Antiretroviral Drug Pharmacokinetics in Hepatitis with Hepatic Dysfunction

David L. Wyles and John G. Gerber
Department of Medicine, Divisions of Infectious Diseases and Clinical Pharmacology, University of Colorado Health Sciences Center, Denver

Chronic viral hepatitis is common among persons with HIV-1 infection, because of shared modes of transmission, and coinfection results in accelerated liver damage, compared with persons with chronic viral hepatitis alone. The use of highly active antiretroviral therapy (HAART) has led to a significant decrease in the morbidity and mortality associated with HIV-1 infection. A number of the medications that are commonly used in HAART regimens are metabolized by the hepatic CYP enzymes, which raises the possibility of significant interactions between antiretroviral medications and hepatic impairment induced by chronic viral hepatitis. Although the data are still very scant, the pharmacokinetics of several antiretroviral medications have been shown to be significantly altered in the presence of liver disease. In the present report, we review the available data and consider potential options, such as dose adjustment and therapeutic drug monitoring, for the administration of antiretroviral therapy to patients with significant hepatic impairment.

Therapy for HIV-1 infection has resulted in substantial decreases in morbidity and mortality due to AIDS-related complications [1]. With this decrease in AIDS-related mortality, there has been an increase in morbidity and mortality associated with chronic liver disease [2, 3]. Estimates of the rate of hepatitis C virus (HCV) coinfection among HIV-1–positive patients ranges from 15% to 30%, with rates of >90% seen in certain high-risk populations [4–7]. End-stage liver disease, which is largely the result of HCV infection, now accounts for up to 50% of deaths among persons with HIV-1 infection [3]. Because hepatic disease can affect the pharmacokinetics of drugs that are metabolized by the liver [8, 9], it is important to understand whether HCV coinfection affects the pharmacokinetics of antiretroviral drugs.

There are few studies that have examined the effect of chronic liver disease or HCV infection on antiretroviral drug metabolism or the extent of that effect. Also, when evaluating the effect of liver disease on drug pharmacokinetics, it is important to understand that an effect on pharmacokinetics can occur because of alterations in cytochrome P450 (CYP) enzyme levels and activity, alteration in liver blood flow in the liver, alterations in hepatic architecture with potential shunting, and alterations in protein binding. The cytochrome P450 family of enzymes is responsible for the metabolism of the majority of antiretroviral drugs, but, for some of the nucleoside reverse-transcriptase inhibitors (NRTIs), hepatic conjugation via UDP-glucuronosyltransferases as well as via alcohol dehydrogenase is important.

Finally, clinicians must be aware of the changes in protein binding that may occur in association with advanced liver disease, and they must be aware of how these changes can affect the interpretation of the total drug concentrations used in therapeutic drug monitoring. Unbound drug is responsible for antiviral activity and, possibly, for some of the toxicities associated with the drug; thus, a decrease in protein binding can decrease total drug concentrations without affecting unbound drug concentrations [10].
EFFECTS OF CHRONIC HEPATITIS ON THE DRUG METABOLIZING FUNCTION OF THE LIVER

Few studies have addressed liver disease due to HCV and its effect on hepatic microsomal enzyme activity. Using antipyrine clearance as a nonspecific measure of hepatic oxidative capacity, Ali et al. [11] found a decrease in antipyrine clearance of 45% (P < .01) among HCV-infected patients (n = 12), compared with control subjects (n = 18). In addition, a significant negative correlation between Child-Pugh scores and antipyrine clearance was observed (r = −0.73; P = .007).

Chronic liver disease may affect the various CYP isoforms differentially, and, thus, an understanding of the enzymes that are involved in drug metabolism will be helpful in predicting the pharmacokinetic effects of HCV infection on specific drugs. George et al. [12], using in vitro liver microsomal preparations, found a 2-fold decrease (P < .001) in the total CYP enzyme content of the livers of 50 patients with cirrhosis, compared with the livers of 21 control subjects. The activity of CYP enzymes in the livers of patients with cirrhosis was also significantly decreased, compared with the activity of CYP enzymes in the livers of control subjects; the greatest effect was on the activity of the CYP 1A2 enzyme (10-fold decrease; P < .01), followed by the activity of the CYP 3A enzyme (2-fold decrease; P < .005), with little change in the activity of the CYP 2E1 and 2C enzymes.

Becquemont and colleagues [13] showed that HCV infection (n = 14) affects the activity of the CYP enzymes. Through the use of prototypical drugs in vivo, they were able to show significant decreases in the activity of the CYP 3A4 and 2D6 enzymes (65% and 81%, respectively; P < .001 for both) in HCV-positive patients, compared with control subjects (n = 35). Conversely, there was no difference in the activity of the CYP 1A2 enzymes between HCV-positive patients and control subjects.

Adedoyin et al. [14] also demonstrated a significant decrease (80%; P < .005) in CYP 2C19 enzyme activity in vivo, but they found no decrease in CYP 2D6 enzyme activity when comparing 10 healthy control subjects and 18 patients with mild-to-moderate liver disease. Other authors have shown a similar effect of chronic liver disease on the CYP 2C19 isoform [15].

In general, the glucuronidation of drugs is not affected by liver disease, including cirrhosis [16]. Fulminant hepatic failure and glucuronidation of zidovudine are exceptions. The data on alcohol dehydrogenase activity in the presence of liver disease are contradictory. Vidal et al. [17] found a significant decrease in alcohol dehydrogenase activity when they used an in vitro liver homogenate assay to evaluate and compare the biopsy specimens of patients with liver disease who either were alcohol abusers (n = 46) or were not alcohol abusers (n = 42) with the biopsy specimens of control subjects who either were alcohol abusers (n = 18) or were not alcohol abusers (n = 17). In a methodologically similar study, Panés et al. [18] found no difference between the activity of alcohol dehydrogenase in patients with liver disease, including cirrhosis, who were not alcohol abusers (n = 24) and that in alcohol abusers with normal liver histologic findings (n = 5).

In aggregate, the available data indicate that chronic liver disease, including liver disease due to HCV, significantly decreases the amount and function of CYP enzymes in the liver. The magnitude of this effect varies on the basis of both the stage of liver disease and the CYP enzyme of interest, because not all CYP enzymes are equally affected. Interpretation of the data for individual CYP isoforms must be undertaken with caution because of the different methodologies and patient populations studied in the individual trials.

THE EFFECT OF LIVER DISEASE ON THE METABOLISM OF ANTIRETROVIRAL DRUGS

NRTIs

The NRTIs (including tenofovir) possess characteristics that make them less susceptible to changes in pharmacokinetics due to hepatic dysfunction. These class characteristics include low protein binding, limited first-pass metabolism, and largely renal elimination [19–26]. Also, when evaluating the effect of liver disease on the pharmacokinetics of NRTIs, it is critical to understand that the unchanged drug is not responsible for efficacy or toxicity [27]. NRTIs are phosphorylated inside cells to the active triphosphate metabolites; the effect of HCV coinfection on the phosphorylation of these drugs has not been well studied, although there is some evidence that nucleoside administration results in more toxicity in HCV-coinfected subjects than in non–HCV-infected subjects [28, 29]. A few small studies of members of this class of drugs (e.g., lamivudine, stavudine, and tenofovir) have been performed, and the results have demonstrated no effect of hepatic dysfunction on the pharmacokinetics of these drugs [30–32].

Zidovudine.

Zidovudine, a thymidine analogue with low protein binding, is rapidly absorbed after oral administration and undergoes first-pass metabolism by hepatic 5′-glucuronidation to yield a bioavailability of 63% [33, 34]. Although the activity of hepatic glucuronyltransferases is generally not altered in the presence of liver disease, the glucuronidation of zidovudine appears to be an exception [16]. In an in vitro liver microsome assay, the glucuronidation of oxazepam, lamotrigine, umbiliferone, and zidovudine—4 drugs that are metabolized solely through glucuronidation—was assessed. There was no change in the glucuronidation of oxazepam, lamotrigine, or umbiliferone in samples from cirrhotic livers (n = 11), compared with control samples (n = 19). Glucuronidation of zidovudine was significantly decreased in samples from cirrhotic livers (P < .001), and the magnitude of the decrease was similar.
to that of the decrease in CYP 3A4 enzyme activity that has been seen in cirrhotic livers.

Taburet et al. [35] evaluated the effect of liver disease on the pharmacokinetics of zidovudine in 14 HIV-negative subjects with biopsy-proven cirrhosis. Compared with control subjects (n = 6), the subjects with cirrhosis had a 70% decrease in the oral clearance of zidovudine (P < .0001) and a 2-fold increase in the maximum plasma concentration (C max) (P < .01) and the half-life (P < .05) of zidovudine. A subsequent study by Fletcher et al. [36], which involved 3 HIV-infected subjects with moderate-to-severe hepatic disease, demonstrated a 63% decrease in the oral clearance of zidovudine after oral administration of a single 200-mg dose, compared with the decrease in oral clearance that was noted among 6 HIV-positive and 6 HIV-negative control subjects.

In the AIDS Clinical Trials Group (ACTG) 062 study, in which the subjects (n = 8) had mild liver disease, the authors reported a 32% decrease in the oral clearance of zidovudine among study subjects, compared with that among healthy volunteers (n = 6) [37]. These data suggest a significant effect of liver disease on the pharmacokinetics of zidovudine. However, the magnitude of this effect has been somewhat variable, which likely reflects the different degrees of hepatic dysfunction in the populations studied.

**Abacavir.** Abacavir has a high oral bioavailability (>80%), with 50% plasma protein binding [38, 39]. Metabolism of abacavir occurs through cytosolic alcohol dehydrogenase and UDP-glucuronosyltransferases [39]. As stated above, the glucuronidation of most drugs is preserved in advanced liver disease. The activity of alcohol dehydrogenase may be affected by liver disease; however, in the presence of liver disease that is not caused by alcohol abuse, this association is less clear [17, 18]. Given the unique metabolism and modest protein binding of abacavir, it is difficult to predict the effect of liver disease on the pharmacokinetics of the drug. In the absence of pharmacokinetic data with regard to liver disease, changes in the pharmacokinetics of abacavir cannot be ruled out.

**Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs)**

Limited data exist on the effect of liver disease on the pharmacokinetics of NNRTIs. NNRTIs are lipophilic drugs that are metabolized by CYP isoforms; thus, hepatic dysfunction could affect the pharmacokinetics of these drugs. Plasma concentrations of NNRTIs do correlate with antiviral efficacy as well as with side effects [40].

**Nevirapine.** Nevirapine has high oral bioavailability and a long half-life of 25–30 h [41]. In addition, nevirapine induces its own metabolism, with steady-state half-lives that are ~50% of those noted after single-dose administration [42]. Elevations in liver enzyme levels are commonly associated with the use of nevirapine [43, 44]. Nunez et al. [45] investigated a possible association between HCV infection, elevated nevirapine levels, and the development of hepatotoxicity. Thirty-two HCV antibody–positive patients were compared with 38 control subjects, and no difference in trough levels of nevirapine (5.8 μg/mL vs. 6.1 μg/mL) was found. However, patients who developed hepatotoxicity of grade 2 or higher had significantly higher nevirapine concentrations (6.5 μg/mL vs. 5.2 μg/mL) than did patients who did not have hepatotoxicity.

**Efavirenz.** Efavirenz is extensively protein bound and possesses a long plasma half-life [46]. Through its effect on the CYP enzymes, efavirenz can alter the pharmacokinetics of other antiretroviral drugs [47, 48]. Case reports documented elevated steady-state concentrations and areas under the curve (AUCs) for efavirenz in 2 patients with hepatic dysfunction who were treated with efavirenz, stavudine, and nelfinavir [49]. In contrast, Fiske et al. [50] evaluated the pharmacokinetics of efavirenz in 20 HIV-negative subjects—10 subjects with chronic liver disease and 10 control subjects—and they found a significantly lower C max (3.72 μmol/L and 5.74 μmol/L, respectively) in the subjects with liver disease but no significant difference in AUCs between the groups evaluated in this single-dose study.

**Protease Inhibitors (PIs)**

PIs are lipophilic drugs that are extensively metabolized by the CYP enzymes. Several drugs in this class also possess narrow therapeutic indices that increase the likelihood of adverse outcomes associated with altered pharmacokinetics. Although the data are still incomplete, more data exist on the interplay of liver disease and the pharmacokinetics of PIs than for the other classes of antiretroviral drugs.

**Nelfinavir.** Nelfinavir is a PI that primarily uses 2 CYP isoforms for metabolism [51]. CYP 3A4 results in the generation of inactive metabolites, and CYP 2C19 is responsible for the generation of the active M8 metabolite [52]. Khaliq et al. [53] first reported, in a study of 8 HIV-positive patients (of whom 6 were coinfected with HCV) with mild-to-moderate liver disease (i.e., Child-Pugh class A or B), decreased oral clearance of nelfinavir with decreased generation of the M8 metabolite. Values were compared with those for historical controls, but no statistical analysis was provided. Regazzi et al. [54] presented data from a large number of patients with HIV/HCV coinfection (n = 38) and showed that the degree of liver pathology, as assessed by biopsy, is correlated with reduced oral clearance of nelfinavir and decreased generation of the M8 metabolite. In subjects with cirrhosis (n = 14), oral clearance of nelfinavir was decreased by 65% (P < .05), and the ratio of the M8 metabolite to nelfinavir was decreased by 80% among those subjects, compared with HIV-positive control subjects (n = 42). Although HIV/HCV-coinfected patients had increased exposure to nelfinavir plus M8, no increase in systemic
toxicity was reported. This finding may be secondary to the fact that the side effects of nelfinavir are mainly topical in the gastrointestinal tract and that increasing plasma concentrations may not be associated with more toxicity.

A trial of therapeutic drug monitoring of nelfinavir in patients with HCV and chronic liver disease was undertaken by Peytavin et al. [55]. The trough concentrations of nelfinavir (dose, 1250 mg b.i.d.) were measured, and dose adjustments were made to maintain concentrations of 0.3–1.0 μg/L. Fifteen of 18 patients required reductions in doses (range, 250–500 mg b.i.d.), on the basis of the criteria set for the study, but there was no detrimental effect on virologic control, and clinical tolerance was unchanged. On the basis of these data, it is difficult to suggest reductions in the nelfinavir dose for patients with HCV/HIV coinfection, because the higher plasma concentration of nelfinavir may enhance efficacy without excess toxicity.

**Indinavir.** The pharmacokinetics of indinavir are altered by coinfection with HCV. Brodie et al. [56] first reported an increased incidence of indinavir-associated nephrolithiasis in coinfected patients. In a cohort of 79 patients, the overall rate of nephrolithiasis was 22%; however, the rate was 37% among patients with HIV/HCV coinfection and 13% among patients who were infected with HIV-1 alone (P = .02). No assessment of plasma concentrations of indinavir was performed in this study. A larger retrospective study also showed a significant association between infection with either HCV or HBV and indinavir-associated nephrolithiasis [57]. In addition, an association between the plasma concentration of indinavir and nephrolithiasis has been shown. In a study of 104 HIV-1–infected patients who were receiving indinavir (800 mg t.i.d.), 17 patients presented with urologic complaints and had plasma concentrations of indinavir measured. Twelve of the 15 patients with measurable indinavir concentrations and nephrolithiasis had concentrations that were greater than the upper limit of the 95% CI for plasma concentrations of indinavir in the control group (n = 14) [58]. In a small GENOPHAR substudy, Bossi et al. [59] reported that plasma concentrations of indinavir (400 mg b.i.d.) boosted with ritonavir (100 mg b.i.d.) are increased in subjects who are coinfected with HBV or HCV. A decrease in the dose of indinavir to 200 mg was possible for these subjects but not for subjects without HBV or HCV coinfection. The findings of these studies support the possible usefulness of therapeutic drug monitoring among subjects with chronic viral hepatitis who are taking indinavir, so that efficacy can be maintained and toxicities, such as nephrolithiasis, can be averted.

**Ritonavir.** Ritonavir undergoes extensive hepatic metabolism, primarily through the CYP 3A isoforms [60]. In a study of single-dose ritonavir, Cameron et al. [61] found a 40% increase in the AUC0–12h and a 27% increase in the Cmax for patients with mild hepatic disease, compared with control subjects. Another study, which evaluated both single-dose and steady-state levels, reported somewhat different results [62]. Subjects with mild hepatic disease (n = 6) showed a 23% increase (P = .03) in the AUC0–12h for ritonavir after receipt of a single 600-mg dose, compared with control subjects (n = 6). However, subjects with moderate hepatic disease (n = 6) did not show any increase in the AUC, compared with control subjects, but they did have a 44% lower Cmax (P = .02). At steady state, there was no significant difference between control subjects and subjects with mild hepatic disease. It should be noted that the dosing of ritonavir was different in the 2 groups: control subjects received 500 mg b.i.d., and subjects with hepatic disease received 400 mg b.i.d. When the same dosing scheme was used for both study groups, subjects with moderate hepatic disease had an AUC and a Cmax that were ~60% lower than those of control subjects (P = .08 and P = .05, respectively), but the minimum plasma concentration (Cmin) of ritonavir was equivalent in all groups. A plausible explanation for these results is a combination of both altered metabolism and absorption of ritonavir in association with more-advanced liver disease.

**Saquinavir.** Saquinavir is available in 2 formulations, hard capsules and soft gel capsules, which are not interchangeable and which result in significantly different plasma pharmacokinetics [63]. Regardless of the formulation used, bioavailable saquinavir is metabolized by the liver, primarily through the CYP 3A enzyme, and, therefore, the pharmacokinetics are likely altered in patients with hepatic dysfunction. A Japanese study described 4 HIV/HCV-coinfected patients with clinically severe liver disease who were treated with saquinavir (1200–1800 mg/day) [64]. Trough concentrations of saquinavir ranged from 182 to 555 ng/mL; such concentrations were higher than those reported for historical controls (46 ng/mL). Although the pathway of metabolism of saquinavir and the limited data on its effects in vivo suggest an effect of liver disease on the pharmacokinetics of saquinavir, the drug has a high therapeutic index and is frequently used with ritonavir; thus, no change in dosing can be recommended for patients with liver disease.

**Lopinavir.** Lopinavir is extensively metabolized by the CYP 3A isoforms [65]. In clinical practice, lopinavir is used in combination with ritonavir (Kaletra; Abbott Labs), which takes advantage of the inhibitory effects of ritonavir on lopinavir metabolism. Recent data on the use of lopinavir and ritonavir demonstrated that ritonavir exposure was increased quite significantly both in HCV-coinfected patients with mild hepatic insufficiency and in HCV-coinfected patients with moderate hepatic insufficiency (n = 12) [66]. The increase in exposure to ritonavir was as much as 185% among patients with moderate hepatic insufficiency, compared with the exposure to ritonavir among control subjects (n = 12). Exposure to lopinavir
Table 1. Use of nucleoside reverse-transcriptase inhibitors (NRTIs) in the treatment of liver disease.

<table>
<thead>
<tr>
<th>NRTI</th>
<th>Standard dosage</th>
<th>Manufacturer recommendation</th>
<th>Author recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>300 mg po b.i.d.</td>
<td>No recommendation(^a)</td>
<td>No change</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>150 mg po b.i.d.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 mg po q.d.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Stavudine</td>
<td>30–40 mg po b.i.d.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Didanosine</td>
<td>125–200 mg po b.i.d.</td>
<td>No recommendation(^b)</td>
<td>No change(^c)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg po b.i.d.</td>
<td>No recommendation(^b)</td>
<td>No change</td>
</tr>
<tr>
<td>Abacavir</td>
<td>300 mg po b.i.d.</td>
<td>No recommendation(^b)</td>
<td>No change</td>
</tr>
</tbody>
</table>

**NOTE.** "Liver disease" is defined as cirrhosis (diagnosed by biopsy or on the basis of clinical evidence) and a Child-Pugh score of \(\geq 5\).

\(^a\) Data suggest a significant effect of hepatic impairment on plasma zidovudine pharmacokinetics. A lack of data precludes altered dosing recommendations. Clinical experience suggests that standard dosing is well tolerated.

\(^b\) Known metabolic pathways would not suggest a significant effect of hepatic impairment.

\(^c\) Should not be coadministered with ribavirin during hepatitis C therapy.

was also increased in subjects with hepatic insufficiency, for whom the \(C_{\text{min}}\) of lopinavir increased by 73% (range, 20%–150%). The authors also found that protein binding of lopinavir was decreased by hepatic insufficiency, so that the percentage of unbound lopinavir increased (0.91% in patients with hepatic insufficiency vs. 0.69% in control subjects; \(P < .01\)). It is impossible to determine whether the altered pharmacokinetics (exposure and protein binding) of lopinavir in these patients were secondary to hepatic insufficiency or to the altered pharmacokinetics of ritonavir.

**Amprenavir.** Amprenavir also undergoes extensive hepatic metabolism, primarily through the CYP 3A isoenzymes [67]. As is the case for most PIs, amprenavir is extensively protein bound to both albumin and \(\alpha_1\)-acid glycoprotein, which are produced heptically [67]. Veronese et al. [68] performed a single-dose pharmacokinetic study of the use of 600 mg of amprenavir for patients with moderate or severe liver disease. Significant \((P < .05)\) increases in the \(AUC_{0-\infty}\) of 146% and 351% were seen for patients with moderate hepatic disease \((n = 10)\) and patients with severe hepatic disease \((n = 10)\), respectively, compared with control subjects \((n = 10)\). There was a significant positive correlation \((r^2 = 0.5884; P = .0001)\) between Child-Pugh scores and the \(AUC_{0-\infty}\) for amprenavir. By use of a linear regression analysis, the authors estimated the dose of amprenavir for a patient with a given Child-Pugh score that would be equivalent to a dose of 1200 mg in a person without liver disease. For patients with Child-Pugh scores of 5–8, the equivalent dose of amprenavir would be 450 mg, and, for patients with Child-Pugh scores of \(\geq 9\), a dose of 300 mg would be appropriate.

**Atazanavir.** Atazanavir is an azapeptidase PI that primarily undergoes hepatic metabolism involving the CYP 3A isoforms [69]. The use of atazanavir is associated with unconjugated hyperbilirubinemia that is secondary to inhibition of bilirubin conjugation. Hepatic impairment does alter the pharmacokinetics of atazanavir. Sixteen patients, 14 of whom had moderate hepatic impairment and 2 of whom had severe hepatic impairment were evaluated after they received a single dose of 400 mg of oral atazanavir [69]. The mean \(AUC_{0-\infty}\) of atazanavir was increased by 42% in study patients, compared with control subjects, and the half-life was prolonged from 6.4 h to 12.1 h. Cahn and colleagues [70] evaluated, for a period of 48 weeks, the efficacy and safety of atazanavir versus nelfinavir in a group of patients who were coinfected with HBV or HCV. No dif-

Table 2. Use of nonnucleoside reverse-transcriptase inhibitors (NNRTIs) in the treatment of liver disease.

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Standard dosage</th>
<th>Manufacturer recommendation</th>
<th>Author recommendation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>200 mg po b.i.d.</td>
<td>No recommendation</td>
<td>No change; should not be used for HCV-positive patients(^a)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg po q.d.</td>
<td>No recommendation</td>
<td>No change</td>
</tr>
</tbody>
</table>

**NOTE.** "Liver disease" is defined as cirrhosis (diagnosed by biopsy or on the basis of clinical evidence) and a Child-Pugh score of \(\geq 5\). HCV, hepatitis C virus.

\(^a\) Data indicate increased fibrosis and fibrosis progression rates among HCV-positive patients who are treated with nevirapine.
Table 3. Use of protease inhibitors (PIs) in the treatment of liver disease.

<table>
<thead>
<tr>
<th>PI</th>
<th>Standard dosage</th>
<th>Manufacturer recommendation</th>
<th>Author recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelfinavir</td>
<td>1250 mg po b.i.d.</td>
<td>No recommendation</td>
<td>No change&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 mg po q8h</td>
<td>600 mg po q8h</td>
<td>600 mg po q8h&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>1200 mg po t.i.d.</td>
<td>No recommendation</td>
<td>No change</td>
</tr>
<tr>
<td>Lopinavir and ritonavir</td>
<td>400/100 mg po b.i.d.</td>
<td>No recommendation</td>
<td>400 mg of lopinavir po b.i.d.&lt;sup&gt;d&lt;/sup&gt; and 100 mg of ritonavir po b.i.d.&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>1200 mg po b.i.d.</td>
<td>450 mg po b.i.d.&lt;sup&gt;e&lt;/sup&gt; or 350 mg po b.i.d.&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1200 mg po q.d. or 600 mg po b.i.d.&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>400 mg po q.d.</td>
<td>300 mg po q.d.&lt;sup&gt;h&lt;/sup&gt;</td>
<td>300–400 mg po q.d.&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**NOTE.** “Liver disease” is defined as cirrhosis (diagnosed by biopsy or on the basis of clinical evidence) and a Child-Pugh score of <6.

<sup>a</sup> Hepatic impairment significantly increases the levels of nelfinavir. Data do not indicate increased toxicity.

<sup>b</sup> If ritonavir is boosted, the indinavir/ritonavir dosage is 200/100 mg po b.i.d.

<sup>c</sup> Consider therapeutic drug monitoring.

<sup>d</sup> Levels are significantly increased, but there are very limited data; consider therapeutic drug monitoring.

<sup>e</sup> Child-Pugh score of 5–8 (roughly class A).

<sup>f</sup> Child-Pugh score of 9–12 (classes B and C).

<sup>g</sup> Moderate hepatic impairment and severe hepatic impairment produce changes in the area under the curve (AUC) for amprénavir that are similar to those in the AUC for ritonavir. In the clinical setting, ritonavir is frequently added to treatment with amprénavir to obtain a consistent plasma concentration.

<sup>h</sup> Child-Pugh class B; not recommended for Child-Pugh class C.

<sup>i</sup> For treatment-experienced patients, atazanavir (400 mg) should be used. Boosting of atazanavir with ritonavir is not recommended.

ference in virologic response was seen between the coinfected group (n = 53) and the group of patients with HIV infection alone (n = 316). Elevations in liver enzyme levels were more common in the coinfected group; however, no difference between atazanavir and nelfinavir was noted. Grade 3 or 4 bilirubin elevations were common in the group receiving atazanavir, but no difference in bilirubin elevations was noted between the coinfected group and the HIV-1–monoinfected group.

**CONCLUSIONS**

NRTIs, as a class, are least affected by hepatocellular dysfunction, because these drugs are not substrates for CYP isoforms. Zidovudine is the only drug for which a significant effect of liver disease on pharmacokinetics has been demonstrated. Nonetheless, no dosing changes are recommended, because of a strong clinical track record of safety, including among patients with hepatic impairment (table 1).

More data may be required for definitive recommendations regarding dosing of NNRTIs for subjects with HCV or HBV coinfection. Preliminary evidence does not suggest a significant effect of liver disease on the pharmacokinetics of nevirapine or efavirenz. A recent report suggested the possibility of nevirapine accelerating the course of HCV in HIV-1–positive patients who are treated with this drug [71]. Although the study was retrospective in nature, the fact remains that, for most patients, other therapeutic alternatives exist and prospective data will be extremely difficult to obtain. We have recommended that nevirapine not be routinely used for HIV-positive patients who are coinfected with HCV (table 2).

The pharmacokinetics of PIs are most consistently influenced by alterations in hepatic metabolism. Despite limited data, enough studies exist to make recommendations about dose alterations for certain PIs for patients with hepatic impairment (table 3). In particular, indinavir, lopinavir and ritonavir, amprénavir, and atazanavir may require dosing adjustments, either because of a narrow therapeutic index or because of large effects of liver disease on the pharmacokinetics of these drugs. However, caution should be exercised in generalizing these recommendations, given the highly variable pharmacokinetics of PIs across the population. As a result, we emphasize that these recommendations are a starting point for the dosing of certain antiretrovirals in patients with liver disease. For many of the PIs for which the therapeutic indices are low, a cogent argument could be made to use therapeutic drug monitoring to avoid excess toxicity while ensuring adequate drug exposure in patients with hepatic dysfunction.

**Acknowledgments**

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References


In an article in the 1 January 2005 issue of the journal (Wyles DL, Gerber JG. Antiretroviral drug pharmacokinetics in hepatitis with hepatic dysfunction. Clin Infect Dis 2005;40:174–81), an error appeared in the dosage of tenofovir listed in table 1. The dosage should read “300 mg po q.d.” (not “300 mg po b.i.d.”); the corrected table appears below. The authors regret this error.

## Table 1. Use of nucleoside reverse-transcriptase inhibitors (NRTIs) in the treatment of liver disease.

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</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>300 mg po b.i.d.</td>
<td>No recommendation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No change</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>150 mg po b.i.d.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 mg po q.d.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Stavudine</td>
<td>30–40 mg po b.i.d.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Didanosine</td>
<td>125–200 mg po b.i.d.</td>
<td>No recommendation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No change</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg po q.d.</td>
<td>No recommendation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No change</td>
</tr>
<tr>
<td>Abacavir</td>
<td>300 mg po b.i.d.</td>
<td>No recommendation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No change</td>
</tr>
</tbody>
</table>

**NOTE.** “Liver disease” is defined as cirrhosis (diagnosed by biopsy or on the basis of clinical evidence) and a Child-Pugh score of >6.<sup>c</sup>

<sup>a</sup> Data suggest a significant effect of hepatic impairment on plasma zidovudine pharmacokinetics. A lack of data precludes altered dosing recommendations. Clinical experience suggests that standard dosing is well tolerated.

<sup>b</sup> Known metabolic pathways would not suggest a significant effect of hepatic impairment.

<sup>c</sup> Should not be coadministered with ribavirin during hepatitis C therapy.

In a letter that appeared in the 1 February 2005 issue of the journal (Hill T, Platzer A, Reyes C. Influenza deaths in spite of immunization and prophylaxis. Clin Infect Dis 2005;40:492–3), an error appeared in the name of the virus subtype mentioned in the letter. The virus subtype identified was H3N2 (not H2N3). The authors regret this error.