# Future Clinical Trials Designs for HIV Prevention

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# Presentation Highlights

HPTN Regional Meeting

- Main issue of presentation
  - We now have many choices for HIV prevention, with a broad range of characteristics and very high effectiveness. We can prevent transmission and acquisition of HIV.
  - There are other prevention possibilities in the pipeline, and we still don't have a vaccine. How are we going to ethically advance new prevention tools?
- Key takeaway
  - For approaches based on ARVs, where there is a track record of high effectiveness, a pathway is comparison against both a standard known-effective drug and a "counterfactual placebo".
  - For approaches not yet proven, the pathway is not yet clear.
- How will this advance HIV prevention efforts?

  Ongoing discernment is needed to discern scientifically valid, ethically appropriate designs for future products.

# HIV prevention successes lead to new challenges for future trial design

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**No ARV-based prevention**

- Up to 2015
- Placebo randomized controlled trials
  e.g. HPTN 035, HPTN 052, iPrEX, Partners PrEP, ASPIRE, RING

**Oral ARV-based Prevention (FTC/TDF)**

- 2015-2022
- Active controlled randomized trials e.g. DISCOVER, HPTN 083/084
- Placebo controlled trials + FTC/TDF as standard of prevention
  e.g. HVTN 704, AMP, MOSAICO

**Long acting ARV-based prevention**

- 2022-
- Designs to evaluate efficacy of new products e.g. implants, longer acting pills/injections

# The HIV prevention toolbox is growing

**Agents for prevention**

- Oral PrEP
- Injectable PrEP
- Vaginal rings
- Monoclonal antibodies
- Microbicides
- Vaccines

**How will this impact the design of clinical trials for new biomedical interventions?**

# Recently completed trials in the era of FTC/TDF

## 1. Compare

Compare proven prevention (STD) to experimental agent (EXP)

Discover:
F/TAF vs TDF/FTC

HPTN 083/084:
CAB-LA vs TDF/FTC

PURPOSE 1/2:
LEN vs TDF/FTC (vs F/TAF)

## 2. Layer

Compare EXP to placebo (PBO) **layered** with use of proven prevention

AMP:
VRC01 vs PBO

HVTN 706
Mosaico vaccine vs PBO

**All pts can use FTC/TDF**

## 3. Combine

Compare existing prevention combined with EXP product

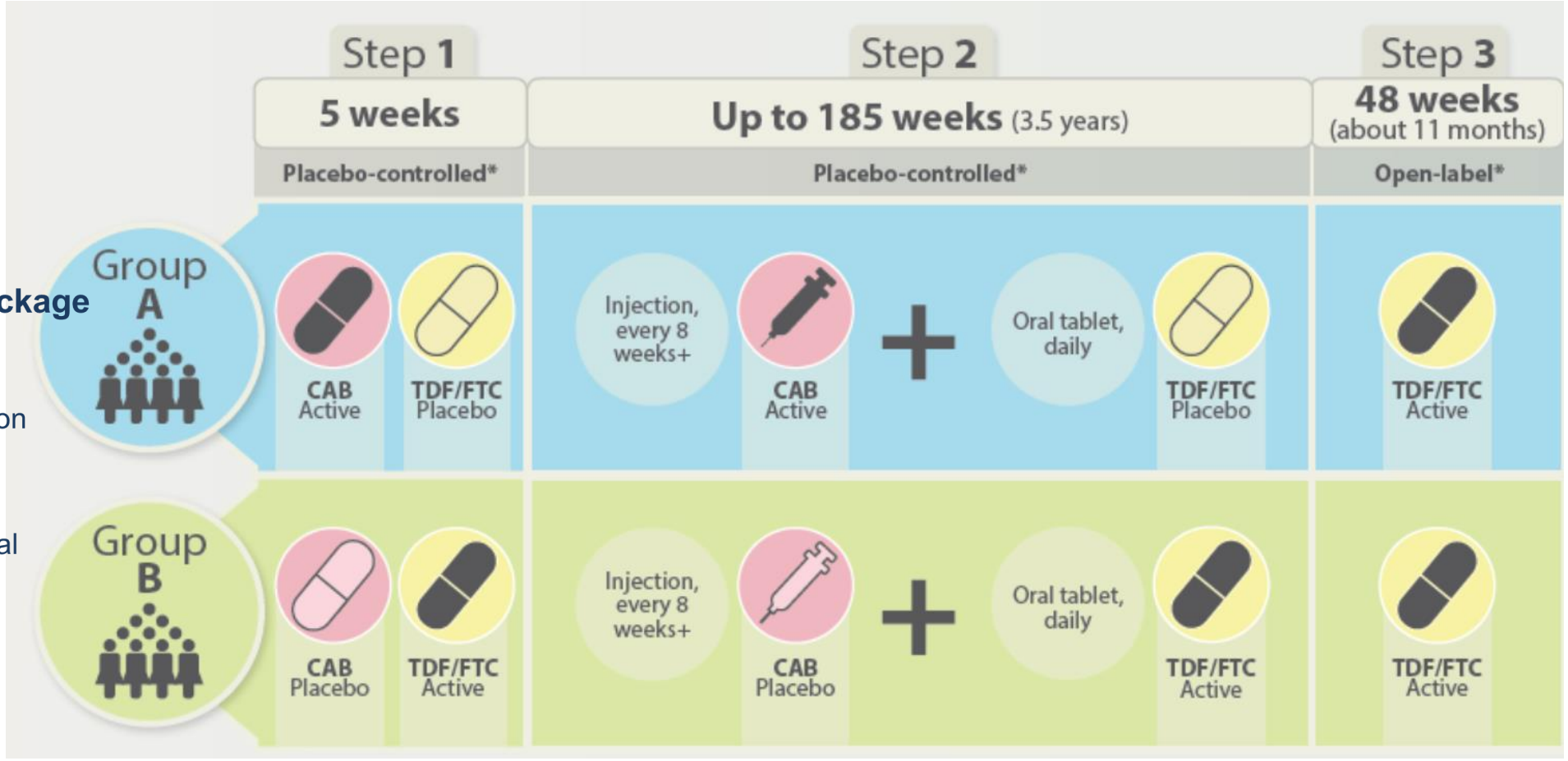
oral PrEP + Placebo


oral PrEP + EXP

# Compare: A participant in an active control trial

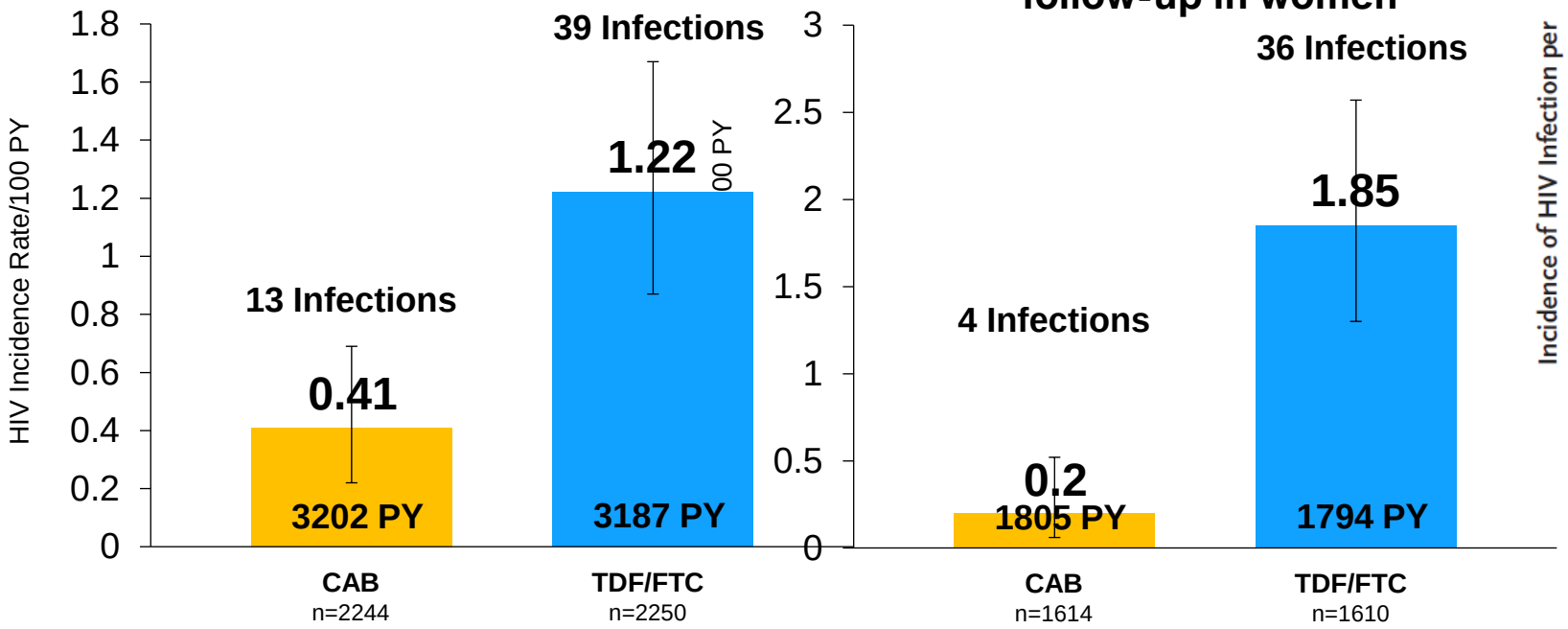
**Optimized prevention package**

- Risk reduction counselling
- Condom and lubricant provision
- PEP counseling and linkage
- Couples counselling
- STI treatment provision/referral
- Contraception



# Compare: Results of the direct comparison trials

**52 HIV infections in 6389 PY of follow-up in MSM/TGW**



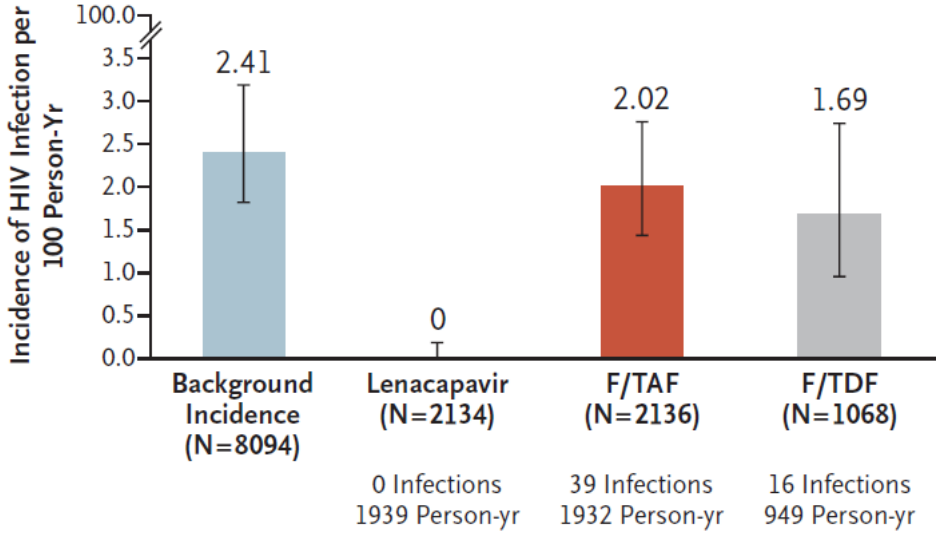

HR = 0.34 (0.1 – 0.62)
*MSM/TGW in the CAB group had an* ***66% lower risk of HIV infection,*** *compared to TDF/FTC group*

**40 infections over 3892 PY of follow-up in women**



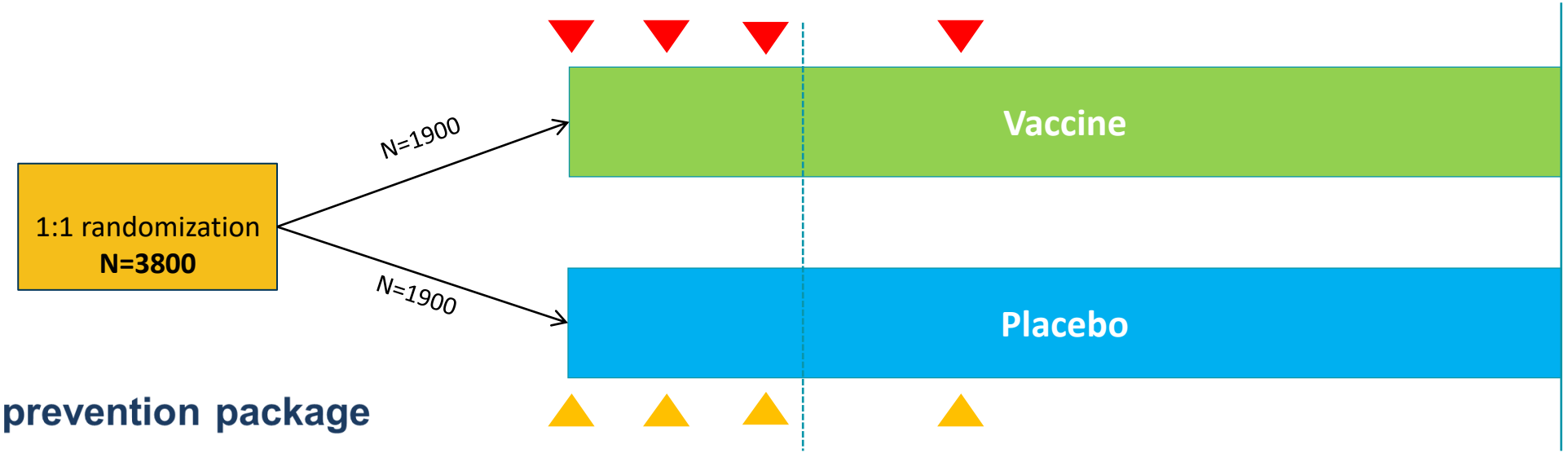

HR = 0.11 (0.01 – 0.31)
*Women in the CAB group had an* ***89% lower risk of HIV infection,*** *compared to TDF/FTC group*

**55 infections over 3920 PY of follow-up in women**




HR = 0.00 (0.00 – 0.04)
*Women in the LEN group had an* ***100% lower risk of HIV infection,*** *compared to background rate of 2.41 (1.82-3.19)*

# Layer: A participant in a placebo controlled trial with access to PrEP




**Optimized prevention package**

- Risk reduction counselling
- Condom and lubricant provision
- PEP counseling and linkage
- Couples counselling
- STI treatment provision/referral
- Contraception
- **PrEP counseling, referral, and linkage**



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# Results of placebo controlled trials with access to PrEP

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HPX3002/HVTN706
N = 3870

| | Vaccine N = 1940 | Placebo N = 1938 |
|---|---|---|
| HIV infections | 113 | 113 |
| HIV incidence | 4.1 | 4.1 |

Efficacy = 0%
95%CI( x-x)

MOSAICO vaccine did not prevent HIV-1 acquisition more effectively than placebo

HVTN 703/HPTN 081
N = 1924 women

| | VRC01 N = 1287 | Placebo N = 637 |
|---|---|---|
| HIV infections | 47 | 29 |
| HIV incidence | 2.49 | 3.10 |

Efficacy = 8.8%
95%CI(-45%–43%)

VRC01 did not prevent HIV-1 acquisition more effectively than placebo

HVTN 704/HPTN 085
N = 2699 MSM/TG

| | VRC01 N = 1791 | Placebo N = 898 |
|---|---|---|
| HIV infections | 60 | 38 |
| HIV incidence | 2.35 | 2.98 |

Efficacy = 27%
95%CI(-12% – 52%)

VRC01 did not prevent HIV-1 acquisition more effectively than placebo

# HIV incidence in recent trials of HIV prevention

| ACTIVE CONTROL | Countries | N enrolled | Number of infections (Exp vs CTL/PBO) | Incidence rate | | |
|---|---|---|---|---|---|---|
| | | | | Exp. | Active control (FTC/TDF) | Detected/Protective FTC/TDF in DBS |
| HPTN 083 (MSM/TGW) | United States, Peru, Brazil, Argentina, Thailand, Vietnam, South Africa | 4541 | 13 vs 39 (stopped early) | 0.41 | 1.22 | 91%/82% |
| HPTN 084 (Women) | South Africa, Botswana, Eswatini, Zimbabwe, Malawi, Kenya, Uganda. | 3224 | 4 vs 36 (stopped early) | 0.20 | 1.86 | 62%/18% |
| PURPOSE 1 (Women) | South Africa, Uganda | 5368 | 0 vs 39 vs 16 (2:2:1) | 0.00 | 1.69 | NA/20% |
| **PLACEBO CONTROL (FTC/TDF access)** | | | | **Exp.** | **Placebo** | |
| AMP MSM/TG (HVTN 704/HPTN 085) | United States, Peru, Brazil, Switzerland | 2699 (3 arm) | 28 & 32 vs 38 | 2.35 | 2.98 | 39%/29% |
| AMP Women (HVTN 703/HPTN 081) | South Africa, Zimbabwe, Malawi, Botswana, Kenya, Mozambique, Tanzania | 1924 (3 arm) | 19 & 28 vs 29 | 2.49 | 3.10 | 4%/0.4% |
| MOSAICO (HPX3002/HVTN 706) | Argentina, Brazil. Italy, Mexico, Peru. Poland. Puerto Rico Spain, USA | 3870 | 113 vs 113 (stopped early) | 4.10 | 4.10 | 9%/5% |

# Five “active-controlled” randomized clinical trials completed

1. DISCOVER (MSM): F/TAF vs FTC/TDF
2. HPTN 083 (MSM/TGW): CAB-LA vs FTC/TDF*
3. HPTN 084 (Women): CAB-LA vs FTC/TDF*
4. PURPOSE 1 (Women): LEN vs F/TAF vs FTC/TDF*
5. PURPOSE 2 (MSM/TG): LEN vs FTC/TDF*

* Stopped early for proven efficacy

Active-controlled trial:

- All participants receive an active product: proven or experimental
- How do you justify randomization to an experimental drug when you an active product that is known to be effective?
- How do you know whether the experimental drug is working or not?

# Three “layered” randomized clinical trials completed

1. MOSAICO (HPX3002/HVTN706): Placebo vs. MOSAICO vaccine
2. AMP (HVTN703/HPTN081; HVTN704/HPTN085)

   Placebo vs. VRC01 10 mg/kg vs. VRC01 30 mg/kg

Placebo-controlled trial:

- No participants are receiving a proven product; all participants were informed about/had access to FTC/TDF PrEP
- How do you justify randomization to placebo when there is a proven drug for HIV prevention?
- The trial is designed to answer whether the biologic works: what is the risk of the layered approach?

# MOSAICO and PrEP

"One of the unique features of the study [MOSAICO] was that as part of the community outreach, clinic staff members first engaged and assessed community acceptance of, and interest in, HIV pre-exposure prophylaxis (PrEP). If community members accepted PrEP, they were navigated to services to begin receiving the preventive medication. However, if community members did not accept PrEP, they were considered for the MOSAICO study. Participants who joined the study and later changed their mind about PrEP were also navigated to PrEP services and remained in the study."

# Trial designs for new HIV prevention products

**Proven action: ARV based products: FTC/TDF; Dapivirine ring; CAB-LA; LEN**

**Unproven action: mAb; vaccines**

# Two possible questions for future trial

Superiority: The new drug is more effective than placebo or active control

- Pick a difference that is a clinically important improvement
- Choose sample size to have high probability of detecting that improvement

Non-inferiority: The new drug is effective and not substantially worse than a known effective drug (active control)

- Pick a difference that is not clinically important (“worse”) = Non-inferiority (NI) margin
- Choose a sample size to have high probability of showing the difference is not worse than that

## High risk to conduct a classical RCT if expected incidence rates are below 1/100 person years

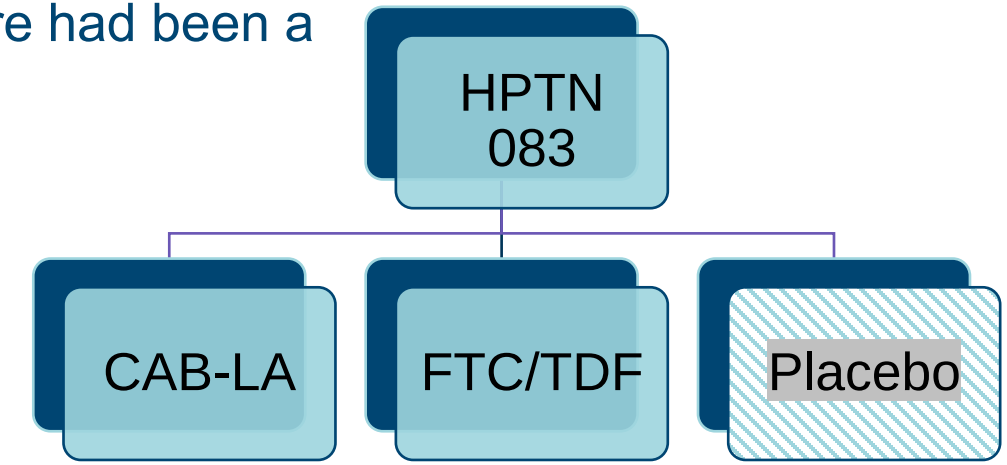
- Expect low rates when participants have access to highly effective (long acting) prevention
- May not gather enough evidence (HIV infections) to prove effectiveness
- Very large sample sizes will be expensive and long
- Large enrollments require expanding enrollment to lower risk populations

## What other approach can we use?

- Estimate what the infection rate “would have been if there had been a placebo”?

  ***“Counterfactual placebo”***

  ***“Background rate of infection”***



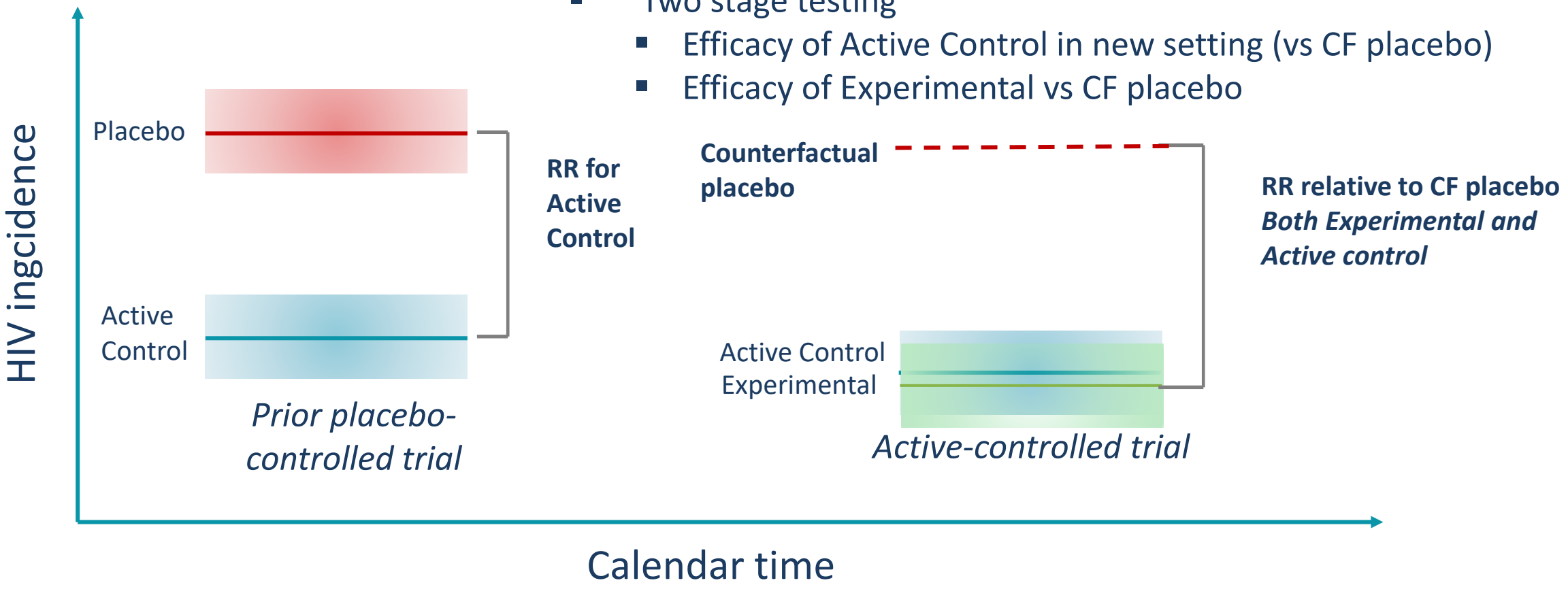
# Comparison for Future Prevention Trials
# Proven classes of agents


## Two long-acting products (“proven” agents)

- Experimental: Injection, infusion, longer acting pill
- Active control:  highly effective, HIV acquisition on proven active-control product <1/100 PYs
- Directly observed dosing
- **Active-control randomized design with a placebo counterfactual**
  - Placebo counterfactual = what would have been observed if there had been a placebo arm

# New Design Framework: Active-controlled Trial with Placebo Counterfactual

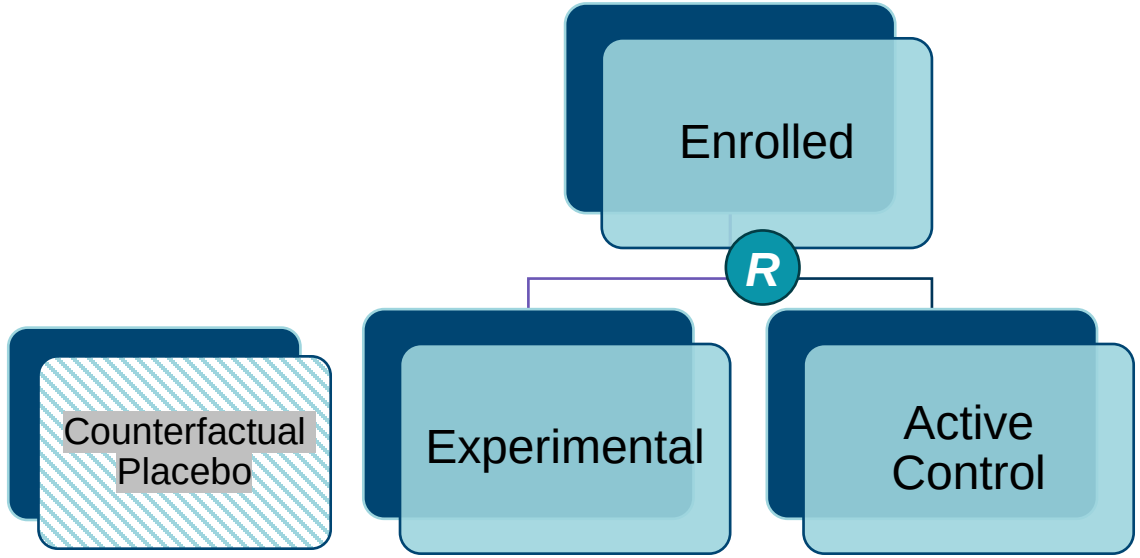
- Theoretical framework derived from NI approach; based on conservative CF placebo estimate
- Two stage testing
  - Efficacy of Active Control in new setting (vs CF placebo)
  - Efficacy of Experimental vs CF placebo




Gao: Submitted Statistics in Medicine "Active-Controlled Trial Design for HIV prevention with a counterfactual placebo"

# Counterfactual Placebo Strategy

- Two arm RCT with Experimental and Active control, with planned placebo counterfactual
  - … requires framework for three groups incorporating uncertainty and defined success criteria
  - … is appropriate for a new agent that is expected to be highly effective
  - … is feasible in terms of sample size
- Likely to be combined with other approaches to ensure efficacy of experimental drug



# Incorporate CHOICE within active control into trial design

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Preference for active control:
Choice of A, B, C

| Has no preference | Has partial preference | Has preference |
|---|---|---|
| Randomized to A, B or C | Randomized to A or B | Chose A |
| | Randomized to B or C | Chose B |
| | Randomized to A or C | Chose C |

Depending on choice preferences and characteristics in cohort, groups can be combined for comparison

Assigned to A vs Assigned to B vs Assigned to C

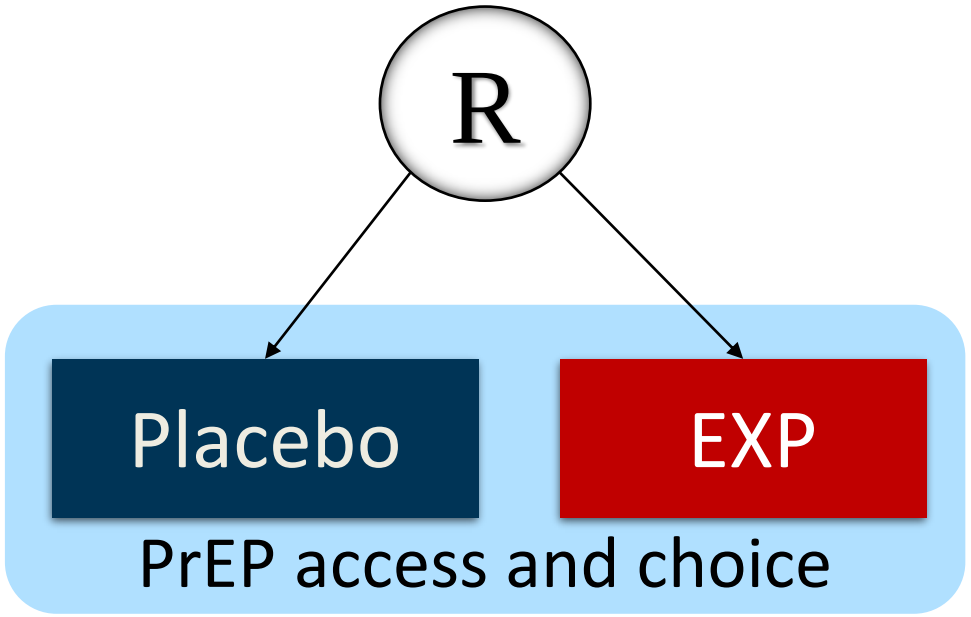
AND/OR

Choice could be compared to assignment

Assigned to A vs Chose A

# Future design for vaccine and mAb

- AMP strategy



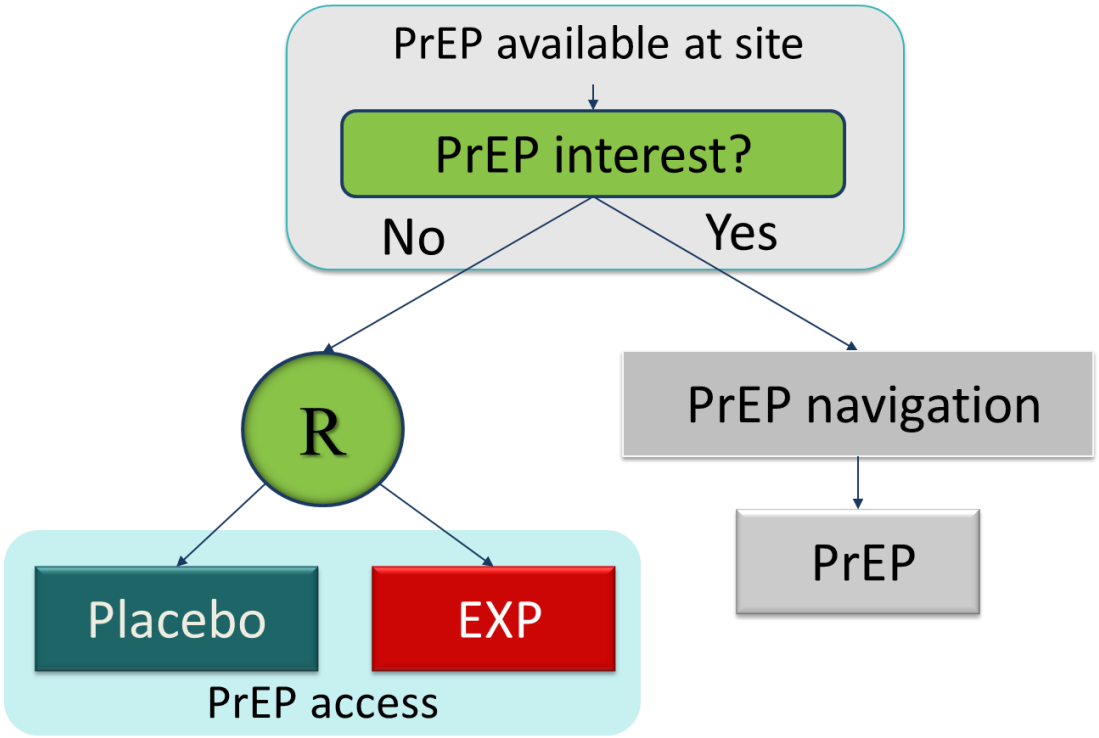

Not clear whether vaccines or mAbs will be as effective as current ARV-based prevention

PrEP choice (e.g. Injectable; FTC/TDF)
With high PrEP use

- HIV risk may be substantially reduced
- Trial design essentially asking whether EXP adds additional benefit

# Future design for vaccine and mAb

- MOSAICO strategy




Not clear whether vaccines or mAbs will be as effective as current ARV-based prevention

PrEP = daily oral : We know many not successful with oral PrEP

PrEP = Injectable

- FDA approved, not yet widely available – this may change
- Don't yet know whether substantial number at risk will not want to use injectable PrEP

# Approaches to Estimating Efficacy Relative to "Counterfactual" Placebo

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## Estimate counterfactual placebo incidence rate

1. Placebo data from external trials

   "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products" Draft FDA Guidance 2023

2. HIV incidence in registrational cohort (e.g. PrEPVacc Trial)
3. Cross-sectional incidence assessed using recency assay (e.g. Lenacapavir trial in women)
4. Estimating placebo incidence using reliable predictor(s) of HIV exposure

## Estimate efficacy of active control compared to counterfactual placebo

5. Using adherence-efficacy relationship of active control
6. Using immune biomarkers of ***effective*** vaccine/mAb as mediators of prevention efficacy

# Summary

- Current set of new prevention studies powered using oral FTC/TDF as SOC or active comparator have completed
  - Most were focused on longer acting products for greater effectiveness
  - Window for this approach in the future is likely narrow
- Sample sizes were uniformly large (3,000-5,000); resource needs are large
  - Continued use of traditionally powered RCT trial design could require 30-50,000 people if PrEP use in trial is highly effective
- Trials of novel ARVs are proceeding with counterfactual placebo assessments planned
  - All include randomization to an active-control Standard
  - Statistical framework for comparison of both Standard and Experimental with CF placebo is novel
  - Discussion with regulatory agencies ongoing

# Open Questions

- Will designs using counterfactual placebo be successful in establishing efficacy?
  - Is it important to have randomization to products known to prevent HIV?
- What will be the path forward for products that might be less efficacious, but still would expand choice?
  - How will we decide the potential future value of new compared to existing products: in terms of efficacy and/or uptake potential?
- What do you think about including product choice in future trials?
  - What is the question that is important to answer?

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