

The Challenge of Hepatitis C in the HIV-Infected Person

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Key Words

HCV, coinfection, liver disease, injection drug use

Abstract

Hepatitis C virus (HCV) coinfection occurs in an estimated one quarter of HIV-infected persons in Europe, Australia, and the United States. As use of highly active antiretroviral drugs has markedly reduced opportunistic infections, HCV-related liver disease has emerged as a leading cause of death. HIV infection adversely affects both the natural history and the treatment of hepatitis C. Because there are no experimental models of coinfection and because the pathogenesis of each infection is incompletely understood, how HIV infection alters hepatitis C is not clear. This review considers the epidemiology, natural history, treatment, and pathogenesis of hepatitis C in HIV-infected persons.

EPIDEMIOLOGY OF HIV/HCV COINFECTION

HIV/HCV-coinfected: infected with both human immunodeficiency virus and hepatitis C virus

Injection drug user (IDU): person who uses illicit drugs by intravenous or subcutaneous injection

It is estimated that 250,000 people in the United States are infected with both human immunodeficiency virus 1 (HIV) and hepatitis C virus (HCV). These HIV/HCV-coinfected persons account for approximately 25% of all HIV-infected persons and 8% of those with hepatitis C (1). Similar proportions of HIV-infected persons are dually infected in Europe and in Australia (2). In sub-Saharan Africa and Asia, where the majority of HIV-infected persons live, the frequency of HIV/HCV coinfection varies, and in many instances remains uncertain. It has been estimated that there are 10 million HIV/HCV-coinfected persons worldwide (<http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050411.7>).

Individuals coinfecting with HIV and HCV comprise a distinct subset of those infected with each virus. Persons who acquired HCV infection through blood transfusions or brief injection drug use are not usually dually infected with HIV. Likewise, those who acquire HIV by sexual exposures are not usually infected with HCV. This point is easiest to appreciate when viewing HCV prevalence by HIV risk factor (**Figure 1**) (3).

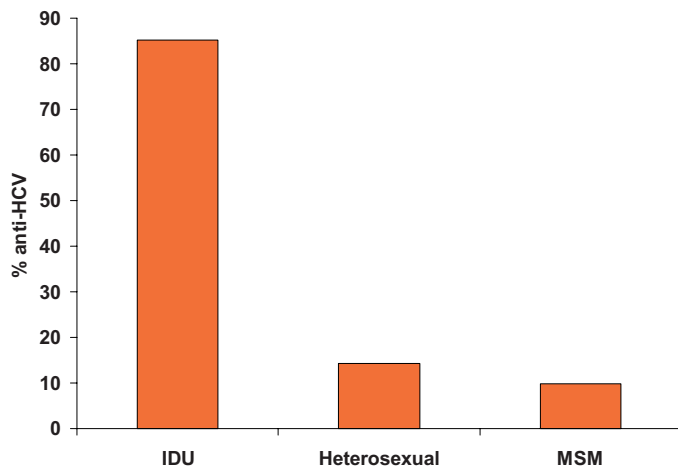


Figure 1

The prevalence of HCV among HIV-infected patients attending the Johns Hopkins HIV Clinic by HIV risk factor (adapted from Reference 3). IDU, injection drug user; MSM, men who have sex with men.

The majority of HIV/HCV-coinfected persons are former or current long-term injection drug users (IDUs). The basis for the strong link between HIV/HCV coinfection and illicit drug use is the greater transmissibility of HCV by this route. In studies from accidental needlestick exposures, HCV is approximately tenfold more transmissible than HIV (4). That, coupled with the greater reservoir of HCV among IDUs, explains why persons who get HIV from injection drug use often already have been exposed to HCV. In one large IDU cohort in Baltimore, the incidence of HCV was eight- to tenfold higher than that of HIV (5). Likewise, in IDUs in virtually all Western cities, including Seattle, Chicago, Los Angeles, Amsterdam, Rome, Sydney, and Melbourne, the incidence of HCV infection is higher than that of HIV. Consequently, the typical HIV/HCV-coinfected person has long-standing injection drug use and a season of HIV infection superimposed on decades of chronic hepatitis C.

Transmission of HCV among HIV-infected men who have sex with men has also been reported, including several recent outbreaks (6, 7). In a detailed analysis of one recent outbreak in the United Kingdom, 60 HIV-infected men who acquired HCV reported more high-risk sexual practices and were more likely to have shared drugs via a nasal or anal route in the preceding year in comparison with 130 controls who did not acquire HCV infection (7). Interestingly, HCV infections occurred in both HIV-infected and HIV-uninfected men in this outbreak (7a). These data must be interpreted in the context of traditionally low rates of HCV in men who have sex with men, even those with HIV infection (8). Although it is difficult to exclude the possibility of unacknowledged or forgotten prior injection drug use in these HCV outbreaks, cumulatively the reports underscore that HCV infection remains a threat to men who have sex with men, and an important reason not to engage in very high-risk practices.

Persons with hemophilia represent a distinct but relatively small fraction of

HIV/HCV-coinfected persons. Transfusion transmission of HCV was a long-standing problem that peaked in the early 1970s and continued until 1991, when effective HCV screening was implemented (9). Transfusion transmission of HIV in the late 1970s and early 1980s led to HIV/HCV coinfection of some, especially those with severe hemophilia (10). As discussed below, rapid progression of liver disease has been documented in HIV/HCV-coinfected persons with hemophilia, so it is important to recognize dual infection in this population.

Each virus also can be transmitted from mother to infant and by heterosexual intercourse. Mothers infected with both HIV and HCV are more likely to transmit each virus to their infants (11, 12). Infants who acquire both infections develop persistent hepatitis C, but little is known about their long-term risk of liver disease (13). It is not clear whether the risk of heterosexual transmission of either virus from HIV/HCV-coinfected persons is greater than from persons with just one infection (10). Although it is not uncommon to detect HCV infection in women who acquired HIV from heterosexual exposures, it is difficult to ascertain how commonly the HCV was also sexually transmitted, since it is difficult to exclude remote illicit drug use.

NATURAL HISTORY OF HEPATITIS C IN PERSONS WITH HIV INFECTION

HIV infection adversely affects the natural history of hepatitis C at all stages. Approximately 30% of HIV-uninfected persons spontaneously clear HCV in the first year of infection. Although spontaneous HCV clearance has been demonstrated in small HCV outbreaks among HIV-infected men, HIV infection reduces the likelihood of spontaneous clearance several-fold (6, 14). In one study of Baltimore IDUs, HCV persistence was detected five times more often in HIV-infected than HIV-uninfected IDUs, and the risk of

persistence was even greater in those with low CD4⁺ lymphocyte counts (14). This fivefold-increased risk of persistence represents cumulative cycles of reinfection among multiply-exposed IDUs rather than the increased risk attributed to a single HCV infection (15). It is not clear whether the risk of HCV persistence is measurably increased in HIV-infected persons with preserved CD4⁺ lymphocyte counts (e.g., >500/mm³).

Among persons who develop persistent hepatitis C, HIV infection increases the viral "set point" as indicated by the plasma level of HCV RNA (16, 17). In some but not all studies, the viral set point continues to increase as HIV-related immunosuppression advances (18). Interestingly, effective antiretroviral therapy is actually associated with a slight increase in HCV RNA, especially in persons with pretreatment CD4⁺ lymphocyte counts <350/mm³ (19).

HIV infection also increases the risk of cirrhosis and liver failure in persons with chronic hepatitis C. The effect of HIV on hepatitis C natural history has been most apparent in cohorts of persons with hemophilia (17). In one large hemophilia cohort, the 16-year cumulative risk of liver failure was 14.0% in HIV/HCV-coinfected persons compared to 2.6% in those with just HCV infection (17). In a meta-analysis that included many of the hemophilia cohorts, the average risk of liver failure was estimated to be sixfold higher in HIV-infected persons than in HCV-infected persons without HIV (20). The impact of HIV on HCV natural history was less apparent in some IDU cohorts, probably because of very high competing mortality (14). However, as the use of antiretroviral therapy has increased among IDUs and overall mortality has diminished, the effect of HIV on liver disease has become more visible.

ANTIRETROVIRAL THERAPY AND HEPATITIS C

There are important interactions between highly active antiretroviral therapy (HAART)

Highly active antiretroviral therapy (HAART): use of three or more antiretroviral compounds, which generally began after 1996

and liver disease. Since the advent of HAART, liver disease has become a leading cause of death among HIV-infected persons (21–23). Estimates vary, but in most large series, liver disease is the second leading cause. In the large D:A:D study, 23,441 HIV-infected persons were followed from December 1999 through February 2004, and 1246 died (23). The primary causes of death were AIDS (31.1%) and liver failure (14.5%) (**Figure 2**). Many of those who died of liver-related causes had effective treatment of HIV. In this series, 54.6% of those who died of liver-related causes had achieved HIV RNA suppression <400 c/ml and half had CD4⁺ lymphocyte counts >200/mm³. This is especially important because these individuals would not be expected to have died of opportunistic infections.

The relative contribution of liver-related mortality is likely to increase. In a population-based study in Denmark, mortality among HIV-infected persons dropped from 124 per 1000 person-years pre-HAART to 38 per 1000 person-years in the early HAART period (1997–1999) and to 25 per 1000 person-years once HAART use was established (2000–2005) (24). Despite this overwhelming overall success, mortality among

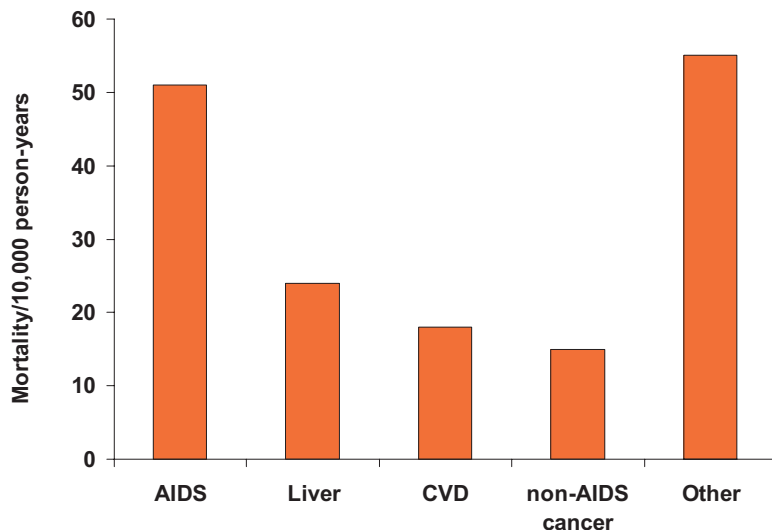
HIV/HCV-coinfected persons did not decline as much. From 2000 to 2005, mortality in HIV/HCV-coinfected persons was 57 per 1000 person-years compared to 19 per 1000 person-years in HCV-uninfected persons. Likewise, a recent review of death certificates in New York City demonstrated a 32.8% increase in non-AIDS-related mortality in HIV-infected persons between 1999 and 2004 (25).

Clearly, the primary effect of HAART on liver-related mortality is a reduction in AIDS-related mortality, which both increases the proportion of mortality attributed to liver-related causes (denominator effect) and allows HIV/HCV-coinfected persons to live long enough to develop liver-related mortality. The finding that half of persons dying of liver-related causes in the D:A:Ds study had HIV RNA suppression <400 c/ml and CD4⁺ lymphocyte counts >200/mm³ underscores this point (23).

What remains unclear is whether HAART directly affects HCV-related liver disease progression. On the one hand, HIV/HCV-coinfected persons are more likely to have grade 3–4 liver toxicity when taking HAART (26). It is conceivable that, like alcohol exposure, HAART-induced liver inflammation

Figure 2

Cause-specific mortality (per 10,000 person-years) among 23,441 HIV-infected persons followed a median of 3.5 years from December 1999 through February 2004 in the Data Collection on Adverse Events of anti-HIV drugs (D:A:D) study. From Reference 23.



could accelerate HCV-related liver disease. Some antiretroviral drugs can also cause hepatic steatosis, which has been linked to accelerated progression to cirrhosis (27). However, significant liver enzyme elevations occur in only ~10% of persons initiating HAART and are often self-limited, and the drugs that cause steatosis (d4T and ddI) are now infrequently used (28).

On the other hand, some data suggest that HAART diminishes progression of HCV-related liver disease, presumably by offsetting the deleterious HIV effect. If this were true, HAART might be indicated in HIV/HCV-coinfected persons at a higher CD4⁺ lymphocyte count to forestall progression of liver disease rather than the current threshold focused on prevention of AIDS. Reduced liver disease was first associated with HAART by Benhamou et al. in a cross-sectional study and has been confirmed by some but not all subsequent work (29–31). One recent prospective study compared HAART exposure and effectiveness in 184 HIV/HCV-coinfected persons who had at least two liver biopsies between January 1998 and July 2006. Forty-one (24%) had significant progression (≥ 2 -point increase in the Ishak scoring system). Between biopsies, HAART was used by 51% of progressors (median exposure 0.6 years) and 65% of nonprogressors (median exposure 1.5 years), a difference that was not statistically significant. Similarly, no significant difference was observed in the proportion of visits with HIV RNA suppression between biopsies among progressors (43%) and nonprogressors (60%) and the median CD4⁺ cell count nadir between biopsies. Methodological differences between studies could explain the apparent discrepancies. Unfortunately, our limited understanding of the pathogenesis of each viral infection and the nature of HAART-induced immune restoration makes it difficult to speculate. At this point, it is fair to conclude that the timing of HAART should chiefly be determined by HIV RNA and CD4⁺ lymphocyte count, not by HCV or liver status.

PREVENTION AND TREATMENT OF HEPATITIS C IN PERSONS WITH HIV INFECTION

The accelerated course of liver disease associated with HIV infection underscores the importance of hepatitis C prevention and treatment. There is no vaccine licensed for prevention of HCV infection and no approved (or effective) form of postexposure prevention of HCV infection. Thus, primary prevention has to be achieved by risk reduction (32). Because most HCV infection results from injection drug use, efforts to reduce drug use or make it safer are central to preventing HCV infection. Recent outbreaks of HCV among HIV-infected men having sex with men demonstrate that, in counseling HIV-infected persons, HCV prevention should be included as one of the reasons to practice safe sex. This advice may be especially important if inhibitions are diminished either because one already has HIV or because one is less concerned about transmitting HIV in the era of HAART.

The goals of HCV treatment are suppression of plasma HCV RNA to an undetectable level (e.g., <50 IU/ml) by the end of treatment and maintenance of suppression six months after treatment is stopped, an end point referred to as a sustained virologic response (SVR) (32, 33). Among both HIV-infected persons and those without HIV, 99% of persons who achieve SVR remain free of active infection five years later (34, 35). Data are sparse, but we generally infer that persons who achieve SVR have a markedly lower risk of developing end-stage liver disease than those with persistent infection.

Although acute HCV infection is uncommonly detected in HIV-infected persons, it is noteworthy that interferon alfa treatment appears to be more effective at this early stage, as is the case in persons without HIV (6, 36). The ideal timing of treatment of acute hepatitis C, the best regimen, and the optimal duration are not known even for patients

Sustained virologic response (SVR):

HCV RNA undetectable six months after therapy is stopped; correlates with long-term “cure”

without HIV. Nonetheless, there is growing consensus that a 24-week course of peginterferon alfa 8–12 weeks after exposure in persons with persistent HCV RNA is reasonable. Beginning treatment even earlier in HIV/HCV-coinfected persons may be justifiable because of the greater risk of persistent infection and lower likelihood of treatment response once persistence has been established.

The best available treatment of chronic hepatitis C in HIV-infected persons is the combination of peginterferon alfa and ribavirin, as shown in 2004 by four “pivotal” studies in which HIV/HCV-coinfected patients were randomized to receive 48 weeks of peginterferon alfa (**Table 1**) (37–40). In the largest study (APRICOT), 868 persons were randomized to receive either standard interferon alfa-2a (3 mU, *tiw*) plus ribavirin (800 mg daily), peginterferon alfa-2a 180 µg per week plus placebo, or peginterferon alfa-2a 180 µg weekly plus ribavirin 800 mg daily. The SVR rates were 12%, 20%, and 40%, respectively (38). For persons with genotype 1 infection, the SVR rate was 29% with peginterferon alfa and ribavirin, whereas SVR was observed in 62% of those with genotype 2 or 3 infection.

The pretreatment level of HCV RNA is an important determinant of response likelihood. In the APRICOT study, SVR rates were >60% in genotype 1–infected persons who were randomized to peginterferon alfa and ribavirin for 48 weeks and had a HCV RNA level ≤800,000 IU/ml compared to 18% for genotype 1–infected persons with higher HCV RNA levels and the same treatment (38). Interestingly, the SVR rate in APRICOT for HIV/HCV-coinfected persons with genotype 1 infection and HCV RNA level ≤800,000 IU/ml (61%) is similar to that reported in a study of HIV-uninfected persons with the same genotype, HCV RNA level threshold, and therapy (55%) (38, 41).

As in persons without HIV infection, failure to suppress HCV RNA on treatment has a high negative predictive value. In the four studies summarized in **Table 1**, <2% of persons whose HCV RNA was still detectable 12 weeks after starting treatment (or whose HCV RNA level was not reduced by at least 2 logs) went on to SVR (37–40).

Other important information also came from the APRICOT study. Pre- and post-treatment liver biopsies were evaluated on 401 subjects (42). A histologic response (reduction of at least 2 points from baseline in the

Table 1 Four pivotal studies of treatment of chronic hepatitis C in HIV-infected persons, published in 2004*

Characteristic	APRICOT	ACTG 5071	RIBAVIC	Barcelona
Number enrolled	868	133	412	95
Peginterferon	2a	2a	2b	2b
Ribavirin	800 mg	600 up to 1g	800 mg	0.8 g, 1 g, 1.2 g ^a
HIV and CD4 ⁺ status	>200/mm ³ or 100–200/mm ³ and HIV RNA <5000 c/ml	>100/mm ³ and HIV RNA <10,000 c/ml	>200/mm ³	>250/mm ³ and HIV RNA <10,000 c/ml
ALT	“elevated” twice	NA	NA	>1.5 ULN
% Genotype 1 ^b	60	77	48	55
% bridging fibrosis or cirrhosis ^b	12	11 (cirrhosis)	39	29
Genotype 1 peg-ribavirin SVR rate ^c	29%	14%	17%	38%

* ALT, alanine aminotransferase; ULN, upper limit of normal; c/ml, copies/ml; NA, not applicable.

^aBased on body weight <65, 65–75, >75 kg.

^bTaken from peginterferon and ribavirin arm; cirrhosis defined as F4–6 MHA1 or F3–4 metavir and Scheurer.

^cRefers to the sustained virologic response (SVR) rate for HIV-infected persons taking peginterferon and ribavirin. Rates are for patients with genotype 1 hcv infection except for the RIBAVIC and Barcelona studies that grouped genotypes 1 and 4.

24-point Ishak modified HAI score) was observed more often in those who received peginterferon plus ribavirin (57%) than in those who received peginterferon plus placebo (39%) or standard interferon plus ribavirin (41%). Among those without SVR, 28% had a histologic response, 48% were unchanged, and 25% worsened. Medication was discontinued in 25% of those taking peginterferon alfa and ribavirin; in 15% this was due to adverse events. The CD4⁺ lymphocyte count dropped an average of 157 cells/mm³, but median CD4⁺ lymphocyte percent did not decline. Hepatic decompensation occurred in 14 of the 860 patients. In each instance, subjects had Child-Pugh scores of 5 or higher at baseline; also associated with decompensation were other markers of cirrhosis such as low platelet counts and dDI use (43). Among those in whom HIV RNA was detected at baseline, HIV RNA levels actually declined an average of 0.696 log₁₀ copies/ml in the peginterferon and ribavirin arm.

It is possible that higher SVR rates can be achieved in HIV-infected persons by longer therapy or by higher doses of peginterferon or ribavirin. In many studies, the ribavirin dose was 800 mg per day to diminish ribavirin-associated anemia, which is a greater problem in HIV-infected persons, especially those taking azidothymidine (AZT) (44). However, ribavirin doses similar to those used in HIV-uninfected persons (1.0 g ≤75 kg and 1.2g >75 kg) are currently recommended for HIV/HCV-coinfected persons (33).

HIV/HCV-coinfected persons have additional safety concerns with peginterferon and ribavirin therapy. Ribavirin-associated anemia may be a greater problem in coinfecting persons than in the HIV-uninfected, a problem that is compounded by concomitant AZT use (44). Ribavirin also raises dDI levels and causes toxicity including fatal hyperlactatemia (45). Although interferon alfa therapy is associated with a dose-related reduction in white blood cell count and absolute CD4⁺ count, the percentage of CD4⁺ cells remains essentially unchanged, and interferon alfa therapy is not as-

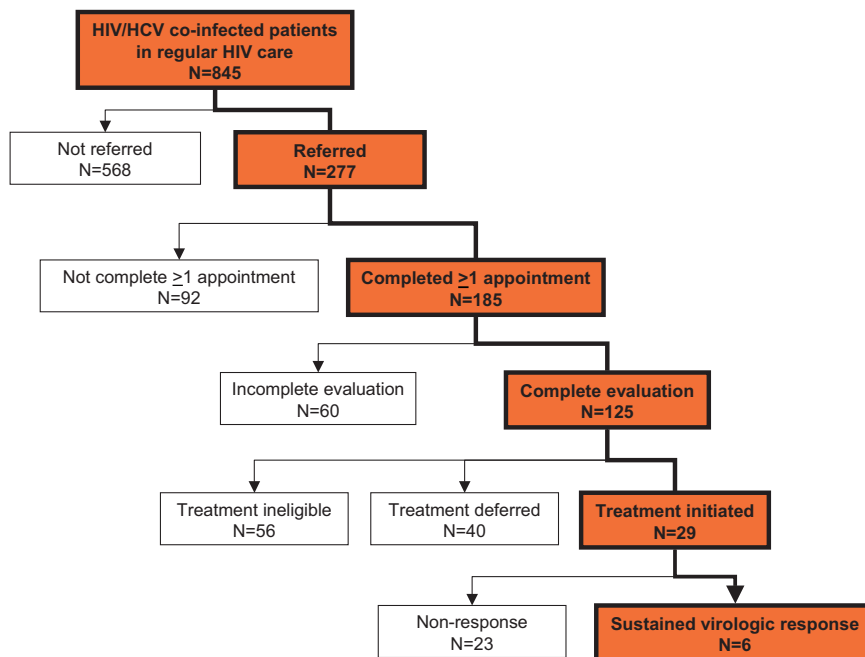
sociated with the development of opportunistic infections (37–40). Liver failure has also occurred in HIV/HCV-coinfected persons on peginterferon alfa and ribavirin therapy, especially when treatment is started in persons who already have Child's B cirrhosis (43).

Peginterferon alfa is contraindicated in persons who already have liver failure. Thus, liver transplantation is the only treatment available for HIV/HCV-coinfected persons with decompensated cirrhosis (that is, Child's B or C cirrhosis) (46). However, transplant remains an investigational procedure, is very expensive, and is unavailable for many HIV/HCV-coinfected persons. Clearly, prevention of liver failure must remain the primary goal.

Unfortunately, the overall effectiveness of HCV treatment of HIV/HCV-coinfected persons is even lower than the efficacy mentioned above. In one university-based HIV clinic in Baltimore, a hepatitis C treatment center was established in 1998, but through 2003 only 277 (33%) of 845 HIV/HCV-coinfected persons were referred to this center for HCV care (**Figure 3**) (47). The overall referral rate increased from <1% in 1998 to 28% in 2003; however, even in 2003, 65% of HIV/HCV-coinfected persons with CD4⁺ cell count >200 cells/ml were not referred. Interestingly, only 67% of 277 patients referred kept their appointment, and only 68% of them completed their pretreatment evaluation. Of the remaining 125, only 69 (55%) were medically eligible for treatment, and 29 (42%) underwent HCV treatment; SVR was achieved by six (21%), who represented only 0.7% of the full cohort. Compared to this predominantly genotype 1 (90%) and African-American (70%) population, higher effectiveness rates are reported in other locations, such as in Spain, where patients are Caucasians with a greater proportion of genotype 3 infection. Nonetheless, these data indicate that the challenge of reducing the burden of liver disease in HIV/HCV-coinfected persons is larger than merely developing more potent antiviral compounds.

Figure 3

Outcome of 845 HIV/HCV-coinfected patients in regular care (at least one visit per year for at least two years) at the Johns Hopkins HIV Clinic after establishment of a hepatitis C treatment center. From Reference 47.



PATHOGENESIS OF HEPATITIS C IN PERSONS WITH HIV INFECTION

The pathogenesis of HIV/HCV coinfection is poorly understood. Direct viral interactions are not likely. HCV chiefly replicates in hepatocytes, which are not known to express CD4⁺ and have not convincingly been shown to support HIV replication. HCV replication in monocytes and lymphocytes has been inferred, but only at low levels and in a minority of cells (19, 48). Given that each virus infects at most a minority of CD4⁺ mononuclear cells, direct viral interactions are unlikely to explain much of the pathogenesis.

HIV infection and the subsequent immune activation markedly affect adaptive immune responses to many infections and immunizations. HIV preferentially infects activated CD4⁺ lymphocytes and affects the function and number of uninfected CD4⁺ lymphocytes, which are necessary for spontaneous clearance of HCV infection (49). The extent of CD4⁺ lymphocyte + lymphocyte depletion (so-called nadir) has also been

linked with the magnitude of reduction in HCV-specific CD8⁺ lymphocyte responses found in HIV-infected persons (who interestingly do not have lower CD8⁺ lymphocyte responses specific to Epstein-Barr virus or cytomegalovirus) (50, 51). CD4⁺ lymphocyte suppression has been correlated with diminished HCV-specific humoral responses (52). Thus, HIV-related CD4⁺ lymphocyte depletion probably contributes to the clinical observation (discussed above) that HIV infection reduces the likelihood of spontaneous HCV clearance.

There is very limited understanding of how HIV accelerates liver disease progression. Increased STAT1 activation and Fas ligand expression in HIV-infected persons may lead to increased hepatocyte apoptosis (53). In one study, HIV/HCV-coinfected persons had greater expression of the profibrotic cytokine transforming growth factor beta 1 than HCV-uninfected persons (54). These studies provide clues to the interaction, but it has been very difficult to learn more in the absence of experimental models.

The nature of CD4⁺ lymphocyte restoration associated with HAART is also poorly understood. Some studies found that HCV-coinfected persons had less robust increases in peripheral CD4⁺ lymphocyte number following HAART, even after adjustment for HIV RNA suppression (55). This finding has not been consistently confirmed, and whether restored peripheral CD4⁺ lymphocytes affect HCV-specific adaptive immunity is unknown (56). The study by Kim et al. (50, 51) suggests that, at least in the near term and for CD8⁺ responses, the degree of initial HIV-related immunosuppression (CD4⁺ lymphocyte nadir) is more important. Interestingly, Chung and coworkers (57) demonstrated that HCV RNA levels in plasma actually increase in the first months after HAART and do so more in persons with low pretreatment CD4⁺ lymphocyte counts. Whether this represents extrahepatic HCV replication in restored CD4⁺ lymphocytes is unknown.

FUTURE DIRECTIONS

In the future, HCV-related liver disease will continue to be a major cause of morbidity and mortality among HIV-infected persons in settings where antiretroviral therapy is provided. In fact, as integrase inhibitors, CCR5 competitors, and other new compounds magnify the antiretroviral impact (and as HIV-infected persons age), the contribution of HCV-related liver disease to morbidity and mortality is likely to increase. Clearly, the greatest challenge is to improve hepatitis C prevention and treatment in HIV-infected persons. A promising anti-HCV drug pipeline makes it likely that potent anti-HCV compounds will be available by 2015. Thus, the major challenge will be to deliver novel treatments to the large proportion of HIV/HCV-coinfected persons not engaged in medical care and to forestall liver disease in the interim by optimizing existing treatment options. A comprehensive synopsis of future

Table 2 Future research priorities to diminish the impact of liver disease in HIV-infected persons (National Institutes of Health Action Plan for Liver Disease Research)

	Short term (0–3 years)	Intermediate term (4–6 years)	Long term (7–10 years)
High risk	Define effects of HIV infection on the liver, including on different populations of liver cells	Develop noninvasive means of detecting early hepatic mitochondrial dysfunction	Develop in vitro or in vivo models of HIV-HCV and HIV-HBV coinfection Develop means to reliably attribute causality of drug-induced liver disease in HIV-infected persons
Intermediate risk	Define safety and efficacy of peginterferon therapy for acute hepatitis C in HIV coinfection	Elucidate mechanisms by which HIV infection accelerates fibrosis and disease progression in HBV and HCV infection Define factors that lead to reactivation of HBV in HIV coinfection and develop means of prevention	Develop noninvasive means of assessing liver disease stage and activity in HIV-infected persons
Low risk	Develop improved regimens of HAV and HBV vaccination Define short- and long-term safety and efficacy of peginterferon and ribavirin in different subpopulations of patients with HIV-HCV coinfection	Define whether long-term peginterferon slows progression of disease in chronic hepatitis C with HIV coinfection Define prevalence, etiology, and severity of different liver disease in different cohorts of HIV-infected patients	Develop optimal therapeutic regimens for chronic hepatitis B in different stages and patterns of disease in HIV-coinfected patients Determine safety and efficacy of new agents for therapy of hepatitis C in HIV coinfection

research priorities to diminish the impact of liver disease in HIV-infected persons is maintained as Chapter 6 of the National Institutes

of Health Action Plan for Liver Disease Research (<http://liverplan.niddk.nih.gov>) (Table 2).

SUMMARY POINTS

1. Because of shared transmission routes, approximately one quarter of HIV-infected persons in the Western world are HCV-coinfected.
2. Liver disease caused by HCV infection is a leading cause of death among HIV-infected persons with access to antiretroviral drugs.
3. HIV accelerates the natural history of hepatitis C and reduces the likelihood of treatment response.
4. Just as in persons without HIV infection, the combined use of peginterferon and ribavirin is the standard of care for treatment of hepatitis C in HIV-infected persons.
5. The pathogenesis of HIV/HCV coinfection is poorly understood.
6. New and more potent treatments for HCV are anticipated and will increase the importance of expanding access to diminish the global impact of liver disease.

DISCLOSURE STATEMENT

The author has served on advisory boards for Human Genome Sciences and Sandhill.

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