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Plasma & Intracellular PK and Renal Safety of TAF 25mg with Boosted PIs and LDV/SOF

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Background

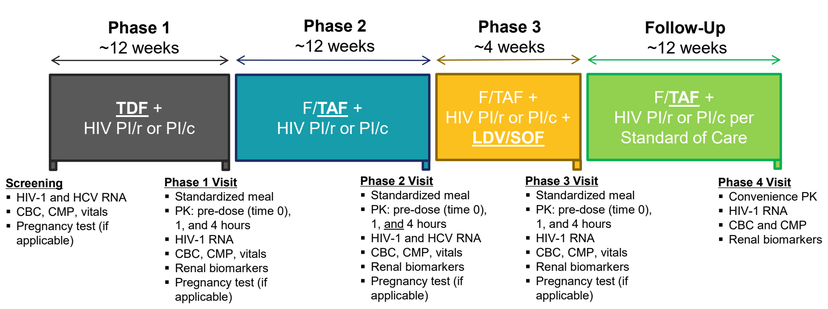
- Up to 16% of persons living with HIV (PLWH) are also co-infected with hepatitis C virus (HCV),[1] and there is a higher risk of liver-related morbidity and mortality in this population.[2,3]
- Several direct-acting antiviral (DAA) therapies with short treatment durations are now available for HCV treatment, including ledipasvir/sofosbuvir (LDV/SOF, Harvoni®, Gilead Sciences, Inc.).[4-7] However, HIV requires lifelong therapy, thus drug-drug interactions between antiretroviral (ARV) medications and DAAs are of concern.[8,9]
- Tenofovir (TFV), in the form of either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), is a key component of multiple recommended ARV regimens.
- TFV use is associated with renal proximal tubule injury, with higher tenofovir exposures corresponding to higher toxicity risk.[10-12]
- LDV/SOF, when co-administered with TDF, increases plasma TFV exposures by 40-98%,[13] and tenofovir-diphosphate (TFV-DP) concentrations by ~3-fold in PBMCs and ~7-18-fold in RBCs (measured in dried blood spots (DBS)).[14,15]
- There are currently no PK or renal safety data for TAF 25mg with boosted PIs and LDV/SOF.

Objectives

- To compare the plasma/intracellular PK and renal safety of boosted PIs with TDF, TAF, and TAF with LDV/SOF in PLWH.

Methods

- Persons living with HIV on TDF with a boosted as standard HIV care were eligible for the study. Ritonavir (RTV, /r) or cobicistat (COBI, /c) were permitted. The study design is detailed in **Figure 1**.
- Adherence was monitored in real-time using wireless pillboxes (Wisepill Technologies®; Capetown, South Africa).



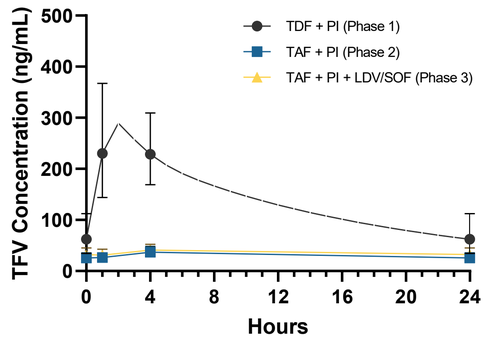
- PBMCs were isolated pre-dose and plasma at every time point. TAF, TFV, and TFV-DP were quantified using validated LC-MS/MS methods.
- Plasma TFV exposures over 24 hours with TDF were calculated using a two-compartment model. Noncompartmental methods were used with TFV from TAF.
- PK and renal biomarkers were log-transformed prior to analysis with mixed models. Results were back-transformed and phase comparisons were reported as GMR (95% CI). P<0.05 was considered statistically significant with no adjustment for multiple comparisons.

Results

Table 1. Baseline Demographics

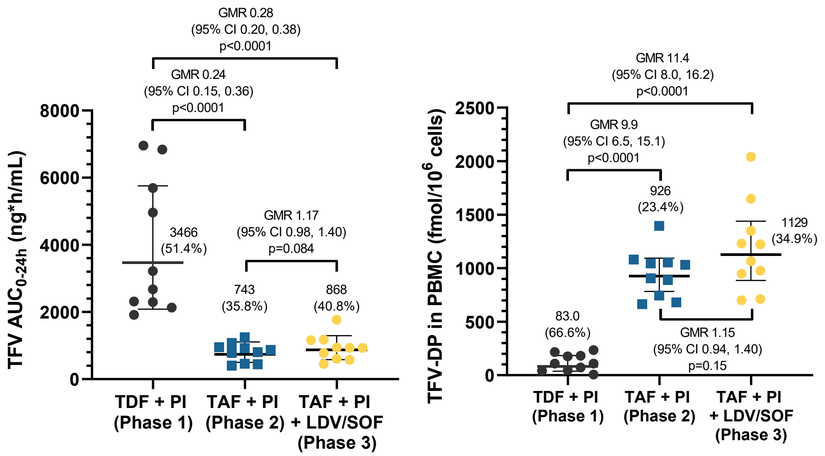
Characteristic	N=10
Sex, n(%)	
Male	9 (90%)
Female	1 (10%)
Race/Ethnicity, n(%)	
White	4 (40%)
Hispanic/Latino	5 (50%)
Black	1 (10%)
Age (yr), mean (SD)	50 (12.3)
Weight (kg), mean (SD)	88.8 (16.6)
eGFR (mL/min/1.73 m2)	91.5 (26.6)
Boosted PI, n(%)	
ATV/r	1 (10%)
DRV/c	5 (50%)
DRV/r	4 (40%)

Figure 2. TFV Plasma Concentration-Time Curves



Data presented as geometric mean (95% CI); TFV curve for TDF generated using post-hoc estimates from two-compartment model; TFV at 24 hours post-dose with TAF imputed from time 0 sampling point.

Figure 3. Plasma TFV exposures (left) and TFV-DP concentrations in PBMCs (right)



Individual summary statistics reflect geometric mean (%CV) and phase comparisons reported as geometric mean ratio (GMR) (95% CI); PBMC phase comparisons reflect estimates after controlling for adherence 1 month prior and time since last dose.

Figure 4. TAF plasma concentrations at 1 hour (left) and 4 hours (right) post-dose

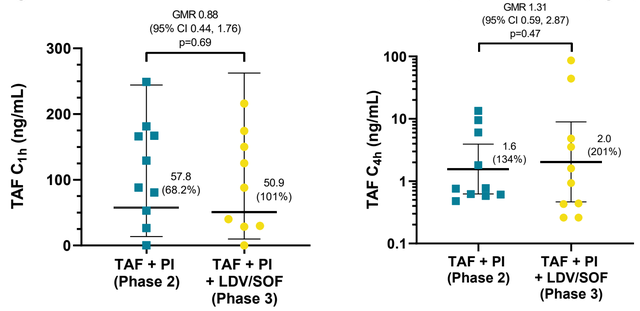


Figure 5. eGFR and urine protein-to-creatinine ratios (UPCR) across phases

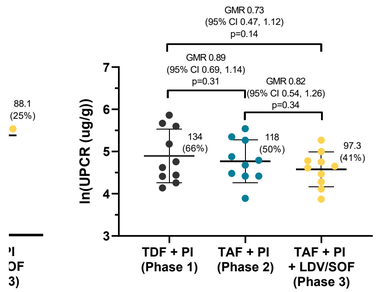
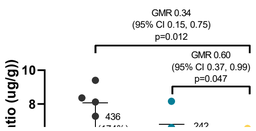


Figure 6. β2-microglobulin:Cr and retinol binding protein (RBP):Cr across phases



Acknowledgements & References

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Conclusions

- Plasma TFV exposures were ~72-76% lower following TAF switch.
- TFV-DP in PBMC increased ~10-fold with TAF 25mg relative to TDF with boosted PIs. This increase is within the range of TFV-DP observed historically with higher TAF doses.
- Unlike TDF, adding LDV/SOF with TAF did not significantly increase plasma TAF/TFV or TFV-DP in PBMC, likely due to differences in hydrolysis pathways between these prodrugs.
- No significant changes in eGFR or UPCR occurred with TAF or TAF with LDV/SOF, but improvements in β2-microglobulin:Cr and RBP:Cr occurred following TAF switch.
- These findings reassure on the safety of TAF + b/PI + LDV/SOF in HIV/HCV-coinfected patients.

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