Indirect Treatment Comparison of Cabotegravir Long Acting for PrEP Versus No PrEP for HIV Prevention

CO156

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Key Takeaways

- **Variation in adherence to TDF/FTC appears to be highly predictive of the effectiveness of TDF/FTC vs. no PrEP for HIV prevention in reducing the risk of acquiring HIV, and variance in adherence accounts for a large degree of heterogeneity across clinical trials**
- **Indirect comparison of CAB-LA vs. no PrEP suggests similar estimates of effectiveness in the HPTN-083 (91%) and 084 (92%) trials, despite the differences in the population, setting and underlying rate of HIV acquisition**
- **Predicted effectiveness of TDF/FTC vs. no PrEP is 75% (083) and 46% (084) at the levels of adherence observed in the HPTN trials**
- **Underlying rates of HIV acquisition for people not receiving PrEP was estimated as 5-6% per 100 PY and 3-4% per 100 PY for the HPTN-083 and -084 trial populations, respectively**

Introduction

- Pre-exposure prophylaxis (PrEP) is the use of an antiretroviral medication to reduce the risk of HIV acquisition[1]
- The efficacy of cabotegravir long acting (CAB-LA) for PrEP vs. oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as PrEP has been demonstrated in two phase 3 randomized controlled trials (RCTs), HPTN-083 (men who have sex with men and transgender women) and HPTN-084 (cisgender women) [2,3]
  - However, as there was no placebo (no PrEP) arm in the HPTN-083 and 084 trials, indirect estimates are required to inform a CAB-LA vs. no PrEP comparison, which is needed for cost-effectiveness modelling of CAB-LA
  - There are wide variations in effectiveness of TDF/FTC observed in clinical trials due to different levels of adherence observed. It is therefore important to account for differences in adherence when conducting an indirect treatment comparison (ITC)
- The aim of this analysis was to perform an ITC of CAB-LA vs. no PrEP via the common comparator of TDF/FTC as PrEP and to estimate how the effectiveness of TDF/FTC vs. no PrEP varies with level of adherence to TDF/FTC as PrEP

Methods

- A systematic literature review (SLR) to identify RCTs evaluating long-acting PrEP, oral PrEP or placebo/no PrEP was conducted (01-Nov-2023)
  - Trials reporting adherence based on detectable tenofovir in plasma were eligible for inclusion in the ITC as an objective and robust adherence metric
- TDF/FTC as PrEP effectiveness is strongly dependent on the level of adherence to the regimen, and heterogeneity in levels of adherence therefore may confound estimates from an ITC between CAB-LA for PrEP and no PrEP[4]
  - A meta-regression was performed to characterise the relationship between TDF/FTC adherence and TDF/FTC effectiveness vs. no PrEP. Several functional forms and sensitivity analyses were investigated to find the best fit
- The levels of TDF/FTC as PrEP adherence seen in the HPTN-083 and 084 trials were then input into the meta-regression equation to generate estimates of TDF/FTC effectiveness vs. no PrEP in these trial populations
- The ITC was conducted on the relative risk (RR) scale of HIV acquisition. A RR of less than one indicates a reduced risk of HIV acquisition with the intervention. Effectiveness was calculated as (1-RR)*100
- The RR of CAB-LA for PrEP vs. no PrEP was estimated as:
  - $RR_{\text{CAB-LA vs no PrEP}} = RR_{\text{CAB-LA vs TDF/FTC}} \times RR_{\text{TDF/FTC vs no PrEP}}$
- The ITC and meta-regression analyses were implemented jointly as a Hierarchical Bayesian model, parameters were estimated using Gibbs sampling as implemented in Just Another Gibbs Sampler (JAGS), model burn-in was 50,000 samples, results were monitored for 50,000 samples and three chains were run

Results

Trials Included in the ITC

- Ten RCTs were included in the ITC, the analysis included trials that reported adherence in terms of detectable levels of tenofovir in blood plasma levels **(Table 1)**
  - Modified Intention to Treat (mITT) results were used for the base case analysis

Table 1. Trials Included in the ITC (mITT)

Trial (primary publication date)	Treatment	Comparator	% Effectiveness (95%CI)	TDF/FTC adherence (detectable in plasma)
Trials that have a placebo comparator				
Partners PrEP (2012)[5]	TDF/FTC	Placebo	63 (83, 20)	0.81
	TDF/FTC	Placebo	71 (87, 37)	0.81
Bangkok Tenofovir Study (2013)[6]	TDF	Placebo	37.6 (67.9, 17.8)	0.66
	TDF	Placebo	78.6 (96.7, 16.8)	0.66
iPrEx Trial (2010)[7]	TDF/FTC	Placebo	44 (63, 15)	0.50
VOICE (2015)[8]	TDF/FTC	Placebo	-4 (27, -49)	0.29
IPERGAY (2015)[9]	On Demand TDF/FTC	Placebo	86 (98, 40)	0.86
Tenofovir 2 (2012)[10]	TDF/FTC	Placebo	49.4 (80.8, -21.5)	0.77
	TDF/FTC	Placebo	80.1 (96.9, 24.6)	0.77
FEM-PrEP (2012)[11]	TDF/FTC	Placebo	6 (41, -52)	0.36
PROUD (2016)[12]	TDF/FTC	Placebo*	86 (96, 64)	0.88
Trials that have a comparator of TDF/FTC				
HPTN-083 (2021)[2]	CAB-LA	TDF/FTC	66 (82, 38)	0.86
HPTN-084 (2022)[3]	CAB-LA	TDF/FTC	88 (95, 69)	0.56

*TDF/FTC deferred for 1 year

Adherence to Oral PrEP

- An SLR of real-world adherence to oral PrEP found that the majority of people taking oral PrEP had poor adherence, where only 3/54 studies showed people with high levels of adherence as measured by detectable tenofovir in urine or plasma[13,14,15]
- While the relationship between oral PrEP effectiveness and adherence is well-established, people may have difficulties with adherence due to factors such as stigma, discrimination, and pill burden
- This suggests that in the real-world setting, adherence to oral PrEP may be lower than observed in clinical trials; therefore, the high levels of effectiveness seen in clinical trials may not translate to the real-world setting
  - Limitations of this review include that there isn't consistent reporting of adherence in real-world studies and the majority of studies included took place in Africa

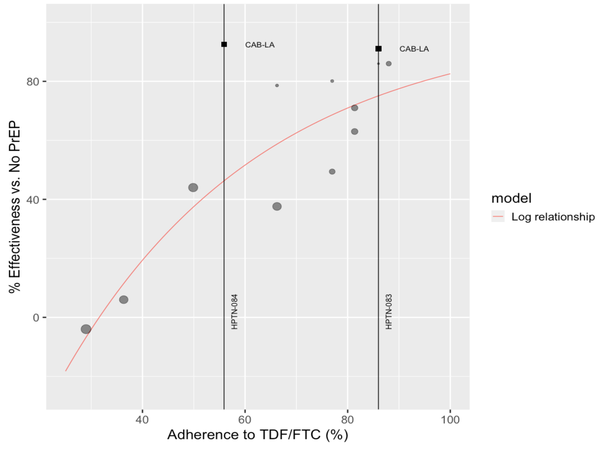
Relationship Between Effectiveness of TDF/FTC and Adherence

- The data show there to be a strong relationship between adherence to TDF/FTC and effectiveness of TDF/FTC vs. no PrEP in reducing HIV acquisition **(Figure 1)**
  - A number of different models and scenarios were explored (linear and log relationship, inclusion of sex as a covariable)
  - Published relationships from earlier trials were considered for comparison[16,17,18]

Relationship Between Effectiveness of TDF/FTC and Adherence

- At the levels of adherence to TDF/FTC observed in the HPTN-083 and HPTN-084 trials, the predicted effectiveness of TDF/FTC vs. no PrEP was greater for HPTN-083 (74.64%) compared with HPTN-084 (46.03%), reflecting the higher level of adherence observed in HTPN-083 (86%) compared with HPTN-084 (56%)
- The adherence to effectiveness relationship displayed in **Figure 1** is specified by the following equations:
  - $Log\ RR = \alpha + \beta . Adherence\ (0\ to\ 1)$
  - α=0.8059, β=-2.5534
  - Effectiveness was calculated as (1-RR)*100

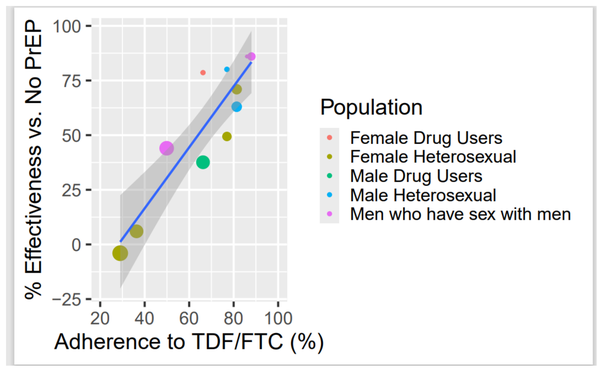
Figure 1. Base Case Relationship Between Effectiveness of TDF/FTC and Adherence



Base Case Relationship Between Effectiveness of TDF/FTC and Adherence

- There was no evidence that population was predictive of effectiveness as there was no obvious deviation from the overall trend between adherence and effectiveness for individual sub-groups (**Figure 2**)
- Furthermore, there was also no deviation from the overall trend for individual regions (Africa, Asia, England, Europe and mixed)

Figure 2. Modelled Relationship Between Effectiveness of TDF/FTC and Adherence by Population



Model Fit

- Lower Deviance Information Criteria (DIC) indicated a better fitting model. A difference of 2 of more is considered significant
- The DIC was similar for the linear relationship (25.73), log relationship + sex (28.35), log relationship (26.42) and log relationship excluding PROUD & Bangkok Tenofovir (19.10)

Model Fit

- The difference in DIC was not significant across models; therefore, the log relationship excluding sex was selected as the base case as it will not predict negative relative risks (effectiveness greater than 100%) **(Figure 2)**

ITC Base Case

- Based on the ITC, the predicted effectiveness of CAB-LA vs. no PrEP was similar for HPTN-083 (91.10%) and HPTN-084 (92.52%) **(Table 2)**
- The underlying risk of HIV acquisition was modelled for individuals in the HPTN-083 and HPTN-084 trials by applying the inverse of the estimated RR for TDF/FTC vs. no PrEP (at the level of adherence seen in the HPTN-083 and -084 trials) to the observed event rates in the TDF/FTC arms **(Table 2)**

Table 2. Base Case Predicted Effectiveness and Underlying Risk of HIV Acquisition

Model	Parameter	Mean score	2.50% CrI	97.50% CrI
Predicted % effectiveness of CAB-LA vs. No PrEP	HPTN-083	91.10	82.87	95.95
	HPTN-084	92.52	83.02	97.38
Predicted % effectiveness of TDF/FTC vs. No PrEP	HPTN-083	74.64	63.92	82.83
	HPTN-084	46.03	35.08	55.6
Predicted underlying risk of infection (No PrEP Event Rate/100 PY)	HPTN-083	5.01	2.96	7.86
	HPTN-084	3.47	2.31	4.93

Limitations

- The HTPN-083 and -084 trials did not include no PrEP arms and there are no trials directly comparing CAB-LA for PrEP vs. no PrEP available to validate the predictions of effectiveness used within the analysis
  - However, the results of the present ITC align with published estimates in previous modelling studies that estimated the background incidence using a counterfactual placebo comparator[19,20]
- There were a number of identified characteristics that showed marked heterogeneity between the trials; however, there were insufficient trials available to include other covariables in the meta-regression model alongside adherence

Conclusions

- Similar estimates of effectiveness for CAB-LA for PrEP vs. no PrEP were seen in the HPTN-083 and -084 trials despite the differences in the population, setting and underlying rate of HIV acquisition. This would support the generalisability of the results of the HPTN-083 and -084 trials to other populations
- Variation in adherence to TDF/FTC as PrEP appears to be highly predictive of the effectiveness of TDF/FTC as PrEP vs. No PrEP. It also appears that variation in adherence explains a large degree of the heterogeneity observed in trial results
  - Adherence to TDF/FTC in practice as shown by the literature is lower than observed in clinical trials; therefore, the effectiveness of TDF/FTC may also be lower in practice

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