Treatment of chronic hepatitis C in patients with HIV/HCV coinfection

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Abstract

Hepatitis C virus (HCV) infection is one of the most frequent causes of comorbidity and mortality in the human immunodeficiency virus (HIV) population, and liver-related mortality is now the second highest cause of death in HIV-positive patients, so HCV infection should be countered with adequate antiviral therapy. In 2011 began the era of directly acting antivirals (DAAs) and the HCV NS3/4A protease inhibitors telaprevir and boceprevir were approved to treat HCV-genotype-1 infection, each one in combination with pegylated interferon alfa (Peg-IFN) + ribavirin (RBV). The addition of the first generation DAAs, strongly improved the efficacy of antiviral therapy in patients with HCV-genotype 1, both for the HCV-monoinfected and HIV/HCV coinfected, and the poor response to Peg-IFN + RBV in HCV/HIV coinfection was enhanced. These treatments showed higher rates of sustained virological response than Peg-IFN + RBV but reduced tolerability and adherence due to the high pill burden and the several pharmacokinetic interactions between HCV NS3/4A protease inhibitors and antiretroviral drugs. Then in 2013 a new wave of DAAs arrived, characterized by high efficacy, good tolerability, a low pill burden and shortened treatment duration. The second and third generation DAAs also comprised IFN-free regimens, which in small recent trials on HIV-positive patients have shown comforting preliminary results in terms of efficacy, tolerability and adherence.

Key words: Hepatitis C virus infection; Human immunodeficiency virus infection; Anti-hepatitis C virus treatment; Directly acting antivirals; HIV/HCV coinfection; Chronic hepatitis C

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Core tip: The combination pegylated interferon alfa + ribavirin has been used infrequently in patients with Human immunodeficiency virus/hepatitis C virus (HIV/HCV) coinfection because of its limited efficacy in these
patients, the high prevalence of medical and psychiatric comorbidities and the high incidence of serious adverse reactions. The introduction of directly acting antivirals has radically changed the scenario of the HIV/HCV coinfection treatment shown comforting preliminary results in terms of efficacy, tolerability and adherence. This paper provides a quick and comprehensive implementation guide to the management of HIV/HCV patients in a historical moment in which it is not yet clear what is the best treatment.

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INTRODUCTION

The percentage of patients with human immunodeficiency virus (HIV) infection who contemporaneously carry the hepatitis C virus (HCV) ranges from 10% to 50% worldwide, reflecting a different diffusion of HCV infection and a different impact of the environmental factors responsible for HCV transmission in each single country.[1-12]

The introduction of highly active antiretroviral therapy (ART) has increased by at least 20 years the average life expectancy of HIV-infected individuals and, consequently, the majority of HIV patients with chronic hepatitis C are at a higher risk of progressing to the more severe forms of the disease. At present HCV infection is one of the most frequent causes of comorbidity and mortality in the HIV population, and liver-related mortality is now the second highest cause of death in HIV-positive patients[13-15]. HCV infection unfavorably influences the natural history of HCV infection by increasing the rate of acute hepatitis C that progresses to chronicity, thus favoring the development of liver cirrhosis, hepatocellular carcinoma (HCC), liver decompensation and liver failure.[16-20]

Therefore, optimized ART should be applied to reduce the unfavorable influence of HIV on HCV-related diseases. Also the HCV infection should be countered with adequate antiviral therapy.

The recent introduction of directly acting antivirals (DAAs) to treat chronic hepatitis C has enhanced the knowledge on the management and treatment of HIV/HCV coinfection.

ANTI-HCV TREATMENT FOR HIV-POSITIVE PATIENTS

The introduction of new, more effective and well-tolerated drugs for the treatment of patients with HIV infection has greatly improved the disease outcome of these patients[21]. In this context, however, the progression of HCV-related liver damage in HIV-positive patients, less evident in the pre-ART era because of the low average survival, has become a major life-threatening clinical condition.[22]. Fewer advances were made in this period in the treatment of HCV[23], at that time based on the combination of pegylated interferon alfa (Peg-IFN) plus ribavirin (RBV), which was poorly tolerated and had a low rate of HCV eradication, especially in HIV-positive patients.[24-26] However, in 2011 the era of DAAs began and the HCV NS3/4A protease inhibitors (PIs) telaprevir (TPV) and boceprevir (BOC) were approved to treat HCV-genotype-1 infection, each one in combination with Peg-IFN + RBV[27-29]. These treatments showed higher rates of sustained virological response (SVR) than Peg-IFN + RBV[30,31] but reduced tolerability[32] and adherence due to the high pill burden. At the same time several pharmacokinetic interactions have been appeared between HCV NS3/4A protease inhibitors and antiretroviral drugs.[33-35]. Finally in 2013 a new wave of DAAs arrived, characterized by high efficacy, good tolerability, a low pill burden and shortened treatment duration.[36-38]. The second and third generation DAAs also comprised IFN-free regimens, which in small recent trials on HIV-positive patients have shown comforting preliminary results in terms of efficacy, tolerability and adherence.[39,40]. Table 1 shows the SVR rate in therapy-naïve patients treated with the different combinations (Table 1). However, the new DAAs are still not available for HIV-positive patients in clinical practice and their high cost may be a handicap to their use in developing countries.

INTERFERON-BASED REGIMENS

Peg-IFN + RBV

The combination Peg-IFN + RBV, although considered the treatment of choice for chronic hepatitis C until 2011, has been used infrequently in patients with HIV/HCV coinfection because of its limited efficacy in these patients, the high prevalence of medical and psychiatric comorbidities and the high incidence of serious adverse reactions. In most studies on chronic hepatitis C monoinfected patients with HCV-genotype 1 or 4, an SVR of almost 50% was achieved. In the APRICOT[41] study, HIV/HCV coinfected patients were treated with Peg-IFN α-2a and a fixed dose of RBV (800 mg/d) for 48 wk and an SVR was obtained in nearly 40% of the cases, in 18% of those with HCV-RNA levels greater than 800000 copies/mL and in 61% of those with a lower HCV load. The current international guidelines suggest prolonging the 48-wk treatment to 72 wk, despite reduced tolerability, for patients with HCV-genotype 1 without a rapid virological response (RVR) (EACS)[42]. With the introduction of DAAs to treat chronic hepatitis C, Peg-IFN + RBV dual therapy should be considered obsolete at least for patients with HCV-genotype 1 or 4.

Peg-IFN + RBV + the first generation DAAs telaprevir or boceprevir

The addition of the first generation DAAs, TPV or BOC, to Peg-IFN + RBV strongly improved the efficacy of
antiviral therapy in patients with HCV-genotype 1, both for the HCV-monoinfected and HIV/HCV coinfected, and the poor response to Peg-IFN + RBV in HCV/HIV coinfected was enhanced with the new combination therapy.

In patients with HIV/HCV coinfection, triple therapy including telaprevir 1125 mg every 12 h or 750 mg every 8 h is administered only for the first 12 wk, followed by a 36-wk Peg-IFN + RBV double therapy. TPV pills should be taken with a fat meal to improve their absorption. In a randomized trial on HIV/HCV-genotype-1 coinfected patients naïve for anti-HCV treatment, the SVR rate was 74% for those treated with telaprevir-based triple therapy and 45% for the control group receiving Peg-IFN + RBV double therapy. Adverse events commonly observed in TPV-based triple therapy included skin rash, pruritus, anemia, and ano-rectal discomfort. In addition, TPV may reduce the glomerular filtration rate and increase RBV concentrations by 55%, inducing in these cases severe anemia. TPV cannot be administered with the ritonavir-boosted PIs used in HIV therapy due to the pharmacokinetic interactions. Thus, despite the enhanced efficacy of telaprevir-based triple therapy in eradicating HCV infection, the number of HIV/HCV patients eligible for this treatment is reduced due to its poor tolerability, interaction with ART and high pill burden.

Predictive factors of a favorable response to treatment, such as mild fibrosis, low HCV-RNA load, IL-28B CC genotype and Caucasian ethnicity should be assessed before starting telaprevir-based triple therapy. Boceprevir is an NS3/4A protease inhibitor approved for treatment of genotype-1 chronic hepatitis C. In these patients treatment with BOC + Peg-IFN + RBV begins after a 4-wk lead-in phase with Peg-IFN + RBV. BOC is stopped at week 36 and Peg-IFN + RBV continued until week 48. Cirrhotic patients or prior null responders should receive BOC + Peg-IFN + RBV until week 48. The SVR rates observed in therapy-naïve HIV + HCV co-infected patients receiving BOC + Peg-IFN + RBV or Peg-IFN + RBV in a phase II trial were 63% and 29%, respectively. Adverse reactions included anemia, dysgeusia, nausea, and neutropenia. BOC cannot be administered with ritonavir-boosted PIs or non-nucleoside retro-transcriptase inhibitors because of the pharmacokinetic interactions. Consequently, the use of the combination BOC + Peg-IFN + RBV for HIV/HCV coinfected patients is very limited.

**Peg-IFN + RBV + a second wave DAA**

In 2013, both sofosbuvir (SOF), a once-a-day oral DAA that inhibits the active site of the HCV NS5B polymerase with an anti-HCV pan-genotypic activity, and simeprevir (SMV), a once-a-day oral DAA that inhibits the HCV NS3/4A protease, were approved by the United States Food and Drug Administration (FDA) to be used in combination with Peg-IFN + RBV to treat patients coinfected with HIV/HCV genotype 1. SOF was also approved to be used in combination with RBV to treat patients coinfected with HIV and HCV genotype 2 or 3. SOF is particularly indicated for patients with HIV/HCV coinfection, since it is well tolerated and no pharmacokinetic interactions with the antiretroviral drugs have been documented.

In a small study from Porto Rico a combination of SOF plus Peg-IFN and RBV given to 23 patients with HIV/HCV coinfection (19 with HCV genotype 1) for 12 wk obtained HCV eradication in 91% of cases; no severe adverse event occurred and only 2 patients discontinued treatment, one due to anemia and one to altered mood.

SMV is a second generation HCV NS3/4A protease inhibitor for the treatment of patients with HCV-genotype-1 infection. The combination of SMV plus Peg-IFN and RBV has been investigated in both HCV-monoinfected and HIV/HCV coinfected patients. An overall 74% SVR rate was obtained in 106 patients coinfected with HIV and genotype-1 HCV treated with this triple therapy and a 79% SVR was achieved in the anti-HCV treatment-naïve patients. In this study, all patients received a 12-wk SMV + Peg-IFN + RBV treatment, followed by double Peg-IFN/RBV response-guided therapy for either 12 or 36 wk. Of note, 89% of naïve or prior relaper co-infected patients without cirrhosis met the inclusion criteria to receive response-guided therapy, which required that serum HCV RNA be undetectable at week 4. Fibrosis stage, HCV sub-genotype, IL28b genotype, and baseline CD4 count above or below 500 did not influence

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**Table 1  Sustained virological response rate in human immunodeficiency virus/hepatitis C virus coinfected patients naïve for anti-hepatitis C virus treatment**

| Ref. | Genotype 1 | Genotype 2 | Genotype 3 | Genotype 4 |
|------|------------|------------|------------|------------|
| Peg-IFN plus ribavirin | 35.6% in 191 patients | 72.4% in 152 patients | 32.6% in 46 patients | |
| Peg-IFN plus ribavirin + boceprevir | 60.7% in 61 patients | - | - | |
| Peg-IFN plus ribavirin + telaprevir | 74% in 38 patients | - | - | |
| Peg-IFN plus ribavirin + sofosbuvir | 79.2% in 52 patients | 91% in 23 patients | - | |
| Peg-IFN plus ribavirin + simeprevir | 73.7% in 227 patients | 84% in 31 patients | - | |
| Peg-IFN plus ribavirin + faldaprevir | 76% in 38 patients | 91% in 57 patients | - | |
| Sofosbuvir plus ribavirin | 67% in 42 patients | 88% in 26 patients | 67% in 42 patients | |
| Sofosbuvir plus ribavirin | 84% in 112 patients | 90% in 19 patients | 91% in 57 patients | 84% in 31 patients |
| Sofosbuvir plus ledipasvir | 100% in 13 patients | - | - | |
| Paritaprevir-r/ombitasvir + dasabuvir + ribavirin | 93.5% in 31 patients | - | - | |

1Therapy-naïve or relapser patients; 2For 24 wk; 3For 12 wk. SVR: Sustained virological response; Peg-IFN: Pegylated interferon alfa.
the SVR rates. The impact of adverse events to SMV + Peg-IFN + RBV (rash, photosensitivity, pruritus, and nausea) was limited in the Phase II/III trials. However, phase III studies, both on mono and coinfected patients, demonstrated that the addition of SMV to the combination Peg-IFN + RBV did not improve the response rate of the dual therapy in patients with HCV-genotype 1a with a baseline NS3 Q80K polymorphism. This polymorphism is detected in nearly one third of subjects infected with HCV-genotype 1a and in only 0.5% of those with HCV-genotype 1b. Screening at baseline for the presence of the NS3 Q80K polymorphism is recommended for patients with HCV-genotype 1a to exclude positive patients from treatment including SMV. Indeed, this polymorphism has a limited effect on SMV activity, but the resistance barrier of this drug appears to be lower in patients carrying the Q80K-variant, resulting in a more frequent emergence of additional mutations and in a higher rate of treatment failure. The United States FDA approval of SMV provides specific recommendations for interactions with commonly prescribed antiretroviral agents. SMV is also a component of several interferon-free combinations currently under study.

Faldaprevir (FDV) is a second generation oral, once-daily HCV NS3/4A protease inhibitor. In the START-Verso 4 trial, a multicenter study, an open-label randomized phase III trial, HIV/HCV therapy-naive or previous relapsers received either FDV 120 mg + Peg-IFN+RBV for 24 wk followed by Peg-IFN + RBV dual therapy for an additional 24 wk or FDV 240 mg + Peg-IFN + RBV for 12 wk followed by a 1:1 randomization to either the same treatment for another 12 wk followed by a 24-wk Peg-IFN + RBV double therapy or to a 12-wk Peg-IFN+RBV double therapy. Due to drug to drug interactions, patients receiving efavirenz were placed in the 120 mg arm, and patients receiving darunavir/ritonavir or atazanavir/ritonavir were randomized to the 120 or 240 mg arms. Patients with an early treatment success stopped treatment at week 24, the others at week 48. Overall, 72% of patients achieved an SVR, the highest rates being observed in patients who had previously relapsed with Peg-IFN + RBV (83%) and in those with IL28b CC genotype (88%); HCV genotype, presence of cirrhosis and FDV dose and duration did not show any major impact on the SVR rate. Adverse events occurred in 7% of patients, neutropenia and bilirubin elevations being the most common grade 3 abnormalities; only 1% of these events were attributed to FDV. The research on this promising drug was stopped in 2014 for commercial reasons.

INTERFERON-FREE REGIMENS

Studies on HIV/HCV coinfected patients

IFN-free clinical trials on HIV/HCV coinfected patients are still in progress, but their preliminary data have shown that these treatments have a greater efficacy in eradicating HCV infection.

PHOTON-1 is the only study on IFN-free treatment of HIV/HCV coinfected patients published at present. In this study, SOF + weight-based RBV were administered to 114 patients with HCV-genotype 1 naïve for anti-HCV treatment for 24 wk and to 68 therapy-naïve patients with genotype 2 or 3 for 12 wk. The SVR rates were 76% in patients with HCV-genotype 1, 88% in those with genotype 2 and 67% in those with genotype 3.

In the phase IIa COSMOS trial, the patients were randomized to SMV + SOF with or without RBV for 12 or 24 wk. The preliminary data for patients in the 12-wk arm showed a 93% SVR rate in prior null-responders to Peg-IFN + RBV and 97% overall. Serious adverse events, anemia and bilirubin increase regarded only patients who received RBV.

In a recent study a combination of SOF plus RBV given for 12 wk to genotype-2 therapy-naïve patients and for 24 wk to all other patients showed an 84% SVR in the 112 therapy-naïve genotype-1 patients, 90% in the 19 naïve genotype-2, 91% in the 57 naïve genotype-3, 84% in the 31 naïve genotype-4, 83% in the 6 therapy-experienced genotype-2 and 86% in the 49 experienced genotype-3 patients.

Ledipasvir (LDV) is an oral NS5A inhibitor administered once daily. In a small trial the combination LDV + SOF ± RBV was administered to HIV/HCV genotype-1 coinfected patients with no evidence of liver cirrhosis. This regimen was well tolerated and the preliminary data showed a 100% SVR12 rate in 12 HCV-genotype-1 patients who were naïve for anti-HIV and anti-HCV treatment.

Daclatasvir (DCV) is an HCV NS5A replication complex inhibitor administered once daily. The safety and efficacy of the combination therapy with DCV + SMV ± RBV were evaluated in the LEAGUE-1 trial, a randomized open-label phase II study enrolling therapy-naïve and null-responder HIV/HCV patients with or without cirrhosis. All patients with HCV-genotype 1b were given a 12-wk treatment with DCV + SMV ± RBV; at week 12 the patients were re-randomized to either an additional 12-wk treatment or to a 12-wk treatment-free follow up. The patients with HCV-genotype 1a received a 24-wk DCV + SMV + RBV treatment. In this study the SVR rate was 67% for patients with HCV genotype 1a and almost 82% for those with HCV genotype 1b.

Ombitasvir, dasabuvir and RBV in patients with HCV-genotype-1 chronic hepatitis and HIV infection. The study is still ongoing, but the preliminary data show an SVR4 in 93.5% of 31 patients treated for 12 wk and in 96.9% of 30 patients treated for 24 wk; an SVR12 was obtained in 93.5% of 31 patients treated for 12 wk. Fatigue, insomnia and headache were the most common side effects, but no patient had a serious adverse event.

Studies on HIV/HCV patients started recently whose results are awaited

The efficacy of SOF + LDV is under evaluation in 100 patients with HIV/HCV-genotype-1 coinfection either untreated for HIV infection (CD4 > 500 cells/mm³) or
with suppressed HIV-1 RNA replication with antiretroviral drugs. (ClinicalTrials.gov Identifier: NCT01878799). Still awaited are the results of the ALLY-2 study on the effect of the combination of SOF + DCV given for 8 or 12 wk to HIV/HCV coinfected patients with HCV genotype 1, 2, 3, 4, 5 or 6.

The C-WORTHY is a study recently started to evaluate the safety and efficacy of the combination of the second generation HCV NS3/4A protease inhibitor MK-5172 + the second generation HCV NS5A inhibitor MK-8742 ± RBV for patients with HCV-genotype 1, both HIV positive and negative. This study design underscores the emerging recognition that HIV-infected patients may not differ from the monoinfected in terms of the effectiveness of oral IFN-free DAA regimens.

A few trials on the efficacy of the combination DCV + SOF for HIV/HCV coinfected patients have recently started and the results are still awaited.

Recent studies on the efficacy of IFN-free DAA regimens for HCV-monoinfected patients, possibly extendible to HIV/HCV coinfection in the near future

Asunaprevir (ASV), a twice-daily NS3/4A protease inhibitor, used in combination with IFN + RBV or in IFN-free regimens, has shown promising results with fewer adverse effects. In HCV-monoinfected patients ASV was studied in a randomized, open-label, 24-wk-treatment study where all 101 patients enrolled received DCV (60 mg) once daily and ASV as follows: 38 with genotype 1b also received ASV (200 mg) twice (DUAL A1) or once daily (DUAL A2), 36 with genotype 1a and 5 with genotype 1b also received ASV twice (QUAD B1) or once daily (QUAD B2) plus Peg-IFN/RBV and 18 patients with genotype 1a and 4 with genotype 1b also received ASV twice daily plus RBV (TRIPLE B3). An SVR12 was obtained in 78% of patients in DUAL A1, 65% in DUAL A2, 95% in QUAD B1, and 95% in QUAD B2. Most patients in the TRIPLE B3 arm developed a virological breakthrough, but aminotransferase elevation grade 3 or 4 was infrequent.

The BMS-791325 (BMS), a twice-daily non-nucleoside NS5B polymerase inhibitor, was investigated in the AI443-014 trial where the efficacy of the oral combination of DCV + ASV + BMS was assessed in a large group of HCV-genotype-1 patients, including cirrhotics. The patients were randomized to DCV/ASV/BMS with BMS dosed at 75 mg or 150 mg. In this combination DCV was given twice daily. The SVR rates were above 90% in both groups. Only 2 of the 166 patients enrolled discontinued treatment due to adverse events.

The SYNERGY trial studied different combinations of DAA in order to achieve high SVR rates with shortened treatment duration in patients with HCV monoinfection. In this study, besides some well-known drugs, the Authors also used two new molecules, GS-9669, a once-daily non-nucleoside HCV NS5B inhibitor, and GS-9451, a once-daily NS3/4A protease inhibitor. The patients were randomized to one of three arms: (1) SOF + LDV for 12 wk; (2) SOF + LDV + GS-9669 for 6 wk; and (3) SOF/LDV/GS-9451 for 6 wk. Patients with cirrhosis were excluded from arms B and C. All patients, with the exception of one in arm B, achieved an SVR. No patient discontinued therapy due to an adverse event. Worthy of note is that most individuals investigated were difficult-to-treat patients because of their Afro-American ethnicity, old age, HCV-sub-genotype 1a, IL28b genotype CT/TT or advanced liver fibrosis.

A 12-wk combination of DCV+SOF ± RBV was investigated in HCV-monoinfected patients with genotype 1, 2, or 3 in the AI444040 study. The study included both therapy-naive patients and previous non-responders to TVP- or BOC-based triple therapy; in both groups 98% of the patients achieved an SVR.

The Turquoise-Ⅱ is a multicenter, randomized, open-label study evaluating the efficacy and safety of a 12-wk or 24-wk treatment with paritaprevir/r + ombitasvir + dasabuvir + RBV in patients with HCV-genotype-1 chronic hepatitis or compensated liver cirrhosis. An SVR12 was observed in 91.8% of patients treated for 12 wk and in 95.9% of those treated for 24 wk.

ART MANAGEMENT IN HIV/HCV COINFECTED PATIENTS DURING TREATMENT WITH DIRECTLY ACTING ANTIVIRALS FOR HCV INFECTION

Despite the remarkable virological response obtained with oral DAAs, the treatment of chronic hepatitis C in HIV patients remains complex and presents multiple challenges. The drug to drug interaction and the high prevalence of severe side effects influence the choice of the ART, and priority should be given to the antiretroviral drugs with fewer side effects and lesser interaction with the DAAs.

The drug to drug interaction in HIV/HCV coinfection mostly regards the use of HCV NS3 protease inhibitors, while the HCV nucleoside and non-nucleoside NS5B polymerase inhibitors and NS5A replication complex inhibitors seem to have minimal effects on the serum concentration of the HIV drugs. Both the anti-HCV and anti-HIV protease inhibitors and NNRTIs are metabolized by the cytochrome p450 pathway and, consequently, multiple complex drug to drug interactions develop that require management in highly experienced clinical centers. In addition, the knowledge on the interaction between anti-HCV protease inhibitors and anti-HIV drugs is in continuous development and even skilled clinicians should consult the www.hep-druginteractions.com web site.

TPV, BOC and SMV interact with CYP3A as inhibitors and substrates, with potential interaction and increased concentrations of drugs metabolized through this pathway and with a reduced TPV or BOC serum concentration due to drug-induced enzymatic activity. A recent study assessed the pharmacokinetic interactions between BOC and the ritonavir (RTV)-boosted protease inhibitors atazanavir (ATV), lopinavir (LPV) and darunavir (DRV)
in a randomized open-label study on 39 healthy adults. The protease inhibitor BOC decreased the exposure of all protease inhibitors; ATV/ritonavir did not significantly affect BOC exposure, whereas BOC was reduced by 45% and 32% when co-administered with LPV/ritonavir and DRV/ritonavir, respectively[75].

In a recent study no significant drug interaction between BOC and raltegravir was found in healthy volunteers[76]. The role of ritonavir in the drug interactions between TPV and ATV was recently investigated. In an open-label, sequential study on HCV/HIV coinfected patients on an RTV-boosted ATV-based antiretroviral regimen (300/100 mg every 24 h) and triple therapy (telaprevir, 1125 mg every 12 h, Peg-IFN + RBV) for genotype-1 chronic hepatitis C, the pharmacokinetic profiles were acquired before and after switching from RTV-boosted to unboosted ATV (200 mg every 12 h). The Authors found RTV responsible for an increase in the dosage of TPV[77]. An open-label crossover study on healthy volunteers evaluated the bioequivalence of BOC and etravirine, an HIV non-nucleoside reverse transcriptase inhibitor, and a reciprocal interaction was demonstrated[78].

The co-administration with efavirenz led to a 20% reduction in the area under curve of TPV, thus requiring an increase in the dosage of TPV[74,78,79]. An open-label crossover study on healthy volunteers evaluated the bioequivalence of BOC and etravirine, an HIV non-nucleoside reverse transcriptase inhibitor, and a reciprocal interaction was demonstrated[80].

The study on the interaction between anti-HCV DAAs and antiretroviral drugs is at its real beginning and further investigation is needed to ensure the optimization of the contemporaneous administration of ART and anti-HCV therapy for HIV/HCV coinfected patients.

**Choice of the best ART during treatment with DAAs**

Precise knowledge of drug interactions and of the adverse events occurring during drug administration is indispensable in order to choose optimized ART and DAAs-based treatment for patients with HIV/HCV coinfecion. Optimized ART should avoid possible interactions with protease inhibitors of HCV and improve drug tolerability and the patients’ adherence. Table 2 shows a list of antiretroviral drugs incompatible with DAA administration. TPV can be safely administered in combination with RTV-boosted ATV, raltegravir, maraviroc, rilpivirine, etravirine or efavirenz (when administered with efavirenz, the TPV dosage should be 1125 mg every 8 h) and with tenofovir/emtricitabine or abacavir/lamivudine[74,78,79,81].

BOC can also be considered in combination with raltegravir, rilpivirine or etravirine and with tenofovir/emtricitabine or abacavir/lamivudine. BOC can be safely administered in combination with raltegravir, rilpivirine and with tenofovir/emtricitabine or abacavir/lamivudine. Some new ART regimens including the integrase inhibitor raltegravir[82] or the entry inhibitor maraviroc[83] have been demonstrated to be safe and their use in HIV/HCV coinfecion should be evaluated in clinical studies.

Concluding on this point, the management of HCV infection for HIV-positive patients is a complex issue. The physicians in care should carefully select the patients for the most suitable treatment and monitor them closely to evaluate the efficacy and tolerability of the drugs administered, their pharmacological interaction, the virus interaction and the patients’ adherence.

**CONCLUSION**

Treatment of chronic hepatitis C for patients with HIV infection is essential to prevent the transition to liver
Factors:
- Age
- Severity of liver disease
- Stability of HIV infection
- Co-morbidities
- Contraindications to IFN
- Treatment adherence

Some examples in real life:
- In young patients with mild chronic hepatitis C and/or instability of HIV infection and/or contraindications to IFN and/or poor adherence to treatments, wait for IFN-free regimes.
- In young patients with severe chronic hepatitis C and controlled HIV infection in the absence of contraindications to IFN, treat with IFN-based regimen.

Figure 1 Factors influencing treatment decision for chronic hepatitis C in human immunodeficiency virus/hepatitis C virus-1 coinfection: treat or defer treatment. HIV: Human immunodeficiency virus; IFN: Interferon.

HCV-RNA-positive genotype-1 patients
- No possibility to defer treatment and no contraindication to IFN: Peg-IFN/Ribavirin.
- Possibility to defer treatment: Wait for: Sofosbuvir/simeprevir or sofosbuvir/daclatasvir or sofosbuvir/ledipasvir or ombitasvir/dasabuvir/paritaprevir.

Figure 2 Treatment of chronic hepatitis C, hepatitis C virus-genotype 1 or 4, in patients with Human immunodeficiency virus/hepatitis C virus coinfection. RVR: Rapid virological response; IFN: Interferon. HCV: Hepatitis C virus.

HCV-RNA positive
- Genotype 2: Sofosbuvir/ribavirin for 12 wk.
- Genotype 3: No contraindication to IFN: Peg-IFN/ribavirin. Contraindication to IFN: Sofosbuvir/ribavirin for 24 wk.

Figure 3 Treatment of chronic hepatitis C, HCV-genotype 2 or 3, in patients with human immunodeficiency virus/hepatitis C virus coinfection. RVR: Rapid virological response; IFN: Interferon.
cirrhosis, the development of HCC and liver failure. The poor tolerability of Peg-IFN + RBV double therapy and of triple therapy with Peg-IFN + RBV + boceprevir or telaprevir has been a serious obstacle to treating chronic hepatitis patients with HIV/HCV-genotype-1 coinfection. These treatment regimens compared to the new DAA-based therapies show lesser efficacy and tolerability because of the more frequent serious adverse events, a higher pill burden and longer period of treatment. Moreover, the first-generation PIs show more pharmacokinetic interactions with antiretroviral drugs than the second and third generation DAA.

At present, treatment decisions range from waiting for all-or-all second or third generation DAA regimens or treating with Peg-IFN/RBV double therapy + sofosbuvir, simeprevir or daclatasvir. A reliable guide in this difficult choice could be the entity of liver fibrosis, detected by liver biopsy or by a sensitive fibroscan assay, and other predictive factors of SVR such as the HCV viral load, the IL-28B genetic profile and the ethnic background (Figure 1). The patients’ adherence, pharmacokinetic interactions between anti-HCV and antiretroviral drugs and sustainability in terms of cost-effectiveness are other important factors to be considered for a rational choice. The achievement of RVR during treatment remains the most sensitive predictor of SVR.

Currently, we deem it reasonable that HIV/HCV-genotype-1 therapy-naïve patients for whom treatment cannot be deferred should be treated with Peg-IFN + RBV dual therapy to establish whether they achieve an RVR during the first month of treatment (Figure 2). In positive cases double therapy should be administered for 12 mo, whereas for patients not achieving an RVR a second generation DAA (sofosbuvir, simeprevir, or daclatasvir) should be added, and this triple therapy administered for 3-6 mo (Figure 2).

Once combinations of second/third generation DAs are licensed for treatment of chronic hepatitis C in HIV/ HCV coinfection, the patients with HCV genotype 1 for whom the treatment has been deferred and those with contraindications to IFN + RBV should be treated with an effective IFN-free DAA-based regimen (Figure 2). The same algorithm can be hypothesized for patients with HCV-genotype 4.

For patients with HIV/HCV genotype-2 coinfection, the treatment choice should be between a 24-wk low-cost Peg-IFN/RBV double therapy and a 12-wk high-cost treatment with sofosbuvir/ribavirin (Figure 3). For patients with HCV-genotype 3, a 24-wk high-cost schedule with sofosbuvir/ribavirin or a 24-wk low-cost Peg-IFN/ribavirin double therapy seem reasonable (Figure 3).

The several ongoing trials will better define the role of the second and third generation DAs in treating chronic hepatitis C in HIV/HCV coinfection, but in the meantime this review article may be of some help in making reasonable therapeutic choices.

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