Supplementary Materials: Supplementary File S6: Research Agenda

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Research Agenda

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Corresponding manuscript: Demidont, A.C. (2025). Bridging the Gap: The PrEP Cascade Paradigm Shift for Long-Acting Injectable HIV Prevention. *Viruses*.

Supplementary File S6: Comprehensive Research Agenda for LAI-PrEP Bridge Period Implementation

Translating LAI-PrEP's extraordinary clinical efficacy into public health impact requires systematic research across multiple domains. This supplementary file outlines a comprehensive research agenda organized by implementation science, clinical, health systems, policy, and equity domains.

S5.1: Implementation Science Research Priorities

Bridge Period Measurement and Characterization

1. **Real-world bridge period duration:** Prospective measurement of median time from prescription to first injection in diverse settings (clinic types, geographic regions, populations). Current estimates (2-8 weeks mentioned in clinical trial protocols) need real-world validation.
2. **Bridge period attrition causes:** Systematic characterization of why individuals do not complete bridge period. Current data (52.9% initiation) lacks detail on causes—is attrition due to: insurance delays? Testing delays? Appointment scheduling barriers? Patient decision to defer? Loss to follow-up? Systematic categorization would enable targeted interventions.
3. **Population-specific bridge period completion rates:** As clinical trial data emerge from PURPOSE-3 (Black and Latina women), PURPOSE-4 (PWID), and PURPOSE-5 (adolescents), prospective measurement of bridge period completion in diverse populations will enable targeted support.
4. **Variation by program model:** Comparative effectiveness of different bridge period support models (integrated vs. standalone clinics, pharmacist-led vs. physician-led, navigator-supported vs. standard, in-person vs. telemedicine). Which models achieve highest completion rates? Which are most cost-effective?

Intervention Development and Testing

1. **Patient navigation intervention efficacy:** Randomized trials of navigation programs targeting bridge period completion in diverse populations (adolescents, women, PWID). What navigation intensity is needed? What costs are justified for completion improvement?

2. **Telemedicine and technology-enabled support:** Pilot and evaluate telemedicine-based bridge period support, text message reminder systems, chatbot-based education tools, and digital tools for insurance/appointment navigation.
3. **Accelerated testing protocol effectiveness:** Trials comparing conservative testing protocols (45-day window) vs. rapid testing protocols (10-18 day window) on bridge period completion and HIV transmission rates. What is the threshold at which improved access outweighs small increased risk?
4. **Financial support mechanisms:** Trials of different financial support models (transportation vouchers, direct payment, bundled support) on bridge period completion. What level of support is effective? What costs can be absorbed by health systems vs. requiring external funding?
5. **Peer support and group education:** Pilot models of peer support groups, cohort-based education, and group navigation sessions. Do social support interventions improve bridge period completion?

S5.2: Clinical Research Priorities

Efficacy and Safety in Underrepresented Populations

1. **Pharmacokinetic variation:** Pharmacokinetic studies of cabotegravir and lenacapavir in diverse populations (different ancestries, body compositions, age groups) to understand whether dosing modifications are needed for different populations.
2. **Safety monitoring in pregnancy and lactation:** PURPOSE-1 included pregnant/lactating participants but with relatively small numbers. Expanded safety monitoring including longer-term infant follow-up is needed.
3. **Drug-drug interactions:** Systematic evaluation of interactions between LAI-PrEP and other commonly used medications (contraceptives, antibiotics, antiretrovirals, MAT medications). Current data exist but may be incomplete.
4. **Injection site reactions: prevention and management:** Research on interventions to prevent or reduce injection site reactions (pre-injection ice, post-injection heat, different injection techniques, pre-treatment with topicals).

Comparability and Sequencing

1. **Head-to-head comparison of cabotegravir vs. lenacapavir:** Which formulation is preferred for different populations? Are there characteristics that predict better outcomes with one vs. another?
2. **Optimal sequencing of LAI-PrEP formulations:** As once-yearly formulations emerge, what is optimal sequence? Start with frequent dosing (every 8 weeks) then switch to longer intervals? Or initiate directly with longest interval tolerable?
3. **Cycling and switching:** Can individuals switch between formulations? Switch between oral and injectable? What are clinical implications of switching?

S5.3: Health Systems Research Priorities

Service Delivery Models

1. **Integration models:** Comparative effectiveness of LAI-PrEP delivered in: (1) HIV specialty clinics, (2) primary care, (3) reproductive health clinics, (4) harm reduction settings, (5) community-based settings. Which integration model achieves best outcomes for which populations?
2. **Workforce and training:** What training duration/content is needed for different cadres (physicians, nurses, pharmacists, community health workers, peer educators) to deliver LAI-PrEP competently and supportively? How to ensure cultural competence and bias reduction?

3. **Technology and EHR integration:** How to design electronic health record (EHR) systems to track bridge period metrics, generate real-time dashboards for program monitoring, and flag individuals at risk of attrition?

Supply Chain and Logistics

1. **Cold chain management:** In resource-limited settings, models for maintaining lenacapavir cold chain from manufacturing through community clinic. Can solar refrigeration work? What is cost?
2. **Inventory forecasting:** Optimal inventory management to avoid stockouts while not over-procuring (shelf-life, storage costs).
3. **Task-shifting in resource-limited settings:** Training and safety of non-physician intramuscular injection administration (nurses, pharmacists, community health workers) in diverse healthcare systems.

S5.4: Policy Research Priorities

Coverage and Financing

1. **Optimal reimbursement models:** How should LAI-PrEP be reimbursed? Episode-based payment (including all bridge period care)? Per-injection? Risk-based? Outcomes-based? Economic analysis of different models' impact on access and quality.
2. **Global funding mechanisms:** As LAI-PrEP scales globally, how to ensure sustainable funding? What is role of public funding vs. Global Fund vs. PEPFAR? How to transition to domestic funding in lower-income countries?
3. **Patient assistance programs:** Optimal design of pharmaceutical manufacturer patient assistance programs to ensure access for uninsured/underinsured while not distorting markets.

Regulatory and Legal

1. **Regulatory pathways for accelerated access:** In resource-limited settings, regulatory approaches that enable faster LAI-PrEP approval without compromising safety (WHO pre-qualification vs. local approval; adaptive pathways).
2. **Legal barriers and solutions:** Policy reform needed to enable harm reduction-based LAI-PrEP delivery in criminalized contexts. What legal protections are needed for healthcare workers and patients?
3. **Intellectual property and generics:** Strategies for ensuring affordable generic access to LAI-PrEP formulations (and lenacapavir in particular) in lower-income countries while incentivizing innovation.

S5.5: Health Equity Research Priorities

Equity Monitoring and Evaluation

1. **Equity metrics:** Development and adoption of explicit health equity metrics for LAI-PrEP programs. Metrics should track: (1) bridge period completion rates by race/ethnicity, gender identity, sexual orientation, housing status, incarceration history, (2) whether gaps narrow over time with targeted interventions, (3) whether LAI-PrEP implementation reduces or exacerbates HIV prevention disparities.
2. **Root cause analysis of equity gaps:** When equity gaps are identified (e.g., Black women have lower bridge period completion than White women), systematic investigation of root causes. Are barriers individual? Structural? Healthcare provider bias?

3. **Longitudinal equity tracking:** Multi-year monitoring to assess whether equity improvements achieved through one intervention are sustained, and whether new gaps emerge as programs scale.

Structural Barrier Reduction

1. **Housing instability:** Research on housing support as component of LAI-PrEP programs. Does providing housing support improve bridge period completion? What intensity of support is needed?
2. **Criminalization and decriminalization:** Evaluation of impact of drug use decriminalization, gender-affirming legal reform, and anti-discrimination legal protections on LAI-PrEP access for criminalized populations.
3. **Healthcare discrimination and bias reduction:** Interventions to reduce discrimination and bias against PWID, transgender persons, and other marginalized groups in healthcare settings providing LAI-PrEP. Impact on bridge period completion.
4. **Income support:** Research on earned income supplements, employment support, or unconditional cash transfers as components of LAI-PrEP programs targeting poverty-related barriers.

S5.6: Implementation Ongoing in Clinical Trials

Several important implementation research studies are underway and will provide critical evidence:

HPTN 102: Post-Trial Implementation in Women

HPTN 102 is a post-trial implementation study following women from PURPOSE-1 and PURPOSE-2, examining real-world bridge period completion, persistence, and barriers in diverse settings. Key outcomes include bridge period success rate, adherence, and adverse events. Results expected 2025-2026.

HPTN 103: Post-Trial Implementation in PWID

HPTN 103 is examining LAI-PrEP implementation in PWID, including bridge period completion and integration with harm reduction services. First-ever prospective data on bridge period completion in PWID will be extraordinarily valuable. Results expected 2025-2026.

EquiPrEP: CDC-Funded Equity Initiative

EquiPrEP is a CDC-funded initiative to increase LAI-PrEP access among populations experiencing HIV-related disparities. Includes implementation sites across US with focus on addressing equity gaps in bridge period completion. Preliminary data suggests bridge period barriers are indeed primary implementation barrier; further results expected 2025.

S5.7: Research Capacity Building

1. **Training future implementation scientists:** Investment in graduate and post-doctoral training in LAI-PrEP implementation science to build global research capacity.
2. **Community-based participatory research (CBPR) models:** Ensuring research is conducted IN PARTNERSHIP with communities rather than ON communities. CBPR approaches for bridge period research will generate more relevant, actionable findings.
3. **Global North-South research partnerships:** Equitable partnerships between researchers in well-resourced countries and those in lower-resource settings, with funding and capacity-building directed to Southern researchers.

4. **Open science and data sharing:** Commitment to open science practices—sharing protocols, raw data, and negative results—to accelerate learning and reduce research duplication.

S5.8: Integration with Broader Implementation Science Frameworks

This research agenda should be integrated with broader implementation science frameworks including:

- **RE-AIM:** Reach (how many eligible individuals are accessed), Efficacy (does intervention work in real-world settings), Adoption (how many providers/programs adopt), Implementation (is it delivered with fidelity), Maintenance (is it sustained over time).
- **CFIR:** Consolidated Framework for Implementation Research domains (intervention characteristics, outer setting, inner setting, individual characteristics, implementation process).
- **Logic models and program evaluation:** Development of explicit logic models for LAI-PrEP bridge period interventions, with clear inputs, activities, outputs, outcomes, and impacts.