Andrew Mujugira, Infectious Diseases Institute, Uganda

Advances in HIV post-exposure prophylaxis

Advancing PEP: Key Findings from the 2026 Johannesburg HIV PEP Summit

AIDS 2026

26–31 July • Rio de Janeiro, Brazil

aids2026.org

Disclosures

Site investigator for Merck EXPrESSIVE-10 clinical trial

Consultant (Merck, Inc., Decera Clinical Education)

AIDS 2026

Why PEP Trial Design Matters Now

The Evidence Gap

No current PEP regimen was approved based on dedicated, large-scale randomized controlled trials (RCTs). Applying stringent RCT requirements to novel candidates creates an artificial barrier when the standard of care itself lacks equivalent evidence. This structural inequity hinders innovation and misses urgent prevention opportunities.

HIV PEP Workshop, May 2026

The Johannesburg workshop brought together a diverse group of stakeholders and leading voices in HIV prevention research, policy, implementation, and regulatory science. The overarching goal was to build consensus on future clinical trials that are simultaneously ethical, acceptable, inclusive, feasible, and efficient.

The challenge in acquiring RCT evidence for HIV PEP is daunting.
However, it is a key justification for adopting innovative trial designs.

Biological Rationale: The Race Against Time

AIDS 2026

1

Founder Population

HIV is established within **2 hours to 3 days** post-exposure, with **~40–50 productively infected cells** in the cervicovaginal or rectal mucosa. Minimal virus in systemic lymphoid tissues at this stage.

2

Local Expansion

Draining lymph nodes amplify infection via immune activation, recruiting susceptible target cells. This phase represents the critical window before systemic dissemination becomes irreversible.

3

Systemic Spread

Without intervention, HIV disseminates systemically. PEP success relies entirely on interrupting this cascade. Early initiation keeps the founder population small; sufficient duration blocks expansion.

Because PEP is initiated when target cells are completely unprotected, its success relies entirely on a race against time. Early initiation keeps the founder population small, while a sufficient duration of treatment blocks local expansion and systemic spread. These two biological pillars determine PEP efficacy.

Sources: Haase, Annu Rev Med. 2011; Miller, J Virol. 2005

Four Candidate PEP Trial Designs

AIDS 2026

Each design is a distinct methodological approach to generating evidence for novel PEP candidates in an ethical, efficient framework.

1

Counterfactual Placebo

Active-controlled trial comparing novel long-acting PEP vs. 28-day oral SOC, augmented by a **mathematically constructed placebo cohort**. No actual placebo arm is enrolled. Draws on PURPOSE 1 and 2 trial precedents and Gao (2025) statistical methodology.

2

Pragmatic Trials

Three concurrent open-label trials (N=300 total) with men who have sex with men, female sexual assault survivors, and occupational exposure cohorts. Primary endpoint: **regimen completion rate**, not biological efficacy.

3

Preference Trial

Blends an RCT with observational choice paths for participants unwilling to be randomized. Modeled after CoVPN 3006. Best suited as an **open-label extension strategy** once biological efficacy is established.

4

Zero Event Trial

Accumulates large volume prospective exposure data to establish a **statistically rigorous upper 95% confidence bound** on the true infection rate. Designed for near zero breakthrough settings where event-driven trials are implausible.

Sources: Gao F, Stat Med. 2025 Mar 15;44(6):e70022; Vielot NJ. Vaccine 2024 Oct 3;42(23):126237

Is The 28-day Regimen Necessary?

AIDS 2026

The Completion Paradox

Only **58% of clients** complete the full 28-day PEP regimen in real-world settings, yet retrospective data still demonstrate high efficacy. This apparent contradiction raises a critical scientific question. Is the full course always necessary?

What the Literature Tells Us

Modeling studies suggest initiating a three-drug regimen within 48 hours post-exposure, achieves 90% efficacy if taken >14 days. However, most real-world clients do not initiate PEP until closer to the 72-hour mark, necessitating the full 28-day course to prevent systemic spread.

The Access Imperative

This biological reality creates a programmatic imperative. Clients must be able to access and initiate PEP within the first 24 hours of exposure. Two strategies have emerged as priority interventions:

PEP-in-Pocket

Pre-positioned regimens enabling immediate self-initiation without healthcare contact

Automated Vending

Automated vending machines providing 24/7 access to PEP starter packs in high-incidence settings

Sources: Zhang, Int AIDS Soc. 2025, Allan-Blitz, J Int AIDS Soc. 2024; Liu, Ann Med. 2023

Design 1: Counterfactual Placebo

Active-controlled trial comparing a novel longer-acting PEP agent against a standard 28-day oral SOC arm, augmented by a modeled counterfactual placebo cohort. No actual placebo arm is enrolled. This design draws on precedents established by the PURPOSE trials and uses statistical methodology formulated by Gao (2025) to ethically estimate absolute efficacy. Counterfactual acquisition risk is estimated at approximately **3 per 10,000 exposures** in virally suppressed-dominant populations.

Sample Size Comparison: Noninferiority vs. Counterfactual Designs

Design Scenario	Total Follow-up (PY)	Total N (2-yr)	Events (Alt. Hypothesis)
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 Counterfactual	9,567	4,784	19

The counterfactual approach reduces required sample size by approximately **70%** relative to a standard noninferiority design without a modeled placebo. This is a substantial efficiency gain, provided the epidemiological assumptions are accepted by regulators.

Source: Gao F, Stat Med. 2025 Mar 15;44(6):e70022

Design 1: Key Limitations

AIDS 2026

Operational Infeasibility

Enrolling approximately **4,000 non-PrEP users** who are at risk and tracking them prospectively for two years is logistically demanding. This requirement necessitates **40 or more clinical sites**, creating substantial infrastructure and administrative burdens that may be unachievable within realistic trial timelines and budgets.

Dynamic Cohorts

Data from the ANRS-Prevenir study in France revealed that **39% of participants** switched from on-demand PrEP to daily PrEP during follow-up. Frequent PEP users routinely transition to PrEP over time (~30%), eroding the integrity of the prospective cohort and introducing significant attrition bias that cannot be easily adjusted for in analysis.

Regulatory Uncertainty

Reliance on modeled epidemiological assumptions to construct the counterfactual placebo introduces multiple points of uncertainty. This erodes confidence among both investigators and regulatory reviewers, who must accept the validity of assumptions they cannot directly verify from trial data. The degree of regulatory acceptance remains uncharted territory.

⚠ Design 1 offers theoretical efficiency gains but faces significant operational and regulatory hurdles that may limit its real-world applicability.

Sources: Molina Lancet HIV 2022; Zhang BMC Public Health 2025

Design 2: Pragmatic Trials

Trial Structure

Three concurrent open-label superiority trials with a total enrollment of **N=300 (100 per trial)**, targeting three clinically and epidemiologically distinct populations:

- Men who have sex with men
- Female sexual assault survivors
- Occupational exposure cohorts

Intervention: single-dose novel long-acting PEP vs. 28-day oral SOC. The primary endpoint is entirely behavioral, i.e., the **proportion of participants completing their assigned regimen**.

Expected Performance

- Novel LA PEP completion: **>99%**
- SOC completion across cohorts: **50–65%**
- Statistical power for superiority: **>95%**

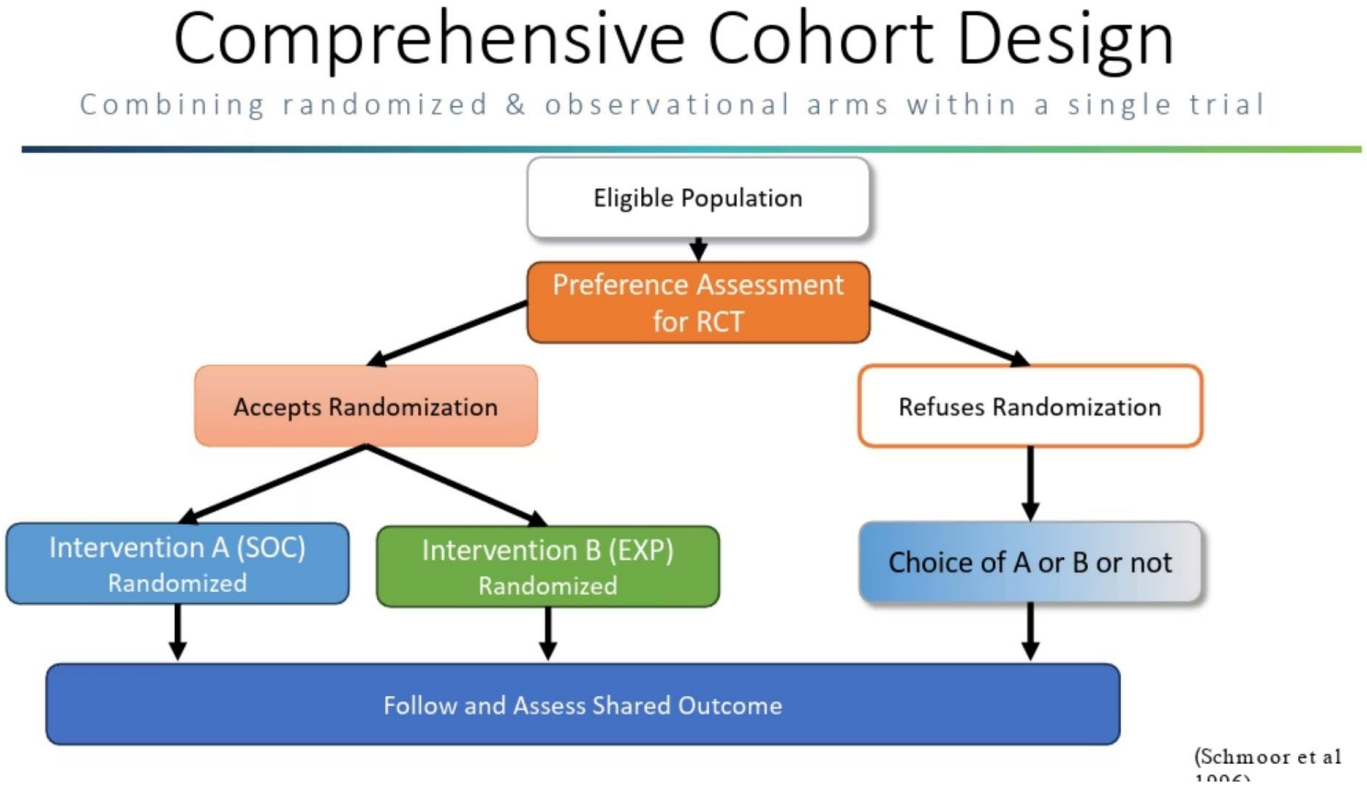
Core Regulatory Limitation

Despite the compelling operational advantages and the realistic prospect of achieving statistical superiority on the completion endpoint, Design 3 faces a fundamental regulatory barrier.

Regulators usually require **confirmation of biological efficacy,** direct evidence that a drug pharmacologically aborts viral replication following exposure, regardless of participant compliance.
Regimen completion, however superior to SOC, does not constitute evidence of biological protection. This design cannot, on its own, satisfy regulatory requirements for product approval or label claims.

Robertson M, HIV PEP Workshop 2006

Design 3: Preference Trial with Hybrid Randomization and Choice



Trial Design

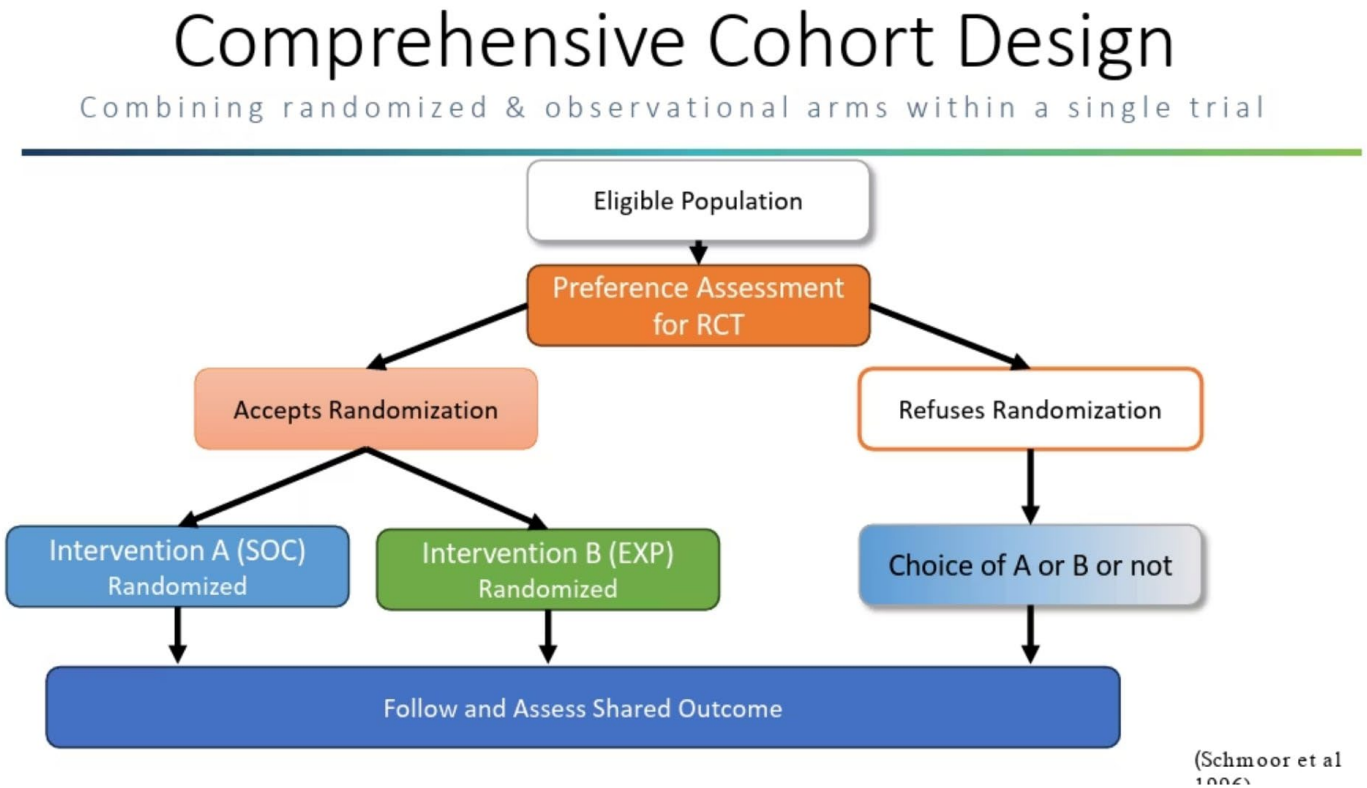
Modeled after CoVPN 3006, this design accommodates participant preferences by creating parallel enrollment paths.

Participants willing to be randomized are assigned to A or B. Those unwilling to be randomized are not excluded. They choose A, B or none, preserving their inclusion in the evidence base while respecting autonomy.

This design is best suited as an open-label extension strategy once a drug has been proven biologically effective. This enables a structured transition from continuous daily PrEP-style use to as-needed PEP-in-pocket deployment in real-world conditions.

CoVPN 3006: Vielot NJ. Vaccine 2024; Brown E. CROI 2026

Design 3: Preference Trial with Hybrid Randomization and Choice



Preference Trial

Pros:

a) Captures real-world preference, selection, and treatment effects simultaneously
b) Provides ministries with real-world data alongside trial data.

Cons:

a) The proportion of participants willing to be randomized is entirely unknown
b) Requires a very large sample size

CoVPN 3006: Vielot NJ. Vaccine 2024; Brown E. CROI 2026

Design 4: The Zero Event Trial

When evaluating highly effective PEP products in low-incidence settings, breakthrough infections are anticipated to be near zero, rendering a traditional event-driven noninferiority trial operationally implausible. The Zero Event Trial is the current consensus design in response to this challenge.

Inferential Shift

Rather than counting breakthrough events, the design accumulates a large volume of prospective PEP exposure data to establish a **statistically rigorous upper 95% confidence bound** on the true underlying infection rate. Evidence is built through the consistent absence of infections, not their occurrence.

Pathway 1: Acute PEP Tracking

Prospective tracking of **individual acute PEP exposures**, documenting timing of initiation, dosing adherence, and outcome at each discrete exposure event. Provides dense per-exposure data suitable for pharmacological modeling.

Pathway 2: PEP-in-Pocket Cohort

Longitudinal enrollment of PEP-in-pocket users with **annual structured follow-up**, capturing repeated exposure events within the same individuals over time. Enables estimation of person-year incidence rates with high precision.

Zero Event Trial – Statistical Benchmarks

Enrolling 1,000–2,000 participants for one year bounds the upper infection limit below **0.3 per 100 person-years**, considered highly persuasive and potentially sufficient to satisfy regulatory efficacy claims without requiring a single breakthrough event to occur during the trial.

N Exposures	Upper 95% Bound	Equivalent Incidence	N Enrolled (1-yr)	Upper 95% Limit
500	0.60%	7.2/100 PY	250	1.2/100 PY
1,000	0.30%	3.6/100 PY	500	0.6/100 PY
2,000	**0.15%**	**1.8/100 PY**	**1,000**	**0.3/100 PY**
5,000	0.06%	0.7/100 PY	1,500	0.2/100 PY
10,000	0.03%	0.4/100 PY	2,000	0.15/100 PY

Each row demonstrates the statistical dividend of scale. Doubling exposure observations halves the upper confidence bound, progressively narrowing the uncertainty envelope around a true zero event outcome. The **1,000–2,000 enrolled participant range** is the consensus for regulatory plausibility.

Zero Event Trial Design (Advantages)

AIDS 2026

1. **High Operational Feasibility**
   This framework is highly realistic and logistically viable when evaluating modern, highly effective PEP candidates in settings where actual clinical breakthrough infections are exceptionally rare.

2. **No Requirement for Active Infection Events**
   The design circumvents the ethical and practical dilemmas of needing to witness a high number of breakthrough infections to establish statistical validity, allowing efficacy claims to be supported even with zero observed events.

3. **Provides a Regulatory-Grade Statistical Upper Bound**
   By generating a clear mathematical upper limit for the true underlying infection rate, it supplies regulators with a standardized, quantifiable index of safety and efficacy.

4. **Measures Per-Exposure Efficacy**
   Addresses what the per-exposure efficacy looks like under a controlled regimen.

5. **Bypasses the Hurdles of Proving Superiority**
   From an analytical design perspective, investigators do not face the large sample size and operational demands required to demonstrate superiority or standard noninferiority over an active comparator.

6. **Sequential Accumulation of Certainty**
   The design allows investigators to systematically increase their level of clinical certainty the more exposure data they successfully log without an infection. Repeating the zero-event observation across hundreds or thousands of exposures progressively solidifies proof that the prevention effect is a biological fact.

7. **Optimized Evidence Generation for Low-Incidence Settings**
   It serves as an ideal mechanism for safety and efficacy evidence accumulation for novel products in populations where background HIV transmission rates are low, but exposures still occur.

Comparing the Four Designs: Decision Framework

Design	Ethical	Feasible	Regulatory Certainty	Sample Efficiency	Biological Evidence
Design 1: Counterfactual Placebo	High	Low	Medium	High	High
Design 2: Zero Event Trial	**High**	**High**	**High**	**High**	**High**
Design 3: Pragmatic Trial	High	High	Low	High	Low
Design 4: Preference Trial	High	Medium	Medium	Medium	Medium

PEP Workshop Consensus

After systematic evaluation, the workshop reached consensus that the **Zero Event Trial (Design 2)** represents the most operationally feasible, ethically sound, and regulatorily credible pathway for generating approval-grade evidence for novel long-acting PEP candidates in contemporary low-incidence settings.

Complementary Designs

Design 3 (Pragmatic Trial) retains value as **supplementary evidence** for label claims related to adherence and access. Design 4 (Preference Trial) is positioned as a post-approval OLE tool. Design 1 (Counterfactual Placebo) remains viable as regulatory precedent for modeled placebo arms is established.

AIDS 2026

Key Takeaways

1 The evidentiary bar should be tailored to the standard of care

Requiring novel PEP candidates to meet RCT standards that existing approved regimens never met is scientifically inconsistent and ethically problematic. Trial design innovation is not a regulatory shortcut; it is a scientific necessity.

2 Biology dictates the 28-day regimen for most real-world clients

Modeling confirms the full course remains necessary for clients initiating at or near 72 hours. PEP-in-pocket and vending machine infrastructure must be treated as trial design prerequisites, not programmatic afterthoughts.

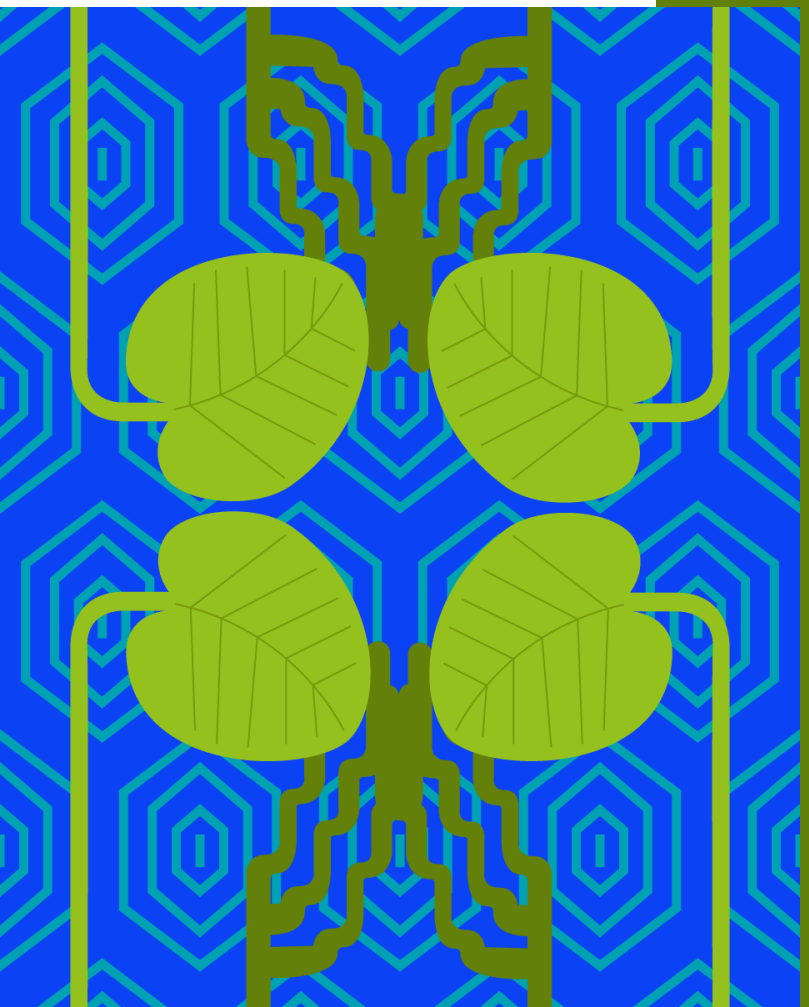
3 Zero Event Trial redefines meaning of "evidence" in near zero incidence settings

Accumulating thousands of zero-event observations provides statistically rigorous, regulatorily credible proof of biological protection. The upper 95% confidence bound is a credible primary efficacy metric, not breakthrough event counts.

4 Regulatory engagement is ongoing

Pre-specification of acceptable upper-bound efficacy thresholds with the FDA is essential before trial initiation. Sequential zero-event accumulation strengthens the biological proof case, but only if regulatory criteria are agreed in advance.

AIDS 2026



Acknowledgements

Forum for Collaborative Research
Deborah Donnell
Mike Robertson
Veronica Miller
Ken Mayer
Sinead Delany-Moretlwe
Logan Donaldson