Pharmacokinetics of Tenofovir Alafenamide, Emtricitabine, and Dolutegravir in a Patient on Peritoneal Dialysis

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BACKGROUND

- People living with HIV (PWH) are at higher risk of developing chronic kidney disease (CKD) than the general population, and therefore more likely to be on kidney replacement therapies (KRT) like peritoneal Dialysis (PD).
- Nucleoside reverse transcriptase inhibitors like the prodrugs tenofovir alafenamide (TAF) and emtricitabine (FTC) and integrase strand transfer inhibitors like dolutegravir (DTG) are commonly used for HIV treatment, therefore dosing data in people on KRT are needed.
- Available data from people with severe CKD or people on hemodialysis (HD) show higher plasma concentrations of FTC and tenofovir (TFV), suggesting lower clearance, but lower concentrations of plasma DTG.
- A single previous case report describes a 46-year-old patient with HIV and HBV on PD on a regimen containing tenofovir disoproxil fumarate (TDF, another prodrug of TFV); TFV trough concentrations confirmed that TFV is partially extracted by PD, but lower TDF dose was still suggested.

CASE STUDY

- A single participant with HIV on once-daily DTG+ TAF/FTC and CKD secondary to Type 1 Diabetes on PD underwent a 2-day intensive PK study to assess TAF, TFV, FTC, and DTG plasma concentrations, as well as peripheral blood mononuclear cell (PBMC) concentrations of the active metabolites TFV-TP and FTC-DP.
- Patient had stably controlled HIV (CD4: 255 cells/mm3 (13.5%); HIV RNA PCR < 20 copies/mL) and had been on continuous 4-cycler PD nightly via an abdominal peritoneal dialysis catheter for a year prior to and during the study.

METHODS

- Blood was collected for plasma and PBMC isolation pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours after the observed dose. Urine was collected cumulatively over two time periods, 0-10 hours, and 10-24 hours post-dose, with urine volume totals recorded.
- PK parameters were compared between the participant and cohorts of PWH, both with normal kidney function and on hemodialysis (HD).
- Non-compartmental analysis in WinNonLin was used to compute PK parameters, including time until maximum plasma concentration (T_{max}), maximal plasma concentration (C_{max}), minimum plasma concentration (C_{min}), and area under the concentration: time curve (AUC_{last}).
- Renal dose and clearance were calculated from the 24-hour cumulative urine volume and the urine drug concentration. Drug concentrations were determined via liquid chromatographic-mass

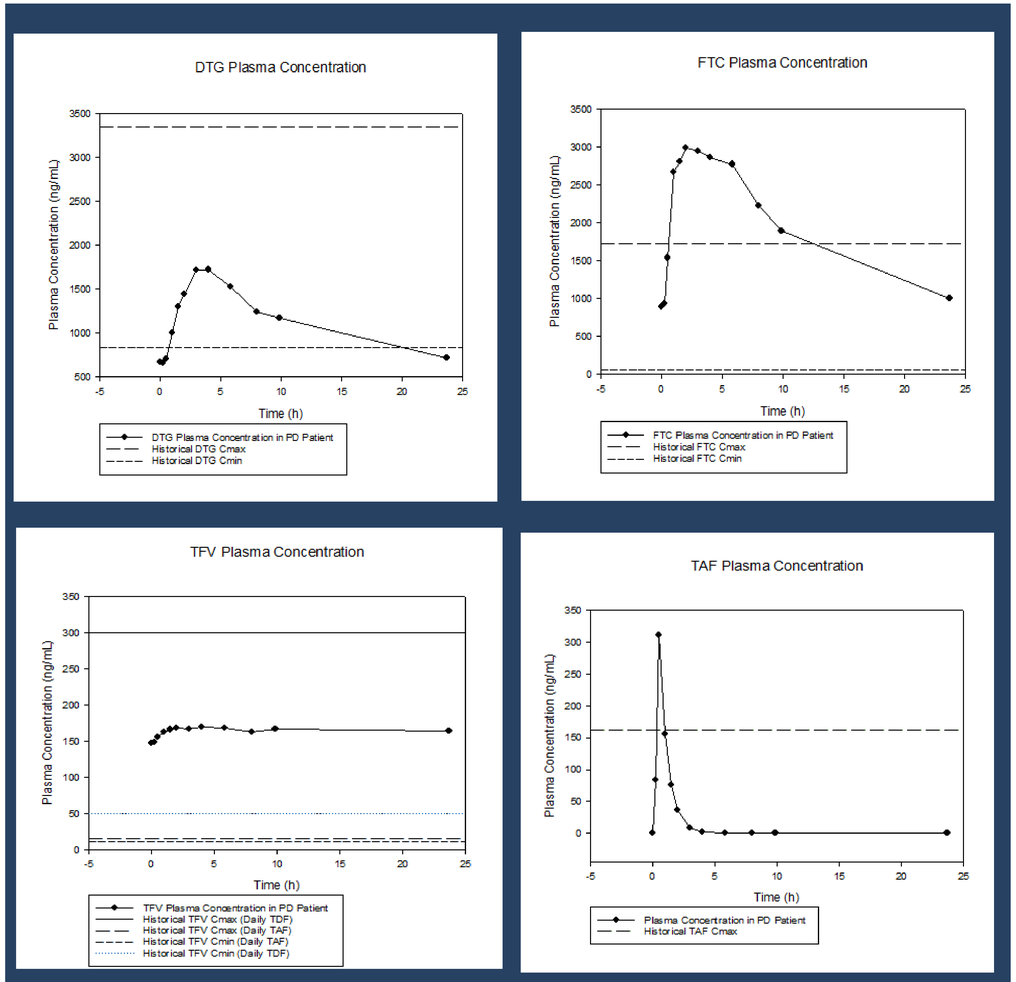
RESULTS

- Plasma pre-dose and 24-hour post-dose trough concentrations were 670 and 718 ng/mL for DTG, 147 and 164 ng/mL for TFV, and 888 and 1006 ng/mL for FTC, respectively, indicating that the participant was not at steady-state for his ART medications.
- Plasma concentration time profiles were plotted in relation to PK values in those with normal renal function.

RESULTS CONT.

- TAF: Cmax 2- and AUClast,1-foldhigher; Cmin below the limit of quantification
- TFV: Cmax 11-, AUClast 13-, and Cmin 15-fold higher
- FTC: Cmax 2-, AUClast 6-, and Cmin 20-fold higher.
- DTG showed the opposite trend: Cmax 0.51, AUClast 0.6, and Cmin 0.9 times those in people with normal renal function.

- Intracellular concentrations in PBMC's were also compared with historical data.
  - TFV-DP: C_{max} and AUC_{last} 2 times higher, but within the range of concentrations observed in those with non-compromised renal function; C_{min} 2 times higher.
  - FTC-TP: C_{max} 5 times higher but within normal range, AUC_{last} 4 and C_{min} 5 times higher, and out of normal range.



Plasma drug concentration versus time plots for each of the four analytes related to the three drugs studied. Dotted reference lines indicate historical C_{max} (long dash) and C_{min} (short dash) for TAF, TFV, FTC, and DTG historical data. TFV plot includes additional historical C_{max} (solid line) and C_{min} (dotted line) from TDF dosing.

CONCLUSIONS

- TFV concentrations were 11-15-fold higher in this participant than what is expected, indicating possible plasma accumulation despite the fact that he was not at steady-state.
  - TFV trough concentrations were 3-fold higher than what would be expected with steady-state TDF dosing in someone with normal renal function,
- FTC C_{max} was modestly higher in our PD patient, but AUC_{last} and C_{min} were many-fold higher, again suggesting plasma accumulation. However, this may not add substantial toxicity risk given the overall tolerability of FTC.
- DTG C_{max}, C_{min}, and AUC_{last} measurements were lower in this participant than in people with normal kidney function, but still above median plasma trough concentrations shown to be sufficient for viral suppression (300 ng/mL).
- Intracellular TFV metabolite concentrations (TFV-DP C_{max} and AUC_{last}) were within the normal range, while C_{min} was slightly above the range; intracellular FTC-TP C_{max} was within normal range, while AUC_{last} and C_{min} were higher compared with historic data. This may be attributable to the 20-fold higher plasma FTC trough concentrations.
- TFV renal clearance was 20-fold lower, and FTC renal clearance was 24-fold lower in this participant on PD than in people with normal renal function, leading to the observed accumulation when usual daily dosing was used.
- Although further studies are needed to confirm our findings, it seems that **adjusted dosing of TAF may be warranted when preservation of residual renal function is desired.**

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