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

Dr. Nkosiphile Ndlovu, Wits RHI on behalf of the PURPOSE 1 Study Team

Summary

What was our main question?

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

What did we find?

- LEN works well and is safe for PrEP in cisgender women
  - 100% efficacious and 100% superior to F/TDF and F/TDF
- Cisgender women on F/TAF got HIV infections at a rate not different from rate of those not on PrEP
- F/TAF protected cisgender women who took it from HIV infection
- 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 potentially help more cisgender women use and stay on PrEP and hopefully to help reduce HIV in cisgender women globally

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

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ORIGINAL ARTICLE

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

L.-G. Bekker, M. Das, Q. Abdool Karim, K. Ahmed, J. Batting, W. Brumskine, K. Gill, I. Harkoo, M. Jaggernath, G. Kigozi, N. Kiwanuka, P. Kotze, L. Lebina, C.E. Louw, M. Malahleha, M. Manentsa, L.E. Mansoor, D. Moodley, V. Naicker, L. Naidoo, M. Naidoo, G. Nair, N. Ndlovu, T. Palanee-Phillips, R. Panchia, S. Pillay, D. Potloane, P. Selepe, N. Singh, Y. Singh, E. Spooner, A.M. Ward, Z. Zwane, R. Ebrahimi, Y. Zhao, A. Kintu, C. Deaton, C.C. Carter, J.M. Baeten, and F. Matovu Kiweewa, for the PURPOSE 1 Study Team*

SCAN ME

Disclosures

- 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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PI, principal investigators

Cisgender women are disproportionately burdened by HIV

Cisgender women's uptake of, adherence to, and persistence on PrEP remains suboptimal globally[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]

- **F/TAF** is smaller than F/TDF; TAF has more plasma stability and more rapid uptake in PBMCs than TDF[9]
- **F/TAF** has demonstrated PrEP efficacy and safety in cisgender men and transgender women who have sex with men[10]

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 cells; SC, subcutaneous. **1.** Joint United Nations Programme on HIV/AIDS. https://aidsinfo.unaids.org (accessed July 5, 2024). **2.** UNAIDS https://www.unaids.org/en/resources/documents/2022/political-declaration_summary-10-targets (accessed July 5, 2024). **3.** de Dieu Tapsoba J, et al. *AIDS Care* 2021;33(6):712-720. **4.** Mugwanya KK, et al. Abstract 993 presented at: Conference on Retroviruses and Opportunistic Infections; March 4-7, 2019; Seattle, WA. **5.** Velloza J, et al. *AIDS Behav* 2023;27(1):279-289. **6.** Chakare T, et al. Abstract OAD0604 presented at: 23rd International AIDS Conference; July 6-10 2020; Brisbane, Australia. **7.** Link JO, et al. *Nature* 2020;584(7822):614-618. **8.** Segal-Maurer S, et al. *N Engl J Med* 2022;386(19):1793-1803. **9.** Lee WA, et al. *Antiviral Therapy* 2022;27(2):13596535211067600; **10.** Mayer KH, et al. *Lancet* 2020;396:239-254.

Study Design and Efficacy Outcomes

PURPOSE 1

Cross-sectional Incidence Cohort

Cisgender women

Not on PrEP, no HIV testing in past 3 months

- **HIV negative and eligible**
- **HIV positive, recency assay data used to estimate RITA background HIV incidence**

Randomized Blinded Cohort

Week 0 — Week 26 — Week 52+

2	**LEN SC every 26 weeks** + oral F/TAF placebo or F/TDF placebo (2:1)		n = 2134
2	**F/TAF oral daily** + SC LEN placebo every 26 weeks	GSI	n = 2136
1	**F/TDF oral daily** + SC LEN placebo every 26 weeks	GILEAD Active control	n = 1068

Prespecified interim analysis
50% of participants completed ≥52 weeks

Primary analysis:[a]
1. LEN vs background HIV
2. F/TAF vs background HIV

Secondary analysis:[b]
1. LEN vs F/TDF
2. F/TAF vs F/TDF

Background HIV incidence

Background HIV incidence is the incidence expected without PrEP, that would have been expected in a placebo group i.e. the counterfactual HIV incidence rate

ClinicalTrials.gov: NCT04994509

[a]IRR assessed using a Wald test or likelihood ratio test if there were zero infections[1]. [b]IRR assessed using Poisson regression or an exact conditional Poisson regression model in case of zero infections
IRR, incidence rate ratio; RITA, recent-infection testing algorithm

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

Baseline Demographics and Clinical Characteristics

Characteristic	LEN, n = 2138	F/TAF, n = 2137	F/TDF, n = 1070
Age, y, median (range)	21 (16–25)	21 (16–26)	21 (16–25)
Age 16 to <18, years, n (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black,[a] n (%)	2135 (99.9)	2136 (100)	1068 (99.8)
Highest education level college/ university, 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

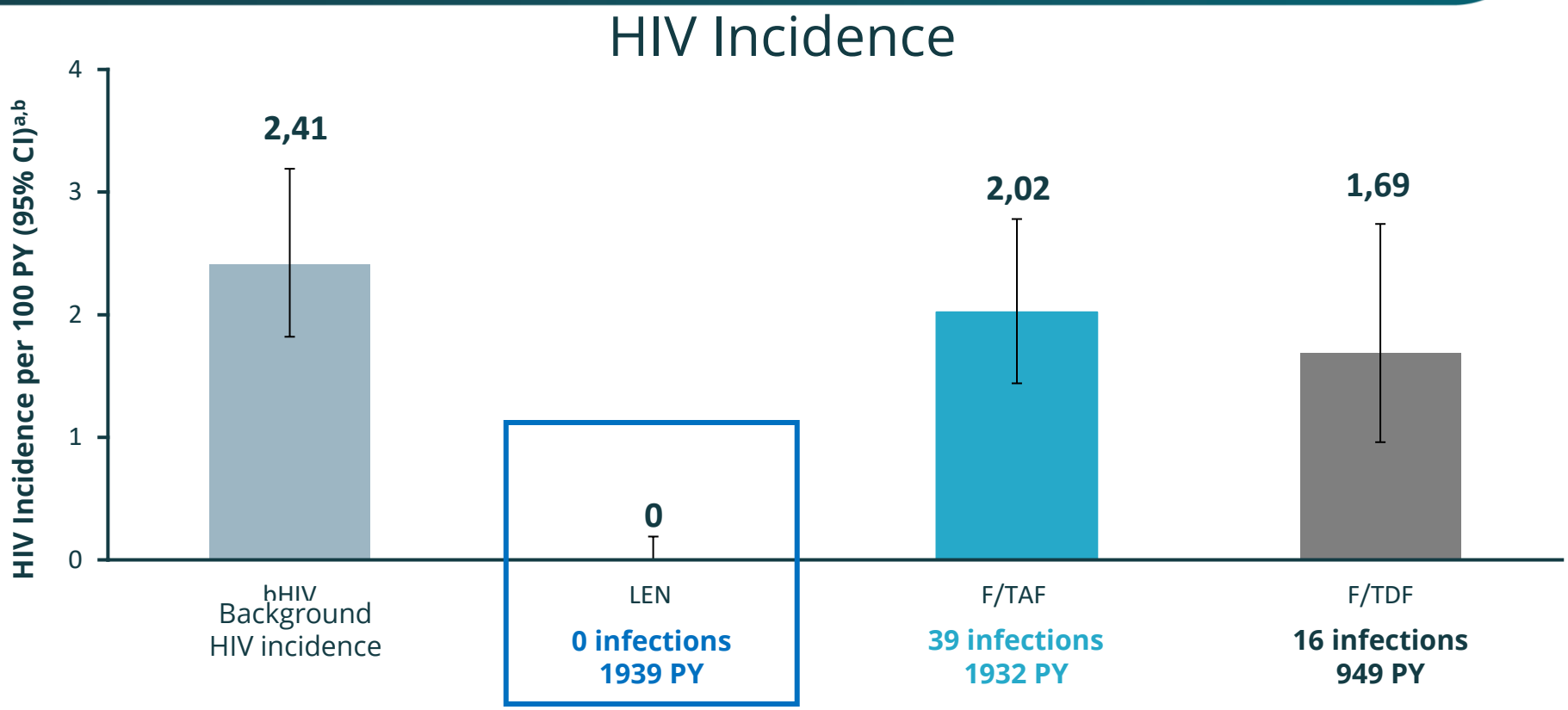
84.3%
South Africa

15.7%
Uganda

Baseline demographics and clinical characteristics were balanced across randomized groups

[a]All non-Black participants were multiracial
Q, quartile; STI, sexually transmitted infection

Zero HIV infections in Cisgender Women on LEN

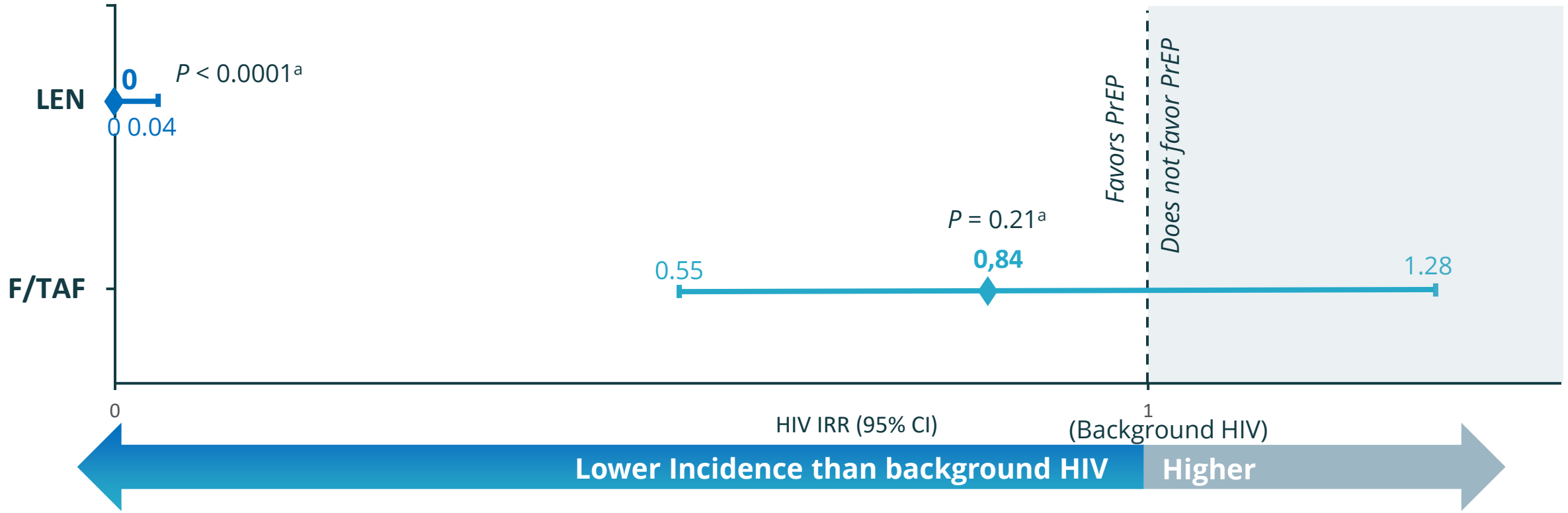


HIV incidence on F/TAF not different from background HIV incidence

[a]Overall n: background HIV incidence group 8094, LEN 2134, F/TAF 2136, F/TDF 1068. [b]95% CIs: background HIV incidence group 1.8, 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

Efficacy Compared With Background HIV Incidence

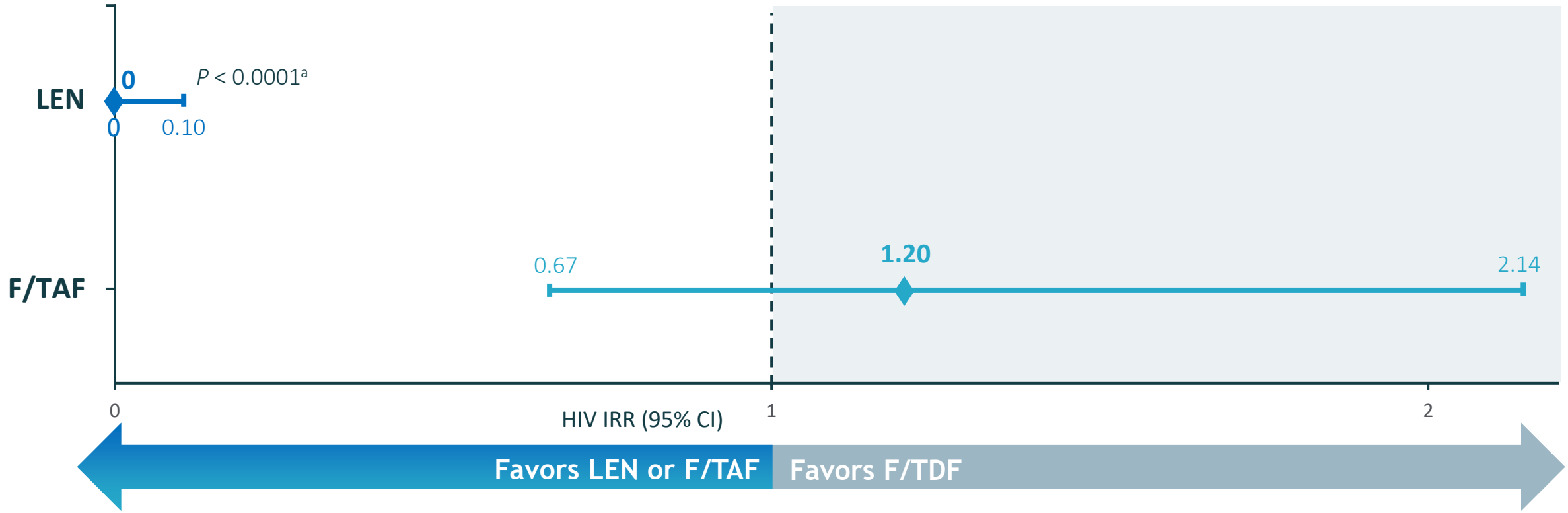


LEN has 100% PrEP efficacy; F/TAF not different from background HIV incidence

[a]HIV IRR vs background HIV assessed using Wald test or a likelihood ratio test if there were zero infections

Secondary Analysis: LEN is 100% Superior to F/TDF

Relative Efficacy Compared with 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 in case of zero infections

Adherence to injections was high while adherence to oral F/TAF and F/TDF was poor

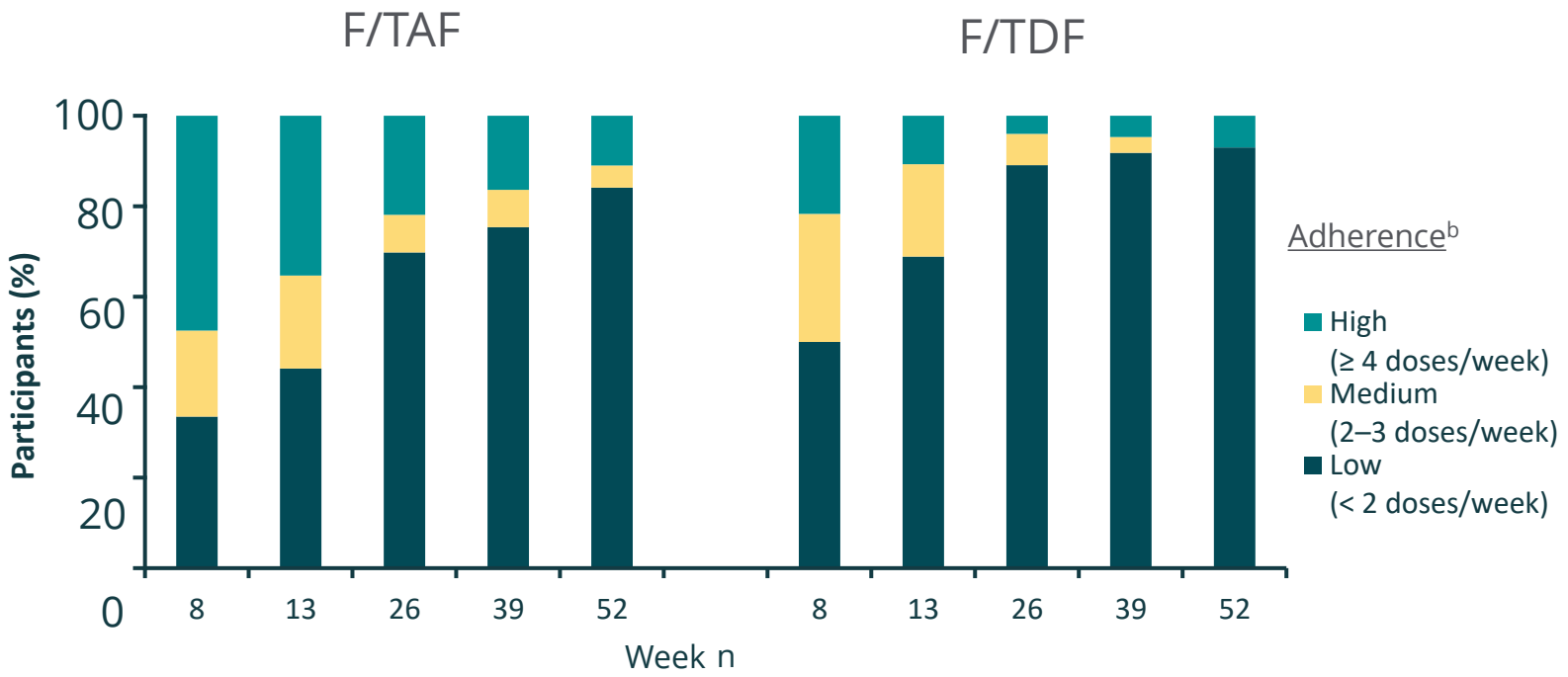
Adherence to Injections

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 to F/TAF and F/TDF by TFV-DP Levels

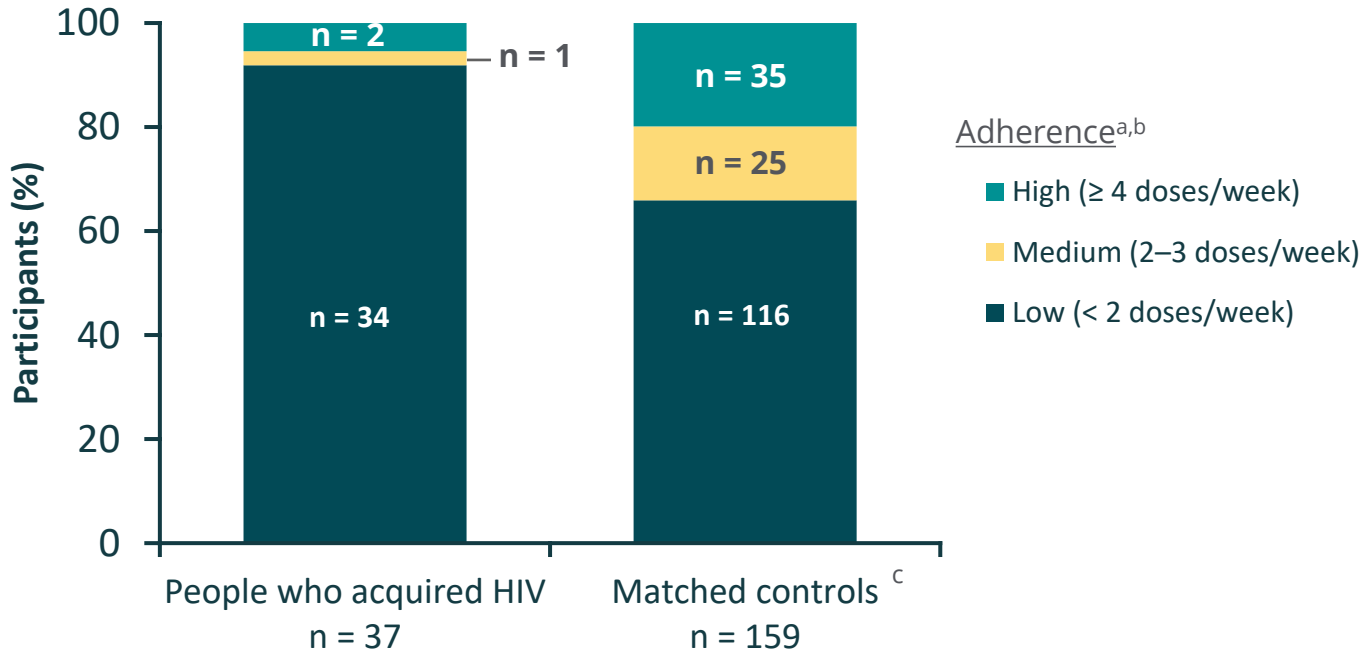


On-time adherence to injections was high
Most participants in both the F/TAF and F/TDF groups had low adherence to oral tablets and adherence declined over time

[a]Adherence to LEN was defined as on-time injection (< 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 F/TDF: low < 350, medium ≥ 350 to < 700, high ≥ 700 fmol/punch). DBS, dried blood spot; TFV-DP, tenofovir diphosphate

High adherence to F/TAF is associated with low chance of HIV infection in a case-control analysis

Case–Control Analysis of Adherence to F/TAF



Within the F/TAF group, those with medium or high adherence had a significantly lower likelihood of HIV infection than those with low adherence (odds ratio 0.11; 95% CI 0.012, 0.49; p = 0.0006)

[a]By TFV-DP DBS levels (adherence cutoffs for F/TAF: low < 450, medium ≥ 450 to < 900, high ≥ 900 fmol/punch and F/TDF: low < 350, medium ≥ 350 to < 700, high ≥ 700 fmol/punch). [b]Missing DBS concentrations imputed for participants with HIV infection based on last concentration prior to HIV diagnosis and decay rate based on the median. [c]Available data shown in stacked bar. Matched control data from the same visit as the HIV diagnosis visit of each case - also matched on investigator site (or city) and presence of rectal STI prior to HIV infection.

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)
Nausea	144 (6.7)	234 (10.9)	142 (13.3)
Vomiting	125 (5.8)	235 (11.0)	107 (10.0)
Laboratory abnormalities, n with baseline result	2126	2113	1053
Any Grade ≥ 1, n (%)	1929 (90.7)	1902 (90.0)	959 (91.1)

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 trials1–4

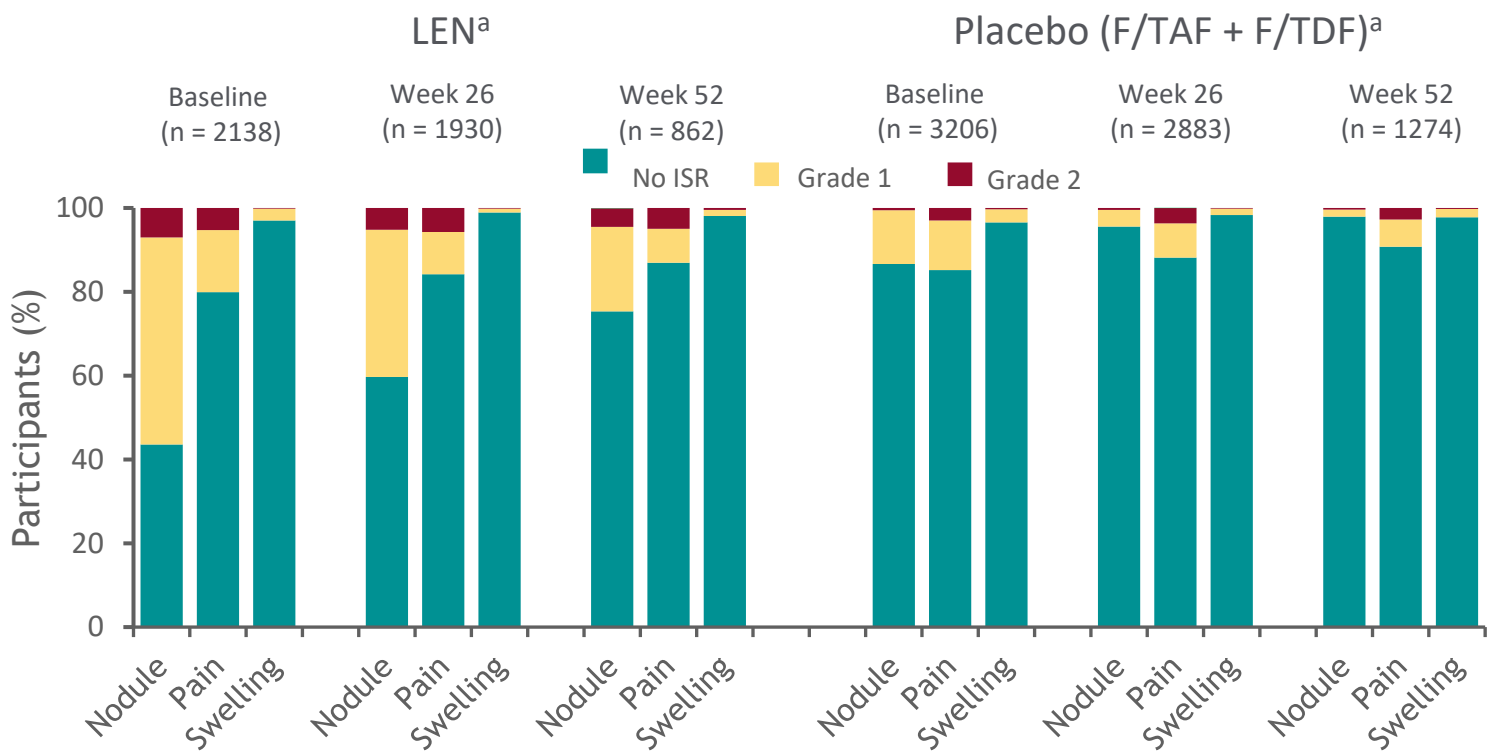
[a]AEs are treatment-emergent in persons who received at least one dose of study drug; AEs exclude injection site reactions; AEs coded according to Medical Dictionary for Regulatory Activities 27.0 and graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs, Version 2. [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.

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;396:239–254. **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 in HIV treatment[1])**

Participants Experiencing ISRs



Among 25,329 injections, only 4 ISRs led to discontinuation

[a]Grade 1 and 2 ISRs are shown. ISR, injection site reaction

1. Kumar P, et al. Poster eP.A.104 presented at EACS: The 19th European AIDS Conference, October 18–21 2023, Warsaw, Poland

Pregnancies were common and outcomes similar to expected rates in the population

Participants and pregnancies[a] 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[a]	105 (54.4)	119 (54.3)	53 (54.1)
Ongoing pregnancies	88 (45.6)	100 (45.7)	45 (45.9)
Live births	54 (28.0)	45 (20.5)	20 (20.4)
Interrupted pregnancies	50 (25.9)	73 (33.3)	32 (32.7)
Induced abortion	30 (15.5)	39 (17.8)	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 population3,4

[a]Includes eight still births: three in the LEN group, four in the F/TAF group, one in the F/TDF group; there were three completed pregnancies (one in each group) with unknown status regarding interruption. [b]Spontaneous miscarriage defined as occurring at < 20 weeks' gestation. **1.** *Obstet Gynecol*. 2018;132(5):e197-e207. **2.** Wilcox et al. *N Engl J Med* 1988; 319:189-194. **3.** Mugo NR et al. *JAMA* 2014;312(4):362-71. **4.** Castagna A et al. Abstract eP.A.104 presented at: 19th European AIDS Conference (EACS); October 18–21, 2023; Warsaw, Poland.

Conclusions and Next Steps

PURPOSE 1

- **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
- 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 NCT identifier: NCT04994509
PURPOSE 2 NCT identifier: NCT04925752
Purpose Studies. Available at: https://www.purposestudies.com/(Accessed July 5 2024)

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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 Herrero, Marjeena 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. Gilead Sciences PURPOSE Team Members: Jared M. Baeten, Andrea Brown, Felicity Blackburn, Christoph Carter, Moupali Das, Chris Deaton, Ramin Ebrahimi, Alexander Kintu, Jenna Scott, Pamela Wong, and Yang Zhao.

Without this village, we would not have been the first to use this novel design, evaluate the first twice-yearly investigational PrEP drug, and intentionally include pregnant and lactating people and adolescents in a Phase 3 Pivotal PrEP Trial