# Utilizing a “Counterfactual Placebo” to Establish Efficacy of Novel HIV Prevention Agents

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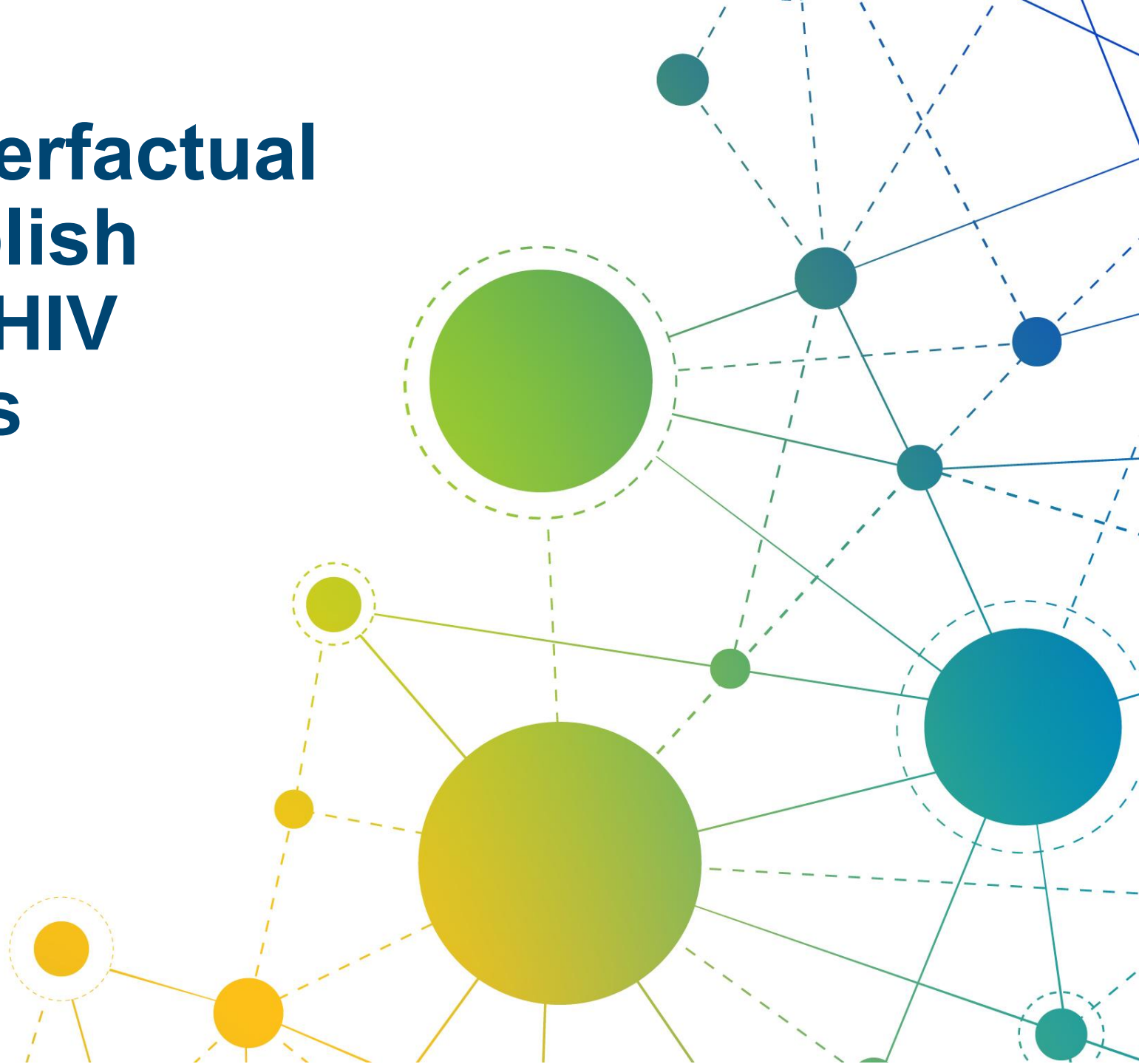

HPTN Annual Meeting

# Presentation Highlights

1. What is the main issue or question the presentation addresses?
   - Traditional designs for efficacy trial may not be feasible in evaluating novel HIV prevention agents, given current landscape for HIV prevention.
2. What is the key finding or ‘takeaway message’?
   - Active-controlled trial augmented by a “counterfactual placebo” may be conducted to evaluate efficacy of an experimental HIV prevention agent with a reasonable sample size.
3. How does the research advance HIV prevention efforts?
   - An efficacy trial is necessary to establish the efficacy of a novel HIV prevention agent and to lay the foundation for ultimate licensure of future HIV prevention products.

# Efficacy of Novel HIV Prevention Agents

HPTN HIV Prevention Trials Network

- The past decade has seen tremendous progress in the development of biomedical agents that are effective as pre-exposure prophylaxis (PrEP) for HIV prevention.
  - Oral PrEP: TDF/FTC, F/TAF
  - Long-acting injectable PrEP: CAB-LA
- For evaluation of new HIV prevention agents, current designs may not be feasible.

# Trial Design for Evaluating Efficacy of Novel HIV Prevention Agents

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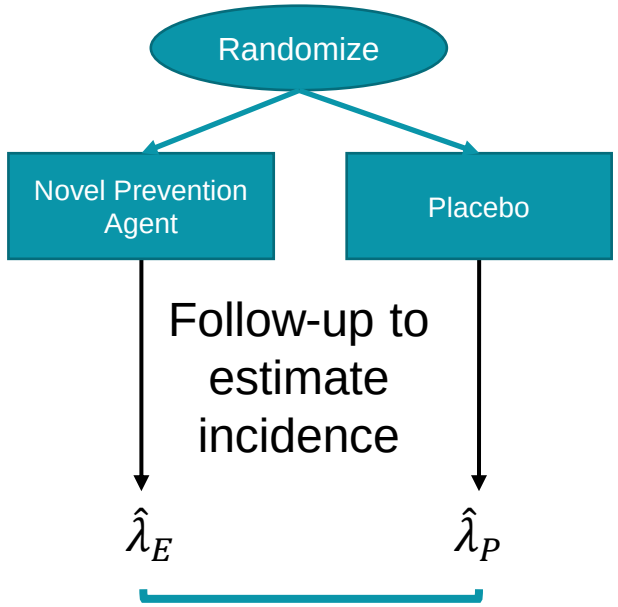
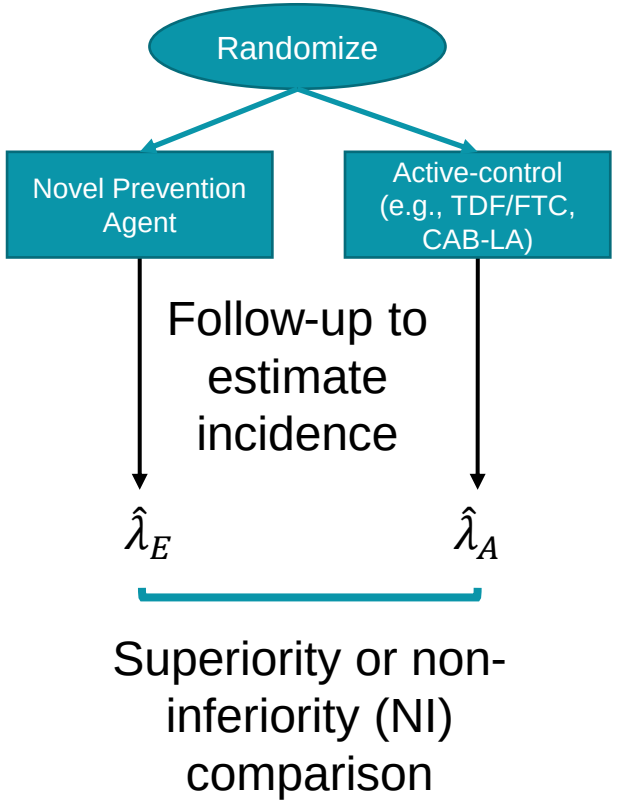
## Placebo-Controlled Trial Design




Randomizing individuals to placebo arm may not be ethical.

## Active-Controlled Trial Design




Active-control has been demonstrated efficacious in a previous trial.

With highly effective active-control (and new agent), the sample size are likely to be prohibitively large.

# Active-Control Design with TDF/FTC as active-control (HPTN 083)

HPTN HIV Prevention Trials Network

- HPTN 083: evaluate efficacy of long-acting cabotegravir (CAB-LA) in MSM/TGW population, with daily oral TDF/FTC as active-control.

Step 1: Determine NI Margin ($\delta$): what we meant by non-inferiority to the active-control.

- Margin M1: active-control efficacy
- Margin M2: proportion preservation of active-control efficacy

It also defines the acceptable prevention efficacy for the experimental agent.

| NI Margin $\delta = \left(\frac{1}{1-M1}\right)^{1-M2}$ | Margin M1 (95% CI lower bound of Active-Control efficacy) | Margin M2 (preservation of Active-Control efficacy) | Non-inferiority |
|---|---|---|---|
| 1.23 | 34.2% | 50% | PE > 44% |

Step 2: Study Design using the NI margin – power = 90%

| Efficacy: Active-Control | Efficacy: Experimental Agent | PY in Each Arm (3% incidence) | # Event: Active-Control | #Event: Exper. Agent |
|---|---|---|---|---|
| 54.5% | 66% | 8,733 | 99 | 74 |

# Active-Control Design with CAB-LA as active-control: A future study design

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- For a future trial to evaluate efficacy for a novel PrEP agent, we may use CAB-LA as active-control.

Step 1: Determine NI Margin ($\delta$): what we meant by non-inferiority to the active-control.

| NI Margin $\delta = \left(\frac{1}{1-M1}\right)^{1-M2}$ | Margin M1 (95% CI lower bound of Active-Control efficacy) | Margin M2 (preservation of Active-Control efficacy) | Non-inferiority |
|---|---|---|---|
| 3.73 | 85% | 31% | PE > 44% |

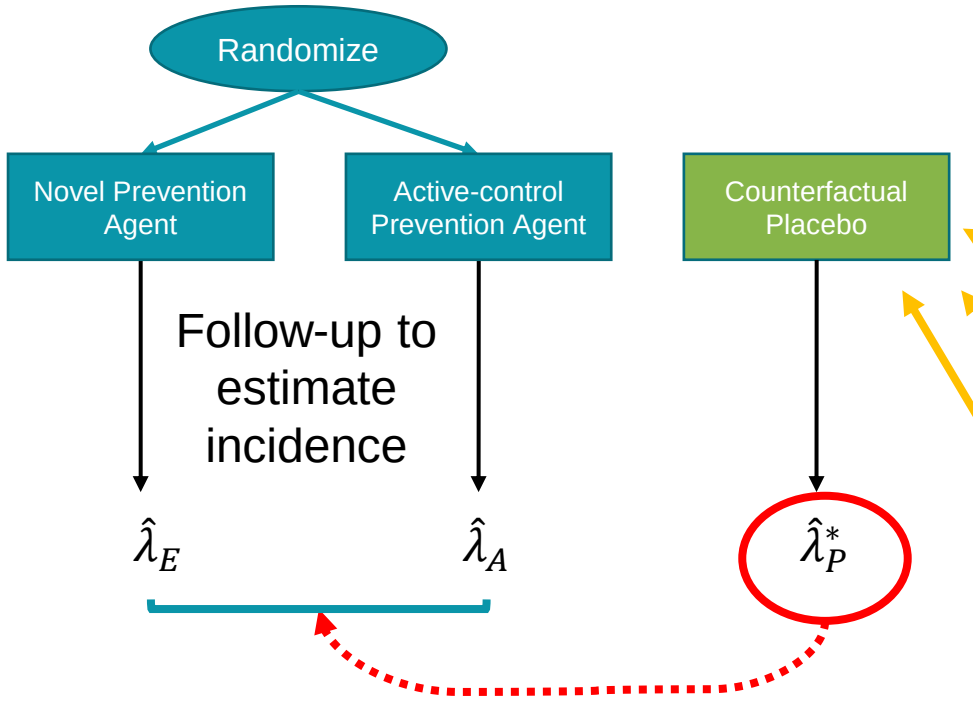
The NI margin is large mainly due to high efficacy of CAB-LA as active-control.

Step 2: Study Design using the NI margin – power = 90%

| Efficacy: Active-Control | Efficacy: Experimental Agent | PY in Each Arm (3% incidence) | # Event: Active-Control | #Event: Exper. Agent |
|---|---|---|---|---|
| 90% | 80% | 13,486 | 40 | 81 |

# Utilizing Counterfactual Placebo

## Active-Controlled Trial Design Augmented by a "Counterfactual Placebo"




Counterfactual placebo: the HIV incidence that would have been observed had a placebo arm been included

- Historical placebo arm
- HIV recency data at screening
- Incidence of other STIs

# Utilizing Counterfactual Placebo

- Non-inferiority comparison between $\lambda_E$ and $\lambda_A$ is equivalent as a relative efficacy comparison under a constancy assumption for the efficacy of the active control

$$H_0: \frac{\log\ \lambda_P - \log \lambda_E}{\log \lambda_P - \log \lambda_A} \leq \gamma \text{ vs } H_a: \frac{\log\ \lambda_P - \log \lambda_E}{\log \lambda_P - \log \lambda_A} > \gamma$$

  - $\gamma$ is the M2 margin in the non-inferiority trial design, which indicates relative efficacy of the experimental agent and active-control.
- Such a hypothesis can also be evaluated utilizing the counterfactual placebo incidence estimate $\hat{\lambda}_A$ through the test statistic

$$T = \frac{\log\ \hat{\lambda}_P^* - \log \hat{\lambda}_E}{\log \hat{\lambda}_P^* - \log \hat{\lambda}_A} - \gamma$$

- We may then strengthen evidence on efficacy of experimental agent utilizing “counterfactual placebo”.

# Active-Control Design with CAB-LA as active-control: A future study design

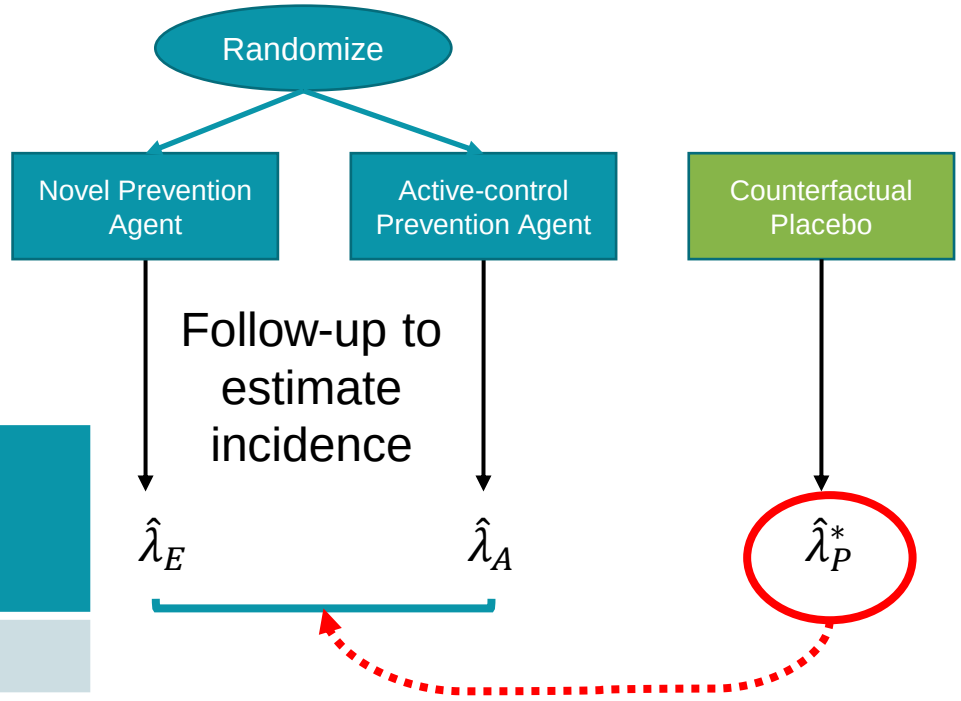
Counterfactual Placebo based on data from external cohorts with 5,500 PYs.

¥ Required counterfactual placebo PYs increased by 1.5 relative to randomized placebo, to offset greater uncertainty in estimating incidence

Study Design – power = 90%

| Efficacy: Active-Control | Efficacy: Experimental Agent | PY in Each Arm (3% incidence) | # Event: Active-Control | #Event: Exper. Agent |
|---|---|---|---|---|
| 90% | 80% | 8,522 | 26 | 51 |

## Active-Controlled Trial Design Augmented by a "Counterfactual Placebo"




May help to determine efficacy of experimental agent

# Summary

- Traditional designs for efficacy trial may not be feasible in evaluating novel HIV prevention agents, given current landscape for HIV prevention.
- Active-controlled trial augmented by a “counterfactual placebo” may be conducted to evaluate efficacy of an experimental HIV prevention agent with a reasonable sample size.

# Acknowledgement

- Deborah Donnell, Ph.D.
- Professor
- Fred Hutchinson Cancer Center

- James P. Hughes, Ph.D.
- Professor Emeritus
- University of Washington

- Holly Janes, Ph.D.
- Professor
- Fred Hutchinson Cancer Center

This work is funded by U.S. National Institutes of Health grants UM1AI068617, R01AI029168, and R01AI177078.