Biostatistical considerations for Future Clinical Trial Design for HIV Prevention

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Design within the ***current context*** of HIV prevention

- Biostatistician's Role: To ensure you get an answer to your question about whether the new product is useful
- Context
  - The intended population for the product
  - The current standard of care

Question changes once successes occur

No ARV-based prevention

- Up to 2012-2015
- Placebo randomized controlled trials
  e.g. HPTN 035, HPTN 052, iPrEX, Partners PrEP, ASPIRE, RING

Daily oral ARV-based Prevention (FTC/TDF)

- 2015-2025
- Active controlled randomized trials of novel ARVs e.g. CAB-LA vs. FTC/TDF
- Placebo controlled trials + FTC/TDF as standard of prevention
  e.g. Vaccine, mAb

Long acting ARV-based prevention

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

Define the question for the clinical trial

“In the context of available, effective, current products…”

1. Is the new product proposed expected to be at least as effective or more effective than the current product?
2. Does the new product have an implementation advantage?
   - Less burden on the health care system
   - Easier to use
   - Less expensive
3. Does the new product have fewer side effects?

Trial designs 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 **layered** with use of proven prevention

AMP:
VRC01 vs Placebo

HVTN 706
Mosaico vaccine vs Placebo

All pts can use FTC/TDF

3. Combine

Compare existing prevention combined with EXP product

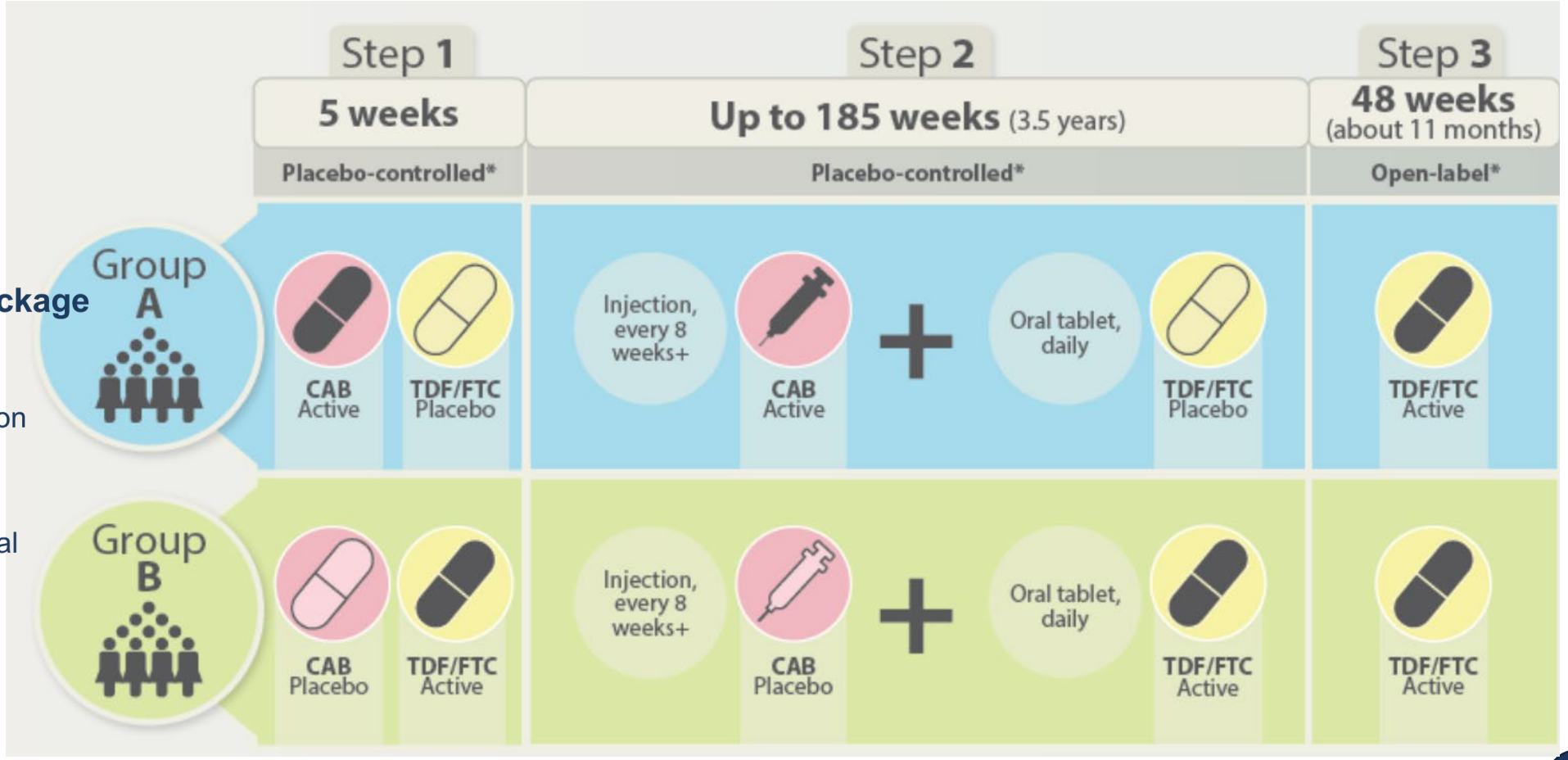
oral PrEP + Placebo

oral PrEP + EXP

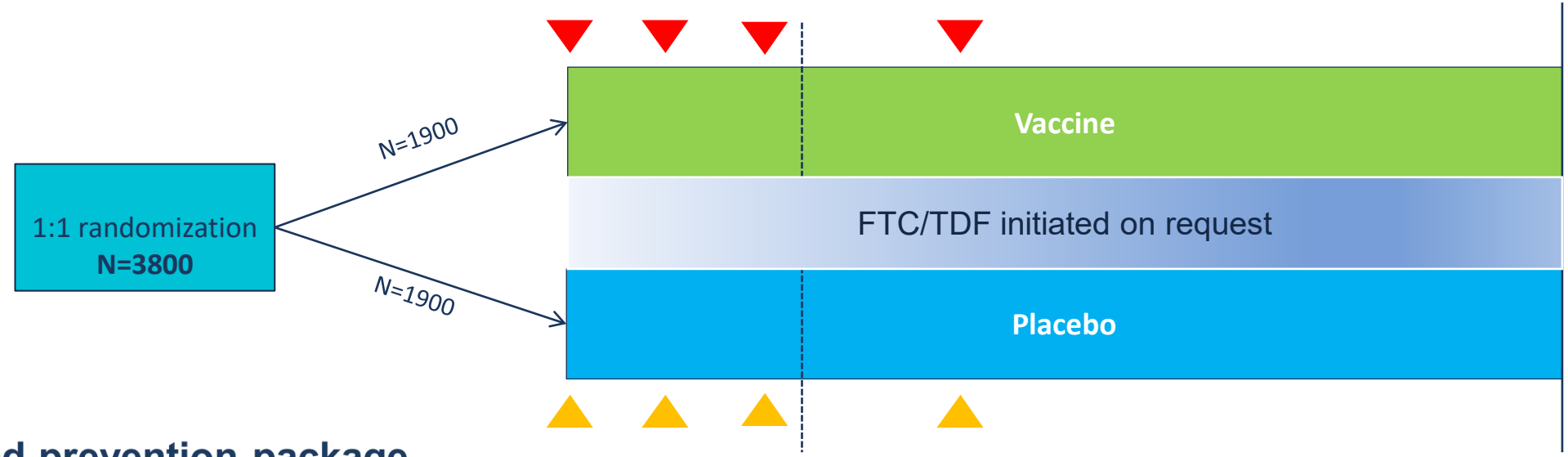
Compare: A participant in an active control trial

Optimized prevention package

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



Layer: A participant in a layer trial



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**

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."

HIV incidence in recent trials of HIV prevention

ACTIVE CONTROL	Countries	N enrolled	Number of infections (Exp vs CTL/PBO)	Incidence rate		Protective FTC/TDF in DBS
				Exp.	Active control (FTC/TDF)	
HPTN 083 (MSM/TGW)	United States, Peru, Brazil, Argentina, Thailand, Vietnam, South Africa	4541	13 vs 39 (stopped early)	0.41	1.22	82%
HPTN 084 (Women)	South Africa, Botswana, Eswatini, Zimbabwe, Malawi, Kenya, Uganda.	3224	4 vs 36 (stopped early)	0.20	1.86	18%
PURPOSE 1 (Women)	South Africa, Uganda	5368	0 vs 39 vs 16 (2:2:1)	0.00	1.69	20%
PURPOSE 2 (MSM/TG/GNB)	United States, Peru, Brazil, Argentina, Thailand, South Africa, Mexico	3265	2 vs 9 (2:1)	0.10	0.93	71%
PLACEBO CONTROL (FTC/TDF background use)				**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	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	0.4%
MOSAICO (HVTN 706)	Argentina, Brazil. Italy, Mexico, Peru. Poland. Puerto Rico Spain, USA	3870	113 vs 113 (stopped early)	4.10	4.10	5%

Future Trial designs for new HIV prevention products

Proven action: ARV based products: e.g. FTC/TDF; Dapivirine ring; CAB-LA injections; LEN

Unproven action: mAb products; vaccines

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

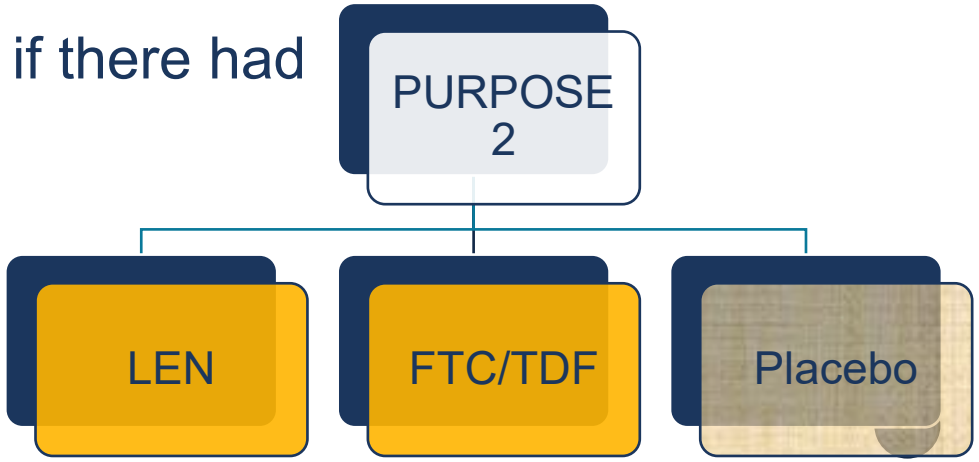
- Expect low rates when participants have access to highly effective (long acting) prevention
- May not gather enough evidence (HIV infections) to prove effectiveness
- Very large sample sizes will be costly
- Large enrollments require expanding enrollment to lower risk populations

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"



Counterfactual Placebo Strategy

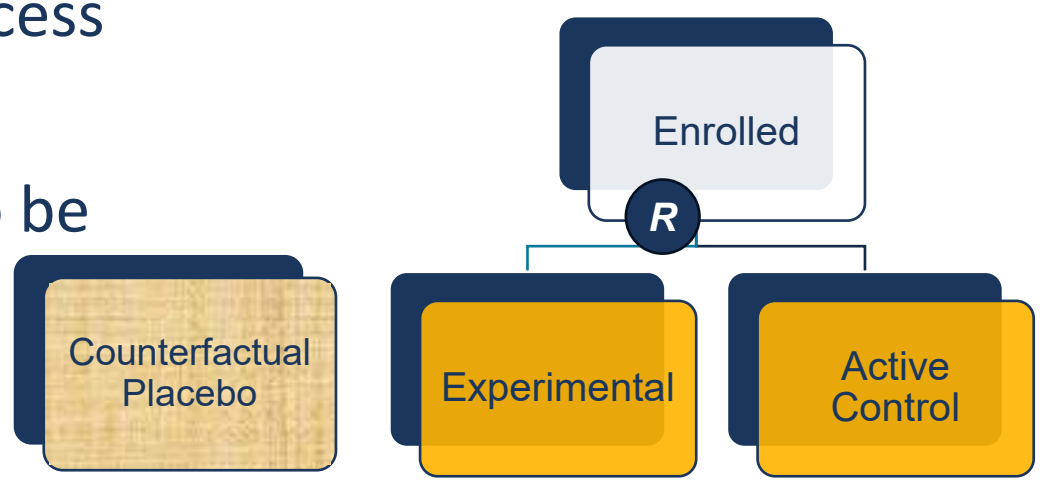
- Two arm RCT with Experimental and Active control, with planned placebo counterfactual

  Developed framework for three groups incorporating uncertainty and defined success criteria

  Is appropriate for a new agent expected to be highly effective

  Feasible in terms of sample size

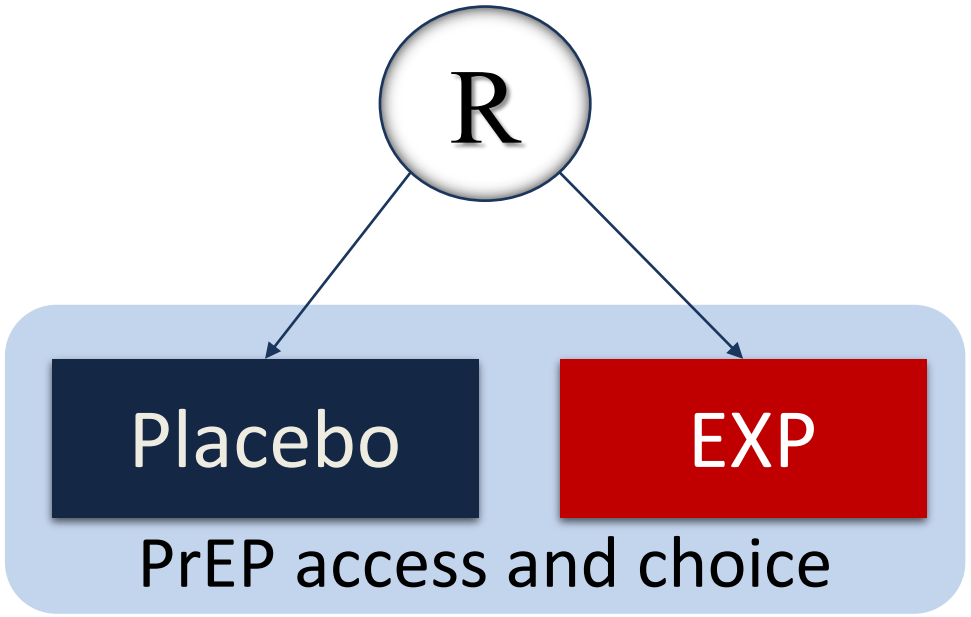
- Likely to be combined with other approaches to ensure adequate evidence for efficacy of experimental drug



Gao F, Janes H, Buchbinder S, Donnell D. Active-Controlled Trial Design for HIV Prevention Trials With a Counterfactual Placebo. Stat Med. 2025 PMID: 40042432.

Future design for vaccine and mAb

- AMP strategy



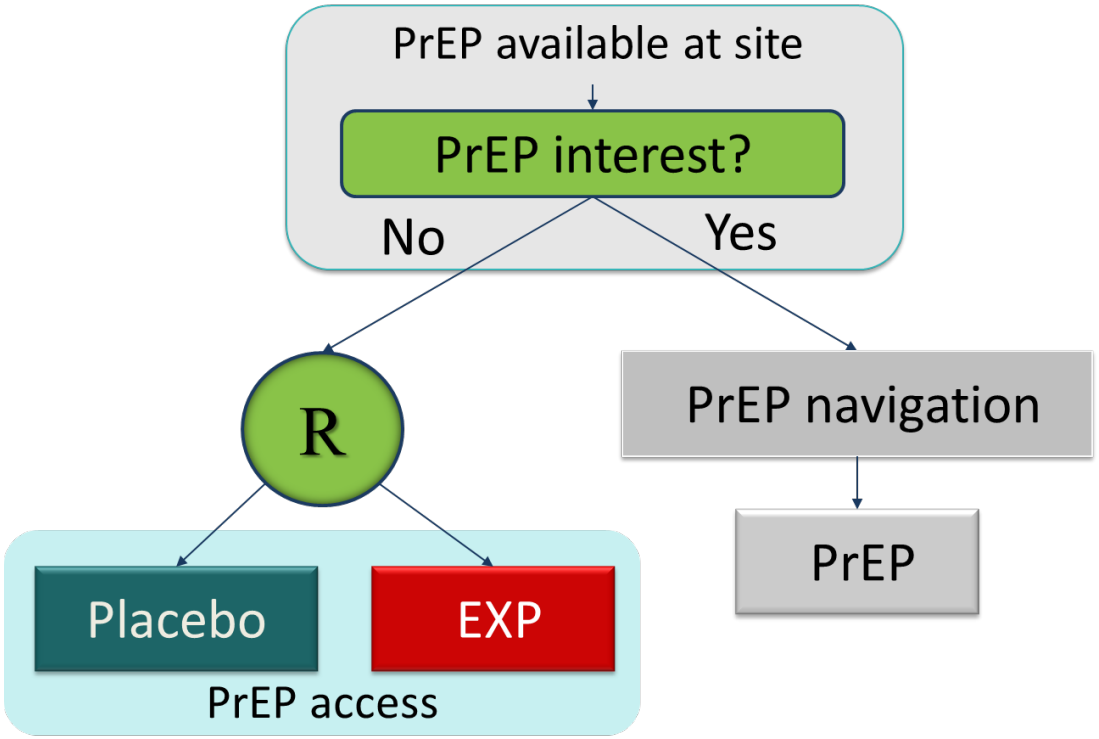
Not clear whether vaccines or mAbs will be as effective as current ARV-based prevention

PrEP choice of Injectable; FTC/TDF

- With high use, HIV risk may be substantially reduced
- With high PrEP use, trial answers 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

- Not yet widely available – hope this will change
- Unknown whether substantial number at risk will not use injectable PrEP

Approaches to Estimating Efficacy Relative to "Counterfactual" Placebo

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 may close e.g. if LEN/CAB replaced by oral FTC/TDF
- 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 high
- Trials of novel ARVs have used counterfactual placebo assessments planned
  - All include randomization to an active-control Standard
  - Statistical framework available for comparison of both Standard and Experimental with CF Placebo
  - Discussion with regulatory agencies ongoing

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Thanks

- Collaborations with statistical colleagues:
  - Fei Gao, Holly Janes, Elizabeth Brown
- HPTN network of scientific colleagues and friends
- UW Global Health: ICRC led by Connie Celum
- AVAC community consultations
- Forum for Collaborative Research