Indirect Treatment Comparison of the Efficacy of Cabotegravir and Lenacapavir for HIV Pre-exposure Prophylaxis (PrEP) Versus No PrEP and Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC)

EPLB005

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Key Takeaways

- In the absence of a head-to-head trial comparing long-acting injectables cabotegravir and lenacapavir for HIV pre-exposure prophylaxis (PrEP), we conducted an indirect treatment comparison (ITC) to assess the efficacy of lenacapavir versus cabotegravir in reducing HIV acquisition risk
- Cabotegravir and lenacapavir offer similar and high efficacy in HIV acquisition risk reduction versus no PrEP or oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), with no evidence of a difference in HIV acquisition risk between lenacapavir and cabotegravir
- Findings from this ITC contribute to the medical evaluation of PrEP options but should not be interpreted in isolation; comprehensive decision-making requires integrating additional clinical factors to fully assess the therapeutic value of various PrEP choices
- This study contributes to the growing body of evidence supporting the diversification of effective HIV prevention strategies, underscoring the progress in addressing the global HIV epidemic and improving outcomes for individuals at risk of HIV acquisition

Introduction

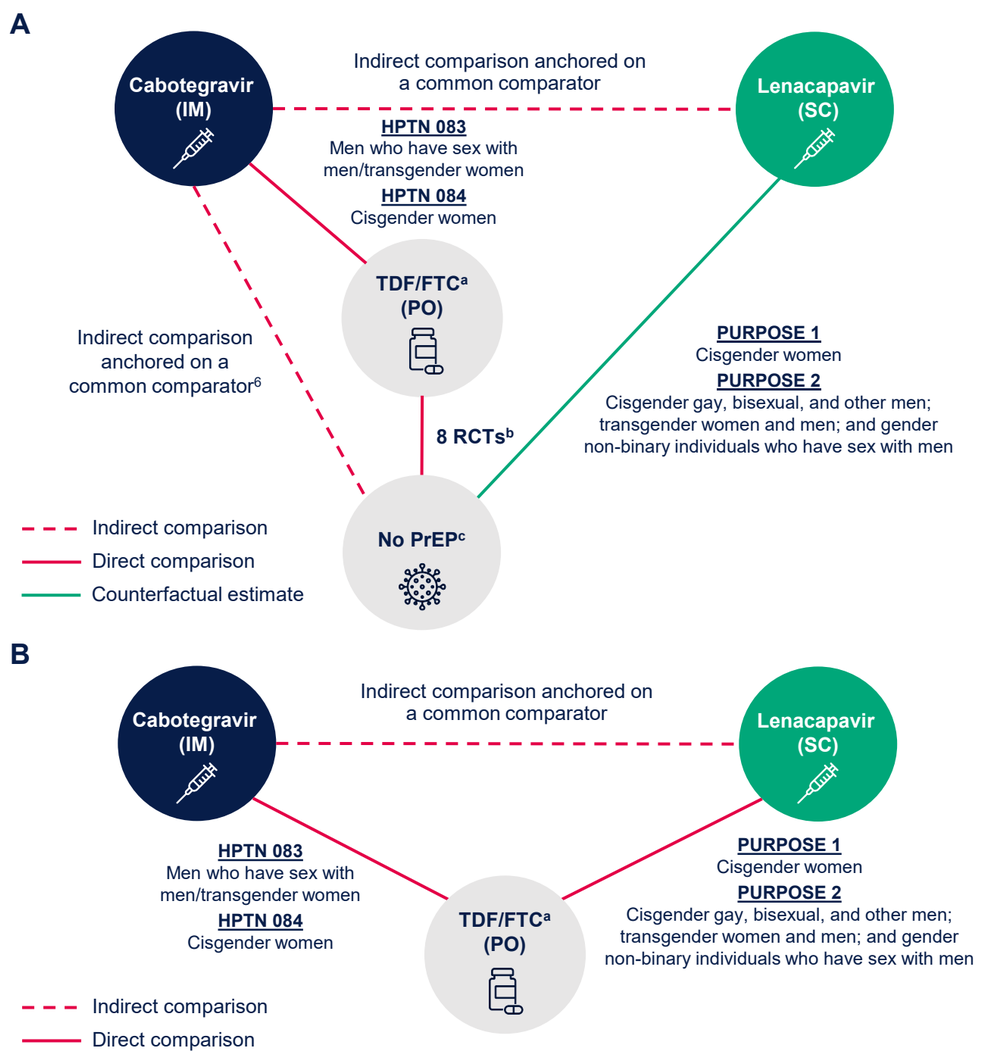
- Long-acting injectable cabotegravir (hereafter referred to as cabotegravir) is the first long-acting injectable approved for pre-exposure prophylaxis (PrEP) and was superior to oral TDF/FTC based on the HPTN 083 and 084 trials[1,2]
- Long-acting injectable lenacapavir (hereafter referred to as lenacapavir) was approved for PrEP on June 18, 2025,[3] based on the PURPOSE 1 and 2 trials[4,5]
- In the absence of a head-to-head trial, we conducted an indirect treatment comparison (ITC) to assess the relative efficacy of lenacapavir versus cabotegravir in reducing HIV acquisition risk

Methods

Study Design

- Leveraging methodology from a prior ITC,[6] this analysis compared cabotegravir and lenacapavir using 2 network approaches
  - Network approach 1 (**Figure 1A**): no PrEP as a common comparator; this leveraged the PURPOSE trials' counterfactual estimate of lenacapavir versus background HIV incidence based on recency assay analyses (ie, no PrEP) and previous research conducted by Hawkins et al to compare cabotegravir versus no PrEP[6]
  - Network approach 2 (**Figure 1B**): daily oral TDF/FTC as a common comparator; this leveraged data from the HPTN and PURPOSE trials, which included TDF/FTC as a direct comparator, using the same methodology from Hawkins et al[6] to account for differences in levels of adherence to TDF/FTC observed between the PURPOSE and HPTN trials
    - The prior published ITC used data from 8 previous randomized controlled trials to inform a meta-regression of TDF/FTC adherence and TDF/FTC effectiveness versus no PrEP[6]
    - The meta-regression, observed adherence in the TDF/FTC arms of the relevant long-acting PrEP trial and the relative effectiveness of long-acting PrEP versus TDF/FTC from that trial, allows for an indirect estimation of the effectiveness of long-acting PrEP versus no PrEP

Figure 1. (A) Network Approach 1 and (B) Network Approach 2



IM, intramuscular; PO, oral; RCT, randomized controlled trial; SC, subcutaneous. [a]Adjusted to the level of TDF/FTC adherence observed in HPTN trials (when used to inform the ITC of cabotegravir versus no PrEP) or PURPOSE trials (when using TDF/FTC as an anchor between cabotegravir and lenacapavir). [b]The 8 RCTs identified from a systematic literature review and used to inform the ITC of cabotegravir versus no PrEP included Partners PrEP, Bangkok Tenofovir Study, iPrEx Trial, VOICE, IPERGAY, TDF2, FEM-PrEP, and PROUD.[6] [c]Defined as background HIV incidence (recency assay) from PURPOSE trials[4,5] and as placebo from Hawkins et al.[6]

Data Sources

- A systematic literature review identified all relevant randomized controlled trials of cabotegravir and lenacapavir for PrEP (HPTN 083, HPTN 084, PURPOSE 1, and PURPOSE 2)
  - Cabotegravir and lenacapavir were evaluated against TDF/FTC in the HPTN and PURPOSE trials, respectively[1,2,4,5]; the PURPOSE trials included a recency assay (background HIV incidence) to provide an estimate of lenacapavir versus no PrEP[4,5]
  - Efficacy inputs for this ITC were derived from re-adjudicated data from the injection phase of the HPTN trials (removal of baseline HIV acquisitions via extended retrospective virologic testing for consistency with the PURPOSE trials)[1,2] or from published PURPOSE trial data[4,5]

Data Analysis

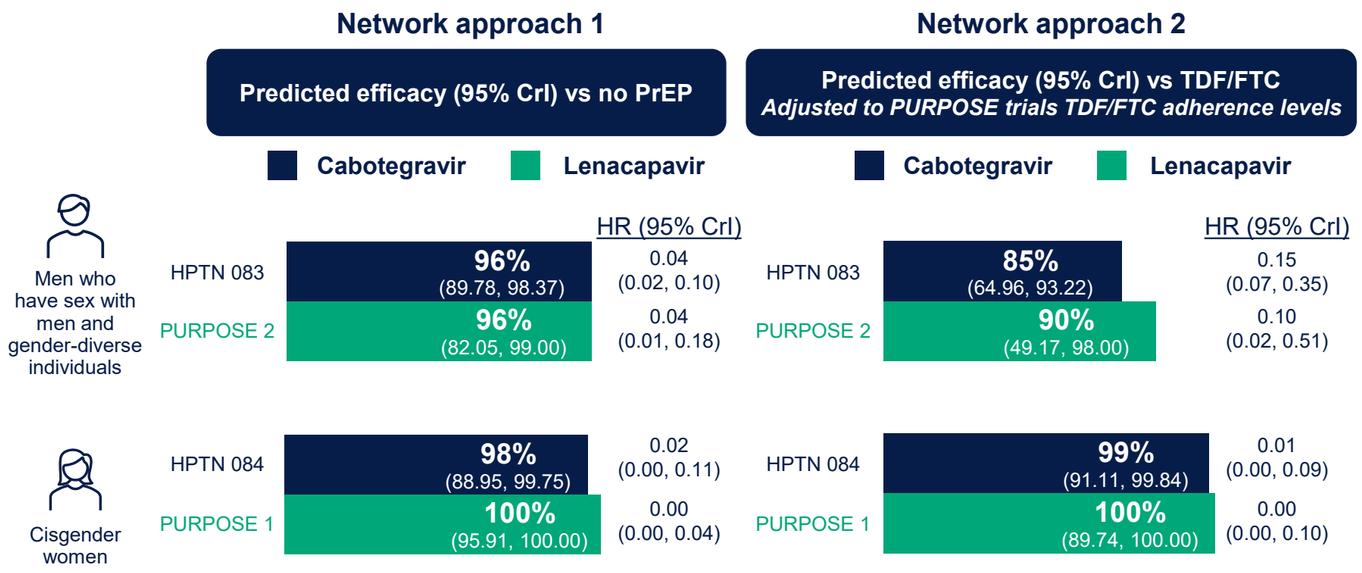
- Data analysis included a base case (aligned with clinical practice, HPTN trial injection phase) and sensitivity analyses (HPTN trial oral lead-in and injection phases)
  - Each analysis was performed using the 2 network approaches
  - The indirect comparisons were Bayesian hierarchical models using the methods described in Hawkins et al,[7] with parameters estimated using Markov Chain Monte Carlo techniques as implemented in Just Another Gibbs Sampler[8]

Results

Predicted Efficacy

- The predicted efficacy of cabotegravir and lenacapavir versus no PrEP or TDF/FTC was high and comparable (**Figure 2**)
  - Sensitivity analyses showed comparable results (data not shown)

Figure 2. Predicted Efficacy of Cabotegravir and Lenacapavir Versus No PrEP or TDF/FTC in the Base Case Analysis[a]

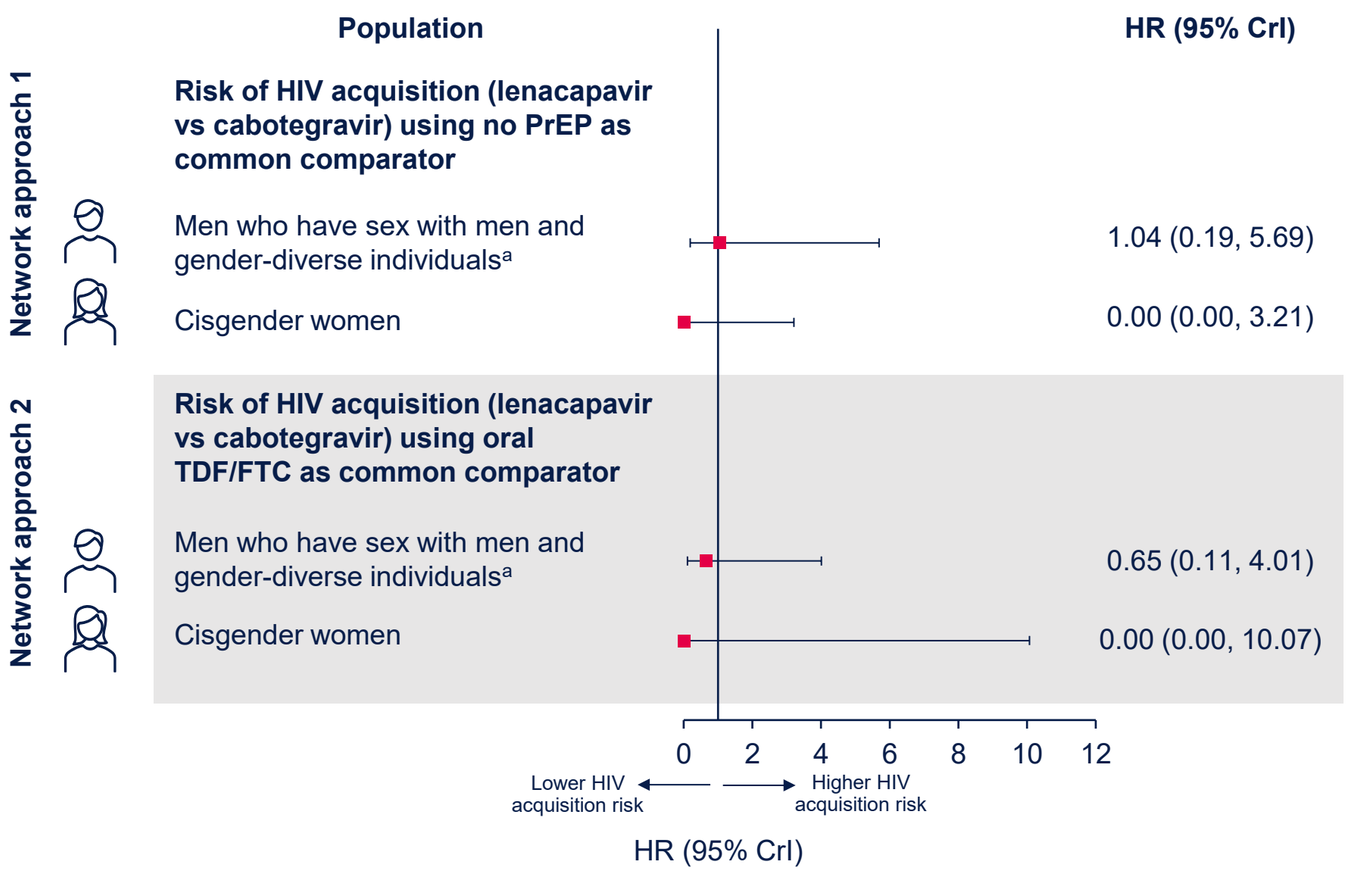


[a]Number of person-years was 5799, 3516, 4821, and 2905 for HPTN 083, HPTN 084, PURPOSE 1,[5] and PURPOSE 2,[4] respectively.

HIV Acquisition Risk for Lenacapavir Versus Cabotegravir

- Given the few HIV acquisitions observed in the HPTN and PURPOSE trials, wide 95% credible intervals (CrIs) for hazard ratios (all crossing 1) were observed in this ITC, as expected with these highly effective PrEP options[1,2,4,5]
- This finding reflected no evidence of superiority between the 2 PrEP options in the base case analysis (**Figure 3**), with comparable results in sensitivity analyses (data not shown)

Figure 3. Lenacapavir Versus Cabotegravir Hazard Ratios (95% CrI) for HIV Acquisition Risk in the Base Case Analysis



CrI, credible interval; HR, hazard ratio. [a]HPTN 083 included men who have sex with men and transgender women.[2] PURPOSE 2 included cisgender gay, bisexual, and other men; transgender women and men; and gender non-binary individuals who have sex with men.[4]

Conclusions

- The lenacapavir versus cabotegravir ITC reflects no evidence of superiority between the 2 long-acting PrEP options, as all 95% credible intervals span 1
- As a head-to-head trial of cabotegravir and lenacapavir could require very large sample sizes and extended observation times due to the low incidence of HIV acquisition with these regimens, this ITC was necessary and provides valuable insights
- Cabotegravir and lenacapavir both offer similar and high efficacy in HIV acquisition risk reduction versus no PrEP and oral TDF/FTC, underscoring the role of long-acting injectables as effective options for PrEP
- Additional research should consider other factors (eg, adverse events [especially injection site reactions], potential drug-drug interactions, real-world data, open label extension data from trials, preference) to achieve a comprehensive clinical value assessment, inform clinical decision-making, and support tailored approaches for people who may benefit from PrEP
- This is the first ITC study to compare the efficacy of cabotegravir and lenacapavir; however, there are limitations
  - Few studies are available, limiting the ability to identify and adjust for additional potential confounding covariables by meta-regression; additionally, adherence measures used in the studies to inform this ITC differed (HPTN, plasma tenofovir; PURPOSE, dried blood spot), and results may also be impacted by variation in trial duration, as median follow-up at time of publication was shorter in the PURPOSE trials (PURPOSE 1, 44.0 weeks; PURPOSE 2, 39.4 weeks)[9] compared with the HPTN trials (HPTN 083, 72.8 weeks; HPTN 084, 64.5 weeks)[1,2]
  - Furthermore, incident HIV acquisitions occurred in the PURPOSE and HPTN trials' open-label extension (OLE) phases (eg, unblinded phase).[3,10,11] These OLE HIV acquisitions were not included in this analysis, which focused exclusively on data from the blinded phase of the trials; however, additional cases from the OLE phases are not expected to alter the conclusions of this ITC

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