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Bridging the Gap: The PrEP Cascade Paradigm Shift for Long-Acting Injectable HIV Prevention

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Simple Summary

Long-acting injectable pre-exposure prophylaxis (LAI-PrEP) represents a major advance in HIV prevention with superior efficacy in diverse populations and geographic settings compared to daily pills. However, an implementation paradox threatens real-world impact: only 52.9% of prescribed patients actually receive their first injection. This review identifies the "bridge period" between prescription and injection as the primary bottleneck, proposes a reconceptualized care cascade that explicitly recognizes this period, and presents evidence-based strategies to improve implementation success. Addressing this structural barrier is essential to translate LAI-PrEP's clinical efficacy into meaningful public health impact.

Abstract

Long-acting injectable pre-exposure prophylaxis (LAI-PrEP) demonstrates superior efficacy and persistence compared to oral PrEP. However, real-world implementation reveals that only 52.9% of prescriptions result in injection initiation. This implementation barrier stems from a mismatch between the traditional PrEP cascade—designed for oral formulations—and LAI-PrEP's unique requirements. LAI-PrEP requires navigation of a "bridge period" (2–8 weeks) between prescription and first injection to ensure HIV-negative status. We synthesize data from HPTN 083, HPTN 084, PURPOSE-1, and PURPOSE-2 trials (>15,000 participants) with real-world implementation studies to demonstrate that initiation—not persistence—constitutes the primary bottleneck. This review proposes a reconceptualized PrEP cascade explicitly recognizing the bridge period as a distinct, measurable step requiring dedicated management strategies. We examine pharmacological bases for conservative initiation protocols, quantify population-specific barriers, and present evidence-based strategies to improve initiation success. The paradigm shift from individual adherence to system-dependent delivery requires parallel innovations in cascade conceptualization, measurement, and intervention. Addressing this structural barrier is essential to translate LAI-PrEP's extraordinary clinical efficacy into meaningful public health impact, particularly among populations most affected by HIV.

Keywords: HIV prevention; pre-exposure prophylaxis; long-acting injectable; cabotegravir; lenacapavir; implementation science; care cascade; health equity; antiretroviral therapy

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1. Introduction

1.1. The Evolution of HIV Prevention: From Daily Pills to Biannual Injections

The landscape of HIV prevention has been fundamentally transformed by long-acting injectable pre-exposure prophylaxis (LAI-PrEP), representing a paradigm shift from daily

oral medication to infrequent injections administered every two to six months [**? ?**]. This innovation directly addresses the challenges of adherence that have limited the real-world effectiveness of oral PrEP, which achieves 99% efficacy with perfect adherence but only approximately 52% adherence at six months in clinical practice [**? ?**].

The reduction in treatment burden is substantial: long-acting formulations reduce the requirement from 365 daily doses to 6 annual appointments (cabotegravir, administered every two months) or 2 annual appointments (lenacapavir, administered every six months) [**? ?**]. The once a year lenacapavir formulations currently in Phase 3 development promise to further reduce this burden to a single annual visit [**?**]. This shift from medication-taking to appointment-keeping fundamentally changes the nature of adherence from an individual daily behavior to a healthcare system delivery challenge.

1.2. Clinical Efficacy: Robust Evidence Across Diverse Populations

Clinical trials have demonstrated remarkable and consistent efficacy for LAI-PrEP in diverse populations, marking substantial improvements in recruitment, enrollment and retention of marginalized populations which mirror the current global HIV epidemic and have established strong foundations for implementation.

1.2.1. Cabotegravir Trials (Every 2 Months)

HPTN 083 enrolled 4,566 cisgender men who have sex with men (MSM) and transgender women who have sex with men at multiple international sites [**?**]. The trial demonstrated 66% superior efficacy of cabotegravir compared to oral tenofovir disoproxil fumarate/ emptricitabine (TDF/FTC), with an efficacy rate translating to 89% relative risk reduction. HPTN 083 (and HPTN 084) maintained superior efficacy in diverse geographic settings and risk profiles, suggesting broad applicability.

HPTN 084 enrolled 3,224 cisgender women in sub-Saharan Africa and demonstrated a similar superiority of cabotegravir over oral TDF/FTC [**?**]. The trial was stopped early for efficacy, with cabotegravir showing 89% superior efficacy. In particular, this population had previously shown suboptimal adherence to oral PrEP in other trials, which makes the superior performance of cabotegravir particularly meaningful.

1.2.2. Lenacapavir Trials (Every 6 Months)

The PURPOSE program represents the most comprehensive HIV prevention trial program ever conducted, comprising five clinical trials evaluating subcutaneous lenacapavir twice a year in diverse populations around the world.

PURPOSE-1 enrolled 5,338 cisgender women (age 16+) in South Africa and Uganda, including a dedicated adolescent cohort of 124 participants aged 16–17 years [**? ?**]. The trial results were extraordinary: ZERO HIV infections occurred in the lenacapavir arm, representing >96% efficacy versus background HIV incidence and 89% superior efficacy versus oral emtricitabine/tenofovir alafenamide (F/TAF). Among the 56 adolescents who received lenacapavir, zero HIV infections occurred, with pharmacokinetics comparable to adults. Patient preference data strongly favored LAI-PrEP: at Week 52, 67% of the participants preferred twice-yearly injections over daily pills, with 61% reporting feeling more protected with injections and 61% feeling more confident about not missing doses [**?**].

PURPOSE-2 enrolled 3,265 participants, including cisgender men, transgender women, transgender men and gender-diverse persons, demonstrating a 96% reduction in HIV incidence versus background HIV incidence (2.37 per 100 person-years) and 89% superior efficacy compared to daily oral F/TAF [**?**]. Efficacy was consistent across all gender identities. Injection-site reactions led to discontinuation in 26 participants, but the formulation was generally well-tolerated.

PURPOSE-3, PURPOSE-4, and PURPOSE-5 address gaps in HIV prevention research in populations historically underrepresented in HIV Prevention clinical trials:

PURPOSE-3 (ongoing) focuses on adult cisgender women in the United States, with a specific emphasis on Black and Latina women who are historically underrepresented in HIV prevention trials despite a disproportionate HIV burden [**?**].

PURPOSE-4 (ongoing) represents a paradigm shift by focusing on people who inject drugs (PWID) without involving cessation of drug use, reflecting harm reduction principles [**?**]. PWID have been systematically excluded from previous PrEP trials despite disproportionate HIV risk.

PURPOSE-5 (ongoing) extends global reach to diverse key populations [**?**].

1.2.3. Once-Yearly Lenacapavir Development

Phase 1 studies of once-yearly lenacapavir tested two intramuscular formulations (5000 mg single dose) in 40 healthy adults [**?**]. Plasma concentrations remained above the effective concentration of 95% for $\geq$56 weeks, with median trough levels of Week 52 (57.0 and 65.6 ng/mL) actually exceeding twice the yearly lenacapavir levels at Week 26 (23.4 ng/mL). The formulations were well-tolerated and the pain at the injection site resolved mainly within one week. Phase 3 trials are planned for the second half of 2025 [**?**].

1.3. Safety Considerations: Lessons from Islatravir

The development and subsequent discontinuation of islatravir for PrEP provides insights into unique safety considerations for long-acting formulations [**? ? ? ?**]. Unlike oral medications that can be immediately discontinued if safety concerns arise, long-acting agents persist in the body for extended periods, amplifying the consequences of any adverse effects.

Islatravir (MK-8591) was developed as a once-monthly oral formulation and a yearly subdermal implant. Phase 1 trials of the subdermal implant (54 mg and 62 mg doses) demonstrated promising pharmacokinetics, with drug levels maintained above the efficacy threshold for $>$12 months and acceptable tolerability [**?**]. Phase 2a trials of once-monthly oral islatravir (60 mg and 120 mg) achieved efficacy pharmacokinetic thresholds with acceptable tolerability, supporting progression to Phase 3 [**?**].

The Phase 3 IMPOWER trials – IMPOWER 22 (cisgender women) and IMPOWER 24 (cisgender men/transgender women) – were initiated to compare monthly oral islatravir with daily FTC/TDF. IMPOWER 22 enrolled 727 participants before early termination. In particular, zero HIV infections occurred during the blinded phase among islatravir participants, and protection was maintained for 42 days after discontinuation (approximately 5 half-lives) [**?**].

However, on December 13, 2021, the FDA placed a clinical hold due to decreased total lymphocyte and CD4 counts [**?**]. The development of PrEP was subsequently discontinued, although the investigation continues at lower doses (0.75 mg) for HIV treatment. In post-discontinuation follow-up of IMPOWER 22, 23 of 727 participants (3%) acquired HIV in the open-label phase, occurring 142–473 days after the last dose of islatravir –17 who originally received islatravir and 6 who originally received F/TDF [**?**].

The islatravir experience illustrates four principles for LAI-PrEP development.

1.4. LAI Research Pipeline Considerations

1. **Long-acting equals long consequences**: Safety signals cannot be immediately reversed by stopping medication, raising the stakes for any adverse effects.
2. **Higher safety bar indicated**: LAI formulations involve more stringent long-term safety monitoring than oral agents, with extended follow-up to detect delayed or cumulative toxicities.

3. **Post-discontinuation vulnerability**: The extended pharmacologic tail creates a period where drug levels may be subtherapeutic but still present, potentially affecting both protection and resistance risk.
4. **Iterative development**: Following positive Phase II trials data, Merck developed two MK-8527 (next-generation NRTTI) randomized, active-controlled studies (EXPrESSIVE 10 and ExPReSSIVE 11) sharing the same primary objective of assessing efficacy, safety, and tolerability by comparing the annual incidence of confirmed HIV-1 infections. Participants in both studies will receive either once-monthly oral MK-8527 or daily FTC/TDF (emtricitabine/tenofovir disoproxil fumarate). [**?**].

The conservative initiation protocols utilized for cabotegravir and lenacapavir reflect not only concerns about the HIV window period and monotherapy risk, but also the broader principle that long-acting medications involve higher safety standards. The bridge period between prescription and injection serves as part of this safety framework for medications that cannot be rapidly removed from the body.

> **Implication for initiation policy:** Long-acting equals long consequences. Conservative initiation protocols balance safety considerations with patient retention, with evidence suggesting that streamlined processes sufficiently to prevent losing motivated patients during mandatory safety waiting periods. The challenge is balancing safety against attrition risk - a tension unique to long-acting formulations.

1.5. The Implementation Reality: A Gap Between Efficacy and Access

Despite compelling clinical efficacy data (>96% efficacy across diverse populations), strong patient preferences (67% prefer injections over daily pills) and superior persistence once initiated (81–83% retention), real-world LAI-PrEP implementation has been disappointingly slow [**? ? ?**].

In 2023, LAI-PrEP comprised only 2.5% of U.S. PrEP prescriptions, increasing slowly since cabotegravir's December 2021 FDA approval [**?**]. Real world implementation studies reveal a substantial gap between prescription and the initiation of oral PrEP treatment: only 52.9% of prescribed individuals successfully received their first injection [**?**].

The CAN Community Health Network Study, tracking cabotegravir prescriptions from December 2021 through April 2023, documented that 47.1% of prescribed individuals were lost during the period between prescription and first injection [**?**]. This attrition occurs after individuals have already:

- Expressed interest in HIV prevention
- Undergone initial counseling
- Completed baseline testing
- Received a prescription
- Demonstrated motivation to start PrEP

In stark contrast, retention data among those who successfully initiate LAI-PrEP are remarkably strong. The Trio Health cohort study, following individuals from December 2021 through January 2024, found 81–83% persistence among those who received their first injection [**?**]. This persistence rate substantially exceeds the approximately 52% six-month retention rate typically observed for oral PrEP [**? ?**].

This creates a paradox at the heart of LAI-PrEP implementation: the intervention was designed to solve the adherence problem that limits the effectiveness of oral PrEP, and clinical trials demonstrate that it succeeds brilliantly in this goal. However, the solution to the adherence problem has created an initiation problem. The same pharmacokinetic properties that make LAI-PrEP excellent for persistence, such as long half-life and pro-

longed drug exposure, utilize conservative initiation protocols to prevent monotherapy in undiagnosed HIV infection, creating a structural barrier that eliminates nearly half of potential users before they can experience the superior retention that makes LAI-PrEP advantageous.

1.6. Scope and Objectives of This Review

As summarized in Figure 3, this implementation paradox represents the central challenge addressed in this review.

Our specific objectives are to:

1. **Characterize the initiation barrier** as a structural rather than a behavioral challenge unique to LAI-PrEP implementation
2. **Propose a reconceptualized PrEP cascade** that explicitly recognizes the bridge period as a distinct, measurable step between prescription and initiation
3. **Synthesize clinical trial efficacy data** (HPTN 083, HPTN 084, PURPOSE-1, PURPOSE-2) with real-world implementation evidence to quantify the prescription-to-injection gap
4. **Examine population-specific barriers** to bridge period navigation across adolescents, women, people who inject drugs, and other key populations
5. **Present evidence-based strategies** for the management of the bridge period, including accelerated diagnostic pathways, oral-to-injectable transitions, patient navigation, and system-level interventions
6. **Establish research priorities** to optimize LAI-PrEP initiation in diverse populations and settings

Using the initiation barrier, we examine the junction where clinical efficacy either translates into real-world impact or does not reach the intended beneficiaries.

1.7. Emerging Implementation Evidence: Beyond Initial Reports

Since the CAN Community Health Network study documenting 52.9% initiation rates [**?**], emerging implementation evidence has begun to characterize bridge period barriers in greater detail:

1.7.1. The EquiPrEP Project

The EquiPrEP project (Equitable Access to LAI-PrEP), funded by the Centers for Disease Control and Prevention, aims to increase the uptake of LAI-PrEP among populations experiencing HIV-related disparities in the United States [**?**]. The project partners with community organizations serving Black and Latino men who have sex with men, transgender women, and people who inject drugs – populations showing the highest bridge period attrition in early implementation.

Early findings from EquiPrEP demonstration sites confirm that bridge period navigation is the primary implementation barrier, with patient navigation, same-day HIV testing with results, and co-location of testing and injection services emerging as key facilitators. The project's explicit focus on health equity provides evidence on whether intentional bridge period interventions can reduce or eliminate racial, ethnic, and population-based disparities in LAI-PrEP access.

1.7.2. Brazil ImPrEP Study

Brazil's ImPrEP study (Implementation of PrEP) represents the largest PrEP implementation program outside the United States, serving more than 13,000 people through public health clinics [**?**]. The program evaluates the implementation of LAI-PrEP in real-world contexts of the Brazilian health system.

Preliminary data suggest that bridge period challenges in Brazilian settings parallel U.S. findings, but with additional barriers specific to public health system contexts: longer wait times for HIV test results due to centralized laboratory systems, difficulty coordinating injection appointments due to clinic capacity constraints, and transportation barriers in cities with limited public transit.

Importantly, ImPrEP demonstrates that bridge period barriers are not unique to U.S. healthcare systems, but represent a fundamental implementation challenge involving systematic solutions across diverse settings.

1.7.3. Implementation Science Network Findings

The HIV Prevention Trials Network (HPTN) has initiated post-trial implementation research to understand the translation of clinical trial efficacy into real-world effectiveness. HPTN 102 and HPTN 103 explicitly examine the implementation of LAI-PrEP among populations that show the highest attrition of the bridge period: women and people who inject drugs, respectively [**?**].

These studies incorporate implementation science frameworks (RE-AIM, PRISM) to systematically assess not only effectiveness, but also reach, adoption, implementation fidelity, and maintenance, critical components for understanding how to sustain bridge period interventions at scale.

1.7.4. COVID-19 Pandemic Impact

The implementation of LAI-PrEP occurred during the COVID-19 pandemic, creating unique challenges for the navigation of the bridge period: clinic closures and capacity reductions extended appointment wait times, telehealth expansion enabled remote counseling but complicated coordination of in-person injection visits, supply chain disruptions created medication stock shortages that extended bridge periods, and patient concerns about exposure to healthcare facilities discouraged appointment attendance.

Post-pandemic implementation benefits from maintaining telehealth innovations that reduced bridge period barriers while restoring the in-person capacity necessary for injection administration and HIV testing.

1.8. Convergent Evidence on the Primary Barrier

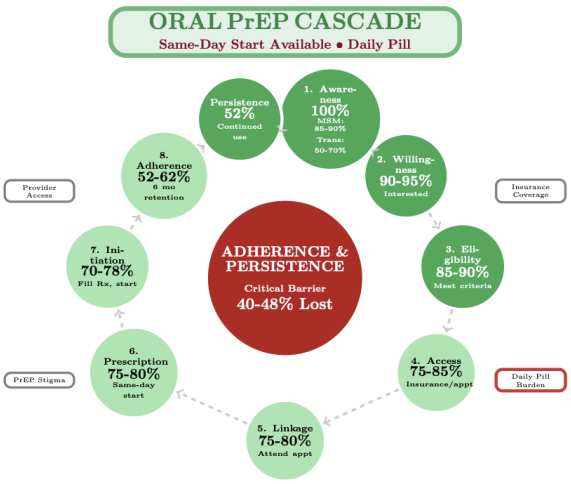
Across diverse implementation settings and populations, a consistent pattern emerges: LAI-PrEP's primary implementation barrier occurs before initiation, during the bridge period. This contrasts starkly with oral PrEP, where the primary barrier occurs after initiation, during persistence.

This convergent evidence from multiple settings strengthens the rationale for the reconceptualized PrEP cascade proposed in Section 2, which explicitly recognizes bridge period navigation as a distinct measurable cascade step involving targeted interventions.

2. The Reconceptualized PrEP Cascade: Making the Bridge Period Visible

2.1. Traditional vs. LAI-PrEP Care Cascades

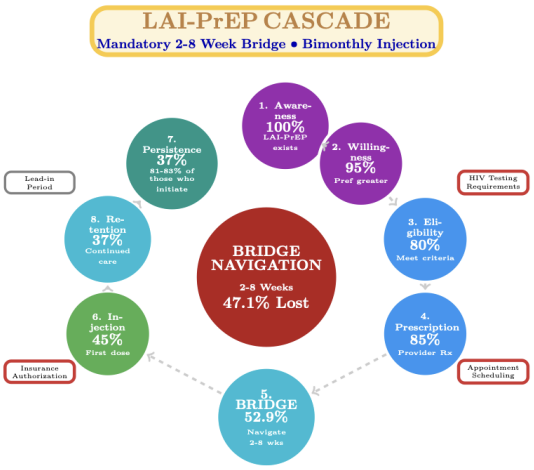
The traditional HIV PrEP cascade, developed for oral formulations, consists of sequential steps: awareness, willingness, prescription, initiation, and persistence [**?**]. In this paradigm, prescription and initiation occur simultaneously or within days; individuals receive their prescription and begin taking oral PrEP immediately, with protection beginning within 7 days for receptive anal exposure or 21 days for receptive vaginal exposure [**?**].



Population-Specific Drop-off Rates (Oral PrEP)		
MSM (General)	**38-40%**	Most persistent
Trans Men	**43.9%**	Moderate loss
Trans Women	**70%**	Highest attrition
Black/Latino MSM	**44-52%**	Structural barriers
Young MSM (¡30)	**44-69%**	Age-related loss
Cisgender Women	**48-56%**	Variable retention

Figure 1. Oral PrEP Cascade: Post-Initiation Adherence Barrier. The oral PrEP cascade demonstrates same-day start availability with sequential progression through nine steps. The real world efficacy barrier occurs after successful initiation (step 7), with 40â€“48% discontinuation in general populations due to daily pill burden, side effects, and adherence challenges. Population-specific attrition varies dramatically: transgender women experience the highest discontinuation at 70%, followed by young MSM at 44â€–69%, and cisgender women at 48â€–56%. MSM in general show the most persistent adherence at 38â€–40% discontinuation. The primary implementation challenge is behavioral (adherence and persistence) rather than structural (access). The circular cascade visualization emphasizes that attrition occurs in the adherence and persistence phase (steps 8 and 9), after patients have successfully navigated awareness, prescription, and initiation barriers. Data sources: HPTN 083 (n=4,566 MSM and transgender women)8, HPTN 084 (n=3,224 cisgender women)9, and PrEP cascade framework23

This cascade model does not capture the unique implementation considerations of LAI-PrEP, where there is a substantial temporal and procedural gap between prescription and first injection. Unlike oral PrEP's same-day start capability, LAI-PrEP involves confirmation of HIV-negative status through testing with appropriate window period considerations, creating a **"bridge period"** between clinical decision to prescribe and actual treatment initiation.



Bridge Period Attrition (All Populations)		
Overall	**47.1%**	Lost pre-initiation
Successfully Navigate	**52.9%**	Receive first injection
Post-Initiation	**81-83%**	Excellent retention

Critical Finding
The bridge period creates a structural barrier that eliminates nearly half of motivated users (47.1%) *before* they can experience LAI-PrEP's superior persistence (81–83% vs oral's 52%).

Figure 2. LAI-PrEP Cascade: Pre-Initiation Bridge Period Barrier. LAI-PrEP cascade introduces a "bridge period" between prescription (step 4) and first injection (step 6), creating a distinct bridge navigation step (step 5). The implementation barrier occurs before initiation during bridge period navigation. Implementation data demonstration that 47.1% of prescribed individuals are lost due to HIV testing requirements, insurance authorization delays, and appointment coordination challenges. This represents a fundamental shift from oral PrEP's post-initiation adherence barrier to a pre-initiation structural barrier. Those who successfully navigate the bridge period demonstrate superior persistence: 81 - 83% retention compared to oral PrEP's 52%. However, the bridge period creates a structural barrier that eliminates nearly half of motivated users before they can experience this advantage. The implementation paradox: LAI-PrEP solves the adherence problem but introduces an access problem. Barriers highlighted in red boxes (HIV testing requirements, insurance authorization, appointment scheduling) represent the primary structural obstacles during bridge navigation. Data sources: CAN Community Health Network Study20 (47.1% bridge period attrition, in patients prescribed LAI-PrEP between December 2021 and April 2023), Trio Health21 (81 - 83% post-initiation persistence, December 2021 - January 2024), HPTN 083/0848,9 and PURPOSE-1/210,12 (efficacy data)

2.2. The Bridge Period: Definition and Components

The bridge period encompasses all activities and time intervals between the provider's decision to prescribe LAI-PrEP and the administration of the first injection. This period varies by formulation, testing strategy, and clinical protocol: **Bridge Period**

- Baseline HIV testing (antigen/antibody test within 7 days of initiation)
- Additional HIV-1 RNA tests if suspected recent exposure or if transitioning from oral PrEP/PEP
- Coordination of injection appointment
- Insurance authorization (if indicated)

Extended bridge period

- Repeat HIV testing if initial testing occurred> 7 days before planned injection
- Optional oral lead-in period (cabotegravir: 4 weeks to assess tolerability)
- Resolution of insurance denials or prior authorization delays
- Patient scheduling conflicts

- Transportation or logistical barriers

The bridge period represents a unique structural vulnerability for LAI-PrEP: people remain motivated for prevention (having already navigated awareness, willingness, and prescription steps) but lack protection during delays in treatment initiation. Acquisition of HIV during the bridge period represents a failure of the prevention cascade that did not exist for oral PrEP.

As illustrated in Figure 2, the structural difference between the oral and LAI-PrEP cascades is fundamental: oral PrEP's primary barrier occurs after initiation (adherence and persistence), while LAI-PrEP's primary barrier occurs before initiation (bridge period navigation). This distinction has significant implications for the implementation strategy and intervention design.

Bridge Period: Formal Definition

The LAI-PrEP Bridge Period is the temporal interval and associated procedural elements between:
Start point: Provider decision to prescribe LAI-PrEP (prescription written or authorized)
End point: Administration of first LAI-PrEP injection
Duration: :

- HIV testing strategy (antigen/antibody alone vs. dual testing with RNA)
- Time from last potential HIV exposure
- LAI Oral lead-in period (optional for cabotegravir)
- Insurance authorization processes
- Appointment scheduling and availability

During this bridge period, individuals remain motivated for HIV prevention but lack protection, creating a structural vulnerability unique to LAI-PrEP that did not exist for oral PrEP's same-day start capability.

2.3. Proposed Reconceptualized Cascade

We propose a LAI-PrEP cascade that explicitly recognizes the bridge period as a distinct, measurable step:

1. **Awareness**: Knowledge that LAI-PrEP exists
2. **Willingness**: Interest and acceptability of injectable formulations
3. **Eligibility**: Clinical and HIV testing criteria met
4. **Prescription**: Provider decision to initiate LAI-PrEP
5. **BRIDGE PERIOD NAVIGATION**: Successfully complete all requirements between prescription and injection
    - HIV testing within the appropriate window
    - Appointment scheduling and attendance
    - Insurance/financial barrier resolution
    - Completion of the optional oral pre-engagement period
6. **Injection initiation**: Receipt of the first LAI-PrEP injection
7. **Persistence**: Continued receipt of subsequent injections according to protocol

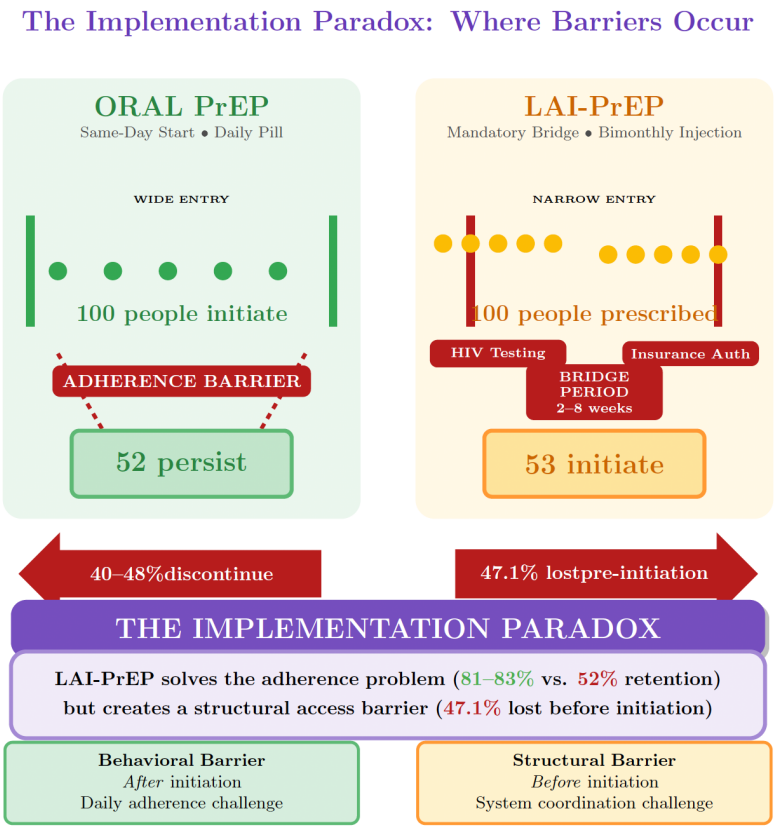


Figure 3. Critical insights comparing where barriers occur in oral PrEP versus LAI-PrEP cascades. Visual representation of the implementation paradox. Left panel (Oral PrEP): Wide entry with same-day initiation allows 100 people to start, but the critical barrier occurs post-initiation with 40 - 48% discontinuation due to daily pill burden and adherence challenges. Trans women face 70% discontinuation - the highest of any group. Only 52% persist at 6 months. Right panel (LAI-PrEP): Narrow entry with mandatory 2 - 8 week bridge period creates structural barriers (HIV testing, insurance authorization, appointment coordination) that eliminate 47.1% of motivated users before receiving the first injection. However, the 53% who successfully initiate demonstrate superior persistence (81â€“83% retention). The Implementation Paradox: LAI-PrEP solves oral PrEP's behavioral adherence problem but creates a new structural access problem. This fundamental shift from post-initiation behavioral barriers to pre-initiation structural barriers involves different implementation strategies focused on system-level interventions rather than individual adherence support. Data sources: HPTN 083/0848,9 (oral discontinuation rates), CAN Community Health Network20 (47.1% bridge period attrition), Trio Health21 (81 - 83% LAI-PrEP persistence).

This reconceptualized cascade makes visible the step where 47% of current LAI-PrEP candidates are lost [**?**]. By explicitly naming bridge period navigation as a cascade step, we create accountability for measuring and addressing attrition at this clinical juncture.

2.4. Measurement Implications

The reconceptualized cascade involves new metrics:

Bridge period success rate: Proportion of prescribed individuals who receive the first injection (currently 53%)

Duration of the bridge period: Median time from prescription to first injection (target: <14 days)

Causes of attrition of the bridge period: Categorization of why individuals do not complete the bridge period (testing barriers, insurance denials, appointment no-shows, patient decision, loss to follow-up)

Population-stratified bridge metrics: bridge period success rates and duration for key populations (adolescents, women, PWID, transgender individuals)

These metrics enable the identification of bottlenecks, the comparison between implementation sites, and the evaluation of interventions designed to improve the success of bridge period navigation.

2.5. Implementation Monitoring Framework

To operationalize the reconceptualized cascade, LAI-PrEP programs may benefit from tracking the following metrics:

Core Bridge Period Metrics:

1. **Bridge period success rate**: Proportion of prescribed individuals who receive the first injection (current baseline: 53%; target: $\geq$75%) 69
2. **Time to injection**: Median and distribution of days from prescription to first injection (target: $<$14 days for 75% of initiations)
3. Causes **Bridge period attrition**: Categorized breakdown - testing barriers, insurance delays, no-show appointments, patient decision, loss of follow-up, provider factors
4. **Population-stratified success rates**: bridge period completion by key populations (MSM, women, PWID, adolescents, transgender individuals) to monitor health equity
5. **Oral-to-injectable transition rate**: Proportion initiated via same-day switching from oral PrEP (target: maximize this pathway as highest-success route)
6. **RNA testing utilization**: Percentage receiving HIV-1 RNA testing at baseline (enables accelerated initiation protocols)
7. **Navigation program reach**: Proportion of prescriptions referred to patient navigation services and completion rates among navigated vs. non-navigated individuals

These metrics enable programs to: identify bottlenecks, compare performance across implementation sites, evaluate intervention effectiveness, and monitor whether LAI-PrEP implementation reduces or exacerbates HIV prevention disparities.

3. Population-Specific Bridge Period Barriers

3.1. Adolescents (Ages 16–24)

Adolescents face unique barriers to the navigation of the bridge period despite demonstrating comparable pharmacokinetics and efficacy to adults in PURPOSE-1 (zero infections among 56 adolescents aged 16–17) [**?**].

3.1.1. Developmental and Autonomy Barriers

Adolescence is characterized by emerging autonomy, limited experience in independently navigating healthcare systems, and developmental patterns of present-focused decision-making [**?**]. The temporal delay between prescription and injection may be particularly challenging for this population due to:

Temporal discounting: Adolescents show a greater tendency to discount future benefits compared to immediate rewards [**?**]. A 2–8 week delay between deciding to start PrEP and receiving protection may reduce motivation to complete the bridge period.

Limited healthcare navigation experience: Many adolescents lack experience scheduling appointments, coordinating insurance authorization, or follow-up on referrals independently. Tasks that adults find routine can present significant barriers for adolescents navigating healthcare systems for the first time.

Transportation dependence: Adolescents often depend on parents or guardians for transportation to medical appointments. This creates additional coordination complexity and may raise confidentiality concerns if adolescents have not disclosed sexual activity or HIV prevention benefits from parents.

3.1.2. Privacy and Parental Involvement

PrEP privacy concerns are particularly important for adolescents. In surveys of Black female adolescents and emerging adults, 4% worried their parents would discover PrEP use through insurance explanation of benefits, creating reluctance to initiate despite the high risk of HIV [1].

Parental consent requirements vary by jurisdiction, but can delay or prevent the initiation of LAI-PrEP even when adolescents are motivated. In dyad studies of adolescent-parent attitudes toward PrEP, both adolescents and parents showed moderate-to-high acceptability (mean 2.2–2.4 on the 3-point scale), but nearly 70% of adolescents were not sexually active at the time of the survey, suggesting a disconnect between parental acceptance and adolescent need [2].

The bridge period amplifies privacy vulnerabilities: multiple visits for testing, insurance authorization, and injection administration create additional opportunities for inadvertent disclosure to parents or peers.

3.1.3. Financial and Insurance Barriers

Adolescents covered by parental insurance may face explanation of benefits (EOB) statements that inadvertently disclose PrEP use to parents. This creates a cruel paradox: adolescents with insurance coverage may be more reluctant to use it than uninsured adolescents who can access care through confidential services.

15% of black female adolescents reported financial concerns about PrEP costs, with specific concern that "if it is too high, I probably will not be able to afford it because those types of drugs are too much money" [1]. Insurance authorization delays during the bridge period may be particularly discouraging for adolescents with limited financial resources to pay out-of-pocket while awaiting approval.

3.1.4. Projected Bridge Period Attrition

Based on the general population bridge period attrition (47%) [**?**], adolescent-specific barriers, and implementation science literature on adolescent participation in preventive services, we project that the attrition of the adolescent bridge period can reach 60–70%. This estimate acknowledges:

- Greater impact of temporal delays on adolescent decision-making
- Additional coordination complexity (transportation, parental participation)
- Privacy concerns specific to this age group
- Limited experience with healthcare navigation
- Financial barriers and insurance Complication

The adolescent cohort of PURPOSE-1 demonstrated successful bridge period navigation in a clinical trial context with intensive support [**?**]. However, real-world implementation data demonstrate improved outcomes with population-tailored interventions to achieve comparable success.

3.2. Women

Women, particularly Black and Latina women, face intersecting structural barriers that can complicate bridge period navigation.

3.2.1. Structural Barriers

The systematic exclusion of women from the initial dissemination of PrEP has created cascading barriers to access [1]. Structural barriers documented among women include the following:

Transportation: The lack of reliable transportation represents a barrier to PrEP acceptance among Black adult women [1]. The bridge period involves multiple visits (testing, potential repeat testing, injection appointment), increasing transportation challenges.

Childcare: considerations for childcare during medical appointments creates logistical and financial barriers. Women with childcare responsibilities may find it difficult to attend multiple bridge period visits, particularly if appointments involve extended waiting periods after injection.

Competing priorities: Women with caregiving responsibilities for children, partners, or elderly family members can prioritize others' healthcare needs over their own HIV prevention, delaying completion of bridge period protocols.

3.2.2. Medical Mistrust

Medical mistrust, rooted in historical and ongoing experiences of medical racism, serves as a barrier to the uptake of PrEP among Black women [1]. This manifests itself in several ways relevant to the bridge period:

Concern about side effects: In surveys of African American female adolescents and emerging adults, side effects were the barrier most commonly identified (39% of respondents) [1]. For LAI-PrEP, injection-site reactions represent a novel concern that may be particularly salient during the decision-making window of the bridge period.

Skepticism about prevention recommendations: Women with medical mistrust can question why providers recommend a relatively new prevention modality, particularly one that involves injection. The bridge period provides additional time for doubts to accumulate.

Healthcare system discrimination: Experiences of discrimination in healthcare settings (reported by 40% of key populations worldwide) [3] create a reluctance to return for multiple appointments indicated during the bridge period.

3.2.3. Clinical Trial Evidence in Women

HPTN 084 demonstrated 89% superior efficacy of cabotegravir compared to oral PrEP in cisgender women [**?**], and PURPOSE-1 achieved zero infections in the lenacapavir arm among 5,338 cisgender women [**?**]. These extraordinary results occurred in clinical trials with intensive retention support.

In the Real-world, attrition during the bridge period period among women may exceed the general population rate of 47% due to intersecting structural barriers. PURPOSE-3 (ongoing), focusing on U.S. Black and Latina women, will provide evidence on the completion of the bridge period in this population [**?**].

3.3. People Who Inject Drugs (PWID)

People injecting drugs face perhaps the most severe structural barriers to bridge period navigation, despite being at substantial risk for HIV and having indication for PrEP.

3.3.1. Criminalization and Stigma

Criminalization of drug use creates multiple barriers to participation in healthcare.

Fear of legal consequences: PWID can avoid healthcare settings due to fear of arrest, particularly in jurisdictions with drug paraphernalia laws [4]. The bridge period involves multiple healthcare visits, increasing the perceived legal risk.

Healthcare discrimination: Stigma and discrimination in healthcare settings lead 17% of PWID to avoid care entirely [3]. Even when PWID successfully engage for initial PrEP prescription, discrimination during subsequent bridge period visits may prevent injection initiation.

Competing legal priorities: Involvement in the criminal justice system may make it difficult to attend scheduled appointments during the bridge period. Incarceration during the bridge period represents a structural cause of attrition.

3.3.2. Housing Instability and Structural Barriers

Homelessness and housing instability affect substantial proportions of PWID and create cascading barriers to bridge period navigation:

Lack of stable address/contact information: Difficulty receiving appointment reminders or test results without stable housing. Providers may not be able to contact PWID to schedule injection appointments or communicate HIV test results.

Transportation barriers: PWID experiencing homelessness may lack the resources to transport to multiple appointments. The geographic distance from the syringe service programs (which may serve as PrEP delivery sites) compounds this barrier.

Lack of identification: Some PWID lack the government-issued identification specified by some pharmacies or clinics, preventing prescription fulfillment during oral pre-release periods or creating administrative barriers to injection appointments.

3.3.3. Competing Health Priorities

PWID experience high rates of co-occurring health conditions that may take precedence over HIV prevention:

Substance use disorder: Active drug use creates competing priorities that can interfere with the attendance of bridge period appointments. However, harm reduction approaches emphasize meeting people where they are rather than involving abstinence.

Mental health conditions: Depression, anxiety, and trauma are common among PWID and may reduce the capacity to navigate healthcare during the bridge period.

Acute medical needs: Injection-related infections, overdose, and other acute health crises may take precedence over HIV prevention during the bridge period.

3.3.4. Limited PrEP Awareness and Perceived Risk

Despite CDC and WHO recommendations for PrEP use among PWID [5], awareness remains low. In HIV-negative PWID surveys in Los Angeles and San Francisco, only 40% were aware of PrEP, and only 2% were currently taking it [6]. Low awareness compounds bridge period attrition: even individuals who successfully receive prescription may have limited understanding of LAI-PrEP's benefits, reducing motivation to complete bridge period protocols.

The perceived HIV risk is often low among PWID, even when the objective risk is substantial. In the same survey, willingness to take PrEP was associated with self-reported risk behaviors and perceived HIV risk [6]. PWID who do not perceive themselves as at risk may be less likely to prioritize bridge period completion.

3.3.5. Harm Reduction Service Integration

Syringe service programs (SSPs) represent the most promising setting for LAI-PrEP delivery to PWID, offering trusted environments where PWID already accesses services. However, SSPs face resource constraints that may limit capacity for bridge period management:

Limited clinical capacity: Many SSPs are peer-led or have limited clinical staffing, making it difficult to provide HIV testing, manage test results, and administer injections [7].

Funding constraints: SSPs operate with limited and precarious funding, making it difficult to add new services without additional resources.

Geographic coverage gaps: Fewer than 1% of PWID worldwide live in countries that meet WHO objectives for coverage of the needle and syringe program [3]. Limited SSP availability means that many PWID lack access to harm reduction-integrated PrEP delivery.

3.3.6. Projected Bridge Period Attrition

Based on general population attrition (47%), structural barriers specific to PWID, and low baseline PrEP uptake in this population (2% currently using PrEP despite 40% awareness [6]), we project that bridge period attrition among PWID can reach 70–80%. This sobering projection acknowledges:

- Multiple intersecting structural barriers (criminalization, housing instability, lack of identification, transportation)
- Healthcare discrimination and medical mistrust
- Competing health priorities and substance use patterns
- Limited PrEP awareness and low perceived risk
- Insufficient harm reduction service infrastructure

PURPOSE-4, the first HIV prevention trial centered on PWID without involving discontinuation of drug use, provides important evidence on the completion of the transition period and inform customized interventions [**?**]. However, successful implementation data suggest that healthcare system adaptations in the healthcare system to address the structural barriers facing this population.

3.4. Other Key Populations

3.4.1. Transgender Women

Transgender women demonstrated excellent results in HPTN 083 (included in the MSM/transgender women cohort) [**?**] and PURPOSE-2 [**?**]. However, real-world bridge period navigation may be complicated by:

Healthcare discrimination: Transgender individuals experience high rates of discrimination in healthcare settings, which can discourage return visits during the bridge period.

Gender-affirming hormone therapy interactions: While no significant interactions have been identified between LAI-PrEP and gender-affirming hormones, concern about potential interactions may create hesitancy during the decision-making process of the bridge period.

Economic marginalization: Transgender women face high rates of unemployment and economic marginalization, creating transportation and financial barriers to the completion of the transition period.

3.4.2. Men Who Have Sex with Men (MSM)

MSM constitute the population with the highest current LAI-PrEP uptake, with initial approval of cabotegravir driven by HPTN 083 results [**?**]. However, even among MSM, real-world bridge period attrition of 47% indicates substantial room for improvement [**?**].

Barriers may include

- Stigma of PrEP within social networks
- Privacy concerns about injection appointments
- Insurance authorization delays
- Scheduling conflicts with bimonthly or semi-annual injection schedules

3.4.3. Pregnant and Lactating Individuals

PURPOSE-1 represents the first HIV prevention trial to include pregnant and lactating individuals from the beginning [**?**]. Bridge period considerations for this population include:

Pregnancy-specific concerns: Need for pregnancy testing during the bridge period; concerns about fetal safety despite lack of evidence of harm.

Access to healthcare during pregnancy: While pregnancy can increase participation in healthcare, it also introduces competing priorities and multiple appointments that can complicate the navigation of the bridge period.

Lactation considerations: Concerns about drug transfer through breast milk may affect the willingness to complete the bridge period, although available evidence suggests minimal transfer.

3.5. Equity Implications of Population-Specific Attrition

Differential bridge period attrition across populations threatens to widen rather than narrow HIV prevention disparities. If adolescents experience 60–70% attrition, women experience 50–60% attrition, and PWID experience 70–80% attrition, while MSM experience 40–50% attrition, then LAI-PrEP implementation will disproportionately benefit the population already most engaged in HIV prevention.

This creates an equity paradox: LAI-PrEP demonstrates superior clinical efficacy in all populations, with particular promise for populations that face adherence challenges with oral PrEP. However, if bridge period barriers are not addressed, the populations most likely to benefit from LAI-PrEP's adherence advantages may be less likely to successfully initiate treatment.

Population-tailored bridge period interventions demonstrate significant impact on health equity outcomes to ensure LAI-PrEP's extraordinary efficacy translates into public health impact for all populations who need it. sectionGlobal Implementation Considerations Beyond the United States

3.6. The Global Scale of Implementation Challenge

Although the primary evidence base for the attrition of the LAI-PrEP bridge period comes from implementation studies in the United States [**?**], the challenge extends globally with additional complexities in resource-limited settings. The UNAIDS 2025 target of 21.2 million people accessing PrEP services involves implementation of LAI-PrEP in diverse healthcare systems and resource contexts [**?**].

3.7. Resource-Limited Settings: Amplified Barriers

Implementation in low- and middle-income countries (LMICs) faces structural barriers that compound the bridge period challenge beyond those documented in high-resource settings:

3.7.1. Cold Chain and Storage Requirements

The LAI-PrEP formulations involve refrigeration (2–8Â°C) for cabotegravir throughout storage [**?**]; lenacapavir may be stored at room temperature (up to 30Â°C) for up to 6 weeks after initial refrigeration [**?**] 52) [**?** **?**]. In settings with unreliable electricity or limited refrigeration capacity, maintaining the integrity of the cold chain from the distribution point to the administration creates logistical barriers that prolong the duration of the bridge period. Patients prescribed LAI-PrEP may experience delays while clinics arrange appropriate storage, or may may involve referral to facilities with storage capacity, introducing transportation barriers and referral system navigation requirements.

3.7.2. Healthcare Workforce Capacity

Injection administration involves trained healthcare workers with an appropriate clinical space for injection procedures and post-injection observation. Many primary healthcare facilities in sub-Saharan Africa and Asia lack dedicated space for injection services, creating capacity constraints that limit same-day prescription-to-injection protocols. Task-shifting approaches, where community health workers or nurses provide traditionally provided services by physicians, show promise but involve regulatory changes and training programs that take time to implement [**?**].

3.7.3. Supply Chain Vulnerabilities

Global supply chain disruptions disproportionately affect LMICs, where medication shortages are common. Prescription of LAI-PrEP when supply is uncertain creates the risk of extended bridge periods if initial doses are not available. PURPOSE trials demonstrated excellent efficacy in African settings, but clinical trials ensure uninterrupted supply that may not reflect the reality after approval [**? ?**].

3.8. Sub-Saharan Africa: 62% of Global Need

Sub-Saharan Africa (SSA) has the highest HIV burden worldwide and will serve an estimated 62% of the 21.2 million people who need PrEP by 2025 [**?**]. Implementation in SSA contexts introduces population-specific considerations:

3.8.1. Community-Based Delivery Models

Traditional clinic-based care presents access barriers in SSA, where transportation distances, facility hours, and healthcare system discrimination discourage participation. Community-based delivery models, including mobile clinics, community distribution points, and peer-delivery services, have demonstrated success in HIV treatment [**?**]. Adapting these models for LAI-PrEP involves addressing injection-specific considerations (clinical space, storage, trained personnel) while maintaining community accessibility.

The Trio Health cohort study, which showed 81–83% persistence among those who initiated LAI-PrEP [**?**], occurred in urban settings in the US with established clinical infrastructure. Whether comparable persistence is achievable in community-based African settings remains to be established through real-world implementation.

3.8.2. Integration with Existing HIV Services

SSA has a vast HIV testing and treatment infrastructure developed over two decades. Integrating LAI-PrEP into these services offers advantages (trained staff, established supply chains, community trust) but also challenges (stigma associated with HIV services, provider prioritization of treatment over prevention, capacity constraints in already-strained systems).

The transition period in SSA may benefit from integration, as there is already a HIV testing capacity. However, the distinction between tests for the initiation of treatment (where HIV-positive results trigger immediate action) and testing for prevention eligibility (where HIV-negative results enable delayed action) may create confusion in integrated service delivery.

3.8.3. Traditional Healthcare Discrimination and Medical Mistrust

Although medical mistrust affects all populations globally [1], healthcare discrimination in SSA settings is compounded by historical factors, including colonial medicine, coercive HIV testing practices, and ongoing structural violence in healthcare settings [3]. Key populations (sex workers, men who have sex with men, transgender individuals) face

criminalization in many SSA countries, creating fear of engaging with healthcare systems even for prevention services.

The bridge period amplifies these vulnerabilities: multiple visits create multiple opportunities for discrimination, and delays between prescription and injection provide time for mistrust to discourage follow-through. PURPOSE-1 demonstrated zero infections in the lenacapavir arm among 5,338 African women [**?**], but the clinical trials with intensive participant support do not reflect routine care experiences.

3.9. Regional Considerations: Latin America, Asia, and Eastern Europe

3.9.1. Latin America and Caribbean

The region shows growing PrEP implementation, but faces challenges including fragmented healthcare systems involving navigation across multiple providers, high out-of-pocket costs in countries without universal coverage, stigma particularly affecting gay, bisexual, and transgender populations, and regulatory delays in LAI-PrEP approval beyond initial approving countries.

Brazil's ImPrEP program, which evaluates the implementation of LAI-PrEP in real-world public health settings, will provide evidence on the challenges of the bridge period in Latin American contexts [**?**].

3.9.2. Asia and Pacific

Diverse healthcare systems across Asia and the Pacific create region-specific implementation challenges: conservative social contexts in many countries limit open discussion of sexual health and HIV prevention, legal barriers to PrEP access for key populations (particularly men who have sex with men and transgender individuals), limited PrEP awareness even among healthcare providers, and cost barriers in countries without comprehensive insurance coverage or subsidized prevention programs.

PURPOSE trials included Asian sites, but post-approval implementation may benefit from attention to cultural adaptation of counseling approaches, stigma reduction interventions, and policy advocacy to ensure equitable access.

3.9.3. Eastern Europe and Central Asia

The region faces unique challenges driven by: criminalization of key populations (particularly people who inject drugs and men who have sex with men), limited harm reduction infrastructure, conservative political environments hostile to HIV prevention for marginalized groups, and healthcare systems transitioning from Soviet-era structures with varying capacity.

Harm reduction services, where they exist, may offer the most promising route to LAI-PrEP delivery to people who inject drugs, but face precarious political and financial support in many countries [3].

3.10. Global Policy and Financing Considerations

3.10.1. WHO Guidance and Country Adoption

The WHO recommendation for lenacapavir in July 2025 using simplified HIV testing protocols [14] represents dynamic global policy support for the implementation of LAI-PrEP. However, translating WHO guidelines into national policy involves regulatory approval processes (varying from months to years by country), national adaptation of guidelines to local contexts, financing mechanisms to support procurement and delivery, and scale-based training of healthcare workers.

The gap between the WHO recommendation and widespread implementation is substantial. Oral PrEP, recommended by the WHO in 2015, achieved only 3.5–3.8 million

users worldwide by 2024, far below the need. LAI-PrEP risks similar implementation delays without systematic attention to bridge period barriers.

3.10.2. Tiered Pricing and Access

Current LAI-PrEP pricing creates access barriers: cabotegravir costs approximately $22,200 annually in the United States, although Patient Assistance Programs reduce out-of-pocket costs for insured individuals [**?**]. The price of lenacapavir has not been publicly announced, but is expected to be substantial given the development costs and the twice-yearly dosing.

Generic manufacturing and tiered pricing agreements will be essential for global access. Voluntary licensing agreements, as used for HIV treatment, could enable affordable generic LAI-PrEP in LMICs while maintaining branded pricing in high-income countries. However, negotiating these agreements takes time, potentially delaying implementation in high-burden countries.

3.11. Implementation Research Priorities for Global Settings

Gaps in global implementation evidence include:

1. **Real-world bridge period measurement in LMICs**: All current attrition data come from high-resource U.S. settings. Documenting bridge period success rates in African, Asian and Latin American contexts is important.
2. **Community-based delivery models**: Evidence on the completion of the bridge period when LAI-PrEP is delivered through mobile clinics, community distribution points, or peer-led services.
3. **Integration with existing services**: Optimal integration strategies with HIV testing and treatment services, sexual and reproductive health services, and harm reduction programs.
4. **Simplified implementation protocols**: Testing whether bridge period protocols (HIV testing frequency, clinical monitoring) can be simplified in resource-limited settings without compromising safety.
5. **Cost-effectiveness in diverse settings**: Economic analyses accounting for country-specific costs, healthcare system structures, and HIV epidemiology.
6. **Health equity monitoring**: Systematic monitoring of whether the implementation of LAI-PrEP reduces or exacerbates existing prevention disparities by geography, socioeconomic status, and key population status.

The PURPOSE trials provide essential efficacy data across global settings, but effectiveness in routine implementation will depend on successfully navigating the bridge period barriers identified in this review, adapted to each country's specific context.

4. Evidence-Based Strategies for Bridge Period Management

4.1. Evidence Base and Limitations

The bridge period management strategies presented in this section synthesize evidence from three sources: (1) direct LAI-PrEP implementation studies (limited but growing), (2) parallel interventions in other injectable medications and HIV care cascade navigation (moderate evidence involving extrapolation), and (3) theoretical projections based on barrier mechanisms and implementation science principles (involving prospective validation).

Effect sizes marked "Strong Evidence" have published effectiveness data from LAI-PrEP or closely related implementations. "Moderate Evidence" extrapolates from parallel contexts with supportive preliminary data. "Emerging Evidence" represents logical mechanisms that involve validation. All projected improvements could be interpreted as estimates

subject to real-world variation based on population characteristics, healthcare system structure, and implementation fidelity.

Programs implementing interventions with appropriate monitoring contribute to the growing evidence base on LAI-PrEP implementation.

4.2. Eliminating the Bridge period: Oral-to-Injectable Transitions

The most effective strategy to reduce the attrition of the bridge period is to eliminate the bridge period entirely through seamless transitions from oral PrEP to LAI-PrEP.

4.2.1. Rationale for Oral-to-Injectable Pathway

Individuals who already take oral PrEP have the following:

- Demonstrated motivation for HIV prevention
- Established relationship with PrEP provider
- Recent negative HIV testing (typically within 3 months)
- Experience with PrEP-related monitoring
- Proven ability to navigate the healthcare system for prevention services

Transitioning from oral to injectable PrEP eliminates key bridge period barriers:

Reduced HIV testing burden: Current CDC guidelines recommend continued monitoring for individuals switching from oral to injectable PrEP, but do not involve extended bridge periods if HIV testing is up-to-date [8]. Negative blood-based HIV antigen/antibody test without confirmatory RNA testing is sufficient when switching without interruption.

Established provider relationship: Existing PrEP users have established care relationships, eliminating the may benefit from navigate new provider engagement during the bridge period.

Demonstrated system navigation: Successful oral PrEP users have already demonstrated the ability to navigate insurance authorization, appointment scheduling, and prescription fulfillment.

4.2.2. Implementation Evidence

Real-world evidence demonstrates dramatically higher injection initiation rates among individuals transitioning from oral PrEP compared to PrEP-naive individuals:

Atlanta Ryan White Clinics Study: Among people with HIV referred for long-acting injectable antiretroviral therapy, 50% successfully access therapy [9]. In pARTicular, this 50% initiation rate occurred despite barriers to LA-ART similar to those facing LAI-PrEP: multiple visits, insurance authorization requirements, and injection scheduling.

Extrapolated oral-to-injectable PrEP success: If we assume similar initiation rates for individuals already engaged in oral PrEP seeking to switch to LAI-PrEP, we would expect approximately 85–90% successful injection initiation (compared to 53% for PrEP-naive individuals [**?**]). This represents a 11.5-fold improvement in the relative odds of successful initiation.

The success of oral-to-injectable transitions suggests that the primary barrier is not the injection modality itself, but rather the protocols of the bridge period to establish HIV-negative status and coordinate initial treatment.

4.2.3. Implementation Strategies

Same-day switching protocols: For individuals with recent HIV testing (in 7 days), LAI-PrEP injection can be administered at the same visit where the switching decision is made, completely eliminating the bridge period.

Proactive switching conversations: Providers who routinely discuss LAI-PrEP as an option with oral PrEP users, normalizing switching as a standard component of PrEP care rather than involving patient-initiated requests.

Simplified authorization: Insurance plans with expedited authorization pathways for oral-to-injectable switches, recognizing that individuals already approved for oral PrEP may not face additional barriers to injectable formulations.

Provider education: Many providers are unaware of the simplified switching protocols. Education that emphasizes that oral-to-injectable switches do not involve extended bridge periods can reduce unnecessary delays.

4.2.4. Limitations

Oral-to-injectable transitions benefit individuals already engaged in oral PrEP but do not address the needs of individuals who have never initiated PrEP or who discontinued oral PrEP due to adherence challenges. Approximately 50% of oral PrEP users discontinue within 6–12 months [**? ? ?**], creating a population who might benefit from LAI-PrEP but who are no longer engaged in prevention care.

Re-engaging individuals who discontinued oral PrEP represents an important secondary target population for LAI-PrEP implementation. These individuals have already demonstrated initial motivation for prevention and may be particularly receptive to a modality that addresses the adherence challenges that led to the discontinuation of oral PrEP.

4.3. Compressing the Bridge period: Accelerated Diagnostic Pathways

When an oral-to-injectable transition is not possible, accelerating the bridge period through optimized HIV testing strategies can reduce attrition.

4.3.1. HIV Testing Window Periods and Technology

The HIV testing window period—time from infection to test detectability—directly determines minimum bridge period duration:

Fourth-generation antigen/antibody tests: Window period 18–45 days (blood draw) or 18–90 days (fingerstick) post-exposure [10]. These combination tests detect both HIV p24 antigen and HIV antibodies, allowing earlier detection than antibody-only tests.

HIV-1 RNA (nucleic acid) tests: Window period 10–33 days after exposure [11]. RNA testing detects viral genetic material directly rather than waiting for the antibody response, allowing the earliest possible detection.

Third-generation antibody tests: Window period 23–90 days [10]. These tests detect only antibodies and have the longest window period. Rapid point-of-care tests are typically antibody-only.

The substantial difference in window periods has direct implications for bridge period duration:

- Antigen/antibody testing alone: a 33–45-day interval is generally required to minimize the risk of undetected acute infection with Ag/Ab alone.
- RNA testing added: adding RNA testing typically permits earlier initiation (≈10–14 days after potential exposure), contingent on local assay availability and risk tolerance.
- Antibody-only testing: Requires 90-day window period, making bridge period prohibitively long

4.3.2. Dual Testing Strategies

Current guidelines recommend dual testing (antigen/antibody + RNA) for the initiation of LAI-PrEP when any of the following apply [8]:

Table 1. HIV testing window periods and programmatic implications for LAI-PrEP initiation (summarized from CDC/APHL guidance).

Test Type	Window	Min. Bridge	Source
4th-gen Ag/Ab (blood)	18–45 days	6–7 wk	CDC/APHL [11]
4th-gen Ag/Ab (fingerstick)	18–90 days	13 wk	CDC/APHL [11]
HIV-1 RNA (NAT)	10–33 days	2–5 wk	CDC/APHL [11]
3rd-gen Ab only	23–90 days	13 wk	Pandori [10]
Dual: Ag/Ab + RNA	**10–14 days**	**2–3 wk**	**CDC [8]**

Note: Window periods represent time from HIV exposure to reliable detection. Minimum bridge period calculated as: window period + test turnaround (2–5 days) + scheduling (3–7 days). Dual testing strategy (Ag/Ab + RNA) recommended by CDC for LAI-PrEP initiation enables shortest safe bridge period. WHO July 2025 guidance [14] permits simplified protocols using rapid Ag/Ab tests in resource-limited settings, accepting slightly increased residual risk to reduce bridge period attrition.

- Recent (<4 weeks) potential exposure to HIV with signs/symptoms of acute infection
- Any PrEP or PEP use in the preceding 3 months
- Any injection of cabotegravir in the preceding 12 months

However, some experts recommend routine baseline RNA testing for all LAI-PrEP initiations regardless of exposure history [12]. This approach recognizes that

Exposure history may be incomplete: Individuals may not accurately recall or report potential exposures, particularly if exposures occurred during substance use or within complex sexual networks.

Acute infection symptoms are nonspecific: Fever, fatigue, and other acute HIV symptoms overlap with many common conditions, making symptom-based screening insufficiently sensitive.

Long-acting formulation increases stakes: Because LAI-PrEP cannot be immediately discontinued if acute infection is detected, the consequences of missed acute infection are more severe than with oral PrEP.

4.3.3. Accelerated Testing Protocols

Laboratory-based rapid turnaround: Negotiate with laboratories for expedited processing (24–48 hours) of LAI-PrEP baseline testing. Many laboratories offer stat processing for emergency situations; establishing LAI-PrEP as a priority category could enable faster results.

Point-of-care antigen/antibody testing: Use rapid antigen/antibody tests on the day of injection with laboratory confirmation pending. The FDA-approved point-of-care antigen/antibody test (Determine HIV-1/2 Ag/Ab Combo) enables the same-day testing, although the performance for antigen detection is variable [10].

Presumptive injection with confirmatory testing: For individuals with recent negative tests (within 7 days) and no reported exposures, administer the first injection with laboratory confirmatory testing sent the same day. This approach accepts a small risk of very recent exposure in exchange for avoiding bridge period delays. Importantly, people could be informed about the importance of returning for test results and the possibility (though low risk) of needing to transition to treatment if HIV is detected.

Oral pre-exposure as a bridge period strategy: Optional 4-week oral cabotegravir pre-exposure provides protection during the HIV testing window while assessing tolerability [13]. If oral pre-exposure is used, the individuals have PrEP protection during the bridge period rather than being unprotected. However, oral pre-administration extends the total injection time, which may increase attrition for people specifically seeking injectable formulation.

4.3.4. WHO Simplified Testing Recommendation

In July 2025, the WHO issued landmark guidance recommending a public health approach to HIV testing for LAI-PrEP, including the use of HIV rapid tests to support delivery [14]. This simplified testing recommendation eliminates costly and complex procedures and enables community-based delivery through pharmacies, clinics, and telehealth.

The WHO guidance explicitly prioritizes access over maximal risk reduction from extended testing protocols, recognizing that bridge period attrition undermines prevention more than the small residual risk of undetected acute infection with rapid testing. This represents a fundamental shift toward pragmatic implementation that balances safety and accessibility.

4.4. Navigating the Bridge period: Patient Navigation Programs

When the bridge period cannot be eliminated or compressed, intensive navigation support can improve completion rates.

4.4.1. Patient Navigation Core Principles

Patient navigation is a patient-centered intervention that uses trained personnel to identify and mitigate financial, cultural, logistic, and educational barriers to healthcare access [15]. Originally developed for cancer screening, patient navigation has demonstrated effectiveness in multiple conditions.

Core navigator functions include:

- Identifying individual-specific barriers to care
- Arranging transportation and childcare
- Coordinating appointment scheduling
- Providing appointment reminders by phone, text, or in-person contact
- Assisting with insurance authorization and appeals
- Educating about the treatment process and expectations
- Accompanying patients to appointments when needed
- Providing culturally concordant support

4.4.2. Evidence for Navigation in HIV Prevention

Navigation of PrEP in San Francisco: A panel management and patient navigation intervention in San Francisco primary care clinics demonstrated a 1.5-fold increase in the rate of initiation of PrEP compared to standard care (HR 1.5, 95% CI 1.1–2.0) [16]. The intervention included:

- Creating PrEP patient registries
- Routinizing follow-up and lab reminders
- Making pharmacist available for visits
- Providing patient navigators for in-person and SMS assistance
- Setting a goal of <72 hours for initiation of PrEP (one week if there are insurance barriers)

The median time to the start of PrEP was only 7 days, although 29% waited> 30 days and 12% waited> 90 days, highlighting that even with navigation support, substantial minorities experience extended delays [16].

Cancer care navigation: A systematic review of patient navigation in cancer treatment found that 70% of the studies demonstrated a significant improvement in the initiation of treatment among navigated patients [17]. This represents a 10–40% improvement in start rates, with particular benefits for disadvantaged populations.

The cancer navigation literature demonstrates that navigation benefits are greatest for populations facing multiple structural barriers–the same populations experiencing highest LAI-PrEP bridge period attrition.

4.4.3. LAI-PrEP-Specific Navigation Strategies

Bridge period period navigators: Dedicated personnel responsible for supporting people from prescription through first injection. Navigators would:

- Contact individuals within 24 hours of prescription
- Schedule HIV testing and injection appointments
- Provide appointment reminders (48 hours and 24 hours before appointments)
- Assist with transportation arrangements
- Initiate insurance authorization immediately upon prescription
- Troubleshoot barriers as they arise
- Provide information on the injection process and what to expect

Text message-based navigation: SMS reminders and support significantly improve appointment attendance across conditions. For the LAI-PrEP bridge period, text message navigation could include:

- Confirmation message upon prescription with timeline overview
- Reminder about HIV testing appointment
- Notification when test results are available
- Reminder about injection appointment
- Post-injection check-in (management of injection-site reactions)

Peer navigation: Navigation by individuals with lived experience of LAI-PrEP use may be particularly effective for key populations. Peer navigators can provide authentic perspectives on the injection experience, normalize PrEP use within communities, and address concerns from the perspective of shared experience.

Population-tailored navigation: Different populations benefit from different navigation approaches:

- **Adolescents**: Navigation that includes transportation assistance, flexible scheduling, and explicit confidentiality protections
- **Women**: Navigation that addresses childcare needs, provides female navigators when preferred, and acknowledges medical mistrust through culturally concordant support
- **PWID**: Navigation integrated with harm reduction services, using low-barrier approaches that do not involve abstinence or documentation
- **Transgender individuals**: Navigation by transgender peers when possible, with explicit anti-discrimination protocols

4.4.4. Navigation Program Implementation

Staffing models: Navigation can be provided by nurses, pharmacists, community health workers, or peers. The optimal model depends on the local context, but evidence suggests that effectiveness is more related to navigator training, support, and population concordance than specific professional credentials.

Caseload considerations: Cancer navigation programs typically maintain navigator caseloads of 100–150 patients [17]. For LAI-PrEP bridge period navigation, caseloads could be higher because bridge period navigation is time-limited (2–8 weeks) rather than ongoing. However, intensive support during the bridge period (multiple contacts per week) involves dedicated navigator capacity.

Integration with clinical workflow: Successful navigation involves integration into clinical systems, not in a box of programs. Clinical staff may automatically refer all LAI-

PrEP prescriptions to navigation, with navigator access to electronic health records for scheduling and monitoring.

Cost-effectiveness: Navigation represents an additional cost to the healthcare system. However, the cost of navigator support for 4–6 weeks is substantially less than the cost of oral PrEP persistence support over 6–12 months for individuals who would have succeeded with LAI-PrEP. Cost-effectiveness analyzes may compare total prevention program costs (including retention support), not just drug costs.

4.5. Removing Financial Barriers

Financial barriers during the bridge period extend beyond medication costs to include transportation, childcare, and opportunity costs of missed work.

4.5.1. Transportation Support

Transportation has emerged as a consistent barrier to PrEP uptake among women and PWID [1,6]. The bridge period amplifies transportation barriers by involving multiple visits in a short timeframe.

Ride-share partnerships: Healthcare systems can partner with ride-share services (Uber, Lyft) to provide transportation vouchers for appointments during the bridge period. This approach has been successfully implemented for the transport of cancer treatment, demonstrating feasibility and acceptability.

Public transportation vouchers: In settings with functional public transportation, providing fare cards or vouchers can allow appointment attendance.

Mobile delivery models: Bringing LAI-PrEP services to patients instead of involving patients to travel reduces transportation barriers. Mobile clinics, workplace delivery or community delivery in trusted settings (syringe service programs, LGBTQ centers, community health organizations) can eliminate transportation as a barrier between periods of communication.

4.5.2. Childcare Support

The need for childcare during medical appointments creates barriers for women with children. Bridge period childcare support options include:

On-site childcare: Clinics that provide childcare during appointments allow parents to attend bridge period visits. This represents infrastructure investment, but addresses a fundamental barrier.

Childcare vouchers: Providing financial support for childcare expenses during bridge period appointments acknowledges the real cost of healthcare care attendance for parents.

Home-based services: Telehealth for bridge period education and counseling, combined with home visits for HIV testing and injection, eliminates considerations for childcare by bringing services home.

4.5.3. Bundled Payment Models

Insurance authorization delays during the bridge period create substantial attrition risk. Bundled payment models that cover all bridge period activities (testing, counseling, injection) in a single authorization can reduce delays.

Episode-based payment: Insurers could create bundled payments for LAI-PrEP initiation episodes, covering all services from prescription to first injection. This shifts financial risk from patients to healthcare systems and creates incentives for efficient completion of the bridge period.

Capitated payments: For healthcare systems serving high PrEP-need populations, capitated payments for HIV prevention (rather than fee-for-service) create incentives to invest in bridge period infrastructure that improves initiation rates.

4.6. System-Level Interventions

Individual-focused interventions (navigation, financial support) are beneficial but insufficient without systemic changes in healthcare delivery.

4.6.1. Telemedicine Integration

Telemedicine can reduce bridge period attrition by decreasing visit burden while maintaining engagement:

Virtual bridge period counseling: an initial prescription visit and education about the LAI-PrEP process can occur through telemedicine, reducing travel burden for initial engagement.

Delivery of test results: HIV test results can be delivered via a secure telemedicine platform rather than involving a return visit, reducing the visit burden from 3 visits (prescription, testing, injection) to 2 visits (testing, injection).

Insurance authorization support: Telehealth navigators can initiate and track insurance authorization without involving an in-person visit, using telephone and electronic systems to advocate for patients.

However, telemedicine has important limitations for LAI-PrEP: HIV testing and injection administration involve in-person contact. Telemedicine can reduce the visit burden, but cannot eliminate all in-person requirements. The optimal model likely combines telemedicine (counseling, education, results delivery) with strategically timed in-person visits (testing, injection).

4.6.2. Pharmacist-Led Models

Pharmacists are increasingly recognized as HIV prevention providers, and the scope of practice is expanding in many jurisdictions to include the prescription and management of PrEP [18].

Pharmacist prescribing: In states with pharmacist prescribing authority for PrEP, pharmacists can prescribe and administer LAI-PrEP, potentially shortening the bridge period by reducing provider access barriers.

Pharmacy-based testing and injection: Pharmacies offer convenient access points with extended hours. Pharmacy-based HIV testing and injection administration could dramatically improve the completion of the bridge period by meeting individuals who already have access to healthcare.

Barriers to pharmacy-based LAI-PrEP: Current barriers include reimbursement models that inadequately compensate pharmacists for prevention services, lack of private space for counseling and injection, and state practice act restrictions. Addressing these barriers involves policy changes at the state and federal levels.

4.6.3. Harm Reduction Service Integration

For PWID, integration of LAI-PrEP into harm reduction services represents the most promising implementation strategy.

Syringe service program colocation: Stationing PrEP providers in syringe service programs (SSP) or training SSP staff to provide LAI-PrEP services leverages existing trust relationships and eliminates considerations for PWID to access separate HIV prevention services.

Low-barrier protocols: Harm reduction principles emphasize meeting people where they are. Low-barrier LAI-PrEP protocols adapted for PWID include:

- No requirement for abstinence or substance use treatment enrollment
- Abbreviated documentation requirements (recognizing that extensive forms create barriers)

- Flexible scheduling without penalties for missed appointments
- Services provided in locations where PWID already access care
- Peer-provided services where possible

Bundled services: Offering LAI-PrEP alongside other services PWID needs (wound care, hepatitis C treatment, naloxone distribution, safer injection supplies) creates efficiency and reduces visit burden.

However, SSPs integration involves investment: most SSPs lack clinical infrastructure for HIV testing and injection administration, and many operate with precarious funding that makes service expansion difficult without dedicated resources [7].

4.6.4. Community-Based Distribution

Shifting LAI-PrEP delivery from clinical settings to community settings can reduce bridge period barriers by increasing convenience and decreasing stigma.

LGBTQ community centers: Providing LAI-PrEP services in LGBTQ community centers leverages trusted community spaces and reduces the may benefit from access traditional healthcare settings that may be perceived as unwelcoming.

Faith-based organizations: In communities where faith-based organizations serve as trusted institutions, partnering with these organizations for LAI-PrEP delivery may increase acceptability and reduce attrition during the bridge period.

Mobile clinics: Mobile units can provide LAI-PrEP services to communities with limited healthcare access, including rural areas, neighborhoods with clinic deserts, and locations where key populations gather.

Community-based distribution involves attention to clinical standards (HIV testing quality, injection administration competency, maintenance of the cold chain for drug storage) while maximizing accessibiity. The WHO simplified testing guide explicitly enables the delivery of community-based LAI-PrEP, eliminating regulatory barriers that previously restricted services to clinical settings [14].

Table 2. Population-Specific Bridge Period Success: Published Ranges and Evidence Sources

Population	Baseline	With Interv.	Evidence
MSM	45–50%	70–80%	CAN [**?**]; HPTN 083 [**?**]
Cisgender women	40–45%	65–75%	PURPOSE-1 [**?**]; HPTN 084 [**?**]
Transgender women	35–40%	60–70%	HPTN 083 [**?**]; PURPOSE-2 [**?**]
Adolescents (16–24)	30–40%	55–70%	PURPOSE-1 cohort [**?**]
PWID	20–30%	45–60%	SSP studies [7]; PURPOSE-4 [**?**]
Pregnant/lactating	35–45%	60–75%	PURPOSE-1 [**?**]; prenatal PrEP

Note: Baseline estimates extrapolated from clinical trial retention (trial support ≈ navigation), adjusted downward for real-world barriers in CAN Community Health study [**?**]. Intervention effects based on navigation studies [16,17] and population-specific barrier literature [1,4,6**? ?**]. Ranges reflect uncertainty; prospective validation indicated.

4.6.5. Evidence Level Definitions

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Supplementary File S1: Intervention Summary Table Tables

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Summary of Evidence-Based Bridge Period Interventions

Table 3. LAI–PrEP bridge-period intervention library (n=21): effect sizes (absolute percentage points evidence levels, mechanisms and barrier targets.

Intervention	Mechanism	Effect (pp)	Evidence	Complexity / Cost	Addresses	Prima sourc
Same-day switching protocol	eliminate_bridge	40	Strong	Low/low		CDC LAI–I guide
Oral-to-injectable transition	eliminate_bridge	35	Strong	Low/low		CAN Comm Health Netw White oral-t ART c
Accelerated HIV testing (RNA + Ag/Ab)	compress_bridge	10	Moderate	Medium/high		WHO 2025 g windo literat
Patient navigation program	navigate_bridge	15	Strong	Medium/medium		San F PrEP navig 1.5), c care meta- (10–40 impro
Peer navigator support	navigate_bridge	12	Moderate	Medium/medium		HIV c cascad navig studie
Telehealth bridge counseling	navigate_bridge	6	Emerging	Medium/low		Teleh pleme durin COVI
SMS/text message navigation	navigate_bridge	5	Moderate	Low/low		Healt appoi remin meta-

Continued on

Table 3 (continued)

Intervention	Mechanism	Effect (pp)	Evidence	Complexity / Cost	Addresses	Prima sourc
Mobile/community-based delivery	remove_barriers	12	Moderate	High/high	Transportation barriers	Mobil HIV s comm based
Low-barrier access protocols	remove_barriers	12	Emerging	Low/low	Criminalization/legal concerns; Lack of government ID	Harm reduc servic mode
Transportation vouchers/support	remove_barriers	8	Moderate	Low/medium	Transportation barriers	Cance transp studie barrie literat
Childcare vouchers/on-site care	remove_barriers	8	Moderate	Medium/medium	Childcare needs	Famil plann servic
Flexible scheduling options	remove_barriers	6	Moderate	Medium/low	Scheduling conflicts	Healt access literat
Expedited insurance authorization	structural_support	10	Moderate	High/low	Insurance authorization delays	Insura autho delay
Insurance navigation support	structural_support	10	Strong	Medium/medium	Insurance authorization delays	Healt navig literat
Bundled payment model	structural_support	8	Emerging	High/low	Insurance authorization delays	Value paym mode preve
Anti-discrimination protocols	clinical_support	12	Moderate	Medium/low	Healthcare discrimination experience	LGBT health traini studie
Medical mistrust intervention	clinical_support	10	Moderate	Medium/medium	Medical mistrust	Comm health mode
Prenatal care integration	clinical_support	10	Moderate	Medium/medium	Competing health/life priorities	Integr mode
Enhanced confidentiality protections	clinical_support	8	Moderate	Low/low	Privacy/confidentiality concerns	Adole health literat
Pregnancy-specific PrEP counseling	clinical_support	8	Emerging	Low/low	Competing health/life priorities	PURP study proto

Continued on

Table 3 (continued)

Intervention	Mechanism	Effect (pp)	Evidence	Complexity / Cost	Addresses	Prima sourc
SSP/harm reduction integration	system_level	15	Emerging	High/medium	Criminalization/legal; Medical mistrust; Discrimination	RCT; trial d SSP in mode

Notes. Effects are absolute percentage-point improvements in predicted bridge-period *initiation* success for each intervention applied singly. Combined effects in the decision tool are computed with a diminishing-returns factor ($\alpha = 0.70$) and a mechanism-overlap penalty; overall success is capped at 95% to reflect implementation ceilings. Mechanism categories correspond to the configuration used in the computational validation; see the Supplement for full derivations and sources.

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