Deborah Donnell Fred Hutchinson Cancer Center, Seattle

Next Gen HIV Prevention Research: Clinical trials in an era of highly effective standards of care

HPTN HIV Prevention Trials Network

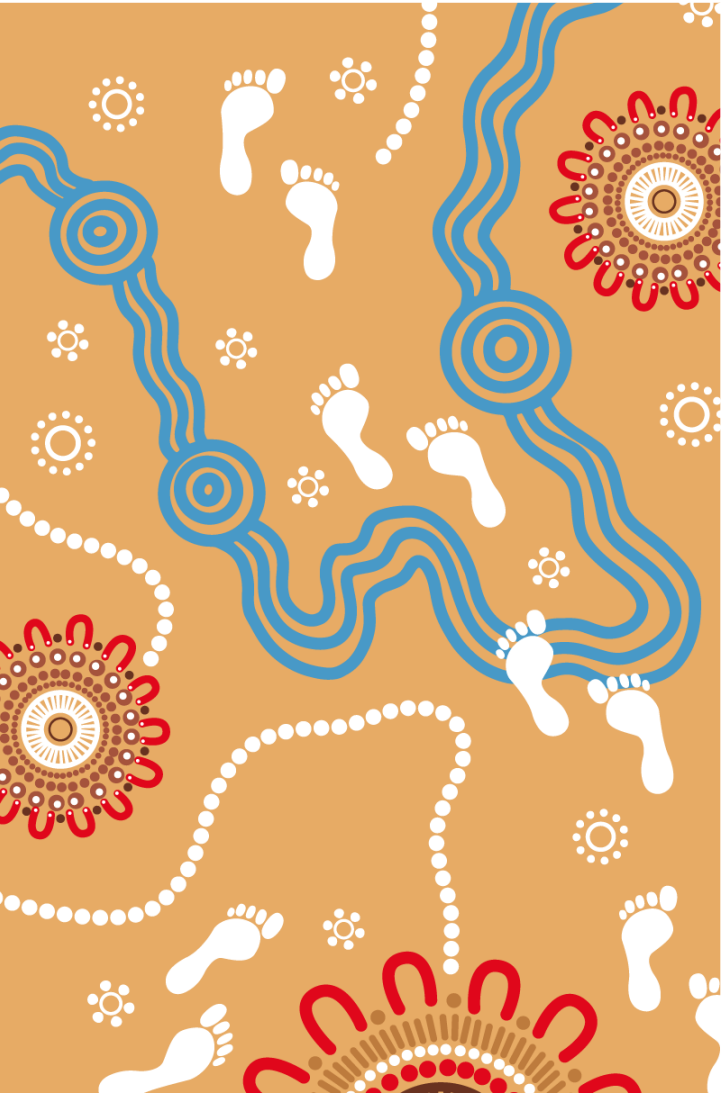
The counterfactual approach: Tools and data sources available for prevention trials

IAS 2023

IAS 2023

Summary

HPTN HIV Prevention Trials Network



What is your main question?

We already have biomedical tools that can prevent 75-90% of HIV infections. How can we conduct trials of new prevention tools, such as vaccines, new ART-based prevention and monoclonal antibodies?

What did you find?

Classical randomized clinical trials that compare an experimental drug against highly effective existing prevention, would require VERY large trials. Instead we could plan trials that estimate HIV infection rates for a "counterfactual placebo", i.e., infection rates without using biomedical prevention.

Why is it important?

Counterfactual approaches to experimental products offer a path to licensing new prevention tools.

The counterfactual approach explained

IAS 2023

- Why consider counterfactuals?
- What do we mean by placebo?
- Parallels/bridge between NI design and counterfactual placebo
- Measurement of counterfactual placebo

HIV incidence with highly active prevention

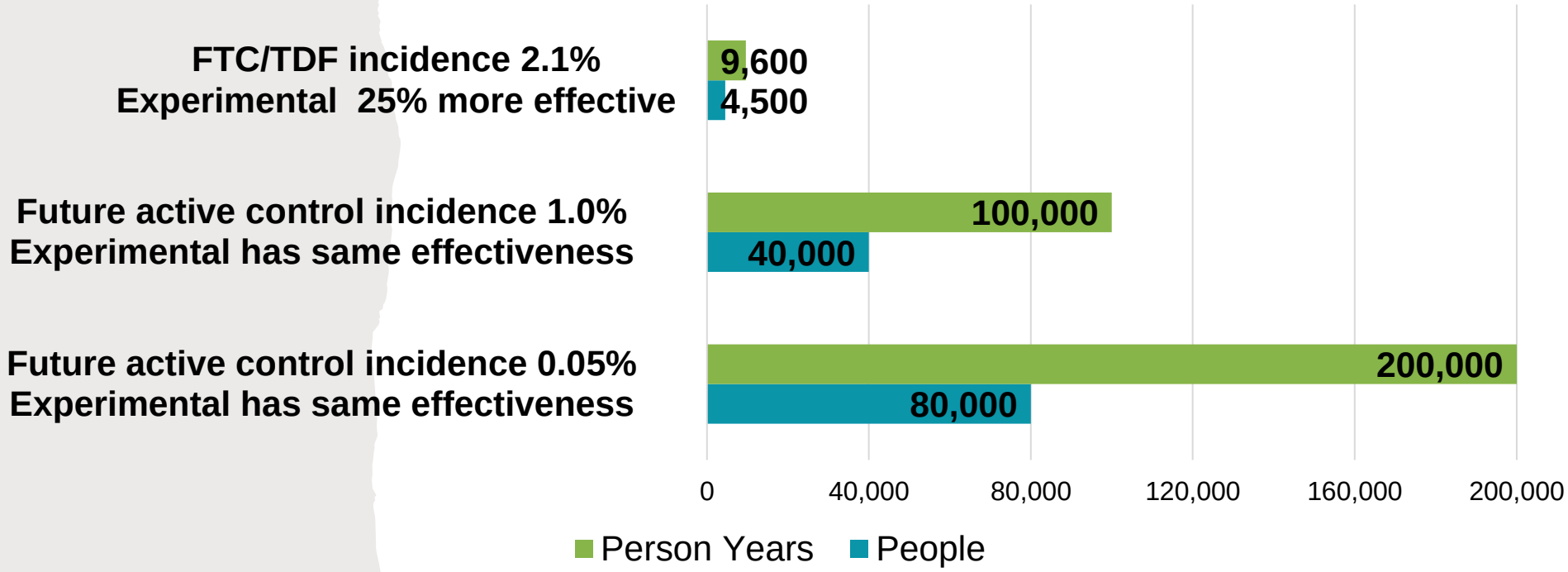
ACTIVE CONTROL	Countries	N enrolled	Number of infections	Incidence rate/100 PY	
				Experimental	Active ctrl (FTC/TDF)
DISCOVER (MSM)	Europe, UK, Canada and Untied States	5399	7 vs 16	0.16	0.34
HPTN 083 (MSM/TGW)	United States, Peru, Brazil, Argentina, Thailand, Vietnam, South Africa	4541	13 vs 39 (stopped 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 randomized trials with highly active control

Illustration: HPTN 083

Goal: Establish CAB-LA is non-inferior to FTC/TDF in MSM+TG

- ***Assumed CAB-LA is 25% better than FTC/TDF***
- ***Assumed FTC/TDF modestly effective***



IAS 2023

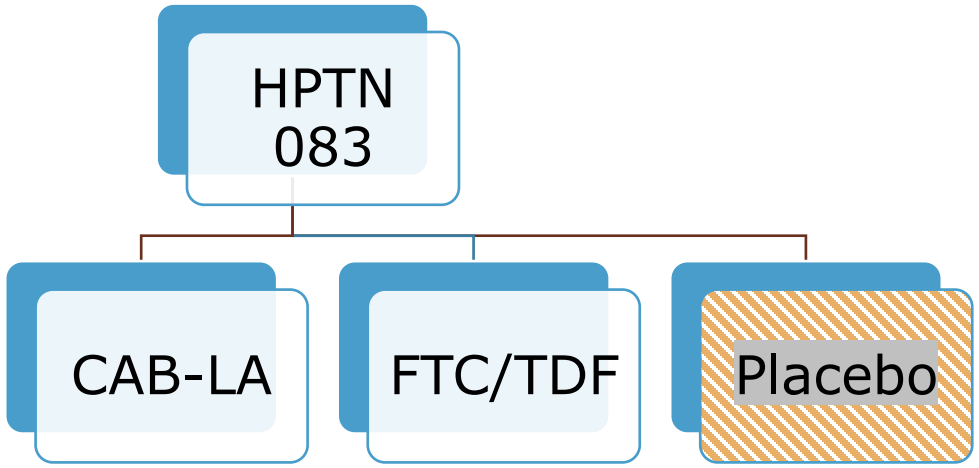
High risk to conduct a classical non-inferiority RCT if incidence rates are below 1/100 person years

- Expect low rates in active arm 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"



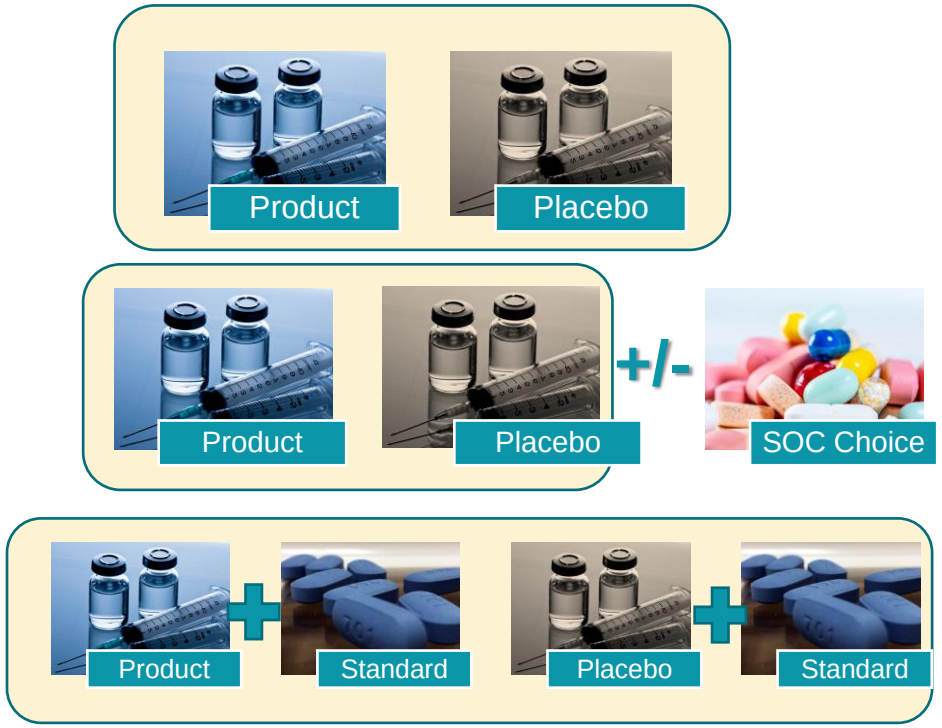
Conceptual selection of “placebo estimand” in study design

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

1. Replacement Placebo
   - Use case: the experimental agent intended to replace an agent

2. Placebo layered with “real world” use of biomedical prevention
   - Use case: experimental can be used with other agents

3. Placebo in combination with other biomedical prevention
   - Use care: Experimental and active agents intended to be used together



Use of placebo in future studies

From “WHO Expert consultation on the use of placebos [in vaccines]” (2013)

- *“Ethics guidance have uniformity on the use of placebos, i.e. that if a proven effective [intervention] exist, the trial [intervention] should generally be tested against it.”*
- *“…must be compelling methodological reasons for the use of placebos, e.g. if using the effective [treatment] as a comparator would not yield scientifically valid results”*
- *“Use of placebos is clearly unacceptable when an effective intervention exists and is currently accessible in the public health system of the country in which the trial is planned”*
- *“A new (low-cost) biologic is being tested against a placebo, because while the existing biologic is known to be effective in the trial country, it is inaccessible to most of the population and is likely to remain so in the future.”*

Challenging ongoing discussion for mAb and vaccines

The intent of the ongoing work on the counterfactual placebo approach:

1. Avoids the use of placebo, as a matter of principle
2. While yielding scientifically valid results.

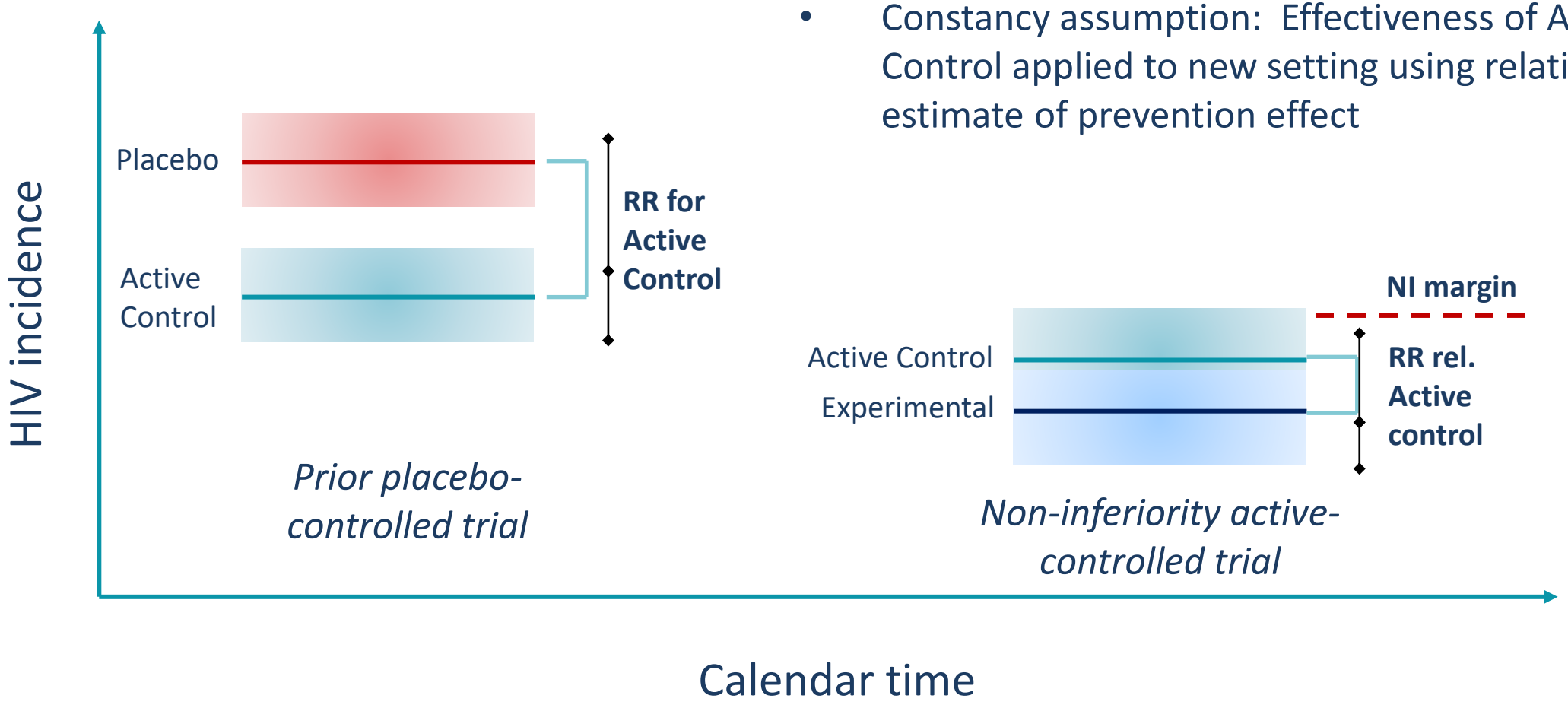
Framework of counterfactual replacement placebo

Goal: To estimate the absolute efficacy of the new product as if we had a placebo arm

- Characteristics of gold-standard placebo-controlled RCT design:
  - For each group/arm
    - Expect balance wrt to measured and unmeasured confounders
    - Same follow-up time distribution in each site
    - Same background exposure risk

- Counterfactual placebo design
  - Randomize participants to active control vs experimental product
  - Include planned estimation(s) of HIV infection rate without biomedical prevention

Active-controlled non-inferiority trial

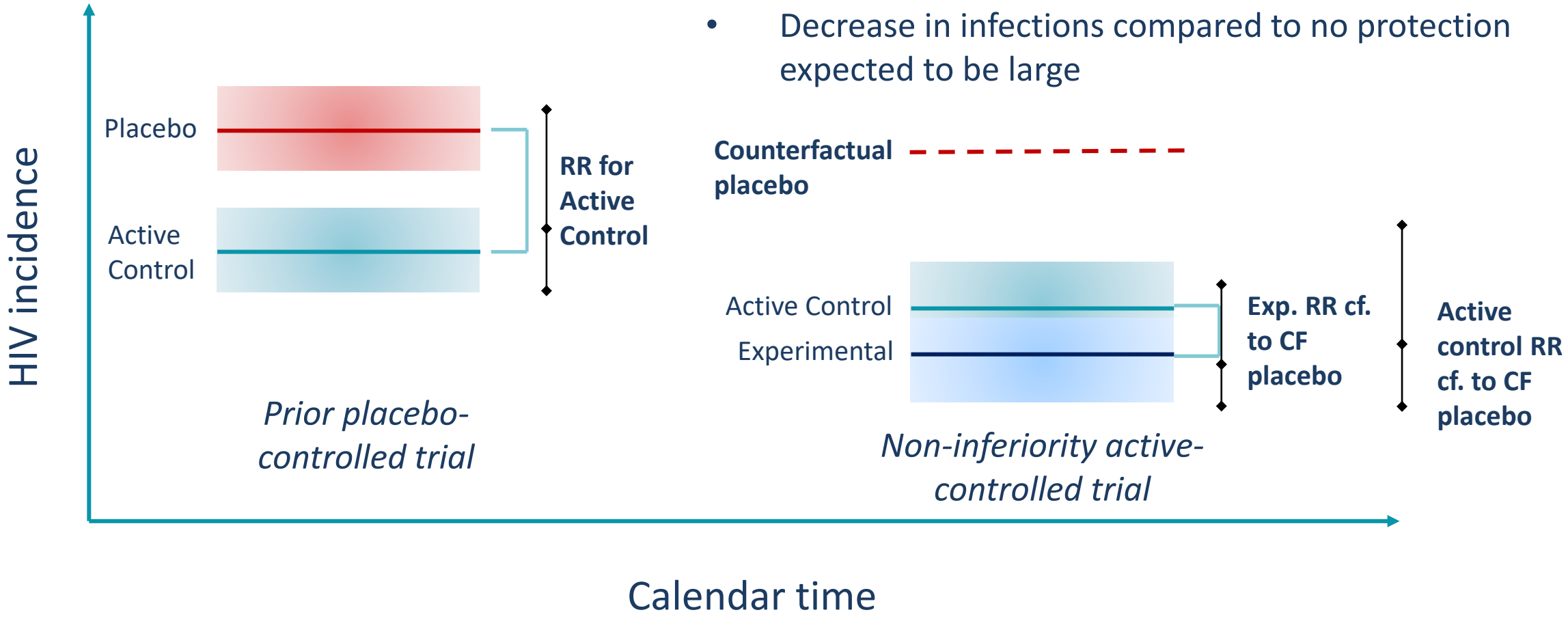


- Constancy assumption: Effectiveness of Active Control applied to new setting using relative estimate of prevention effect

RR = Relative risk

Active-controlled trial with placebo counterfactual

- Infections on active control expected to be too small to achieve statistical accuracy
- Decrease in infections compared to no protection expected to be large



Tools and data to measure counterfactual placebo

- Placebo incidence rates from external trials or cohort
  - Counterfactual efficacy using external concurrent trials (JIAS Donnell 2023)
  - Registrational cohort (PrEP VACC trial)
  - “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products” (Draft Guidance 2023)
- Recency assay estimate of incidence
  - Estimate the incidence rate in eligible population during screening
- Assess efficacy of active control based on adherence in trial
  - Need model predicting efficacy based on adherence
  - Model available for TDF/FTC; not yet for CAB-LA (Glidden JIAS 2021, Anderson CID 2023)
- Assess counterfactual incidence based on biomarker of exposure
  - Need model predicting HIV based on biomarker of exposure (e.g. STI rates)

What are the cautions with using a counterfactual?

- Do not have protection of randomization
  - Estimates need to be corrected for characteristics of cohort related to HIV incidence
- Efficacy estimates intrinsically less statistically reliable
  - Replication (multiple trials) remain important
  - Strong and consistent absolute efficacy results needed
- Ecological trends in HIV incidence
  - Risk of bias in counterfactual efficacy estimates (both high and low)
  - PrEP use and increased ARV treatment may decrease incidence over time
- Experimental products with modest efficacy may not advance
  - Observation of more infections on experimental than (highly) active control may lead to early termination

Summary

- Valid counterfactual placebo estimates offer feasible trials yielding scientifically valid results without continued use of placebo
- Trials of novel ARVs are proceeding with counterfactual placebo assessments planned
  - All use randomization to an active-control standard
- Statistical frameworks to better understand assumptions and study performance are under development. Important to
  - Appropriately protect conclusions against uncertainty of estimates
  - Characterize veracity of effectiveness (sensitivity analyses)
- Data from completed trials are testing different potential approaches to counterfactual-based estimates
- Gaining experience from field-testing placebo counterfactual measures

Thank you

Deborah Donnell
deborah@fredhutch.org

| @HIVptn

HPTN
HIV Prevention Trials Network