MK-8504 and MK-8583 (Tenofovir Prodrugs) Single-Dose PK and Antiviral Activity in HIV Infection

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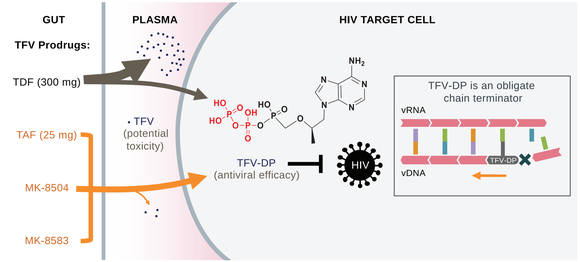
BACKGROUND

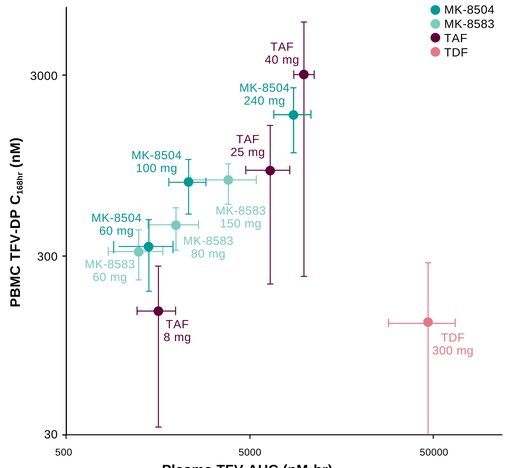
- HIV-1 treatments with improved safety and ease of administration are needed[1,2]
- Tenofovir (TFV) is converted to active TFV-diphosphate (TFV-DP) to inhibit reverse transcriptase and HIV replication[3,4] (**Figure 1**)
- MK-8504 and MK-8583 are novel TFV prodrugs, with potential for weekly dosing and reduced toxicity due to efficient intracellular conversion to TFV-DP and low plasma TFV levels
- Similar to tenofovir alafenamide (TAF), MK-8504 and MK-8583 exposure results in high intracellular levels of active TFV-DP and low plasma TFV levels[5] (**Figure 2**)

Figure 1. TFV Prodrugs: Pharmacokinetics (PK) and Mechanism of Action[3,4]



TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TFV-DP, TFV-diphosphate; vDNA, viral DNA; vRNA, viral RNA. Figure adapted from Ray et al. 2016.[3]

Figure 2. Exposure of MK-8504, MK-8583, TAF, and Tenofovir Disoproxil Fumarate (TDF)[5]

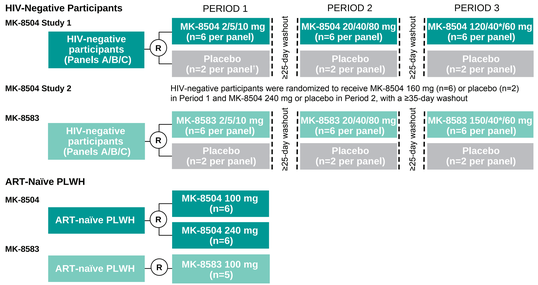


Plasma TFV AUC was computed as day 10 AUC_{0-24} multiplied by 7 for TAF and TDF (QD), and as single-dose AUC_{0-inf} for MK-8504 and MK-8583 (QW). For TAF and TDF, day 10 PBMC C_{168hr} was used as a surrogate of PBMC TFV-DP C_{168hr}. Error bars represent standard deviation. AUC, area under the curve; AUC_{0-24}, AUC from time 0 to 24 hours post dose; AUC_{0-inf}, AUC from time 0 extrapolated to infinity; C_{168hr}, concentration at 168 hours; C_{trough}, average concentration over the dosing interval at steady state; PBMC, peripheral blood mononuclear cell; QD, once daily; QW, once weekly; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TFV-DP, TFV-diphosphate.

METHODS

- The Phase 1 clinical program investigated the single-dose PK, antiviral activity, and safety of MK-8504 and MK-8583 (**Figure 3**)

Figure 3. Design of MK-8504 and MK-8583 Single-Dose Studies



Studies with a placebo were double-blinded; all treatments were single oral doses. *Doses with a high-fat meal. †One participant discontinued and was replaced. ART, antiretroviral therapy; PLWH, people living with HIV; R, randomized.

RESULTS

MK-8504 and MK-8583 Single Doses in HIV-Negative Participants

Baseline Characteristics

- MK-8504 Study 1: Median age 49 years (range, 23–55); 20 of 25 participants male
- MK-8504 Study 2: Median age 57 years (range, 50–60); 7 of 8 participants male
- MK-8583: Median age 40 years (range, 22–53); 20 of 24 participants male

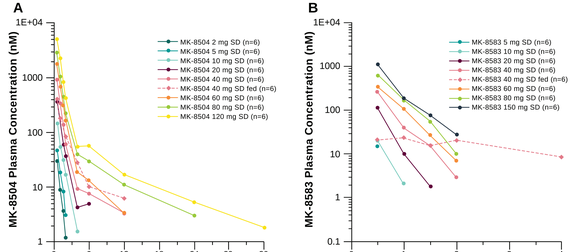
Safety

- MK-8504 and MK-8583 were generally well tolerated; all adverse events (AEs) were mild or moderate in intensity; no serious AEs, events of clinical interest, or deaths; no trends between AE incidence and increasing dose; only one discontinuation in a placebo-treated participant

MK-8504 and MK-8583 Plasma Concentration

- MK-8504 2–240 mg apparent terminal half-life ($t_{1/2}$) was 0.4–8.6 hours (median time to maximum concentration [T_{max}] 0.5 hours) (**Figure 4A**)
- MK-8583 2–150 mg fasted apparent terminal $t_{1/2}$ was 0.2–0.4 hours (median T_{max} 0.5 hours) and 40 mg fed apparent terminal $t_{1/2}$ was 1.0 hour (median T_{max} 1.5 hours) (**Figure 4B**)

Figure 4. Mean MK-8504 (A) and MK-8583 (B) Plasma Concentration Over Time

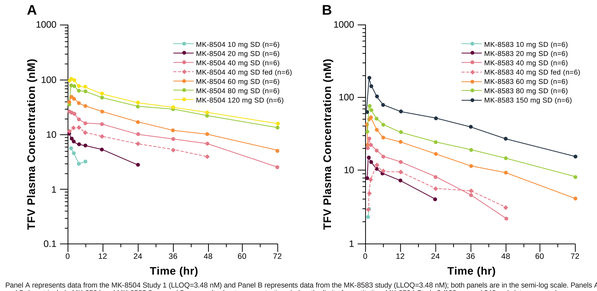


Panel A represents data from the MK-8504 Study 1 (LLOQ=1.76 nM) and Panel B represents data from the MK-8583 study (LLOQ=1.67 nM); both panels are in the semi-log scale. Panel B does not include MK-8583 2 mg results due to concentrations below the limit of quantitation. MK-8504 Study 2 (160 mg and 240 mg) data are not shown. LLOQ, lower limit of quantitation; SD, single dose.

TFV Plasma Concentration

- After MK-8504 administration, TFV apparent terminal $t_{1/2}$ was 20–38 hours (median T_{max} 1–4 hours); and after MK-8583 administration, TFV apparent terminal $t_{1/2}$ was 19–30 hours (median T_{max} 1–4 hours) (**Figure 5**)
- After MK-8504 administration, geometric mean (GM) area under the curve from time 0 to the last measurable concentration ranged from 1 to 5520 nM•hr; and after MK-8583 administration, it ranged from 5 to 3107 nM•hr

Figure 5. Mean TFV Plasma Concentration Over Time After MK-8504 (A) and MK-8583 (B)

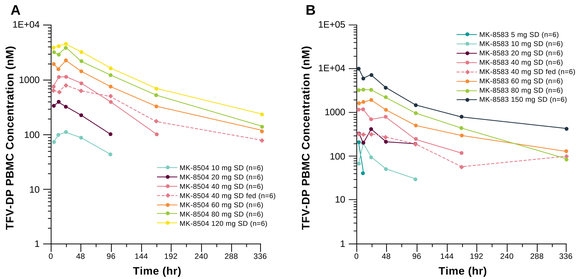


Panel A represents data from the MK-8504 Study 1 (LLOQ=3.48 nM) and Panel B represents data from the MK-8583 study (LLOQ=3.48 nM); both panels are in the semi-log scale. Panels A and B do not include MK-8504 and MK-8583 2 mg and 5 mg results due to concentrations below the limit of quantitation. MK-8504 Study 2 (160 mg and 240 mg) data are not shown. LLOQ, lower limit of quantitation; SD, single dose; TFV, tenofovir.

TFV-DP Peripheral Blood Mononuclear Cell (PBMC) Concentration

- After MK-8504 administration, TFV-DP apparent terminal $t_{1/2}$ was 48–115 hours (median T_{max} 12–24 hours); and after MK-8583 administration, TFV-DP apparent terminal $t_{1/2}$ was 65–192 hours (median T_{max} 4–24 hours) (**Figure 6**)
- Intracellular PK target was set at ≥100 nM at 168 hours, based on *in vitro* and clinical exposure response data, which was achieved at the following doses:
  - MK-8504 60, 80, 120, 160, and 240 mg fasted; and 40 mg fed
  - MK-8583 40, 60, 80, and 150 mg fasted

Figure 6. Mean TFV-DP PBMC Concentration Over Time After MK-8504 (A) and MK-8583 (B)



Panel A represents data from the MK-8504 Study 1 (raw concentration assay LLOQ=0.162 nM) and Panel B represents data from the MK-8583 study (raw concentration assay LLOQ=0.162 nM); both panels are in the semi-log scale. Panel A does not include MK-8504 2 mg and 5 mg results and panel B does not include MK-8583 2 mg results due to concentrations below the limit of quantitation. MK-8504 Study 2 (160 mg and 240 mg) data are not shown. LLOQ, lower limit of quantitation; PBMC, peripheral blood mononuclear cell; SD, single dose; TFV-DP, tenofovir-diphosphate.

MK-8504 and MK-8583 Single Doses in Antiretroviral Therapy (ART)-Naïve People Living with HIV (PLWH)

Baseline Characteristics

- MK-8504: Median age 36 years (range, 24–45); all participants male; median baseline HIV RNA level 4.3 log_{10} copies/mL (range, 3.5–5.9)
- MK-8583: Median age 26 years (range, 22–49); all participants male; median baseline HIV RNA level 4.4 log_{10} copies/mL (range, 4.1–5.0)

Safety

- MK-8504 and MK-8583 were generally well tolerated; most AEs were mild or moderate in intensity; no serious AEs, events of clinical interest, or deaths

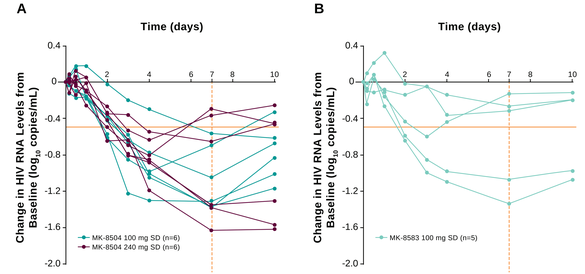
MK-8504 and MK-8583 PK

- PK observed in PLWH were similar to HIV-negative participants

Antiviral Activity

- Mean difference in HIV RNA reduction from baseline at 7 days post dose compared with historical placebo (pooled from monotherapy studies in PLWH) was 1.03 and 0.92 log_{10} copies/mL for MK-8504 100 mg and 240 mg, respectively, and 0.60 log_{10} copies/mL for MK-8583 100 mg (**Figure 7**). In the MK-8583 study, three participants did not meet the target reduction in HIV RNA (target of 0.5 log_{10} copies/mL) 7 days post dose (**Figure 7B**)
- No observed relationship between TFV-DP PBMC trough concentrations and antiviral efficacy. Across the two studies, 15 of 16 participants with evaluable PBMC samples achieved the target TFV-DP concentration of ≥100 nM at 7 days post dose
- No genetic-resistant variants identified

Figure 7. Change in HIV RNA Levels From Baseline After MK-8504 (A) and MK-8583 (B)



Panel A represents data from the MK-8504 study and Panel B represents data from the MK-8583 study. Each line corresponds to the change in HIV RNA level from baseline for a participant. Horizontal line represents a minimal efficacy target reduction in HIV RNA levels of 0.5 log_{10} copies/mL at 7 days. SD, single dose.

CONCLUSIONS

- Single doses of MK-8504 and MK-8583 were generally well tolerated in HIV-negative adults and ART-naïve PLWH
- MK-8504 and MK-8583 were rapidly converted to TFV-DP and achieved target trough concentrations at most doses evaluated, including at low doses
- MK-8504 and MK-8583 generally led to lower TFV plasma concentrations than TDF[5]
- MK-8504 and MK-8583 achieved and maintained target HIV RNA levels in some participants, but overall results were variable. It is possible that virologic efficacy could be improved with daily administration of MK-8504 or MK-8583 as part of a combination antiretroviral drug regimen
- Collectively, these data raise questions about the potential efficacy and feasibility of TFV prodrugs in intermittent extended-interval oral dosing regimens

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