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Lipid-lowering therapy in HIV-infected patients: relationship with antiretroviral agents and impact of substance-related disorders

Cindy Bednasz, **Barry S. Zingman**, **Amneris E. Luque**, **Margaret A. Fischl**, **Barbara M. Gripshover**, **Charles S. Venuto**, **Jie Gu**, **Zekun Feng**, **Robin DiFrancesco**, **Gene D. Morse**, and **Qing Ma**

Translational Pharmacology Research Core, Center of Excellence in Bioinformatics and Life Sciences and School of Pharmacy and Pharmaceutical Sciences, University at Buffalo; Montefiore Medical Center, Albert Einstein College of Medicine, Einstein/Montefiore Center for AIDS Research; University of Miami; Case Western Reserve University/University Hospitals of Cleveland; University of Rochester

Abstract

BACKGROUND—The use of combination antiretroviral therapy (cART) has significantly decreased the morbidity and mortality associated with HIV infection. Lipid disorders, including lipodystrophy, hypertriglyceridemia, hypercholesterolemia, and dyslipidemia, remain the most commonly reported metabolic disorders among those treated with long-term cART. Mounting evidence suggests an association between drug abuse and poor glycemic control and diabetes complications. Substance related disorders (SRD) may increase the risk of metabolic syndrome.

MATERIALS AND METHODS—The aim of this retrospective cohort study was to examine the relationship between SRD, cART, and lipid-lowering agent use in an HIV infected population. A total of 276 subjects with HIV infection were included, 90 (33%) received lipid-lowering agents, and 31 (34%) had SRD. Patients received efavirenz or protease inhibitor-based cART for at least 6 months. Prescription information was retrieved from the medical records. The primary outcome was the use of lipid-lowering agents including statins, fibrates and fish oil. The impact of SRD and cART was assessed on the lipid-lowering agent use.

RESULTS—Smoking was prevalent among subjects with SRD (84% *vs.* 15%, $p<0.001$). Statins were the mainstay for the management of dyslipidemia (66%), followed by the fibrates (24%), omega-3 fatty acids (5%), nicotinic acid (3%) and the cholesterol absorption inhibitors (3%). Use of statins or fibrates was significantly higher among subjects without SRD than those with (40% *vs.* 23%, $p=0.005$). The type of cART, including efavirenz and protease inhibitors, appeared to have no significant impact on the use pattern of lipid-lowering agents. Lopinavir/r was mostly prescribed for subjects with SRD (25% *vs.* 8%, $p=0.02$).

CONCLUSIONS—Among HIV-infected patients, statins remain the mainstay for the management of dyslipidemia in routine clinical care, followed by fibrates. A significant high risk

Corresponding author: Qing Ma, PhD, Translational Pharmacology Research Core, Center of Excellence in Bioinformatics and Life Sciences, Department of Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, Buffalo, NY 14214, USA, Phone: (716)881-7500, ; Email: qingma@buffalo.edu
Center for Human Experimental Therapeutics, University of Rochester, Rochester, NY 14642

of metabolic disorders among patients with SRD is implicated by heavy tobacco use and prevalent lopinavir/r-based treatment. Significantly low rate of lipid-lowering agent use in this population underscores the importance of lipid disorder scrutiny and cART treatment optimization for HIV-infected patients with SRD.

Keywords

substance-related disorders; HIV; metabolic disorder; dyslipidemia; lipid-lowering therapy; statins; fibrates

Introduction

Although the use of combination antiretroviral therapy (cART) targeting the human immunodeficiency virus (HIV) has significantly decreased the morbidity and mortality associated with the HIV infection, issues such as lipodystrophy, hypertriglyceridemia, hypercholesterolemia and diabetes still plague those treated with protease inhibitors (PIs). While dyslipidemia has been associated with the use of non-nucleoside-reverse transcriptase inhibitors, PI-based regimens appear to have significantly higher prevalence, ranging from 28–80% (1–5). The mechanism of PI-induced dyslipidemia is not fully understood, but might involve PI binding to cytoplasmic retinoic acid-binding protein type 1 (CRABP-1) which is structurally similar to the catalytic region of HIV-1 protease (6). Notably, there is conflicting results about the risk of myocardial infarction association with the use of PIs (7–9).

Statins are considered as first line treatment for primary hypercholesterolemia. Fluvastatin, pitavastatin and pravastatin (except for pravastatin with darunavir/r) have the least potential for drug-drug interactions, according to the guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (10). Simvastatin and lovastatin are contraindicated with PIs due to an increased risk of myopathy and rhabdomyolysis as a result of drug interactions (10). Fibrates, such as gemfibrozil and fenofibrate, are also commonly used in hypercholesterolemia, hypertriglyceridemia and mixed dyslipidemia. No clinically relevant interaction has been noted between PIs and fibrates (11).

The global HIV epidemic continues to grow, and is associated with substance-related disorders (SRD) (12–16). This underscores the need to develop individualized treatment programs that provide clinical care for both HIV and SRD in an integrated setting (17–26). Although it is well appreciated that cART adherence is important to achieve sustained viral suppression, many clinicians often indicate that this goal is a challenge in patients with SRD due to poor adherence (27–31). In addition, patients with SRD are often perceived to have comorbidities 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 (32–35). There is evidence that suggests those with a history of drug abuse are more likely to have poor glycemic control and diabetes complications (36, 37). SRD *per se* may increase the risk of metabolic syndrome (38). This retrospective analysis aims to examine the relationship between SRD, antiretroviral therapy and lipid lowering agent use.

Methods

Patient Population

This was a retrospective cohort study that examined 276 subjects from four HIV treatment and research centers including Bronx, New York; Rochester, New York; Miami, Florida and Cleveland, Ohio. Subjects were eligible for the study if they had a confirmed HIV-1 infection, were >18 years of age, and on either an efavirenz- or PI-based combination ART regimen with dual nucleoside analogs for >6 months. Data was obtained from a therapeutic drug monitoring registry maintained by the University at Buffalo. This was a secure, interactive website (www.tdm.buffalo.edu) that was developed by the pharmacology laboratory for centralized data entry. The data of interest was from a period spanning from May 2003 to May 2007. The data entry process included adherence verification for antiretrovirals and concurrent medications according to the prescribed dosing schedule. Information was extracted from this registry, including baseline demographics, presence or absence of active SRD, plasma HIV-1 RNA viral load, CD4 cell count, co-infection status (HCV or HBV), ART utilization, and concomitant medication profile.

Antiretroviral therapy, Lipid Lowering Agents and Substance-Related Disorders

Antiretroviral therapy was categorized into efavirenz (EFV), atazanavir (ATV), lopinavir/ritonavir (LPV/r), or other PI-based regimens. Lipid lowering agents were divided into the following classes: statins, fibrates, omega-3 fatty acids, nicotinic acids and cholesterol absorption inhibitors. A complete list of medication in each class is listed in appendix-1. The number of prescriptions a subject received toward each drug class was used to quantify medication utilization.

Subjects with active substance use were identified between 2003 and 2007 according to the National Institute on Drug Abuse (http://www.drugabuse.gov/) criteria (see (39) for additional information). Subjects were categorized as SRD positive (SRD+, n=130) or negative (SRD−, n=146) based on individual reporting on the use of the following substances within 30 days before their entry visit: opiates or benzodiazepines not prescribed by a physician, anabolic steroids, cigarettes, alcohol, cocaine, barbiturates, “club” drugs, phencyclidine, amphetamines, inhalants, marijuana, or treatment for opioid addition, such as with methadone, levo-alpha-acetylmethadol, naltrexone, naloxone or buprenorphine. SRD− patients might have a history of smoking, alcohol or marijuana use. The determination of SRD− was at the discretion of the clinician.

The difference in utilization of lipid lowering agents and ART was examined between SRD+ and SRD− groups. Additional analyses was performed to explore specific lipid lowering agent(s) used by SRD+ and SRD− subjects, and by those receiving PI-based regimens (ATV, LPV/r, other PI-based) or NNRTI-based regimens (EFV).

Statistical Analysis

Differences between patients with and without active SRD were compared by the $\chi 2$ and Fisher’s exact tests for categorical variables, while continuous variables were compared by the Student’s t-test. The Yates continuity correction was used for the 2x2 contingency tables.

Statistical analysis was performed using Minitab, and $p < 0.05$ (two-sided) was considered significant.

Results

Data from 90 subjects, 33% of 276 total enrollment in the study, between 2003 and 2007 was retrospectively evaluated from 4 different HIV treatment and research centers for use of lipid-lowering agent prescriptions. Overall, 34% (n=31) of the subjects were SRD+. Approximately 25% of the subject population were female, and the majority of subjects were African Americans (32%), Caucasians (32%) and Hispanics (32%). A significant difference was found in smoking status between the SRD+ and SRD− groups (84% *vs.* 15%, respectively, p<0.001). The demographic characteristics of the study population are summarized in Table 1.

The difference in use of lipid-lowering agents in the SRD+ and SRD− groups is listed in Table 2. Overall, 23% (30/130) of subjects with SRD received statins or fibrates treatment, in comparison to 40% (58/146) without SRD (p=0.005). Statins and fibrates had comparable use within the SRD+ and SRD− groups (statins: 68% *vs.* 65%, p=0.87, fibrates: 21% *vs.* 26%, p=0.76). Omega-3 fatty acids, nicotinic acid and cholesterol absorption inhibitor were the least utilized agents and did not show a statistical difference between the two groups. Twenty one percent (21%) of subjects (19/90) used combination lipid-lowering agents.

Statins were the mainstay of dyslipidemia treatment for HIV-infected patients (66%), followed by fibrates (24%), omega-3 fatty acids (5%), nicotinic acid (3%) and the cholesterol absorption inhibitor (3%). Atorvastatin was the most frequently prescribed statin in both the SRD+ and SRD− groups, followed by pravastatin (Figure 1); with fenofibrate being the most commonly prescribed fibrate (Figure 2). When looking at interactions between utilization patterns of antiretrovirals and lipid lowering agents within the SRD+ group, there was a comparable trend of statin use in the ATV, LPV/r, and EFV groups and comparable fibrate use in all four groups (Table 3). While 30% of patients (58/193) on PI-based antiretroviral regimen received statins or fibrates, 36% on EFV (26/73) required either statin or fibrate containing lipid lowering treatment (p=0.141). In the SRD− group, LPV/r group had the greatest number of statins users, followed by EFV, other-protease inhibitors, and ATV (Table 3). No difference was noted between PI-based and efavirenz-based regimens in the use of statins and fibrates (89% *vs.* 91%, respectively, p=1.00). Fibrates were mostly used in the ATV group, with comparable use between the remaining groups. Comparing the use of antiretrovirals between the SRD+ and SRD− groups, a significant difference was noted in the use of LPV/r between the SRD+ and SRD− groups (25 *vs.* 8%, p=0.02) (Table 4).

The lipid parameters between SRD+ and SRD− groups were summarized in Table 5. While total cholesterol and LDL appeared to be largely under control with borderline high (~200 mg/dL) and near optimal (~110 mg/dL) levels, respectively, for subjects receiving lipid-lowering agents regardless their SRD status, the average triglyceride levels remained high for both groups (>250 mg/dL), particularly among those with SRD (329 mg/dL), suggesting suboptimal triglycerides management with lipid-lowering therapy.

Discussion

This retrospective analysis of drug utilization data from a multicenter study explored the effect of SRD on lipid lowering medication use in an HIV-infected population. We identified a statistically higher rate of lipid-lowering medication use in those without SRD. The parent study was not powered to distinguish between the increased risk in those already on cART, cART-induced dyslipidemia, or effects of SRD on lipid metabolism. The 90 patients included in this analysis undergoing lipid-lowering treatment, accounted for a significant portion of 275 subjects (33%) enrolled in the parent study, indicating the clinical relevance of lipid management as well as cardiovascular complications in HIV-infected patient population.

Statins (66%) were the most commonly prescribed medication for dyslipidemia in this analysis, followed by fibrates (24%), omega-3 fatty acids (5%), cholesterol absorption inhibitors (3%) and nicotinic acid (2%), regardless of SRD status. These prescribing patterns were consistent with the clinical outcomes associated with statins and other lipid-lowering agents when used for treatment of dyslipidemia and primary prevention of cardiovascular disease. Atorvastatin was the most prescribed (72%), followed by pravastatin (19%), rosuvastatin (5%) and simvastatin (4%) suggesting efficacy remained the first priority in the lipid management. Although the CURVE study demonstrated atorvastatin 10, 20 and 40 mg produced greater reduction in low-density lipoprotein (LDL) cholesterol at equivalent doses of simvastatin, pravastatin, lovastatin and fluvastatin; cautions should be exercised with atorvastatin and most PI co-administration, except tipranavir, which is contraindicated with atorvastatin use. For co-administration, atorvastatin should be started with a low dose and gradually titrated to higher doses (10). Despite of a favorable drug interaction profile, pravastatin only accounted for 19% prescription likely due to its low efficacy. Pitavastatin has the least potential for drug-drug interactions with PIs, but was not available during the study period (10, 40, 41). Simvastatin is contraindicated with all PIs, but safe with concurrent use of efavirenz.

While the association between LPV/r and dyslipidemia was implicated in a number of studies, non-nucleoside reverese transcriptase inbhibitors, particularly nevirapine, have demonstrated a more lipid-friendly profile than LPV/r with an HDL increase and a remarkable reduction in total cholesterol/HDL ratio (42). In the present study, there was no significant difference in statin or fibrate use between the protease inhibitor and efavirenz groups (30% *vs.* 36%, p=0.141), consistent with previous findings from the 2NN study and ACTG A5142 study that efavirenz and ritonavir-enhanced PIs had similar and significant potential of inducing dyslipidemia (43, 44).

Substance-related disorders, particularly high cigarett smoking rate, are well estabolished cardiovascular risk factors commonly found in patients with HIV infection. In the present study, the SRD+ group had a remarkably higher percentage of subjects smoking compared to that in the SRD− group (84% *vs.* 15%, $p<0.001$). Evidence has revealed that cigarette smoking promoted systemic atherosclerosis by damaging the arterial endothelium, suggesting that smoking might contribute to the pathogenesis of dyslipidemia that requires lipid-lowering medication use (45). As well, a recent national survey has estimated a

significantly higher rate of smoking in the SRD positive population than that in the general population (46). Current IDSA guideline recommends smoking cessation regardless of cardiovascular risk due to its multiple adverse effects on metabolism, drug interactions, bone health and cardovascular system (47). Signifantly more prescriptions of statins and fibrates among subjects without SRD noted in the present study (40% *vs.* 23%, p=0.005) confirmed the high prevalence of dyslipidemia among HIV-infected patient population and reinforced the importance of proper management using statins and fibrates regardless SRD status. High triglyceride levels were noted in this study, particularly among patients with SRD indicating an urgent need for triglyceride management with more potent lipid-lowering regimens. The analysis of interactions between lipid-lowering agent use, SRD status and cART indicated no significant relationship likely due to the small sample size; thus, in order to distinguish the contribution of these factors to the increased risk of dyslipidemia and metabolic disorders, a large clinical study would be warranted.

Additional analysis of cART use and SRD revealed that statistically more SRD+ subjects received LPV/r-based regimen compared to those in the SRD− group (25% *vs.* 8%, p=0.02). This finding might reflect more severe HIV disease and suboptimal treatment outcomes among HIV-infected subject with SRD since LPV/r is typically reserved as the second-line treatment. A number of previous studies demonstrated that LPV/r-based regimens have the highest risk of dyslipidemia and metabolic syndrome among cART (1, 4), representing a unique challenge for management of dyslipidemia among HIV-infected subjects with SRD undergoing LPV/r-based treatment.

Several limitations might interfere the validity of findings from this study, including a small sample size, the retrospective cross-sectional design, misclassification of medications, and selection bias. The data might not be representative of the HIV-infected population although they were collected from four different institutions. Misclassification of medications could occur, *e.g.*, benzodiazepines might be used for anticonvulsant purposes and as sleeping aid, while methadone could be used for substance-related disorders and pain control (48). Lastly, selection bias was also possible since the subjects were enrolled from four different research centers and each center, and clinician might have different opinions for defining active SRD. Nevertheless, the study assessed the relationship between lipid lowering agents, SRD status, and cART and identified a high prevalence of dyslipidemia among HIV-infected patients requiring lipid lowering medications regardless their SRD status.

Conclusions

The study demonstrated a high prevalence of lipid lowering medication use among HIV-infected patients regardless their SRD status. Statins were the mainstay for the lipid management, followed by fibrates. Notably, the majority of SRD+ patients receiving lipid-lowering agents were smokers and on LPV/r-based regimens. This combination could substantially increase the risk of atherosclerosis and cardiovascular complications. The limitations of this study might have precluded statistical significance, however, future studies with a large sample size are warranted to investigate the impact of SRD and cART on development of dyslipidemia as well as lipid management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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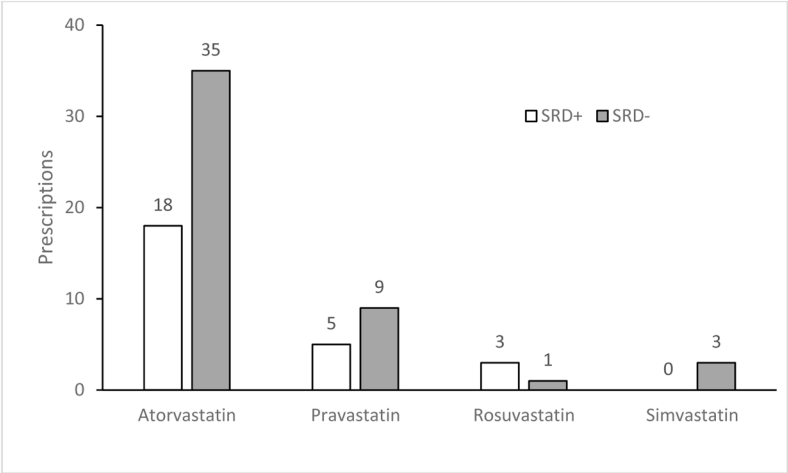

Figure 1.

Prescriptions of HMG CoA reductase inhibitors among HIV-infected subjects with and without SRD

SRD: substance-related disorders

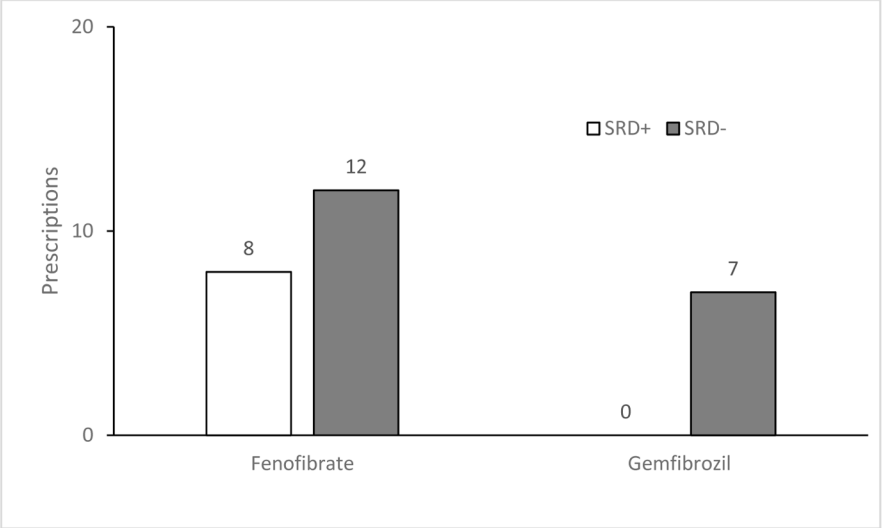

Figure 2.

Prescriptions of fibrates among HIV-infected subjects with and without SRD

SRD: substance-related disorders

Table 1

Characteristics of study subjects

Characteristics	SRD+ n (%)	SRD− n (%)
No. of Subjects	31 (34)	59 (66)
Age (y) **Mean (SD)**	44 (8)	48 (8)
BMI **Mean (SD)**	27.7 (5.1)	22.5 (5.9)
Male	24 (77)	41 (70)
Ethnicity		
African American	13 (42)	16 (27)
Caucasian	11 (36)	18 (31)
Hispanic	6 (19)	23 (39)
Others	1 (3)	2 (3)
Glucose (mg/dL) **Mean (SD)**	94 (43)	118 (78)
Hepatitis C	6 (19)	12 (20)
CD4 count (cells/mm^3) **Mean (SD)**	645 (343)	554 (277)
HIV viral load (c/ml) **Mean (SD)**	3690 (13,181)	4183 (15,645)
Substance-related disorders		
Tobacco *	26 (84)	9 (15)
Alcohol	12 (39)	17 (29)
Cocaine	2 (6)	
Methadone or buprenorphine	2 (6)	
Marijuana	4 (13)	10 (17)
Protease inhibitor use	21 (68)	39 (66)

* $p<0.001$.

SRD: substance-related disorders. Age, BMI, glucose, CD4 count, and HIV viral load are expressed as mean (standard deviation, SD).

Table 2

Use of lipid-lowering agents in HIV-infected subjects with or without substance-related disorders –n (%)

Prescriptions	SRD+	SRD−	Total	*p*
Statins	26 (68)	48 (65)	74 (66)	0.87
Fibrates	8 (21)	19 (26)	27 (24)	0.76
Omega-3 fatty acids	2 (5)	4 (5)	6 (5)	1.00 *
Nicotinic acids	1 (3)	1 (1)	2 (2)	1.00 *
Cholesterol absorption inhibitor	1 (3)	2 (3)	3 (3)	1.00 *
Total	38 (34)	74 (66)	112 (100)	

* Fisher's exact test. SRD: substance-related disorders.

Table 3

Use of lipid lowering agents per antiretroviral regimen in HIV-infected patients with and without substance-related disorders – n (%)

	Efavirenz		Atazanavir		Lopinavir/r		Other PIs	
	SRD+	**SRD−**	**SRD+**	**SRD−**	**SRD+**	**SRD−**	**SRD+**	**SRD−**
Statins	7 (78)	16 (70)	8 (67)	13 (50)	7 (70)	5 (83)	5 (56)	15 (71)
Fibrates derivatives	1 (11)	5 (22)	3 (25)	9 (35)	3 (30)	1 (17)	2 (22)	4 (19)
Omega-3 fatty acids	1 (11)	2 (8)	1 (8)	3 (12)				1 (5)
Nicotinic acid							1 (11)	1 (5)
Cholesterol absorption inhibitor				1 (3)			1 (11)	
	Efavirenz		**Protease inhibitors (including atazanavir, lopinavir/r and others)**					
	SRD+	SRD−	SRD+		SRD−			
Statins or fibrates	8 (89)	21 (92)	28 (90)		47 (89)			

PIs: protease inhibitors; SRD: substance-related disorders.

Table 4

Use of cART regimens with or without SRD

Prescription –n (%)	SRD+	SRD−	Total	*p*
Atazanavir	12 (30)	26 (34)	38 (33)	0.80
Efavirenz	9 (23)	23 (30)	32 (28)	0.50
Lopinavir/r	10 (25)	6 (8)	16 (14)	0.02
Other protease inhibitors	9 (23)	21 (28)	30 (26)	0.71

cART: combination antiretroviral therapy, SRD: substance-related disorders

Table 5

Lipid parameters in HIV-infected patients with or without SRD

	SRD+	SRD−	*p*
Triglyceride (mg/dL)	329 (178)	257 (164)	0.062
Total cholesterol (mg/dL)	211 (40)	204 (44)	0.399
HDL (mg/dL)	43 (10)	47 (16)	0.165
LDL (mg/dL)	112 (27)	114 (38)	0.930

Mean (SD), SRD: substance-related disorders, LDL, low-density lipoprotein cholesterol, HDL, high-density lipoprotein cholesterol