

VI. HIV Treatment in HIV/HCV Coinfection

Summary

There are many unresolved questions regarding treatment of HIV in people coinfecting with HIV and HCV. There are no United States treatment guidelines created specifically for HIV/HCV coinfection. This creates confusion among coinfecting people and their clinicians, and variations in patient care. The optimal sequencing of treatment for HIV and HCV is unclear. Treating HIV first may prevent HCV disease progression by preserving the immune system; however, some studies have reported a blunted immune response to antiretroviral therapy in coinfecting persons (Greub 2000; Law 2002; Torriani 2001; Zala 2004).

Antiretroviral-induced hepatotoxicity—abnormal elevations in liver enzyme levels—is a significant concern among coinfecting persons. HCV coinfection increases the risk for hepatotoxicity. Protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and nucleoside analog reverse transcriptase inhibitors are all associated with hepatotoxicity. The mechanism of liver toxicity differs by class of drug, as well as by agents within a class. Several factors may contribute to hepatotoxicity, such as flares of preexisting hepatitis due to immune restoration; genetic factors that influence drug metabolism; pharmacokinetic (drug-drug) interactions; heavy alcohol consumption; and perhaps even hepatitis C genotype. Treating HCV first may decrease the risk of hepatotoxicity by improving the condition of the liver (Uberti-Foppa 2003).

Coinfecting persons may be more vulnerable to certain antiretroviral-associated side effects and toxicities such as lipoatrophy and diabetes. Antiretroviral agents should be selected carefully by coinfecting patients and their clinicians. In some instances, antiretroviral agents may need to be changed, or treatment discontinued. HCV-related liver damage may compromise hepatic metabolism of antiretrovirals, thus increasing the potential for side effects, toxicities, and interactions with other drugs commonly used by people with HIV. Data on antiretroviral drug levels in people with hepatic impairment are scant. More information is needed.

Care, Treatment, and Research Issues

Treatment Guidelines and Provider Education

Currently, there are no United States guidelines for the care and treatment of HIV/HCV-coinfecting persons. Coinfection-specific guidelines are needed to ensure that coinfecting individuals receive optimal care for HIV and HCV. Coinfecting individuals are not always referred to a liver specialist. If specialty care is available, coinfecting persons may need to coordinate their care between infectious disease doctors and gastroenterologists. Some infectious disease physicians routinely offer referral to a gastroenterologist or hepatologist, but others do not. Infectious disease doctors have said that some gastroenterologists and hepatologists prefer not to treat coinfecting persons, while some liver specialists report that some infectious disease doctors are not providing adequate care to those with liver disease.

The American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) have collaborated on *Practice Guidelines for Diagnosis, Management and*

Treatment of Hepatitis C (Strader 2004). The *Practice Guidelines* include less than two pages on the diagnosis, natural history, and treatment of hepatitis C in coinfecting persons. These guidelines are a first step towards establishing consistent standard of care for hepatitis C in HIV-positive persons.

Current resources include the *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (DHHS 2003), the *Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus* (USPHS/IDSA 2001), the *Consensus Statement on the Management of Hepatitis C: 2002* (NIH 2002), and the *AASLD/IDSA's Practice Guidelines for Diagnosis, Management and Treatment of Hepatitis C* (Strader 2004). These resources need to be integrated into guidelines for the care and treatment of HIV/HCV coinfection. In the meantime, other resources available to coinfecting individuals, clinicians, educators, and advocates include:

- The British HIV Association (BHIVA) *Guidelines for Treatment and Management of HIV and Hepatitis C Coinfection* (BHIVA Coinfection Guidelines Committee 2003);
- The HIV-HCV International Panel's *Care of Patients with Chronic Hepatitis C and HIV Co-infection* (Soriano 2004);
- The Australasian Society for HIV Medicine (ASHM) *Coinfection HIV & Viral Hepatitis. A Guide for Clinical Management* (2003);
- *Coinfection by HIV and Hepatitis A, B and C Virus in Adult Patients* (GESIDA/PNS 2003).

Initiatives for provider education must accompany treatment guidelines. The need for provider education is underscored by surveys of clinician adherence to both the United States *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* (DHHS 2004) and the *Treatment Recommendations for Patients with Chronic Hepatitis C: 2002 Version 3.0* from the Department of Veteran's Affairs (VA). The survey of clinician adherence to the DHHS Guidelines reported that only 6% (116/1,933) of coinfecting persons had been vaccinated against the hepatitis A virus (HAV), although the Guidelines recommend HAV vaccination for all susceptible coinfecting individuals (Teshale 2002).

The VA's *Treatment Recommendations for Patients with Chronic Hepatitis C: 2002 Version 3.0* states that,

All patients with HIV should be tested for hepatitis C . . . Patients infected with both HIV and hepatitis C appear to be at higher risk of liver disease progression than those with HCV infection alone. Therefore, they should be seriously considered for HCV therapy.

A recent review of patient and provider surveys, and of laboratory, pharmacy, and administrative medical records from the VACS-3 cohort (881 HIV-positive veterans) revealed that 79.5% (700/881) had been tested for antibodies to HCV, yet only 21.7% (65/300) of anti-HCV-positive individuals had HCV-RNA testing performed. Sixty-five individuals had no contraindications for HCV treatment, yet only 18% received a liver biopsy, and only 3% were prescribed HCV treatment. Overall, the investigators found that of the approximately 5,510 coinfecting veterans in the VA system,

only 2.5% (138) had been prescribed HCV treatment (Fultz 2003b).

Until there are U.S. coinfection treatment guidelines and tools—such as an algorithm to help determine which coinfecting individuals should be offered HCV treatment—as well as widespread initiatives to educate clinicians on the care and treatment of coinfecting individuals, many HIV/HCV-coinfecting people will continue to receive substandard care.

HIV Treatment in Coinfecting Persons

When to Start Antiretroviral Therapy

The United States DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* recommend initiation of antiretroviral treatment in all symptomatic HIV infected persons and in those with CD4 cell counts below 200/mm³. For those with CD4 cell counts of 200–350/mm³ “treatment should be offered, although [it is] controversial” and for those with CD4 cell counts over 350/mm³ “some” clinicians would initiate therapy in those with HIV RNA levels over 55,000 copies/mL, while “most” experienced clinicians would recommend deferring therapy for those with HIV RNA levels below that level (DHHS 2004).

The optimal time for initiating antiretroviral therapy in coinfecting persons is not established. It may be beneficial to initiate antiretroviral therapy in coinfecting individuals at a higher CD4 count than that which is currently recommended by the *Guidelines*. Some evidence suggests that coinfecting persons have a blunted immune response to HAART, although this remains controversial (Greub 2000; Law 2002; Law 2004; Pineda 2002; Torriani 2001; Zala 2004). Starting HIV treatment at higher CD4 cell counts may help coinfecting individuals preserve and maintain high CD4 cell counts.

HAART may delay HCV disease progression by increasing CD4 cell counts, because the risk of cirrhosis increases with CD4 counts below 200/mm³ (Allory 2000; Goedert 2002; Lesens 1999; Ragni 2001). A retrospective analysis of the effect of HAART on survival of HIV/HCV-coinfecting persons reported significant reductions in overall and liver-related mortality ($P < 0.001$ and $P = 0.018$, respectively) with triple-combination therapy vs. nucleoside analog reverse transcriptase inhibitors alone or no HIV treatment (Qurishi 2003). Maintaining a CD4 cell count $> 200/\text{mm}^3$ increases the likelihood of achieving a sustained virological response to HCV treatment with standard interferon (Mauss 1998; J. F. Sanchez 1994; Soriano 1996). Although CD4 cell percentages often increase during interferon therapy, absolute CD4 cell counts decrease (Ballesteros 2002; Chung 2002b; Hoffman-Terry 2002; Soriano 1995; Torriani 2004). Concomitant or pre-emptive use of HAART may be necessary to prevent CD4 cell counts from dropping below 200/mm³ during HCV therapy. Absolute CD4 cell count and CD4 percentage usually return to baseline after completion of HCV therapy (Chung 2004; Torriani 2004).

On the other hand, HAART-mediated immune reconstitution may exacerbate HCV infection, at least in the initial weeks of HAART. Some studies have found that antiretroviral therapy may increase HCV RNA levels, although others have not (Chung 2002a; Masiota-Bernard 2001; Qurishi 2003; Torriani 2002; Torre 2001; Rutschmann 1998; Zylberberg 1998b). After initiation of HAART, Chung and colleagues found greater increases in HCV RNA among individuals with

lower baseline CD4 cell counts. In 10 individuals with baseline CD4 cell counts $<350/\text{mm}^3$, HCV RNA increased by 0.44 log at 16 weeks and 0.59 log at 48 weeks. HCV RNA increased by 0.26 log at week 16 and 0.1 log at week 48 in the 30 individuals with a baseline CD4 cell count >350 (Chung 2002c). The clinical implications of these increases in HCV RNA are unknown.

The decision to initiate antiretroviral therapy depends on a number of non-clinical factors as well, but in the absence of large, prospective, long-term clinical trials, coinfecting persons and clinicians lack the information they need in order to make key HIV treatment decisions.

Sequencing of Treatment for HIV and HCV

For coinfecting individuals with CD4 counts in the range of $300\text{--}400/\text{mm}^3$, there are compelling arguments for treating either virus first, but there is no completed research addressing this question. In those with high CD4 counts, the presence of advanced liver disease makes HCV treatment the priority. Offering liver biopsy to assess liver damage will help to inform the decision making process, as biochemical and virological tests are not reliable surrogate markers for fibrosis or cirrhosis and the need for HCV treatment cannot be definitively assessed without a liver biopsy (Mendes-Corréa 2003; Merchante 2003; Sterling 2003). Individuals with CD4 counts $\leq 200/\text{mm}^3$ need HIV treatment first. Those with high CD4 cell counts and mild liver disease may not need to treat either virus immediately.

Immune activation is associated with HIV disease progression in untreated individuals, and has been identified as a key element in HIV pathogenesis (Giorgi 1999; Grossman 2002; Liu 1998). During treatment with antiretroviral therapy, persistent immune activation has been associated with decreased CD4 cell gains (Anthony 2003). Coinfection with HCV has been associated with increased immune activation (Hunt 2003; Valdez 2000). Treating hepatitis C first may decrease or eliminate its contribution to immune activation if a sustained virological response is achieved. On the other hand, early initiation of antiretroviral therapy may decrease immune activation. Higher levels of immune activation have been observed in individuals who initiate HAART at low CD4 cell counts (Lange 2002). However, immune activation appears to decrease as the duration of viral suppression increases (Hunt 2003).

• Treating HIV First

The arguments for treating HIV first include the well-recognized risk of progression to AIDS in untreated HIV disease and the known efficacy of antiretrovirals against HIV. Virological suppression of HIV may slow fibrosis progression (Braü 2004b). Maintaining a high CD4 cell count may reduce the risk of HCV disease progression. Furthermore, preserving the immune system may slow HCV disease progression, allowing coinfecting individuals to defer HCV therapy until more effective and less toxic HCV therapies reach the market. Finally, maintaining a high CD4 cell count with HAART may contribute to the success of future HCV treatment, as standard interferon-based regimens are more effective in those with CD4 cell counts $>500/\text{mm}^3$ (Mauss 1998; J. F. Sanchez 1994; Soriano 1996).

● Treating HCV First

The rationale for treating HCV first is informed by data on the natural history of HCV in HIV-positive individuals, as HCV infection is known to progress more rapidly in coinfecting persons. A proportion of coinfecting persons treated for HCV may achieve a sustained virological response. Although treating hepatitis C does not invariably result in eradication of hepatitis C, some virological non-responders may have improved liver histology. HCV mono-infection studies (see Chapter V, Hepatitis C Treatment) have reported that HCV disease progression may stabilize or that there may be a reversal of liver damage after treatment, even in the absence of an SVR. This may apply in coinfection as well, although the long-term histological and clinical benefits of pegylated interferon-based regimens in mono- or coinfecting persons are currently unknown.

Even in the absence of an SVR, many clinicians and researchers have speculated that treating HCV first may lower the risk of antiretroviral hepatotoxicity by improving overall liver health. Uberti-Foppa and colleagues studied the effect of pretreatment for HCV on the risk for hepatotoxicity after initiation of HAART in an unrandomized, prospective study of 105 coinfecting participants. HIV and HCV parameters of all participants were similar at baseline. Sixty-six chose to be pretreated for HCV (with standard interferon monotherapy or standard interferon plus ribavirin) prior to initiating antiretroviral therapy. The risk for discontinuation of anti-HIV therapy was significantly greater among individuals who were not pretreated for HCV (RR=10.4; 95% CI, 1.6–66; P=0.0127) and those with elevated liver enzyme levels before initiation of HAART. The discontinuation risk increased with ALT elevations (for increases of 10 U, 50 U and 100 U, the risk ratios were 1.14, 1.96 and 3.86, or 1.014 per unit of ALT; P=0.005). The probability of remaining on HAART for 24 months was 95% ± 4.5% in the pretreated group versus 85% ± 15.4% in the non-pretreated group, suggesting that pretreatment of hepatitis C may increase tolerability of antiretroviral therapy. All of those who achieved an SVR were able to tolerate HAART (Uberti-Foppa 2003). Although a baseline assessment of liver histology was available, post-treatment liver biopsies were not performed in this study.

Assessment of baseline and post-treatment liver histology must be included in future studies.

● Treating HIV and HCV Simultaneously

Both viruses may be treated at the same time, although side effects may be unendurable for some individuals. In the absence of prospective, randomized studies, treatment decisions should be made on an individualized basis.

HIV Treatment Issues in HIV/HCV Coinfection

Hepatotoxicity

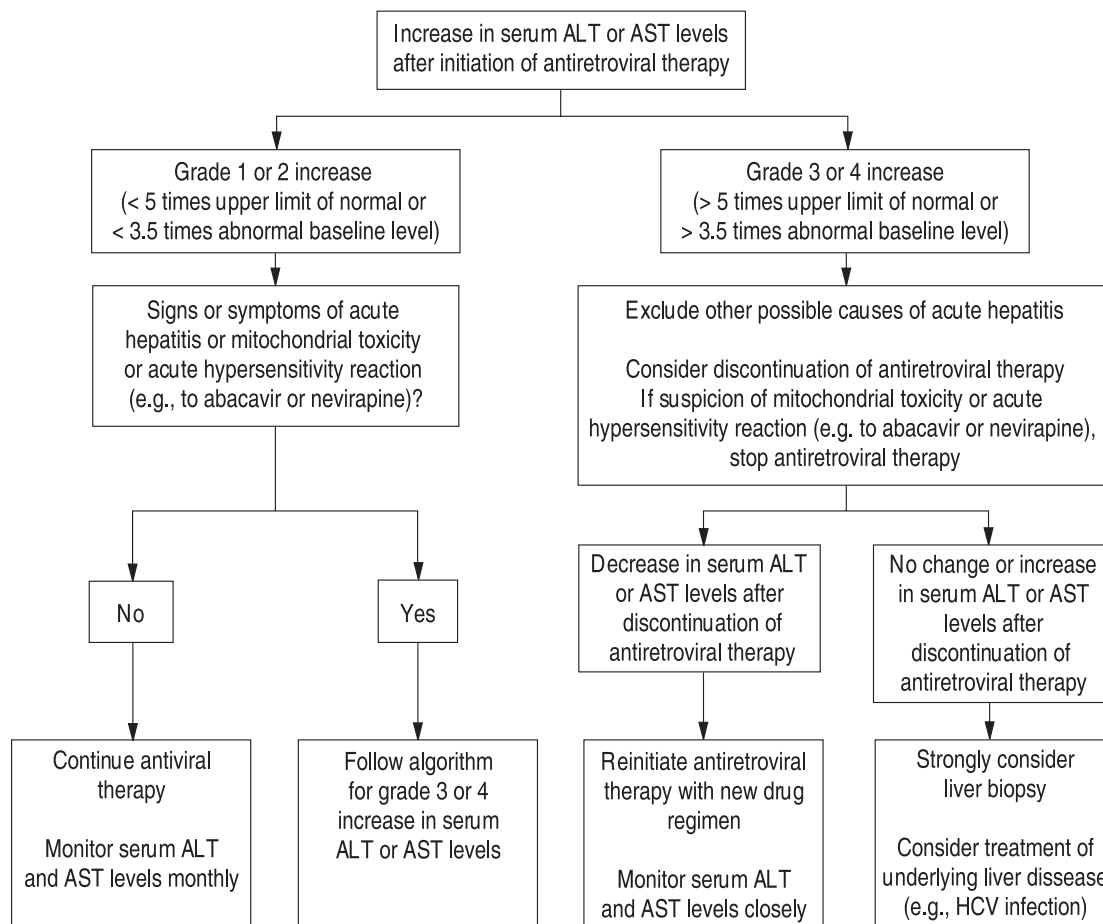
One of the most vexing areas in care and treatment for coinfecting individuals is the potential for hepatotoxicity from antiretrovirals or other ancillary medications commonly used to treat HIV disease, opportunistic infections, complications and co-morbidities. Antiretroviral-related hepatotoxicity is characterized by abnormal elevations in liver enzyme levels and, in some instances, flares of symptomatic hepatitis after initiation of HAART. In some cases, antiretroviral

agents may need to be switched or discontinued. Although people who are not HCV-coinfected also experience HAART-related hepatotoxicity, the risk is greater for coinfecting people (Aceti 2002; Bonnet 2002; Bonfanti 2001; den Brinker 2000; S. M. Imperiale 2002; Law 2003; Martinez 2001; M. Núñez 2001; Reisler 2002; Savès 1999; Sulkowski 2000a; Sulkowski 2000b; Torriani 2000; Zylberberg 1998a).

Several mechanisms may cause or contribute to hepatotoxicity, such as direct toxicity of antiretrovirals, pharmacokinetic interactions, drug-induced mitochondrial damage in liver cells, and enhanced immune responses to hepatitis C after HAART-mediated immune restoration. Host factors are involved as well; hereditary differences in the genes encoding drug-metabolizing enzymes may alter the risk for hepatotoxicity. Heavy alcohol use has been associated with an increased risk for hepatotoxicity (Aceti 2002; Lana 2001; M. Núñez 2002). The stage of HIV disease at initiation of HAART, and the immunologic response to therapy may contribute as well.

Much remains unknown about hepatotoxicity. The relationship between the degree of liver damage present at initiation of HAART and the incidence of hepatotoxicity has not been thoroughly examined. Research must include baseline assessments of liver histology at initiation of HAART in order to determine when hepatotoxicity is likely to occur, since ALT levels are not an adequate surrogate for HCV disease progression (Kouvatsos 2002). Antiretroviral regimens for coinfecting persons must be carefully selected, and regular monitoring of liver enzyme and bilirubin levels is required.

Table 1. Clinical Management of Antiviral-Associated Hepatotoxicity in HIV/HCV Coinfection



Sulkowski 2003d

There is no universal definition for hepatotoxicity. Different studies have used different parameters to define hepatotoxicity, ranging from AST and ALT levels that are 5–10 times the upper limits of normal to levels >10 times the upper limits of normal. When ALT and AST levels are elevated at baseline, definitions have ranged from >200 above baseline to 3.5 times the baseline amount. Adopting or developing a uniform characterization of hepatotoxicity, such as the AIDS Clinical Trials Group parameters (see Table 2) will benefit research and clinical care. Definitions of, and parameters for, liver toxicity must be included in coinfection treatment guidelines.

Table 2. AIDS Clinical Trials Group Parameters for Liver Transaminase Elevations*

	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Potentially life-threatening
AST (SGOT)	1.25–2.5 x ULN**	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN
ALT (SGOT)	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN
GGT	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN
ALK PHOS	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN

AIDS Clinical Trials Group 1992

*For more information on liver transaminases, see Chapter IV, Diagnostics.

**ULN = upper limit of normal.

Antiretrovirals and Hepatotoxicity

Three classes of antiretroviral agents—protease inhibitors (PIs), nucleoside analog reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs)—may cause hepatotoxicity, although their causal mechanisms may vary by class and by individual agent (Bonnet 2002; John 1998; Lana 2001; Martín-Carbonero 2002; M. Núñez 2001; Rutschmann 1998; Savès 1999; Sulkowski 2000a; Sulkowski 2000b).

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

All of the NNRTIs have been associated with elevations in liver enzymes. They may interfere with liver function and affect metabolism of drugs by inhibiting or inducing the liver’s cytochrome P450 system. Drugs may build up to hepatotoxic levels, or be excreted too rapidly, leading to drug failure and the emergence of drug-resistant virus. The NNRTI nevirapine (Viramune®) may induce fulminant hepatitis, which can be fatal.

- Nevirapine

With nevirapine (Viramune®), potentially life-threatening clinical hepatitis may develop, with two-thirds of cases developing within six to twelve weeks after starting the drug. Symptoms may include fatigue, appetite loss, nausea, jaundice, a swollen or tender liver, rash, and fever, with or without elevated liver enzyme levels. In February of 2004, nevirapine’s manufacturer, Boehringer Ingelheim, added to the boxed warning on the drug’s label: “Severe, life threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and

hepatic failure, has been reported in patients treated with Viramune®. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Women, and patients with higher CD4 counts, are at increased risk of these hepatic events. Women with CD4 counts >250 cells/mm³, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of these events. Patients with signs or symptoms of hepatitis must discontinue Viramune® and seek medical evaluation immediately.” The manufacturer states, “Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment. The greatest risk of severe rash or hepatic events (often associated with rash) occurs in the first six weeks of therapy. However, the risk of any hepatic event, with or without rash, continues past this period and monitoring should continue at frequent intervals.” (Boehringer Ingelheim. Dear Health Care Provider Letter. 2004a).

An analysis of data from several clinical trials revealed that the incidence of hepatic events was 12 times greater among women with CD4 cell counts >250 cells/mm³ than in women with CD4 cell counts <250/mm³ (11% vs. 0.9%). For men, the incidence of hepatic events was greatest in those with CD4 cell counts >400/mm³ (6.3% vs. 2.3% among men with CD4 cell counts <400/mm³). Some cases of hepatic adverse events were asymptomatic. Nevirapine discontinuation did not always stop progression of liver injury (Boehringer Ingelheim 2004a). In a 468-person treatment trial that compared lamivudine (3TC; Epivir®) to emtricitabine (FTC; Emtriva™) in combination with stavudine (d4T; Zerit®) grade 4 liver enzyme elevations occurred among 9.4% (36/385) of those who received nevirapine vs. 0% of those who received efavirenz (Sustiva™). Grade 4 elevations occurred among 12% of females vs. 6% of males (P=0.05). Two participants died from liver failure (Bartlett 2001).

The risk for nevirapine-related hepatic adverse events is greater among individuals who have elevated liver enzymes at initiation of therapy, as well as in those who are coinfecting with hepatitis C (Martínez 2001). Sulkowski and colleagues examined the incidence of nevirapine-related hepatotoxicity among 568 individuals, 43% (244/563) of whom were coinfecting. They reported that only 32% of cases of nevirapine-related hepatotoxicity occurred during the first 12 weeks of therapy. Overall, nevirapine-related hepatotoxicity was observed in 19.3% (23/119) of coinfecting individuals vs. 12.4% (17/137) of those with HIV alone (Sulkowski 2000a). In coinfecting individuals, nevirapine plasma concentrations over 6 mcg/ml have been associated with a 92% risk for hepatotoxicity (Gonzalez 2002).

- Efavirenz

With efavirenz, Sulkowski and colleagues observed severe hepatotoxicity among 15.3% (19/124) of coinfecting recipients vs. 3.2% (6/188) of those with HIV alone (RR 4.8; 95% CI, 2.0–11.8). Half of the episodes of efavirenz-associated hepatotoxicity occurred during the first twelve weeks of therapy. Adding a protease inhibitor to an efavirenz-containing regimen increased the likelihood of severe hepatotoxicity among coinfecting persons (Sulkowski 2000a).

Table 3. ALT and AST Levels Before, During, and After Treatment by HCV Status and Use of Nevirapine or Efavirenz

	Nevirapine HCV +	Nevirapine HCV –	P value	Efavirenz HCV +	Efavirenz HCV –	P value
Baseline ALT	37 (24–61)	24 (14–41)	<0.0001	36 (25–52)	26 (19–41)	<0.0001
Maximum ALT	88 (47–134)	47 (28–99)	<0.0001	56 (32–98)	35 (21–55)	<0.0001
Change in ALT	37 (10–82)	16 (1–60)	<0.01	17 (-2–49)	6 (-6–24)	<0.01
Baseline AST	47 (35–70)	28 (20–44)	<0.0001	48 (36–73)	29 (22–40)	<0.0001
Maximum AST	84 (57–144)	45 (28–80)	<0.0001	84 (39–148)	37 (26–56)	<0.0001
Change in AST	32 (6–87)	10 (0–36)	<0.001	19 (-3–79)	6 (-5–21)	<0.001

Sulkowski 2002a

Protease Inhibitors (PIs)

All protease inhibitors (PIs) are metabolized in the liver. PIs may cause elevated liver enzyme levels at any time during treatment. Protease inhibitors affect hepatic metabolism by inhibiting or inducing the liver’s cytochrome P450 system, so drugs may build up to hepatotoxic levels or be cleared too rapidly, leading to therapeutic failure and the emergence of drug resistance. Of the PIs, full-dose ritonavir (Norvir®) has most often been associated with elevated liver enzymes (Aceti 2002; Bonfanti 2001).

• Full and Boosting Doses of Ritonavir

Ritonavir is an extremely powerful cytochrome P450 CYP3A4 metabolic inhibitor, often used to boost levels of other protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz™), fosamprenavir (Lexiva™), indinavir (Crixivan®), and saquinavir (Fortovase®). Ritonavir is coformulated with lopinavir in Kaletra®. It is rarely administered at the full dose of 600 mg twice daily due to poor tolerability and the availability of other treatment options.

Sulkowski and colleagues evaluated the incidence of severe hepatotoxicity from full-dose ritonavir among a cohort of 294 HIV-positive persons, 158 of whom were coinfecting (53.7%). The overall risk for hepatotoxicity was fivefold greater from full-dose ritonavir than saquinavir, indinavir, and nelfinavir (Viracept®), regardless of HCV status. Severe hepatotoxicity occurred in 30% (6/30) of coinfecting individuals receiving full-dose ritonavir, and among 30% (9/30) with HIV alone (Sulkowski 2000b).

Aceti and colleagues retrospectively analyzed hepatotoxicity among 1325 individuals, 731 HCV-coinfecting, who received protease inhibitors as part of their HIV treatment regimen. HCV coinfection significantly increased the risk for hepatotoxicity after six months of HAART (OR 6.79; 95% CI, 3.66–9.16; P<0.0001). Liver toxicity (of any grade) occurred more frequently among coinfecting persons receiving full-dose ritonavir than in those with HIV alone (P=0.006), and more often with full-dose ritonavir than other protease inhibitors (26.1% (17/65) for ritonavir vs. 17.3% (9/52) for nelfinavir, 16.5% (41/248) for saquinavir, and 11.7% (44/375) for indinavir). Severe liver toxicity

occurred more frequently in coinfecting persons taking full-dose ritonavir (20% (13/65)) than any other protease inhibitor (5% (12/248) for saquinavir; 1.86% (7/375) for indinavir; and 0% (0/52) for nelfinavir) (Aceti 2002).

Low-dose ritonavir has also been associated with an increased risk for hepatotoxicity in coinfecting persons. In an analysis of the incidence of liver toxicity among 120 individuals (52 coinfecting) after initiation of a regimen containing lopinavir/ritonavir (Kaletra®), Soriano and colleagues reported a 4% overall cumulative incidence of grade 3 and grade 4 hepatotoxicity at 12 months. The cumulative incidence of hepatotoxicity rose to 8% among coinfecting individuals, although there was no significant difference in lopinavir/ritonavir levels by HCV status (Soriano 2003).

Sulkowski and colleagues reported hepatotoxicity data from 1,061 HIV-positive persons, 488 (46%) coinfecting. Although 405 (83%) coinfecting persons did not experience hepatotoxicity, their risk for developing hepatotoxicity was twice as high as that of the HIV-positive, HCV-negative group. The risk was greatest for those receiving combinations including higher doses of ritonavir (Sulkowski 2003c).

Table 4. Incidence of Hepatotoxicity (Grade 3/4) by HCV Status and Antiretroviral Agent

	Nelfinavir N=605	Lopinavir + 200 mg RTV* N=89	Indinavir + 200-400 mg RTV** N=92	Saquinavir + 400 mg RTV*** N=273
All	11.1%	9%	12.8%	17.2%
HCV/HIV coinfecting	15.8%	12.8%	14.8%	26.2%
HIV mono-infection	6.5%	6%	10%	11.4%

Sulkowski 2003c

*Lopinavir is coformulated with 100 mg of ritonavir and is taken twice daily.

**Indinavir can be combined with different doses of ritonavir; in this study, ritonavir doses ranged from 200 to 400 mg/day.

***Saquinavir has been combined with different doses of ritonavir; in this study, participants received 400 mg of each per day.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

The NRTIs are not metabolized through the cytochrome P450 system. These drugs can cause hepatotoxicity by damaging mitochondria, the small, rod- or oval-shaped bodies inside of cells that produce energy. NRTI-induced mitochondrial dysfunction may cause hyperlactatemia (mild to serious elevations in serum lactate levels), sometimes accompanied by liver enzyme elevations and hepatic steatosis (liver tissue degeneration marked by fat globules in the cells) (Lonergan 2000). Lactic acidosis—a rare but life-threatening consequence of mitochondrial toxicity—has been linked with the use of all NRTIs, and particularly with zalcitabine (ddC; Hivid®), didanosine (ddI; Videx®), stavudine, and zidovudine (AZT; Retrovir®) (Boubaker 2001; Brinkman 2000; Falcó 2002; Fortgang 1995; John 2001; Marceau 2003; K. D. Miller 2000). The symptoms of lactic acidosis may include weakness, abdominal pain and distention, nausea, vomiting, diarrhea, muscle aches, ascending neuromuscular weakness, elevations in liver enzyme levels, and shortness

of breath. Severe NRTI-induced lactic acidosis is often accompanied by hepatic steatosis, hepatomegaly (swollen liver), and hepatic failure (Bienvenu 2001; Fortgang 1995; K. D. Miller 2000; Mokrzycki 2000; Olano 1995).

Mitochondrial abnormalities have been detected in liver tissue from individuals using NRTIs (Batisse 2002; Van Huyen 2003). In addition, hepatitis C has been associated with mitochondrial abnormalities in liver tissue (Barbaro 1999). NRTIs may exacerbate HCV-induced mitochondrial toxicity. Verruci and colleagues examined liver tissue samples from 39 coinfecting individuals, 34 of whom had been using antiretroviral therapy (including NRTIs) for a median duration of 8.7 years; the other 5 had never been treated for HIV. All 34 had mitochondrial abnormalities in their liver tissue, as did 3/5 in the untreated group. Although some abnormalities (polymorphism, crystalline inclusions, and hyperplasia) were found in all 39, certain abnormalities (glycogen inclusions, reduction or loss of cristae, and reduction of matrix density) were present only among those who had received antiretroviral therapy (Verucchi 2004). These data are limited by small sample size of the treatment-naïve group and the absence of a comparator group with HCV mono-infection. A larger study is warranted.

- **“D” Drugs: Didanosine (ddI), Stavudine (d4T), and Zalcitabine (ddC)**

Walker and colleagues examined serum lactate levels and liver tissue samples from 94 people with hepatitis C, 80 coinfecting. Participants were grouped as coinfecting, no antiretroviral therapy at biopsy (N=11); coinfecting, uninterrupted antiretroviral therapy (N=69); and HCV-mono-infecting (N=14). Thirty-four coinfecting individuals were using a “d” drug (didanosine (ddI), stavudine (d4T), zalcitabine (ddC)) as part of their antiretroviral therapy. Their hepatic mitochondrial DNA (mtDNA) was significantly decreased ($P < 0.0001$ for “d” drugs vs. non-“d” drugs). Dual “d” drug therapy further reduced hepatic mtDNA by 53% ($P < 0.0001$ for stavudine plus didanosine vs. stavudine alone). There was no significant difference in hepatic mtDNA levels by HIV status or use of antiretroviral therapy without “d” drugs, and the difference in mtDNA could not be attributed to any other variables. Only three individuals had lactate levels equal to, or above, the upper limits of normal. All were using stavudine, and two were also using didanosine; their hepatic mtDNA levels were significantly lower than all untreated participants ($P = 0.003$) as well as the other 31 individuals using “d” drugs ($P = 0.017$). Serum lactate levels at liver biopsy were higher among those using antiretroviral therapy than among untreated persons; among treated persons, there were no significant differences in lactate levels by antiretroviral agent (Walker 2004).

Drug Interactions

Inhibiting or inducing hepatic drug metabolism via the cytochrome P450 system leads to drug interactions between antiretroviral agents and other drugs. Ritonavir, in particular, is a potent inhibitor of the hepatic metabolism of other drugs, which “...may create the potential for serious and/or life threatening reactions such as cardiac arrhythmias, prolonged or increased sedation, and respiratory depression” (Abbott 2003).

Alterations in the capacity for hepatic metabolization of antiretrovirals may result in accumulation of drugs to toxic levels, decreases to suboptimal levels or increased potential for interactions, side effects, and toxicities. There is abundant potential for interactions among antiretroviral agents;

drugs used as prophylaxis for opportunistic infections; ancillary medications for the complications of HIV disease and side effects of antiretroviral therapy; hormonal contraceptives; and treatments for other conditions including methadone, anti-anxiety drugs, vitamins, supplements, and herbal preparations.

For more information on specific drug-drug interactions among medications used for treatment of hepatitis C, antiretroviral agents, and immunosuppressants, see Chapter VII, HCV Treatment in HIV/HCV Coinfection.

Pharmacokinetics of Antiretroviral Agents

The liver's capacity to metabolize drugs may be compromised by damage from hepatitis C. George and colleagues compared 50 cirrhotic livers (which were removed during transplantation) and 21 normal livers. They discovered a significant reduction in cytochrome P450 in the cirrhotic livers (George 1995). Although the livers studied were damaged enough to warrant transplantation, and HCV was not the only cause of cirrhosis, this research sheds some light on metabolic impairment resulting from liver damage. The impact of liver damage on antiretroviral drug levels has not been adequately explored; only a small body of data is available. More research is required.

Table 5. Dosing Recommendations for Persons with Hepatic Dysfunction

Nucleoside Reverse Transcriptase Inhibitors	Daily Dose	Dosing in hepatic impairment
Abacavir (<i>Ziagen</i>)	300 mg bid	No dosage recommendation
Didanosine (<i>Videx</i>)	Weight >60 kg: 400 mg qd or 200 mg bid Weight <60 kg: 250 mg qd or 125 mg bid	No dosage recommendation
Emtricitabine (<i>Emtriva</i>)	200 mg qd	No dosage recommendation
Lamivudine (<i>Epivir</i>)	300 mg qd or 150 mg bid	No dosage recommendation
Stavudine (<i>Zerit</i>)	Weight >60 kg: 40 mg bid Weight <60 kg: 30 mg bid	No dosage recommendation
Tenofovir (<i>Viread</i>)	300 mg qd	No dosage recommendation
Zalcitabine (<i>Hivid</i>)	0.75 mg tid	No dosage recommendation
Zidovudine (<i>Retrovir</i>)	300 mg bid	No dosage recommendation
Non-Nucleoside Reverse Transcriptase Inhibitors	Daily Dose	Dosing in hepatic impairment
Delavirdine (<i>Rescriptor</i>)	400 mg tid	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (<i>Sustiva</i>)	600 mg qd	No dosage recommendation; use with caution in patients with hepatic impairment
Nevirapine (<i>Viramune</i>)	200 mg bid	No data available; avoid use in patients with moderate to severe hepatic impairment

Protease Inhibitors	Daily Dose	Dosing in hepatic impairment	
Amprenavir (<i>Agenerase</i>)	1200 mg bid	Child-Pugh Score	Dose
		5–8	450 mg bid
		9–12	300 mg bid
Atazanavir (<i>Reyataz</i>)	400 mg qd	Child-Pugh Class	Dose
		Class B	300 mg qd
		Class C	not recommended
Fosamprenavir (<i>Lexiva</i>)	1,400 mg bid	Child-Pugh Score	Dose
		5–8	700 mg bid
		9–12	not recommended
Indinavir (<i>Crixivan</i>)	800 mg q8h	For mild-to-moderate hepatic insufficiency due to cirrhosis: 600 mg q8h	
Lopinavir/Ritonavir (<i>Kaletra</i>)	400/100 mg bid (coformulated)	No dosage recommendation; use with caution in patients with hepatic impairment	
Nelfinavir (<i>Viracept</i>)	1250 mg bid	No dosage recommendation; use with caution in patients with hepatic impairment	
Ritonavir (<i>Norvir</i>)	600 mg bid	No dosage adjustment in mild hepatic impairment; no data for moderate to severe impairment, use with caution	
Saquinavir (<i>Fortovase</i>) soft gel cap	1200 mg tid	No dosage recommendation; use with caution in patients with hepatic impairment	
Fusion Inhibitor	Daily Dose	Dosing in hepatic impairment	
Enfuvirtide (<i>Fuzeon</i>)	90 mg SQ q 12h	No dosage recommendation	

Department of Health & Human Services 2004

● Nucleoside Reverse Transcriptase Inhibitors

○ Abacavir

There are no data on the pharmacokinetics of abacavir (Ziagen®) in persons with hepatic impairment.

○ Didanosine

There are no data on the pharmacokinetics of didanosine in persons with hepatic impairment.

○ Emtricitabine

The pharmacokinetics of emtricitabine have not been studied in persons with hepatic impairment (Gilead package insert 2003).

o Lamivudine

The pharmacokinetics of lamivudine did not differ in individuals with hepatic impairment; safety and efficacy for individuals with hepatic decompensation have not been evaluated (Glaxo Smith Klein package insert 2002).

o Stavudine

The pharmacokinetics of a single 40 mg dose of stavudine have been evaluated in five HIV-negative individuals with cirrhosis (Child-Pugh Class B and C); the pharmacokinetics of stavudine were unaltered in these individuals (Bristol Myers Squibb package insert 2002).

o Tenofovir

The pharmacokinetics of a single 300 mg dose of tenofovir have been evaluated in 24 HIV-negative persons; 7 had moderate hepatic impairment, 8 had severe hepatic impairment, and the other 8 were unimpaired controls. The pharmacokinetics of tenofovir were not substantially altered in persons with moderate or severe hepatic impairment (Kearney 2004).

o Zalcitabine

No data are available on the pharmacokinetics of zalcitabine in persons with hepatic impairment.

o Zidovudine

Data on the pharmacokinetics of zidovudine in persons with hepatic impairment are limited; because it is metabolized in the liver, dose reduction may be necessary (Glaxo Wellcome package insert 2001).

• Non-Nucleoside Reverse Transcriptase Inhibitors

o Delavirdine

Delavirdine (Rescriptor ®) has not been studied in persons with hepatic impairment.

o Efavirenz

A study monitoring levels of efavirenz reported that 50% (6/12) of coinfecting participants had minimum concentrations (C_{min}) that were above the upper limit of the therapeutic range. The dosing in this group was decreased from 600 mg qd to 400 mg qd; after a mean interval of six months, all had maintained undetectable HIV RNA (Jeantils 2003).

o Nevirapine

The pharmacokinetics of a single 200 mg dose of nevirapine have been studied in 10 HIV-negative individuals: 6 had mild hepatic impairment, and 4 had moderate hepatic impairment.

One individual with moderate hepatic impairment had a significant increase in the area under the curve (AUC; a measurement of the total amount of a drug in blood) of nevirapine. Nevirapine is not recommended for persons with severe hepatic impairment (Boehringer Ingelheim package insert 2004b). Vigilant monitoring for signs and symptoms of clinical hepatitis and elevated liver enzyme levels, especially during the first 18 weeks of treatment, is crucial. Nevirapine can cause severe and life-threatening hepatic events.

- **Protease Inhibitors**

- **Amprenavir and Fosamprenavir**

Amprenavir has been evaluated in persons with hepatic impairment. Veronese and colleagues compared drug levels in three groups of ten: a control group (no cirrhosis), a moderate cirrhosis group, and a severe cirrhosis group. A linear relationship between the AUC of amprenavir and the severity of liver disease was identified; with AUC increased 2.5-fold in the group with moderate cirrhosis, and by 4.5-fold in the group with severe cirrhosis (Veronese 2000); see Table 5 for dosing recommendations.

Fosamprenavir, a prodrug of amprenavir, has not been evaluated in persons with hepatic impairment, nor are there any data on ritonavir-boosted fosamprenavir.

- **Atazanavir**

The concentration of atazanavir is increased in people with hepatic impairment. After a single 400 mg dose of atazanavir, the AUC was 42% greater in 16 individuals with moderate to severe hepatic impairment than that of study volunteers without hepatic impairment. Hepatic impairment decreased clearance of atazanavir; its mean half-life was 12.1 hours vs. 6.4 hours in persons without hepatic impairment. Individuals with "...underlying hepatitis B or C viral infections or marked elevations in liver transaminases prior to treatment may be at risk for developing further transaminase elevations or hepatic decompensation" (Bristol Myers Squibb package insert 2003). There are no data on ritonavir-boosted atazanavir in persons with hepatic impairment.

- **Indinavir**

Indinavir has been studied in 12 people with mild-to-moderate hepatic impairment and evidence of clinical cirrhosis. After one 400 mg dose, the AUC was approximately 60% greater and the half-life of indinavir was extended (2.8 ± 0.5 hours vs. 1.8 ± 0.4 hours with no hepatic impairment) (Merck package insert 2001). There are no data on ritonavir-boosted indinavir in persons with hepatic impairment.

- **Lopinavir/Ritonavir**

Levels of lopinavir/ritonavir (LPV/r) are higher in persons with HCV-related liver disease. Arribas and colleagues conducted a pharmacokinetic evaluation of drug levels among 24 individuals (12 HIV-positive controls; 6 HCV-coinfected with mild hepatic impairment and 6 HCV-coinfected with moderate hepatic impairment). They reported that the AUC of lopinavir was 0.98–1.96 times

greater in mild hepatic impairment and 0.89–1.76 times greater with moderate hepatic impairment. The AUC of ritonavir was 41% greater with mild hepatic impairment and 185% higher with moderate hepatic impairment (Arribas 2003).

o Nelfinavir

Regazzi and colleagues studied the clinical pharmacokinetics of nelfinavir. They looked at plasma concentrations of the drug in 42 HIV-positive individuals, and two groups of HIV/HCV-coinfected individuals (24 without cirrhosis and 14 with cirrhosis). Nelfinavir levels were significantly higher in both groups of coinfecting persons. The AUC increased by 58% in coinfecting non-cirrhotics and by 155% in coinfecting cirrhotics (Regazzi 2003). The implications for dosing are unclear; a reduced dose of nelfinavir could result in suboptimal drug levels. There are no data on ritonavir-boosted nelfinavir in persons with hepatic impairment.

o Saquinavir

The pharmacokinetics of saquinavir and ritonavir-boosted saquinavir have not been studied in people with hepatic impairment.

● Fusion Inhibitors

o Enfuvirtide

The pharmacokinetics of enfuvirtide (T-20; Fuzeon®) in persons with hepatic impairment have not been studied.

Immune Reconstitution and Hepatotoxicity

Transient flares of hepatitis after initiation of HAART—characterized by significant increases in liver enzyme levels and in some cases, symptomatic hepatitis—may be the result of HAART-mediated immune reconstitution. John and colleagues reported two cases of symptomatic hepatitis after initiation of HAART. One had been taking dual nucleoside analog reverse transcriptase inhibitors; adding a protease inhibitor increased the CD4 cell count from 266/mL to 416/mL. The other had a history of multiple opportunistic infections; therapy with two nucleoside analog reverse transcriptase inhibitors and a protease inhibitor increased the CD4 cell count from 32/mL to 138/mL. Although both were anti-HCV-negative prior to initiation of HAART, a look at stored samples of their plasma revealed that each had detectable HCV RNA prior to initiating HAART. Both individuals developed antibodies to HCV after an immunological response to HAART (CD4 cell increase of >100 after four weeks of therapy) (John 1998).

The degree of virological and immunologic responses to HAART has been associated with hepatotoxicity in some studies, although this association remains controversial. Gavazzi and colleagues reported that increased liver enzyme levels occurred only in coinfecting individuals with persistently undetectable HIV RNA after initiation of HAART. The achievement of undetectable HIV RNA levels correlated with an increase in CD8 cells. The authors speculate that these cytotoxic CD8 cells could be responsible for liver enzyme elevations and suggested further analysis of immunologic

and histological parameters (Gavazzi 2000).

Puoti and colleagues examined the incidence of severe hepatotoxicity (defined as ≥ 10 times the upper limit of normal or, if elevated at baseline, ≥ 5 times the amount of baseline) after initiation of antiretroviral therapy among a cohort of 755 HIV-positive individuals, 513 coinfecting. Severe hepatotoxicity was experienced by 26 individuals, 25 of whom were coinfecting. Overall, 5% (25/513) of coinfecting persons experienced severe hepatotoxicity; 58% (15/26) with baseline CD4 cell counts of $<200/\text{mm}^3$. Seven of the individuals who experienced severe hepatotoxicity died from liver failure. A direct correlation between peak elevations in ALT levels and CD4 cell increase from baseline was observed ($P<0.001$). Paired pre- and post-treatment hepatotoxicity biopsy samples were available from 2 individuals; both showed worsening of HCV disease (Puoti 2003).

However, immune-mediated exacerbation of hepatitis C is not a universal phenomenon, and the contribution of immune reconstitution to hepatotoxicity remains controversial. Zylberberg and colleagues examined paired biopsy samples (pre-HAART and after 12 months of antiretroviral therapy) from 25 coinfecting individuals, finding no significant relationship between immune reconstitution and histological progression of HCV disease (Zylberberg 2003). Martín-Carbonero and colleagues retrospectively studied liver injury among 42 coinfecting persons. They did not identify an association between elevated liver enzymes and increases in HCV RNA, or virological and immunological responses to HAART. They measured liver enzyme levels, HIV- and HCV RNA levels and CD4 cell counts at baseline, and every three months for at least six months after initiation of antiretroviral therapy. Those who developed hepatotoxicity had their HIV and HCV RNA levels measured, and a CD4 cell count when their liver enzymes reached a peak. Baseline and peak liver enzyme measurements were compared with measurements in those who did not experience hepatotoxicity. Although immune reconstitution syndrome occurred more frequently in coinfecting persons who initiated HAART with baseline CD4 cell counts of $<200/\text{mm}^3$, liver enzyme elevations did not (Martín-Carbonero 2002).

The extent of immunologic and virological responses to HAART may influence the likelihood of developing hepatotoxicity. After one year of HAART, Aceti and colleagues found that hepatotoxicity was more common in coinfecting persons with no increase in CD4 cell counts than those with CD4 cell increases (20.9% vs. 10.2%; $P=0.017$). Additionally, liver toxicity was more common in coinfecting individuals who had increases in HIV RNA after a year of HAART than in those who had stable or decreasing HIV RNA levels (34% vs. 13%; $P=0.18$) (Aceti 2002).

HAART may have beneficial or detrimental effects on ALT levels, according to individual characteristics. Torre and colleagues retrospectively studied CD4 cell counts, HIV and HCV RNA levels, and changes in ALT levels among 323 coinfecting individuals over a follow-up period of at least two years. Individuals with normal baseline ALT had significant increases in ALT at 12, 18, 24, and 30 months, while those with elevations in ALT >4 times the upper limit of normal at initiation of HAART showed significant decreases in ALT at 12, 18, 24, 30, and 36 months. Participants with immune recovery—defined as an increase in CD4 cell count of ≤ 200 – $\geq 400/\text{mm}^3$ —had significant increases in ALT 6 months after initiation of therapy, but levels decreased for the 36 months of follow-up (Torre 2001).

Table 6. Duration of HAART, CD4 Cell Increases, and Changes in ALT

Months on HAART	# w/immune recovery*	Increase in DC4	Change in ALT
6	8	467.7 ± 288.1	+65.0 ± 51.3
12	12	450.0 ± 125.2	-21.0 ± 84.1
18	25	449.1 ± 154.7	-22.0 ± 76.6
24	25	493.4 ± 153.8	-31.8 ± 62.9
30	16	549.2 ± 203.5	-15.6 ± 59.0
36	6	537.8 ± 65.8	-57.7 ± 84.4

Torre 2001

HCV Genotype and Hepatotoxicity

Hepatitis C genotype may contribute to the risk for hepatotoxicity. Núñez and colleagues evaluated 70 coinfecting individuals initiating HAART. They discovered that those with HCV genotype 3 were at greater risk for developing any grade of liver enzyme elevation than individuals with genotypes 1, 2, or 4. Severe liver enzyme elevations (defined as either ≥ 5 times above the upper limit of normal, or, when baseline ALT and AST levels were abnormal, elevations ≥ 3.5 -fold above baseline) were more frequent among individuals with HCV genotype 3 (OR, 4.4; 95% CI, 1.2–16.1; $P=0.02$). The incidence of severe liver enzyme elevations by genotype was as follows: genotype 1, 13% (5/39); genotype 2, 0% (0/3); genotype 3, 33% (7/21); and genotype 4, 0% (0/7). In a multivariate analysis, the only significant factors associated with the development of severe hepatotoxicity were heavy alcohol intake and HCV genotype 3 ($P=0.004$ for heavy alcohol use; $P=0.01$ for HCV-3) (M. Núñez 2002). Another study, however, did not find a relationship between transaminase elevations and HCV genotype (Gavazzi 2000).

Metabolic Complications: HCV and HAART

Careful selection of antiretroviral regimens for coinfecting persons is warranted, as risk for developing HAART-related metabolic complications (lipoatrophy, fat redistribution, pre-diabetic conditions such as insulin resistance, glucose intolerance, and hyperglycemia, as well as diabetes itself) appears to increase with HCV coinfection (Crane 2004; Duong 2001; Mehta 2003b; Patroni 2002; Rodriguez-Guardado 2003; Torti 2002; Zylberberg 2000). Conversely, coinfection with HCV may decrease total serum cholesterol, low-density lipoprotein cholesterol (LDL), and triglycerides.

Lipoatrophy and Fat Redistribution

Lipoatrophy may occur more frequently in coinfecting individuals. Zylberberg and colleagues examined a cohort of 226 HIV-positive individuals (46 coinfecting) for lipodystrophy, which they classified as pure lipoatrophy, pure truncal adiposity, and a mixed syndrome. Although prevalence of lipodystrophy did not differ by HCV status, pure lipoatrophy was significantly more prevalent among coinfecting individuals (46.2% vs. 27.6% of those with HIV alone; $P<0.03$) (Zylberberg 2000). Duong and colleagues also found an association between hepatitis C, fat redistribution, and other metabolic abnormalities. They analyzed data from 226 individuals; 121 had HCV

monoinfection, and 105 were HIV-positive, using antiretroviral therapy. Of the 105, 29 were coinfecting. Although the coinfecting participants had a greater duration of HIV infection, there was no significant difference in duration of antiretroviral therapy between groups. Pure lipodystrophy was significantly more common among coinfecting persons than in those with HIV alone (41% (12/29) vs. 14% (11/76); $P=0.006$) (Duong 2001).

Rodriguez-Guardado and colleagues retrospectively analyzed the development of lipodystrophy among 88 persons receiving antiretroviral therapy, 51 coinfecting. In this study, lipodystrophy was classified as facial and/or limb lipodystrophy, with or without increased fat in the abdomen. Baseline characteristics—CD4 cell count, HIV RNA, sex, and age—did not differ significantly between groups, nor did use of specific nucleoside analog reverse transcriptase inhibitors. Lipodystrophy was more common among coinfecting persons than in those with HIV alone (45% (23/51) vs. 30% (11/37); $P=0.0031$) (Rodriguez-Guardado 2003).

Although these results are preliminary, they merit further investigation in larger studies.

Insulin Resistance, Glucose Elevations, and Diabetes

HCV itself has been associated with diabetes; individuals with HCV monoinfection are 11 times more likely to develop diabetes than those who do not have HCV (Mehta 2003a). Diabetes is more prevalent among coinfecting people than in those with HIV alone. Butt and colleagues assessed the prevalence of actual diabetes among a cohort of 41,262 HIV-positive male veterans, 17.9% (7,386) HCV-coinfecting. Diabetes was significantly more prevalent in coinfecting persons (19.7% vs. 13.7% in those with HIV alone; $P<0.001$) (Butt 2003). Crane and colleagues retrospectively studied new cases of diabetes among 699 HIV-positive patients of an urban clinic; from 1996 to 2003, 40 of those individuals developed diabetes. New-onset diabetes developed significantly more often in coinfecting people than in those with HIV alone (43% vs. 23%; $P<0.01$), and coinfection increased the odds for developing diabetes 2.1-fold (95% CI, 1.1–4.2) (Crane 2004).

HCV coinfection and use of protease inhibitors have been associated with an increased risk for hyperglycemia (elevated glucose levels in the blood; a sign of diabetes). In a retrospective analysis of data from 1,230 individuals who initiated HAART between 1996 and 2002, hyperglycemia was more prevalent among coinfecting individuals (5.9% vs. 3.3%; $P=0.03$) than in those with HIV alone. New-onset hyperglycemia also occurred more frequently among coinfecting persons (5.8% vs. 2.8%; $P=0.01$) than in those with HIV alone. Both HCV coinfection and use of a protease inhibitor were independent risk factors for developing hyperglycemia (adjusted relative hazard (ARH), 5.02; 95% CI, 1.39–18.16 for protease inhibitor therapy and ARH 2.28; 95% CI, 1.23–4.22 for coinfection). Coinfecting individuals who received a protease inhibitor had the greatest incidence of hyperglycemia (5.6 cases per 100 person-years) (Mehta 2003b).

HAART increases the risk for diabetes and it has been implicated in the development of two conditions that are precursors to diabetes: insulin resistance and glucose intolerance (Dube 2000; Hardy 2001; Metha 2000). HCV coinfection appears to contribute to the risk. Duong and colleagues identified a relationship between insulin resistance, antiretroviral therapy, and HCV in a study of 226. Of the 226, 105 were taking HAART and 29 were coinfecting; 121 had HCV alone. Insulin resistance was significantly higher in individuals with HCV, both mono- and coinfecting

(0.21 ± 0.34 for HCV mono-infection; 0.25 ± 0.28 for coinfection) than in those HIV alone (0.04 ± 37 ; $P=0.01$ and $P=0.03$, respectively). HCV coinfection—in the context of antiretroviral therapy—was linked significantly with the development of insulin resistance (OR, 8.9; 95% CI, 2.61–110.29; $P=0.003$).

Cholesterol and Triglycerides

HCV coinfection appears to exert an inhibitory effect on total serum cholesterol, low-density lipoprotein cholesterol (LDL), and triglycerides. This may occur because of hepatic metabolic dysfunction. A number of other factors may contribute as well, including diet, heredity, age, sex, race, and antiretroviral regimen. The hepatitis C virus itself may have an effect on cholesterol levels. A part of hepatitis C's envelope, called E2, binds with serum lipoproteins. Low-density lipoproteins carry cholesterol from the liver into the tissues via the bloodstream, and high-density lipoproteins (HDL) recycle cholesterol from the tissues to the liver via the bloodstream. When hepatitis C virions bind with lipoproteins, the uptake of LDL may increase, thereby lowering serum cholesterol levels (Wünschmann 2002).

Torti and colleagues retrospectively analyzed changes in cholesterol and triglyceride levels after initiation of HAART in a cohort of 205 HIV-positive individuals, 112 HCV-antibody positive. Median follow-up was 21.4 months. By multivariate analysis, the presence of antibodies to HCV was negatively associated with cholesterol ($P<0.0001$) (Torti 2002). Another retrospective study of elevations in cholesterol among 282 individuals on their first HAART regimen reported that the presence of antibodies to HCV was significantly associated with smaller increases in cholesterol ($P<0.001$), regardless of antiretroviral regimen (Patroni 2002). These findings are supported by data from the Veterans Aging Cohort 3 Site Study (VACS 3), which found an independent association with lower levels of both LDL and HDL cholesterol and HCV coinfection among HIV-positive individuals receiving antiretroviral therapy ($P<0.001$) (Stapleton 2002).

Recommendations

Develop guidelines for the care and treatment of HIV/HCV-coinfected individuals.

Despite the resources available to physicians who care for coinfecting individuals in the United States, no one has yet integrated the recommendations from the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents (DHHS 2003), the National Institutes of Health's 2002 Consensus Statement on the Management of Hepatitis C (NIH 2002) and the Practice Guidelines for Diagnosis, Management and Treatment of Hepatitis C (Strader 2004) into specific recommendations for care and treatment of persons with HIV/HCV coinfection. Care and treatment for HIV/HCV coinfection is not always consistent or well coordinated; some infectious disease doctors providing care for both HIV and HCV may be more focused on HIV disease. Referral to a gastroenterologist is not always feasible. When referral is possible, the gastroenterologist may not be well informed about the clinical management of HIV. Adapting, integrating, and updating existing recommendations under the aegis of the DHHS Guidelines Panel could address these concerns. Coinfection-specific care and treatment guidelines would provide an essential resource for coinfecting individuals and their clinicians, as well as for treatment educators and advocates.

Investigate treatment strategies for HIV/HCV coinfection.

It is still unclear when antiretroviral therapy should be initiated in coinfecting individuals. Some studies have found a blunted immune response to HAART in coinfecting individuals (Greub 2000; Torriani 2001). Earlier initiation of HAART may help to preserve immune function and delay HCV disease progression, as end-stage liver disease (ESLD) occurs more frequently in individuals with low CD4 cell counts (Goedert 2002; Ragni 2001). Thus, for coinfecting individuals, it is now critical to investigate whether earlier initiation of HAART—possibly at higher CD4 cell counts than today's recommended threshold of 200–350 CD4 cells/mm³—will decrease the progression rate and incidence of ESLD among coinfecting individuals. Alternatively, since it may be possible to eradicate HCV in people who experience a sustained virological response (SVR) to therapy, early initiation of HCV treatment in HIV-positive individuals should also be explored. Preemptive treatment of HCV, even if an SVR is not achieved, may improve tolerability of antiretroviral agents; this requires Congress and NIH to allocate sufficient resources to carry out long-term treatment strategy studies.

Establish a universal definition for hepatotoxicity and characterize its severity.

Coinfecting individuals often have elevated liver enzyme levels, which may be due to both liver disease and hepatotoxicity of anti-HIV medications (Staples 1999). A universal definition of hepatotoxicity for research and clinical practice is needed to increase the consistency and interpretability of results from clinical trials, to guide antiretroviral treatment decisions, and to enable the collection of consistent adverse event data.

Hepatitis C coinfection significantly increases the risk of hepatotoxicity from HAART (Lana 2001). In some cases, individuals must discontinue HAART altogether because of liver toxicity; in other instances, only a particular drug must be switched. Hepatotoxicity has multiple causes, such as

underlying liver diseases unrelated to HCV, fatty liver, alcohol consumption, genetic variation, antiretrovirals, and other medications.

We need to be able to differentiate between transient elevations in liver enzymes and clinically significant indicators of progressive liver damage. Studies must include liver biopsy, so that the relationship between liver histology and hepatotoxicity may be more fully characterized. NIH and industry must support hepatotoxicity research.

Explore pharmacokinetics and drug levels in coinfecting individuals.

Up to 90% of HIV-positive individuals receive at least one hepatotoxic drug (Orenstein 2002). The potential for drug interactions in HIV-positive individuals is abundant even without hepatitis C coinfection; often, people take hormonal contraceptives, lipid-lowering agents, methadone or buprenorphine, anti-anxiety medications, prophylaxis against opportunistic infections, vitamins, herbs, supplements, and antiretrovirals.

The liver metabolizes several important antiretrovirals; HCV-related liver damage may compromise the liver's ability to metabolize these drugs. HIV drug levels may be elevated in individuals with liver disease, increasing side effects, interactions, and toxicities. Alternatively, levels can also decrease, allowing loss of viral suppression. The incidence and severity of complications from antiretroviral therapy among coinfecting individuals needs further investigation and documentation. The contribution of a specific class or agent to interactions, side effects, and complications also needs further exploration. Drug interactions between antiretrovirals and drugs used for opiate addiction treatment must be characterized. The FDA must mandate pharmacokinetic evaluation of antiretroviral agents in coinfecting persons and individuals with hepatic impairment prior to approval.

List of Terms Used in This Chapter

Area under the curve (AUC): a measurement of the total amount of a drug in blood, defined by graphing the change in drug levels over a 24-hour period, then calculating the area under the curve.

BID: twice daily.

Cristae: distinctly structured folds projecting from the inner membrane into the matrix of mitochondria in liver cells.

Crystalline inclusions: an accumulation of crystals inside of a cell.

CYP3A4: one of six isoenzymes responsible for 90% of the oxidative metabolism of drugs in human beings. CYP designates the root, 3, the family, A, the subfamily and 4 designates the gene.

Cytochrome p450 (CYP): the CYP isoenzymes are involved with the metabolism of drugs and other substances. These are located mainly in liver cells where most CYP metabolism occurs, although some are present in the small intestine, kidney, lungs and brain.

Glycogen inclusions: an accumulation of glycogen in the liver.

Hepatic Steatosis: degeneration of liver tissue marked by accumulation of fat globules.

Hepatomegaly: swollen liver.

Hyperlactatemia: mild to serious elevations in serum lactate levels.

Hyperplasia: abnormal increase of cell growth in tissue and/or organs.

Lactic acidosis: a rare but life-threatening sequelae of mitochondrial toxicity, lactic acidosis occurs when lactate acid levels accumulate in the bloodstream.

Lipoatrophy: loss of fat under the skin.

Lipodystrophy: abnormal metabolism of fat, resulting in loss or accumulation of fat under the skin.

Matrix: the area between the inner and outer membrane of mitochondria in liver cells.

Polymorphism: occurring in many different forms.

Pro-drug: an inactive precursor to a pharmacologically active metabolite.

Q8H: every eight hours.

Q12H: every twelve hours.

QD: once daily.

SQ: subcutaneous; an injection under the skin.

TID: three times daily.

Truncal adiposity: fat in the main part of the body.