State of HIV prevention clinical research: Updates on PrEP

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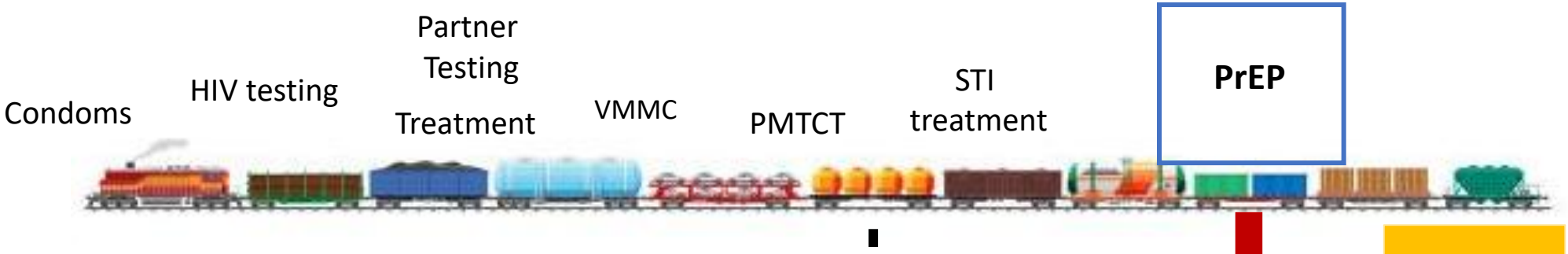
11 June 2025

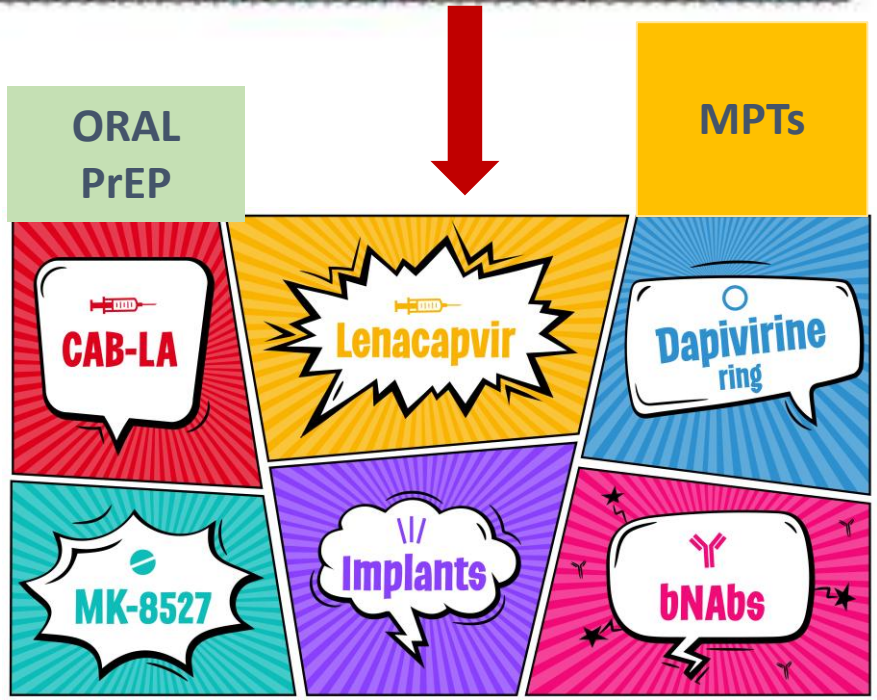
Key points

- Significant strides have been made in HIV prevention
  - The early years of the epidemic were scary, with many unknowns on HIV.
  - In the 90s – only methods for HIV prevention were condoms and abstinence
- Pre-exposure prophylaxis (PrEP) began in 2012 with the approval of oral TDF/FTC taken once a day.
- Since then, PrEP options have expanded rapidly to suit different people.
  - Current PrEP options
  - PrEP research pipeline
- In the era of highly efficacious PrEP how have clinical trials changed over time (from placebo-controlled trials, to active-control, to external controls)?

HIV prevention interventions

THE HIV PREVENTION TRAIN





Strategies:

- Behavior Change (delay sexual debut, mutual monogamy, etc.)
- Condom use
- VMMC
- PrEP
- PEP
- MPTs
- **Preventive vaccine***

Slide adapted from Linda-Gail Bekker

The dapivirine vaginal ring

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Features

- A flexible silicone vaginal ring
- Slowly releases the ARV dapivirine over one month
- Shelf-life: Up to 60 months when stored at or below 30ºC
- No cold chain needed for storage

Benefits

- Woman-initiated
- Self-inserted monthly
- Discreet
- Does not interfere with sex and menses

Two phase III trials showed a monthly dapivirine vaginal ring was well tolerated and reduced HIV incidence by ~30% compared to placebo

Higher effectiveness seen in OLE and based on drug levels

MTN microbicide trials network

27% reduction

Moderate efficacy & shown to be safe

International Partnership for Microbicides

Population Council
Ideas. Evidence. Impact.

31% reduction

CROI 2024

Additional Research

- Additional studies in AGYW (REACH), pregnant (DELIVER) and breastfeeding (B-PROTECTED) women

Vaginal ring to reduce the risk of HIV infection for women in non-EU countries with high disease burden

News 24/07/2020

EMA's human medicines committee (CHMP) has adopted a positive opinion for Dapivirine Vaginal Ring (dapivirine) used to reduce the risk of infection with the human immunodeficiency virus type 1 (HIV-1), in combination with safer sex practices when oral pre-exposure prophylaxis (PrEP) is not used, cannot be used or is not available. Placed in the vagina, the ring slowly releases the antiretroviral medicine dapivirine over a period of 28 days.

This is the eleventh medicine recommended by EMA under EU Medicines for all (EU-M4All), a mechanism that allows the CHMP to assess and give opinions on medicines that are intended for use in countries outside the European Union under Article 58 of Regulation (EC) No 726/2004.

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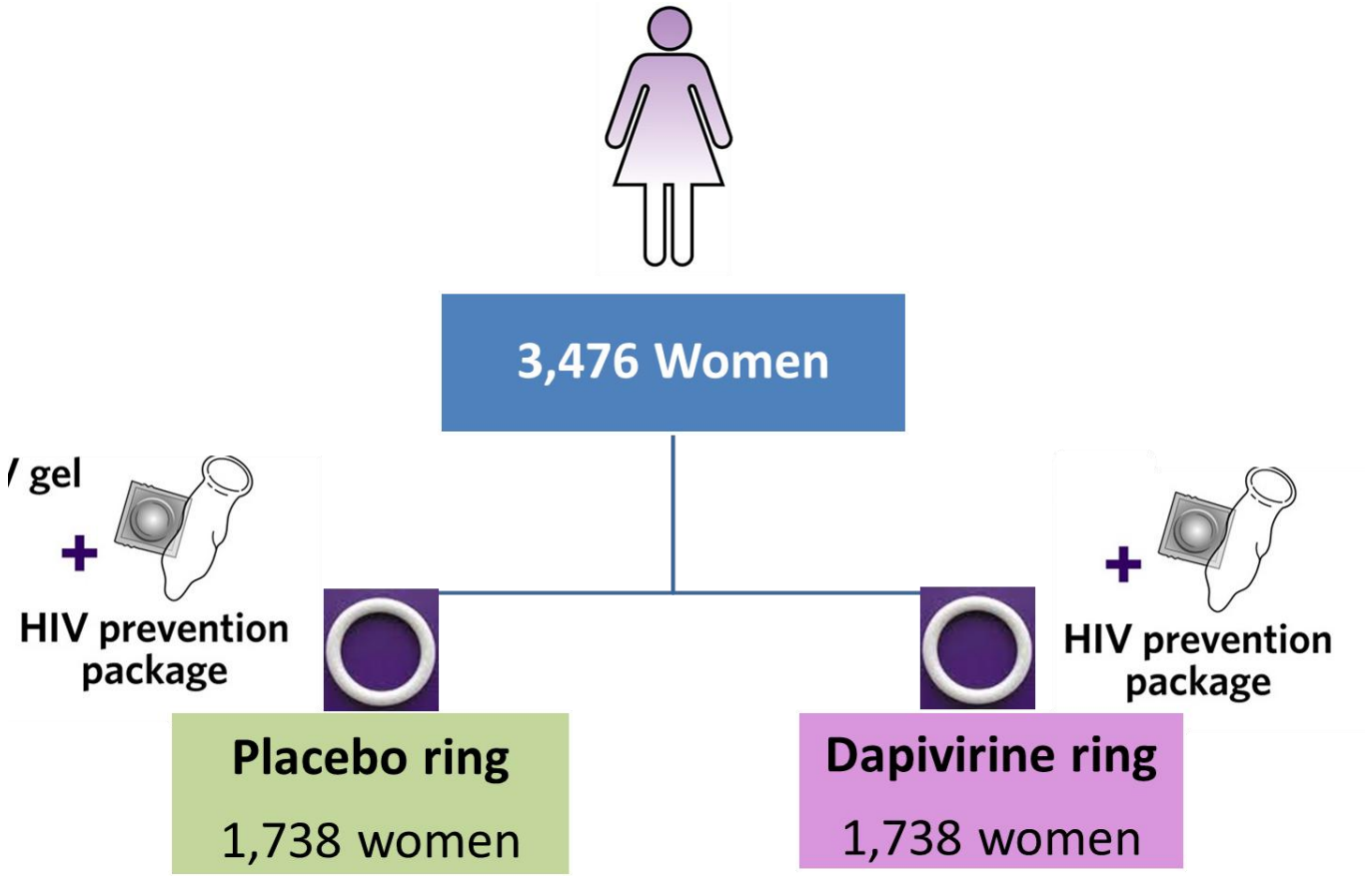
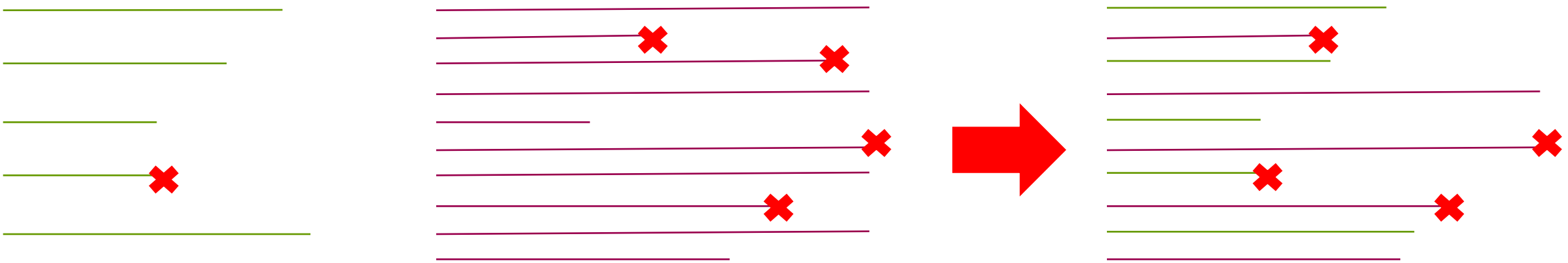
ASPIRE study design



HIV-1 incidence comparison in HOPE OLE

- HIV-1 incidence is compared by randomly sampling individual data from MTN-020/ASPIRE.
  - Sampling a similar distribution of risk (defined by age, site, and STI)



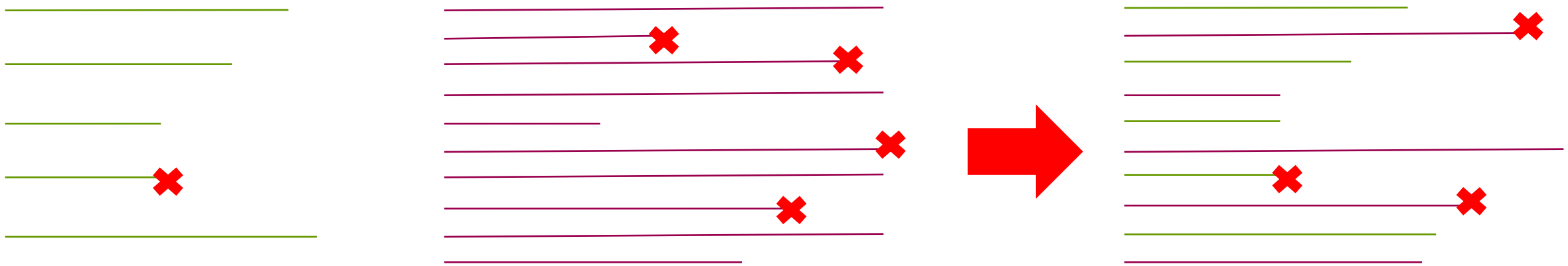
MTN-025/HOPE open-label

MTN-020/ASPIRE placebo arm

Comparison

HIV-1 incidence comparison

- This sampling was then repeated 10,000 times (bootstrapping), and a range of HIV-1 incidences in the sampled MTN-020/ASPIRE population was generated.



MTN-025/HOPE open-label

MTN-020/ASPIRE placebo arm

Comparison

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Long acting injectables

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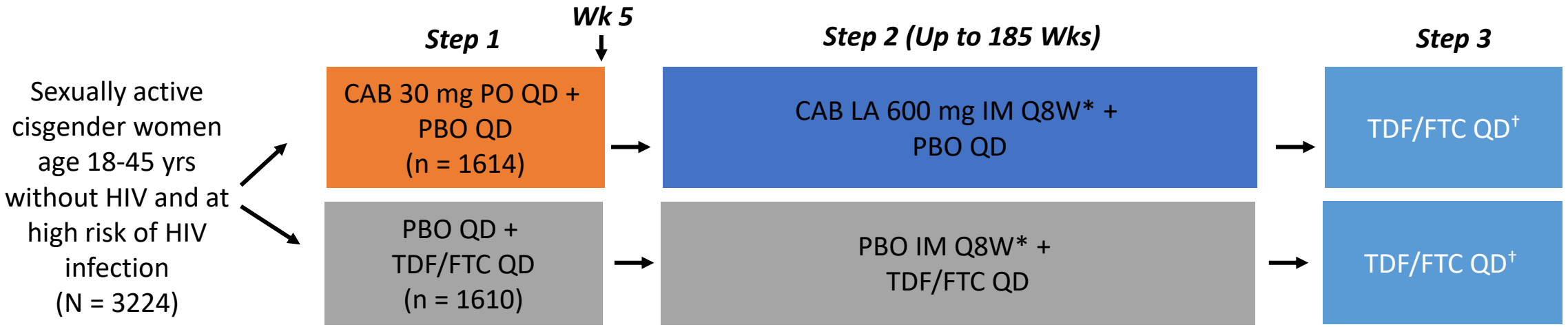
HPTN 084: Study design

- Multicenter, randomized, double-blind phase IIb/III trial in participants without HIV



*First 2 doses given 4 wks apart then every 8 wks thereafter.
†Open-label TDF/FTC initiated maximum 8 wks after last injection for up to 48 wks.

- Primary endpoints: incident HIV infections in Steps 1 and 2, grade ≥ 2 AEs
- Secondary endpoints: incident HIV infection during follow-up, safety

Delany-Moretlwe. HIVR4P 2021. Abstr HY01-02. NCT02720094.

Slide credit: clinicaloptions.com

CAB-LA Ultra-Long Acting (ULA)

- Two strategies for less frequent dosing:
  - Increase volume and/or concentration of current CAB-LA (200mg/mL)
  - Develop ultra-long acting formulation with longer terminal half-life
- Tested increased volume of CAB200 (equivalent to 800mg, 1600mg, 3200mg) SC with human recombinant hyaluronidase
  - All had injection site reactions (ISR), severity increased with increasing dose
  - Not pursuing this strategy
- Tested CAB-ULA (800mg, 1200mg, 1600mg in 2-3mL) IM and SC
  - Half-life more than 2x greater (IM) and 6x greater (SC) than CAB200
  - ISR similar for IM CAB-ULA and CAB200 (69%)
  - ISR greater for SC CAB-ULA (100%)

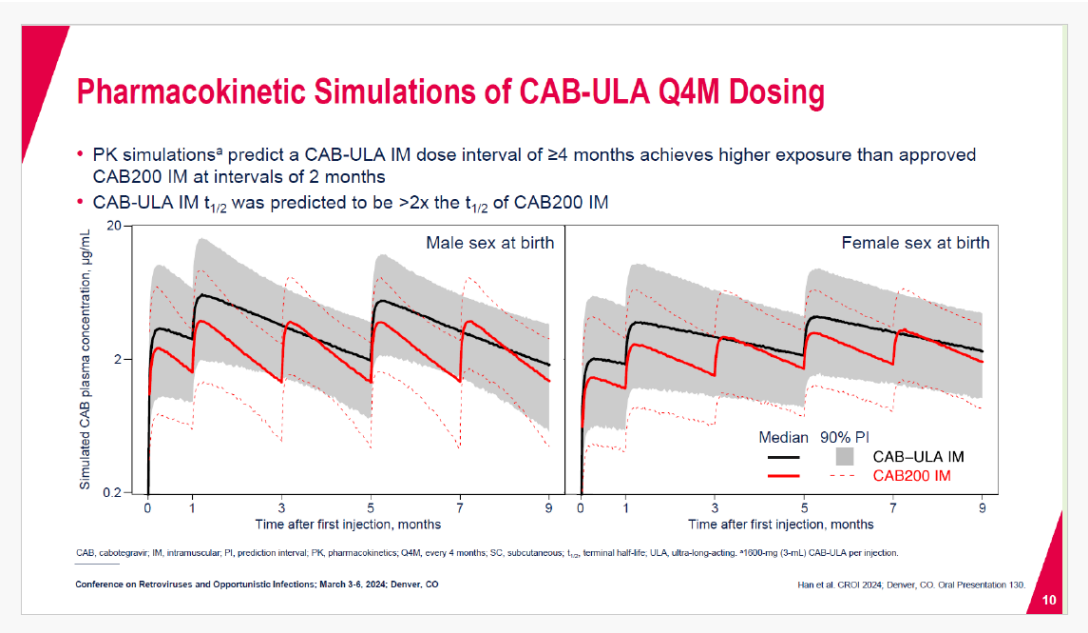
Han, Abstract #130, CROI 2024

Slide courtesy of Susan Buchbinder

HPTN Annual Meeting

ULA CAB LA PK and next steps

- CAB-ULA (q 4 months) next steps
- Conducting a Phase 1 single arm, repeat dose study
- Participants get 9 months of CAB-LA, then switched to CAB-ULA (every 4 months) to 23 months
- Study the pharmacokinetics, safety, and tolerability of switching to CAB-ULA from CAB-LA in healthy adults



Slide courtesy of Susan Buchbinder

Lenacapavir

- Lenacapavir acts as a capsid inhibitor, with disruption of multiple stages in HIV's life cycle
- Has the potential to work against HIV strains that have developed resistance to multiple other classes
- Subcutaneous injectable formulation displays a long half-life

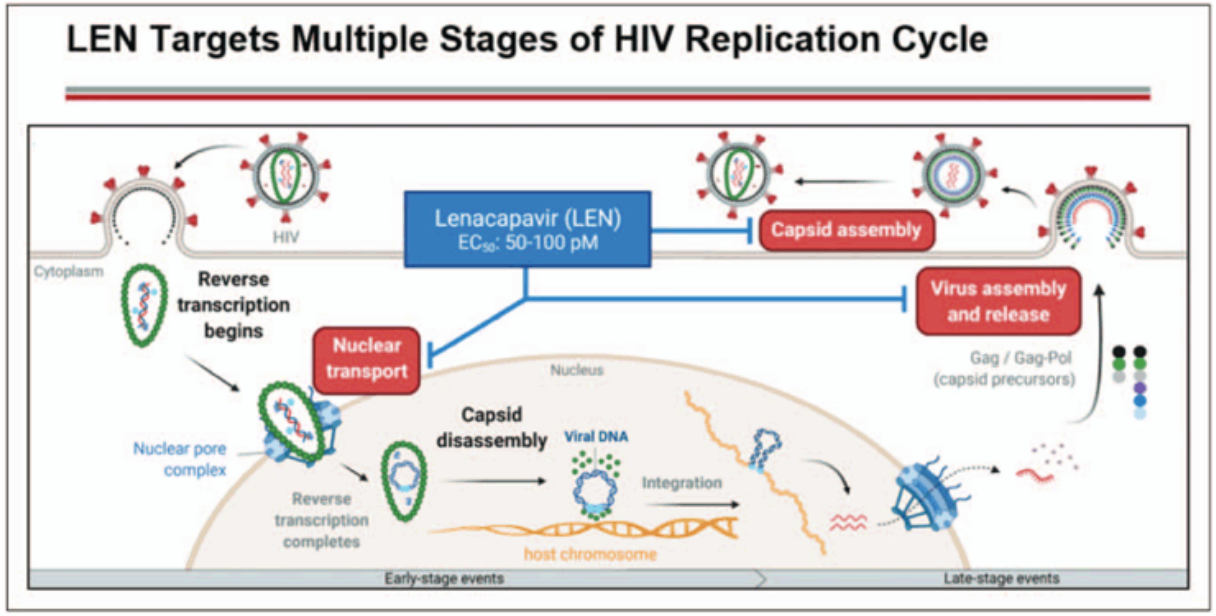
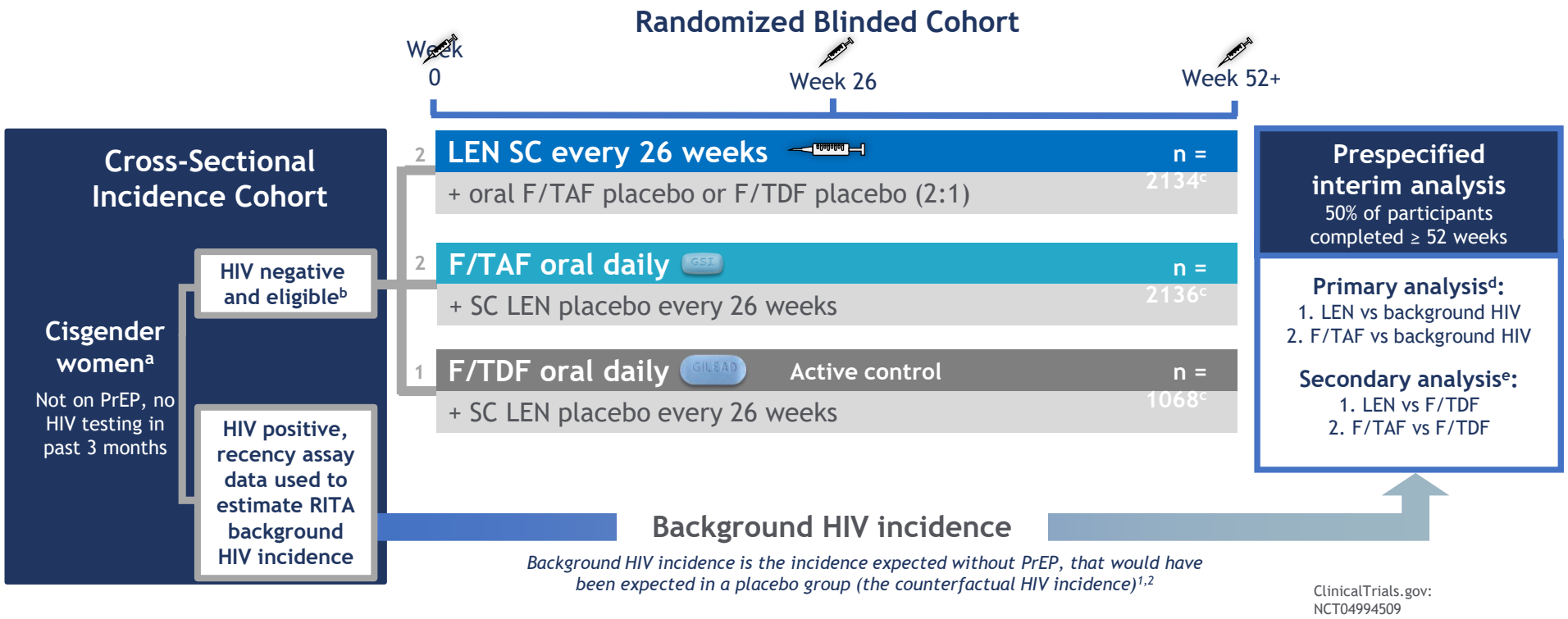


FIGURE 1. Lenacapavir targets multiple stages of the HIV replication cycle. Adapted from [4**,5].

PURPOSE 1

Study design for cisgender women

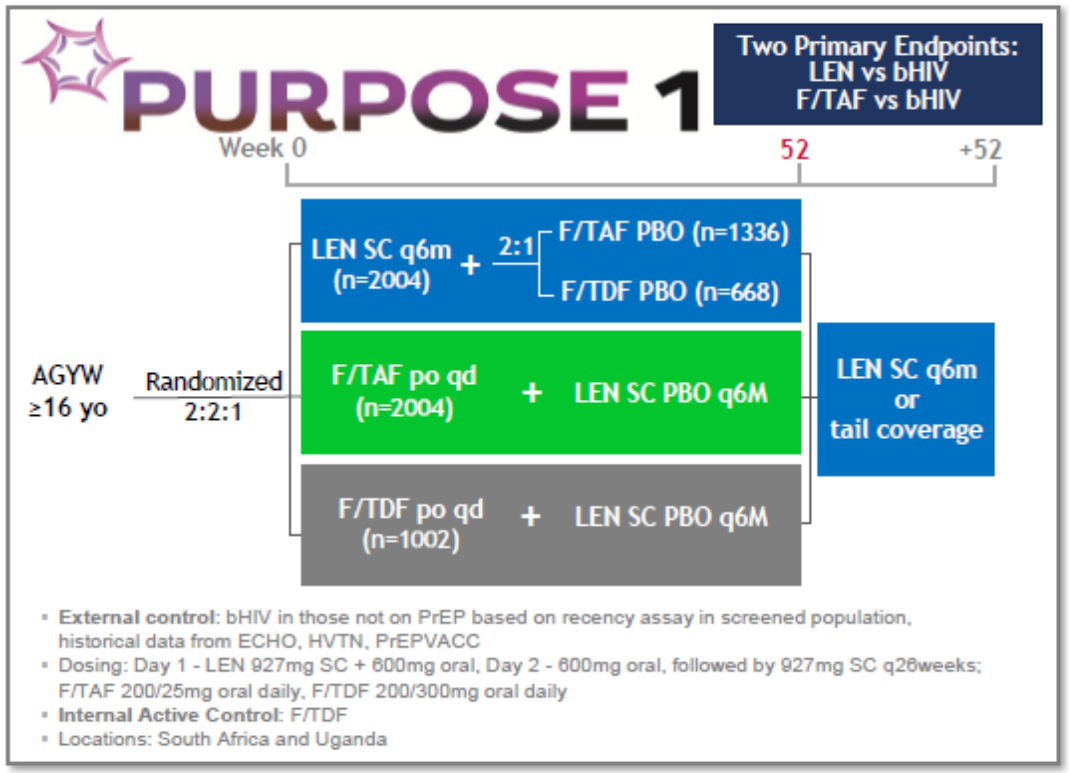


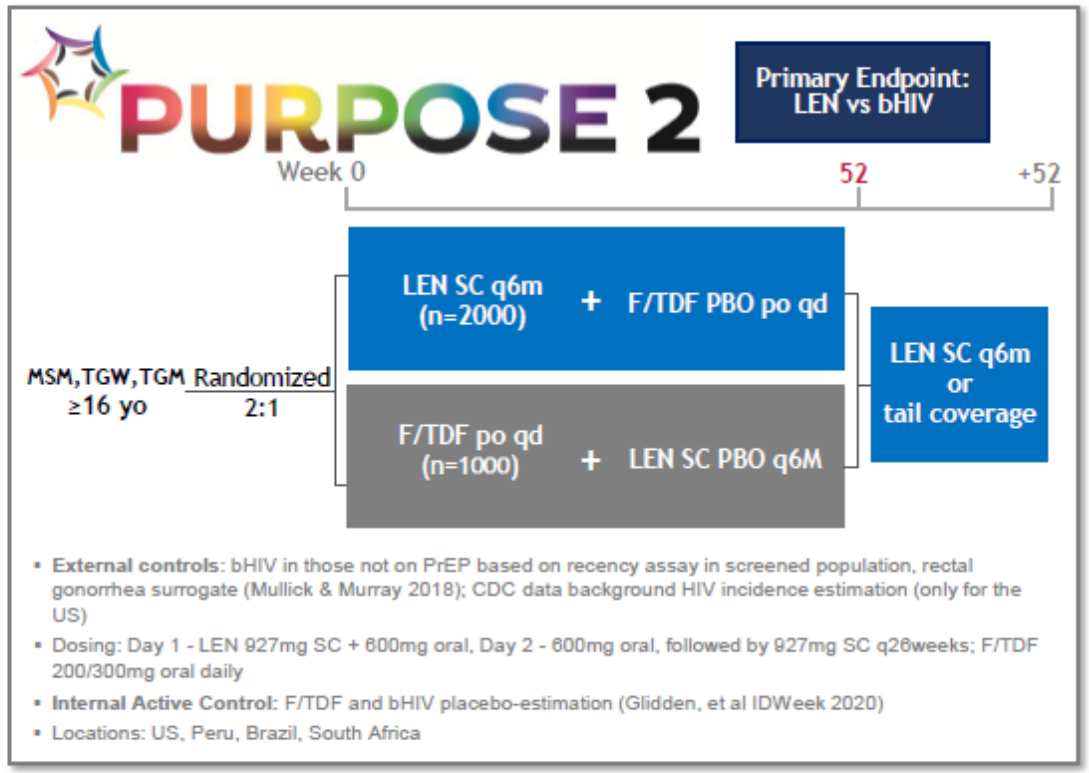
[a]The first participant was screened in August 2021, the 50th percentile participant was randomized in May 2023, and the last participant was randomized in September 2023. [b]Eligibility criteria included: weight ≥35 kg, eGFR ≥60 ml/min, not pregnant. [c]n numbers represent the full analysis set for 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.

‡

LEN for Pre-Exposure Prophylaxis (PrEP): The PURPOSE Studies

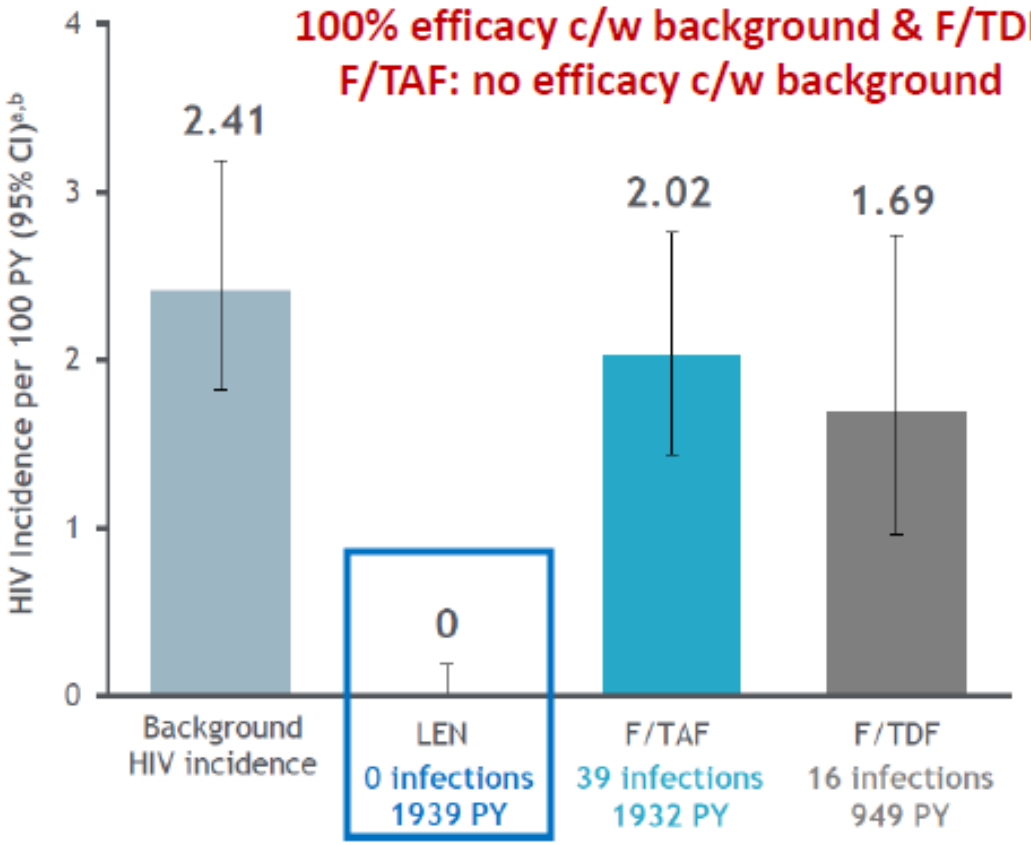




These studies used a counterfactual analysis for primary efficacy analysis

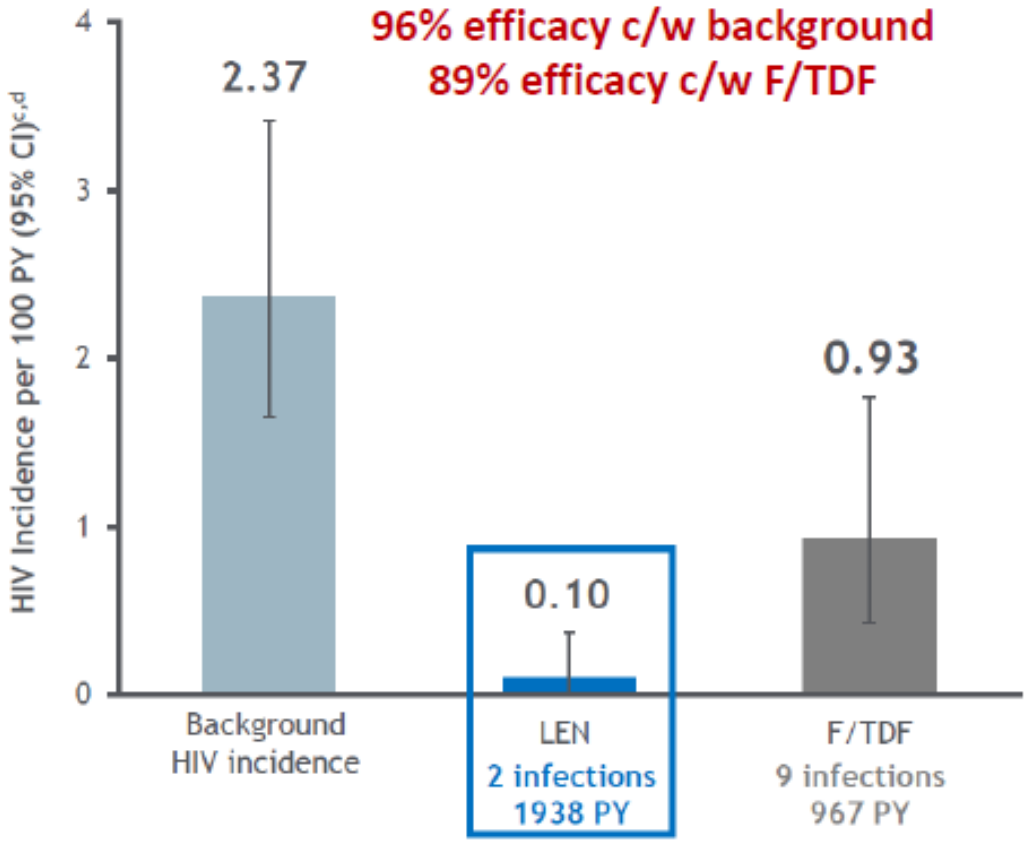
AGYW, adolescent girls and young women; bHIV, background HIV incidence; LEN, lenacapavir; PBO, placebo; SC, subcutaneous
Data on file, Gilead Sciences

PURPOSE 1: Zero HIV Infections in Cisgender Women Receiving LEN



Median follow-up duration: 44.0 weeks

PURPOSE 2: Two HIV Infections in Participants Receiving LEN



Median follow-up duration: 39.4 weeks

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

Bekker, NEJM 2024; Kelley, NEJM 2024

Once-yearly formulation of LEN

Singh et al, Abstract 154, CROI 2025

Study Design

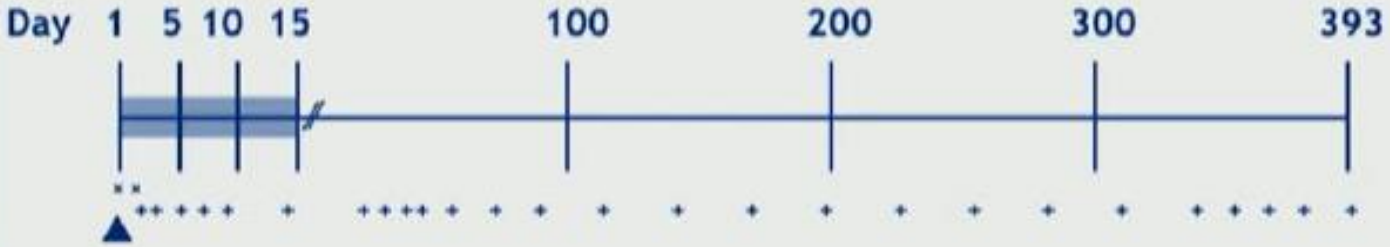
Open-label, Phase 1 study evaluating the PK, safety, and tolerability of a single 5000 mg[a] IM dose of two free-acid LEN formulations: Formulations 1 and 2

Cohort 1: Formulation 1 (5% EtOH; n = 20)

Cohort 2: Formulation 2[b] (10% EtOH; n = 20)

Study Population

- Healthy participants with a low likelihood of HIV acquisition
- Aged 18-55 years
- BMI ≤ 35.0 kg/m²



- Clinic inpatient observation
- ▲ Study drug dosing: two 5-mL IM gluteal injections
- × Intensive PK sample (≤ 5 minutes before dose, and 2, 4, 8,12, 24 and 36 hours post dose)
- \+ Single anytime PK sample[c] follow-up: Days 22-43 (± 1 day), Days 57-141 (± 3 days), Days 169-393 (± 5 days)

Safety Assessments

- Laboratory evaluation
- Investigator-reported AEs
- Participant-reported outcomes including pain measures on a qualitative scale

PK Analysis/Outcomes

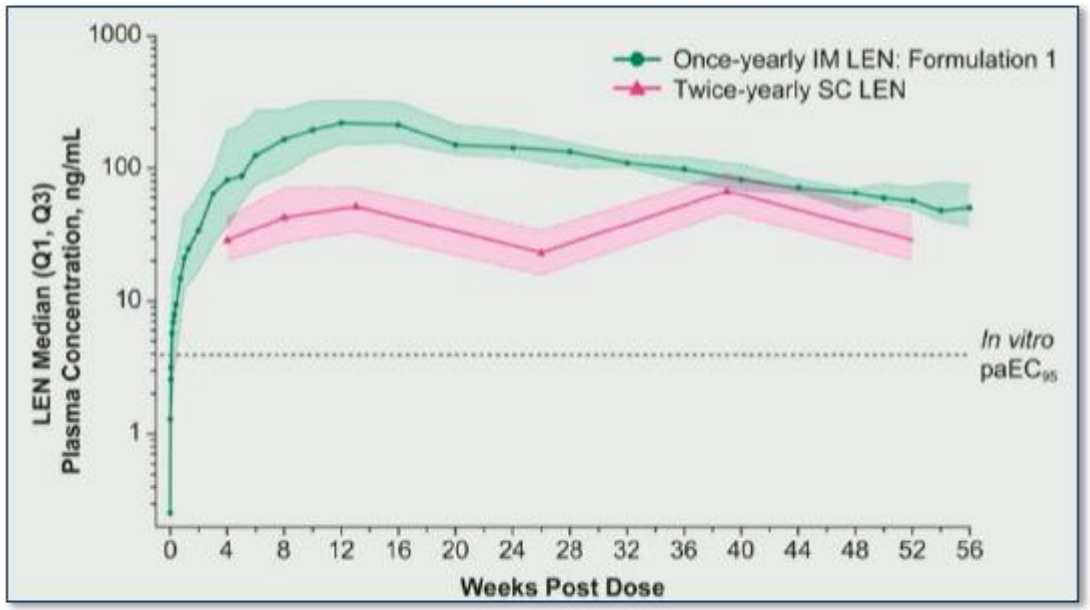
- PK ($AUC_{Days\ 1\text{-}365}$, C_{max}, T_{max}, and C_{trough})
- Compared LEN concentrations between once-yearly IM and twice-yearly SC LEN

[a]2 × 5 mL of 500 mg/mL. [b]Half of participants who received Formulation 2 were pretreated for approximately 10 minutes with an ice pack at the site of injection. [c]A single anytime PK sample was collected on Days 3, 4, 6, 8, 10, 15, 22, 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 351, 365, 379, and 393, and at the early termination visit (if applicable).

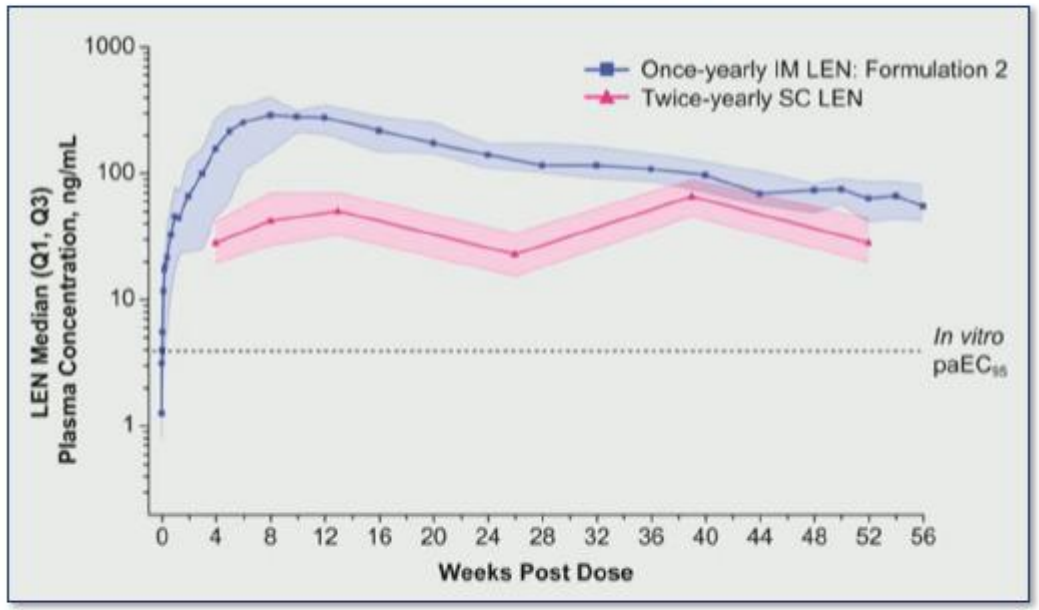
AE, adverse event; **AUC**, area under the concentration-time curve; $AUC_{Days\ 1\text{-}365}$, area under the concentration-time curve for the once-yearly dosing interval calculated from days 1-365; **BMI**, body mass index; C_{max}, observed peak plasma concentration; C_{trough}, estimated trough concentration at the end of 364 days; **EtOH**, ethanol; **IM**, intramuscular; **LEN**, lenacapavir; **PK**, pharmacokinetic; T_{max}, time to reach peak plasma concentration.

Once-yearly LEN formulations maintain higher plasma conc's than twice-yearly LEN thru 56 wks

Formulation 1



Formulation 2



Slide courtesy of Susan Buchbinder

Singh et al, Abstract 154, CROI 2025

LEN – What next?

- 6-monthly subcutaneous injection under regulatory review
- Yearly formulation: favorable pharmacokinetic profile
  - Delivered intramuscularly (no subcutaneous nodules)
  - Most participants reported no or mild injection site pain
  - ISP typically resolved within 1 week
  - Good tolerability - Pre-treatment with ice diminished pain ratings on days 1 and 1 for formulation 2
- Bridging study planned for PrEP indication

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Long acting oral formulations

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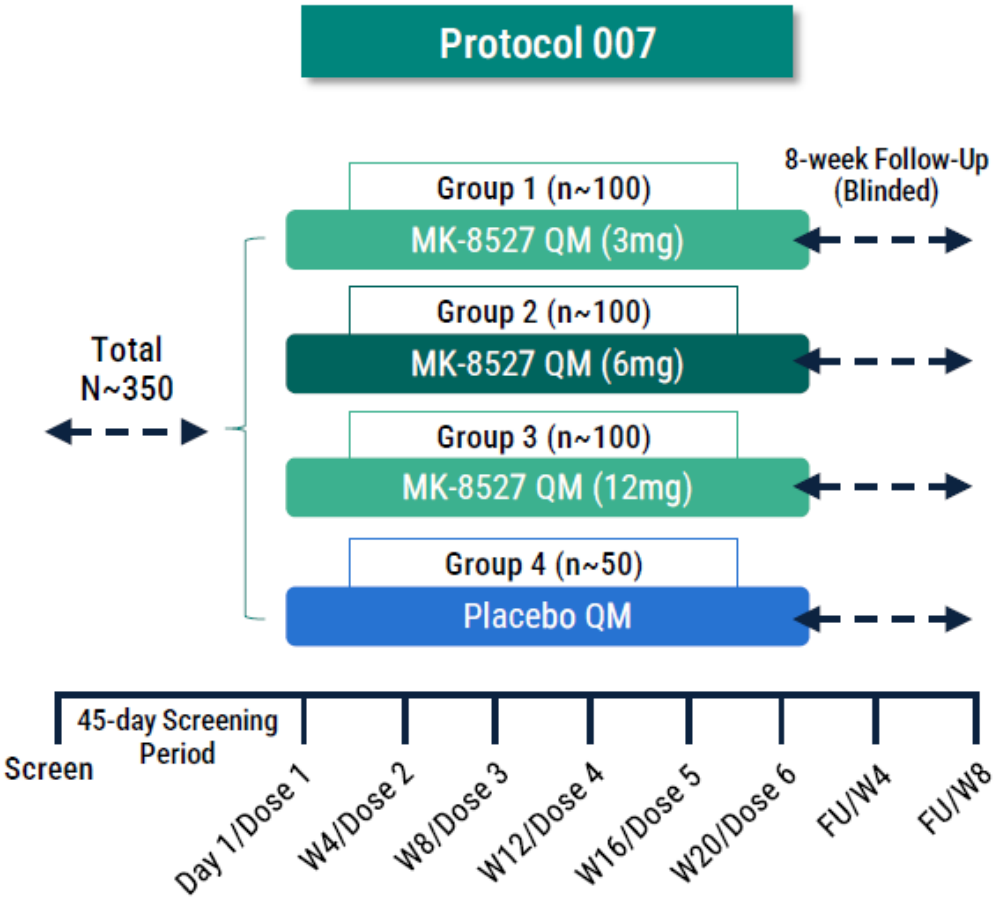
MK-8527: New NRTTI

- Islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI) reduced CD4+ counts at doses tested for monthly oral PrEP
- MK-8527 another novel NRTTI tested in 2 Phase 1 trials:
  - Ascending single dose (0.5mg – 200mg)
  - Multiple doses (5-40mg 3x/week)
- MK-8527 was well tolerated, all drug-related AEs were mild/moderate and resolved
  - After single dose, 5mg-200mg all above target levels for protection
  - In multiple dose trial, across all doses the terminal half-life of the intracellular form was 216-291 hours
- PK profile supports weekly (or less frequent dosing)
- Currently underway is Protocol 007, results expected anytime now
- Phase 3 trials planned in cis-women and cis-men/transgender/ non-binary populations



Phase 2 randomized (2:2:2:1), double-blind, dose-ranging study of monthly oral MK-8527

Gillespie, Abstract 129, CROI 2024; Figure courtesy of Rebecca Plank

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Other drug delivery formulations

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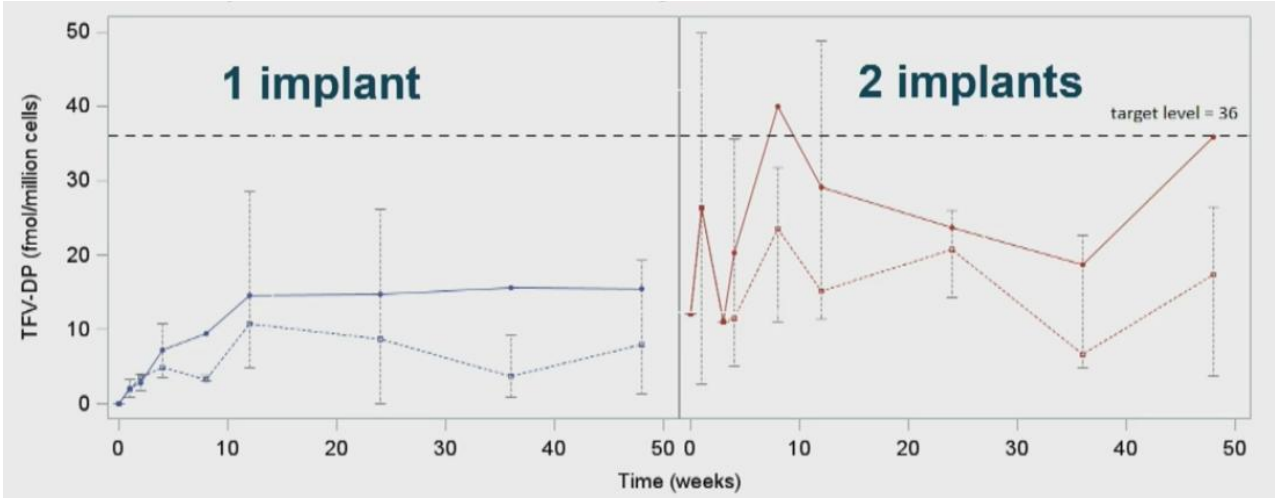
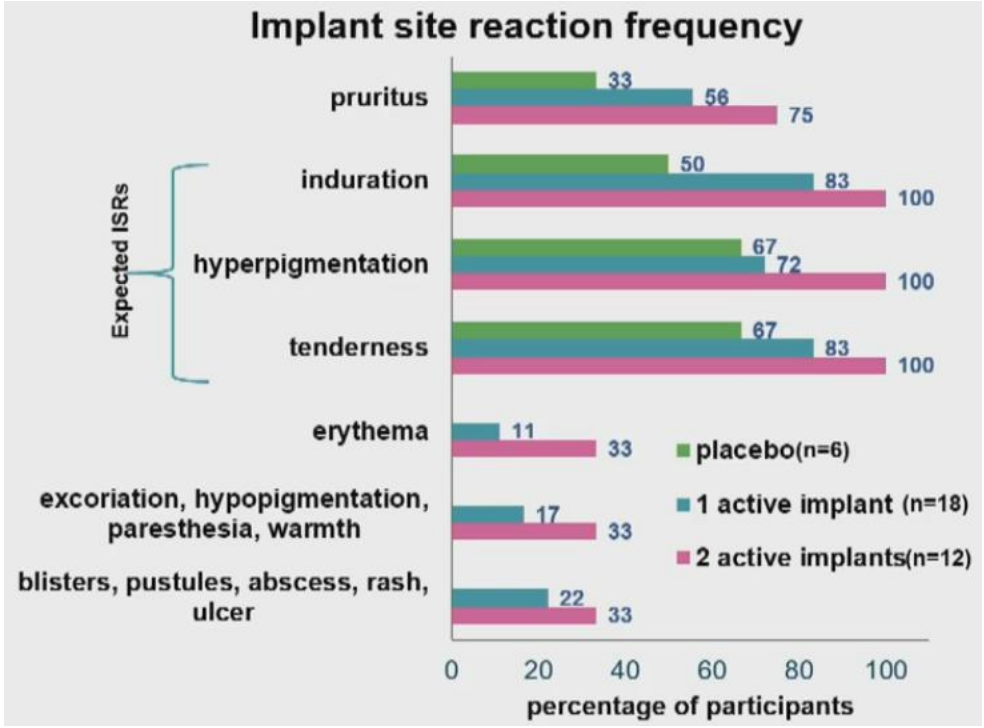
TAF silicone implant CAPRISA 018

PK



- Lower than planned drug release:
  2 implants had median TFV-DP of 14.8, below target of 36 fmol/10^6 cells

Safety



- 33% of TAF implants (vs. 17% of placebo implants) removed early

Gengiah TN et al, Abstract 123, CROI 2024

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Multi-purpose prevention technologies

MPTs

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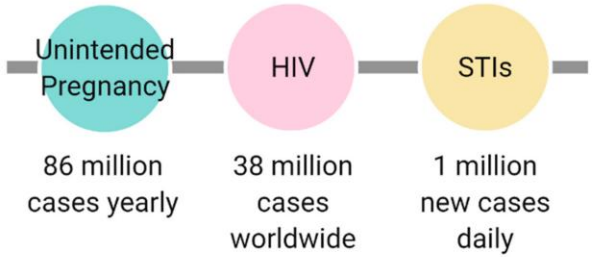
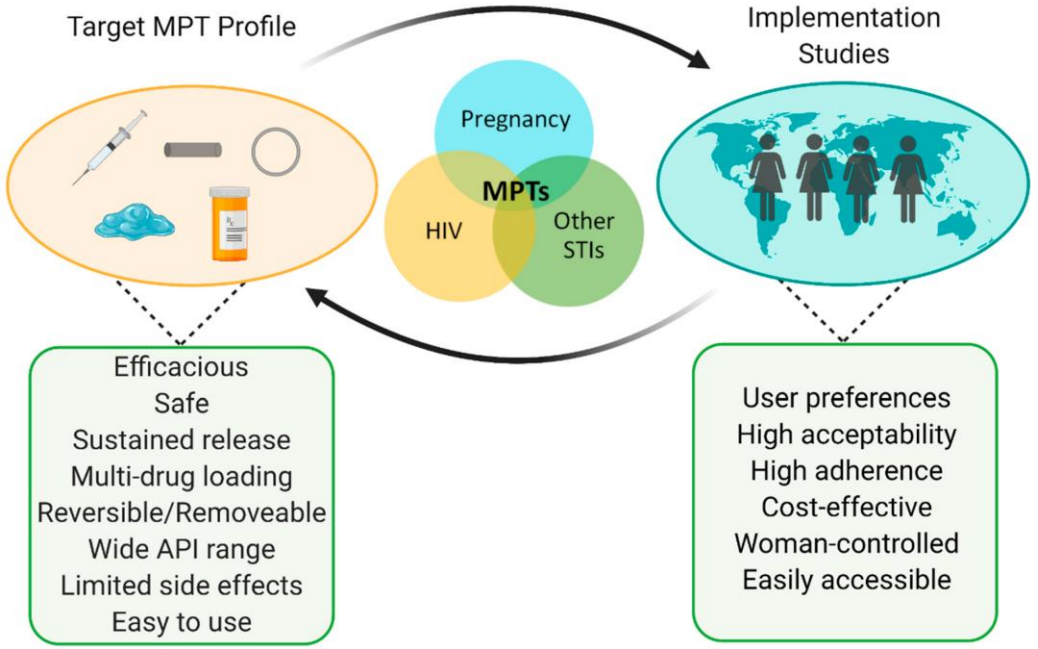
The Pipeline of MPTs

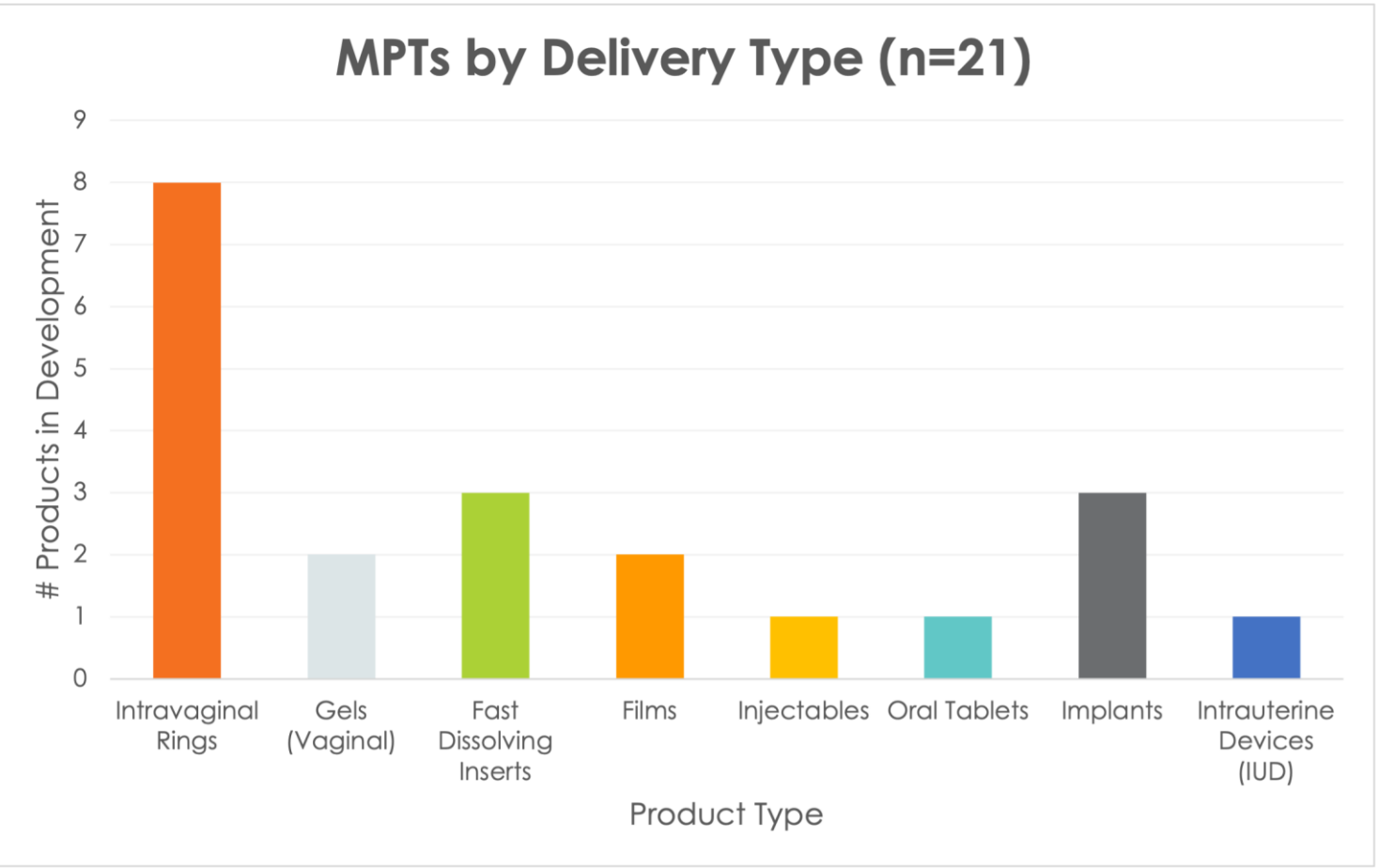
- Oral PrEP, dapivirine vaginal ring, cabotegravir and lenacapavir will not address the needs of all people who need HIV prevention.
- Products which are less costly, more acceptable, **provide added value** and have less impact on health systems are needed.
- MPTs may have added value for users, but the MPT pipeline will require investment to move these products forward.





Slide courtesy of Sharon Hillier

MPTs in development



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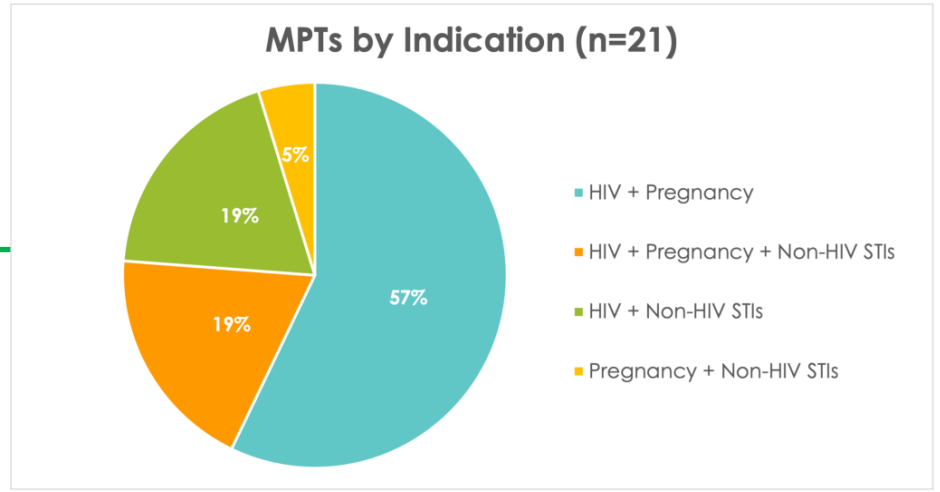

MPTs in phase 1 or nearing phase 1

- 90 day Dapivirine ring with LNG (Pop Council)
- TAF/EVG insert with or without doxycycline (CONRAD)
- 30 day Dapivirine film with LNG (Pitt)
- Nonhormonal non ARV multipurpose ring (Oak Crest)

Other MPTs

- Dual Prevention Pill (HPTN-104)
- VivaGel (StarPharma)
- Yaso Gel
- Lactic acid gel (Pop Council)
- Griffithsin fast dissolving insert (Pop Council)

New HIV prevention technologies: Conclusion

- We need a diversity of prevention options and programs to address the diverse needs of individuals at risk for HIV infection
- The HIV prevention field is evolving faster than ever
- Expedite the research and development of a range of products that are **acceptable**, **affordable**, **scalable** and **deliverable** in settings where they are needed most.
- Products that:
  - End-users indicate they are likely to use,
  - Could be manufactured and distributed locally and at low cost,
  - Are likely be easy to deliver, with minimal burden on healthcare systems,
  - Meet the needs of Ministries of Health and national health programs.
  - Will offer significant potential to curb HIV
- The bar for developing next-generation HIV prevention options and designing HIV prevention clinical trials continues to rise

Acknowledgements

My sincere gratitude to the following colleagues who contributed to this slide set

- Caroline Murombedzi
- Jochen Buck
- Marc Baum
- Sharon Hillier
- Susan Buchbinder


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos

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Study design approaches for future active-controlled HIV prevention trials

The **evolution of HIV pre-exposure prophylaxis (PrEP) clinical trial design and analysis** reflects progress in our understanding of the virus, HIV prevention, statistical methodologies, ethical frameworks, and public health needs.

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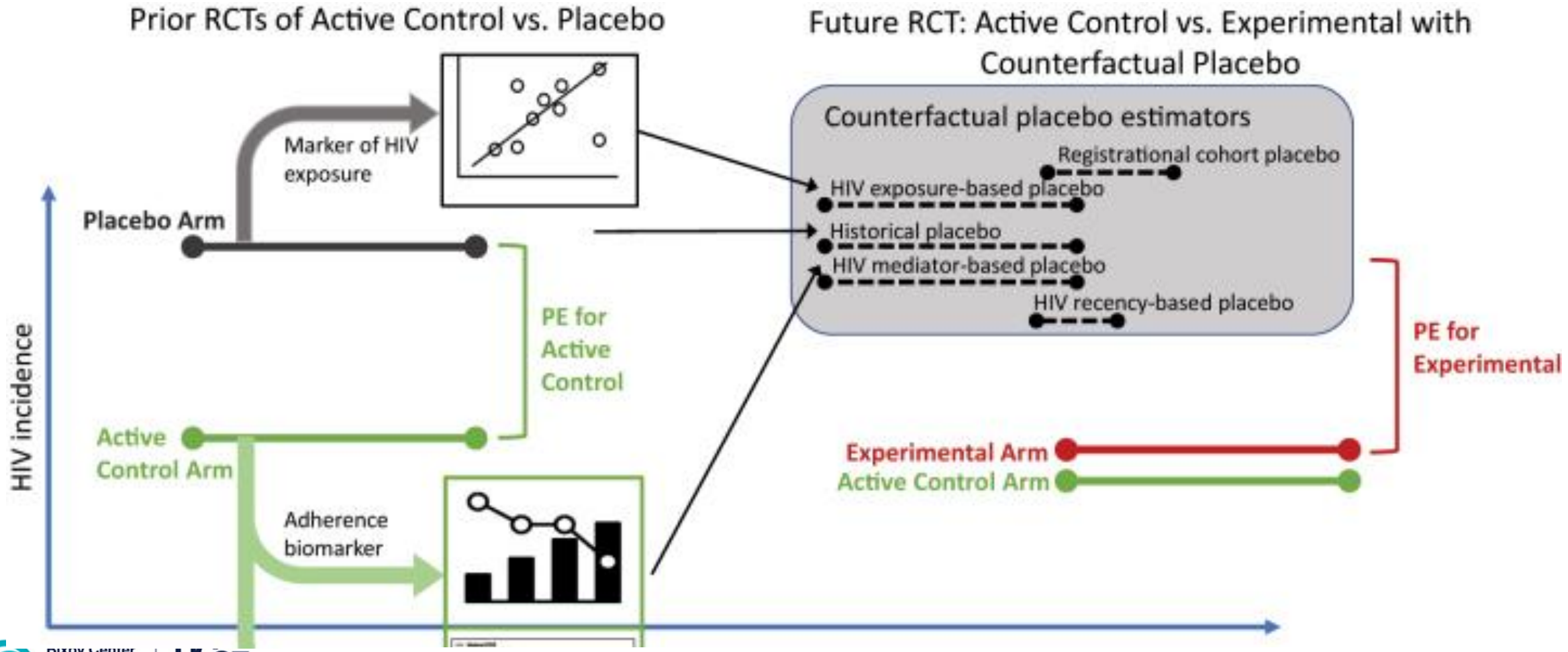
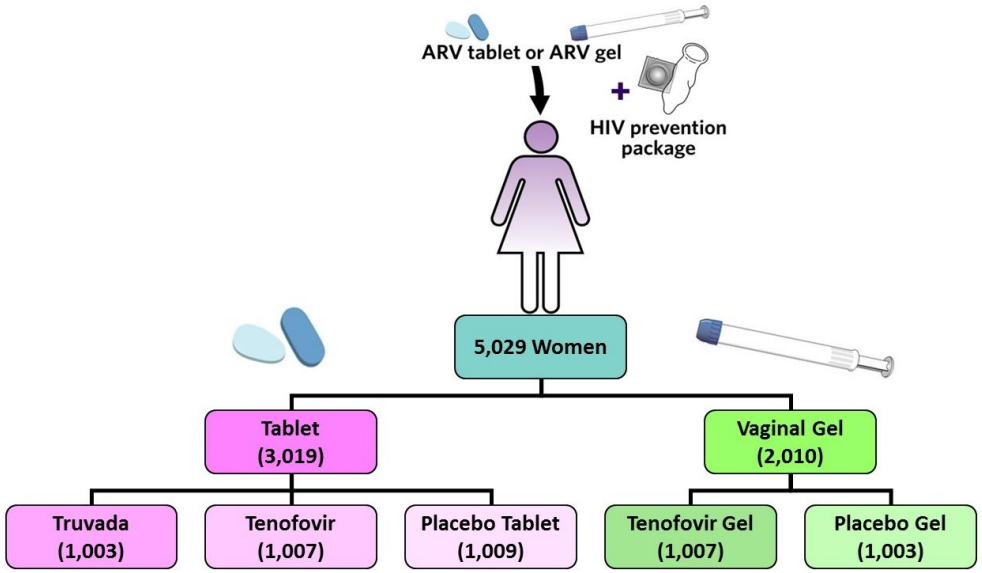
Multiple approaches for inferring prevention efficacy (PE) of an experimental intervention relative to placebo, based on data from an active-controlled trial



Donnell D, Kansiime S, Glidden DV, Luedtke A, Gilbert PB, Gao F, Janes H. Study design approaches for future active-controlled HIV prevention trials. Stat Commun Infect Dis. 2024 Jan 22;15(1):20230002. doi: 10.1515/scid-2023-0002. PMID: 38250627; PMCID: PMC10798828.

Earlier HIV prevention trials



VOICE Study – Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women (MTN-003)

- **POC** - To determine whether antiretroviral drugs particularly **tenofovir-based regimens**, could prevent HIV infection.
- **Designs:** Randomized controlled trials, often placebo-controlled.
- **Participants:** High-risk populations (e.g., MSM, sero-discordant couples, sex workers, cis gender women).
- **Endpoints:** HIV seroconversion (primary); safety; adherence measured via self-report or pill count.
- **iPrEx (2010):** MSM and transgender women; showed ~44% reduction in HIV incidence.
- **Partners PrEP, TDF2, FEM-PrEP, VOICE:** Varying efficacy, raising questions about adherence and biological factors (e.g., vaginal vs rectal transmission, vaginal inflammation).

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Conceptual approaches to inferring prevention efficacy of an HIV prevention intervention relative to a counterfactual placebo.

- **Registrational cohort** A registrational cohort, or trial 'run-in', is enrolled and followed for incident HIV
- **Recency assays during trial screening** HIV recency assays, applied to individuals screened for active-controlled trial participation
- **External trial placebo arm data** Placebo arm data for historical or concurrent placebo-controlled HIV prevention trials
- **Biomarker of HIV exposure** HIV incidence/exposure biomarker association estimated using historical placebo cohort data.
- **ARV drug concentrations as mediators of ARV PE** Drug concentration of ARV is established as mediator of PE.
- **Immune biomarkers as mediators of mAb/vaccine PE** Immune biomarker established as mediator of protection in prior placebo-controlled trial(s).

Donnell D, Kansiime S, Glidden DV, Luedtke A, Gilbert PB, Gao F, Janes H. Study design approaches for future active-controlled HIV prevention trials. Stat Commun Infect Dis. 2024 Jan 22;15(1):20230002. doi: 10.1515/scid-2023-0002. PMID: 38250627; PMCID: PMC10798828.

Event driven oral PrEP for women

There is new information about how women can take PrEP which includes:

- How quickly PrEP can start to work.
- Number of doses needed for daily and event-based dosing.
- How long after sex one needs to continue daily dosing if they want to stop PrEP.

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Model-based predictions of protective HIV pre-exposure prophylaxis adherence levels in cisgender women

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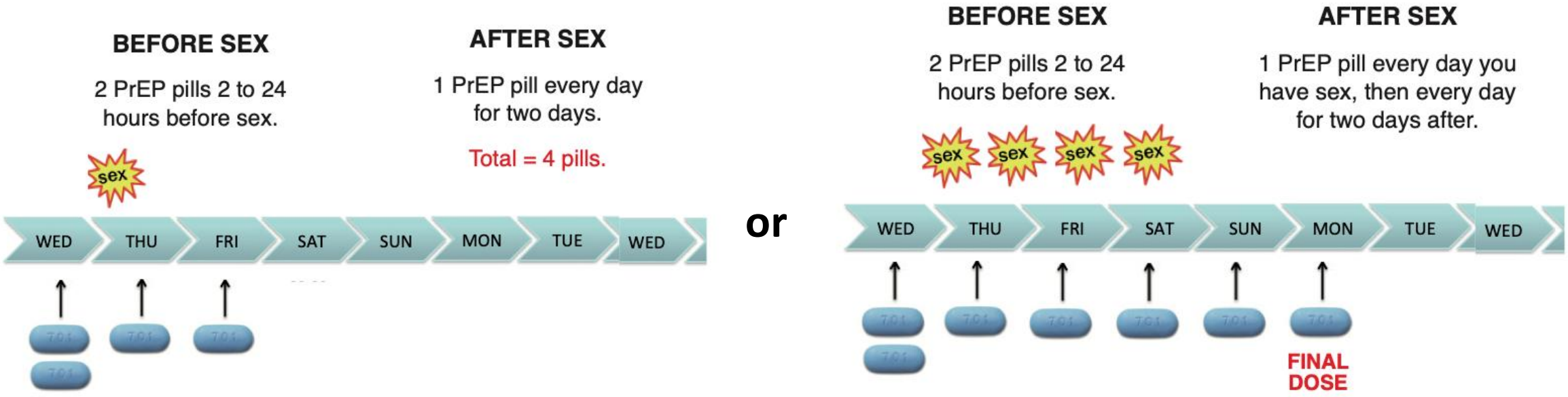
PBMC drug levels support 2:1:1 dosing for cisgender women

- A double dose (two pills) of PrEP can achieve optimal protection within two hours
- Post-sex daily doses must be taken as recommended.



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