PURPOSE

Prevention with PURPOSE

HIVR4P 2024

Twice-Yearly Lenacapavir for HIV Prevention in Cisgender Gay, Bisexual, and Other Men, Transgender Women, Transgender Men, and Gender-Nonbinary People who Have Sex With Partners Assigned Male at Birth: Interim Analysis Results From the PURPOSE 2 Study

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- Chair of Category H (HIV) for the 2024 IDWeek Program Committee
- Vice Chair for the HIV Medicine Association
- Gilead Sciences, Inc., funded the study and designed the study with input from the PIs and G-CAG. The PIs and study staff gathered data; Gilead Sciences, Inc., monitored conduct of the trial, received the data, and performed analyses. The PURPOSE 2 Study Team all vouch for the data and analysis
- Medical writing support was provided by Heather Davies, PhD, of Aspire Scientific (Bollington, UK), and was funded by Gilead Sciences, Inc.

CME, continuing medical education; G-CAG, Global Community Advisory Group; PI, principal investigator.

Summary

What is your main question?

- Does twice-yearly LEN work for HIV prevention (pre-exposure prophylaxis, PrEP) in cisgender gay, bisexual, and other men; transgender women; transgender men; and gender nonbinary people who have sex with partners assigned male at birth?

What did you find?

- Twice-yearly LEN significantly reduced HIV incidence by 96% compared with background HIV incidence, and by 89% compared with daily oral F/TDF

Why is it important?

- LEN prevents HIV, is safe, and the twice-yearly dosing may reduce clinic and user burden and could increase PrEP uptake, adherence, and persistence in populations disproportionately affected by HIV. This may help to reduce disparities in HIV acquisition worldwide

F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir.

Populations Disproportionately Affected By HIV Incidence Need New HIV Prevention Choices

The uptake of, adherence to, and persistence on oral PrEP remains suboptimal in non-White and gender-diverse populations who are disproportionately affected by HIV incidence[1-6]

We need to develop new PrEP options

LEN is a first-in-class, multistage HIV-1 capsid inhibitor with high potency and a long half-life, supporting twice-yearly SC injection[7,8]

In the recent Phase 3 PURPOSE 1 trial, LEN was demonstrated to be highly efficacious and well tolerated for HIV prevention in cisgender women[9]

We evaluated the safety and efficacy of twice-yearly SC LEN for HIV prevention in cisgender gay, bisexual, and other men; transgender women; transgender men; and gender nonbinary individuals who have sex with partners assigned male sex at birth

SC, subcutaneous. **1.** Klein H, Washington TA. *J Gay Lesbian Soc Serv*. 2020;32:99-114. **2.** Baral SD, et al. *Lancet Infect Dis*. 2013;13:214-22. **3.** Kanny D, et al. *MMWR Morb Mortal Wkly Rep*. 2019;68:801-6. **4.** Poteat T, et al. *J Acquir Immune Defic Syndr*. 2016;72(suppl. 3):S210-9. **5.** Sullivan PS, et al. *J Int AIDS Soc*. 2020;23:e25461. **6.** Torres TS, et al. *Lancet Reg Health Am*. 2023;28:100642. **7.** Segal-Maurer S, et al. *N Engl J Med*. 2022;386:1793-803. **8.** Link JO, et al. *Nature*. 2020;584:614-18. **9.** Bekker L-G, et al. N Engl J Med. 2024;391:1179-92.

PURPOSE 2 Key Eligibility Criteria

Screening Incidence Cohort

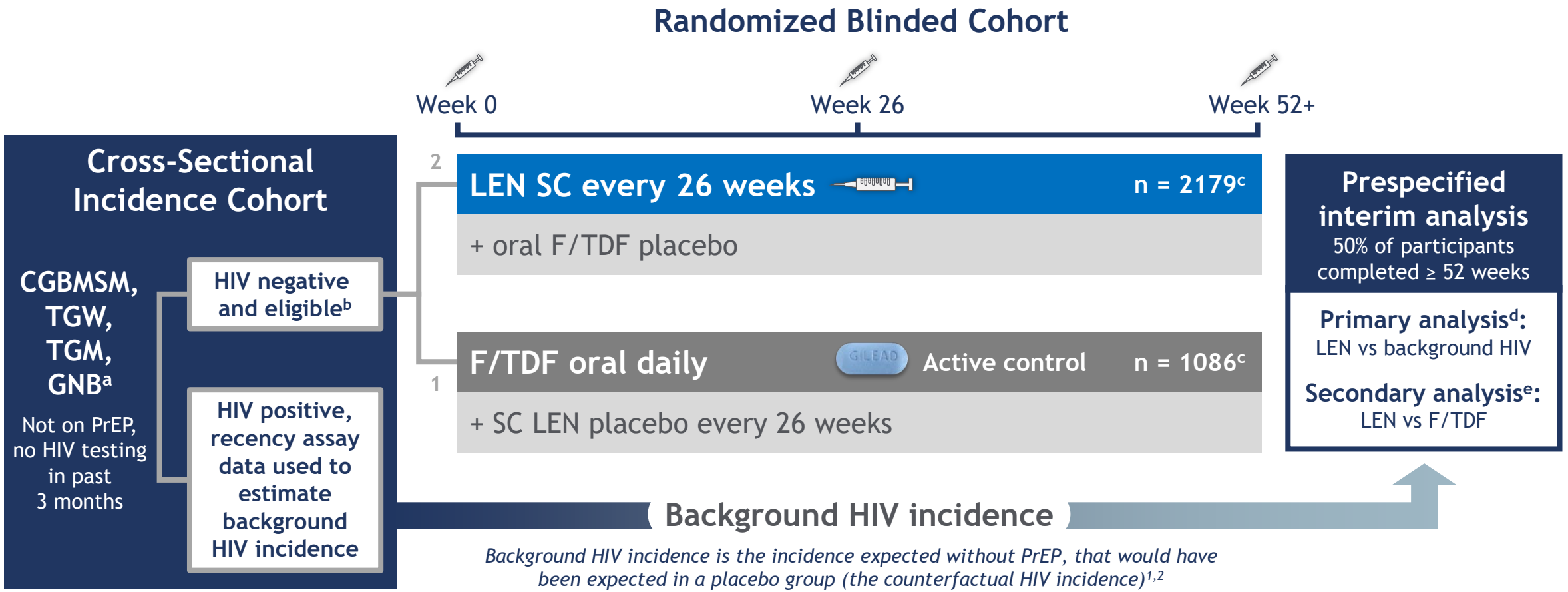
- CGM, TGW, TGM, and GNB who have condomless receptive anal sex with partners assigned male at birth and at risk for HIV-1 infection
- Age ≥ 16 years at screening
- HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3M
- Sexually active with ≥ 1 partner assigned male at birth (condomless receptive anal sex) in the last 12M and one of:
  - Condomless receptive anal sex with ≥ 2 partners in the last 12W
  - History of syphilis, rectal gonorrhea, or rectal chlamydia in the last 24W
  - Self-reported use of stimulants with sex in the last 12W
- No oral PrEP or PEP use in the last 12W or any prior use of long-acting injectable PrEP

Randomized Blinded Cohort

- Negative local rapid 4th generation HIV-1/2 Ab/Ag, central 4th generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative NAAT
- eGFR ≥ 60 mL/min at screening
- Body weight ≥ 35 kg

[a]Including F/TDF or F/TAF. Ab, antibody; Ag, antigen; eGFR, estimated glomerular filtration rate; M, months; NAAT, nucleic acid amplification testing; PEP, postexposure prophylaxis; W, weeks.

PURPOSE 2 Study Design

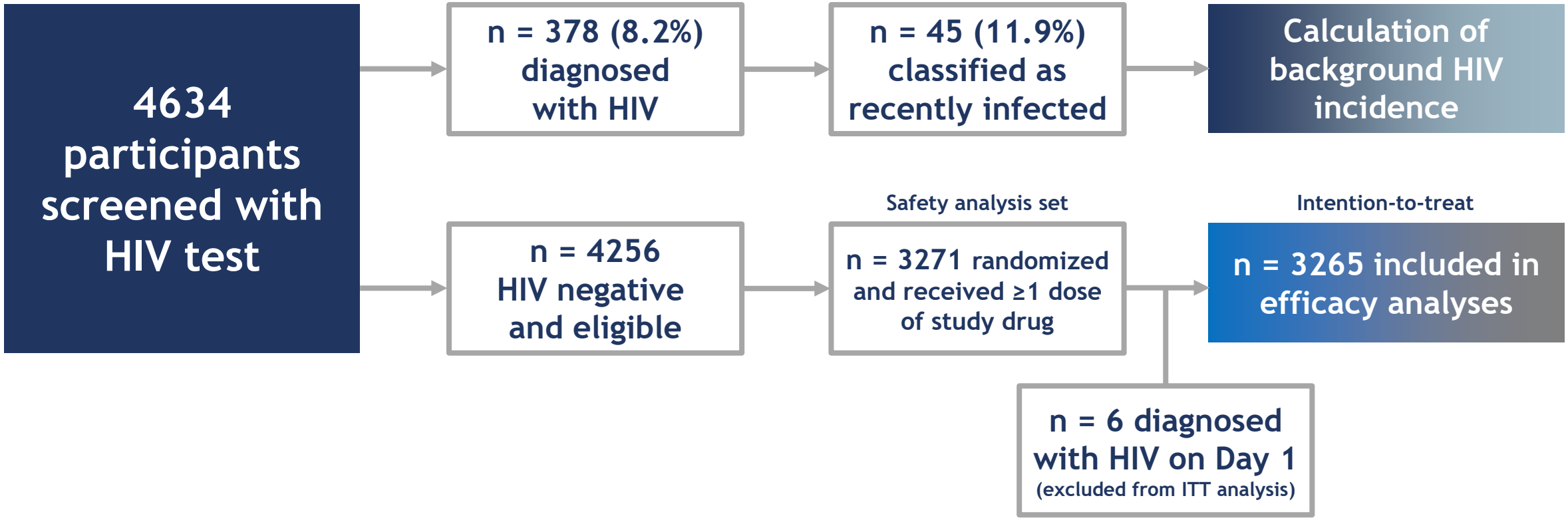


ClinicalTrials.gov: NCT04925752

On Days 1 and 2, all participants received a pharmacologic loading dose of 600 mg oral LEN or matched oral placebo. [a]The first participant was screened in June 2021, the 50th percentile participant was randomized in August 2023, and the last participant was randomized in December 2023. [b]Eligibility criteria included: age ≥16 years, 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.[1,2] [e]IRR was assessed using Poisson regression. CGBMSM, cisgender gay and bisexual men who have sex with men; GNB, gender nonbinary individuals; IRR, incidence rate ratio; TGM, transgender men; TGW, transgender women.

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

Incidence Cohort: Enrolled from June 2021 to December 2023



ITT, intention-to-treat

Baseline Characteristics

Characteristic	LEN, n = 2183	F/TDF, n = 1088
Age, years, median (range)	28 (17-74)	29 (17-73)
Age 16 to ≤ 25, years, n (%)	752 (34.4)	344 (31.6)
Non-White race,[a] n (%)	1453 (66.8)	742 (68.3)
Hispanic/Latine ethnicity,[b] n (%)	1378 (63.2)	675 (62.0)
Gender identity, n (%)		
Cisgender man	1697 (77.7)	846 (77.8)
Gender-diverse	486 (22.3)	242 (22.2)
STIs, n (%)		
Chlamydia or gonorrhea[c,d]	382 (18.2)	207 (20.0)
Syphilis	84 (3.8)	43 (4.0)
No prior HIV test, n (%)	597 (27.3)	306 (28.1)
Any prior lifetime use of PrEP, n (%)	515 (23.6)	249 (22.9)
Self-reported use of stimulants with sex in last 12 wks, n (%)	491 (22.5)	271 (24.9)

Participants

Brazil 35.6%

US 20.6%

Peru 13.7%

Thailand 11.9%

South Africa 10.9%

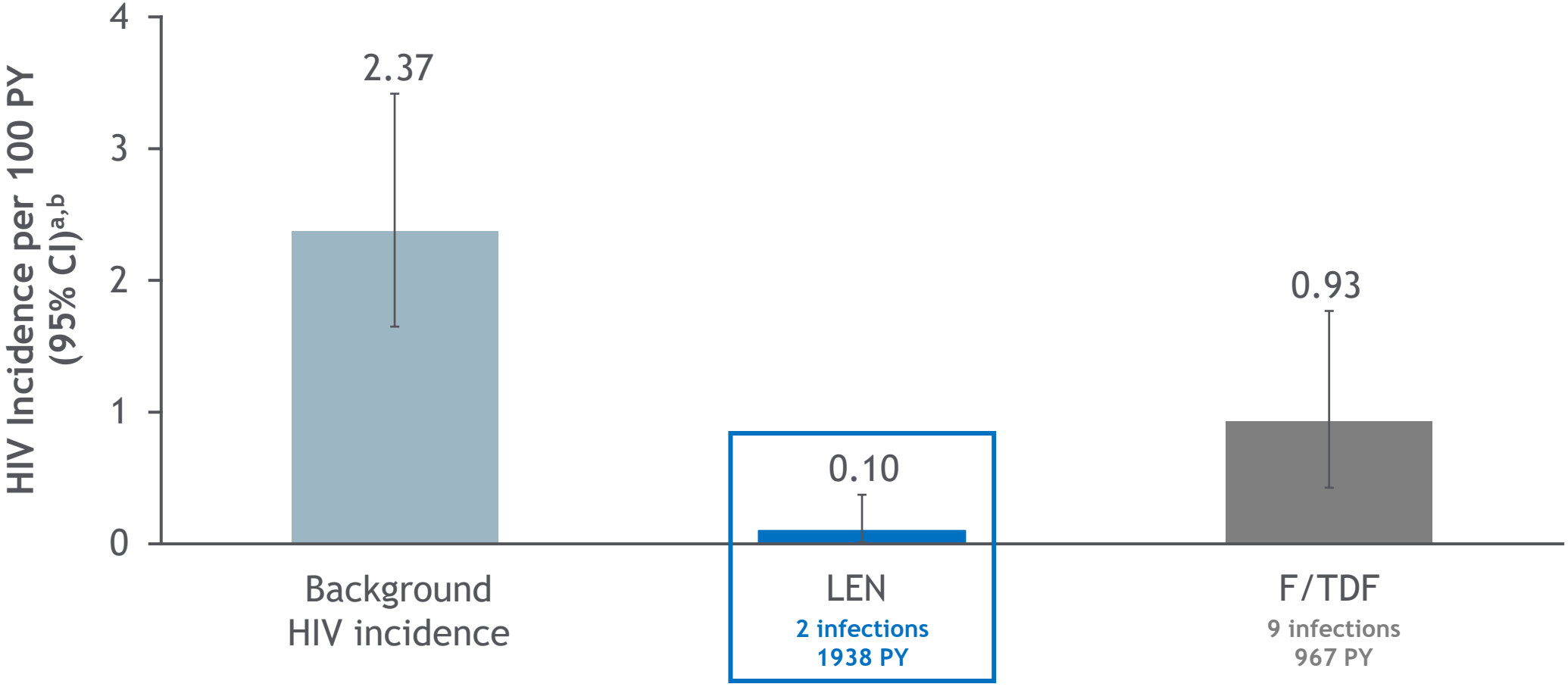
Argentina 6.9%

Mexico 0.4%

Baseline demographics and clinical characteristics were balanced between randomized groups

Six participants were subsequently determined to have had HIV infection at the time of randomization, and thus 3265 were included in the modified intention-to-treat efficacy analysis. [a]Race data were unavailable for eight participants in the LEN group and two participants in the F/TDF group. [b]Ethnicity data were unavailable for one participant in the LEN group. [c]LEN: n = 2096; F/TDF: n = 1036. ITT participants with any STI while at risk of HIV in study. Testing for T vaginalis was performed at investigator discretion (1 T vaginalis diagnosed at baseline in the LEN group). [d]Diagnoses for chlamydia or gonorrhea were based on rectal, pharyngeal, and urine testing at a central laboratory. STI, sexually transmitted infection.

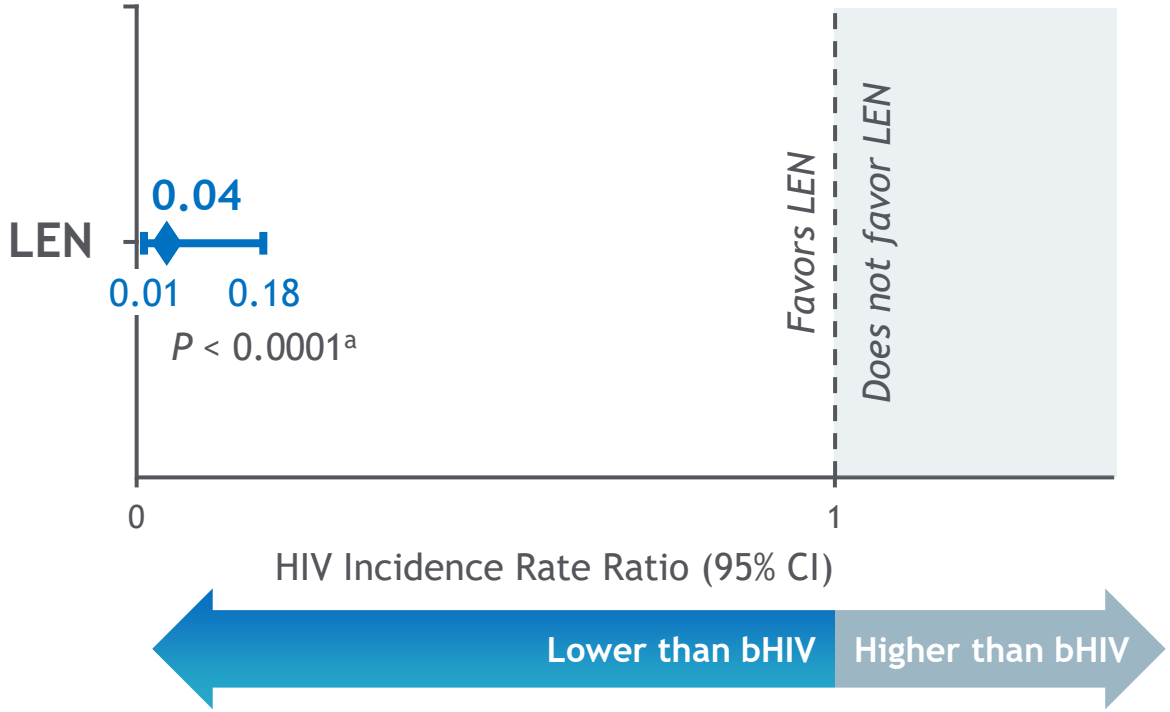
Two HIV Infections in Participants Randomized to LEN



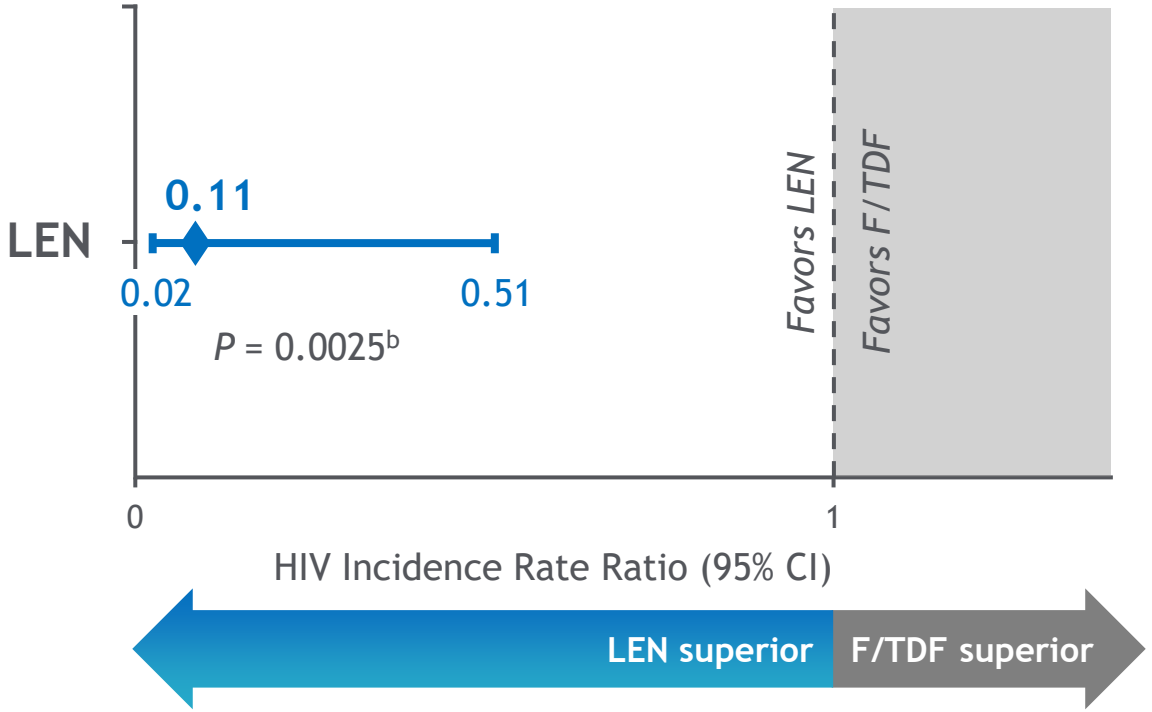
Median follow-up: 39.4 weeks

[a]Overall n: background HIV incidence group 4634; LEN, 2179; F/TDF, 1086. [b]95% CIs: background HIV incidence group 1.649, 3.417; LEN 0.012, 0.373; F/TDF 0.426, 1.768.
CI, confidence interval; PY, person-years.

Primary Analysis:
LEN Superior to bHIV Incidence



Secondary Analysis:
LEN Superior to F/TDF



LEN reduced HIV infections by 96% compared with background HIV incidence and by 89% compared with daily oral F/TDF

[a]HIV IRR vs background HIV was assessed using a Wald test[1]; [b]HIV IRR vs F/TDF assessed using Poisson regression.
bHIV, background HIV incidence.

1. Gao F, et al. *Stat Commun Infect Dis*. 2021;13:20200009.

LEN and F/TDF Are Safe and Well Tolerated

Adverse Event,[a] n (%)	LEN, n = 2183	F/TDF, n = 1088
Any	1607 (74)	803 (74)
Grade ≥ 2	1173 (54)	594 (55)
Grade ≥ 3	91 (4)	65 (6)
Serious AEs	71 (3)	43 (4)
AEs leading to discontinuation of study drug	7 (< 1)	7 (< 1)[b]
AEs occurring in ≥ 5% of participants, n (%)		
Rectal chlamydia infection	289 (13)	128 (12)
Oropharyngeal gonococcal infection	283 (13)	119 (11)
Rectal gonococcal infection	233 (11)	99 (9)
Upper respiratory tract infection	148 (7)	77 (7)
Diarrhea	146 (7)	75 (7)
Headache	119 (5)	76 (7)
Influenza	120 (5)	66 (6)
Latent syphilis	114 (5)	44 (4)
Nausea	89 (4)	67 (6)
Laboratory abnormalities, n with ≥ 1 post-baseline result[c]		
Any Grade ≥ 1, n (%)	1822 (85)	937 (87)

4 deaths in the LEN group and 2 deaths in the F/TDF group[d]; none related to study drug per investigator

Median change from baseline in eGFR:

- Week 26: +1.2 mL/min in the LEN group vs -3.0 mL/min in the F/TDF group ($P < 0.0001$)
- Week 52: +0.6 mL/min in the LEN group vs -2.9 mL/min in the F/TDF group ($P = 0.0024$)

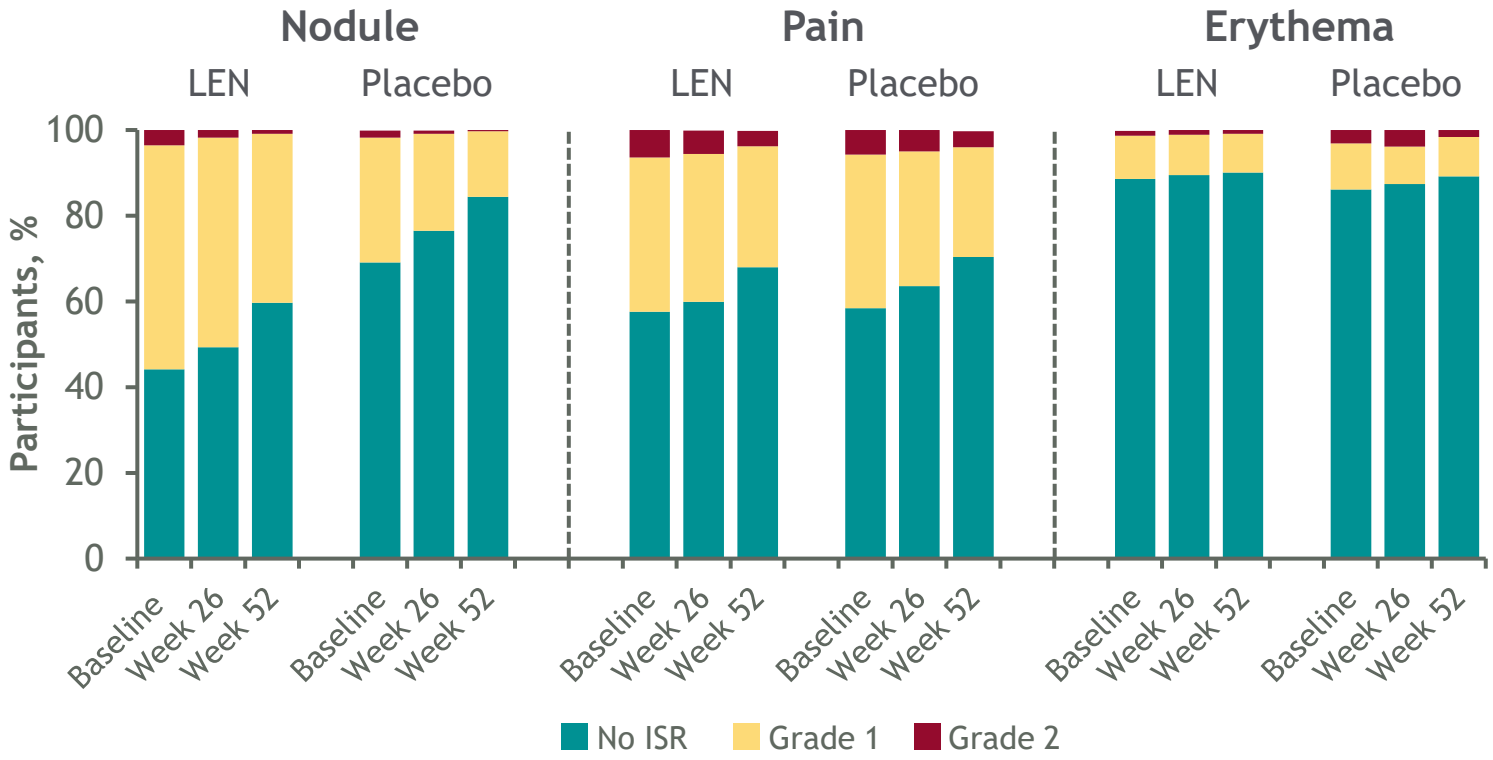
The frequency of adverse events and laboratory abnormalities was similar between arms, with the exception of changes in eGFR (significantly different at Week 26 and Week 52). Safety was consistent with prior LEN and F/TDF trials[1-5]

[a]Excluding injection-site reactions; AEs coded according to Medical Dictionary for Regulatory Activities, Version 27.0, and graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.
[b]AEs leading to discontinuation of study drug in > 1 participant in any group: decreased creatinine renal clearance (2 participants in the F/TDF group). [c]Among participants with post-baseline results: LEN n = 2153; F/TDF n = 1071.
[d]LEN group: cerebrovascular accident and pulmonary thromboembolism, car collision, sudden death with an undetermined cause, and suicide; F/TDF group: intracranial hemorrhage and undetermined cause. AE, adverse event.

1. Gupta SK, et al. *Lancet HIV*. 2023;10:e15-23. **2.** Ogbuagu O, et al. *Lancet HIV*. 2023;10:e497-505. **3.** Mayer KH, et al. *Lancet*. 2020;396:239-54. **4.** Baeten JM, et al. *N Engl J Med*. 2012;367:399-410.
5. Bekker L-G, et al. N Engl J Med. 2024;391:1179-92.

Injection-Site Reaction Frequency and Grade Diminish With Subsequent Injections

- LEN is injected into the SC space and forms a drug depot that may be palpable under the skin but is usually not visible
- As the drug elutes over time, the depot gets smaller, and the nodules resolve or reduce in size substantially prior to the next injection
- **The frequency of ISRs, including nodules, decreased with subsequent doses (also observed previously in PURPOSE 1[1] and with HIV treatment[2])**



Among 15,239 LEN or placebo injections, only 29 participants discontinued due to AEs of ISRs; 26 in LEN group and 3 in the F/TDF group

AEs coded according to Medical Dictionary for Regulatory Activities, Version 27.0. Subcutaneous nodules, injection-site pain, and erythema were the most commonly reported ISRs; over the period of study, they occurred in 63.4%, 56.4 %, and 17.3% of participants in the LEN group, respectively, versus 39.2%, 53.4%, and 19.4% of participants given placebo injections; Grade 1 and 2 ISRs are shown, Grade 3 ISRs in the LEN group: n = 4 pain, n = 3 erythema; F/TDF group: n = 1 pain. LEN n: baseline, 2183; Week 26, 1859; Week 52, 744. Placebo n: baseline, 1088; Week 26, 946; Week 52, 379. ISR, injection-site reaction.

1. Bekker L-G, et al. N Engl J Med. 2024;391:1179-92. **2.** Kumar P, et al. Abstract EPB184 presented at the 24th International AIDS Conference, July 29 to August 2, 2022; Montreal, Canada.

PURPOSE 2 Conclusions

- There were only two incident HIV infections among 2179 participants receiving twice-yearly LEN for HIV prevention
  - LEN reduced HIV incidence by 96% compared with background HIV incidence, and by 89% compared with daily oral F/TDF
- LEN and F/TDF were safe and well tolerated
- All trial participants are being offered open-label LEN
- LEN continues to represent a novel, highly effective tool for HIV prevention that is not dependent on daily oral adherence

Twice-yearly LEN offers an efficacious, safe, and well-tolerated choice for PrEP in cisgender men, transgender women, transgender men, and gender-diverse people and has the potential to increase PrEP uptake and to reduce the global burden of HIV

PURPOSE 2 Pending Analyses

Adherence/PK

- Adherence to F/TDF measured via tenofovir-diphosphate levels in dried blood spots
- PK for LEN measured in plasma

Detailed data on HIV seroconversions among those assigned to LEN

- LEN PK
- Resistance
- Sexual and other behavior

PK, pharmacokinetics

PURPOSE 2 Next Steps

Global regulatory filings are urgently in progress so that LEN, if approved, can be authorized for all those who need or want PrEP, particularly those most disproportionately affected by HIV

Gilead has been developing a strategy to enable broad, sustainable access globally

- Royalty-free, voluntary licensing agreements are in place with six pharmaceutical manufacturers to make generic LEN available in 120 high-incidence, resource-limited countries, covering LEN for HIV prevention, if approved, and treatment in HTE adults with MDR HIV
- These agreements are just one component of Gilead's overall global strategy to enable broad, sustainable access to lenacapavir for PrEP, if approved, prioritizing timely regulatory filings, engagement with partners and governments, and manufacturing planning, including for Argentina, Brazil, Mexico, Peru, and the United States

Please see the full access statements at Gilead.com[a,b]

PURPOSE 1 NCT identifier: NCT04994509; PURPOSE 2: NCT04925752; PURPOSE 3: NCT06101329; PURPOSE 4: NCT06101342. PURPOSE studies available at: https://www.purposestudies.com (accessed Oct 4, 2024).
[a]https://www.gilead.com/company/company-statements/2024/updated-statement-on-access-planning-in-high-incidence-resource-limited-countries-for-lenacapavir-for-hiv-prevention (accessed Oct 4, 2024).
[b]https://www.gilead.com/news/news-details/2024/gilead-signs-royalty-free-voluntary-licensing-agreements-with-six-generic-manufacturers-to-increase-access-to-lenacapavir-for-hiv-prevention-in-high-incidence-resource-limited-countries (accessed Oct 4, 2024).
FR, France; HTE, heavily treatment-experienced; MDR, multidrug-resistant; PWID, people who inject drugs; NCT, National Clinical Trial; UK, United Kingdom; US, United States.

PURPOSE 2

Acknowledgments

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PURPOSE 2 Study Team

Maribel Acevedo-Quiñones, Allison L Agwu, Suvaporn Anugulruengkitt, Anchalee Avihingsanon, Joanne Batting, Jose A Bazan, Paul Benson, Vladimir Berthaud, Jill Blumenthal, Indira Brar, Cynthia Brinson, Carlos Roberto Brites Alves, Pedro Cahn, Thomas B Campbell IV, Valeria D Cantos, Michelle Cespedes, Ploenchan Chetchotisakd, Jesse Clark, Meredith Clement, Katya Corado, Gonzalo Corral, Catherine Creticos, Gordon Crofoot, Edwin Dejesus, Ricardo S Diaz, Craig Dietz, Susanne Doblecki-Lewis, David F Dougherty, Ian Frank, James W Galbraith, Jorge Antonio Gallardo Cartagena, Aditya Gaur, Beatriz Gilda Jegerhorn Grinsztejn, Marcus Guimaraes De Lacerda, Michael Guyton-Nunley, Shawn Hassler, Christine Heumann, Juan Carlos Hinojosa Boyer, Theo Hodge, Moises A Huaman, Richard Kaplan, Colleen F Kelley, Sasisopin Kiertiburanakul, Javier R Lama Valdivia, Anthony LaMarca, Marcelo Losso, Christopher Lucasti, Morakane Alicia Caroline Makwela, Weerawat Manosuthi, Kenneth H Mayer, Eric G Meissner, Ivan Melendez-Rivera, Anthony Mills, Kathryn Mngadi, Caryn G Morse, Karam Mounzer, Nkosiphile Ndlovu, Richard M Novak, Onyema Ogbuagu, Alma Minerva Perez Rios, Nittaya Phanuphak, Jose Henrique Pilotto, Jorge Pinto, Jose Valdez Ramalho Madruga, Moti Ramgopal, Jeffrey Reeves, Lina Rosengren-Hovee, Peter J Ruane, Kamla Sanasi-Bhola, Breno Santos, Tanya Schreibman, Hyman Scott, Namrata Shah, Peter Shalit, Jihad Slim, LaShonda Spencer, Khuanchai Supparatpinyo, Javier Valencia, Cornelius N Van Dam, Olivia T Van Gerwen, Ricardo Vasconcelos, Jose Gabriel Vasquez Cerro, Jennifer Veltman, Robert Woolard, Kimberly Workowski, Ashraf Zadshir, Zwelethu Zwane

PURPOSE 2

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