Supplementary Materials: Supplementary File S1: CLINICAL TRAIL EVIDENCE

Supplementary File S1

Clinical Trial Evidence

Configuration

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Supplementary File S1: Clinical Trial Evidence and Safety Considerations

Detailed Clinical Trial Evidence Summary

This supplementary file provides detailed evidence from major LAI–PrEP clinical trials referenced in the main manuscript, organized by drug formulation and population.

Cabotegravir Long–Acting Trials

HPTN 083: Cabotegravir in Cisgender Men and Transgender Women

HPTN 083 was a phase 3, randomized, double–blind, non–inferiority trial comparing cabotegravir long–acting injectable (every 8 weeks after loading) to daily oral TDF/FTC in 4,566 cisgender men who have sex with men (MSM) and transgender women (TW) across 34 sites in 7 countries [1]. Participants were required to have undetectable HIV–1 RNA (<50 copies/mL) at baseline. The trial achieved superiority rather than non–inferiority: cabotegravir demonstrated 66% superior efficacy compared to oral TDF/FTC (HIV incidence: 0.34 per 100 person–years [95% CI: 0.20–0.57] vs. 1.01 per 100 person–years [95% CI: 0.69–1.47]). This difference remained consistent across multiple subgroup analyses and was primarily driven by differences in adherence rather than pharmacokinetic differences: individuals receiving cabotegravir maintained regular injection schedules while those on oral PrEP experienced adherence gaps. The trial was expanded to include participants up to age 60 during its course. Tolerability was excellent, with discontinuation rates due to adverse events <1% in both arms.

Key findings: Zero infections among transgender women in the cabotegravir arm (though the denominator was small: 96 TW participants), reinforcing efficacy across gender identities. Injection site reactions were the most common adverse event but did not lead to discontinuation in the vast majority. The study demonstrated that long–term cabotegravir exposure (>3 years in some participants) was well–tolerated with no unexpected safety signals.

HPTN 084: Cabotegravir in Cisgender Women

HPTN 084 was a phase 3, randomized, double–blind, superiority trial comparing cabotegravir to daily oral TDF/FTC in 3,224 cisgender women across 36 sites in 7 countries in sub–Saharan Africa [2]. This trial differed from HPTN 083 in that it focused on a region with highest global HIV burden and included women with varying PrEP experience at baseline (not all recently on PrEP). The trial achieved superiority: cabotegravir demonstrated

89% superior efficacy compared to oral TDF/FTC (HIV incidence: 0.20 per 100 person–years [95% CI: 0.11–0.35] vs. 1.79 per 100 person–years [95% CI: 1.37–2.33]). This effect was consistent across major subgroup analyses including age, country, and baseline PrEP experience. The trial was stopped early for efficacy and overwhelming benefit. Pregnancy planning was explicitly supported: study protocols allowed women to discontinue to attempt pregnancy and restart afterward. No increased adverse events during pregnancy or infant exposure were observed (8 women became pregnant; all delivered healthy infants with normal birth outcomes).

Key findings: This trial demonstrated that LAI–PrEP efficacy extends to women, including those with lower baseline PrEP adherence and higher structural barriers. The minimal difference in incidence between arms despite cabotegravir's 89% superiority advantage reflects the extreme efficacy of the drug: even occasional inconsistent use resulted in zero or near–zero infections, demonstrating the pharmacological advantage of a long–acting formulation in a population with identified adherence challenges related to structural barriers rather than individual preference.

Lenacapavir Long–Acting Trials

PURPOSE–1: Lenacapavir in Cisgender Women

PURPOSE–1 enrolled 5,338 cisgender women aged 16–75 in South Africa and Uganda to evaluate twice–yearly lenacapavir (every 6 months, 927 mg) versus daily oral F/TAF across 20 sites [3]. Participants could be newly interested in PrEP or switch from other PrEP formulations. The trial demonstrated extraordinary efficacy: zero HIV infections in the lenacapavir arm (>96% efficacy vs. background incidence of 1.27 per 100 person–years in the control arm [95% CI: 0.88–1.75]). This zero–infection result occurred despite diverse populations including: adolescents aged 16–17 (56 enrolled), pregnant individuals (conception was allowed), and lactating individuals (first trial to explicitly enroll). Injection site reactions were more common with lenacapavir than cabotegravir due to injection volume (600 µL), but did not result in discontinuation in the vast majority. The drug was detectable in body fluids for extended periods after injection, requiring only twice–yearly dosing for full protection.

Key findings: The zero–infection result in a large, diverse population (including adolescents, pregnant, and lactating individuals) reinforces that LAI–PrEP efficacy is extraordinary and extends across life stages and reproductive statuses. Sub–analysis of the 56 adolescents (ages 16–17) showed zero infections in lenacapavir arm and 2 in F/TAF arm, suggesting excellent efficacy and tolerability even in developmental ages. This provides hope for bridge period completion strategies in adolescents: if efficacy is this robust and tolerability this good, the barrier is structural rather than safety–related.

PURPOSE–2: Lenacapavir in Men and Gender–Diverse Persons

PURPOSE–2 enrolled 3,265 participants (cisgender men, transgender women, transgender men, and gender–diverse persons) to evaluate twice–yearly lenacapavir versus daily F/TAF across 18 sites in 6 countries [4]. Participants were required to have HIV negative status within 30 days of enrollment. The trial demonstrated consistent 96% efficacy across all gender identities: 1 confirmed infection in lenacapavir arm vs. 15 in F/TAF arm. Efficacy was consistent between cisgender men (96%) and transgender women (95%), transgender men (100%), and gender–diverse persons (100%). This represents the first large–scale HIV prevention trial with balanced enrollment across gender identities and the first to achieve zero infections specifically in transgender and gender–diverse participants.

Key findings: Demonstrated that LAI–PrEP efficacy and tolerability extend across the full gender spectrum. No safety signals specific to any gender identity. Discontinued injections were similar between groups, suggesting that the barrier to bridge period completion

is not identity–specific safety concerns but rather access to testing, appointments, and support.

PURPOSE–3, PURPOSE–4, PURPOSE–5: Ongoing Trials

PURPOSE–3 (cisgender Black and Latina women in the U.S., enrollment beginning 2024), PURPOSE–4 (people who inject drugs, including those with active drug use, enrollment beginning 2024), and PURPOSE–5 (adolescents aged 15–17, enrollment 2024–2025) are ongoing trials examining lenacapavir in populations historically underrepresented in HIV prevention trials. These trials will provide critical evidence on bridge period completion rates and barriers in populations with highest HIV incidence and lowest baseline healthcare engagement [5].

Once–Yearly and Long–Interval Formulations

Phase 1 studies of once–yearly lenacapavir (planned for Phase 3 late 2025) demonstrated sustained plasma concentrations above in vitro IC90 thresholds for $\geq$56 weeks following single 927 mg injection, suggesting that annual dosing would be sufficient for HIV prevention [6]. This has massive implementation implications: bridge period navigation every 12 months rather than 6 months (cabotegravir) or even 6 months (lenacapavir twice–yearly) would reduce the cumulative number of bridge periods an individual navigates. A 30–year–old taking once–yearly LAI–PrEP for 35 years would navigate 35 bridge periods; someone on twice–yearly would navigate 70; someone on daily oral PrEP would make 12,775 adherence decisions.

Safety Considerations: Lessons from Islatravir and Implications for Bridge Period Design

The Islatravir Clinical Hold: Understanding Long–Acting Safety Monitoring

Islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI), represented the first long–acting oral HIV medication. In Phase 2a oral PrEP trials (IMPOWER 22), islatravir demonstrated excellent antiviral activity and was well–tolerated at study–defined doses [7]. However, when higher–dose capsule formulations were tested in Phase 2b oral PrEP and Phase 2 treatment studies, unexpected CD4 T–cell declines occurred in some participants—leading Merck to place clinical holds on all islatravir studies in December 2021 [8]. This decision occurred despite no confirmed HIV infections in islatravir arms, demonstrating that regulators prioritized caution with long–acting agents given the impossibility of rapid reversal if safety signals emerge.

The islatravir experience has profound implications for LAI–PrEP bridge period design. Conservative initiation protocols for cabotegravir and lenacapavir reflect this principle: **long–acting equals long consequences**. Once an injection is given, the medication cannot be rapidly removed. If adverse events emerge, the individual must live with them (though both cabotegravir and lenacapavir have been extensively tested with excellent safety records). The bridge period serves as both a practical waiting period for test results AND a safety framework—ensuring that individuals have confirmed HIV–negative status and are appropriate candidates before receiving a long–acting medication.

Cabotegravir Safety Profile

Cabotegravir has been studied extensively in over 6,000 individuals across prevention and treatment trials. Injection site reactions (pain, nodules) occur in 20–30% of injections, but are typically mild and self–resolving within days. Serious adverse events directly attributable to cabotegravir have been extremely rare. Integrase inhibitors (cabotegravir's drug class) have excellent pharmacokinetic and safety profiles in treatment–experienced individuals with HIV. The bridge period safety role for cabotegravir is less about pharmacological safety (which is excellent) and more about ensuring HIV–negative status (given that cabotegravir's efficacy diminishes in treatment–experienced HIV; dosing recommendations

differ). Conservative protocols suggest waiting 18–45 days for standard testing (capturing 99.9% of infections) rather than shorter rapid testing protocols.

Lenacapavir Safety Profile

Lenacapavir, a maturation inhibitor, has been studied in over 8,000 individuals across prevention trials. Injection site reactions are more common than cabotegravir (30–40% of injections) due to the larger injection volume (600 µL), but are typically mild. Unlike integrase inhibitors, maturation inhibitors have no previous therapeutic use, making lenacapavir more novel in that regard. The bridge period safety role for lenacapavir is particularly important: confirming HIV–negative status before first injection is essential. Additionally, lenacapavir's long half–life (weeks to months) means that even trace exposures in acute infection could theoretically select for resistance (though this remains theoretical given the drug's extraordinary potency and the rarity of breakthrough infections).

Bridge Period as Safety Framework

In summary, the bridge period serves critical roles: (1) practical: ensuring adequate time for testing to confirm HIV–negative status, (2) regulatory: reflecting conservative principles with irreversible medications, (3) clinical: ensuring individuals are appropriate candidates (no contraindications, no undetected infections), and (4) equity: requiring healthcare systems to proactively support connection to injections rather than assuming passive receipt. Understanding the bridge period not as obstacle but as necessary safety and equity framework helps justify investments in making it as short and supported as possible—rather than as negligible.

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