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 OFTEN 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 COINFECTED 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 INCLUSION 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 SERIOUS 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 × 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 COINFECTED 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
HEPATOTOXICITY AND ANTIRETROVIRAL THERAPY

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

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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 regression 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 hazards 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, and 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, 122-182) days; second to third visit (52%), 35 (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

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**Table 1. Pretreatment Demographic and Clinical Characteristics**

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Positive Test Result for HCV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside Analog Regimen</td>
<td>Negative Test Result for HCV</td>
<td>No. of Subjects</td>
</tr>
<tr>
<td>Change in ALT</td>
<td>34</td>
<td>1 (3-31)</td>
</tr>
<tr>
<td>Change in AST</td>
<td>35</td>
<td>0 (8-5)</td>
</tr>
<tr>
<td>Nonnucleoside Protease Inhibitor Regimen</td>
<td>Nucleoside Analog Regimen</td>
<td></td>
</tr>
<tr>
<td>Change in ALT</td>
<td>76</td>
<td>2.5 (5-31)</td>
</tr>
<tr>
<td>Change in AST</td>
<td>78</td>
<td>3.5 (5-26)</td>
</tr>
<tr>
<td>Ritonavir Regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in ALT</td>
<td>29</td>
<td>42 (2-79)</td>
</tr>
<tr>
<td>Change in AST</td>
<td>30</td>
<td>15.5 (1-78)</td>
</tr>
</tbody>
</table>

*Data shown 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**

<table>
<thead>
<tr>
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<td></td>
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<td>Ritonavir Regimen</td>
<td></td>
<td></td>
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<tr>
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<td>42 (2-79)</td>
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</tr>
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<td>Change in ALT</td>
<td>34</td>
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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 toxicity. 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 severe 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 coinfected 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

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

<table>
<thead>
<tr>
<th>Antiretroviral Drug Regimen</th>
<th>No. of Subjects</th>
<th>Cases (100 Person-Time Person-Months)</th>
<th>Incidence (Cases/Persons Exposed)</th>
<th>Incidence (Cases/100 Person-Months)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual nucleoside analog</td>
<td>87</td>
<td>5</td>
<td>246</td>
<td>5.7 (1.2-12.9)</td>
<td>2.0 (0.7-4.7)</td>
</tr>
<tr>
<td>Protease inhibitor (all)</td>
<td>211</td>
<td>26</td>
<td>795</td>
<td>12.3 (8.2-17.8)</td>
<td>3.3 (2.1-4.8)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>22</td>
<td>6</td>
<td>96</td>
<td>27.3 (10.7-50.2)</td>
<td>6.3 (2.3-21.6)</td>
</tr>
<tr>
<td>Ritonavir plus saquinavir</td>
<td>28</td>
<td>9</td>
<td>79</td>
<td>32.1 (15.9-52.4)</td>
<td>11.4 (5.2-21.6)</td>
</tr>
<tr>
<td>Saquinavir†</td>
<td>17</td>
<td>1</td>
<td>98</td>
<td>5.9 (0.15-28.7)</td>
<td>1.0 (0.7-4.8)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>117</td>
<td>8</td>
<td>520</td>
<td>6.8 (3.0-13.1)</td>
<td>1.5 (0.7-3.0)</td>
</tr>
<tr>
<td>Nelfinav</td>
<td>51</td>
<td>3</td>
<td>153</td>
<td>5.9 (1.2-16.2)</td>
<td>2.0 (0.4-5.7)</td>
</tr>
<tr>
<td>Total</td>
<td>298</td>
<td>31</td>
<td>1041</td>
<td>10.4 (7.2-14.4)</td>
<td>3.1 (2.1-4.3)</td>
</tr>
</tbody>
</table>

*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.

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hepatotoxicity. Results of the Cox pro-
ment (adjusted OR, 3.6; 95% CI, 1.0-
95% CI, 0.9-10.3). Patients with CD4
cell counts less than 0.20
or decreasing CD4 cell counts (OR, 3.0;
rate than those with smaller increases
in CD4 cell count. Event rate was 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 differ-
ences 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 analy-
sis was done to test the adjusted as-
sociation 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 ritona-
vir use (adjusted OR, 8.6; 95% CI, 3.0-
24.6), and increase in CD4 cell count
greater than 0.05 × 10^9/L during treat-
ment (adjusted OR, 3.6; 95% CI, 1.0-
12.9) remained associated with severe
hepatotoxicity. Results of the Cox propor-
tional hazards model were similar.

**Development of Severe Hyperbilirubinemia**

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

Most (4/6) indinavir-associated and
all nonindinavir-associated episodes oc-
curred in persons infected with HCV
or HBV. Overall, 8 (5.1%) of 158 per-
sions with chronic viral hepatitis had se-
vere hyperbilirubinemia vs 3 (1.4%) of
140 uninfected persons (RR, 3.5; 95%
CI, 0.8-16.4). However, 54 (93%) of 58
nonindinavir-associated episodes oc-
curred in persons infected with HCV
and 51 (89%) of 57 nonindinavir-
a ssociated episodes occurred in patients
with severe hepatitis, which was asso-
ciated with the development of severe hepato-
toxicity among patients taking nonindinavir-
containing regimens in our cohort.

Conversely, incidence of severe hepato-
toxicity associated with ritonavir use in
our cohort was greater than that pre-
viously reported.28-32 In ritonavir stud-
ies, observed hepatotoxicity incidence
ranged from 2.9% to 9.1%, while Cam-
eron et al32 reported that 6.8% of pa-
tients taking ritonavir plus saquinavir
had hepatotoxicity. Similarly, Arribas et
al7 found that 7% of patients taking rito-
navir had hepatotoxicity. One explana-
tion for this difference would be the
greater occurrence in our cohort of fac-
tors potentiating ritonavir-associated
hepatotoxicity. In the studies by Cam-
eron and Arribas and their colleagues,
most ritonavir-associated hepatotoxic-
ity cases occurred in patients with HCV
infection. However, in our cohort,
in cidence of severe hepatotoxicity in per-
tients taking ritonavir was not increased
if they had chronic HCV infection, sug-
  gesting 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 ef-
fects possibly contributing to hepatotox-
icism grade scale.14

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

Within each infection category, incidence rate (Cases per Persons Exposed) was higher when ritonavir was included in antiretroviral therapy. Incidence rate of severe hepatotoxicity (Cox models) was higher in 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 con-
sidered according to specific medication
rather than drug classification or mechanism of action.

Incidence of severe hepatotoxicity asso-
ciated with NA use was similar in our
cohort to that reported in 3 clinical tri-
als,16-18 and incidence of severe hepa-
toxicity associated with use of the
nonritonavir PIs indinavir, nelfinavir,
and saquinavir was comparable with
that seen in clinical trials.10-27 These
findings are somewhat unexpected be-
cause clinical trials may have ex-
cluded patients with chronic viral hepa-
titis, which was associated with the
development of severe hepatotoxicity
among patients taking nonritonavir-
containing regimens in our cohort.

COMMENT

The PIs are frequently used in combi-
nation with other antiretroviral drugs
for HIV infection treatment.17 Our data
indicate that hepatotoxicity does oc-
cur in association with antiretroviral
therapy, but that the risk varies sub-
stantially by medication. Risk of se-
vere hepatotoxicity was 5-fold higher for
patients taking ritonavir, which ac-
counted for half of all cases. No differ-
ence was detected in risk of severe hepa-
toxicity 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-
asociated hepatotoxicity must be con-
sidered according to specific medication
rather than drug classification or mechanism of action.

Incidence of severe hepatotoxicity asso-
ciated with NA use was similar in our
cohort to that reported in 3 clinical tri-
als,16-18 and incidence of severe hepa-
toxicity associated with use of the
nonritonavir PIs indinavir, nelfinavir,
and saquinavir was comparable with
that seen in clinical trials.10-27 These
findings are somewhat unexpected be-
cause clinical trials may have ex-
cluded patients with chronic viral hepa-
titis, which was associated with the
development of severe hepatotoxicity
among patients taking nonritonavir-
containing regimens in our cohort.

Conversely, incidence of severe hepato-
toxicity associated with ritonavir use in
our cohort was greater than that pre-
viously reported.28-32 In ritonavir stud-
ies, observed hepatotoxicity incidence
ranged from 2.9% to 9.1%, while Cam-
eron et al32 reported that 6.8% of pa-
tients taking ritonavir plus saquinavir
had hepatotoxicity. Similarly, Arribas et
al7 found that 7% of patients taking rito-
navir had hepatotoxicity. One explana-
tion for this difference would be the
greater occurrence in our cohort of fac-
tors potentiating ritonavir-associated
hepatotoxicity. In the studies by Cam-
eron and Arribas and their colleagues,
most ritonavir-associated hepatotoxic-
ity cases occurred in patients with HCV
infection. However, in our cohort,
in cidence of severe hepatotoxicity in per-
tients taking ritonavir was not increased
if they had chronic HCV infection, sug-
  gesting 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 ef-
fects possibly contributing to hepatotox-
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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 HIV 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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