Future Trial Designs for HIV Prevention

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Key Takeaways

- 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

Three eras of HIV prevention trials

HPTN Regional Meeting

No effective biomedical prevention	• Adult trials all placebo controlled
Oral FTC/TDF approved for prevention	• ARV-based: Active control FTC/TDF • Vaccine and mAb: allowed concurrent use of FTC/TDF
CAB-LA approved for prevention	• With uptake and access can prevent ~90% of infections • Future: ???

Comparison for future prevention trials

Experimental = unproven agent e.g. triple mAb, monthly pill, vaccine

Active agent = a proven agent e.g. TDF/FTC, CAB-LA

1. Experimental vs Active Agent(s)
   Selected agent or choice
2. Experimental vs. Placebo
   All with access to active agent(s)
3. Experimental vs. Placebo
   Among persons not currently choosing to use any active agent

Comparison for future prevention trials

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HIV incidence in recent trials of HIV prevention

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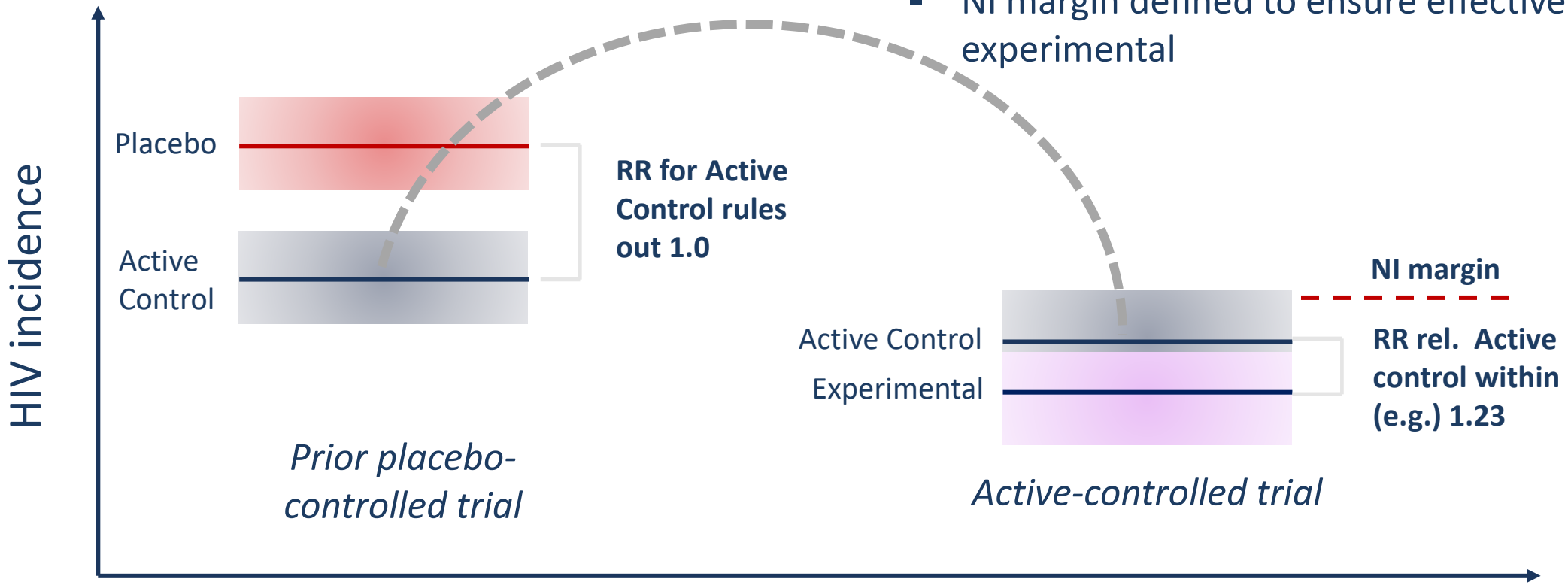
ACTIVE CONTROL	Countries	N enrolled	Number of infections	Incidence rate/100 PY	
				Experimental	Active ctrl (FTC/TDF)
DISCOVER (MSM)	Europe, UK, Canada and Untied States	5399	7 vs 16	0.16	0.34
HPTN 083 (MSM/TGW)	United States, Peru, Brazil, Argentina, Thailand, Vietnam, South Africa	4541	13 vs 39 (stopped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

Usual strategy: Active-controlled non-inferiority trial

- Constancy assumption: Effectiveness of Active Control applies in new setting
- NI margin defined to ensure effectiveness of experimental



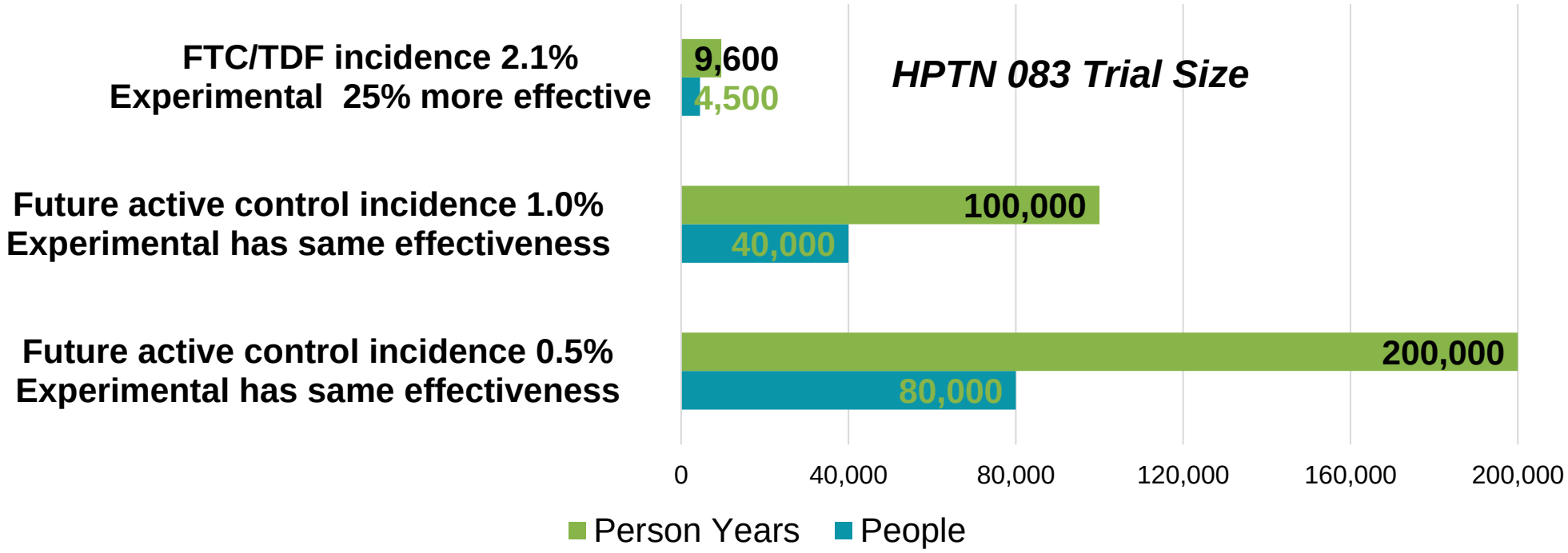
RR = Relative risk

Sample size for randomized non-inferiority trials with highly effective active control

Illustration: HPTN 083

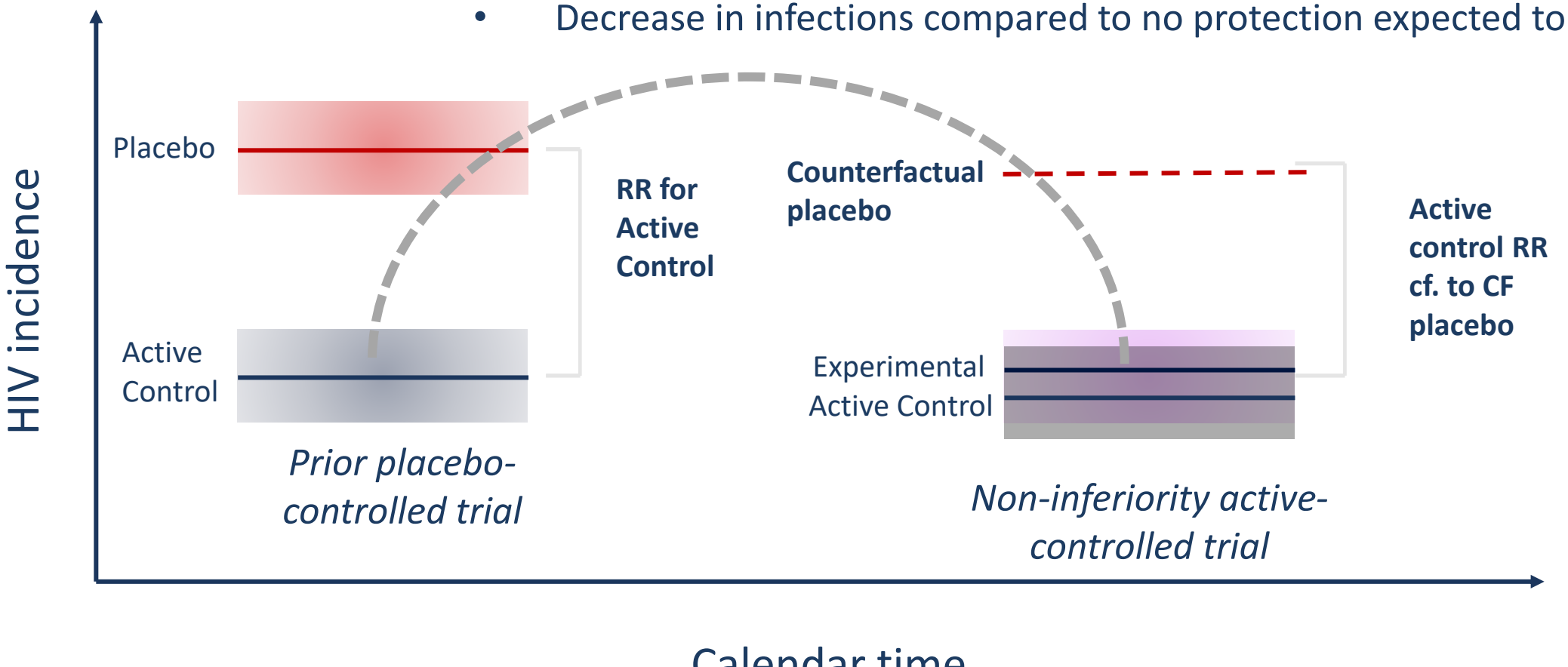
Goal: Establish CAB-LA is non-inferior to FTC/TDF in MSM+TG

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



New strategy proposed: Active-controlled trial with placebo counterfactual

- Constancy assumption: Effectiveness of Active Control applies in new setting
- Expected infections on active control too small to achieve statistical accuracy
- Decrease in infections compared to no protection expected to be large



Estimating efficacy relative to “Counterfactual” placebo

How do we do this?

Approaches to estimating efficacy relative to "counterfactual" placebo

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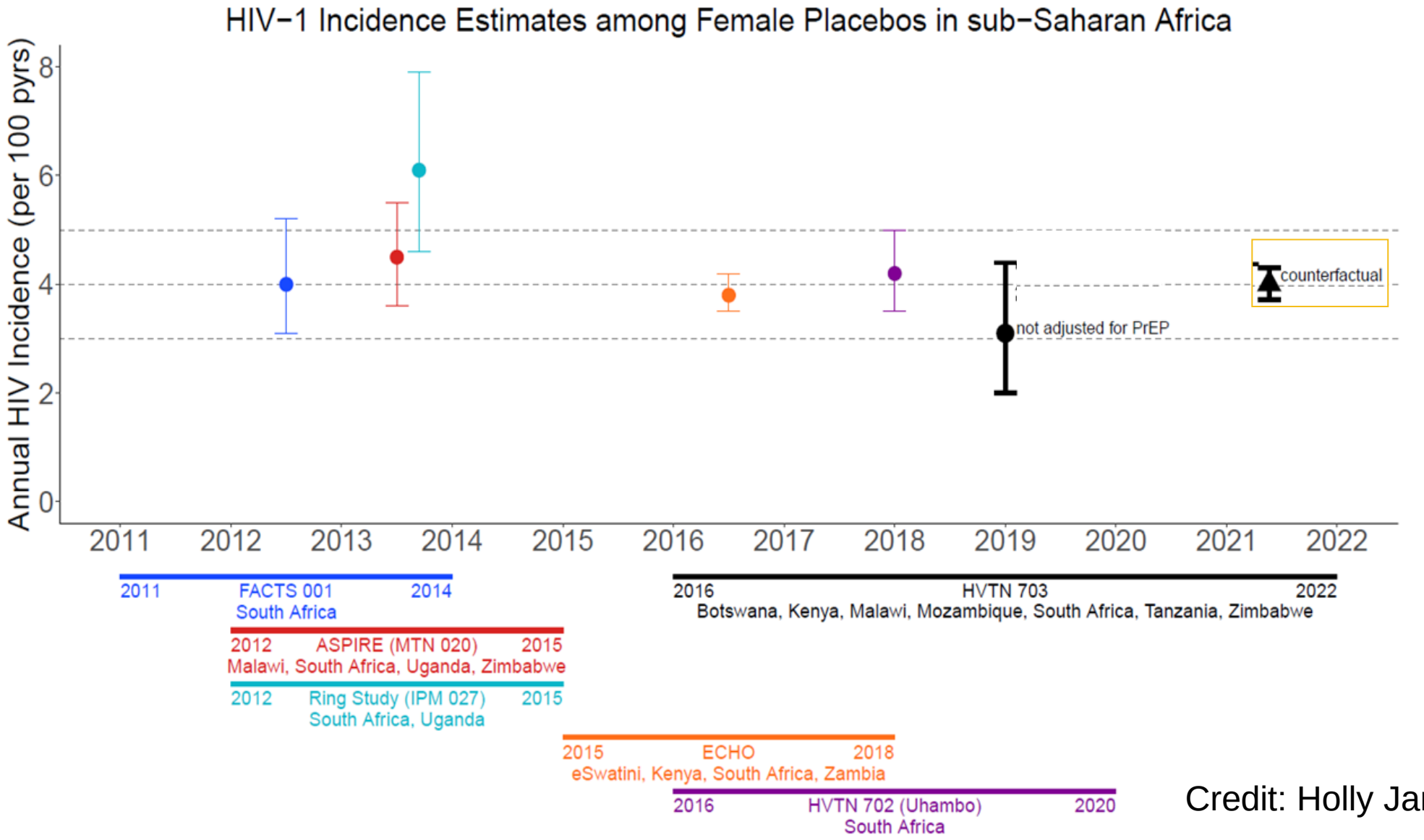
Estimate counterfactual placebo incidence rate

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

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 (monoclonal Ab and vaccine)

1. Historical data for specific populations

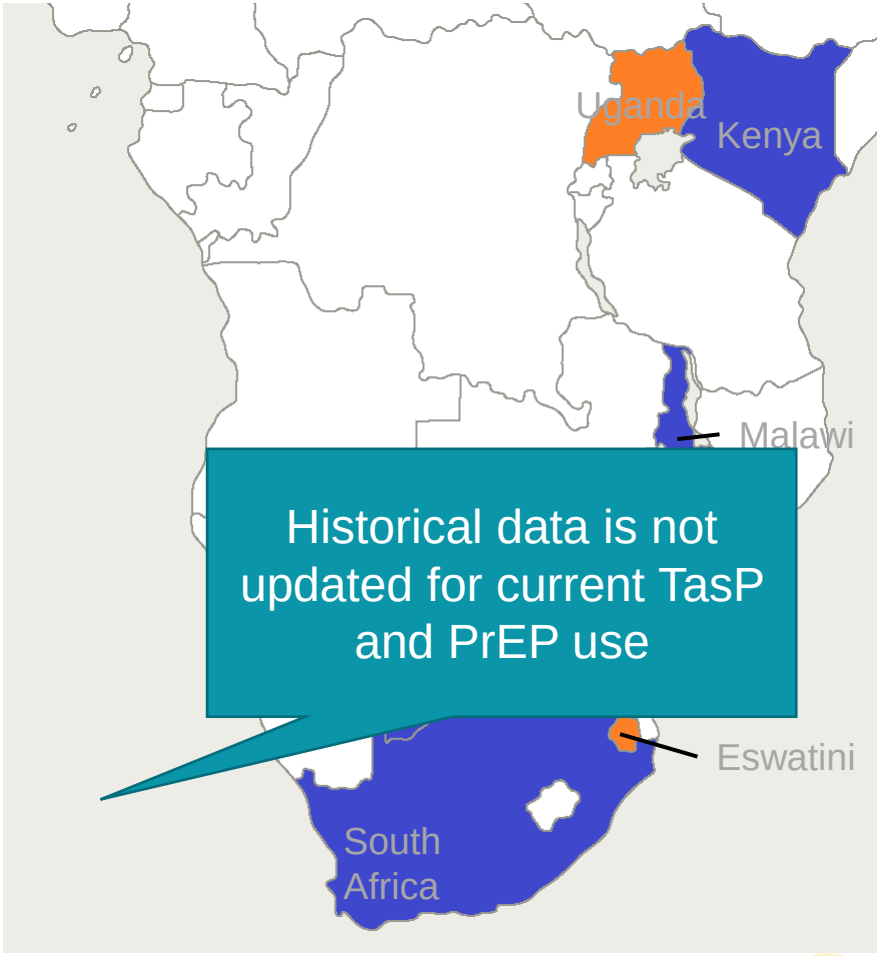


Credit: Holly Janes

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%)**

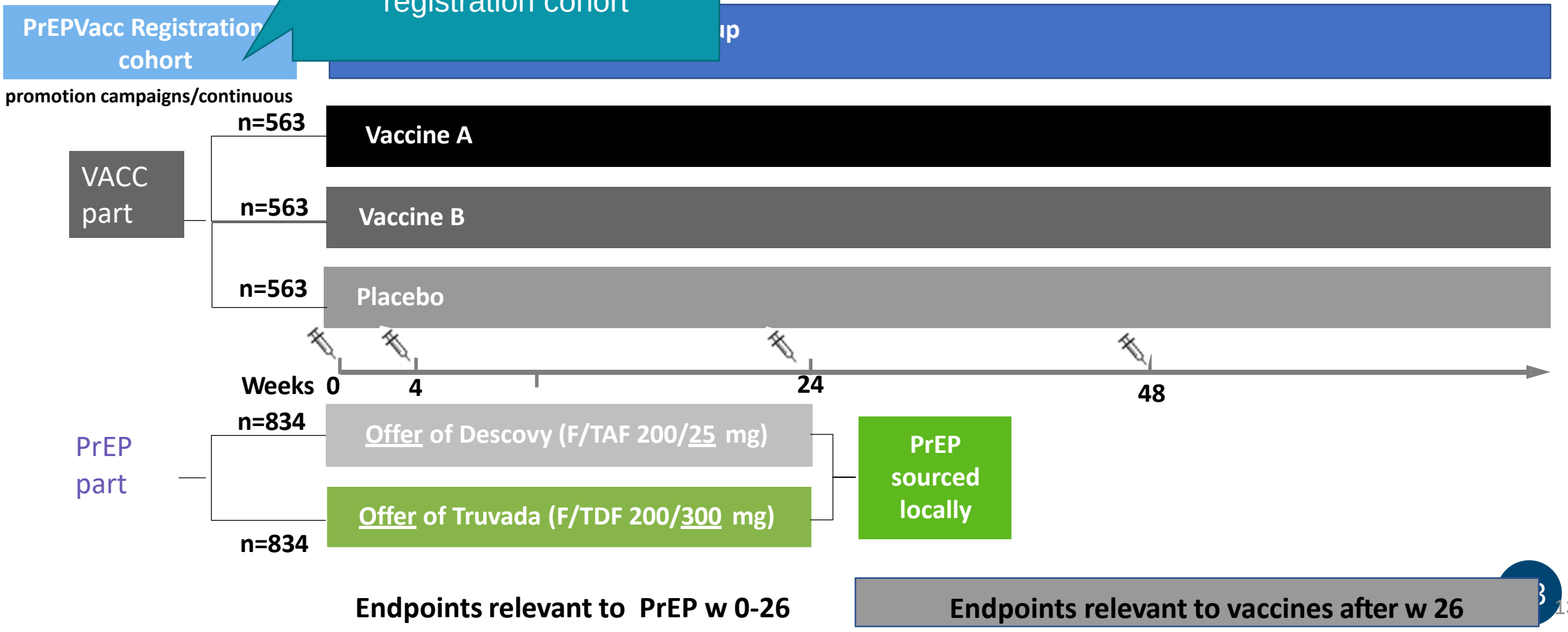


JIAS 2023, Donnell. Counterfactual estimation of efficacy against placebo for novel PrEP agents using external trial data: example of injectable cabotegravir and oral PrEP in women

2. Registrational cohort as counterfactual

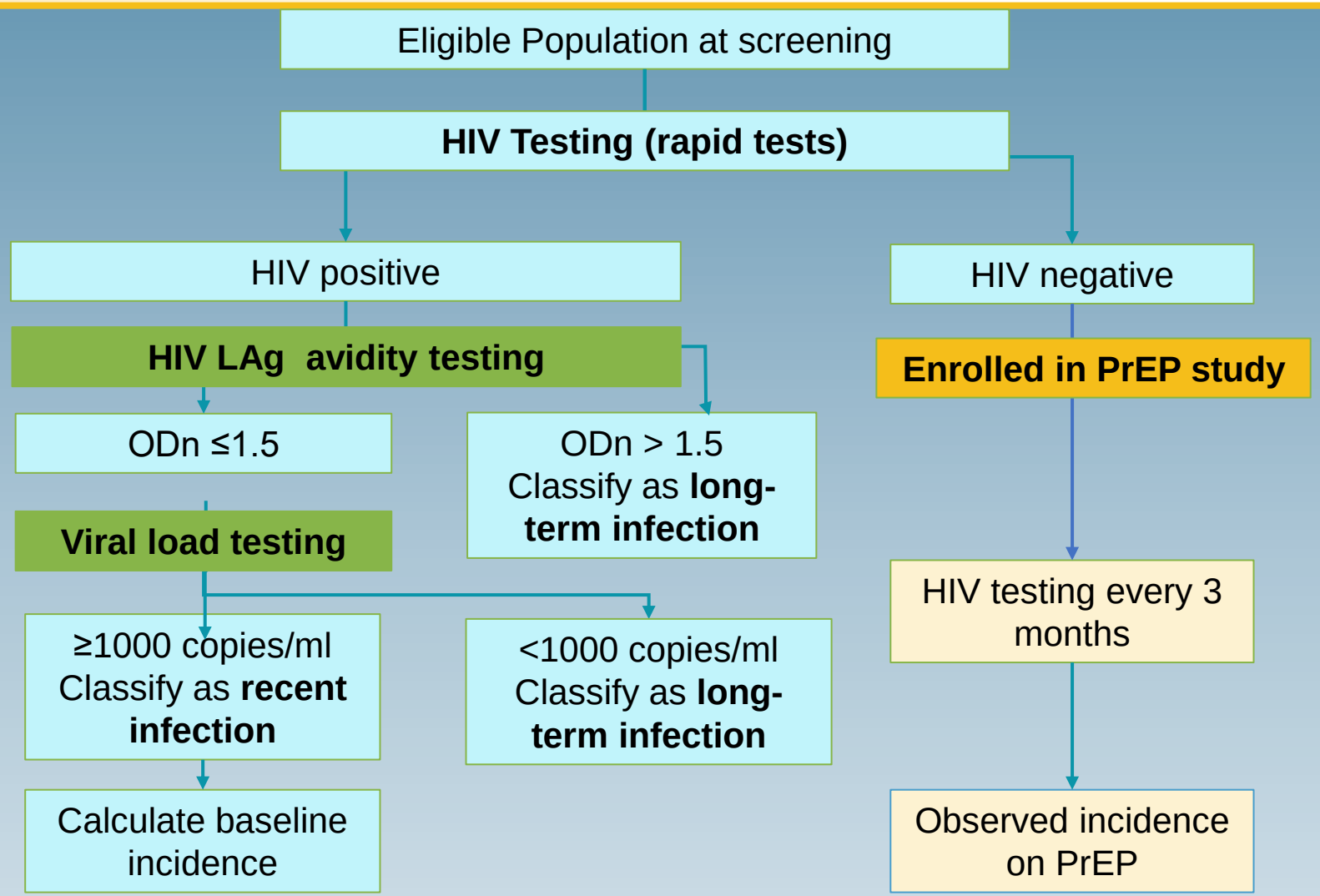
- A Phase II … rophylactic HIV vaccine trial with a concurren… pare F/TAF PrEP to TDF/FTC PrEP

Increasingly expect effective use of PrEP in the registration cohort



2. Counterfactual using Recency Testing Algorithm (RITA) at Screening

- Limiting Antigen Avidity Enzyme Immunoassay (LAg) results (normalized optical density ODn)
- Viral load
- LAg avidity and viral load results:[1-3]
  - ODn >1.5 classify as **long-term infection** (no viral load testing)
  - ODn ≤1.5 + VL≥ 1000 copies/ml classify as **recent infections**
  - ODn ≤ 1.5 + VL < 1000 copies /ml classify as **long-term infection**
  - Incidence estimate validated for 2 year window



1. Duong YT et al. Recalibration of the limiting antigen avidity EIAhttps://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC4339840&blobtype=pdf
2. https://www.sediabio.com/wp-content/uploads/2021/05/LN-6039-09PackageInsertLAgAvidityEIA.pdf
3. Oliver et al ; Validation of the Limiting Antigen Avidity Assay in Rakai, Uganda: https://doi.org/10.1089/aid.2018.0207

2. Counterfactual using Recency Testing Algorithm (RITA) at Scr

- Limiting Antigen Avidity Enz… Immunoassay (LAg) results (normalized optical density ODn)
- Viral load
- LAg avidity and viral load results:[1-3]
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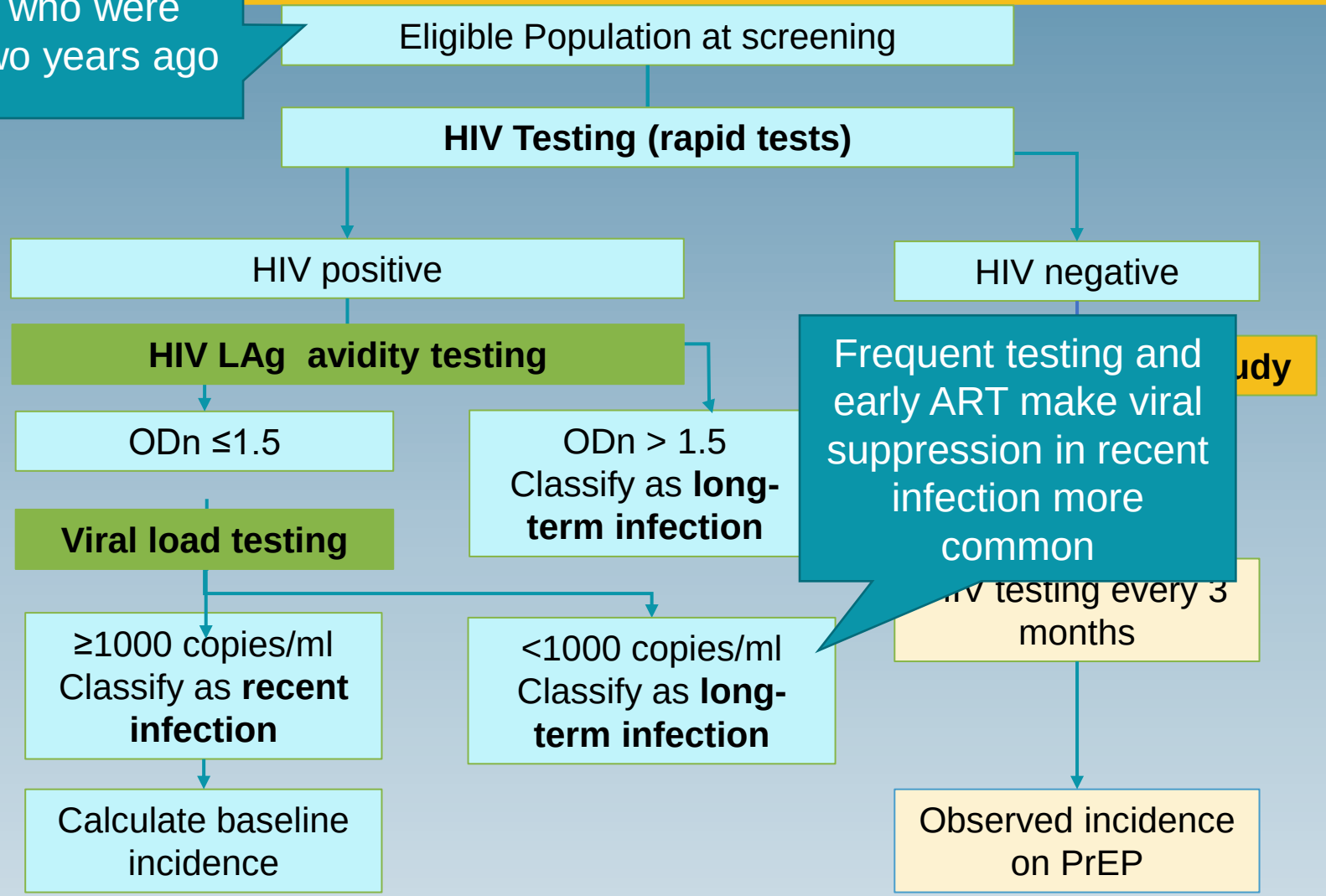
  - Incidence estimate validated for 2 year window

Representative of eligible population who were uninfected two years ago



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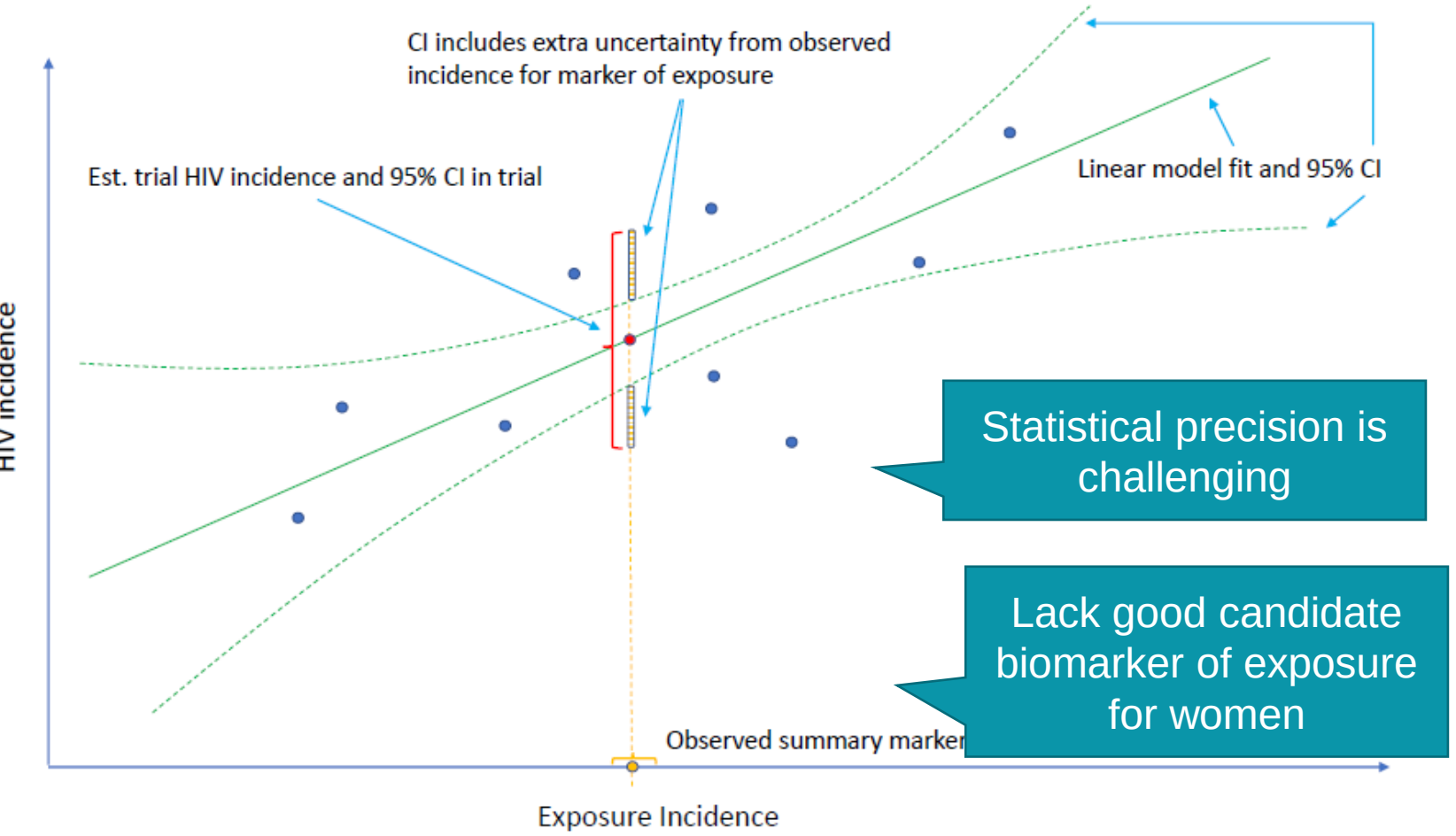
4. Estimating HIV incidence using biomarker of HIV exposure

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



Statistical precision is challenging

Lack good candidate biomarker of exposure for women

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

Clinical trials, Zhu, under revision

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 navigate this path (e.g. Forum for Collaborative Research PrEP project)
- Our common goal is to ensure a future with a multiple highly effective, readily available and widely used biologics

Thank you

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