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Management Complexities of HIV/HCV Coinfection in the Twenty-First Century

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INTRODUCTION

Due to shared risk factors, approximately one-third of patients with human immunodeficiency virus-1 infection (HIV) are coinfected with chronic hepatitis C virus (HCV) infection [1,2]. HIV coinfection accelerates the course of HCV-associated liver disease, and compared to those infected with chronic HCV alone (i.e., HCV-monoinfected), there is more rapid progression of hepatic fibrosis in HIV/HCV-coinfected individuals [3–5]. Thus, as HIV has become a chronic illness due to the effectiveness of highly active antiretroviral therapy (HAART), HCV-related liver disease has emerged as a major cause of morbidity and mortality among HIV-infected patients in the developed world [6–8].

Since HIV/HCV coinfection is prevalent and increases the risk of HCV-associated liver disease, effective anti-HCV therapy is critical for the long-term survival of these patients. Among HIV-infected individuals, HCV therapy can lead to viral eradication [9–12], may halt or regress hepatic fibrosis, even in the absence of viral eradication [13,14], and has been shown to be cost-effective [15]. However, a variety of complexities, including overall reluctance by patients and providers to initiate HCV therapy, increased hepatotoxicity of antiretroviral therapy, drug-drug interactions, and adverse effects of HCV therapy, have made management of chronic HCV infection a major challenge in the HIV-infected population.

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In this article, we review the: 1) epidemiology of HCV among HIV-infected individuals, 2) effect of HIV on the natural history of chronic HCV, 3) impact of antiretroviral therapy on HCV coinfection, and 4) management of chronic HCV in the HIV-infected person.

EPIDEMIOLOGY OF HCV INFECTION IN HIV

HIV and HCV are transmitted efficiently by percutaneous exposure to contaminated blood, through sexual intercourse, and from mother to infant. Since both viruses have similar routes of transmission, coinfection with HCV is common among HIV-infected individuals. In the United States, a cross-sectional analysis of two large HIV trials (N=1687) demonstrated that the overall prevalence of HCV coinfection was 16.1% (95% confidence interval [CI], 14.3%–17.8%) [1]. Approximately 80% of these patients were infected with HCV genotype 1, and 75% had high HCV RNA levels (i.e., >800,000 IU/mL) [1]. Similar HCV prevalence rates have been demonstrated among HIV-infected populations in France [16], Germany [17], Switzerland [18], and Greece [19]. In contrast, the prevalence of HCV infection in the general U.S. population is 1.6% [20].

The prevalence of HCV infection varies with the mode of transmission of HIV. As such, chronic HCV has been reported in up to 90% of HIV-infected hemophiliacs [21–23] and 90% of HIV-positive injection drug users [2,24–27]. However, transmission of HIV and HCV through blood products has been reduced markedly in the United States by screening of blood donations for both viruses [28]. In contrast, the incidence of HCV infection among HIV-infected homosexual men has risen recently, and unprotected anal intercourse, traumatic sexual practices, and concomitant sexually transmitted diseases have been the main risk factors for HCV acquisition [29].

The risk of perinatal transmission of HCV is increased for infants born to HIV/HCV-coinfected mothers. A recent meta-analysis of 10 studies demonstrated that the risk for HCV vertical transmission among HIV/HCV-coinfected mothers was 2.82 (95% CI, 1.8–4.5) compared to HCV-monoinfected mothers [30]. The cumulative incidence of HCV infection is 17.1% in infants born from HIV/HCV-coinfected mothers compared with 5.4% for those born to mothers with only HCV infection [31–33]. Higher HCV RNA levels are associated with increased perinatal transmission [32].

EFFECT OF HIV ON THE NATURAL HISTORY OF HCV

HIV infection adversely affects every aspect of the natural history of chronic HCV. While 14% to 45% of HCV-monoinfected individuals spontaneously clear HCV after acute infection, HCV clearance occurs in only 5% of HIV/HCV-coinfected persons, and less often in those with lower CD4 cell counts [34–36]. HIV/HCV coinfection is associated with higher HCV RNA levels compared to HCV-monoinfected patients [5,37–40], and HCV RNA levels increase as CD4 cell count decreases, suggesting that HIV-induced immune deficiency allows for increased HCV replication [5,38].

In addition, liver fibrosis progression is accelerated in HIV/HCV patients, with a more rapid progression to cirrhosis compared with HCV-monoinfected individuals [3,5]. HIV/HCV-coinfected persons are at higher risk for advanced hepatic fibrosis and cirrhosis compared to HCV-monoinfected individuals [3,5,37,41–44]. Among 67 HIV/HCV-coinfected patients undergoing paired liver biopsies separated by a median of 2.8 years, Sulkowski et al [45] demonstrated that 28% of patients had an increase of at least 2 modified Ishak stages of hepatic fibrosis. Among those with mild fibrosis on initial biopsy, 26% had a two-stage progression on follow-up biopsy.

HIV/HCV coinfection increases the risk of hepatocellular carcinoma compared to HIV-monoinfected patients (adjusted hazard ratio [HR], 5.35; 95% CI, 2.34–12.20) [46] but not compared to HCV-monoinfected (adjusted HR, 0.84; 95% CI, 0.55–1.27) [47]. This cancer presents sooner after cirrhosis develops [48] and more commonly as infiltrating and multifocal lesions [49] in HIV/HCV patients compared to those with chronic HCV alone.

The effect of HIV on HCV-related end-stage liver disease has been examined exclusively in patients with hemophilia. These studies show that the cumulative incidence of hepatic failure is 11% to 35% over a mean follow-up of 10 to 24 years from initial factor concentrate exposure, corresponding to a yearly incidence of 1.5%/year [21–23,50–52]. The results also indicate a 3- to 21-fold increase in the risk of end-stage liver disease in HIV/HCV-coinfected patients compared to HCV-monoinfected patients.

HIV coinfection decreased the median survival time of patients with HCV-associated end-stage liver disease compared to HCV-monoinfected patients (16 mo versus 48 mo; $p<0.001$) in a Spanish cohort [53]. The risk of death in HIV-infected patients is substantially higher in HIV/HCV patients compared to those with chronic HCV alone (relative risk [RR], 2.26; 95% CI, 1.51–3.38) [53]. Predictors of death among HIV/HCV coinfected patients were Child - Pugh score (HR, 1.20; 95% CI, 1.08–1.37), CD4 cell count less than 100 cells/mm^3 (HR, 2.48; 95% CI, 1.52–4.06), and hepatic encephalopathy at the time of decompensation (HR, 2.45; 95% CI, 1.41–4.27) [54].

With the increased longevity of HIV patients due to potent antiretroviral therapy and the prophylaxis of traditional opportunistic pathogens, HCV-related liver disease has emerged as a major cause of morbidity and mortality in this population [6,7,55–58]. Results from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, a collaborative network of 11 HIV cohorts from North America, Europe, and Australia, demonstrate that HCV-related liver disease is now the second leading cause of death in the HIV population [8]. Among 23,441 HIV-infected patients enrolled in the study between December 1999 and February 2004 and followed for a median of 3.5 years, 1246 deaths occurred and 181(14.5%) were liver-related. Among these liver-related deaths, 66% were due to chronic HCV, 17% were due to chronic hepatitis B, and 7% were due to both hepatitis B and HCV. In addition, recent data from the Strategies for Management of Antiretroviral Therapy (SMART) study demonstrate that mortality rates among HIV/viral hepatitis-coinfected individuals are nearly four times that of HIV-monoinfected persons [59].

In summary, these data clearly show that chronic HCV is more severe in HIV/HCV-coinfected patients. A greater proportion of HIV/HCV patients develop chronic HCV, and HIV/HCV patients are at substantially higher risk for liver-related complications such as cirrhosis, end-stage liver disease, and hepatocellular carcinoma compared to HCV-monoinfected patients. In addition, HCV-associated liver disease is now the major cause of morbidity and mortality among HIV-infected patients in the developed world.

IMPACT OF ANTIRETROVIRAL THERAPY ON HCV INFECTION

Effect of Antiretroviral Therapy on the Natural History of HCV

Recent cohort studies have shown that use of HAART, in particular achieving HIV suppression, is associated with better hepatic outcomes in HIV/HCV-coinfected patients. Mehta et al [60] reported that detectable HIV RNA (adjusted odds ratio [OR], 3.4; 95% CI, 1.6–7.1) and shorter cumulative HAART exposure (adjusted OR per year of exposure, 0.8; 95% CI, 0.70–0.96) were associated with necroinflammatory activity among coinfected persons. Bräu et al [61] found that HIV/HCV patients with HIV RNA suppression had a slower fibrosis progression rate than those with detectable HIV RNA (0.122 versus 0.151 Ishak fibrosis units/year;

p=0.013) but similar to that of HCV-monoinfected patients (0.122 versus 0.128 Ishak fibrosis units/year; p=0.52). Similarly, Verma et al [62] reported that HIV/HCV-coinfected persons on HAART had comparable liver histology findings to those of HCV-monoinfected persons. In a study of 162 HIV/HCV-coinfected individuals who underwent a liver biopsy, absence of protease inhibitor therapy as part of the antiretroviral regimen was an independent predictor of progression to cirrhosis (RR, 4.74; 95% CI, 1.34–16.67) [63].

Use of HAART has also been shown to be associated with reduced liver-related mortality among HIV/HCV-coinfected individuals. A German cohort study that followed coinfected patients over a 12-year period showed that HAART was an independent predictor of liver-related survival (OR, 0.106; 95% CI, 0.020–0.564) [64]. Among HIV/HCV-coinfected patients with pre-existing hepatic failure, HAART was associated with improved survival (HR, 0.5; 95% CI, 0.30–0.90), and 40% of HIV/HCV patients receiving HAART were alive after three years compared to 18% not on HAART [54]. Finally, the recent D:A:D study [8] showed that there was little change in the liver-related death rate with increasing cumulative duration of HAART use.

Taken together, the available data suggest that HAART favorably affects the course of HCV in HIV-infected patients, decreases the rate of death due to liver disease, and should not be withheld from HIV/HCV-coinfected persons dues to fears of toxicity (see next section).

Hepatotoxicity of Antiretroviral Therapy in HCV Coinfection

While use of HAART has had enormous benefits for HIV/HCV patients, liver toxicity associated with these medications remains a concern for physicians who treat this population. Four main mechanisms of antiretroviral-related hepatotoxicity have been described in HIV-infected individuals: 1) mitochondrial toxicity; 2) hypersensitivity reactions involving the liver; 3) direct drug toxicity; and 4) immune reconstitution following HAART initiation in the presence of hepatitis coinfection [65]. More than one mechanism may occur simultaneously.

Among studies of HIV-infected persons, the AIDS Clinical Trial Group scale of liver toxicity typically has been employed to categorize the severity of liver injury [66]. Severe hepatotoxicity, the primary outcome in the majority of hepatotoxicity studies in the HIV population, has been defined as either a grade 3 (5.1 to 10 times upper limit of normal) or 4 (>10 times upper limit of normal) change in aspartate aminotransferase and/or alanine aminotransferase levels during HAART treatment or >3.5-fold increase in these levels above baseline if aminotransferases are elevated at HAART initiation [67].

Using these criteria, studies have shown that HCV coinfection increases the risk of severe hepatotoxicity in HIV-infected patients treated with HAART [67–75]. Discontinuation of HAART is more frequent and occurs earlier among HIV/HCV-coinfected patients than for those with HIV alone [76]. Moreover, the risk of severe hepatotoxicity with HAART is increased for HIV/HCV-coinfected patients with advanced (METAVIR stage 3 or 4) fibrosis (RR, 2.75; 95% CI, 1.08–6.97) [77]. However, anxiety related to hepatotoxicity should not, as it often does, dissuade or delay patients and physicians from initiating a therapy that may attenuate HCV-related liver disease and reduce liver-related mortality.

Given the increased risk of hepatotoxicity in the HIV/HCV population, eradication of HCV with antiviral therapy might improve tolerance to HAART. In a recent study among 132 HIV/HCV-coinfected patients treated with interferon-based therapy in Spain, the yearly incidence of severe hepatotoxicity was greater in patients who did not achieve a sustained virologic response (i.e., SVR, defined as an undetectable HCV RNA at the end of treatment and 24 weeks later) than in those who did (12.9% versus 3.1%; p<0.001) and in patients with advanced liver fibrosis than in those without it (14.4% versus 7.6%; p=0.003) [78]. Failure to achieve SVR

(OR, 6.13; 95% CI, 1.83–37.45) and use of either didanosine or stavudine as part of the antiretroviral regimen (OR, 3.59; 95% CI, 1.23–10.42) were independent predictors of hepatotoxicity after interferon therapy. These data demonstrate that achieving SVR after anti-HCV treatment can reduce the risk of hepatotoxicity during antiretroviral therapy, which should further encourage the treatment of chronic HCV in HIV.

Certain antiretroviral medications and/or classes may be more likely to produce elevated aminotransferases or lead to clinically apparent hepatotoxicity (Table 2). The use of the nucleoside analogues stavudine, didanosine, or their combination can lead to a higher rate of hepatic steatosis in the coinfected population [79]. The non-nucleoside reverse transcriptase inhibitor nevirapine has been shown to increase the risk of severe hepatotoxicity in HIV/HCV-coinfected patients, and elevations in aminotransferase levels may develop 4 to 6 months after initiation of the medication [67,80,81]. Nevirapine use has also been associated with more advanced hepatic fibrosis (adjusted OR, 2.56; 95% CI, 1.02–6.58) in a cross-sectional study of 152 coinfected patients who underwent a liver biopsy [82]. In contrast, the majority of HIV/HCV patients who initiate a protease inhibitor-containing regimen do not experience treatment-limiting hepatotoxicity. Although liver enzyme elevations may develop with any protease inhibitor, lopinavir/ritonavir, fosamprenavir/ritonavir, and nelfinavir appear to be less hepatotoxic [83] and tipranvir/ritonavir most hepatotoxic [84]. An unconjugated hyperbilirubinemia can occur during atazanavir and indinavir therapy but does not reflect liver damage and is related to the inhibition of the uridine diphosphate glucuronosyl transferase enzyme [85,86]. Dual protease inhibitor therapy does not increase the rate of hepatotoxicity [87]. Data on the hepatotoxicity of fusion inhibitors, integrase inhibitors, and chemokine receptor antagonists in HIV/HCV patients are lacking.

INTEGRATING HCV CARE IN HIV PRACTICE

Multidisciplinary Approach

HIV/HCV-coinfected patients should be referred to a hepatologist or infectious diseases physician with expertise in HIV/HCV coinfection to provide more information about diagnosis, natural history, and therapeutic options. Clinical management should subsequently be multidisciplinary, with input from advanced practice nurses, psychiatrists, pharmacists, dieticians, and addiction management experts [88].

Support and education are crucial to the management of chronic HCV in HIV-infected patients, and health care providers should provide additional educational materials and offer referral to support groups to those undergoing evaluation for established HCV infection. Patients should be counseled to prevent liver damage and HCV transmission.

Screening for Drug and Alcohol Abuse

Heavy alcohol consumption, particularly in quantities greater than 50 g per day (approximately 3 drinks), can worsen the course and outcome of chronic HCV [89] and may compromise antiviral therapy by decreasing adherence or interfering with the antiviral action of interferon-based therapy [90]. Efforts to diagnose and treat alcohol abuse should be performed in all HIV/HCV-coinfected patients before beginning HCV therapy, and relapse into drug and alcohol use should be repeatedly assessed. Treatment for drug and alcohol abuse should be made available to all who want and need it. Safe levels of alcohol consumption in HIV/HCV patients remain unclear, but even moderate levels of consumption may accelerate disease progression [91]. All HIV/HCV-coinfected patients should therefore be advised to abstain from alcohol [92,93].

Treatment of Neuropsychiatric Disorders

Neuropsychiatric disorders, particularly depression, are common among HIV/HCV-coinfected patients [94] and are a frequent adverse effects of pegylated interferon therapy [9–11]. Identification and treatment of neuropsychiatric disorders should be pursued prior to and during HCV therapy [91]. Referral to a psychiatrist should also be considered.

Immunization Against Hepatitis A and B

HIV/HCV-coinfected individuals should be tested for prior exposure to hepatitis A virus infection (anti-hepatitis A IgG antibody) and previous or concurrent hepatitis B virus infection (hepatitis B surface antigen, anti-hepatitis B core IgG antibody, and anti-hepatitis B surface antibody). Acute infection with hepatitis A or B in those with underlying chronic HCV increases the risk for fulminant hepatitis and can result in high morbidity [95,96]. Despite evidence of decreased response in HIV-infected persons, hepatitis A and B vaccination should be performed in those who are seronegative for these viruses [97].

Liver Fibrosis Assessment

Evaluation of liver histology with a liver biopsy is the best tool for assessing the likelihood of progression of hepatic injury and is a better predictor of subsequent clinical events than hepatic aminotransferase elevations, HCV genotype, or HCV RNA level [98,99]. In one study, 29% of HIV/HCV patients with persistently normal alanine aminotransferase levels had advanced fibrosis on liver biopsy [100]. As such, many experts recommend a liver biopsy in HIV/HCV-coinfected patients to assess the extent of underlying liver damage. The liver biopsy can help guide HCV treatment decisions, permits direct determination of the degree of necroinflammation, and allows detection of other hepatic abnormalities (e.g., steatosis, iron overload, and concomitant infections) [101]. Evaluation of liver histology with a liver biopsy can also inform the need for hepatocellular carcinoma screening, which is recommended once cirrhosis is present.

Despite the value of the liver biopsy, it possesses a number of limitations that have contributed to low acceptance by HIV/HCV-coinfected patients, in particular, its invasive nature, occasionally serious complications [101], sampling error due to the small size of the extracted tissue and inherent heterogeneity of hepatic fibrosis [102,103], and high cost [104]. As a result, non-invasive modalities to evaluate hepatic fibrosis have been increasingly examined in HIV/HCV population [105]. These non-invasive tools are currently divided into two major categories: 1) serum biochemical markers (e.g., AST-to-platelet ratio index, SHASTA, FIB-4, FibroTest, FibroSure) [106–109], and 2) imaging techniques, primarily elastometry (FibroScan) [110,111]. These tools have high predictive value in identifying advanced hepatic fibrosis and cirrhosis, but they have been imprecise in distinguishing among the intermediate stages of hepatic fibrosis [112]. In addition, serum fibrosis markers have generally been less reliable in coinfected patients because of the inflammatory nature of HIV disease and co-administration of medications that may interfere with test results.

Given the accelerated progression of HCV-related liver disease among HIV-infected patients, improvements in the efficacy of HCV therapy in the HIV population, the high predictive value of the early virological response to HCV therapy (at week 12 of treatment) to identify who will and who will not respond, and the acknowledged limitations of the liver biopsy, current HIV/HCV coinfection management guidelines no longer require that a liver biopsy be performed prior to initiation of HCV therapy [112].

HCV Treatment

Pegylated Interferon plus Ribavirin—Given the accelerated progression to end-stage liver disease among HIV/HCV patients, treatment of chronic HCV should be considered in all coinfected patients [113]. Combination pegylated interferon plus ribavirin for 48 weeks represents the standard of care for treating chronic HCV in HIV-infected individuals, as it is for HCV-monoinfected persons. As with HCV-monoinfected patients, the primary goal of treatment is viral eradication (i.e., SVR) [91,112]. A second potential benefit of HCV therapy is a reduction in the risk of liver-related complications. Among a Spanish cohort of antiretroviral-treated HIV/HCV-coinfected patients, receipt of HCV therapy was associated with improved survival, and no episodes of hepatic decompensation were noted among subjects who achieved SVR [114]. In an Italian retrospective cohort study, HIV/HCV-coinfected patients with cirrhosis who received a mean of nine months of pegylated interferon plus ribavirin without virologic response were less likely to develop adverse liver-related outcomes (i.e., ascites, jaundice, encephalopathy, variceal bleeding, hepatocellular carcinoma, or death) compared with age- and Child-Pugh score-matched coinfected patients who had not received HCV therapy [115].

Three randomized, controlled trials (AIDS Clinical Trials Group [ACTG] Study 5071, AIDS Pegasys Ribavirin International Co-infection Trial [APRICOT], and ANRS HC-02 RIBAVIC trial) were published in 2004 demonstrating that pegylated interferon plus ribavirin is the optimal therapy for chronic HCV among HIV-infected patients [9–11]. There were notable differences in type of pegylated interferon use, dose regimen of ribavirin, and type of coinfected patients enrolled between the studies, and these are highlighted in Table 1. These differences make it impossible to compare overall results between these clinical trials.

In each study, the highest SVR rates were observed in the pegylated interferon plus ribavirin arms. SVR rates for HCV genotype 1-infected persons in these arms were 14% for ACTG 5071, 17% for RIBAVIC, and 29% for APRICOT [9–11]. For subjects infected with HCV genotypes 2 or 3, SVR rates were considerably higher: 44% (RIBAVIC), 62% (APRICOT), and 72% (ACTG 5071) [9–11], emphasizing the importance of HCV genotype as a predictor of SVR, as in studies of HCV-monoinfected patients. Similarly, low pretreatment HCV RNA level (≤800,000 IU/mL) is also associated with SVR [9]. This was highlighted in the APRICOT study where SVR rates were 61% among persons with HCV genotype 1 and a baseline HCV RNA ≤800,000 IU/mL who were randomized to pegylated interferon plus ribavirin [9]. In contrast, the SVR rate was only 18% for those with genotype 1 and HCV RNA >800,000 IU/mL who received pegylated interferon plus ribavirin. Additional predictors of SVR that have been reported include absence of prior history of injection drug use [10], detectable HIV RNA [10], age ≤40 years [11], baseline alanine aminotransferase level greater than 3 times the upper limit of normal [11], antiretroviral therapy with a non-nucleoside reverse transcriptase inhibitor or protease inhibitor [116], and non-black race [116]. The early virologic response, defined as ≥2 log IU/mL decrease in HCV RNA level after 12 weeks of therapy, has high predictive value in patients with coinfection [9–11]. Thus, if a patient has not had an early virologic response, the likelihood of SVR is negligible. Extending therapy in patients who do not have an early virologic response will not increase SVR rates [117].

The SVR rates reported in the pivotal HIV/HCV treatment trials are considerably lower than those reported for HCV-monoinfected patients (42–52% in HCV genotype 1 and 78–84% for genotypes 2 and 3). Possible reasons for the poorer SVR rates among HIV/HCV-coinfected patients include: 1) high HCV RNA levels in subjects with HIV coinfection, 2) qualitative defects in both the cellular and innate immune response, 2) and lower doses of ribavirin or dose escalation administered in the treatment trials (due to concern for potential increased risk of hematologic toxicity in this population). Recently, the Spanish Pegasys Ribavirina España Coinfección (PRESCO) study examined whether administration of weight-based ribavirin

(1000 mg daily if body weight <75 kg and 1200 mg if >75 kg) in combination with pegylated interferon, as is used in HCV-monoinfected patients, improves SVR rate in HIV/HCV patients [118,119]. Substantial improvements in virologic outcomes were reported, with SVR achieved in 72.4% of HCV genotype 2 or 3 patients and 35% of genotype 1 or 4 patients. Only 3% of patients stopped HCV therapy due to severe anemia. As such, recent HIV/HCV management guidelines now recommend weight-based ribavirin dosing in HIV-positive persons undergoing combination HCV therapy.

In addition to virologic response, HCV therapy can halt or regress hepatic fibrosis in HIV/HCV-coinfected patients, even in the absence of SVR [13,14]. Data from the APRICOT trial show that 70% of patients who achieved SVR with pegylated interferon plus ribavirin had a two-stage improvement in Ishak fibrosis score on a repeat liver biopsy 24 weeks after the end of HCV treatment. Among those who did not achieve SVR, 43% receiving pegylated interferon plus ribavirin arm had this histologic response. Combination HCV therapy has also been shown to decrease progression of HCV-related fibrosis in HIV-infected individuals [14]. For coinfected patients who have not responded to HCV therapy or who have relapsed after treatment, clinical trials are currently examining whether the long-term administration of interferon can prevent liver fibrosis progression even in the absence of SVR [120]. New agents with specific anti-HCV activity are being tested [121], and clinical trials examining the efficacy and safety of these drugs in coinfected patients should be prioritized without waiting for the final results of phase III trials conducted in HCV-monoinfected patients.

Adverse Effects of HCV Therapy—The toxicities and intolerabilities of HCV therapy tend to dominate HCV treatment in HIV-infected patients, but these do not lead to treatment discontinuation more frequently among HIV/HCV-coinfected patients (12–17% withdrawal rates in randomized trials [9–11]) compared to HCV-monoinfected patients (14–22% withdrawal rates in clinical trials [12,122]).

Results from the APRICOT study show that pegylated interferon reduces HIV RNA levels approximately 1.0 log copies among subjects with detectable HIV RNA [9].In the same study, HCV therapy precipitated a decrease in absolute CD4 cell counts throughout the 48-week treatment phase of the study and then returned to baseline values by 24-weeks after completing HCV therapy [9]. Despite the decrease in CD4 cell counts, the CD4 cell percentage is typically unchanged, and clinical progression to the acquired immune deficiency syndrome was not observed in any subject in APRICOT during the study period. Cooper et al [123] recently compared infection rates between HIV/HCV-coinfected and HCV-monoinfected patients receiving interferon-based therapy for chronic HCV. Rates of infection did not differ by HIV status, and HIV was not found to be an independent predictor of infection during HCV therapy.

Leukopenia and thrombocytopenia are both dose-related adverse effects of pegylated interferon. In particular, use of granulocyte colony-stimulating factor was allowed in two of the pivotal HIV/HCV coinfection treatment trials to improve leukopenia [9,10]. Anemia is also a common adverse effect during combination anti- HCV therapy [124]. It arises because of the suppression of erythropoiesis induced by interferon [125] and the reversible hemolysis induced by ribavirin [126,127]. Reduction of the ribavirin dose had been recommended if anemia developed during HCV therapy, but this is associated with reduced SVR rates [122]. Recombinant human erythropoietin can counteract the anemia associated with HCV therapy in HIV/HCV-coinfected subjects and helps avoid ribavirin dose reduction [128], maximizing the effectiveness of antiviral therapy. The use of hematopoietic growth factors in HIV/HCV patients has been associated with an improved clinical response to pegylated interferon plus ribavirin therapy [129].

A recent retrospective cohort study found that the incidence of significant weight loss (defined as loss of at least 5% of baseline body weight) was substantially greater in dually-treated HIV/HCV-coinfected subjects compared to either treated HCV- or HIV-monoinfected subjects [130]. Among 192 patients (N=63 HIV/HCV-coinfected, N=64 HCV-monoinfected, N=65 HIV-monoinfected), significant weight loss occurred in 48 (76%) HIV/HCV subjects versus 25 (39%) HCV subjects ($p<0.001$) and 2 (3%) HIV subjects ($p<0.001$), yielding an adjusted HR of 2.76 (95% CI, 1.67–4.55) and 38.5 (95% CI, 8.5–174.7), respectively. The degree of weight loss was also greater among the HIV/HCV cohort compared to both monoinfected cohorts. Body weights for HIV/HCV-coinfected and HCV-monoinfected subjects were stable before initiation of HCV therapy, but both cohorts lost weight after HCV treatment initiation, with the rate of weight loss being greater for dually-treated HIV/HCV subjects. Receipt of more than two nucleoside reverse transcriptase inhibitors increased the risk of clinically significant weight loss (adjusted HR, 8.17; 95% CI, 2.37–28.20), suggesting that mitochondrial toxicity might play some role in weight loss during dual HIV/HCV therapy.

Drug-Drug Interactions During HCV Therapy—An additional concern for dually-treated HIV/HCV-coinfected patients is the potential for drug-drug interactions between ribavirin and the nucleoside reverse transcriptase inhibitors included in the antiretroviral regimen (Table 2). A retrospective cohort study among 217 HIV/HCV patients receiving pegylated interferon plus ribavirin found that zidovudine use was associated with a greater mean hemoglobin decline at four weeks of HCV therapy (3.1 vs. 2.1 gm/dL; $p<0.001$) compared to non-users [131]. By week 12 of HCV therapy, zidovudine use was more frequently associated with ribavirin dose reduction (52% vs. 18%; $p<0.001$) and erythropoietin use (49% vs. 23%; $p<0.001$) compared to those who did not receive the drug. Zidovudine likely exacerbates ribavirin-related anemia by inhibiting the hematopoietic response to ribavirin-induced hemolysis. Thus, it is advisable to avoid zidovudine use during HCV therapy, and providers should considering switching to an alternative nucleoside reverse transcriptase inhibitor prior to initiation of HCV treatment [112].

Since ribavirin increases the intracellular active metabolite of didanosine [132], concomitant use of both medications increases the likelihood of mitochondrial toxicity that may lead to pancreatitis and symptomatic lactic acidosis [133–136]. In both the APRICOT and RIBAVIC trials, didanosine use increased the risk of hepatic decompensation when used in conjunction with ribavirin [137,138]. As a result, ribavirin should not be administered to person taking didanosine as part of their HAART regimen.

A recent retrospective substudy of the RIBAVIC trial reported that abacavir use increased the risk of early virologic failure to combination HCV therapy (OR, 4.9; 95% CI, 1.5–16.1), possibly due to intracellular competition between ribavirin and abacavir, both guanasine analogues, for activation through phosphorylation [139]. However, in a Spanish cohort that controlled for serum ribavirin levels, abacavir use was not associated with early virologic failure, suggesting that appropriate weight-based ribavirin dosing and adherence are important when abacavir is part of the antiretroviral regimen [140].

Advanced Liver Disease—The management of advanced liver disease in HIV/HCV-coinfected patients is complex. Patients with cirrhosis should have regular monitoring for evidence of decompensation and hepatocellular carcinoma. Individuals with decompensated liver disease are generally not candidates for HCV therapy because treatment increases the risk of life-threatening complications [138]. HIV therapy may improve hepatic outcomes and survival in coinfected patients with liver failure [54]. However, administration of these medications in this setting is challenging due to alteration of hepatic metabolism and the risk of drug-induced liver injury. Of note, hepatic metabolism of non-nucleoside reverse-

transcriptase inhibitors, particularly efavirenz, is impaired in coinfected patients with cirrhosis, but no similar effect is seen for protease inhibitors [141].

Orthotopic liver transplantation is an option for coinfected patients with decompensated liver disease. However, HIV coinfection is a major determinant of poor outcomes and death in HCV-infected persons undergoing liver transplant [142]. De Vera et al [143] demonstrated substantially reduced five-year survival after liver transplantation among HIV/HCV-coinfected compared to HCV monoinfected patients (33% versus 72%; p=0.07). In addition, 22% of coinfected patients were unable to tolerate HAART post-transplant, which was a major determinant of death. Early treatment of HCV post-transplant may be a potential strategy to reduce these adverse outcomes, but more study is needed and ongoing in this area.

SUMMARY

Due to shared routes of transmission, HCV coinfection is common among HIV-infected persons. Due to the effectiveness of antiretroviral therapy, chronic HCV has now emerged as a major cause of morbidity and mortality in this population. Since chronic HCV is highly prevalent among HIV-infected patients and has a rapid disease progression, antiviral therapy with pegylated interferon plus ribavirin is critical for the long-term survival of HIV/HCV patients. Additional studies are needed to examine the natural history of chronic HCV in HIV/HCV-coinfected patients, identify the appropriate treatment candidates, and identify additional interventions that can improve response to antiviral therapy.

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Table 1

Data from pegylated interferon plus ribavirin arms from four pivotal studies examining the treatment of chronic hepatitis C virus infection in HIV-infected individuals.

Characteristic	**ACTG 5071 (N=133)**	**APRICOT (N=868)**	**RIBAVIC (N=412)**	**PRESCO (N=389)**
Site	U.S.	U.S., Europe, Australia	France	Spain
Peginterferon formulation	Peginterferon α-2a	Peginterferon α-2a	Peginterferon α-2b	Peginterferon α-2a
Ribavirin dose	600 mg/d – 1000 mg/d	800 mg/d	800 mg/d	1000 mg/d – 1200 mg/d
HCV genotype 1 (%)	77	61	48	51
Bridging fibrosis/cirrhosis (%)	11	12	39	27
On antiretroviral therapy (%)	85	84	83	67%
CD4 cell count (/mm^3)	453 (median)	520 (mean)	547 (median)	540 (mean)
Undetectable HIV RNA (%)	61 (<50 copies/mL)	60 (<50 copies/mL)	70 (<400 copies/mL)	NR
SVR rate, genotype 1 (%)	14	29	17	35
SVR rate, genotype 2/3 (%)	73	62	44	72
Withdrawal rate (%)	12	25	39	45

HIV=human immunodeficiency virus; SVR=sustained virologic response; NR=not reported

Table 2

Specific antiretroviral concerns in HIV/HCV-coinfected persons.

Drug	Comment	Recommendation
Abacavir	• May decrease virologic response to HCV therapy, especially when serum ribavirin levels low, possibly by competing with ribavirin for phosphorylation at an intracellular level [139,140]	• Ensure adequate weight-based ribavirin dosing • Emphasize ribavirin adherence
Didanosine	• Can have increased intracellular levels when administered with ribavirin [132] • May be associated with hepatic steatosis in coinfected persons [79] • Increased risk of lactic acidosis and pancreatitis when administered with ribavirin [133–136] • Increased risk of hepatic decompensation during HCV therapy in coinfected patients with cirrhosis [137,138]	• Concomitant use with ribavirin contraindicated
Nevirapine	• Increased rate of severe hepatotoxicity in HIV/HCV-coinfected persons [67,80, 81] • May be associated with hepatic fibrosis in coinfected individuals [82]	• Consider alternate antiretroviral agent in coinfected persons
Stavudine	• May be associated with hepatic steatosis in HIV/HCV-coinfected persons [79]	• Consider avoiding use of stavudine, if possible
Zidovudine	• Can potentiate ribavirin-induced anemia, possibly through suppression of hematopoiesis [131]	• Avoid concomitant use with ribavirin • Monitor hemoglobin levels closely if no other antiretroviral options