

Hepatotoxicity Associated With Antiretroviral Therapy in Adults Infected With Human Immunodeficiency Virus and the Role of Hepatitis C or B Virus Infection

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ABNORMAL LEVELS OF LIVER ENZYMES are common among persons infected with human immunodeficiency virus (HIV), and may be caused by multiple factors, including medication toxicity and coinfection with hepatitis C virus (HCV) or hepatitis B virus (HBV).¹⁻³ Coinfection with HCV and HIV is common, occurring in 50% to 80% of individuals who acquired HIV through parenteral exposures. Chronic HBV infection occurs in 10% to 15% of persons infected with HIV.^{2,4}

Anecdotal evidence suggests that chronic viral hepatitis may be associated with increased risk of antiretroviral-associated hepatotoxicity, particularly during the use of protease inhibitors (PIs).⁵⁻¹⁰ However, the actual incidence of drug-induced hepatotoxicity and role of chronic viral hepatitis are poorly understood since anecdotal reports generally omit the number of exposed persons and may focus attention on exceptional cases or high-risk populations. Conversely, clinical trials are frequently restricted to persons at low risk for adverse events.^{11,12} Also, clinical trials underrepresent minority groups, women, and injection drug users, and may exclude those with chronic HCV or HBV infection.

Context Use of antiretroviral drugs, including protease inhibitors, for treatment of human immunodeficiency virus (HIV) infection has been anecdotally associated with hepatotoxicity, particularly in persons coinfecting with hepatitis C or B virus.

Objectives To ascertain if incidence of severe hepatotoxicity during antiretroviral therapy is similar for all antiretroviral drug combinations, and to define the role of chronic viral hepatitis in its development.

Design Prospective cohort study.

Setting University-based urban HIV clinic.

Patients A total of 298 patients who were prescribed new antiretroviral therapies between January 1996 and January 1998, 211 (71%) of whom received protease inhibitors as part of combination therapy (median follow-up, 182 days) and 87 (29%) of whom received dual nucleoside analog regimens (median follow-up, 167 days). Chronic hepatitis C and B virus infection was present in 154 (52%) and 8 (2.7%) patients, respectively.

Main Outcome Measure Severe hepatotoxicity, defined as a grade 3 or 4 change in levels of serum alanine aminotransferase and aspartate aminotransferase, evaluated before and during therapy.

Results Severe hepatotoxicity was observed in 31 (10.4%) of 298 patients (95% confidence interval [CI], 7.2%-14.4%). Ritonavir use was associated with a higher incidence of toxicity (30%; 95% CI, 17.9%-44.6%). However, no significant difference was detected in hepatotoxicity incidence in other treatment groups, ie, nucleoside analogs (5.7%; 95% CI, 1.2%-12.9%), nelfinavir (5.9%; 95% CI, 1.2%-16.2%), saquinavir (5.9%; 95% CI, 0.15%-28.7%), and indinavir (6.8%; 95% CI, 3.0%-13.1%). Although chronic viral hepatitis was associated with an increased risk of severe hepatotoxicity among patients prescribed nonritonavir regimens (relative risk, 3.7; 95% CI, 1.0-11.8), most patients with chronic hepatitis C or B virus infection (88%) did not experience significant toxic effects. Rate of severe toxicity with use of any protease inhibitor in patients with hepatitis C infection was 12.2% (13/107; 95% CI, 6.6%-19.9%). In multivariate logistic regression, only ritonavir (adjusted odds ratio [AOR], 8.6; 95% CI, 3.0-24.6) and a CD4 cell count increase of more than $0.05 \times 10^9/L$ (AOR, 3.6; 95% CI, 1.0-12.9) were associated with severe hepatotoxicity. No irreversible outcomes were seen in patients with severe hepatotoxicity.

Conclusions Our data indicate that use of ritonavir may increase risk of severe hepatotoxicity. Although hepatotoxicity may be more common in persons with chronic viral hepatitis, these data do not support withholding protease inhibitor therapy from persons coinfecting with hepatitis B or C virus.

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Given the increasing complexity of HIV treatment regimens and high prevalence of coinfection with hepatitis C and B infection, clinicians need accurate information regarding the risk

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of hepatotoxicity associated with antiretroviral drugs to guide appropriate use of these drugs. In the absence of such assessments, clinicians may be reluctant to prescribe some antiretroviral drug regimens to patients with chronic viral hepatitis. The objective of this study is to determine the incidence of severe hepatotoxicity following antiretroviral therapy initiation, and to define the role of chronic viral hepatitis in the development of antiretroviral-associated hepatotoxicity.

METHODS

Treatment outcomes were analyzed in a heterogeneous cohort of patients receiving medical care from January 1996 to January 1998 in the Johns Hopkins Hospital HIV Clinic. In this urban, university-based setting, all patients undergo a comprehensive evaluation as previously described.¹³ The HCV and HBV serologies are routinely performed by a licensed commercial lab. Patients with a reactive serum HCV antibody by immunoassay and those with a positive HBV surface antigen by immunoassay with neutralization (≥ 2 occasions with a minimum interval of 6 months) were considered to have chronic infection.

Clinicians and social workers used standardized instruments to record data about patient demographics, social practices, clinical variables, and laboratory test results. These data were abstracted from patient charts and the Johns Hopkins Hospital laboratory database at enrollment and every 6 months by trained staff using standard data collection forms. Data on clinical outcomes, such as new illnesses, hospitalization, and death, and records of prescribed medications were included. Medication prescriptions are recorded by name, dose, and number dispensed in the patient chart, which is updated including telephoned and mailed prescriptions at each clinical encounter. Validity checks of prescriptions and of medication-associated adverse events were done via chart review on a sample (10%) of the collected data and discrepancies found in less than 1% of abstractions. Approval for the study was obtained

from the institutional review board of Johns Hopkins Hospital.

Hepatotoxicity was examined for all patients receiving new antiretroviral regimens during the study period, for all of whom follow-up aminotransferase levels were available. Patients were classified based on antiretroviral regimen: patients taking PIs (as part of combination therapy) for the first time were the PI group whereas those prescribed dual nucleoside analog (NA) regimens were the NA group. No patients received the antiretroviral regimen for less than 45 days, and all had pretreatment liver enzyme levels measured within 6 months of new drug regimen initiation. According to written practice guidelines, all patients receiving new antiretroviral therapies had laboratory evaluations prior to therapy and at regular intervals during treatment. The standard clinic visit schedule for patients with new regimens was 4 weeks after therapy initiation and then every 12 weeks. At each visit, standard laboratory assessment was done by the Johns Hopkins Hospital Clinical Pathology Laboratory. Standard laboratory testing included complete blood cell count, serum chemistries, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBR), CD4 cell count, and plasma HIV RNA level (using reverse transcriptase-polymerase chain reaction).

The change in serum ALT, AST, and TBR from pretreatment levels to highest level during treatment was categorized via a standardized toxicity grade scale (modified from that used by the AIDS Clinical Trials Group¹⁴). Patients with pretreatment serum AST and ALT levels within normal range (AST < 35 U/L and ALT < 31 U/L) were classified based on changes relative to the upper limit of normal (ULN): grade 0 (< 1.25 ULN); grade 1 (1.25 - $2.5 \times$ ULN); grade 2 (2.6 - $5 \times$ ULN); grade 3 (5.1 - $10 \times$ ULN); and grade 4 ($> 10 \times$ ULN). To avoid selection bias favoring inclusion of persons with chronic viral hepatitis, patients with elevated pretreatment serum AST and ALT levels (higher than the ULN) were classified based on changes relative to base-

line value rather than ULN: grade 0 ($< 1.25 \times$ baseline); grade 1 (1.25 - $2.5 \times$ baseline); grade 2 (2.6 - $3.5 \times$ baseline); grade 3 (3.6 - $5 \times$ baseline); and grade 4 ($> 5 \times$ baseline). Changes in serum TBR were classified based on changes relative to ULN: grade 0 ($< 1.1 \times$ ULN); grade 1 (1.1 - $1.5 \times$ ULN); grade 2 (1.6 - $2.9 \times$ ULN); grade 3 (3 - $5 \times$ ULN); and grade 4 ($> 5 \times$ ULN).

Severe hepatotoxicity (the primary study outcome) was defined as grade 3 or 4 change in AST or ALT levels during antiretroviral treatment. If AST and ALT grades were discordant, the higher of the 2 was used for classification. Severe hyperbilirubinemia was defined as grade 3 or 4 change in serum TBR levels during treatment, and was analyzed independent of serum ALT and AST changes because of the association of indinavir use with elevated serum TBR. Incidence rate of severe toxicity was determined following initiation of PI-containing and NA regimens. Medical records were reviewed on all cases of severe hepatotoxicity to exclude other potential causes of hepatic disease such as acute viral hepatitis, acute cholecystitis, other infectious processes, acetaminophen and other nonantiretroviral drug toxicity, and alcoholic hepatitis. Toxicity was considered causally related to antiretroviral medications if there was no likely alternative explanation after chart and laboratory review and/or discontinuation of the medication was temporally associated with hepatic enzyme improvement. To exclude the possibility that drug therapy changes occurred at toxicity grades 1 or 2, medical records were reviewed for all patients with grade 2 hepatotoxicity and those with grade 1 hepatotoxicity with ALT or AST levels greater than 100 U/L and who continued therapy for less than 90 days.

Incidence rate was calculated both as number of episodes per persons exposed during the study period and as number of episodes of severe hepatotoxicity per 100 person-months of use for each regimen. Poisson regression was used to determine 95% confidence intervals (CIs). Intraindividual paired comparisons of liver function

tests and other laboratory markers were done with the nonparametric Wilcoxon signed rank test. The nonparametric Mann-Whitney test was used to compare these values between groups of subjects. Univariate logistic regres-

sion and stepwise multivariate logistic regression were performed to analyze risk factors associated with hepatotoxicity development. To evaluate the possibility of bias due to differences in follow-up time, a Cox proportional haz-

ards analysis was done. Data were analyzed with Stata software (Intercooled Stata 5.0, College Station, Tex).

RESULTS

Patients

From January 1996 to January 1998, 381 patients who were prescribed a new antiretroviral regimen met inclusion criteria. Patient follow-up was sufficient for the 298 subjects who comprised the study cohort. Patient pretreatment characteristics are shown in TABLE 1. Of these subjects, 87 received NA regimens and 211 patients received PI-containing regimens (ritonavir, 22 patients; ritonavir plus saquinavir [hard gelatin capsule formulation], 28; indinavir, 117; nelfinavir, 51; and saquinavir, 17). Patients receiving NA regimens were more likely to be black and use injection drugs, while those receiving PIs had lower CD4 cell counts and higher plasma HIV RNA levels. There were no significant differences between groups regarding age, sex, HBV surface antigen and HCV antibody status, and pretreatment serum AST, ALT, or TBR levels. Also, there was no significant difference in prescription of ritonavir, nelfinavir, and indinavir by HCV antibody status ($P = .07$, $P = .65$, $P = .12$, respectively). During the study period there were 25 deaths (14 in the PI group and 11 in the NA group, $P = .11$).

Median duration of follow-up was 182 (interquartile range, 122-297) days for PI users and 167 (interquartile range, 121-182) days for NA users. Median time from therapy initiation to first visit (100% of subjects available) was 43 (interquartile range, 27-77) days; first to second visit (75%), 40.5 (interquartile range, 13-64) days; second to third visit (52%), 35 (interquartile range, 8-77) days; and third to fourth visit (35%), 20 (interquartile range, 2-50) days.

Serum Hepatic Aminotransferase Levels Before and During Therapy

Median time from pretreatment serum AST and ALT to therapy initiation was 7 (interquartile range, 0-28) days for the NA group and 20 (interquartile range, 2-47) days for the PI group. Patients infected with HCV had

Table 1. Pretreatment Demographic and Clinical Characteristics*

	Protease Inhibitor Regimen (n = 211)	Dual Nucleoside Analog Regimen (n = 87)	P Value
Age, median (interquartile range), y	37 (31-42)	36 (32-40)	.54
Sex			
Male	163 (77)	60 (69)	.28
Female	48 (23)	27 (31)	
Race			
Black	151 (72)	71 (82)	.02
White	57 (27)	13 (15)	
Other	3 (1)	3 (3)	
Injection drug use	104 (49)	56 (60)	.02
Hepatitis C virus antibody positive	102 (48)	52 (60)	.07
Hepatitis B surface antigen positive	7 (3.3)	1 (1.1)	.29
Alanine aminotransferase, median (interquartile range), U/L	32.5 (19-49.5)	32 (20-47)	.52
Aspartate aminotransferase, median (interquartile range), U/L	38 (26-57)	41 (28-59)	.23
Total bilirubin, median (interquartile range), $\mu\text{mol/L}$	10.3 (6.8-13.7)	10.3 (8.6-11.9)	.25
CD4 cell count, median (interquartile range), $\times 10^3/\text{L}$	1.09 (0.33-2.94)	2.15 (0.41-3.83)	.01
≤ 100	101 (48)	28 (32)	.01
101-200	43 (20)	14 (16)	.40
≥ 201	67 (32)	45 (52)	.001
Human immunodeficiency virus RNA, median (interquartile range), copies/mL	55 000 (16 000-156 531)	23 000 (5108-68 000)	.004
$< 40 000$	20 (22)	35 (64)	.005
$\geq 40 000$	107	20	

*Values are expressed as number (percentage) unless otherwise indicated.

Table 2. Changes in Serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels During Antiretroviral Therapy by Hepatitis C Virus (HCV) Antibody Status*

	No. of Subjects	Negative Test Result for HCV	No. of Subjects	Positive Test Result for HCV	P Value
Nucleoside Analog Regimen					
Change in ALT	34	1 (-3 to 11)†	52	10.5 (-2 to 44)	.07
Change in AST	35	0 (-8 to 14)†	52	15 (-5 to 48)	.01
Nonritonavir Protease Inhibitor Regimen ‡					
Change in ALT	76	2.5 (-5 to 23)	81	14 (-2 to 40)	.09
Change in AST	78	3.5 (-5 to 26)	82	12 (-3 to 46)	.27
Ritonavir Regimen					
Change in ALT	29	42 (2 to 79)	20	20.5 (4 to 67)	.78
Change in AST	30	15.5 (-1 to 78)	20	19 (5 to 140)	.39

*Data shown are expressed as median values (interquartile range). $P < .01$ for comparisons for change in ALT and AST during therapy (except as noted below) using the Wilcoxon signed rank test.

† $P = .14$ for change in ALT and $P = .68$ for change in AST during therapy using the Wilcoxon signed rank test.

‡Includes indinavir, nelfinavir, and saquinavir.

higher pretreatment AST and ALT levels than HCV-uninfected subjects ($P < .001$ for both). Median time to highest AST or ALT level was 71 (interquartile range, 42-123) days in the PI group and 89 (interquartile range, 47-147) days in the NA group. During therapy, serum AST and ALT levels increased significantly in all treatment groups except in patients not infected with HCV taking NAs (TABLE 2). The magnitude of increase in aminotransferase levels was similar for patients infected and uninfected with HCV, except in those prescribed NAs, for whom AST increases were greater in persons infected with HCV.

Development of Severe Hepatotoxicity

Severe (grade 3 or 4) hepatotoxicity was seen in 31 (10.4%) of 298 patients (95% CI, 7.2%-14.4%) (FIGURE 1; TABLE 3). Median therapy duration before detection of severe hepatotoxicity was 118 (interquartile range, 63-156) days. Incidence of severe toxicity in ritonavir users was greater than that in patients prescribed NA regimens, indinavir, nelfinavir, and saquinavir (without concurrent ritonavir use), and ritonavir use was associated with 48% of all cases of severe hepatotoxicity. Use of ritonavir was associated with a higher incidence of toxicity (30%, 95% CI, 17.9%-44.6%). Incidence of toxicity associated with ritonavir plus saquinavir was similar to that with ritonavir alone. Likewise, risk of se-

vere toxicity with use of NA regimens was similar to that with regimens containing indinavir, nelfinavir, or saquinavir (without concurrent ritonavir use). One patient taking indinavir discontinued antiretrovirals due to grade 1 hepatotoxicity.

Hepatotoxicity and Chronic Viral Hepatitis

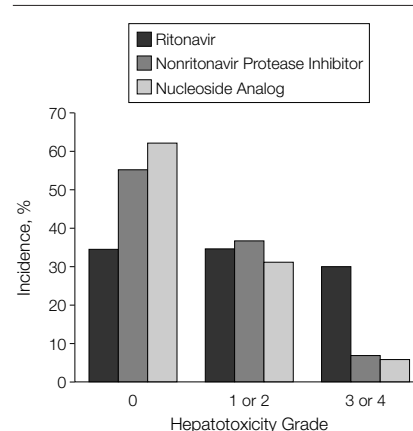
Hepatotoxicity (any grade) was seen in 83 (54%) of 154 persons infected with HCV vs 56 (39%) of 144 uninfected persons ($P = .009$). Rate of severe toxicity with any PI in coinfecting patients was 12.2% (13/107; 95% CI, 6.6%-19.9%). Of ritonavir users, severe hepatotoxicity was seen in 6 (30%) of 20 patients infected with HCV and 9 (30%) of 30 uninfected patients (relative risk [RR], 1.0; 95% CI, 0.4-2.4). In nonritonavir PI users, severe hepatotoxicity was seen in 7 (8.1%) of 87 persons infected with HCV and 4 (5.1%) of 79 uninfected persons (RR, 1.6; 95% CI, 0.5-5.2). In NA users, all 5 cases of severe hepatotoxicity occurred in persons infected with HCV ($P = .06$). Two of 8 persons with chronic HBV infection had severe hepatotoxicity; both received indinavir and 1 was infected with HCV. Three additional patients (of a total of 4) with both chronic hepatitis C and B virus infection did not develop severe hepatotoxicity. Overall, in nonritonavir PI and NA users, 13 (9.4%) of 138 patients with chronic HCV or HBV infection developed severe hepatotoxicity vs 3 (2.7%)

of 110 uninfected patients (RR, 3.7; 95% CI, 1.0-11.8). However, 139 (88%) of 158 patients with evidence of chronic hepatitis C or B virus infection did not have severe hepatotoxicity during antiretroviral therapy (FIGURE 2).

Risk Factors for Development of Severe Hepatotoxicity

Univariate logistic regression analysis showed that ritonavir use was associated with severe hepatotoxicity (OR, 6.2; 95% CI, 2.8-13.7). Patients experiencing a CD4 cell increase of greater

Figure 1. Incidence Rate (Cases per Persons Exposed) of Hepatotoxicity During Antiretroviral Therapy, by Drug Regimen



Antiretroviral treatment categories are ritonavir-containing regimens, including ritonavir and ritonavir plus saquinavir; nonritonavir protease inhibitor regimens, including indinavir, nelfinavir, and saquinavir; and dual nucleoside analog (nonprotease inhibitor) regimens. Hepatotoxicity is categorized using a standardized toxicity grade scale.¹⁴

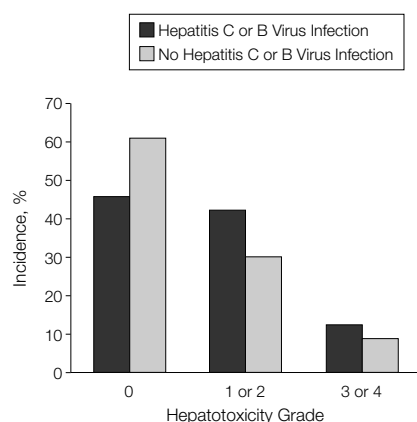
Table 3. Incidence and Relative Risk of Severe Hepatotoxicity Associated With Antiretroviral Regimens*

Antiretroviral Drug Regimen	No. of Subjects	Cases	Person-Time (100 Person-Months)	Incidence (Cases/Persons Exposed) (95% CI)	Incidence (Cases/100 Person-Months) (95% CI)	Relative Risk (95% CI)
Dual nucleoside analog	87	5	246	5.7 (1.2-12.9)	2.0 (0.7-4.7)	1.0
Protease inhibitor (all)	211	26	795	12.3 (8.2-17.5)	3.3 (2.1-4.8)	2.2 (0.9-5.4)
Ritonavir (single protease inhibitor)	22	6	96	27.3 (10.7-50.2)	6.3 (2.3-21.6)	4.8 (1.6-14.1)
Ritonavir plus saquinavir	28	9	79	32.1 (15.9-52.4)	11.4 (5.2-21.6)	5.6 (2.1-15.3)
Saquinavir†	17	1	98	5.9 (0.15-28.7)	1.0 (0.7-4.8)	1.0 (0.1-8.2)
Indinavir	117	8	520	6.8 (3.0-13.1)	1.5 (0.7-3.0)	1.2 (0.4-3.5)
Nelfinavir	51	3	153	5.9 (1.2-16.2)	2.0 (0.4-5.7)	1.0 (0.3-4.1)
Total	298	31	1041	10.4 (7.2-14.4)	3.1 (2.1-4.3)	NA

*CI indicates confidence interval; NA, not applicable. Because use of individual drugs was studied, some overlap during the study period occurred; thus, the individual numbers of subjects and cases and the person-time for specific protease inhibitor categories do not equal the "Total."

†Saquinavir hard gelatin capsule formulation without concurrent ritonavir prescription. The case occurring in a subject receiving saquinavir alone (ie, not in combination with ritonavir) is also counted in the indinavir category because the subject was taking both drugs at the time of toxicity.

Figure 2. Incidence Rate (Cases per Persons Exposed) of Hepatotoxicity During Antiretroviral Therapy, by Hepatitis C or B Virus Infection Status



Categories of infection are chronic hepatitis C or B virus infection and no evidence of chronic viral hepatitis (data for all antiretroviral drug regimens included). Hepatotoxicity is categorized using a standardized toxicity grade scale.¹⁴

than $0.05 \times 10^9/L$ had a higher event rate than those with smaller increases or decreasing CD4 cell counts (OR, 3.0; 95% CI, 0.9-10.3). Patients with CD4 cell counts less than $0.20 \times 10^9/L$ had a higher incidence of severe toxicity (OR, 2.2; 95% CI, 0.9-5.3). Event rate was also higher in patients with elevated pretreatment ALT and/or AST levels (OR 2.5; 95% CI, 1.0-5.7). There were no statistically significant differences by sex, age, race/ethnicity, injection drug use, HCV antibody and HBV surface antigen status, pretreatment HIV RNA level, and change in HIV RNA level during treatment.

Multivariate logistic regression analysis was done to assess the adjusted association between antiretroviral drug use, demographic characteristics, and laboratory parameters. This model included variables with a significance level of $P < .10$ on univariate analysis. After multivariate adjustment, only ritonavir use (adjusted OR, 8.6; 95% CI, 3.0-24.6), and increase in CD4 cell count greater than $0.05 \times 10^9/L$ during treatment (adjusted OR, 3.6; 95% CI, 1.0-12.9) remained associated with severe hepatotoxicity. Results of the Cox proportional hazards model were similar.

Development of Severe Hyperbilirubinemia

Severe hyperbilirubinemia was seen in 10 (3.4%) of 298 patients who took antiretrovirals (95% CI, 1.7%-6.3%) for a total of 1041 person-months for an incidence rate of severe hyperbilirubinemia of 1.0 case per 100 person-months (95% CI, 0.5-1.8). Median therapy duration before hyperbilirubinemia detection was 72 (interquartile range, 30-132) days. Indinavir use was associated with 60% of cases, and severe hyperbilirubinemia occurred in 6 (5.2%) of 116 indinavir users vs 4 (2.2%) of 179 persons taking other antiretroviral drugs (RR, 2.3; 95% CI, 0.7%-8.0%). Severe hyperbilirubinemia occurred in 3 patients with severe hepatotoxicity, of whom 2 received indinavir.

Most (4/6) indinavir-associated and all nonindinavir-associated episodes occurred in persons infected with HCV or HBV. Overall, 8 (5.1%) of 158 persons with chronic viral hepatitis had severe hyperbilirubinemia vs 3 (1.4%) of 140 uninfected persons (RR, 3.5; 95% CI, 0.8-16.4). However, 54 (93%) of 58 indinavir recipients with chronic viral hepatitis did not develop severe hyperbilirubinemia.

Clinical Outcomes

After development of severe hepatotoxicity, antiretroviral therapy was stopped in 25 of 31 patients. It was continued in 6 individuals, including 3 taking ritonavir plus saquinavir, without clinically significant consequences during the study period. Four individuals died within 90 days of having severe hepatotoxicity; none of the deaths were due to liver-related events.

COMMENT

The PIs are frequently used in combination with other antiretroviral drugs for HIV infection treatment.¹⁵ Our data indicate that hepatotoxicity does occur in association with antiretroviral therapy, but that the risk varies substantially by medication. Risk of severe hepatotoxicity was 5-fold higher for

patients taking ritonavir, which accounted for half of all cases. No difference was detected in risk of severe hepatotoxicity in persons receiving other PIs vs NAs alone. Likewise, more than half of cases of severe hyperbilirubinemia were associated with indinavir use. The data suggest that antiretroviral-associated hepatotoxicity must be considered according to specific medication rather than drug classification or mechanism of action.

Incidence of severe hepatotoxicity associated with NA use was similar in our cohort to that reported in 3 clinical trials,¹⁶⁻¹⁸ and incidence of severe hepatotoxicity associated with use of the nonritonavir PIs indinavir, nelfinavir, and saquinavir was comparable with that seen in clinical trials.¹⁹⁻²⁷ These findings are somewhat unexpected because clinical trials may have excluded patients with chronic viral hepatitis, which was associated with the development of severe hepatotoxicity among patients taking nonritonavir-containing regimens in our cohort.

Conversely, incidence of severe hepatotoxicity associated with ritonavir use in our cohort was greater than that previously reported.²⁸⁻³² In ritonavir studies, observed hepatotoxicity incidence ranged from 2.9% to 9.1%, while Cameron et al³² reported that 6.8% of patients taking ritonavir plus saquinavir had hepatotoxicity. Similarly, Arribas et al⁷ found that 7% of patients taking ritonavir had hepatotoxicity. One explanation for this difference would be the greater occurrence in our cohort of factors potentiating ritonavir-associated hepatotoxicity. In the studies by Cameron and Arribas and their colleagues, most ritonavir-associated hepatotoxicity cases occurred in patients with HCV infection. However, in our cohort, incidence of severe hepatotoxicity in persons taking ritonavir was not increased if they had chronic HCV infection, suggesting that the effect is largely due to the medication.

Ritonavir is a potent inhibitor of the cytochrome P450 system, which may have pharmacokinetic and metabolic effects possibly contributing to hepatotox-

icity by increasing drug concentrations or interfering with liver function.^{33,34} However, these hypotheses could not be further investigated in this study.

In our cohort, in patients not taking ritonavir, there was a trend toward increased risk of hepatotoxicity in patients with chronic hepatitis B or C virus infection. Similarly, Rodriguez-Rosado et al⁸ found that chronic HCV infection was associated with 2.8-fold greater risk of hepatotoxicity with use of highly active antiretroviral therapy. Our data also agree with the report of increased drug-induced hepatotoxicity risk in HCV-infected persons receiving tuberculosis treatment.³⁵ While the mechanism of drug-related toxicity in patients with chronic viral hepatitis is not known, some studies have suggested that hepatic injury may be due to enhanced HCV replication and CD8 cell activity during highly active antiretroviral therapy-associated immune reconstitution, although other studies have failed to confirm this.³⁶⁻⁴⁰ In our cohort, CD4 cell recovery was associated with severe hepatotoxicity; however, this finding may reflect medication adherence rather than immune-mediated liver injury. Because our study did not examine hepatitis C RNA or CD8 cell levels, the association of immune reconstitution and hepatotoxicity could not be further examined.

The study has several potential limitations. First, because patients were not randomly assigned to drug therapies, selection bias could have occurred if clinicians were less likely to prescribe PIs to patients with viral hepatitis, leading to underestimation of risk for such patients. However, patients infected with HCV, who were receiving PIs, had higher HIV RNA and lower CD4 cell levels than those receiving NA regimens, and there were no differences in the pretreatment AST and ALT levels, suggesting antiretroviral drug selection was based on HIV disease parameters. Second, because follow-up assessments were not standardized, ascertainment bias could have occurred if 1 group of patients was monitored more closely, leading to in-

creased detection of toxicity in that group. Third, if antiretroviral adherence was lower with specific medications or patient groups, such as injection drug users, then our risk estimates could be higher for those with better adherence. However, previous studies from this and other cohorts suggest that historical injection drug use is not associated with antiretroviral nonadherence, and that injection drug users and persons not using injection drugs, who are infected with HIV have similar clinical outcomes.^{41,42}

Fourth, if antiretroviral drugs were stopped at differential rates due to disparate rates of events such as grade 1 or 2 hepatotoxicity, other drug-related adverse events, or virologic failure, then our incidence estimates may be biased. However, we found little evidence that clinicians stopped prescribing antiretroviral drugs due to grade 1 and 2 toxicity. Furthermore, studying the same cohort population, Lucas et al⁴³ reported that incidence of adverse events was similar with indinavir use (20.6%) and nelfinavir use (21.8%) but statistically significantly higher with ritonavir use (48.7%). Thus, if bias occurred as a result of differential adverse event rates, it would lead to an underestimate of RR of hepatotoxicity associated with ritonavir use vs other PIs, resulting in a conservative risk estimate. Lucas et al⁴³ also found that virologic failure rates were similar for all PI regimens.

Fifth, we assumed all persons with detectable HCV antibody had chronic viral hepatitis, which may influence our estimate of association with hepatotoxicity. If not all patients with reactive HCV antibody were viremic or had HCV-related hepatitis, then the effect of HCV infection could be underestimated. However, we have found that more than 90% of persons infected with HIV with reactive HCV antibody have detectable plasma HCV RNA, suggesting our case definition is acceptable.⁴⁴ Finally, our ability to detect differences in the risk of hepatotoxicity associated with specific drugs may be limited by the relatively small number of episodes observed during therapy with each medication.

In conclusion, ritonavir was associated with the greatest hepatotoxicity risk, while risk was similar with nelfinavir, indinavir, and NA regimens. Despite the frequency of hepatotoxicity in this cohort, no deaths were associated with toxicity and most patients infected with HCV tolerated antiretroviral therapies. However, controlled studies are needed to confirm these results and to further define the mechanism of interaction between drug-induced hepatotoxicity and chronic viral hepatitis. These data suggest that antiretroviral therapies should not be withheld from persons infected with HIV with chronic viral hepatitis, and may also support the practice of continuing antiretroviral therapy in the presence of mild-to-moderate hepatic aminotransferase elevations with careful clinical monitoring.

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