Reflections on use of counterfactual placebo in HIV prevention trial design

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Why consider counterfactual designs?

- Why do we have to consider counterfactuals?
- Parallels/bridge between NI designs and counterfactual placebo
- Statistical frameworks to retain scientific rigor
- Measurement of counterfactual placebo

HIV incidence in recent trials of HIV prevention

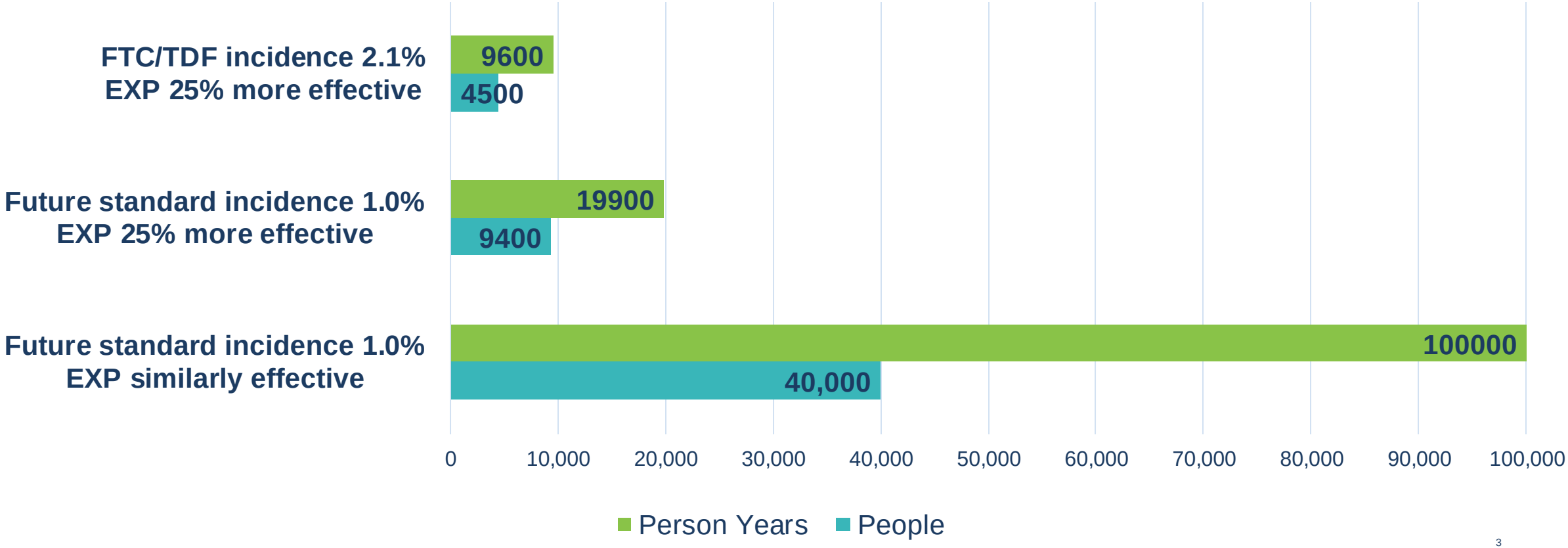
ACTIVE CONTROL	Countries	N enrolled	Number of infections	Incidence rate/100 PY	
				Experimental	Active ctrl (FTC/TDF)
DISCOVER (MSM)	Europe, UK, Canada and Untied States	5399	7 vs 16	0.16	0.34
HPTN 083 (MSM/TGW)	United States, Peru, Brazil, Argentina, Thailand, Vietnam, South Africa	4541	13 vs 39 (stopped early)	0.41	1.22
HPTN 084 (Women)	South Africa, Botswana, Eswatini, Zimbabwe, Malawi, Kenya, Uganda.	3224	4 vs 36 (stopped early)	0.20	1.86
PLACEBO CONTROL (FTC/TDF background use)				**Experimental**	**Placebo**
AMP MSM/TG (HVTN 704/HPTN 085)	United States, Peru, Brazil, Switzerland	2699 (3 arm)	28 & 32 vs 38	2.35	2.98
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
HVTN 702 (Men and Women)	South Africa	5404	138 vs 133	3.37	3.28

Sample size for fully powered non-inferiority trials

Decreasing number of infection events = Larger trials

Example: HPTN 083: Show CAB-LA is non-inferior to FTC/TDF in MSM+TG

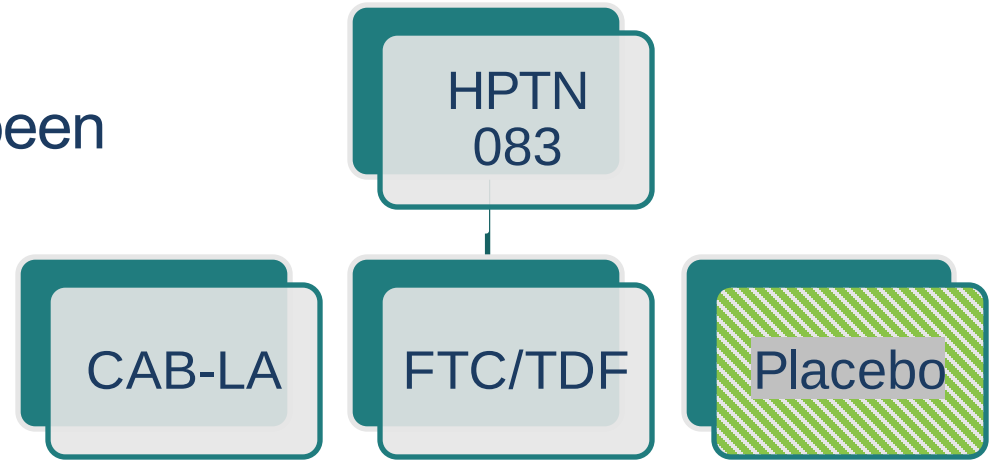
assuming CAB-LA is 25% better than FTC/TDF



- High risk to conduct a classical RCT if 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 cost very large $$
  - Large enrollments require expanding enrollment to lower risk populations

What other approach can we use?

- Estimate what the infection rate "would have been if (counter-to-fact) there had been a placebo"
  "Counterfactual placebo"



Conceptual framework of counterfactual placebo

Placebo: a substance with no therapeutic effect, made identical in appearance to experimental biologic, used as a control in testing new drugs.

Goal: Estimate the effect of an experimental biologic relative to a placebo, if, counter to fact, the trial had a randomized placebo arm

Characteristics of gold-standard placebo-controlled RCT design:

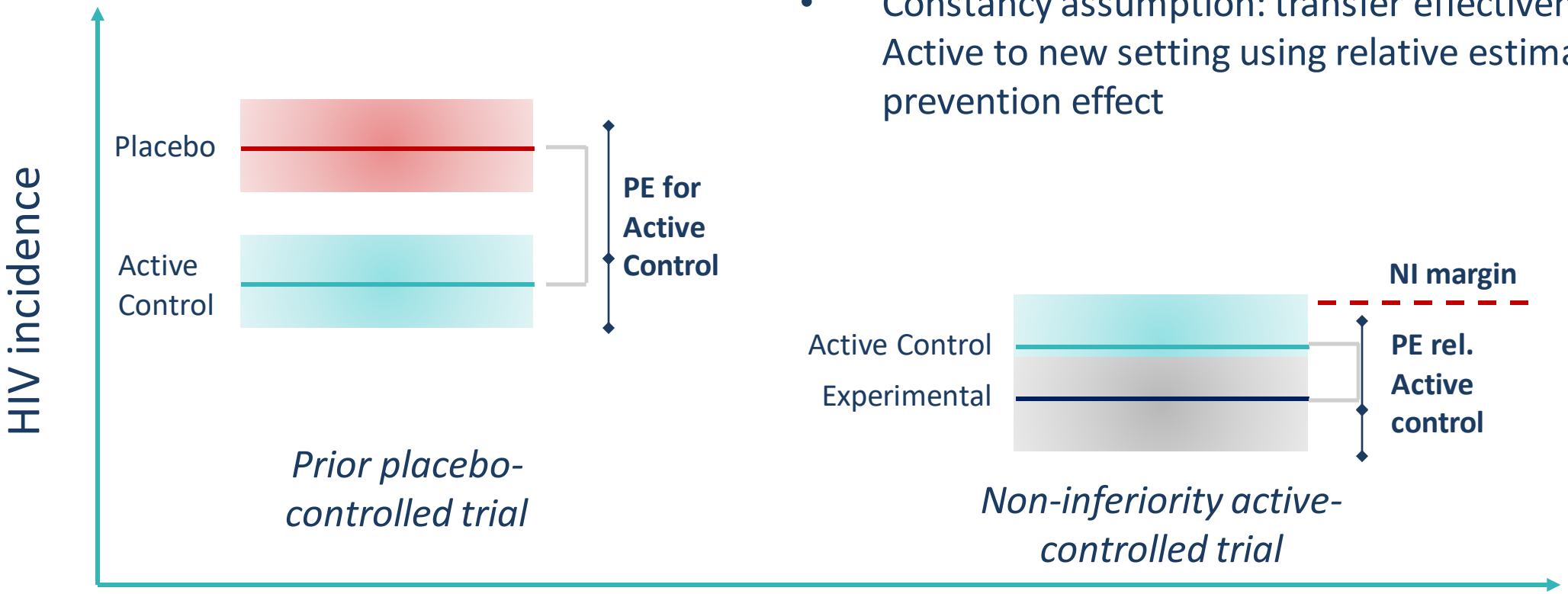
Within each group/arm:

- Expected balance wrt to measured and unmeasured confounders
- Same follow-up time distribution in each site
- Same background exposure risk

Bridge between non-inferiority and counterfactual designs

Superiority to Non-inferiority trial

- Constancy assumption: transfer effectiveness of Active to new setting using relative estimate of prevention effect



The non-inferiority trial design as the gold standard

1. Randomized – internal validity of Experimental versus established Standard (as active control)
2. Non-inferiority margin used to define success criterion for effectiveness

   The NI margin is based on prior placebo-controlled RCT results from an external trial

   No efficacy estimate relative to Placebo, only to Standard

   Accepted principles for this comparison

   A. **Constancy**: NI Margin should … account for bias or lack of reliability in the estimate of the effect of Standard

   B. **Effect preservation**: NI Margin should … achieve preservation of a percentage of the effect of Standard (e.g. 50%)

Implementation of these principles for NI

A. **Constancy**: Prevention effect of standard (A) compared to placebo (P) is constant in prior and future trials:

$$\log(\lambda_P) - \log(\lambda_A) = \log(\lambda_{P^0}) - \log(\lambda_{A^0}) \quad \left[\text{Equiv. } \frac{\lambda_P}{\lambda_A} = \frac{\lambda_{P^0}}{\lambda_{A^0}}\right]$$

- The NI trial is not done under the same conditions as the prior trial
- The effect in the prior trial is subject to measurement uncertainty

Implement: Use conservative estimate of (relative) effect from placebo-controlled trial(s):

$$\log \widehat{\lambda}_{P^0} - \log \widehat{\lambda}_{A^0} < z_\alpha \sigma_{PA^0}$$

B. **Success Criterion**: NI Margin should … achieve preservation of a percentage of the effect of Standard (e.g. 50%)

- The experimental arm (E) must be "not unacceptably worse" than Standard:
- 95-95 formulation of the NI-margin (δ) with preservation of effect (γ) defines NI margin

$$\delta = (1-\gamma)\left(\log \widehat{\lambda}_{P^0} - \log \widehat{\lambda}_{A^0} + z_\alpha \sigma_{PA^0}\right)$$

Statistical Framework for Counterfactual placebo design

Constancy assumption and preservation of effect motivates a formulation of a counterfactual hypothesis based on measurement of placebo, active and experimental:

$$\mathrm{K_o}: \frac{\log(\lambda_P) - \log(\lambda_E)}{\log(\lambda_P) - \log(\lambda_A)} \leq \gamma \text{ vs. } \mathrm{K_a}: \frac{\log(\lambda_P) - \log(\lambda_E)}{\log(\lambda_P) - \log(\lambda_A)} > \gamma$$

Fei Gao

$\lambda_P, \lambda_A, \lambda_E$ HIV rates in future placebo, active control and experimental
$\lambda_{P0}, \lambda_{A0}$ HIV rates from previous placebo-controlled trial

Assumed Future Trial Experimental Context

- Randomized trial with experimental and active-control arm(s)
  - Internal validity of direct causal comparison λ_A, λ_E
- "Counterfactual placebo" measured in context of prior/current RCT
  - High quality ascertainment of incidence or effect λ_P
  - High quality measurement of cohort characteristics (needed b/c not-randomized)
- Trial goal to reliably establish sufficient evidence from:
  - Active control group satisfies constancy:

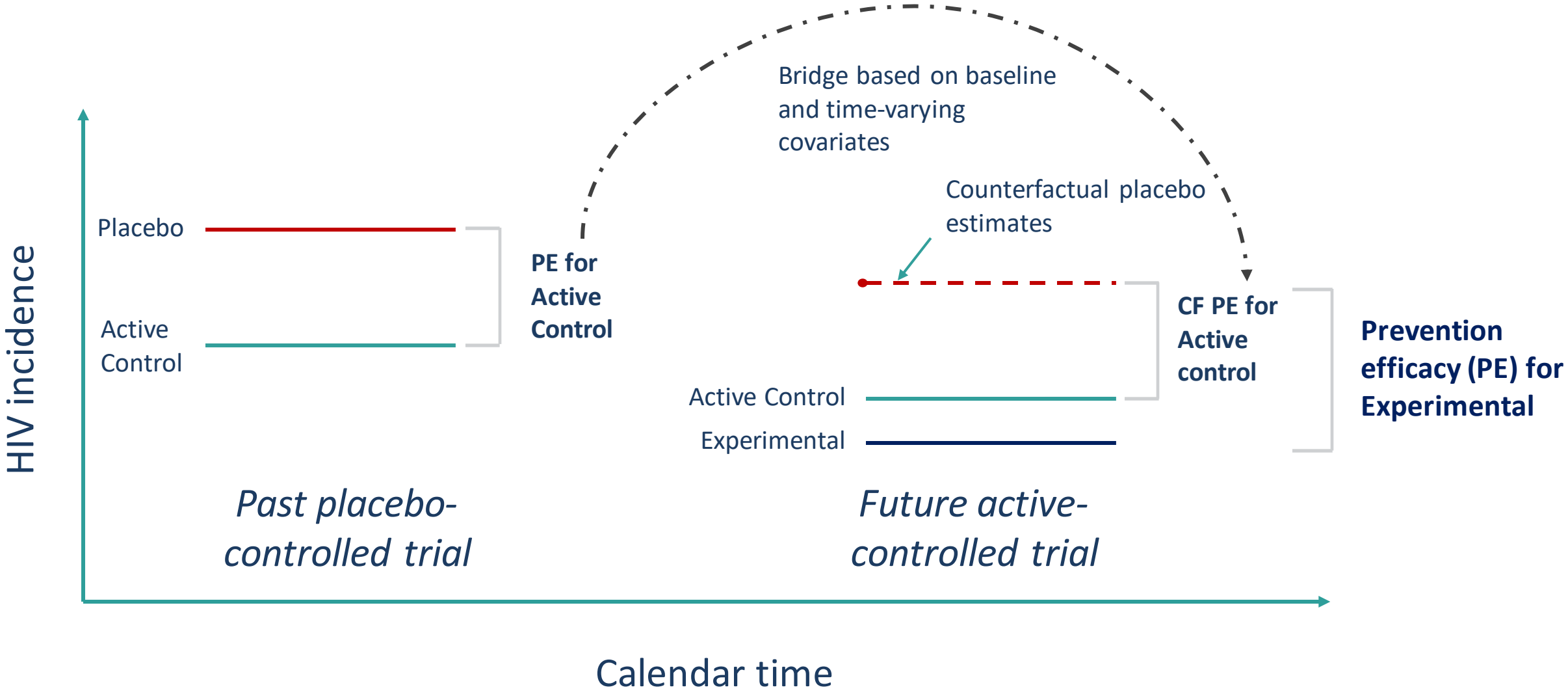
$$\log(\lambda_P) - \log(\lambda_A)$$

  - Experimental and active-control groups have "similar" infection rates:

$$\log(\lambda_E) - \log(\lambda_A)$$

  - Experimental (and active-control) groups have lower infection rates than "placebo

$$\log(\lambda_P) - \log(\lambda_E)$$


Bridge based on baseline and time-varying covariates
Counterfactual placebo estimates
Placebo
Active Control
PE for Active Control
Active Control
Experimental
CF PE for Active control
Prevention efficacy (PE) for Experimental
HIV incidence
Past placebo-controlled trial
Future active-controlled trial
Calendar time

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Approaches to estimating efficacy relative to “Counterfactual” placebo

Approaches under investigation

1. Bridging from contemporary “placebo” data
   - Registrational Cohort/Post trial access data – same participants
   - Placebo data from external trials – different participants
2. Cross-sectional incidence assessed during screening for enrollment in “untreated” participants
3. Bridging active control efficacy using adherence-efficacy relationship of active control
4. Assessing placebo risk using reliable predictors of HIV exposure risk

Counterfactual efficacy using external trials

Counterfactual study	CAB-LA Incidence	Counterfactual Placebo Incidence	Efficacy of CAB-LA versus Placebo (95% CI)
Five Country (AMP Women)	0.19	2.62	**93% (76%-98%)**
Three Country (ECHO)	0.23	4.47	**95% (79%-99%)**
South Africa (HVTN 702 Vaccine)	0.28	4.21	**93% (73%-98%)**

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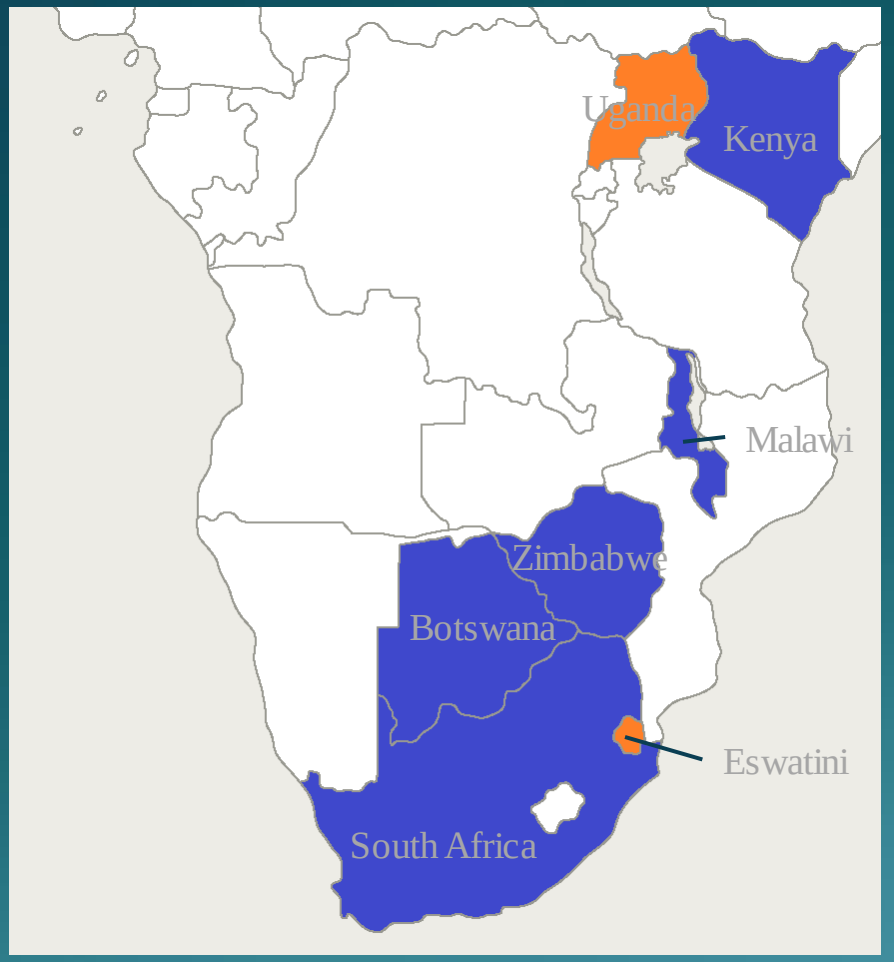

Summary

- Trials of novel ARVs are proceeding with counterfactual placebo assessments planned
  - All include randomization to an active-control Standard
  - Comparison of both Standard and Experimental with CF Placebo are available; non-randomized assessment with CF placebo appears primary
- Statistical frameworks to better understand assumptions and study performance are under development
- It is not clear (to me) if standards to “establish effectiveness” amongst placebo, active and experimental “arms” have yet been defined.
- Data from completed trials are available for testing different potential approaches to bridging
- Attention to appropriately protect against uncertainty of constancy-type assumptions and understand veracity of effectiveness are needed

THANK YOU

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