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Pharmacokinetics of Two Common Antiretroviral Regimens in Older HIV-Infected Patients: A Pilot Study

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Abstract

Background—The pharmacokinetics (PK) of antiretrovirals (ARVs) in older HIV-infected patients are poorly described. Here, the steady-state PK of 2 common ARV regimens (tenofovir [TFV]/emtricitabine [FTC]/efavirenz [EFV]; TFV/FTC/atazanavir [ATV]/ritonavir [RTV]) in older non-frail HIV-infected patients are presented.

Methods—HIV-infected subjects ≥ 55 years old not demonstrating the frailty phenotype were enrolled in an unblinded, intensive-sampling PK study. Blood plasma (for TFV, FTC, EFV, ATV, and RTV concentrations) and peripheral blood mononuclear cells (PBMCs; for tenofovir diphosphate [TFV-DP] and emtricitabine triphosphate [FTC-TP] concentrations) were collected at 11 time points over a 24-hour dosing interval. Drug concentrations were analyzed using validated LC-UV or LC-MS/MS methods. Noncompartmental pharmacokinetic analysis was used to estimate PK parameters ($AUC_{0–24hr}$, C_{max}). These parameters were compared to historical values from the general HIV-infected population.

Results—Six subjects on each regimen completed the study. Compared to the general population, these elderly subjects had 8–13% decreased TFV $AUC_{0–24hr}$ and C_{max}, and 19–78% increased FTC and RTV $AUC_{0–24hr}$ and C_{max}. Decreased ATV $AUC_{0–24hr}$ (12%) and increased C_{max} (9%) were noted, while EFV exposure was unchanged (5%) with a 16% decrease in C_{max}. Intracellular nucleoside/tide metabolite concentrations and AUC are also reported for these subjects.

Conclusions—This study demonstrates that the PK of these ARVs are altered by 5–78% in an older HIV-infected population. Implications of PK differences on clinical outcomes, particularly with the active nucleoside metabolites, remain to be explored. This study forms the basis for further study of ARV PK, efficacy, and toxicity in older HIV-infected patients.

Keywords

Pharmacokinetics; Aging; Intracellular Pharmacokinetics

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Introduction

As a direct result of improved antiretroviral (ARV) treatment, patients with chronic HIV infection in the United States are living longer. As such, non-AIDS related diseases are an increased cause of death (1). From 2006 to 2009, the 60–64 year age group saw the largest increases in patients living with HIV/AIDS with the largest age demographic in the 44–49 (19%) age group (2). These numbers will continue to increase as life expectancy increases. An estimated one-half of those living with HIV will be >50 years old by 2015 (2).

Although older HIV-infected adults typically demonstrate excellent virologic response to the initiation of antiretroviral therapy (3, 4), immunologic recovery is frequently diminished compared to younger patients (3, 5), with a slower and blunted recovery of $CD4^+$ cells after ARV initiation. This results in increased mortality and an overall worse prognosis. Every 10 years of additional chronological age provides 35 fewer $CD4^+$ cells/μL during a year of treatment (6, 7). Advanced disease at diagnosis (4) and senescence may partially explain this phenomenon. However, the contribution of altered ARV PK and the resultant risk for adverse events has not been investigated.

Known physiologic changes during aging can affect drug absorption, distribution, metabolism, and excretion, and these changes have been shown to affect clinical outcomes (8, 9). However, little is known about these effects on the PK of ARVs used to treat this growing population of HIV-infected patients. Modest evidence suggests that cellular activation, such as that seen with aging and HIV infection, may increase intracellular phosphorylase activity in the elderly (10), potentially resulting in increased toxicity of nucleoside reverse transcriptase inhibitors (NRTIs) (11). The active intracellular phosphorylated forms of tenofovir and emtricitabine, two such agents, have not been studied in older patients (12–14).

The present investigation sought to characterize the PK of two common, first-line ARV regimens in HIV-infected patients ≥55 years old in order to provide PK parameter estimates for optimal sample design for a population pharmacokinetic/pharmacodynamic (PK/PD) investigation of the effects of aging on ARVs.

Methods

Study Design and Population

Twelve HIV-infected adults ≥ 55 years old were recruited from the University of North Carolina (UNC) Healthcare Infectious Diseases Clinic in Chapel Hill, NC. The protocol was approved by the UNC Biomedical Institutional Review Board and the protocol listed on ClinicalTrials.gov (NCT01180075). Six currently adherent subjects for each of two regimens: either TFV 300mg/FTC 200mg/EFV 600mg administered once daily (Atripla™, Bristol-Myers Squibb, New York, NY) or TFV 300mg/FTC 200mg (Truvada™, Gilead Sciences, Foster City, CA), ATV 300mg (Reyataz™, Bristol-Myers Squibb, New York, NY), and RTV 100mg (Norvir™, Abbott Laboratories, Chicago, IL) administered once daily provided informed consent and underwent screening. This was a convenience sample, selected to provide preliminary PK information for future work. Adherence was defined as ≤3 missed doses in the previous 30 days, with no missed doses in the 3 days immediately preceding pharmacokinetic sampling. Subjects received their regimen for at least 2 weeks prior to sample collection. Screening consisted of vital signs, a physical exam, basic laboratory studies (performed within 45 days of enrollment), and frailty phenotyping. Frailty phenotyping was performed as in Fried et al (15) by the Clinical and Translational Research Center Bionutrition Core at UNC, and includes answering questions regarding unintentional weight loss, fatigue, and physical activity, in addition to measuring grip strength and walk

times. Subjects with unstable vital signs, abnormal lab values meeting DAIDS Grade 1 anemia (hemoglobin < 8.5 mg/dL) or DAIDS Grade 2 criteria for other lab abnormalities, or displaying the frailty phenotype were excluded. Cognitive status was not assessed and cognitive impairment was not an exclusion criteria. For subjects receiving ATV, Grade 2 total bilirubin elevations (up to 2.5 times the upper limit of normal) were allowed, with clinical documentation that the elevation was related to ATV administration and clinically insignificant. Subjects receiving concomitant medications expected to alter the PK parameters of a study drug ≥30% were excluded; subjects receiving ATV were excluded for concomitant proton pump inhibitor or a histamine-2 receptor inhibitor therapy.

PK Visit

Subjects were admitted to the NC TraCS Institute Clinical and Translational Research Center (CTRC) approximately 2 hours prior to their home dosing time of the ARV regimen for vital signs, a complete blood count (CBC) to check for anemia prior to sampling, a brief physical exam, and adherence questioning. Subjects also completed dosing cards for the 3 days prior to their PK visit, and cards were reviewed by study personnel at admission. Blood samples were was collected in K_2EDTA tubes (BD Diagnostics, Franklin Lakes, NJ) for plasma processing and CPT tubes (BD Diagnostics, Franklin Lakes, NJ) for peripheral blood mononuclear cells (PMBCs) at −0.5, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours following a witnessed dose. Subjects receiving TFV/FTC/EFV took their dose on an empty stomach and did not eat for at least 4 hours post-dose; TFV/FTC/ATV/RTV subjects took their dose with a standard research meal at their typical time of medication administration. A whole blood sample was also obtained for future pharmacogenomic analyses. Adverse event questionnaires(16) were administered prior to discharge. Subjects returned for a brief follow-up visit within 30 days of the PK visit which included vital signs, a CBC, a brief physical exam, and adverse event questionnaires.

Sample Collection and Processing

Within 1 hour after collection, K_3EDTA tubes stored on ice were processed by centrifugation at 3000×g at 4°C for 10 minutes. The resultant plasma was aliquoted into labeled cryovials, and stored at −80°C until analysis. Within 2 hours after collection, CPT tubes stored at room temperature were centrifuged at 1300×g for 30 minutes at room temperature with the brake off. After washing the gel with cold 0.9% normal saline, the PBMC-containing plasma was centrifuged at 350×g for 10 minutes at 4°C. After discarding the supernatant, cells were resuspended in red blood cell lysis buffer and allowed to sit at room temperature for 2 minutes. After adding 10mL cold 0.9% normal saline and centrifugation at 300×g for 5 minutes at 4°C, cells were prepared for counting using Trypan blue exclusion and a Countess Cell Counter. After counting, cells were lysed with 70:30 methanol:water solution, and the methanolic extracts obtained after 15 minutes on ice followed by centrifugation at 800×g for 10 minutes at 4°C were stored at −80°C until analysis.

Concentration Analysis

Tenofovir, emtricitabine, efavirenz, atazanavir, and ritonavir concentrations in plasma were determined using validated HPLC-UV methods (17, 18). All methods were validated as mandated by the industry guidance set by the US DHHS, FDA, and CDER (19). For all the above analytes, the dynamic range is 10–10,000 ng/mL. Tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) concentrations were determined using validated LC-MS/MS methods with an Agilent 1200 HPLC system connected to an Agilent 6410 triple quadrupole mass spectrometer (Agilent Technologies, Santa Clara, CA). Briefly, methanolic extracts underwent protein precipitation with 1:1 methanol/1mM ammonium phosphate solution containing the internal standards (^{13}C TFV, ^{13}C ^{15}N FTC, ^{13}C TFV-DP),

followed by evaporation to dryness under nitrogen and reconstitution with 1mM ammonium phosphate. The analytes were eluted from a Waters Xbridge™ C18 (2.1 × 20 mm, 5μm particle size) analytical column (Waters Corporation, Milford, MA) in series with a Thermo Scientific BioBasic AX (50 × 2.1mm 5μm particle size) column (Thermo Fisher Scientific, Waltham, MA). Data were collected using Agilent LC-MS/MS MassHunter Chromatography Software, with positive ion m/z transitions of 448.1/270.1 (TFV-DP) and 488.1/130 (FTC-TP) using electrospray ionization. The dynamic range of the assay is 1–1,000 ng/mL; raw concentration values are normalized for cells counts and molecular mass of the analyte, with final concentration values reported as femtomoles/10^6 cells. All calibrators and quality controls samples were within 15% of the nominal value for both within-day and between-day runs.

All drug concentrations were performed in the UNC Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Laboratory. The lab participates in national and international proficiency testing of its methods, and consistently achieves >95% accuracy in this testing.

Pharmacokinetic and Statistical Analysis

After preliminary graphical analysis, noncompartmental analysis for each drug was performed using Phoenix Win Nonlin v6.1 (Pharsight, Inc; Cary, NC). The maximal concentration (C_{max}) and time of maximal concentration (T_{max}) were determined from visual inspection. Area-under-the-concentration-time curve over 24 hours (AUC) was determined using the trapezoidal rule (linear up/log down interpolation). Terminal half-life was calculated from the log-linear slope of the elimination phase. PK parameter estimates for extracellular drugs (TFV, FTC, EFV, ATV, RTV) were compared to values reported either in the drug's Full U.S. Prescribing Information or the literature. Due to the variable nature of intracellular metabolite concentrations, AUC (linear trapezoidal rule) and average PBMC concentrations across dosing intervals are presented.

To compare these results with published PK parameters for extracellular drugs in the general HIV-infected population, the mean or median PK parameter available in the literature, that as closely represented the study design and data analysis as possible, was used to calculate ratios for C_{max} (peak concentrations) and AUC (drug exposure) of older cohort:general population. For each subject, the parameter of interest was divided by the literature value, and the median ratio for all subjects is reported. Statistical comparisons were made using the Wilcoxon Rank Sum test in SAS JMP7 (SAS Institute, Cary, NC) at a significance level of $\alpha = 0.05$. Due to differing sampling schemes and analytical methodologies between our study and other published reports of TFV-DP and FTC-TP, statistical comparisons were not made for these metabolites.

Results

Subject Demographics and Safety Evaluation

Twelve subjects were screened and enrolled. Demographic data for subjects by regimen are presented in Table 1. Overall, the average age was 59.7 ± 3.9 years, BMI was 29.9 ± 5.4 kg/m^2, and CrCL was 70.1 ± 17.6 ml/min (mean/standard deviation). Equal numbers of Caucasians and African Americans were enrolled on each regimen, and half of all subjects were female. Eleven of twelve subjects had undetectable HIV RNA concentrations at screening; 1 subject, who had initiated TFV/FTC/EFV within the last month, had a viral load of 1372 copies/mL at screening which was <50 copies/mL 3 months later. Mean CD4+ lymphocyte counts were 818 ± 370 cells/mm^3 for all subjects. Subjects reported no missed doses, and all doses in the 3 days prior to the PK visit were taken within 3 hours of the

scheduled administration time. With the exception of one TFV/FTC/ATV/RTV subject who had a dose that was 1.5 hours late, all other doses immediately prior to the PK visit were taken within 30 minutes of the scheduled administration time.

This cohort of older HIV-infected subjects tolerated intensive PK sampling well. No subjects experienced significant changes in CBC values between sampling and follow-up. One subject reported developing a sore throat that spontaneously resolved and deemed by the study physician not to be related to the study intervention.

Noncompartmental Analysis

Concentration-time profiles for each drug are presented in Figure 1a–e. NCA parameter estimates are reported in Table 2 for each drug in each regimen. TFV and FTC parameter estimates are provided separately for each regimen. The terminal half-life and T_{max} for FTC were statistically different between regimens ($p< 0.05$); no statistically significant differences were observed for TFV PK parameters by regimen (all $p>0.05$).

A summary of comparisons to historical values in the adult HIV-infected population for both regimens is presented in Table 3. Compared to published values for TFV (20), FTC (21), and EFV (22), several differences are noted. The $AUC_{0\text{-}24hr}$ and C_{max} of TFV are slightly lower in the TFV/FTC/EFV cohort, with a median ratio of 0.92 for $AUC_{0\text{-}24hr}$ and a median ratio of 0.87 for C_{max}. In contrast, the $AUC_{0\text{-}24hr}$ and C_{max} of FTC were found to be higher in our cohort, with a median ratio of 1.75 for $AUC_{0\text{-}24hr}$ and median ratio of 1.26 for C_{max}. For EFV, $AUC_{0\text{-}24hr}$ was similar to historic controls (median ratio of 1.05), with a lower C_{max} (median ratio of 0.84). These differences did not achieve statistical significance.

For the subjects receiving TFV/FTC/ATV/RTV, comparison to the same TFV (20)/FTC (21) reference parameters indicates similar results for FTC (median ratios of 1.31 for both $AUC_{0\text{-}24hr}$ and C_{max}) and TFV (median ratio 0.90 for $AUC_{0\text{-}24hr}$ and 0.94 for C_{max}). For ATV/RTV co-administered with TFV at a dose of 300mg ATV + 100mg RTV (23), ATV exposures in this cohort are lower (median ratio of 0.88 for $AUC_{0\text{-}24hr}$) with a higher C_{max} (median ratio of 1.09). For RTV, higher $AU_{0\text{-}24hr}$ C and C_{max} were seen, with a median $AUC_{0\text{-}24hr}$ ratio of 1.19 and a median C_{max} ratio of 1.78. These differences did not achieve statistical significance.

Intracellular Metabolite Analysis

For TFV-DP, the median/IQR $AUC_{0\text{-}24hr}$ and the mean concentration over the dosing interval by regimen are reported in Table 4. The comparator available in the literature (24) included mean concentrations over the dosing interval, with a reported value of 76.1 fmol/10^6 cells compared to 128 ± 78 fmol/10^6 cells (mean ± standard deviation) for EFV subjects and 112 ± 78 fmol/10^6 cells for ATV/r subjects in this study, suggestinghigher TFV-DP concentrations in older subjects.

Median/IQR $AUC_{0\text{-}24hr}$ and mean concentration over the dosing interval for FTC-TP are also reported by regimen in Table 4. The comparator available in the literature (21) includes the median 4-hr post-dose concentration, with a reported value of 4000 fmol//10^6 cells compared to 3110 (2100, 4120) fmol/10^6 cells (median/IQR) for EFV subjects and 3100 (2389, 3346)) fmol/10^6 cells for ATV/r subjects in this study, suggesting lower FTC-TP concentrations in older patients.

Discussion

In this PK study of 2 of the recommended first-line ARV regimens (25) in older HIV-infected adults, noncompartmental PK parameters were similar to historic controls. ATV,

EFV, and RTV all undergo significant CYP450-mediated metabolism, and liver mass is known to decrease with age (26–28). Based on a population PK report, higher EFV exposures were expected (29), potentially due to decreased auto-induction of EFV metabolism through CYP3A, but was not seen in this small study of non-frail subjects ≥55 years. Owing to its acid-dependent absorption profile and the potential effects of altered metabolism (30), decreased ATV exposures were expected. Although exposure was similar, peak concentrations decreased, which may be explained by altered absorption (23, 30). RTV concentrations and exposure did increase, however given the complicated PK profile of this drug, it is not possible to determine what factors may be influencing this observation at this time, and merits further exploration.

The observed difference between FTC terminal elimination half-life and T_{max} in the TFV/FTC/EFV and TFV/FTC/ATV/RTV regimens does not appear to be related to a drug-drug interaction or differences in renal function between groups; although the mean creatinine clearance value in the EFV group is lower, this is primarily driven by a single subject. TFV, which is also renally cleared, shows similar trends, but exposure and peak concentrations were lower. Both drugs are substrates for drug transporters (31), and the potential effects of aging on drug transport activity has not been well categorized (32). A recent publication in aged mice suggests both age-related and gender-specific changes in transporter expression (33); these data offer a basis for further exploration of transporter effects on TFV and FTC disposition.

This is one of the few studies to collect intensive PBMC samples and report TFV-DP and FTC-DP values at 11 points over a 24 hour dosing regimen, and the first to look at these metabolites specifically in the elderly population. The observed changes between concentrations in the dosing interval compared to historical data may reflect differences in the intracellular metabolic pathways for the drugs due to increased cellular activation in older patients. FTC is preferentially metabolized in resting cells (34), whereas TFV may be metabolized in either resting or activated cells (35). In the study used for comparison for TFV-DP (24), a polymorphism in gene coding for MRP-4 and tenofovir renal clearance were related to intracellular concentrations, suggesting that alterations in transporter activity could contribute to altered TFV-DP concentrations in older patients.

As chronologic age alone may not adequately describe physiologic changes that occur with disease processes, studying frail older individuals may provide new insight. Frailty is described as a clinical syndrome of decreased functional reserves that increases morbidity and mortality. Frailty is likely due to altered biochemical processes in the body as demonstrated by increased concentrations of inflammatory markers such as TNF-α, IL-6, and CRP (15). A characteristic phenotype has been described (15) and applied to the HIV population, which demonstrates this phenotype at earlier ages than the general population (36, 37). Significant decreases in drug clearance of 50% or greater have been demonstrated in the frail elderly for acetaminophen (38), metoclopramide (39), and antipyrine (40) compared to younger, healthier subjects. This increase in exposure is likely due to a combination of decreased renal clearance and cytokine-induced down-regulation of metabolic enzymes (41). Increased exposure likely contributes to increased toxicity of drugs in frail patients.

The overall goal of this investigation was to use intensive PK sampling and parameters in otherwise healthy HIV-infected population, and so frail subjects were purposefully excluded. Only older subjects were enrolled to provide estimates of PK parameters in this population; 55 years of age was selected at the time of study initiation. Subsequent research and discussion in the literature suggests that HIV-infected patients may be considered “elderly” at age 50 rather than 55 years of age (42).

Due to the small numbers of subjects involved in this investigation, traditional statistical comparisons have limited ability to show differences between these subjects and historic controls. A limitation of this report is the use of historical controls rather than concomitant enrollment of younger subjects using the same study design and analytical methods for drug concentrations. For the extracellular drugs studied, study designs for the comparator data used similar intensive-sampling schemes and analytical methods, and therefore statistical comparisons are presented. For the intracellular metabolites, intensive-sampling schemes are rarely used due to the complexity of cell processing, and analytical methodology varies considerably from laboratory to laboratory. As data for comparison using the methods employed here were not readily available in the literature, values are provided only as a point of reference without formal statistical comparisons.

These data will be used to design a larger, population-based PK/PD study in HIV-infected patients to quantify differences based on age or other patient-specific characteristics differences, frailty being one characteristic. Population PK/PD modeling seeks to characterize variability in drug disposition and effect in a patient population in order to make dosing recommendations based on patient characteristics, and is a powerful and increasingly accepted (43) tool for identifying sub-populations that may benefit from alternative dosing strategies. Ultimately, population PK/PD modeling aims to inform clinicians of any necessary dosing recommendations specific for older HIV-infected populations.

In conclusion, this investigation provides rationale and background for further examination into the area of ARV pharmacokinetics and aging. Subsequent investigations will include the enrollment of a cohort with a broad age range and the presence of the frailty phenotype for a population PK/PD analysis.

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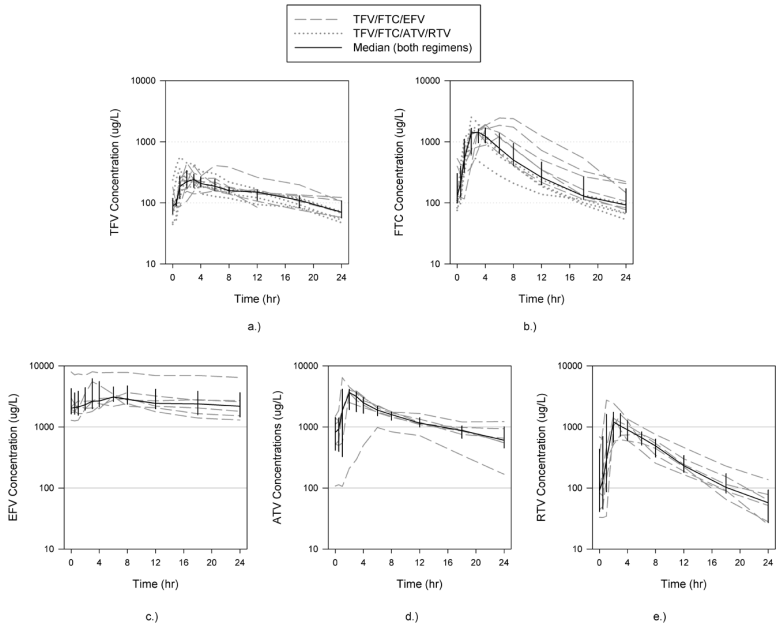

Figure 1.

Table 1

Subject Demographics by Regimen. Data presented as mean ± standard deviation, or number (percentage). Creatinine clearance was calculated using the Cockcroft-Gault equation ($\frac{(140 - age) \times bodyweight}{72 \times \text{serum creatinine}}$, multiplied by 0.85 for females[1]; actual body weight was used unless the subject was >20% above their ideal body weight, and then adjusted body weight was used).

Baseline Characteristics	TFV/FTC/EFV Subjects (n = 6)	TFV/FTC/ATV/RTV Subjects (n = 6)
Age (yrs)	60.7 ± 5.4	58.7 ± 1.4
Race		
Caucasian	3 (50%)	3 (50%)
African American	3 (50%)	3 (50%)
Sex		
Female	4 (66.7%)	2 (33.3%)
Male	2 (33.3%)	4 (66.7%)
Duration with HIV (yrs)	14.3 ± 10.3	8.4 ± 3.9
Duration on current regimen (yrs)	3.5 ± 3.65	3.4 ± 1.7
CD4+ T-cell count (cells/mm^3)	683 ± 226	952 ± 455
HIV RNA <50 copies/mL	5/6	6/6
Creatinine clearance (mL/min)	69.4 ± 25.0	70.9 ± 7.46
BMI (kg/m^2)	27.6 ± 5.6	32.2 ± 4.5

[1] Cockcroft D, Gault M. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31–41.

Table 2

Noncompartmental PK parameter estimates for each drug, by regimen.

Regimen	Drug	terminal half-life (hr)	T_{max} (hr)	C_{max} (ug/L)	C_{24hr} (ug/L)	$AUC_{0–24hr}$ (hr*ug/L)
TFV/FTC/EFV	TFV	13.7 (12.4, 31.6)	3.0 (1.5, 12)	295 (223, 421)	96.8 (66.5, 112)	3.43×10^3 (3.05×10^3, 4.05×10^3)
	FTC	6.24 (5.07, 6.57)	4.0 (2.1, 6.1)	1780 (1410, 2050)	126 (81.0, 210)	1.41×10^4 (1.03×10^4, 1.91×10^4)
	EFV	44.9 (26.6, 68.2)	4.5 (3.0–8.0)	3403 (2840, 6120)	2180 (1460, 3620)	6.08×10^4 (4.60×10^4, 9.60×10^4)
TFV/FTC/ATV/RTV	TFV	11.1 (9.47, 14.1)	1.5 (1.0–2.1)	319 (275, 417)	62.1 (51.0, 80.9)	3.33×10^3 (2.92×10^3, 4.23×10^3)
	FTC	8.53 (7.49, 9.66)	1.9 (1.0–6.0)	1840 (1470, 2130)	78.5 (62.8, 116)	1.05×10^4 (8.54×10^3, 12.4×10^4)
	ATV	6.00 (3.75, 12.0)	2.0 (1.0–6.0)	3750 (2120, 4610)	605 (452, 1000)	3.47×10^4 (2.55×10^4, 3.85×10^4)
	RTV	5.61 (4.18, 7.05)	2.5 (1.0–6.0)	1440 (725, 1880)	57.3 (27.2, 92.5)	6.54×10^3 (7.87×10^3, 1.25×10^4)

TFV: tenofovir; FTC: emtricitabine; EFV: efavirenz; ATV: atazanavir; RTV: ritonavir; T_{max}: time of maximal concentration; C_{max}: maximal concentration; C_{24hr}: concentration at the end of the 24 hr dosing interval; $AUC_{0–24hr}$: area under the concentration-time curve from 0 to 24 hours

Table 3

Median ratios for each drug, by regimen, in comparison to literature values.

	TFV/FTC/EFV			TFV/FTC/ATV/RTV			
	TFV	**FTC**	**EFV**	**TFV**	**FTC**	**ATV**	**RTV**
AUC_{0-24hr}	↓ 0.92	↑ 1.75	↔ 1.05	↓ 0.9	↑ 1.31	↓ 0.88	↑ 1.19
C_{max}	↓ 0.87	↑ 1.26	↓ 0.84	↓ 0.94	↑ 1.31	↑ 1.09	↑ 1.78

TFV: tenofovir; FTC: emtricitabine; EFV: efavirenz; ATV: atazanavir; RTV: ritonavir; C_{max}: maximal concentration; AUC_{0-24hr}: area under the concentration-time curve from 0 to 24 hours.

Table 4

Tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) mean concentrations over a dosing interval and area under the concentration-time curve (AUC), by regimen.

Regimen	Analyte	Mean Concentration over Dosing Interval (fmol/10^6 cells; mean ± SD)	AUC (hr•fmol/10^6 cells; median/IQR)
EFV	**TFV-DP**	128 ± 78	2410 (1450, 5030)
ATV/r		112 ± 77	2110 (1470, 2720)
EFV	**FTC-TP**	2830 ± 830	69400 (53500, 79000)
ATV/r		3160 ± 1190	64400 (56400, 70100)

EFV: efavirenz; ATV/r: (atazanavir/ritonavir); SD: standard deviation; IQR: interquartile range