PHARMACOKINETICS OF TWICE-DAILY TAF IN ADULTS WITH HIV-ASSOCIATED TB ON BIC/FTC/TAF AND RIFAMPICIN

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BACKGROUND

Tenofovir alafenamide fumarate (TAF) is a pro-drug of tenofovir (TFV) with less renal and bone toxicity than tenofovir disoproxil fumarate (TDF). However, unlike TDF, TAF has been shown to interact with rifampicin (RIF) in healthy volunteers. The pharmacokinetics (PK) of TAF when co-administered with RIF has not been evaluated in people with HIV (PWH) and tuberculosis (TB).

METHODS

- We conducted a nested PK sub-study within INSIGHT (NCT04734652, a 48-week study of bictegravir (BIC) vs dolutegravir-containing ART in adults with HIV-TB)
- We evaluated the PK of plasma TFV and intracellular TFV-diphosphate (TFV-DP) in individuals initiated on a BIC/emtricitabine (FTC)/TAF regimen dosed twice-daily (BD) until 2 weeks post RIF-based TB treatment and once-daily (QD) thereafter until 48 weeks.
- Participants underwent regular clinical and safety monitoring during study follow-up visits.
- Plasma and dried blood spot (DBS) samples were collected during TB treatment at weeks 4 and 12 (pre-dose, 1, 2, 4, 6, and 8-12h post-dose) and after TB treatment at week 32 (pre-dose, 1, 2, 4, 6-8, and 24-25h post-dose).
- TFV-DP concentration was quantified from a full DBS spot and converted to fmol/3mm punch.
- Non-compartmental PK analyses were conducted using the PKanalix2024R1 software.

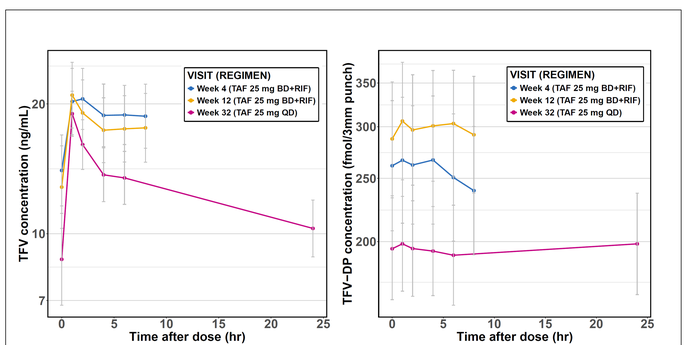

Figure 1: Geometric mean of TFV and TFV-DP concentration at each time point with their 95% CI error−bars

RESULTS

- We enrolled 43 participants in the PK sub-study; Median (IQR) age and weight were 35 (30-39) years and 57 (52-64) kg; 77% were male; 100% black race.
- A total of 119 and 122 PK profiles were evaluable for TFV and TFV-DP respectively
- Geometric least square mean ratio (GLSMR) (90% CI) AUC_{0-24} for TFV was 1.28 (1.10, 1.50) and 1.24 (1.06, 1.45) at weeks 4 and 12 on TAF BD with RIF relative to week 32 on QD TAF without RIF. GLSMR (90% CI) C_{avg} for TFV-DP was 1.62 (1.42-1.86) at weeks 12 vs week 32 with and without RIF, respectively (Table 1).
- Overall, 95% of participants achieved viral suppression at week 24 in the BIC arm, there were no BIC/FTC/TAF drug related adverse events in the study including no treatment discontinuations.

Twice-daily TAF with rifampicin achieved intracellular TFV-DP concentrations similar or higher than once-daily TAF and similar TFV-DP concentrations to those previously reported with TDF

Table 1: Pharmacokinetic parameters of TFV and Intracellular TFV-DP

	Geometric mean (CV%)			GLSMR (90% CI)	
Tenofovir (TFV) PK parameters	**TAF 25mg BD+RIF Week 4 (N=40)**	**TAF 25mg BD+RIF Week 12 (N=40)**	**TAF 25 mg QD Week 32 (N=39)**	**TAF BD+RIF (Week 4) vs TAF QD (Week 32)**	**TAF BD+RIF (Week 12) vs TAF QD (Week 32)**
AUC_{0-24} (ng·h/mL)	370 (59%)	356 (66%)	305 (47%)	1.28 (1.10, 1.50)	1.24 (1.06, 1.45)
C_{max} (ng/mL)	23 (55%)	22 (60%)	19 (40%)	1.21 (1.05, 1.40)	1.23 (1.07, 1.41)
	Geometric mean (CV%)			**GLSMR (90% CI)**	
Tenofovir diphosphate (TFV-DP) PK parameters	**TAF 25mg BD+RIF Week 4 (N=40)**	**TAF 25mg BD+RIF Week 12 (N=41)**	**TAF 25 mg QD Week 32 (N=41)**	**TAF BD+RIF (Week 4) vs TAF QD (Week 32)**	**TAF BD+RIF (Week 12) vs TAF QD (Week 32)**
C_{avg} (fmol/3mm punch)	259 (80%)	301 (70%)	195 (61%)	1.33 (1.17-1.52)	1.62 (1.42-1.86)

AUC_{0-24} was calculated by multiplying the extrapolated AUC_{0-12} by 2 for TAF 25 mg BD + RIF.
AUC_{0-24}=area under the concentration-time curve from 0 to 24 hours; BD=twice-daily; Cavg= average concentration during the dosing interval; CI=confidence interval; Cmax= maximum concentration; CV=coefficient of variation; GLSMR=geometric least square mean ratio; QD=once-daily; RIF=rifampicin; TAF=tenofovir alafenamide; TFV=tenofovir; TFV-DP= tenofovir diphosphate.

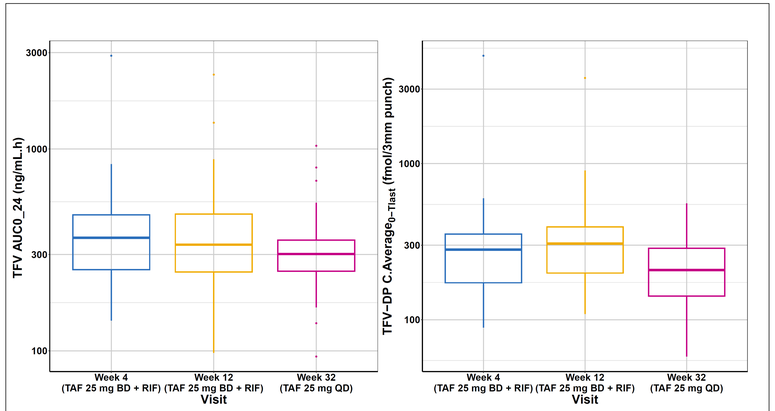

Figure 2: Boxplots of TFV AUC_{0-24} and TFV-DP C_{avg} during TAF BD with RIF at weeks 4 and 12 and TAF QD alone at week 32

CONCLUSIONS

Twice-daily TAF with RIF achieved intracellular TFV-DP concentrations similar to those with once-daily TAF alone. Plasma TFV was lower and intracellular TFV-DP concentrations were similar to those previously reported with TDF. Twice-daily TAF achieved sufficient exposures to overcome RIF enzyme-inducing effects in adults with HIV and TB. These data support the use of TAF in a fixed dose combination of BIC/FTC/TAF in PWH and TB and fills the knowledge gap for TAF PK with RIF.

REFERENCES

[1]Naidoo et al Efficacy, Safety, and PK of BIC/FTC/TAF in adults with HIV and tuberculosis on rifampicin at week 24.In CROI; Denver; Mar 2024, abstract 211

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