PURPOSE
Prevention with PURPOSE

IAS 2025

Estimation of the Counterfactual HIV Incidence in the PURPOSE Trials

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13th International AIDS Society (IAS) Conference on HIV Science; July 13-17, 2025; Kigali, Rwanda

Acknowledgments and Presenter Disclosures

Acknowledgments

I want to begin my talk by extending my deepest gratitude to the PURPOSE trial participants who have shared their time, experiences, and bodies for the purposes of this research, and their families and communities, the global community advisory and accountability groups, the site staff and investigators, and the members of the PURPOSE study teams. Much of the fight against HIV and AIDS relies upon people living with HIV and people who want or need PrEP continuing to put themselves forward and this research and our fight against HIV and AIDS is indebted to those past and present.

Disclosures

- Lillian Brown is an employee of, and holds stock in, Gilead Sciences, Inc.
- Gilead Sciences funded and designed the trials with input from the PIs and Global Community Advisory Group. The PIs and study staff gathered data; Gilead Sciences, Inc., monitored conduct of the trial, received the data, and performed analyses. The PURPOSE 1 and 2 Study Teams all vouch for the data and analysis
- Medical writing support was provided by Jenna Steere, PhD (Aspire Scientific Ltd, UK), and was funded by Gilead Sciences, Inc.

PURPOSE 1 PURPOSE 2

G-CAG, Global Community Advisory Group; PI, principal investigator; PrEP, pre-exposure prophylaxis.

Summary

What is your main question?

- How did the bHIV incidence in PURPOSE 1 and PURPOSE 2 estimated by a RITA compare with additional counterfactual estimates?

What did you find?

- RITA-based bHIV for PURPOSE 1 and PURPOSE 2 was consistent with conservative incidence estimates
- The F/TDF efficacy-adherence estimate was most similar to RITA-based bHIV
- Varying RITA parameters had minimal impact on the bHIV estimates

Why is it important?

- It is important that bHIV estimates are conservative and comparable. These findings support RITA-based bHIV estimates as comparators in future HIV prevention trials

To access a copy of this presentation, please scan the QR code*

bHIV, background HIV incidence; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **RITA**, recent infection testing algorithm.

Challenges in HIV Prevention Clinical Trial Design

Superiority to placebo

- Placebo use is unethical[1]

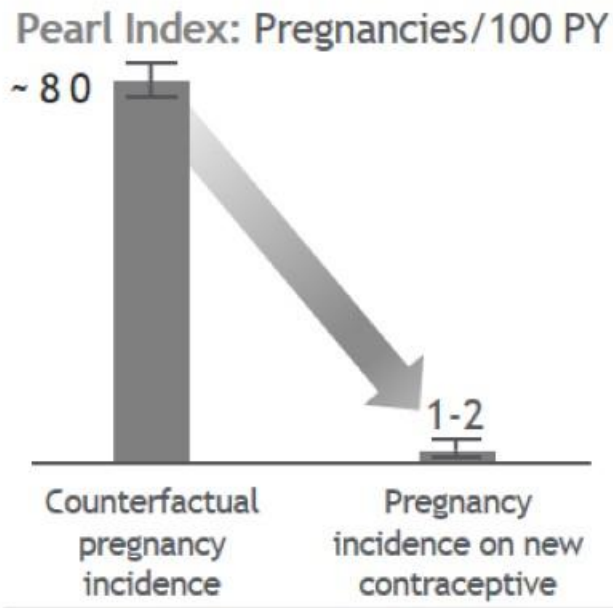
Superiority to active comparator

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

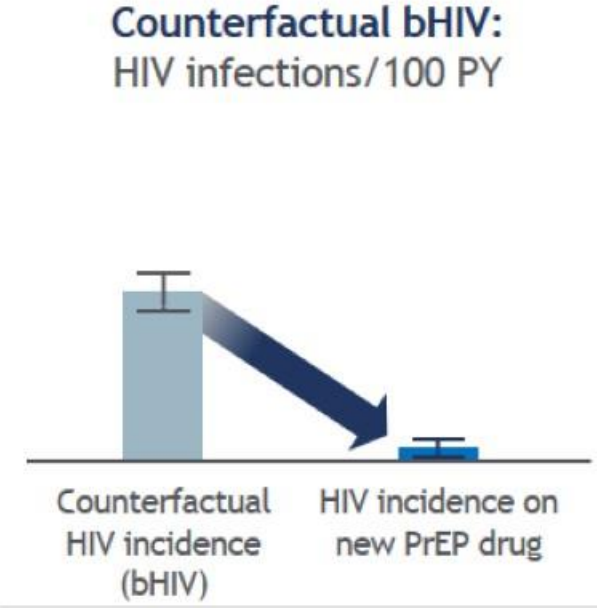
Noninferiority to active comparator

- Large cohort sizes with long duration[3]
- Infeasible in certain populations[1]

Counterfactual incidence is used in contraceptive trials



Counterfactual incidence design was chosen for the PURPOSE trials



Counterfactual HIV incidence design was used in the PURPOSE 1 and 2 trials[4,5] to address these challenges

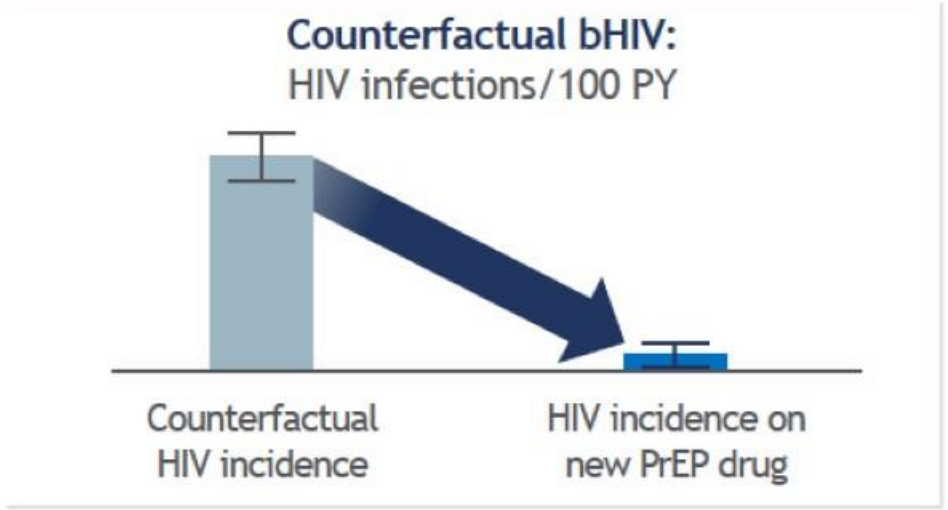
bHIV, background HIV incidence; PrEP, pre-exposure prophylaxis; PY, person-years. 1. Janes H, et al. *Lancet HIV*. 2019;6:e475-82. 2. Cutrell A, et al. *HIV Clin Trials*. 2017;18:177-88. 3. Grobler AC, Karim Abdool SS. *AIDS*. 2012;26:529-32. 4. Bekker LG, et al. *N Engl J Med*. 2024;391:1179-92. 5. Kelley CF, *N Engl J Med*. 2025;392:1261-76.
Figures adapted from Parkin, F, et al. *ePoster* PEC307 presented at: IAS; July 18-21, 2021 virtual congress

Different Methods to Estimate Counterfactual HIV Incidence

- HIV incidence from prior clinical trials; run-in cohorts[1]
- HIV surveillance data[2]
- Rectal gonorrhea-HIV incidence relationship[3]
- Acute HIV infections between screening and baseline[4]
- VOICE risk score[5]
- F/TDF adherence-efficacy relationship[4]

Recency assay and RITA

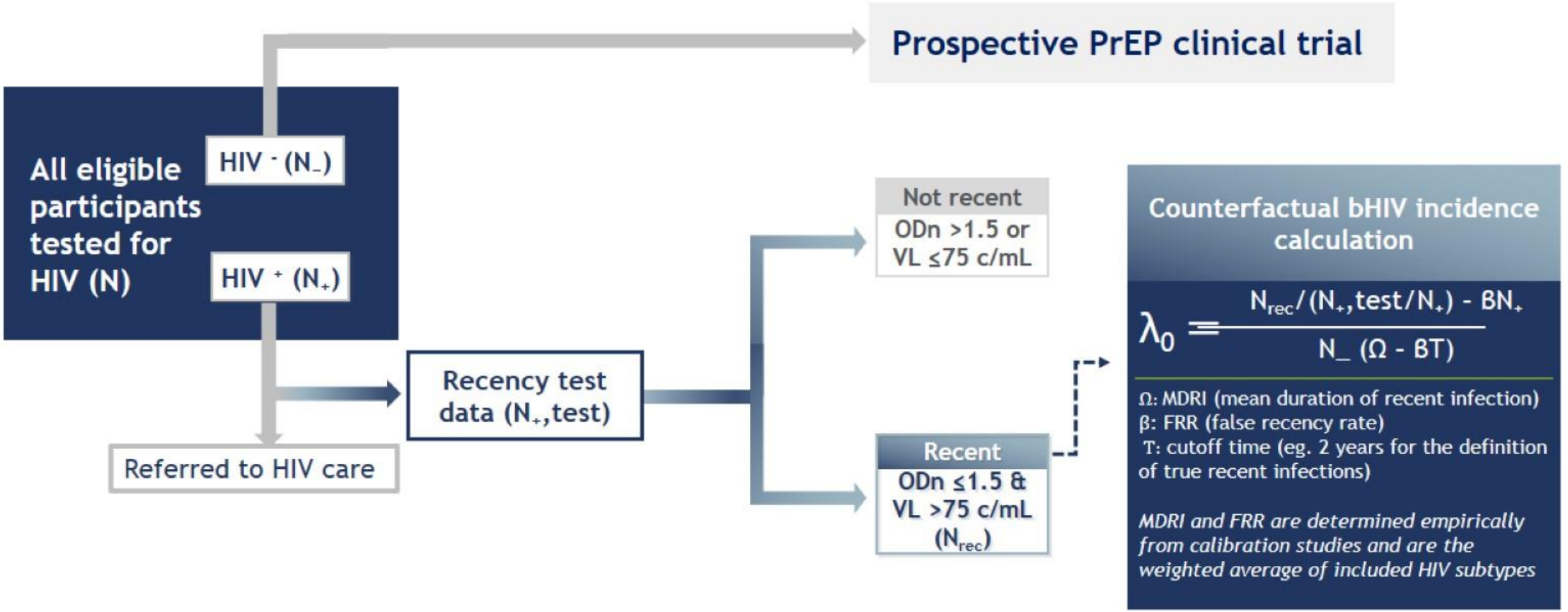
Optimal approach to estimating the counterfactual background HIV incidence (bHIV) using a RITA



This analysis compares the RITA-estimated bHIV from PURPOSE 1 and PURPOSE 2 primary analyses to the estimated bHIV using alternative RITA parameters and to other counterfactual methods

bHIV, background HIV; F/TDF, emtricitabine/tenofovir disoproxil fumarate; PrEP, pre-exposure prophylaxis; PY, person-years; RITA, recent infection testing algorithm. 1. Kusemererwa S, et al. *Medicine (Baltimore)*. 2021;100:e27719. 2. Mera R, et al. *J Int AIDS Soc*. 2019;22:e25433. 3. Mullick C, et al. *J Infect Dis*. 2020;221:214-7.
4. Glidden D, et al. *J Int AIDS Soc*. 2021;24:e25744. 5. Balkus JE, et al. *J Acquir Immun Defic Syndr*. 2016;72:333-43.

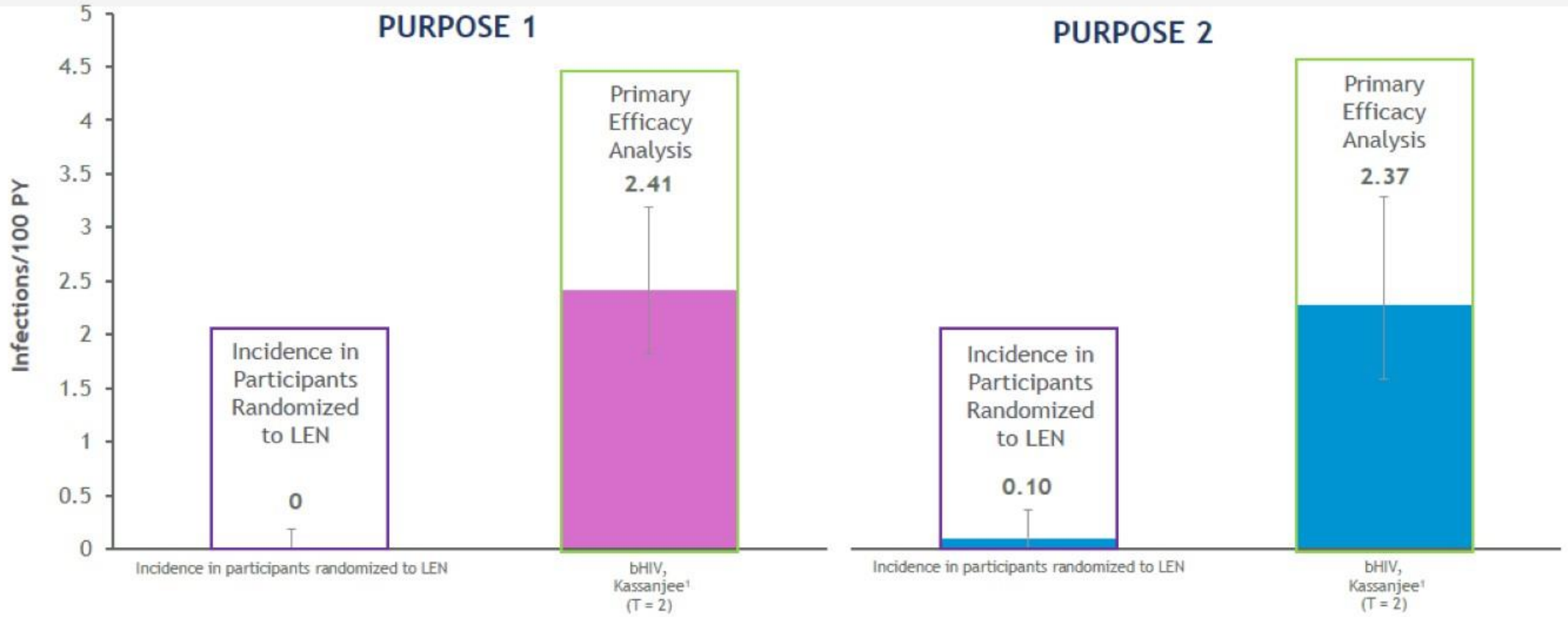
Applying a RITA to Estimate bHIV in a PrEP Clinical Trial[1,2]



bHIV, background HIV; c/mL, copies per mL; FRR, false recency rate; MDRI, mean duration of recent infection; ODn, normalized optical density; PrEP, pre-exposure prophylaxis; 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.

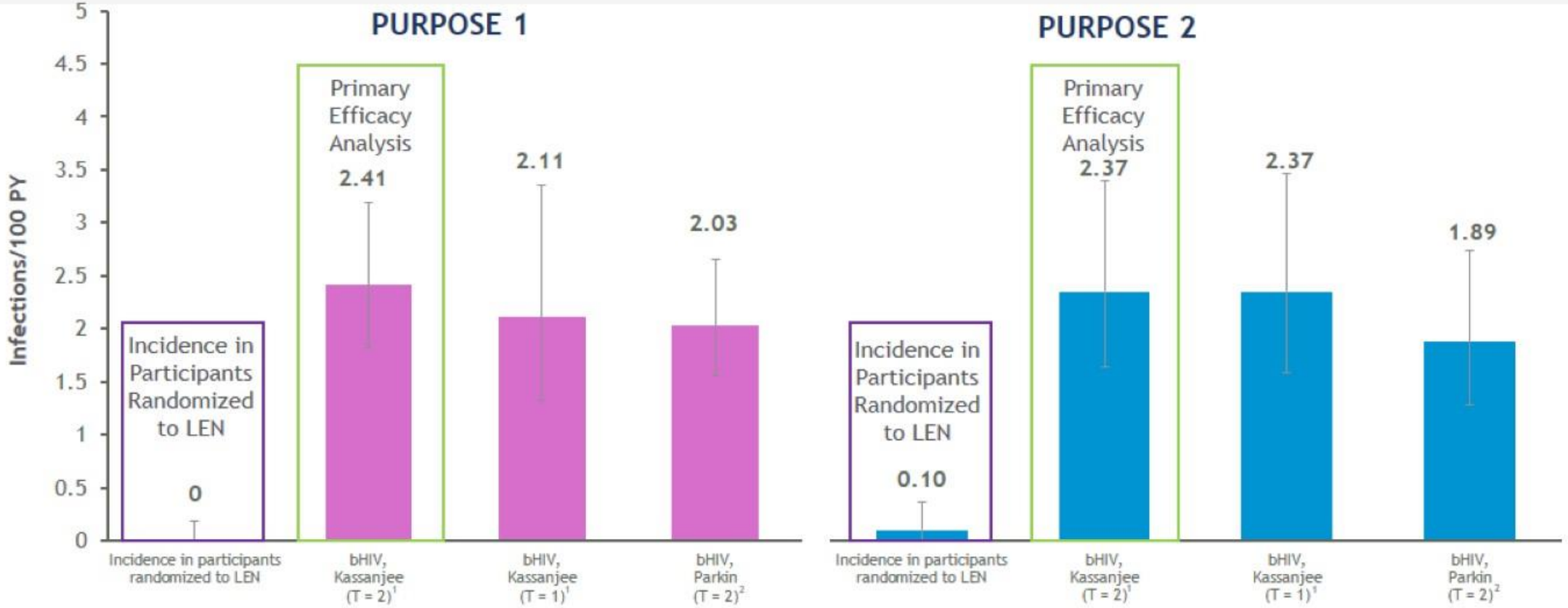
Estimated bHIV using RITA in PURPOSE 1 and PURPOSE 2



PURPOSE 1 reported zero incident cases of HIV in cisgender women receiving LEN
PURPOSE 2 reported two incident cases of HIV in participants receiving LEN

Recent infections identified using Sedia LAg-EIA limiting antigen enzyme immunoassay, normalized optical density threshold of 1.5, and viral load threshold of 75 copies/mL.
bHIV, background HIV incidence; **CI**, confidence interval; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **LAg-EIA**, limiting antigen-enzyme immunoassay; **LEN**, lenacapavir; **PY**, person-years; **RITA**, recent infection testing algorithm; **T**, recent time cutoff. 1. Kassanjee R, et al. *AIDS*. 2016;30:2361-71.

Comparison of Estimated bHIV Using Alternative RITA parameters in PURPOSE 1 and PURPOSE 2

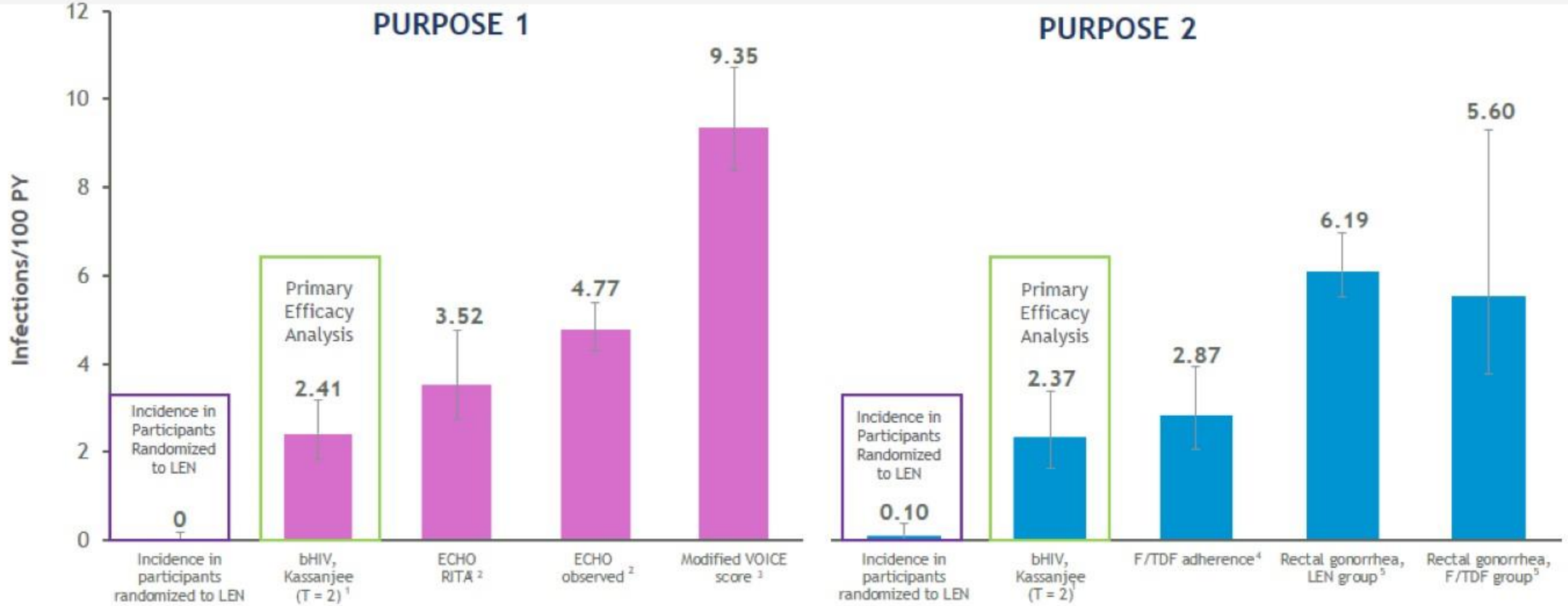


Varying RITA parameters had minimal impact on the bHIV estimate

Recent infections identified using Sedia LAg-EIA limiting antigen enzyme immunoassay, normalized optical density threshold of 1.5, and viral load threshold of 75 copies/mL. Pink columns are bHIV estimates derived from PURPOSE 1 data using RITA parameters as described in citations noted. Blue columns are bHIV estimates derived from PURPOSE 2 data using RITA parameters.

bHIV, background HIV incidence; **CI**, confidence interval; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **LAg-EIA**, limiting antigen-enzyme immunoassay; **LEN**, lenacapavir; **PY**, person-years; **RITA**, recent infection testing algorithm; **T**, recent time cutoff. 1. Kassanjee R, et al. *AIDS*. 2016;30:2361-71. 2. Parkin N, et al. *Clin Pharmacol Ther*. 2023;114:29-40

Comparison of Estimated bHIV Using RITA and Alternative Counterfactual Estimates in PURPOSE 1 and PURPOSE 2



Estimated bHIV was comparable and conservative compared to alternative counterfactual estimates

Recent infections identified using Sedia LAg-EIA limiting antigen enzyme immunoassay, normalized optical density threshold of 1.5, and viral load threshold of 75 copies/mL. Pink columns 1-2 and 5 (from left to right) are bHIV estimates derived from PURPOSE 1 data, columns 3 and 4 are bHIV estimates derived from ECHO data, and columns 1-4 use RITA parameters as described in citations noted. All blue columns are bHIV estimates derived from PURPOSE 2 data, columns 1-2 (from left to right) use RITA parameters. **bHIV**, background HIV incidence; **CI**, confidence interval; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **LAg-EIA**, limiting antigen-enzyme immunoassay; **LEN**, lenacapavir; **PY**, person-years; **RITA**, recent infection testing algorithm; **T**, recent time cutoff. 1. Kassanjee R, et al. *AIDS*. 2016;30:2361-71. 2. Cox S, et al. Poster presented at: IAS; July 23-26, 2023; Brisbane, Australia. 3. Balkus JE, et al. *J Acquir Immune Defic Syndr*. 2016;72:333-43. 4. Glidden DV, et al. *J Int AIDS Soc*. 2021;24:e25744. 5. Mullick C, Murray J. *J Infect Dis*. 2020;221:214-7.

Conclusions

- This analysis supports the counterfactual trial design and the choice of RITA for estimating the background HIV incidence
- Reducing bias in the cross-sectional incidence cohort is critical to the success of the RITA-based counterfactual HIV incidence study design
- RITA-based background HIV incidence estimates for PURPOSE 1 and PURPOSE 2 were consistent with conservative incidence estimates
  - A conservative estimate is preferential in a randomized trial setting as it increases the rigor of the evaluation

These findings support RITA-based background HIV incidence estimates as comparators in future HIV prevention trials

RITA, recent infection testing algorithm.

Accelerating Access for Global HIV Prevention

Expansive licensing	Rapid technology transfer	Simultaneous submissions
Earliest and geographically broadest (120 countries) voluntary licensing strategy ever for an antiretroviral	Agreements with 6 generics & full technology transfer within 3 months; Global Fund 2 million people for 3 years	US Approval June 2025 EU, EUM4All, South Africa, Brazil, Canada, Australia, Switzerland & more coming
Expediting Regulatory Review	**WHO endorsement**	**Manufacturing readiness**
EU-M4all application enables faster reviews in low- and middle-income countries	Guidelines released July 14, 2025 & prequalification later this year will facilitate global adoption	Gilead-supplied no-profit product & partnership agreements, bridging to sustainable generic supply

Collaborative implementation science studies to inform sustainable access, eg South Africa (Project PrEP, UNITAID/Wits RHI; ALIGN, Gates Foundation/Desmond Tutu Health Foundation) and Brazil (ImPrEP, IUNITAID/Fiocruz)