

Genotypic Resistance in HIV-Infected Naive Patients Receiving Abacavir Plus Lamivudine and Efavirenz

To the Editor:

Thymidine nucleoside analogues have been the backbone of most highly active antiretroviral therapy (HAART) regimens for several years. Reported associations of stavudine and, to a lesser degree, zidovudine with mitochondrial toxicity, lipoatrophy, and certain metabolic changes have favored the use of nonthymidine nucleoside analogues as first-line compounds, however.^{1,2} Tenofovir (TDF)- and abacavir (ABC)-containing regimens combined with emtricitabine (FTC) or lamivudine (3TC) and a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI) have shown good efficacy and tolerability in several clinical trials and are now extensively used in nucleoside fixed-dose combinations as part of first-line regimens.²⁻⁵

The physician's choice of the first nucleoside reverse transcriptase inhibitor (NRTI) option may be influenced by the intrinsic toxicity of these agents: hypersensitivity reactions with ABC and renal toxicity with TDF. Another factor that may have an impact on the choice of a first regimen is the resistance profile, which can condition future sequencing options. In patients with virologic failure, the key mutations selected are K65R in those receiving TDF (although it is rare in 2-class regimens) and L74V, Y115F, and K65R in those receiving ABC. Emergence of these mutations raises concern as to the efficacy of the next options used. K65R selection occurs less commonly with administration of ABC/3TC than with TDF, but the association of L74V and M184V typically compromises ABC and didanosine (ddI) activity. Although ABC/3TC/EFV has been evaluated in clinical trials, extensive data regarding its resistance profile are not available.^{4,5}

Primary resistance to antiretrovirals may contribute to virologic failure. Several studies have recently shown an increase in primary resistance rates in various geographic areas,^{6,7} and a genotypic resistance test is now recommended before initiation of HAART in patients with chronic HIV infection.⁸

The ABCDE study was a 96-week, randomized, multicenter trial performed in a cohort of antiretroviral-naive patients, where ABC was compared with stavudine, both associated with 3TC/efavirenz (EFV).⁹ The patients receiving ABC presented with a notably lower incidence of lipoatrophy and a better lipid profile. In addition, a trend favoring ABC was observed in the intent-to-treat analysis when comparing the proportion of patients with a viral load <50 copies/mL.⁹ The incidence and patterns of resistance mutations at baseline and at virologic failure were also assessed in this study and are presented herein.

Among the 237 patients enrolled in the trial up to June 2002, genotype resistance testing (ViroSeq HIV-1 genotyping system; Abbott Diagnostics, Abbott Park, IL) was performed in 227 (96%) patients at baseline and in those with virologic failure and a confirmed HIV-1 RNA load >500 copies/mL. The International AIDS Society (IAS) algorithm (August 2006)¹⁰ was used to evaluate the presence of mutations associated with resistance.

Among the 227 patients with genotype testing at baseline, several resistance mutations were detected alone or in combination in 12 (5.3%) patients. Mutations associated with nucleoside analogue resistance were observed in 9 (4%) patients, and mutations associated with NNRTI resistance were observed in 3 (1.3%). No major PI-associated resistance mutations were detected (Table 1).

Twenty-seven (12%) patients presented with virologic failure during follow-up. In 7 patients, the HIV-1 RNA level was 50 to 500 copies/mL, and in 1 case, the HIV-1 RNA level could not be amplified. Thus, genotype resistance results were available in 19 patients. In 12 patients (63%), no resistance mutations were detected, and in all cases, there had been poor adherence and/or discontinuation of therapy. Five

of the 12 patients reinitiated the same regimen, reaching an HIV-1 RNA level <50 copies/mL after a median period of 3 months.³⁻⁶ Resistance mutations were detected in 7 of the 19 patients with virologic failure and resistance testing (37%); 5 were new (not detected at baseline) resistance mutations, as detailed in Table 1.

Overall, virologic failure occurred in 4 (33.3%) of 12 patients with resistance mutations at baseline; these included 2 of 9 patients with baseline mutations associated with nucleoside analogue resistance and 2 of 3 patients with baseline mutations associated with NNRTI resistance. The fact of not presenting with primary resistance was associated with a significantly lower risk of virologic failure (odds ratio [OR] = 0.028, 95% confidence interval [CI]: 0.005 to 0.148). The mutation pattern seen at failure in patients with or without baseline resistance mutations is shown in Table 1.

With regard to NNRTIs, both patients with the K103N mutation at baseline failed at 6 and 12 months (in the first case, the M184V mutation was also selected at failure). Nevertheless, it is interesting that the patient with the Y181C mutation, which confers high-level resistance to delavirdine and nevirapine, but only low-level resistance to EFV, had a durable virologic response up to the end of the study period.

Summarizing the results, in this 96-week trial, only 3% (7 of 227) of patients had virologic failure associated with the presence of resistance mutations. Most patients with virologic failure and a viral load >500 copies/mL were poorly adherent; hence, the drug pressure on HIV, if any, did not suffice to develop resistance. Of note, K65R and L74V were not selected during the study period. Stavudine did not show an advantage in terms of resistance as compared with ABC. Although the prevalence of resistance mutations at baseline was relatively low (mainly regarding NNRTI-associated resistance), their presence had a clinical impact, with one third of the patients presenting with virologic failure.

Our results agree with previous studies showing that ABC/3TC/EFV is

TABLE 1. Resistance Mutations Detected at Baseline and/or Virologic Failure*

Patient	Arm†	Resistance Mutations at Baseline	Resistance Mutations at Failure	Month of Virologic Failure
0117	ABC	—	M184V, K103N, P225H	12
0215	d4T	M41L, T215D	M41L, T215Y/D/A/S, K103N	6
0226	ABC	K103N	K103N	12
0304	d4T	K103N	K103N, M184V	6
0606	d4T	M41L, T215C	M41L, T215C	15
0810	ABC	—	M184V, G190A	18
1901	ABC	—	K103N	21
0122	d4T	M41L	No failure	—
0142	d4T	M41L, T215A	No failure	—
0152	ABC	Y181C	No failure	—
0217	ABC	T215S, L210W/R	No failure	—
0312	ABC	T215D	No failure	—
0605	ABC	D67N	No failure	—
1602	ABC	A62V	No failure	—
1925	d4T	V75I	No failure	—

*Twelve patients had resistance mutations at baseline; 4 (33%) of the 12 had virologic failure (2 cases with new mutations). Three other patients without baseline mutations had resistance mutations at virologic failure.

†Plus 3TC and EFV.

d4T indicates stavudine.

associated with a low incidence of virologic failure related to the development of resistance mutations, with M184V- and EFV-associated mutations being the most prevalent. The absence of K65R and L74V also fits in with results from other clinical trials, which have reported a low prevalence of these mutations.^{4,11}

Recent reports from the United States and Europe have indicated that the prevalence of HIV-1 primary resistance to antiretroviral drugs is growing, at least in some geographic areas.^{6,7} We did not detect this trend, particularly with respect to NNRTI resistance. It should be noted that our patients were enrolled up to mid-2002 and that some changes in the prevalence of primary resistance may have occurred over the past years. Our data agree with recent Spanish reports, however, in which a reduction or at least a stabilization of primary resistance rates has been observed in recent HIV-1 seroconverters, ranging from 33% in 1997 to 7.7% in 2004.^{12,13} In another multicenter study with newly diagnosed HIV-infected patients from January 2004 onward, the prevalence of primary resistance was only 4%.¹⁴ These data may vary in the future; thus, surveillance studies should be conducted to identify modifications in the prevalence of primary mutations associated with resistance.

It has been suggested that standard methods may not detect the presence of minor baseline populations of reverse transcriptase- or PI-resistant strains, which may be associated with subsequent

virologic failure.^{15,16} If this was the case in this trial, few patients seem to have been affected, because only 4 (1.8%) of 224 developed NNRTI-associated mutations at virologic failure in the absence of resistance mutations at baseline.

Finally, although the proportion of patients with baseline resistance was low, the rate of virologic failure in these patients, mainly when NNRTI mutations were present, highlights the benefits of performing genotype resistance testing in naive patients, particularly if an NNRTI-containing regimen is given.

In conclusion, a small incidence of resistant mutations at failure and a resistance pattern preserving most therapeutic options, together with its known efficacy and tolerability, are the advantages of ABC/3TC/EFV as a first-line regimen. At present, at least in our area, the resistance profile seems to have a lower impact than other factors on clinical decisions regarding the best HAART options to give to naive patients.

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No Evidence of Relation Between Peripheral Neuropathy and Presence of Hemochromatosis Gene Mutations in HIV-1-Positive Patients

To the Editor:

Peripheral neuropathy (PN) is a frequent complication of HIV infection, but its actual mechanisms are largely unknown.¹ Kallianpur et al² showed that patients with HFE (hemochromatosis) gene mutations, the C282Y heterozygosis mutation in particular, had a decreased risk of PN. It has been hypothesized that peripheral nervous system damage is facilitated by decreased iron storage related to HIV infection and that HFE mutations compensate for this phenomenon. Although this observation has potential implications for patient risk assessment and treatment, it has been obtained in a limited population under specific highly active antiretroviral therapy

(HAART), including stavudine (d4T) and didanosine (ddI). Moreover, diagnosis of PN was based on patient self-reporting of symptoms without any confirmation by electromyography. In this study, we aimed at assessing the possible protective effect of HFE mutations, taking into account potential codeterminants of PN, whose diagnosis was confirmed by electromyography.

A case-control study was performed. All patients with a diagnosis of PN confirmed by electromyography (ie, cases) among HIV-positive patients attending the Clinic of Infectious and Tropical Diseases of the University of Brescia were studied. Patients who did not have signs or symptoms of PN (ie, controls) were selected from the same clinic and matched with cases for the following factors: age (± 5 years), gender, reported history of alcohol abuse (defined as alcohol consumption exceeding 60 g of ethanol per day), hepatitis C virus (HCV) antibody (Ab) reactivity, hepatitis B surface antigen (HBsAg)-positive serostatus, and concomitant diabetes. The possible influence of other factors that may also cause PN was explored: risk factors for HIV acquisition; nadir CD4⁺ T-cell count; occurrence of previous major opportunistic infections (eg, 1993 Centers for Disease Control and Prevention [CDC] clinical class C); exposure to dideoxynucleoside analogues (ddX), such as d4T, ddI, and zalcitabine; and HIV RNA level. To reduce confounding, we excluded patients with other strong risk factors for PN (eg, exposure to drugs toxic for the nerves, cancer, autoimmune diseases).

Analyses of exons 2 and 4 of the HFE gene, mainly aimed at detecting the H63D and C282Y mutations, were performed by denaturing high-performance liquid chromatography (HPLC) as previously described.³

The data were analyzed by a conditional logistic regression model to account for matched case-control data and to identify variables associated with outcome (ie, PN). Variables reaching $P \leq 0.2$ on univariate analysis were put into the multivariable model, including HFE gene mutations. Results are expressed as odds ratios (ORs) with their 95% confidence intervals (CIs). Analyses were performed with STATA (STATA Statistical Software, release 9.0; Stata Corporation, College Station, TX).

We studied 57 HIV-positive patients with from PN and 57 HIV-positive controls. Patient characteristics used for matching were as follows: 95% Italian nationality, 82% male gender, mean age of 45 (SD = 5) years, 61% HCV-Ab-positive serostatus, 19% alcohol abusers, and 5% diabetics. Most patients (35 [61%] of 57) in the case group had 3 or more possible risk factors for PN (among alcohol abuse, diabetes, HCV-Ab reactivity, CD4 nadir <100 cells/mm³, CDC clinical class C, HIV RNA >5 log₁₀ copies/mL at the time of electromyography, and ddX exposure). The prevalence of HFE gene mutations did not seem significantly different between the cases and the controls. Sixty-three percent of patients in the case group had no HFE mutations, 25% had H63D heterozygosis, 5% had H63D homozygosis, and 7% had C282Y heterozygosis. Among the controls, 73% had no HFE mutations, 25% had H63D heterozygosis, and 2% had H63D homozygosis.

Table 1 shows results of the conditional logistic regression analysis. In the univariate model, the following variables seemed to be significantly associated with the risk of PN: intravenous drug use (IVDU) as a risk factor for HIV acquisition, nadir CD4⁺ T-cell count, 1993 CDC clinical class C, and HIV RNA level. Moreover, exposure to d4T was associated with a risk of PN, but the association did not reach statistical significance. Conversely, HFE mutations were not associated with protection from PN, whereas a trend toward increased risk was found for the presence of H63D homozygosis (OR = 3.04, 95% CI: 0.31 to 29.63; $P = 0.338$). In the multivariable analysis, IVDU and HIV RNA level emerged as the only 2 factors significantly associated with the risk of PN.

Our study did not show any apparent protective role of HFE mutations (including C282Y) for PN in HIV-positive patients on HAART. The prevalence of HFE gene mutations in the group of HIV-positive patients with a confirmed diagnosis of PN was even higher than that found in the Italian general population in the same region (15% in the general population vs. 30% in our HIV-positive population for H63D homozygosis and 5% vs. 7% for C282Y heterozygosis).⁴ Although a low

TABLE 1. Factors Associated With PN (Univariate and Multivariable Conditional Regression Analysis)

	Cases (N = 57)	Controls (N = 57)	Unadjusted			OR	Adjusted		P
			OR	95% CI	P		OR	95% CI	
Qualitative factors (%)									
IVDU	61%	42%	4.66	1.34 to 16.24	0.01	9.18	1.52 to 55.28	0.02	
1993 CDC clinical class C	49%	26%	3.17	1.26 to 7.93	0.01	2.85	0.71 to 11.47	0.14	
d4T exposure	61%	47%	2.33	0.9 to 6.07	0.08	2.24	0.62 to 8.03	0.22	
ddI exposure	49%	58%	0.58	0.23 to 1.48	0.26	—	—	—	
Zalcitabine exposure	14%	19%	0.63	0.2 to 1.91	0.41	—	—	—	
H63D heterozygosis	25%	25%	1.06	0.42 to 2.7	0.90	1.23	0.27 to 5.64	0.79	
H63D homozygosis	5%	2%	3.04	0.31 to 29.63	0.34	42.74	0.35 to 5279.46	0.13	
C282Y heterozygosis	7%	0%	—	—	—	—	—	—	
Quantitative factors, mean (SD)									
CD4 ⁺ T-cell count at nadir value (cells/mm ³)	119 (115)	155 (103)	1.00	0.99 to 1.00	0.04	1.00	1.00 to 1.01	0.47	
HIV RNA (log ₁₀ copies/mL)	3.19 (1.51)	1.95 (0.86)	2.39	1.43 to 4.01	0.001	3.57	1.55 to 8.21	0.003	

prevalence of C282Y heterozygosis was found in our population, an apparent paradoxical effect was demonstrated, because all 4 patients with C282Y heterozygosis presented with PN. Moreover, diverse HFE mutation patterns that could also lead to iron loading were found at a significant prevalence in our population, but none of them was associated with protection from PN. For instance, Kallianpur et al² did not find any statistical association between H63D heterozygosis and protection from PN. In our study, H63D homozygosis was not associated with PN, although its effect on iron loading could be superior to that produced by the heterozygosis pattern. Therefore, the protective mechanism of iron loading hypothesized by others² needs to be re-evaluated.

The only 2 factors independently associated with the risk of PN were IVDU and a high HIV RNA level. Our data are consistent with a particularly high prevalence of PN in patients who acquired HIV through IVDU.⁵ IVDU was a risk factor independently of HCV or alcohol abuse; thus, a possible neuro-pathogenic effect of recreational drugs by themselves could be postulated. Moreover, in univariate analysis, advanced viroimmunologic and clinical conditions as well as exposure to d4T were associated with an increased risk of PN. Our findings go in the same direction as those of others,⁶ suggesting that HIV by itself, host factors, and the effect of drugs (eg, d4T) are codeterminants in influencing the risk of PN, perhaps more importantly than HFE gene mutations. More studies are needed to support whether iron deficiency is implicated in the etiology of PN, and thus the need of

iron supplementation to treat or prevent PN.

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Is Phosphatemia the Best Tool to Monitor Renal Tenofovir Toxicity?

To the Editor:

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue of adenosine-5'-monophosphate that has proven efficacy in treating antiretroviral-naïve and -experienced HIV-infected patients.^{1,2} It

offers several advantages, including a once-daily formulation with single-tablet administration, a low level of cross-resistance, and a low risk of dyslipidemia and thymidine analogue-related toxicity. As with other nucleotide analogues, cases of proximal tubular dysfunction with urinary loss of phosphorus have been reported, including severe toxicity such as Fanconi syndrome.³⁻⁵ For these reasons, it is recommended to monitor phosphatemia and creatinine clearance every 3 months to detect renal toxicity. The pharmaceutical laboratory recommends assessment for proximal dysfunction in cases in which phosphatemia is less than 0.48 mmol/L and/or creatinine clearance is less than 50 mL/min per 1.73 m². Interestingly, the ratio of the maximal tubular reabsorption rate of phosphate and the glomerular filtration rate (TmPO₄/GFR) that corresponds to the value of phosphatemia greater than which phosphate is excreted in the urine is normally higher than 0.8 mmol/L. We hypothesized that in case of TDF renal toxicity, bone phosphate stock could initially compensate renal loss, thus preventing the early detection of toxicity through the monitoring of phosphatemia. To test this hypothesis, we proposed to monitor the capacity of the kidney to reabsorb phosphate through an ambulatory screening for the TmPO₄/GFR and to compare these results with the concomitant phosphatemia.

The study population included HIV-infected patients receiving TDF as part as their ongoing antiretroviral therapy in the Department of Infectious Diseases. The TmPO₄/GFR was estimated as described by Bijvoet,⁶ using measurement of phosphate and creatinine in fasting blood samples and urine collected in the morning. In patients for whom ambulatory estimates of the TmPO₄/GFR were lower than <0.8 mmol/L, we checked this estimate against a complete evaluation of phosphate and calcium homeostasis in the Department of Physiology to confirm urinary phosphate loss and to look for another cause of renal loss. Bone mineral density evaluation by dual-energy x-ray absorptiometry (DEXA) was performed in patients with a confirmed decrease in the TmPO₄/GFR.

Ninety patients receiving TDF for a mean interval of 15 months were

evaluated. At the time of the screening, 60 patients had undetectable HIV plasma RNA (<50 copies/mL). None had phosphatemia less than 0.48 mmol/L or creatinine clearance less than 50 mL/min per 1.73 m². An estimated TmPO₄/GFR less than 0.8 mmol/L, suggesting an impairment of renal phosphate transport, was found in 29 (32%) patients. Among those, only 8 had phosphatemia between 0.5 and 0.8 mmol/L (Fig. 1).

Eighteen of the 29 patients with a TmPO₄/GFR less than 0.8 mmol/L underwent a complete evaluation of phosphate and calcium homeostasis. Decreased proximal reabsorption of phosphate was confirmed in 11 (61%) of 18 patients, whereas all had a normal GFR (mean of 97 ± 5 mL/min per 1.73 m²) and plasmatic ionized calcium (mean of 1.21 ± 0.02 mmol/L). Among these 11 patients, 7 had phosphatemia greater than 0.8 mmol/L. Secondary hyperparathyroidism (parathormone [PTH] values greater than 60 pg/mL and 25(OH)-vitamin D level less than 25 ng/mL) was detected in 3 of 11 patients and could explain the observed decrease in proximal phosphate reabsorption. In the 8 other patients, no other cause was detected, suggesting possible renal proximal toxicity of TDF. Eight of the 11 patients had a DEXA scan to monitor bone mineralization. Osteopenia (T-score <-1) was observed in 6 patients at the lumbar spine or the hip. Among them, 4 had phosphatemia less than 0.8 mmol/L.

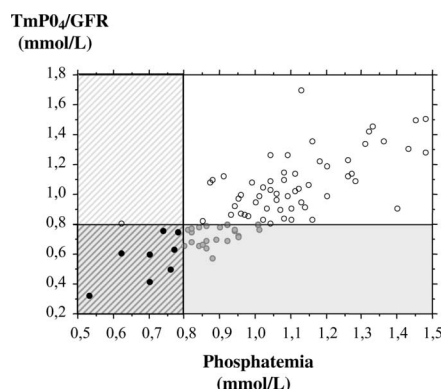


FIGURE 1. TmPO₄/GFR estimation and phosphatemia in 90 patients receiving tenofovir (■, patients with a decreased TmPO₄/GFR and hypophosphatemia; ■, patients with a decreased TmPO₄/GFR with normal phosphatemia; □, patients with a normal TmPO₄/GFR and phosphatemia).

Since the introduction of TDF, the rate of TDF renal toxicity and the methods to detect it have been a subject of debate.⁷⁻⁹ Symptomatic severe acute proximal toxicity leading to an interruption in the prescription of TDF has been reported with a frequency of 0.39%.⁷ The occurrence of mild asymptomatic toxicity has been estimated through phosphatemia monitoring and measurement of creatinine level. It was estimated to be <1% for hypophosphatemia less than 1 mg/L and 7% for a 5-μmol/L increase in serum creatinine.⁸ These rates have to be compared with those of the 30% of patients with a decrease in phosphate reabsorption in our study and that of Badiou et al.⁹ The detection of a mild alteration of renal proximal function is difficult, because renal loss of phosphate can be compensated by bone loss to maintain normal phosphatemia. This probably explains why phosphatemia remained normal in 60% of the patients with proven renal loss of phosphate in our study. This result showed that monitoring phosphatemia lacks the sensitivity to detect renal toxicity; thus, we propose the use of TmPO₄/GFR estimation for the assessment of TDF toxicity. TmPO₄/GFR estimation is practical to perform and more sensitive than phosphatemia in the detection of renal loss of phosphate. We acknowledge that the positive and negative predictive values of this test could not be estimated here, because a complete exploration of phosphate and calcium metabolism was not performed in patients with a normal estimated TmPO₄/GFR. The complete evaluation of calcium and phosphate metabolism in 18 patients revealed the frequency of other disturbed parameters involved in the decrease in renal phosphate reabsorption, such as the modification of vitamin D and PTH metabolism observed in 27% of the patients. TDF remained the only identified cause of tubular toxicity in 72% of the patients. Modification of vitamin D metabolism has recently been demonstrated in HIV-infected patients with a decrease in 25- or 1-α-hydroxylation and 1,25(OH)₂ vitamin D degradation.^{10,11} Vitamin D is the major known regulator of intestinal phosphate absorption, and, through its regulation of PTH, it also affects renal phosphate reabsorption. Our results suggest that vitamin D and PTH

concentrations should be checked before imputing renal phosphate loss to TDF toxicity.

Our patients showed neither other alterations of proximal function nor glomerular filtration alteration. Because no follow-up monitoring was conducted, however, we cannot rule out the possibility of a decrease in renal function during the course of TDF chronic toxicity.

In conclusion, using an estimated TmPO_4/GFR , we demonstrated a urinary loss of phosphate despite normal phosphatemia in 23% of patients receiving TDF. Because long-term consequences of this mild toxicity are currently not known, a pragmatic approach might be to monitor renal tubular function on a regular basis. In case of worsening function, the interruption of TDF should be weighed against the potential benefit of this nucleotide in the therapeutic strategy for each patient.

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Safety of Statin Therapy in HIV/Hepatitis C Virus–Coinfected Patients

To the Editor:

Hypercholesterolemia after highly active antiretroviral therapy (HAART)–related toxicity in lipid metabolism¹ might require treatment with lipid-lowering drugs, such as statins. The risk of hepatotoxicity of statins and their interaction with the hepatic metabolism

of protease inhibitors (PIs) at the level of cytochrome P450 have limited their prescription, however, particularly in HIV/hepatitis C virus (HCV)–coinfected patients. The estimated risk of aminotransferase abnormalities with statins is 0.2% to 2.7%, but a more recent analysis did not confirm the statin-related hepatotoxicity in a low-risk population.² Few data are available about the hepatotoxicity of statins in chronic liver diseases. Recently, Khorashadi et al³ evaluated the incidence of aminotransferase increase in HCV infection, and neither significant hepatotoxicity nor a significant difference between hepatitis C–positive and hepatitis C–negative treated patients was found. To our knowledge, no data have shown the impact on the liver of statin use in HIV/HCV coinfection. The aim of this study was to assess whether statin therapy increased the risk of hepatotoxicity in an HIV-positive/HCV-positive population compared with an HIV-positive/HCV-negative population.

We retrospectively reviewed all HIV-positive patients, followed as outpatients, who had the use of statins included in their clinical history. Two groups of patients were compared: group A included patients with HIV/HCV coinfection, as defined by HCV RNA positivity, who started statin therapy at least 6 months after diagnosis of hepatitis C, and group B consisted of HIV-positive, HCV/hepatitis B virus (HBV)–negative subjects also starting statin therapy. Patients with alcohol abuse or concomitant hepatotoxic medications other than antiretrovirals and patients on anti-HCV treatment were excluded.

We considered as significant an increase of liver function test (LFT) results ≥ 1.5 the baseline values (defined as the mean of 3 consecutive controls within 6 months before the introduction of a statin) or if results were above the upper limit of normal for those with normal values at study entry.

Demographic data and laboratory test results were collected at baseline. LFT results obtained 6 months after initiation of statin therapy were considered for the analysis. We registered the type of statin and any other concomitant medication, particularly antiretroviral drugs. Quantitative HCV RNA (branched DNA; Siemens Medical Solutions USA) was collected when available.

Statistical analysis was performed using the χ^2 or Fisher exact test, and distributions of continuous variables were compared using the Mann-Whitney test for independent samples. All tests were 2-sided, with 5% type I error (α).

Among the 1421 HIV-1-infected patients currently referred to our clinic, 80 patients who have been treated with statin therapy for hypercholesterolemia were included: 38 patients in group A (HIV positive/HCV positive) and 42 patients in group B (HIV positive/HCV negative). A total of 76.2% of patients were male, and the median (25th to 75th percentiles) age was 45.5 (42 to 54) years, with a significant difference between the 2 groups ($P = 0.0006$ and $P = 0.001$, respectively), because a higher percentage of patients in group A were male and younger. Baseline median LFT results were significantly higher in group A (alanine aminotransferase [ALT]: 49.5 vs. 27 IU/L, $P = 0.0006$; gamma-glutamyl transferase [GGT]: 72 vs. 40 IU/L in groups A and B, respectively, $P = 0.006$). The overall mean \pm SD value of the CD4⁺ count was 556.4 \pm 259.6 cells/ μ L, and the median HIV level (25th to 75th percentiles) was 50 (50 to 80) copies/mL without significant differences between groups.

The most frequently prescribed statin was atorvastatin (63.7%), followed by pravastatin (28.7%), rosuvastatin (5%) and simvastatin (2.5%), without a significant difference between the 2 groups. The distribution of antiretroviral regimens was also similar, with 36 patients (45%) taking 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 1 PI, 39 patients (48.7%) taking 2 NRTIs plus 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), and 5 patients (6.2%) taking no antiretroviral drugs. HCV RNA

quantification and genotyping were available for 24 patients with HCV RNA median values (25th to 75th percentiles) of 1,702,027 (910,458 to 2,778,835) IU/mL and for 15 patients harboring genotype 1, 8 with genotype 3, and 1 with genotype 2.

As shown in Figure 1A, the fold change of liver enzymes was low in both groups of subjects, with no significant difference. No difference in the percentage of patients developing an increase in aspartate aminotransferase (AST), ALT, or GGT ≥ 1.5 baseline level emerged between groups A and B (see Fig. 1B): 7.9% versus 4.8% for AST, 7.9% versus 14.3% for ALT, and 15.8% versus 14.3% for GGT in groups A and B, respectively ($P =$ not significant [NS]). The higher increase of GGT (from 50 to 158 IU/L and from 74 to 118 IU/L in groups A and B, respectively) was observed in 2 patients in group A, who were both taking simvastatin. None of the patients discontinued statins because of liver toxicity or modified their antiretroviral regimen because of drug interaction.

Interestingly, overall percentages of 40%, 42.5%, and 37.5% of patients underwent a reduction in LFT values (AST, ALT, and GGT, respectively) after statin introduction. The median percentage (25th to 75th percentiles) reductions in AST, ALT and GGT were -18% (-0.4 to -26), -28% (-0.9 to -47), and -19% (-1.3 to -23), respectively, in group A and -25% (-1 to -33), -20% (-11 to -34), and -18% (-0.9 to -26), respectively, in group B, without a significant difference between the 2 groups and with no correlation with cholesterol reduction. Furthermore, no correlation was found between PI or NNRTI including HAART or between the statin used, with respect to LFT result increase

from baseline, although a trend emerged for GGT ($P = 0.059$), because both patients taking simvastatin had a marked increase in GGT. We found a positive correlation between patients who underwent a reduction in ALT and those with higher baseline values of ALT. In the 18 patients in group A with a reduction of ALT while on statin therapy the a median (25th to 75th percentile) baseline ALT value was 70.5 IU/L (50 to 110) compared with 31 IU/L (22 to 57) of the 20 subjects with ALT increment, ($P = 0.0038$). Sixteen patients in group B with a reduction in ALT had a baseline median ALT value of 37.5 IU/L (27.5 to 47) versus 21 IU/L (18 to 32) of the 26 who presented ALT increase ($P = 0.0007$).

Finally, a significant reduction in cholesterol levels was observed ($P = 0.01$) in both groups.

The Infectious Disease Society of America's guidelines for the management of dyslipidemia in HIV-infected subjects on HAART do not provide any recommendation for the treatment of HCV-coinfected patients,⁴ who are at a higher risk of hepatotoxicity. Therefore despite the potential usefulness of statins, their use is still debated because of the uncertain risks.

In our experience, statin use in HIV/HCV-coinfected patients showed a low elevation in LFT values. Only 7.9% of coinfecting patients on statin therapy experienced an increase in ALT ≥ 1.5 times the baseline values, which was lower than that observed in the HCV-negative group. Furthermore none of our patients demonstrated an increase in liver enzymes ≥ 3 times the upper limit of normal, as set by the American Heart Association⁵ for dose reduction or statin suspension.

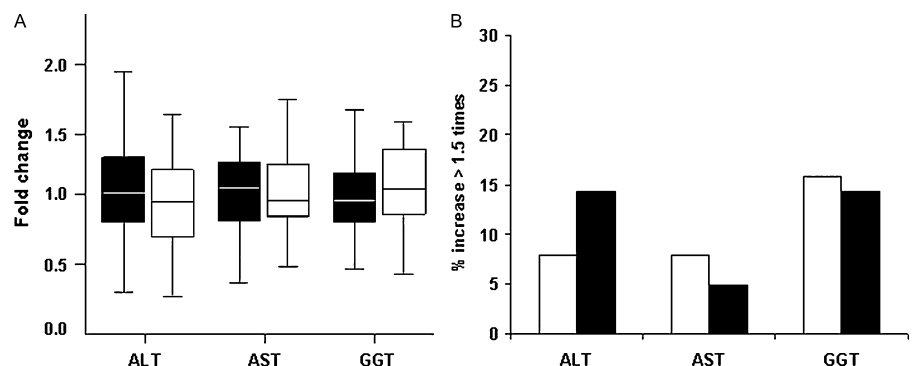


FIGURE 1. A, Fold change from baseline of liver enzyme values 6 months after the introduction of statin therapy. No significant difference emerged between the study groups. B, Percentage of patients with an increase in LFT results ≥ 1.5 times baseline values or above the upper limit of normal for those with normal baseline values at study entry. No significant difference emerged between the study groups (\square , group A; \blacksquare , group B).

The PI inhibition of the cytochrome P450-CYP3A4, resulting in an increase in statin area under the curve (AUC), may account for the major increase of GGT observed in 2 subjects treated with simvastatin.

Recently, Khorashadi et al³ found an association between statin therapy and the reduction of median LFT values in patients with hepatitis C. In a percentage of our HIV-infected patients, we also observed an improvement in the median LFT values but without a difference between HCV-positive and HCV-negative patients. Recent reports showed a promising effect of statins in reducing aminotransferases in nonalcoholic fatty liver disease (NAFLD).⁶ The hypothesis that treatment of hyperlipidemia may improve LFT abnormalities attributable to NAFLD might partially explain our results, considering that HCV and HIV infections as well as the use of anti-retrovirals favor the emergence of non-alcoholic steatohepatitis, although we did not find a correlation between a reduction in LFT results and cholesterol improvement. Another intriguing hypothesis is that statins may modulate immune response by induction of anti-inflammatory activity.^{7,8} Patients with

HIV-1 or HIV/HCV coinfection demonstrate a chronically activated inflammatory response with high levels of circulating inflammatory cytokines; moreover, liver inflammation is enhanced by HAART-related chronic toxicity. The anti-inflammatory activity of statins may account for the amelioration of LFT results in both groups, with the correlation found between patients with a decrease in ALT and higher values of ALT at baseline possibly expressing liver inflammation.

Our results suggest that the use of atorvastatin, pravastatin, and rosuvastatin is safe in HIV and HIV/HCV-coinfecting patients with hypercholesterolemia.

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