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THERAPEUTIC DRUG MONITORING OF PROTEASE INHIBITORS AND EFAVIRENZ IN HIV-INFECTED INDIVIDUALS WITH ACTIVE SUBSTANCE RELATED DISORDERS

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Abstract

Background—Achieving targeted antiretroviral (ART) plasma concentrations during long-term treatment in HIV-infected patients with substance related disorders (SRD) may be challenging due to a number of factors including medication adherence, co-infection with hepatitis B or C virus, medication intolerance and drug interactions. One approach to investigate these factors is to conduct therapeutic drug monitoring (TDM) to measure ART exposure during treatment. The objective of this study was to utilize TDM to compare efavirenz and protease inhibitor pharmacokinetics in patients with and without SRDs.

Methods—This was a multi-center, cross-sectional open-label study in patients with HIV-1 infection receiving ART, with active (n=129) or without (n=146) SRD according to National Institute on Drug Abuse criteria. 275 subjects who were receiving either protease inhibitor- or efavirenz-based ART regimens for more than 6 months were enrolled at four HIV treatment centers with an equal distribution of SRD and non-SRD at each site. Patients were instructed during enrollment visits with regard to the importance of adherence prior to and after study visits. Demographics and routine clinical laboratory tests were recorded.

Results—Among the 275 patients, 47% had SRD with at least one substance. There were no significant differences between SRD and non-SRD groups for race, gender, age, or CD4 count at entry. A significantly higher proportion of patients with SRD had an entry HIV RNA plasma concentration > 75 copies/ml compared to patients without SRD (40% vs. 28%, p=0.044). Logistic regression modeling revealed an association between HIV RNA plasma concentration and African-American race (p=0.017). A significantly higher proportion of SRDs also had an efavirenz or protease inhibitor trough concentration below the desired range (23% vs. 9%, p=0.048). Significantly lower trough concentrations were noted in patients with SRDs receiving atazanavir (0.290 vs. 0.976 μg/mL) or lopinavir (3.75 vs. 5.30 μg/mL).

Conclusions—The pharmacokinetic data indicate differences between HIV-infected patients with and without SRD that may influence viral load suppression during long-term ARV treatment. These findings require additional investigation in a randomized design with more intensive

pharmacokinetic assessment to identify individual factors that are contributing to suboptimal ARV exposure in patients with SRDs.

BACKGROUND

The global HIV epidemic continues to grow, and in many countries is associated with substance related disorders (SRDs). [1–5] This underscores the need to develop individualized treatment programs that provide clinical care for both HIV and SRDs in an integrated setting.[6–15] Furthermore, achieving successful antiretroviral therapy in HIV-infected patients with SRDs is often considered to be complicated by a number of factors that may lead to suboptimal antiretroviral exposure.. [16–21] Although it is well appreciated that ART adherence is important to achieve sustained viral suppression, many clinicians often indicate that this goal is a challenge in patients with SRDs due to anticipated poor adherence. [22–26] In addition, patients with SRDs are often perceived to have co-morbidities that preclude successful antiretroviral adherence. Disease complexity factors such as co-infection with tuberculosis, malaria, hepatitis B and C, or behavioral health disorders and cancer may influence antiretroviral exposure. [27–30] Another contributing factor in complexity in these patients is the multiple medications that are commonly prescribed which may result in negative pharmacokinetic interactions and unpredictable plasma concentrations of antiretrovirals. [31–40]

In this study, we utilized TDM as a clinical research strategy to compare efavirenz and HIV-1 protease inhibitor pharmacokinetics in patients with and without active SRDs. Clinical interest in TDM is based on the observed inter-individual variation in antiretroviral pharmacokinetics that results in a wide range of drug exposure from fixed-dose ARVs in combination regimens. Thus, TDM may serve as measurement of pharmacokinetic effects which could better characterize antiretroviral drug exposure among HIV-infected populations with and without SRDs. The clinical utility of TDM may also benefit from the rapid evolution in the availability of phenotypic assays that generate a target inhibitory concentration, *e.g.* EC_{50}, as a basis for adjusting individual ARV dosages. [33, 41–49] The inhibitory quotient (IQ) is a calculation that reflects the relationship between the drug concentration and the relative susceptibility of the virus to a particular drug. [50] In general, the higher the IQ, the more likely the drug exposure is sufficient to inhibit viral replication. However, a recent randomized trial did not demonstrate a benefit to TDM-guided combination antiretroviral therapy (cART). [51] As mentioned above, an important pharmacologic factor that contributes to interest in utilizing TDM in patients with SRDs and others is the potential for lower plasma ARV concentrations that may result from complex drug interactions, thus resulting in lower IQs and subsequent treatment failures.

The objective of our study was to compare efavirenz and HIV-1 protease inhibitor plasma concentrations during chronic treatment in HIV-infected patients with and without active SRD on combination antiretroviral therapy.

METHODS

This study was conducted from May 2003 through May 2007. Patients > 18 years of age with confirmed HIV-1 infection were enrolled at four HIV treatment and research centers in Bronx, New York, Rochester, New York, Miami, Florida and Cleveland, Ohio. Subjects with active substance abuse were identified by the clinical investigators according to the National Institute on Drug Abuse (http://www.drugabuse.gov/) criteria (see reference 67 for detailed information). The participants were receiving either an efavirenz- or PI-based combination ART regimen with dual nucleoside analogs for more than 6 months. The study

protocol was reviewed and approved by the University at Buffalo Institutional Review Board (IRB) and the IRB at each participating clinical site.

Patients were identified by the clinical investigators and the details of the study were carefully discussed with the subject prior to enrollment. The subject was asked to read and sign the consent form that was approved by each site. Subjects continued to receive their prescribed antiretrovirals and concurrent medications. All prescribed medications were continued as clinically indicated and changes during the pharmacokinetics study period were recorded. Throughout the study, adherence was monitored by self-reporting as part of routine clinical procedures. Prior to the collection of blood samples, the date, time, and amount of the last three doses of all antiretrovirals and concurrent medications were reported by the patient to the clinician and documented. Blood samples for ARV assays were processed and shipped according to the pharmacology laboratory standard operating procedures.

Pharmacokinetic sampling included a trough sample visit and a directly observed therapy visit. Adherence assessment and counseling were provided at enrollment and prior to each scheduled visit. Subjects took their scheduled ARV doses at the same time for at least four days before the pharmacokinetic sampling visits. Telephone contact was attempted four days before each visit to review the importance of adherence to the medication regimen leading up to the TDM sample visits. On the day of the trough sample visit, subjects arrived at the clinic without taking medications that morning and plasma samples were collected. The DOT visit included a pre-dose sample, plus three additional samples collected following observed medication administration for planned pharmacokinetic modeling, which is currently ongoing.

A secure, interactive website (www.tdm.buffalo.edu) was developed by the pharmacology laboratory for centralized data entry. The data entry process included adherence verification for antiretrovirals and concurrent medications according to the prescribed dosing schedule. Demographic data, active SRD information, and clinical chemistry results including plasma HIV-1 RNA viral load, and CD4+ counts were also recorded. A standard protocol for pharmacokinetic sample collection was used in all four HIV treatment centers.

The laboratory used a high performance liquid chromatography (HPLC) method previously developed, validated, and certified in our laboratory by the New York State Department of Health. [52] Atazanavir was subsequently added to this method and was re-approved. Over the study period, the variation of the assay averaged ≤ 11% across all control levels and all analytes. The accuracy of the drug concentrations reported was validated by participation in the AIDS Clinical Trials Group (ACTG) Proficiency Testing Program. [53, 54] The following literature values for concentrations were used to determine if troughs (C_{trough}) were below, within and above the target ranges: saquinavir 0.2 – 0.4 μg/ml, indinavir 0.15 – 0.20 μg/ml, nelfinavir 1.0 – 1.4 μg/ml, amprenavir 0.3 – 0.7 μg/ml, lopinavir 0.9 – 1.2 μg/ml, atazanavir 0.3 – 1.0 μg/ml and efavirenz 1.0 – 4.0 μg/ml. [55]

Differences between patients with and without active SRD were compared by the Kruskal-Wallis test for continuous variables, and by the $\chi 2$ and Fisher's exact tests for categorical variables. Associations of patient characteristics with CD4+ cell count and plasma HIV RNA were determined using logistic regression models. Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC), and $P < 0.05$ was considered as statistically significant.

RESULTS

Of the 275 patients enrolled, 47% (n=129) had a clinician-identified active substance-related disorder. Table 1 summarizes the active SRDs that were present among the enrolled patients. Tobacco (56%), alcohol (29%), marijuana (16%), and methadone or buprenorphine (15%) were the most commonly used substances in this cohort, while 41% used multiple substances. The demographic characteristics of the study population are summarized in Table 2. The enrolled patients completed 694 study visits. In general, our approach to educate the patient about the importance of accurate medication administration prior to the clinic visit for pharmacokinetic sample collection was successful. Out of the 694 study visits, 88% of patients took their antiretrovirals on a schedule that resulted in an accurate trough sample collection. In addition, the use of a DOT visit provided an additional opportunity to include the subject in the study and further increase confidence in the self-reported adherence information.

A significant difference between patients with and without active SRD was noted in the proportion below, within and above target trough concentration ranges (Table 3). 23% of patients with active SRD had trough concentrations below the target range, compared with 9% in non-SRDs (p=0.048). The median C_{trough} for atazanavir was 0.290 μg/mL (IQR 0.0936-0.714 μg/mL) and 0.967 μg/mL (IQR 0.330–0.931 μg/mL) in the SRD (n=32) and non-SRD arms (n=35), respectively. The median C_{trough} for lopinavir was 3.75 μg/mL (IQR 2.59–6.11 μg/mL) and 5.30 μg/mL (IQR 3.25–7.19 μg/mL) in the SRD (n=26) and non-SRD arms (n=22), respectively. The median C_{trough} for efavirenz was 1.917 μg/mL (IQR 1.221–4.078 μg/mL) and 2.371 μg/mL (IQR 1.690–3.634 μg/mL) in the SRD (n=24) and non-SRD (n=29) arms, respectively. Comparing the active SRD arm with the non-SRD arm, higher concentrations were observed in patients without active SRD, the differences for atazanavir were statistically significant ($p = 0.001$), but not for lopinavir or efavirenz ($p = 0.111$ and $p = 0.211$, respectively).

Active substance use status was correlated with the HIV RNA concentration at entry (Table 3). At the time of TDM, 71% of patients without SRD had an HIV-1 RNA < 75 copies/ml compared to 60% of patients with active SRD (p=0.044). Table 4 illustrates the multivariate linear regression models of the estimated effects of substance use status on HIV RNA concentration and CD4+ lymphocyte count. No patient characteristics were associated with CD4+ cell counts at entry. African American race was the only factor associated with plasma HIV RNA below 75 copies/ml at entry following multivariate analysis (p=0.017, OR 0.457).

Table 5 summarizes the concurrent medications that the patients were receiving during the study period. The table includes primary categories including central nervous system (40%), cardiovascular and renal (15%), antimicrobials (13%), anti-inflammatory (6%), endocrine (7%), and gastrointestinal agents (3%). A number of patients were receiving a medication from more than one of the categories.

DISCUSSION

Individual ARV pharmacokinetics may be affected by variability in drug absorption, protein binding, CYP450 metabolism, and efflux pump (e.g., P-glycoprotein) activity. [56, 57] Drug interactions in HIV-infected patients commonly occur when cART regimens are selected and the patient is already taking other medications. [58] In addition, many patients with active substance use experience drug interactions from SRD treatment with methadone or buprenorphine. [31, 39, 59] Furthermore, active substance is often an important consideration that may influence NNRTI and PI pharmacokinetics during periods of

irregular adherence. Lastly, additional medications for co-morbidities such as hyperlipidemia and depression may lead to drug interactions resulting in an unpredictable pharmacokinetic profile. [39]

Our findings suggest the use of TDM to determine net pharmacokinetic effects in patients with SRD. In addition, our data indicate that substance users can be monitored during a TDM program given adequate adherence counseling and primary care follow up. Furthermore, HIV clinicians should consider complex drug interactions and co-morbidities as interactive pharmacologic factors within an individual patient that, when considered together, are important aspects of delineating individual antiviral exposure during chronic ARV dosing. [6–9] Although these factors are logical and are likely a part of clinical care to varying degrees, some consideration should be given to examining alternative approaches to managing HIV infection that include the use of TDM to identify patients who may benefit from more extensive pharmacokinetic evaluation [33, 41–48].

Another aspect of using TDM to evaluate NNRTI and PI pharmacokinetics is the relationship between adherence and NNRTI and PI plasma concentration measurements. The integration of adherence measurements with pharmacokinetics to arrive at conclusions about drug exposure has been previously described. [60, 61] In our study, patients were able to demonstrate short-term adherence to their regimens in a manner that allowed TDM to be used to gain estimates of drug exposure. Although we excluded some patients in this analysis who were not able to have their samples drawn within the desired range for sample collection times, we anticipate that all of the data will be used in conjunction with pharmacokinetic modeling approaches that will be employed to generate AUC values and predicted trough concentrations.

In the present study, the observed concentration distribution of atazanavir, lopinavir and efavirenz among patients without SRD was consistent with previously reported data. The mean ATV trough concentration of 0.956 μg/mL was higher than that noted in the British TDM study, 0.774 μg/mL [62], but similar to that reported by European Medicine Agency, 0.862 μg/mL. The possible reasons for the higher than expected ATV trough concentrations may include the diverse patient population in our study: 40% African Americans and 34% Hispanics, and our attempts to promote adherence. To our knowledge, this is the first report indicating significantly lower ATV trough concentrations (~3 fold) among patients with active SRD. For LPV, the median (IQR) of 5.30 μg/mL (3.25–7.19 μg/mL) was similar to that observed in a recent ACTG A5073 study, 5.60 μg/mL (3.30–8.20 μg/mL) [63]. Active SRD resulted in a ~30% decrease in LPV mean trough concentrations. For efavirenz, the median (IQR) EFV trough concentration of 2.371 μg/mL (IQR 1.690–3.634 μg/mL) among patients without active SRD was consistent to that reported 2.011μg/mL (IQR 1.539–2.556 μg/mL) [64]. However, the impact of active SRD was minimal as the EFV trough concentrations were similar between SRD and non-SRD arms.

The observations in this study indicated low PI concentrations in patients with active substance use. In particular, there were statistically significant differences in ATV troughs among patients with and without active SRD. There are a number of potential causes of lower PI concentrations in substance users in our study. First, self-report may overestimate adherence in patients with HIV [65, 66]. Therefore, it is possible that incomplete adherence led to the differences in trough concentrations in these groups and active substance users in our study may have been less adherent than patients without SRD. However, if adherence fully explained the differences in PI trough concentrations between groups, we might have seen a disparity in the EFV trough concentrations. Second, the relatively small number of patients in each group limits the statistical power of the observations. A trend toward lower

median trough concentrations was noted in patients with SRD taking LPV (3.75 *vs.* 5.30 μg/mL, p=0.111). The same trend is true for EFV (1.917 *vs.* 2.371 μg/mL, p=0.211).

A significantly lower proportion of antiretroviral-treated patients with active SRD failed to suppress HIV (HIV RNA ≤ 75 copies/ml) thus leading to a greater potential for treatment failure. This finding is consistent with previous results from retrospective studies. [18] In addition, patients with SRD had higher rates of inadequate PI and/or efavirenz exposure than those without SRD, possibly increasing the emergence of resistant HIV in this population. TDM of PIs and efavirenz represents a research tool that provides a "pharmacokinetic phenotype" that reflects individual differences in pathophysiology, genetics, and other factors that make it challenging to predict ARV pharmacokinetics particular among HIV patients with SRD.

Our data also highlight the number of CNS acting drugs that are prescribed in combination with antiretrovirals. Although we have grouped these drugs together for the purpose of summarizing them, it is interesting to note the extensive use of anti-anxiety agents, antidepressants and antipsychotics. In particular, the striking number of CNS acting drugs suggests that more rigorous attention to the initiation of antiretrovirals, particularly efavirenz, is an important consideration in substance users.

There are a few limitations of the present study. First, the relatively small sample size has weakened the statistical power of these observations. Second, the large inter-patient variability in the point evaluation of pharmacokinetics, *i.e.* trough concentrations could have underestimated the impact of substance use. In this case, the development of a pharmacokinetic model will allow samples to be collected during a range of time points, with subsequent model-derived trough concentrations then used to individualize dosing. These types of analyses will allow our dataset to be examined for the importance of maximum, minimum or time-averaged PI or EFV exposure as predictors of antiviral response or long-term toxicity. In addition, a detailed analysis of possible substance-drug and drug-drug interactions and their effects on antiretroviral therapy should be performed at individual substance and agent level.

In summary, TDM provides a clinical research tool for determining the net pharmacokinetic effects of contributing factors that are present in patients with HIV and active substance use. Despite the wide interindividual variability of trough concentrations, a significant association between substance use and low ATV trough concentrations was observed. These pharmacokinetic differences may also influence viral load suppression during long-term ARV treatment. These findings require additional investigation with more intensive pharmacokinetic assessment to identify individual factors that are contributing to suboptimal ARV exposure in patients with SRDs.

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Table 1

Prevalence of Active Substance Use (n=275)

Substance	N (%)
Alcohol	80 (29)
Cocaine	29 (11)
Heroin	5 (2)
Marijuana	43 (16)
Prescription opioids	45 (15)
Tobacco	154 (56)
Multiple substance use	113 (41)

Table 2

Characteristics of the study population (Mean ± SD)

Characteristic	All	SRD	Non-SRD	*P*
No. of subjects	275	129	146	--
Males (%)	173	84 (65)	89 (61)	0.352
Age, years	46 ± 7	45 ± 7	46 ± 7	0.467
Body weight, kg	78.4 ± 18.7	79.1 ± 20.4	77.7 ± 17.1	0.967
CD4 counts, cells/mm^3	458 ± 288	472 ± 317	444 ± 259	0.995
HIV-1 viral load, log_{10} copies/mL	2.2 ± 1.2	2.3 ± 1.2	2.2 ± 1.2	0.331
Albumin, g/dL	4.27 ± 0.46	4.29 ± 0.46	4.26 ± 0.45	0.660
Presence of HCV antibodies, %	34	43	27	0.002
Ethnicity				
African Americans (%)	115 (42)	56 (43)	59 (40)	0.991
Caucasians (%)	66 (24)	33 (26)	33 (23)	0.169
Hispanics (%)	83 (30)	34 (26)	49 (34)	0.118
Others (%)	11 (4)	6 (5)	5 (3)	0.605

Table 3

Comparison of plasma HIV RNA concentrations and plasma trough concentrations between HIV-infected patients with and without active substance related disorders.

Characteristics	SRD	Non-SRD	*P*
Baseline HIV RNA (%) [a]			
HIV RNA below detection	77 (60)	104 (71)	0.044
HIV RNA detectable	52 (40)	42 (29)	
Target trough concentration (%) [b]			
Below	18 (23)	6 (9)	0.048
Within	51 (65)	49 (71)	
Above	10 (13)	14 (20)	

[a] HIV RNA ≤ 75 copies/ml;

[b] Trough concentration ranges (μg/ml) are defined as follows: atazanavir 0.3 – 1.0, fosamprenavir (amprenavir) 0.3 – 0.7, lopinavir 0.9–1.2, nelfinavir 1.0–1.4, saquinavir 0.2–0.4, efavirenz 1.0–4.0.

Table 4

Logistic regression model of factors associated with CD4+ cell count and plasma HIV RNA among HIV-infected patients with/without active SRD

CD4+ cell count

Variables	Univariate *P* Value	Multivariate *P* Value
Race	0.778	0.742
Gender	0.755	0.909
Known substance use	0.496	0.570
BMI	0.703	0.639
Age at first visit, years	0.427	0.752

HIV RNA Concentration < 75 copies/ml

Variables	Univariate *P* Value (OR)	Multivariate *P* Value (OR)
African-American race	0.016 (0.466)	0.017 (0.457)
Gender	0.131 (1.485)	0.251 (1.388)
Known substance use	0.045 (1.672)	0.116 (1.539)
BMI	0.608 (1.014)	0.395 (1.020)
Age at first visit, years	0.008 (1.047)	0.098 (1.032)

OR: odds ratio

Table 5

Concomitant Medications

Drug Category	SRD	Non-SRD	Total (%)
Central nervous system	172 (53)	150 (47)	322 (40)
Renal and cardiovascular	44 (41)	63 (59)	107 (13)
Vitamins	46 (44)	58 (56)	104 (13)
Antimicrobials	52 (57)	40 (43)	92 (11)
Endocrine	31 (41)	44 (59)	75 (9)
Analgesic/Anti-inflammatory	21 (57)	16 (43)	37 (5)
Gastrointestinal	11 (58)	8 (42)	19 (2)