

Supplementary Materials: SUPPLEMENTARY FILE S5:
POPULATION GUIDANCE

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Population Guidance

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Supplementary File S5: Population-Specific Implementation Guidance

This supplementary file expands on population-specific bridge period barriers and implementation strategies referenced in Section 3 of the main manuscript. Each population section includes epidemiologic context, bridge period barriers specific to that population, and evidence-based strategies to improve navigation.

S2.1: Adolescents (Ages 16–24)
Epidemiologic Context

Adolescents represent approximately 8% of global HIV infections but account for disproportionate percentages of incident infections in key regions. In sub-Saharan Africa, adolescents aged 15-19 represent 12% of the population but account for 29% of new HIV infections [1]. In the United States, adolescents aged 13-24 represent 21% of new HIV diagnoses and have unique epidemiology: transgender youth are 6-7 times more likely to be HIV-positive than cisgender youth [2]. Gay and bisexual male adolescents represent 82% of new HIV diagnoses in adolescent males. These epidemiologic patterns mean that adolescent-targeted LAI-PrEP programs could reach populations with extraordinary HIV incidence.

Bridge Period Barriers Specific to Adolescents

Developmental Factors: Temporal Discounting and Future Orientation

Neurobiological research demonstrates that temporal discounting—the tendency to discount future benefits in favor of immediate rewards or concerns—peaks in adolescence [3,4]. For a prescribed adolescent, the immediate requirement to navigate a bridge period (appointments, testing, multiple visits) competes against the abstract future benefit of HIV prevention. This is not a failure of individual adolescents but a predictable neurobiological developmental pattern. LAI-PrEP implementation strategies must account for this: reducing the number of bridge period visits, making visits immediately rewarding (supportive environments, peer presence), and emphasizing near-term benefits (simplicity of future dosing) alongside distant HIV prevention benefits.

Healthcare Navigation and Insurance Barriers

Adolescents typically have limited experience navigating healthcare independently. Insurance-related bridge period barriers are amplified for this population: adolescents

may not know how to appeal insurance denials, may not know that explanation of benefits documents arrive in household mailboxes, and may not know how to seek pre-authorization. Additionally, adolescents dependent on parental insurance face privacy concerns: if insurance requires pre-authorization or generates denial letters, parental discovery is possible.

Surveys of Black female adolescents aged 16–24 found that 34% reported concerns about parental discovery of PrEP through insurance documentation as a barrier to initiation [5]. For adolescents with non-supportive parents, this risk is real and substantial. Some adolescents are in foster care, have unstable housing, or lack parental engagement—creating additional complexity for insurance and appointment navigation.

Educational Access and Literacy

Informed consent for LAI-PrEP requires understanding testing protocols, safety profiles, efficacy expectations, and side effects. For adolescents with lower health literacy (which varies widely by education access and individual background), bridging this knowledge gap during the bridge period requires more intensive education. Interactive, youth-friendly education resources (rather than dense clinical documentation) improve understanding and engagement.

Appointment Adherence and Transportation

Adolescents may have limited transportation options, school/work commitments that conflict with appointment scheduling, and may not independently manage calendar systems for appointment reminders. Bridge period success requires frequent appointments (baseline visits, testing follow-up, pre-injection visits). Each appointment creates an opportunity for non-attendance.

Projected Bridge Period Attrition in Adolescents

Synthesizing general population attrition (47%) with adolescent-specific barriers (developmental discounting, healthcare navigation complexity, insurance/privacy concerns, transportation challenges), we project adolescent bridge period attrition may reach 60–70% without targeted interventions. This would mean that <40% of prescribed adolescents would receive first injection. However, adolescents demonstrate excellent persistence in PURPOSE-1 (zero infections among 56 adolescents in lenacapavir arm), suggesting that once they navigate the bridge period, they engage well with long-acting treatment.

Evidence-Based Strategies for Adolescent Bridge Period Support

1. **Adolescent-Centered Care Environments:** Integrate LAI-PrEP into existing adolescent clinics and teen health centers rather than requiring navigation to adult-oriented specialty settings.
2. **Peer Navigation and Education:** Enroll adolescents who have successfully received LAI-PrEP to provide peer mentoring, normalize the experience, and provide credible role models.
3. **School-Based or Community-Based Access:** Minimize transportation barriers by bringing services to adolescents through school health centers, community centers, or community health worker models.
4. **Insurance/Coverage Navigation:** Train adolescent-focused staff to manage insurance barriers including pre-authorization, appeals, and alternative payment options.
5. **Parent Engagement (When Safe):** For adolescents with supportive parents, parental involvement reduces bridge period barriers. For adolescents with non-supportive parents or complex family situations, strategies should preserve autonomy and privacy.
6. **Flexible Scheduling:** Offer extended hours, weekend appointments, and virtual visits for education/follow-up to reduce school and work conflicts.

7. **Psychosocial Support:** Integrate mental health support, recognizing that anxiety, depression, or trauma history may complicate bridge period engagement.

S2.2: Women (Including Transgender Men and Gender-Diverse Persons)

Epidemiologic Context

Cisgender women represent 48% of global HIV infections, with women aged 15-49 accounting for approximately 21 million infections globally. In sub-Saharan Africa, women represent 57% of new HIV infections [1]. Women's HIV incidence remains concentrated among key populations: female sex workers, women in serodiscordant partnerships, and incarcerated women. Pregnancy and lactation are important considerations: approximately 1,200 pregnant women are newly infected with HIV globally each year, and pregnancy planning and postpartum care are central to women's lives. Transgender men and gender-diverse persons with reproductive capability face unique HIV prevention needs that LAI-PrEP can address.

Bridge Period Barriers Specific to Women

Structural and Caregiving Barriers

Women, particularly Black and Latina women, face intersecting structural barriers: transportation access (lower rates of car ownership), childcare responsibilities (essential childcare during appointments), and competing caregiving priorities (elder care, sick family members) [5]. These barriers are not individual failures but structural inequities. A woman with three children may find it logistically impossible to attend multiple bridge period appointments without childcare support or may face transportation barriers if partner/family has sole access to vehicle. Single mothers may lack flexibility at work to attend appointments.

Medical Mistrust and Healthcare Discrimination

Women, particularly Black and Indigenous women, experience well-documented medical racism and discrimination in healthcare settings. This history creates rational medical mistrust: women are underdiagnosed with conditions, have pain complaints dismissed, and experience discrimination in reproductive healthcare [6]. For LAI-PrEP, this manifests as skepticism about side effect information, concerns about injectable medications, and reluctance to trust prevention recommendations. A 2023 survey of Black women considering LAI-PrEP found that 39% identified side effects as the primary barrier—reflecting both legitimate concerns about medication side effects AND heightened skepticism about pharmaceutical claims [5].

Pregnancy and Reproductive Planning

While PURPOSE-1 explicitly enrolled pregnant and lactating individuals and demonstrated safety, pregnancy creates bridge period complexity: some testing protocols require HIV testing at pregnancy confirmation, adding another requirement before first injection. Pregnancy planning (whether to delay LAI-PrEP to attempt pregnancy, or continue LAI-PrEP if already initiated) requires nuanced discussion. Postpartum care and lactation-related barriers (loss of healthcare focus after pregnancy, competing demands of newborn care) can affect persistence even if bridge period is successfully navigated.

Projected Bridge Period Attrition in Women

Synthesizing general population attrition (47%) with women-specific barriers (transportation, caregiving, medical mistrust, pregnancy complexity), we project women's bridge period attrition may reach 55–65% without targeted interventions. This would mean that 35–45% of prescribed women would receive first injection.

Evidence-Based Strategies for Women's Bridge Period Support 131

1. **Trauma-Informed Care:** Implement trauma-informed practices recognizing that many women (particularly those with HIV exposure history) have experienced gender-based violence or other trauma. 132
2. **Integrated Sexual and Reproductive Health:** Situate LAI-PrEP within comprehensive sexual and reproductive health clinics rather than as standalone service. 133
3. **Address Medical Mistrust Directly:** Provide transparent information about side effects, involve women in decision-making, and create spaces to discuss historical medical racism. 134
4. **Support for Caregiving Responsibilities:** Provide childcare during appointments, flexible scheduling for competing caregiving demands, and telehealth options for follow-up visits. 135
5. **Transportation Support:** Provide transportation vouchers, partner with transportation services, or bring services to community locations accessible via public transportation. 136
6. **Pregnancy-Specific Counseling:** Provide clear information about LAI-PrEP continuation in pregnancy/lactation, emphasize zero-infection results in PURPOSE-1, and support reproductive planning discussions. 137
7. **Community Health Worker Models:** Employ community health workers from women's communities to provide culturally congruent support and navigation. 138

S2.3: People Who Inject Drugs (PWID) 139

Epidemiologic Context 140

Globally, an estimated 12 million people inject drugs, of whom approximately 1.4 million are HIV-positive [7]. In the United States, injection drug use accounts for 9% of new HIV diagnoses, but this percentage is rising due to the opioid epidemic. Key regions with high PWID HIV prevalence include Eastern Europe (particularly among people injecting in prisons), Southeast Asia, and North America. PWID have historically been underrepresented in HIV prevention research, with the first major HIV prevention trial specifically focused on PWID (PURPOSE-4) only just beginning enrollment in 2024 [8]. This historical exclusion from research reflects broader healthcare marginalization of PWID. 141

Bridge Period Barriers Specific to PWID 142

Criminalization and Fear of Legal Consequences 143

In jurisdictions where drug use is criminalized, PWID rationally fear healthcare engagement due to legal consequences. Fear of legal consequences (that healthcare facilities might report them to law enforcement) is one of the top-cited barriers to healthcare access among PWID [9]. This creates paradox: LAI-PrEP could be provided through syringe service programs (SSP), harm reduction settings where PWID congregate, yet many SSPs are also underfunded and under-resourced specifically because of criminalization and societal stigma. 144

Housing Instability and Unstable Contact Information 145

Substantial proportions of PWID experience housing instability (28-40% depending on region), creating cascading barriers: no stable address means appointment reminders don't reach them, no phone access means no text reminders, transportation from shelters to appointments is complex, and maintaining engagement with healthcare systems is nearly impossible. Bridge period requires multiple appointments—each requiring the individual to remember the date and location and be able to access transportation. 146

Medical Mistrust and History of Iatrogenic Harm 147

PWID have experienced profound medical discrimination, including forced treatment, incarceration for drug-related charges despite seeking healthcare, and dismissal of health 148

concerns in medical settings [10]. This creates rational medical mistrust: healthcare systems have historically harmed PWID through policies like mandated detoxification, criminal reporting, and systematic exclusion. For LAI-PrEP, this manifests as skepticism about injectable medications and concerns about being tracked or surveilled through healthcare systems.

Competing Acute Health and Survival Priorities

For an individual experiencing housing instability or struggling with active opioid use, navigating bridge period appointments competes against immediate survival needs: securing housing, obtaining food, managing withdrawal, obtaining substances to prevent withdrawal. These are not failures of motivation but rational prioritization of immediate survival over abstract future prevention benefits. Bridge period navigation requires sufficient stability and executive function to attend multiple appointments—resources that may be lacking for PWID in active crisis.

Projected Bridge Period Attrition in PWID

Synthesizing general population attrition (47%) with PWID-specific barriers (criminalization fears, housing instability, medical mistrust, competing survival priorities), we project PWID bridge period attrition may reach 70–80% without targeted interventions. This would mean that only 20–30% of prescribed PWID would receive first injection. This projection is sobering but underscores the need for extraordinarily intensive support for PWID bridge period navigation.

Evidence-Based Strategies for PWID Bridge Period Support

1. **Integration with Syringe Service Programs (SSPs):** Locate LAI-PrEP services within existing SSPs where PWID already congregate, rather than requiring navigation to separate clinic locations.
2. **Same-Appointment Testing and Injection:** Where feasible, reduce the number of bridge period appointments by conducting testing and first injection in same setting (after appropriate waiting period).
3. **Low-Threshold Entry:** Eliminate or minimize preconditions for LAI-PrEP access (do not require detoxification, drug abstinence, or documented housing as conditions for access).
4. **Legal Protections and Confidentiality:** Clearly communicate confidentiality protections, include legal advocacy as part of LAI-PrEP programs, and partner with organizations defending PWID rights.
5. **Peer Navigation and Support:** Employ peer navigators (people with lived experience of injection drug use and HIV/PrEP) to provide credible support and navigation.
6. **Address Housing and Basic Needs:** Provide or connect to housing support, food assistance, and other basic needs to reduce competing survival priorities during bridge period.
7. **Harm Reduction and Medication-Assisted Treatment (MAT) Integration:** Integrate LAI-PrEP with MAT (methadone, buprenorphine) and harm reduction services to address the full spectrum of PWID health needs.
8. **Flexible Contact and Reminder Systems:** Use multiple contact methods (text, phone, in-person at SSP, email) and don't assume stable housing or phone access.

S2.4: Other Key Populations

Transgender and Gender-Diverse Persons

Transgender women and gender-diverse persons are disproportionately affected by HIV, with HIV prevalence among transgender women estimated at 14.7% globally—38 times higher than the general adult population [11]. Yet transgender persons face profound

healthcare discrimination, including discrimination within HIV care settings. Barriers to bridge period completion include: fear of discrimination in healthcare settings, legal barriers to medical documentation (misgendering in medical records creates additional trauma), limited access to gender-affirming healthcare more broadly (meaning if LAI-PrEP provider is non-affirming, entire care experience is compromised), and economic marginalization limiting ability to afford healthcare.

HPTN 083 enrolled transgender women (though the denominator was relatively small) and PURPOSE-2 demonstrated excellent outcomes across transgender and gender-diverse participants. Evidence-based strategies include: employing transgender staff, ensuring electronic health records use correct names and pronouns, integrating gender-affirming care with LAI-PrEP, and explicitly addressing healthcare discrimination in patient education.

Incarcerated and Formerly Incarcerated Persons

Approximately 1 million incarcerated people globally are HIV-positive. Within prisons, HIV prevalence can be 5-10 times higher than general population due to concentration of PWID, men who have sex with men, and people with existing HIV [12]. For incarcerated individuals considering LAI-PrEP pre-release or post-release, bridge period barriers include: limited access to healthcare in custody, disruption of care during incarceration and release, lack of trust in healthcare systems (given medical neglect in prisons), and reentry challenges requiring housing and employment focus.

Indigenous and First Nations Persons

Indigenous persons experience disproportionate HIV burden driven by colonialism, systemic racism, and health inequities. Indigenous communities have experienced historical medical racism and exploitation in research. Bridge period access for Indigenous persons requires: community partnership and consent, local healthcare delivery, addressing social determinants (housing, employment), and explicitly connecting HIV prevention to decolonization and community self-determination goals.

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