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Concise Review

Current concepts in the management and treatment of hepatitis C in HIV-infected patients

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Abstract

Chronic hepatitis C virus (HCV) infection is very common among HIV-positive patients who were infected through intravenous drugs use or contaminated blood products (e.g., hemophiliacs). An increase in liver-related deaths among HIV-positive subjects co-infected with HCV has been acknowledged over the last years. HIV infection has a negative impact on the natural history of chronic hepatitis C, accelerating the progression of liver fibrosis. Moreover, interactions between anti-HIV and anti-HCV drugs are of concern, and a lower response to anti-HCV therapy limits its benefit in the HIV/HCV-coinfected population. Regarding treatment monitoring, the stopping rule at week 12 recommended for HCV-monoinfected individuals, seems to be equally valid in HIV-infected patients. This finding is of great value, since it allows to offer treatment in the absence of contraindication (e.g., low CD4 counts, alcohol abuse, etc), discontinuing it as soon as at 12 weeks after initiation when no chances of cure are anticipated, saving costs and deleterious side effects. There are important barriers to HCV treatment in HIV/HCV-coinfected patients, which are necessary to be addressed in order to increase the eligibility and applicability of HCV therapy in this population. In addition, strategies aimed to improve tolerance of the HCV medication with adequate support as well as to enhance the response to current available therapies, including individualized tailoring of drug dosages and length of treatment, should be pursuit to enhance the rate of treatment success. Finally, new anti-HCV drugs currently under development are eagerly awaited for the growing number of HCV/HIV-coinfected patients non-responders or relapsers to the current therapy.

Key words: Hepatitis C, HIV, interferon-α, ribavirin, liver.

The problem of HCV and HIV coinfection

Liver disease is nowadays one of the most common causes of morbidity and mortality among HIV-infected individuals in areas with a high number of intravenous drug users, in whom the prevalence of hepatitis C virus (HCV) infection is high.[1-6] The increased weight of liver complications among HIV-infected patients is a result of the dramatic decrease in opportunistic infections as consequence of the widespread use of highly active antiretroviral therapy (HAART), and of aging of the cohorts with chronic liver disease.[7]

There are bidirectional interferences between HCV and HIV infections that have clinical consequences and make very complex the management of coinfected individuals.[8] Acute HCV infection more easily evolves into chronic hepatitis in HIV-infected individuals, especially in those with more advanced stage of immune deficiency. Once chronic HCV infection is established, HCV-RNA levels are much higher in HIV-coinfected subjects compared to HCV-monoinfected individuals, both in plasma and in the liver.[9,10] The progression of liver fibrosis is accelerated in HIV/HCV-coinfected patients, especially when immune deficiency is more profound.[11-14] As a consequence, progression to end-stage liver disease occurs faster in this population,[15-18] including the development of hepatocellular carcinoma at younger ages.[19] Overall, 25% of HIV-coinfected patients will develop cirrhosis within 15 years after initial HCV infection, while this only occurs in 5% of those without HIV infection.

Clinical studies examining whether there is an influence of HCV on HIV disease progression have shown conflicting results, some demonstrating an others failing to prove association between HCV infection and faster HIV disease progression.[8] Conflicting results also exist

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regarding a possible negative influence of HCV infection on CD4 recovery using HAART, with some clinical studies evidencing significantly lower CD4 cell gains in HCV-positives compared to HCV-negatives and others showing no differences.[20,21] HCV may influence negatively HIV disease through indirect ways, such as making antiretroviral treatment discontinuation more frequent due to an increased risk of liver toxicity.[22]

The worsened clinical outcome of chronic hepatitis C and the higher risk of liver toxicity using HAART in the face of HIV/HCV-coinfection are two reasons for pursuing anti-HCV treatment in these patients if feasible. However, there are currently many opened questions regarding treatment of hepatitis C in HIV/HCV-coinfected subjects, a relatively novel area.[23,24] Experts in the field are making great efforts to achieve consensus and develop practical guidelines for the management of these patients.[25,26] This review attempts to provide an updated overview on the treatment of chronic hepatitis C in HIV-coinfected patients.

Epidemiology of HIV/HCV-coinfection

In the United States, it is estimated that 30% of the 800,000 HIV-infected living individuals are coinfected with HCV.[27,28] Similar prevalences (33%) have been estimated for Western Europe.[29] HCV and HIV are both transmitted by whole blood and blood products, being HCV 10 times more infectious than HIV. Coinfection with HIV and HCV is therefore frequent in persons with increased blood exposure such as HIV-positive intravenous drug users and hemophiliacs, who have a prevalence of coinfection of 60-90%.[27,28,30] Although sexual transmission of HCV is infrequent, what explains the low rate of HCV coinfection among homosexual HIV-infected subjects, recent reports of small epidemics of acute HCV infection have been associated with homosexual relationships.[31]

Assessment and management of chronic hepatitis C in HIV-infected subjects

Current guidelines recommend that all HIV-infected individuals should be screened for HCV antibodies by ELISA.[25,26] Above 85% of anti-HCV antibody positive subjects show detectable HCV-RNA in the setting of HIV infection.[25] Subjects with repeatedly elevated aminotransferase levels of unclear cause and negative HCV antibody should also be tested for HCV-RNA, although the presence of HCV infection despite negative serology (occult hepatitis C) is very rare, and mainly described in patients with very severe immunodeficiency.[9,25,33,34] If HCV-RNA is positive, the HCV genotype should be determined.

HIV/HCV-coinfected patients are recommended to be vaccinated against hepatitis A virus if they have not been previously exposed or immunized, since acute hepatitis A may be more severe in the presence of underlying chronic C hepatitis.[32]

Anti-HCV treatment in HIV/HCV-coinfection: results from randomized clinical trials

The current standard treatment for HCV is the combination of pegylated IFN (peg-IFN) and RBV. Four randomized studies assessing the efficacy and safety of this therapy in HIV/HCV-coinfected patients have been published.[35-38] *Table I* summarizes the main results of these studies. Sustained virological response (SVR) ranged from 27% to 44%. The different results may be explained by study-to-study differences, person-to-person differences (genotype, age, viral load, race, weight, treatment tolerability, etc..), and by the presence of mitigating fac-

Table I. Main randomized clinical trials assessing HCV treatment with pegylated interferon and ribavirin in HIV/HCV-coinfected patients.

	ACTG5071	APRICOT	RIBAVIC	Barcelona
Reference	36	35	37	38
No. with PegIFN+RBV	66	289	205	52
RBV dose (mg/day)	600-1,000	800	800	800-1,200
Pegylated IFN	IFN-α-2a	IFN-α-2a	IFN-α-2b	IFN-α-2b
Intravenous drug users	—	62%	81%	75%
Cirrhotics	11%	15%	40% (F3-F4)	19%
Genotypes 1-4	77%	67%	69%	63%
Normal ALT levels	—	0%	15%	0%
Mean CD4 count (cells/mm^3	—	520	525	512
On HAART	—	84%	82%	94%
Tx discontinuation	—	25%	41%	25%
Response (ITT)				
End of treatment	41%	49%	36%	52%
Sustained	27%	40%	27%	44%
Genotypes 2/3	73%	62%	43%	53%
Genotypes 1/4	14%	29%	16%	38%

ITT: Intent to treat analysis.

tors such as alcohol intake, ongoing intravenous drug use, CD4 counts < 200 cells/mm^3, renal failure, and anemia.

The ACTG 5071 study included 66 coinfected patients from several centers in the United States. Subjects were treated with a fixed dose of 180μg/week of peg-IFN alpha-2a along with RBV.[36] All subjects began RBV at doses of 600 mg per day and increased up to 1,000 mg 12 weeks later if the tolerance was acceptable. In this trial, 77% of patients carried HCV genotype 1, which tends to show a poorer response to HCV therapy. End-of-treatment response (EOR) was reached by 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, a multicenter French trial conducted by the Agence Nationale de la Recherche sur le SIDA (ANRS), evaluated 205 HIV/HCV-coinfected patients treated with a weight-adjusted dose (1.5 μg/kg/week) of peg-IFN alpha-2b plus a fixed dose of 800 mg of RBV per day.[37] While the overall SVR in this study was 27%, equal that in the prior American study, the proportion of subjects with HCV genotypes 2 or 3 achieving SVR was much lower. However, the RIBAVIC trial had a high drop-out rate (38%), which was not due to early virological failure.

The APRICOT is the largest trial conducted so far in HIV/HCV-coinfected patients assessing the response to peg-IFN and RBV.[35] It assessed 289 subjects receiving at least one dose of peg-IFN alpha-2a 180 μg/week plus a fixed dosage of 800 mg of RBV per day. In contrast with the prior two trials, this study was conducted by the pharmaceutical industry (Roche) and included patients from several countries and continents, what was reflected in a lower proportion of patients with the less favorable genotype 1 (60%). The overall rate of SVR was 40%, but dropped to 29% in patients with HCV genotype 1. A close monitoring of patients and strict inclusion criteria resulted in a relatively low number of discontinuations in this trial (25%). The better response rates seen in APRICOT with respect to other trials may be explained, at least in part, by differences in the study populations. In addition, the lower RBV dosages of only 600 mg per day given initially in the ACTG A5071 could have contributed to its lower response rate.

In a much smaller trial, performed in Barcelona (Spain), pegylated IFN-α-2b was given along with RBV at dosages from 800 to 1,200 mg/day according to body weight, and compared to standard IFN-α-2b.[38] SVR was above 40% in this study, which included a very selected population with a relatively low proportion of poor-responder genotypes 2-3 and cirrhotics.

Much higher responses for HCV genotypes 2 or 3 compared to HCV-1 were seen in all these trials. For instance, in the APRICOT study, the percentages of EOT (64%) and SVR (62%) were very close. This low proportion of relapses should be highlighted, and suggests that extending treatment beyond 24 weeks for genotypes 2/3 may be advisable to avoid relapses in HIV/HCV-coinfected patients.[39] At this time is unclear whether prolonging therapy beyond 12 months in HCV genotypes 1 or 4 may equally lead to reduced relapse rates.

Given that the use of peg-IFN plus RBV improves the response among HIV-positive patients with chronic hepatitis C, it should be considered the treatment of choice in this population.[25,26] Nevertheless, treatment responses are still lower than in HCV-monoinfected subjects. The underlying reasons are not well understood, but are most likely multiple. In *Table II* are summarized both, the facts observed evidencing a poor response, and the reasons which may explain it. Since both peg-IFN and RBV act, at least in part, as immunomodulatory agents, immune defects driven by HIV infection might negatively impact on the performance of these drugs, even in patients with high CD4 counts and undetectable plasma HIV-RNA. On that regard, immune responses against HCV have been found to be important determinants of HCV-RNA clearance in subjects undergoing anti-HCV therapy.[40] Likewise, intrahepatic CD8 responses were associated to the success of IFN therapy according to a recent study performed in HIV/HCV-coinfected subjects.[41]

Assessment of candidates for anti-HCV therapy

Given the ominous clinical outcome of patients when chronic hepatitis progresses to end-stage-liver-disease (ESLD), treatment should be entertained in all HIV/HCV-coinfected subjects before reaching late stages of liver cirrhosis. Severe psychiatric diseases or the presence of other conditions may contraindicate treatment with IFN and RBV,[42] but once those have been ruled out, a complete assessment of the HCV infection should be pursuit in these patients.

Table II. Factors accounting for the lower response to anti-HCV therapy in HIV/HCV-coinfected subjects.

Observations
Slower plasma HCV-RNA clearance on treatment
Lower end-of-treatment responses
More frequent relapses after treatment discontinuation
Poorer immune responses under interferon-based treatment
Possible explanations
Less activity of anti-HCV therapy due to HIV-related immune dysfunction
Poor profile for treatment response in most of HIV/HCV-coinfected patients
More advanced liver fibrosis stage
High HCV RNA levels
Predominance of genotype 1
Higher prevalence of liver steatosis (alcohol, nucleoside analogues)
Use of lower than optimal doses of ribavirin in most trials
Higher proportions of treatment withdrawals due to side effects
Lower drug compliance

Once HCV-RNA has been demonstrated in HCV antibody positive subjects, then quantification of HCV-RNA levels and especially HCV genotyping give the most valuable information on the probability of achieving response to therapy, being higher HCV-RNA levels and genotypes other than 2/3, poor prognostic factors.[42]

As summarized in *Figure 1*, the third element in the evaluation of chronic HCV infection is liver histology. The need of liver biopsy before prescribing anti-HCV therapy was under hot debate past years, but currently many experts feel that outside academic purposes is not needed in most cases. Liver histology allows staging of HCV hepatic damage and may predict the time to develop cirrhosis. It may also provide information to rule out other causes of liver damage.[43-46] The controversy may be less justified in HCV/HIV-coinfected patients, in whom the fibrosis progression rate is much higher than in HCV-monoinfected persons[14,15,18,19] and other causes of liver disease can be rule out by serum markers (i.e., hemochromatosis) or interview (i.e., alcohol). Anti-HCV therapy will be almost always warranted considering the extent of histological damage in coinfected patients.[47] Nearly half of coinfected patients may show unexpected cirrhosis or pre-cirrhosis after 40 years of age.[14] Overall, 50% of patients will have cirrhosis 25 years after initial HCV infection. Since currently the mean age of HIV/HCV-coinfected patients in Western countries is 40 years, and that the majority started to exchange needles when they were about 20 years-old, it is expected that many of them already have significant liver fibrosis. These subjects, if not treated, are at high risk to develop liver complications within the coming decade.

Supporters of pre-therapy liver biopsy argued that the limited efficacy and important side effects of IFN-based therapies in HIV-coinfected subjects made necessary to assess the histological damage and prescribe the treatment only to patients who really needed it and had prospects to achieve response. However, given that liver damage is a dynamic process and fibrosis progression rate is accelerated in HCV/HIV-coinfected patients,[11-13] if treatment is not offered to patients with lack of or minimal fibrosis, liver biopsy should be repeated at 2-4 year intervals. This option may be limited by the costs and the reluctance of patients to undergo the procedure several times. On that regard, a recent analysis has pointed out the cost-effectiveness of prescribing anti-HCV therapy in HCV/HIV-coinfected individuals without prior liver biopsy.[48]

Given the 'cons' of liver biopsy, including the invasive character of the procedure, non-invasive tools have emerged to assess liver fibrosis [49]. There are currently 6 available serological tests, being the FibroTest the most validated. Their specificity ranges from 41% to 91% and their sensitivity from 41% to 90%. The problem in HIV infection is that there are several markers that may be dependent on HIV-related factors: transaminase elevations may reflect drug hepatotoxicity, total bilirubin may be elevated by certain antiretrovirals (i.e., indinavir and arazanavir), thrombocytopenia may be caused by HIV itself, and the MELD score system for transplant candidates has not been validated yet for HIV-infected patients. Nevertheless, there are reports claiming the applicability of serum markers of fibrosis also in HIV-coinfected subjects.[50] Two indexes have been proposed for HIV/HCV-coinfected patients, the SHASTA index (hialuronic acid, AST and albumin) and the FIB-4 (age, platelets, AST, ALT).

Hepatic elastography (FibroScan®), a technique developed to measure liver elasticity has recently been validated alone and in combination with serum markers to assess liver fibrosis in HCV-monoinfection, and it is currently being studied in HCV/HIV-infected cohorts. It is easy to perform, and discriminates accurately advanced stages of fibrosis,[51] for which it has a specificity of 91% and a sensitivity of 56%. Obesity, but not steatosis could interfere with the measurement of liver elasticity.

Although a liver biopsy may give valuable information, fibrosis markers and FibroScan® could stage liver disease as accurately as biopsy, and save most patients from it. Liver biopsy could be spared only for those cases in which results of serum marker tests and elastography are discordant *(Figure 1)*. There is a need for performing longitudinal studies to assess the risk for disease progression with novel non-invasive techniques, and for validating these new tools in HIV+ patients.

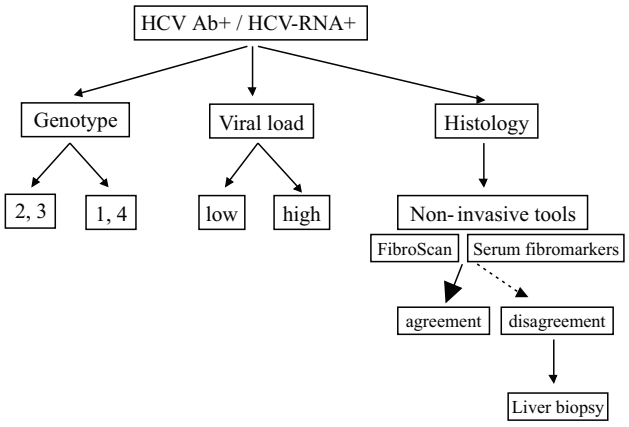

Figure 1. Algorithm for evaluating prescription of HCV treatment.

Candidates for HCV therapy among HIV-coinfected patients

Response to anti-HCV therapy seems to be superior with better immunological status according to some studies, although this has not been confirmed by others.[35,37,52] Candidates to receive anti-HCV therapy ideally should have above 350 CD4 cells/mm^3, a usually feasible threshold if antiretroviral therapy is used appropriately. In sub-

jects with CD4 counts between 200 and 350 cells/ mm^3 and already under HAART, the decision to treat HCV infection must be made taking into account other factors, such as the estimated length of HCV infection, the severity of liver disease, the extent of HIV suppression, and classical predictors of response to anti-HCV therapy such as HCV genotype and viral load.[53,54]

Anti-HCV therapy should be deferred in individuals with less than 200 CD4+ T cells/mm^3. IFN-based therapies decrease CD4 counts, what may pose patients at risk for developing opportunistic infections if their baseline counts are low. Therefore, they should be treated with antiretroviral therapy as a priority, and receive prophylaxis for opportunistic infections. Later on, once their CD4 counts have risen and their plasma HIV-RNA is under control, the prescription of anti-HCV therapy should be re-assessed.

In antiretroviral-naive individuals with HCV/HIV-coinfection, chronic hepatitis C should be treated first if the CD4 counts do not warrant immediate antiretroviral therapy. However, in patients with CD4 counts above 350 cells/mm^3 but high plasma HIV-RNA levels, it is unclear whether suppression of HIV replication should be attempted first, deferring anti-HCV therapy until attaining undetectable HIV viremia. Finally, the greater efficacy of anti-HCV therapy with higher CD4 counts should be balanced against a higher risk of interactions between antiretrovirals and anti-HCV drugs.[23]

Regarding liver disease stage, patients with liver decompensation (ascites, gastrointestinal bleeding, hepatic encephalopathy, etc.) should not be treated, given their higher risk to develop serious side effects with the current approved drugs. These patients should be assessed for liver transplantation. However, treatment should be attempted in patients with compensated cirrhosis (Child-Pugh class A), since they have poor prognosis in the short-term if HCV is not cleared.[55,56]

Individuals with prior history of severe neuropsychiatric disorders should not be treated, since IFN can exacerbate these conditions. Subjects currently engaged in heavily alcohol intake and/or illegal drug addiction practices should delay treatment, whereas all efforts should be devoted to put them into detoxification programs. Patients on methadone are acceptable candidates for anti-HCV therapy. However, up to one third of them may need adjustments in methadone dosage.[57] This is due to psychological demands rather than to pharmacological interactions between anti-HCV drugs and methadone. Ideally, a multidisciplinary team, including experts in addiction medicine and psychologists/psychiatrics should take care of these patients.[58,59]

Subjects with repeated normal liver enzymes might benefit from current anti-HCV therapy, particularly those infected with HCV genotypes 2 or 3.[42] However, more information on liver damage in this subgroup of HCV/HIV-coinfected patients is needed to balance the cost-benefit of anti-HCV therapy in them.[23] Preliminary data from the RIBAVIC trial suggest, however, that liver fibrosis may be recognized in a substantial proportion of coinfected patients with normal ALT levels and unexpectedly the response was lower in this subset of patients.[37]

In summary, all HIV-positive persons with chronic HCV infection should be considered as potential candidates for anti-HCV therapy, given their higher risk of progression to end-stage liver disease and increased risk of liver toxicity after beginning antiretroviral therapy, compared to HIV-negatives. The timing for anti-HCV treatment should be decided on an individual basis. Severe neuropsychiatric disorders, alcohol and drug abuse and advanced liver cirrhosis contraindicate current anti-HCV treatment. However, methadone use and early cirrhosis are not contraindications for therapy. Treatment of patients with CD4 counts below 200 cells/mm^3 is risky and should be avoided.

There seems to be important barriers in the treatment of HCV infection in HIV/HCV-coinfected subjects. Both the eligibility (patients without contraindications for treatment) of coinfected subjects for HCV treatment (<30%) and the applicability (patients actually receiving therapy) (<10%) have been too low.[60-63] Therefore, efforts are needed to increase the suitability of the coinfected population to be treated for HCV.

Monitoring of anti-HCV therapy - the 12 weeks 2-log rule

Almost all HCV-monoinfected individuals clearing the virus under anti-HCV therapy show a virological response soon after initiating treatment.[42,64,65] Thus, assessment of plasma HCV-RNA titers early on treatment may permit to identify who would benefit from prolonging therapy and who would not. A decline in plasma HCV-RNA greater than 2 logs and/or to undetectable levels at week 12 of therapy has been shown to predict sustained response in HCV-monoinfected subjects. In contrast, it is very rare to achieve that goal in patients without that early virological response, and therefore, anti-HCV therapy may be discontinued at that point in them.[42] This so-called "2-log rule" is of great importance because side effects and costs can be spared in those early non-responders, given their lack of prospects for HCV eradication.

Kinetic studies, however, suggest that HCV clearance induced by IFN-based therapy might be delayed in the setting of HIV infection.[66] As a consequence, there was a concern about the reliability of the 2 log rule in HCV/HIV-coinfected patients. Nevertheless, data from recent trials, including those from ACTG A5071, RIBAVIC and APRICOT, suggest that despite a slower initial HCV-RNA decay in HIV-coinfected patients, all those who attain SVR showed a decline greater than 2 logs at week 12 of therapy.[35-37,67,68] Furthermore, a more recent report has demonstrated the negative predictive value of

the 2 log rule at week 12 in coinfected patients.[69] In that study, the only difference between HIV-positive and HIV-negative subjects with hepatitis C was that the proportion of patients reaching virological responses at any given time point was much lower in the coinfected population. Therefore, the principles guiding anti-HCV therapy in HIV-negatives seem equally applicable to HIV-coinfected patients.

There is a second phase of clearance of HCV-RNA in subjects on HCV therapy, which accounts for the steadily destruction of infected liver cells.[70,71] This second HCV-RNA decay is also delayed in HIV/HCV-coinfected subjects, and has been associated with a poorer immune response against HCV.[72] The slower decay in HCV-RNA in the setting of HIV infection could explain the more frequent relapse rate in early virological responders seen in HIV-coinfected patients. Therefore, it seems necessary to reconsider the appropriate duration of therapy in HIV/HCV-coinfected patients. This observation seems to apply particularly to HCV genotype 3, since relapses are uncommon in HIV-negative subjects infected with this genotype while it may occur in up to one third of HIV/HCV-coinfected patients treated for only 6 months.[39] Recent studies in which treatment was provided for 12 months to individuals with HCV genotypes 2 and 3, have proven that relapses are dramatically reduced using a more prolonged duration of therapy.[35-37] Therefore, HIV/HCV-coinfected subjects carrying genotypes 2 or 3 should be treated during 12 months.

Side effects of HCV therapy and interactions with antiretrovirals

Adverse events of anti-HCV drugs can be grouped in 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 side effects such as alopecia and thyroid dysfunction, may develop on rare occasions.[42,73] They lead to treatment discontinuation in around 15% of HCV-monoinfected patients, and to dose reductions of either peg-IFN and/or RBV in other 20-25% of subjects.[64,74] Higher treatment discontinuation rates have been recorded in some studies conducted in HIV-coinfected persons.[37]

Hematologic toxicity, especially anemia, is one of the most limiting side effects of anti-HCV therapy. Although it occasionally may be caused by IFN, anemia is most often secondary to RBV, and due to extravascular hemolysis.[73] Dose reductions and temporary discontinuation of the drug may allow to overcome it. Since appropriate RBV exposure seems crucial for attaining higher sustained response rates, particularly in patients carrying HCV genotype 1, any effort to keep patients on adequate doses of the drug should be made.[74,75] The administration of recombinant erythropoietin has been proposed as an useful strategy in the management of RBV-related anemia.[76,77] Although some studies in HCV-monoinfected subjects have shown increased hemoglobin levels, better quality of life and opportunities to keep adequate RBV doses, an increase in virological responses has not been proven so far with EPO.[77] In this regards, the new RBV pro-drug under development, viramidine, which produces less anemia is much more promising.[78]

Treatment with peg-IFN may result in decreases in white cell counts, and neutropenia is a frequent side effect. The use of granulocyte colony stimulating factor (GCS-F) may be considered in some cases, but there are weak data to support its use. In addition, the occurrence of bacterial infections seems to be infrequent (<2% in the APRICOT study).[35] Likewise, CD4 cell counts may drop to risky values for developing opportunistic infections.[79] However, the occurrence of opportunistic events in patients with good control of their HIV infection under anti-HCV treatment is rather uncommon. Nevertheless, prophylaxis with cothrimoxazole should be prescribed when counts decrease to levels below 200 cells/mm^3.

Special attention should be paid to symptoms of depression, a disorder relatively frequent at HIV clinics, which may arise or be aggravated with peg-IFN therapy. Early treatment of depression may be enough to overcome it without discontinuing anti-HCV therapy. Decreases in the dose of peg-IFN may also occasionally be helpful. The use of "pre-emptive" antidepressants has been advocated in individuals with history of depression, but more studies are needed to support this approach.

HCV treatment in the presence of HIV infection is more complicated due to the interferences between RBV and some antiretrovirals. Intracellular levels of some HIV nucleoside analogues might be decreased by RBV, but the interactions have no clinical consequences. However, higher toxicity has been seen with the concomitant use of didanosine (ddI) and RBV, and even more when stavudine (d4T), ddI and RBV are used together.[80] This is due to the enhancement of mitochondrial toxicity.[81] Hepatic decompensation, sometimes with fatal outcome[82] has been described with the co-administration of these drugs in cirrhotic patients. Besides this adverse event, lactic acidosis and pancreatitis have been reported with the combined use of RBV and ddI, and therefore ddI should be avoided in patients receiving anti-HCV therapy.[25]

It is also advisable to avoid zidovudine (AZT) if possible when anti-HCV therapy is initiated, because it has been shown that anemia is more frequent and severe in patients taking AZT along with RBV.[83] Moreover, in a recent study in which there was a correlation between RBV plasma levels and anemia, higher RBV concentrations were found among patients receiving AZT.[83]

Improving success of hepatitis C treatment in HIV-coinfected subjects

Table III includes several strategies that may increase the number of HIV/HCV-coinfected patients successfully treated of their chronic hepatitis C. The low eligibility and applicability of HIV/HCV-coinfected subjects for receiving anti-HCV treatment has already been reported.[60-63] Therefore, the first effort needed is to improve the population of candidates for therapy. In some of these reports, poor compliance with follow-up visits was one of the most common causes for rejecting HIV/HCV-coinfected patients for receiving HCV therapy. Drug and alcohol abuse are also often reported as barriers to treat hepatitis C in this population. Preliminary data from a multidisciplinary HIV/HCV-coinfection program aimed to address barriers to successful HCV care in this population are encouraging.[84]

The high proportion of HCV treatment discontinuations in some of the trials conducted in HIV-coinfected patients, even surpassing one third of recruited patients, should not be ignored. Although it may reflect more frequent serious adverse events in this population compared to HIV-negatives, in whom it is usually lower than 15%,[64,74] it might also reflect that some HIV physicians are not familiar enough with the management of side effects of anti-HCV therapy. Special efforts should be made to follow very closely and to appropriately manage the side effects derived from anti-HCV medications in coinfected patients to avoid unnecessary discontinuations.

Regarding dosages of anti-HCV drugs, higher doses of RBV (1,000-1,200 mg/day *versus* 800 mg/day) have been shown to be more effective in HCV-monoinfected patients with genotype 1.[75] There are limited data on the safety and efficacy of RBV doses above 800 mg/day in the HIV/HCV-coinfected population, but in one study RBV was given at weight-based dosages (800-1,200 mg/day) without safety concerns.[38] Two recent reports showed higher early and sustained responses in HIV/HCV-coinfected subjects with more elevated RBV plasma levels, suggesting that also in this setting is important to maximize the exposure to RBV.[83,85]

It has been mentioned earlier that, contrary to HCV-monoinfected patients, treatment should be given for 48 weeks to HIV/HCV-coinfected patients with HCV genotype 3, and that might decrease the number of relapsers after initial response. Relapses in HIV-positive patients coinfected with HCV genotypes 1 or 4 treated for 12 months occur in 20-30% of patients. In this population, the benefit of prolonged periods of therapy, at least among early virological responders, should be investigated, since results from HCV-monoinfected subjects are promising using that strategy (less than 15% relapses with 18 months of treatment).[86] Moreover, tailoring the duration of treatment according to early kinetics might be another strategy to maximize the proportion of SVR. Thus, patients with slower declines during the first weeks of therapy could benefit from receiving more prolonged therapy than those showing a rapid decline of HCV RNA levels.[87] However, extending the treatment to patients who had not attained adequate virological response at week 12, has been proven not to increase SVR in HIV/HCV-coinfected subjects.[88]

Table III. Strategies to enhance the success of HCV therapy in HIV/HCV-coinfected patients.

Increase eligibility for treatment
• Increase CD4 with antiretroviral therapy
• Inform patients on the outcome of chronic hepatitis C
• Treat psychiatric conditions
• Address alcohol, drug use and social issues
• Not delay treatment until late stage liver disease is established
Reduce premature discontinuations
• Inform patients about side effects
• Provide treatments for side effects
• Close follow-up
• Psychological support
Increase virological effectiveness, individually tailoring treatment
• Maximize dose of ribavirin
• Prolong treatment

Open questions and anti-HCV drugs under development

Although great progress has been made in the treatment of chronic hepatitis C in HIV-infected subjects, especially with the advent of the pegylated forms of IFN, many questions still remain unanswered regarding the use of IFN-based therapies in this population *(Table IV)*. Even paying particular attention, a large group of patients will be unable to be treated with the current drugs.

Although the combination of peg-IFN plus RBV should be considered the treatment of choice in HCV/HIV-coinfected patients, this combination has significant toxicity and its effectiveness is limited. Therefore, it is necessary to develop new drugs with novel mechanisms of action and less toxic for the treatment of HCV infection. Several compounds are currently under investigation for the treatment of HCV.

Valopicitabine (NM283) is a new nucleoside analogue that has been shown in an early phase I/II trial to significantly reduce HCV-RNA plasma levels in monotherapy in patients with prior failure to current anti-HCV therapy. In a phase IIa study recently reported, NM283 combined with pegylated IFNα-2b was shown to reduce by a mean of -3.01 $\log_{10}$ HCV-RNA levels by week 12 of therapy.[88] VX-950 is an HCV protease inhibitor orally administered. In a phase Ib study, treatment with VX-950 was well tolerated and decreased HCV-RNA levels 4 $\log_{10}$ after 14 days of treatment in subjects infected by HCV genotype 1.[89] PEG-alfacon, a pegylated form of the consensus IFN, and CPG 10101 (Actilon) the first of a new class of antiviral immunomodulatory drugs, are also under evaluation.[90,91]

Table IV. Open questions regarding the treatment of chronic hepatitis C in HIV-infected patients.

Assessment prior to treatment
• Use of non-invasive methods for assessment of liver fibrosis
Candidates for treatment
• Timing
• CD4 cell count threshold
• HCV treatment for subjects with no evidence of liver fibrosis?
Treatment provided
• Ribavirin dose
• Duration of treatment
Management of toxicities
• Use of epoietin?
• Concurrent ART, particularly zidovudine
Management of non-responders and relapsers

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