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Pharmacokinetics of Antiretroviral Regimens Containing Tenofovir Disoproxil Fumarate and Atazanavir-Ritonavir in Adolescents and Young Adults with Human Immunodeficiency Virus Infection▽†

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The primary objective of this study was to measure atazanavir-ritonavir and tenofovir pharmacokinetics when the drugs were used in combination in young adults with human immunodeficiency virus (HIV). HIV-infected subjects ≥18 to <25 years old receiving (≥28 days) 300/100 mg atazanavir-ritonavir plus 300 mg tenofovir disoproxil fumarate (TDF) plus one or more other nucleoside analogs underwent intensive 24-h pharmacokinetic studies following a light meal. Peripheral blood mononuclear cells were obtained at 1, 4, and 24 h postdose for quantification of intracellular tenofovir diphosphate (TFV-DP) concentrations. Twenty-two subjects were eligible for analyses. The geometric mean (95% confidence interval [CI]) atazanavir area under the concentration-time curve from 0 to 24 h (AUC_{0-24}), maximum concentration of drug in serum (C_{max}), concentration at 24 h postdose (C_{24}), and total apparent oral clearance (CL/*F*) values were 35,971 ng · hr/ml (30,853 to 41,898), 3,504 ng/ml (2,978 to 4,105), 578 ng/ml (474 to 704), and 8.3 liter/hr (7.2 to 9.7), respectively. The geometric mean (95% CI) tenofovir AUC_{0-24}, C_{max}, C_{24}, and CL/*F* values were 2,762 ng · hr/ml (2,392 to 3,041), 254 ng/ml (221 to 292), 60 ng/ml (52 to 68), and 49.2 liter/hr (43.8 to 55.3), respectively. Body weight was significantly predictive of CL/*F* for all three drugs. For every 10-kg increase in weight, there was a 10%, 14.8%, and 6.8% increase in the atazanavir, ritonavir, and tenofovir CL/*F*, respectively ($P \leq 0.01$). Renal function was predictive of tenofovir CL/*F*. For every 10 ml/min increase in creatinine clearance, there was a 4.6% increase in tenofovir CL/*F* ($P < 0.0001$). The geometric mean (95% CI) TFV-DP concentrations at 1, 4, and 24 h postdose were 96.4 (71.5 to 130), 93.3 (68 to 130), and 92.7 (70 to 123) fmol/million cells. There was an association between renal function, tenofovir AUC, and tenofovir C_{max} and intracellular TFV-DP concentrations, although none of these associations reached statistical significance. In these HIV-infected young adults treated with atazanavir-ritonavir plus TDF, the atazanavir AUC was similar to those of older adults treated with the combination. Based on data for healthy volunteers, a higher tenofovir AUC may have been expected, but was not seen in these subjects. This might be due to faster tenofovir CL/*F* because of higher creatinine clearance in this age group. Additional studies of the exposure-response relationships of this regimen in children, adolescents, and adults would advance our knowledge of its pharmacodynamic properties.

An increasing number of adolescents and young adults are being infected with human immunodeficiency virus (HIV) (27). However, when new antiretroviral drugs are developed, pharmacokinetic studies are performed in adults and then in children, leaving the adolescent age group often underrepresented. Growth and development are not linear processes (12); thus, antiretroviral pharmacokinetics in adolescents and young adults may differ from those in young children and older adults (4, 15, 26).

Once-daily antiretroviral drugs may be preferred in the treatment of HIV-infected young adults to improve adherence to treatment regimens (24). Tenofovir disoproxil fumarate (TDF [Viread]; Gilead Sciences, Foster City, CA), a nucleotide reverse transcriptase inhibitor, and atazanavir (Reyataz; Bristol Myers Squibb, Princeton, NJ), a protease inhibitor, represent highly efficacious once-daily agents for the treatment of HIV (2, 7, 11, 20, 22, 23). Antiretroviral regimens, including TDF and ritonavir-boosted atazanavir, have proven efficacious in HIV-infected adults (18). Unfortunately, there are no intensive pharmacokinetic data on these agents in combination in HIV-infected adolescents or young adults. Additionally, a high rate of virologic failure was recently observed in a study of

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adolescents switched to a once-daily regimen that included atazanavir-ritonavir (16). In this study, three of four previously virologically suppressed adolescents who experienced virologic failure upon switching to atazanavir-ritonavir were on TDF. This report highlights the need to fully characterize the pharmacokinetics and potential interactions of antiretroviral drugs in adolescents before prescribing them in this patient population.

Children and adolescents have faster apparent oral clearances of atazanavir and tenofovir than adults. Thus, they require higher doses on a mg/m^2 basis to achieve similar exposures (9, 15). The age or size when clearance slows to adult values is unknown and likely differs among antiretroviral drugs. Additionally, there is a bidirectional drug-drug interaction between TDF and atazanavir. In HIV-infected adults, TDF causes an approximate 25% decrease in the atazanavir area under the concentration-time curve (AUC) when the drug is given as either unboosted or ritonavir-boosted atazanavir, and the unboosted atazanavir minimum concentration of drug in serum (C_{min}) is reduced 40% when the drug is given with TDF (25). Conversely, the tenofovir AUC and maximum concentration of drug in serum (C_{max}) are increased 37% and 34%, respectively, in the presence of atazanavir in healthy volunteers (1). The magnitude of this interaction is not well characterized in HIV-infected adults, and there are no intensive pharmacokinetic data on this interaction in children and adolescents.

The primary objective of this study was to determine the pharmacokinetics of atazanavir-ritonavir and tenofovir when used in combination to treat HIV-infected adolescents and young adults. Secondary objectives included evaluating predictors of atazanavir and tenofovir plasma pharmacokinetics and describing and evaluating predictors of the intracellular concentrations of tenofovir diphosphate (TFV-DP).

(This study was presented at the Eighth International Workshop on Clinical Pharmacology of HIV Therapy, April 16–18, 2007, Budapest, Hungary, as oral abstract 12.)

MATERIALS AND METHODS

Subjects. HIV-infected persons ≥18 to <25 years old on a stable antiretroviral regimen containing 300 mg TDF once daily plus 300/100 mg atazanavir-ritonavir once daily plus at least one other nucleoside reverse transcriptase inhibitor for at least 28 days were eligible to participate. There were no CD4 count or viral load restrictions. Subjects who were pregnant, required active therapy for a malignancy, had a gastrointestinal condition which could interfere with drug administration or absorption, alanine or aspartate aminotransferase values >5 times the upper limit of normal, serum creatinine ≥2.5 times the upper limit of normal, concurrent treatment with a protease inhibitor other than atazanavir-ritonavir or a nonnucleoside reverse transcriptase inhibitor, hemoglobin of ≤7 g/dl, or a severe clinical toxicity(ies) were excluded. Subjects could not be on the following agents within 1 week prior to the intensive pharmacokinetic visit: antiarrhythmics; warfarin; antiepileptics; itraconazole; voriconazole; astemizole; terfenadine; rifampin; irinotecan; cidofovir; valganciclovir; midazolam; triazolam; bepridil; diltiazem; nifedipine; verapamil; ergot derivatives; cisapride; herbal products, including but not limited to St. John's wort, garlic supplements, and echinacea; lovastatin; simvastatin; cyclosporine; tacrolimus; fluticasone; investigational drugs; pimozide; clarithromycin; erythromycin; or proton pump inhibitors.

This study was conducted through the Adolescent Trials Network for HIV/AIDS Interventions. The study was approved by the institutional review boards at each site recruiting subjects, and all subjects provided written informed consent.

Design. This was a multisite, open-label, 24-h, intensive pharmacokinetic study. Subjects were contacted via telephone for the 2 days preceding the intensive pharmacokinetic visit to ensure adherence to and appropriate timing of medication administration. For the intensive pharmacokinetic visit, subjects were admitted fasting, a predose concentration for quantification of atazanavir, ritonavir, and tenofovir was obtained, a light-fat meal (400 to 500 kcal and 13 g fat) was consumed, and an observed dose of study medication was administered (time 0). Blood was obtained at the following intervals postdose for quantification of atazanavir, ritonavir, and tenofovir plasma pharmacokinetics: 1, 2, 4, 6, 8, 12, and 24 h. Peripheral blood mononuclear cell samples (PBMCs) were obtained at 1, 4, and 24 h postdose for quantification of intracellular TFV-DP concentrations.

Bioanalyses. (i) Atazanavir-ritonavir in plasma. Plasma was separated and frozen at −70°C within 30 min of blood collection. Atazanavir and ritonavir plasma concentrations were measured using a simultaneous, validated, reversed-phase high-performance liquid chromatographic (HPLC) UV detection method (University of Colorado antiviral pharmacology laboratory, Denver, CO). Briefly, after the addition of internal standard, a liquid-liquid extraction procedure with t-butylmethylether at basic pH was used to prepare the samples. The chromatographic separation of the compounds and the internal standard was accomplished on a Waters YMC HPLC 100- by 4.6-mm reversed-phase octyl column with a 3-micron particle size (Waters Corp., Milford, MA). The mobile phase consisted of 54.7% 20 mM acetate buffer–45.3% acetonitrile, pH 4.9, with an isocratic flow rate of 1 ml/min. Detection and quantification of the drugs was at 212 nm. For both atazanavir and ritonavir, the assay was linear over the range of 20 to 20,000 ng/ml, with a minimum limit of quantification of 20 ng/ml using 0.2 ml of human plasma. The standard curves generated had coefficients of determination greater than 0.9988. Precision and accuracy were measured in quality controls at 75, 750, and 7,500 ng/ml, and all accuracies were within 15% of the nominal concentration, with percent relative standard deviations of less than 10%.

(ii) Tenofovir in plasma. Plasma concentrations of tenofovir were determined by a validated LC-tandem mass spectrometry (LC-MS-MS) assay (University of Colorado antiviral pharmacology laboratory, Denver, CO) (6). Briefly, after the addition of adefovir as the internal standard, trifluoroacetic acid was used to produce a protein-free extract. Ten-microliter aliquots of the samples were injected into the HPLC column with the mobile phase (3% acetonitrile–1% acetic acid, aqueous) flowing isocratically at 0.2 ml/min with 7-min sample run times. Chromatographic separation was achieved with a Polar-PR Synergi 2-mm by 150-mm reversed-phase analytical column. Detection of tenofovir was achieved by electrospray ionization MS-MS (TSQ quantum; Thermo Fisher, San Jose, CA) in the positive ion mode using 288/176 and 274/162 transitions, respectively. The method was linear from 10 to 750 ng/ml, with a minimum quantifiable limit of 10 ng/ml when 0.25-ml aliquots were analyzed. Accuracy and precision were within ±15%.

(iii) Intracellular TFV-DP. PBMCs were isolated using 8-ml citrate cell preparation tubes, and a hemocytometer was used to obtain the cell count. An indirect method was developed that first isolated TFV-DP from tenofovir-monophosphate and tenofovir. TFV-DP was then dephosphorylated with acid phosphatase to form tenofovir. Tenofovir was desalted and concentrated, making its tandem mass spectral detection possible. Intracellular TFV-DP concentrations in PBMCs were determined with a validated LC-MS-MS assay using a TSQ quantum (ThermoElectron, San Jose, CA) (University of Colorado antiviral pharmacology laboratory, Denver, CO) (13). The assay was linear in the range of 50 fmol to 10,000 fmol per sample. The minimal quantifiable limit is 10 fmol/million cells when 5 million cells are analyzed. Accuracy and precision are within ±15%.

Pharmacokinetic analyses. The atazanavir, ritonavir, and tenofovir AUCs for the 0- to 24-h dosing intervals (AUC_{0-24}) were determined by using the linear-log trapezoidal rule and noncompartmental methods (WinNonLin version 5.0.1; Pharsight Corporation, Mountain View, CA). The C_{max}, time to C_{max} (T_{max}), and concentration at 24 h postdose (C_{24}) values were determined visually. The total apparent oral clearance (CL/F) was determined as dose/AUC_{0-24}.

Statistical analyses. This study was designed to enroll 30 individuals, with the goal of accruing 20 evaluable subjects. The following criteria were applied a priori to consider a subject's concentrations evaluable: (i) subject had to have pharmacokinetic samples obtained at the following times during the 24-h study period: predose and 1, 4, 8, 12, and 24-h postdose, and (ii) subject must have been adherent to medication administration as evidenced by detectable predose atazanavir (>20 ng/ml) and tenofovir plasma (>10 ng/ml) concentrations.

Creatinine clearance was estimated by using the Cockcroft-Gault equation (5). Adjusted body weight was used in the Cockcroft-Gault formula if a subject was ≥130% of ideal body weight.

Linear regression analyses were used to evaluate predictors of atazanavir, ritonavir, and tenofovir pharmacokinetics. Data were log transformed to reduce skewness when necessary. All statistical tests were performed in SAS version 9.1 (SAS, Cary, NC). There were no adjustments made for multiple comparisons.

TABLE 1. Characteristics of study subjects[a]

Subject characteristic	Value (median [range])
Age (yr)	23 (18.6–24.9)
Weight (kg)	70.3 (46.9–131.6)
Body surface area (m^2)	1.86 (1.45–2.62)
Serum creatinine (mg/dl)	0.8 (0.6–1.3)
Total bilirubin (mg/dl)	1.6 (0.4–4.7)
Creatinine clearance (ml/min)[b]	129 (78.9–274.8)
CD4 count (cells/mm^3)	430 (12–959)

[a] Twenty-two subjects were evaluated.
[b] Estimated using the Cockcroft-Gault equation.

RESULTS

Twenty-five (11 female and 14 male) subjects enrolled and completed the study. The data for three subjects were excluded from the plasma analyses due to tenofovir and/or atazanavir predose concentrations below the limits of assay detection (i.e., nonadherence). Thus, 22 subjects were eligible for the pharmacokinetic analyses. Of the 22 subjects eligible for the data analyses, all subjects were Tanner stage 5. The racial distribution for the 22 subjects was 14 black, 2 white, 5 other or mixed, and 1 unknown. Six of these subjects were of Hispanic or Latino ethnicity. In addition to atazanavir-ritonavir and TDF, concomitant antiretroviral drugs included emtricitabine (n = 17), delayed-release didanosine (n = 2), stavudine (n = 1), and abacavir and lamivudine (n = 2). Seventy-three percent of subjects had viral loads of <400 copies/ml. Among those with detectable HIV-1 RNA values, the values ranged from 431 to 27,914 copies/ml. The characteristics of the study subjects are shown in Table 1.

The geometric mean (95% confidence interval [CI]) atazanavir, ritonavir, and tenofovir plasma pharmacokinetic parameters are shown in Table 2. In regression modeling, gender and race were not predictive of atazanavir or tenofovir pharmacokinetics. No significant association between atazanavir concentrations and total bilirubin levels was observed in this study. Ritonavir concentrations were associated with atazanavir concentrations. For every 1,000 ng/hr/ml increase in the ritonavir AUC, there was, on average, a 6.4% increase in the atazanavir AUC (P = 0.02). Weight was associated with both the atazanavir (Fig. 1) and tenofovir CL/F. For every 10-kg increase in weight, there was, on average a 10% increase in the atazanavir CL/F (P = 0.0005) and a 6.8% increase in the tenofovir CL/F (P = 0.003). The relationships were similar for body surface area and the atazanavir (P = 0.004) and tenofovir (P = 0.013) CL/F values. When data for the four patients weighing >120 kg were removed, the slopes for both drugs remained similar, though the P values were no longer significant (P value of 0.1 for atazanavir clearance and P value of 0.2 for tenofovir). Renal function was predictive of tenofovir CL/F. For every 10 ml/min increase in creatinine clearance, there was, on average, a 4.6% increase in the tenofovir CL/F ($P < 0.0001$) (Fig. 2). This association remained significant even after the data for the subject with an estimated creatinine clearance of 274 ml/min was removed (P = 0.003). There was no association between HIV-1 RNA level and atazanavir or tenofovir pharmacokinetics.

Multiple regression confirmed the contribution of weight to the atazanavir CL/F and renal function to the tenofovir CL/F. When weight, gender, and race were included in a multivariate model, weight remained the only significant predictor of atazanavir CL/F (P = 0.0015). When renal function, weight, race, and gender were included in a multivariate model, only estimated creatinine clearance remained significantly predictive of the tenofovir CL/F (P = 0.008).

The intracellular TFV-DP concentrations for 21 subjects are shown in Fig. 3. One subject had suspect samples (hemolyzed, very-low cell counts, and concentrations above the limits of assay detection), and that subject's data were therefore excluded from these analyses. The geometric mean (95% CI) TFV-DP concentrations at 1, 4, and 24 h postdose were 96.4 (71.5 to 130), 93.3 (68 to 130), and 92.7 (70 to 123) fmol/million cells. There was an association between renal function, tenofovir AUC, and tenofovir C_{max} and intracellular TFV-DP concentrations, although none of these associations reached statistical significance. For every 10 ml/min increase in creatinine clearance, there was, on average, a 4% decrease in intracellular TFV-DP concentrations (P = 0.12). For every 1,000 ng · hr/ml increase in the tenofovir AUC, there was, on average, a 25% increase in TFV-DP (P = 0.16). For every 100 ng/ml increase in the tenofovir C_{max}, there was, on average, a 21% increase in TFV-DP concentrations (P = 0.15).

DISCUSSION

These are the first intensive pharmacokinetic data on the combination of atazanavir-ritonavir and TDF in young adults. The atazanavir concentrations observed in our patients in the presence of tenofovir were similar to what was previously observed in older adults receiving this combination (25). The Puzzle 2 pharmacokinetic substudy included 10 HIV-infected males aged 33 to 59 receiving atazanavir-ritonavir plus TDF and at least one other nucleoside reverse transcriptase inhibitor. In that study, the mean (percent coefficient of variation [%CV]) atazanavir $AUC_{0\text{-}24}$, C_{max}, C_{24}, and CL/F values were 39,231 ng · hr/ml (59), 3,443 ng/ml (41), 665 ng/ml (84), and 9.8 liter/hr (51), very similar to the values observed in our patients. This compares with mean (%CV) atazanavir $AUC_{0\text{-}24}$, C_{max},

TABLE 2. Geometric mean atazanavir, ritonavir, and tenofovir plasma pharmacokinetic parameters[a]

Drug	Value (geometric mean [95% CI])			
	$AUC_{0\text{–}24}$ (ng · hr/ml)	C_{max} (ng/ml)	C_{24} (ng/ml)	CL/F (liter/hr)
Atazanavir	35,971 (30,853–41,898)	3,504 (2,978–4,105)	578 (474–704)	8.3 (7.2–9.7)
Ritonavir	7,840 (6,292–9,769)	842 (664–1,064)	71 (53–102)	12.8 (10.3–16)
Tenofovir	2,762 (2,392–3,041)	254 (221–292)	60 (52–68)	49.2 (43.8–55.3)

[a] Pharmacokinetics for 22 subjects were measured.

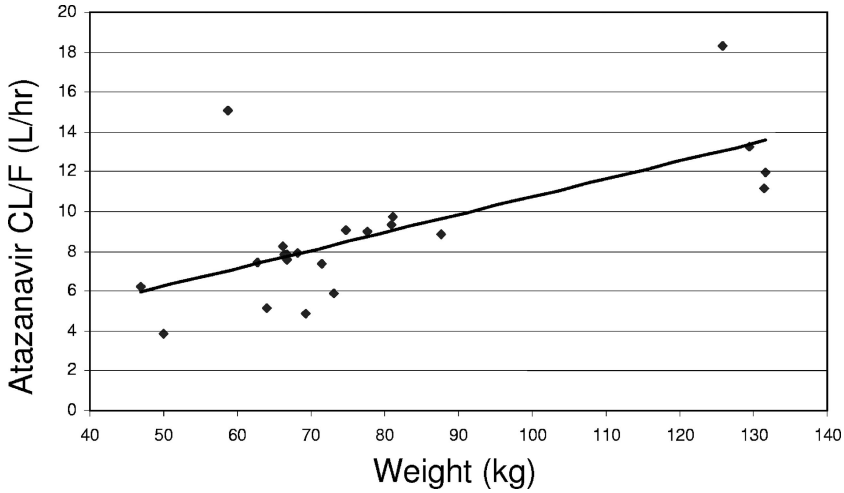

FIG. 1. Weight (in kilograms) is shown on the *x* axis. Atazanavir CL/*F* (in liters/h) is shown on the *y* axis. For every 10-kg increase in weight, there was, on average, a 10% increase in atazanavir CL/*F* ($P = 0.0005$).

C_{min}, and CL/*F* values of 53,761 ng · hr/ml (66), 5,233 ng/ml (58), 862 ng/ml (97), and 5.6 liter/hr (66) when atazanavir is administered without TDF in HIV-infected adults (Reyataz product information; Bristol-Myers Squibb). We also found weight to be significantly predictive of atazanavir CL/*F*. These data suggest that higher doses of atazanavir may be required in very-large patients to achieve the same exposures. Unlike the results of several previous studies (17, 19, 21), we did not detect a strong and statistically significant correlation between atazanavir concentrations and total bilirubin levels. The atazanavir AUC and C_{max} values were very weakly (positively) correlated with total bilirubin concentrations (0.02 and 0.04, respectively) in this study. The correlation between the atazanavir C_{min} and total bilirubin was 0.37, and this increased to approximately 0.5 if we removed the data for three subjects with total bilirubin concentrations of >4 mg/dl. We can only assume that the correlation with C_{min} and total bilirubin concentrations was not significant in our study due to the small sample size and also, possibly, the racial heterogeneity of our patient population. The majority of our subjects were African American; however, several previous studies identifying a correlation included mainly Caucasian subjects. Also, it could be possible that UGT1A1 activity is greater in this age group. There are no published data correlating bilirubin and atazanavir concentrations in children or adolescents.

The tenofovir prescribing information reports the mean (%CV) tenofovir $AUC_{0\text{-}24}$ and C_{max} from seven patients as 3.3 μg · hr/ml (42) and 326 ng/ml (37) (tenofovir [Viread] prescribing information; Gilead, Foster City, CA [accessed January 14, 2007]), very similar to the values observed in our patients. In the aforementioned Puzzle 2 substudy, the tenofovir $AUC_{0\text{-}24}$, C_{max}, and C_{24} values were 2.3 μg · hr/ml, 234 ng/ml, and 45 ng/ml (28), also comparable to the concentrations observed in our patients. A separate study of 28 healthy volun-

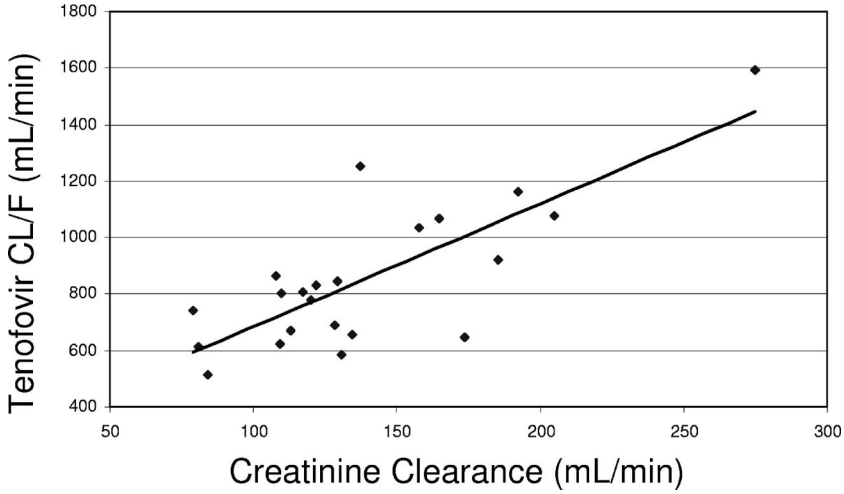

FIG. 2. Creatinine clearance (in milliliters/minute, estimated using the Cockcroft-Gault equation) is shown on the *x* axis. Tenofovir CL/*F* (in milliliters/minute) is shown on the *y* axis. For every 10 ml/min increase in creatinine clearance, there was, on average, a 4.6% increase in tenofovir CL/*F* ($P < 0.0001$).

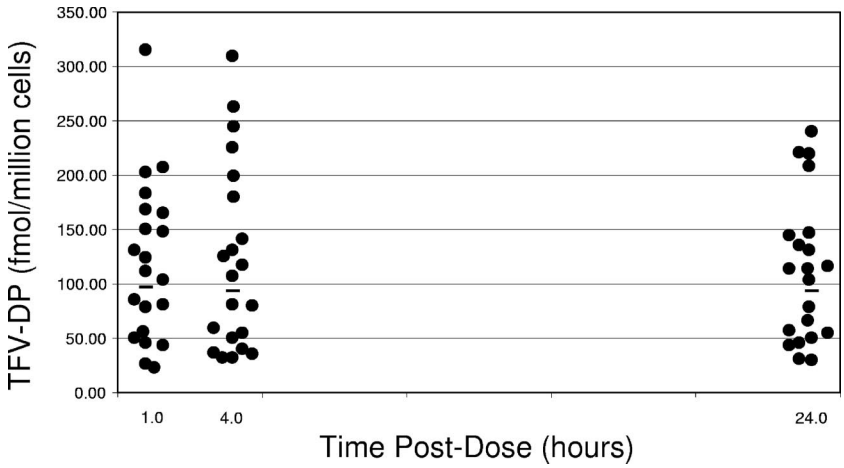

FIG. 3. Time postdose (in hours) is shown on the *x* axis. Intracellular TFV-DP concentrations (in femtomoles/million cells) are shown on the *y* axis. The horizontal lines indicate the geometric mean TFV-DP concentrations at each of the three time points. The geometric mean (95% CI) TFV-DP concentrations at 1, 4, and 24 h postdose were 96.4 (71.5 to 130), 93.3 (68 to 130), and 92.7 (70 to 123) fmol/million cells.

teers aged 19 to 43 found that the tenofovir $AUC_{0\text{-}24}$, C_{max}, and C_{24} values were increased 37%, 34%, and 29%, respectively, when TDF was given with atazanavir-ritonavir (1). Based on those findings, we anticipated that tenofovir concentrations in our patients would be higher than the values reported in the literature for tenofovir without a protease inhibitor, but this was not the case. The lower-than-anticipated tenofovir concentrations found in our study subjects may be due to faster tenofovir clearance as a result of increased creatinine clearance in this young age group. Indeed, we found estimated creatinine clearance to be significantly predictive of tenofovir clearance. Tenofovir concentrations were also lower in obese subjects.

This was the first study to describe TFV-DP concentrations in young adults and in combination with atazanavir-ritonavir. The TFV-DP concentrations observed in this study were similar to those described previously by Hawkins et al. (8) in subjects 31 to 65 years of age (median, 85 to 110 fmol/million cells) and by Kiser et al. (14) in subjects aged 25 to 60 (mean ± standard deviation, 76 ± 40 fmol/million cells). The previous study by Kiser at al. also found tenofovir AUC and renal function to be associated with intracellular TFV-DP concentrations (14).

There are limitations to this study. First, this was an observational trial that did not allow within-person comparisons of changes in tenofovir pharmacokinetics after the addition of atazanavir-ritonavir and/or changes in atazanavir pharmacokinetics after the addition of tenofovir. Therefore, we are only able to describe our subjects' pharmacokinetic parameters and make comparisons to historical data. Also, several PBMC pellet samples arrived hemolyzed or frozen. These were included in the analyses, which may have affected TFV-DP quantification in unpredictable ways.

Although we may have expected higher tenofovir concentrations in our subjects, based on a previous interaction study of healthy volunteers, the atazanavir concentrations observed in this study were similar to historical data. The fact that 16 of 22 subjects had HIV-1 RNA less than or equal to 400 copies/ml suggests that the tenofovir and atazanavir exposures were therapeutic in the majority of these subjects. There are some concentration-effect data for atazanavir with which to compare our data. In the BMS-089 study, in which subjects received stavudine and lamivudine in combination with either atazanavir alone or ritonavir-boosted atazanavir, 85% of treatment-naïve subjects with atazanavir troughs between 327 to 764 ng/ml had an undetectable viral load at week 48 of treatment (3). However, there are very limited data correlating tenofovir levels with response. A previous study of TDF in 18 children aged 8.3 to 16.2 found that tenofovir serum AUCs in virologic responders (median, 3,800 ng · hr/ml) were higher than in nonresponders (median, 2,510 ng · hr/ml) (10). The geometric mean tenofovir exposures in our study subjects (2,762 ng · hr/ml) were closer to the exposures in the "virologic nonresponder" subjects in that study. Considering that atazanavir and atazanavir-ritonavir have been shown to increase tenofovir concentrations in prior studies, our findings provide a basis for concern about tenofovir exposures in young adults not receiving atazanavir-ritonavir or another protease inhibitor. Specifically, could tenofovir exposures in young adults be even lower when used in regimens that do not include atazanavir or ritonavir? If they are lower, does this have implications for virologic response in this age group? Unfortunately, there are very limited concentration-effect data with tenofovir; thus, it is currently unclear what the lower threshold for tenofovir exposures should be. The lack of exposure-response relationships in our study may also be a function of the heterogenous patient population included (i.e., the study included treatment-naïve and experienced subjects, and the other nucleoside reverse transcriptase inhibitor(s) the subjects were taking were not controlled for).

In conclusion, the pharmacokinetic characteristics of atazanavir, ritonavir, and tenofovir in these young adults are consistent with historical data, though we anticipated higher tenofovir concentrations, based on a tenofovir/atazanavir-ritonavir interaction study of healthy volunteers. Additional studies of exposure-response relationships of this regimen in children, adolescents, and adults would advance our knowledge of its pharmacodynamic properties.

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