIV prevention has made significant strides, but challenges remain.
- Clinical trials are crucial for developing new prevention tools.
- Need for continuous innovation to achieve epidemic control.

Three eras of HIV prevention trials



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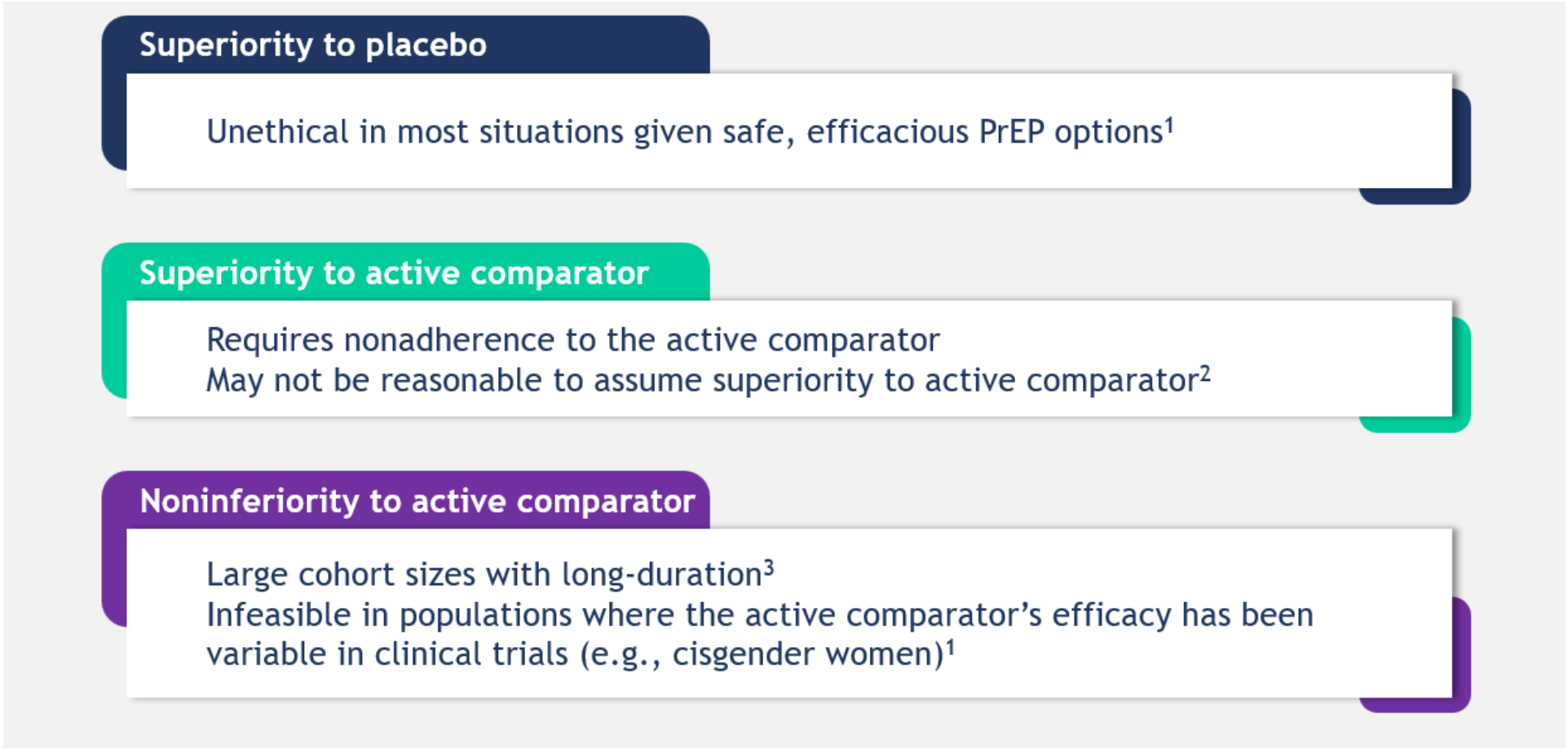
Challenges facing HIV prevention clinical trial designs



- 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.

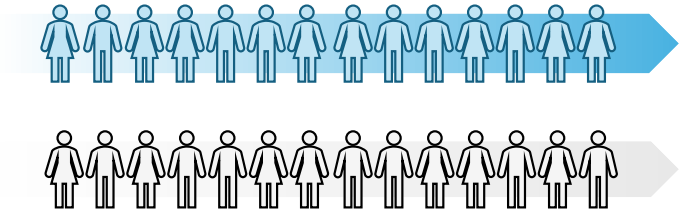
Counterfactual Design

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

Counterfactual trial design

\+ Intervention
factual

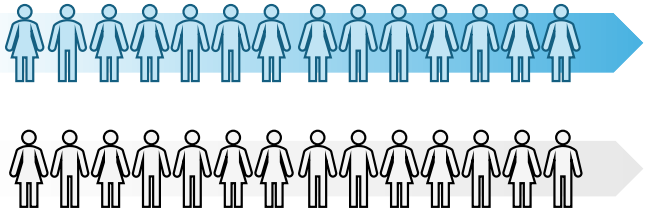
– Intervention
counterfactual estimate



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.

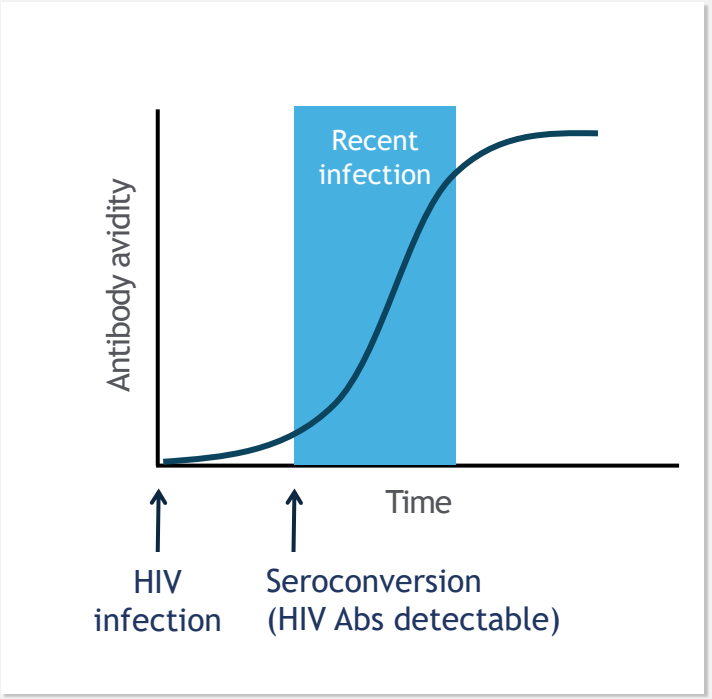
What is a Recency Assay?

- The recency assay provides a powerful tool for distinguishing recent from long-standing HIV infections.

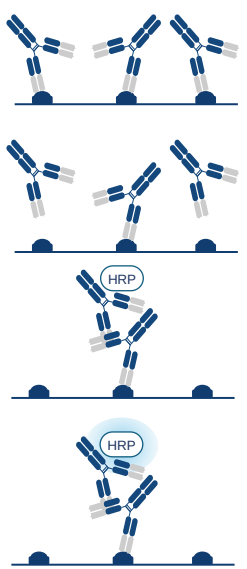
  - **Definition:** A laboratory test that identifies individuals who have been infected with HIV within a relatively short, defined period (e.g., within 6-12 months)
  - **Commonly Used Assays:** Limiting Antigen (LAg) Avidity Assay
  - **Biological Basis:** Typically measures the maturation of the HIV antibody response. Newer assays also incorporate viral load or other biomarkers
  - **Output:** Classifies individuals as "recent" or "long-term" infection

What does a recency assay measure?

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

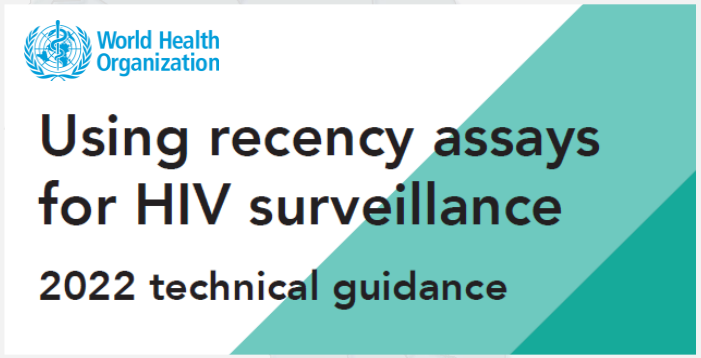
- Abs, antibodies; Ag, antigen; HIV, human immunodeficiency virus; HRP, horseradish peroxidase; IgG, immunoglobin G; LAg, limiting Ag; ODn, normalized optical density; TMB, 3,3',5,5'-tetramethylbenzidine.

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

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

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

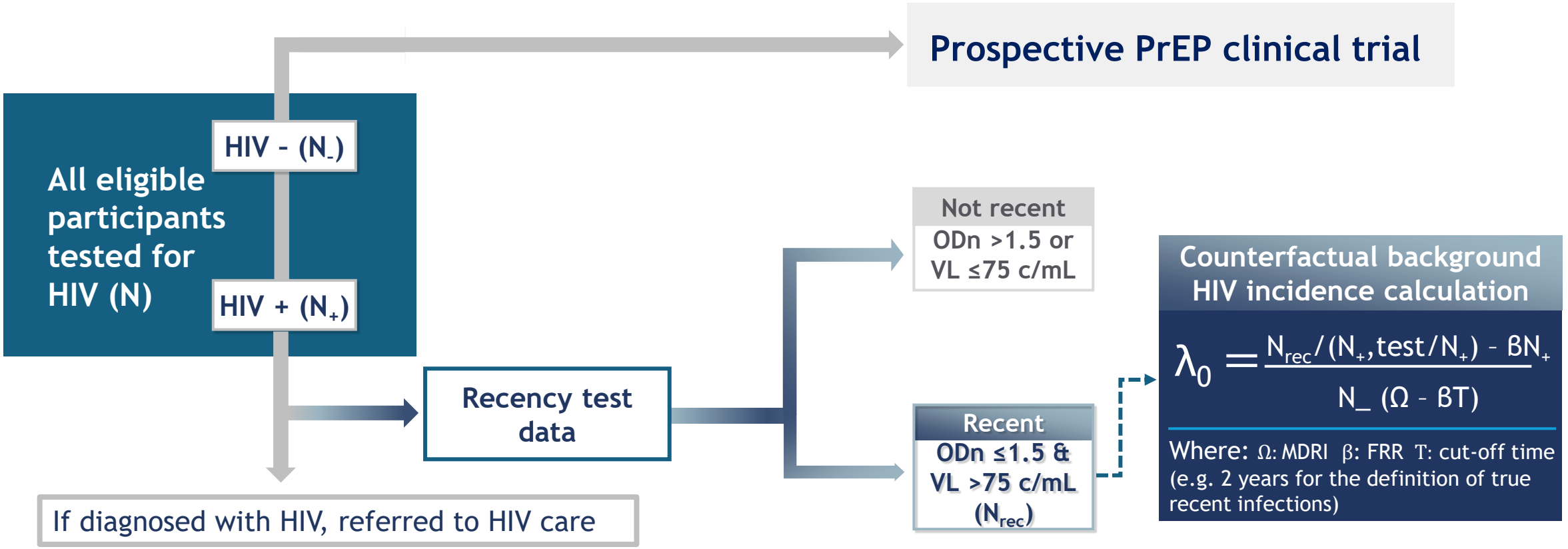


RITAs are used to **understand HIV incidence trends** at the population level

- 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.

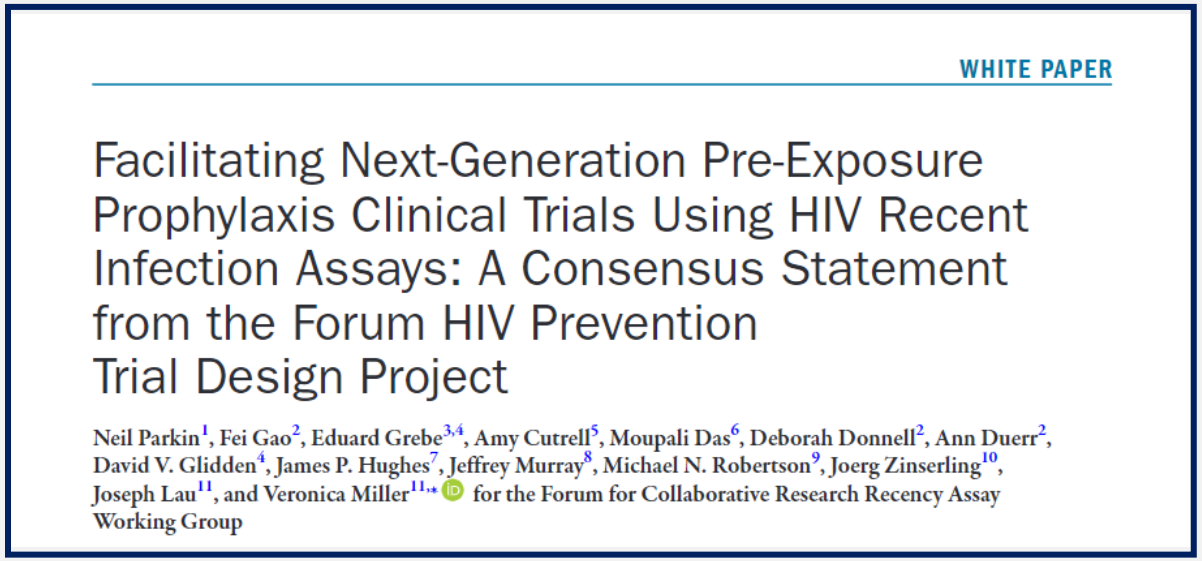
Applying the RITA to estimate bHIV incidence in a PrEP clinical trial[1,2]



- 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.

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


WHITE PAPER

Facilitating Next-Generation Pre-Exposure Prophylaxis Clinical Trials Using HIV Recent Infection Assays: A Consensus Statement from the Forum HIV Prevention Trial Design Project

Neil Parkin[1], Fei Gao[2], Eduard Grebe[3,4], Amy Cutrell[5], Moupali Das[6], Deborah Donnell[2], Ann Duerr[2], David V. Glidden[4], James P. Hughes[7], Jeffrey Murray[8], Michael N. Robertson[9], Joerg Zinserling[10], Joseph Lau[11], and Veronica Miller[11,*] for the Forum for Collaborative Research Recency Assay Working Group

Regulatory agencies

FDA

European Medicines Agency — Science Medicines Health

SAHPRA — South African Health Products Regulatory Authority

Federal Institute for Drugs and Medical Devices

Intergovernmental / governmental agencies

UNAIDS

CDC

World Health Organization

Academic / non-profit

University of Washington

London School of Hygiene & Tropical Medicine

WVCTSI — West Virginia Clinical and Translational Science Institute

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

Drug developers

MERCK

ViiV Healthcare

Diagnostics

SEDIA BIOSCIENCES CORPORATION

MaximBio

THE FORUM For Collaborative Research℠

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

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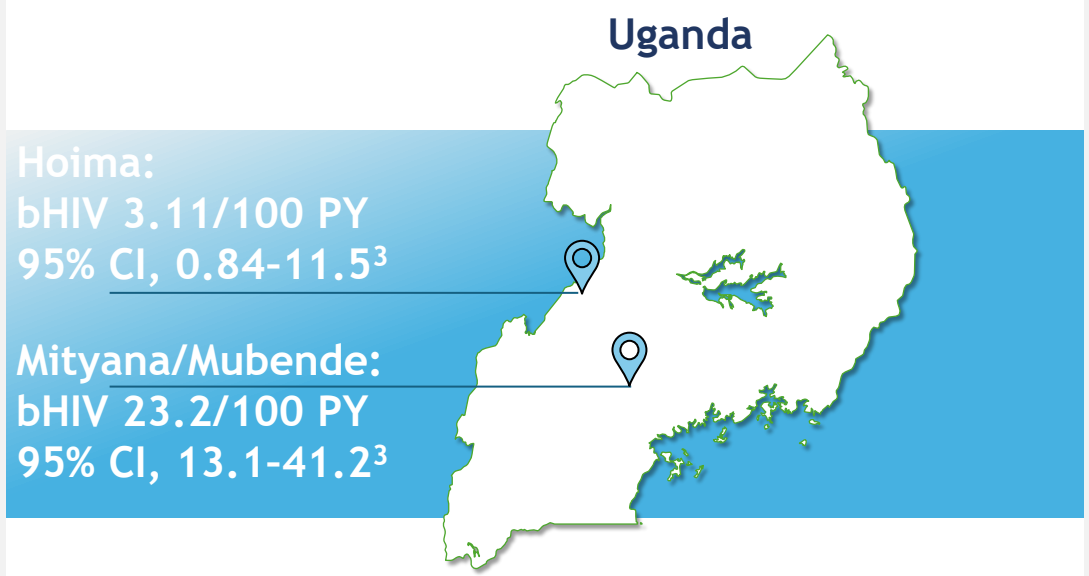
Parkin N, et al. *Clin Pharmacol Ther*. 2022;15:3083-94.

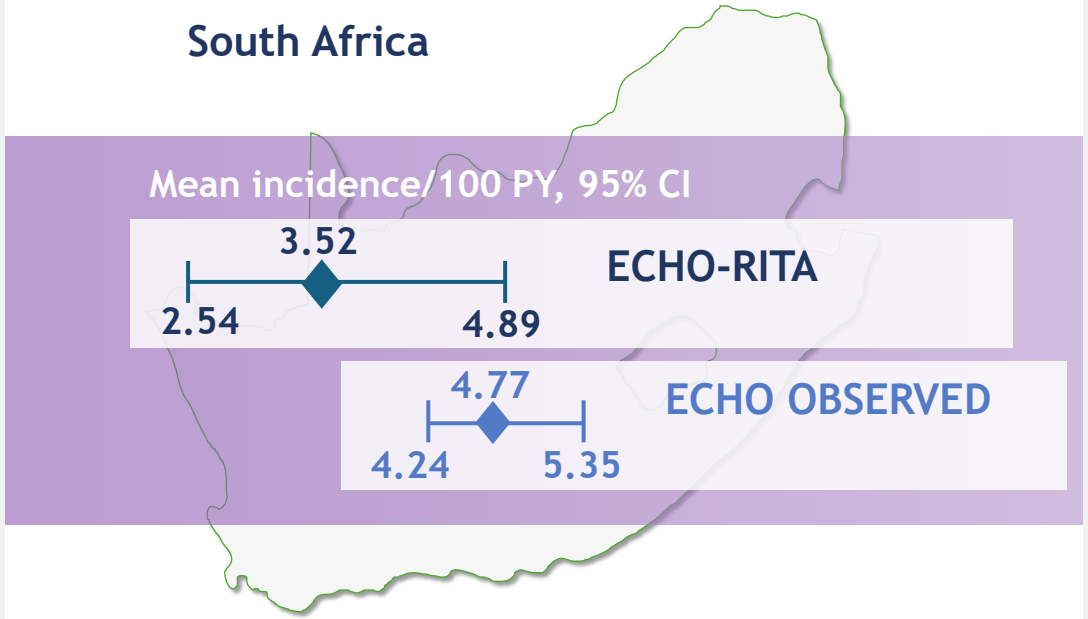
SIENA & ECHO-RITA results support use of Recency assays to estimate bHIV in Uganda and South Africa

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

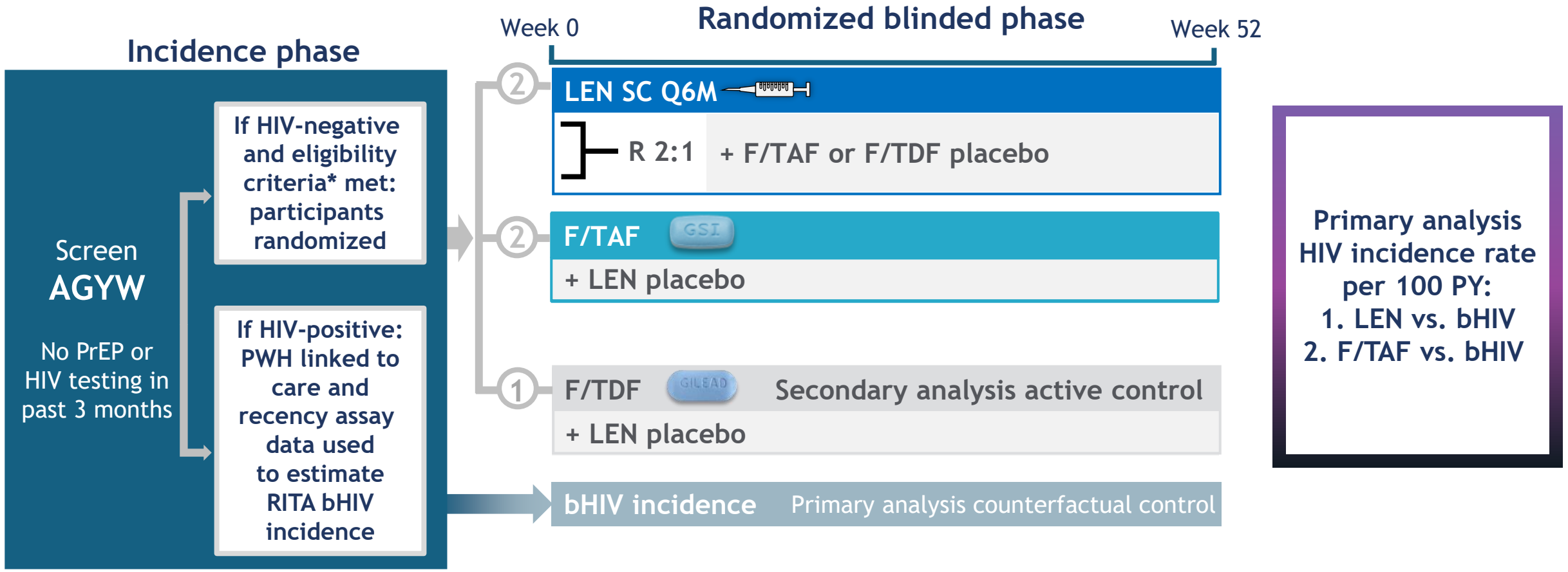
- AGYW, adolescent girls and young women; bHIV, background HIV; CI, confidence interval; ECHO, The Evidence for Contraceptive Options and HIV Outcomes; EIA, enzyme immunoassay; HIV, human immunodeficiency virus; LAg, limiting antigen avidity;
PY, person years; RITA, recent infection testing algorithm;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



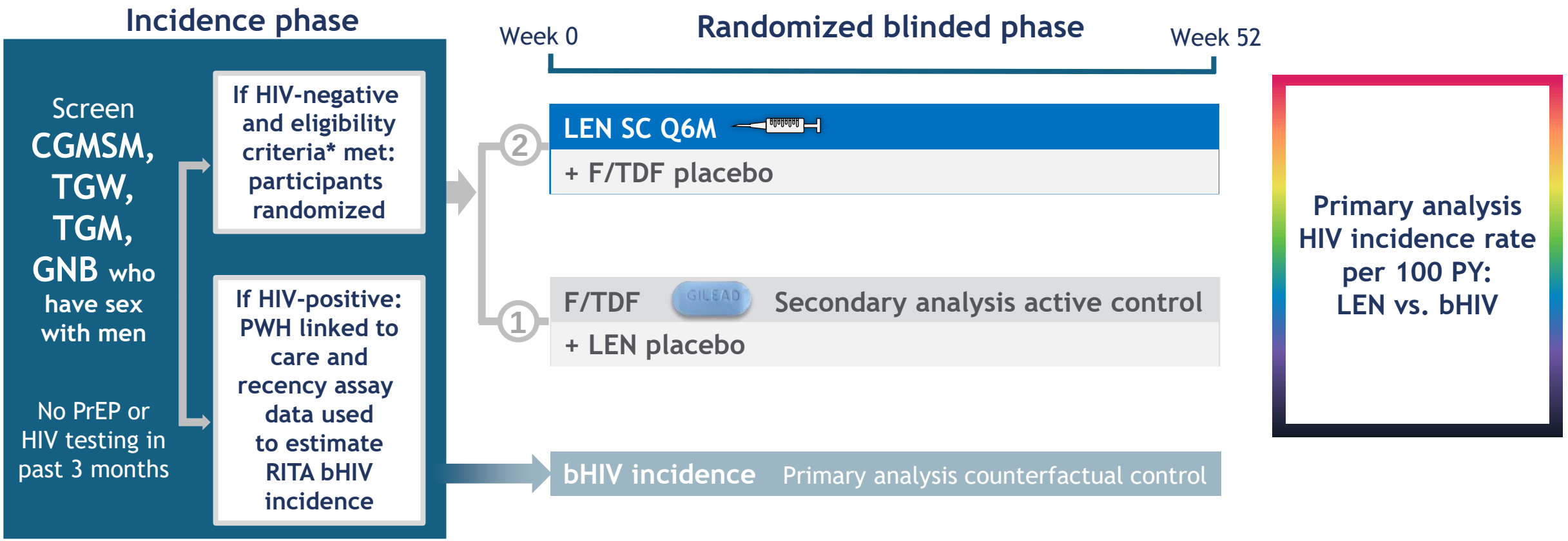
*High-level eligibility criteria: eGFR=> 60 ml/min, >=35 kg

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

Advantages of Incorporating Recency Assays in Trial Designs

- Recency assays offer significant benefits for the efficiency, ethics, and interpretability of HIV prevention trials:

  - **Reduced Sample Size Requirements:** By leveraging background incidence, trials can be smaller.
  - **Shorter Trial Durations:** Faster assessment of intervention efficacy.
  - **Enhanced Ethical Acceptability:** Minimizes the need for placebo arms, particularly in high-incidence settings.
  - **Real-World Relevance:** Provides incidence data directly relevant to ongoing transmission dynamics.
  - **Improved Resource Allocation:** Directs prevention efforts to areas with ongoing transmission.

Conclusions

- Increasing availability and use of long-acting PrEP presents a significant hurdle for evaluating the effectiveness of new prevention methods

- Innovative trial designs and tools like the recency assay are essential for accelerating HIV prevention efforts
  - Aligns with the FDA's "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products" (Draft Guidance 2023)
  - Collaborative engagement all key stakeholders essential in navigating this evolving landscape – researchers, communities, funders, and policy makers

- The field continues to evolve, with ongoing efforts to refine trial designs and maximize the utility of tools like recency assays.

Acknowledgements

- Research participants – SIENA, ECHO, PURPOSE 1 & 2 studies
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- Forum for Collaborative Research Forum

Questions

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