The Pharmacokinetics of Tenofovir and Tenofovir Diphosphate Following Administration of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate

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Abst#_6

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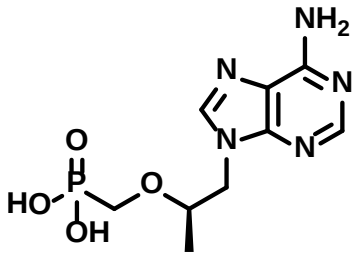
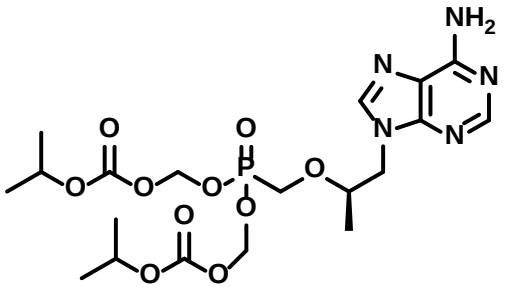
Disclosures

- All coauthors are employees of Gilead Sciences
- These studies were funded by Gilead Sciences

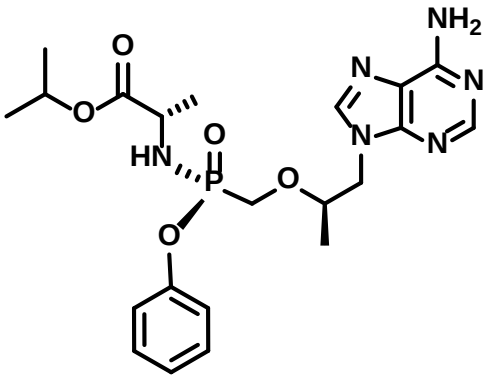
Introduction



Tenofovir (TFV)



Tenofovir disoproxil fumarate (TDF)



Tenofovir alafenamide (TAF)

- TDF is a preferred NRTI in US/EU guidelines
  - A component in the approved single-tablet regimen (STR) containing elvitegravir 150 mg (EVG, E), cobicistat 150 mg (COBI, C), emtricitabine 200 mg (FTC, F) and TDF 300 mg (E/C/F/TDF; Stribild®, STB)
- TAF is an investigational prodrug of TFV with distinct metabolism designed to maximize antiviral potency and clinical safety
  - A component in the fixed-dose combination F/TAF and E/C/F/TAF STR

Introduction

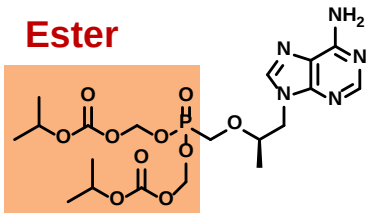
TDF has limitations and can be improved

- Nephrotoxicity
  - Dose adjustment in renal insufficiency
  - Declining GFR, proteinuria, urinary phosphate wasting, glycosuria
- Osteopenia/osteoporosis
  - Associated with loss of bone mineral density
- Likely relationship between TFV exposure and renal + bone toxicity
  - High-dose subcutaneous TFV administered to nonhuman primates causes PRT dysfunction and bone demineralization
  - Positive correlation between TFV clearance and/or AUC and renal + bone effects[1]

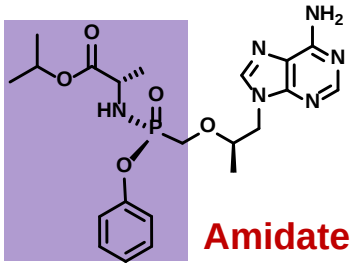
1. Van Rompay KK, et al. AAC. 2008;52:3144-60.

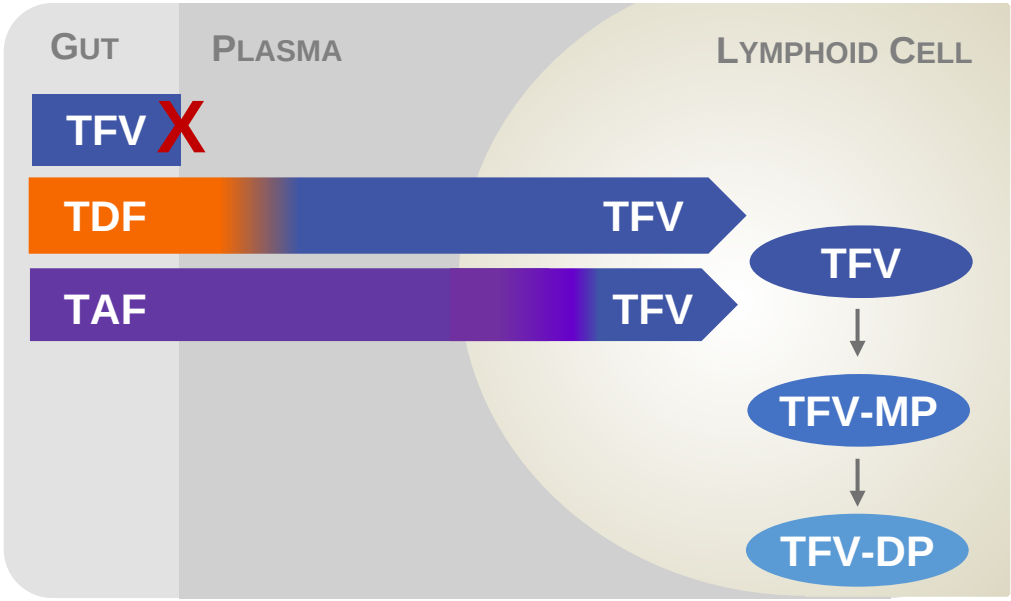
TAF: Targeted Prodrug of Tenofovir (TFV)

TDF (Prodrug)



TAF (Targeted Prodrug)



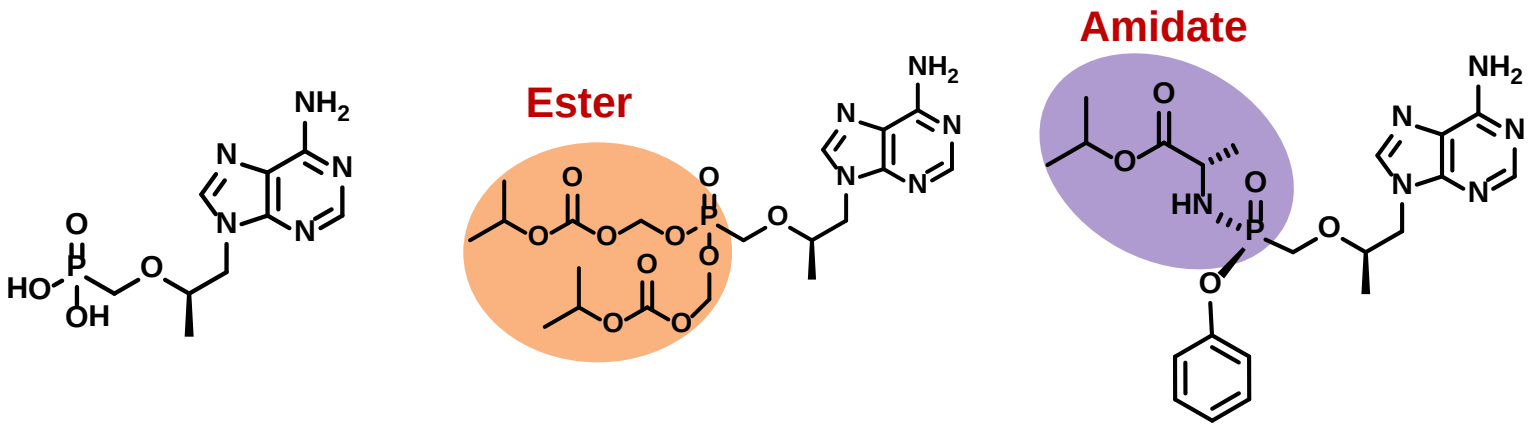


- TAF is more stable in plasma compared to TDF[1]
- Intact TAF transits directly into target cells where it is activated to tenofovir disphosphate (TFV-DP)[1-3]
  - ↑ intracellular levels of active moiety TFV-DP
  - ↓ circulating TFV relative to TDF may ↓ nephrotoxicity

1. Lee WA, et al. Antimicrob Agents Chemother 2005;49:1898-906; 2. Birkus G, et al. Antimicr Agents Chemo 2007;51:543-50;
3. Babusis D, et al. Mol Pharm 2013;10:459-66.

TAF Is More Stable in Plasma vs TDF; Lower Dose Provides Higher Potency, Lower TFV Systemic Exposures

TFV | **TDF (Prodrug)** | **TAF (Prodrug)**



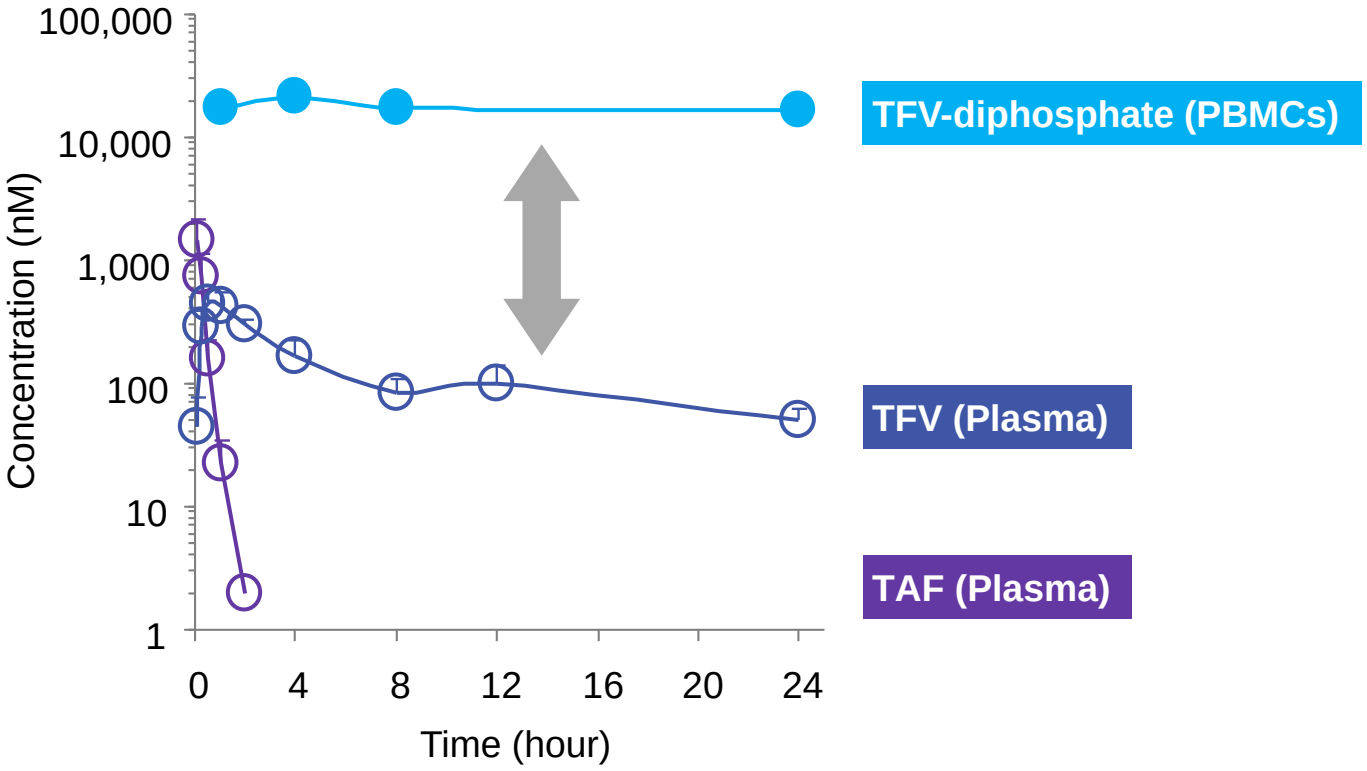
	$T_{1/2}$ [min]	
	Human plasma	T-cell extract
TVF	Stable	Stable
TDF	0.4	71
TAF	90	28

TDF: Hydrolysis in blood is fast, hydrolysis in T-cells is relatively slow
TAF: More stable in blood, hydrolysis in T-cells faster than TDF

Lee WA, et al. Antimicrob Agents Chemother 2005;49:1898-906.

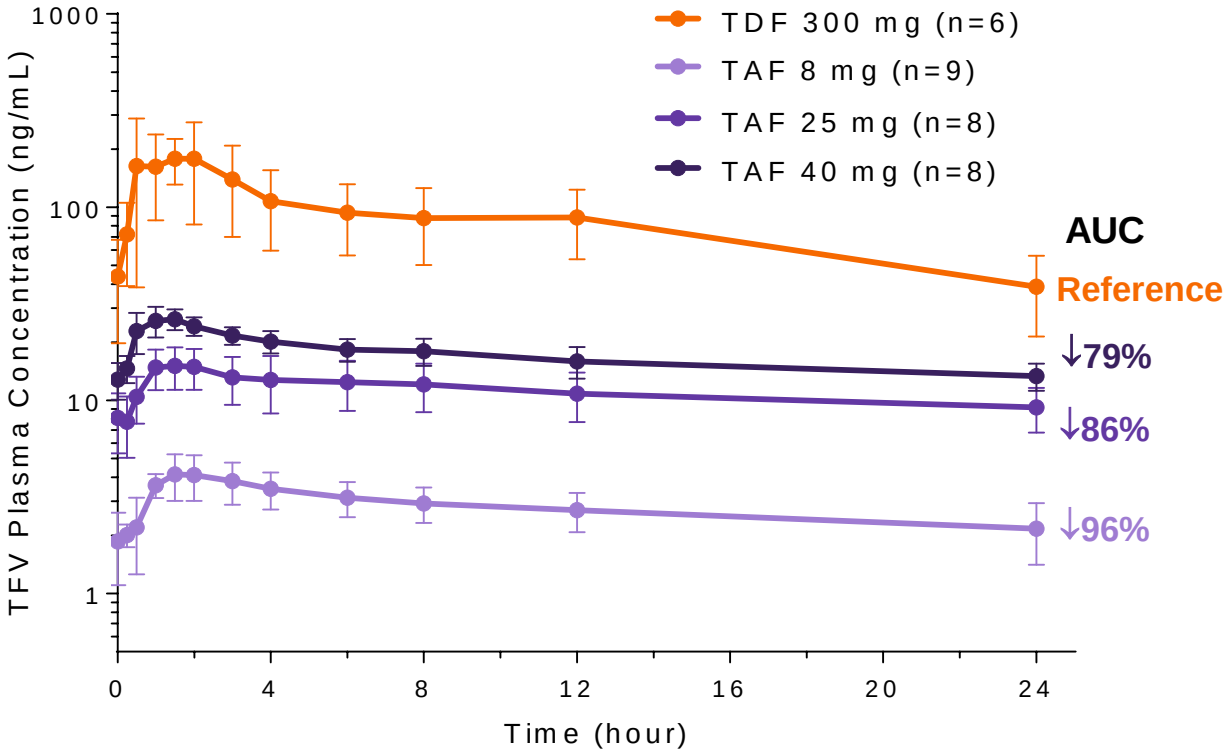
TAF Nonclinical PK in Dogs

Oral PK in Dogs (5 mg/kg)

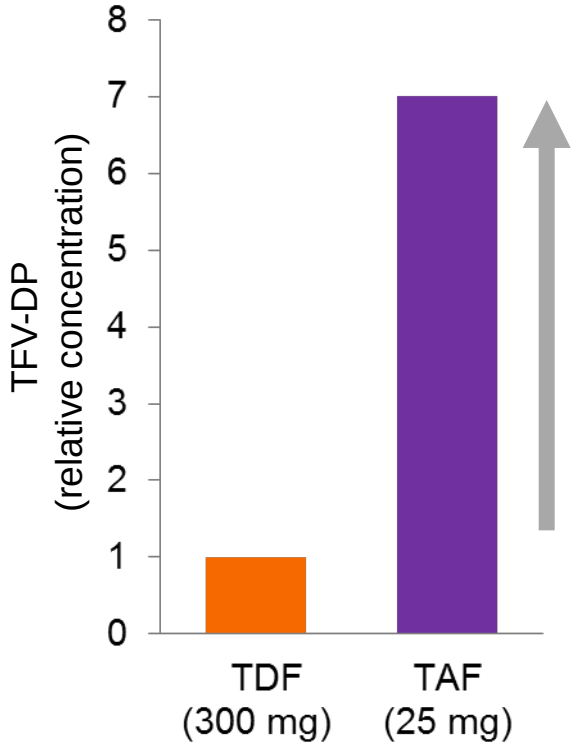


Lee et al. Antimicrob Agents Chemother 2005;49:1898-906.

Clinical POC PK: TFV Lower in Plasma and TFV-DP Higher in PBMCs With TAF vs TDF



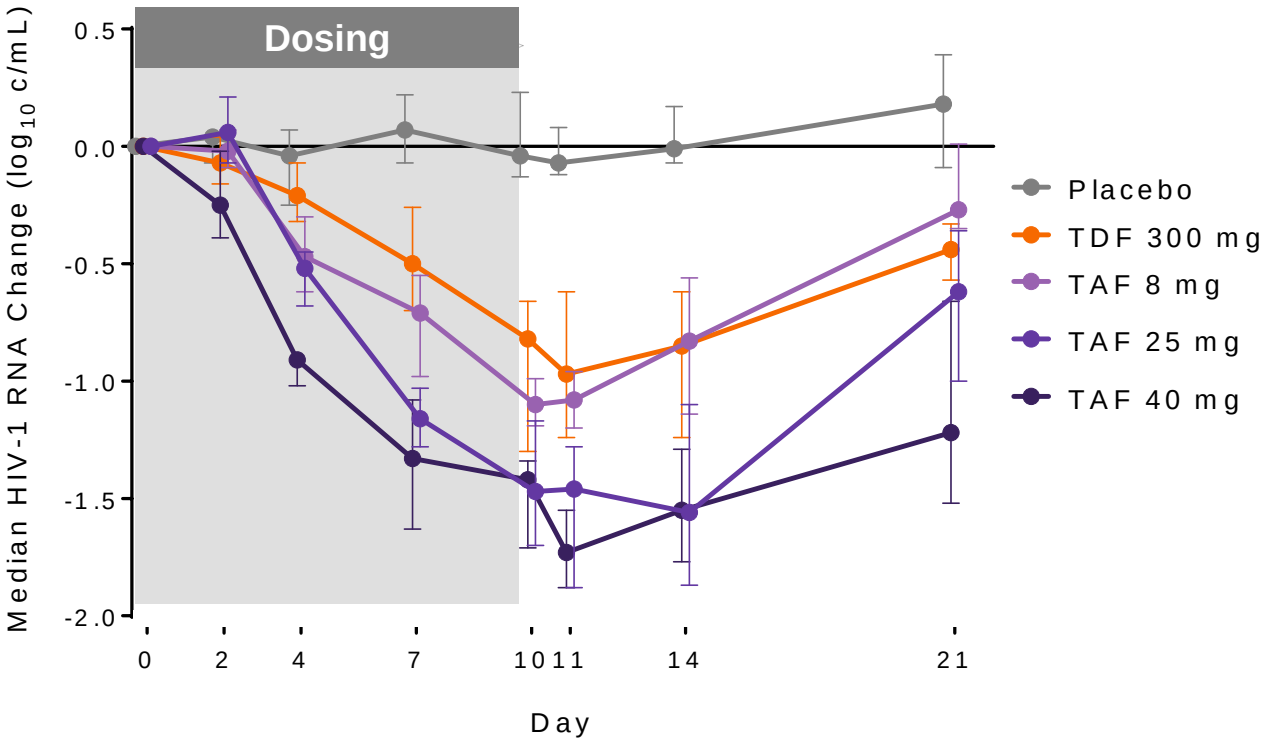
Up to 7x More TFV-DP in PBMCs



- Proof-of-concept study in treatment-naïve HIV-infected subjects

Ruane P, et al. J Acquir Immune Defic Syndr 2013;63:449-5.

Based on Clinical POC PK and Antiviral Activity, TAF 25 mg Selected for Phase 2/3



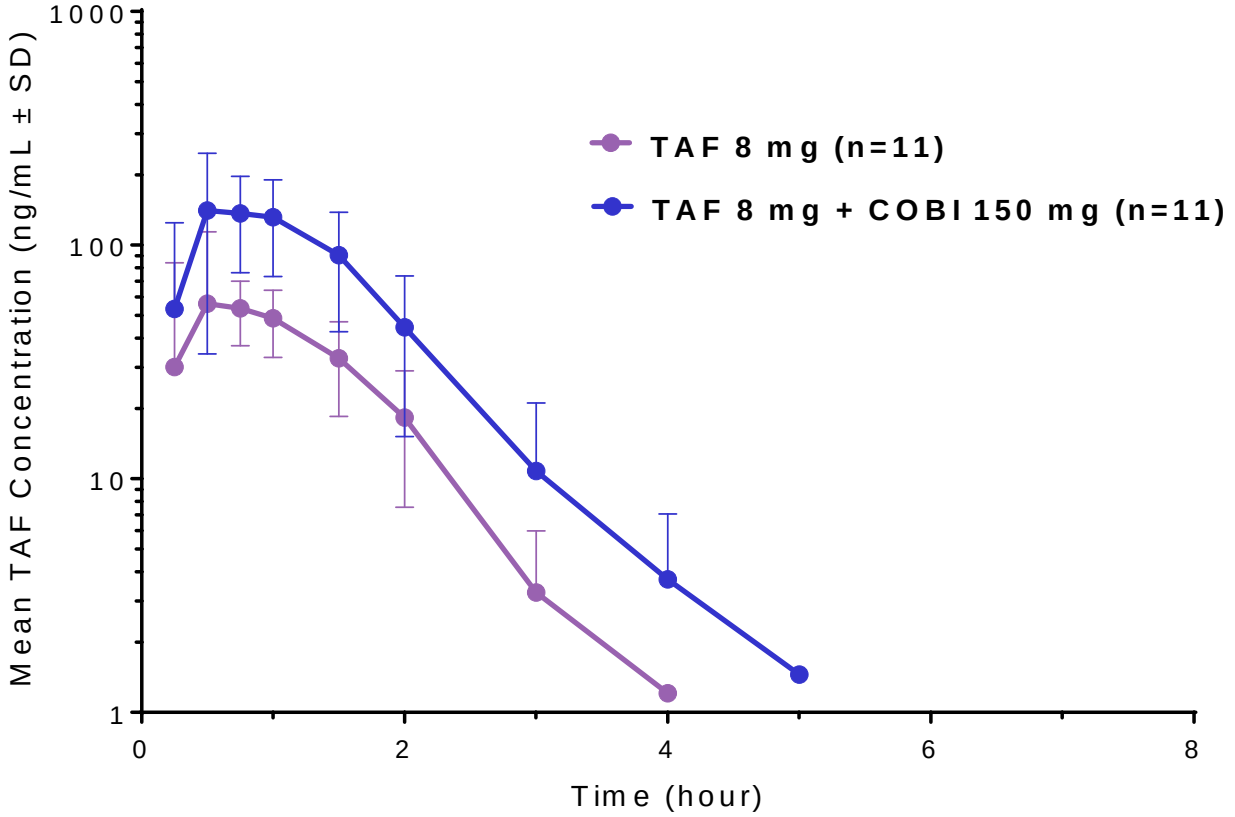
TAF 8 mg: similar anti-HIV activity to TDF 300 mg

TAF 25 mg: more potent anti-HIV activity than TDF 300 mg

- Higher intracellular TFV-DP: potential for improved efficacy
- Lower plasma TFV: potential for improved safety
- Selected for further clinical development

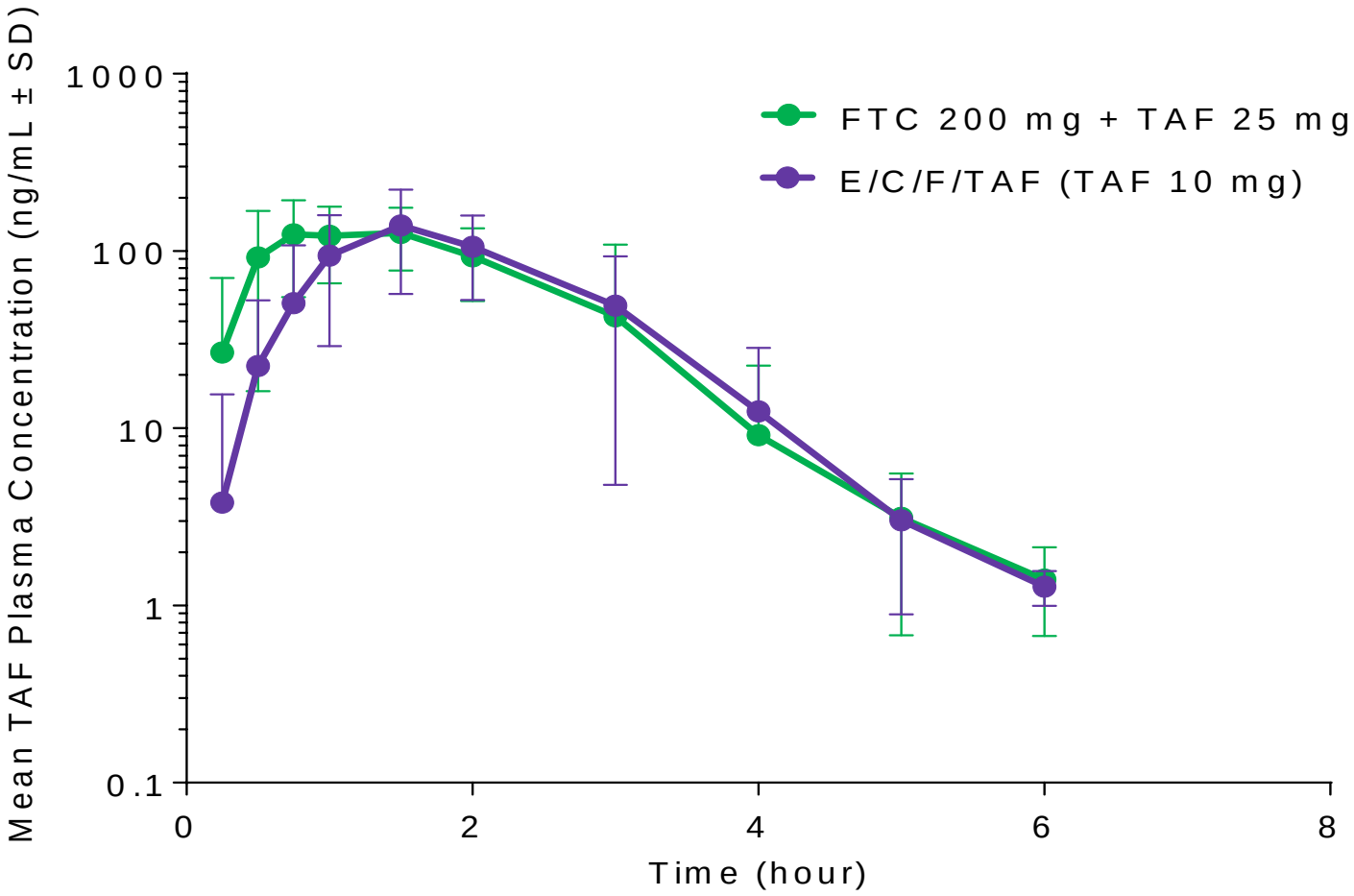
Ruane P, et al. J Acquir Immune Defic Syndr 2013;63:449-5.

TAF Availability Increased by COBI via Inhibition of Intestinal Pgp

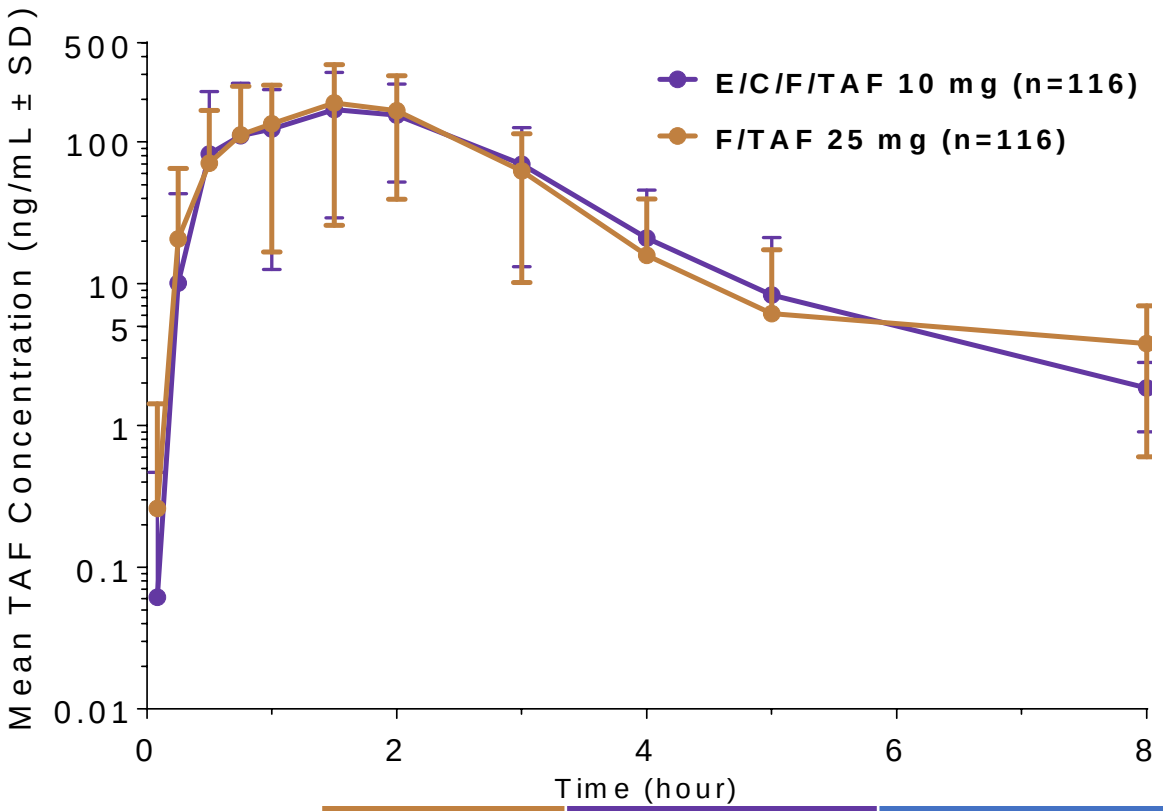


	TAF	
Mean (%CV)	**TAF 8 mg + COBI**	**TAF 8 mg**
AUC_{last} (ng•h/mL)	188 (27)	81 (44)
C_{max} (ng/mL)	142 (33)	71 (73)

TAF 10 mg in E/C/F/TAF STR



F/TAF 25 mg FDC was Shown to be Bioequivalent to E/C/F/TAF STR



TAK PK Parameter Mean (%CV)	F/TAF 25mg	E/C/F/TAF 10 mg	GMR (90% CI)
AUC_{last} (ng·h/mL)	374 (43)	369 (41)	100 (96.5, 104)
AUC_{inf} (ng·h/mL)	396 (43)	390 (39)	98.5 (94.6, 103)
C_{max} (ng/mL)	281 (63)	268 (60)	104 (95.5, 112)

*F/TAF (200/25 mg) (test) vs E/C/F/TAF (reference)

Objective of Phase 2/3 PK Substudy

- Evaluate the PK of plasma TFV and intracellular TFV-DP in peripheral blood mononuclear cell (PBMC) in HIV-infected subjects receiving either E/C/F/TAF or the approved STB

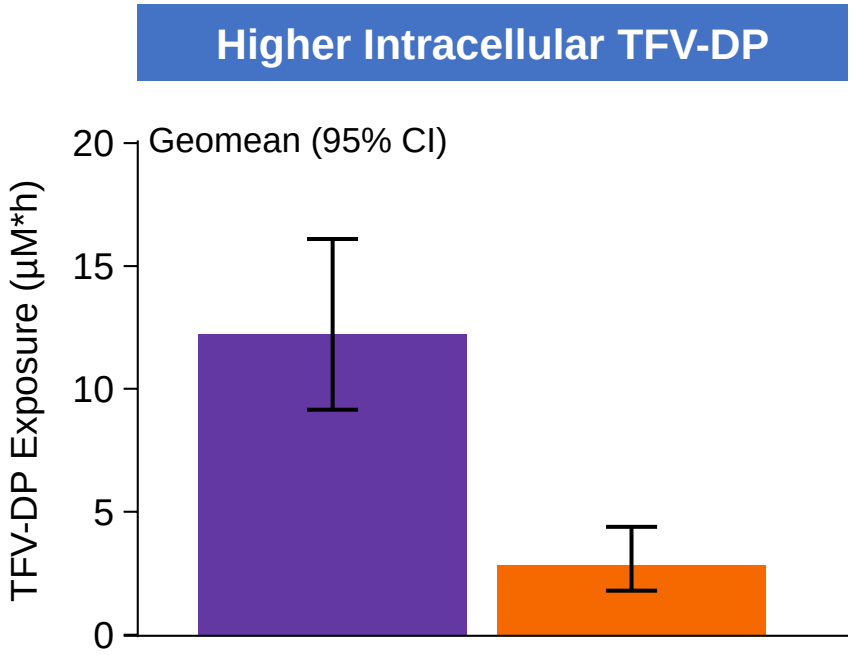
Phase 2/3 PK Substudy Design and Methods

- One Phase 2 and two Phase 3 randomized, double-blind, multi-site studies were conducted to evaluate the safety and efficacy of E/C/F/TAF vs STB in antiretroviral treatment-naïve adult subjects
- Studies designed with a PK Substudy at or between Weeks 4 or 8 to evaluate steady-state TFV and TFV-DP in subjects receiving E/C/F/TAF vs STB
- Data pooled across all 3 studies
- Plasma TFV
  - E/C/F/TAF: n=55
  - STB: n=36
- Intracellular TFV-DP
  - E/C/F/TAF: n=31
  - STB: n=19

Phase 2/3 PK Substudy Data Analysis

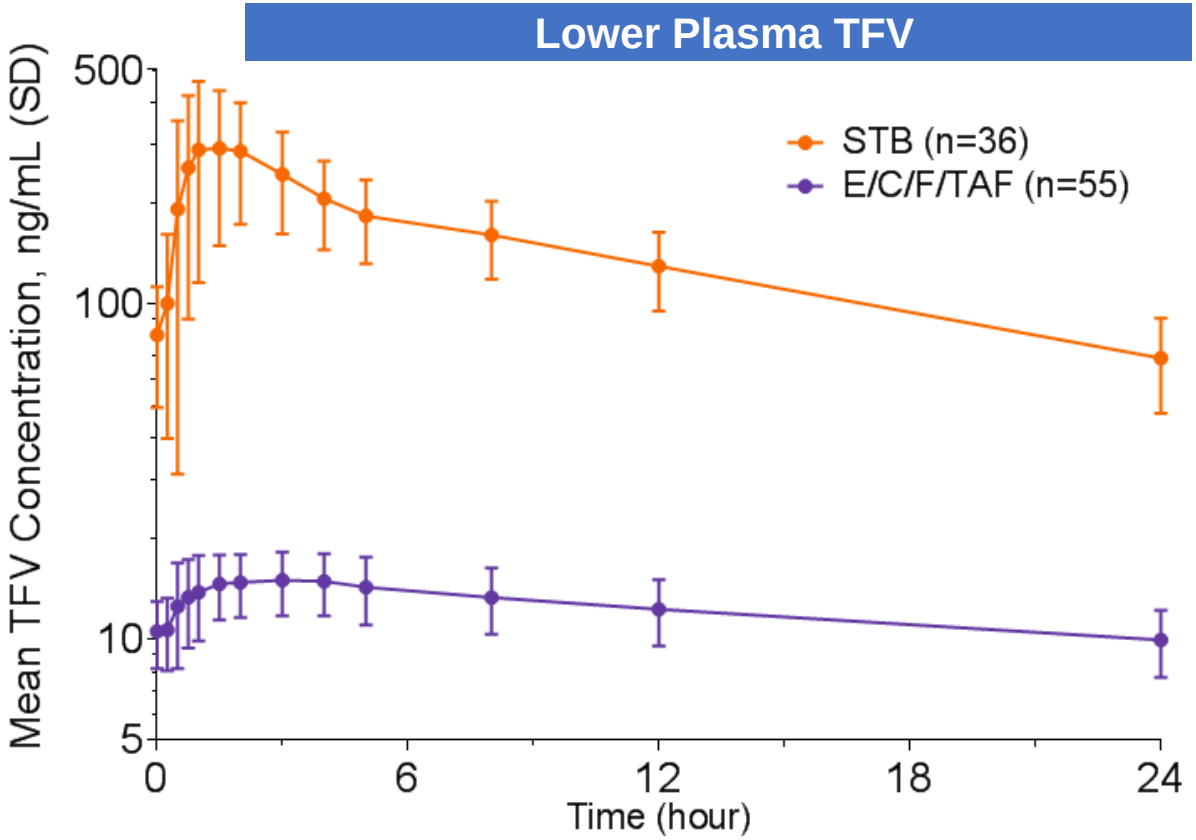
- Bioanalyses conducted by QPS
  - Plasma TFV concentrations were determined via LC/MS/MS
  - Intracellular PBMC TFV-DP concentrations were determined via LC/MS/MS in combination with PBMC cell counting via DNA quantitation procedure
- PK parameters estimated using noncompartmental methods and WinNonlin® software v6.3
- A parametric (normal theory) ANOVA was used for generation of 90% CI for geometric mean ratio (GMR) for TFV and TFV-DP
  - Test treatment: E/C/F/TAF
  - Reference treatment: STB

Intracellular TFV-DP 4.4-Fold Higher Following E/C/F/TAF vs STB



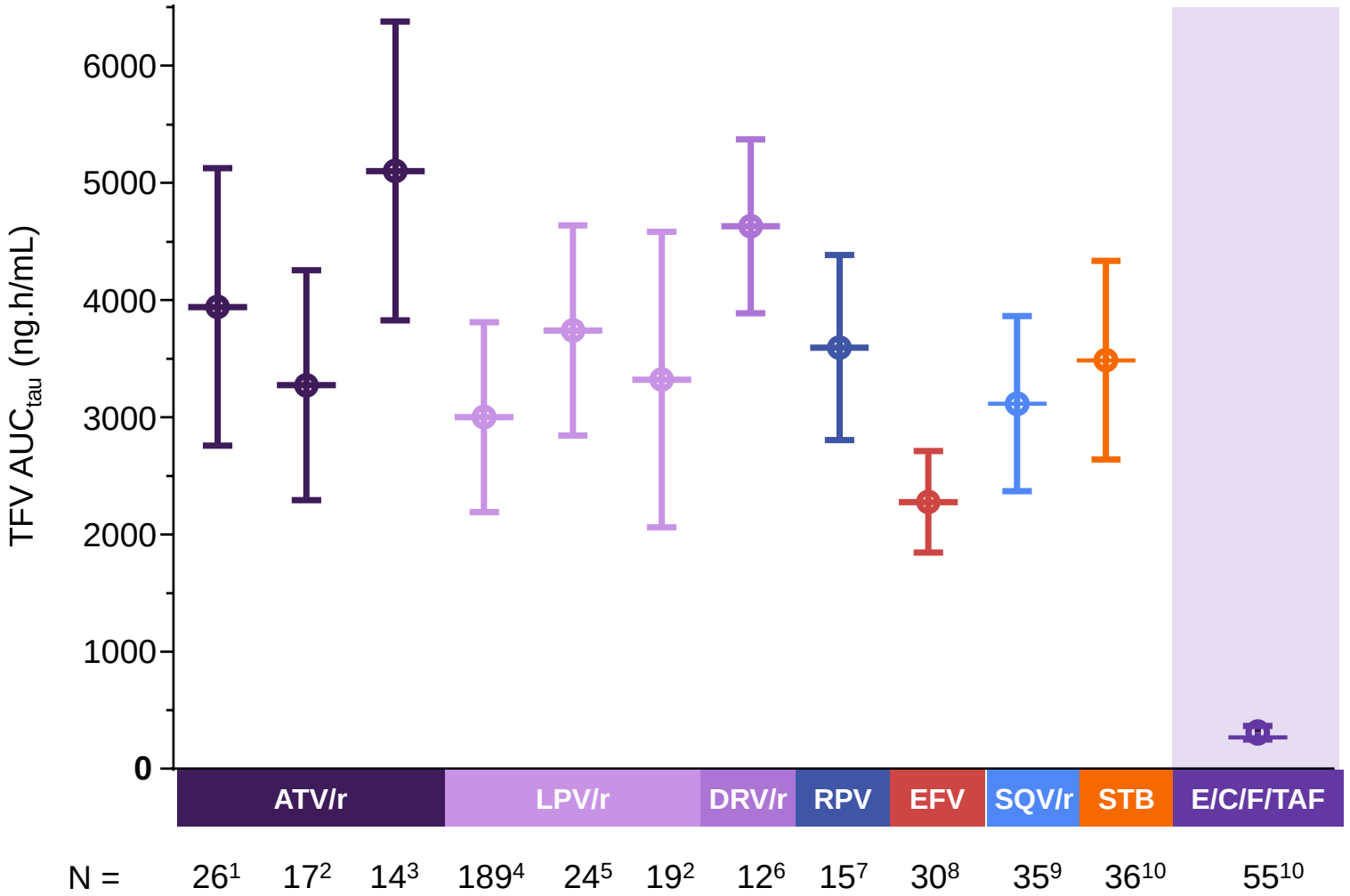
TFV Geomean	E/C/F/TAF n=31	STB n=19	GMR (90% CI)
AUC_{tau} (ng·h/mL)	12.2	2.79	437 (286, 669)

Plasma TFV 91% Lower Following E/C/F/TAF vs STB



TFV Mean (%CV)	E/C/F/TAF	STB	GMR (90% CI)
AUC_{tau} (ng·h/mL)	307 (19)	3480 (24)	8.90 (8.20, 9.65)
C_{max} (ng/mL)	17.4 (19)	420 (28)	15.0 (13.5, 16.7)
C_{tau} (ng/mL)	10.5 (22)	71.7 (31)	4.21 (3.84, 4.62)

TFV Exposure Following TDF-Containing Regimens vs E/C/F/TAF



1. Gilead Study 0114; 2. Zhu. 9th IWCPHT. 2008; Abs 023; 3. Agarwala, 6th IWCPHT. 2005; Abs 16; 4. Jullien V, et al. Antimicrob Agents Chemother. 2005;49:3361-6; 5. Kearney BP, et al. J Acquir Immune Defic Syndr 2006;43:278-83; 6. Hoetelmans RM, et al. Br J Clin Pharmacol 2007;64;655-61 7. Hoetelmans. 6th IWCPHT. 2005; Pos 2.11; 8. Gilead Study GS-US-236-0120; 9. Chittick GE, et al. Antimircrob Agents Chemother 2006;50:1304-10; 10: Gilead Study 0102, 0104, and 0111

Conclusions

- Administration of E/C/F/TAF resulted in markedly higher intracellular TFV-DP concentrations with substantially lower plasma TFV relative to STB
- Higher intracellular concentrations from E/C/F/TAF versus STB demonstrate stable and effective loading of the active moiety TFV-DP into the target cells by TAF
- Lower plasma TFV exposures from E/C/F/TAF versus STB or other TDF-containing regimens may potentially reduce off-target effects associated with TFV, in particular renal and bone toxicity

Acknowledgments

We extend our thanks to study participants and their families as well as the study teams.