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The Prevalence and Risk Factors for Abnormal Liver Enzymes in HIV Positive Patients Without Hepatitis B or C Coinfections

Richard K. Sterling, M.D.[1,4], **Steven Chiu, M.D.**[2], **Kenny Snider, Pharm. D.**[3], and **Daniel Nixon, D.O.**[4]

[1]Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University Health System, Richmond, Virginia

[2]Virginia Commonwealth University School of Medicine, Virginia Commonwealth University Health System, Richmond, Virginia

[3]Department of Pharmacy, Virginia Commonwealth University Health System, Richmond, Virginia

[4]Division of Infectious Disease, Virginia Commonwealth University Health System, Richmond, Virginia

Abstract

Background—Abnormal liver enzymes (LFTs) are frequently seen in HIV patients. Because HCV and HBV overshadow other possible variables, little is known about the prevalence and predictive factors of abnormal LFTs in the absence of viral hepatitis.

AIMS—To determine the prevalence and factors associated with abnormal LFTs defined as > 1.25 ULN.

Methods—A retrospective analysis of HIV clinic patients was performed. Variables were determined at the time of abnormal LFTs or by history and included diabetes mellitus (DM), hypertension (HTN), dyslipidemia, HCV and HBV status, metabolic syndrome (MS), and HAART use (NRTI, NNRTI, and PI).

Results—Patients without HCV/HBV (n=679/1208) were younger, Caucasian, had a BMI > 30 and had dyslipidemia. The prevalence of elevated LFTs in those without HCV/HBV were AST 20%, ALT 15%, and ALP 43% compared to 64%, 46%, and 63% in those with HCV (all p<.0001) and 98% were mild-moderate (grade 1–2). While AST was highly correlated with ALT, neither was associated with increased ALP. In those without HCV/HBV, increased AST was associated with HTN, HIV RNA, and absence of PI use; increased ALT was associated with HTN, HIV RNA, CD4 < 200, MS, and absence of PI use; while increased ALP was associated with age, BMI, CD4%, DM, and NRTI use.

Conclusions—Mild-moderate increased liver enzymes are common in HIV patients without HCV/HBV and absence of PI use is independently associated with elevations in both AST and ALT while features typical of hepatic steatosis (DM and BMI) are only associated with increased ALP.

Address Correspondence to: Richard K. Sterling, MD, Professor of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University Medical Center, 1200 E. Broad St, West Hospital, Room 1492, Richmond, VA 23298-0341, Ph: 804-828-4060, Fax: 804-828-4945, rksterli@hsc.vcu.edu.

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Introduction

HIV infection is a global health concern with an estimated 1 million infected in the United States and 42 million worldwide (www.UNAIDS.org). With the advent of highly active antiretroviral therapy (HAART), which combines various nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs), the morbidity and mortality related to HIV have significantly decreased (1;2). As a result, patients are now living longer with HIV infection and other co-morbidities and hepatic events have emerged as a key issue in the management of HIV-infected patients (3).

Abnormal liver chemistries (aspartate aminotransferase: AST, alanine aminotransferase: ALT, and alkaline phosphatase: ALP) are common and occur in 40–60% of patients on current HAART regimens even in the absence of HCV or HBV (4–6) and their management remains a challenge (7). This high proportion is far greater than expected in the general population of 8% (8). Because the main focus on liver disease in patients with HIV has been on coinfection with hepatitis C virus (HCV) and hepatitis B virus (HBV), there has been little attention to other causes of liver diseases in the absence of HCV and HBV (9, 10). Furthermore, most clinical studies on hepatoxicity have focused on those with severe liver enzyme elevations (defined as ≥ 5x the upper limit of normal (ULN) (5;11–13). However, the majority of patients with abnormal liver chemistries have mild to moderate liver enzyme elevations (1.25 to 4 x ULN). Because this group of patients has largely been ignored, there are little data in these individuals without viral hepatitis that develop mild to moderate elevations in liver enzymes. To address this issue, we performed a retrospective analysis of outpatients attending our HIV clinic to determine the prevalence and risk factors associated with abnormal liver enzymes in a cohort of HIV infected patients without HCV or HBV coinfection.

Methods

Patients

We performed a retrospective cross sectional analysis of all adult patients currently attending the Virginia Commonwealth University Health System (VCUHS) HIV clinic. We excluded patients under age 18 and inmates as required by our Institutional Review Board (IRB) for the study of Human Subjects for this analysis. Of over 1600 patients, charts on 1208 were available for review. Charts that were missing from the file room at the time of review were assumed to be missing at random. The following data was recorded: age, gender, race, weight, body mass index (BMI), % BMI > 30, HIV RNA level by a commercial assay, % with undetectable HIV RNA (< 400 copies/ml), CD 4 count, % with CD4 < 200, CD4%, diabetes mellitus (DM: defined by listed diagnosis or on anti-DM medication), hypertension (HTN: defined by listed diagnosis or on anti-HTN medication), dyslipidemia (defined by listed diagnosis or on a lipid lowering medication), and HAART use (% NRTI, NNRTI, and PI as well as individual agents) at the time of abnormal liver enzymes. For analysis purposes, we defined the metabolic syndrome (MS) as the presence or absence of 2 or more of the following features: DM, HTN, dyslipidemia, or obesity (BMI ≥ 30). While measuring antibodies to HCV and HBV surface antigen was performed on all HIV patients, HCV RNA and HBV DNA was not performed on all subjects. Therefore, we defined HCV and/or HBV coinfection as the presence of absence of anti-HCV or HBV surface antigen, respectively. To minimize data entry errors, a random sample of 50 subjects had their data verified and all outlier values were confirmed or corrected.

Statistical analysis

We defined abnormal liver enzymes according to the NIH-NIAI Guidelines (AIDS Clinical Trial Group) as follows: grade 0: < 1.25 x ULN, grade 1: 1.25–2.5 ULN, grade 2: 2.6–5.0 ULN, grade 3: 5.1–10 x ULN, and grade 4: > 10 x ULN. For analysis, abnormal liver enzymes were defined as grade 1 or higher at any time point. Clinical variables were determined at the time of abnormal liver enzymes if present or by history and chart review. Variables were dichotomized as presence or absence of DM, HTN, dyslipidemia, HCV antibody positive, HBV surface antigen positive, metabolic syndrome, and HAART use at the time of abnormal liver enzymes.

Continuous variables were assessed for normality. Mean and standard deviation (SD) were used to describe continuous variables and proportions to describe categorical data. Univariate analysis was used to determine factors associated with abnormal AST, ALT, and ALP in the cohort as well as those with and without HCV or HBV. Analysis of variance was used to compare continuous variables and Pearson chi square to compare categorical variables. Stepwise multivariable logistic regression (MLR) with a p value of 0.25 to enter and 0.10 to remain in the model was then used to identify independent predictors of elevated AST, ALT, and ALP in the cohort as well as those with and without HCV and HBV coinfections. All tests were two-sided and a p value < 0.05 was considered statistically significant. All analyses were performed by JMP IN 6.0 (SAS Institute, Cary, NC). This retrospective analysis was approved by the Institutional Review Board (IRB) for the study of Human Subjects at VCUHS.

Results

Of over 1600 patients, charts on 1208 were available for review. The characteristics of the cohort are shown in table 1. The mean age was 42 years, 63% were male, 25% were Caucasian, and 22% had a BMI > 30. Overall, 24% had antibodies to HCV, 7.1% were positive for HBV surface antigen, and 1% were positive for both HCV and HBV. HCV and HBV antibody status were missing in 67 (5%) and 226 (18%) respectively. Of the cohort, 66% were taking HAART. Of these, 99%, 41.3%, and 59% were on a NRTI, NNRTI, and PI, respectively. Looking at individual agents, of those on HAART (n = 802), 35% were taking zidovudine (AZT), 58% were on lamuvidine, 17% were on didanosine (ddI), 13% were on stavudine (d4T), 52% were on tenofovir, 24% on emtricitabine (usually combined with tenofovir), 18% were on abacavir, 28% were on efavirenz, 13% on nevirapine, 21% on lopinavir, 9% on nelfinavir, 2% on saquinavir, 3% on indinavir, 1% on amprinavir, 2% on atzanavir, 2% on fosamprenavir, and 40% were on ritonivir (low dose combined with another PI).

Elevated AST, ALT, and ALP were observed in 31.5%, 23.8%, and 46.9% of the cohort. The overwhelming majority of elevations in liver enzymes were mild to moderate grade 1–2 with only 1–2% having elevations greater than 5 x ULN (grade 3–4). AST was highly correlated with ALT (r = .80, p<.0001) while neither were correlated with increased ALP. An isolated increased ALP was observed in 315/798 (39%) of those with normal AST and ALT compared to 166/259 (64%) with elevated AST or ALT (p < .0001).

Table 2 compares the characteristics in those with available data in those with (n = 294) and without HCV or HBV (n = 679). Those with HCV or HBV were older (p<.0001), African American (p = .0007), have a lower BMI (p = .027), less likely to have a BMI > 30 (p = .03), and less likely to have dyslipidemia (p < .0005). Those with HCV or HBV coinfection were also more likely to have elevated AST, ALT and ALP (p< .0001 for each). However, 30–40% of those coinfected had normal liver enzymes. Although no significant differences in NRTI, NNRTI, and PI use when analyzed by class of medication, those with HCV or

HBV were more likely to be on nevirapine (12 vs. 6%; p = .026) and nelfinavir (12 vs. 4%; p <.0001) and less likely to be on efaverinz (13 vs. 22%; p = .008).

Because HCV and HBV coinfection was the strongest predictor of abnormal liver enzymes in the entire cohort (p < .0001 for AST, ALT, and ALP), it may mask other factors. Therefore, we focused on the risk factors of abnormal liver enzymes in those without HCV and HBV. In this group (n = 679), increased AST, ALT, and ALP were observed in 134 (19%), 103 (15%), and 291 (42%) respectively. While AST was correlated with ALT (r = . 36, p = .0007), it was not correlated with ALP and an isolated ALP was observed in 39%. Factors associated with increased liver enzymes in patients without coinfection are shown in tables 3a–c. Increased AST and ALT were independently related to presence of HTN, HIV RNA level, and inversely with PI use (p < .0001) while the metabolic syndrome was only associated with increased ALT. Increased ALP was associated with BMI > 30, DM, and CD4%, and NRTI use. In comparison, in the cohort with HCV without HBV, increased AST was observed in 144 (64%) and was only associated with race (p = .0352); increased ALT was observed in 46.6% and both univariate and multivariable analysis failed to identify any significant factor associated with increased AST or ALT in these individuals supporting the "masking" effect of HCV coinfection. Conversely, increased ALP was observed in 140 (61%) of those with HCV coinfection and associated with DM (p = .0487), NRTI use (p < . 0001), and PI use (p = .0004).

There were no significant differences in either class of HAART medication used or individual medications between those with or without HCV coinfection. The relative risk (RR) of elevated liver enzymes and HAART use in those with and without HCV or HBV coinfections are seen in table 4. While only d4T was associated with elevated AST, several agents were inversely associated with increased ALT. NRTI, NNRTI, and PI use as well as several individual agents were positively associated with increased ALP. In comparison, no class or individual agent was associated with increased AST while only indinavir was associated with increased ALT (RR 2.19; 95% CI 1.89–2.53) in those coinfected. Conversely, several agents were associated with increased ALP. Because of concerns of increased liver enzymes in patients on NNRTIs, we compared those on efaverinz or nevirapine in the entire cohort and found no significant differences in increased AST regardless of the presence of HCV while use of nelfinavir was inversely associated with increased ALT only in those with HCV or HBV coinfection (RR 0.54, 95% CI .28–1.0; p = . 037). Conversely, increased ALP was positively associated with efaverinz but this was limited to those without HCV or HBV (RR 1.29, 95% CI 1.07–1.55; p = .012).

Discussion

Our study in over 1200 unselected HIV patients has several important findings and is the first attempt to quantify the prevalence and factors associated with elevated LFTs in HIV patients without HCV or HBV coinfection. First, in the absence of HCV or HBV, defined by the presence or absence of anti-HCV or HBV surface antigen, the prevalence of elevated liver enzymes was high (15–43%). Second, the majority of liver enzyme elevations were mild-moderate (1.25–5 x ULN). Third, increases in ALP were the most common abnormality seen in 43% and did not correlate with increased AST or ALT. And forth, PI use was independently associated with absence in elevations in both AST and ALT while features typical of hepatic steatosis (DM and increased BMI) were only associated with increased ALP.

Abnormal liver enzymes (AST, ALT, and ALP) can be classified as either hepatocellular (increases in AST and ALT), cholestatic (increases in ALP), or mixed (14). Because patterns can have differing etiologies and pathogenic mechanisms, it is important to analyze them

independently. Increased liver enzymes are frequently seen in those with HIV and may be due to a variety of factors including viral hepatitis coinfections, alcohol, opportunistic infections, steatohepatitis, and concomitant medications including HAART (15). However, because most studies have focused on individuals that are coinfected with HBV or HCV or in those with severe (grade 3–4) elevations, factors associated with abnormal liver enzymes, particularly those with grade 1–2, in patients with HIV in the absence of viral hepatitis have not been explored.

In a recent report in a large cohort of 5957 HIV patients, the prevalence of abnormal ALT and AST (defined as greater than upper limit of normal) in those without HCV (n = 3997) was 55% and 76% respectively and lower than those with HCV coinfection (83% for ALT and 92% for AST) (9). Importantly, 86% of these patients without HCV were also HBV surface antigen negative suggesting another etiology for increased liver enzymes. Of those without HCV, 53% were on HAART and another 30% were on an antiretroviral medication. Importantly, analyses for factors associated with increased liver enzymes were not performed. Conversely, in a study by Maida and colleagues cryptogenic liver disease, defined as increased liver enzymes in the absence of HCV and HBV coinfections, was identified in only 17 of 3200 (0.5%) HIV positive subjects (10). However, they excluded patients with severe obesity, grade 3 to 4 dyslipidemias, hyperglycemia, insulin resistance, and/or ultrasonographic evidence of fatty liver, all established risk factors for elevated liver enzymes (16). Interestingly, even in the absence of risk for hepatic steatosis, liver histology in 5 of the 17 patients who underwent biopsy demonstrated steatosis and inflammation. In their analysis, only longer ddI exposure was identified as an independent predictor of chronic liver enzyme elevations.

The high frequency of increased ALP in those without HCV or HBV coinfection has not previously been reported in those with HIV. In the study by Rockstroh (9), no data on ALP was provided. In the study by Maida (10), among those 17 with increased liver enzymes, ALP was elevated in 16. However, it is not clear if an isolated ALP met their criteria for cryptogenic liver disease. This high proportion of increased ALP compared to AST and ALT is different than reported from large drug induced liver registries of severe hepatitis in the general population which found hepatocellular pattern of injury more common (52–58%) than a cholestatic pattern (20–26%) (17;18). In the current study, increased ALP was more common than AST or ALT and associated with a BMI > 30 and DM, both associated with hepatic steatosis. This finding was not surprising given that an isolated ALP has been observed in patients with nonalcoholic fatty liver disease (NAFLD) (19). Although increased ALP was also associated with NRTI, NNRTI, and PI class use on univariate analysis, only NRTI use was identified on multivariate logistic regression. Independent predictors of increased AST and ALT in those without HCV or HBV coinfections were HTN while PI use was protective. While a HIV < 400 copies was not, a low CD4 < 200 and presence of the metabolic syndrome were also associated with increased ALT.

There are several potential mechanisms that are specific to HIV medications that can result in liver enzyme elevations. Because not all drugs within each class have similar effects on the liver, we also were able to look at individual drugs within each class and observed that only d4T was associated with increased AST while no specific agent was associated with increased ALT. Conversely, several agents were associated with increased ALP. Although the use of nevirapine has been associated with cholestatic liver enzyme elevations (20), we found no association in increased ALP and nevirapine use in the absence of HCV coinfection.

Causes of increased liver enzymes in those with HIV can include direct cytopathic effects of HIV on either hepatocytes or biliary epithelia or specific drug toxicity of HAART. There are

several potential mechanisms that are specific to HIV medications that can result in liver enzyme elevations. PIs have been associated with the development of insulin resistance (IR) and dyslipidemia, both risk factors for steatosis (21–27). In addition, both ddI and d4T have been associated with steatosis in HCV coinfected patients (28–30). Our findings of d4T support these prior observations. The inverse relationship of PI and increased liver enzymes may have several possible explanations. Several studies in HIV-HCV coinfected patients have shown that PI use is associated with lower fibrosis progression (31; 32). However, data were not provided on the impact of PI use on liver enzymes and their relationship to liver pathology in those without HCV is unknown. PI use has been reported to affect hepatocyte apoptosis which may impact on liver enzymes (33). Therefore, the ability of HAART and other drugs to disrupt the normal production or elimination of reactive oxygen species in the liver may be an important factor relating to their potential cause of abnormal liver enzymes (15). However, this area has not been well studied and requires further research.

Both IR and dyslipidemia are pathogenic mechanisms associated with NAFLD and non-alcoholic steatohepatitis (NASH) which often present as asymptomatic liver enzyme elevations and may explain elevations in liver enzymes in some of these individuals (19). We observed that both HTN and DM, components of the metabolic syndrome, were independently associated with elevated liver enzymes, particularly, elevations in ALP. This was not unexpected given the association of isolated ALP elevations in those with steatohepatitis (16, 34). Therefore, in the absence of viral hepatitis, these enzyme elevations are most likely due to hepatic steatosis. Because NASH is now recognized as a significant cause of cirrhosis with associated morbidity and mortality, its recognition as a long term complication of HAART is important to the management of those living with HIV. Although we did not have histology, our findings that DM, BMI, and NRTI use are associated with elevated liver enzymes supports these previous observations.

The prevalence of steatosis in those with HIV is unknown in those without HCV coinfection. Several recent reports in HIV-HCV coinfected patients have found a high proportion (40–75%) with steatosis (29; 35–39) that is greater than expected (40) from the general population and associated with increased weight or BMI (28; 29; 38), hyperglycemia (28), lipodystrophy (38), d4T (28), NRTI (29) and PI use (28). Conversely, in a cohort of 92 coinfected patients, Monto found a low (2%) prevalence of significant steatosis (>33%) compared to 9% in HCV controls which was unrelated to HIV therapy (37). However, because hepatic steatosis is associated with increased fibrosis progression (28), its presence is clinically significant.

There are several limitations of our analysis. First, we did not differentiate those with transient from those with persistent liver enzyme elevations and we defined abnormal liver enzymes as any elevation at any time. We also did not take into account renal function, alcohol use, concurrent medication use, coexisting liver diseases other than HCV or HBV that may also have caused increases in liver enzymes. Furthermore, confirmation of HCV infection by RNA, HBV DNA or E antigen status in those with HBV surface antigen may have resulted in misclassification of subjects. We did not directly measure IR nor take into account the normal fluctuations in liver enzymes and changes in HAART use over time. There also were missing data on HCV and HBV in a small proportion of patients which may have impacted our results. Furthermore, there are several additional causes of increased ALP, including primary biliary cirrhosis (PBC), biliary tract diseases (primary sclerosing cholangitis (PSC), sarcoidosis, gallstones, HIV cholangiopathy), and infiltrating tumors. In addition, elevations in ALP are not specific for liver disease and may also be elevated in bone diseases. Because ultrasound was not routinely performed in patients with elevated liver enzymes, that information was not included in our analysis. We also did not specifically look for PBC, sarcoidosis, biliary tract and bone diseases which are uncommon

in our population and do not explain the observed high prevalence of increased ALP. Also, gamma glutamyl transferase (GGT) was not routinely obtained on all patients, especially those with isolated elevations in ALP. However, the majority of cases of increased ALP reported by Maida were associated with increased gamma glutamyl transferase (GGT) suggesting liver rather than bone origin (10). The most important limitation of our findings was lack of histology in these patients. Therefore, the clinical significance of these mild liver enzyme elevations could not be assessed. Nevertheless, given these limitations, this study represents the first attempt to describe the prevalence and potential factors associated with abnormal liver enzymes in unselected HIV patients without HCV and HBV coinfections.

In conclusion, elevated liver enzymes are common in those with HIV, even in those without obvious HCV or HBV coinfections. In the absence of HCV or HBV, absence of PI use is independently associated with elevations in both AST and ALT while features typical of hepatic steatosis, DM and increased BMI, were associated with increased ALP. These observations need to be confirmed in prospective cohorts and ongoing studies with liver histology will determine the clinical significance of asymptomatic liver enzyme elevations. Until additional data are available, clinicians caring for those with HIV should monitor all their patients with mild to moderate liver enzyme elevations, regardless of the presence of HCV or HBV coinfections, and consider liver biopsy to assess the etiology and significance of this common clinical scenario.

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Abbreviations

LFTs	liver function tests
HIV	human immunodeficiency virus
HCV	hepatitis C virus
HBV	hepatitis B virus
ULN	upper limits of normal
DM	diabetes mellitus
IR	insulin resistance
HTN	hypertension
MS	metabolic syndrome
HAART	highly active antiretroviral therapy
NRTI	nucleoside/tide reverse transcriptase inhibitor
NNRTI	non nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
RNA	ribonucleic acid
BMI	body mass index
AST	aspartate aminotransferase
ALT	alanine aminotransferase

ALP	alkaline phosphatase
MLR	multivariate logistic regression
AZT	zidovudine
LAM	lamivudine
ddI	didanosine
d4T	stavudine
FTC	emtricitobine
ABAC	abacavir
EFV	efavirenz
NVP	nevirapine
LOP	lopinavir
NEL	nelfinavir
AMP	amprinavir
ATZ	atazanavir
RIT	ritonavir
IND	indinavir

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Table 1

Characteristics of subjects.

Variable	
N	1208
Age (years) *	42.14 (9.7)
Gender (% male)	63.7
Race (% Caucasian)	24.7
Weight (kg) *	78.46 (18.7)
BMI *	26.46 (6.3)
% BMI ≥ 30	22.3
% HIV RNA < 400 copies	41.3
CD 4 (cells/mm^3) *	445 (326)
CD4% *	23.04 (17.5)
% CD4 < 200	23.9
Diabetes (%)	7.6
Hypertension (%)	27.3
Dyslipidemia (%)	25.6
Metabolic Syndrome (%)	22.1
Anti-HCV positive (%)	24.3
HBV surface antigen + (%)	7.1
Elevated AST (%)	31.5
Elevated ALT (%)	23.8
Elevated ALP (%)	46.9
Elevated bilirubin (%)	10.7
NRTI/NNRTI/PI use (%)	66/27/40

* mean (SD)

Table 2

Comparison of those with (n = 294) and without (n = 679) HCV or HBV.

	Anti-HCV −	Anti HCV +	p-value
Age (yrs)*	40.8 ± .36	46.0 ± .61	<.0001
% male	63	65	NS
% white	17	3	.0007
BMI	27 ± .24	25 ± .41	.027
BMI > 30 (%)	25	17	.03
DM (%)	6	7	NS
HTN (%)	25	32	NS
Dyslipidemia	28	16	.0005
Metabolic Syn	23	18	NS
CD 4 count	449 ± 12	456 ± 21	NS
HIV RNA <400	41	36	.03
% CD 4 < 200	24	21	NS
% ALT Elevated	15	44	<.0001
% AST Elevated	19	63	<.0001
% ALP Elevated	43	61	<.0001
NTRI use (%)	63	65	NS
NNRTI use (%)	28	25	NS
PI use (%)	36	41	.052

mean ± standard error; NS = not significant

BMI = body mass index; DM = diabetes mellitus; HTN = hypertension; Syn = syndrome; NTRI; nucleoside reverse transcriptase inhibitor; NNRTI = non- nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

Table 3a

Factors associated with increased AST in those without HCV or HBV (n = 134/679).

Variable	Univariate	Mulitvariate	
	P value	OR (95% CI)	P value
Gender (male/female)	.0221		
HTN (yes/no)	.05	1.45 (1.07–1.95)	.0142
HIV RNA	<.0001	.997 (.996–.999)	.0012
CD 4 (increasing)	.0006		
CD4 < 200 (yes/no)	<.0001		
CD4%	<.0001		
PI use (no/yes)	.0009	.49 (.32–.73)	< .0001

HTN = hypertension; PI = protease inhibitor

Table 3b

Factors associated with increased ALT in those without HCV or HBV (n = 103/679).

Variable	Univariate	Mulitvariate	
	P value	OR (95% CI)	P value
Gender (male/female)	.0221		
HTN (yes/no)	.05	1.45 (1.07–1.95)	.0142
HIV RNA	.0008	.998 (.997–.999)	.02
CD 4 (increasing)	.008		
CD4 < 200 (yes/no)	<.0196	1.57 (1.14–2.15)	.0049
CD4%	<.0001		
Metabolic syndrome (yes/no)	.04	1.41 (1.00–2.00)	.043
NRTI (no/yes)	.0039		
PI use (no/yes)	.0005	.59 (.40–.83)	.0038

HTN = hypertension; NTRI; nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

Table 3c

Factors associated with increased ALP in those without HCV or HBV (n = 297/679).

Variable	Univariate	Mulitvariate	
	P value	OR (95% CI)	P value
Age	< .0001	.97 (.95–.98)	.0007
BMI > 30	.20	1.25 (1.03–1.52)	.021
HIV RNA < 400 copies/ml	.017		
CD 4	.05		
CD4 < 200 (yes/no)	.0012		
CD4%	.0001	1.43 (1.18–1.73)	.0002
DM (yes/no)	.0027	1.42 (1.02–1.95)	.037
Dyslipidemia (yes/no)	.0341		
Metabolic syndrome	.042		
NTRI use (yes/no)	<.0001	1.31 (1.08–1.60)	.0059
NNRTI use (yes/no)	.0035		
PI use (yes/no)	.0046		

BMI = body mass index; DM = diabetes mellitus; NTRI; nucleoside reverse transcriptase inhibitor; NNRTI = non- nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

Table 4

Relative risk (RR) of HAART with elevated liver enzymes

Total Cohort (n = 1208)			HCV/HBV Negative (n = 679)			HCV/HBV Positive (n = 223)		
Elevated AST (> 1.25 upper limit normal)								
Drug	**RR (95%C)**	**p**	**Drug**	**RR (95%C)**	**p**	**Drug**	**RR (95%C)**	**p**
PI (class)	.78 (.65–.93)	.0054	PI (class)	.55 (.38–.79)	.0009	none		
Stavudine	1.35 (1.06–1.73)	.028	Stavudine	1.66 (1.09–2.52)	.037			
Tenofovir	.74 (.61–.90)		Tenofovir	.61 (.42–.87)	.006			
Emtricitabine	.68 (.52–.90)		Emtreicitabine	.51 (.28–.91)	.014			
Atzanavir	.66 (.51–.88)		Atzanavir	.35 (.17–.72)	.001			
Ritonavir	.71 (.58–.88)		Ritonavir	.53 (.35–.81)	.0022			
Elevated ALT (> 1.25 upper limit normal)								
None			NRTI (class)	.59 (.41–.84)	.0039	Nelfinavir	.54 (.28–1.0)	.037
			PI (class)	.47 (.30–.74)	.0009	Indinavir	2.19 (1.89–2.53)	.046
			Tenofovir	.61 (.39–.94)	.023			
			Atzantavir	.39 (.07–.87)	.012			
			Ritonavir	.50 (.30–.83)	.005			
Elevated ALP (> 1.25 upper limit normal)								
NRTI (class)	1.52 (1.31–1.76)	<.0001	NRTI (class)	1.31 (1.11–1.57)	.0035	NRTI (class)	1.65 (1.26–2.14)	<.0001
NNRTI (class)	1.21 (1.07–1.37)	.038	NNRTI (class)	1.55 (1.26–1.91)	<.0001	PI (class)	1.43 (1.18–1.75)	.0004
PI (class)	1.30 (1.16–1.47)	<.0001	PI (class)	1.28 (1.08–1.53)	.0048	Lamivudine	1.32 (1.08–1.61)	.0078
Zidovudine	.78 (.67–.92)	.002	Zidovudine	.75 (.59–.96)	.016	Tenofovir	1.42 (1.18–1.61)	.0012
Lamivudine	1.15 (1.02–1.30)	.016	DidanosineI	1.45 (1.12–1.79)	.0018	emtricitobine	1.41 (1.15–1.72)	.016
Stavudine	1.27 (1.07–1.51)	.0126	Tenovovir	1.43 (1.21–1.70)	<.0001	Abacavir	1.36 (1.09–1.69)	.042
Didanosine	1.28 (1.09–1.50)	.0043	Emtricitabine	1.27 (1.03–1.5)	.0385	Atazavir	1.51(1.27–1.80)	.0015
Tenovovir	1.41 (1.25–1.59)	<.0001	Efaverinz	1.29 (1.07–1.55)	.012	Ritonavir	1.31 (1.07–1.59)	.027
Emtricitabine	1.18 (1.02–1.36)	.035	Lopinavir	1.41(1.16–1.71)	.0022			
Efaverinz	1.20 (1.04–1.38)	.0124	Ritonavir	1.24 (1.04–1.48)	.0285			
Lopinavir	1.29 (1.12–1.49)	.0015						
Saquinavir	1.51 (1.11–2.07)	.049						

Total Cohort (n = 1208)			HCV/HBV Negative (n = 679)			HCV/HBV Positive (n = 223)		
Elevated AST (> 1.25 upper limit normal)								
Drug	RR (95%C)	p	Drug	RR (95%C)	p	Drug	RR (95%C)	p
Ritonavir	1.25 (1.11–1.42)	.0005						