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Estimating HIV incidence in the era of long-acting PrEP

HPTN HIV Prevention Trials Network

Novel scientific approaches for establishing efficacy of new biologics in the era of long-acting PrEP

IAS 2023

23 – 26 July · Brisbane and virtual

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Summary

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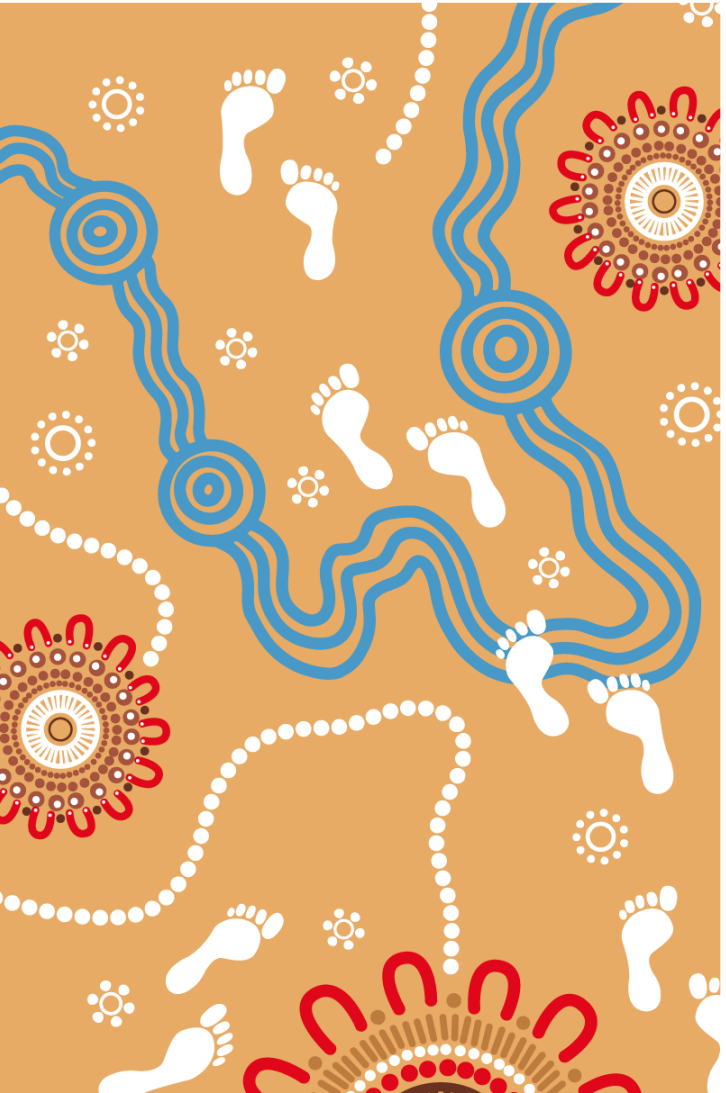

What is your main question?

We have multiple ARV-based forms of HIV protection, most recently an injection of cabotegravir every 8 weeks that prevents 90% of HIV infections in both men and women. With such effective prevention available, how will we approach future testing of potential HIV vaccines or other novel biologics?

What did you find?

When novel biologics are also expected to be highly effective, a potential strategy is to estimate the infection rate we would have expected if no product were used, using a "counterfactual placebo" strategy. Several ways to estimate this placebo counterfactual rate are available and being evaluated.

Why is it important?

We need to ensure that we have reliable evidence of the effectiveness of novel products, even as we have multiple proven choices available for HIV prevention

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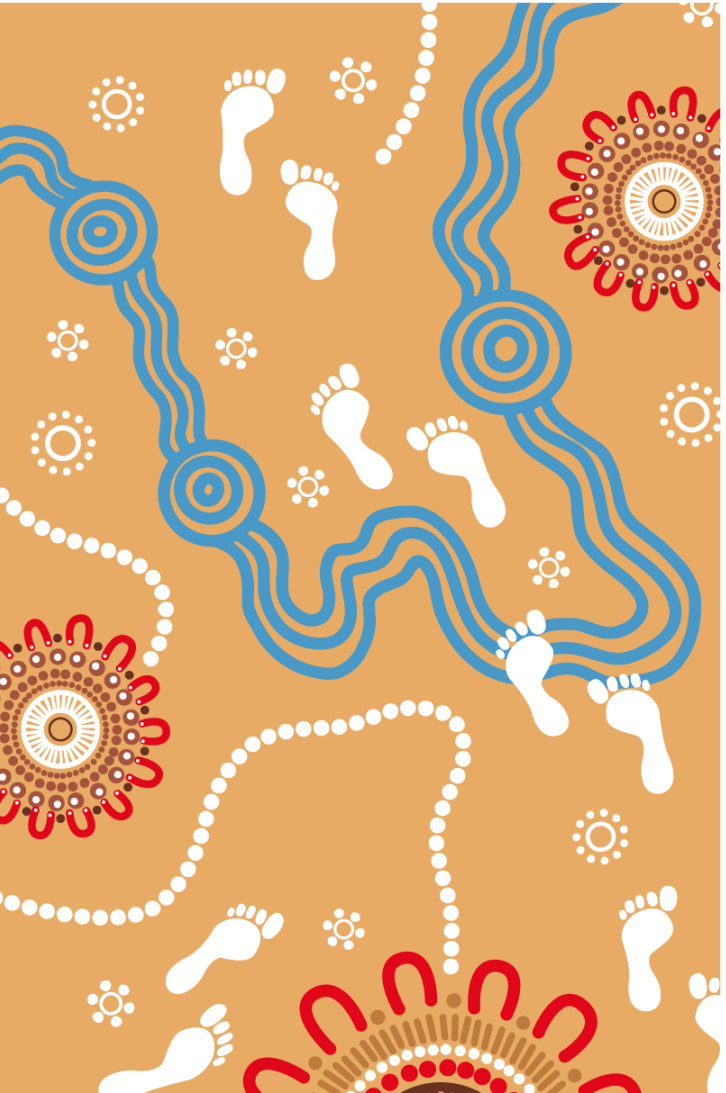


No effective biomedical prevention

- No effective biomedical prevention

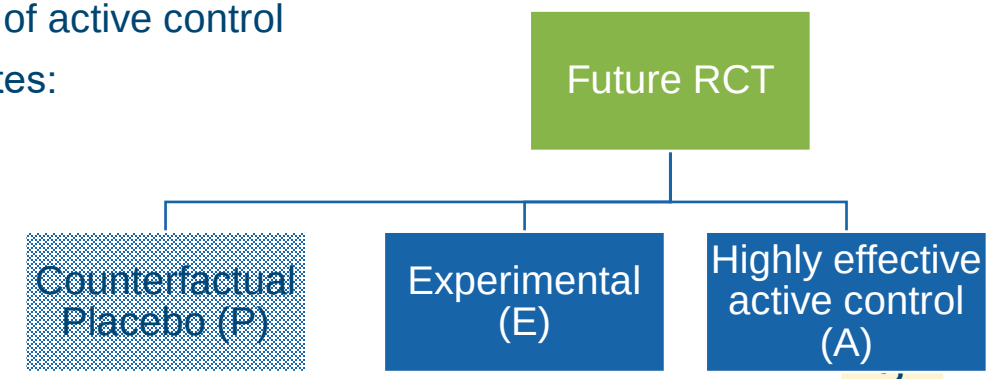
Potential Future Trial Experimental Context

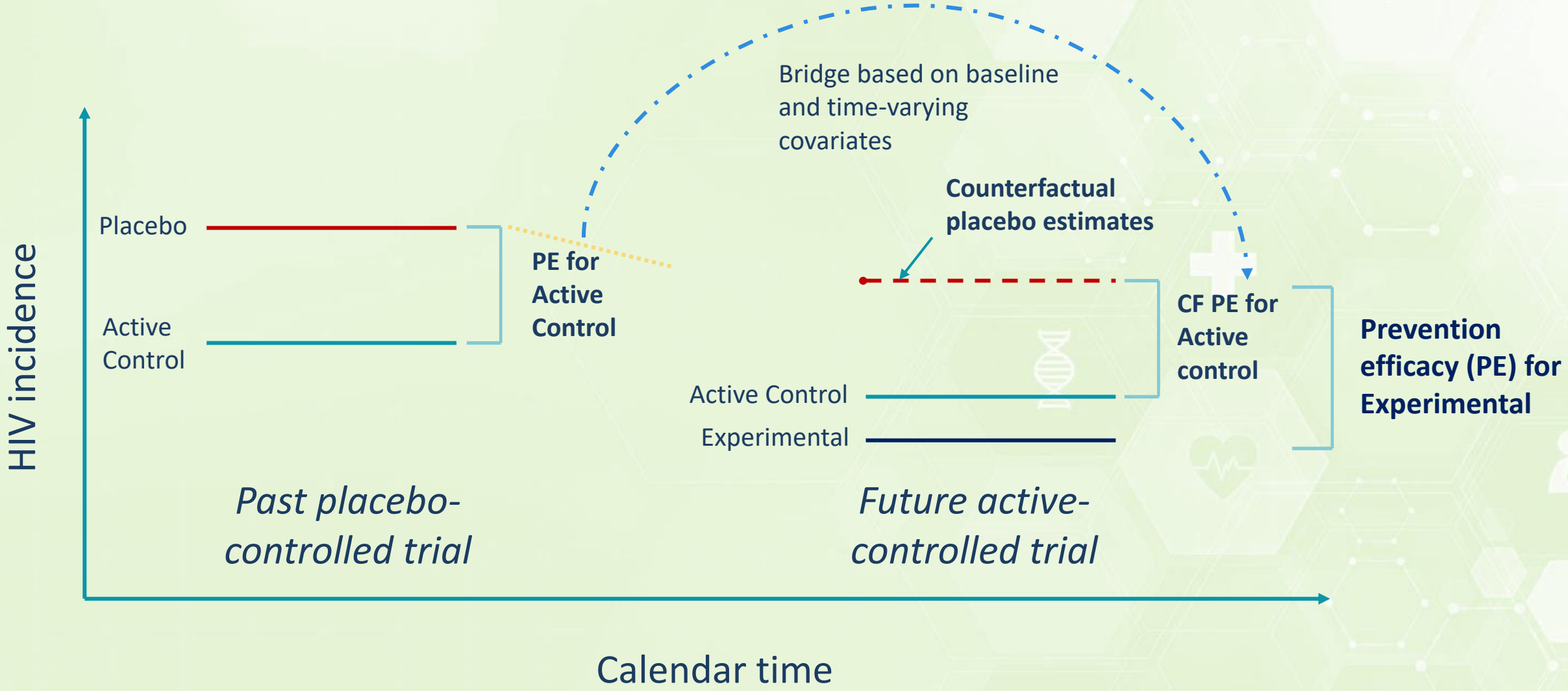
- Randomized trial with experimental (E) and active-control arm (A)
  - Active-control highly effective (75-90% prevention efficacy)
  - Internal validity of direct comparison of incidence rates: λ_A, λ_E
- Additional information contributed by "counterfactual placebo" applied to context of prior/current RCT
  - High quality estimate of HIV incidence without biomedical prevention (λ_P) and/or high quality estimate of active control effectiveness $(\frac{\lambda_A}{\lambda_P})$
  - High quality measurement of cohort characteristics (needed b/c not randomized)
- Trial goal to reliably establish sufficient evidence of effectiveness of experimental from:
  - Active control is preventing HIV infection in the trial

    $\log(\lambda_P) - \log(\lambda_A)$ demonstrates known prevention effect of active control
  - Experimental and active-control groups have "similar" infection rates:

    $\log(\lambda_E) - \log(\lambda_A)$
  - Experimental group has 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

Novel estimands utilizing the counterfactual placebo

- Traditionally, HIV prevention active-control trials use
  - Rate Ratio: $\frac{\lambda_E}{\lambda_A}$ or $\log(\lambda_E) - \log(\lambda_A)$ or
  - Rate difference: $\lambda_E - \lambda_A$
- Alternative estimands under consideration
  - Averted Infection Ratio: $\frac{\lambda_P - \lambda_E}{\lambda_P - \lambda_A}$ *(Dunn, Glidden)*
    - selected for the F/TAF vs TDF/FTC question in the PrEP VACC trial
  - Placebo counterfactual NI: $\frac{\log(\lambda_P) - \log(\lambda_E)}{\log(\lambda_P) - \log(\lambda_A)}$ *(Gao)*
    - Direct connection to NI design justification

λ_P, λ_A, λ_E HIV rates in future placebo, active control and experimental

Approaches to estimating efficacy relative to “Counterfactual” placebo

Approaches to estimating efficacy relative to "counterfactual" placebo

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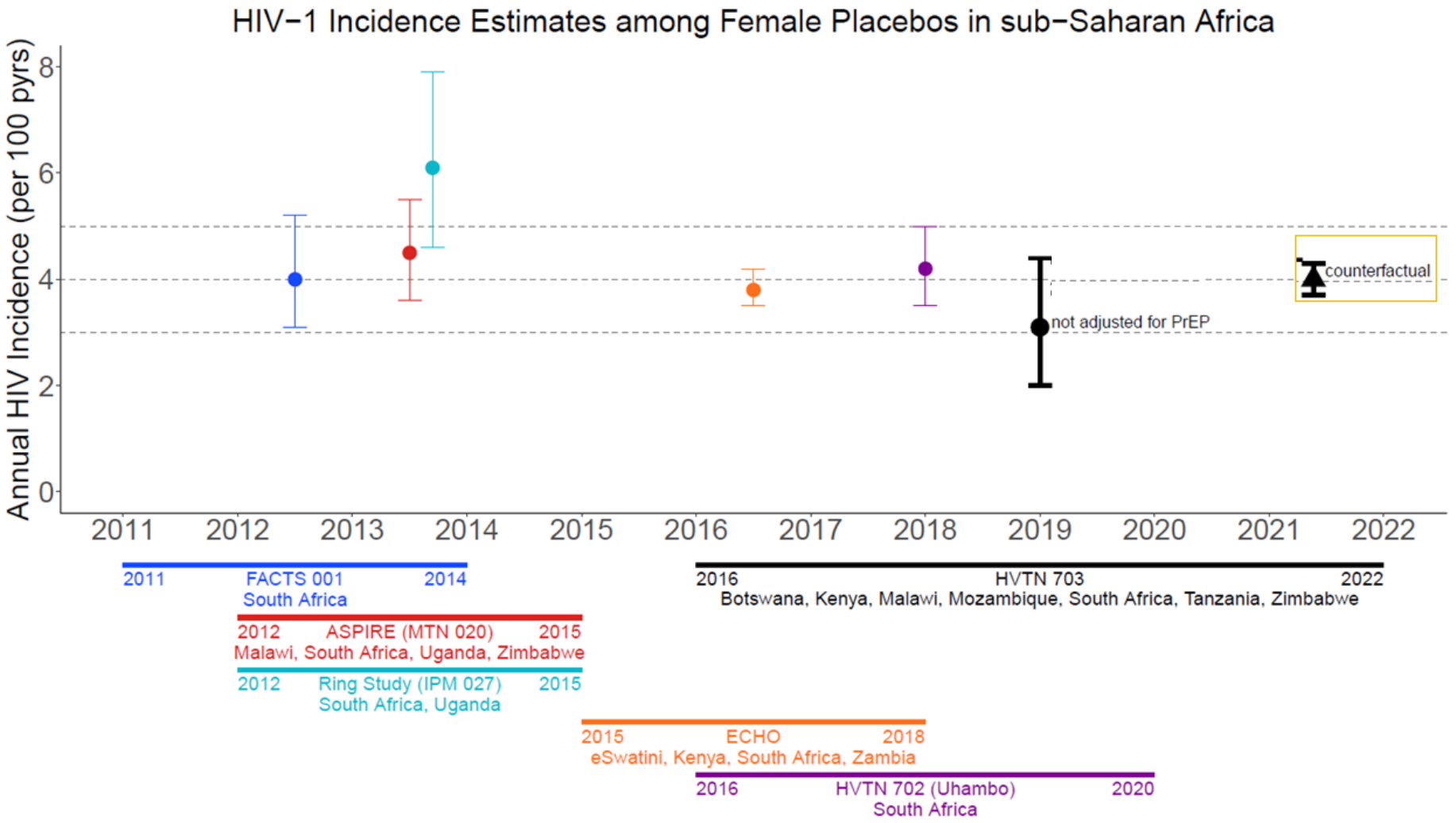
Estimate counterfactual placebo incidence rate

1. Placebo data from external trials
2. HIV incidence in registrational cohort *[Eugene's talk]*
3. Cross-sectional incidence assessed using recency assay during screening for enrollment in "untreated" participants [*Moupali's talk*]
4. Estimating placebo incidence using reliable predictor(s) of HIV exposure risk

Estimate efficacy of active control to counterfactual placebo

5. Using adherence-efficacy relationship of active control
6. Using immune biomarkers of effective vaccine/mAb as mediators of prevention efficacy (monoclonal Ab and vaccine)

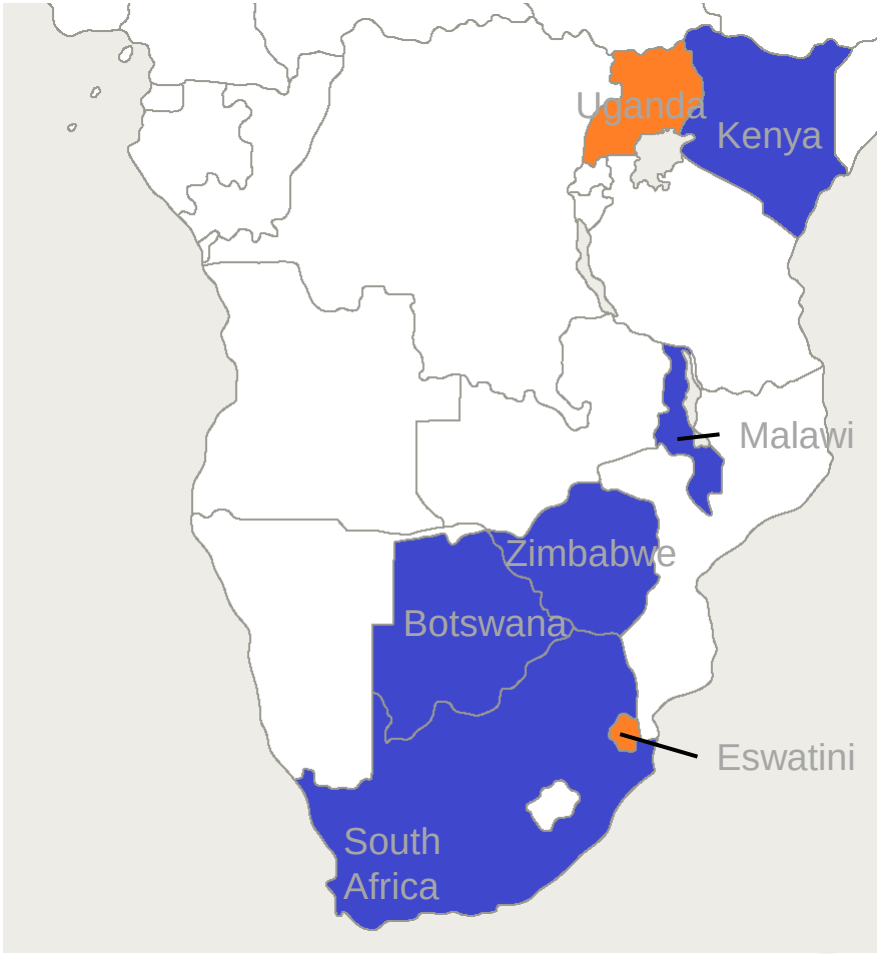
1. Historical data by specific population



1. Counterfactual efficacy using external trial data

IDEA: HIV incidence data from other trials in the same regions and population remains a valid estimate of current HIV incidence

Counterfactual study	CAB-LA Incidence	Counterfactual Placebo Incidence	Efficacy of CAB-LA versus Placebo (95% CI)
Five Country (HVTN 703)	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%)**



JIAS 2023, Donnell

4. Estimating HIV incidence using biomarker of exposure (e.g. Rectal GC)

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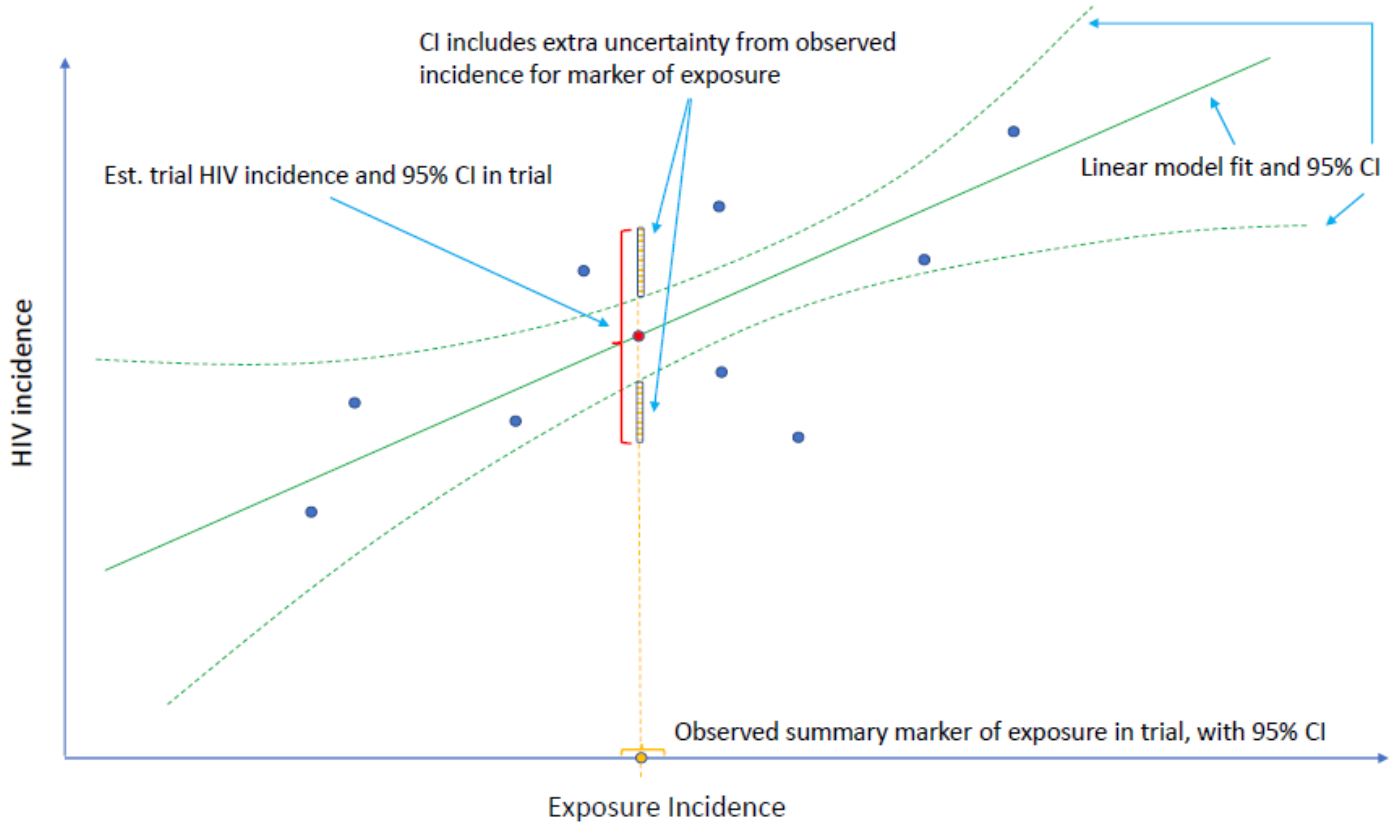
IDEA: Biomarker of sexual exposure can be used to estimate HIV exposure and risk of HIV infection



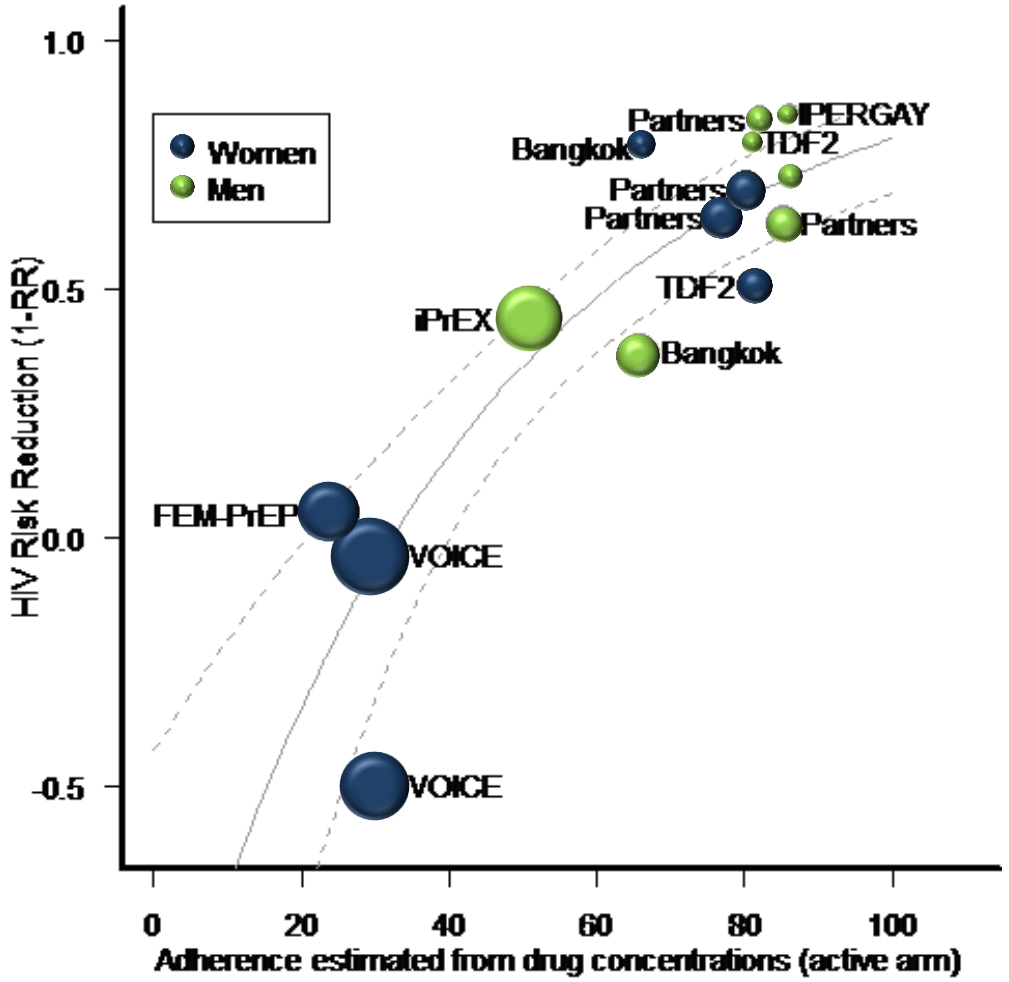
Assumptions

- Multiple placebo-controlled trials with HIV incidence and exposure biomarker,
- Relationship between placebo HIV incidence and exposure biomarker holds across trials
- Biomedical intervention in future trials does not affect exposure biomarker

Clinical trials, Zhu, under revision

5. Counterfactual efficacy: adherence-efficacy relationship of active control

IDEA: Adherence biomarker of active control in future used to estimate its effectiveness in trial population



Assumptions

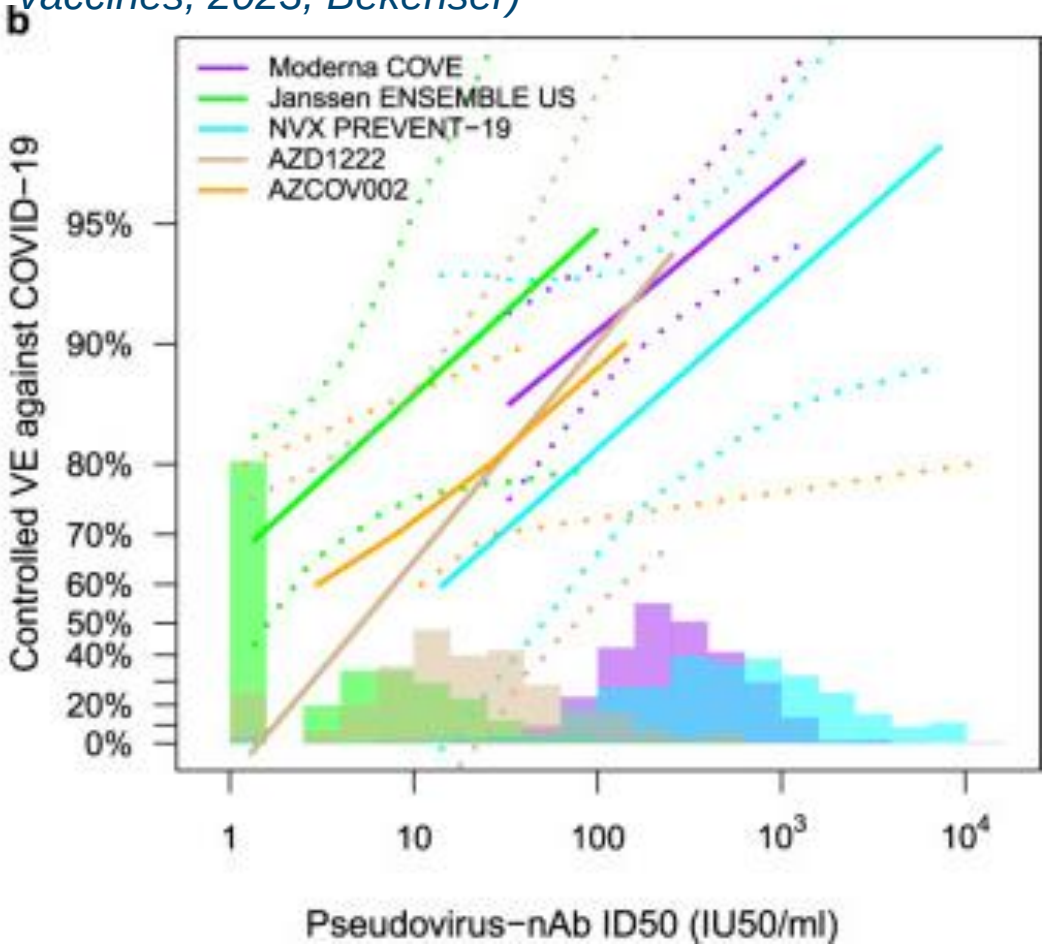
- Adherence biomarker accurately estimates the active control prevention efficacy;
- Adherence-efficacy dose-response association holds across the historical and active-controlled trials
- Same biomarker used in all trials

Glidden, 2012, JIAS

6. Establish an immune correlate/mediator of protection (vaccine/mAb)

IDEA: Immune biomarker of future vaccine used to estimate its effectiveness in trial population

- Correlates of protection for COVID-19 vaccines *(Nature vaccines, 2023, Bekenser)*



Assumptions

- Multiple placebo-controlled trials of successful vaccine that establish an immune marker
- Immune marker applies to new intervention
- Subsequent vaccine approval commonly based on validated immunological marker surrogate endpoints

Conclusions

- Long-acting PrEP, when readily available and widely used, will create a challenge for assessing the prevention efficacy of new products
- Efficacy estimates based on counterfactual placebo approach offers a path forward
  - FDA “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products” (Draft Guidance 2023)
  - Careful and thoughtful engagement with regulators, clinical trialists, biostatisticians, community stakeholders needed to ensure we have a variety of highly effective, readily available and widely used biologics

Thank you

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