Population Pharmacokinetics of Tenofovir (TFV) and Tenofovir Diphosphate (TFVdp) in the Blood, Semen, and Mononuclear Cells of HIV-Negative and Positive Men Receiving Tenofovir Disoproxil Fumarate (TDF) or Tenofovir Alafenamide (TAF)

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Objectives: To evaluate the differences of blood and semen population pharmacokinetics of TFV and its active intracellular anabolite, TFVdp, from two different TFV formulations (TDF and TAF) in HIV-negative (TDF) and positive (TDF or TAF) men.

Methods: 6 blood and semen samples per subject were collected from 24 men (n=8/arm). Blood plasma (BP), peripheral blood mononuclear cells (PBMC), seminal plasma (SP), and seminal mononuclear cells (SMC) were analyzed to measure extracellular TFV and intracellular TFVdp concentrations using LC-MS/MS. A Noncompartmental analysis (NCA) was performed to characterize the pharmacokinetics of TFV from each dosage form and a subsequent population pharmacokinetic model for TDF (TAF model under development) was constructed in NONMEM 7.3.0.

Results: Compared to TDF, TAF has been shown to increase TFVdp PBMC concentrations while decreasing TFV BP concentrations. The aforementioned NCA revealed higher than expected TFV SP and TFVdp SMC concentrations following TAF administration. To further understand these findings, population pharmacokinetic modelling was initiated. A 2-compartment TDF model with first order absorption best described TFV BP pharmacokinetics. PBMC, SP, and SMC compartments were best linked to the TFV central compartment by a fraction of the overall BP TFV clearance (determined by OFV and AIC improvement, goodness-of-fit plots, and %RSE). A model schematic and parameter estimates are shown in figure1.

Conclusions: Tenofovir pharmacokinetics in the male genital tract vary by tenofovir dosage form (TDF vs TAF). These differences may have important implications for viral replication within this compartment. A population pharmacokinetic model can help postulate hypotheses for future studies to elucidate the different mechanisms underlying TFV and TFVdp disposition in this viral sanctuary.