Plasma and Intracellular Pharmacokinetics of Tenofovir in Patients Switched from TDF to TAF

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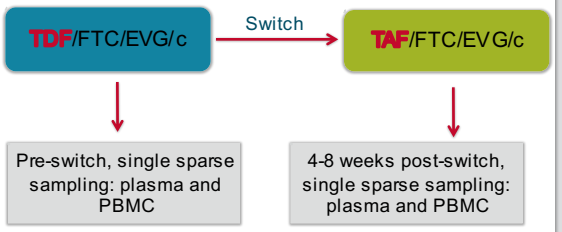
Background

- Current HIV treatment guidelines recommend two nucleoside analogue reverse transcriptase inhibitors (NRTIs), plus a third agent.
- Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), both pro-drugs of tenofovir (TFV), are each first line NRTIs according to the US Department of Health and Human Services Adult and Adolescent Treatment Guidelines.
- Tenofovir alafenamide has been shown to have an improved safety profile as compared to tenofovir disoproxil fumarate, resulting in lower rates of renal and bone toxicity.[1,2,3]
- Tenofovir alafenamide results in higher intracellular penetration (4.4 fold) and lower plasma concentrations (90% lower) compared to tenofovir disoproxil fumarate.[4]
- Intraindividual comparisons of plasma and intracellular pharmacokinetics of TFV and its intracellular metabolite, tenofovir-diphosphate (TFV-DP) have not been described in patients switching from TDF to TAF.

Methods

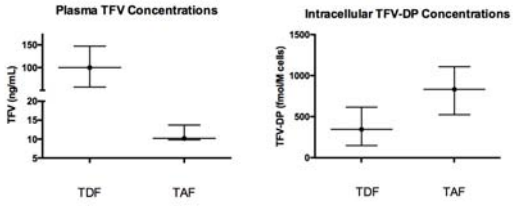
- Prospective, non-randomized, crossover, pharmacokinetic study of 30 HIV-infected patients
- Inclusion Criteria: HIV RNA < 20cpm, receiving TDF/emtricitabine (FTC)/elvitegravir (EVG)/cobicistat(c) based ART
- All patients switched to TAF-containing ART: TAF/FTC/EVG/c
- A single, sparse blood sample of plasma and PBMC were collected pre-switch and 4-8 weeks post-TAF switch.
- LC/MS/MS determination of plasma TFV and intracellular TFV-DP
- PBMC cell enumeration via droplet digital quantification of Rnase P (RPP30)[5]
- Patient characteristics summarized with descriptive statistics (median, IQR)
- Pharmacokinetic data summarized as geometric mean ratio (GMR) and compared with Wilcoxon signed-rank test

Study Scheme



Pharmacokinetic Data

Metric	Pre-Switch TFV Plasma Conc. (ng/mL)	Post-Switch TFV Plasma Conc. (ng/mL)	Pre-Switch TFV-DP Intracellular Conc. (fmol / M cells)	Post-Switch Intracellular Conc. (fmol / M cells)
Median	100.0	10.2	346.9	834.7
Q1,Q3	57.1, 147.3	9.8, 13.7	149.3, 617.4	526.0, 1110.0
Time Post Dose	11.2 (4.1- 18.6)		10.8 (2.7 – 17.4)	
GMR Post : Pre Switch	0.10; p<0.001		2.4; p=0.004	



- 30 participants completed both study visits.

Results

Table 1: Baseline Participant Demographics

Characteristic	Metric	Total (N=30)
Age	Median (range)	39 (25,58)
Female gender	n (%)	4 (13%)
Race / Ethnicity	Black Non-Hispanic, n (%)	10 (33%)
HIV-1 RNA	Undetectable (<20cpm), n (%)	30 (100%)
CD4 cells/mm^3 at entry	Median (range)	632 (429,713)
TDF-based ART duration at pre-switch visit, (weeks)	Mean (SD)	82.8 (38.6)
TAF-based ART duration at post-switch, (weeks)	Mean (SD)	5.9 (1.5)

Observations and Conclusion

- These results confirm intra-individual plasma TFV concentrations decrease ~90% after switching from TDF to TAF- based ART which is consistent with inter-individual results
- Intracellular TFV-DP concentrations increased ~140% in PBMCs after switching from TDF to TAF–based ART, slightly lower than what has been observed in parallel group studies
- A novel droplet digital PCR method of cell enumeration was validated for use with intracellular pharmacokinetic studies

References

[1]Sax, Paul E., et al. "Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials." *The Lancet* 385.9987 (2015): 2606-2615.

[2]Sax, Paul E., et al. "Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 67.1 (2014): 52-58.

[3]Mills, Anthony, et al. "Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate in the First Protease Inhibitor–Based Single-Tablet Regimen for Initial HIV-1 Therapy: A Randomized Phase 2 Study." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 69.4 (2015): 439-445.

[4]Custodio, J., W. Garner, and C. Callebaut. "The pharmacokinetics of tenofovir and tenofovir diphosphate following administration of tenofovir alafenamide versus tenofovir disoproxil fumarate (Abstract 6)." *16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy*. 2015.

[5]Ravi Dyavar Shetty et al. "Normalization of antiretroviral drug concentrations in tissue mononuclear cells using highly sensitive RNase P droplet digital polymerase chain reaction based cell enumeration assay." (Abstract 12R1100) *American Association of Pharmaceutical Sciences. 2016*

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