THE FORUM FOR COLLABORATIVE RESEARCH

THE HIV POST-EXPOSURE PROPHYLAXIS (PEP) SUMMIT

A two-day summit co-hosted by the Forum for Collaborative Research and Wits RHI

May 11 – 12, 2026

Johannesburg, South Africa

1608 Rhode Island Avenue NW
Washington, DC 20036
www.forumresearch.org

THE FORUM For Collaborative Research℠
Berkeley's Hub for Regulatory Science

University of the Witwatersrand WITS RHI

UC Berkeley Public Health

CONTENTS

INTRODUCTION

The HIV PEP Summit brought together a diverse group of stakeholders and leading voices in HIV prevention research, policy, implementation, and regulatory science to accelerate HIV prevention research by building consensus on the future of clinical trials that are ethical, acceptable, inclusive, feasible, and efficient. The summit was organized by the Forum for Collaborative Research (Forum) of the University of California, Berkeley, and the Wits Reproductive Health and HIV Institute (RHI) of the University of the Witwatersrand. The Forum for Collaborative Research has a longstanding commitment to convening experts in trial design, pharmaceuticals, regulation, ethics, and community to confront these challenges. By partnering with Wits RHI, a premier African research institute renowned for its leadership in HIV and sexual health, the summit underscored the value of African leadership and innovation in shaping the future of HIV prevention research.

BACKGROUND

HIV PEP is a prevention option taken following a potential exposure to HIV within 72 hours, but ideally as soon as possible. PEP is a prevention tool, along with Pre-Exposure Prophylaxis (PrEP), testing/treatment, and prevention of mother to child transmission, that contributes to the anti-retroviral (ARV) implementation spectrum that may lead to end the HIV pandemic. PEP is often observed in two scenarios: an emergency setting where someone may have inadvertently been exposed to HIV, as in an assault or an occupational exposure, or in an on-demand (PEP in pocket) context. This summit and the clinical trial discussions predominantly focused on the former, with some implementation considerations for on-demand PEP.

Despite the use of HIV PEP for many years, little human PEP efficacy or effectiveness data exist. There is also no regulatory indication for HIV PEP; antiretroviral drugs that have been approved for treatment or prevention are used off-label according to national guidelines. This usually consists of a 28-day oral regimen that is often uncompleted and complicates HIV PEP implementation. The possibility of future regulatory indications provides opportunities for better program/financial coverage and to inform the best implementation practice.

New opportunities for PEP are on the horizon, with new drugs and delivery/dosing modes that may lead to simpler implementation and program options. This provides an opportunity for consensus development on the roles of pre-clinical and human PK/PD data in future regulatory decisions, along with feasible and pragmatic clinical trial designs to collect necessary data. Robust evidence is needed to generate both new and effective guidelines and a potential regulatory approval for PEP, and these are not mutually exclusive endeavors. The HIV PEP Summit in Johannesburg focused on a product agnostic path of evidence generation for both normative guidelines and regulatory approval. The importance of the African region in HIV research and the active participation of diverse stakeholder groups in shaping clinical trials were highlighted in this summit. This includes the collaboration with Wits RHI, numerous African regulatory authorities and normative bodies, and

specific regional/implementation needs and programs. Further, implementation models from other regions, including the US and Brazil, were highlighted to round out the diverse perspectives on PEP.

Finally, the summit highlighted key populations that may benefit from HIV PEP implementation and product approval, especially young women/adolescent girls and sexual assault providers. Participants discussed important settings where HIV PEP may have a significant role in prevention, including sexual assault/emergency care centers, community-based settings, pharmacy-based dispensing, and PEP in pocket/ dispensing machines. End-user and implementation setting considerations must be emphasized when building consensus on data collection and trial designs that may lead to future successful HIV prevention.

This report summarizes the key discussions and outcomes from the summit, highlighting key challenges identified and collaborative strategies proposed to accelerate HIV PEP clinical research and potential clinical trial designs that may improve confidence in regional guidelines or possible approval from regulatory authorities.

PRECLINICAL MODELS, PK/PD, AND EXISTING KNOWLEDGE

PRECLINICAL MODELS

There is immense value in macaque models in HIV prevention research. They allow for highly controlled conditions to regulate the exact timing of virus exposure and the subsequent administration of antiretroviral drugs. These models serve as the gold standard for clinically evaluating PrEP by accurately predicting the clinical efficacy of daily, on-demand, and long-acting injectable regimens. In fact, early macaque studies with tenofovir in the mid-1990s provided the foundational proof of concept showing that both the timing of PEP initiation and the total duration of treatment are critical to prevention success.

Animal data from these models reveal that within hours to 7 days after the virus crosses the mucosa, a small founder population is rapidly established, typically between 2 hours and 3 days. This early stage is highly focal, consisting of a small cluster of roughly 40 to 50 productively infected cells primarily located in cervicovaginal tissues or rectal mucosa, with minimal virus present in systemic lymphoid tissues. Following this initial phase, local expansion occurs in the draining lymph nodes, inducing immune activation that recruits susceptible target cells in a process known as signal amplification, which eventually leads to systemic dissemination and viremia. 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.

Researchers utilize different exposure models to test these prevention dynamics. The high-dose model exposes animals to a massive viral dose that causes a shortened eclipse phase, a larger founder population, and a 100% infection rate after a single exposure, making it historically useful for testing long-acting PEP drugs. Conversely, the low-dose model involves repeated lower-dose exposures and features a longer eclipse phase of 8 to 10 days that closely mimics human HIV, requiring multiple exposures to establish an infection. Key findings across these models show that a combination of long-acting cabotegravir (CAB) and rilpivirine (RPV) initiated 24 hours post-exposure protected four out of six animals in high-dose models, though the breakthrough infections experienced significantly delayed seroconversion and delayed RNA detection alongside selecting for RPV resistance. Meanwhile, weekly oral islatavir initiated 24 hours post-exposure was highly protective, yielding 100% protection with two to four weekly doses. However, a 7-day daily oral regimen of potent drugs like FTC/TAF or FTC/TAF boosted with elvitegravir (EVG) showed zero efficacy at 24 hours post-exposure in the high-dose model, demonstrating that intense viral challenges can completely overwhelm short-duration PEP unless the viral challenge is titrated down to a lower dose. In repeated low-dose models, two doses of FTC/TDF given 2 and 24 hours post-exposure yielded 75% efficacy, whereas two doses of FTC/TAF showed no protection, and short three-drug combinations like FTC/TAF boosted with EVG provided 80% to 100% efficacy if initiated very early within 6 hours, losing efficacy by 24 hours. Ultimately, macaque data indicate that if PEP is started within 24 hours of exposure when the viral founder population is still tiny, a short course of a few oral doses or on-demand regimens may suffice, but initiation at 24 hours or later requires long-duration PEP spanning weeks via long-acting oral or injectable agents.

When evaluating animal model designs, low-dose, repeated, exposure models are preferred over high-dose exposures to evaluate the sustained strength of an intervention over time. While high-dose exposures infect 100% of control animals easily, they risk overwhelming the drug intervention; therefore, researchers aim for a calibrated lower dose that still reliably infects controls to maintain statistical power without masking the protective capabilities of the drug. Current benchmark studies utilize adult macaque models, although infant macaque models were studied in the 1990s for the prevention of mother-to-child transmission (PMTCT), and thus there is a gap in active neonatal or infant PEP modeling.

PHARMACOKINECTIC AND PHARMACODYNAMIC CONSIDERATIONS

It is biologically plausible that drug concentrations required to prevent HIV in a PrEP setting should also be effective for PEP. The generally accepted target for prevention is an Inhibitory Quotient of 4 (IQ4), which represents four times the protein-adjusted 95% effective concentration. However, validating this target in prospective clinical trials is incredibly difficult because researchers must randomize patients to an intervention rather than to a specific drug concentration, and existing post-hoc correlations between drug concentration and prevention failure are heavily biased by "adherence pollution" -meaning drug concentrations often just serve as a surrogate for a patient's overall drug-taking behavior and risk level. Bridging PK and efficacy data from PrEP trials to PEP is also limited because PrEP assumes a patient has not yet encountered the virus, whereas PEP

assumes exposure has already occurred, meaning PEP must rapidly achieve target concentrations in the effect compartment to succeed. Nevertheless, bridging is highly valuable for safety, as using safety data from HIV-negative participants in PrEP trials can eliminate the need for massive, separate safety studies for PEP indications. Furthermore, advanced PK modeling is a powerful tool to determine how fast a regimen hits target levels, evaluate the need for oral loading doses, predict the impact of circulating drug resistance, and select the best candidate products. For example, modeling showed that the candidate drug MK-8527 can reach effective plasma concentrations within one hour of oral dosing, and modeling was successfully used to design lenacapavir's updated dosing regimen by moving the subcutaneous dose to Day 1 instead of Day 8, a change accepted by regulatory agencies without requiring entirely new trials.

A formal PEP label will likely require a window of administration after exposure and a statement on futility, but gathering the definitive human data required to define these windows is ethically and logistically challenging because researchers cannot intentionally delay standard-of-care PEP to find out when it fails. Additionally, active drug metabolites display discrepancies depending on where they are measured; for instance, single-dose intracellular tenofovir diphosphate persists far longer than plasma tenofovir but takes several hours to hit effective target levels in peripheral blood mononuclear cells (PBMCs). Compounding this, regulatory bodies do not currently accept tissue or intracellular drug concentrations in package inserts as surrogates for PK exposure due to analytical and assay performance issues. This creates a notable oral versus injectable paradox: while injectables offer an incredibly attractive "one-and-done" workflow for emergency rooms to ensure full compliance without needing complex patient follow-up, the pharmacological reality is that standard oral drugs achieve effective, protective concentrations faster than long-acting injectables.

PEP treatment duration and whether the standard 28 days is truly necessary must be evaluated. Real-world compliance is low, with only about 33% of patients completing the full 28-day PEP regimen, yet retrospective data still show high efficacy. However, 2024 modeling data demonstrate that the full 28-day regimen remains critical for most individuals. While a 14-to-20-day course might suffice if a three-drug PEP regimen is initiated within a 24-hour window, most real-world individuals do not start PEP until closer to the 72-hour mark. With this biological rationale, explaining that delayed initiation after 24 hours allows the virus to replicate and establish a localized population, necessitating a full 28-day course to prevent systemic spreading. This biological reality strongly supports programmatic "PEP-in-pocket" strategies or automated vending machines to ensure patients can access and initiate PEP within the first 24 hours of exposure.

Pharmacokinetics and dosing strategies across different exposures present a challenge. Tenofovir diphosphate concentrations are historically lower in the female genital tract than in rectal tissues, and there is a knowledge gap regarding PEP efficacy specifically against vaginal routes of exposure in macaque models. Despite this, overemphasis on vaginal tissue concentrations has previously hindered PrEP progress, given that Peripheral Blood Mononuclear Cell (PBMC) drug levels correlate much more reliably with clinical trial outcomes. Although, it is likely a combination of both, local tissue concentrations are uniquely vital for PEP to halt early replication, while systemic circulation protects against deeper spread. Drug half-lives and resistance, particularly within long-acting

cabotegravir and rilpivirine (CAB/RPV) studies, may be a concern where delayed infection was detected in animals up to 3 and 10 months post-exposure. Because rilpivirine has a significantly longer half-life than cabotegravir in animals, cabotegravir cleared rapidly, leaving a long "tail" of standalone rilpivirine. This dual-rate clearance led to the emergence of rilpivirine-specific resistance due to low-level, ongoing viral replication, even when standard assays showed undetectable viremia.

LEVELS OF EVIDENCE: CONSIDERATIONS FOR GUIDELINES AND REGULATORY APPROVAL

GUIDELINE CONSIDERATIONS

Detailed processes through which scientific evidence is evaluated are used to formulate clinical guidelines. Utilizing the GRADE methodology[1], a major and troubling disparity in the certainty of evidence across different HIV prevention methods was highlighted. While Pre-Exposure Prophylaxis (PrEP) guidelines enjoy a high level of certainty backed by multiple robust randomized controlled trials (RCTs), Post-Exposure Prophylaxis (PEP) guidelines have historically been forced to rely on small, non-comparative observational trials, which ultimately results in a low or very low certainty of evidence. Under standard GRADE rules, a designation of very low certainty mandates that committees issue only conditional recommendations. However, the United States has actively begun removing "conditional" language from its guidelines to prevent clinical provider confusion and to maintain strong confidence in insurance coverage for patients. An ironic discrepancy was noted where guideline committees in the United States and Canada arrived at entirely different certainty grades while evaluating the exact same scientific data. This leaves room for a neutral body like AVAC or the Forum to host informal discussions to better align international scientific interpretations. In potential future prevention products, such as MK-8527, clinical researchers must generate data of much higher certainty regarding core clinical workflows. This includes defining the optimal duration for PEP, such as comparing a two-dose regimen against the standard 28-day course, establishing appropriate follow-up intervals, and successfully integrating self-testing strategies, all while navigating unique challenges in the United States like political hurdles and a loss of domestic subject matter expertise.

Global PEP guidelines and their real-world implementation are in an opportunistic position, as upcoming data on new products like MK-8527 are poised to directly shape future international policies. The WHO's preferred PEP regimen evolved from a 2014 standard backbone consisting of TDF/3TC or FTC to the pivotal 2016 inclusion of dolutegravir (DTG), a choice driven by DTG's high genetic barrier to resistance and high global availability. In 2024, the WHO focused heavily on improving drug access and implementing task shifting to combat dismal real-world PEP completion

[1] GRADE Book. Cited 2026 Jul 6. Available from: https://book.gradepro.org/guideline/overview-of-the-grade-approach

rates, which sit at just 56% globally due to prohibitively high private-sector costs and limited physical delivery points. The WHO's Guideline Development Group intentionally pushed through a strong recommendation for delivering PEP in community settings, such as pharmacies, community-based organizations (CBOs), and automated vending machines, despite the available data possessing a very low certainty of evidence. Because future PEP innovations are highly unlikely to have randomized controlled trials due to ethical and logistical constraints, guideline committees will have to lean heavily on biological plausibility, animal models, and pharmacokinetic/pharmacodynamic (PK/PD) studies. Future WHO considerations will focus on whether new drugs can stand alone as monotherapy or require pairing, whether the post-exposure eligibility window can expand beyond the current 72 hours, and how to successfully coordinate with local regulators to expand the types of healthcare workers permitted to dispense antiretroviral therapies.

REGULATORY CONSIDERATIONS

PEP is an established clinical practice, typically a 28-day regimen initiated within 4 to 72 hours, but it exists in a regulatory "grey zone" because no antiretroviral product currently includes PEP as an official indication, meaning all clinical use is technically off-label. In Europe and Norway, the decision to administer PEP relies on patient consent and the HIV status of the exposure source; if the source is HIV-negative or well-controlled, PEP is discontinued, but if the source's status is unknown or consent for testing is refused, the treatment is fully administered.

Despite the belief that current oral regimens have high efficacy when adherence is perfect, real-world completion rates are frequently compromised by tolerability issues or a patient's inability to return for "starter pack" refills. Longer-acting oral agents could potentially improve adherence, but for PEP to be successful, these candidates must achieve therapeutic pharmacological levels rapidly. This is a challenge for long-acting injectable agents designed to last for weeks, which may require an initial period of daily dosing to monitor adverse reactions. Critically, monthly oral MK-8527 does not require loading doses and is expected to reach target concentrations within an hour of dosing.

From a regulatory standpoint, the most logical development path for new PEP candidates is to first secure a standard treatment or prevention indication, which ensures that the manufacturing process, nonclinical data, and extensive safety dossiers are already established before expanding into PEP. While pragmatic clinical trials—often using standard-of-care as a comparator—have been conducted to improve clinical recommendations, these studies generally focus on safety and tolerability rather than meeting the rigorous requirements for a formal regulatory indication. Developers should seek early scientific advice from regulators to navigate these requirements, as there is no "one-size-fits-all" approach. Furthermore, because the EMA approves specific drug products rather than regimens, any combination of drugs from different manufacturers would require complex, parallel marketing authorization submissions. Ultimately, while no formal regulatory guidelines for PEP development currently exist at the EMA, the dialogue between developers and regulators through scientific advice procedures is the most viable path toward establishing formal evidence standards and potential future regulatory guidelines.

The South African Health Products Regulatory Authority (SAHPRA) regulatory perspectives on Post-Exposure Prophylaxis (PEP) largely align with the EMA's approach, emphasizing the critical need for regulatory harmonization and data quality. In the South African context, while national guidelines clearly dictate the clinical approach, specifying the 72-hour initiation window and the requirement for baseline HIV testing, these guidelines are distinct from the regulator's role. Because no antiretroviral drugs currently hold an official label indication for PEP, their use remains off-label, which creates significant complications for reimbursement and insurance payers. There is a necessity for rigorous, standardized data if developers wish to move beyond off-label use. If an applicant were to pursue a formal PEP indication, SAHPRA would require a comprehensive Target Product Profile (TPP) covering clinical efficacy, safety, and drug-drug interactions, particularly concerning comorbidities common in South Africa such as TB and diabetes. Because randomized controlled trials for PEP are currently lacking, if developers intend to use real-world evidence or real-world data to support an application, they must ensure the documentation, monitoring, and follow-up associated with those studies are of the highest quality. Furthermore, SAHPRA operates through global collaboration, frequently relying on assessments from the EMA and the US FDA to streamline their own authorization processes. This "reliance" mechanism allows SAHPRA to authorize products more efficiently when they have already been evaluated by trusted international authorities. SAHPRA plays a leadership role on the African continent; many other African nations often rely on SAHPRA's own assessments. Consequently, SAHPRA conducts thorough, exhaustive reviews of submitted data to ensure that both efficacy and safety are well-established.

Finally, manufacturers must embed robust monitoring systems via proactive pharmacovigilance, either through clinical trials or real-world observational studies, to capture adverse drug reactions and outcomes. While national clinical guidelines are essential for guiding daily practice, a close, collaborative relationship between health ministries and regulators is required to ensure that new PEP drug combinations—whether they evolve into three-drug, two-drug, or potentially single-drug regimens—are brought into the regulatory fold with the necessary scientific backing.

ETHICAL AND STRATEGIC PRIORITIES

- **Systemic Improvement:** The focus should not solely be on new tools, but on improving the resilience and resourcing of existing PEP programs. PEP is currently viewed as a "missed opportunity" in HIV prevention.
- **Reframing Promotion:** The inability of manufacturers to market off-label products may limit PEP awareness. Public health entities could take the lead in promoting HIV prevention tools generically, rather than relying on manufacturer-driven marketing campaigns.
- **Epistemic Humility:** Acknowledgment that stakeholders must be humble about the limits of their knowledge, avoid over-commitment to specific unproven ideas, and recognize that what is "right" in one clinical context (like PrEP) may not be directly translatable to PEP.

KEY INSIGHTS

The path forward for Post-Exposure Prophylaxis (PEP) requires a critical balance between regulatory rigor and practical public health implementation. The current regulatory landscape is nuanced because no current PEP regimen was approved based on dedicated, large-scale randomized controlled trials (RCTs). Consequently, applying stringent requirements to new PEP candidates—when the standard of care itself lacks such evidence—creates an artificial barrier that could hinder innovation and miss urgent prevention opportunities.

- **The "Bright Shiny Object" Caution:** Ethically there must be caution against "chasing bright shiny objects", new products or methodologies that promise improved results, without sufficient validation. There is a risk that solving one implementation hurdle (e.g., adherence via long-acting agents) may introduce new, unanticipated complications, such as resistance patterns or complex follow-up requirements.
- **Regulatory Efficiency:** To improve approval timelines at the national level harmonization and reliance must be utilized. By utilizing the WHO's "Good Reliance Practices," national regulators can leverage evaluations from internationally recognized bodies (such as the EMA and FDA), which facilitates quicker access to priority products. However, regulators cannot act without formal submission from drug manufacturers, whose commercial priorities may not always align with public health needs.
- **Defining Evidence for PEP:** The field must move beyond traditional trial designs. Since PEP is urgent rather than emergent, the use of real-world "surrogate" markers, such as time-to-initiation and 28-day completion rates, may be used to establish pharmacological effectiveness. Drawing a parallel to cardiovascular medicine, where blood pressure serves as a surrogate for cardiac outcomes, standardized real-world data could potentially satisfy regulatory requirements for PEP indications.
- **The Data Gap:** The lack of global, systematic data collection on PEP usage remains a challenge. While global reporting mechanisms (like the UN's GAM) track PEP policy, they currently lack the infrastructure to collect quality-assured, standardized data on PEP utilization. The creation of a global protocol for data sharing or establishing registries like those used for ARV use in pregnancy, could fill this evidentiary vacuum.

By fostering better resource allocation, leveraging proactive pharmacovigilance, and maintaining a pragmatic approach to evidence, the aim is to ensure future PEP innovations are integrated effectively into health systems.

CLINICAL TRIAL DESIGNS AND STATISTICAL CONSIDERATIONS

CLINICAL TRIAL DESIGNS

Historically, PEP has been underfunded and sidelined in favor of daily PrEP, lacking global monitoring metrics despite the real-world challenges of PrEP pill burden, unpredictable risk windows, and poor adherence. Implementation data reveal that a significant portion of individuals prefer PEP's episodic nature over continuous PrEP, as only 11% to 49% of PEP users across various implementation studies eventually transition to PrEP. This low transition rate provides a strong real-world signal that trial designs must accommodate people who prefer an episodic, PEP-based prevention strategy, rather than a long-term daily regimen.

Evaluating new long-acting PEP agents presents scientific, logistical, and ethical trial design hurdles, primary among them being an incredibly low HIV acquisition rate, as evidenced by a systematic review showing only one infection among over 3,000 PEP users. Additionally, PEP trials suffer from short evaluation windows of ~one-month, severe recruitment barriers due to a strict 72-hour post-exposure timeline, and complexities in obtaining trauma-informed consent from highly vulnerable individuals, such as sexual assault survivors at police stations. Compounding these issues, no fully powered human efficacy trial has ever been conducted for standard of care PEP, and long-acting injectable agents require four to seven days to achieve protective drug levels. To overcome the statistical challenge of expecting near-zero events in either study arm, researchers propose shifting the efficacy goal to establishing that acquisition rates approach zero, utilizing consensus-based thresholds borrowed from contraceptive trials and leveraging early HIV RNA testing to detect endpoints as early as one-week post-exposure.

To generate robust evidence for long-acting PEP, a collaborative and creative approach is necessary to address challenges and understand the tradeoffs between methodology. Individual short-course randomized controlled trials (RCTs) focus on per-exposure efficacy but are hindered by immense sample size demands and re-randomization complexities, while long-term individual RCTs track repeat PEP users pragmatically but risk high dropout rates if participants dislike their assigned regimen. Cluster RCTs simplify site-level implementation by randomizing venues like pharmacies or clinics but incur high costs and risks of participant contamination across sites. Non-randomized choice designs fully respect participant autonomy and eliminate ethical concerns but suffer from statistical confounding since a person's choice often aligns with their perceived exposure risk. Ultimately, the hybrid preference trial, utilizing a comprehensive cohort design, is highlighted as an efficient approach because it runs randomized and observational arms simultaneously, allowing investigators to distinguish treatment, selection, and preference effects while providing regulatory bodies and ministries with real-world implementation data.

Design	Study Population	Primary Outcomes / Endpoints	Key Advantages	Key Challenges
1. Individual RCT (Short-Course)	General PEP seekers.	HIV infection status at 1 month.	Focuses on per-exposure efficacy; individuals randomized to SOC or long-acting PEP.	Exceptionally hard to power due to near-zero expected events; complex rerandomization required for repeat exposures.
2. Individual RCT (Long-Term)	Repeat PEP-strategy users followed for > 6 months.	HIV incidence over extended follow-up.	Pragmatic, unblinded design; better statistical power as differential adherence increases observed incidence.	Difficult to locate and recruit clients who prefer repeat PEP over PrEP; risk of differential loss-to-follow-up.
3. Cluster RCT	Clients at randomized delivery sites (pharmacies/clinics).	Cluster-adjusted HIV incidence.	Simpler site-level implementation.	High implementation costs, large required sample sizes, and a high risk of site contamination if participants seek specific clusters.
4. No Randomization (100% Choice)	PEP seekers given full autonomy to choose their regimen.	Observed HIV incidence.	Eliminates ethical consent concerns; respects participant choice.	Strong confounding factors, as a participant's choice of regimen may correlate directly with their perceived exposure risk.
5. Preference Trial (Hybrid)	PEP seekers (comprehensive cohort design).	HIV incidence, adherence, drug levels, and acceptability.	Captures real-world preference, selection, and treatment effects simultaneously; provides ministries with real-world data alongside trial data.	The proportion of participants willing to be randomized is entirely unknown; requires a very large sample size.

TOTALITY OF EVIDENCE

It is evident there is a distinct regulatory paradox: while Post-Exposure Prophylaxis (PEP) is globally utilized and thoroughly integrated into clinical guidelines, no specific drug currently holds official regulatory approval for a PEP indication. Securing formal regulatory approval is critical because it may foster public and clinical confidence in PEP's safety and efficacy, enable broad promotional campaigns, and significantly streamline insurance reimbursement pathways. However, executing

traditional clinical efficacy trials to secure this approval is entirely unfeasible. Because PEP is already accepted as effective, utilizing a placebo control would be highly unethical, requiring researchers to use an active comparator instead. Yet, no active PEP comparator possesses randomized trial data to establish its baseline efficacy. Historical data rely primarily on outdated AZT monotherapy case studies, and standard multi-drug regimens have never undergone formal efficacy testing. Furthermore, because the background HIV transmission rate per exposure is exceptionally low (such as an uncorrected 1.38% for receptive anal intercourse, which plummets further when factoring in localized viral suppression rates), any trial attempting to measure a difference in infections would demand massive, logistically impossible sample sizes ranging into the thousands or tens of thousands.

To bypass this experimental logjam, a "Totality of Evidence" regulatory framework is proposed, arguing that regulatory flexibility is fully justified when traditional human trials are either unethical or impossible. This approach gathers multiple streams of validation to build a compelling case for a new HIV PEP drug approval without relying on a traditional efficacy trial. First, it leverages strong mechanistic and pharmacodynamic evidence. Both the underlying pathophysiology of HIV transmission and the replication-suppressing mechanism of antiretroviral drugs are thoroughly understood. Second, it incorporates robust pharmacokinetic and pharmacodynamic (PK/PD) profiles, specifically tissue PK data, to demonstrate that a drug achieves rapid onset and maintains protective concentrations above the target threshold for at least 28 days. Third, it uses concrete efficacy data from non-human primate studies as a clear proof-of-concept. Finally, it relies on cross-indication clinical data, meaning that if a drug is already approved for HIV treatment or Pre-Exposure Prophylaxis (PrEP), a PEP indication can safely be pursued as a straightforward label extension.

Crucially, because preclinical and PK data alone are insufficient to secure approval, the totality of evidence strategy proposes to integrate a small-scale, pragmatic human clinical trial. In this instance the proposed trial is designed to target the primary reason PEP fails in the real world: regimen completion rates. Real-world data show that PEP does not fail because the underlying drugs are ineffective; rather, it fails because patients struggle to adhere to a grueling 28-day regimen, resulting in an average completion rate of only 55%. Completion rates drop as low as 45% to 52% among female sexual assault survivors and max out around 60% to 70% for healthcare workers experiencing occupational exposure. Novel long-acting, single-dose PEP agents eliminate this compliance barrier, automatically guaranteeing near 100% completion while removing daily pill burdens and the social stigma of family members or colleagues discovering a 30-day medication bottle.

To demonstrate this clinical advantage, a specific "strawman" proposal was presented that outlines three small, open-label, randomized pragmatic superiority trials across key populations: men who have sex with men (MSM), female sexual assault survivors, and individuals with occupational exposures. By enrolling just 100 participants per trial (50 randomized to standard of care and 50 to the single-dose agent), researchers would possess over 95% statistical power to prove the single-dose regimen's superiority in completion rates. The clinical trial workflow would mirror standard PEP delivery timelines, featuring baseline consenting and HIV testing on Day 0, followed by safety check-

ins, pill counts, and secondary HIV testing at Week 4, with long-term follow-up testing extending to Week 12 and Week 24. Ultimately, implementing these high-completion, single-dose PEP options fulfills a vital public health imperative, offering a transformative tool that could successfully prevent tens of thousands of infections over a ten-year period among the 200,000 individuals who seek emergency post-exposure care annually.

Strawman Proposals for Pragmatic Superiority Trials

Specific configurations proposed for the three distinct pragmatic superiority clinical trials designed to measure HIV PEP regimen completion rates in different populations:

Trial Feature / Parameter	Trial 1: MSM	Trial 2: Female Survivors of Sexual Assault	Trial 3: Occupational Exposure
Target Population	Men who have sex with men (MSM)	Female survivors of sexual assault	Healthcare workers
Primary Mode of Exposure	Receptive anal intercourse	Vaginal and/or anal exposure	Needlestick, blood splashes, etc.
Sample Size Allocation	Total N = 100 (50 per arm)	Total N = 100 (50 per arm)	Total N = 100 (50 per arm)
Expected Long-Acting (LA) Completion	>95%	>95%	>95%
Expected Standard of Care (SOC) Completion	56%	50%	65%
Statistical Power to Show Superiority	>95%	>95%	>95%

STATISTICAL CONSIDERATIONS AND FURTHER DESIGNS

There are mathematical and logistical constraints that create a statistical impasse for traditional HIV Post-Exposure Prophylaxis (PEP) clinical trials. Because PEP is the established standard of care, utilizing a placebo control group is highly unethical, yet executing a standard active-controlled superiority or non-inferiority trial is practically impossible due to exceptionally low clinical event rates. In high-prevalence areas where baseline HIV prevalence ranges between 15% and 30%, the

widespread success of Treatment as Prevention (TasP) and 95-95-95 targets ensures that most people living with HIV are virally suppressed. Consequently, data across multiple African nations show that the risk of encountering a partner with an unsuppressed viral load during an exposure is very low, ranging from 1.13% to 8.14%, which means only about 4% of individuals prescribed PEP were exposed to active viremia. When this 4% exposure probability is multiplied by the already minimal per-act transmission risks, such as 1% to 2% for receptive anal intercourse or 0.08% for receptive vaginal intercourse, the combined real-world risk drops to a mere 3 infections per 10,000 PEP distributions. For every 10,000 potential exposures, researchers would expect only 1 to 5 actual seroconversions without PEP, making true drug breakthroughs nearly impossible to observe.

This mathematical reality explains why historical human HIV PEP data provide an insufficient basis for regulatory approval. Past observational and randomized trials, such as the MiPEP, RAL-PEP, and MARAVI-PEP studies, relied on small sample sizes that maxed out at roughly 250 participants and could only evaluate regimen completion rates, which varied widely from 38% to 71%. Because these cohorts yielded effectively zero or one single breakthrough infection, they failed to generate the statistical efficacy data required by regulators. To bypass this limitation, researchers have evaluated alternative models like a longitudinal "PEP-in-pocket" (PIP) prevention strategy designed for individuals who want intermittent post-exposure coverage rather than continuous daily PrEP. However, monitoring a PIP strategy long-term introduces a scientific caveat because almost all breakthrough infections in these settings occur when a participant completely fails to take their medication rather than from a biological failure of the drug itself, leaving it unclear if this approach answers the core efficacy questions that regulators demand.

Another alternative framework is an active-controlled trial design augmented by a mathematically modeled "counterfactual placebo," which estimates the background HIV incidence rate that would have occurred if a placebo arm were ethically permissible. Drawing precedent from the recent PURPOSE trials and utilizing advanced statistical methodologies published by Gao in 2025, a counterfactual baseline can be constructed through localized prevalence data, viral suppression rates, explicit exposure types, or HIV recency data at screening. Assuming a two-year follow-up, a 2% counterfactual placebo rate, 90% standard of care efficacy, and a 68% non-inferiority margin, this model significantly reduces trial size compared to a traditional non-inferiority design. Specifically, a traditional active-controlled non-inferiority trial would require 25,107 person-years of follow-up, a sample size of 12,554 participants, and 50 observed events. In contrast, a counterfactual-augmented design reduces these requirements to 7,611 person-years and 3,806 participants to capture 14 events, while a conservative counterfactual model demands 9,567 person-years and 4,784 participants to capture 19 events. Even with these massive reductions, enrolling nearly 4,000 participants represents an immense hurdle for PEP trials that have historically struggled to accrue even 300 individuals.

Because observing active breakthrough events is fundamentally unrealistic, researchers could alternatively plan a near-zero event cohort trial to establish an upper statistical bound of infection risk by tracking large groups of PEP users in high-risk environments. As the size of a zero-infection cohort scales over a one-year follow-up period, the upper 95% confidence limit for the annual

infection rate drops significantly, providing a rigorous body of evidence for regulatory review. For instance, tracking a cohort of 250 participants with zero infections establishes an upper 95% limit of 1.2 infections per 100 person-years, which falls to 0.6 for 500 participants, 0.3 for 1,000 participants, 0.2 for 1,500 participants, and reaches 0.15 for 2,000 participants. Ultimately, traditional randomized clinical trials are entirely unfeasible for a PEP indication due to low transmission rates. While utilizing zero-event cohorts to prove a strict upper bound of risk offers a viable path forward, obtaining any form of direct human efficacy evidence requires longitudinal follow-up under a structured PEP prevention strategy.

Statistical Upper 95% Confidence Bounds (1-Year Follow-Up)

N Exposures Accumulated	Upper 95% Bound		N Participants Enrolled	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

Enrolling 1,000 to 2,000 participants with one-year follow-up can successfully prove an upper infection bound below 0.3/100 PY, potentially satisfying efficacy claims without needing a single observed infection.

HIV PEP IMPLEMENTATION

SEXUAL ASSAULT CLINICS IN SOUTH AFRICA

HIV PEP implementation and the operational framework of Clinical Forensic Medicine (CFM) Services (also known as Medico-Legal Services) in Johannesburg is dynamic. While antiretroviral therapy (ART) and oral Pre-Exposure Prophylaxis (PrEP) programs are highly mature, with 79% of South Africa's public primary healthcare facilities offering oral PrEP and Gauteng achieving a 99% facility coverage rate, HIV PEP availability remains less widespread across standard facilities. To bridge this gap in Johannesburg, which is home to more than 600,000 people living with HIV, the Medico-Legal Services network operates eight specialized clinics. The primary hub is the Hillbrow Community Health Centre. These centers function as specialized Gender-Based Violence (GBV) units dedicated to

examining and supporting victims of sexual offences and domestic violence. Services are rendered by specially trained healthcare professionals and GBV social workers to any individual in need, entirely irrespective of race, culture, or nationality. Medico-Legal Mandates and Clinical Protocols. The clinics execute a dual "medico-legal" mandate by simultaneously managing urgent preventative healthcare and gathering forensic evidence for the legal system. The standard clinical protocol for a victim's first visit involves initiating PEP (antiretrovirals), dispensing emergency contraception (the morning-after pill), and conducting testing or treatment for STIs and Hepatitis B. There is a strict window for qualifying for both PEP and emergency contraception within 72 hours of the incident. To prevent secondary traumatization, the clinics employ an integrated internal referral pathway. Specially trained doctors, nurses, and counselors handle HIV testing, immediate treatment initiation, and handoffs to mental health or long-term care within the same facility footprint.

Client volumes at the clinic display monthly fluctuations. In early 2026 PEP provision numbers rose steadily from January to April. Across these services, more females than males receive care. Case surges routinely align with school holidays, when unsupervised minors frequently present late, and month-ends. While adult late-reporting is low (around 1% to 2%), individuals under 18 frequently delay seeking help past the 72-hour window due to fear and secrecy. On a broader scale, system-wide data for the April 2025 to March 2026 financial year shows South African healthcare systems managed 48,500 new sexual assault cases and issued PEP to over 49,000 individuals nationwide. Nationally, 83% of primary healthcare clinics now report PEP uptake; in the Gauteng region specifically, 327 out of 372 primary healthcare clinics are actively equipped to provide PEP.

Despite national availability of HIV PEP, healthcare workers face difficulties in patient compliance and retention. Key challenges include unreliable patient information (false addresses or dead phone numbers), missed follow-up appointments, and poor compliance to the required treatment course. To counter poor return rates and lower the community's HIV burden, the clinic has shifted its clinical strategy: if a victim refuses an on-site HIV test, staff do not withhold medication; instead, they immediately dispense a full 28-day supply of the modern TLD regimen (rather than a traditional 7-day starter pack). This modern regimen minimizes the drug-resistance risks associated with older configurations. Furthermore, the clinic distributes HIV self-testing kits so patients can safely check their status at home rather than facing the logistical barriers of traveling back to the clinic. Multi-Sectoral Support Systems and Future Innovations to facilitate comprehensive legal justice and mental recovery, the CFM clinics rely heavily on an external network of institutional support. This includes the South African Police Service's (SAPS) specialized Family Violence, Child Protection, and Sexual Offences (FCS) unit for secure patient transport and crime-scene evidence retrieval. Global healthcare systems face immense structural pressures, and future frameworks must prioritize patient empowerment and simpler technologies.

PHARMACY DELIVERY IN KENYA

Traditional public HIV clinics face severe client access barriers, including pervasive stigma for HIV-uninfected individuals, long wait times, travel distances, and highly restrictive hours of operation, as

they frequently close on weekends and only operate during mid-day hours on weekdays. Furthermore, despite updated national guidelines, public facilities have historically rationed post-exposure prophylaxis (PEP) sparingly, focusing almost exclusively on occupational exposures and sexual assault cases while overlooking broader community needs. In contrast, private pharmacies are highly ubiquitous—with Kenya possessing over 7,000 licensed pharmacies, 11,000 pharmaceutical technologists, and 3,000 pharmacists—and they offer discreet, non-stigmatizing, and rapid care with extended evening and weekend hours. Because roughly half of the population in low- and middle-income countries regularly utilize pharmacies for sexual and reproductive health commodities, they represent a convenient, pre-established platform for community-led prevention.

HIV PEP pharmacy delivery has progressed through a series of iterative studies beginning in 2020, starting with a multi-stakeholder mobilization meeting involving the Ministry of Health, the Pharmacy and Poisons Board, laboratory regulators, and end-user populations to chart out a legal operational pathway. An initial 12-month pilot was rolled out across four pharmacies (two in high-incidence Kisumu and two in moderate-incidence Kiambu) delivering oral pre-exposure prophylaxis (PrEP) and charging a 300 KES fee (~$3) to align with the profit-driven nature of private retail. This was followed by a 6-month pilot extension across 12 pharmacies that introduced PEP and STI testing while waiving client fees to maximize affordability. The pilot extensions proved successful, yielding over 99% client acceptability and 92% provider acceptability, with no pharmacy staff reporting that the services were difficult to deliver. Crucially, the extension study reached populations traditionally omitted from clinic-based prevention: among the PEP clients enrolled, 58% were male, 49% were under the age of 25, 83% were unmarried, and the vast majority sought care due to recent unprotected sex (48%) or condom breakage (46%) rather than sexual assault (4%).

Building on these pilots, a large cluster-randomized controlled trial (cRCT) spanning 60 to 75 pharmacies was launched in June 2023 and completed in July 2025 to evaluate varying business and operational models. The trial compared a client-sustained arm (charging individuals 250 KES), an implementer-sustained arm (free to clients, with a third party or government paying a 250 KES reimbursement per visit to the pharmacy), a counselor-supported arm designed to alleviate the pharmacist's time burden by introducing a dedicated HIV testing services counselor (free to clients, with a 100 KES provider incentive), and the standard of care which simply referred clients to public clinics. Aggregated data from this trial, which enrolled 4,772 clients, revealed a previously unrecognized demand for PEP over PrEP, with PEP accounting for 68% of all participants compared to just 32% for PrEP. These pharmacy PEP seekers were representative of acute-risk groups, consisting of 57% men, 62% unmarried individuals, and 35% youth under 25, with 91% explicitly reporting condomless sex within the preceding 72 hours.

While private pharmacies are a remarkably promising mechanism for expanding HIV prevention, long-term sustainability hinges on resolving key operational and structural hurdles. Because anti-retroviral commodities were provided for free by the Kenyan government during the trials, establishing robust public-private partnerships (PPPs) and sustainable cost-sharing business models

will be vital moving forward. Furthermore, there remain regulatory policy barriers regarding the scope of clinical practice for pharmacists beyond dispensing, a mismatch in standard risk screening tools that fail to evaluate immediate 72-hour exposure windows, and an unmet need to boost HIV testing compliance post-PEP completion potentially via HIV self-testing.

INNOVATIVE DELIVERY IN BRAZIL

São Paulo's innovative public health strategy is designed to scale up HIV PEP and PrEP delivery. Catering to a massive urban center of over 12 million inhabitants with approximately 100,000 people historically diagnosed with HIV/AIDS, the municipality coordinates a combined prevention grid across 120 specialized health service sites. The program's core objective is to bypass conventional clinical bottlenecks by embedding prophylaxis distribution points directly within local communities, prioritizing availability during high-risk off-hours like nights and weekends. This non-traditional framework developed through a structural multi-year timeline: while Brazil introduced PEP in 1999, São Paulo built PEP into its Combination Prevention guidelines in 2015, expanded it across city emergency medical networks and Testing and Counseling Centers (CTAs) in 2019, and launched targeted transgender care through the SampaTrans Network in 2020. Simultaneously, in 2020, São Paulo became the first Brazilian city to pass trailblazing municipal regulations authorizing nurses, pharmacists, and dentists to prescribe PrEP and PEP.

To effectively lower institutional access barriers, the city deployed low-threshold community strategies starting in 2021, including "PrEP on the Street" mobile interventions targeting sex clubs, cultural spaces, and public squares, alongside a mobile clinic minibus called the "City's CTA". Operating Thursday through Sunday from 5:00 PM to 10:00 PM, these mobile outreach efforts completed over 3,400 activities, logging 10,000 consultations, administering more than 218,000 multi-pathogen rapid tests, and distributing 1,800 standalone PEP kits while seeing their highest relative demand from cisgender men and non-white communities. In 2023, the city further decentralized clinical spaces by opening the "Jorge Beloqui Prevention Station" directly inside a major subway hub. Operated by a lean team of just six medical and front-desk professionals, this metro-station clinic functions Tuesday through Saturday from 5:00 PM to 11:00 PM, facilitating an average of 80 daily consultations and delivering 6,120 PEP regimens between June 2023 and March 2026. Crucially, while a significant portion of metro clinic users are white cisgender men, roughly 50% of the individuals accessing this transit site reside in the city's underserved outskirts.

In tandem with physical outreach, São Paulo integrated high-tech digital workflows to make prevention completely on-demand, launching the "SPrEP" online telehealth channel in 2023 and automated medication vending machines in 2024. Built directly into the municipal e-SaúdeSP mobile app, SPrEP provides virtual provider consultations daily—including weekends and holiday shutdowns like Christmas and New Year's—from 6:00 PM to 10:00 PM. This virtual telehealth channel facilitated 23,150 consultations and 5,760 PEP provisions from June 2023 to March 2026, capturing clear sub-population trends: although cisgender women represent only 6% of overall

SPrEP users, an overwhelming 77% of those women utilize the app exclusively to secure emergency PEP. To fulfill prescriptions seamlessly, the city set up automated PrEP and PEP vending machines across five critical subway stations (Luz, Vila Sônia, Santana, Consolação, and Brás) operating from 4:40 AM to midnight, with select locations extending to 24-hour service on weekends. To access the automated machines, clients use a digital verification QR code generated during their virtual SPrEP teleconsultation, a protocol that yielded approximately 12,000 medication pickups, 8,200 PrEP provisions, and 3,600 PEP provisions between June 2024 and March 2026.

The macro epidemiological data demonstrate that occasional/consensual sexual exposure represents the primary driver of prevention-seeking behavior in the city, prompting citywide annual PEP provisions to more than double from 15,461 in 2020 to 37,296 in 2025. Cumulatively, São Paulo administered over 153,000 PEP courses from 2020 to 2025, and by 2024, its 83,500 registered PrEP users accounted for an incredible 20% of all PrEP patients across Latin America and the Caribbean. These extensive, structurally varied community networks have triggered an epidemiological turnaround, resulting in nine consecutive years of falling municipal HIV transmission rates. Total annual new HIV infections dropped 56% from 3,138 cases in 2016 down to 1,662 cases in 2025, particularly pronounced among vulnerable youth aged 15 to 29. By removing cost barriers and ensuring that all PEP and PrEP resources are distributed entirely for free under the public healthcare framework, São Paulo remains on track toward its ultimate target of eliminating the urban HIV epidemic.

DELIVERY IN THE UNITED STATES

Nonoccupational Post-Exposure Prophylaxis (nPEP) in the United States is a critical but severely underutilized tool within the broader prevention toolbox. The US healthcare system presents glaring regional and demographic disparities in prevention access. For instance, while southern states account for 53% of new HIV diagnoses, they only represent 39% of PrEP users. A similar equity gap exists racially, with Black individuals comprising 38% of new diagnoses but making up only 15% of PrEP users. Within this fractured landscape, PEP should ideally act as a safety net, yet data show it is rarely deployed effectively.

Real-world data from urban STI clinics in Seattle and Minneapolis highlight that PEP initiation rates remain persistently low, accounting for less than 1% of total clinic visits across 2024 and 2025. Furthermore, successfully linking patients to long-term PrEP within six months varies widely by region, hovering around 12% to 16% in Seattle compared to roughly 40% to 41% in Minneapolis. To contextualize a "1% preference rate" a parallel can be drawn to contraception. In 2018, only 1% of US women noted event-driven emergency contraception as their preferred method, yet public health data reveal that 26% of women aged 15 to 49 have relied on it at least once in their lives. This comparison suggests an unaddressed emergency demand for PEP that may currently be suppressed by systemic barriers.

The PEP care cascade experiences sharp drop-offs at every stage: only about 66% of individuals who would benefit from PEP seek care, 59% receive a full prescription, 38% complete the 28-day course, and only 36% attend follow-up visits. A tracking window from October 2025 to April 2026 at Hennepin County Medical Center (HCMC) exposes how insurance hurdles actively disrupt acute care, forcing sexual assault survivors to walk away with incomplete 4-to-7-day "starter packs". Financially, navigating a single course of PEP in the US is challenging, often totaling an estimated $7,000 per course. This exorbitant price tag includes emergency department encounter fees ranging from $900 to $2,000, medication costs of approximately $4,200 for a 28-day regimen of drugs like BIC/FTC/TAF (Biktarvy) and ~ $800 for baseline laboratory panels required by the CDC, which mandate non-rapid HIV tests, pregnancy tests, hepatitis B serologies, and kidney/liver function checks. Because of this pricing structure, patients frequently receive confusing or financially devastating "surprise bills," or the healthcare system simply swallows the uncompensated cost.

A complex web of system-level and individual-level hurdles may delay or completely block rapid access to PEP within the 72-hour window. Systemically, current CDC guidelines are complex and mandate case-by-case assessments, which can negatively impact clinical confidence; only 40% of emergency department providers report feeling comfortable prescribing PEP. On an individual level, patients face long emergency room wait times, financial anxiety, pill burdens, and the prolonged emotional strain of a month-long regimen paired with multi-month follow-up testing. Privacy fears are so pervasive that 50% of insured individuals choose to withhold their insurance information from clinics. Compounding this is institutionalized stigma; patients are frequently driven away from care after discovering judgmental medical coding in their electronic charts, such as explicit labels designating "high-risk homosexual behavior".

To meet patients where they are, there is an urgent need to decentralize and demedicalize PEP delivery. Proposed strategies include expanded telehealth models with remote lab testing, "PEP in pocket" approaches for forward-planning, and pharmacist-prescribed medications. However, innovative international solutions, like the PEP and PrEP vending machines utilized in São Paulo, Brazil, face rigid regulatory roadblocks in the United States. State legislatures and public health departments prohibit automated dispensing unless the FDA grants an over-the-counter regulation status for these medications. Ultimately, creating an effective public health model for PEP requires establishing affordable access outside traditional health insurance, designing shorter drug courses with rapid onset and higher "forgiveness" for missed doses, simplifying institutional guidelines, and critically rethinking the necessity of mandatory baseline labs.

KEY INSIGHTS

Structural Gaps, Policy Inconsistencies, and Low PEP Utilization

- **Outdated Global Policy and Omission:** Globally, PEP has been left behind compared to advancements in PrEP and tuberculosis (which has achieved shorter drug regimens). The World Health Organization's last major PEP guideline update occurred a decade ago when

Dolutegravir (DTG) was added in 2016. Furthermore, regional prevention frameworks routinely omit PEP; for example, Zambia's DSD (Differentiated Service Delivery) guidelines only mention PEP once as a passing example.

- **The Pitfalls of Clinic Integration:** While consolidating public facilities into centralized spaces (combining outpatient, emergency, and primary care) is intended to streamline health systems, it has created long queues and massive wait times. This directly undermines PEP delivery, which requires rapid administration as a time-sensitive emergency service.

Regulatory, Legal, and Ethical Hurdles to Decentralization

- **Rigid Drug Scheduling:** In South Africa and Zimbabwe, PEP is classified as a strict Schedule 4 drug requiring a physician's prescription, meaning pharmacists cannot independently prescribe or dispense it. This severely limits access compared to emergency contraception, which sits at a more accessible Schedule 2 over-the-counter status.
- **The Missing Metric ("PEP Watch"):** Scaling up PEP is hindered by a critical lack of operational data. While global platforms like PrEP watch track PrEP initiations worldwide to drive implementation strategies, no equivalent data tracking hub exists for PEP.
- **The Economic Justification Dilemma:** Ministries of Health frequently hesitate to fund PEP because its "number needed to treat" is 10,000 to prevent just five seroconversions, leading policymakers to question if the upfront investment is more cost-effective than simply treating those five infections later.
- **The Fragility of Funding:** Clinical operations remain highly vulnerable to volatile international funding. This reality reinforces the urgent public health need for simpler, ultra-affordable, and "forgiving" PEP regimens that do not rely on complex, daily pill adherence or heavy medical infrastructure.

FUTURE HIV PEP TRIAL DESIGNS

DESIGN 1: COUNTERFACTUAL PLACEBO

- **Concept:** An active-controlled trial comparing a novel longer-acting PEP agent against a standard 28-day oral Standard of Care PEP 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 estimate absolute efficacy ethically.
- **Counterfactual Modeling:** The counterfactual placebo is mathematically constructed from background epidemiological parameters: HIV prevalence, risk of viremic exposure (using the 95-95-95 cascade), per-act transmission probability, and frequency of exposure events. In virally suppressed-dominant populations, this combined estimate yields an acquisition risk of approximately $3/10{,}000$ per exposure.

- **Sample Size Advantages:** Incorporating a counterfactual cohort substantially minimizes the required participant enrollment and follow-up person-years (PY) compared to standard non-inferiority (NI) active-controlled trials.

Sample Size Impact (2-Year Follow-Up Cohort)
(Powered under a counterfactual placebo rate of 2/100 PY, SOC PEP efficacy of 90% [incidence of 0.2/100 PY], and an NI margin of 68%)

Design Scenario	Total Follow-up (PY)	Total N (2-Year Follow-up)	# Events (Alternative 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

Discussion & Critiques:

- *Feasibility Concerns:* This design is operationally unfeasible. Enrolling around 4,000 non-PrEP users who are at risk and tracking them prospectively for two years is incredibly slow and logistically challenging.
- *Dynamic Cohorts:* A non-PrEP cohort is highly unstable over two years. Data from the *Prevenir* study in France revealed that 40% of participants switched study arms (e.g., between on-demand and daily PrEP) during follow-up. Over a multi-year period, frequent PEP users often gain the confidence to transition into PrEP users.
- *High Point of Uncertainty:* Relying on modeled epidemiological assumptions introduces many points of uncertainty, eroding confidence among both investigators and regulators.

DESIGN 2: 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 non-inferiority trial operationally implausible. Instead, this design shifts the inferential goal toward accumulating a large volume of prospective PEP exposure data to establish a statistically rigorous upper 95% confidence bound on the true infection rate.

Statistical Upper 95% Confidence Bounds (1-Year Follow-Up)

N Exposures Accumulated	Upper 95% Bound		N Participants Enrolled	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

Enrolling 1,000 to 2,000 participants with one-year follow-up can successfully prove an upper infection bound below 0.3/100 PY, potentially satisfying efficacy claims without needing a single observed infection.

Discussion & Critiques:

- *Confounding Transmission Routes:* Possible challenge of handling participants with overlapping risk profiles. For instance, if a participant enters the trial following a single sexual assault exposure but is also an active injection drug user, their ongoing exposures undermine the "single event" premise of the analysis.

DESIGN 3: PRAGMATIC COMPLETION TRIALS

A randomized, open-label pragmatic superiority clinical program consisting of three concurrent trials. Rather than tracking biological HIV efficacy, it focuses entirely on a behavioral endpoint: the proportion of participants who complete their assigned PEP regimen. It specifically evaluates a single-dose novel long-acting (LA) PEP agent against the standard 28-day daily oral standard of care PEP.

Cohort Specifications (Total N = 300; 100 per trial)

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

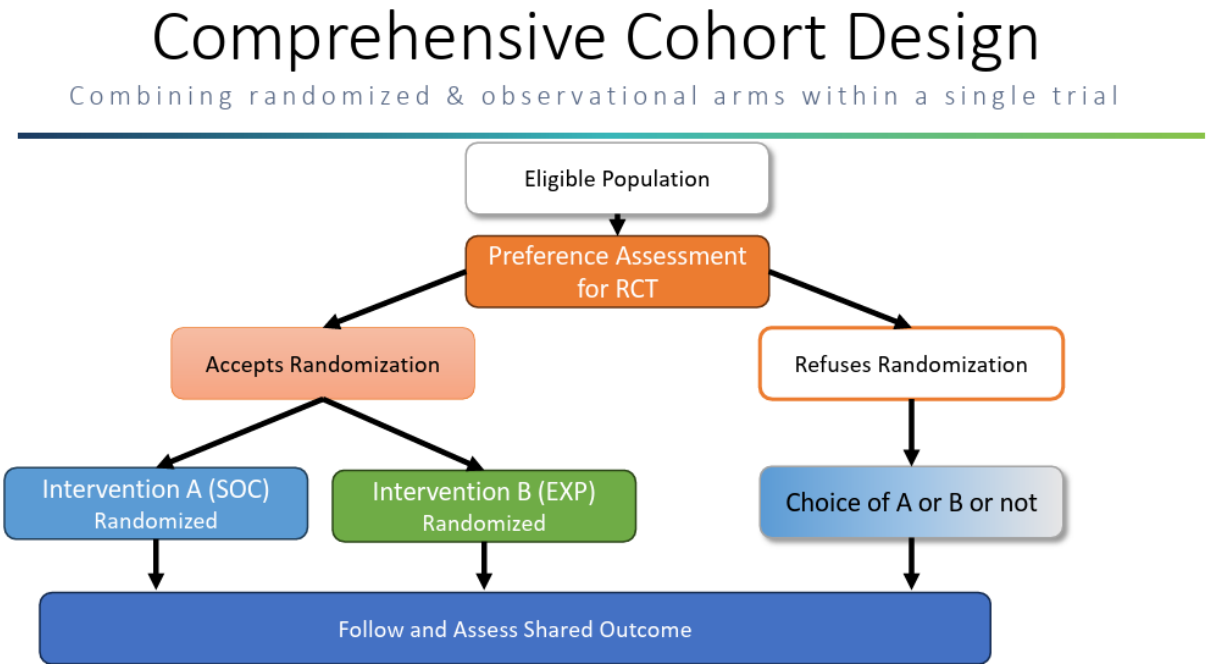
Even if daily oral SOC completion rates track as high as 80% in the real world, each micro-trial retains roughly $\sim 90\%$ *statistical power to demonstrate the behavioral superiority of single-dose PEP. The longitudinal follow-up includes HIV testing, safety, and pharmacokinetic (PK) tracking across Day 0, Week 4, Week 12, and Week 24.*

Discussion & Critiques:

- *Design Flaw:* A completion trial comparing a single-dose long-acting agent (which inherently features immediate $\sim 100\%$ completion) against a 28-day daily oral pill regimen feels "facetious" because the statistical outcome is a foregone conclusion.
- *Completion vs. Effectiveness:* The core limitation of this framework is that regimen completion does not equal biological effectiveness. Regulators (such as Marian Gruber and Kim Strub from the FDA) require absolute confirmation that a drug biologically prevents the establishment of HIV infection when taken *after* an exposure, regardless of compliance.
- *Proposed App-Based Enhancements:* Instead of simple completion, the study could integrate an app to collect data on *why* participants felt at risk, *when* they exposed themselves, and exactly how many hours elapsed before the first dose entered their system—parameters much more vital to clinical success than raw completion rates.

DESIGN 4: PREFERENCE / COMPREHENSIVE COHORT

Modeled after CoVPN 3006 and psychological/addiction treatment frameworks, this design blends a randomized controlled trial (RCT) with observational choice paths. Participants willing to be randomized enter Path 1 (assigned to novel LA PEP vs. oral SOC PEP). Participants unwilling to be randomized are not excluded; instead, they are permitted to self-select their preferred intervention, dividing into Path 2 (active choice of novel long-acting PEP) or Path 3 (active choice of standard 28-day oral SOC PEP). This design simultaneously tracks real-world treatment selection, preference effects, and clinical outcomes.



Discussion & Critiques:

- *Open-Label Extensions:* a preference design would serve well as a follow-on strategy during an Open-Label Extension (OLE) phase of a successful trial. Once a drug is proven effective, patients can be offered the choice to transition from continuous daily use to an as-needed PEP or "PEP-in-pocket" setting.

CROSS-CUTTING THEMES AND OPERATIONAL OBSTACLES

Defining the Core Question: Traditional Emergency PEP vs. On-Demand Prevention Strategy

Traditional PEP dictates that an individual presents acutely to a clinic *after an emergency, unintended exposure* to prevent the establishment of an infection. However, "PEP-in-pocket" (PIP) used repeatedly as-needed transitions into an *on-demand prevention strategy*. For regulatory and guideline clarity, the research must target traditional emergency presentations. Nonetheless, any long-acting

PEP design requires a baseline understanding that if the drug exhibits high efficacy, it functions fundamentally as both PrEP and PEP.

Logistical Recruitment Bottlenecks

A major obstacle is the low volume of acute PEP presentations. For example, Fenway Health, the busiest PEP provider in New England, receives only about two acute PEP requests per week. Consequently, a 4,000-person study (such as Design 1) would require an implausible infrastructure of 40 or more distinct clinical sites to succeed. Conversely, a distinct, highly accessible population exists: individuals who refuse continuous PrEP because they do not feel they are at constant risk, but who are eager to keep "PEP-in-pocket" for episodic exposures.

Efficacy vs. Compliance in Regulatory Packages

While a pragmatic completion trial (Design 3) provides clear data on compliance, the FDA and other regulators view compliance merely as a component of a package, not a replacement for efficacy data. Regulators must be convinced that the drug pharmacologically aborts viral replication post-exposure. Designs that completely bypass efficacy or rely on highly variable counterfactual models face steep regulatory hurdles.

Observational Center Frameworks vs. Voluntary Registries

Researchers favor structured, prospective observational studies conducted at specific community centers or pharmacies over voluntary "registries". The term "registry" implies voluntary reporting, which introduces severe reporting bias and undermines data rigor. For a zero-event or observational study to carry scientific weight, every exposure and drug dispensation must be meticulously documented by clinicians at designated study hubs.

The Myth of Informed Consent as an Operational Burden

Securing research consent from acute PEP patients should not be an operational barrier. Because prescribing emergency PEP already mandates an intensive public health and clinical consent conversation regarding side effects, toxicities, and the absolute necessity of strict adherence, formalizing a properly constructed research consent adds no real operational weight and can enhance patient compliance.

CONSENSUS DESIGN AND TAKEAWAYS

THE ZERO-EVENT TRIAL DESIGN FOR HIV PEP CLINICAL TRIALS

The Zero Incidence, or Zero-Event, Trial Design is developed for clinical scenarios where breakthrough infections are anticipated to be near-zero or extremely rare. In these contexts, conducting a conventional event-driven non-inferiority clinical trial becomes operationally implausible due to the inability to accumulate enough endpoints. To overcome this, the zero-event trial fundamentally shifts the core inferential goal of the research program. Rather than tracking and

comparing observed infection events across comparative groups, the design focuses entirely on accumulating a large, statistically sufficient volume of prospective PEP exposure data. The ultimate analytical objective is to establish a mathematically rigorous upper 95% confidence bound on the true underlying infection rate.

This design can be operationalized through two primary pathways:

- **Single PEP Exposure Design**: Tracking participants immediately following a single, discreet acute encounter where PEP is prescribed and used.
- **Longitudinal PEP Cohort:** Distributing a product via a "PEP-in-pocket" (PIP) framework and tracking a cohort over a full year, measuring safety and outcomes whenever individual exposure events happen to occur over time.

ADVANTAGES OF THE ZERO-EVENT DESIGN

Strengths and advantages of implementing a Zero-Event Trial Design include:

- **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.
- **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.
- **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.
- **Measures Per-Exposure Efficacy**: Addresses what the per-exposure efficacy looks like under a controlled regimen.
- **Bypasses the Hurdles of Proving Superiority**: From an analytical design perspective, investigators do not face the steep sample size and operational demands required to demonstrate superiority or standard non-inferiority over an active comparator.
- **Sequential Accumulation of Certainty**: The architecture 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 instances progressively solidifies proof that the prevention effect is a biological fact.
- **Optimized Evidence Generation for Low-Incidence Settings**: It serves as an ideal mechanism for safety and efficacy evidence accumulation for novel products deployed in populations where background HIV transmission rates are low, but exposures still occur.

STATISTICAL BENCHMARKS FOR EFFICACY AND BOUNDS

The statistical utility of the Zero-Event design relies entirely on the volume of data accumulated. The following tables illustrate how increasing the number of recorded exposures or expanding the enrolled participant cohort shrinks the upper 95% confidence limit, thereby reinforcing the statistical evidence of efficacy.

Statistical Upper 95% Confidence Bounds by Accumulated Exposures

N Exposures Accumulated	Upper 95% Confidence Bound	Equivalent Incidence Rate
500	0.60%	7.2 / 100 Person-Years (PY)
1,000	0.30%	3.6 / 100 Person-Years (PY)
2,000	0.15%	1.8 / 100 Person-Years (PY)
5,000	0.06%	0.7 / 100 Person-Years (PY)
10,000	0.03%	0.4 / 100 Person-Years (PY)

Statistical Upper 95% Confidence Limits by Cohort Enrollment (1-Year Follow-Up)

N Participants Enrolled	Upper 95% Confidence Limit
250	1.2 / 100 Person-Years (PY)
500	0.6 / 100 Person-Years (PY)
1,000	0.3 / 100 Person-Years (PY)
1,500	0.2 / 100 Person-Years (PY)
2,000	0.15 / 100 Person-Years (PY)

As contextualized by these projections, enrolling a longitudinal cohort of approximately 1,000 to 2,000 participants for a single year of structured follow-up provides sufficient statistical power to bound the upper infection limit below 0.3 per 100 person-years. This level of rigorous bounding is considered highly persuasive and potentially sufficient to satisfy regulatory efficacy claims without requiring a single actual breakthrough event to occur during the trial.

STAKEHOLDER PERSPECTIVES

Zero-Event Trial Design is an alternative to complex, unfeasible modeling exercises like the Counterfactual Placebo Design. The data derived from zero-event models carry real-world persuasiveness because it rules out unacceptable, elevated infection rates. However, for this design to remain rigorous and acceptable to bodies like the FDA, the study must operate under a foundational regulatory assumption that high clinical adherence directly translates to biological protection. Additionally, the design of the trial itself could be kept logistically simple, making it well-suited for implementation across decentralized networks like community health centers or specialized hubs.

NEXT STEPS

The Forum is hosting a satellite session at the AIDS 2026 conference in Rio de Janeiro to build on the summit's discussions. Additional in-person or virtual meetings will be considered. Furthermore, the Forum plans to invite summit participants to collaborate on a manuscript to be published in a peer-reviewed journal to publicize the deliberations and recommendations. Further deliberations between relevant stakeholders, including regulators, are likely to occur to reach final consensus. The summit closed with the appreciation of participants for their commitment to advancing HIV prevention research.