PURPOSE
Prevention with PURPOSE

AIDS 2024

Twice-Yearly Lenacapavir or Daily Oral Emtricitabine/Tenofovir Alafenamide for HIV Prevention in Cisgender Women: Interim Analysis Results from the PURPOSE 1 Study

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Summary

What is your main question?

- Does twice-yearly LEN or daily oral F/TAF work for HIV prevention (pre-exposure prophylaxis, PrEP) in cisgender women?

What did you find?

- Zero women receiving LEN acquired HIV
  - 100% efficacious and better than F/TDF at preventing HIV infection
- The rate of HIV infections was not reduced by F/TAF
  - However, women who were adherent to F/TAF had a lower chance of HIV infection than those who did not take the F/TAF tablets as directed
- LEN, F/TAF, and F/TDF were safe and well tolerated

Why is it important?

- Twice-yearly LEN works well, is safe, and is a discreet choice to help more cisgender women use and stay on PrEP and hopefully to reduce HIV incidence in cisgender women worldwide

F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; PrEP, pre-exposure prophylaxis.

Disclosures

- Honoraria for advisories from Gilead Sciences, Merck (Pty) Ltd, ViiV Healthcare
- Research grants to the Desmond Tutu Health Foundation to conduct implementation science obtained from Johnson and Johnson, ViiV healthcare
- Served on the Data Safety Monitoring Board for the PrEPVACC HIV Vaccine trial
- Gilead Sciences funded the study and designed the study with input from the PIs and G-CAG. The PIs and study staff gathered data; Gilead Sciences monitored conduct of the trial, received the data, and performed analyses. The PURPOSE 1 Study Team all vouch for the data and analysis
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G-CAG, Global Community Advisory Groups; PI, principal investigators

Cisgender Women Need New HIV Prevention Choices

Cisgender women's uptake of, adherence to, and persistence on PrEP remains suboptimal globally.[1-4]
We need to develop new PrEP options

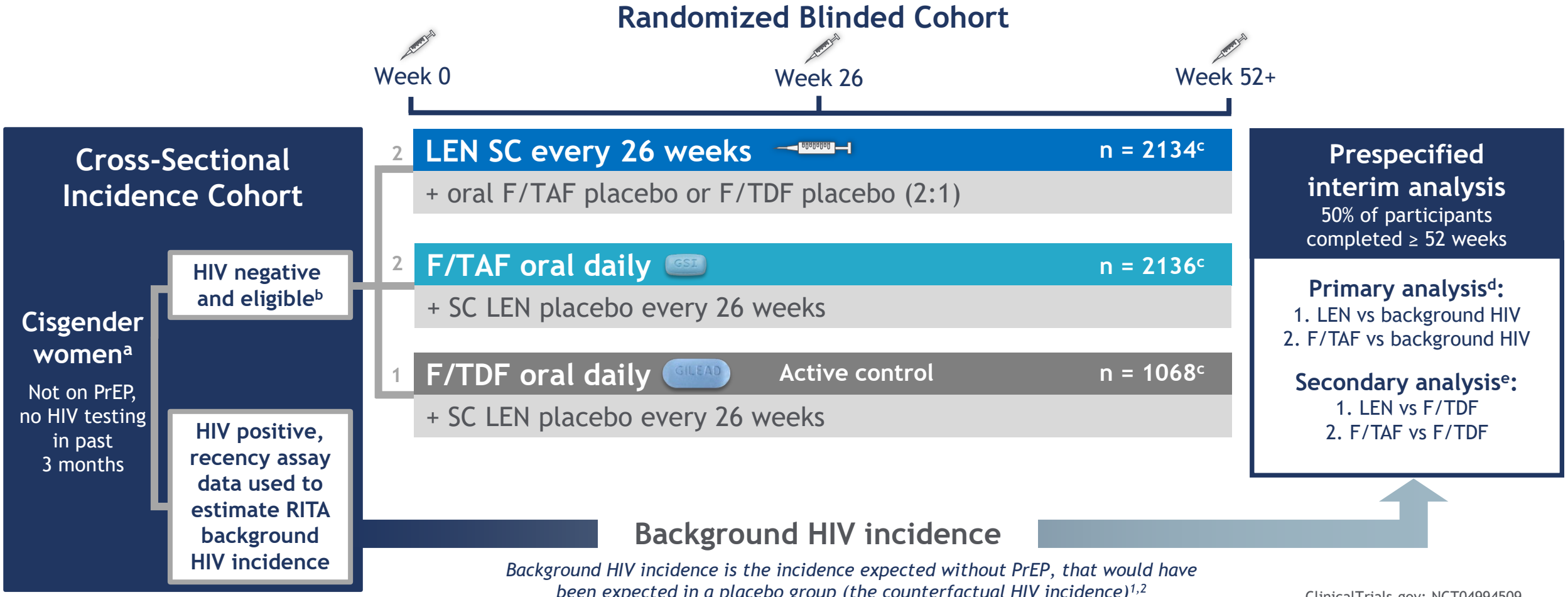
LEN is a **first-in-class**, multistage HIV-1 capsid inhibitor with **high potency** and a **long half-life**, supporting **twice-yearly SC injection**[5,6]

- **F/TAF** is administered in a smaller tablet than F/TDF; TAF has more plasma stability and more rapid uptake in PBMCs than TDF[7]
- **F/TAF** has demonstrated PrEP efficacy and safety in cisgender men and transgender women who have sex with men[8]

We evaluated the safety and efficacy of twice-yearly SC LEN or daily oral F/TAF for HIV prevention in cisgender women

PBMC, peripheral blood mononuclear cell; SC, subcutaneous. **1.** de Dieu Tapsoba J, et al. *AIDS Care*. 2021;33(6):712-20. **2.** Mugwanya KK, et al. Abstract 993 presented at: Conference on Retroviruses and Opportunistic Infections; March 4-7, 2019; Seattle, WA. **3.** Velloza J, et al. *AIDS Behav*. 2023;27(1):279-89. **4.** Chakare T, et al. Abstract OAD0604 presented at: 23rd International AIDS Conference; July 6-10, 2020; Brisbane, Australia. **5.** Link JO, et al. *Nature*. 2020;584(7822):614-18. **6.** Segal-Maurer S, et al. *N Engl J Med*. 2022;386(19):1793-803. **7.** Lee WA, et al. *Antiviral Therapy*. 2022;27(2):13596535211067600; **8.** Mayer KH, et al. *Lancet*. 2020;396:239-54.

PURPOSE 1 Study Design



[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.

Baseline Characteristics

Characteristic	LEN, n = 2138	F/TAF, n = 2137	F/TDF, n = 1070
Age, years, median (range)	21 (16-25)	21 (16-26)[a]	21 (16-25)
Age 16 to <18, years, n (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black race,[b] n (%)	2135 (99.9)	2136 (100)	1068 (99.8)
Highest education level college/university,[c] n (%)	183 (8.6)	198 (9.3)	109 (10.2)
Marital status, n (%)			
Married	26 (1.2)	30 (1.4)	17 (1.6)
Living with primary partner	148 (6.9)	132 (6.2)	73 (6.8)
STIs, n (%)			
Chlamydia trachomatis	520 (24.3)	562 (26.3)	263 (24.6)
Neisseria gonorrhoeae	197 (9.2)	178 (8.3)	90 (8.4)
Trichomonas vaginalis	154 (7.2)	165 (7.7)	82 (7.7)
Syphilis	57 (2.7)	63 (2.9)	29 (2.7)
Any prior use of PrEP, n (%)	143 (6.7)	121 (5.7)	71 (6.6)
Any prior HIV testing, n (%)	1713 (80.1)	1731 (81.0)	860 (80.4)
Median time since last HIV test, months (Q1, Q3)	6.8 (4.7, 11.5)	6.6 (4.8, 11.0)	6.5 (4.6, 11.0)

Participants

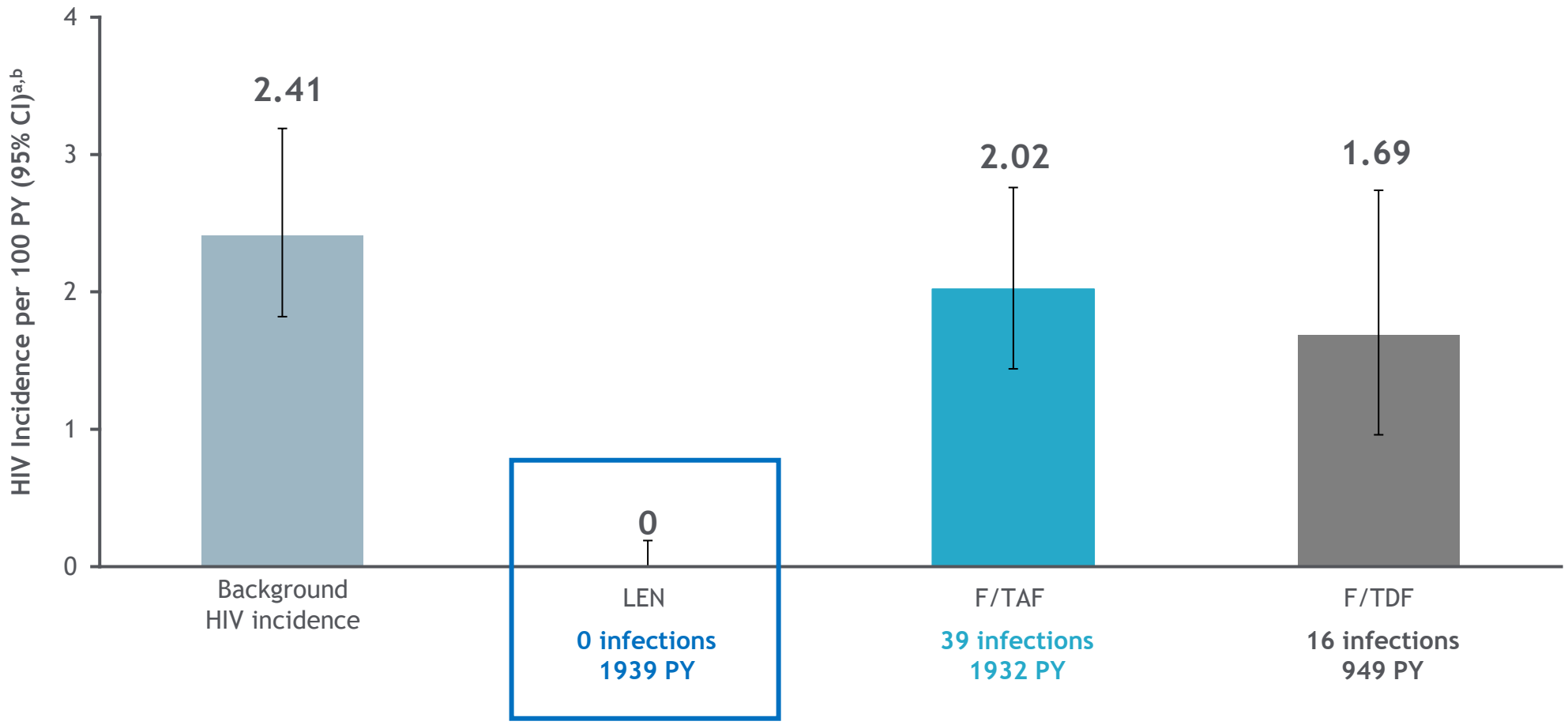
84.3%
South Africa

15.7%
Uganda

Baseline demographics and clinical characteristics were balanced across randomized groups

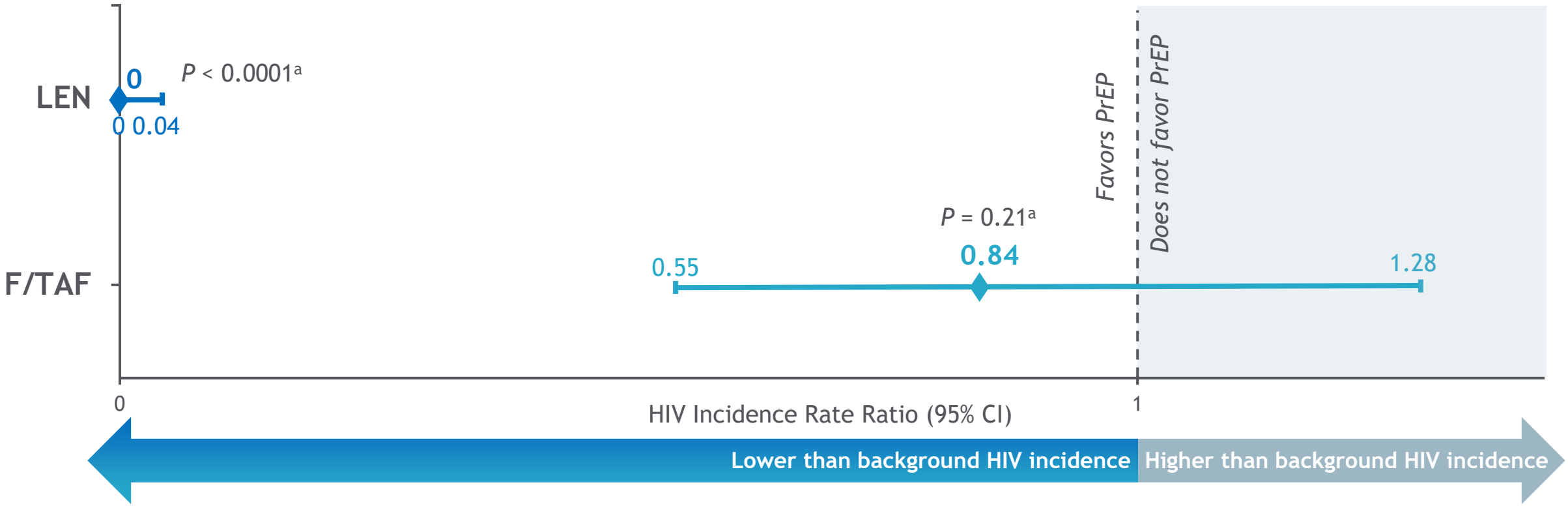
Seven participants were subsequently determined to have had HIV infection at the time of randomization, and thus 5338 were included in the modified intention-to-treat efficacy analysis. [a]One participant was aged 25 years at screening but turned 26 by randomization—this was not a violation of eligibility criteria. [b]All non-Black participants were multiracial; [c]Sample size LEN: 2136; F/TAF: 2134; F/TDF: 1069
Q, quartile; STI, sexually transmitted infection.

Zero HIV Infections in Cisgender Women receiving LEN



[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.

Primary Analysis: LEN has 100% Efficacy for PrEP

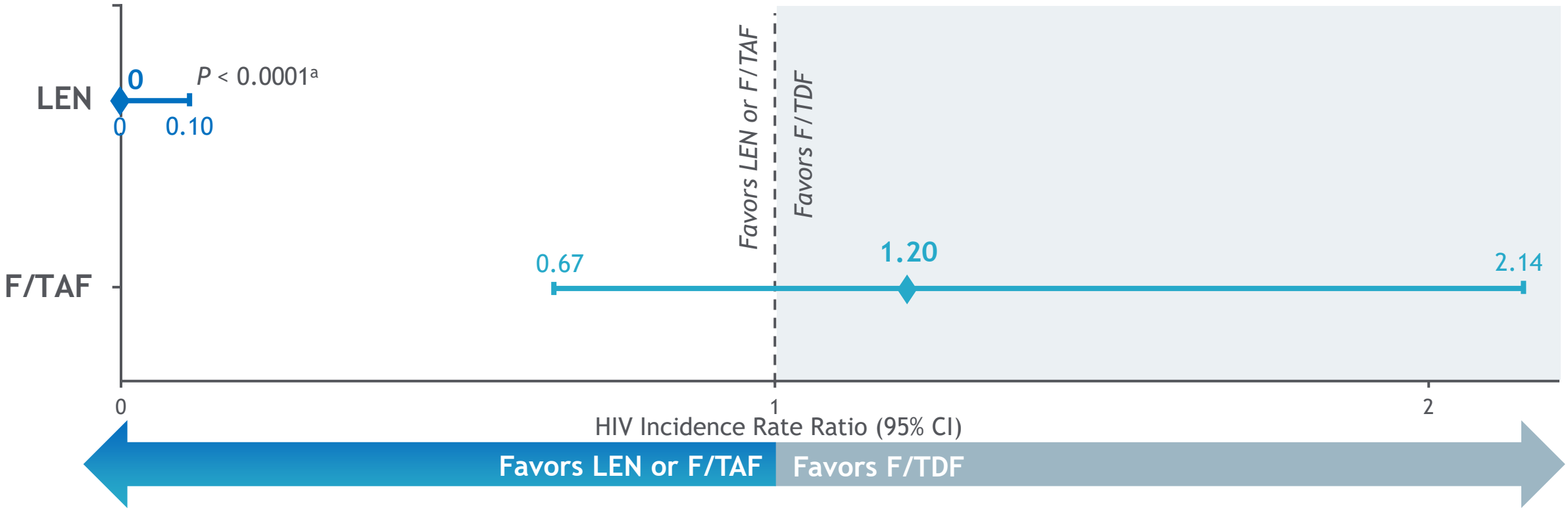


LEN has 100% PrEP efficacy; F/TAF not different from background HIV incidence

[a]HIV IRR vs background HIV was assessed using a likelihood ratio test (LEN, due to zero infections), and a Wald test (F/TAF).[1,2]

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

Secondary Analysis: LEN is Superior to F/TDF



LEN has 100% superiority to F/TDF; F/TAF not numerically different from F/TDF

[a]HIV IRR vs F/TDF assessed using an exact conditional Poisson regression model (LEN, due to zero infections).

Adherence to Injections Was High While Adherence to Oral F/TAF and F/TDF Was Poor

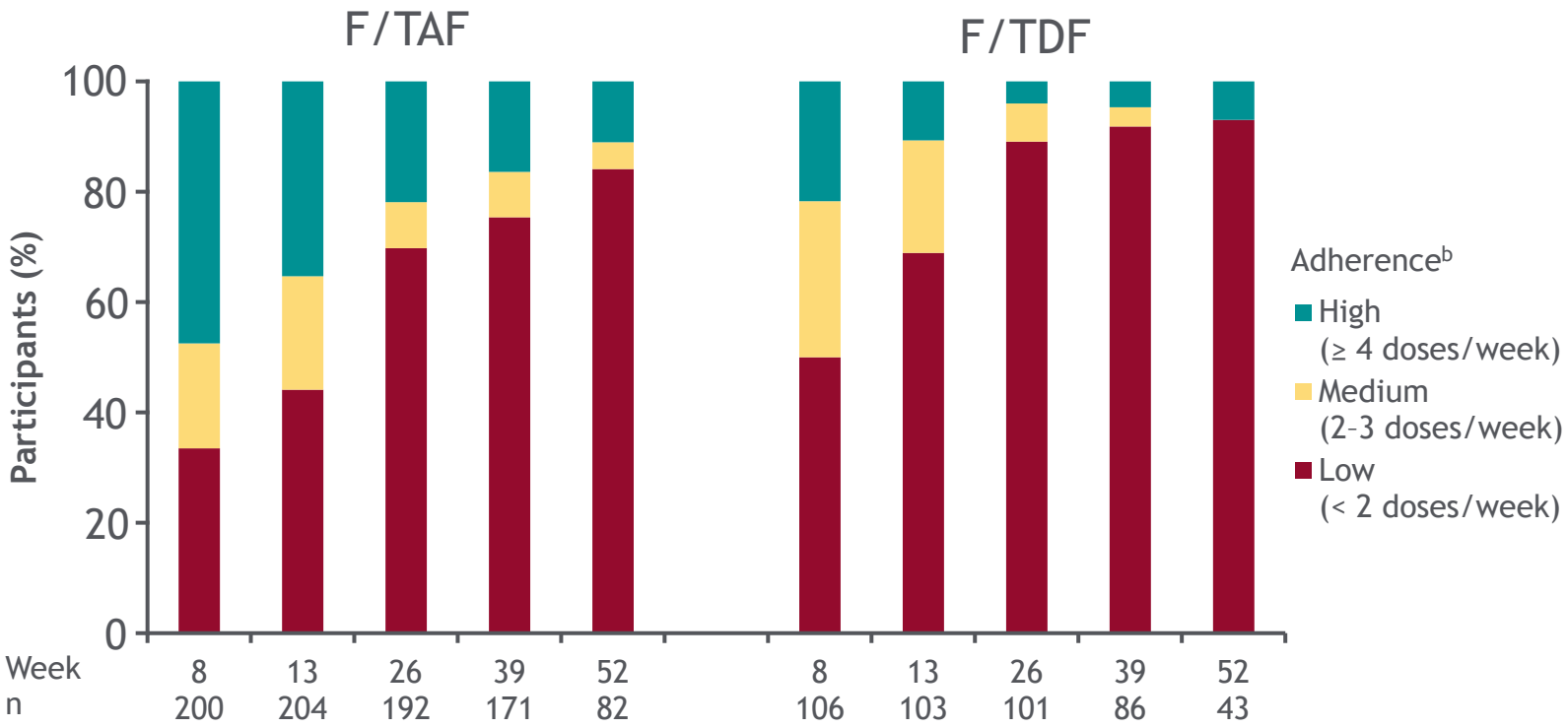
Injection Adherence in All Participants

Injections were on time[a] for:

- **91.5% (4545/4967) at Week 26**
- **92.8% (2025/2181) at Week 52**

On-time injection similar on LEN and placebo (F/TAF and F/TDF)

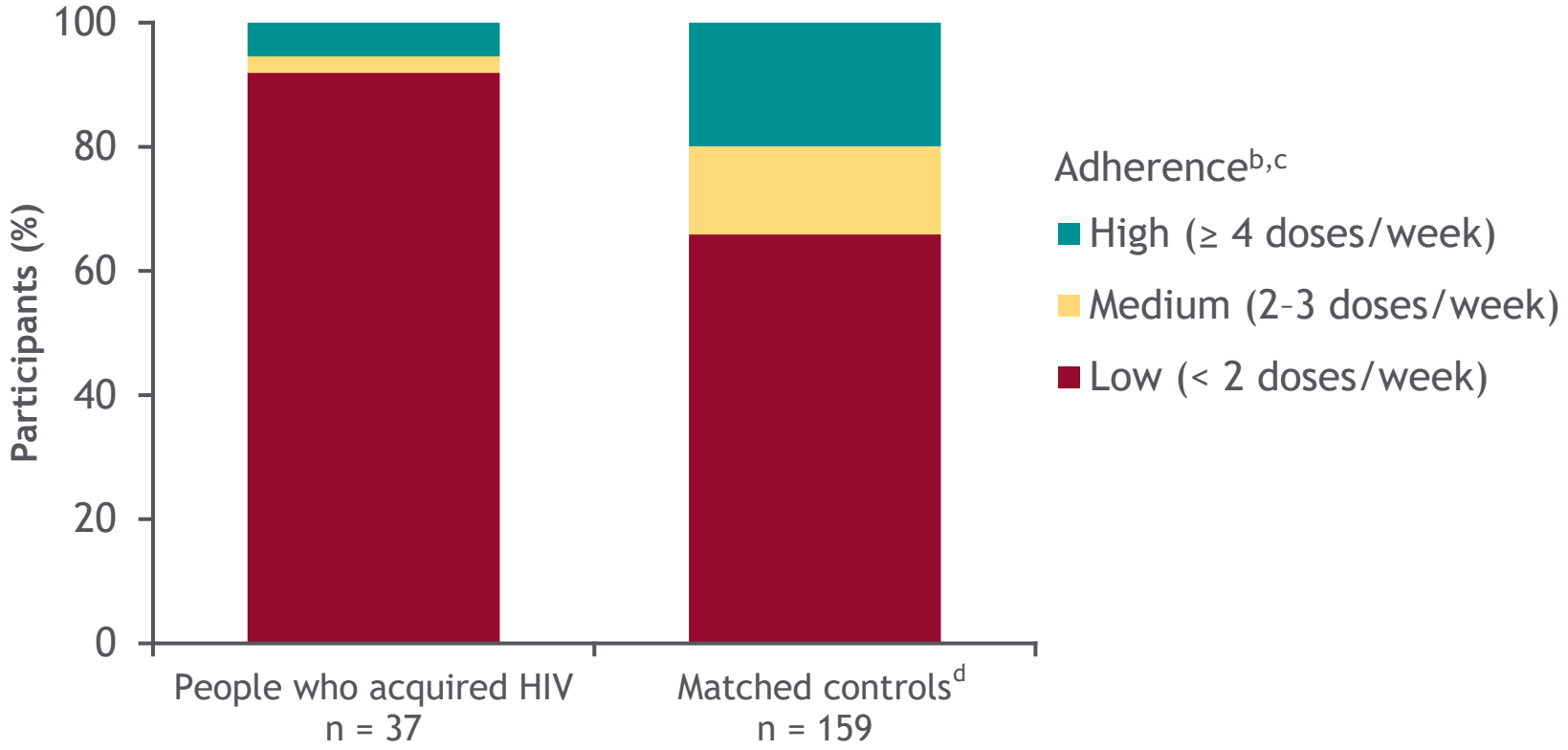
Adherence by TFV-DP Concentration in 10% Cohort



On-time adherence to injections was high
Most participants in both the F/TAF and F/TDF groups had low adherence to oral tablets, and adherence declined over time

[a]Adherence to LEN was defined as on-time injections (< 28 weeks from the last injection), and participants who presented late required negative HIV testing to reinitiate study product, which included reloading with oral LEN or placebo. [b]Preselected 10% sample of participants assessed for TFV-DP concentrations in DBS (adherence cutoffs for F/TAF: low < 450, medium ≥ 450 to < 900, high ≥ 900 fmol/punches; and for F/TDF: low < 350, medium ≥ 350 to < 700, high ≥ 700 fmol/punch). DBS, dried blood spot; TFV-DP, tenofovir diphosphate.

Lower Chance of HIV Infection Associated With Medium or High Adherence to F/TAF: A Matched Case-Control Analysis[a]



A significantly lower likelihood of HIV infection is associated with medium or high adherence compared with low adherence (odds ratio 0.11; 95% CI 0.012-0.49; *P* = 0.0006)

[a]Conditional logistic regression. Controls matched on site and baseline VOICE score from the same visit as the HIV diagnosis visit of each case. Each of 37 case participants contributed 1 sample. A trial participant could serve as a control for more than case participant; 159 participants contributed 176 samples to be used as matched controls. [b]By TFV-DP DBS levels (adherence cutoffs for F/TAF: low < 450, medium ≥ 450 to < 900, high ≥ 900 fmol/punch; and for F/TDF: low < 350, medium ≥ 350 to < 700, high ≥ 700 fmol/punch). [c]Missing DBS concentrations imputed for participants with HIV infection based on last concentration prior to HIV diagnosis, and decay rate based on the median half-life. [d]Available data shown in stacked bar.

LEN and F/TAF Are Safe and Well Tolerated

Adverse Events[a], n (%)	LEN n = 2138	F/TAF n = 2137	F/TDF n = 1070
Any	1631 (76.3)	1665 (77.9)	830 (77.6)
Grade ≥ 2	1111 (52.0)	1078 (50.4)	533 (49.8)
Grade ≥ 3	88 (4.1)	95 (4.4)	50 (4.7)
Serious AEs	59 (2.8)	85 (4.0)	35 (3.3)
AEs leading to discontinuation of study drug	5 (0.2)[b]	2 (<0.1)[c]	0
AEs occurring in ≥10% of participants, n (%)			
Headache	285 (13.3)	352 (16.5)	155 (14.5)
Urinary tract infection	307 (14.4)	305 (14.3)	163 (15.2)
Genitourinary chlamydia infection	300 (14.0)	317 (14.8)	129 (12.1)
Upper respiratory tract infection	271 (12.7)	274 (12.8)	121 (11.3)
Nausea	144 (6.7)	234 (10.9)	142 (13.3)
Vomiting	125 (5.8)	235 (11.0)	107 (10.0)
Laboratory abnormalities, n with ≥1 post-baseline result	2126	2113	1054
Any Grade ≥ 1, n (%)	1929 (90.7)	1904 (90.1)	959 (91.0)

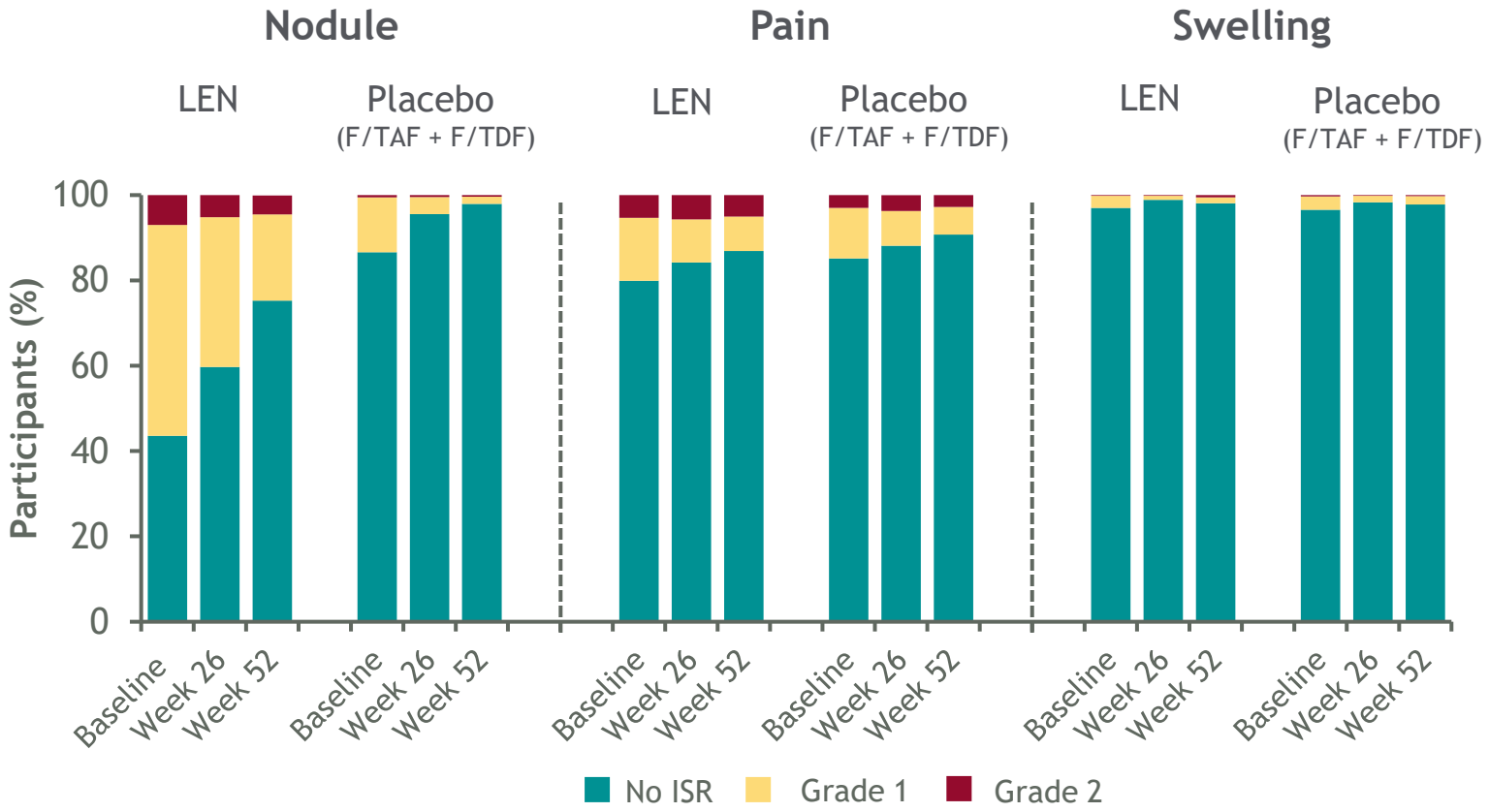
Six deaths[d] all in the F/TAF group; none related to study drug per investigator

Adverse events were consistent with prior LEN, F/TAF and F/TDF trials[1-4]

[a]AEs are treatment emergent in persons who received at least one dose of study drug; AEs exclude 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 AEs, Version 2.1. [b]n = 1 for each of: nausea, decreased creatinine renal clearance, increased hepatic enzyme, spontaneous miscarriage, suicide attempt/major depression. [c]n = 1 for each of: suicide attempt/depressive symptoms/drug overdose, angioedema. [d]Asphyxia secondary to strangulation, non-accidental burns, knife stab to chest, hemorrhage due to traffic accident, autopsy-confirmed ischemic cardiomyopathy, and ovarian cancer. AE, adverse event. **1.** Gupta SK, et al. *Lancet HIV*. 2023;10(1):e15-e23. **2.** Ogbuagu O, et al. *Lancet HIV*. 2023;10(8):e497-e505. **3.** Mayer KH, et al. *Lancet*. 2020;396:239-54. **4.** Baeten JM, et al. *N Engl J Med*. 2012;367:399-410.

Injection Site Reaction Frequency Diminishes 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
- **ISRs, including nodules, decreased with subsequent doses (also observed with HIV treatment[1])**



Among 25,329 injections, only four ISRs led to discontinuation

Grade 1 and 2 ISRs are shown. LEN n: baseline, 2138; Week 26, 1930; Week 52, 862. Placebo (F/TAF + F/TDF) n: baseline, 3206; Week 26, 2883; Week 52, 1274.
ISR, injection site reaction

1. Kumar P, et al. Abstract EPB184 presented at the 24th International AIDS Conference, July 29 to August 2, 2022; Montreal, Canada.

Pregnancies Were Common and Outcomes Similar to Expected Rates in the Population

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)

Expected spontaneous miscarriage rate[1,2]:

- **~10-20% of clinically recognized pregnancies**
- **~30% of biochemically detected pregnancies**

Available pregnancy outcomes were similar to those expected for the population[3]

[a]Completed uninterrupted pregnancies which includes live births and 8 still births: 3 in the LEN group, 4 in the F/TAF group, and 1 in the F/TDF group. [b]Spontaneous miscarriage defined as occurring at < 20 weeks' gestation.

1. ACOG Committee on Practice Bulletins—Gynecology. *Obstet Gynecol*. 2018;132(5):e197-e207. **2.** Wilcox AJ, et al. *N Engl J Med*. 1988;319:189-94. **3.** Mugo NR, et al. *JAMA*. 2014;312(4):362-71.

PURPOSE 1 Conclusions

- There were zero HIV infections in cisgender women receiving twice-yearly LEN for HIV prevention
  - LEN HIV prevention efficacy was superior to both background HIV incidence and F/TDF
- Daily oral F/TAF and F/TDF adherence was poor
  - HIV protection was strongly associated with F/TAF adherence
- LEN and F/TAF were safe and well tolerated
- All trial participants are being offered open-label LEN
- This novel study design creates a path forward for future PrEP options or HIV vaccine trials

Twice-yearly LEN offers an efficacious, safe, and discreet choice to improve PrEP use among cisgender women and reduce the global burden of HIV

PURPOSE 1 Next Steps

The regulatory filing for lenacapavir will include the results of PURPOSE 1 and PURPOSE 2, if positive, to ensure approval for those most disproportionately affected by HIV

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

Please see the full access statement at Gilead.com[a]

PURPOSE 1 NCT identifier: NCT04994509; PURPOSE 2: NCT04925752; PURPOSE 3: NCT06101329; PURPOSE 4: NCT06101342. PURPOSE Studies. Available at: https://www.purposestudies.com/ (Accessed July 5, 2024)
[a]https://www.gilead.com/news-and-press/company-statements/updated-statement-on-global-access-planning-for-lenacapavir-for-hiv-prevention. CGMSM, cisgender men who have sex with men; FR, France; GNB, gender non-binary people; PWID, people who inject drugs; TGM, transgender men; TGW, transgender women; NCT, national clinical trials; UK, United Kingdom; US, United States.

PURPOSE 1

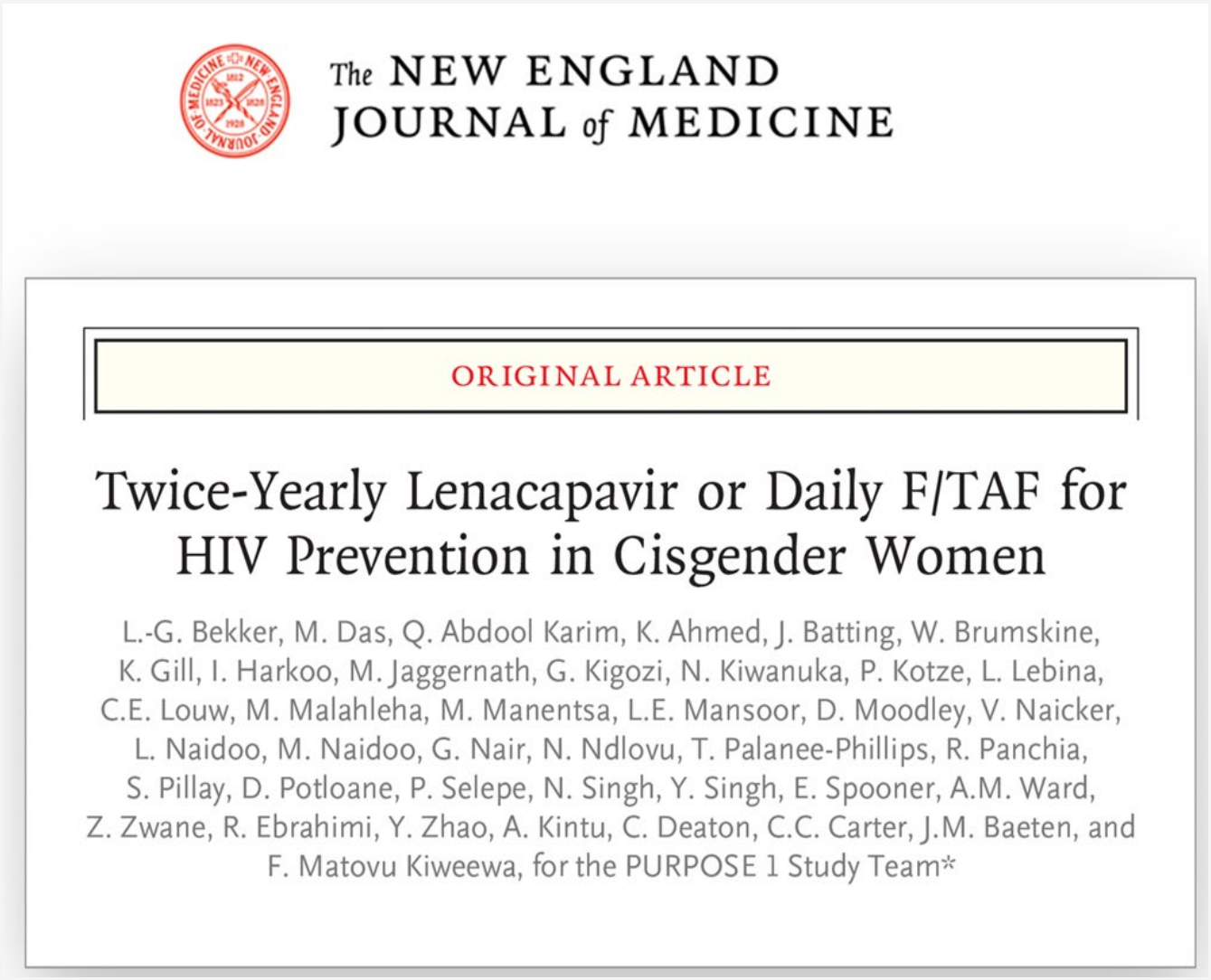
Acknowledgments

We extend our gratitude to the trial participants, their families and communities, the investigators and site staff, our Global Community Accountability and Advisory Group, and the members of the PURPOSE 1 study team

PURPOSE 1 Study Team

Quarraisha Abdool Karim, Khatija Ahmed, Dos Santos Ankomisyani, Joanne Batting, Johanna Alida Baumgarten, Trevor Beattie, Ngundu Behuhuma, Linda-Gail Bekker, Mags Beksinska, Gabriella Benade, William Brumskine, Sithandiwe Buthelezi, Valmy Craffert, Alicia Catherine Desmond, Nkosilathi Dlodlo, Nokuphiwa Doncabe, Linamandla Douglas, Phillip du Preez, Megan Easton, Carla Edeling, Vinodh Aroon Edward, Lindsey Faul, Katherine Gill, Nicole Glover, Thasha Gounden, Vaneshree Govender, Nicole Gracie, Willem Hanekom, Ishana Harkoo, Chiara Ilett, Manjeetha Jaggernath, Nitesha Jeenarain, Lindsay Jeffrey, Alex Jemba, Samuel Kabwigu, Edrine Kalule, Priya Kassim, Lindsay Kew, Reolebogile Kgoa, Johara Khan, Mlungisi Khanyile, Zainab Kharva, Noluthando Khiya, Khensani Khoza, Godfrey Kigozi, Ronald Kisitu, Noah Kiwanuka, Carla Kloppers, Philip Kotze, Limakatso Lebina, Cheryl E Louw, Mmatshepho Maditsi, Philisiwe Makhoba, Heeran Makkan, Morakane Alicia Caroline Makwela, Moelo Malahleha, Mookho Malahleha, Malebo Mampane, Mmatsie Manentsa, Leila Mansoor, Flavia Matovu Kiweewa, Valerie Mlotshwa, Mbalizethu Mntambo, Rorisang Mofokeng, Dhayendre Moodley, Mgcini Moyo, Timothy Muwonge, Vimla Naicker, Kavitha Naidoo, Logashvari Naidoo, Megeshinee Naidoo, Gonasagrie Nair, Joan Nakakande, Gertrude Nakigozi, Fred Nalugoda, Joyce Namale Matovu, Anusha Nana, Esther Nantambi, Terusha Navsaria, Nkosiphile Ndlovu, Theodorah Ndzhukule, Tanya Nielson, Nomfundo Ntuli, Thesla Palanee-Phillips, Ravindre Panchia, Menoka Pillay, Saresha Pillay, Disebo Potloane, Sunai Ramdhani, Caro-Lee Saal, Khanyile Saleni, Ni Ni Sein, Pearl Selepe, Melissa Senne, Nishanta Singh, Yashna Singh, Jennifer Smit, Elizabeth Spooner, Ali Ssetaala, Nicola Thomas, Andrew Tlagadi, Mishka Valjee, Amy M. Ward, Ben Wasswa, Zinhle Ayanda Zwane, Zwelethu Zwane.

PURPOSE 1



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

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To access a copy of this presentation, a link to the published NEJM manuscript, a copy of the Global Community Advisory and Accountability Group poster (Danielle Campbell et al., AIDS 2024, TUPEC210), and other supplemental information, please scan the QR code

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