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# Truvada for PrEP® (FTC/TDF) Results From Study HPTN 084

This document is in response to your request for information regarding Truvada for PrEP® (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF] for HIV-1 pre-exposure prophylaxis [PrEP]) and its data from the phase 3 study HPTN 084.

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**The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.**

## Summary


### Product Labeling[1]

FTC/TDF is indicated in at-risk adults and adolescents weighing ≥35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating FTC/TDF for HIV-1 PrEP.

### Study HPTN 084 on FTC/TDF for Cisgender Women

Study HPTN 084 was a phase 3, double-blind, double-dummy, active-controlled, superiority study assessing the relative efficacy and safety of once-daily oral CAB for 5 weeks followed by Q2M IM CAB for PrEP (n=1614) vs once-daily oral FTC/TDF (n=1610) for PrEP in sexually active, cisgender women aged 18 to 45 years.[2,3]

- Both regimens were highly effective in preventing HIV, with a pooled HIV incidence of 1 per 100 PY (95% CI: 0.73–1.4) during the blinded period.[2]
- In the ITT population, Q2M IM CAB for PrEP was superior to once-daily oral FTC/TDF for PrEP at preventing HIV through to Week 153 (88% relative risk reduction; *P*<0.0001).[2] In the combined blinded and unblinded periods, HIV acquisition occurred in 6 participants in the CAB group and in 56 participants in the FTC/TDF group.[3]
- In both treatment groups, participants who acquired HIV had suboptimal adherence (defined as <2 doses/week in the FTC/TDF group).[2,3]
- Q2M IM CAB for PrEP and once-daily oral FTC/TDF for PrEP were both well tolerated. During the blinded period, ISRs were reported by 38% of participants in the CAB group and by 10.8% of participants in the FTC/TDF group.[2]
- Over the course of 3 years, weight gain was similar between the two groups (CAB, +2.4 kg/year; FTC/TDF, +2.1 kg/year; *P*=0.041 [threshold for significance was *P*<0.025]).[2]

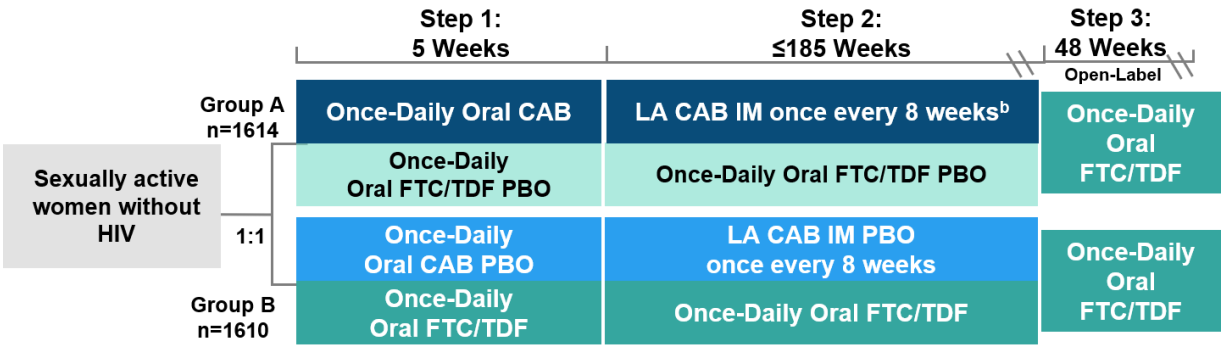
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# Study HPTN 084 on FTC/TDF for Cisgender Women

## Study Design and Demographics[2]

Study HPTN 084 was a phase 3, double-blind, double-dummy, active-controlled, superiority study assessed the relative efficacy (incidence of HIV acquisition) and safety (occurrence of Grade ≥2 AEs or laboratory abnormalities) of 5 weeks of once-daily oral CAB followed Q2M IM CAB for PrEP (n=1614) vs once-daily oral FTC/TDF (n=1610) for PrEP in sexually active, cisgender women aged 18 to 45 years in Africa. Participants were randomly assigned 1:1 to receive either Q2M IM CAB or once-daily oral FTC/TDF (Figure 1). Participants who discontinued Q2M IM CAB injections due to safety concerns or for other reasons were offered open-label once-daily oral FTC/TDF for 48 weeks.

**Figure 1. HPTN 084: Study Design[2a]**




Abbreviation: PBO=placebo.
[a]Blinded trial was stopped in November 2020.
[b]Participants were administered a 4-week interval load of IM CAB at Weeks 5 and 9, followed by injections at 8-week intervals.

At baseline, the median age of participants was 25 years, 54.7% of participants had ≥2 sex partners in the last month, 34.3% had a partner who was HIV positive or whose HIV status was unknown, and the median Vaginal and Oral Interventions to Control the Epidemic risk score was 6.

## Efficacy Results

### Blinded period[2]

Both regimens were highly effective in preventing HIV, with a pooled HIV incidence of 1 per 100 PY (95% CI: 0.73–1.4). Forty participants acquired HIV (CAB, n=4; FTC/TDF, n=36) over 3898 PY (Table 1).

**Table 1. HPTN 084: Incidence of HIV During the Blinded Period[2,3]**

| Parameters | CAB (n=1614) | FTC/TDF (n=1610) |
|---|---|---|
| HIV acquisition, n | 4[a] | 36[b] |
| Tested positive during Step 1 | 1 | 1 |
| Tested positive during Step 2 | 1[c] | 35 |
| Tested positive during Step 3 | 1[d] | 0 |
| PY | 1956 | 1942 |
| HIV incidence (95% CI) | 0.15 (0.03–0.45)[e] | 1.85 (1.3–2.57) |

[a]Included 1 participant who was found to be HIV positive at baseline and was reclassified accordingly.
[b]In 98% of those assigned to receive FTC/TDF and subsequently acquired HIV (n=35), poor adherence or nonadherence to once-daily oral FTC/TDF was observed.
[c]In this participant, 3 of the 9 CAB injections were delayed.
[d]Participant was not adherent to once-daily oral FTC/TDF.
[e]After exclusion of 1 participant who was HIV positive at baseline.

In the ITT population, which omitted participants who tested positive for HIV before randomization, participants in the CAB group had an 88% lower risk of acquiring HIV than participants in the FTC/TDF group over the 153-week period (HR, 0.12; 95% CI: 0.05–0.31; *P*<0.0001). Upon analysis of new incidences of HIV acquisition only, participants in the CAB group had a 91% lower risk of acquiring HIV than participants in the FTC/TDF group (HR, 0.09; 95% CI: 0.04–0.27; *P*<0.0001).

### *Seroconversion data*

While it was previously reported that there were 4 HIV acquisitions in the CAB group, 1 participant was found to have had HIV during enrollment and was reclassified as having HIV at baseline.[2] Two participants with incident HIV did not receive any CAB injections: 1 participant completed the oral lead-in phase but was late for the first injection, and the second participant was switched to open-label FTC/TDF due to pregnancy.[4]
The third participant had 3 of her 9 CAB injections delayed; at this participant's first visit after being diagnosed with HIV, her CAB concentrations were <4 × the paEC$_{90}$. No major INSTI-R mutations were detected in any of the 4 participants in the CAB group who acquired HIV.[2]

The 36 HIV acquisitions in the FTC/TDF group were all classified as incident infections, with 98% of new HIV incidences (35/36) occurring in participants with poor or inconsistent adherence (equating to <2 doses/week) based on TFV and TFV-DP levels. One incidence occurred in a participant with partial adherence (4–6 doses/week). NNRTI-R mutations were detected in 9 participants[4] (mainly K103N mutations); 1 of these participants had an additional M184V mutation.[2]

### *Adherence data*[2]

Injection coverage (defined as CAB or placebo injections received on time or <2 weeks delayed) was estimated to be 93.1% of the 3599 PY on study (CAB, 93% of 1805 PY; FTC/TDF [placebo injection], 93.1% of 1794 PY). In a random subset of 405 participants who received once-daily oral FTC/TDF, 55.9% of the 1939 plasma samples that were evaluated had detectable TFV (≥0.31 ng/mL), and 41.9% had concentrations consistent with adherent once-daily dosing (≥40 ng/mL).

## Combined blinded and unblinded period[3]

During the combined blinded and unblinded periods, the CAB group (n=1613) had an 89% lower risk of acquiring HIV than the FTC/TDF group (n=1610). Six new incidences of HIV in the CAB group were observed over 3334 PY (HIV incidence, 0.18 per 100 PY), and 56 were observed over 3292 PY in the FTC/TDF group (HIV incidence, 1.7 per 100 PY; HR, 0.11; 95% CI: 0.05–0.24). Of the 3 participants in the CAB group who acquired HIV during the unblinded period, 1 participant tested positive during Step 2, and 2 participants who never received an injection tested positive during the annual follow-up. The participant who tested positive during Step 2 had no quantifiable CAB during the oral lead-in, received her first injection, and had detectable HIV RNA levels 28 days later, at which point the CAB injection was not given. All 3 of the new HIV acquisitions in the CAB group were associated with poor or inconsistent treatment adherence. Additional information for the 20 participants in the FTC/TDF group who acquired HIV during the unblinded period was not reported.

# Safety Results

## Blinded period[2]

Both Q2M IM CAB and once-daily oral FTC/TDF were well tolerated (Table 2). Permanent study discontinuation due to AEs was reported in 17 participants (1.1%) in the CAB group and in 23 participants (1.4%) in the FTC/TDF group. A total of 66 participants experienced SAEs, 6 of which were deemed drug-related. In the CAB group, 2 of the serious treatment-related AEs included hospitalization due to fetal distress and respiratory tract infection (each, n=1); hospitalizations in the FTC/TDF group included investigations of increased transaminases (n=2), hepatotoxicity (n=1), and seizure (n=1).

ISRs were reported in 38% of participants in the CAB group and in 10.8% of participants in the FTC/TDF group (Q2M IM CAB placebo), with ISRs of Grade ≥2 in severity reported in 12.6% and 1.6% of participants, respectively. No participants discontinued therapy due to ISRs.

**Table 2. HPTN 084: Grade ≥2 AEs Reported in ≥10% of Participants, SAEs, and Deaths During the Blinded Period[2]**

| Safety Parameter, n (%) | CAB (n=1614) | FTC/TDF (n=1610) |
|---|---|---|
| Any Grade ≥2 AEs | 1487 (92.1) | 1486 (92.3) |
| Decreased CrCl | 1166 (72.2) | 1197 (74.3) |
| SCr increased | 340 (21.1) | 330 (20.5) |
| Gastrointestinal disorders[a] | 334 (20.7) | 370 (23) |
| Abnormal uterine bleeding[a] | 311 (19.3) | 306 (19) |
| Upper respiratory tract infection[a] | 276 (17.1) | 312 (19.4) |
| Headache[a] | 276 (17.1) | 280 (17.4) |
| Chlamydia[a] | 261 (16.2) | 287 (17.8) |
| Urinary tract infection[a] | 229 (14.2) | 209 (13) |
| Amylase increased | 169 (10.5) | 149 (9.3) |
| Any SAEs | 33 (2) | 33 (2) |
| Deaths | 3 (0.2)[b] | 0 |

[a]Includes similar terms in the Medical Dictionary for Regulatory Activities (MedDRA) that fall within this preferred term.
[b]None of the deaths were considered study-drug related.

In the ITT population, an initial increase in weight of +0.4 kg (95% CI: 0.27–0.51) was reported in those receiving Q2M IM CAB vs once-daily oral FTC/TDF (*P*<0.001). Over the course of 3 years, mean (95% CI) weight gain was similar between the two groups: CAB, +2.4 (1.9–3) kg/year; FTC/TDF, +2.1 (1.9–2.4) kg/year; *P*=0.041 (threshold for significance was *P*<0.025).

Pregnant or breastfeeding women were excluded from enrollment, and all participants were required to use an effective form of modern contraception during the study. If participants became pregnant during the study, they received open-label once-daily oral FTC/TDF throughout pregnancy and breastfeeding. Live-born infants were evaluated for congenital anomalies at 12 months after delivery. Forty-nine pregnancies (CAB, n=29; FTC/TDF, n=20) were reported; among the 31 known pregnancy outcomes (CAB, n=18; FTC/TDF, n=13), there were 13 and 10 live births in the CAB and FTC/TDF groups, respectively. No congenital anomalies were reported.

## Unblinded period[3]

No new safety concerns were identified during the unblinded period (Table 3). Among the AEs of Grade ≥2 in severity, 80% were assessed as unrelated to the treatment drug.

**Table 3. HPTN 084: Grade ≥2 AEs Reported in ≥10% of Participants, SAEs or Expedited AEs, and Deaths During the Unblinded Period[3]**

| Safety Parameter, n (%) | CAB (n=1440) | FTC/TDF (n=1425) |
|---|---|---|
| Any Grade ≥2 AEs | 1194 (83) | 1197 (84) |
| CrCl decreased | 562 (39) | 584 (41) |
| Chlamydia | 225 (16) | 228 (16) |
| Gastrointestinal disorders | 211 (15) | 174 (12) |
| SCr increased | 168 (12) | 170 (12) |
| Any SAEs or expedited AEs[a] | 26 (2) | 22 (2) |
| Deaths | 2 (0.1) | 0 |

[a]Expedited AEs were required to be reported within a 3-day time period.[5]

### *Combined blinded and unblinded period[3]*

In the combined blinded and unblinded period, there were 132 confirmed pregnancies (CAB, n=63; FTC/TDF, n=69; including those mentioned above). Among the 79 known pregnancy outcomes (CAB, n=42; FTC/TDF, n=37; included pregnancies with multiple births), there were 31 and 30 live births in the CAB and FTC/TDF groups, respectively. The remaining 18 pregnancies (CAB, n=11; FTC/TDF, n=7) resulted in pregnancy loss. No congenital anomalies were reported.

# References

1. Enclosed. Gilead Sciences Inc, TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
2. Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. *Lancet.* 2022;399:1779-1789.
3. Delany-Moretlwe S, Hughes JP, Bock P, et al. Long acting injectable cabotegravir: updated efficacy and safety results from HPTN 084 [Presentation]. 2022.

4. Marzinke MA, Delany-Moretlwe S, Agyei Y, et al. Long-acting injectable PrEP in women: laboratory analysis of HIV infections in HPTN 084 [Poster]. Paper presented at: 11th International AIDS Society (IAS) Conference on HIV Science Virtual; 18-21 July, 2021.
5. (DAIDS) DoA. *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.* January 2010.

# Abbreviations

AE=adverse event
CAB=cabotegravir
FTC=emtricitabine
HPTN=HIV Prevention Trials Network
HR=hazard ratio
IM=intramuscular
INSTI-R=integrase strand transfer inhibitor resistance
ISR=injection site reaction
NNRTI-R=non-nucleos(t)ide reverse transcriptase inhibitor resistance
$paEC_{90}$= protein-adjusted concentration necessary to achieve 90% viral inhibition
PrEP=pre-exposure prophylaxis
PY=person years
Q2M=once every 2 months
SAE=serious adverse event
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate

# Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Truvada US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.

# Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

# Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 https://www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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