III. The Natural History of HIV/HCV Coinfection

Summary

In the United States, an estimated 16–25% of HIV-positive individuals are coinfected with HCV (Sherman 2002a; Tedali 2003b; Thomas 2002); as many as 90% of the people who acquired HIV through injection drug use are coinfected with HCV. In 1999, hepatitis C was classified as an opportunistic infection of HIV disease.

Before the use of effective prophylactic drugs and the advent of highly active antiretroviral therapy (HAART), many coinfected people died from other opportunistic infections before serious hepatitis-C-related liver damage developed. Now that AIDS-related mortality has decreased dramatically, end-stage liver disease (ESLD) has become a leading cause of death for HIV-infected individuals (Bica 2001; Martín-Carbonero 2001; Monga 2001; Quintana 2002; Rosenthal 2003).

Cohort studies of coinfected hemophiliacs and injection drug users have reported that coinfection with HIV accelerates HCV disease progression (Eyster 1993; Rockstroh 1996; Sánchez-Quijano 1995; Telfer 1994). Coinfected persons with advanced HIV disease (CD4 cell counts <200/mL) are at greater risk of developing cirrhosis (Allory 2000; Goedert 2002; Lesens 1999; Ragni 2001).

While it is clear that HIV infection accelerates HCV disease progression, the effect of HCV on HIV disease progression is controversial. A majority of pre-HAART-era studies did not find any differences according to HCV serostatus in HIV progression or survival (Dorrucci 1995; Macías 1998; Wright 1994). In the HAART era, however, there are new questions; conflicting data about the efficacy of HAART in coinfected individuals have emerged. Some studies have reported that immune responses to HAART are blunted in coinfected people, but the effect of HCV coinfection on the immunological response to HAART remains controversial, as this finding has not been consistent across studies (Chung 2002a; Greub 2000; Rockstroh 2004; Sulkowski 2002; Torriani 2001; Zala 2004).

Although HAART increases survival of HIV-positive people, coinfection with HCV increases the risk of liver-related death (Backus 2004; Fultz 2003a; Rimland 2004; Rockstroh 2004). Coinfected people and their medical providers are left with questions and uncertainties. If HIV disease is controlled with HAART, will hepatitis C be less aggressive as well? Will coinfected individuals fully reap the benefits of HAART? Is there a tipping point when the amount of damage to the immune system will result in acceleration of HCV disease? Information from randomized clinical trials will help inform treatment decisions about which disease to treat first and when to start treatment. In the meantime, balancing the immunological benefit of HAART with its potential hepatotoxicity is a huge concern.

HCV and Immunosuppression

Indirect evidence that HIV may influence HCV disease progression through immune suppression can be found in studies of HCV in immunocompromised people, such as people with congenital immune deficiencies and individuals taking immunosuppressive drugs following transplants. In people with immune deficiencies unrelated to HIV infection, accelerated HCV disease progression

has been observed (Bjorkander 1988; Collier 1997). One study followed a cohort with primary hypogammaglobulinemia who were infected from contaminated intravenous immune globulin treatments between 1982 and 1986. Fifteen of 17 persons were biopsied within 10 years of infection. All 15 had abnormal liver histology; 6 had cirrhosis (Bjoro 1994).

End-stage liver disease from hepatitis C is the leading indication for liver transplantation in the United States (Charlton 1998; Shuhart 1997). Hepatitis C infection almost always returns after transplantation. In the setting of post-transplant immunosuppression, hepatitis C can become more aggressive and have a more rapid course, although disease severity varies among recipients. In one study of transplant recipients, moderate-to-severe hepatitis or cirrhosis was identified in 25% of transplant recipients during a median follow-up period of 25 months (Zhou 1996). Gane and colleagues looked at 130 persons who survived for at least 30 months after transplantation. In this group, 10 (8%) developed cirrhosis during a median follow-up interval of 51 months (range: 24–138 months), and 35 (27%) developed moderate chronic hepatitis over 35 months of follow-up (range: 6–127 months). Seventy individuals (54%) developed mild chronic hepatitis after a median interval of 35 months (range: 6–103 months), and 15 individuals had no evidence of chronic hepatitis after a median follow-up period of 20 months (range: 6–103 months) (Gane 1996).

Acute HCV in HIV-Positive Individuals

HIV-positive people are less likely to achieve spontaneous viral clearance of HCV infection (Augenbraun 2003; Bhagani 2003; Danta 2003; Mehta 2002; Thomas 2000a). Mehta and colleagues evaluated the incidence of spontaneous viral clearance of HCV among 98 injection drug users with previous, resolved HCV infection (three HIV-positive) and 164 with no evidence of HCV exposure (three HIV-positive). They reported that individuals with a previous, resolved HCV infection were 12 times less likely to develop chronic hepatitis C after a new HCV infection than those with no previous exposure to HCV, although none of the three HIV-positive participants who became infected with HCV achieved spontaneous viral clearance despite having a prior, resolved infection (Mehta 2002).

Thomas and colleagues also found an increased likelihood of HCV chronicity among a group of HIV-positive injection drug users; the odds of chronicity increased with lower CD4 cell counts. For those with more than 500 CD4 cells, the odds ratio was 0.64 (95% CI, 0.26–1.36). In individuals with CD4 cell counts between 200 and 499, the odds ratio was 0.64 (95% CI, 0.36–1.14) and for those with less than 200 CD4 cells, the odds ratio was 0.31 (95% CI, 0.13–0.73). The adjusted odds ratio for spontaneous viral clearance of HCV among HIV-negative persons was 2.19 (95% CI, 1.26–3.47) (Thomas 2000a).

HIV-positive women and individuals with higher CD4 cell counts may be less likely to develop chronic HCV infection. Augenbraun and colleagues studied the incidence of HCV infection among members of the Women's Interagency HIV Study (WIHS) by testing samples from 2,628 women, 2,059 HIV-positive. Overall incidence of new HCV infections was low; it was slightly higher among HIV-negative women (3.3 cases per 1,000 person-years vs. 2.7 cases per 1,000 person-years for HIV-positive women). All participants were screened for anti-HCV at enrollment; subsequent samples were stored. The last available sample from women with no evidence of HCV was tested

for anti-HCV; if anti-HCV was detected, samples stored between the enrollment visit and the last visit were tested for anti-HCV. Samples from women who developed anti-HCV were tested for HCV RNA. Fourteen new HCV infections were identified; ten in HIV-positive women. While five women—two HIV-positive—achieved spontaneous viral clearance, chronic HCV developed in nine women, eight of them HIV-positive (Augenbraun 2003).

Danta and colleagues identified 23 cases of acute HCV infection in a cohort of HIV-positive men who have sex with men (MSM). The mean CD4 cell count at the time of HCV diagnosis was 600/μL. Spontaneous viral clearance occurred in 17% (4/23). The mean CD4 cell count at diagnosis was significantly higher among those who achieved spontaneous viral clearance (801 vs. 556; P<0.05) (Danta 2003).

Hemophiliacs with HIV/HCV Coinfection

HIV/HCV coinfection is a significant problem among hemophiliacs who were treated with clotting factors prior to the institution of viral inactivation techniques; an estimated 70% to 90% became infected with HCV, and 60% to 95% of the hemophiliacs who received clotting factor before 1985 were infected with HIV (Eyster 1993; Eyster 1994; Ragni 1993). Cohort studies of coinfected hemophiliacs have been a rich source of natural history data, as dates of infection can usually be estimated from records of when clotting factors were received, and several cohorts were followed for over 15 years.

There are some limitations to the information from cohorts of coinfected hemophiliacs. Since the majority of hemophiliacs are white males, the influence of race and sex on HCV disease progression cannot be determined from these studies. The course of disease in hemophiliacs infected with HCV and HIV may differ from that in people who acquired these infections through other routes, due to possible differences in the volume of inoculum and the potential for repeated infections. A majority of hemophiliacs were infected with HCV before they contracted HIV, so it is not possible to analyze potential differences in the natural history of coinfection according to the sequence of acquiring each infection (Eyster 1993; Ragni 2001). Due to the risk of bleeding from liver biopsy on hemophiliacs, assessment of HCV-related liver disease progression in hemophiliac cohorts has relied on biochemical testing and clinical features; information about liver histology is usually unavailable. Additionally, information about alcohol consumption was not consistently collected across studies. Despite these limitations, these studies have produced evidence of accelerated HCV disease progression among coinfected hemophiliacs.

Eyster and colleagues followed a cohort of hemophiliacs from 1973 until 1992. They found a higher incidence of liver failure among hemophiliacs who were coinfected; 8.8% (8/91) developed liver failure vs. none of the 58 hemophiliacs with HCV alone. In another cohort of 181 HCV-infected hemophiliacs (40% coinfected with HIV), hepatic decompensation occurred in 11 individuals; 10 of the 11 were HIV-coinfected. HIV-coinfected individuals were 21 times more likely to develop hepatic decompensation than those with HCV alone, and the median time from first exposure to clotting factor to hepatic decompensation was 16.5 years (range: 7.7–22.9 years) (Telfer 1994).

A low CD4 cell count appears to be an independent risk factor for HCV disease progression in

coinfected individuals. Goedert and colleagues followed 1,816 HCV-infected hemophiliacs, 1,192 (65.6%) of whom were coinfected with HIV. The estimated 16-year cumulative incidence of ESLD in coinfected individuals was 14.0% (95% CI, 11.6–16.4%). vs. 2.6% in those with HCV alone (95% CI, 1.0–4.3%). Coinfection with HIV increased the risk of developing ESLD by eight-fold (relative hazard 7.9; 95% CI, 4.2–15.2). The risk of developing ESLD among coinfected individuals with CD4 cell counts under 200 was doubled (relative hazard 2.1; 95% CI, 1.3–3.3). Ragni and colleagues found that ESLD in coinfected hemophiliacs occurred only at very low CD4 cell counts. A group of 157 HCV-infected hemophiliacs, 85 of whom were coinfected, was followed from 1978 until 1999. By 1999, ESLD was the second leading cause of death in coinfected individuals; 16% of coinfected individuals progressed to ESLD after a mean 18 years' (estimated) duration of HCV infection. No ESLD was reported among coinfected hemophiliacs with CD4 cell counts >150/mL.

Injection Drug Users with HIV/HCV Coinfection

Cohort studies of people who acquired HCV infection from injection drug use have provided important information about coinfection, although cofactors including HCV re-infection, regular use of street drugs, and nonsterile injection practices may also contribute to hepatitis C disease progression.

This research, too, has reported more rapid progression to cirrhosis among coinfected individuals than among those with HCV alone. In a study of 547 individuals who acquired hepatitis C from injection drug use (116 of whom were coinfected with HIV), Soto and colleagues observed stark differences in HCV disease progression by HIV status. Ten years after acquiring HCV, 14.9% (13/87) of coinfected individuals developed cirrhosis versus 2.6% (7/272) of those with HCV alone. The mean interval from HCV infection to cirrhosis was 23.2 years among individuals with HCV alone vs. 6.9 years in coinfected individuals (P<0.001) (Soto 1997).

Based on data from a pre-HAART-era, long-term retrospective cohort study of 160 HCV-infected IDUs (80 of whom were HIV-coinfected), Di Martino and colleagues developed a model that projected a higher risk of cirrhosis among coinfected individuals. Over 12 to 180 months, a higher prevalence of cirrhosis among coinfected people was recorded: 17.5% were cirrhotic vs. 7.5% of those with HCV alone. Alcohol consumption of more than 80 grams per day was associated with an eleven-fold increase in the risk of mortality from cirrhosis among coinfected individuals. Based on these findings, they calculated a significantly higher actuarial rate of cirrhosis in coinfected persons. The projected risk of cirrhosis among coinfected individuals at 10 years after HCV infection was 7% as compared to 3% in those with HCV alone; at 20 years, the risk increased to 37% among coinfected individuals as compared with 10% among those with HCV monoinfection. The cirrhosis risk at 25 years jumped to 69% for coinfected individuals, but remained stable at 10% in those with HCV alone. As in the hemophiliac cohorts, the risk of cirrhosis increased in coinfected individuals with CD4 cell counts below 200 (Di Martino 2001).

Although exact rates and outcomes vary, these studies present a consistent picture of accelerated hepatitis C disease progression in HIV-positive individuals. The variations may be attributable in part to high rates of HIV-related mortality before HAART, when HIV-related deaths preceded cirrhosis and ESLD in these cohorts. For example, Goedert and colleagues reported that in up

to 16 years of follow-up of 1,167 coinfected hemophiliacs, AIDS-related deaths reached a cumulative incidence of 45% (95% CI, 6–48.3%), compared to an estimated 16-year cumulative incidence of ESLD in coinfected individuals of 14.0% (95% CI, 11.6–16.4%).

Survival of Coinfected Injection Drug Users in the HAART Era

Injection drug use has been associated with an increased risk of death for coinfected people in the HAART era. Voirin and colleagues analyzed data from a cohort of 2,710 HIV-positive individuals, 469 coinfected, in Lyon, France. They evaluated the effects of HAART, HCV coinfection and injection drug use on survival in the pre-HAART (prior to 1996; N=1,240) and the post-HAART era (1996–2002; N=1,470). After HAART became available, three-year and five-year mortality rates decreased among all groups (HIV only, HIV/HCV and HIV/HCV plus injection drug use). After controlling for age and baseline CD4 cell count, the risk of death after 1996 HAART era was not substantially different for HIV/HCV coinfection (HR, 0.76; 95% CI, 0.28–2.08; P=0.59) than for HIV alone. The risk of death was substantially higher for HIV/HCV coinfection plus injection drug use (HR, 2.92; 95% CI, 1.63–5.23; P<0.001) (Voirin 2003).

Rapidly Progressive HCV in HIV-Positive Individuals: Pre-HAART

Most data on disease progression in coinfected persons come from research on individuals believed to have acquired HCV before becoming infected with HIV. A small body of data from the pre-HAART era provides information about rapidly progressive HCV acquired subsequent to, or at the same time as, HIV infection. These reports suggest rare scenarios in which underlying HIV infection can dramatically accelerate the course of HCV disease.

Martin and colleagues reported three cases of post-transfusion non-A, non-B hepatitis infections among HIV-positive men who were at least 60 years of age; all three developed cirrhosis within three years of the onset of hepatitis (P. Martin 1989). In another case, a 48-year-old health care worker acquired HIV and HCV from a needlestick accident in July 1990. At the time, additional exposure to blood occurred from a spill; blood from the collection tube seeped under the cuffs of the health care worker's gloves and onto chapped skin with open cracks, increasing the total amount of blood that the health care worker was exposed to. The source patient was HIV-positive and had a history of injection drug use, but had not been tested for hepatitis C. The health care worker developed antibodies to HIV between 8 and 9 months after this exposure. HCV seroconversion occurred between 9 and 13 months after the exposure. Less than three years after the needlestick, the health care worker died as a result of complications from hepatic failure. Testing of stored samples from the source patient and the health care worker provided phylogenetic evidence of transmission. The causes of such lengthy incubation periods (her HIV seroconversion at 9 months was one of the longest ever recorded, and her HCV seroconversion also occurred after an unusually long interval after the exposure) and such rapid disease progression remain unclear, but the authors suggest that the simultaneous acquisition and potential interaction between the two viruses might be involved (Ridzon 1997).

Did HCV Worsen HIV in the Pre-HAART Era?

Pre-HAART-era studies generally found no differences in HIV progression or survival between coinfected individuals and those with HIV alone. These studies have certain limitations; for instance, follow-up generally lasted only a few years, and detailed information about trends in CD4 cell counts and viral load was not available. On the whole, however, the data from these studies suggest that HCV infection does not dramatically alter the course of HIV disease over short periods of time (Dorrucci 1995; Macías 1998; Wright 1994). For example, a longitudinal study of 416 HIV-positive individuals (with known dates of seroconversion) compared the rate of clinical and immunologic progression of HIV disease between coinfected individuals (214/416) and those with HIV alone (202/416). During a follow-up period of 30 months, no statistically significant differences were observed between the two groups; endpoints were progression to AIDS and reaching a CD4 cell count below 100 (Dorrucci 1995).

Piroth and colleagues did not find an association between HCV coinfection and HIV clinical progression in a study of 238 HIV-infected individuals, half of whom were coinfected with HCV. Accelerated CD4 cell count decline was observed among a subset of the 27 coinfected persons with CD4 cell counts above 600 (P=0.05), but no difference in CD4 cell count changes or clinical progression was noted for individuals with lower CD4 cell counts (Piroth 1998). While hepatitis C itself may not significantly worsen the course of HIV disease, HCV-related liver disease might be a prognostic factor for accelerated HIV disease progression. A study by Lesens and colleagues evaluating a cohort of 147 HCV-infected hemophiliacs, 81of whom were coinfected with HIV, reported a more rapid progression to AIDS in coinfected individuals who developed liver disease (P<0.03) (Lesens 1999).

Prognostic Factors Among Coinfected Individuals

Benhamou and colleagues matched 122 coinfected individuals to 122 individuals with HCV alone and analyzed prognostic factors known to be involved in fibrosis progression. HIV status, presence of severe immunosuppression (defined as a CD4 cell count under 200), gender, age at infection with HCV (over or under 25), and alcohol consumption (>50 or ≤ 50 grams/day) were considered in a multivariate analysis of fibrosis progression. The median CD4 cell count in coinfected persons was 305/μL. Seventy-four of 122 coinfected persons were receiving antiretroviral therapy, although treatment regimens and durations varied widely. Among the coinfected participants, alcohol consumption over 50 grams/day, a CD4 count ≤ 200/μL, and age at HCV infection >25 were independently associated with an accelerated fibrosis progression rate. Notably, HIV status was not associated with fibrosis progression in this analysis after controlling for CD4 cell count (Benhamou 1999).

To determine the rate of fibrosis progression, Benhamou and colleagues then examined 24 paired liver biopsies from 12 coinfected individuals. The observed progression rate was the difference in METAVIR score (see Cahpter IV, Diagnostics) between the two biopsies divided by the amount of time that had elapsed (in years) between them. To estimate the rate of fibrosis progression using results from only one liver biopsy, a model from Poynard and colleagues was used. In this model, the estimated rate of fibrosis progression per year was calculated as the ratio between the fibrosis stage at the time of biopsy (using the METAVIR system) and the estimated duration of infection in

years (Poynard 1997). (The model from Poynard and colleagues is based on cross-sectional data, estimated duration of infection, and an assumption of linear fibrosis progression, which may affect the accuracy of these estimates.) To validate their estimate of fibrosis progression, Benhamou and colleagues compared progression rates from the paired biopsies with estimated rates.

Overall, liver fibrosis progressed at a faster rate in coinfected individuals. Without HCV treatment, the median time to cirrhosis in HIV-coinfected individuals was 26 years vs. 34 years in those with HCV alone. The authors cited two examples: a coinfected individual with a CD4 cell count of ≤ 200/μL and alcohol intake of >50 grams/day would have a liver fibrosis progression rate of 0.250 fibrosis units per year (median expected time to cirrhosis of 16 years), while another coinfected individual with a high CD4 cell count and alcohol intake <50 grams/day would have a fibrosis progression rate of 0.111 fibrosis units per year (median expected time to cirrhosis of 36 years) (Benhamou 1999).

Figure 1. Median Expected Time to Cirrhosis According to CD4 Count and Alcohol Consumption
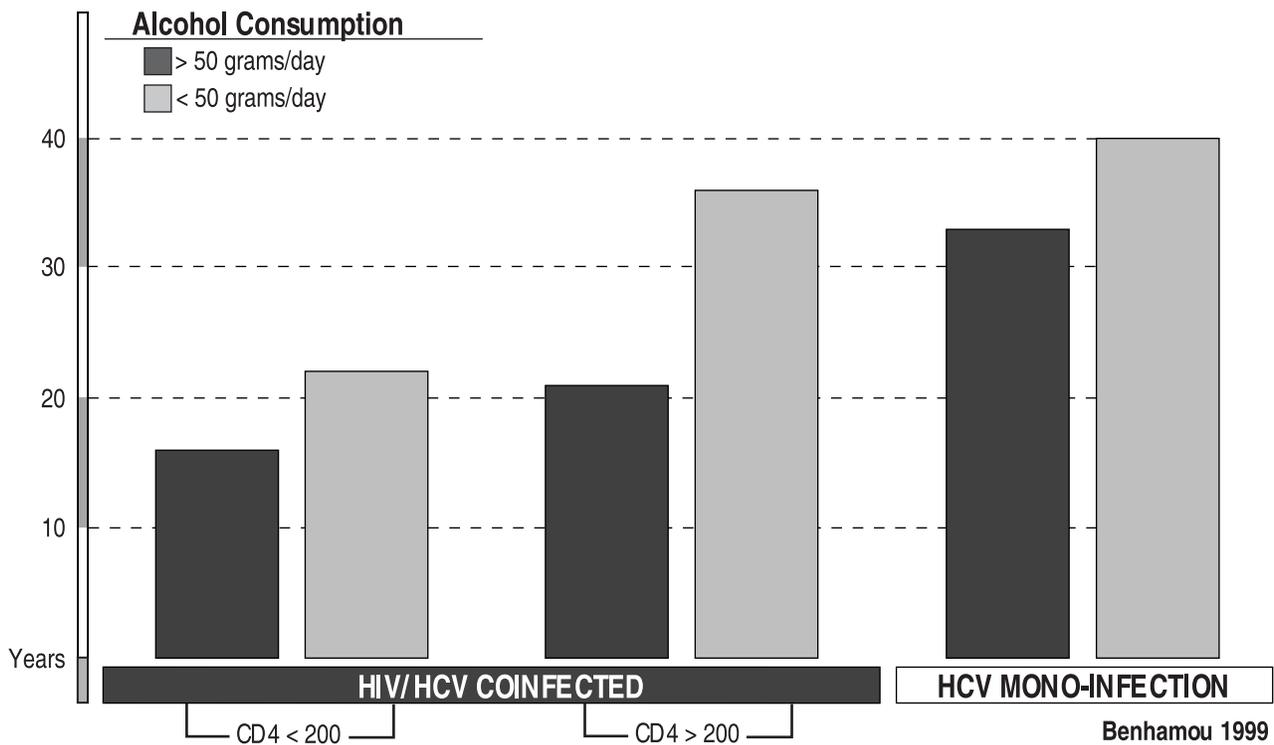
A direct look at biopsy samples from 492 coinfected individuals with an estimated median duration of infection of 14 years found more advanced liver damage than that seen in those with HCV monoinfection of similar estimated duration. Liver fibrosis was evaluated using the METAVIR system. No fibrosis (F0) was found in 13.2%, while 35% had a METAVIR score of F1, 19% had a METAVIR score of F2, 21% were scored as F3, and 12% as F4 (cirrhosis). The three strongest predictors of severe liver fibrosis (F3 or F4) were duration of HCV infection of over 15 years (OR, 3.6; 95% CI, 1.5–4.4), infection with HCV at over 20 years of age (OR, 3.3; 95% CI, 1.9–5.6), and a history of alcohol consumption of more than 80 grams/day (OR, 2.5; 95% CI, 1.5–4.4). No association of fibrosis with CD4 cell count, the HCV genotype or virus load, sex, or use of HAART was

observed, although 57% of participants had never received antiretrovirals (Martín-Carbonero 2003).

Martín-Carbonero and colleagues examined biopsy specimens from 914 coinfected individuals with elevated alanine aminotransferase (ALT, a liver enzyme; see Sidebar, Chapter IV, Diagnostics) levels. Overall, 57% had moderate-to-serious liver damage (METAVIR score of F2, F3 and F4), while only 10% had a METAVIR score of F0. They reported that predictors of severe liver fibrosis were age of >35 years (OR, 2.95; 95% CI, 2.08–4.18), consumption of >50 grams of alcohol/day (OR, 1.61; 95% CI, 1.1–2.35) and a CD4 cell count <500/mm^3 (OR, 1.43; 95% CI, 1.03– 1.98.) The median duration of HCV infection was 16 years; age at liver biopsy ranged from 33 to 41. Duration of HCV infection was not included in the multivariate analysis due to a strong correlation with age (Martín-Carbonero 2004).

Because data on duration of HIV infection and nadir CD4 cell counts were not included in this analysis, it is difficult to assess the influence of HIV disease on fibrosis progression. Severe liver fibrosis is more common among coinfected persons with advanced HIV disease; in this study, it was significantly more common among individuals using antiretroviral therapy than among the untreated (39% vs. 28%; P<0.05). The greater prevalence of severe liver disease among those on antiretroviral therapy could be due to advanced HIV disease requiring treatment, antiretroviral-induced hepatotoxicity, use of alcohol and drugs, or a combination of these and other factors.

Important questions persist in interpreting the increased HCV disease progression rates observed in coinfected individuals: does the presence of HIV itself accelerate HCV disease progression, or are higher rates of fibrosis progression associated primarily with immune deficiency? In a retrospective assessment of fibrosis progression in coinfected individuals, Puoti and colleagues found an association between CD4 cell counts <500/mm^3 and more severe fibrosis (OR, 3.2; 95% CI, 1.1–9.2). After controlling for CD4 cell depletion, HIV infection itself was not associated with severe fibrosis (Puoti 2001); however, in a case-controlled study of 116 HCV-infected individuals, 56 of whom were coinfected with HIV, Allory and colleagues found increased necroinflammatory activity in coinfected individuals, especially in those with high CD4 cell counts (>500/ml) (Allory 2000). This would support the theory that HIV infection itself, even prior to significant immune depletion, may accelerate the progression of liver fibrosis. The potential influence of HAART on these findings is not clear, as participants who were taking more than two antiretroviral drugs were excluded by Puoti and colleagues, and the use of HAART was not reported by Allory and colleagues.

Additional Screenings and Vaccinations

Vaccinations for hepatitis A and hepatitis B are recommended for coinfected individuals (Centers for Disease Control, *Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons, 2002*). HCV-infected individuals are at risk for fulminant hepatitis A, which can be life-threatening (Koff 2001; Pramoolsinsap 1999; Vento 1998; Vento 2000). Hepatitis B infection in combination with HIV and/or HCV has been associated with more aggressive liver disease, as well as with increases in morbidity and mortality (Cropley 2000; Liaw 2000; Ockenga 1997; Piliero 2002). Although vaccinations for hepatitis A and B are safe in HIV-positive individuals, their immuno-genicity is decreased among HIV-positive individuals, especially those with low CD4 cell counts (Bruguera 1992; Hess 1995; Neilson 1997; Puoti 2002). CDC estimates that 66–75% of HIV-positive individuals will experience protective antibody responses after vaccination for HAV.

The CDC estimate may be high. Weissman and colleagues assessed the immune response to HAV vaccination in 123 HIV-positive individuals. Most were receiving antiretroviral therapy at the time of vaccination (102/123). Only half of those vaccinated (61/123) had an antibody response (positive IgG titer). Responders had significantly higher CD4 cell counts at vaccination than non-responders (486/mm^3 vs. 358/mm^3; P=0.02), and were more likely to be female than male (40% vs. 13.5%; P=0.001). Those with a CD4 cell count of <200/mm^3 at vaccination were less likely to respond (14% vs. 35%; P=0.02). Although nadir CD4 cell count was slightly higher among vaccine responders, the difference was not significant (Weissman 2004).

The efficacy of HBV vaccination in HIV-positive individuals is unclear, Tedali and colleagues reported that response to HBV vaccination among 51 of 198 HIV-positive individuals who received ≥ 1 dose of HBV vaccine. More than 70% were receiving antiretroviral therapy at vaccination. Only 37.2% (19/51) were responders. Those who had a CD4 cell nadir of >200/ mm^3, undetectable HIV RNA and high CD4 cell counts at vaccination were more likely to respond. Most responders had a CD4 cell nadir of >200/ mm^3 (84.2 % vs. 46.9%; P=0.008) and undetectable HIV RNA at vaccination (63.2% vs. 33.3%; P=0.04).The median CD4 cell count at vaccination was higher among responders (584 vs. 384/mm^3), although the difference did not reach statistical significance. Although use of HAART was not significant, those with undetectable HIV RNA and higher CD4 cell counts were more likely to be receiving HAART (Tedali 2004).

Strategies for optimizing the immunogenicity of HBV vaccination in HIV-positive people are necessary. Additional boosters or higher dosing have been suggested as possible interventions (Centers for Disease Control and Prevention, Recommendations of the Advisory Committee on Immunization Practices (ACIP): *Use of Vaccines and Immune Globulins in Persons with Altered Immunocompetence; 1993*).

Coinfection at Birth or in Early Childhood

HAART has substantially increased the life expectancy for those infected with HIV at birth (de Martino 2000; Gortmaker 2001), and HCV acquired at birth or early in childhood usually progresses slowly (Casiraghi 2004; Guido 1998; Kage 1997). The effect of untreated HIV on HCV disease progression in adolescents who were HIV/HCV coinfected at birth or during early childhood is unknown.

Thuret and colleagues evaluated biopsy samples from seven coinfected adolescents, six of whom received antiretroviral therapy for 9–14 years. All had CD4 cell counts >200/mm^3; CD4 cell counts ranged from 275 to 1,100 cells/mm^3. Six of seven had detectable HIV RNA, ranging from 3,162 to 54,954 copies/mL . HCV RNA levels ranged from 316,227 to 794,328 copies/mL.

Overall, METAVIR fibrosis and inflammation scores (see Chapter IV, Diagnostics) reflected mild liver disease. The authors found that one feature—intralobular inflammation—which is common in coinfected adults, was more marked in these coinfected children and adolescents than their HCV monoinfected peers (Thuret 2003).

Table 1. Mode of, and Age at Acquisition, CD4 count at Biopsy, Liver Histology & Disease Activity in Seven Coinfected Adolescents

Mode of transmission & age at infection	Sex/age at biopsy	CD4 count at biopsy	Disease activity	Fibrosis
Transfusion at birth	M/17.5	512	Mild	Moderate
Transfusion at 4 weeks	M/16.5	377	Mild	Mild
Transfusion at birth	F/16.5	1078	Mild	Moderate
Mother-to-infant at birth	F/16	275	Mild	Mild
Mother-to-infant at birth	F/13	1061	Mild	Mild
Clotting factor; 4 years	M/17.5	470	Mild	Moderate
Clotting factor; 4 years	M/17.5	1100	Mild	Moderate

Thuret 2003

Coinfection in the Era of Highly Active Antiretroviral Therapy (HAART)

Data collected during the HAART era provide a description of the current impact of coinfection and antiretrovirals on HIV-related hospital admissions. The benefits of HAART have been reflected in a survey of 327,306 HIV-related hospitalizations in 1996, 1998, and 2000. While hospital admissions for opportunistic infections decreased significantly (from 41% to 29% of all HIV-related hospitalizations; $P<0.001$), admissions for liver-related complications rose significantly (from 13% to 18%; $P<0.001$) (Gebo 2003).

Data on the impact of HAART on survival of coinfected people are emerging. Fultz and colleagues analyzed data from 36,419 HIV-positive participants in the Veteran's Aging Cohort Study (VACs) and 35,708 HIV-negative participants. Almost 20% of HIV-positive participants were coinfected with HCV (7,138/36,419), while 9% (3,214/35,708) HIV-negative participants were infected with HCV. The risk of death from HIV disease before 1996 was greater than the risk of death from coinfection after 1996 (Fultz 2003a).

Table 2. The Risk of Death From HIV, HCV, and HIV/HCV Before and After 1996

Infections	Pre-1996	Post-1996
HIV	10.2	2.7
HCV	0.3	1.2
HIV/HCV	2.2	2.6

Fultz 2003a

Although HCV coinfection increases the risk of liver-related death in people with HIV, HAART has significantly decreased AIDS-related and liver-related deaths (Backus 2004; Rimland 2004; Rockstroh 2004; Qurishi 2003; Voirin 2003). Qurishi and colleagues looked at the effect of antiretroviral therapy on liver-related mortality in a group of 285 coinfected persons treated for

63

HIV between 1990 and 2002. A total of 25 people died from liver disease during the study period; two treated with HAART, five with nucleoside analog reverse transcriptase inhibitors only, and 18 were untreated. Antiretroviral therapy significantly decreased liver-related mortality (P=0.018), and use of HAART was a significant predictor of liver-related survival (P<0.005) (Qurishi 2003).

Figure 2. Effect of HIV Treatment on Liver-related Mortality Rates

Qurishi 2003
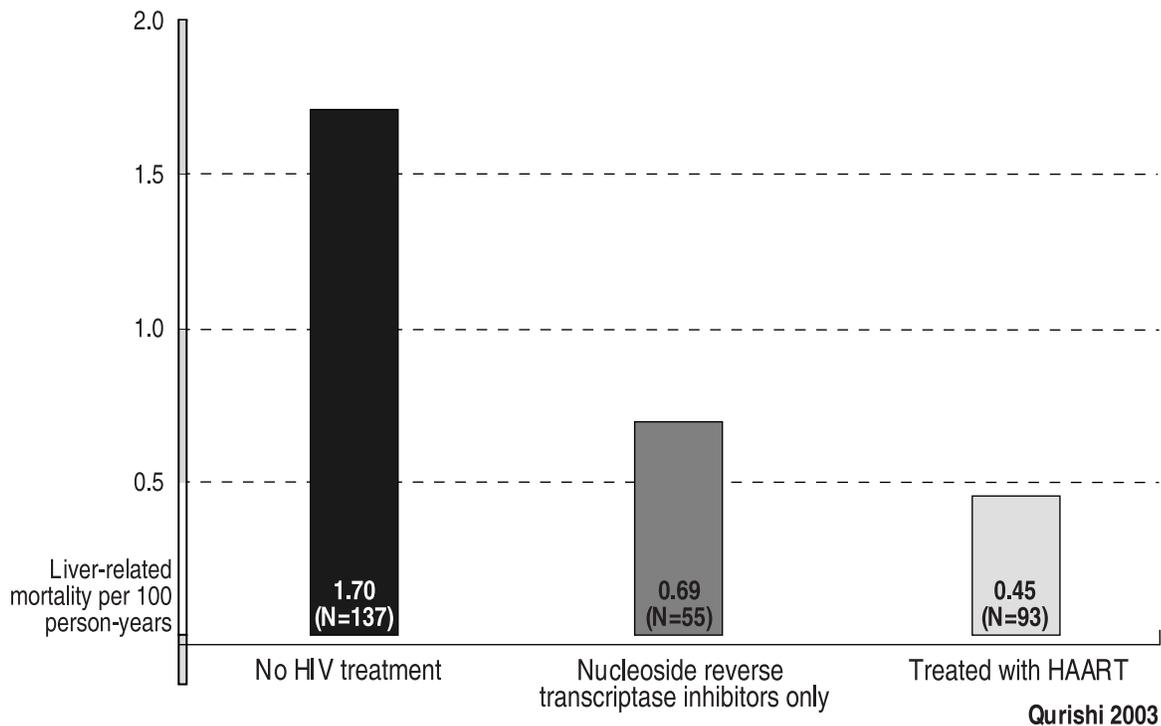
Rockstroh and colleagues evaluated data from 4,957 EuroSIDA cohort participants, 1,685 coinfected with HCV. HCV coinfection did not have a significant effect on progression to AIDS or on immunological or virological response to HAART. However, the risk of liver-related mortality was significantly greater among coinfected persons (IRR [incidence rate ratio] for liver-related mortality 3.18; 95% CI, 1.23–6.18; P<0.014) (Rockstroh 2004).

Backus and colleagues found that coinfection with hepatitis C did increase the risk of death in people with HIV, although the risk was far greater among those who were not taking HAART, regardless of HCV status. They evaluated Veteran's Administration (VA) National Immunology Case Registry (ICR) records from 12,216 HIV-positive individuals, 4,668 (37%) coinfected; all initiated HAART between January 1997 and February 2003. The mean length of follow-up was 3.5 years. Records included history of AIDS-defining conditions; use of antiretroviral therapy prior to HAART; CD4 cell count and HIV RNA within one year of initiation of HAART; measurement of exposure to HAART from prescription records; HCV treatment; and substance abuse and psychiatric diagnoses. Three sources were used to collect death data (Social Security Administration, VA beneficiary records and ICR).

Psychiatric diagnosis, alcohol abuse and drug use were significantly more common among those coinfected with HCV (P<0.001 for each). Coinfected people were more likely to have been

treated with nucleoside analog reverse transcriptase inhibitors (NRTIs) prior to initiation of HAART (48.8% vs. 38.8%; P<0.0001) and had a shorter duration of HAART (21.3 months vs. 24.9; P<0.0001).

Although HCV coinfection increased the risk of death (HR, 1.38; 95% CI, 1.26–1.51; P<0.0001), being off HAART was associated with a greater risk of death regardless of HCV status (HR, 3.91; 95% CI, 3.53–4.33; P<0.0001) (Backus 2004). This analysis controlled for variables including age; HIV RNA and CD4 at baseline; prior AIDS; pretreatment with NRTIs; HCV treatment; psychiatric diagnoses and use of alcohol and drugs; and HIV caseload of the facility.

Rimland and colleagues reported mortality data from The HIV Atlanta VA Cohort Study (HAVACS) a group of 2,506 HIV-positive individuals, 30–35% coinfected. Prospective data collected from 1981 until the end of 2003 were analyzed for rates and causes of death prior to and during the HAART era. In 1997, the mortality rate decreased from 26.1 per 100 to 6.7 per 100; it has remained stable since then. Death rates from AIDS and opportunistic infections decreased significantly (58.1% prior to 1996 vs. 38% after 1996; P=0.00002). Although deaths from HBV and HCV-related end-stage liver disease (ESLD) increased from 3.8% (27/707) to 6.7%(29/435) after 1996, the ESLD death rate per 100 patients did not change significantly (1.77 before 1996; 1.75 after 1996). In total, 19 deaths were attributed to HCV; four occurred before 1996 (Rimland 2004). Given the high prevalence of HCV coinfection in this cohort, the increase in ESLD-related deaths was not substantial.

Although antiretroviral therapy has significantly reduced AIDS-related mortality and liver-related mortality among coinfected persons, all 20 approved antiretroviral agents have been associated with severe and life-threatening events (DHHS 2004; Qurishi 2003). Reisler and colleagues estimated the incidence and predictors of non-AIDS defining grade 4 (serious or life threatening) events, AIDS events and death among a cohort of 2,947 individuals receiving antiretroviral therapy from December 1996 until the end of December 2001. A subset of 1,628 participants was tested for hepatitis B and C; 17.9% (291/1,628) were HCV coinfected. The risk of death after the first grade 4 event was similar to that of the first AIDS-defining event (5.68 and 6.95, respectively).

Serious and life-threatening liver events—liver enzyme elevations to >10 times the upper limit of normal (ULN); bilirubin elevations >5 times ULN, clinical or fulminant hepatitis, toxic hepatitis, fatty liver, cirrhosis, and hepatic encephalopathy—were the most common grade 4 events in this cohort. Any grade 4 liver event significantly increased the risk of death (HR, 3.49; 95% CI, 2.38–5.12; P=0.0001). HCV coinfection significantly increased the risk of developing a grade 4 liver event (HR, 2.74; 95% CI, 1.29–5.84; P=0.009) (Reisler 2003).

Impact of HAART on Fibrosis Progression

The impact of highly active antiretroviral therapy on fibrosis progression is controversial. Teasing out the contribution of a particular antiretroviral agent, or class of agents to fibrosis progression is difficult. Without sequential biopsy samples, individual fibrosis progression rates cannot be pinpointed. In most studies, fibrosis progression rates are estimated with a model that assumes linearity; this assumption is not always correct. The duration of a person's HIV and their HCV, the severity of their HIV disease, their age, use of alcohol and other drugs and variations in individual

fibrosis progression rates may make conclusions about HAART's effect(s) on fibrosis difficult.

Benhamou and colleagues evaluated the impact of protease inhibitors on fibrosis progression in a retrospective analysis of data from 182 coinfected people; 63 of them were treated for HIV with a protease inhibitor. They considered age, alcohol consumption, CD4 cell count and HIV RNA. For HCV, mode and duration of infection, age at infection, genotype and liver biopsy specimens were evaluated. Fibrosis progression rates were estimated with a model that assumed linear progression from the time of infection until biopsy. Use of a protease inhibitor was significantly associated with a lower stage of liver fibrosis (P=0.03). The authors suggested that fibrosis progression might be stabilized by reducing alcohol intake (from >50 grams/day to <50 grams/day) and maintaining a high CD4 cell count with combination therapy including a protease inhibitor (Benhamou 2001).

Macías and colleagues evaluated data and biopsy samples from 152 HIV/HCV coinfected people with a known or estimated duration of HCV infection. A majority had been treated for HIV (105/152) (Macías 2004). They reported that HIV therapy that included nevirapine (a non-nucleoside reverse transcriptase inhibitor) was significantly associated with a more rapid fibrosis progression rate, although the drug's actual contribution to accelerated fibrosis progression is unclear. Recipients of nevirapine were older, and more likely to have clinical AIDS (25% vs. 6% of the non-HAART group). Both aging and advanced HIV disease have been associated with accelerated fibrosis progression.

For more information on antiretroviral agents, see Chapter V, HIV Treatment in HIV/HCV Coinfection.

HCV and HAART: New Questions about Immune Reconstitution

While the introduction of HAART has provided the opportunity for controlling HIV, concerns have been raised about the immunologic benefits of antiretroviral therapy for coinfected persons. In research conducted before the HAART era, HCV was not generally shown to have a significant influence on HIV disease progression. In the post-HAART era, coinfected individuals appear to respond well to therapy as measured by HIV RNA levels (Chung 2002a), although conflicting results have emerged from more recent studies examining whether hepatitis C coinfection affects the likelihood and extent of immunologic response to antiretroviral therapy. One large cohort study showed a blunted CD4 cell response to HAART in coinfected persons as compared to those with HIV alone (Greub 2000); another showed no significantly diminished CD4 cell responses to HAART among coinfected persons (Sulkowski 2002).

The Swiss Cohort Study

The Swiss Cohort Study provided the first indications of reduced immune reconstitution among coinfected persons taking HAART. A cohort of 3,111 HIV-positive individuals, 1,157 (37.2%) of them HCV-antibody-positive, began HAART regimens containing two nucleoside reverse transcriptase inhibitors and a protease inhibitor between June 1, 1996, and May 31, 1999. The median follow-up time was 28 months. There were some small but significant differences between the HCV-seropositive and HCV-seronegative groups. While 58.9% of coinfected individuals were treatment naïve at baseline, only 52.3% of those with HIV alone were treatment naïve (P<0.001).

The HCV-seropositive participants were more likely to have had an AIDS diagnosis at baseline (27.7% vs. 23.5%; P=0.009) and lower median baseline CD4 cell counts (172 [range: 70–322] vs. 222 [range: 90–373]; P<0.001). The presence of antibodies to HCV was also associated with active drug use, lower income, less education, female sex, and younger age.

While more than half of the entire cohort maintained undetectable HIV viral loads (<400 copies/mL), there were significant differences in CD4 cell increases after initiation of HAART. HCV-positive individuals had smaller increases in CD4 cell counts; this group was 21% less likely to see CD4 cell count increases of at least 50/μL. Blunted CD4 increases were seen in coinfected individuals at all baseline CD4 strata, as well as in those with undetectable HIV RNA levels; however, no association was found between anti-HCV positivity and either the likelihood of achieving an undetectable HIV viral load after initiation of antiretroviral therapy or the time to subsequent virological failure (two consecutive viral load measurements >400 copies/mL).

The risk of clinical progression to an AIDS-defining event or death was higher among HCV-seropositive individuals. The estimated probability for clinical progression at two years was 6.6% (95% CI, 5.6–7.9) with HIV alone and no active injection drug use (IDU). The probability of clinical progression increased to 9.7% (95% CI, 7.4–12.7) for HCV-seropositive individuals without active IDU, and rose to 15.0% (95% CI, 12.2–18.4) for HCV-seropositive individuals with active IDU. The hazard ratio for clinical progression was 2.07 (95% CI, 1.40–3.06) for anti-HCV-positive individuals as compared to those with HIV alone.

HCV seropositivity was strongly associated with active injection drug use in this cohort (odds ratio 45.4; 95% CI, 30.8–66.8). The overwhelming majority of HCV-seropositive individuals had a history of IDU (87.7%, vs. 4.8% in the HCV-seronegative group; P<0.001) (Greub 2000). Data from other research suggest that IDU—either through direct effects on the immune system or by influencing treatment adherence and utilization of medical care—can play a role in HIV disease outcomes. Opiates may have an effect on the immune system (Carr 1995; G. Nunez 1999; Peterson 1998; Rouveix 1992; Roy 1996). In one study, IDUs reported a 35% rate of nonadherence to HAART as compared to a 24% rate in nonusers and 17% in former users. Smaller CD4 cell increases were observed in the active users (65 CD4 cells vs. 122 in former users and 116 in nonusers) (Lucas 2001).

Although HCV prevalence was not reported in the Lucas study, it would presumably be comparable to that between active and former IDUs, given that most IDUs acquire HCV within a year of initiating injection drug use. This would suggest that current IDU may independently reduce CD4 cell gains for those on HAART, either directly through the immune system or through poorer adherence. The Swiss Cohort Study attempted to discount the potentially confounding influence of IDU in its evaluation of treatment outcomes for HCV-seropositive individuals. It reported that differences in CD4 cell gains and clinical outcomes persisted even when active IDUs were excluded from the analysis; however, determination of active injection drug use was based on patients' reports and physicians' observations, which may have underestimated the extent of injection drug use in the HCV-seropositive group.

The Baltimore Study

Sulkowski and colleagues analyzed data from a cohort of 1,955 HIV-positive individuals, 873 of them anti-HCV-positive. HAART was given to 54% of the HCV-seropositive participants and 67% of the HCV-seronegative participants (total n=1,199). The median length of follow-up for HCV-seropositive individuals was 2.19 years; for those with HIV alone, median follow-up was 2.00 years.

HCV status did not influence the response to HAART, despite differences in baseline characteristics between HCV-seropositive and HCV-seronegative participants. Eighty-five percent of HCV-seropositive individuals had a history of IDU, compared with 13% of the HCV-seronegative participants (P<0.001). The HCV-seropositive group also had lower absolute CD4 cell counts at entry (median, 237 vs. 266; P=0.02) and were less likely to have received prior antiretroviral therapy (P<0.001). Virological response to HAART was equivalent among the HCV-seropositive and HCV-seronegative participants; 29% of both groups achieved well-controlled HIV RNA levels (defined as < 400 copies/mL on at least 75% of clinic visits). Among those with well-controlled HIV RNA, no detectable difference was observed between HCV-seropositive and HCV-seronegative participants in immunologic responses to HAART at one, two, and three years after initiation of anti-HIV treatment.

In HAART recipients, there were no significant HCV-serostatus-related differences in the risk of acquiring an AIDS-defining illness (RH, 1.09; 95% CI, 0.88–1.34) or in the risk of death (RH, 1.22; 95% CI, 0.22–1.61). In a subgroup of HCV-seropositive individuals with CD4 cell counts between $50/\mu L$ and $200/\mu L$, the risk of death was higher than that for HCV-seronegative individuals, especially for those who had received HAART. After multivariate analysis, however, death was independently associated with total exposure (in years) to HAART, percentage of clinic visits with detectable HIV RNA levels, older age, and baseline CD4 cell count—not with HCV seropositivity (RH, 1.01; 95% CI, 0.65–1.56) (Sulkowski 2002).

In the Baltimore cohort, there were 187 deaths among the 1,199 individuals who received HAART (15.6%). There were 6 deaths in the subgroup of 208 individuals with durable viral control (2.9%). After controlling for use of HAART, there was no difference in the mortality rate between groups by HCV serostatus. The Baltimore cohort had a higher mortality rate than the Swiss Cohort Study (181 deaths [5.8%] among 3,111 participants). In the Swiss Cohort Study, there were 20 deaths among the subgroup of 1,596 with well-controlled HIV RNA (1.3%). A greater frequency of non-AIDS-related deaths (such as liver disease, drug overdose, and violence) among HCV-seropositive individuals was noted in both cohorts.

The demographic differences between the Baltimore cohort and the Swiss cohort are significant: in the Swiss cohort, IDUs were more likely to be female, white, and young; in the Baltimore study, IDUs were more likely to be male, African-American, and in their late thirties. Information about adherence was not provided for either study, and virological control has been used as a surrogate. There are many confounding variables involved and it may not be possible to elucidate the many external factors that can influence individual disease progression such as poor nutrition, host and virological differences, other co-morbid conditions, variable HIV treatment histories, differing stages of HIV disease, pre-existing liver damage, and other individual prognostic factors.

The Aquitaine Cohort

A French HIV cohort study found an association between severely elevated aspartate aminotransferase levels (AST) and poorer survival on antiretroviral therapy, although the presence of antibodies to HCV was not associated with mortality. In this prospective study, 995 HIV-positive individuals—576 of whom were HCV-antibody-positive—were treated with antiretroviral therapy (consisting of dual nucleosides or triple combinations with a protease inhibitor) and followed for a median of 35 months. At baseline, median CD4 cell counts did not differ significantly between the HCV-positive and HCV-negative groups (189 vs. 213; P=0.3), although mean HIV RNA was slightly lower in anti-HCV-positive individuals (4.07 $\log_{10}$ vs. 4.34 $\log_{10}$; P=0.02; based on 366 available samples). At 24 months, HCV serostatus was not associated with a significant difference in median CD4 cell increases (+82/mm^3 for HCV/HIV vs. +105/mm^3 for HIV alone) or mean HIV-RNA changes (-1.35 $\log_{10}$ vs. -1.60 $\log_{10}$). At 48 months, the overall median CD4 cell increase was +146 mm^3. Those taking a protease inhibitor had significantly higher median CD4 cell increases (+191/mm^3, compared with +81/mm^3 in those taking only dual nucleosides) and larger HIV-RNA decreases (-1.89 $\log_{10}$ vs. -1.27 $\log_{10}$).

No association between HCV seropositivity and poorer survival was detected. After three years, the probability of survival among HCV-seropositive individuals was 89.7% (95% CI, 86.8–92.6), while the survival probability for those with HIV alone was 92.0% (95% CI, 88.7–95.4); however, large elevations in AST levels—seen in 15% of HCV-seropositive individuals and in 7% of those with HIV alone—were significantly associated with poorer survival (HR for elevations >200 IU/l of 2.30; 95% CI, 1.32–4.03; P=0.004) (Rancinan 2002). This is cause for concern, since coinfected individuals often have elevated AST levels, which may be due to both liver disease and hepatotoxicity of anti-HIV medications (Staples 1999).

The AIDS Clinical Trials Group Analysis

Chung and colleagues retrospectively compared the virological and immunologic responses to 16 weeks of HAART by looking at stored plasma samples from 40 coinfected individuals and 129 with HIV alone who participated in two antiretroviral treatment trials, ACTG 348 and ACTG 320. There were no significant differences by HCV status in baseline CD4 cell counts, HIV-RNA levels, or the initial antiretroviral regimen. Stored plasma samples from 40 coinfected participants and 129 with HIV alone were evaluated. At week 16, there were no significant differences in mean CD4 cell increases between the two groups. Coinfected individuals with baseline CD4 cell counts >350/mm^3 had greater CD4 cell increases than did HCV-seronegative individuals in the same CD4 strata (+145/mm^3 vs. + 82/mm^3; P=0.0331). They also had significantly larger decreases in HIV RNA (-2.55 $\log_{10}$ vs. -2.02 $\log_{10}$; P=0.02) and a higher rate of HIV suppression to <500 copies/mL (97.4 vs. 84.4%; P=0.04) (Chung 2002a).

Although 48-week data were provided—showing no significant differences in virological and immunologic response between groups—treatment regimens diverged after week 24 and samples were not uniformly available. A longer, prospective study with a larger sample size is needed to determine if disparities in immunologic responses to HAART by HCV status are consistent in each CD4 cell strata.

Making Sense of Conflicting Results

The contrasting results from these studies will need to be resolved by additional research. The constraints and limitations in the study designs and data collected make definitive answers elusive. For example, HCV-RNA data were not consistently gathered across studies; the reliance on HCV-antibody results without confirmatory testing for the presence of the virus may not have accurately represented the distribution of chronic hepatitis C infection. In the Baltimore cohort, participants with antibodies to HCV were not tested for HCV RNA. This decision was based on previous research by one of the study authors, in which 90% of HIV-positive individuals with antibodies to HCV also had detectable HCV RNA, and results from a similar cohort where the HCV antibody test was found to be more than 99% accurate in HIV-positive individuals (Thio 2000; Thomas 2000a). In the Swiss Cohort, only a small subgroup of HCV-seropositive individuals was tested for HCV RNA; of the 56 individuals tested, 14 (25%) had undetectable HCV RNA (Greub 2000). Without a second HCV-RNA test, it is not possible to distinguish a current HCV infection from a prior, resolved infection, as people with chronic HCV may be intermittently viremic (see Chapter IV, Diagnostics).

In addition, individuals with advanced HIV disease may not produce antibodies to HCV; HCV-RNA testing may be necessary in this population to confirm or rule out active HCV infection (Busch 2001). There were 460 HCV-seronegative participants in the Swiss cohort with AIDS at baseline; a portion of this group may have been infected with HCV but undiagnosed because they did not produce antibodies to HCV.

Because these studies examined the effect of HCV on HIV, information about the severity of HCV disease was not collected. Without data on HCV-RNA levels, liver enzyme levels, and actual liver histology, it is impossible to determine the severity of HCV disease, which may in itself have had an effect on response to HAART.

The long-term effects of HAART on HCV disease progression require further study. HAART increases HCV-RNA levels, especially in individuals with CD4 cell counts below 350 (Chung 2002a; Rutschmann 1998). Coinfected individuals with normal baseline ALT levels have seen ALT flares after immune reconstitution from initiation of HAART (Chung 2002a; Torre 2001; Torriani 2002b). Does the degree of HAART-mediated immune reconstitution influence long-term HCV disease progression? Clinical trials that incorporate assessment of HIV and HCV disease progression are needed to increase our understanding of the complex interrelationship between these two viruses. In the meantime, developing treatment strategies for coinfected individuals must become a priority.

Recommendations

Establish prospective longitudinal cohort studies of the natural history of HIV/HCV coinfection in the era of HCV treatment and HAART.

In the HAART era, new questions and conflicting data about the efficacy of HAART in coinfected individuals have emerged (Greub 2000; Law 2002; Sulkowski 2002). We need to increase our understanding of the complex interrelationship between these two viruses, and the impact of HAART and immune restoration on HCV progression. So far, most studies that have examined the effect of HCV on responses to HAART and clinical progression of HIV disease have not collected information about the progression or severity of underlying HCV disease. Without data on actual liver histology, it is impossible to determine the severity of HCV disease, which may in turn affect an individual's ability to respond to HAART.

Well-designed, prospective longitudinal cohorts will be essential to following infected populations; defining prognostic factors and other cofactors for progressive disease; observing changing treatment outcomes over time; and generating productive hypotheses for pathogenesis, prevention, and treatment studies. Because treatment modalities for HIV and HCV will continue to evolve, cohort studies must be large enough and long enough to measure and account for variations in treatment, as well as other cofactors such as access to health care, drug and alcohol use, race/ethnicity, and sex. Barriers to enrollment such as invasive needle biopsies can be addressed by being restricting those procedures to intensified substudies, if necessary. In any case, full participation of coinfected persons and advocates will be essential in planning and implementing such cohort studies. The National Institutes of Health and the Centers for Disease Control and Prevention must support these studies.

Develop strategies to enhance HAV and HBV vaccine immunogenicity in HIV-positive individuals.

Although vaccinations for hepatitis A and B are safe in HIV-positive individuals, vaccine immuno-genicity is decreased, especially in persons with low CD4 cell counts (Bruguera 1992; Hess 1995; Neilson 1997; Puoti 2002; Tedali 2004; Weissman 2004). CDC estimates that only 66–75% of HIV-positive individuals develop protective antibody responses after vaccination for HAV. Response rates to HAV vaccination in HIV-positive people may be lower than the CDC estimate; one study reported response to HAV vaccination in only 49% of HIV-positive individuals (Weissman 2004).

The efficacy of HBV vaccination in HIV-positive individuals is suboptimal; a strategy to enhance immunogenicity is needed. Additional doses of HBV vaccine may improve HBV vaccine response in people with HIV (CDC 1993).

Research on interventions to enhance the immunogenicity of HAV and HBV vaccines in HIV-positive persons should be made a priority by the National Institutes of Health.

List of Terms Used in This Chapter

Actuarial rate: a model projecting future risk.

Aspartate aminotransferase (AST): a liver enzyme.

HIV–treatment naïve: an individual who has never taken anti-HIV medications is referred to as treatment naïve.

Hypogammaglobulinemia: an immune deficiency in which the body's production of antibodies and, in some cases, other immune responses are insufficient.

Log: Because viral loads can range from <5 copies/mL to tens of millions of copies, researchers sometimes use logarithmic—rather than linear—metrics to describe viral load levels. For example, a one-log decrease—or a 90% decrease—in viral load would be a reduction from 1 million to 100,000. A two-log decrease would be a reduction to 10,000. A one-log increase in viral load from 1 million would be a rise to 10 million.

Phylogenetic analysis: testing performed on a virus to identify genetic "family resemblance" among viral strains.