Novel study designs for new HIV prevention products

Deborah Donnell

Fred Hutchinson Cancer Research Center
University of Washington
May 2024

Clinical Trial Design Academy for Advocates

FRED HUTCH
CURES START HERE™

HIV prevention successes lead to new challenges for future trial design

No ARV-based prevention

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

Oral ARV-based Prevention (FTC/TDF)

- 2015-2021
- Active controlled randomized trials e.g. DISCOVER, HPTN 083/084
- Placebo controlled trials + FTC/TDF standard of prevention
  e.g. HVTN 704, AMP, MOSAICO

Long acting ARV-based prevention

- 2022-
- Designs to evaluate efficacy of new products e.g. implants, longer acting pills/injections

The HIV prevention toolbox is growing

Agents for prevention

- Oral PrEP
- Injectable PrEP
- Vaginal rings
- Monoclonal antibodies
- Microbicides
- Vaccines

How is this impacting the design of randomized clinical trials for new biomedical interventions?

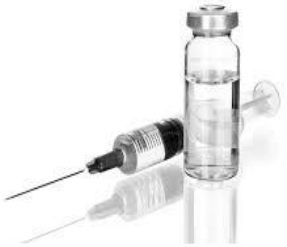
HPTN
HIV Prevention
Trials Network

With an effective product, three design choices in future RCTs

1. Compare

Compare experimental product (EXP) to existing prevention (FTC/TDF)

FTC/TDF



EXP

2. Layer

Compare EXP to placebo (PBO) on top of use of existing prevention

3. Combine

Compare existing prevention combined with EXP product

FTC/TDF+ Placebo

FTC/TDF + EXP

Recently completed trials 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

2. Layer

Compare EXP to placebo (PBO) layered with use of proven prevention

AMP:
VRC01 vs PBO

HVTN 706
Mosaico vaccine vs PBO

All pts can use FTC/TDF

3. Combine

Compare existing prevention combined with EXP product

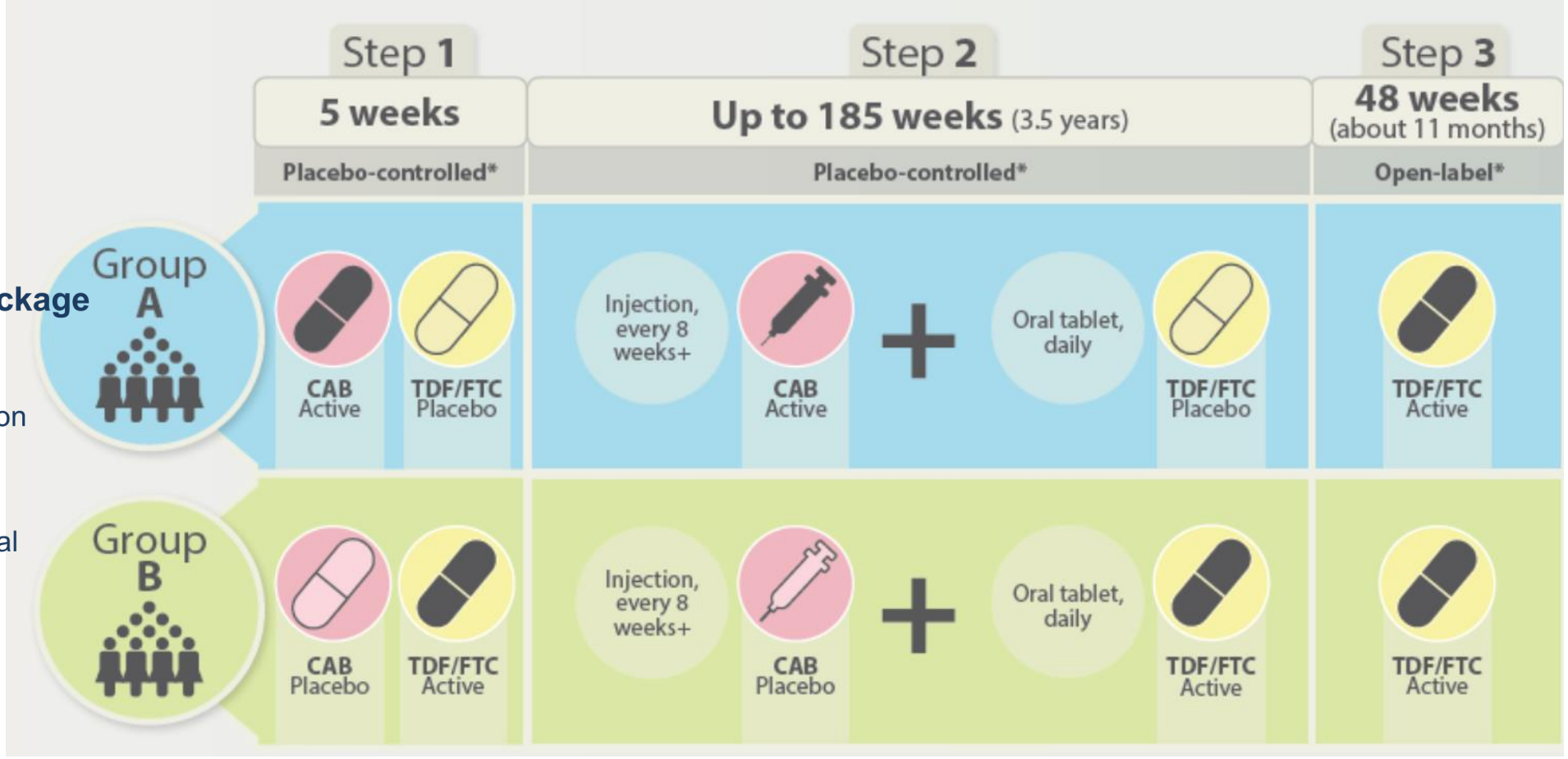
oral PrEP + Placebo

oral PrEP + EXP

Compare: A participant in an active control trial

Optimized prevention package

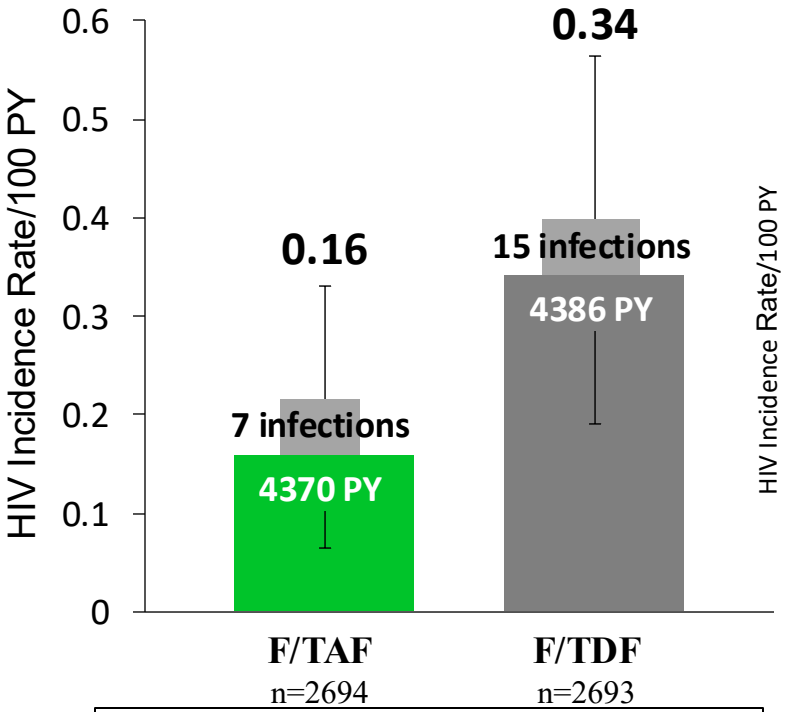
- Risk reduction counselling
- Condom and lubricant provision
- PEP counseling and linkage
- Couples counselling
- STI treatment provision/referral
- Contraception



Compare: Results of the direct comparison trials

DISCOVER

22 HIV infections in 8756 PY of follow-up in MSM

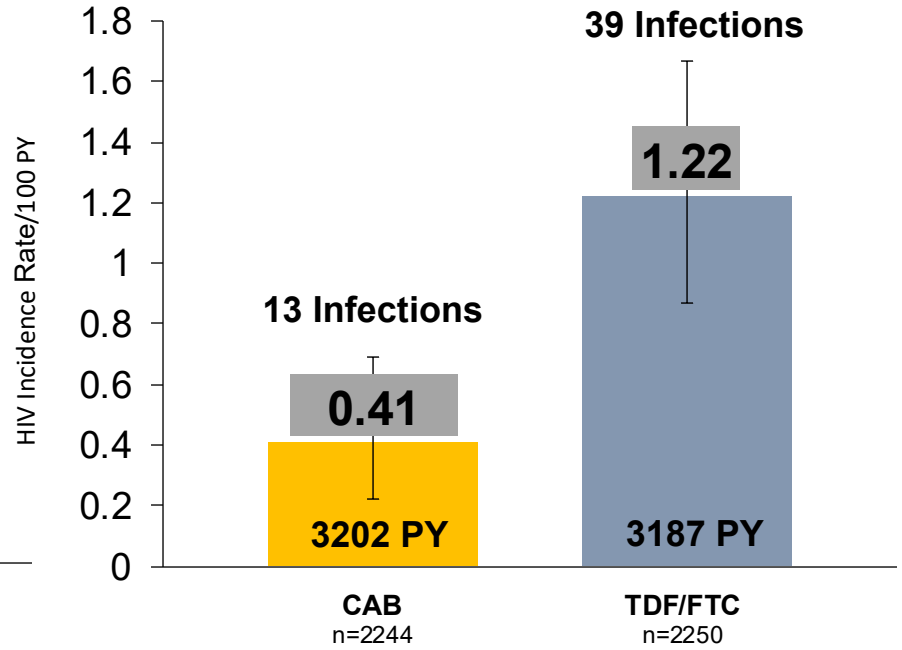


HR = 0.47 (0.19 – 1.15)

*F/TAF is **noninferior** to F/TDF for HIV prevention*

HPTN 083

52 HIV infections in 6389 PY of follow-up in MSM/TGW



HR = 0.34 (0.1 – 0.62)

*MSM/TGW in the CAB group had an **66% lower risk of HIV infection,** compared to TDF/FTC group*

HPTN 084

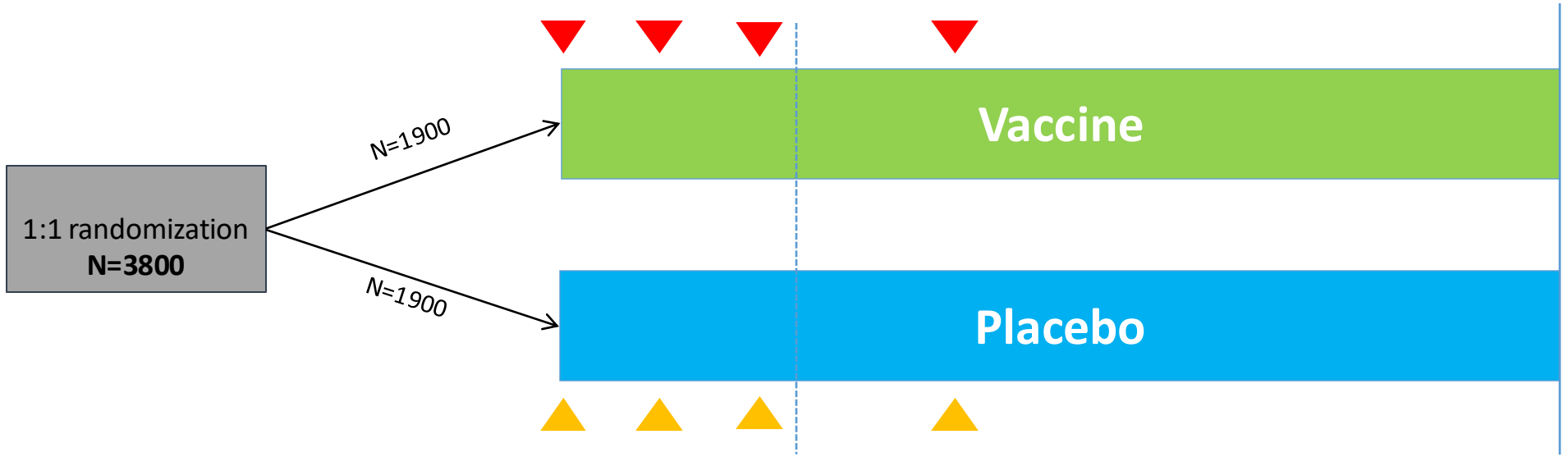
40 infections over 3892 PY of follow-up in women

	CAB N = 1614	TDF/FTC N = 1610
HIV infections	4	36
HIV incidence	0.20	1.86

HR = 0.11 (0.01 – 0.31)

*Women in the CAB group had an **89% lower risk of HIV infection,** compared to TDF/FTC group*

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**

Results of the Layered trials

- HVTN 706
  N = 3870

	Vaccine N = 1940	Placebo N = 1938
HIV infections	113	113
HIV incidence	4.1	4.1

Efficacy = 0% 95%CI(x-x)

MOSAICO vaccine did not prevent HIV-1 acquisition more effectively than placebo

- HVTN 703/HPTN 081
  N = 1924 women

	VRC01 N = 1287	Placebo N = 637
HIV infections	47	29
HIV incidence	2.49	3.10

Efficacy = 8.8% 95%CI(-45% – 43%)

VRC01 did not prevent HIV-1 acquisition more effectively than placebo

- HVTN 704/HPTN 085
  N = 2699 MSM/TG

	VRC01 N = 1791	Placebo N = 898
HIV infections	60	38
HIV incidence	2.35	2.98

Efficacy = 27% 95%CI(-12% – 52%)

VRC01 did not prevent HIV-1 acquisition more effectively than placebo

Three “active-controlled” randomized clinical trials completed

1. DISCOVER: F/TAF vs FTC/TDF
2. HPTN 083: CAB-LA vs FTC/TDF
3. HPTN 084: CAB-LA vs FTC/TDF

Active-controlled trial:

- All participants receive an active product: proven or experimental
- How do you justify randomization to an experimental drug when you have something that is known to work?
- How do you work out whether the experimental drug is working or not?

Three “layered” randomized clinical trials completed

1. MOSAICO (HVTN706): Placebo vs. MOSAICO vaccine
2. AMP (HVTN703/HPTN081)
    1. Women : Placebo vs. VRC01 10 mg/kg vs. VRC01 30 mg/kg
    2. MSM (HVTN704/HPTN085): Placebo vs. VRC01 Low vs. VRC01 High

Placebo-controlled trial:

- No participants are receiving a proven product; all participants were informed about FTC/TDF PrEP
- How do you justify randomization to placebo when there is a proven drug for HIV prevention?
- The trial is designed to answer whether the biologic works: what is the risk of the layered approach?

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 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	Incidence rate		
				Exp.	Active control (FTC/TDF)	Detected/Protective FTC/TDF in DBS
DISCOVER (MSM)	Europe, UK, Canada and Untied States	5399	7 vs 16	0.16	0.34	84-93%
HPTN 083 (MSM/TGW)	United States, Peru, Brazil, Argentina, Thailand, Vietnam, South Africa	4541	13 vs 39 (stopped early)	0.41	1.22	91%/82%
HPTN 084 (Women)	South Africa, Botswana, Eswatini, Zimbabwe, Malawi, Kenya, Uganda.	3224	4 vs 36 (stopped early)	0.20	1.86	62%/18%
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	39%/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	4%/0.4%
HVTN 706 (MSM/TG)	Argentina, Brazil. Italy, Mexico, Peru. Poland. Puerto Rico Spain, USA	3870	113 vs 113 (stopped early)	4.10	4.10	9%/5%

Trial designs for new HIV prevention products

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

Unproven action: mAb products; vaccines

Two possible questions for future trial

- Superiority: The new drug is more effective than placebo or active control
  - Pick a difference that is a clinically important improvement
  - Choose sample size to have high probability of detecting that improvement
- Non-inferiority: The new drug is effective and not substantially worse than a known effective drug (active control)
  - Pick a difference that is not clinically important (“worse”) = Non-inferiority (NI) margin
  - Choose a sample size to have high probability of showing the difference is not worse than that

Non-inferiority Trial Efficacy

- Compare Experimental to Active Control

  If they were the same expect $\frac{\text{\# Infections with injectable PrEP}}{\text{\# Infections with oral PrEP}} \approx 1$

  NI Margin = “How much more than 1 is acceptable”

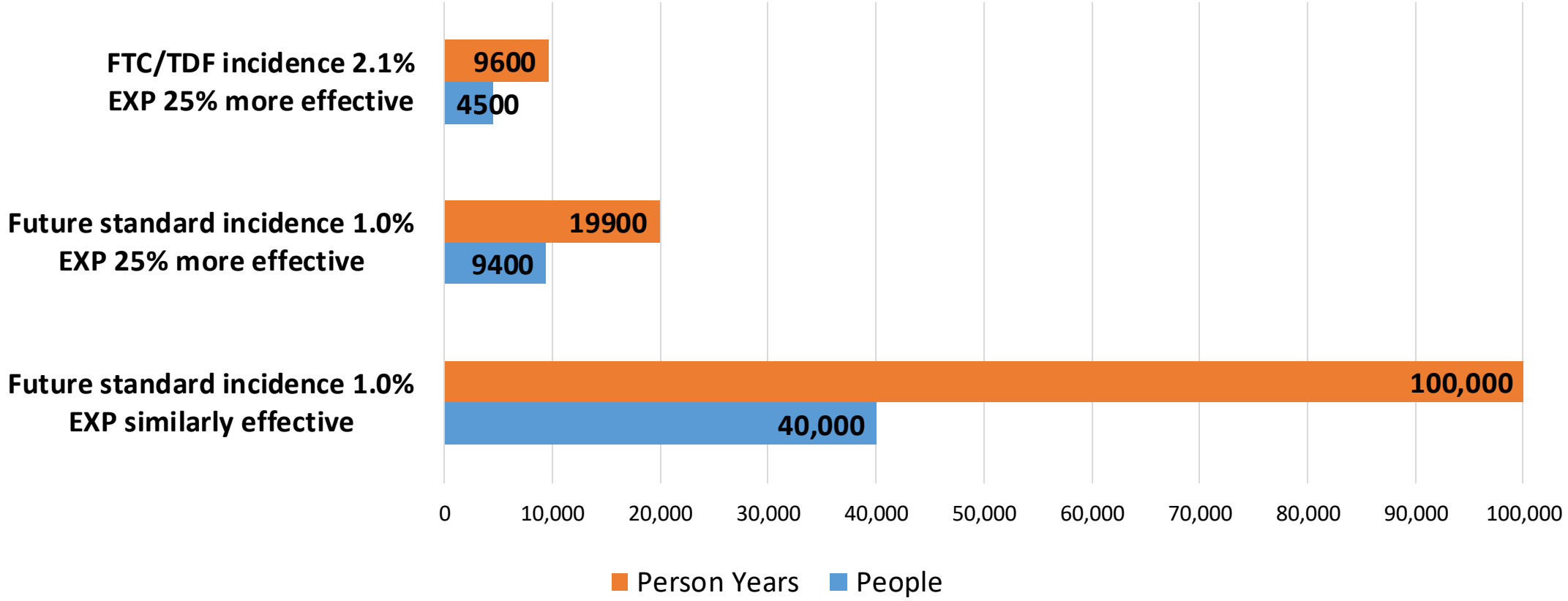
- Standard of evidence = 95%CI around Prevention Efficacy does not include the NI margin
- Dilemma of NI trial: Rates can be the same because
  a) ***Both*** are effective
  b) ***Neither*** are effective
- Assumption that active control (e.g. oral PrEP) is working as it did in prior trials

Non-inferiority design for future trials using active control

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

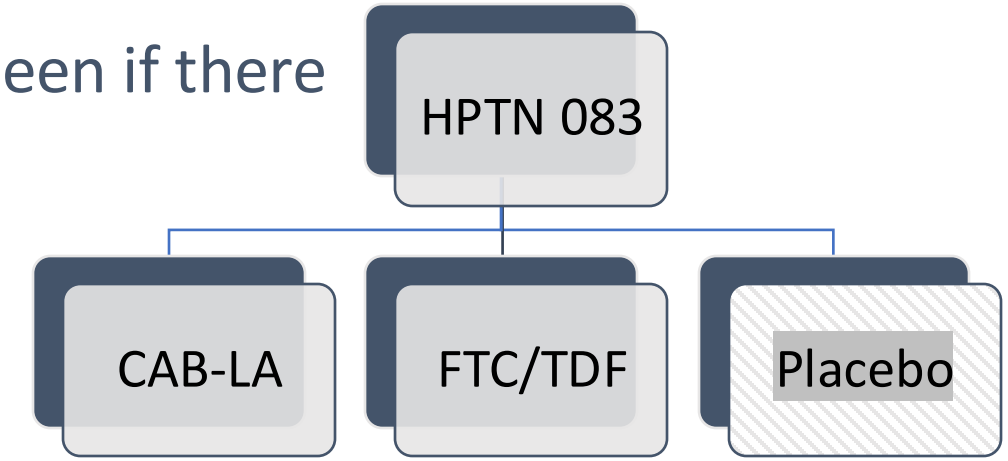


- High risk to conduct a classical RCT if incidence rates are below 1/100 person years
  - Expect low rates when participants have access to highly effective (long acting) prevention
  - May not gather enough evidence (HIV infections) to prove effectiveness
  - Very large sample sizes will be costly
  - 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"



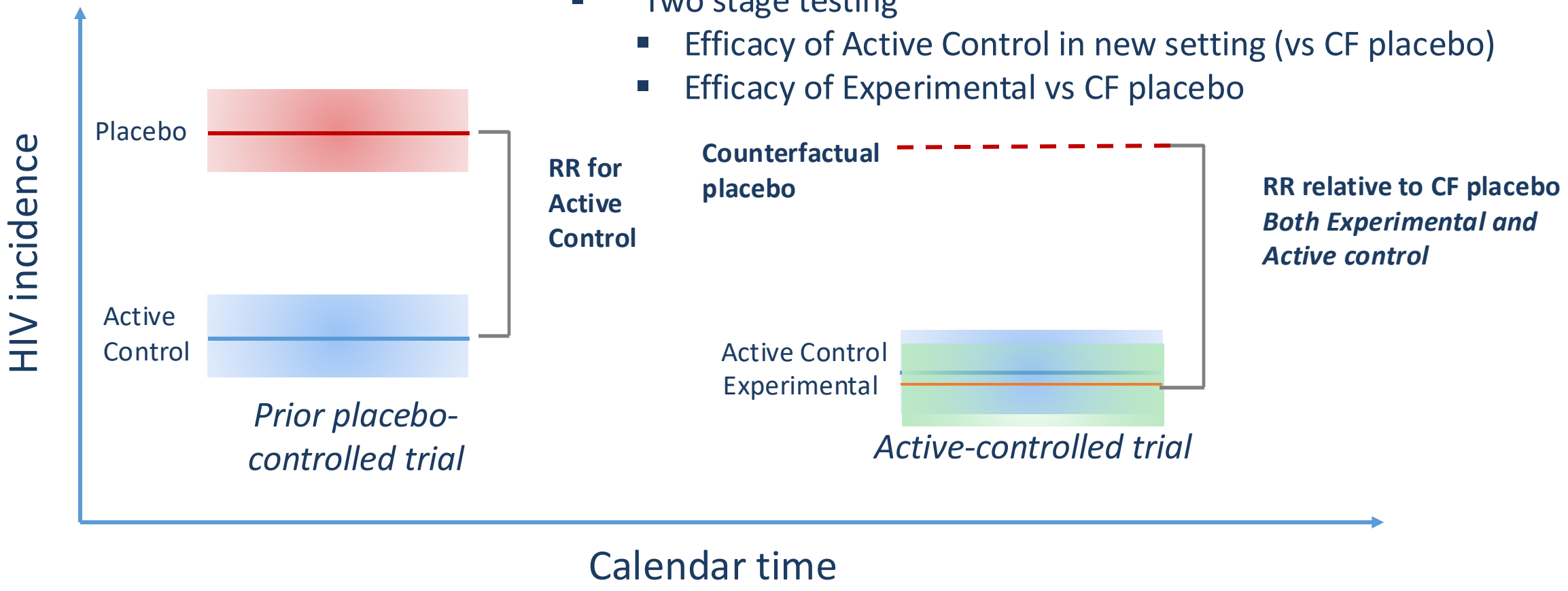
Comparison for Future Prevention Trials

Two long-acting products

- Experimental: Injection, infusion, longer acting pill
- Active control: highly effective, HIV acquisition on proven active-control product <1/100 PYs
- Directly observed dosing
- **Active-control randomized design with a placebo counterfactual**
  - Placebo counterfactual = what would have been observed if there had been a placebo arm

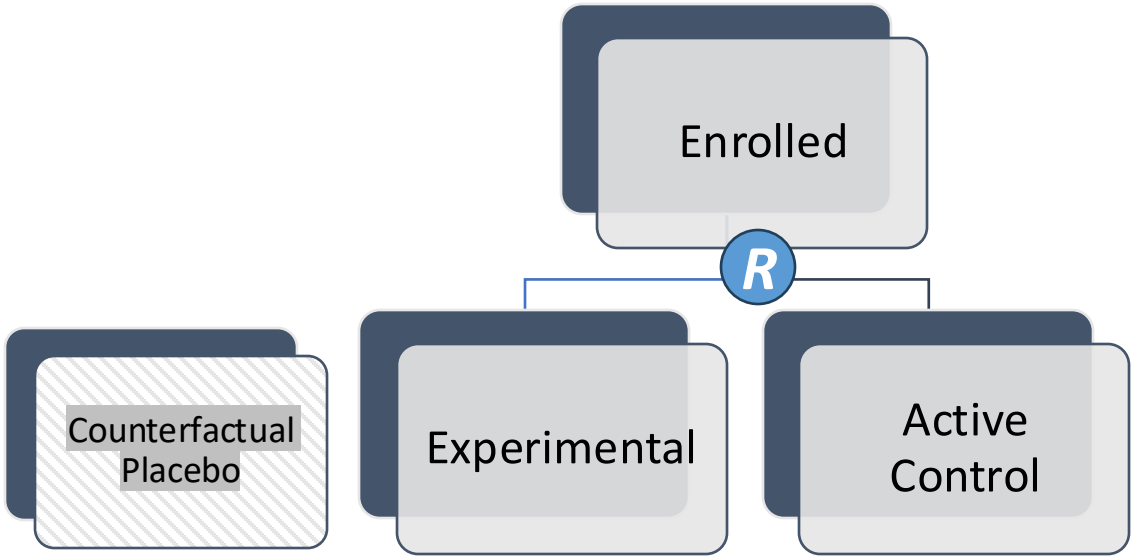
New Design Framework: Active-controlled Trial with Placebo Counterfactual

- Theoretical framework derived from NI approach; based on conservative CF placebo estimate
- Two stage testing
  - Efficacy of Active Control in new setting (vs CF placebo)
  - Efficacy of Experimental vs CF placebo



Counterfactual Placebo Strategy

- Two arm RCT with Experimental and Active control, with planned placebo counterfactual
  - … requires framework for three groups incorporating uncertainty and defined success criteria
  - … is appropriate for a new agent that is expected to be highly effective
  - … is feasible in terms of sample size
- Likely to be combined with other approaches to ensure efficacy of experimental drug



Incorporate CHOICE within active control into trial design

HPTN HIV Prevention Trials Network

Preference for active control: Choice of A, B, C

Has no preference	Has partial preference	Has preference
Randomized to A, B or C	Randomized to A or B	Chose A
	Randomized to B or C	Chose B
	Randomized to A or C	Chose C

Depending on choice preferences and characteristics in cohort, groups can be combined for comparison

Assigned to A vs Assigned to B vs Assigned to C

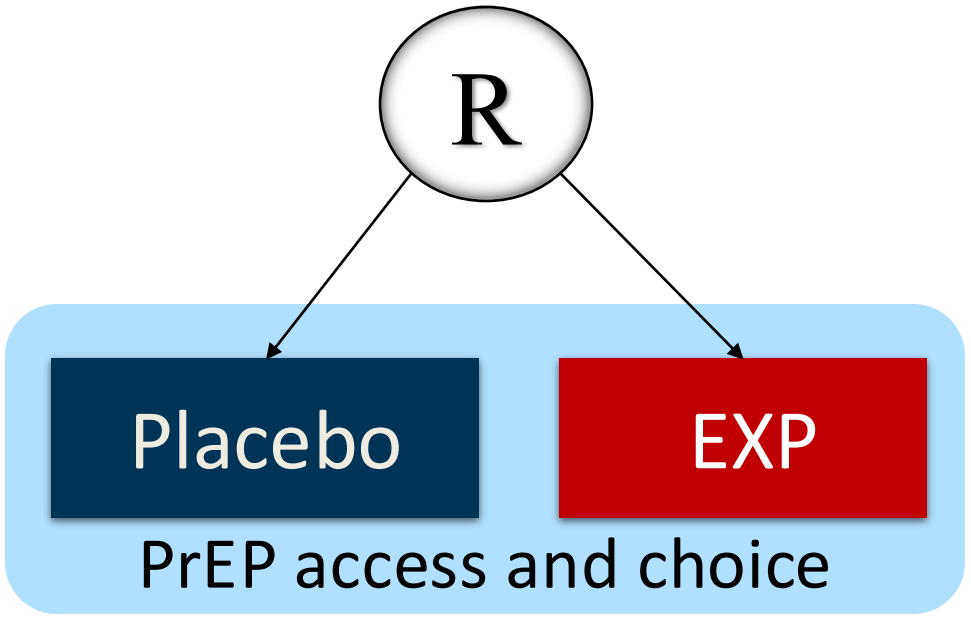
AND/OR

Choice could be compared to assignment

Assigned to A vs Chose A

Future design for vaccine and mAb

- AMP strategy



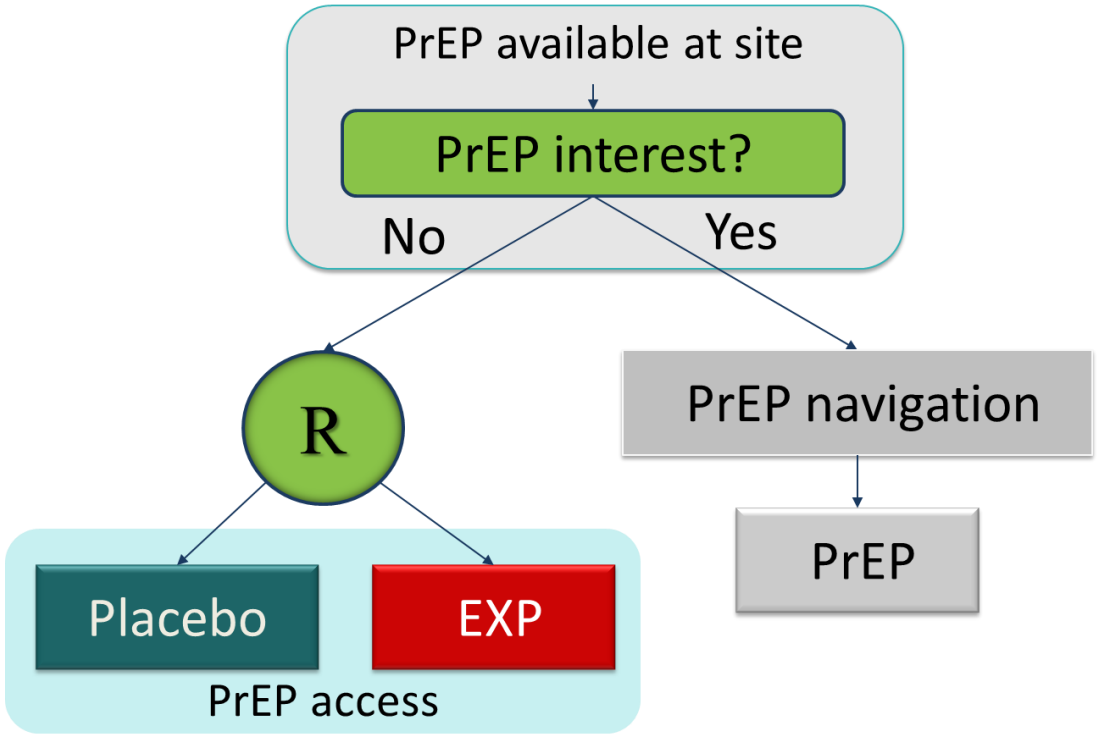
Not clear whether vaccines or mAbs will be as effective as current ARV-based prevention

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

- FDA approved, not yet available
- Don't yet know 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

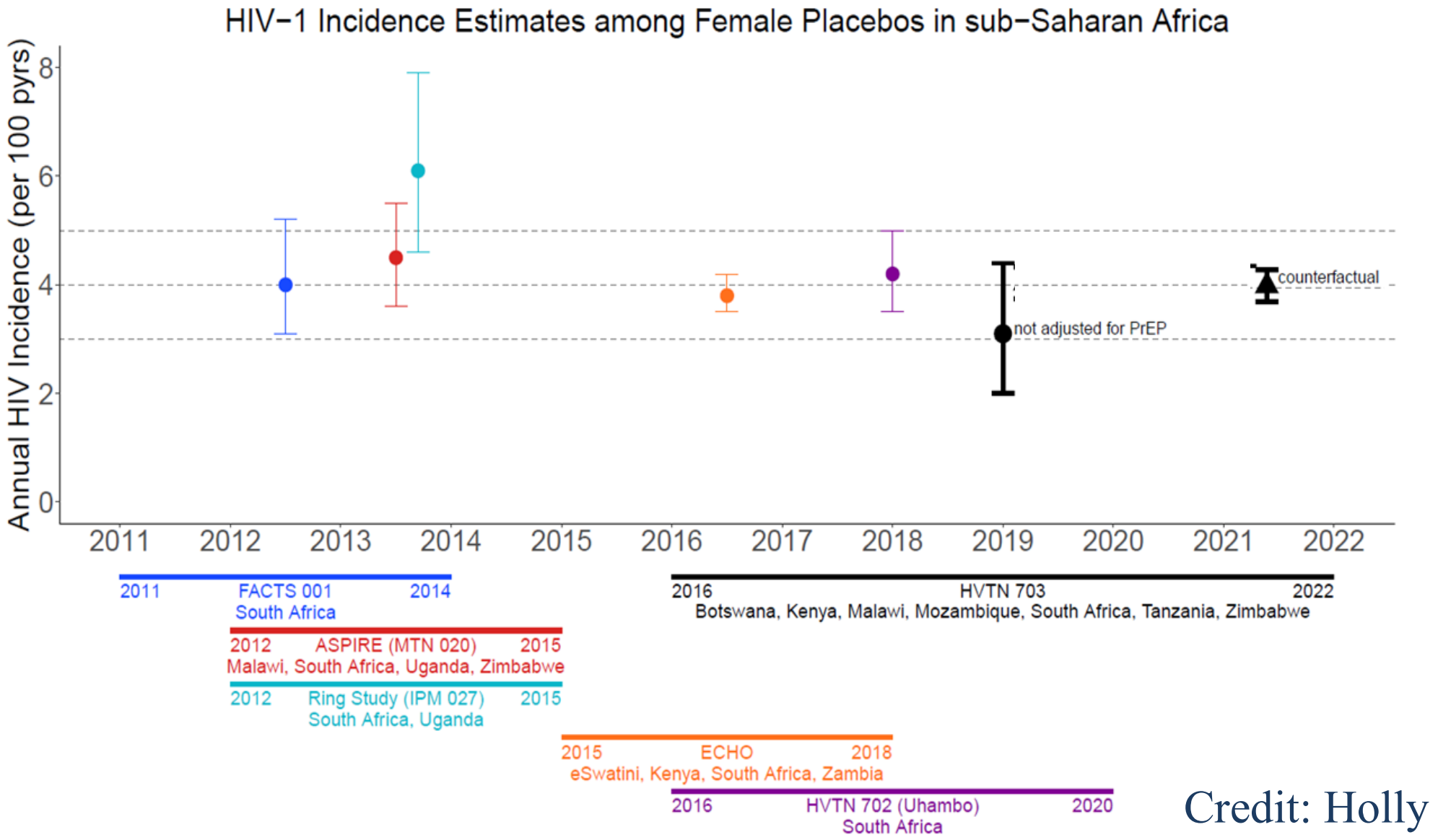
Estimate efficacy of active control compared to counterfactual placebo

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

Specific approaches

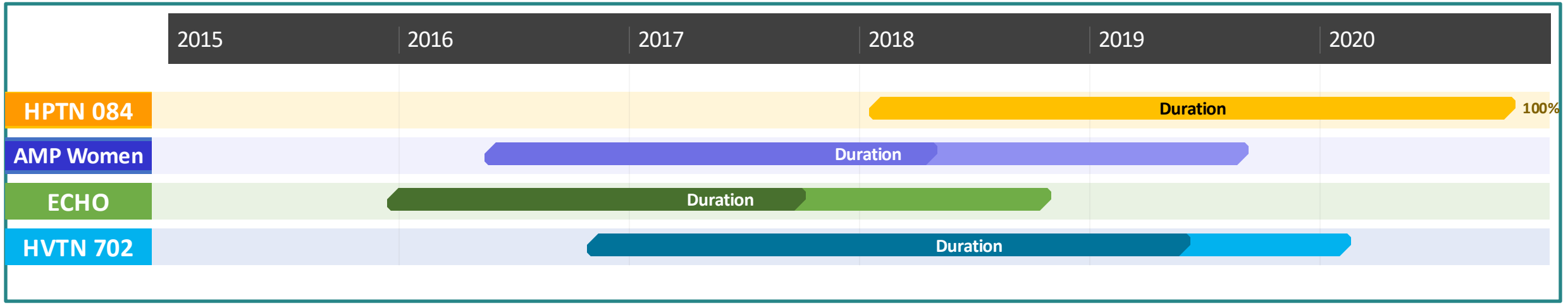
Currently implemented in trials in the field today

1. Historical data for specific populations



Credit: Holly Janes

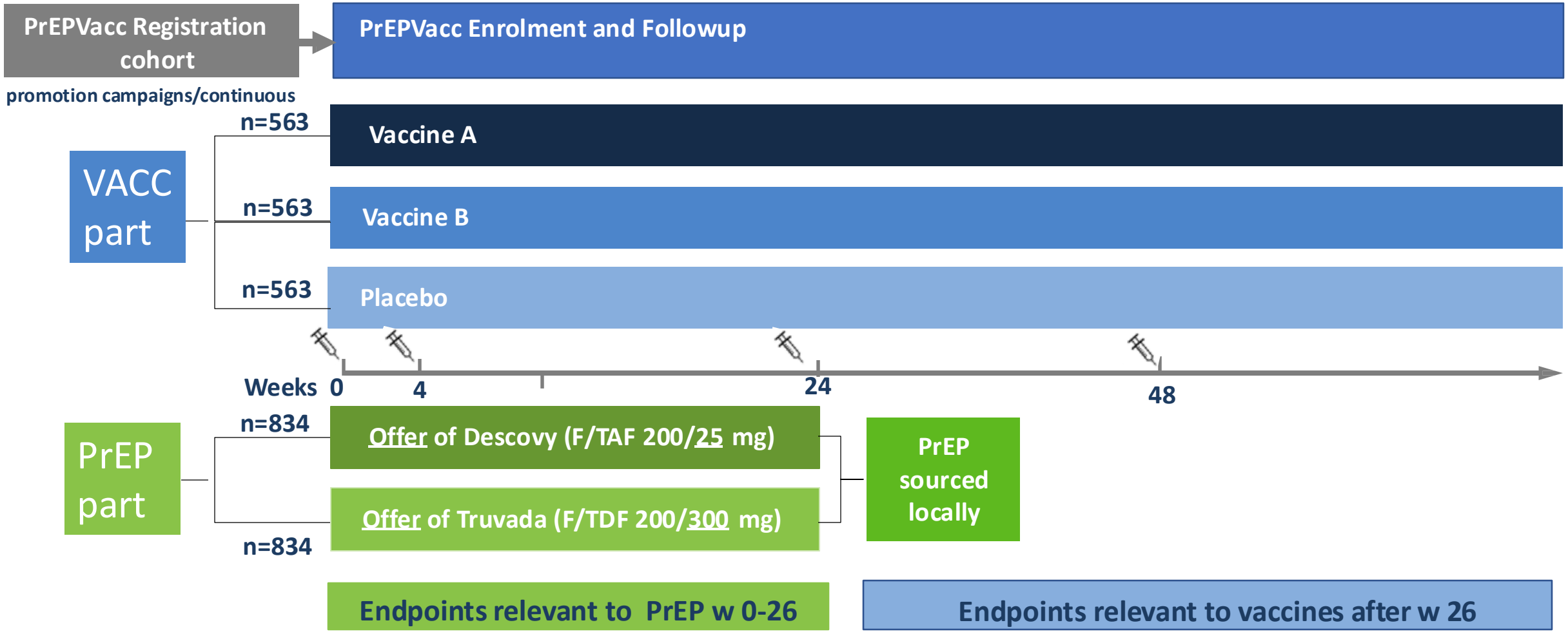
1: “Placebo” for HPTN 084 relied on follow-up from contemporary trials in same settings



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%)**

2: Registrational cohort : PrEPVacc trial

- A Phase III three-arm, two-stage prophylactic HIV vaccine trial with a concurrent randomization to compare F/TAF PrEP to FTC/TDF PrEP



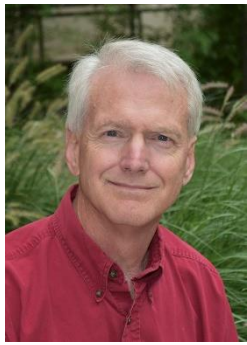
3: Cross-sectional recency assay

Fei Gao

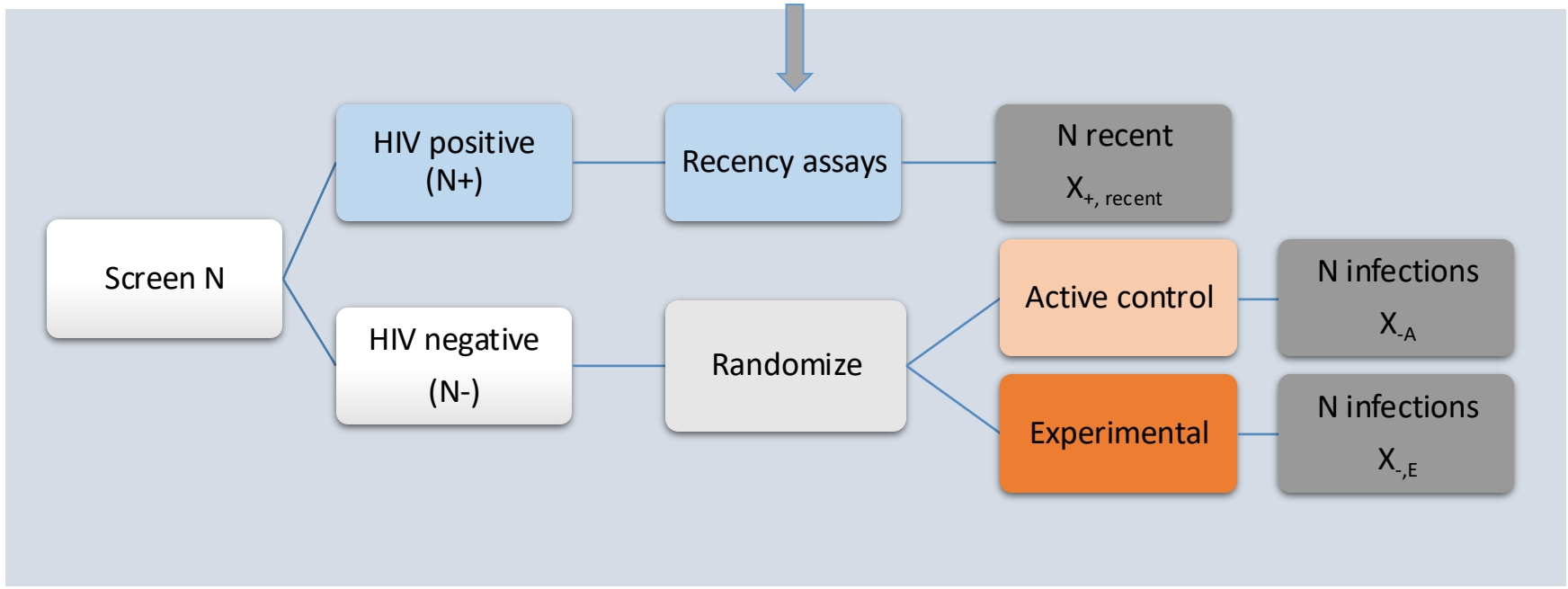
Counterfactual placebo

Active Arm

Experimental arm



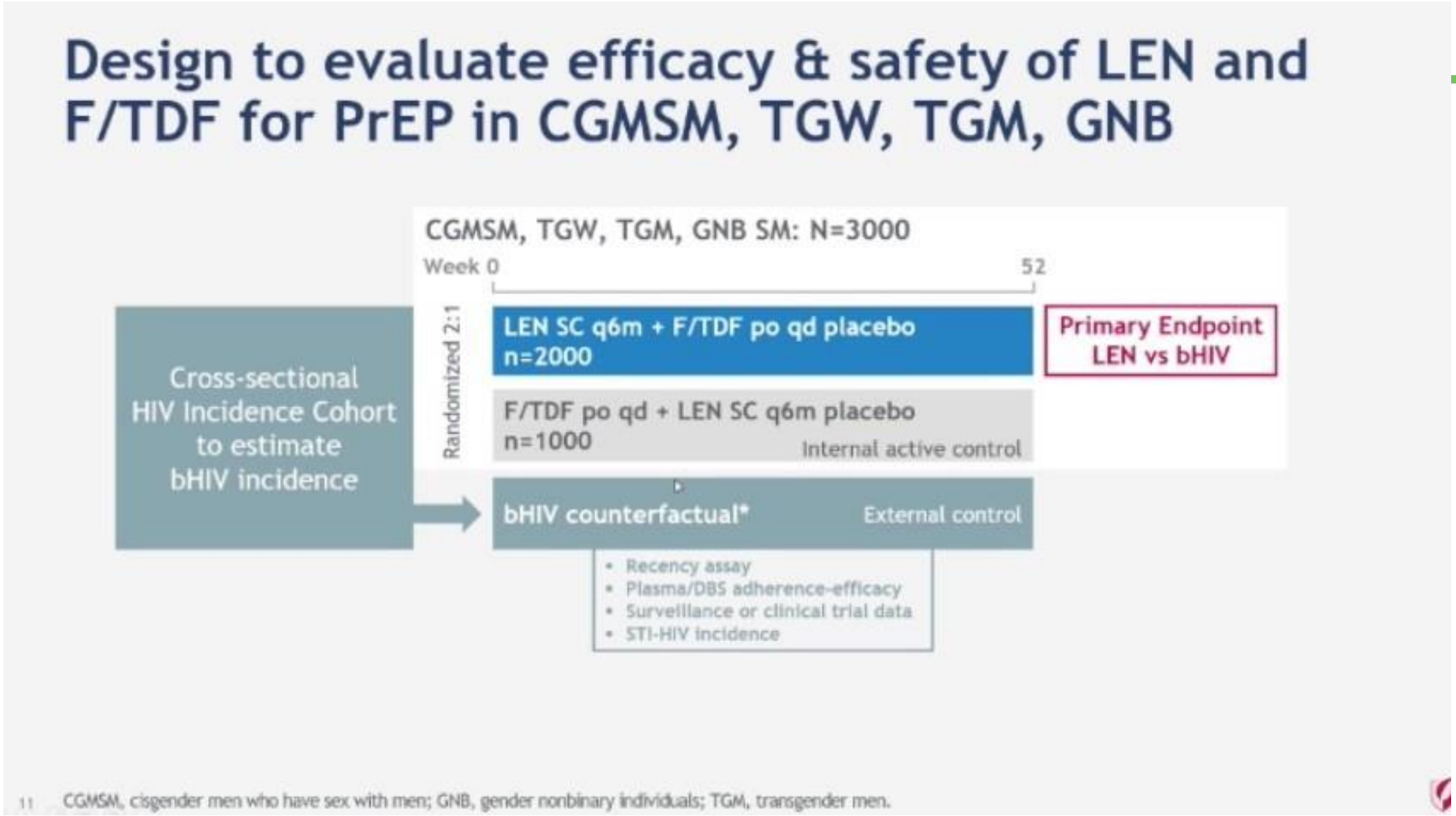
Jim Hughes



- N_-: number of HIV-negative subjects
- N_+ : number of HIV-positive subjects
- N_{rec} : number of test-recent subjects

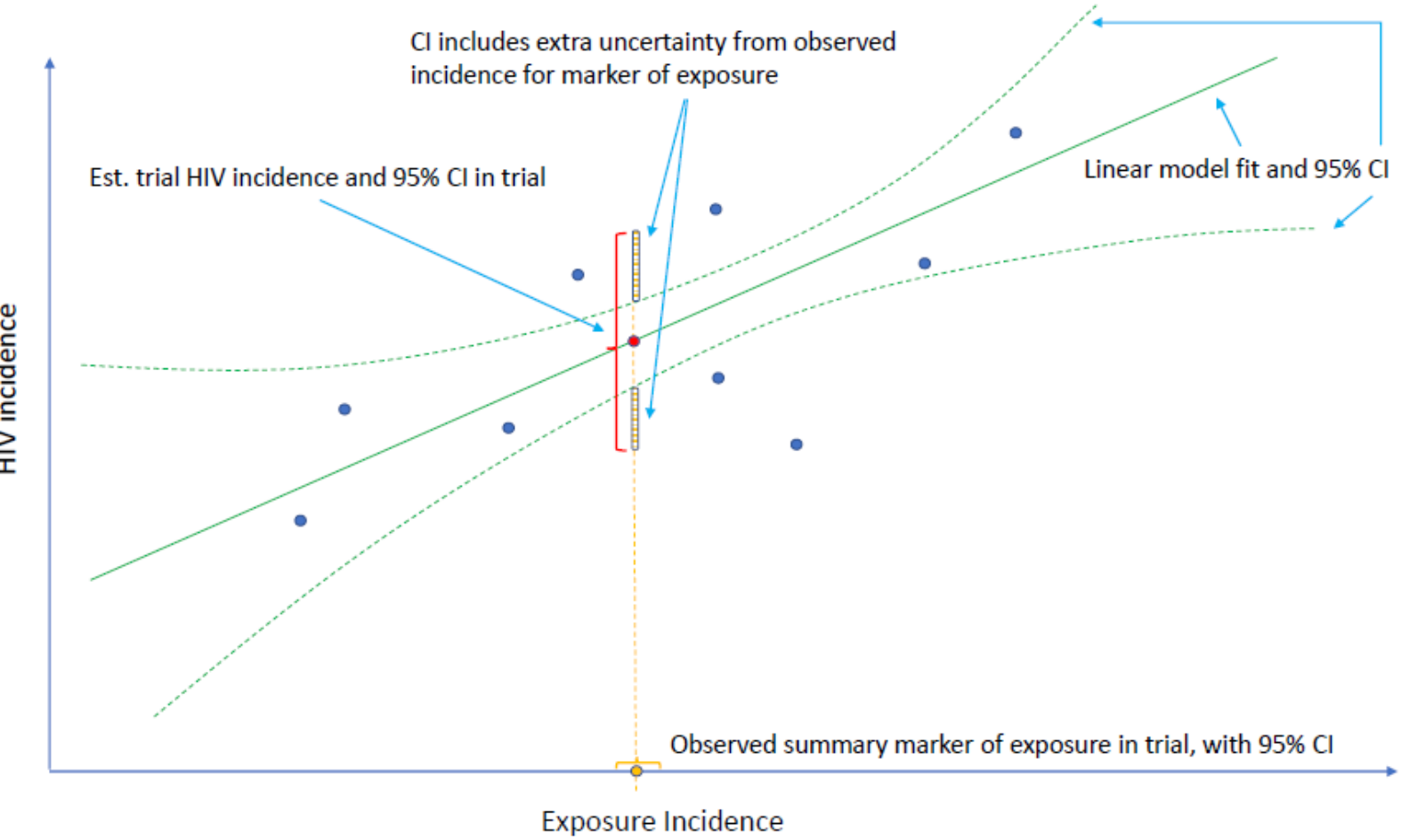
- Incidence estimated by $\frac{N_{rec}}{N_- \times MDRI}$
  - MDRI (mean duration of infection): the mean duration of test-recent for an HIV-positive subject.

3: Trial of Lenacapavir: Recency assay



4. Estimating HIV incidence using biomarker of HIV exposure

IDEA: Biomarker of sexual exposure (b/c correlated with HIV exposure, (e.g. Rectal GC in MSM) can be used to estimate risk of HIV infection



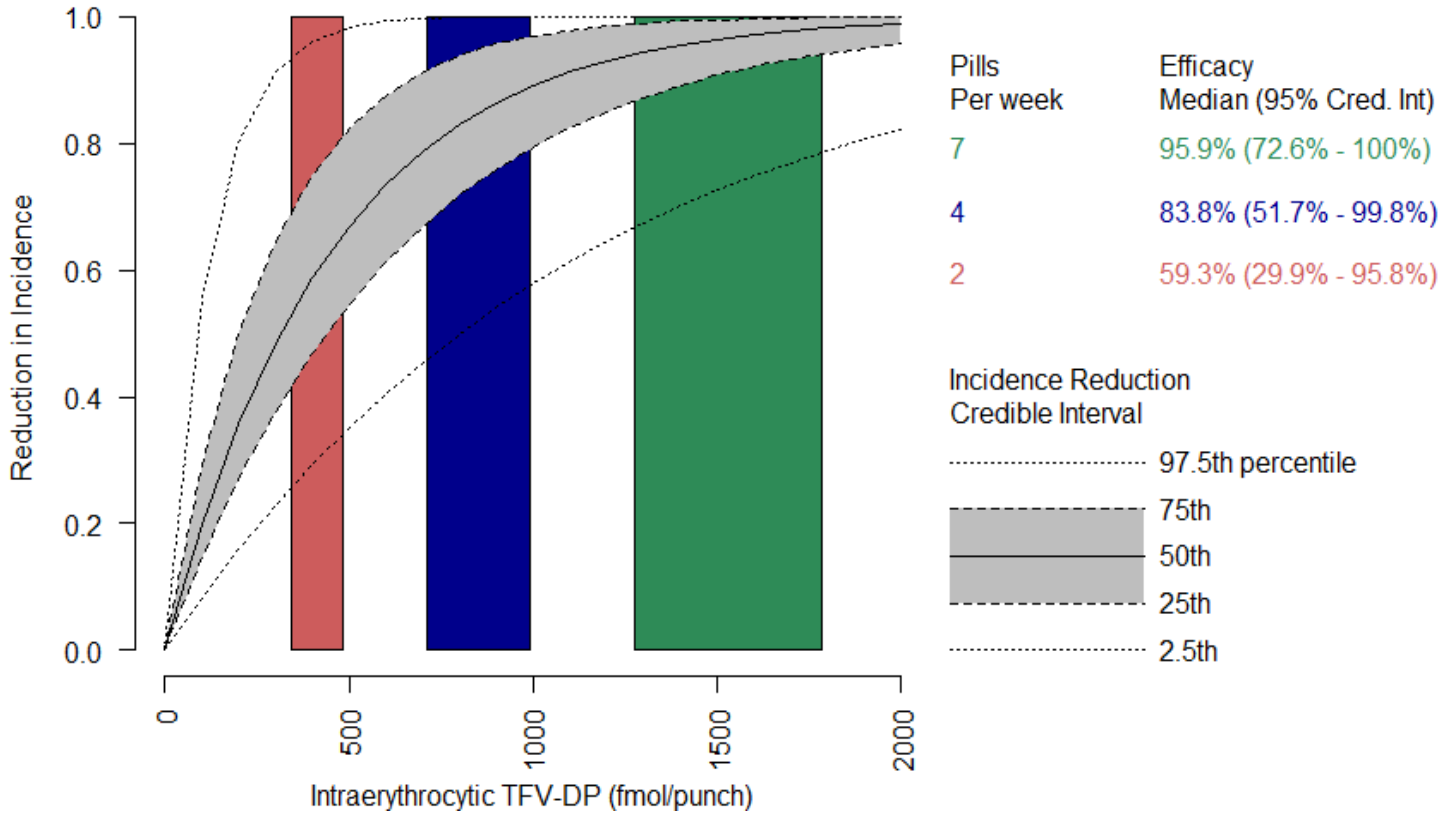
Assumptions

- Multiple observations with "placebo" 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

Mullick and Murray JID 2019
Zhu, Clinical trials, 2024

Estimating incidence using adherence-effectiveness relationship for active control

$$\text{Effectiveness (adherence)} = \frac{Inc_{active\ control}(adherence)}{Inc_{placebo}}$$



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 with FTC/TDF as SOC or active comparator have completed
  - Most were focused on longer acting products for greater effectiveness
  - Window for this approach in the future is likely narrow
- Sample sizes were uniformly large (3,000-5,000); resource needs are large
  - In future, RCT trial design approach could require 30-50,000 people
- Trials of novel ARVs are proceeding with counterfactual placebo assessments planned
  - All include randomization to an active-control Standard
  - Statistical framework for comparison of both Standard and Experimental with CF Placebo
  - Discussion with regulatory agencies ongoing

Open Questions

- Will designs using counterfactual placebo be successful in establishing efficacy?
  - Is it important to have randomization to products known to prevent HIV?
- What will be the path forward for products that might be less efficacious, but still would expand choice?
  - Are there limits to testing new products in terms of efficacy and/or uptake potential?
- What do you think about including product choice in future trials?
  - What is the question that is important to answer?