Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV–HIV International Panel

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AIDS 2007, **21**:1073–1089

Keywords: HCV, HIV, liver, interferon, ribavirin

Introduction

Chronic hepatitis C (HCV) infection is currently one of the most clinically relevant comorbidities in the HIV population; overall, it affects one third of HIV-positive individuals [1]. Progression to end-stage liver disease occurs faster in coinfected patients [2–4] and decompensated cirrhosis is one of the main causes of hospitalization and death in this population [5–8]. However, the risk of hepatotoxicity using antiretroviral drugs is increased in subjects with underlying HCV infection [9,10]. Therefore, the optimal management of chronic HCV in HIV-positive patients is currently a priority.

Several guidelines for caring for HCV infection in HIV-positive individuals have been released [11–15]. Because new and relevant information has recently appeared, it is convenient to update them. Eleven areas have been identified in which new recommendations are particularly needed:

- management of patients with persistently normal aminotransferases
- liver fibrosis assessment: when and how
- predictors of response to anti-HCV therapy in coinfected patients
- optimal dosages of pegylated interferon (pegIFN) and ribavirin (RBV)
- optimal duration of anti-HCV therapy
- treatment of non-responders and/or relapsers
- care of patients with end-stage liver disease
- treatment of acute HCV infection in HIV-infected individuals
- management of patients with multiple hepatitis viruses
- interactions between HCV medications and antiretroviral drugs
- hepatotoxicity of antiretroviral drugs.

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ISSN 0269-9370

Patients with persistently normal aminotransferases

The exact definition of persistently normal aminotransferases is not well established in patients with chronic HCV infection. Fluctuations in aspartate/alanine aminotransferases (AST/ALT) are frequent in HCV-related liver disease and differences in the prevalence of persistently normal ALT may reflect the length of follow-up and/or the number of biochemical determinations made [16–18]. We propose a definition requiring the demonstration of normal ALT in at least three consecutive tests made at least 2 months apart each, over a period of 12 months. One third of individuals who initially meet these criteria, however, may show ALT elevations as the period of observation extends [19–22].

Therefore, the characterization of patients with normal ALT should not be based on sporadic determinations of liver enzymes, and the term 'asymptomatic' or 'healthy' HCV carrier is inappropriate [22].

A further consideration is that the so-called 'normal' limit of aminotransferases has to be revisited, since recent studies have shown that aminotransferase levels in subjects without any liver injury [23] or in persons free of liver-related death on follow-up [24] are definitely lower than those accepted as normal in the past.

The degree of aminotransferase elevation generally reflects the extent of liver inflammation. Around 25% of HCV-monoinfected patients show persistently normal ALT [19–22,25] and liver disease is generally less severe in this group [25–28]. Women tend to show more frequently persistently normal ALT than men [28], as well as subjects infected with HCV genotype 4 [29–31]. In contrast, patients with HCV genotype 3 show normal ALT less frequently [31]. As expected considering the immune-mediated nature of HCV-related liver disease, there is little correlation between serum HCV RNA and aminotransferases [32].

Few studies have been conducted so far in coinfected patients with normal ALT. Only 7–9% of this population show persistently normal liver enzymes [31,33]. Exposure to antiretroviral drugs, alcohol abuse and other conditions explain, on the one hand, the lower rate of normal ALT in HIV-positive patients with chronic HCV infection. On the other hand, significant liver fibrosis has been reported in up to 25–40% of coinfected patients with normal ALT [31,33], a prevalence higher than the 10–30% reported in HCV-monoinfected individuals [28,34]. In two recent studies, 12–14% of coinfected patients with normal ALT had cirrhosis on liver biopsy [33,35].

Since less than 15% of HCV-monoinfected individuals with minimal or absent liver fibrosis progress to cirrhosis within 15 years [36], and most patients with normal ALT have mild liver disease [37], these individuals have formerly not been considered for HCV therapy. Moreover, flares in ALT activity and lower treatment responses were reported in the past in patients with normal ALT exposed to IFN, which further discouraged their treatment. However, recent studies in HCV-monoinfected patients have alerted clinicians to the higher liver fibrosis progression in initially mild chronic HCV infection [38] and similar responses to pegIFN plus ribavirin RBV have been obtained in patients with normal than with elevated aminotransferases [39].

Recommendation

Given that the prevalence of and progression to advanced liver fibrosis in patients with normal ALT is higher in HIV-positive patients [31,33], these patients should be considered for anti-HCV therapy. Treatment should be recommended based on patient's motivation, disease duration, fibrosis stage and virological profile regardless ALT levels [40].

Liver fibrosis assessment: when and how?

The extent of hepatic fibrosis is the best prognostic factor of disease progression in patients with chronic HCV infection, and therefore it is worth considering this before initiating HCV therapy. Liver biopsy has been for many years the only tool to assess hepatic fibrosis. It has the advantage of providing additional information on other relevant histological findings, such as necroinflammation and steatosis. However, the development of non-invasive tools for staging hepatic fibrosis has been prompted by the several limitations of liver biopsy, such as its invasive nature, with occasional serious and even life-threatening complications [41]; sampling error owing to relatively small size and/or fragmentation of examined tissue [42] and/or to the inherent heterogeneity of hepatic fibrosis [43]; low acceptance by most patients; and relatively elevated cost [44].

Non-invasive procedures to assess liver fibrosis are currently divided into two major categories: imaging techniques, such as elastometry (FibroScan) [45–48] and serum biochemical markers (i.e., Fibrotest, APRI, SHASTA, FIB-4, Forn's index, etc.) [49–53]. These tools are generally accurate in discriminating between lack of fibrosis and advanced fibrosis but are less precise in distinguishing between intermediate fibrosis stages. Their predictive value is particularly good for advanced hepatic fibrosis and cirrhosis [54]. However, serum fibrosis markers are generally less reliable in coinfected patients, given the inflammatory nature of HIV disease and/or the frequent prescription of drugs in this population that may interfere with some fibrosis markers in the blood [55,56], as with bilirubin elevations in atazanavir therapy, gamma-glutamate transaminase abnormalities with non-nucleoside reverse transcriptase inhibitors, or cholesterol elevations associated with some protease inhibitors. In

contrast, fibrosis staging using elastometry seems to be more reliable in this setting, avoiding such interference [48,57]. Elastometric measurements can be made in 10 min, be repeated periodically, are inexpensive and have more than 90% positive predictive value for advanced fibrosis [45–47].

When the diagnosis of a hepatic disease is clear by other means, as occurs with chronic HCV infection using virological markers (serum HCV RNA), the need for a liver biopsy to stage hepatic fibrosis and guide treatment decisions is currently no longer justified in most instances [58,59]. The higher response to pegIFN–RBV compared with that to standard IFN, the faster progression of HCV-related liver disease in the HIV setting and the chance to assess the virological response at earlier timepoints to identify who will and who will not respond to therapy are all factors that allow the opportunity to prescribe HCV therapy to most patients while avoiding a liver biopsy [59]. The availability of easier means to assess liver fibrosis accurately has permitted this invasive procedure to be abandoned in most cases in routine clinical practice outside academic purposes. Moreover, these new tools have opened further opportunities to improve our knowledge of the natural history of HCV-related liver damage. Large cross-sectional and longitudinal studies have allowed recognition of (1) HCV genotype 3 as an independent predictor of accelerated liver fibrosis [60]; (2) different fibrosis thresholds in cirrhotic patients for developing distinct complications (e.g., esophageal varices, ascites or bleeding) [61]; and (3) of the possibility that severe liver fibrosis, including cirrhosis, can partially revert in at least a subset of patients who clear HCV after IFN therapy [62–64].

The information needed about hepatic fibrosis in chronic HCV infection is limited to that required to divide patients into those with and those without fibrosis (the latter group has not immediate need to be treated) and to recognize liver cirrhosis. Treatment is particularly needed for those with compensated cirrhotic disease; moreover, they should undergo periodic screening for esophageal varices and hepatocarcinoma, and overall are more prone to experience liver toxicity under antiretroviral therapy [65]. With this view, the distinction of histopathological stages of hepatic fibrosis based on a liver biopsy is currently unnecessary, avoiding the inherent problems derived from intra- and interobserver variations [66] and the other limitations mentioned above. Figure 1 summarizes the main variables that should be assessed before prescribing HCV therapy.

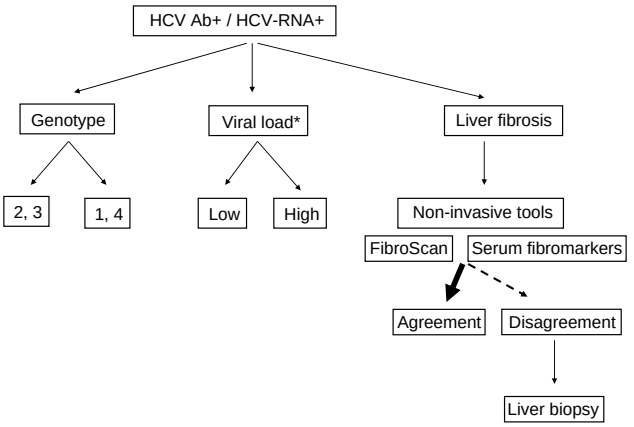

Fig. 1. Main variables to assess in patients considered as candidates for hepatitis C (HCV) therapy. *Low viral load defined as HCV RNA < 500 000–800 000 IU/ml. Ab, antibody.

Recommendation

Information on liver fibrosis staging is important for therapeutic decisions in coinfected patients. However, a liver biopsy is not mandatory for considering the treatment of chronic HCV infection. A combination of non-invasive methods to assess liver fibrosis accurately predicts hepatic fibrosis in most cases.

Predictors of response to hepatitis C therapy

Baseline serum HCV RNA and HCV genotype are the main predictors of sustained virological response (SVR) to pegIFN–RBV in coinfected [11,14,67,68] as in HCV-monoinfected patients. Several other variables, however, may influence treatment responses, although generally to a lesser extent (Table 1). They can be grouped in three

Table 1. Factors associated with sustained virological response to HCV therapy.

Host	Virus	Treatment
Genetic (white ethnicity)	Genotypes 2–3	Adequate peginterferon dose
Younger age	Low baseline HCV RNA load	Weight-based ribavirin dose
Minimal liver fibrosis	Undetectable HCV RNA at week 4	Good adherence
Low body mass index		No concurrent didanosine or zidovudine
Lack of insulin resistance		
Use of adjuvant growth factors when needed		
Lack of hepatic steatosis		
Higher CD4 cell count		
No polysubstance abuse		
No psychiatric disease		

categories, determining a better outcome as follows: (1) host (younger age, non-black ethnicity, lower body mass index, lack of insulin resistance), (2) HCV status (elevated ALT, less advanced hepatic fibrosis), and (3) treatment schedule (optimal doses of pegIFN and/or RBV, enough length of therapy, good adherence). In addition, treatment outcomes could be better depending on some HIV variables, such as higher CD4 cell counts [69] or low HIV load, although it may just reflect a better tolerance of the anti-HCV medication in this subset of patients [70].

Particular attention has recently been paid to the negative impact of insulin resistance on HCV treatment response [71]. Insulin resistance is quite prevalent in coinfected patients at least in part because of the use of certain antiretroviral drugs [72,73]. Therefore, prevention of insulin resistance and/or its adequate management (even considering treatment with insulin-sensitizer agents when indicated) might improve HCV treatment outcomes in coinfected patients [74].

As in HCV-monoinfected patients, treatment adherence should be encouraged as much as possible. The '80/80/80' rule is equally valid in coinfected patients, meaning that subjects who take more than 80% of pegIFN and of RBV doses during at least 80% of planned period of therapy respond significantly better than the rest [75]. Therefore, adequate selection of treatment candidates [76], psychological and/or psychiatric support [77] and use of growth factors to avoid dose reductions of either pegIFN and/or RBV [78,79] must all be encouraged in order to maintain adequate doses of anti-HCV medications in the majority of patients.

The kinetics of HCV load in response to pegIFN–RBV is a reliable indicator of treatment efficacy. The availability of sensitive quantitative tools to closely monitor HCV decays under treatment has permitted the recognition of early time-points with high predictive value of SVR. Overall, the early virological response to HCV therapy divides patients into those sensitive and those refractory to therapy. Nearly 20% of HCV-monoinfected subjects do not show a significant reduction in HCV viremia (defined as a decline $>1\log$ IU/ml) during the first month of pegIFN–RBV [80], and this figure increases up to 30% in coinfected patients [81]. In virological responders, the best positive predictive value for SVR is achieved when a negative serum HCV RNA is attained at week 4 of therapy (rapid virological response, RVR), while the best negative predictive value for SVR is seen when HCV RNA falls $<2\log$ IU/ml at week 12 [67,68,82–86]. Higher baseline HCV RNA levels in coinfected patients compared with HCV-monoinfected individuals may explain why they achieve undetectable HCV viremia at week 4 less frequently and, therefore, achieve SVR less often [87]. Coinfected patients may show slower HCV decays on HCV therapy [88]. Interestingly, this could be overcome at least partially using higher RBV doses [81].

The so-called '2-log stopping rule' refers to the strong predictive value of non-response at the week 12 assessment of virological response [80]. The failure to achieve HCV RNA declines $>2\log$ IU/ml (early virological response) at this time point permits the premature discontinuation of anti-HCV therapy, avoiding side effects and costs, when there is no chance of attaining the main goal of anti-HCV therapy, which is eradication of HCV infection. Fortunately, this rule works as well in coinfected as in HCV-monoinfected patients [67,68,82–86]. By comparison, a negative serum HCV RNA 6 months after completing anti-HCV therapy, which defines SVR, correlates with the long-term clearance of serum HCV as well as with histological and clinical improvements in most patients [89–91]. Therefore, 'occult' HCV infections with the potential worry of late HCV relapses are very rare.

Recommendation

The achievement of SVR can be predicted on the basis of negative serum HCV RNA at week 4 of therapy. On the other hand, a reduction $<2\log$ IU/ml in HCV RNA at week 12 and/or the presence of detectable viremia at week 24 both predict lack of SVR; accordingly these patients should be advised to stop prematurely anti-HCV therapy.

Optimal dosages of pegylated interferon and ribavirin

Adequate exposure to RBV is crucial to maximize responses to anti-HCV therapy [92–94]. Weight-based dosing seems well able to balance the highest efficacy and the lowest limiting toxicities of the drug, namely anemia. Pharmacokinetic studies have shown a good correlation between RBV plasma levels and HCV RNA responses [95,96]. Therefore, the use of fixed low doses of RBV (800 mg/day) in most trials conducted so far in coinfected patients could explain lower SVR [67,68,82–85,97–100]. The use of higher RBV doses (1000–1200 mg/day) in the PRESCO trial has confirmed this assumption, since the overall SVR in this trial (50%) is the highest reported so far in coinfected patients [101]. Figure 2 shows the proportion of patients achieving SVR in pivotal trials as a function of distinct doses of RBV and HIV status. Clearly, while HCV/HIV-coinfected patients may respond less, low RBV exposure may further impair treatment outcomes.

Optimal exposure to RBV could be particularly important in coinfected patients if the main mechanism of RBV action is hypermutagenesis [93,94,102,103].

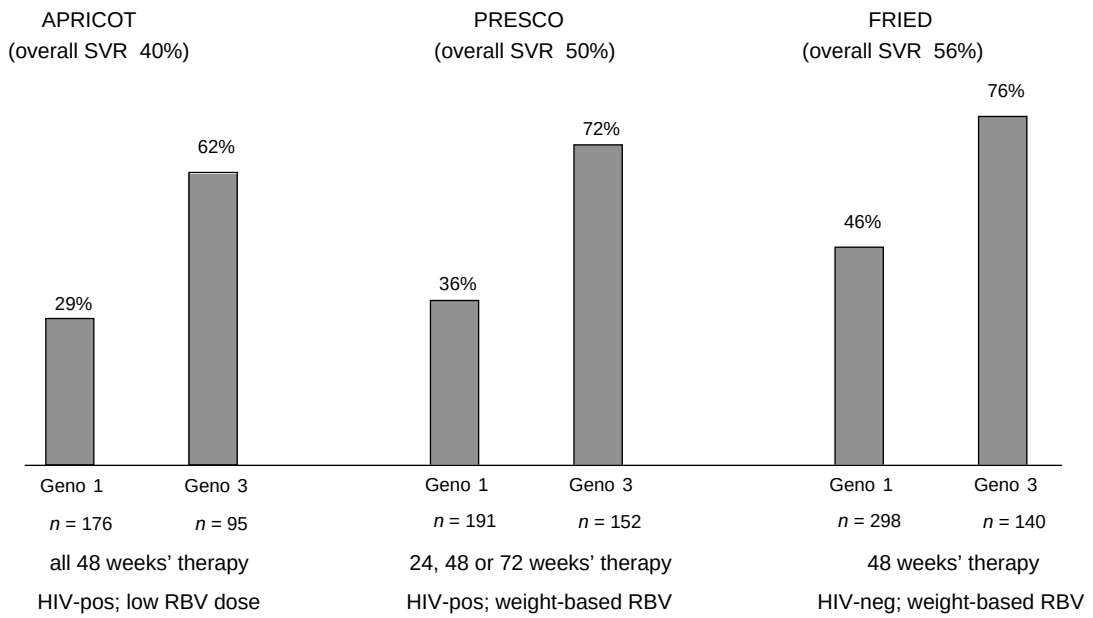

Fig. 2. Proportion of patients with sustained virological response (SVR) in three different large trials in HIV-positive (pos) and HIV-negative (neg) patients using low or weight-based ribavirin (RBV) doses (intent-to-treat analysis).

Causing errors in the virus replication cycle, RBV activity should be maximized in HIV-positive individuals, in whom the immune-mediated effects of IFN are compromised. Moreover, the benefit of adequate RBV exposure might not be limited to patients infected with HCV genotypes 1–4 and may expand to genotype 3 [81]. In HCV-monoinfected individuals, a flat RBV dose of 800 mg/day is enough for genotype 3 [104], as long as therapy is provided for at least 24 weeks. However, shorter periods of therapy seem to require greater RBV doses in order to minimize relapses [105,106].

Anemia is the main drawback of increasing RBV dosing and may force a reduction in RBV dosage. When dose adjustments are made within the first weeks of therapy, reduced SVR may be expected [107], especially in patients with HCV genotypes 1–4. The use of zidovudine with pegIFN–RBV significantly increases the risk of developing severe anemia [108]. Therefore, when possible, zidovudine should be avoided and the use of erythropoetin should be encouraged in patients developing anemia under pegIFN–RBV in order to avoid the need for RBV dose reductions [78,79].

The efficacy of higher doses of pegIFN in coinfected patients has been explored in a few studies. In the CORAL-1 trial, the administration of 270 μg/week of pegIFN alpha-2a for the first 4 weeks did not improve the early virological response, whether measured as the proportion of patients with undetectable HCV load at week 4 or as reductions of >2 log IU/ml HCV RNA at week 12, when compared with the administration of standard doses (180 μg/week) [109]. However, the size of the study population in that study was relatively small and nearly half the patients carried non-1 HCV genotypes. In contrast, data from studies conducted in HCV-monoinfected individuals suggest that there is a subset of patients who may benefit from exposure to higher doses of pegIFN [110] and this issue still warrants further investigation.

Recommendation

The current treatment of chronic HCV infection in HIV-positive persons should be pegIFN at standard doses plus weight-based RBV (1000 mg/day if <75 kg and 1200 mg/day if >5 kg).

Optimal duration of therapy

Studies conducted in HCV-monoinfected patients have shown that RVR, defined as undetectable HCV load at week 4, in patients treated with pegIFN–RBV may allow therapy to be shortened safely. Accordingly, treatment for only 12–16 weeks in patients with HCV genotype 3 [105,106] or for only 24 weeks in HCV genotype 1 [111,112] have been proposed for patients with RVR.

The picture seems to be slightly different in coinfected patients. First, HCV load is generally higher in this population, which could explain why a smaller proportion reaches undetectable viremia at week 4 despite showing good early virological response [87]. Second, HCV clearance driven by IFN could be delayed in the HIV setting [86,88]. Third, the relapse rate upon completion of treatment might be increased in coinfected patients. This was shown to be the case for 24 weeks of therapy in HCV genotypes 2–3 in earlier trials [98,113].

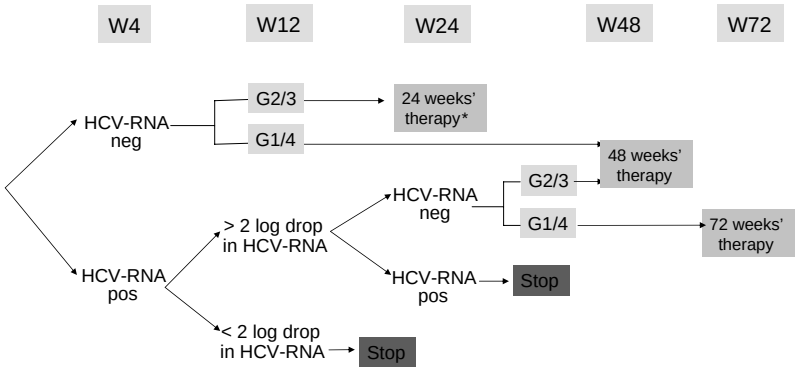

Fig. 3. Proposed optimal duration of hepatitis C (HCV) therapy in HCV/HIV-coinfected patients. *In patients with baseline low viral load and minimal liver fibrosis. W, week; neg, negative; pos, positive; G, genotype.

For all these reasons, prior guidelines have recommended that duration of treatment in coinfected patients should be 48 weeks regardless HCV genotype [12,15]. It is important to note that the 2 log IU/ml rule at week 12 is also highly predictive of non-SVR in coinfected patients [12,15], which permits premature cessation of anti-HCV therapy when there is no chance of achieving a cure.

Recent studies, however, have questioned these simple views to some extent. In a retrospective study conducted in coinfected patients with HCV genotypes 2–3, the subset who reached undetectable HCV RNA at week 4 could safely stop therapy at week 24, with minimal risk of relapse [114]. Similar findings have been reported in another recent Irish study [115]. However, a retrospective substudy of the APRICOT trial has shown that patients with HCV genotype 1 with low baseline HCV RNA and RVR obtained high rates of SVR (61%) and did not relapse [116], suggesting that shorten periods of therapy could have been enough in those patients. Overall, all these preliminary data encourage the provision of shorten periods of therapy on the basis of viral response at week 4, and clearly studies specifically designed to confirm this hypothesis in coinfected patients are needed. It might be the case that relapses could be limited to the subset of patients with high baseline HCV load and/or advanced fibrosis despite experiencing RVR, in whom 48 weeks of therapy would still be advisable [117].

In some patients with slow virological response, extended periods of treatment may permit SVR to be achieved [118]. Detectable viremia at week 4 seems to identify a subset of patients with genotypes 1–4 who may benefit from longer duration of therapy provided that it proves to be effective (> 2 log IU/ml fall in HCV RNA at week 12 followed by undetectable viremia at week 24) [119,120]. However, the main problem with extended periods of therapy is compliance [119,121,122]. This may be particularly problematic in coinfected individuals, given that a poor tolerance of the medication has largely impacted negatively on outcomes in many trials [68,99]. Clinical trials designed to prove the efficacy of extended periods of therapy in coinfected patients without RVR are, therefore, encouraged.

At this time, the information available supports the principle that shorter periods of therapy (24 weeks) could be advised in patients with HCV genotypes 2–3 with RVR, as long as HCV load is low, there is good adherence, there is not advanced hepatic fibrosis and weight-based RBV dosing is provided. For the rest of the patients with HCV genotypes 2–3, 48 weeks of therapy could still be advisable. In patients with HCV genotypes 1–4, extension of treatment beyond 48 weeks could be recommended in the absence of RVR if the medication is well tolerated (Fig. 3). However, as previously noted, high drop-out rates might limit the benefit of this strategy [101,123].

Recommendation

The current treatment of chronic HCV infection in HIV-positive persons should be pegIFN plus weight-based RBV for 48 weeks. Patients infected with HCV genotype 2–3 and RVR could benefit from shorter (24 weeks) courses of therapy. In contrast, carriers of HCV genotypes 1 and 4 with early virological response (week 12) but not RVR (week 4) might benefit from extended (60–72 weeks) courses of therapy.

Treatment of non-responders and/or relapsers

A growing number of coinfected patients have already been exposed to IFN-based therapies without achieving SVR. These patients continue to be at risk for progression to end-stage liver disease, including the development of hepatocellular carcinoma [89]. Table 2 summarizes the distinct situations affecting these subjects, each of which may require a distinct approach.

Patients failing prior suboptimal therapies (i.e., shorter duration, low RBV doses, monotherapy with standard

Table 2. Classification of and interventions for patients coinfected with hepatitis C and HIV who are non-responders/relapsers to prior interferon-based therapies.

Category	Recommended intervention
Suboptimal prior treatment schedules: interferon (monotherapy or with ribavirin); low ribavirin doses; short length of therapy	Retreatment using combination therapy with peginterferon plus weight-based ribavirin doses
Limiting toxicities and poor adherence	Optimal support (psychiatric, pharmacists, use of hematopoietic growth factors)
Virological failure	Maintenance therapy in patients with advanced liver fibrosis; wait until new antiviral drugs come to the market in the rest

IFN), who prematurely interrupted therapy owing to side effects, or who were poorly adherent to the medication are not strictly treatment (virological) failures and could be better considered as treatment-experienced patients. This group should firstly be retreated according to current standards in coinfection. The available data indicate that subjects who failed a prior course of suboptimal therapy may achieve acceptable but lower SVR rates than IFN-naive patients [124]. Overall, the chances for treatment response in pretreated patients are higher as the efficacy of the previous regimen was lower [125]. Finally, the efficacy of pegIFN–RBV retreatment also depends on whether it was truly virological non-response or relapse to the prior suboptimal regimen, and overall responses tend to be better in the latter.

Non-responders should be defined as adherent patients who received an optimal course of therapy with pegIFN–RBV at weight-adjusted doses and failed to achieve early virological response ($>2\log$ IU/ml decline in HCV RNA at week 12) or undetectable HCV load at week 24. Relapsers are patients who experienced HCV rebound after stopping a complete course of therapy. Retreatment of any of these patients rarely permits SVR to be achieved, although relapsers might benefit more than virological non-responders. Extension of treatment and/or use of higher than recommended doses of HCV medications may slightly improve response rates [110], although SVR rarely will go beyond 20%.

When the achievement of SVR is not feasible, the goal of therapy may be switched to halting or delaying progression of liver disease. Interestingly, hepatic fibrosis improves in 35–43% of coinfected patients despite not attaining SVR [85,126]. Since paired liver biopsies in these studies were performed at baseline and shortly after completion of treatment, it should be highlighted that this benefit most likely will vanish as time passes, as demonstrated in studies conducted both in HCV-monoinfected [63,64,91,127] and in coinfected [62,89] patients followed for longer periods of time. However, these observations underline that histological improvements while on HCV therapy or shortly thereafter mainly reflect the antifibrotic effects of IFN [128,129] and provide the rationale for assessing whether maintenance therapy with pegIFN alone could ameliorate liver disease deterioration when HCV eradication is not feasible. Large trials in HCV-monoinfected (EPIC[3], HALT-C, Co-PILOT) and coinfected (HRN-004, SLAM-C) virological non-responders are currently under way to prove this hypothesis [130]. Several caveats should be kept in mind with respect to these trials in coinfected patients. First, it is not known whether CD4 cell count declines, and broader immune effects of IFN may be harmful in these patients when the drug is provided for long periods. Second, side effects and quality of life issues will limit the long-lasting administration of pegIFN in a substantial proportion of these patients.

New antiviral drugs against HCV are urgently needed, particularly for the already large and rapidly growing pool of coinfected patients who failed to clear HCV with the current medication. Accelerated progression of liver disease will shorten their lives in the absence of urgent access to those medications. Table 3 summarizes the main anti-HCV drugs in the pipeline. Trials exploring 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 individuals. With the appropriate close monitoring of safety issues, regulatory agencies should encourage these studies.

Recommendation

Non-responders and relapsers to prior courses of HCV therapy are a heterogeneous population and therapeutic interventions in them should be individualized.

Table 3. New anti-HCV compounds in development.

Drug types	New compounds
Modified interferons	Albuferon, consensus interferon
Polymerase inhibitors: nucleoside analogs	NM283, R126, R1479, MK-0608
Polymerase inhibitors: non-nucleoside analogs	HCV-796, BI-2071
Protease inhibitors	VX-950, SCH-3034, BMS-5339, GS-9132, BI-1335, BI-1230

Management of end-stage liver disease

The management of coinfected persons with advanced liver cirrhosis is complex. They should be evaluated for staging of liver disease and management of liver-related complications such as portal hypertension, encephalopathy, ascites and hepatocellular carcinoma. Because of an increased risk of life-threatening complications during pegIFN–RBV therapy, persons with hepatic decompensation are not typically candidates for therapy [131,132], unless easy access to orthotopic liver transplantation is available. Antiretroviral therapy may significantly improve short- and mid-term outcomes in HIV-positive patients with hepatic decompensation [133] and, therefore, HAART should not be discouraged. However, the effective treatment of HIV in persons with advanced cirrhosis may be challenging owing to alterations in hepatic metabolism of antiretroviral drugs and risk of drug-induced liver injury [134].

At this time, orthotopic liver transplantation is the primary treatment option for eligible coinfected patients with Child–Pugh stage B or C cirrhosis (Table 4) [135–138]. In a recent study [138], cumulative survival among 24 HIV-positive HAART recipients was similar to that among age- and race-comparable HIV-negative recipients. At 12, 24 and 36 months after orthotopic liver transplantation, respective estimated survival rates were 87%, 73% and 73% among HIV-positive patients and 87%, 82% and 78% among HIV-negative patients. However, when only HCV-infected patients were considered, there was an almost significant trend toward worse survival in coinfected transplant recipients compared with HCV-monoinfected controls. The respective estimated survival rates at 1, 2 and 3 years were 87%, 81% and 75% in HCV-monoinfected subjects and 80%, 57% and 57% in coinfected patients. Factors independently associated with poor survival were post-transplant intolerance to HAART, CD4 cell counts < 200 cells/μl, detectable plasma HIV RNA and HCV infection [138].

Recommendation

HIV infection should no longer be considered a contraindication to orthotopic liver transplantation. However, coinfected patients present unique and highly complex problems post-transplantation, including rapidly progressive recurrent HCV infection and drug interactions (mainly between immunosuppressive agents and protease inhibitors). Accordingly, orthotopic liver transplantation in this population should be limited to transplant centers experienced in the management of such patients, where a multidisciplinary team including surgeons, hepatologists, pharmacologists and infectious diseases physicians can work in concert.

Treatment of acute hepatitis C

Outbreaks of HCV infection among homosexual men have been reported in several large European cities [139–144]. This observation is striking since HCV was not believed to be efficiently transmitted by sexual contact, as hepatitis B virus (HBV) or HIV. High levels of sexual promiscuity, certain particularly traumatic sex practices and ulcerative sexually transmitted diseases have all been associated with these outbreaks [140,141].

Up to 25–30% of HIV-negative individuals with acute HCV infection may show spontaneous viral clearance within the first 12 weeks following initial exposure [145]. Younger age, female sex and symptomatic acute infection are all associated with a higher chance of spontaneous HCV recovery. Conversely, patients with HIV enter into chronic HCV infection more frequently [146,147]. Therefore, early therapeutic intervention in acute HCV infection is particularly indicated in patients with HIV disease, although treatment should not be instituted before 12 weeks of estimated exposure in order to exclude spontaneous HCV clearance [148]. However, further delays should be discouraged since these may reduce treatment responses [149].

Treatment of acute HCV infection in HIV-positive patients seems to provide a lower rate of cure [143,144,147] than in HIV-negative patients [149,150]. Since the antiviral activity of IFN may be mediated through the cytokine network, immunological abnor-

Table 4. Criteria for liver transplantation in HIV-infected patients with end-stage liver disease.[a]

Criteria	Details
Inclusion criteria	Undetectable plasma HIV-RNA (generally, < 50 IU/ml)
Additional inclusion criteria if participant has a history of HIV-related cancers or opportunistic infections	CD4 cell count > 100 cells/μl; requirement for children will be based on child's age; some participants with certain HIV-related diseases must have > 200 cells/μl for the 6 months prior to entry
	Willing to take medication to prevent certain infections.
	If participant has hepatitis B or C, willing to undergo frequent monitoring including liver biopsies, and specific antiviral treatment
	Willing to submit laboratory test results within 7 days of blood draw
	Willing to notify the transplant team before changing any medications
Exclusion criteria	Pregnancy, significant wasting

[a]From the National Institute of Allergy and Infectious Diseases (http://www.hivtransplant.com).

malities in the HIV setting could negatively influence IFN efficacy [151].

However, the rates of HCV clearance obtained in HIV-positive patients treated during the acute phase are much higher (up to 80%) [147,152] than in chronic HCV infection. HCV genotypes 2–3 respond better than genotypes 1–4 [143]. More elevated ALT levels during the acute episode and rapid viral clearance on therapy predict better chances of SVR. In contrast, patient's age, CD4 cell count, HIV or HCV load and having symptomatic infection do not seem to influence treatment response [153]. At this time, it is unclear whether adding RBV to pegIFN would offer any advantage when treating acute HCV infection in HIV-positive individuals. However, given the worse prognosis of HCV infection in HIV-positive persons, it seems worthwhile to provide RBV to ensure maximal clearance of HCV. Following the advice for HIV-negative persons, 24 weeks of therapy is the recommended duration of treatment of acute HCV infection in HIV-positive patients regardless HCV genotype.

Recommendation

Acute HCV infection in HIV-positive persons should be treated for 24 weeks with a combination of pegIFN plus weight-based RBV. However, responses are lower than in HIV-uninfected persons.

Management of patients with multiple hepatitis viruses

The prevalence of multiple viral hepatitis (HBV/HCV, HBV/hepatitis D, HBV/HCV/hepatitis D) in HIV-positive patients is below 3% in developed countries, but higher than in the general population [154–156]. Patients carrying HBV/HCV infections seem to have a reciprocal inhibition of virus replication, with one virus predominating over the other [157]. Moreover, this predominance may fluctuate over time, with one virus taking over from the other intermittently [158]. However, in patients with severe immunosuppression, replication of all these viruses may occur simultaneously [159]. In most HIV-positive patients with relatively good immune status, viral interference seems to favor HCV over HBV replication rather than the opposite [160]. However, it is noteworthy that the proportion of subjects with HCV antibodies showing negative serum HCV RNA is much higher in patients carrying HBV surface antigen (HBsAg) [161].

Progression of liver disease seems to be further accelerated in HIV-positive patients dually coinfected with HBV and HCV [162]. Moreover, these individuals are more prone to develop hepatocellular carcinoma [163]. Liver-related mortality is increased in HIV-positive patients with multiple viral hepatitis compared with those with HBV or HCV monoinfection [164]. This higher fatality is maintained even when antiretroviral drugs with anti-HBV activity, such as lamivudine, are used [165].

A few studies have examined the efficacy and safety of IFN–RBV in patients with dual HBV/HCV infections. While one study found a lower SVR for HCV in patients with HBsAg compared with HCV-monoinfected individuals (43% versus 60%) [166], most studies have concluded that results are similar [167,168]. There is little information on the efficacy of pegIFN–RBV in HIV-positive patients coinfected with HBV/HCV. Moreover, few data exist regarding the influence of anti-HBV medications on HCV replication in HBV/HCV-infected patients. The treatment of all replicating viruses should be pursued, mainly in patients with advanced liver fibrosis. During therapy of one virus, replication of the other should be actively monitored since reactivations of latent infections may occur [169,170].

Finally, the treatment of chronic hepatitis D in HIV-positive patients with IFN is rarely effective [171]. However, recent data using pegIFN for longer than 18 months in HIV-uninfected persons have shown that is relatively safe and effective [172]. Consequently, long-term therapy with pegIFN could be advisable in HIV-positive patients with chronic hepatitis D and advanced liver fibrosis on an individual basis.

Recommendation

Multiple viral hepatitis is not uncommon in HIV-positive individuals and worsens liver damage. Complex and dynamic viral interactions occur and making the management of these patients difficult. When possible, treatment of all replicating viruses should be pursued.

Interactions between anti-HIV drugs and those for hepatitis C

The concomitant administration of antiretroviral drugs might affect the activity of pegIFN–RBV therapy in at least two ways. First, it may increase the risk of side effects via overlapping toxicities, such as anemia and/or neutropenia when using zidovudine with RBV [108]. Since RBV exposure is critical to maximize the response to anti-HCV therapy, it is advisable to avoid zidovudine when other antiretroviral drugs are used. Given that RBV increases the phosphorylation of the active intracellular metabolites of didanosine, a higher incidence of pancreatitis, lactic acidosis and decompensated cirrhosis have been reported in patients treated with these two drugs [131,132,173,174] and, therefore, this combination is currently contraindicated.

A second mechanism by which HIV nucleoside analogs might influence HCV therapy could be via interference

Table 5. Mechanisms of drug-related liver damage in HIV-infected patients.

Mechanism	Drug
Mitochondrial toxicity	Nucleoside reverse transcriptase inhibitors (especially didanosine and stavudine); tends to occur after prolonged exposure
Hypersensitivity	Nevirapine, abacavir; occurs early, usually within 12 weeks; often associated with rash; HLA-linked; not favored by HCV or HBV
Direct toxicity (intrinsic and idiosyncratic)	Protease inhibitors and non-nucleoside reverse transcriptase inhibitors; occurrence can vary by agent; dose-dependence for intrinsic damage
Immune reconstitution	Chronic HBV (unclear for HCV); occurs within the first month following initiation of HAART

HBV, hepatitis B virus; HCV, hepatitis C virus.

with the activity of RBV against HCV, a concern that has not been proven so far. However, studies on this issue are particularly needed for purine analogs, such as tenofovir and abacavir. Preliminary reports have shown that the pharmacokinetics of RBV is not affected by the concomitant use of tenofovir [175]. The use of RBV with tenofovir might increase the phosphorylated metabolites of tenofovir within the cells, as occurs with didanosine, since both drugs are adenosine analogs. However, there is no evidence of an enhanced risk of tenofovir-associated nephrotoxicity, nor an impaired response to anti-HCV therapy when RBV and tenofovir are combined [176,177]. Similar information has not been reported yet for abacavir, which like RBV is a guanosine analogue.

In-vitro studies have shown that the active metabolites of RBV may reduce the phosphorylation of other nucleoside analogs in the intracellular compartment [178], which might reduce the activity of antiretroviral therapy. However, clinical observations [179] and a pharmacokinetic study [180] have not confirmed any clinical relevance of these interactions.

Enhanced mitochondrial damage seems to be the most common pathway for explaining the deleterious interactions between RBV and some nucleoside analogs, such as didanosine and stavudine [173,174,181]. Moreover, HIV and HCV by themselves may cause mitochondrial DNA depletion in distinct cell types, further favoring these toxicities [182].

Recommendation

While didanosine should never be used with RBV, zidovudine should also be avoided when possible.

Hepatotoxicity of antiretroviral drugs

Liver enzyme elevations in HIV-positive patients are multifactorial [183,184]. In patients exposed to antiretroviral therapy, four different mechanisms of hepatotoxicity have been described (Table 5): (1) mitochondrial damage in patients receiving nucleoside analogs [185,186]; (2) hypersensitivity reactions involving the liver (e.g., taking nevirapine, efavirenz, or abacavir) [187]; (3) direct liver injury, as using full doses of ritonavir [188]; and (4) immune reconstitution phenomena, mainly in severely immunosuppressed patients with underlying chronic HBV infection [189]. In patients with HCV infection, drug-related hepatotoxicity can be mediated by any of these mechanisms but hypersensitivity reactions are most likely [190–192].

Nucleoside analogs may contribute to the occurrence of liver steatosis, which is frequently found in HIV-positive patients [193]. Steatohepatitis accelerates the progression of liver fibrosis in patients with chronic HCV infection. Insulin resistance, dyslipidemias and lipodystrophy are associated with liver steatosis. In patients carrying HCV genotype 3, steatosis is more prevalent, and this could explain both a faster progression of liver fibrosis [60] and a higher incidence of hepatotoxicity [194,195]. The so-called 'd-drugs' (didanosine and stavudine) are the drugs most frequently involved in liver-related mitochondrial toxicity [196]. More alarming, the long-term use of didanosine has recently been recognized as an independent factor for developing advanced liver fibrosis in HIV-positive patients in whom other causes of liver damage were excluded [197].

Non-nucleoside reverse transcriptase inhibitors may cause liver damage in the context of hypersensitivity reactions or by direct toxic effects. It is of interest that the clinical presentation varies according to the mechanism of liver toxicity (Table 6). Almost all studies show that nevirapine is more hepatotoxic than efavirenz [198–200]. The presence of underlying chronic HCV infection enhances the risk of developing liver enzyme elevations in

Table 6. Clinical presentation of antiretroviral-related liver toxicity.

	Early onset	Late presentation
Interval	1–4 weeks	4–8 months
Mechanism	Immune mediated	Direct toxicity, cumulative
Dose-related	No	Yes
Role of HCV	No	Yes
Role of CD4 cell count	Yes	No
More common drugs	Abacavir, nevirapine	Stavudine, didanosine, nevirapine, ritonavir, tipranavir

HCV, hepatitis C virus.

patients receiving nevirapine, which generally occurs after 4–6 months of therapy [198,201,202]. This second peak of incidence of hepatotoxicity under nevirapine therapy is not related with any hypersensitivity reaction [187,202] nor with increased levels of the drug as a consequence of chronic HCV-related liver disease [203].

Most protease inhibitors have been associated with episodes of liver toxicity, with lopinavir/low-dose ritonavir, fosamprenavir/low-dose ritonavir and nelfinavir being less hepatotoxic [204,205] and tipranavir/low-dose ritonavir most hepatotoxic [206]. Hyperbilirubinemia is often associated with atazanavir and/or indinavir therapy but does not reflect liver damage and is related to the inhibition of UDP-glucuronosyltransferase [207]. It is remarkable that low-dose ritonavir used as booster for other protease inhibitors does not cause hepatotoxicity [208].

Despite all concerns regarding the relatively high incidence of liver toxicity using antiretroviral drugs in HIV-positive patients with chronic HCV infection, the benefits outweigh this risk. Many reports have clearly demonstrated lower rates of liver-related mortality in coinfected patients taking HAART, even in those with end-stage liver disease [209], compared with patients not receiving antiretroviral drugs or treated with suboptimal combinations [164,210]. Since severe immunosuppression accelerates HCV-related liver fibrosis progression [2,4,211], it may be advisable to start HAART without unnecessary delays in coinfected patients and even consider earlier initiation of treatment [212]. Elevated plasma HIV RNA seems to be largely responsible for the accelerated course of hepatic fibrosis in coinfected patients [213], and accordingly time on successful HAART has been shown to protect from rapid liver fibrosis progression [214].

Recommendation

Patients with chronic HCV infection have an increased risk of liver enzyme elevations following exposure to most antiretroviral drugs. The management of hepatotoxicity should be based on the knowledge of the mechanisms involved for each drug. Treatment of HCV infection may reduce the chances for further development of liver toxicity in these patients.

Acknowledgements

We would like to thank Pablo Barreiro, Marina Nuñez and Javier Garcia-Samaniego for helpful comments.

Sponsorship: This work was supported in part by grants from Fundación Investigación y Educación en SIDA (IES), Red de Investigación en SIDA (RIS), the European VIRGIL Network, Agencia Lain Entralgo and Schering-Plough.

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