HIV Post-Exposure Prophylaxis: Clinical Trial Designs

Evaluating novel PEP-in-pocket prevention strategies for non-PrEP users —from counterfactual placebo approaches to zero-event trials, preference-based designs, and pragmatic trials focused on PEP regimen completion rates.

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The PEP-in-Pocket Prevention Gap

Despite growing interest in PEP-in-pocket (PIP) as a prevention strategy for individuals who decline PrEP, robust longitudinal evidence remains sparse. Prior trials have been small, and pharmacy-based PrEP programs have not attempted systematic longitudinal follow-up of PEP users.

Limited Trial Data

PEP randomized trials have enrolled small cohorts — insufficient to power efficacy conclusions or characterize preference patterns at population scale.

No Longitudinal Follow-Up

Pharmacy PrEP programs have not tracked PEP users over time, leaving critical gaps in long-term behavior and breakthrough infection risk.

Key Unanswered Question

Are breakthrough infections driven by **failure to use PEP** (behavioral) or **failure of PEP** (pharmacologic)? Trial design must distinguish these mechanisms.

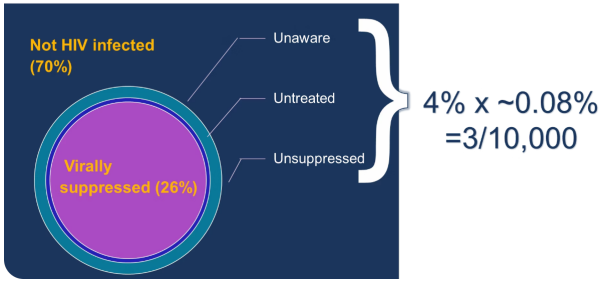
DESIGN 1

Counterfactual Placebo Design

An active-controlled trial augmented by a modeled **counterfactual placebo** —the HIV incidence that would have been observed had a no-PEP arm been included. This draws on precedent from the PURPOSE trials and statistical methods by Gao (*Statistics in Medicine*, 2025), enabling efficacy estimation without an unethical placebo arm.

1	2	3
Novel PEP Arm	**SOC PEP Arm**	**Counterfactual Placebo**
Investigational longer-acting agent; HIV incidence tracked prospectively over 2 years.	Standard 28-day oral PEP; active comparator benchmark for non-inferiority testing.	Modeled HIV acquisition risk from recency data at screening and population-level epidemiologic parameters —no actual placebo arm enrolled.

The counterfactual is constructed from: HIV prevalence, risk of viremic exposure (95-95-95 cascade), per-act transmission probability, and frequency of exposure events. Combined estimate: **~4% × ~0.08% = 3/10,000 per exposure** in suppressed-dominant populations.



DESIGN 1 — SAMPLE SIZE

Counterfactual Design: Sample Size Impact

A 2-year follow-up cohort is powered under: counterfactual placebo rate of **2/100 PY**, SOC PEP efficacy of **90%** (incidence 0.2/100 PY), and a non-inferiority margin of **68%**. Counterfactual augmentation substantially reduces required sample size.

Design Scenario	Total Follow-up (PY)	Total N (2-yr f/u)	# Events (alt)
NI: SOC vs. Novel PEP (no counterfactual)	25,107	12,554	50
SOC vs. Novel PEP **with Counterfactual**	7,611	3,806	14
SOC vs. Novel PEP **with Conservative CF**	9,567	4,784	19

Given low transmission risk and high PEP effectiveness, breakthrough infections are expected to reflect primarily **failure to use PEP** rather than pharmacologic failure — a key interpretive consideration for any observed events.

DESIGN 2

Zero-Event Trial Design

When breakthrough infections under effective PEP are anticipated to be extremely rare, a conventional event-driven non-inferiority trial becomes operationally implausible. The **near-zero event trial** shifts the inferential goal: accumulate sufficient PEP exposure data to establish a statistically rigorous upper bound on the infection rate.

Single PEP Exposure Design

N Exposures	Upper 95% Bound
500	0.60% (7.2/100 PY)
1,000	0.30% (3.6/100 PY)
2,000	0.15% (1.8/100 PY)
5,000	0.06% (0.7/100 PY)
10,000	0.03% (0.4/100 PY)

PEP Cohort (1-Year Follow-Up)

N Enrolled	Upper 95% Limit
250	1.2/100 PY
500	0.6/100 PY
1,000	0.3/100 PY
1,500	0.2/100 PY
2,000	0.15/100 PY

Enrolling ~1,000–2,000 participants with one-year follow-up can establish an upper bound below 0.3/100 PY—potentially sufficient to support efficacy claims without a single observed infection.

DESIGN 3

Pragmatic Trials: PEP Completion Rates

A three-trial clinical program evaluating **single-dose PEP versus 28-day SOC**, designed to demonstrate superior completion rates across key exposure populations. Design: randomized, open-label, pragmatic superiority trials. Primary endpoint: proportion completing PEP regimen. Total N=300 (100 per trial).

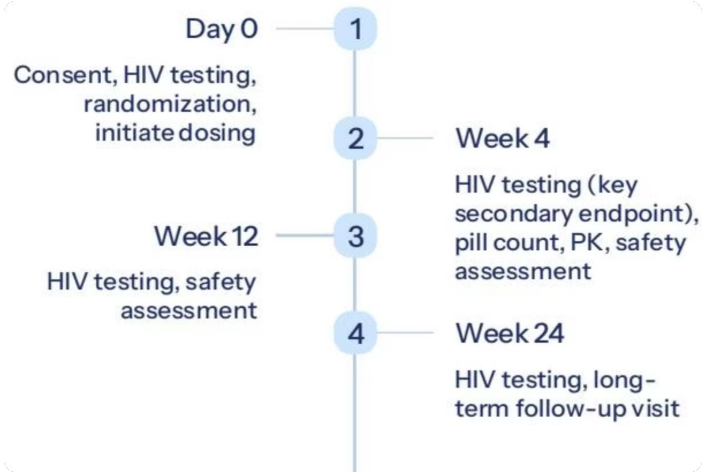
	Trial 1: MSM	Trial 2: Female Sexual Assault Survivors	Trial 3: Occupational Exposure
Exposure	Receptive anal intercourse	Vaginal and/or anal exposure	Needlestick, blood splash, etc.
Sample Size	N=100 (50/arm)	N=100 (50/arm)	N=100 (50/arm)
Expected LA Completion	>95%	>95%	>95%
Expected SOC Completion	56%	50%	65%
Power to Show Superiority	>95%	>95%	>95%

Even if SOC completion rates are as high as **80%**, each study retains **~90% statistical power** to demonstrate superiority of single-dose PEP.

DESIGN 3 — TRIAL TIMELINE

Trial Structure & Follow-Up Schedule

Hypothesis: Single-dose PEP achieves superior completion vs. 28-day SOC. The trial follows participants from Day 0 through Week 24 with HIV testing, pharmacokinetic, and safety assessments at key timepoints.



DESIGN 4

Preference Trial: Hybrid Randomization & Choice

Modeled on CoVPN 3006 and mental health/addiction treatment preference trials, this **Comprehensive Cohort Design** randomizes willing participants to novel long-acting PEP vs. SOC PEP, while allowing unwilling participants to self-select their preferred agent. This uniquely enables simultaneous estimation of treatment, selection, and preference effects.

Path 1: No Preference (Randomized)

Undecided participants are **randomized** to SOC or long-acting PEP. Unwillingness to be randomized is **not** an exclusion criterion.

Path 2: Long-Acting PEP (Choice)

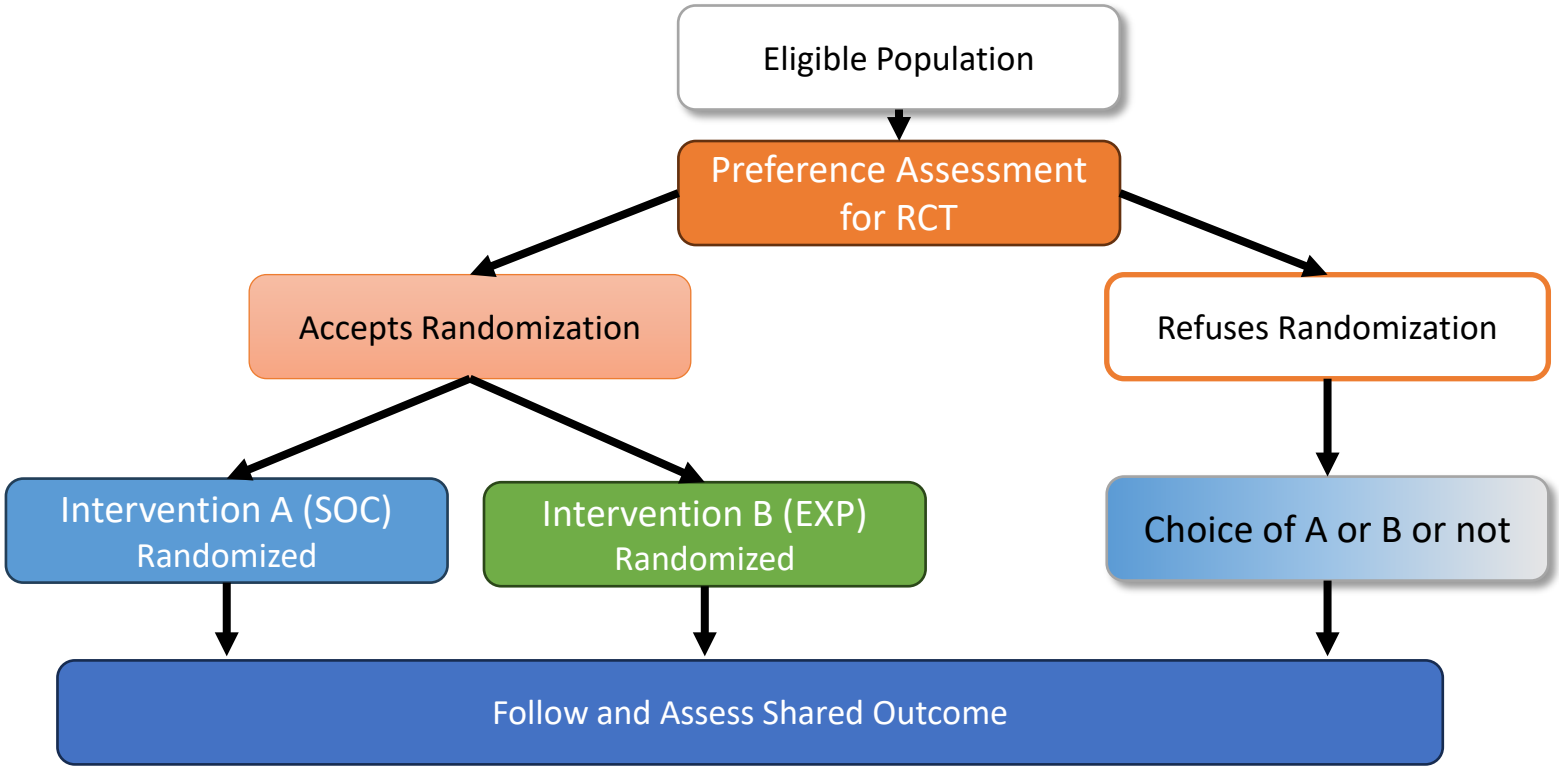
Participant actively selects the novel longer-acting PEP formulation. Drug levels assessed at weeks 2, 4, and 6.

Path 3: SOC PEP (Choice)

Participant actively selects standard 28-day oral post-exposure prophylaxis based on personal preference.

Comprehensive Cohort Design

Combining randomized & observational arms within a single trial



(Schmoor et al 1996)

Comparing All Four Design Approaches

Each design addresses a distinct evidentiary need — from efficacy estimation to adherence superiority and real-world preference. The table below summarizes the key trade-offs.

Design	Strengths (Pros)	Limitations (Cons)	Best Suited For
Design 1: Counterfactual Placebo	Avoids unethical placebo arm; reduces sample size ~3× vs. standard active-control; enables absolute efficacy estimation of each agent	Relies on modeled assumptions for counterfactual; validity depends on accuracy of epidemiologic parameters; complex statistical methodology	Comparative efficacy of novel vs. SOC PEP where placebo is unethical
Design 2: Zero-Event Trial	Feasible when infections are extremely rare; provides regulatory-grade upper bound; no observed events required	Cannot demonstrate superiority or non-inferiority directly; upper bound may not satisfy all regulatory bodies; no comparative arm	Safety/efficacy evidence accumulation for highly effective PEP in low-incidence settings
Design 3: Pragmatic Completion Trials	Directly addresses the behavioral adherence gap; high power with small N=100/trial; covers three key exposure populations	Does not measure HIV efficacy; open-label design introduces performance bias; completion ≠ effectiveness	Demonstrating single-dose PEP superiority on adherence across MSM, sexual assault, and occupational cohorts
Design 4: Preference/Comprehensive Cohort	Captures real-world treatment selection; estimates preference, selection, and treatment effects simultaneously; maximizes enrollment by including non-randomizable participants	Preference cohorts may be confounded; more complex analysis; results may be harder to interpret for regulatory purposes	Implementation science; understanding who chooses which PEP and why in real-world settings