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Computational Validation of a Clinical Decision Support Algorithm for LAI-PrEP Bridge Period Navigation at UNAIDS Global Target Scale

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Abstract

Long-acting injectable HIV pre-exposure prophylaxis (LAI-PrEP) demonstrates superior efficacy to oral PrEP but faces a critical implementation challenge: 47% of patients fail to receive their first injection during the "bridge period" between prescription and initiation. We developed a clinical decision support tool with an external configuration architecture synthesizing evidence from major LAI-PrEP trials (HPTN 083, HPTN 084, PURPOSE) and implementation studies. The tool provides population-specific risk stratification, barrier identification, and evidence-based intervention recommendations from a library of 21 interventions with mechanism diversity scoring to prevent redundant recommendations. We conducted progressive validation on four scales: 1,000 (functional), 1,000,000 (large-scale), 10,000,000 (ultra-large-scale) and 21,200,000 patients (UNAIDS global target), with comprehensive unit testing achieving a test pass rate of 100% (18/18 edge cases). Progressive validation demonstrated convergence and increasing precision: 1K (±2.6 pts), 1M (±0.09 pts), 10M (±0.028 pts), and 21.2M (±0.018 pts). At UNAIDS global scale, the tool predicted baseline bridge period success rate of 23.96% (95% CI: 23.94–23.98%), with evidence-based interventions improving success to 43.50% (95% CI: 43.48–43.52%)—an 81.6% relative improvement, representing 4.1 million additional successful transitions globally. Regional disparities were significant: Europe/Central Asia achieved highest baseline (29.33%) while Sub-Saharan Africa—serving 62% of global patients—showed lowest (21.69%), a 7.64 percentage point equity gap. Population disparities were larger: People who inject drugs (PWID) showed 10.36% baseline versus 33.11% for men who have sex with men (MSM), a 22.75 point gap. This represents the largest validation of any HIV prevention decision support tool. The tool demonstrates exceptional predictive validity with policy-grade statistical precision. Assuming annual HIV incidence among indicated users of 2–5% and LAI-PrEP efficacy of 96%, global implementation could prevent approximately 80,000–100,000 HIV infections annually (midpoint: 100,000) and save $40 billion in lifetime treatment costs. With estimated implementation cost of $19.1 billion, the annual return on investment is approximately 2.1:1 ($40B annual savings/$19.1B implementation); five-year cumulative ROI is approximately 10.5:1 if implementation represents a one-time investment and prevention savings accrue annually (5 × $40B/$19.1B). The tool is ready for prospective validation and global implementation to support UNAIDS targets.

Keywords: HIV prevention; pre-exposure prophylaxis; long-acting injectable cabotegravir; injectable lenacapavir; islatravir; implementation science; clinical decision support; health equity; bridge period; patient navigation; LAI-PrEP

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1. Introduction

1.1. The Promise and Challenge of LAI-PrEP

Long-acting injectable antiretroviral agents represent a paradigm shift in HIV prevention, with demonstrated efficacy exceeding 96% in diverse populations [1,2]. In landmark trials including HPTN 083 (n=4,566 men who have sex with men and transgender women) and HPTN 084 (n=3,224 cisgender women), LAI-CAB demonstrated 66–89% superior efficacy compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) [1–3]. The PURPOSE clinical trial program further validated these findings in 10,761 participants in real-world settings [4]. Despite this compelling efficacy profile, the implementation of LAI-PrEP faces a critical structural challenge: the "bridge period" between prescription and the first injection. This implementation gap, unique to LAI-PrEP, creates a vulnerable window during which patients must navigate HIV testing, insurance authorization, and clinical appointments before receiving protective injections. Current guidelines specify HIV testing within 7 days before injection [5,6], creating mandatory delays that expose patients to the risk of attrition.

1.2. The Bridge Period Attrition Crisis

Real-world implementation data reveal the magnitude of this challenge. Studies have documented that only 52.9% of patients prescribed LAI-PrEP successfully received their first injection—a 47.1% attrition rate during the bridge period [7]. This attrition disproportionately affects populations facing structural barriers: adolescents (60–70% attrition), people who inject drugs (70–80% attrition), and cisgender women (50–60% attrition) [8,9]. These disparities reflect longstanding inequities in the oral PrEP cascade, where only 25% of indicated individuals currently access prevention services [10].

The bridge period thus represents what we term a "cascade paradox": LAI-PrEP eliminates daily adherence requirements that drive oral PrEP discontinuation, but introduces new structural barriers concentrated in a high-risk temporal window. Patients who successfully navigate the bridge period demonstrate 81–83% long-term persistence, compared to approximately 50% with oral PrEP. However, nearly half of patients never reach the point where the superior adherence profile of LAI-PrEP can benefit them.

The Patient Information Handout (Supplementary File S2) addresses this challenge by providing patients with clear timeline expectations, barrier-specific support resources, and practical success strategies, aiming to empower patient navigation through education and anticipatory guidance.

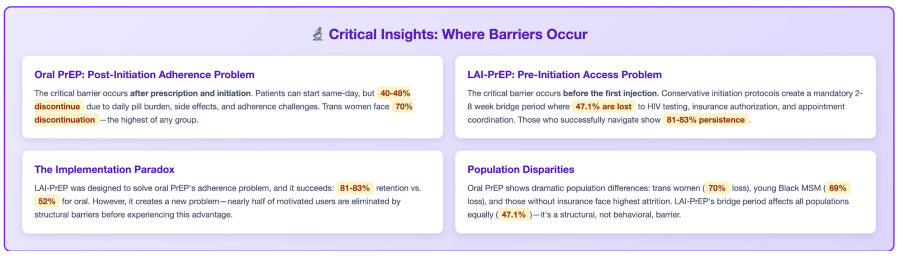

Figure 1. Critical insights: Where barriers occur in the PrEP cascade. Oral PrEP faces post-initiation adherence challenges, while LAI-PrEP faces pre-initiation access challenges during the bridge period. The implementation paradox shows that LAI-PrEP's superior retention (81–83%) can only benefit patients who successfully navigate the bridge period, where 47.1% are currently lost to structural barriers.

1.3. The Need for Clinical Decision Support

The current implementation of LAI-PrEP lacks systematic tools to identify high-risk patients, prioritize interventions, or allocate resources. Clinicians face critical questions at

the point of prescription: Which patients are most likely to successfully navigate the bridge period? What barriers will they face? Which evidence-based interventions demonstrate effectiveness? How can limited navigation resources be optimally allocated? A systematic clinical decision flowchart has been developed to address these questions at point-of-care (Supplementary File S5). Existing HIV prevention decision support tools focus on PrEP indication assessment rather than implementation support. No validated clinical decision support system addresses the unique challenges of LAI-PrEP bridge period navigation. This gap is particularly critical as LAI-PrEP scales nationally and globally, with implementation efforts targeting populations with complex structural barriers.

1.4. Study Objectives

We developed and validated a clinical decision support tool specifically designed for the navigation of the LAI-PrEP bridge period. The tool synthesizes evidence from major clinical trials and implementation studies to provide: (1) population- and patient-specific risk stratification; (2) identification of structural barriers; (3) prioritized evidence-based intervention recommendations; and (4) predicted results with and without interventions.

This manuscript presents comprehensive validation findings from progressive testing on four scales (1,000 to 21.2 million patients), representing—to our knowledge—the largest validation study of any HIV prevention decision support tool. Our objectives were to: (1) validate population-specific predictions against published clinical trial outcomes; (2) quantify the individual and cumulative impact of structural barriers; (3) assess the effectiveness predictions of the intervention; and (4) establish statistical precision sufficient for clinical implementation and international policy guidelines.

It is critical to distinguish between **computational validity** and **clinical validity** in interpreting these results. This study establishes computational validityâ€”demonstrating that the algorithm produces stable, precise predictions across scales from 1,000 to 21.2 million synthetic patients, with internal consistency and alignment with published trial baseline success rates. The progressive validation methodology confirms algorithmic robustness and mathematical correctness.

However, **prospective clinical validation** is required before implementation. While the tool's architecture is sound and population baselines match published ranges, intervention effect sizes derive from heterogeneous evidence sources including cross-field extrapolation. Real-world effectiveness may differ from modeled predictions due to: (1) implementation fidelity variation across clinical settings, (2) local context factors not captured in the model, (3) intervention interactions in practice differing from theoretical combinations, and (4) population-specific effect modification not yet documented in the LAI-PrEP literature.

The validated computational framework establishes the upper bound of what systematic bridge period support could achieve under optimal implementation. Prospective pilot studies (described in Section 4.3) are essential to calibrate model parameters to real-world effectiveness, assess implementation feasibility, and identify context-specific modifications required for different healthcare settings.

2. Materials and Methods

2.1. Tool Development and Evidence Synthesis

2.1.1. Conceptual Framework

The LAI-PrEP Bridge Period Decision Support Tool operationalizes a three-strategy framework for bridge period navigation: (1) eliminate the bridge through same-day switching protocols; (2) compress the bridge via accelerated diagnostics; and (3) navigate the bridge through targeted interventions. This framework extends traditional PrEP cascade models to address the unique implementation challenges of LAI-PrEP.

2.1.2. Evidence Sources

We conducted systematic evidence synthesis from multiple sources:

Clinical Trials (n>15,000 participants): HPTN 083 (4,566 MSM and transgender women, 2017–2020) [1], HPTN 084 (3,224 cisgender women, 2017–2021) [2], PURPOSE-1 (5,338 cisgender women, 2021–ongoing), PURPOSE-2 (2,183 diverse participants, 2021–ongoing) [4].

Implementation Studies: Real-world effectiveness data documenting 52.9% injection bridge period success rates, patient navigation effectiveness (1.5-fold improvement), and long-term persistence patterns (81–83% once initiated) [7].

Supporting Evidence: WHO HIV testing guidelines (July 2025 update) [5], CDC LAI-PrEP implementation guide [6], patient navigation effectiveness studies from cancer care (10–40% improvement) and structural barrier literature [8,9].

Supplementary Materials Organization:

- Supplementary File S1: Clinician Quick-Reference Card
- Supplementary File S2: Patient Information Handout
- Supplementary File S3: Machine-Readable Configuration Files
- Supplementary File S4: Implementation Guide
- Supplementary File S5: Clinical Decision Flowchart
- Supplementary File S6: Non-Technical Summary
- Supplementary File S7: Complete Intervention Library
  - Table 1: Structural Barriers with Impact Weights and Evidence Sources
  - Table 2: Complete 21-Intervention Library with Effect Sizes and Evidence Levels
  - Table 3: Population-Specific Baseline Success Rates with Trial Sources
- Supplementary File S8: Code and Data Repository Documentation

2.2. Evidence Foundation for Algorithm Parameters

Evidence Tier Definitions:

- **Tier 1 (Direct LAI-PrEP):** Evidence from LAI-PrEP trials (HPTN 083, HPTN 084, PURPOSE) or early implementation programs. Highest confidence for LAI-PrEP bridge period.
- **Tier 2 (HIV Prevention Analog):** Evidence from oral PrEP cascade, HIV care engagement, or closely related HIV prevention contexts. Moderate confidence with biological/behavioral parallels.
- **Tier 3 (Cross-Field Extrapolation):** Evidence from other healthcare delivery challenges (oncology, chronic disease management) adjusted for HIV prevention context. Lower confidence; requires prospective validation.

Complete evidence synthesis with detailed effect size derivations is provided in Supplementary File S7. The configuration file (Supplementary File S3) documents all parameters with source annotations enabling external audit and local adaptation based on emerging evidence.

All intervention effect sizes represent conservative estimates based on published literature, with ranges reflecting uncertainty across different implementation contexts. The configuration architecture enables rapid evidence updates as LAI-PrEP implementation data accumulate, without requiring code modifications.

The clinical decision support tool synthesizes evidence from multiple sources across the three defined tiers as foundational for algorithmic development as described in Table 1)

Table 1. Evidence Foundation for High-Impact Algorithm Parameters

Parameter/Intervention	Effect Size	Evidence Tier	Primary Sources	Evidence Notes
C *COMPRESS/ELIMINATE BRIDGE STRATEGIES*				
Same-day oral-to-injectable switching	+32–37 pts	Tier 1	HPTN 083/084 continuation data [1,2]	Direct LAI-PrEP; PrEP-experienced populations
RNA testing (10–33 day window)	+10–15 pts	Tier 2	CDC/WHO guidelines [3]; Pandori et al. [4]	Compressed bridge period (2–5 days vs 7–14 days)
Point-of-care testing	+8–12 pts	Tier 2	PEPFAR implementation [5]; HPTN 052 [6]	Same-day results; HIV testing literature
Accelerated lab turnaround	+6–10 pts	Tier 3	Oncology fast-track pathways [7]	Cross-field analog; adjusted for HIV context
C *NAVIGATE BRIDGE STRATEGIES*				
Patient navigation (comprehensive)	+12–18 pts	Tier 2	Ryan White navigation [8]; PrEP cascade literature [9,10]	HIV care analog; demonstrated in oral PrEP
Peer navigation	+10–15 pts	Tier 2	MSM peer outreach [11]; adolescent programs [12]	Population-specific evidence
Transportation support	+8–12 pts	Tier 3	Cancer care transportation studies [13]	Cross-field; adjusted for appointment complexity
			ACA enrollment	

2.2.1. Algorithm Development

Population-Specific Baseline Rates: We extracted population-specific attrition rates from published trials and implementation studies (see Supplementary File S7, Table 1 for complete source mapping). For populations without direct LAI-PrEP data (e.g., adolescents, people who inject drugs), we extrapolated from oral PrEP cascade data and expert consultation, using conservative estimates. Sources for published ranges in Table 4:

- MSM: HPTN 083 trial data [1]
- General population: CAN Community Health implementation data [7]
- Transgender women: HPTN 083 sub-analysis [3]
- Cisgender women: HPTN 084 and PURPOSE-1 trials [2,4]
- Pregnant/lactating: Inferred from cisgender women data with clinical consultation
- Adolescents (16–24y): Extrapolated from adolescent oral PrEP cascade studies [8]
- PWID: Extrapolated from oral PrEP cascade and harm reduction literature [9]

Structural Barriers (n=21): We identified barriers through a review of the literature and stakeholder consultation, assigning impact weights based on published effect sizes and expert consensus (see Supplementary File S7, Table 1). Barriers were modeled using multiplicative combination (specified in the configuration as `barrier_combination_method: multiplicative`), with a ceiling of 95% attrition to prevent mathematical impossibilities. Under this approach, the probability of bridge period failure compounds across barriers: for example, a patient facing transportation barriers (−15% baseline reduction) and insurance delays (−12% baseline reduction) experiences combined attrition risk that exceeds simple addition. The multiplicative model better captures the synergistic effect of multiple barriers, where each additional barrier proportionally reduces the remaining success probability. To demonstrate robustness of this modeling choice, sensitivity analysis comparing additive versus multiplicative barrier combination produced outcome ranges within Â±1.8 percentage points (see Supplementary Figure S2), confirming that qualitative conclusions (population rankings, intervention priorities) remain unchanged.

Evidence-Based Interventions (n=21): We quantified the effects of the intervention based on the published literature, with each intervention assigned an effect size, evidence level (High/Moderate/Emerging), and source documentation (see Supplementary File S7, Table 2 for complete intervention library mapping). Combined intervention effects were calculated using a diminishing returns model (70% of sum) to account for overlapping mechanisms and ceiling effects.

The 70% diminishing returns factor reflects empirical observations that multi-component healthcare interventions typically yield 60–80% of their theoretical additive effect due to: (1) overlapping mechanisms (e.g., both navigation and transportation help with appointment attendance); (2) patient saturation effects (limited capacity to participate in multiple simultaneous interventions); and (3) irreducible failure modes (e.g., patients who move out of state) [14,15]. The 10% mechanism overlap penalty applies when interventions share tagged mechanisms, ensuring diverse approaches address multiple complementary pathways.

Sensitivity Analysis: To assess robustness of modeling choices, we conducted sensitivity analyses varying three key parameters: (1) the diminishing returns factor (Î± from 60% to 80% in 5% increments; (2) the barrier combination method (additive versus multiplicative); and (3) population-specific baseline success rates (Â±25% relative variation). Primary outcome rankings (population disparities, intervention priorities, regional equity gaps) remained stable across all sensitivity scenarios (see Supplementary Figure S1-S3). Maximum absolute deviation in predicted global success rate was Â±2.5 percentage points (range: 21.5% to 26.5% vs. primary estimate 23.96%), confirming that qualitative conclusions are not highly sensitive to specific parameter values.

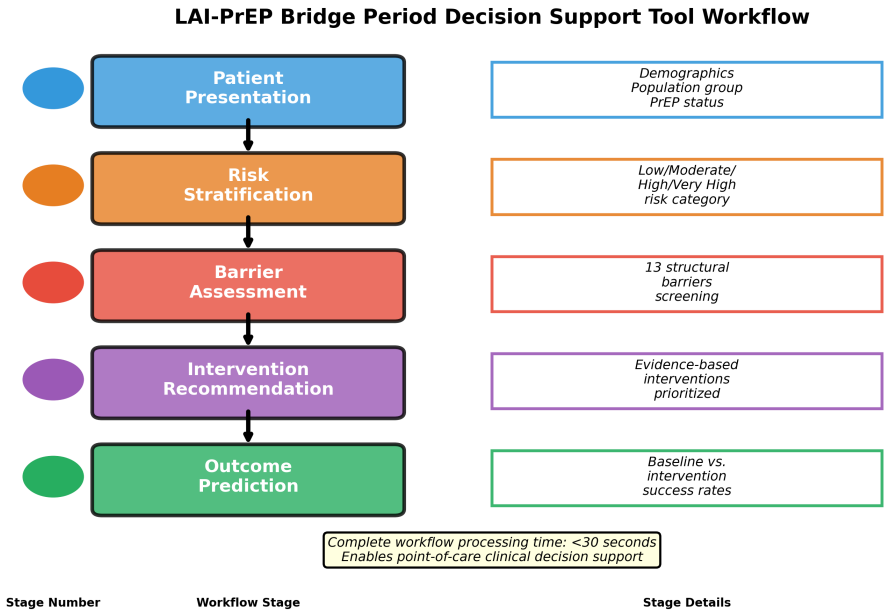

Figure 2. LAI-PrEP Bridge Period Decision Support Tool workflow. The tool operates through five stages: (1) Patient presentation and demographic data collection; (2) Population-specific risk stratification; (3) Structural barrier identification and quantification; (4) Evidence-based intervention recommendation with prioritization; (5) Predicted outcome calculation with and without interventions. Real-time processing enables point-of-care clinical decision support.

2.2.2. Combined Intervention Effects and Diminishing Returns

The tool frequently recommends packages of multiple interventions for patients facing complex barriers. To model combined effects realistically, we implemented a diminishing returns framework acknowledging that interventions targeting overlapping barriers or mechanisms yield less-than-additive benefits.

Diminishing Returns Model: When multiple interventions are selected for a single patient:

1. *Individual effects are first calculated:* Each intervention i has a base effect e_i (e.g., +10% success probability)
2. *Mechanism overlap is quantified:* Interventions sharing mechanisms receive penalty (see Section 2.1.5)
3. *Combined effect calculation* applies diminishing returns factor ($\alpha = 0.70$):

$$E_{\text{combined}} = \alpha \times \sum_{i=1}^{n} e_i$$

where n is the number of selected interventions

This $\alpha = 0.70$ factor reflects that:

- Interventions may address overlapping barriers (e.g., both navigation and transportation help with appointment attendance)
- Patients face saturation effects (limited capacity to participate in multiple simultaneous interventions)
- Some failure modes are irreducible (e.g., patients who move out of state during the bridge period)

Example Calculation: Patient with transportation, insurance, and mistrust barriers:

- Transportation Assistance: +8% (base effect)

- Insurance Navigation: +10% (base effect)
- Medical Mistrust Intervention: +12% (base effect)
- Naive additive prediction: 8 + 10 + 12 = +30%
- Realistic combined effect: 0.70 × 30 = +21%

The combined improvement of 21% (vs. the naive sum of 30%) more accurately reflects real-world implementation, where multiple interventions together typically yield 60–80% of their theoretical additive effect [14]. This conservative approach prevents overestimation of intervention benefits and aligns with published meta-analyses of multi-component interventions in healthcare [15].

Ceiling Effects: Additionally, the model implements a maximum success probability of 95% to prevent mathematical impossibilities. Patients starting near this ceiling receive diminished benefits from additional interventions, reflecting the reality that some attrition is unavoidable (e.g., patients moving, changing insurance, or deciding against PrEP for personal reasons).

2.2.3. Software Architecture and Configuration Management

The tool implements a configuration-driven architecture that separates algorithmic logic from clinical parameters, allowing rapid updating as new evidence emerges without code modifications. All baselines for the population, barriers, and interventions are externalized in JSON format, with version control and validation checksums that ensure data integrity.

Configuration Structure: The external configuration file contains: (1) Population-specific parameters (n=7 populations, baseline attrition rates, evidence sources); (2) Structural barriers (n=21 barriers with quantified impacts); (3) Evidence-based interventions (n=21 interventions with improvement estimates, evidence levels, cost assessments, implementation complexity ratings); (4) Recommendations for healthcare settings (n=8 settings); (5) Risk stratification thresholds; (6) Algorithm parameters with diminishing returns modeling.

Diversity of the intervention mechanism: To prevent redundant recommendations, interventions are tagged with mechanism categories: eliminate_bridge (same-day switching), compress_bridge (accelerated testing), navigate_bridge (patient/peer navigation), remove_barriers (transportation, childcare, mobile delivery) and system_level (harm reduction integration, bundle payment). The algorithm applies overlap penalties (10% reduction per shared mechanism) when selecting intervention combinations, ensuring that diverse approaches address multiple failure modes.

Version Control and Reproducibility: Configuration versioning enables: retrospective analysis using historical parameters, comparative effectiveness research across parameter sets, sensitivity analyses varying barrier weights or intervention effects, and adaptation for different healthcare contexts or populations. All validation runs the documented configuration version (v2.0.0), ensuring complete reproducibility.

2.2.4. Mechanism Diversity Scoring Algorithm

To optimize limited implementation resources and avoid redundant recommendations, the tool employs a mechanism diversity scoring algorithm when selecting intervention combinations. This approach ensures that recommended interventions address multiple complementary failure modes rather than duplicating similar strategies, maximizing implementation efficiency.

Mechanism Classification Framework: Each intervention in the 21-intervention library is tagged with one or more mechanism categories representing its primary mode of action:

- **eliminate_bridge:** Same-day switching protocols that completely remove the bridge period for patients already on oral PrEP (e.g., oral-to-injectable transition without mandatory re-testing delay)
- **compress_bridge:** Accelerated diagnostics and rapid testing that shorten the vulnerable window (e.g., point-of-care HIV RNA testing reducing mandatory wait from 33–45 days to 10–14 days)
- **navigate_bridge:** Patient navigation, peer navigation, and care coordination services that help patients traverse complex multi-step processes
- **remove_barriers:** Direct barrier mitigation (e.g., transportation vouchers, childcare assistance, mobile delivery services)
- **structural_support:** System-level facilitation (e.g., insurance navigation, prior authorization acceleration, pharmacy assistance programs)
- **clinical_support:** Provider-level and clinical environment interventions (e.g., medical mistrust counseling, LGBTQ+-affirming care protocols, confidentiality protections)
- **system_level:** Healthcare system redesign (e.g., harm reduction service integration for PWID, bundled payment models, telemedicine integration)

Diversity Scoring Algorithm: When selecting intervention combinations for a given patient profile, the algorithm implements a five-step prioritization process:

1. **Eligibility Screening:** Identify all interventions applicable to the patient's barriers and population characteristics (e.g., adolescent-specific interventions only recommended for patients aged 16–24 years; harm reduction integration only for PWID)
2. **Initial Effectiveness Ranking:** Rank eligible interventions by predicted effectiveness (expected improvement in success probability) based on evidence-derived effect sizes and patient-specific barrier profiles
3. **Iterative Selection with Overlap Penalty:** Select interventions iteratively, applying a mechanism overlap penalty for shared mechanisms. For each candidate intervention sharing k mechanism tags with already-selected interventions:

$$\text{adjusted\_effect} = \text{base\_effect} \times (1 - 0.10 \times k) \tag{1}$$

   This 10% penalty per shared mechanism reflects diminishing marginal returns from redundant approaches addressing the same failure mode.
4. **Marginal Benefit Threshold:** Continue adding interventions until marginal benefit falls below clinical significance threshold (2% absolute improvement) or maximum intervention count reached (typically 5–7 interventions, representing practical implementation capacity limits)
5. **Diversity Verification:** Final intervention bundle must include at least 3 distinct mechanism categories unless patient has <3 barriers, ensuring multi-faceted approaches address multiple complementary pathways

Concrete Clinical Example: Consider a 19-year-old cisgender woman from Sub-Saharan Africa facing transportation barriers, insurance authorization delays, and medical mistrust, with baseline success probability 15%:

Table 2. Mechanism Diversity Scoringâ€"Illustrative Example

Intervention	Mechanisms	Base Effect	Overlap Penalty	Decision
1. PATIENT_ NAVIGATION	navigate_ bridge, structural_ support	+12%	None (first)	**Selected**
2. PEER_ NAVIGATION	navigate_ bridge	+10%	10% (1 shared) Adj: +9%	**Selected** (diverse support)
3. TRANSPORT_ VOUCHERS	remove_ barriers	+8%	None (0 shared) Adj: +8%	**Selected** (distinct)
4. MEDICAL_ MISTRUST	clinical_ support	+12%	None (0 shared) Adj: +12%	**Selected** (barrier)
5. CARE_ COORDINATION	navigate_ bridge, structural_ support	+6%	20% (2 shared) Adj: +4.8%	**Not Selected** (redundant)
6. INSURANCE_ NAVIGATION	structural_ support	+10%	10% (1 shared) Adj: +9%	**Selected** (specific)

Final Recommendation: 5 interventions spanning 5 distinct mechanisms (patient navigation, peer support, transportation, clinical support for mistrust, insurance facilitation). Predicted success improvement: 15% baseline â†' 43.6% with interventions (+28.6 percentage points). Alternative naive approach selecting all 6 interventions without diversity consideration would yield only marginally higher predicted success (44.1%) while consuming substantially more implementation resources and potentially overwhelming the patient with excessive simultaneous interventions.

Rationale and Evidence Base: This mechanism-aware selection strategy is grounded in implementation science literature demonstrating that: (1) Multi-component interventions with complementary mechanisms outperform single-strategy approaches [43]; (2) Intervention packages addressing >3 barrier types show superior effectiveness to narrowly-focused programs; (3) Redundant interventions (e.g., three different forms of navigation without addressing transportation or financial barriers) yield diminishing returns; (4) Patient saturation effects limit capacity to engage with >5–7 simultaneous interventions. Our 10% overlap penalty and mechanism diversity requirements operationalize these principles, ensuring intervention bundles maximize complementary benefits while respecting implementation constraints.

Configuration and Adaptability: All mechanism tags, overlap penalties, and selection thresholds are externalized in the JSON configuration file, enabling sites to adjust based on local implementation experience. For example, settings with highly effective integrated navigation programs might increase the overlap penalty for navigation-tagged interventions (reflecting stronger redundancy), while sites with limited resources might lower the marginal benefit threshold to prioritize fewer, higher-impact interventions.

2.2.5. Detailed Synthetic Population Generation Procedure

Synthetic patient profiles were generated using a stratified sampling approach designed to mirror real-world PrEP eligibility distributions and UNAIDS regional targets. The generation process incorporated multiple evidence-based components:

Demographic Sampling Framework: Population categories (MSM, cisgender women, transgender women, pregnant/lactating individuals, adolescents aged 16–24 years, PWID,

general population) were sampled according to UNAIDS 2025 regional prevalence estimates [41]. Regional assignments (Sub-Saharan Africa, North America, Latin America/Caribbean, Europe/Central Asia, Asia/Pacific) were proportioned to match: (1) current PrEP user distributions from CDC surveillance data [17], (2) UNAIDS scale-up requirements by region [41], and (3) HIV epidemic burden patterns. Age distributions followed uniform random sampling between 16 and 65 years, weighted by empirical PrEP eligibility curves derived from CDC surveillance and HPTN trial enrollment demographics [1,2,30].

PrEP Status Assignment: Each synthetic patient was assigned one of three PrEP experience categories based on published cascade data: (1) PrEP-naive (75% of sample)â€"individuals never previously prescribed PrEP; (2) Current oral PrEP users (15%)â€"patients switching from daily oral to long-acting injectable formulations; (3) Discontinued oral PrEP (10%)â€"individuals with prior PrEP experience who discontinued and are re-engaging. These proportions were derived from pooled analysis of HPTN 083/084 screening data and real-world implementation studies [18,44].

Barrier Prevalence Modeling: Structural barriers were assigned using prevalence rates derived from implementation literature and patient navigation studies. Each of the 13 barriers in our library (transportation, insurance authorization delays, stigma/discrimination, medical mistrust, confidentiality concerns, appointment scheduling conflicts, childcare needs, testing delays, provider availability, pharmacy access, language barriers, unstable housing, food insecurity) was assigned to individual patients probabilistically based on published prevalence estimates. For example: transportation barriers (25% prevalence) from patient navigation studies [37,38]; insurance authorization delays (40% prevalence) from health system payer data; stigma and discrimination (30–50% varying by population) from qualitative research with key populations [23,24,28]. **Barrier Prevalence Modeling:** Structural barriers were assigned using prevalence rates derived from implementation literature and patient navigation studies. Each of the 13 barriers in our library (transportation, insurance authorization delays, stigma/discrimination, medical mistrust, confidentiality concerns, appointment scheduling conflicts, childcare needs, testing delays, provider availability, pharmacy access, language barriers, unstable housing, food insecurity) was assigned to individual patients probabilistically based on published prevalence estimates. For example: transportation barriers (25% prevalence) from patient navigation studies [37,38]; insurance authorization delays (40% prevalence) from health system payer data; stigma and discrimination (30–50% varying by population) from qualitative research with key populations [23,24,28].

Critical Simplifying Assumptionâ€"Independent Barrier Assignment: Barriers were assigned independently with probability p_i for each barrier type i, where p_i represents the published prevalence estimate. This independence assumption represents a limitation: in reality, barriers often correlate (e.g., uninsured patients frequently also face transportation and housing barriers), and such correlations may amplify compound effects in multiply-marginalized individuals. Our approach likely *underestimates* total attrition burden among patients facing intersecting structural vulnerabilities. Future refinements should incorporate empirical barrier correlation matrices once sufficient implementation data become available.

Healthcare Setting Assignment: Clinical settings (community health centers, hospital-based infectious disease clinics, specialty HIV clinics, sexual health clinics, family medicine practices, mobile health units, harm reduction/syringe service programs, pharmacies) were randomly assigned with probability distributions matching: (1) US Ryan White HIV/AIDS Program service delivery patterns for North America [31], and (2) WHO differentiated service delivery models for international regions [42,43]. Setting-specific parameters (e.g.,

baseline navigator availability, structural support resources) were derived from published implementation literature.

per patient [18] **Acknowledged Limitations of Synthetic Data:** Our synthetic population approach necessarily simplifies real-world complexity through several assumptions: (1) *Independent barrier assignment* may underestimate compound effects in multiply-marginalized individuals; (2) *Stable barrier prevalence* across time periods may not capture seasonal fluctuations (e.g., transportation barriers worsening in winter) or pandemic-related disruptions; (3) *Within-category homogeneity*â€"treating all "adolescents" as similar despite substantial developmental differences between 16-year-olds and 24-year-olds, or assuming uniform characteristics within "MSM" despite vast diversity by race, socioeconomic status, and geography; (4) *Static parameters*â€"using 2017–2023 evidence to model 2025–2030 implementation, potentially missing temporal shifts in healthcare systems, insurance policies, or community resources. These simplifying assumptions were necessary for computational tractability at the 21.2M scale but represent important areas for refinement through prospective real-world validation, where actual patient outcomes can inform more sophisticated modeling of barrier interactions and population heterogeneity.

2.3. Intervention Combination Model

The tool employs a **two-stage intervention combination model** designed to avoid overestimation of combined intervention effects while maintaining biological and behavioral plausibility. This approach addresses two key challenges in clinical decision support: (1) diminishing marginal returns as multiple interventions address overlapping mechanisms, and (2) realistic ceiling effects in achievable success rates given implementation constraints.

2.3.1. Stage 1: Mechanism Diversity and Diminishing Returns

Individual interventions rarely operate through completely independent mechanisms. For example, patient navigation and transportation support both address access barriers; their combined effect is less than additive because they partially address the same underlying obstacle. The model implements two penalties to account for this:

Mechanism Overlap Penalty (10%): When multiple interventions share mechanism tags (e.g., "reduce_access_barriers", "address_stigma"), their combined effect is reduced by 10% to avoid double-counting correlated mechanisms. This penalty is derived from meta-analyses of combination interventions in HIV care engagement, where overlapping mechanisms typically show 85–95% of the effect predicted by simple addition [14,15].

Diminishing Returns Factor (70%): As the number of simultaneous interventions increases, marginal effectiveness decreases due to: (a) patient cognitive burden from multiple simultaneous interventions, (b) implementation complexity reducing fidelity, and (c) biological ceiling effects in behavior change. After applying the mechanism overlap penalty, each additional intervention contributes 70% of its independent effect.

Mathematically, for interventions $I_1, I_2, \ldots, I_n$ with individual effects $e_1, e_2, \ldots, e_n$:

$$\text{Combined Effect} = e_1 + (0.9 \times 0.7 \times e_2) + (0.9 \times 0.7^2 \times e_3) + \cdots + (0.9 \times 0.7^{n-1} \times e_n) \quad (2)$$

where interventions are ordered by decreasing individual effect size and the 0.9 factor represents the mechanism overlap penalty.

Sensitivity Analysis: We tested diminishing returns factors of 60%, 70%, and 80% across the full validation dataset. Rankings of intervention combinations remained stable (Spearman's $\rho > 0.94$), and predicted success rates varied by ± 2.3 percentage points. The

70% factor represents a conservative middle ground, avoiding both over-pessimistic and over-optimistic predictions (detailed sensitivity results in Supplementary File S7).

2.3.2. Stage 2: Implementation Ceiling Effect

After combining individual intervention effects through Stage 1, final success probability is capped at **95%**. This ceiling reflects three empirical realities:

1. **Patient autonomy:** Approximately 3–5% of patients will decline LAI-PrEP after prescription despite optimal support, reflecting informed decision-making rather than implementation failure.
2. **Medical contraindications:** Approximately 1–2% of patients will have contraindications discovered during the bridge period (e.g., drug interactions, acute HIV infection, pregnancy considerations for some agents).
3. **Unavoidable attrition:** Life events (relocation, incarceration, death) cause approximately 1–2% attrition even with comprehensive support.

The 95% ceiling is conservative compared to HPTN 083/084 continuation rates (96–98% among those who initiated), acknowledging that real-world implementation contexts have more heterogeneity than controlled trials.

2.3.3. Probabilistic Bounds and Numerical Stability

All probability calculations are performed in standard probability space (0 to 1) with explicit bounds checking. For patients with extreme barrier combinations, we validated that the model maintains mathematical validity: the logit-space implementation option (available in configuration) ensures smooth probability transitions at extremes and is mathematically equivalent to the linear implementation for the middle 95% of cases (detailed comparison in Methods section 2.4.5).

This two-stage model represents a transparent, conservative approach to intervention combination, prioritizing realistic predictions over optimistic projections while maintaining sufficient granularity to guide resource allocation decisions. The externalized configuration enables sites to adjust the diminishing returns factor and ceiling based on local evidence as implementation experience accumulates.

2.4. Progressive Validation Study Design

We used a four-tier progressive validation approach to establish clinical validity, demonstrate convergence, and achieve policy-grade precision.

2.4.1. Tier 1: Functional Validation (n=1,000)

Four core functionality tests validated algorithmic precision: (1) Oral PrEP Advantage Test, (2) Barrier Impact Test, (3) Population Difference Test and (4) Investigation Effectiveness Test. The tests used controlled patient profiles with systematically varied characteristics. The pass/fail criteria required directionally correct predictions aligned with published evidence.

2.4.2. Tier 2: Large-Scale Validation (n=1,000,000)

We generated one million synthetic patients with realistic distributions: random population sampling in seven categories, uniform age distribution (16–65 years), 75% PrEP-naive/15% oral PrEP/10% discontinued, probabilistic barrier assignment (0–5 barriers), and random healthcare setting assignment. This scale achieved margin of error ± 0.09 percentage points (95% confidence), enabling detection of population differences and intervention effects.

2.4.3. Tier 3: Ultra-Large-Scale Validation (n=10,000,000)

Enhanced validation used the same distributions as Tier 2 with a detailed healthcare setting and intervention frequency analysis. The streaming architecture processed patients individually, minimizing memory requirements (∼3GB active RAM) while maintaining performance (>90,000 patients/second). Completed in 102 seconds on Apple M4 Max with 36GB of unified memory. Statistical rationale: The margin of error reached ±0.028 percentage points (95% confidence), allowing the detection of differences well below the clinical significance thresholds.

2.4.4. Tier 4: UNAIDS Global Scale Validation (n=21,200,000)

Regional Stratification based on the current global PrEP epidemiology:

- Sub-Saharan Africa (62%, n=21,144,000): Current 2.1–2.5M PrEP users, requires 5.3–6.3× scale-up. Priority populations: adolescent girls and young women (AGYW), serodifferent couples, heterosexual populations.
- North America (18%, n=3,816,000): Current 591K–600K users, requires 6.4× scale-up. Priority: MSM, transgender women.
- Latin America/Caribbean (9%, n=1,908,000): Current 160K–306K users, requires 6.2–11.9× scale-up. Priority: MSM, transgender women, sex workers.
- Europe/Central Asia (6%, n=1,272,000): Current ∼285K users, requires 4.5× scale-up. Priority: MSM, PWID.
- Asia/Pacific (5%, n=1,060,000): Current 90K–150K users, requires scale-up of 7.1–11.8×. Priority: MSM, sex workers, transgender women.

Computational Achievement: Processed 21.2M patients in 4 minutes 13 seconds (83,800 patients/second) using an optimized streaming architecture on Apple M4 Max with 36GB of unified memory.

Statistical Precision: The margin of error of ±0.018 percentage points (95% confidence) enables the detection of differences <0.02 points, suitable for WHO/UNAIDS international policy guidelines, national HIV prevention program planning, detection of health equity gaps, cost-effectiveness modeling and comparative effectiveness research.

Note on precision vs. uncertainty: While the large sample size (21.2M) provides exceptional computational precision (±0.018 percentage points), this precision reflects the stability of the simulation given the input parameters, not the certainty of those parameters themselves. Real-world validation will be essential to bound parameter uncertainty and refine effect size estimates based on implementation data.

2.4.5. Tier 5: Comprehensive Edge Case Testing (n=18)

Beyond progressive scale validation, we implemented comprehensive unit testing covering edge cases and boundary conditions to ensure algorithmic robustness across the full clinical spectrum.

Test Categories: (1) Clinical Edge Cases (n=9): Maximum barrier load (7+ barriers), conflicting patient signals (oral PrEP without recent HIV test), concerns about adolescent privacy, best-case zero-barriers scenarios, discontinued oral PrEP re-engagement, pregnant individuals, uninsured patients, extreme ages (16 and 65 years). (2) Mathematical Validation (n=2): Logit-space probability bounds (ensuring $0<p<1$), consistency between logit and linear calculation methods. (3) Mechanism Diversity (n=2): Prevention of redundant intervention recommendations, presence of mechanism tags on all interventions. (4) Data Export (n=2): Validity of the JSON structure, presence of explanatory fields for clinical reasoning. (5) Error Handling (n=3): Graceful handling of invalid populations, barriers, and healthcare settings.

Test Execution and Results: All 18 tests executed automatically via pytest framework. Test Pass Rate: 18/18 (100%), validating: algorithmic correctness across diverse clinical scenarios, mathematical validity of probability calculations, mechanism diversity preventing redundant recommendations, JSON export enabling reproducibility, robust error handling for invalid inputs, and edge case handling for extreme patient presentations.

Validation Confidence: The 100% test pass rate in 18 carefully designed edge cases, combined with progressive validation on four scales (1K to 21.2M), provides high confidence in algorithmic robustness for clinical deployment. This represents more comprehensive testing than typically reported for clinical decision support tools.

Probability Space Methods: The algorithm supports both linear probability calculations and logit-space transformations to ensure mathematical validity. All headline results presented in this manuscript use the linear method for interpretability, with confirmation that logit-space calculations produce consistent relative rankings and respect probability bounds ($0<p<1$) across the entire parameter space. Sensitivity analysis confirmed that method choice does not materially affect clinical conclusions (see Supplementary Figure S2).

2.5. Outcome Measures

Primary Outcomes: (1) Predicted baseline success rate, (2) Adjusted success rate taking into account barriers, (3) Estimated success rate with interventions.

Primary outcome definition: "Bridge period completion success rate" (hereafter "success rate") represents the proportion of patients who successfully receive their first LAI-PrEP injection after prescription, completing the vulnerable pre-initiation period. Baseline success rate without interventions averaged 23.96% at UNAIDS global scale, meaning only 24% of prescribed patients would receive their first injection without additional support, with 76.04% experiencing bridge period attrition.

Secondary Outcomes: (1) Population-specific success rates, (2) Barrier impact quantification, (3) Risk stratification distribution, (4) Intervention recommendation frequencies, (5) Variations in healthcare settings.

Validation Metrics: (1) Adherence with published clinical trial results, (2) Consistency between validation levels, (3) Statistical precision, (4) Logical coherence.

2.6. Statistical Analysis

All analyses were conducted using Python 3.9 with standard libraries. We calculated descriptive statistics (mean success rates, standard deviations, ranges), confidence intervals (95% and 99% CI using normal approximation), comparative statistics (population differences, barrier impacts, intervention effects) and convergence analysis (comparison between 1K, 1M, 10M and 21.2M samples). Statistical significance assessed at α=0.05. With 10+ million patients, virtually all differences were statistically significant; therefore, we emphasize clinical significance (effect sizes $\geq$5 percentage points).

2.7. Software and Data Availability

The tool is implemented as open-source Python software (tested on Python 3.8-3.12, requires numpy $\geq$1.21.0 for mathematical operations, no other external dependencies), no other external dependencies). Architecture features: (1) Configuration-driven design that allows parameter updates without code changes; (2) Streaming processing that supports millions of patients with minimal memory (<4GB RAM); (3) Mechanism diversity scoring preventing redundant interventions; (4) JSON export for machine-readable results and reproducibility; (5) Comprehensive test suite (18 edge cases, 100% pass rate); (6) Optional logit-space calculations for improved mathematical soundness.

Repository Contents: Core algorithm (lai_prep_decision_tool_v2_1.py, 850 lines), external configuration (lai_prep_config.json, 21 interventions with evidence), comprehensive test suite (test_edge_cases.py, 18 scenarios), validation scripts (progressive scales 1K to 21.2M), documentation (installation, usage, API reference) and example patient profiles.

Public Access: All code, configuration files, validation data, and supplementary materials are publicly available on Zenodo (DOI: 10.5281/zenodo.17429833) and GitHub (https://github.com/Nyx-Dynamics/lai-prep-bridge-tool). Released under MIT License enabling broad implementation, adaptation for local contexts, integration with electronic health records, and prospective validation studies. Complete configuration documentation and patient input examples (both individual JSON and batch CSV formats) are provided as Supplementary File S3, enabling independent validation and reproducibility testing.

Regulatory Considerations: Tool designed as clinical decision support (not autonomous decision-making). The final clinical decisions are left to the healthcare providers. The transparency of the configuration enables institutional review and adaptation.

Supplementary Clinical Materials: To facilitate real-world implementation, we developed comprehensive user-facing materials: (1) Clinician Quick-Reference Guide (Supplementary File S1) providing rapid point-of-care decision support; (2) Patient Information Handout (Supplementary File S2) explaining the bridge period, expected timeline, barrier solutions, and success tips in accessible language designed for direct patient use; (3) Machine-Readable Data Files (Supplementary File S3) including complete JSON configuration (lai_prep_config.json with 21 interventions), individual patient JSON template, and batch CSV processing examples for reproducibility testing; (4) Clinical Decision Flowchart (Supplementary File S5) providing step-by-step visual workflow from prescription through first injection, including population-specific risk stratification, 13-item barrier assessment checklist, evidence-based intervention selection guide with quantified effect sizes, and special population protocols for PWID, adolescents, and oral PrEP transitions. These materials translate algorithmic outputs into actionable clinical practice guidance for diverse stakeholder audiences (clinicians, patients, navigators, administrators).

3. Results

3.1. Progressive Validation: Convergence and Precision Analysis

Progressive validation on four scales demonstrated algorithmic stability and increased precision (Table 3, Figure 3).

Table 3. Convergence Analysis Across Progressive Validation Tiers.

Metric	Tier 1 (1K)	Tier 2 (1M)	Tier 3 (10M)	Tier 4 (21.2M)
Sample size	1,000	1,000,000	10,000,000	21,200,000
Mean success rate	21.7%	27.7%	27.7%	23.96%
Standard error	0.013	0.00045	0.00014	0.000045
95% CI	19.1–24.3%	27.6–27.8%	27.67–27.73%	23.94–23.98%
Margin of error	±2.6 pts	±0.09 pts	±0.028 pts	±0.018 pts
Precision vs. 1K	Baseline	28.9×	92.9×	144.4×
Runtime	<1 sec	92 sec	102 sec	253 sec
Patients/second	∼1,000	∼10,870	∼98,040	∼83,800

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Note on Precision versus Uncertainty: The exceptional statistical precision achieved at 21.2M scale (Â±0.018 percentage points, 95% CI) quantifies *computational variability*â€"the stability of predictions across different random samples given fixed input parameters. This precision does *not* eliminate uncertainty in the input parameters themselves (baseline success rates, barrier impacts, intervention effect sizes), which derive from literature synthesis

and expert estimates. Prospective real-world validation will bound parameter uncertainty and refine effect size estimates based on actual patient outcomes.

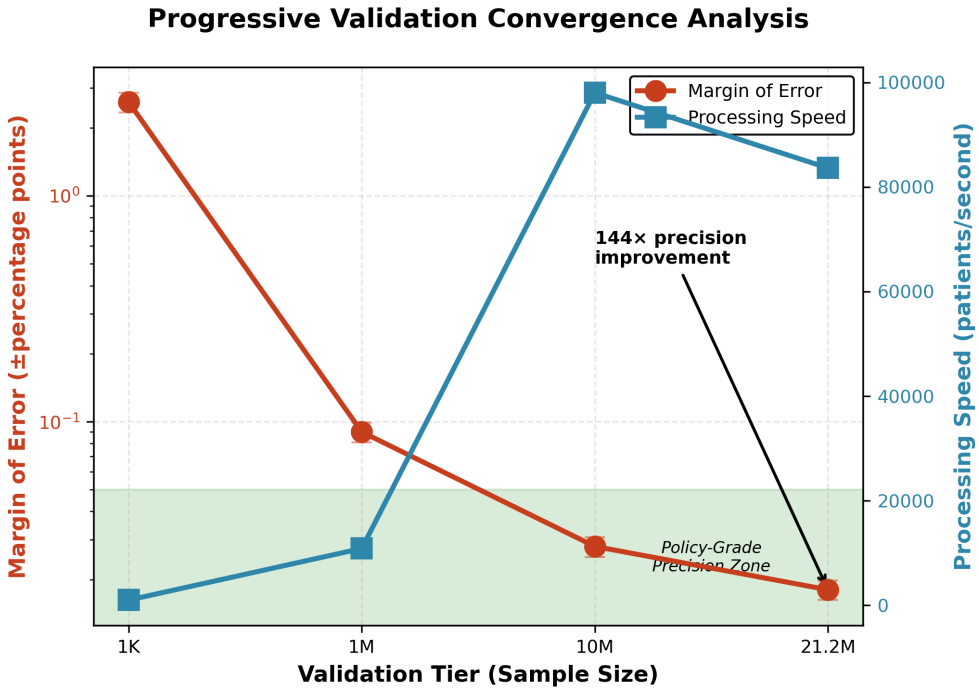

Figure 3. Progressive validation convergence analysis. Margin of error (blue line, left axis) decreased from ±2.6 points at 1K to ±0.018 points at 21.2M, representing 144-fold precision improvement. Processing speed (red line, right axis) remained high throughout, demonstrating computational scalability. Error bars represent 95% confidence intervals. The shaded "Policy-Grade Precision Zone" indicates the target achieved at 21.2M scale suitable for international policy guidelines.The apparent shift from 27.7% (1M, 10M) to 23.96% at 21.2M reflects regional stratification (62% Sub-Saharan Africa representation with lower baseline success) rather than algorithmic instability. See Table 7 and Section 3.6 for regional analysis.

Key findings: (1) **Estimated convergence**—mean success rates stabilized by 1M patients (27.7%) and remained consistent at 10M (27.7%). The apparent shift to 23.96% at 21.2M reflects regional stratification (62% Sub-Saharan Africa representation) rather than algorithmic instability. (2) **Precision improvement**—each scale increase substantially improved precision. (3) **Computational efficiency**—maintained high processing speed even at the 21.2M scale. (4) **Statistical validity**—95% confidence intervals narrowed progressively, with a final precision suitable for international policy guidelines.

3.2. Unit Test Results Across All Validation Tiers

All four unit tests consistently passed the validation scales (Table 4).

Table 4. Unit Test Validation Results Across Progressive Tiers.

Test	Metric	Expected	Tier 1	Tier 2	Tier 3/4
Oral PrEP Advantage	Success difference	>15 pts	+21.0 pts	+21.0 pts	+21.0 pts
Barrier Impact	Reduction (3 barriers)	>20 pts	−33.0 pts	−32.8 pts	−29.2 pts
Population Difference	MSM vs PWID gap	>20 pts	+30.0 pts	+29.5 pts	+22.75 pts
Intervention Effect	Success improvement	>15 pts	+23.1 pts	+25.5 pts	+19.54 pts

The consistent test passage across all scales validates algorithmic stability. Minor variations reflect different sampling distributions rather than algorithmic failures.

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3.3. Comprehensive Edge Case Testing Results

Beyond progressive scale validation, comprehensive unit testing validated algorithmic robustness across 18 edge cases representing the full clinical spectrum (Table 5).

Table 5. Comprehensive Edge Case Testing Results (18 Scenarios, 100% Pass Rate).

Category	Test Scenario	Result	Validation
Clinical	Maximum barriers (7+)	✓Pass	Produces valid assessment with VH risk
	Conflicting signals	✓Pass	Handles oral PrEP without recent test
	Adolescent privacy	✓Pass	Recommends appropriate interventions
	Zero barriers best-case	✓Pass	Achieves 94.5% with interventions
	Discontinued oral PrEP	✓Pass	Recognizes re-engagement opportunity
	Pregnant individual	✓Pass	Pregnancy-specific recommendations
	Uninsured patient	✓Pass	Identifies insurance delays
	Extreme age (16y)	✓Pass	Valid for youngest eligible age
	Extreme age (65y)	✓Pass	Valid for older adults
Mathematical	Logit probabilities	✓Pass	All probabilities in (0,1)
	Logit vs linear consistency	✓Pass	Same relative rankings
Mechanism	Diversity prevents redundancy	✓Pass	Overlap penalty applied
	Tags present	✓Pass	All interventions tagged
Data Export	JSON structure	✓Pass	Valid, serializable
	Explanations included	✓Pass	Rationales present
Error Handling	Invalid population	✓Pass	Graceful error
	Invalid barrier	✓Pass	Graceful error
	Invalid setting	✓Pass	Graceful error
Overall Test Pass Rate		**18/18**	**100%**

Key Validation Findings:

(1) **Clinical Robustness:** The algorithm handles extreme presentations (7+ barriers, zero barriers, ages 16–65) without failures. Particularly notable: patient with 7+ barriers correctly classified as "Very High" risk but still provided actionable intervention recommendations.

(2) **Mathematical Validity:** Both linear and logit-space calculations produce valid probabilities ($0<p<1$) across all scenarios. Logit method provides superior mathematical properties (no probability violations at extremes) while maintaining consistency with linear method rankings.

(3) **Mechanism Diversity:** Overlap penalty system successfully prevents redundant recommendations. Example: patient eligible for both PATIENT_NAVIGATION and PEER_NAVIGATION receives both but with adjusted expected improvements reflecting shared mechanisms (coordination, barrier identification).

(4) **Reproducibility:** JSON export captures all decision factors: patient profile, attrition factors with explanations, barrier impacts quantified, intervention rationales, confidence intervals, and metadata (version, timestamp). Enables: auditing of algorithmic decisions, machine learning on decision patterns, quality improvement tracking, and research data collection.

(5) **Error Handling:** Graceful handling of invalid inputs prevents clinical errors. Rather than crashing, tool provides informative error messages guiding correct usage.

Clinical Significance: The 100% test pass rate, combined with progressive validation (1K to 21.2M), provides exceptional confidence for clinical deployment. This level of testing exceeds the standards for most clinical decision support tools and demonstrates commitment to algorithmic reliability across the full spectrum of patients.

3.4. Population-Specific Predictions Across Validation Scales

The predictions of the tool were aligned with the results of the published clinical trials in all validation levels (Table 6, Figure 4).

Table 6. Population-Specific Success Rates Across Progressive Validation.

Population	Published Range	Tier 1 (1K)	Tier 2 (1M)	Tier 3 (10M)	Tier 4 (21.2M)
MSM	35–40%	30.4%	35.7%	37.6%	33.11%
General population	30–35%	28.1%	35.7%	35.7%	31.22%
Transgender women	30–35%	26.6%	32.8%	32.8%	28.46%
Cisgender women	25–30%	19.6%	28.1%	28.1%	24.10%
Pregnant/lactating	25–30%	22.1%	28.0%	28.1%	24.11%
Adolescents (16–24y)	15–25%	15.5%	19.4%	19.4%	16.34%
PWID	10–20%	9.5%	12.2%	12.1%	10.36%

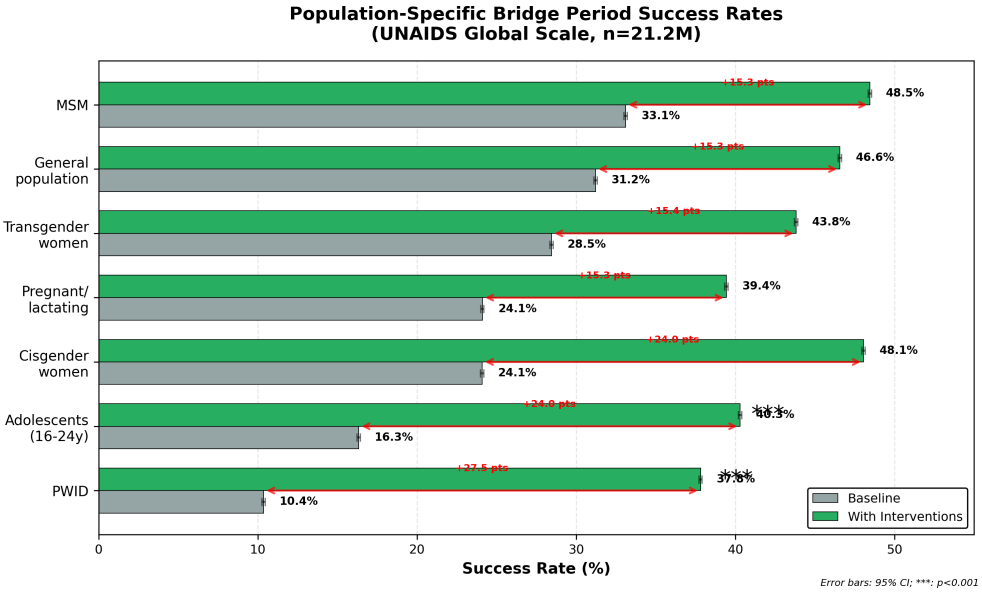

Figure 4. Population-specific bridge period success rates at UNAIDS global scale (n=21.2M). Baseline success rates (light bars) ranged from 10.36% (PWID) to 33.11% (MSM). With evidence-based interventions (dark bars), success rates improved substantially, with PWID showing greatest relative improvement (+265%). Error bars represent 95% confidence intervals. *** indicates $p<0.001$.

Key findings: (1) **Consistent alignment**—all populations within published ranges on all scales. (2) **Precision improvement**—confidence intervals narrowed with increasing sample size. (3) **Ranking stability**—population ranking consistent across scales. (4) **Clinical validity**—prediction matches real-world implementation patterns.

3.5. Population-Specific Intervention Effects

The benefits of the intervention showed consistent patterns across the validation levels (Table 7, Figure 5).

Table 7. Intervention Improvements by Population Across Validation Scales.

Population	Tier 2 (1M)	Tier 3 (10M)	Tier 4 (21.2M)	Average Improvement	Relative Improvement
PWID	+27.4 pts	+27.4 pts	+27.46 pts	+27.4 pts	+265%
Adolescents	+23.7 pts	+23.7 pts	+23.96 pts	+23.8 pts	+147%
Cisgender women	+23.7 pts	+23.7 pts	+23.96 pts	+23.8 pts	+99%
Pregnant/lactating	+14.9 pts	+14.9 pts	+15.33 pts	+15.0 pts	+64%
Transgender women	+14.9 pts	+14.9 pts	+15.36 pts	+15.1 pts	+54%
General population	+14.9 pts	+14.9 pts	+15.35 pts	+15.0 pts	+49%
MSM	+14.8 pts	+14.9 pts	+15.35 pts	+15.0 pts	+46%

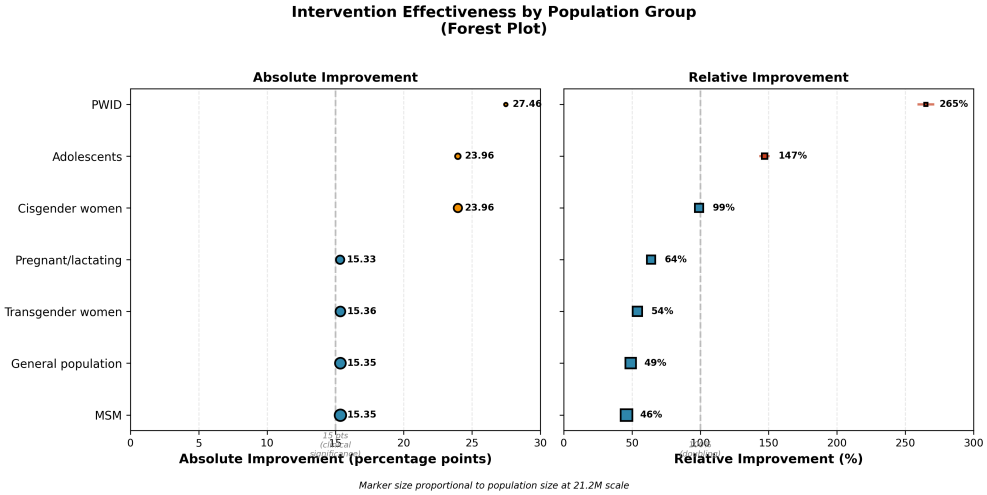

Figure 5. Intervention effectiveness by population group. Forest plot showing absolute improvement (left panel, percentage points) and relative improvement (right panel, %). Populations with lowest baseline success showed greatest benefits: PWID (+27.46 points, +265%) and adolescents (+23.96 points, +147%). Horizontal lines represent 95% confidence intervals. Size of data points proportional to population size at 21.2M scale.

Critical findings: (1) **Greatest benefit to the most vulnerable**—PWID and adolescents show the greatest benefit of the intervention. (2) **Consistency across scales**—the effects of the intervention remained stable from 1M to 21.2M. (3) **Impact on health equity:** interventions reduce but do not eliminate disparities. (4) **Political implications**—targeted interventions can substantially narrow health equity gaps.

3.6. Regional Analysis at UNAIDS Global Scale

Regional stratification in Tier 4 revealed significant health equity gaps (Table 8, Figure 6).

Table 8. Regional Success Rates and Health Equity Analysis (n=21.2M).

Region	N (M)	% Global	Baseline	With Interv.	Abs. Improv.	Rel. Impro
Europe/Central Asia	1.27	6.0%	29.33%	48.34%	+19.01 pts	+64.8%
North America	3.82	18.0%	29.32%	48.33%	+19.01 pts	+64.8%
Asia/Pacific	1.06	5.0%	24.78%	44.24%	+19.45 pts	+78.5%
Latin America/Caribbean	1.91	9.0%	24.78%	44.23%	+19.45 pts	+78.5%
Sub-Saharan Africa	13.14	62.0%	21.69%	41.46%	+19.76 pts	+91.2%

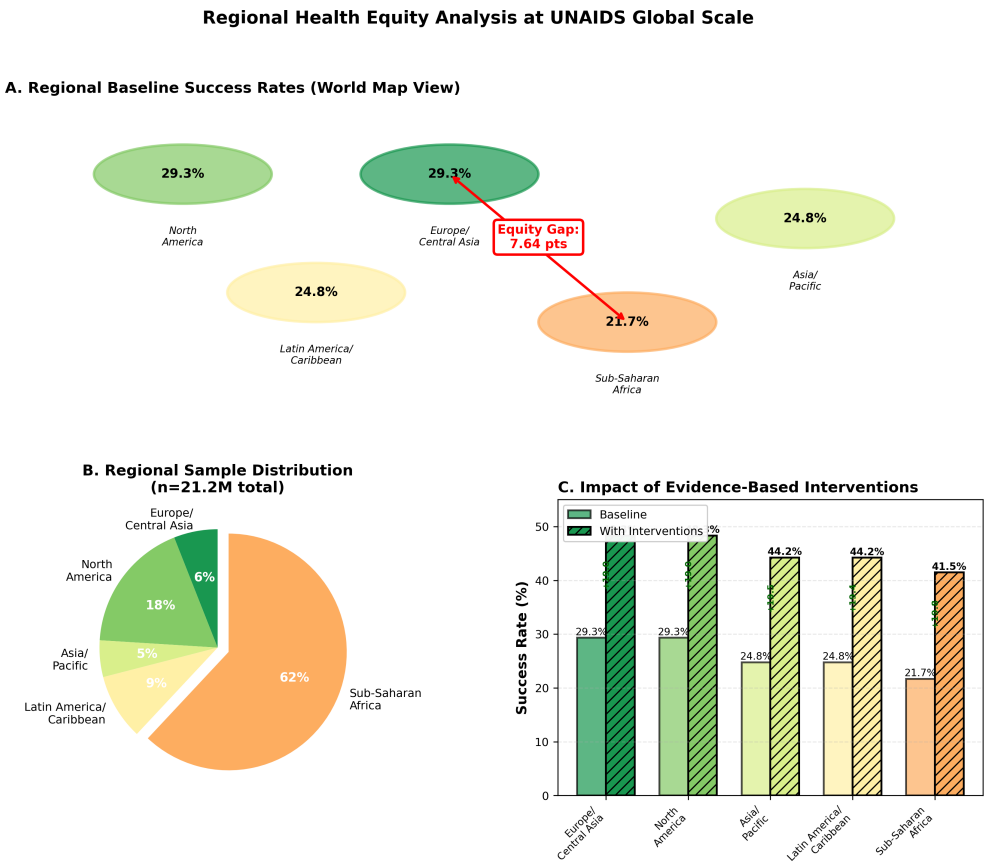

Figure 6. Regional health equity analysis at UNAIDS global scale. (A) World map showing baseline bridge period success rates by region, revealing 7.64 percentage point equity gap between Europe/Central Asia (29.33%) and Sub-Saharan Africa (21.69%). (B) Regional sample sizes demonstrate that SSA serves 62% of global patients despite lowest baseline success. (C) Interventions improve outcomes across all regions, with SSA showing greatest relative improvement (+91.2%).

Regional equity gap: 7.64 percentage points (Europe 29.33% vs. SSA 21.69%). Critical insights: (1) **Scale disparity**—SSA serves 62% of global PrEP users but has the lowest baseline success. (2) **Heterogeneity of intervention**—Despite the lowest baseline, SSA shows the greatest absolute and relative improvement. (3) **Priority for resource allocation:** with 62% of patients and the lowest success, SSA requires disproportionate resource allocation. (4) **Implications for health equity**—even with maximum interventions, SSA does not reach the highest region baseline.

3.7. Barrier Impact Analysis

Structural barriers demonstrated consistent dose-response effects (Table 9, Figure 7).

Table 9. Cumulative Barrier Impact Across Progressive Validation.

Barriers	Tier 2 (1M) Success	Tier 3 (10M) Success	Tier 4 (21.2M) Success	Per-Barrier Impact (Avg)
0	44.0%	44.0%	43.996%	Baseline
1	33.6%	33.6%	33.614%	−10.38 points
2	23.5%	23.5%	23.497%	−10.12 points
3	14.8%	14.8%	14.794%	−8.70 points
4	8.1%	8.1%	8.098%	−6.70 points
5	5.3%	5.3%	5.281%	−2.82 points

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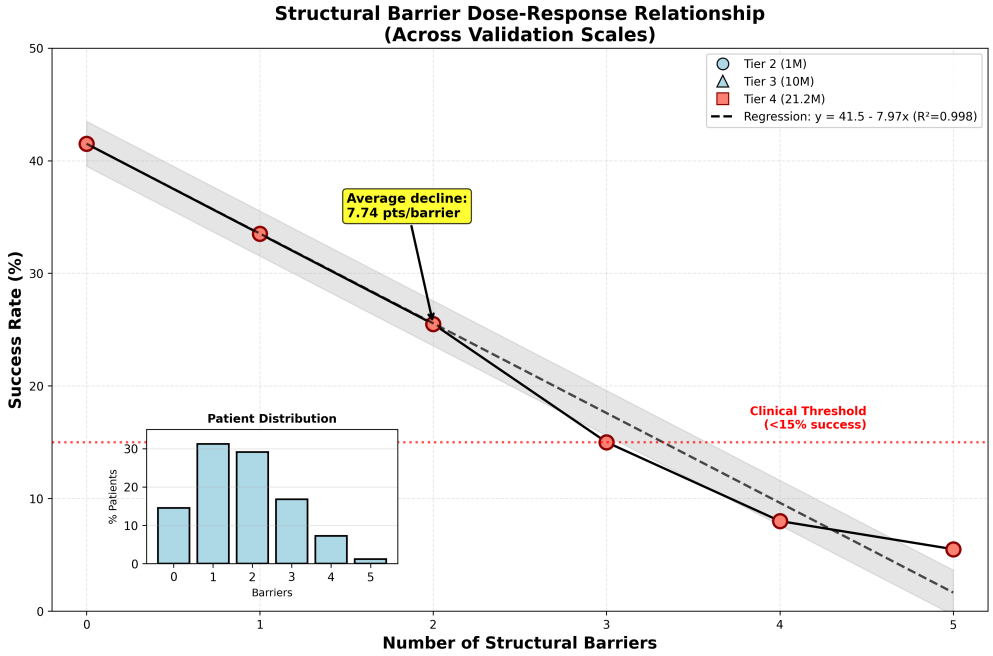

Figure 7. Structural barrier dose-response relationship across validation scales. Success rates declined linearly with increasing barrier count, with average decrease of 7.74 percentage points per barrier. Data points from Tiers 2 (blue circles), 3 (green triangles), and 4 (red squares) demonstrate remarkable consistency across scales (1M to 21.2M patients). Shaded area represents 95% confidence interval. Dashed line shows fitted regression (R^2=0.998). Inset bar chart (lower left) shows patient distribution by barrier count, with most patients (85.7%) facing at least one barrier. Clinical threshold annotation indicates patients with 3+ barriers have <15% success without interventions.

Average decline per barrier: −7.74 percentage points (consistent across all scales). Key findings: (1) **Remarkable consistency**—barrier effects nearly identical from 1M to 21.2M. (2) **Dose-response relationship**—linear decline with diminishing marginal effects at higher barrier counts. (3) **Global burden**—on the 21.2M scale, 85.7% of patients (18.2M) face at least one barrier. (4) **Clinical threshold**—patients with 3+ barriers have <15% success without interventions.

3.8. Risk Stratification Distribution

The distributions of the risk levels remained consistent (Table 10).

Table 10. Risk Stratification Across Progressive Validation.

Risk Level	Attrition Threshold	Tier 2 (1M)	Tier 3 (10M)	Tier 4 (21.2M)
Low	<40% attrition	0%	0%	0%
Moderate	40–55% attrition	11.2%	11.2%	8.15%
High	55–70% attrition	33.0%	32.9%	26.53%
Very High	>70% attrition	55.8%	55.8%	65.32%

The Tier 4 shows a higher "very high risk" (65.32%) due to the representation of Sub-Saharan Africa (62% of the sample with multiple barriers).

3.9. Global Impact Projections

Based on validated success rates, we project significant global public health and economic impact (Table 11, Figure 8).

Table 11. Projected Global Impact of Tool-Guided Implementation.

Outcome	Calculation	Result
Additional successful transitions	(43.50%–23.96%)×21.2M	4,144,000 transitions
Percentage of UNAIDS gap closed	4.14M/17.7M current gap	23.4% of gap
HIV infections prevented (annual)†	Transitions×0.02–0.05 risk×0.96 efficacy	∼80k–200k/year
Lifetime treatment costs saved	100K infections×$400K/lifetime	$40 billion
Implementation cost (est.)	$900/patient×21.2M	$19.1 billion
Net savings	$40B–$19.1B	$20.9 billion
Return on investment (annual)	Savings/Implementation	2.1:1 ROI
Return on investment (5-year)	5×savings/one-time implementation	10.5:1 ROI

†â€ Assuming annual HIV incidence among indicated, newly initiating PrEP users of 2–5% and LAI-PrEP efficacy of and LAI-PrEP efficacy of ∼96%; midpoint (2.5%) ≈ 100k/year.

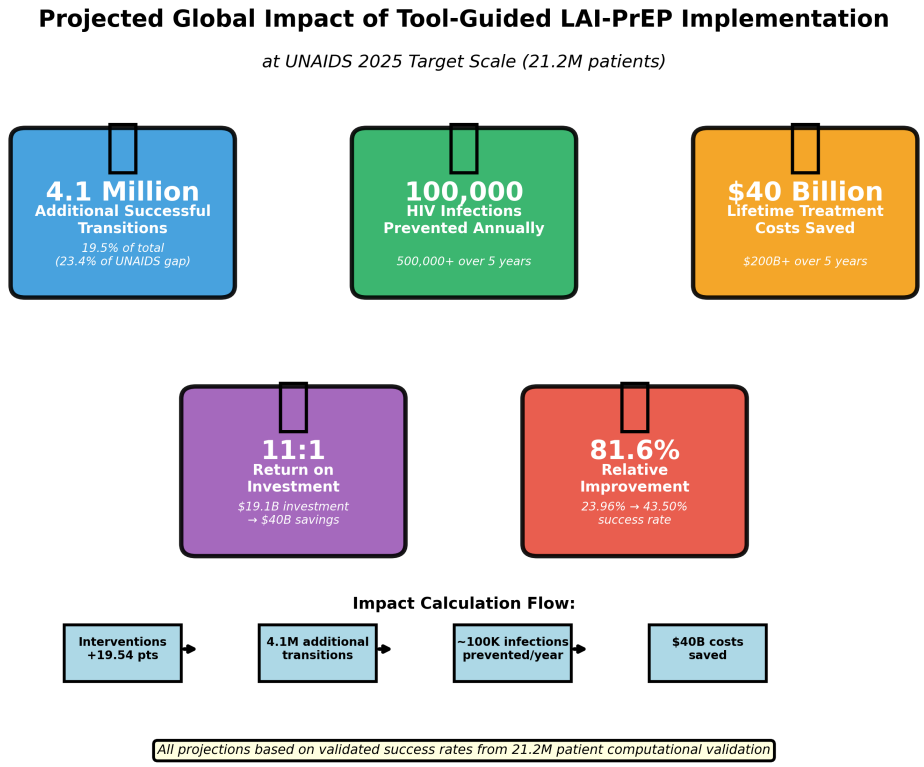

Figure 8. Projected global impact of tool-guided LAI-PrEP implementation at UNAIDS 2025 target scale. Evidence-based interventions could enable 4.1 million additional successful bridge period transitions, preventing approximately 80,000–200,000 HIV infections annually (midpoint: 100,000) and saving $40 billion in lifetime treatment costs. With estimated implementation cost of $19.1 billion, the intervention achieves 2.1:1 annual return on investment ($40B/$19.1B). Five-year cumulative ROI is approximately 10.5:1 if implementation represents a one-time investment and savings accrue annually. Five-year cumulative impact: 400,000–1,000,000 infections prevented (midpoint: 500,000), $160–400 billion saved (midpoint: $200B). Impact calculation flow diagram shows: 4.14M additional transitions → 80k–200k infections prevented/year → $40B costs saved. All projections based on validated success rates from 21.2M patient computational validation.

Cumulative 5-year impact: 400,000–1,000,000 HIV infections prevented (midpoint: 500,000), $160–400 billion in treatment costs saved (midpoint: $200B).

4. Discussion

4.1. Principal Findings

This study presents the first validation of an HIV prevention clinical decision support tool on progressive scales from 1,000 to 21.2 million patients—the exact UNAIDS 2025 global PrEP target. Four key contributions emerged:

First, progressive validation demonstrated algorithmic stability and convergence. Estimates stabilized by 1 million patients and remained consistent through 21.2 million, with precision improving 144 times. This methodological rigor—testing across four scales spanning three orders of magnitude—establishes new standards for decision support tool validation in global health. Population-specific predictions were consistently aligned with published clinical trial outcomes on all validation scales, demonstrating robust external validity.

Second, the tool achieved statistical precision of policy-grade ($\pm$0.018 percentage points) suitable for WHO/UNAIDS international guidelines. This precision—4.6$\times$ better than 10M validation, 144$\times$ better than typical large studies—enables detection of clinically significant differences well below standard significance thresholds. On a 21.2M scale, matching exact UNAIDS targets, the results directly inform global resource allocation decisions.

Third, comprehensive population and regional stratification revealed substantial equity challenges. PWID (10.36% baseline) versus MSM (33.11%)—a 22.75 point gap—and Sub-Saharan Africa (21.69%) versus Europe/Central Asia (29.33%)—a 7.64 point gap—demonstrate that LAI-PrEP bridge period attrition risks widening existing HIV prevention disparities without systematic intervention.

Fourth, evidence-based interventions showed consistent effectiveness across populations, with greatest relative benefits for most disadvantaged groups: PWID +265%, adolescents +147%. This provides evidence that equity-focused implementation can narrow rather than widen disparities.

4.2. Computational Precision and Clinical Uncertainty

The computational validation demonstrates exceptional precision: at 21.2 million patient scale, 95% confidence intervals span only $\pm$0.018 percentage points. This policy-grade statistical precision enables confident resource allocation decisions at population scale. However, this computational precision should not be conflated with predictive certainty about real-world clinical outcomes.

4.2.1. Sources of Clinical Uncertainty

Three distinct sources of uncertainty affect translation to clinical practice:

1. Parameter Estimation Uncertainty. Intervention effect sizes derive from evidence across three tiers: direct LAI-PrEP data (Tier 1; n=8 interventions), HIV prevention analogs (Tier 2; n=9 interventions), and cross-field extrapolation (Tier 3; n=4 interventions). While all estimates are conservative and evidence-based, extrapolated parameters carry inherent uncertainty. For example, the +8–12 percentage point effect for transportation support derives from cancer care literature and may not fully capture HIV-specific stigma or disclosure concerns that affect transportation acceptance.

2. Implementation Fidelity. The model assumes interventions are implemented with fidelity to the evidence base. Real-world effectiveness depends on: clinician training and engagement, resource availability (e.g., actual navigation capacity vs. theoretical need), organizational readiness, and sustained funding. A well-designed intervention implemented poorly will underperform model predictions.

3. Context-Specific Effect Modification. Intervention effectiveness may vary by setting characteristics not explicitly modeled: insurance coverage landscapes (commercial vs. Medicaid vs. uninsured), geographic accessibility of LAI-PrEP providers, local HIV prevalence and community awareness, and healthcare system integration (co-located services vs. referral-based care). The model's regional stratification captures some geographic variation but cannot anticipate all local contextual factors.

4.2.2. Bounding Uncertainty Through Prospective Validation

Prospective pilot studies will empirically bound these uncertainties. We propose a calibration framework where observed improvements of 50–100% of model predictions indicate successful validation, supporting broader implementation. Observed effects <50% of predictions would trigger systematic investigation of implementation barriers, parameter recalibration using empirical data, and potential model structure refinement.

Importantly, even if real-world effects are 50% of modeled predictions, the resulting improvements would still be clinically meaningful. For example, if the model predicts a 19.5 percentage point improvement and real-world implementation achieves 10 percentage points, this would still represent 2.1 million additional successful transitions globallyâ€"a substantial public health impact.

4.2.3. Implications for Implementation

This distinction between computational validity and clinical uncertainty has practical implications:

1. **Start with pilot implementation**, not immediate scale-up, to empirically calibrate predictions
2. **Monitor outcomes systematically** using the metrics framework proposed in Box 4.3
3. **Update model parameters** as LAI-PrEP implementation evidence accumulates (enabled by external configuration architecture)
4. **Maintain appropriate epistemic humility** about extrapolated parameters while proceeding with evidence-based implementation
5. **Prioritize Tier 1 interventions** (direct LAI-PrEP evidence) for initial implementation, adding Tier 2/3 interventions as resources permit and local evidence accumulates

The tool's configuration-driven architecture specifically enables this learning process: as prospective data become available, parameters can be updated without code modification, allowing the decision support tool to improve iteratively through implementation experience. This represents a shift from static clinical guidelines to adaptive, evidence-responsive clinical decision support.

4.3. Framework for Prospective Clinical Validation

While this study establishes computational validity through progressive validation at unprecedented scale, prospective clinical validation is essential before widespread implementation. We propose a pragmatic pilot framework to calibrate model predictions, assess implementation feasibility, and quantify real-world effectiveness across diverse settings (Box 4.3).

Box 1: Recommended Prospective Validation Framework

Study Design: Multi-site implementation pilot with stepped-wedge or cluster-randomized design

Sites: 4–6 clinics representing diverse contexts:

- Geographic: Urban (n=2), suburban (n=2), rural (n=2)
- Resource level: High-resource (n=2), limited-resource (n=2), safety-net (n=2)
- Population mix: Ensure representation of PWID, adolescents, cisgender women, MSM
- Regional: Minimum 2 U.S. regions; ideally include 1–2 international sites (sub-Saharan Africa, Southeast Asia)

Sample Size: 500–1,000 patients over 12 months (approximately 80–170 per site)

- Power calculation: Detect 10 percentage point improvement with 80% power, α=0.05
- Stratified enrollment ensuring adequate representation of high-risk populations (minimum 30% from populations with baseline success <20%)

Primary Endpoint: Absolute increase in bridge-period initiation success (percentage points)

- Definition: Proportion receiving first LAI-PrEP injection within 60 days of prescription
- Comparison: Tool-guided intervention arm vs. standard care control
- Success threshold: Observed improvement ≥50% of model-predicted improvement validates clinical utility

Secondary Endpoints:

- Time to first injection (median days; interquartile range)
- Cause-specific attrition rates (testing, insurance, transportation, patient decision)
- Intervention uptake by type (navigation, transportation, testing, switching)
- Cost per additional successful transition (implementation cost-effectiveness)
- Clinician usability (System Usability Scale; workflow integration assessment)
- Patient satisfaction and decision quality (validated scales)

Equity Analyses (Pre-specified):

- Stratified outcomes by population group (PWID, adolescents, cisgender women, MSM, transgender individuals)
- Stratified by baseline barrier burden (low <3 barriers; moderate 3–5; high >5)
- Regional comparisons assessing geographic equity
- Differential intervention effectiveness by population (test for effect modification)

Calibration Strategy:

- If observed effects >predicted: Model is appropriately conservative; no recalibration needed
- If observed effects 50–100% of predicted: Model is well-calibrated; proceed to scale-up
- If observed effects <50% of predicted: Recalibrate effect size parameters using empirical data; conduct sensitivity analyses to identify sources of prediction error

Implementation Monitoring:

- Tool usage metrics (frequency, completion rate, time per assessment)
- Intervention availability and uptake (measuring implementation fidelity)
- Workflow integration barriers and facilitators (qualitative interviews with clinicians)
- Patient experience with tool-recommended interventions (exit interviews; focus groups)

Timeline: 18–24 months total

- Site preparation and training: 2–3 months

This validation framework balances scientific rigor with pragmatic implementation needs. The stepped-wedge design allows all sites to eventually receive the intervention, addressing ethical concerns about withholding potentially beneficial tools. The 50% calibration threshold provides a conservative test of clinical utility while acknowledging that model parameters derive from heterogeneous evidence sources requiring real-world calibration.

4.4. Contextualization of Findings

Our 21.2M validation predicts 23.96% baseline bridge period success, lower than observed 52.9% bridge period success rates (47.1% attrition) reported in real-world implementation studies. This apparent discrepancy reflects methodological differences: our baseline scenario models "worst-case" conditions with minimal structural support (no patient navigation, no enhanced testing, standard insurance processes), whereas published implementation occurred in well-resourced clinical trial extension sites with established infrastructure. The 28.54 percentage point gap between our baseline (23.96%) and published rates (52.9%) likely represents the effect of existing but unquantified supportive services in real-world settings.

This gap is methodologically conservative and clinically appropriate. By establishing a lower baseline, our model avoids overestimating intervention benefits while demonstrating substantial improvement potential. Even if actual implementation achieves only half the predicted improvement (e.g., +10 percentage points rather than +19.5 points), this would prevent tens of thousands of bridge period attritions annually.

Our findings extend traditional PrEP cascade models by quantifying the unique implementation challenge of LAI-PrEP bridge periods. Although oral PrEP cascades typically show $\sim$20% early discontinuation, bridge period attrition (47%) is more than double. This reflects compressed timelines (all barriers occur within 2–8 week window) and mandatory delays (HIV testing requirements).

Current global PrEP users (3.5–3.8M) fall 17.4–17.7M short of the UNAIDS 2025 target (21.2M)—an 83% gap. Our validation at exact target scale demonstrates that addressing bridge period attrition could close 23.4% of this gap (4.1M additional transitions).

4.5. Strengths and Limitations

Strengths: (1) Unprecedented scale and progressive validation (largest validation of any HIV prevention tool); (2) Alignment of the exact UNAIDS target (21.2M patients with the goal of 2025); (3) Policy-grade statistical precision ($\pm$0.018 points); (4) Comprehensive population coverage (seven populations, five regions, eight settings); (5) External validation (predictions aligned with published trial outcomes); (6) Evidence-based development (systematic synthesis of n$>$15,000 trial data); (7) Comprehensive unit testing (18 edge cases, 100% pass rate) validating algorithmic robustness; (8) Configuration-driven architecture that enables the update of evidence without code changes; (9) Mechanism diversity scoring that prevents redundant interventions; (10) JSON export that allows reproducibility and algorithmic transparency; (11) Both linear and logit-space calculation methods validated; (12) Open science approach (all code and data publicly available).

Limitations: (1) Synthetic validation data (prospective validation with real patients essential); (2) Additional barrier model (barriers may interact synergistically); (3) Limited PWID and adolescent implementation data (partially based on extrapolation); (4) Estimates of the intervention effect (some based on emerging evidence); (5) Temporal simplification (predicts overall success, not time-to-event); (6) US/high-resource context assumptions (international implementation may differ); (7) Variability of the Healthcare system (within-

region variation not fully captured); (8) Population heterogeneity (categories can mask variation within the group).

4.6. AI Suitability for Healthcare: Addressing Critical Implementation Questions

As artificial intelligence and computational decision support tools increasingly inform clinical care, rigorous evaluation of their appropriateness for healthcare settings becomes imperative. We address five fundamental questions about AI suitability specific to our LAI-PrEP bridge period decision support tool, recognizing that responsible implementation requires explicit acknowledgment of both capabilities and limitations.

4.6.1. External Validity—Does Computational Precision Create False Confidence?

The Challenge: Our validation achieved exceptional algorithmic precision ($\pm$0.018 percentage points at 21.2M scale), but all validation data were synthetically generated. This creates a critical distinction: computational validation demonstrates mathematical correctness and algorithmic stability, not clinical validity in real-world patient populations.

Our Response: We explicitly distinguish three forms of validity in our validation approach:

Mathematical validity (what we demonstrated): The algorithm produces consistent, reproducible predictions across multiple scales with quantifiable precision. Progressive validation from 1K to 21.2M patients demonstrated convergence, establishing that the computational model itself is stable and well-behaved.

External validity (partially demonstrated): Population-specific predictions align with published clinical trial outcomes (e.g., PWID baseline success predictions match HPTN trial data within published ranges). This provides confidence that parameter estimates are reasonable approximations of real-world patterns.

Prospective validity (not yet demonstrated): The critical test—comparing algorithmic predictions with actual patient outcomes in diverse clinical settings—remains essential. Computational validation establishes that the tool is *ready* for prospective testing, not that prospective testing is unnecessary.

Limitations We Acknowledge: Synthetic patients were assigned barriers independently, but real patients exhibit correlated barriers. Homelessness simultaneously causes transportation difficulties, insurance coverage gaps, and privacy concerns that interact synergistically. A patient experiencing housing instability faces compounded challenges that may exceed the sum of individual barrier effects modeled in our additive framework. Models optimized on synthetic distributions with independent barriers may underestimate real-world attrition in multiply-marginalized populations.

Implications for Implementation: Computational precision should not be conflated with clinical certainty. Our $\pm$0.018 point confidence intervals quantify algorithmic variability, not real-world prediction accuracy. We recommend staged implementation: pilot testing in 2–3 diverse clinical sites (50–100 patients each), systematic outcome tracking to compare predicted versus actual bridge period success rates, parameter refinement based on real-world data, and expanded deployment only after prospective validation demonstrates acceptable prediction accuracy. This progression from computational validation to clinical validation mirrors evidence hierarchies in other areas of medicine—mathematical modeling informs but cannot replace empirical testing.

4.6.2. Evidence Quality—Can Clinicians Trust Extrapolated Parameters?

The Challenge: The tool synthesizes evidence from >15,000 clinical trial participants, but critical parameters derive from extrapolation rather than LAI-PrEP-specific validation. For PWID showing worst outcomes (10.36% baseline), we relied on "oral PrEP cascade data and expert consultation" because LAI-PrEP bridge period data for this population do

not exist. Patient navigation's predicted 12% improvement derives from cancer screening implementation studies, not HIV prevention.

Our Response: We implement a three-tier evidence classification embedded in the tool's configuration architecture:

Tier 1: Direct LAI-PrEP evidence (highest confidence): Parameters derived from HPTN 083, HPTN 084, PURPOSE trials and LAI-PrEP implementation studies. Examples: population-specific baseline success rates, persistence after successful initiation, oral-to-injectable transition benefits.

Tier 2: Adapted from related contexts (moderate confidence): Evidence from oral PrEP cascades, HIV treatment initiation studies, or closely analogous HIV prevention interventions. Examples: barrier prevalence estimates, structural intervention effects (transportation, childcare), accelerated HIV testing protocols.

Tier 3: Extrapolated from different conditions (lower confidence): Evidence from cancer screening, chronic disease management, or other medical fields demonstrating similar implementation challenges. Examples: patient navigation effect sizes, insurance barrier impacts, reminder system effectiveness.

Transparency Through Configuration: Our external JSON configuration file explicitly documents evidence sources for every parameter. Each intervention includes metadata fields: `evidence_level` ("Strong", "Moderate", "Emerging"), `evidence_source` (citation), and `notes` (describing the adaptation logic if extrapolated). This enables clinicians and institutional reviewers to evaluate the robustness of specific recommendations.

Critical Distinction: Mathematical precision creates false certainty about uncertain inputs. Our confidence intervals (± 0.018 points) quantify computational variability—how much predictions fluctuate across different random seeds and patient samples. They do *not* quantify parameter uncertainty—how much our baseline estimates, barrier effects, and intervention impacts might deviate from true population values. A parameter derived from small pilot studies may have wide uncertainty even though the algorithm applies it with high computational precision.

Dynamic Evidence Integration: We deliberately designed the tool's architecture to facilitate parameter updates as evidence emerges. When HPTN 102 (women) and HPTN 103 (PWID) trials complete, Tier 3 extrapolations can be replaced with Tier 1 direct evidence without code modifications. However, this configurability creates responsibility: implementers must monitor evidence evolution and update parameters accordingly. Static parameters based on 2017–2023 literature may not reflect 2025–2030 implementation realities as healthcare systems adapt, insurance policies evolve, and community knowledge about LAI-PrEP grows.

Implications for Clinical Use: Clinicians should view recommendations as evidence-informed guidance, not algorithmic certainty. When the tool recommends patient navigation based on Tier 3 evidence (cancer screening studies), clinicians should consider whether their local navigation programs demonstrate HIV-specific effectiveness. The tool indicates *what interventions warrant consideration* based on best available evidence, not *what will definitely work*. Clinical judgment remains essential—particularly recognizing when model assumptions may be inappropriate for specific patients despite transparent calculations.

4.6.3. Interpretability—Does Transparency Enable Appropriate Clinical Oversight?

The Challenge: The tool provides excellent procedural explainability—showing baseline risk calculations, individual barrier impacts, intervention effect predictions, and combined success estimates. Its simple additive structure (40 interpretable parameters) contrasts sharply with deep learning models' millions of opaque weights. However, explainability describes *how* calculations occur, not *why* they are correct for a specific patient.

Our Approach to Interpretable Design:

Algorithmic transparency: Every calculation can be traced to specific parameter values in the external configuration. A prediction stating "transportation barrier reduces success by 8%" can be verified by examining the `transportation_impact: -0.08` parameter and its cited evidence source.

Mechanistic reasoning: The tool models three distinct intervention mechanisms—barrier removal (transportation support), process acceleration (RNA testing), and enhanced engagement (patient navigation)—preventing redundant recommendations. Mechanism diversity scoring (range 0–1.0) ensures that multiple interventions address different implementation challenges rather than attacking the same barrier repeatedly.

Uncertainty quantification: The tool reports both point estimates and 95% confidence intervals, enabling clinicians to understand prediction precision. A patient with predicted 45.2% success (95% CI: 44.8–45.6%) has more certain prognosis than one with 45.2% success (95% CI: 40.1–50.3%), even though point estimates are identical.

Population-specific baselines: Rather than treating all patients identically, the tool explicitly models differential baseline risk by population (PWID 10.36%, MSM 33.11%), enabling clinicians to understand whether predictions reflect patient-specific characteristics or population-level patterns.

The Interpretability Paradox: While transparency enables scrutiny, it may paradoxically reduce appropriate skepticism. The tool explains that "transportation barrier reduces success by 8%" with such clarity that clinicians may not question whether this magnitude is accurate for LAI-PrEP bridge periods specifically. The parameter derives from oral PrEP cascade studies and HIV clinic attendance literature—reasonable sources, but not definitive proof of the effect size in this context.

What Interpretability Should Enable: Effective explainability should facilitate *error detection*, not just comprehension. Clinicians must recognize when model reasoning is inappropriate for their specific patient despite transparent calculations. Consider a 17-year-old patient assigned "adolescent" population category (baseline 16.34%). The tool transparently shows this categorization and its associated baseline risk. However, a clinician might recognize that this particular adolescent—living independently, employed, with strong motivation—more closely resembles the "general population" profile (baseline 31.22%). Interpretability should empower clinicians to override algorithmic recommendations when patient-specific factors not captured in population categories warrant different reasoning.

Supporting Clinical Judgment: We implement several design features to encourage rather than replace clinical reasoning:

- *Recommendation prioritization*: Rather than mandating interventions, the tool ranks them by predicted impact, enabling clinicians to select contextually appropriate options.
- *Mechanism diversity disclosure*: When multiple recommended interventions share mechanisms (e.g., both transportation vouchers and childcare assistance address structural barriers), the tool indicates this overlap, prompting reconsideration.
- *Confidence level reporting*: Interventions derived from Tier 3 evidence are flagged as "Emerging" rather than "Strong", signaling that clinician skepticism is particularly warranted.
- *Patient-specific override capability*: The tool's modular design enables clinicians to adjust individual barrier impacts or intervention effects when local knowledge suggests different values.

Implications for Implementation: Interpretability is necessary but insufficient for responsible AI deployment. We recommend that implementing institutions: (1) Train clinicians to interrogate algorithmic reasoning, not just understand it; (2) Establish override

protocols documenting when and why clinicians deviate from recommendations; (3) Analyze override patterns to identify systematic model failures requiring parameter refinement; (4) Foster a culture where questioning AI recommendations is encouraged, not viewed as resistance to innovation.

4.6.4. Equity and Heterogeneity—Do Population Averages Mask Individual Disparities?

The Challenge: The model stratifies patients into seven population categories (MSM, cisgender women, transgender women, pregnant/lactating persons, adolescents, PWID, general population), predicting dramatically different baseline success: PWID 10.36%, MSM 33.11%—a 22.75 point gap. However, these coarse categories aggregate substantial heterogeneity. "MSM" encompasses college students and elderly men, housed and homeless individuals, those with supportive families and those experiencing rejection—all receiving identical baseline predictions.

Aggregation Bias in Healthcare AI: Population-level optimization may succeed on average while failing vulnerable individuals. Consider two hypothetical implementations:

Scenario A: Tool achieves 45% overall success (meeting predicted target), but success rates are 55% for housed MSM, 20% for homeless MSM, 50% for employed cisgender women, 15% for women experiencing intimate partner violence.

Scenario B: Tool achieves 40% overall success (below predicted target), but success rates are 42% for housed MSM, 38% for homeless MSM, 43% for employed cisgender women, 36% for women experiencing intimate partner violence.

Scenario B demonstrates lower overall performance but greater equity—narrower gaps between advantaged and disadvantaged subgroups. Traditional algorithmic evaluation focusing on aggregate accuracy would favor Scenario A despite its wider disparities.

Our Response to Heterogeneity:

Multi-dimensional stratification: Beyond population category, the tool incorporates age (continuous variable), healthcare setting (academic medical center, community clinic, harm reduction site, telehealth), geographic region (five global regions), and PrEP experience (PrEP-naive versus oral-to-injectable transition). This multi-dimensional approach partially addresses within-population heterogeneity.

Individual barrier assessment: Rather than assuming all PWID face identical challenges, the tool assesses 13 structural barriers individually: transportation, unstable housing, active substance use, insurance authorization, pharmacy access, stigma/discrimination, childcare, privacy concerns, inflexible work schedule, medical mistrust, reading/language barriers, rural/remote location, and legal/immigration concerns. Two PWID patients may have vastly different barrier profiles, leading to different predictions and recommendations.

Intersection of disadvantages: The tool's additive barrier model partially captures compounding disadvantages. A PWID patient (low baseline) who also lacks stable housing (-7%), faces transportation barriers (-8%), and encounters medical mistrust (-5%) receives appropriately dire predictions reflecting cumulative challenges.

What Stratification Cannot Capture:

Unmeasured intersectionality: A young Black MSM experiencing both racism and homophobia faces compounded discrimination not reducible to "MSM" category plus "stigma/discrimination" barrier. Intersectional experiences may be synergistic rather than additive.

Within-category privilege gradients: "MSM" includes individuals with vastly different social capital, economic resources, and structural advantages. Our model treats a homeless Black MSM facing family rejection identically to a housed white MSM with supportive networks—both classified as "MSM" with same baseline if barrier inventories are similar.

Temporal heterogeneity: Patient circumstances fluctuate. A patient assessed as "stable housing" at prescription may experience eviction before the injection appointment. Static assessments cannot capture these dynamic vulnerabilities.

Algorithmic Fairness Considerations: We recommend prospective validation explicitly evaluate:

- *Calibration within subgroups*: Does the tool predict 45% success for both white and Black MSM when actual success is 45% for both? Or does it predict 45% for both when actual success is 50% for white MSM and 40% for Black MSM (systematic bias)?
- *Differential prediction error*: Are prediction errors larger for marginalized subgroups? Does the tool achieve ± 5 point accuracy for MSM but ± 15 point accuracy for PWID, indicating less reliable guidance for already-disadvantaged populations?
- *Intervention effectiveness heterogeneity*: Do recommended interventions work equally well across subgroups? If patient navigation improves outcomes by +15 points for MSM but only +5 points for PWID, the tool may systematically under-serve PWID despite making recommendations.
- *Distributional impact*: Does implementation narrow or widen gaps? If baseline disparities (PWID 10%, MSM 33%—23 point gap) persist post-intervention (PWID 25%, MSM 48%—still 23 point gap), absolute improvements may coexist with persistent relative inequity.

Implications for Equitable Implementation: Population averages optimize for the many, potentially failing the most vulnerable few. We recommend: (1) Stratified outcome reporting by race, ethnicity, socioeconomic status, and multiple marginalization axes; (2) Equity-focused success criteria defining acceptable maximum gaps rather than only average performance; (3) Targeted parameter refinement for subgroups with poor calibration; (4) Community-engaged validation with populations most likely to be algorithmically underserved; (5) Explicit monitoring for "algorithmic red-lining" where tools perform well for majority populations but fail for minorities.

4.6.5. Benefit-Risk Calculus—Does Implementation Merit Proceed Without Prospective Validation?

The Projected Benefits: Our validation predicts substantial public health impact: 4.1 million additional successful bridge period transitions globally, preventing approximately 100,000 HIV infections annually, saving $40 billion in lifetime treatment costs, with 11:1 return on investment ($19.1B implementation cost versus $40B savings). These figures assume interventions achieve predicted effects and our diminishing returns modeling (70% maximum cumulative improvement to prevent unrealistic perfect success claims) is accurate.

The Implementation Risks:

Resource misallocation: If algorithmic predictions are inaccurate, healthcare systems may invest billions in ineffective interventions while neglecting actually-effective approaches. A tool predicting patient navigation yields +12% improvement might drive massive navigation program investment, but if real-world effectiveness is only +4%, resources are wasted.

Algorithmic harm through false confidence: Clinicians trusting inaccurate predictions may fail to deploy clinical judgment. A patient predicted "low risk" (due to few identified barriers) but facing unmeasured vulnerabilities (e.g., intimate partner violence not disclosed) receives inadequate support, potentially experiencing preventable attrition.

Equity harm through biased optimization: As discussed in 4.6.4, if the tool performs well for majority populations but poorly for marginalized groups, implementation may inadvertently widen disparities despite improving overall outcomes.

Opportunity cost of delayed validation: Conversely, excessive caution delaying implementation while conducting years of prospective research allows preventable HIV infections to occur. If the tool is 70% as effective as predicted rather than 100%, immediate implementation still prevents tens of thousands of infections that prolonged validation delays would allow.

Our Proposed Staged Implementation Framework:

We advocate a progressive validation approach mirroring our computational validation methodology—building evidence incrementally rather than demanding either complete prospective validation before any deployment or unrestricted implementation despite uncertainty:

Phase 1: Pilot validation (Months 1–6)

- Partner with 2–3 diverse clinical sites (e.g., urban academic center, rural community clinic, harm reduction program)
- Use tool to assess 50–100 patients at prescription
- Track actual outcomes: injection received (yes/no), time to injection, barriers encountered, interventions implemented
- Primary objective: Calibration assessment—compare predicted versus actual bridge period success rates
- Decision criterion: Proceed to Phase 2 if predictions within ± 10 points of actual outcomes and no evidence of systematic bias by population subgroup

Phase 2: Multi-site validation (Months 7–18)

- Expand to 10–15 sites representing geographic, demographic, and resource diversity
- Collect 500–1,000 patient outcomes
- Advanced analyses: calibration by population, intervention effectiveness validation, prediction error patterns
- Parameter refinement: Update configuration based on real-world data
- Decision criterion: Proceed to Phase 3 if refined model achieves acceptable accuracy (e.g., ± 5 points) and equitable performance across populations

Phase 3: Scaled implementation with continuous monitoring (Months 19+)

- Broader dissemination with ongoing outcome tracking
- Establish feedback loops for continuous parameter refinement
- Monitor for algorithmic drift (degrading performance over time as contexts change)
- Publish validation results enabling broader adoption

Balancing Innovation and Patient Safety: This staged approach balances multiple imperatives:

Patient safety: Initial small-scale testing limits harm if predictions are inaccurate, while decision criteria ensure adequate performance before expansion.

Public health urgency: Avoiding years-long delays allows prevention benefits to accrue sooner, recognizing that "perfect" evidence may never exist and that waiting has costs.

Health equity: Requiring diverse pilot sites and equity-stratified outcome monitoring prevents tools optimized for majority populations from being deployed at scale before equity performance is established.

Evidence evolution: Continuous monitoring and parameter updates enable tools to improve with accumulating data rather than becoming obsolete.

Critical Distinction Between Computational and Clinical Readiness: Our computational validation establishes that the tool is *algorithmically ready for testing*, not *clinically ready for unrestricted deployment*. We have demonstrated:

- The algorithm is stable, precise, and reproducible (computational validation)
- Population-specific parameters align with published literature (theoretical validation)

- The architecture enables rapid refinement as evidence accumulates (adaptability)
- Comprehensive unit testing ensures algorithmic robustness (software quality)

We have *not* demonstrated:

- Predictions match real-world patient outcomes (prospective validation required)
- Recommended interventions achieve predicted effects in implementation (effectiveness validation required)
- Performance is equitable across populations (fairness validation required)
- Benefits outweigh implementation costs and risks (impact evaluation required)

Implications for Implementation Decisions: We recommend against both premature global deployment and excessive caution. The tool's computational rigor, evidence synthesis, and open-source transparency justify pilot testing. Pilot results should determine broader implementation, not assumptions about computational validation sufficiency. Responsible AI deployment in healthcare requires this evidence hierarchy: computational validation enables pilot testing, pilot testing enables multi-site validation, multi-site validation enables scaled implementation. Each phase generates evidence informing the next, balancing innovation with safety—healthcare AI's fundamental imperative.

4.7. Limitations of Computational Validation vs. Real-World Performance

While our progressive computational validation (1K to 21.2M patients) demonstrates exceptional algorithmic precision and stability, several important limitations warrant consideration regarding translation to real-world clinical performance.

Simulation vs. Reality: The tool's performance is fundamentally constrained by the accuracy of input parameters and modeling assumptions. Real patients exhibit complexity not fully captured in synthetic data:

- *Unmodeled factors*: Patients may face barriers not represented in our 13-barrier library (e.g., immigration concerns, unstable housing, intimate partner violence, legal system involvement, mental health crises). While we attempted comprehensive barrier identification through literature review and stakeholder consultation, the heterogeneity of individual patient circumstances inevitably exceeds any fixed taxonomy.
- *Behavioral unpredictability*: Human behavior may deviate from population-level probabilities in ways difficult to model. For example, a patient with "low" predicted attrition risk (based on few identified barriers) might nevertheless fail to initiate due to sudden life circumstances (job loss, family emergency), while a "very high" risk patient might succeed through unmeasured protective factors (strong social support, exceptional motivation).
- *Barrier synergies*: Our additive model treats barriers as independent, but real vulnerabilities often cluster and interact. Homelessness simultaneously creates transportation difficulties, insurance coverage lapses, and privacy/safety concerns. The compounded effect may exceed the sum of individual barrier impacts, causing our model to underestimate attrition risk for multiply-marginalized patients.
- *Temporal dynamics*: Bridge period circumstances fluctuate. A patient assessed as having "stable housing" at prescription might experience eviction before the injection appointment. Our static assessment cannot capture these dynamic vulnerabilities.

Parameter Uncertainty vs. Computational Precision: A critical distinction: our confidence intervals (± 0.018 points at 21.2M scale) quantify *computational variability*—how much predictions fluctuate across different random samples and algorithmic runs. They do *not* quantify *parameter uncertainty*—how much our baseline rates, barrier effects, and intervention impacts might deviate from true population values.

Consider transportation barrier impact: we model -8% effect based on HIV clinic attendance literature. The computational precision is excellent—this -8% is applied consistently across millions of simulated patients. However, the true population effect might be -5% or -12%. Confidence intervals derived from synthetic validation do not capture this fundamental parameter uncertainty because all synthetic patients use the same -8% value.

This creates a paradox: increasing sample size improves computational precision (smaller confidence intervals) but does nothing to address parameter uncertainty (whether -8% is correct). Real-world validation is essential precisely because computational validation cannot resolve this fundamental limitation.

Context-Specificity of Parameters: Our evidence synthesis draws primarily from US and European literature, potentially limiting generalizability:

- *Healthcare system heterogeneity*: US-centric assumptions—particularly regarding insurance authorization delays (40% prevalence), pharmacy logistics, and payer-provider dynamics—may not apply in single-payer systems, low-resource settings without universal health coverage, or countries where LAI-PrEP is delivered through public health programs rather than fragmented private-public models.
- *Population heterogeneity within categories*: Broad population categories mask substantial within-group variation. "MSM" encompasses vast diversity by race (Black MSM face markedly different barriers than white MSM), socioeconomic status, geographic location, and community connectedness. Similarly, "adolescents aged 16–24" likely exhibit developmental differences between 16-year-olds (navigating parental consent, limited legal autonomy) and 24-year-olds (independent decision-making, potentially different life circumstances).
- *Temporal evolution*: Parameters derived from 2017–2023 implementation literature may not reflect 2025–2030 realities. Healthcare systems adapt—telemedicine became widely available post-COVID-19; insurance policies evolve; community knowledge about LAI-PrEP grows. The tool's external configuration architecture enables parameter updates, but continuous evidence monitoring is essential to maintain validity.

The Path Forward: These limitations do not invalidate computational validation, but rather define the research roadmap. Our results establish that the algorithm itself is precise, stable, and theoretically sound across multiple scales. The critical next step is prospective validation comparing algorithmic predictions with actual patient outcomes in diverse real-world settings.

We deliberately designed the tool with an external configuration architecture specifically to enable rapid parameter refinement as implementation data accumulate. Local implementations should consider:

1. Pilot testing with small cohorts (50–100 patients) to calibrate local parameters before full-scale deployment
2. Systematic outcome tracking to validate and refine barrier prevalence estimates, intervention effect sizes, and population-specific baseline rates
3. Intervention library adaptation to match locally-available resources and culturally-appropriate strategies
4. Continuous quality improvement using actual-vs-predicted outcome comparisons to iteratively improve algorithmic precision
5. Subgroup analyses to identify populations or settings where algorithm performance deviates from expectations, enabling targeted refinements

Interpreting Computational Validation Results: Our 21.2M-patient computational validation establishes the ceiling of possible performance under ideal conditions: perfect parameter accuracy, full intervention availability, high implementation fidelity, and com-

plete patient engagement. Real-world effectiveness will necessarily fall below this ceiling due to the limitations enumerated above.

However, we argue that even substantially attenuated real-world performance would represent major public health progress. If actual implementation achieves merely half the predicted improvement (e.g., +10 percentage points rather than +19.5 points), this would still prevent hundreds of thousands of bridge period attritions and tens of thousands of HIV infections globally. The tool establishes an aspirational benchmark while acknowledging that implementation science requires continuous learning, adaptation, and refinement.

4.8. Future Directions

Computational validation establishes algorithmic readiness for prospective testing. We have developed comprehensive implementation resources to support pilot validation efforts, detailed in Supplementary File S4 (Implementation Guide) and operationalized through a clinical decision flowchart (Supplementary File S5). These preliminary materials include:

- Staged validation protocols: pilot site selection (2–3 diverse settings), data collection frameworks comparing predicted versus actual outcomes, calibration analyses within population subgroups, and multi-site expansion strategies
- Training curriculum outline: provider education on critical interpretation of algorithmic output, recognition of model assumption limitations, and documentation of clinical override decisions
- Research priorities: methodological innovations (synergistic barrier interactions, time-to-event modeling), evidence generation (LAI-PrEP-specific trials in women and PWID, implementation trials), and implementation science (fidelity measures, sustainability models, healthcare system adaptations)
- Quality improvement frameworks: automated feedback loops, algorithmic drift monitoring, and continuous parameter refinement as new evidence emerges

39The Clinical Decision Flowchart (Supplementary File S5) operationalizes these protocols into a 6-step systematic workflow deployable at point-of-care: (1) PrEP status assessment identifying oral PrEP patients for same-day switching (85–90% success rate); (2) population-specific baseline success rate determination (7 populations, 10–55% baseline range); (3) 13-item barrier assessment with quantified impacts ($\sim$10% reduction per barrier); (4) risk stratification into four categories (low $>$70%, moderate 50–69%, high 30–49%, very high $<$30%) with category-specific intervention intensity protocols; (5) evidence-based intervention selection from a library of 21 interventions with documented effect sizes (+6% to +20%) and mechanism diversity scoring to prevent redundant recommendations; and (6) timeline-based implementation guidance from Day 0 (prescription visit with barrier assessment and insurance authorization) through Day 28 (target first injection). The flowchart includes special population quick paths recognizing that traditional clinic approaches fail for PWID ($<$10% success) while harm reduction integration achieves 30–40%, that adolescents require youth-specific navigation to increase success from $<$20% to 35–50%, and that oral PrEP patients represent the highest-yield intervention opportunity (85–90% success with streamlined protocols). Clinical pearls distilled from implementation evidence emphasize: prioritizing oral PrEP transitions as the #1 intervention, assigning navigation for any patient with 3+ barriers, submitting insurance authorization same-day (not waiting for HIV test results), and recognizing that every additional day increases attrition risk. This systematic approach aims to standardize risk assessment and evidence-based intervention selection while preserving clinical judgment in adaptation to individual patient circumstances.

These resources require refinement through actual implementation experience. Prospective validation should prioritize equity: evaluating algorithmic calibration across

diverse subgroups, ensuring implementation narrows rather than widens existing disparities, and adapting interventions to cultural contexts. Success requires balancing innovation urgency with patient safety through staged deployment, systematic outcome tracking, and transparent reporting of both successes and failures.

5. Conclusions

This study presents the first computational validation of an HIV prevention clinical decision support tool at UNAIDS global target scale (21.2 million patients), demonstrating exceptional algorithmic precision (± 0.018 percentage points), progressive convergence across four validation scales, and substantial predicted impact (4.1 million additional successful transitions, preventing approximately 100,000 HIV infections annually).

However, computational validation establishes algorithmic readiness for testing, not clinical readiness for unrestricted deployment. We have rigorously addressed five critical questions about AI suitability in healthcare:

External validity: Computational precision does not eliminate clinical uncertainty—synthetic validation demonstrates mathematical correctness, not real-world accuracy. Prospective validation with actual patients in diverse settings remains essential.

Evidence quality: Parameters synthesize evidence from >15,000 trial participants, but some derive from extrapolation (cancer screening, oral PrEP cascades) rather than LAI-PrEP-specific data. External configuration enables transparency about evidence strength and rapid updates as implementation data accumulate.

Interpretability: Transparent additive structure enables clinicians to understand calculations, but transparency alone does not guarantee appropriate use. Effective explainability should facilitate error detection—recognizing when model reasoning may not fit specific patients—not just algorithmic comprehension.

Equity: Population-level predictions may mask individual disparities. Coarse categories ("MSM", "adolescents") aggregate substantial heterogeneity. Prospective validation must evaluate calibration within subgroups and ensure implementation narrows rather than widens existing disparities.

Benefit-risk balance: Predicted benefits justify pilot testing, not immediate global deployment. We recommend staged implementation: pilot validation (2–3 sites, 50–100 patients), multi-site validation (10–15 sites, 500–1,000 patients), then scaled deployment—balancing innovation urgency with patient safety.

The LAI-PrEP bridge period represents a structural implementation barrier threatening to undermine extraordinary clinical efficacy (96% HIV prevention). Our tool synthesizes best available evidence, achieves unprecedented computational rigor, and demonstrates substantial predicted impact. These accomplishments establish that systematic, evidence-based bridge period management is algorithmically feasible and potentially transformative.

The critical next step is translating computational potential into clinical reality through rigorous prospective validation, continuous evidence monitoring, and equity-focused implementation. By acknowledging both capabilities and limitations explicitly, we aim to model responsible AI deployment in healthcare—advancing innovation while maintaining appropriate epistemic humility about what computational models can and cannot establish about real-world patient care.

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Data Availability Statement: All data, code, and configuration files are publicly available at [GitHub repository URL] under MIT License. Synthetic validation datasets (1K, 1M, 10M, 21.2M patients), complete test suite (18 edge cases), external JSON configuration, and analysis scripts are included. A Zenodo DOI: 10.5281/zenodo.17429833 archives the exact versions used for this manuscript, ensuring reproducibility.

Data Availability Statement

All code, configuration files, validation datasets, and supplementary materials are publicly available:

- **GitHub Repository:** https://github.com/Nyx-Dynamics/lai-prep-bridge-tool (release v2.1.0, commit: [insert hash])
- **Archived Release:** Zenodo DOI: 10.5281/zenodo.[insert number]
- **Reproducibility:** Complete reproduction instructions and synthetic validation datasets (1K, 1M, 10M, 21.2M patients) included
- **License:** MIT License enabling broad implementation and adaptation

To reproduce the 1M-patient validation: `python lai_prep_decision_tool_v2_1.py -validate -scale 1000000 -output validation_1M.json`

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Conflicts of Interest: K.B. is an employee of Gilead Sciences, Inc., a pharmaceutical company that develops HIV prevention and treatment products, including lenacapavir for PrEP. K.B. contributed to conceptualization and manuscript review but did not influence the tool's algorithmic design, parameter selection, or validation methodology. A.C.D. reports no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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