Key messages from recent international HIV conferences

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Latest cures using stem-cell transplants

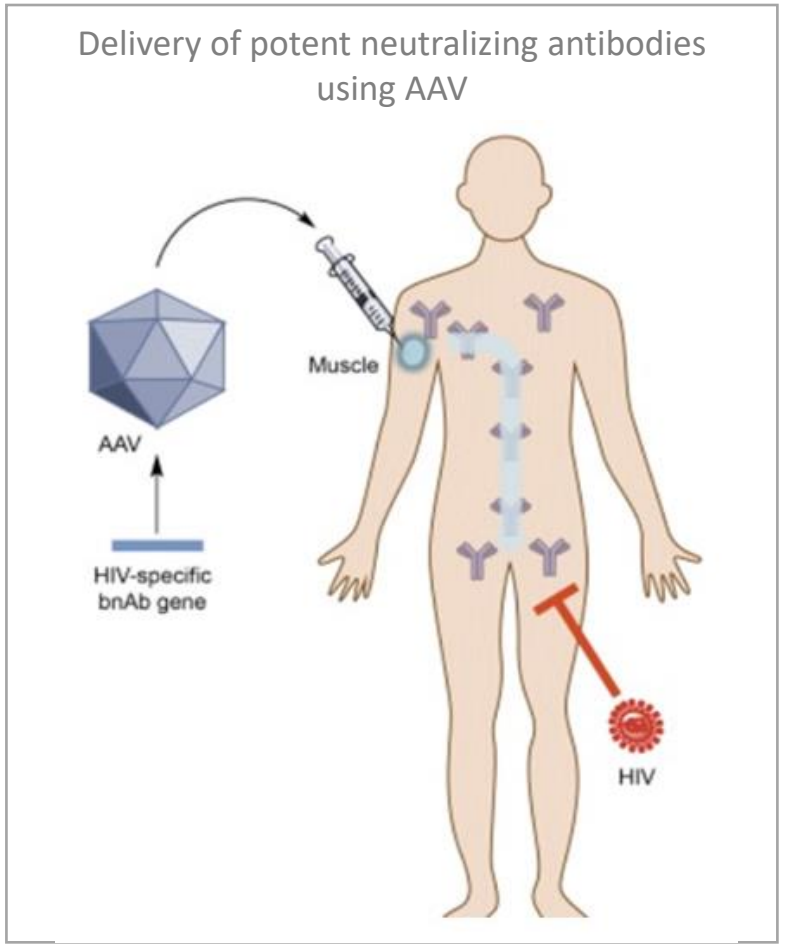
- The case of the "next Berlin patient", the seventh person cured of HIV using a stem-cell transplant, was presented at AIDS 2024.
- The donor had one copy of CCR5-negative gene out of two (heterozygous)
  - 5 of the previously cured cases received stem cells that were CCR5-negative homozygous (CCR5Δ32/Δ32).
- He has been aviremic off ART for nearly six years
- This is promising for future HIV cure strategies based on gene therapy, because it suggests that possibly not every single piece of CCR5 should be eliminated to achieve remission.

Marc Franke, Paul Edmonds, Adam Castillejo.© Gonzalo Bell / IAS

Approaches to Cure HIV

Using

- Broadly neutralizing antibodies (bNAbs)
- Genetic engineering
  - excising latent proviral HIV genome using AAV9 multiplex CRISPR-SaCas9 technology was safe and did not result in off-target DNA damage (n=6).
  - follow up will be critical in assessing the safety of gene editing
- Transcription inhibition



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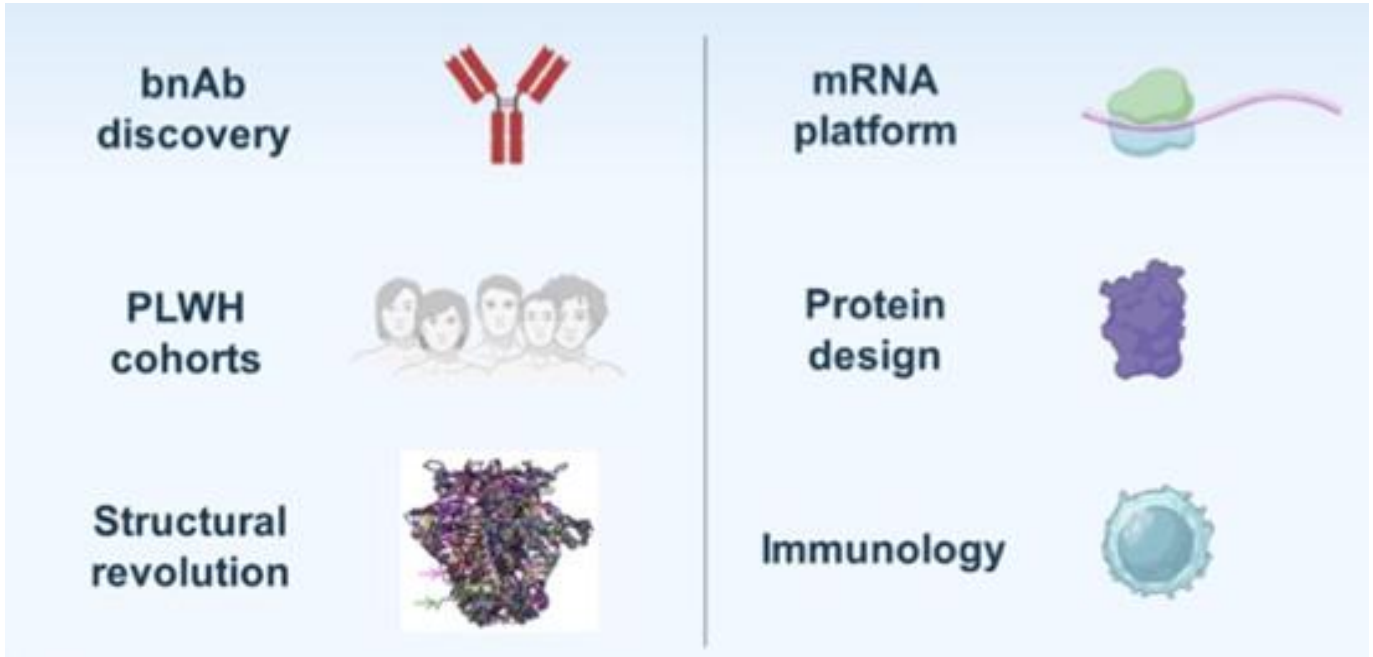
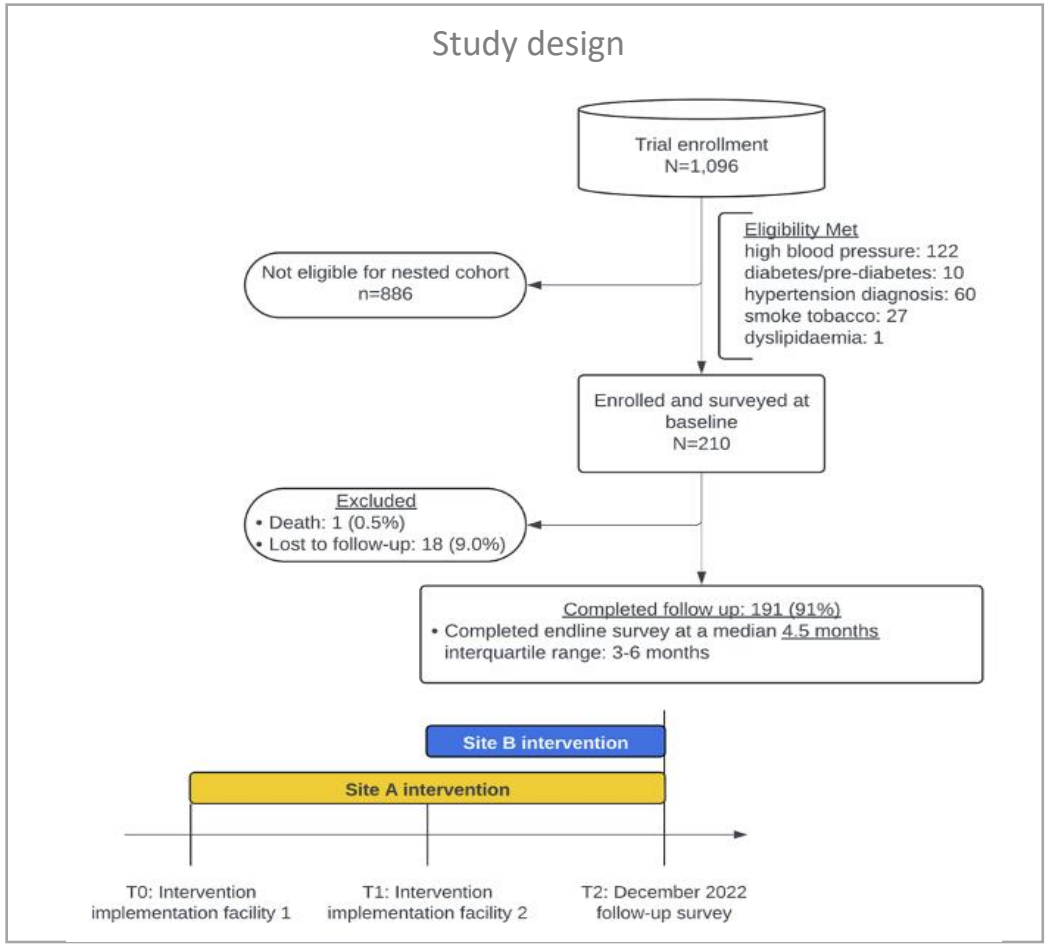
- While we may seem no nearer to an HIV vaccine than we were 10 years ago, we now have the knowledge, experience and tools to accelerate vaccine research and pursue multiple strategies in a way we never could before.



Innovation as the engine for acceleration to a vaccine

- In Zambia, a package was introduced and a study evaluated whether the package improved blood pressure control without compromising HIV viral suppression.
- The package of integrated HIV/NCD services included:
  - "One stop shop" for NCD/HIV services
  - WHO-PEN protocols, algorithm and training materials adapted for Zambia
  - NCD clinical information added to HIV electronic medical records
  - Access to screening and laboratory monitoring for diabetes and hyperlipidemia
  - Strengthened NCD medication supply chain, with multi-month dispensing
- Clinic workflows were re-organized, using task-shifting (to nurses and community health workers) and task-sharing (team-based care and referrals).

- The study evaluated whether the package improved blood pressure control without compromising HIV viral suppression.
- "Dual control" of both blood pressure and HIV was assessed in participants with cardiometabolic NCDs or risk factors.
  - 191 of 1,096 participants were eligible (had hypertension, pre-diabetes, diabetes or dislipidemia, or smoked).
- The cohort was 70% female, median age 49, with a median 12 years since their HIV diagnosis.



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- There was improvement in blood pressure control, defined as systolic blood pressure <140mmHg and diastolic blood pressure <90mmHg.
- There was also a 74% increase in the rate of dual (blood pressure and HIV) control.

Control of blood pressure and HIV

Outcome	Adjusted* risk ratio (95% CI)
Dual control	**1.74 (1.43, 2.12)**

*adjusted for age and sex

Outcome	Baseline Proportion (95% CI)	Follow-up Proportion (95% CI)
Blood pressure (BP) control	**36.1%** (29.3, 43.4%)	**57.3%** (49.7, 64.7%)
HIV control (<1,000 copied/ml)	**84.8%** (78.9, 89.6%)	**95.3%** (91.2, 97.8%)
Dual control	**30.9%** **(24.4, 38.0%)**	**53.6%** **(46.0, 61.6%)**

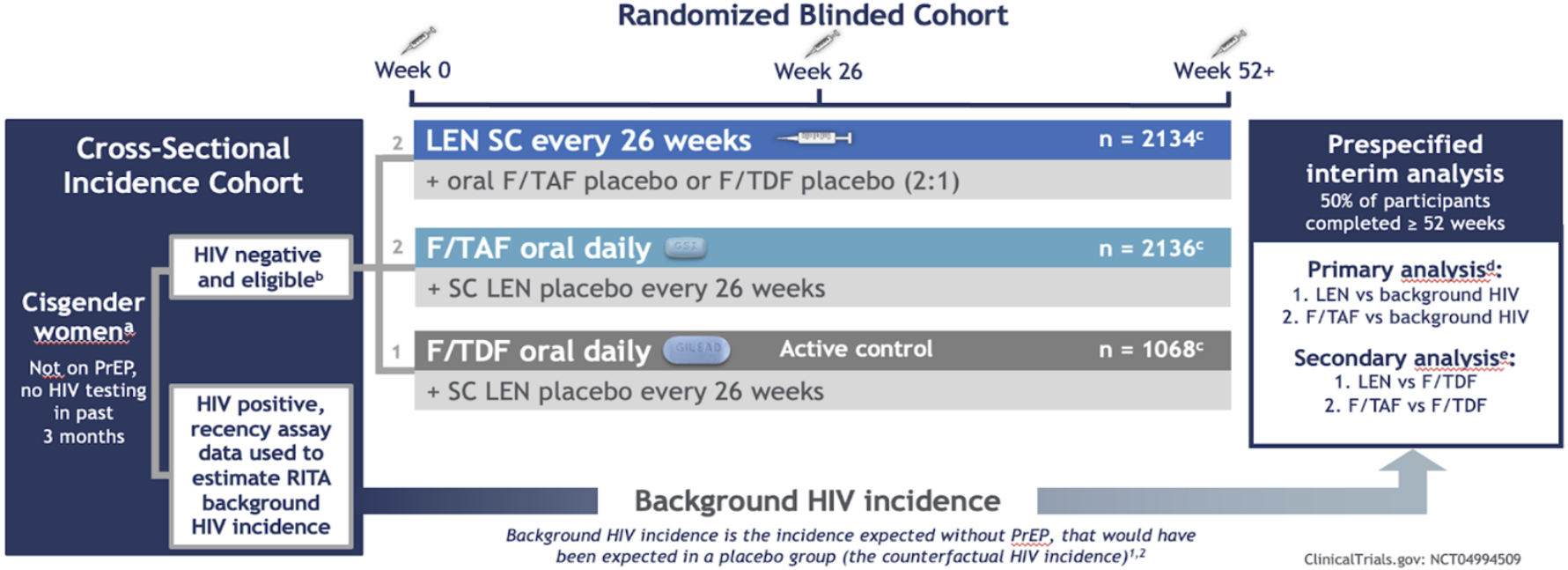
Long-acting lenacapavir PrEP

- A double-blinded randomized control trial evaluated three PrEP options, including long-acting lenacapavir (PURPOSE 1).
- Lenacapavir is a novel capsid inhibitor with a long half-life, administered by subcutaneous injection every six months.
- The study recruited 5,338 young women aged 16-25 in South Africa and Uganda.

Linda-Gail Bekker. © Gonzalo Bell / IAS

Bekker SS0407

Study design

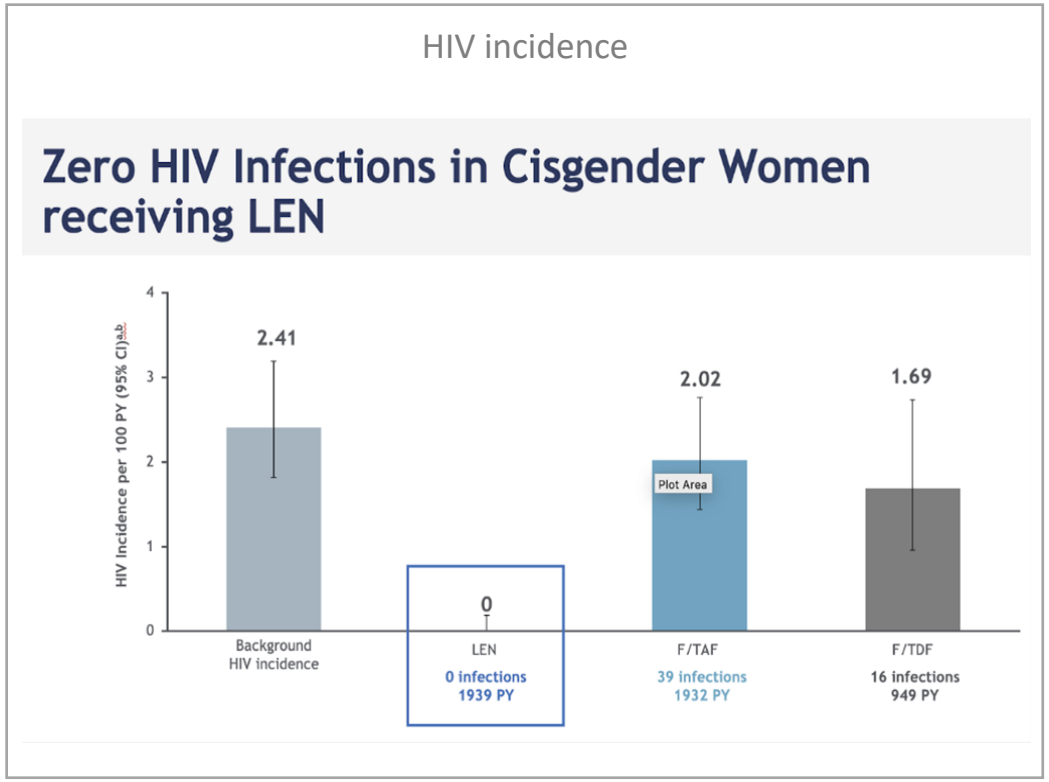


- Participants were randomized 2:2:1 to receive either:
  - Lenacapavir injections every six months (LEN SC)
  - Daily oral emtricitabine and tenofovir alafenamide (F/TAF)
  - Daily oral emtricitabine and tenofovir disoproxil fumarate (F/TDF)

Bekker SS0407

- There were 5,338 participants in the study: median age was 21, 99.9% were Black, 92% single.
- The group was vulnerable to HIV acquisition:
  - Over a third tested positive for a sexually transmitted infections at study entry.
  - Background HIV incidence was 2.41 per 100 person-years.

- 55 study participants acquired HIV – but none were in the lenacapavir arm.
- Lenacapavir reduced HIV incidence by:
  - 100% as compared with background HIV incidence
  - 100% as compared with F/TDF
- However, HIV incidence with F/TAF was not significantly different from background HIV incidence or from incidence with F/TDF.



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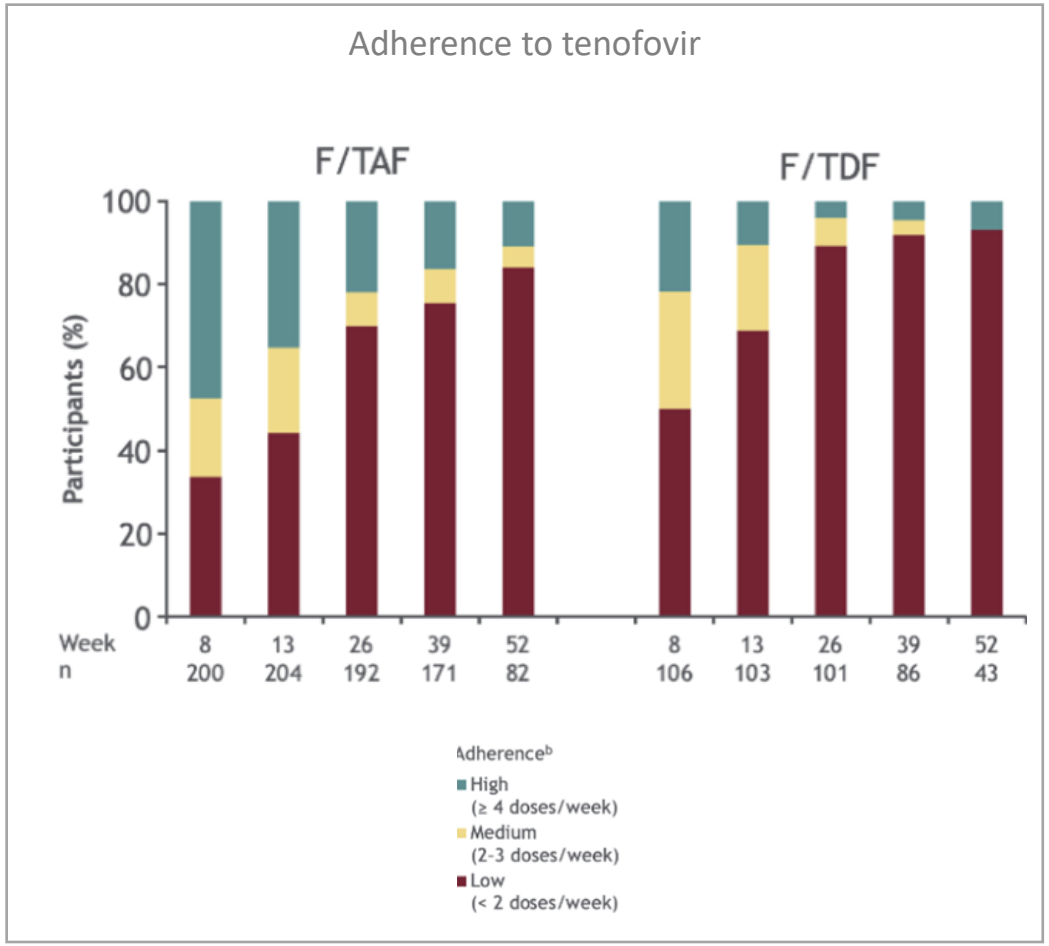
- 92% of lenacapavir injections were on time.
- In contrast, adherence to oral PrEP was low and decreased over time.
- Poor adherence explains the poor results for the two oral PrEP arms.
- Participants with medium or high adherence to oral PrEP were less likely to acquire HIV than those with low adherence.



Bekker SS0407

- The products used were safe and well tolerated: less than 5% of participants in each group experienced severe (grade 3) adverse events.
- Injection site reactions (ISRs) were experienced by 69% of lenacapavir recipients:
  - Frequency decreased with subsequent doses.
  - Among 25,329 injections, only four ISRs led to discontinuation.
  - Nodules (harmless, usually invisible, small lumps under the skin) were the most common ISR.
- Participants were not required to use contraception.
  - There were 510 pregnancies (including 193 in the lenacapavir group).
  - Available pregnancy outcomes were similar to those expected in the population.

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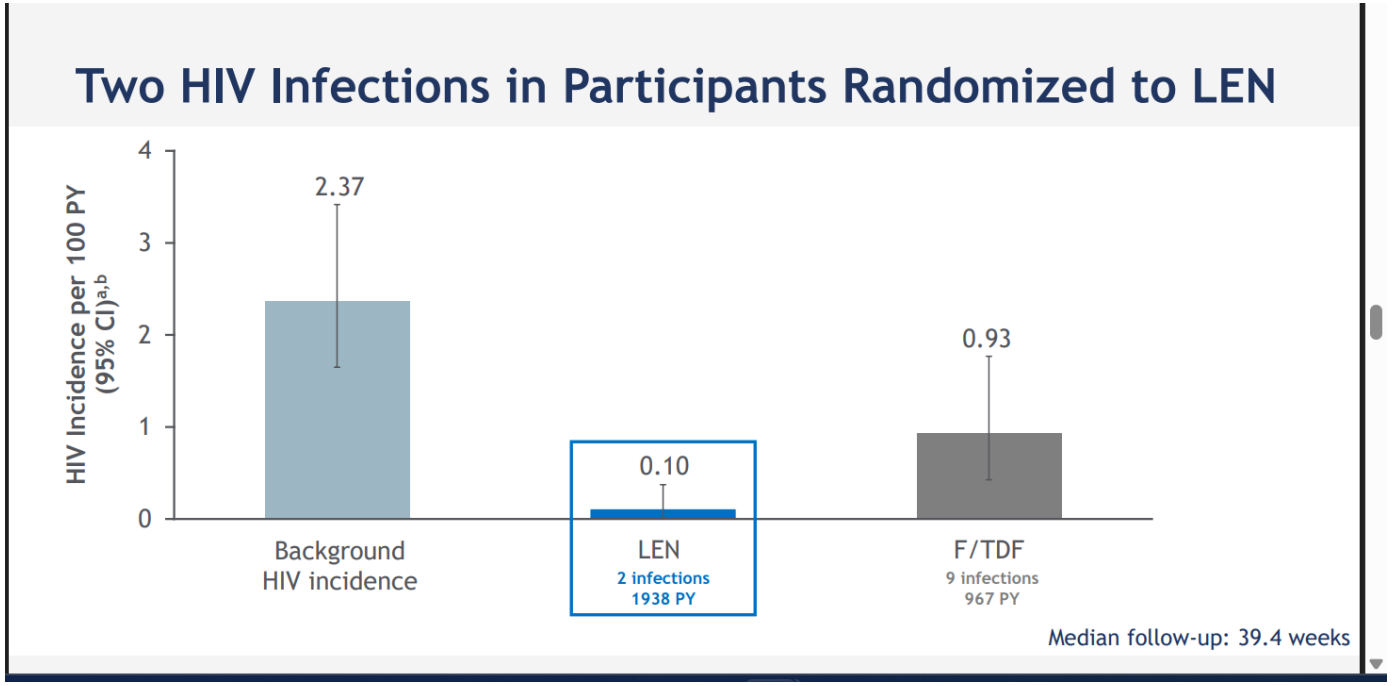
Purpose 2



- Trial was conducted among men who have sex with men and trans women in Argentina, Brazil, Mexico, Peru, South Africa, Thailand and the United States.
- Only two HIV acquisitions occurred among 2,179 trial participants who were randomized to receive subcutaneous lenacapavir every six months.

Kelley OA02

IAS PURPOSE 1 & 2 trials: Lenacapavir conclusions

In women without prior HIV infection, PrEP with twice-yearly SC LEN resulted in no infections

- HIV incidence with LEN was significantly lower than background and FTC/TDF incidence
- Adherence to PrEP with oral FTC/TAF and FTC/TDF was poor
- Medium or high FTC/TAF adherence associated with lower odds of HIV infection
- SC LEN and oral FTC/TAF were well tolerated and safe

In MSM and non-binary men, PrEP with twice-yearly SC LEN resulted in 2 infections

- HIV incidence with LEN was significantly lower than background and FTC/TDF incidence

- **FDA is reviewing lenacapavir data June 2025**

Promising results on longer acting IM lenacapavir

- IM LEN demonstrated plasma concentrations above the threshold associated with protective efficacy for twice-yearly subcutaneous LEN over >12 months.

- Injection-site reactions were mostly mild to moderate, with pain resolving within a week, and pretreatment with an ice pack significantly reduced discomfort.

- These findings suggest that once-yearly IM LEN could enhance PrEP adherence by offering a long-acting, low-maintenance alternative

Jogiraju et al Abstract #154

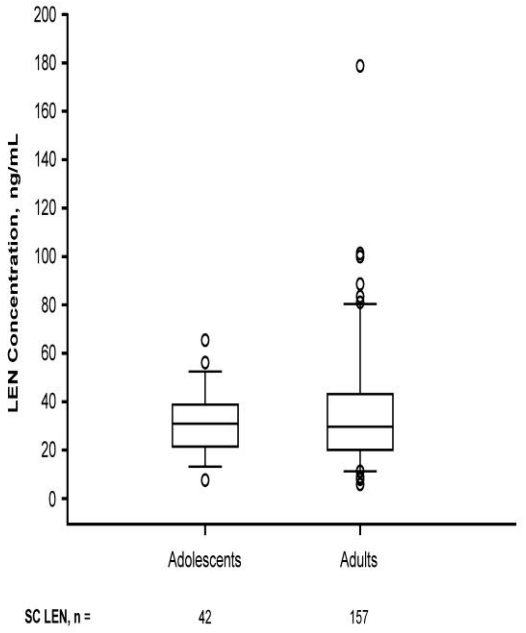
Additional sub-studies from PURPOSE 1

Safety of LEN among adolescents:

- Assessed pharmacokinetics, safety, and efficacy of twice-yearly LEN in adolescent girls (16–17 years) compared to young women (18–25 years)

- Results showed comparable LEN plasma concentrations, adverse events, and laboratory findings between adolescents and adults, with no HIV infections observed among LEN recipients.

Figure. Boxplots[a] of LEN Plasma Concentrations After Week 26 (C_{trough}) in the Randomized Blinded Phase of the PURPOSE 1 Study (Adolescents vs Adults[b])



[a]Data from the preliminary analysis are presented.
[b]Excludes participants who became pregnant and those who received oral LEN bridging.
Values below the limit of quantitation were treated as zero. Black box = Q1 and Q3; horizonal line inside box = median; whiskers = 5th and 95th percentiles.
C_{trough}, trough concentration; LEN, lenacapavir; Q, quartile; SC, subcutaneous.

Gill et al Abstract #120

Additional sub-studies from PURPOSE 1

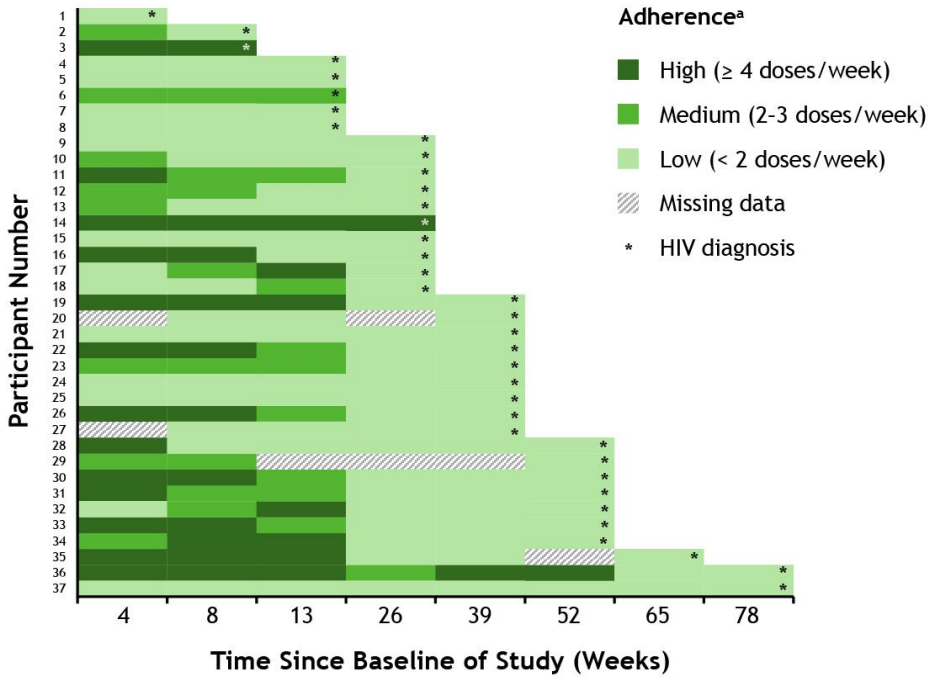
Adherence to F/TAF

- PURPOSE 1 highlighted that nearly all HIV infections in participants receiving daily oral FTC/TAF were linked to low adherence, with rare instances of transmitted drug resistance and minimal delays in HIV diagnosis.

- Among 37 participants who acquired HIV, 35 exhibited suboptimal adherence or nonadherence, reinforcing the importance of adherence for oral PrEP effectiveness.

- However, a lower chance of HIV infection was associated with medium or high adherence.

Figure. Longitudinal Adherence of PURPOSE 1 Participants Diagnosed With Incident HIV in the F/TAF Group



Each row represents a single participant. Each box represents DBS-based adherence for the corresponding time period. DBS data were unavailable for two participants receiving F/TAF.
[a]By TFV-DP DBS levels (adherence cutoffs: low < 450, medium ≥ 450 to < 950, high ≥ 950 fmol/punch).
DBS, dried blood spot; F/TAF, emtricitabine plus tenofovir alafenamide; TFV-DP, tenofovir diphosphate.

CROI Conference on Retroviruses and Opportunistic Infections

Kiweewa et al. Abstract 194

A novel monthly pill for HIV-1 PrEP - MK-8527

- MK-8527 is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) that is phosphorylated intracellularly to its active form, MK-8527-TP
- Preclinical studies in a rhesus macaque model and Phase 1b trials determined that a once-monthly oral dose of at least 6mg of MK-8527 is expected to maintain MK-8527-TP levels above the threshold for protection in over 90% of the population
- Phase 2 trials will evaluate 3, 6, and 12 mg doses among adults with a low chance of HIV exposure

Kapoor et al. Abstract # 1232

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On-demand oral PrEP for cisgender women

- Simulations predicted that the standard 2-1-1 IPERGAY regimen provides >80% protection for 5 days post-sex, while extending dosing to 4 days was predicted to achieve > 80% protection for 7 days.
- With this model, investigators predicted that 2-2-2-2 dosing would provide 95% protection for 7 days, and 2-1-1-1 would provide 84% at 7 days.
- Investigators suggested that the 2-1-1-1 regimen would balance safety, efficacy, and tolerability while maintaining a level of effectiveness similar to what was reported with four weekly doses of oral PrEP in clinical trials.
- Altogether, these findings support further evaluation of extended on-demand PrEP dosing strategies in cisgender women to enhance HIV prevention options, especially for those who find it challenging or stigmatizing to take a daily pill

CROI Conference on Retroviruses and Opportunistic Infections

Stansfield et al. Abstract 1290

Preferences for injectable PrEP vs daily pills

- A quantitative survey (N=5218) found that about two-thirds of respondents preferred twice-yearly injections over daily pills, with 61% feeling more protected and more confident about their adherence with injections.
- A qualitative sub-study of 108 adolescent girls and young women echoed these findings, emphasizing the convenience, ease of adherence, and reduced stigma associated with injectable PrEP.
- Altogether, these findings show that the majority preferred injectable PrEP, but with a notable proportion of participants still favoring oral PrEP.
- This data reinforces the need for expansion of injectable PrEP and for diverse options, including oral PrEP, to improve uptake and persistence.

Montogomery et al. Abstract #1234

Thank You