Deborah Donnell
Professor, Vaccine and Infectious Disease

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Statistical Considerations for PEP trials

Fred Hutch Cancer Center

Disclosure

I have served as a scientific advisor to **Merck & Co., Inc.**

I receive research funding from the **NIH** and the **Bill & Melinda Gates Foundation**.

"Given the established challenges of conducting traditional RCTs for a PEP indication, the working group continues to evaluate alternative pathways for obtaining a formal regulatory label."

HIV Post-Exposure Prophylaxis Working Group:
April 15th, 2026

"Placebo-controlled trials are unethical as PEP is already the standard of care, and superiority trials are nearly impossible due to low event rates. "

HIV Post-Exposure Prophylaxis Working Group:
February 11th, 2026

"A randomized, active-controlled design to evaluate the performance of a novel PEP candidate against current standard-of-care practice…traditional design likely unfeasible"

HIV Post-Exposure Prophylaxis Working Group:
March 12th, 2026

Statistical considerations

Risk of exposure

Infection risk

Effect size

Statistical considerations

By the numbers: Risk of exposure

TasP Era

- Risk of exposure to an untreated PLWH in a high prevalence setting
  - Prevalence of HIV: 15-30%
  - Probability of non-suppressed VL (95-95-95)

Risk of exposure

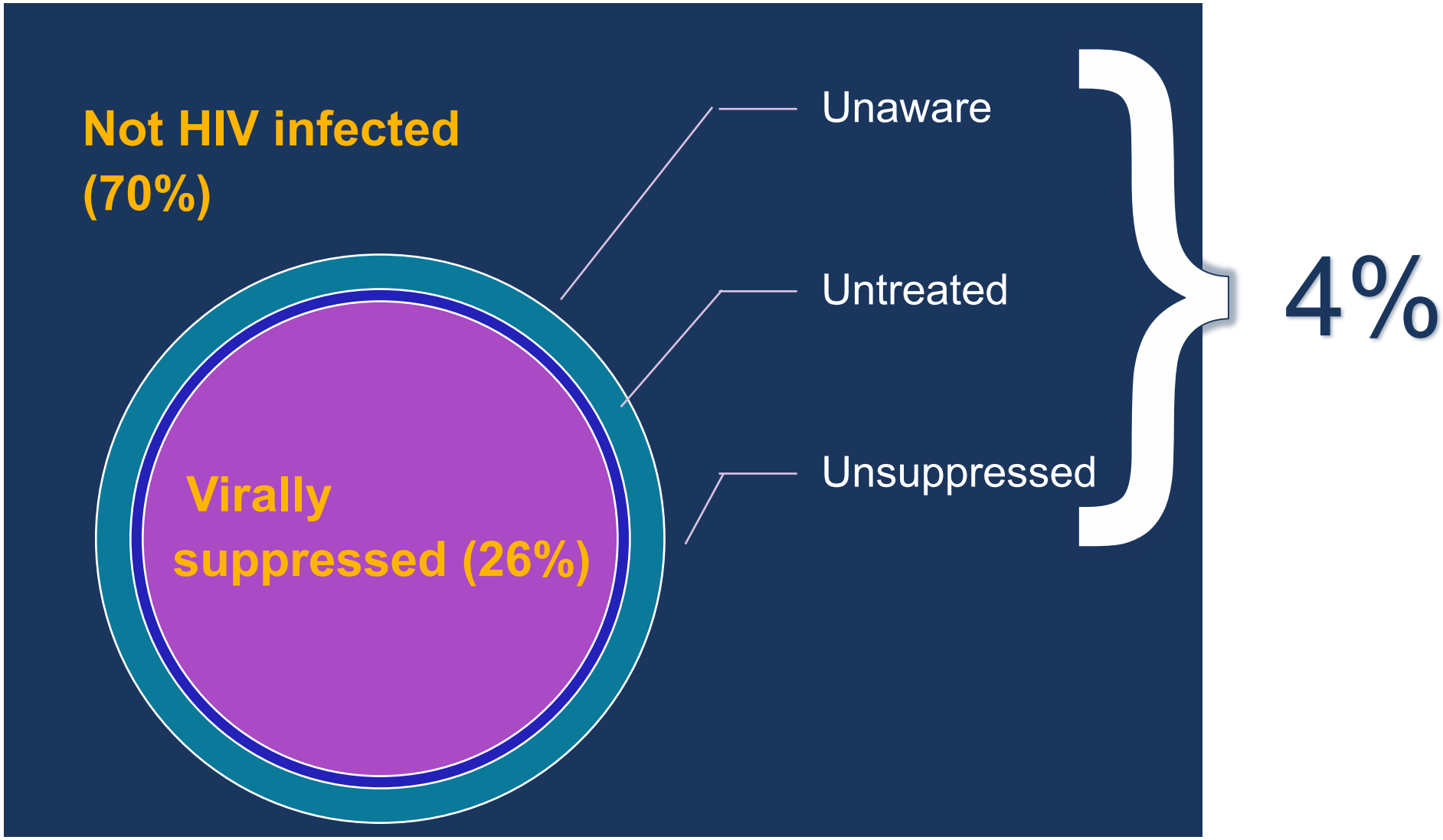
Infection risk

Effect size

Risk of a viremic exposure

Country	Know HIV status (%)	On ART (%)	Virally suppressed (%)	Adult HIV prevalence – women (%)	Adult HIV prevalence – men (%)	Viremic exposure from women	Viremic exposure from men
Eswatini	94–95	98	98	30.4	18.7	2.96%	1.82%
Botswana	95	95	92	26.2	15.2	4.45%	2.58%
Lesotho	~95	~94	~98	23.5	13.4	2.93%	1.67%
Zimbabwe	~95	~95	~95	13.0	7.9	1.85%	1.13%
Namibia	~91	~92	~90	15.7	9.3	3.87%	2.29%
South Africa	~92	~75–77	~92	22.3	11.0	8.14%	4.02%

Risk of a Viremic Exposure Is Low



Statistical considerations

By the numbers: Infection risk from PLWH not virally suppressed

Pre HAART ERA (Boily 2009)

- Low-income country (2009), w/o commercial sex
  - Female-to-male **0.38% per act** [95% CI 0.13-1.10] and
  - Male-to-female **0.30% per act** [95% CI 0.14-0.63]
  - Male-to-male **1.7% per act** [95%CI 0.3-8.9]

TasP Era

- Risk of infection from a single exposure with PLWH (no ART/no condom; CDC/Patel 2014):
  - Receptive anal: ~1–2%
  - Insertive anal: ~0.1%
  - Receptive vaginal: ~0.08%
  - Insertive vaginal: ~0.04%

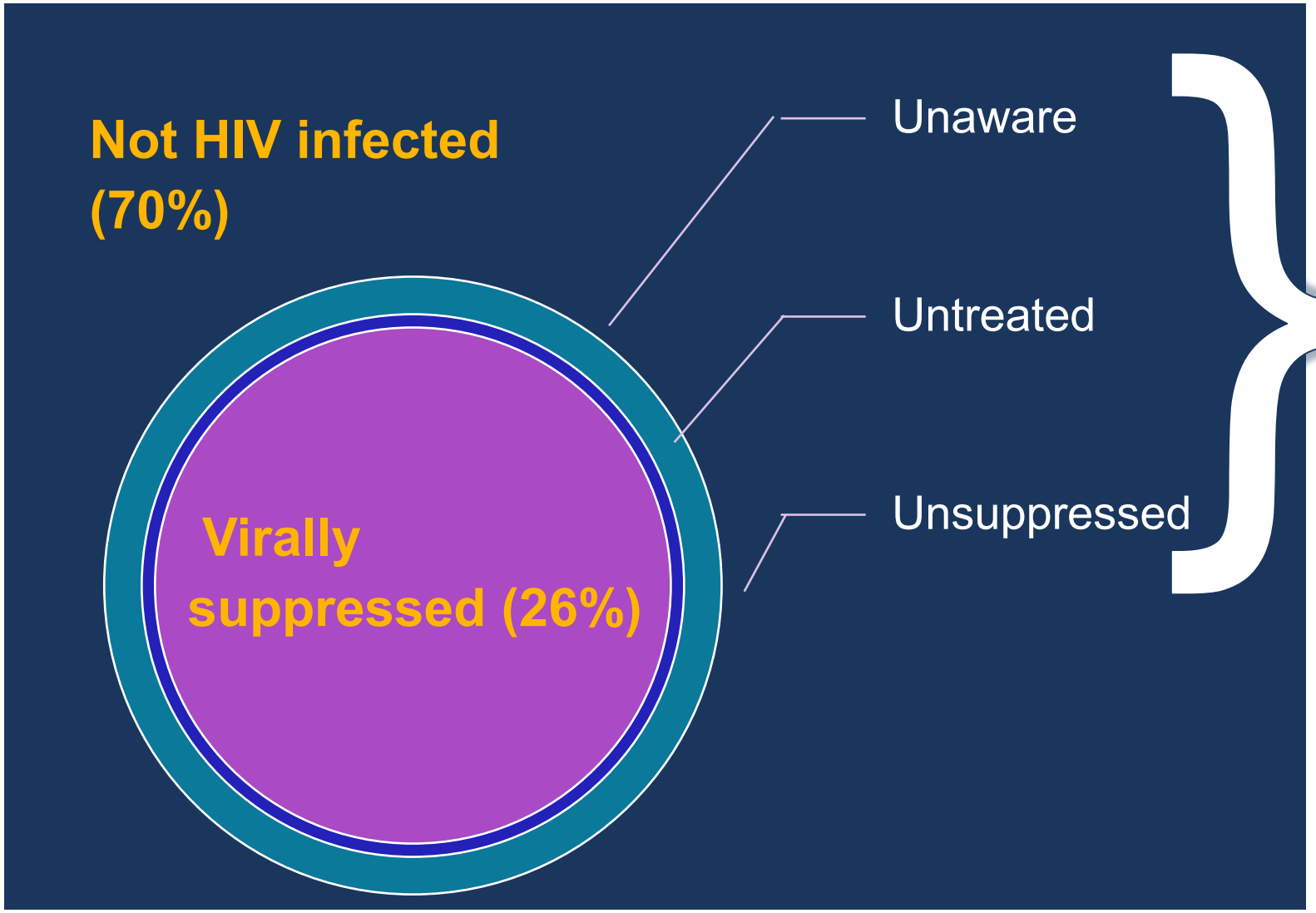
Risk of infection from a viremic sexual exposure is very small

Risk of exposure

Infection risk

Effect size

HIV Transmission Risk from a Single Sex Encounter Is Very Low



4% x ~0.08%
=3/10,000

Statistical considerations

By the numbers: Effect size

- No PEP efficacy studies
- PrEP trials efficacy of all drugs when taken exceed 90%
- Oral PEP coverage over 28 day is modest, but PEP breakthroughs are rarely observed
- SOC effectiveness likely to be high ~90%

Risk of exposure

Infection risk

Effect size

Very, very small risk of infection per PEP dispense

For every 10,000 people you give PEP for a potential exposure

- *Without* PEP, expect ~1-5 seroconversions
- ***With*** PEP, expect 0 (i.e. 0.1-0.5).

PEP trials in humans

Primary endpoint: adherence/coverage

	N	PY	Seroconversion	
Observational				
Toronto PEP-in-Pocket	43	32 PY	0	Rashotte et al., Int J STD AIDS
Toronto multi-year PEP-in-Pocket cohort	111	179 PY	0	Billick et al., JAIDS (2023)
Randomized		**Completion**		
MiPEP Trial	213	71%/65%	0	Milinkovic et al., J Antimicrob Chemother (2017)
RAL-PEP Trial (Barcelona)	243	43%/43%	1 (Day 90)	Leal et al, J Antimicrob Chemother (2017)
MARAVI-PEP Trial	237	38%/44%	0	Leal et al, J Antimicrob Chemother (2016)

Mimic PrEP approach: follow-up on PEP prevention “strategy”

Follow PEP users over time e.g. Propose PEP-in-pocket prevention strategy for non-PrEP users

- Little data to evaluate preference for strategy
  - PEP-in-pocket trials small
  - Pharmacy PrEP did not attempt longitudinal follow-up of PEP users
- Breakthrough infections from failure to use PEP: is this our question?

Strawman concept

Enroll and follow participants who choose a PEP-in-pocket prevention strategy

Randomize to

- PEP SOC (28 day oral treatment) vs
- Novel PEP (longer acting)

Assume PEP SOC is 90% effective (no data)

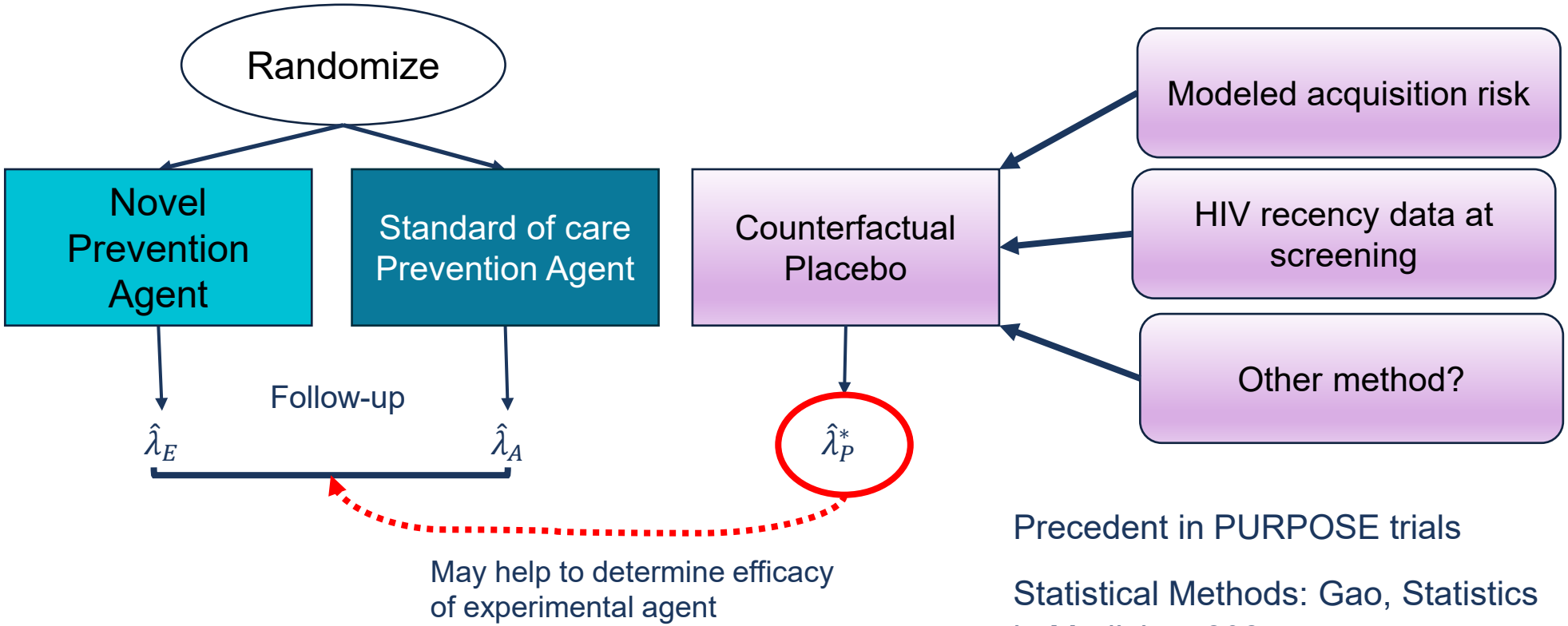
- Assume background rate of 2/100 person year (lower risk)
- Lack of efficacy data motivates explicit estimation of infection rate without PEP (counterfactual placebo)

Goal to show novel PEP is similarly effective (e.g. rule out less than 68%)

Counterfactual Placebo Design

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



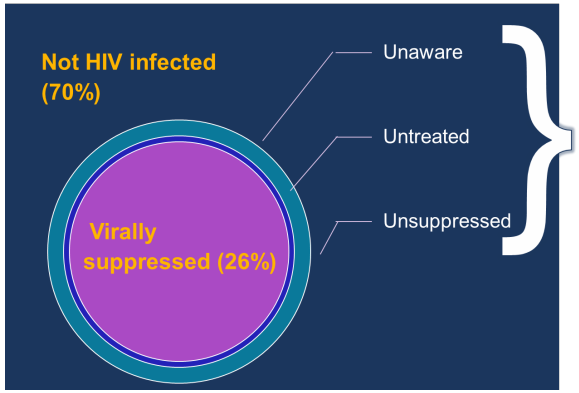
Precedent in PURPOSE trials

Statistical Methods: Gao, Statistics in Medicine, 2025

PEP counterfactual

Counterfactual placebo: the HIV incidence that would have been observed had a placebo (no PIP) arm been included

- Have no PEP efficacy trials
- Recency testing – not on PrEP, interested in PEP-in-pocket
- Modelling a reliable estimate of risk of HIV acquisition without PEP
  - HIV prevalence
  - Risk of viremic HIV exposure (95-95-95)
    - Unknown infection
    - Known, Untreated infection
    - Unsuppressed, treated infection
  - Risk of acquisition from (type of) sexual risk exposure



4% x ~0.08% =3/10,000

Sample Size For Counterfactual-Augmented design

- **Enroll and follow a cohort on PIP for 2 years**
- **Assume counterfactual placebo rate of 2/100 person years**
- Active control efficacy of 90%; incidence rates of 0.2/100 person years
- NI Margin of 68%; equivalent to testing experimental product efficacy 68% vs 90%.

	Non-Inferiority	SOC vs Novel PEP with Counterfactual	SOC vs Novel PEP with Conservative CF
Total Follow-up PY	25,107	7,611	9,567
Total N (2-year f/u)	12,554	3,806	4,784
#Events (alt)	50	14	19

- Given low transmission risks and PEP effectiveness, breakthrough infections may occur primarily for failure to use PEP, rather than failure of PEP

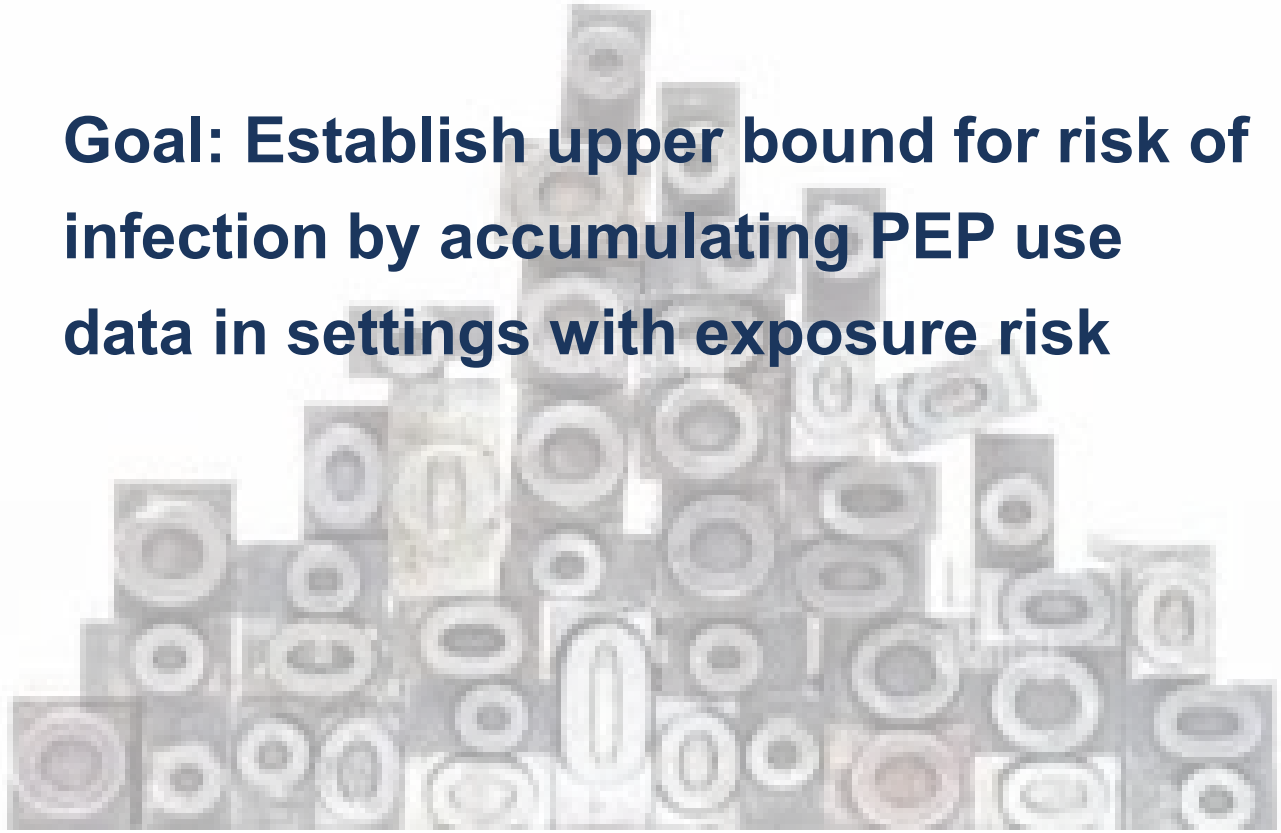
Alternatively:

Get data on HIV infection risk in humans on PEP

Low expectation of seeing any breakthrough infections

Plan a (near)-zero event trial

Goal: Establish upper bound for risk of infection by accumulating PEP use data in settings with exposure risk



Zero event “evidence”

Upper bound for the infection probability/rate using PEP if 0 events observed

PEP Exposure		PEP cohort (followed for one year)	
N	Upper 95% bound on event probability (per 100 exposure months (100 PY))	N	Upper 95% limit on event rate (per 100 PY)
500	0.60% (7.2/100 PY)	250	1.2/100 PY
1000	0.30% (3.6/100 PY)	500	0.6/100 PY
2000	0.15% (1.8/100 PY)	1000	0.3/100 PY
5000	0.06% (0.7/100 PY)	1500	0.2/100 PY
10000	0.03% (0.4/100 PY)	2000	0.15/100 PY

Conclusion

- It is infeasible to conduct a traditional RCT strategy for a PEP indication
- Obtaining evidence that supports low risk/low rates of infection with PEP in humans would require follow-up with a PEP prevention strategy
  - Enrollment larger than PrEP trials
  - Unclear whether there is a demand for PEP as a prevention strategy
  - PEP breakthrough probability at time of use would be secondary analysis
- Acquiring human data about HIV risk with PEP use could elicit an upper bound for risk of infection.