Management of Patients with
HCV/HIV Co-infection

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INTRODUCTION

Both HIV and hepatitis C virus (HCV) infections are global public health problems. Currently, more than 42 million people are estimated to have HIV worldwide, while HCV infection is found in 2-3% of the world’s population, which represents around 175 million people [1]. Overall, nearly 10 million people are co-infected with both HIV and HCV.

Transmission of either HCV or HIV is frequent throughout parenteral exposure to contaminated blood and blood products, with HCV being 10 times more infectious than HIV. Co-infection with both viruses is therefore frequent in this population. For instance, HCV can be found in 70-90% of HIV-positive hemophiliacs and in 60-80% of HIV-positive intravenous drug users (IDUs) [2]. In contrast, sexual transmission of hepatitis C is rare, which explains the low 4-8% rate of HCV co-infection among HIV-positive homosexual men [3]. However, small epidemics of acute hepatitis C have been reported among homosexuals in London and Berlin, which seem to be associated with many sexual partners and blood shedding sexual practices [4, 5] Taking these differences in transmission among different risk groups into account, around one third of HIV-positive persons are estimated to be co-infected with HCV in Europe and the United States [6, 7].
Around 85% of HCV antibody-positive HIV co-infected individuals show HCV viremia [8, 9], a rate that is slightly above the 75% reported among HIV-negative individuals with HCV-positive serology. Thus, HIV seems to favor hepatitis C chronicity after initial exposure. Moreover, higher plasma HCV RNA levels (1 log on average) are found in HIV-positive individuals compared to hepatitis C patients without HIV [10]. In one study conducted among hemophiliacs, plasma HCV RNA levels increased 10-fold within the first 2 years after HIV seroconversion [11].

The distribution of HCV genotypes in the HIV population reflects the main route of HCV transmission. Genotype 1b accounts for more than two thirds of post-transfusion HCV infections and accordingly is the predominant genotype among hemophiliacs [12]. In contrast, genotypes 1a and 3a are much more frequent among IDUs [13]. However, recent evidence suggests that HCV genotypes 1 and 4 are becoming more frequent than genotype 3 in Europe, while the frequency of HCV-3 is steadily decreasing [14]. Given the prognostic value of HCV genotypes and HCV load on treatment response, co-infected patients should be generally considered as a difficult-to-treat population.

**NATURAL HISTORY OF CHRONIC HEPATITIS C IN HIV-POSITIVE PATIENTS**

There is no doubt that HIV accelerates the progression of HCV liver disease, especially when HIV-associated immunodeficiency progresses [15, 16]. In the American Multicenter Hemophilia Cohort study, liver failure occurred in 9% of multitransfused HCV/HIV co-infected hemophiliacs with no AIDS-defining condition [15]. In contrast, during the same period, no cases of liver failure were observed among HCV-positive hemophiliacs without HIV infection. Subsequently, several studies have confirmed the unfavorable course of hepatitis C in HIV co-infected patients, particularly in the setting of advanced CD4 depletion [16, 17]. The time interval between HCV acquisition and the development of cirrhosis is significantly shortened in co-infected subjects. Overall, within 10-15 years after the initial HCV infection, 15-25% of HCV/HIV co-infected patients develop cirrhosis [18-21], compared to 4-6% of HIV-negative patients with hepatitis C. It is important to note that co-infected hemophiliacs who died from advanced liver disease were 10 years younger than HIV-
negative hemophiliacs with hepatitis C [22]. Moreover, several reports have also emphasized the occurrence of hepatocellular carcinoma at a younger age and after a shorter duration of hepatitis C infection in HCV/HIV co-infected individuals [23]. Finally, in a recent European study including 914 patients co-infected with hepatitis C and HIV, who underwent liver biopsy, the distribution of METAVIR liver fibrosis stages was F0 in 10% of patients, F1 in 33%, F2 in 22%, F3 in 22% and F4 in 13%, clearly showing the increased severity of liver fibrosis in this population [24]. In that study, the best predictor of severe liver fibrosis was age: nearly 50% of HCV/HIV co-infected patients over 40 years had bridging fibrosis or cirrhosis (Figure 1). It should also be stated that the mean age of HIV-positive individuals being treated in European and North American clinics is 40-45 years old.

![Figure 1: Liver fibrosis stage according to age in HCV/HIV co-infected patients [24]](image)

Recent evidence suggests that the immune restoration that follows the use of antiretroviral therapy might reverse the unfavorable course of hepatitis C in co-infected patients. A study in 162 HCV/HIV
Hepatitis C

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co-infected individuals who underwent liver biopsy, demonstrated that use of protease inhibitors as part of the highly active antiretroviral therapy (HAART) regimens resulted in significantly reduced rates of fibrosis progression [25]. These findings have been further confirmed by a recent long-term cohort analysis showing that HCV/HIV co-infected individuals on HAART had significantly lower liver-related mortality than patients receiving either suboptimal (1 or 2 HIV drugs) or no antiretroviral therapy [26]. Overall, the data available suggest that HAART has a favorable impact on the further course of hepatitis C in co-infected patients. These benefits of HAART seem to largely outweigh the risks of increased liver toxicity in this population [7]. Thus, HAART should be offered to all HCV/HIV co-infected patients using the general guidelines of antiretroviral treatment [27].

However the short and long-term success of HAART in HCV/HIV co-infected patients, is limited by an increased risk of hepatotoxicity [28, 29]. Multiple studies have demonstrated that underlying hepatitis C is an independent predictor of liver enzyme elevations after initiating HAART [30-33]. Further studies have shown a significantly increased risk of liver toxicity in co-infected patients especially with the protease inhibitor ritonavir (at doses of 600mg bid) and with nevirapine [34, 35]. Moreover, the use of “d-nucleosides” (didanosine [ddi], Zerit [d4T], Hivid [ddC]), especially the combination of d4T plus ddl has been found to result in an increased rate of hepatic steatosis in co-infected patients [36-39]. Therefore, d-nucleosides (especially the combination of d4T plus ddl) should be avoided, when possible, in HCV/HIV co-infected patients.

Liver disease due to chronic hepatitis C is now a leading cause of morbidity and mortality among HIV infected patients in the developed world, where the classic opportunistic complications of severe immunodeficiency have declined dramatically thanks to the widespread use of potent antiretroviral therapies [40-43]. Initial trials with interferon and much later with interferon plus ribavirin provided disappointing response rates and high drop-out rates due to adverse events in HCV/HIV co-infected patients [44-48]. However, the recent availability of the new pegylated forms of interferon (pegylated interferon) provides better maintenance of effective interferon levels for over a week after a single injection, allowing weekly subcutaneous administration of the drug. The first results with the pegylated interferon plus ribavirin combination are now available and the
improved performance of this combination in several trials is encouraging for HIV-positive patients with hepatitis C. As a result, new guidelines about how to manage HCV/HIV co-infected patients have recently been released [49] and will be the main body of discussion of this review.

THE BEST HIV-POSITIVE CANDIDATES FOR HCV THERAPY

All HIV infected individuals should be screened for HCV antibodies in serum or plasma. HCV-antibody negative but HCV RNA-positive cases may exist, mainly in patients with severe cellular immune suppression due to HIV [10, 50, 51]. Those with repeatedly elevated aminotransferase levels should be tested for HCV load and HCV genotype, to assess anti-HCV therapy.

All HIV-positive patients with chronic HCV infection should be considered as potential candidates for anti-HCV therapy, due to the higher risk of progression to end-stage liver disease and increased risk of liver toxicity after beginning antiretroviral therapy, compared to HIV-negative patients [49]. Since response to HCV therapy is dependent on the CD4 count [44, 52], ideally it should only be prescribed when the CD4 count is above 350 cells/µL, a threshold which is relatively easy to obtain in most instances when antiretroviral therapy is properly used. Besides, this is currently the immunological cut-off for beginning antiretroviral therapy in drug-naive patients [27]. In subjects with CD4 counts between 200 and 350 cells/µL, who are already receiving long-term antiretroviral therapy, the decision to treat HCV should take into account other factors, such as the estimated length of HCV infection, the severity of liver disease, the extent of suppression of HIV replication, and classical predictors of response to anti-HCV therapy, such as HCV genotype and HCV load [53, 54].

Finally, anti-HCV therapy should be postponed in individuals with less than 200 CD4+ T cells/µL, since the response rate is very low in this subgroup of patients [44, 52]. Moreover, the risk of opportunistic infections in the short-term may be high and may worsen with HCV therapy [55, 56]. Therefore, these patients should be treated with antiretroviral therapy and receive prophylaxis for opportunistic infections first. Later on, when their CD4 counts have risen and their plasma HIV RNA is under control, the possibility of HCV therapy should again be assessed.
Patients with prior liver decompensation (ascites, gastrointestinal bleeding, hepatic encephalopathy, etc) should not be treated, due to the higher risk of serious side-effects using the current approved drugs, pegylated interferon and ribavirin. These patients should be assessed for liver transplantation. However, patients with compensated cirrhosis (Child-Pugh class A) must be treated, since their chance of response is currently relatively high and are ultimately those who will benefit most from HCV clearance.

Individuals with a prior history of severe neuropsychiatric disorders should not be treated, since interferon can exacerbate these conditions. Individuals who have heavy alcohol intake and/or are addicted to illegal drugs should delay treatment, and all efforts should be made to put them onto detoxification programs. Patients on methadone are acceptable candidates for anti-HCV therapy. Up to one third of patients may require adjustment in methadone dosage [57]; however, this is for psychological reasons rather than pharmacological interactions between HCV drugs and methadone. Ideally, a multidisciplinary team, including experts in addiction, psychologists/psychiatrists and infectologists should treat these patients [58, 59].

Based on the 2002 NIH Consensus Conference recommendations [60], subjects with repeated normal liver enzymes may benefit from current HCV therapy, particularly those infected with HCV genotypes 2 or 3. However, more data on liver damage in this subgroup of HCV/HIV co-infected patients are needed to balance the cost-benefit of anti-HCV therapy [49]. Preliminary data from the APRICOT trial suggest that liver fibrosis may be recognized in a substantial proportion of co-infected patients with normal ALT levels, although treatment response rates seem to be lower in this population.

In drug-naive individuals with HCV/HIV co-infection, chronic hepatitis C should be treated first if the CD4 count does not require antiretroviral therapy. However, in patients with CD4 counts above 350 cells/µL but high plasma HIV RNA (i.e., above 50,000 copies/mL), it is not clear whether suppression of HIV replication should be done first, postponing anti-HCV therapy until after HIV viremia becomes undetectable. In these patients, a possible greater efficacy of HCV therapy should be weighed against a greater risk of interactions between antiretroviral and HCV drugs [49].
THE ROLE OF LIVER BIOPSY IN TREATMENT DECISIONS

The value of liver biopsy before prescribing HCV therapy is under debate [61-64]. Liver histology allows staging of HCV liver damage and predicts the development of cirrhosis in the short-mid term. At the same time, it may rule out other causes of liver damage, such as hemochromatosis, alcoholic steatosis, Wilson’s disease, autoimmune hepatitis, etc., although these conditions may be identified by other non-invasive means [61-64].

This controversy is less a problem in HCV/HIV co-infected patients, because the rate of advanced liver fibrosis is much higher than in HCV monoinfected persons [20-24]. Anti-HCV therapy will almost always be justified because of the extent of histological damage in HCV/HIV co-infected patients [65]. Moreover, nearly half of co-infected patients may show unexpected cirrhosis or pre-cirrhosis [24]. The main predictor of advanced fibrosis stages seems to be age, reflecting the estimated duration of HCV infection. On average, nearly half of patients will have cirrhosis 25 years after first exposure to HCV. The mean age of co-infected patients is currently 40 years old, and most are former intravenous drug users who began to exchange needles when they were about 20 years old, thus many of them should now have significant liver fibrosis. Therefore, if they are not treated, a rapid increase in liver complications among HIV infected persons should occur over the next decade.

Those in favor of a liver biopsy before treating chronic hepatitis C in HIV co-infected patients argue that side-effects, the risk of interactions with antiretroviral treatment and the relatively low efficacy of current anti-HCV therapy in this population are major limitations so that medication should only be prescribed for those who histologically really need it. However, liver damage is a dynamic process and progression of fibrosis is accelerated in HCV/HIV co-infected patients [66, 67], so those who support this point of view should be reminded that if treatment is not offered to patients without or with minimal fibrosis, liver biopsy should be repeated at 2-3 year intervals. However, this option would be refused by many patients and may significantly increase costs. Accordingly, a recent analysis has demonstrated the cost-effectiveness of therapy in co-infected individuals [68].
TREATMENT RESULTS IN HCV/HIV CO-INFECTED PATIENTS

In the last few months, the final results of large trials assessing the efficacy and safety of pegylated interferon plus ribavirin in co-infected patients have been released. Most of these studies have been performed by European investigators [69-72]. However, the trials about this treatment modality in co-infected patients that had the greatest public impact appeared in February 2004, when three large comparative trials were presented orally at the 11th Retrovirus Conference, in San Francisco, CA. In contrast to many prior studies, these three pivotal trials all provided treatment for 12 months to all patients, irrespective of their HCV genotype. Besides, due to concerns on drug interactions and further toxicities, lower than recommended doses of ribavirin were prescribed. Moreover, only patients with a relatively good immunologic status were recruited into these trials, acknowledging that severely immunosuppressed patients should not be treated.

Table 1 summarizes the main treatment schedules and results of the main trials conducted in co-infected patients assessing the efficacy and safety of pegylated interferon plus ribavirin.
### Table 1: Response to pegylated interferon plus ribavirin in HCV/HIV co-infected patients; results of pivotal studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Treatment schedule</th>
<th>Discont. due to adverse events</th>
<th>End-of-treatment response*</th>
<th>Sustained virological response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pérez-Olmeda et al. [69]</td>
<td>68</td>
<td>pegylated interferon alpha-2b 1.5µg/kg/week + ribavirin 800mg/d 48 weeks (genos 1 &amp; 4) and 24 weeks (genos 2 &amp; 3)</td>
<td>15%</td>
<td>40%</td>
<td>28%</td>
</tr>
<tr>
<td>Voigt et al. [70]</td>
<td>72</td>
<td>pegylated interferon alpha-2b 1.5µg/kg/week + ribavirin 800mg/d 48 weeks (genos 1 &amp; 4) and 24 weeks (genos 2 &amp; 3)</td>
<td>17%</td>
<td>46%</td>
<td>26%</td>
</tr>
<tr>
<td>Ballesteros et al. [71]</td>
<td>28</td>
<td>pegylated interferon alpha-2b 1.5µg/kg/week + ribavirin 800mg/d 48 weeks (genos 1 &amp; 4) and 24 weeks (genos 2 &amp; 3)</td>
<td>29%</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>Moreno et al. [72]</td>
<td>35</td>
<td>pegylated interferon alpha-2b 0.5µg/kg/week + ribavirin 800mg/d 48 weeks (all genos)</td>
<td>17%</td>
<td>40%</td>
<td>31%</td>
</tr>
<tr>
<td>Chung et al. [73]</td>
<td>66</td>
<td>pegylated interferon alpha-2a 180µg/week + ribavirin 600mg/d (increased to 1000mg/d at week 12) 48 weeks (all genos)</td>
<td>12%</td>
<td>41%</td>
<td>27%</td>
</tr>
<tr>
<td>(geno 1:29%)</td>
<td></td>
<td></td>
<td>(geno 3:80%)</td>
<td>(geno 1:14%)</td>
<td>(geno 3:73%)</td>
</tr>
<tr>
<td>Perronne et al. [74]</td>
<td>205</td>
<td>pegylated interferon alpha-2b 1.5µg/kg/week + ribavirin 800mg/d 48 weeks (all genos)</td>
<td>38%</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>(genos 1-4:16%)</td>
<td></td>
<td></td>
<td>(genos 2-3:43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torriani et al. [75]</td>
<td>289</td>
<td>pegylated interferon alpha-2a 180µg/week + ribavirin 800mg/d 48 weeks (all genos)</td>
<td>12%</td>
<td>49%</td>
<td>40%</td>
</tr>
<tr>
<td>(genos 1-4:16%)</td>
<td></td>
<td></td>
<td>(genos 2-3:64%)</td>
<td></td>
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</tbody>
</table>

*results based on intent-to-treat analyses.
Hepatitis C

The AIDS Clinical Trials Group (ACTG) 5071 included 66 co-infected patients from several centers located in the United States. Subjects were treated with a fixed dose of 180µg/week of pegylated interferon-alpha-2a (Pegasys) plus ribavirin [73]. All subjects began ribavirin at doses of 600mg/day and increased up to 1000mg over the last weeks if the tolerance was acceptable. In this trial, 77% of patients carried HCV genotype 1, which tends to respond less well to HCV therapy. End-of-treatment-response (EOTR) was reached in 41% of patients, but sustained virological response (SVR) only was maintained by 27% (14% in subjects with HCV genotype 1 and 73% in those with other genotypes).

The RIBAVIC trial was a multicenter French study performed by the Agence Nationale de la Recherche Scientifique, in which 205 co-infected patients were treated with a weight adjusted dose (1.5µg/kg/week) of pegylated interferon-alpha-2b (pegylated Intron) plus a fixed dose of 800mg of ribavirin [74].

AIDS Pegasys Ribavirin International Co-infection Trial (APRICOT) is the largest trial so far in co-infected patients assessing the response to current HCV therapy. A total of 289 co-infected patients from several countries and continents received at least one dose of pegylated interferon-alpha-2a (Pegasys) 180µg/week plus a fixed dose of 800mg of ribavirin per day [75]. The overall rate of SVR was 40%, but it dropped to 29% in patients with HCV genotype 1. Close monitoring of patients and strict inclusion criteria provided a relatively low discontinuation rate in this trial (25%), whereas in the French RIBAVIC trial up to 38% of patients did not complete therapy [74].

Much better response rates were obtained for HCV genotypes 2 or 3 compared to genotype 1 in all these trials. For instance, in the APRICOT trial the rate of EOTR was 64%, with a rate of SVR of 62%. This low relapse rate for these genotypes should be mentioned, and suggests that extending treatment beyond 24 weeks for those particular genotypes appears necessary to avoid relapses in the setting of HIV infection [76]. In prior studies in which co-infected patients with HCV genotypes 2 or 3 were treated for only 24 weeks, relapse rates were recognized in more than one third of patients [76].

In summary, the use of pegylated interferon plus ribavirin improves the rate of SVR in HIV-positive patients with chronic hepatitis C and therefore should be considered the best treatment choice in this population, as it is in HCV monoinfected individuals.
The best response rates were seen in the APRICOT trial, although some differences existed between the studies. For example, the lower ribavirin dosages of 600mg per day given initially in ACTG A5071 could explain the lower response rates. Similarly, discontinuation rates of nearly 40% significantly penalized the response in the RIBAVIC trial. Other features, such as the proportion of patients with HCV genotype 1, with cirrhosis, or who were intravenous drug users could also further explain the lower response rates in those trials (see Table 2).

<table>
<thead>
<tr>
<th></th>
<th>ACTG 5071</th>
<th>APRICOT</th>
<th>RIBAVIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. on pegylated + ribavirin</td>
<td>67</td>
<td>289</td>
<td>205</td>
</tr>
<tr>
<td>IDUs</td>
<td>80%</td>
<td>62%</td>
<td>81%</td>
</tr>
<tr>
<td>Cirrhotics</td>
<td>11%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>Genotypes 1-4</td>
<td>77%</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>Mean CD4 count</td>
<td>492</td>
<td>520</td>
<td>525</td>
</tr>
<tr>
<td>With HAART</td>
<td>85%</td>
<td>84%</td>
<td>82%</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>–</td>
<td>25%</td>
<td>42%</td>
</tr>
<tr>
<td>EOTR (ITT)</td>
<td>41%</td>
<td>49%</td>
<td>36%</td>
</tr>
<tr>
<td>SVR (ITT)</td>
<td>27%</td>
<td>40%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Table 2: Mean characteristics of the study populations and results of the three pivotal studies reported at the 11th Retrovirus Conference (February 2004).

The reason why anti-HCV therapy obtains such a poor response in the setting of HIV infection are multiple (Table 3) [49]. Since both pegylated interferon and ribavirin act, at least partially, as immunomodulatory agents, subtle immune defects due to HIV infection might have a negative influence on the performance of these drugs, even in patients with high CD4 counts and undetectable plasma HIV RNA under antiretroviral therapy.
Use of lower than optimal doses of ribavirin in most trials.
Less activity of anti-HCV therapy in the setting of HIV-related immune dysfunction.
More advanced liver fibrosis stage.
Higher rate of steatosis (alcohol, nucleoside analogs).
Unfavorable HCV virological features (high HCV RNA titers).
Lower initial HCV RNA clearance on treatment.
More frequent relapses after treatment discontinuation.
Higher rate of treatment withdrawals due to side-effects.
Lower drug compliance.

Table 3: Factors explaining the lower response rates to HCV therapy in HCV/HIV co-infected patients.

In addition, we also mentioned that there was a high rate of HCV treatment discontinuation in some of the trials performed in HIV co-infected patients, sometimes more than one third of recruited patients. Although this may reflect a higher rate of serious adverse events in this population compared to HIV-negative patients, which is usually less than 15% [77, 78], it might also suggest that some HIV physicians are not familiar with the management of side-effects of anti-HCV therapy. Thus, efforts to minimize side-effects with preventive symptomatic treatments and appropriate management of complications are critical to ensure completion of HCV therapy in most patients.

MONITORING THE RESPONSE TO HCV THERAPY IN HIV-POSITIVE PATIENTS

Individuals with HCV alone who will clear HCV RNA with HCV treatment show a virological response soon after beginning therapy [60, 78, 79]. Therefore, early assessment of serum or plasma HCV RNA titers after starting treatment may help identify who will benefit
from prolonging therapy and who will not. Those HIV-negative patients who show a decline in HCV RNA greater than 2 logs and/or to undetectable levels at 12 weeks of therapy, may eventually reach a sustained response. In contrast, almost none of those who have HCV RNA reductions of less than 2 logs at 12 weeks achieve this goal. Therefore, HCV therapy may be discontinued at week 12 based on this virological criteria in early non-responders [60]. This guide to HCV therapy can spare side-effects and cost in individuals with no chance of cure. In HCV/HIV co-infected patients these considerations are even more crucial, since interactions between antiretrovirals and HCV drugs are frequent and issues related to poor compliance in subjects under polymedications are highly relevant [49].

Kinetic studies suggest that HCV clearance after beginning therapy with interferon may be delayed in the setting of HIV infection [80] (Figure 2a). Therefore, concern exists about the reliability of the 2 log HCV RNA reduction rule at 12 weeks: it might not work in HCV/HIV co-infected patients. However, data from several recent trials, included those from ACTG A5071, RIBAVIC, APRICOT and others suggest that despite a slower decay in HCV/RNA in HIV co-infected patients after beginning HCV therapy, all subjects who will reach SVR show a greater decline than 2 logs at week 12 of therapy [71-75]. Furthermore, a more recent report has demonstrated the predictive value of the 2 log rule at week 12 in co-infected patients in a better designed study [81]. In this study, the only difference between HIV-positive and HIV-negative subjects with hepatitis C was that the proportion of patients reaching virological response at any given time point was much lower in the co-infected population (see Figure 3), but it did not deny the predictive value of SVR using early virological assessments. Therefore, the principles guiding anti-HCV therapy in HIV-negatives may also apply to HIV co-infected patients (see Figure 4).
Figure 2: Hepatitis C virus kinetics under interferon therapy. Influence of HIV infection [49]: a) early phase; b) second phase.
Figure 3: Virological response at different time points in HIV-positive [81] versus HIV-negative patients [78].
Figure 4: Algorithm for the treatment of chronic hepatitis C [60].
* In patients with high baseline HCV loads, treatment might be prolonged beyond 24 weeks despite the recognition of detectable viremia at that time if a reduction greater than 2 logs was observed at week 12 of therapy.
** In the light of higher relapse rates in the setting of HCV-HIV co-infection, patients with HCV genotypes 2-3 showing good virological responses at earlier time-points should be advised to prolong therapy up to 12 months.

Patients with high HCV loads may have a good early virological response but may not reach undetectable viremia at week 24, even though they will clear HCV much later [82]. This subset of patients represents less than 3% of HCV monoinfected individuals, but may be larger in HIV co-infected patients, who frequently have higher baseline HCV RNA titers and who may have slower HCV RNA decays on treatment [10, 80]. In this situation, extending treatment for 12 months may be advisable since it may allow the patient to reach SVR.
There is a second phase of clearance of HCV RNA in subjects on long-term HCV therapy, which explains the steady destruction of infected cells (hepatocytes) [83, 84]. A slower decay in HCV RNA in the presence of HIV infection (see Figure 2b) could explain why the early discontinuation of therapy might result in higher relapse rates in virological responders. We have already mentioned that the most recent data support this notion, and make it necessary to reconsider how long to continue HCV therapy in HCV/HIV co-infected patients with an early virological response. This particularly applies to HCV genotype 3, since relapses are uncommon in HIV-negative subjects infected with this genotype while it may occur in one third of HCV/HIV co-infected patients treated for only 6 months [76], based on what is recommended in HIV-negative patients [60]. Recent studies such as RIBAVIC and APRICOT, which provided treatment for 12 months to patients with HCV genotypes 2 and 3, have proven that relapses are markedly reduced using the extended period of therapy. Therefore, co-infected individuals with HCV genotypes 2 or 3 should be treated for 12 months instead of for shorter periods. Relapses in HCV genotypes 1 or 4 in co-infected patients treated for 12 months occur in 20-35% of patients. In this population, the benefit of long periods of therapy, at least among early virological responders, should be investigated, since results from patients with HCV alone have recently shown a reduction in relapse rate to less than 15% when HCV treatment is extended to 18 months [85].

Patients with HCV alone who do not clear HCV RNA during HCV treatment might benefit from long-term therapy with interferon alone [86-88]. Maintenance therapy with interferon may provide histological improvement and even reduce the risk of hepatocellular carcinoma. It is currently being investigated as an alternative approach in large trials (i.e., hepatitis long-term treatment against cirrhosis (HALT-C) and EPIC). Whether this strategy could be considered in some HCV/HIV co-infected individuals with advanced fibrosis who did not respond virologically to HCV therapy, should be further investigated. The use of lower doses of pegylated interferon (half those recommended at first line) may improve tolerance and facilitate long-term administration of the drug. However, this potential benefit should be weighed against an expected reduction in the quality of life due to the long-term prescription of a drug administered subcutaneously, which often causes side-effects, including a reduction
in the CD4 count which is considered undesirable in most HIV-positive patients.

**MANAGEMENT OF SIDE-EFFECTS OF HCV THERAPY IN HIV-POSITIVE PATIENTS**

Side-effects of HCV treatments are common, and include five main categories: influenza-like symptoms (headache, fever, asthenia, myalgias, decreased appetite), hematologic abnormalities, neuropsychiatric disorders (depression, irritability, insomnia), gastrointestinal symptoms (nausea, diarrhea), and inflammation at injection sites. In addition, other adverse events are rare but include alopecia and thyroid dysfunction [60, 89]. Overall, they result in treatment discontinuation in around 15% of patients with HCV infection alone, and to dose reductions of either pegylated interferon and/or ribavirin in another 20-25% [77, 78]. Higher treatment discontinuation rates have been found in some studies in HIV co-infected persons [71, 74]. The lack of expertise in the management of HCV treatment-related side-effects by doctors as well as insufficient information to patients both help explain these high drop-out rates. These aspects should therefore be properly addressed in the future. When possible, hepatitis C in HIV co-infected patients should be treated by medical teams with expertise in the field.

The hematologic abnormalities may be due to either pegylated interferon or ribavirin. Anemia due to ribavirin typically is mild and due to extravascular hemolysis, and is accompanied by an increase in reticulocytes. Although ribavirin dose reductions may reduce anemia, the usefulness of recombinant erythropoietin (r-EPO) has been shown in these patients [90]. Supplements of folinic acid are advisable. Otherwise, the dose of ribavirin should be reduced to half when hemoglobin (Hb) drops below 10g/dL, and it needs to be discontinued if it goes below 8.5g/dL. However, ribavirin exposure appears crucial to obtain higher sustained response rates, especially in patients with HCV genotype 1 [77, 91]; therefore any efforts to keep patients on adequate doses of the drug (i.e., using r-EPO) should be favored.

Leukopenia, especially neutropenia and less frequently lymphocytopenia, may develop with pegylated interferon. Patients should be informed about the risk of reduced CD4+ counts [44, 55, 56] which mostly affect absolute CD4 number but not the percentage of cells. Moreover, it reverses after discontinuing interferon therapy
[92]. For neutropenia, the use of therapeutic growth factors, such as granulocyte colony stimulating factor (GCS-F), may be considered and may be better than reducing pegylated interferon doses, especially in patients with HCV genotype 1, who seem to be particularly sensitive to pegylated interferon doses.

**INTERACTIONS BETWEEN ANTIRETROVIRAL DRUGS AND HCV MEDICATIONS**

Since anemia is a frequent side-effect during ribavirin treatment, attention should be paid to patients who are taking azidothymidine (AZT), which is also known to cause anemia. Thus, in patients with AZT-related anemia this drug should be discontinued before prescribing ribavirin. Alternatively, Hb values should be closely monitored during the first 6 weeks of therapy [49].

Mitochondrial damage is a result of the inhibition of mitochondrial polymerase gamma by nucleoside analogs [93, 94]. Ribavirin can enhance intracellular concentrations of phosphorylated ddi metabolites, and result in a higher risk of toxicity [95-97]. Several cases of pancreatitis and/or lactic acidosis have been reported, and the FDA now warns against the risk of giving ribavirin and ddi concomitantly. Therefore, subjects who begin treatment with ribavirin should not use ddi concomitantly [49]. The role of d4T in the development of lactic acidosis in these patients has also been shown in the RIBAVIC and APRICOT trials, mainly when used concomitantly with ddi [74, 98].

More recently, cases of liver decompensation, some fatal, have been reported in subjects receiving ribavirin with ddi [74, 98]. All these cases occurred in patients with cirrhosis, and hypothetically ddi and ribavirin acted synergistically leading to liver failure. Therefore, the concomitant administration of ddi and ribavirin should be contraindicated in subjects with advanced liver fibrosis.

Finally, several observations have shown that ribavirin could potentiate subcutaneous fat loss when used concomitantly with some nucleoside analogs, mainly d4T [99]. In this form, severe weight loss mimicking progression of lipoatrophy could be another characteristic side-effect due to the interaction of ribavirin and antiretroviral drugs. Patients should be informed in advance about the risk of this complication and, when possible, drugs with a lower lipodystrophic profile should be prescribed.
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