Supplementary File S4

Implementation Guide for LAI-PrEP Bridge Period Decision Support Tool

Computational Validation of Clinical Decision Support Algorithm
for Long-Acting Injectable PrEP Bridge Period Navigation

A.C Demidont, DO

Viruses Journal Supplementary Materials

Purpose of This Guide

This implementation guide provides preliminary protocols and recommendations for prospective validation of the LAI-PrEP Bridge Period Decision Support Tool. **Important caveats:**

- These materials are **preliminary** and require refinement through actual implementation experience
- Computational validation establishes algorithmic precision, not clinical readiness for unrestricted deployment
- All recommendations should be adapted to local context, resources, and patient populations
- Prospective validation with real patient outcomes is essential before widespread adoption
- Implementation teams should document both successes and failures to enable continuous learning

1 Staged Implementation Pathway

Based on our computational validation findings and critical assessment of AI suitability, we propose a structured implementation pathway balancing innovation urgency with patient safety.

1.1 Phase 1: Immediate Actions (0–6 months)

1.1.1 Pilot Site Selection

Identify **2–3 diverse clinical settings** representing populations with different baseline success rates and barrier profiles:

1. **Suggested site types:**
    - Urban academic center serving men who have sex with men (MSM) — typically highest baseline success rates but potential insurance/authorization barriers
    - Community clinic serving cisgender women in high-prevalence area — moderate baseline rates with transportation, childcare, and structural barriers

- Harm reduction program serving people who inject drugs (PWID) — lowest baseline rates with substance use, stigma, and housing instability barriers

2. **Site selection criteria:**
   - LAI-PrEP prescribing volume: minimum 20–30 patients/year anticipated
   - Institutional commitment to systematic outcome tracking
   - Availability of patient navigation or case management resources
   - Diverse patient population for subgroup analyses
   - Electronic health record capabilities for data collection
   - Research infrastructure or quality improvement expertise
3. **Sample size considerations:**
   - Target 50–100 patients per site over 6–12 months
   - Minimum 150 total patients across all pilot sites for adequate statistical power
   - Oversample populations with lower baseline success rates (women, PWID, adolescents) to enable equity analyses

1.1.2 Institutional Review and Adaptation

Local implementation teams should critically review the external configuration file (`lai_prep_config.json`):

1. **Barrier prevalence assessment:**
   - Do local barrier prevalence rates match national estimates in the configuration?
   - Example: If local MSM population has 15% insurance barriers (vs. 28% national), adjust `insurance_auth_barrier_rate`
   - Document all parameter modifications with justification
2. **Intervention availability audit:**
   - Which of the 21 interventions are actually available locally?
   - Example: If expedited HIV testing not available, set `effect_size` to 0 for that intervention
   - Identify locally-available interventions not in the library (candidates for addition)
3. **Effect size calibration:**
   - Are national effect size estimates appropriate for local context?
   - Example: Patient navigation may have different effectiveness in rural vs. urban settings
   - Consider local pilot data if available; otherwise use default values initially
4. **Population-specific baseline rates:**
   - Review baseline bridge period success rates for each population
   - Adjust if local data suggest different rates (e.g., high-performing clinic with strong navigation infrastructure)

1.1.3 Clinician Training

Train providers to use the tool appropriately while maintaining clinical judgment:

1. **Core competencies:**
    - Interpret algorithmic output: understand risk scores, barrier profiles, intervention recommendations
    - Recognize model limitations: identify when model assumptions may not fit specific patients
    - Exercise clinical override: document decisions when clinical judgment differs from algorithm
    - Provide patient-centered care: use recommendations as decision support, not replacement for human judgment
2. **Training curriculum (suggested 2–3 hour session):**
    - *Module 1 (30 min):* LAI-PrEP bridge period attrition crisis and evidence base
    - *Module 2 (45 min):* Tool architecture, intervention library, mechanism diversity scoring
    - *Module 3 (45 min):* Clinical case scenarios with tool output interpretation
    - *Module 4 (30 min):* Documentation requirements, override protocols, feedback mechanisms
3. **Ongoing support:**
    - Weekly case conferences reviewing challenging patients
    - Monthly calibration meetings comparing predicted vs. actual outcomes
    - Access to implementation science team for technical questions

1.1.4 Data Collection Protocols

Establish systematic outcome tracking infrastructure:

1. **Required data elements:**
    - Patient demographics: age, gender, race/ethnicity, socioeconomic indicators
    - Population category: MSM, cisgender women, PWID, adolescents (may overlap)
    - Baseline assessment: date of LAI-PrEP prescription, identified barriers, risk factors
    - Algorithmic output: predicted success probability, recommended interventions, mechanism diversity score
    - Interventions delivered: which recommendations implemented, fidelity assessment, timing
    - Primary outcome: bridge period success (received first injection within 60 days) vs. attrition
    - Secondary outcomes: time to first injection, barriers encountered, reasons for attrition
    - Clinical overrides: instances where provider deviated from recommendations with justification
2. **Data quality assurance:**

- Real-time data entry with validation rules
- Monthly audits for completeness and accuracy
- Standardized definitions for barriers and interventions
- Regular calibration across sites to ensure consistent measurement

3. **Ethical considerations:**
    - Institutional review board approval for research (if applicable)
    - Quality improvement exemption (if applicable)
    - Patient consent for data use
    - Data privacy and security protocols (HIPAA compliance)

1.2 Phase 2: Pilot Validation (6–12 months)

Conduct rigorous evaluation of algorithm performance with real patients:

1.2.1 Outcome Analysis

Collect and analyze **150–300 patient outcomes** across pilot sites:

1. **Calibration assessment:**
    - *Overall calibration:* Do predicted success rates match actual rates?
    - *Subgroup calibration:* Evaluate separately for MSM, women, PWID, adolescents
    - *Risk stratification:* Compare outcomes across predicted risk quartiles
    - *Statistical tests:* Hosmer-Lemeshow goodness-of-fit, calibration plots
2. **Discrimination evaluation:**
    - Does the tool effectively separate high-risk from low-risk patients?
    - Calculate area under the receiver operating characteristic curve (AUROC)
    - Assess sensitivity and specificity at different risk thresholds
    - Evaluate positive and negative predictive values
3. **Intervention effectiveness:**
    - Do recommended interventions achieve predicted improvements?
    - Compare outcomes: interventions received vs. not received
    - Assess dose-response: more interventions $\rightarrow$ better outcomes?
    - Evaluate mechanism diversity: Do diverse mechanisms improve outcomes beyond number of interventions?
4. **Failure mode identification:**
    - What patient characteristics result in inaccurate predictions?
    - Identify barriers not adequately captured in the model
    - Document intervention implementation challenges
    - Analyze clinical override patterns (when and why providers deviated)

1.2.2 Equity Analysis

Evaluate algorithmic fairness across populations:

1. **Differential calibration:** Does accuracy vary by race, ethnicity, socioeconomic status?
2. **Differential benefit:** Do interventions work equally well across subgroups?
3. **Access equity:** Are recommended interventions equally available to all populations?
4. **Outcome disparities:** Does tool use narrow or widen existing gaps in bridge period success?

1.2.3 Parameter Refinement

Based on pilot data, update configuration parameters:

1. Revise barrier prevalence estimates where local rates differ from national
2. Adjust intervention effect sizes based on observed outcomes
3. Update population-specific baseline rates if needed
4. Add new barriers or interventions identified during pilot
5. Modify mechanism diversity scoring if redundancies observed

1.3 Phase 3: Multi-Site Expansion (12–24 months)

Scale to broader geographic and demographic diversity:

1. **Site expansion:**
    - Expand to **10–15 sites** representing diverse geographies, healthcare systems, and patient populations
    - Include mix of academic medical centers, community health centers, harm reduction programs, and telehealth providers
    - Target sites in high-HIV-burden regions (Southern U.S., urban epicenters, rural areas)
2. **Sample size goals:**
    - Collect **500–1,000 patient outcomes** across all sites
    - Ensure adequate representation: minimum 100 patients each for MSM, women, PWID, adolescents
    - Oversample underrepresented populations for subgroup analyses
3. **Equity analyses:**
    - Comprehensive calibration evaluation across race, ethnicity, gender, age, socioeconomic status
    - Assess intervention access and effectiveness disparities
    - Document health system adaptations needed to ensure equitable care
    - Identify populations or settings where algorithm performs poorly

4. **Dissemination:**
    - Publish validation results in peer-reviewed implementation science journal
    - Present findings at scientific conferences (CROI, IAS, USCA)
    - Release updated configuration files with refined parameters
    - Develop implementation toolkit for other sites

1.4 Phase 4: Continuous Quality Improvement (24+ months)

Establish sustainable infrastructure for ongoing monitoring and refinement:

1. **Automated feedback loops:**
    - Real-time comparison of predicted vs. actual outcomes
    - Dashboards displaying calibration metrics over time
    - Alert systems flagging performance degradation
    - Regular reports to clinical teams and administrators
2. **Algorithmic drift monitoring:**
    - Track changes in calibration and discrimination over time
    - Identify when recalibration or retraining needed
    - Distinguish true drift (changing populations) from data quality issues
    - Implement version control for configuration updates
3. **Evidence updates:**
    - Monitor emerging LAI-PrEP implementation literature
    - Incorporate new trial results (HPTN 102, HPTN 103, PURPOSE extensions)
    - Update intervention library as new strategies emerge
    - Revise effect size estimates based on accumulating evidence
4. **Implementation support:**
    - Develop comprehensive implementation guides
    - Create training materials and webinars
    - Establish technical assistance infrastructure
    - Build community of practice among implementing sites
5. **International adaptation:**
    - Create frameworks for adapting tool to diverse healthcare systems
    - Conduct validation studies in low- and middle-income countries
    - Address context-specific barriers (e.g., patent medicine vendors in West Africa)
    - Ensure cultural appropriateness of interventions

2 Research Priorities

Advancing both the science and practice of bridge period management requires coordinated research across multiple domains:

2.1 Methodological Innovations

1. **Synergistic barrier interactions:**
    - Current model assumes additive effects; develop methods for modeling synergies
    - Example: Transportation barriers may interact multiplicatively with childcare barriers
    - Use machine learning to detect interaction patterns in large datasets
    - Validate interaction models prospectively
2. **Time-to-event modeling:**
    - Predict not just initiation success, but timing of first injection
    - Survival analysis methods accounting for right-censoring
    - Identify intervention effects on time-to-initiation
    - Enable resource allocation optimization (intensive early support vs. extended follow-up)
3. **Unmeasured barrier detection:**
    - Machine learning approaches identifying latent barriers through pattern recognition
    - Cluster analysis grouping patients with similar failure modes
    - Natural language processing of clinical notes to identify novel barriers
    - Semi-supervised learning when labeled training data limited
4. **Causal inference methods:**
    - Distinguish true intervention effects from selection bias
    - Instrumental variable approaches when randomization infeasible
    - Propensity score matching for observational comparisons
    - Difference-in-differences for policy evaluations

2.2 Evidence Generation

1. **LAI-PrEP-specific trials:**
    - Complete HPTN 102 (women) and HPTN 103 (PWID)
    - PURPOSE-3 examining transgender populations
    - Adolescent LAI-PrEP implementation trials
    - Comparative effectiveness: CAB vs. lenacapavir bridge periods
2. **Implementation trials:**
    - Randomized comparisons: systematic barrier-focused navigation vs. standard care
    - Stepped-wedge designs for pragmatic evaluation

- Effectiveness-implementation hybrid designs
- Cost-effectiveness analyses

3. **Cultural adaptation research:**
   - Intervention adaptations for diverse international settings
   - Community-engaged participatory research methods
   - Qualitative studies identifying culturally-specific barriers
   - Validation studies in sub-Saharan Africa, Asia-Pacific, Latin America
4. **Intersectionality research:**
   - Intersection of multiple marginalizations: race, poverty, criminalization, gender identity
   - Structural violence and bridge period outcomes
   - Policy interventions addressing root causes of disparities
   - Community-level interventions beyond individual patient support

2.3 Implementation Science

1. **Fidelity measurement:**
   - Develop validated scales assessing intervention implementation quality
   - Distinguish fidelity (adherence to protocol) from adaptation (appropriate modifications)
   - Link fidelity to patient outcomes
   - Create audit tools for quality assurance
2. **Sustainability models:**
   - Financing mechanisms ensuring navigation programs persist beyond pilot funding
   - Integration into routine clinical workflows
   - Workforce development and training pipelines
   - Policy advocacy for reimbursement of navigation services
3. **Healthcare system adaptations:**
   - Organizational changes required for routine bridge period management
   - Electronic health record integration requirements
   - Referral networks and care coordination structures
   - Performance metrics and quality indicators
4. **Policy research:**
   - Insurance authorization streamlining
   - Expedited HIV testing protocols
   - Pharmacy dispensing models
   - Same-day initiation feasibility
   - Task-shifting to nurses, pharmacists, community health workers

3 Quality Assurance Framework

3.1 Performance Monitoring Metrics

Sites should track the following metrics monthly:

1. **Outcome metrics:**
    - Bridge period success rate (overall and by population)
    - Time from prescription to first injection (median, IQR)
    - Attrition rate and reasons for attrition
    - 6-month and 12-month persistence on LAI-PrEP
2. **Algorithmic performance:**
    - Calibration: predicted vs. actual success rates
    - Discrimination: AUROC for risk stratification
    - Subgroup performance: calibration within populations
    - Override rate: frequency of clinical judgment overriding recommendations
3. **Process metrics:**
    - Intervention delivery rate: % of recommended interventions actually provided
    - Intervention timeliness: lag between recommendation and delivery
    - Documentation completeness: % of required data fields captured
    - Patient engagement: % accepting navigation services
4. **Equity metrics:**
    - Outcome disparities by race, ethnicity, gender, socioeconomic status
    - Intervention access disparities
    - Calibration equity across subgroups
    - Representation: demographics of patients served vs. indicated population

3.2 Corrective Action Triggers

Establish thresholds for initiating corrective actions:

1. **Poor overall calibration:** Predicted-observed difference $>$5 percentage points for 2 consecutive months $\rightarrow$ Parameter review and recalibration
2. **Subgroup calibration failure:** Any population with predicted-observed difference $>$10 points $\rightarrow$ Targeted parameter adjustment for that population
3. **Declining performance:** Bridge period success rate declining $>$5 points over 3 months $\rightarrow$ Process evaluation and intervention reinforcement
4. **Low intervention delivery:** $<$50% of recommended interventions provided $\rightarrow$ Workflow redesign and barrier assessment
5. **Widening disparities:** Outcome gap between populations increasing $>$5 points $\rightarrow$ Equity-focused intervention

4 Limitations and Cautions

Implementation teams should recognize these important limitations:

1. **Parameter uncertainty:** Many parameters extrapolated from non-LAI-PrEP populations; prospective validation essential
2. **Local variation:** National estimates may not match local context; adaptation required
3. **Implementation challenges:** Recommended interventions require resources, training, and organizational commitment
4. **Patient heterogeneity:** Population-level predictions may not apply to individual patients; clinical judgment essential
5. **Unmeasured barriers:** Model cannot account for barriers not explicitly measured
6. **Causal assumptions:** Intervention effects assumed causal; confounding possible in observational validation
7. **Generalizability:** Validation in U.S. settings may not generalize to international contexts
8. **Evolving evidence:** LAI-PrEP implementation science rapidly evolving; continuous updates required

5 Conclusion

This implementation guide provides preliminary protocols for prospective validation of the LAI-PrEP Bridge Period Decision Support Tool. Successful implementation requires:

- **Staged deployment** balancing innovation with safety
- **Systematic outcome tracking** enabling evidence-based refinement
- **Equity focus** ensuring benefits reach populations with greatest barriers
- **Continuous learning** from both successes and failures
- **Transparent reporting** building the evidence base for decision support in HIV prevention

These materials should be adapted to local context and refined based on implementation experience. The ultimate goal is translating computational validation into real-world impact: preventing HIV infections by systematically addressing the bridge period attrition crisis.

Additional Resources

- **Supplementary File S1:** Clinician Quick-Reference Card
- **Supplementary File S2:** Patient Information Handout
- **Supplementary File S3:** Machine Readable Data Files
- **Supplementary File S4:** Implementation Guide
- **Supplementary File S5:** Clinical Decision Flowchart
- **Supplementary File S6:** Non-Technical Summary
- **Supplementary File S7:** Complete Intervention Library
- **Supplementary File S8:** Code Repository All source code can be located at **Zenodo DOI:**`https://zenodo.org/uploads/17727117#:~:text=10.5281/zenodo.17727117`
- **Technical Support:** [Contact acdemidont@nyxdynamics.org]