Comparative Effectiveness and Toxicity of Statins Among HIV-Infected Patients

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Background. Dyslipidemia is common and is often treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins). Little is known about the comparative effectiveness of statins among human immunodeficiency virus (HIV)–infected patients. This study compared the effectiveness and toxicity of statins among HIV-infected patients in clinical care.

Methods. We conducted a retrospective cohort study of patients starting their initial statin medications at 2 large HIV clinics ($N = 700$). The primary observation was change in lipid levels during statin therapy. Secondary observations included whether individualized National Cholesterol Education Program (NCEP) goals for low density lipoprotein cholesterol (LDL-C) and non–high density lipoprotein cholesterol (non-HDL-C) levels were reached, and toxicity rates. We used linear regression to examine change in lipid levels, controlling for baseline lipid values and demographic and clinical characteristics. We conducted secondary analyses using propensity scores to address confounding by indication.

Results. The most commonly prescribed statins were atorvastatin ($N = 303$), pravastatin ($N = 280$), and rosuvastatin ($N = 95$). One year after starting a statin therapy, patients who received atorvastatin or rosuvastatin had significantly greater decreases in total cholesterol, LDL-C, and non-HDL-C than patients on pravastatin. The likelihood of reaching NCEP goals for LDL-C levels was higher with the use of rosuvastatin (OR 2.1; $P = .03$) and atorvastatin (odds ratio [OR], 2.1; $P = .001$) compared with that of pravastatin. The likelihood of reaching NCEP goals for non-HDL-C levels was higher for rosuvastatin (OR 2.3; $P = .045$) but not atorvastatin (OR, 1.5; $P = .1$) compared with pravastatin. Toxicity rates were similar for all 3 statins: 7.3% for atorvastatin, 6.1% for pravastatin, and 5.3% for rosuvastatin.

Conclusions. Our findings suggest that atorvastatin and rosuvastatin are preferable to pravastatin for treatment of HIV-infected patients with dyslipidemia, due to greater declines in total cholesterol, LDL-C, and non-HDL-C, with similar lower toxicity rates.

Metabolic abnormalities such as dyslipidemia among human immunodeficiency virus (HIV)–infected patients result in significant morbidity, including increased cardiovascular disease risk [1]. Guidelines for managing dyslipidemia among HIV-infected individuals recommend statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase inhibitors) to treat elevated low density lipoprotein cholesterol (LDL-C) and non–high density lipoprotein cholesterol (non-HDL-C) levels above the thresholds set by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [2, 3]. Whereas statin use among HIV-infected individuals is increasing [4, 5], little is known about the comparative effectiveness and toxicity of these medications in routine care.

Previous studies of statins and HIV infection have been limited by small sample size [6–13], short follow-up time or cross-sectional study design [13–15]. Most

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did not examine the effectiveness of different statins [6, 11], or were conducted before the availability of statins now in widespread use [6, 7, 13, 16]. Thus, questions remain regarding the comparative effectiveness of statins among HIV-infected individuals.

We conducted this large, longitudinal study among a cohort of HIV-infected patients to compare the effectiveness and toxicity of statins in clinical care. This study is unique because of its large sample size; comparison of individual statins, including those more recently incorporated into clinical care; and systematic evaluation of reasons for discontinuing statin medications, including symptomatic toxicity.

METHODS

Study Setting

This observational study was conducted among patients from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort [17]. Patients from 2 CNICS sites—the University of Alabama at Birmingham and University of Washington—were included in this study.

Study Participants

HIV-infected individuals aged ⩾18 years who started statins between 1 January 2000 and 1 March 2008 were eligible for the study. We included no data collected prior to 2000 because of concerns about changing practice patterns. Patients were followed up until statin discontinuation, switch to another statin, addition of another lipid-lowering agent, loss to follow-up, or 1 May 2008, whichever occurred first. Patients who started a statin while receiving other lipid-lowering agents were excluded. Change in statin dose was considered a continuation of the same regimen, as done previously [6]. Study procedures were approved by both the University of Washington and the University of Alabama at Birmingham institutional review boards.

Source of Data

The CNICS data repository integrates comprehensive clinical data from all outpatient and inpatient encounters, including demographic, clinical, laboratory, and medication data [17]. Reasons for stopping medications, including medication toxicity, are documented by the treating clinician in the electronic medical record at discontinuation or are captured by systematic review of all clinician progress notes recorded at the time of discontinuation.

Lipid Outcomes and Other Key Variables

We examined lipid levels over time, including levels of total cholesterol, LDL-C, high density lipoprotein cholesterol (HDL-C), triglycerides, and non-HDL-C (calculated by subtracting HDL-C from total cholesterol values) [18]. Lipid values were measured as part of clinical care; however, fasting status was not routinely available.

We controlled for year of statin initiation. We examined indicator variables for each year and for earlier and later time periods (2000–2004, 2005–2008). We examined indicator variables for baseline antiretroviral medications by class (no medication vs protease inhibitor [PI]–based vs non-nucleoside reverse transcriptase inhibitor [NNRTI]–based), and by individual medications. Body mass index (BMI) was categorized as underweight ($<$18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese ($\geqslant$30 kg/m^2). We used an imputed height based on age, race, and sex for 28 individuals (4%) with missing baseline height. We estimated each patient's 10-year coronary heart disease risk using the Framingham formula [3]. We determined individualized NCEP goals for LDL-C and non-HDL-C levels based on risk factor and Framingham risk category [3].

Toxicity was classified as *potentially serious* if elevations of creatine phosphokinase (CPK) levels to greater than 2 times normal levels, or doubling of creatinine or liver enzyme values were associated with statin discontinuation. Toxicity was classified as *symptomatic* if symptomatic complaints (e.g., myalgias, gastrointestinal symptoms, and fatigue) without accompanying laboratory abnormalities were associated with statin discontinuation.

Statistical Analysis

We used *t* tests, χ^2 tests, and 1-way analyses of variance to compare baseline characteristics by statin as well as lipid levels at follow-up versus baseline. We used linear regression to determine factors associated with lipid level changes 12 months after initiating a statin, controlling for baseline lipid levels and demographic and clinical characteristics. We performed sensitivity analyses in which we modeled changes in lipid levels at 3, 6, 18, and 24 months after statin initiation and in which we did not censor individuals who started another lipid-lowering medication.

We generated propensity scores using multinomial logistic regression [19] to address potential confounding by indication due to choice of initial statin. Variables evaluated for inclusion in propensity scores included demographic and clinical characteristics such as presence of diabetes mellitus, BMI, calendar period, antiretroviral medication class, and specific antiretroviral medications. This approach addressed the possibility that use of individual statins may have differed by antiretroviral medication regimen.

We used χ^2 tests to compare the proportion of patients who reached their individualized NCEP LDL-C or non-HDL-C goals [3] for each statin. We used logistic regression to compare the probability of reaching NCEP LDL-C or non-HDL-C goals adjusting for age, race, sex, CD4$^+$ cell count nadir, baseline antiretroviral medication class, and baseline LDL or non-HDL

lipid value. We used χ^2 tests to compare adverse event rates. We considered 2-tailed P values of $<.05$ statistically significant.

RESULTS

Study-inclusion criteria were met by 700 patients. Mean (SD) age was 43 (8) years, 86% were men, and mean (SD) $CD4^+$ cell count nadir was 182 (180) cells/μL (Table 1).

The 3 most commonly prescribed statins were atorvastatin ($N = 303$; 43%), pravastatin ($N = 280$; 40%), and rosuvastatin ($N = 95$; 14%). Dose data were not available on all patients, but among the subset of patients with complete dose data ($N = 320$), the median starting dose was 10 mg for atorvastatin, 20 mg for pravastatin, and between 5 and 10 mg for rosuvastatin. Median doses at study end were 20 mg for atorvastatin, 40 mg for pravastatin, and 10 mg for rosuvastatin. Another 22 patients

Table 1. Clinical and Demographic Characteristics of Study Patients by Type of Initial Statin ($N = 700$)

Characteristic	Atorvastatin, no. (%) ($n = 303$)	Pravastatin, no. (%) ($n = 280$)	Rosuvastatin, no. (%) ($n = 95$)	Other,[a] no. (%) ($n = 22$)	P[b]
Sex					
Male	266 (88)	233 (83)	85 (89)	18 (82)	
Female	37 (12)	47 (17)	10 (11)	4 (18)	.3
Age at initiation of initial statin, years					
<30	8 (3)	17 (6)	10 (11)	2 (9)	
30–39	118 (39)	92 (33)	45 (47)	11 (50)	
40–49	125 (41)	122 (44)	30 (32)	5 (23)	
⩾50	52 (17)	49 (17)	10 (11)	4 (18)	.01
Race					
White	215 (71)	189 (68)	67 (71)	17 (77)	
Black	61 (20)	73 (26)	27 (28)	5 (23)	
Hispanic	19 (6)	11 (4)	0	0	
Other	8 (3)	7 (3)	1 (1)	0	.2
HIV-transmission risk factor					
MSM	178 (59)	161 (58)	51 (54)	12 (55)	
IDU	41 (14)	34 (12)	8 (8)	2 (9)	
Heterosexual	64 (21)	62 (22)	24 (25)	5 (23)	
Other	20 (7)	23 (8)	12 (13)	3 (14)	.7
CD4+ cell count nadir, cells/μL					
0–200	188 (62)	185 (66)	56 (59)	15 (68)	
201–350	69 (23)	61 (22)	17 (18)	3 (14)	
>350	46 (15)	34 (12)	22 (23)	4 (18)	.2
Initial HIV-1 RNA level, copies/mL					
0–9999	37 (12)	24 (9)	0	2 (9)	
10,000–99,999	46 (15)	42 (15)	0	1 (5)	
⩾100,000	220 (73)	214 (76)	95 (100)	19 (86)	<.001
Body mass index					
<18.5	7 (2)	5 (2)	1 (1)	1 (5)	
18.5–25	102 (34)	102 (36)	42 (44)	12 (55)	
25.1–30	129 (43)	108 (39)	30 (32)	5 (23)	
>30.0	65 (21)	65 (23)	22 (23)	4 (18)	.3
Diabetes mellitus					
No	265 (87)	224 (80)	80 (84)	16 (73)	
Yes	38 (13)	56 (20)	15 (16)	6 (27)	.05
Antiretroviral therapy regimen					
PI-based	129 (43)	143 (51)	28 (29)	1 (5)	
NNRTI-based	85 (28)	54 (19)	29 (31)	6 (27)	
None	89 (29)	83 (30)	38 (40)	15 (68)	<.001

NOTE. IDU, injection drug users; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] Other statins, include simvastatin ($N = 14$), fluvastatin ($N = 5$), and lovastatin ($N = 3$).

[b] P values based on χ^2 tests comparing all 4 groups.

Table 2. Baseline Laboratory Values among Patients Starting Commonly Prescribed Statins (*N* = 678)

	Atorvastatin		Pravastatin		Rosuvastatin		
	Mean	SD	Mean	SD	Mean	SD	*P*
Total cholesterol, mg/dL	239	56	240	58	219	38	.004
LDL-C, mg/dL	140	36	141	40	134	30	.3
Triglyceride, mg/dL	373	375	322	244	310	238	.08
HDL-C, mg/dL	38	10	40	14	40	12	.1
BMI, kg/m^2	27	5	27	6	26	5	.3
AST,[a] U/L	30	18	34	27	32	21	.2
ALT,[a] U/L	36	27	39	44	33	21	.2
Creatinine,[b] mg/dL	1.0	.3	1.1	.8	1.1	.3	.2
Glucose,[c] mg/dL	105	49	106	51	106	53	.9

NOTE. Comparisons between statins were made using 1-way analyses of variance. To convert total cholesterol, LDL-C, non-HDL-C, or HDL-C values to mmol/L, multiply by .0259. To convert triglyceride values to mmol/L, multiply by .0113. ALT alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SD, standard deviation.

[a] Baseline AST and ALT data available on 664 patients. Data available from a median of 2 d before starting therapy (interquartile range, 0– 21 d).

[b] Baseline creatinine data available on 676 patients. Data available from a median of 13 d before starting therapy (interquartile range, 0– 36 d).

[c] Baseline glucose data available on 675 patients. Data available from a median of 19 d before starting therapy (interquartile range, 0– 91 d).

received other statins: simvastatin (N = 14; 2%), lovastatin (N = 3; <1%), and fluvastatin (N = 5; <1%). Median (interquartile range [IQR]) follow-up while receiving an initial statin was 19 months (7–40 months). The distribution of baseline lipid values, other laboratory values, and BMI stratified by statin is in Table 2. Patients who started rosuvastatin were younger, had a higher HIV-1 RNA level (Table 1) and slightly lower baseline total cholesterol values (Table 2).

Mean total cholesterol, LDL-C, triglyceride, and non-HDL-C levels were lower than baseline values at periods up to 24 months (Figure 1). HDL-C values did not change significantly over time.

We excluded patients receiving simvastatin, lovastatin, or fluvastatin from adjusted analyses due to small numbers. Patients treated with atorvastatin had greater decline in total cholesterol, LDL-C, and non-HDL-C values than patients treated with pravastatin, whereas those receiving rosuvastatin had greater decline in total cholesterol, LDL-C, triglyceride, and non-HDL-C values at 12 months in adjusted analyses (Table 3). Findings are similar in models that also adjust for diabetes mellitus. Findings at time points from 3 to 24 months and results of sensitivity analyses including propensity scores were similar to 12 month findings in Table 3 (data not shown). Findings were similar in sensitivity analyses

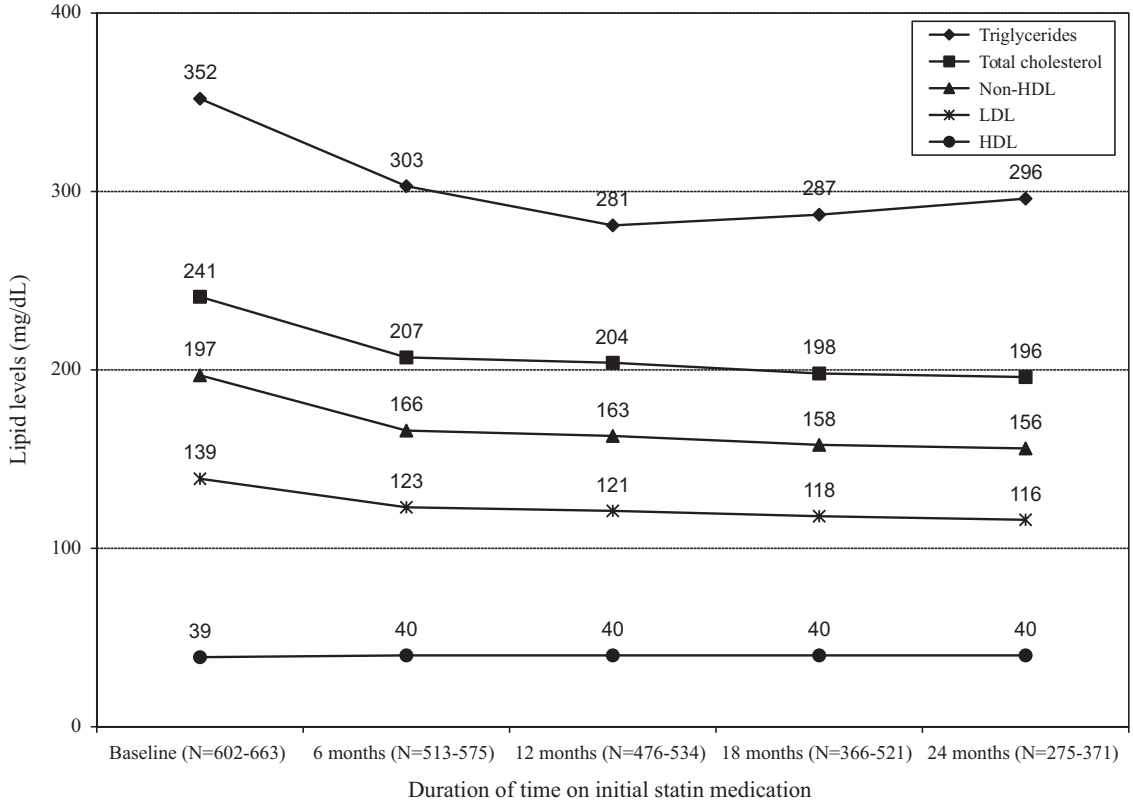

Figure 1. Lipid levels among human immunodeficiency virus (HIV)–infected patients initiating their initial statin medication (N = 700).

Table 3. Decrease in Plasma Lipid Concentrations After 12 Months of Statin Therapy Compared With Baseline by Individual Statin in Adjusted Analyses

	Total cholesterol (n = 502)			LDL-C (n = 468)			Triglycerides (n = 505)			Non-HDL-C (n = 433)			HDL-C (n = 460)		
Statin	mg/dL	95% CI	*P*	mg/dL	95% CI	*P*	mg/dL	95% CI	*P*	mg/dL	95% CI	*P*	mg/dL	95% CI	*P*
Pravastatin	25	16–34	Ref	12	5–19	Ref	24	−17 to 65	Ref	26	17–35	Ref	1.1	−.7 to 2.9	Ref
Atorvastatin	39	31–48	<.001	26	20–32	<.001	60	23–66	.06	39	31–47	.002	.6	−1.1 to 2.2	.5
Rosuvastatin	43	31–55	.004	23	14–32	.01	83	29–137	.03	47	35–59	.001	+.6[a]	−1.6 to 3.0	.1

NOTE. Models were adjusted for baseline lipid values, age, race, sex, baseline antiretroviral therapy (none, protease inhibitor–based, or non-nucleoside reverse transcriptase inhibitor–based), and CD4+ cell count nadir. To convert total cholesterol, LDL-C, non-HDL-C, or HDL-C values to mmol/L, multiply by .0259. To convert triglyceride values to mmol/L, multiply by .0113. CI, confidence interval; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein; non-HDL-C, non–high density lipoprotein cholesterol.

[a] HDL-C levels among patients on rosuvastatin increased .6 mg/dL. All other values in the table indicate the decrease in mean lipid levels after 12 months of statin therapy compared with baseline values.

that did not censor patients who started another lipid-lowering agent.

National Cholesterol Education Program Goals

Based on the Framingham formula, the estimated mean 10-year coronary heart disease risk at statin initiation was 10% (median, 6%; IQR, 3%–16%) for the study cohort. Lipid goals based on NCEP criteria did not differ among patients by statin. Among patients receiving their initial statin for 12 months, LDL-C goals were met by 374 (71%) of 530 patients who had 12-month LDL-C data, and non-HDL-C goals were met by 292 (62%) of 473 patients who had 12-month non-HDL-C data. Of 700 patients, 53% were receiving the initial statin without other lipid-lowering medications and had an LDL-C level below their NCEP goal at 12 months; 42% were receiving the initial statin and had a non-HDL-C level below their NCEP goal at 12 months. The likelihood of reaching NCEP goals differed by statin. Patients who received rosuvastatin (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.1–3.9; $P = .03$) or atorvastatin (OR, 2.1; 95% CI, 1.4–3.2; $P = .001$) were more likely to reach NCEP LDL-C goals at 12 months than patients who received pravastatin in adjusted analyses. Patients who received rosuvastatin were also more likely to reach NCEP non-HDL-C goals at 12 months compared with patients who received pravastatin (OR, 2.3; 95% CI, 1.0–5.0; $P = .045$). Patients receiving atorvastatin appeared more likely to reach non-HDL-C goals at 12 months, although this was not statistically significant (OR, 1.5; 95% CI, .9–2.4; $P = .1$).

Toxicity

Toxicity associated with discontinuing statin therapy occurred rarely (in 6.4% of cases), with similar rates across the 3 commonly used statins: 6.1% for pravastatin, 7.3% for atorvastatin, and 5.3% for rosuvastatin. Among the 44 patients who experienced toxicities, 15 (2.2% of all study participants) had potentially serious toxicity and 29 (4.3%) had symptomatic toxicity. An elevation in CPK level (with or without a decline in renal function) was the most common potentially serious toxicity followed by elevations in liver enzymes. Five patients had CPK-level elevations between 1000 and 10,000 U/L (4 on pravastatin, 1 on rosuvastatin), and 1 had an elevation >10,000 U/L (on atorvastatin). Among 29 patients with symptomatic toxicity, the most common symptoms were myalgias/arthralgias (62%), gastrointestinal symptoms (21%), and fatigue (7%). Overall, 49 patients (7.2%) discontinued statins without any laboratory abnormalities or symptoms reported in the medical record. The rate of discontinuation for unknown reasons was similar across the 3 statins.

DISCUSSION

In this observational cohort study, HIV-infected patients in clinical care who received rosuvastatin or atorvastatin had greater declines in total cholesterol, LDL-C, triglyceride, and non-HDL-C values than patients who received pravastatin. The greatest improvement in dyslipidemia was observed among those receiving rosuvastatin. These findings were consistent across a series of sensitivity analyses, including the use of different durations of follow-up and propensity scores to account for confounding by indication. A higher proportion of individuals receiving rosuvastatin reached NCEP goals for non-HDL-C levels, and higher proportions of those receiving rosuvastatin or atorvastatin reached NCEP goals for LDL-C levels. Approximately one-third of patients had not reached NCEP goals at 12 months. Toxicity associated with discontinuing statin therapy occurred in 6.4%. These rates were similar for the 3 commonly used statins.

Results from studies of the effectiveness and toxicity of statins among HIV-infected individuals may differ from results for the general population for several reasons. The patterns of dyslipidemia commonly seen among HIV-infected individuals differ

from those in persons without HIV infection [20] and may be less responsive to treatment [21]. Second, drug interactions between statins and antiretroviral medications may impact the metabolism, effectiveness, and toxicity risk associated with particular statins [13, 22–25].

Previous studies of HIV-infected patients suggested that statins decrease total cholesterol levels by 11%–25% and triglyceride levels by 0%–40% [6, 16, 21, 26]. Our results are consistent with these findings. Treatment with a statin for 12 months was associated with mean declines of 15% in total cholesterol, 13% in LDL-C, 20% in triglycerides, and 17% in non-HDL-C levels. Treatment was not associated with significant HDL changes.

Small studies have demonstrated modest improvements in lipid levels among HIV-infected individuals with use of pravastatin [7, 11, 12], atorvastatin [9, 12], and rosuvastatin [12, 14, 27]. However, few studies have compared the lipid-lowering effectiveness of individual statins. One trial reported greater decreases in total cholesterol and LDL-C levels with rosuvastatin than with atorvastatin or pravastatin, but no differences in triglycerides; however, only 28 patients received rosuvastatin [12].

We found a nonsignificant increase in HDL-C levels at 12 months among those receiving rosuvastatin. A lack of improved HDL-C levels in patients on rosuvastatin has been seen in some studies [14, 28] but not others [29] including a study of HIV-infected persons [27]. HDL-C may increase as much as 10% with rosuvastatin among those without HIV [29]. Our results are consistent with the idea that combined (mixed) dyslipidemia in HIV-infected patients may be more difficult to treat [21, 30] and thus raises the question of whether combination therapy with additional lipid-lowering agents may be needed.

National Cholesterol Education Program Goals

Regardless of statin, higher proportions of patients in this study reached NCEP goals than those in studies reported previously [6, 8, 30]. These differences may be due to several factors, including greater use of more lipid-tolerant antiretroviral regimens, longer follow-up, more potent statins, and heightened provider awareness of the importance of treating lipid abnormalities.

A substantial proportion of HIV-infected individuals receiving statins did not reach individualized NCEP goals while receiving an initial statin alone. This was particularly the case for non-HDL-C levels. Other studies have also reported difficulty meeting NCEP goals, especially among HIV-infected individuals [6, 8, 10, 30]. Rosuvastatin appeared to be better than pravastatin for reaching individualized NCEP LDL-C and non-HDL-C goals.

Toxicity

Adverse events associated with statins among individuals without HIV infection are uncommon [31]. Most reports of toxicity in HIV-infected persons included small numbers of patients [13, 15, 27, 32] or did not compare the effects of statins [15, 21, 27]. In contrast to data for laboratory toxicities, data for symptomatic toxicity such as myalgia are rarely collected and reported [16, 32]. We found low toxicity rates associated with statin discontinuation that did not vary across the 3 commonly used statins. The rate of CPK elevations was lower than that reported previously [6], despite our use of a very low cutoff point for CPK elevations to increase sensitivity. This may reflect more limited use of simvastatin. Furthermore, CPK elevations may occur even in the absence of statins and often are asymptomatic.

A number of drug interactions with statins have been described that may increase toxicity risk among HIV-infected individuals [33]. Until recently, pravastatin and rosuvastatin were thought to be safer than other statins because the metabolism of these statins did not utilize the cytochrome P450 (CYP450) 3A4 enzyme system influenced by many antiretroviral medications. However, recent studies have demonstrated increased plasma levels (expressed as area under the plasma concentration–time curve [AUC] and maximum concentration [Cmax] values) of these statins associated with particular antiretroviral medications [25, 34] (For a table of selected examples of these associations, see Supplementary Appendix Table 1). These increased levels may be the result of inhibition of the organic anion transporting polypeptide (OATP) 1B1 that facilitates statin uptake into the liver [22]. The disposition of pravastatin and rosuvastatin may be more dependent than other statins on OATP1B1. Consistent with this theory, a study found that atazanavir-ritonavir was associated with increased rosuvastatin levels. This finding led the authors to conclude that the maximum dose of rosuvastatin with atazanavir-ritonavir should be 10–20 mg, similar to current recommendation of a maximum rosuvastatin dose of 10 mg when used with lopinavir-ritonavir [34]. Although increased statin levels may enhance the effectiveness of the drugs, this benefit may come with the expense of enhanced toxicity. To date there are no known interactions between rosuvastatin and NNRTIs [22].

Treatment of Dyslipidemia Among HIV-Infected Individuals

Guidelines from the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group recommend the use of pravastatin or atorvastatin in HIV-infected individuals with elevated LDL-C or non-HDL-C and moderately elevated triglyceride values (200–500 mg/dL) [2]. These guidelines also emphasize the importance of considering pharmacokinetic and pharmacodynamic interactions between lipid-lowering drugs and other medications. More recent studies have recommended including rosuvastatin [26, 35] among the statins preferred for use in HIV-infected individuals, and European guidelines have included rosuvastatin with the caveat that the initial dose is low

when patients are receiving antiretroviral therapy, particularly PIs [36, 37]. The current study provides additional empiric data supporting these recommendations for using rosuvastatin among those with HIV. Further, among the 28 patients who started rosuvastatin while on a ritonavir-boosted PI regimen, no toxicity was noted. Rosuvastatin may be a particularly good choice in the setting of NNRTI-based therapy [22], given its greater effectiveness and lack of proven interactions, although additional pharmacokinetic studies would be useful. In addition, rosuvastatin also requires less dose-escalation than other statins [38]. Traditionally, pravastatin has been the preferred statin among HIV-infected individuals because of a lower risk of drug interactions [34]. However, our findings suggest that the lipid-lowering effectiveness of pravastatin was significantly less than that of rosuvastatin or atorvastatin.

Strength and Limitations

Strengths of this study include the large sample size, longitudinal follow-up, and comprehensive clinical data. This study examined the comparative impact of individual statins in clinical care rather than in a trial, which can sometimes lack generalizability due to broad exclusion criteria.

As with any observational study, there may be confounding factors for which adjustment is not possible. We conducted sensitivity analyses using a propensity-score approach to investigate the potential for confounding by indication related to individual statins, and our results were essentially unchanged. However, the possibility of unmeasured confounding factors still exists. Other limitations are as follows: (1) We looked for toxicities only when statins were stopped or changed, so toxicity that did not result in therapy changes may have been missed. (2) Providers may have varied in toxicity documentation and may have neglected to record all reasons for discontinuing a drug; (3) Lipid values were measured in clinical care so we could not confirm fasting status, but have no reason to suspect that fasting status would vary by statin. (4) Only 2 clinical sites were included, so findings may not generalize to all HIV-infected patients. (5) The study lacks information regarding adherence to statins, genetic factors, diet, and exercise; however, we would not expect these factors to vary by statin.

We did not restrict patients to particular dosing regimens for each statin, so dose-escalation intensity may vary by statin, though in general dose escalations are not as aggressive as they should be in clinical care [39]. The advantage of this approach is that it allowed us to examine the effectiveness of statins as they are actually prescribed in clinical care.

Longer-term follow-up is necessary to determine the impact of statins on cardiovascular events among HIV-infected patients. The failure to reach NCEP goals for one-third of patients highlights the frequent need for more aggressive dose escalation and the use of other medications in addition to statins [40]. Although many HIV-infected individuals have a good LDL-C response to statin therapy, triglyceride and HDL-C levels can be more difficult to treat. Significant benefits are likely achieved with any improvement in lipid parameters [11].

CONCLUSIONS

Atorvastatin and rosuvastatin were associated with greater improvements in lipid levels than pravastatin among HIV-infected individuals in clinical care. Approximately one-third of patients failed to reach individualized NCEP goals. Toxicity associated with statin discontinuation was uncommon and did not differ across statins. Current recommendations include treatment of HIV-associated dyslipidemia with statins and emphasize the use of pravastatin or atorvastatin. Our findings are consistent with the recent British guidelines that include a recommendation to use rosuvastatin [37].

Supplementary Material

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/).

Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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