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Optimal Management of HIV-HCV Coinfection

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Abstract Around 25 % of HIV-positive individuals are HCV coinfected. HIV infection clearly worsened the natural history of chronic HCV infection, and despite the improved cares of comorbidities (chronic alcohol intake, metabolic syndrome, poor immune status by an earlier and better immune restoration with antiretrovirals (ARV), and finally by a decreasing hepatotoxicity of ARV), liver-related mortality remains one of the main causes of mortality in HIV/HCV-coinfected patients as compared to HIV monoinfected patients. Treatment options in HIV-HCV-coinfected patients have been greatly improved in the last few years. The treatment of acute HCV infection in HIV-positive individuals using the association of pegylated interferon/ribavirin (PEG-IFN/RBV) (with a first-generation protease inhibitor in genotype 1-infected patient) will allow a HCV virologic cure in around 80 %. In chronically infected patients, the PEG-IFN/RBV association has demonstrated an efficacy of 20–40 % in genotype 1 and higher in other genotypes, and increasing with optimization of dosing and duration, stopping rules and ART adjustment; the adjunction of telaprevir or boceprevir for genotype 1 increased the chance of HCV cure to around drug-70 % with drug interaction concerns. Physicians are today, in 2014, in a period of transition between the standard treatment combining PEG-IFN and RBV with or without first-generation HCV protease inhibitors according to HCV genotype and oral combinations of different classes of direct-acting antivirals (DAAs) with a pangenotypic antiviral potency and a fair safety which will clearly change the prognosis of HIV/HCV-infected patients. The DAA combination removes HIV-infected patients (like cirrhotics or liver transplant recipients) as difficult-to-treat patients.

Keywords HIV · AIDS · Hepatitis C virus; PEG-IFN · RBV · Protease Inhibitors

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Introduction

Around 25 % of HIV-positive individuals are HCV coinfected. HIV infection clearly worsened the natural history of chronic HCV infection [1, 2], but the negative impact of HIV infection on HCV natural history is now debated mainly because of improved control of comorbidities (chronic alcohol intake, metabolic syndrome, poor immune status), an earlier treatment of HCV infection with increasing therapeutic effectiveness, an earlier and better immune restoration with antiretrovirals (ARV), and finally a decreasing hepatotoxicity of ARV as compared to that of the first-generation analogs (steatosis, toxic hepatitis, mitochondrial toxicity) [3]. However, recent data suggest that despite all these improvements, liver-related mortality remains one of the main causes of mortality in HIV/HCV-coinfected patients as compared to HIV-monoinfected patients. Despite the harmful impact of HIV on HCV with an increased morbidity and mortality, and even though eradication of HCV modifies the long-term prognosis of these patients, access to HCV treatment in coinfected patients has been limited even if it is now improving (around half of them has been treated in France, as an example) [4]. Recently, the development of the first anti-HCV direct-acting antiviral (DAAs) allowed to improve the rate of virologic recovery in coinfected patients with rates similar to those achieved in HCV-monoinfected patients. In the next future, the oral combination of DAAs will allow to achieve a high rate of virologic cure with similar results than in HCV-monoinfected patients with a short duration of therapy and a

fair tolerance; the high rate of viral clearance, even if counterbalanced with an increase risk of drug interactions and adverse events in HIV-positive patients, is about to change the management of HIV/HCV-coinfected patients [3].

Epidemiology of HCV/HIV Coinfection

Reciprocal Impact of HIV and HCV on Natural Histories

While there is no effect of HCV infection on HIV infection and disease progression, HIV negatively impacted HCV progression. Approximately 25 % of people living with HIV infection are coinfected with HCV with a classical more rapid progression to fibrosis occurring twice as fast than in HCV-monoinfected patients. After 10 to 15 years of HCV infection without specific treatment, 25 % of HIV-coinfected patients developed cirrhosis, as compared to 2–10 % of HCV monoinfected patients [2]. The risks of complications of cirrhosis are five times higher in HCV/HIV-coinfected patients than in HCV-monoinfected individuals [2]. In France, it has been shown that annual mortality associated with HBV or HCV infection was substantial (4000–5000 cases) [5]. Male gender, older age, HIV infection, and especially excessive alcohol consumption were associated with increased mortality rates. Steatosis is frequent (higher than 80 %) in HIV-infected patients and increases the risk of progression of fibrosis. The role of insulin resistance, observed in one out of three coinfected patients, is more controversial. As in patients with HCV monoinfection, insulin resistance seems to be predictive of a poor response to pegylated interferon (PEG-IFN) and ribavirin (RBV) treatment [6], but this is still under debate [7].

Do the improvement of the immune restoration and the use of less hepatotoxic drugs change significantly the harmful impact of HIV? This remains debated because in parallel with an earlier HIV treatment of HCV-infected patients with increasingly effective therapeutic schedules resulting in earlier and better immune restoration with antiretrovirals (ARV) which are less hepatotoxic compared to first-generation analogs, control of liver comorbidities (chronic alcohol intake, metabolic syndrome, poor immune status) improved. A recent nationwide study to assess whether HCV hastens overall and non-liver mortality in HIV-infected patients was conducted by a retrospective, longitudinal analysis of the French National Hospital database. All HIV-infected patients receiving hospital care from January 2008 to December 2012 were included, and their medical trajectory was tracked in all French hospitals with the use of the International Classification of Diseases (ICD-10), medical procedures, and in-hospital mortality as recorded per stay [8]. Of 69,913 HIV-infected patients (male 65.2 %; mean age 42.3 years), 2366 deaths occurred in 248,885 patient years. Overall mortality was higher in 8283 (7.5 %) HIV/HCV patients as compared to 59,476 (2.8 %) HIV patients (hazard ratio [HR] 1.79, $P<0.0001$), while it did not differ in 2154 (3.9 %) HIV/HBV patients (HR 1.21, $P=0.09$). Non-liver-related mortality as well as non-liver, non-AIDS-related mortality remained higher in HIV/HCV-coinfected patients (HR 1.36, $P<0.0001$ and HR 1.43, $P<0.0001$, respectively), suggesting a persisting harmful impact of HCV infection on HIV infection. In summary, at the HAART era, HCV infection increased overall and non-liver-related mortality in HIV-infected patients although this was not found in HIV/HBV infected patients who had sustained and complete HBV virosuppression with nucleotide analog treatment. Thus, viral suppression should be recommended for HCV coinfection as it is for HBV coinfection [8].

At the opposite, the positive impact of HCV viral suppression is confirmed. In an observational Spanish cohort study [9], 626 of 1599 HIV/HCV-coinfected patients (39 %) had a sustained virologic response (SVR): failure to achieve an SVR was associated not only with an increased risk of liver-related events and liver-related death but also with higher rates of HIV progression and mortality not related to liver disease.

The future availability of new anti-HCV direct-acting antivirals (DAAs), more potent and better tolerated than historical standard of care (SOC) using PEG-IFN and RBV, should then modify the prognosis of HCV/HIV-coinfected patients.

Acute HCV Hepatitis

One of the peculiar patterns of HCV infection in HIV-positive patients is the occurrence and increasing prevalence of acute cases. HCV transmission occurs in high-risk groups, namely drug users and patients with high-risk sexual practices (exposure to blood). HCV is more easily transmitted in patients with sexually transmitted diseases (genital ulcers) and HIV infection.

Over the past years, a rise in the incidence of acute hepatitis C was observed especially in HIV-positive men having sex with men [10], in relation with unsafe sex practice and recreational drug use. This outbreak was associated with particular social networks, and phylogenetic analysis identified specific clusters of HCV strains circulating in different western countries. In recent years, even without randomized control studies, data from clinical studies or cohort gave many insights into definition, natural course, and anti-HCV treatment to optimize the management of acute hepatitis C in HIV-positive patients.

Acute HCV infection is defined arbitrarily as occurring within the first 6 months after exposure to HCV. Most acute HCV infections are asymptomatic [11], and the first marker of HCV infection is the serum HCV-RNA detection as early as 1 week post-infection; the detection of anti-HCV antibodies (Ab) is delayed (only two thirds of HIV-positive patients are anti-HCV-positive at 3 months) [12]. The two criteria for the diagnosis of acute HCV infection recommended in HIV-positive individuals by the European AIDS Treatment

Network (NEAT) [12] are as follows: (1) positive anti-HCV Ab with a negative anti-HCV Ab documented in the previous 12 months or (2) positive HCV-RNA with negative anti-HCV Ab and a negative HCV-RNA documented in the previous 12 months.

The rate of spontaneous HCV clearance is below 15 % in HIV-positive patients [13] as compared to 25 % in HIV negative. IL28B genotypes strongly influence HCV clearance like in HIV-negative patients. In HIV-positive patients, non-black ethnicity, younger age, female gender, sexual transmission, HBV coinfection, higher HIV load, ALT peak, and higher CD4 count have been reported to be associated with a higher rate of HCV clearance. Patients who spontaneously recovered should be re-checked for HCV-RNA within the 3 months since some of them may have detectable HCV-RNA suggesting immune escape more than re-infection (personal experience).

HCV Treatment in HCV/HIV-Coinfected Patients

Treatment of Acute Hepatitis C

Treatment of acute HCV should be begun within 12 weeks after diagnosis if HCV-RNA is still detectable: the NEAT consensus recommended to decide a treatment in patients who have not shown a drop in HCV-RNA of more than 2 log at week 4 or are still positive at week 12. In the majority of the published cohorts, the treatment started around week 12 [11, 14–19]; if the treatment started later, at week 24 [20], between weeks 12 and 36 [21] or between weeks 12 and 48 [22], there is no evidence of a lower SVR rates.

Recommendations are to treat acute HCV infection in HIV-infected patients with 24 weeks of PEG-IFN and RBV combination therapy, even if the addition of RBV has not been shown to be beneficial in HIV-negative patients [23].

By using a combination of PEG-IFN alpha 2a or 2b (PEG-IFN) and RBV (RBV) during 24 to 48 weeks, SVR rates are high, from 47 to 91 % [11, 14–19]. The rapid virologic response (RVR) at week 4 is the best predictor of SVR, and other factors including adherence, ALT peak, early virologic response (EVR) at week 12, longer duration of treatment, or genotype non-1 are less predictive.

If the benefit of the adjunction of RBV to PEG-IFN is very likely [10] with a more rapid HCV-RNA decline with PEG-IFN and RBV than with PEG-IFN alone [14], the dosing of RBV is less clear between weight-based (1000 or 1200 mg/day) or fixed doses (800 mg/day or 1000 mg/day): weight-based RBV dosing should be preferred and especially because genotype 1 and 4 are the most prevalent [10].

The European consensus recommended to modulate the duration of the treatment in relation with RVR at week 4 [12]. In patients with RVR, a treatment duration of 24 weeks seems to be sufficient, whereas a treatment of 48 weeks have to be proposed to patients without RVR but with EVR at week 12 [12]. Adding on telaprevir to PEG-IFN and RBV in acute genotype 1 HCV of HIV-infected men decreased the treatment duration (12 weeks for 81 % of patients) and increased the SVR rates from 63 % in the control group to 84 % in the telaprevir group [24].

With the new DAAs and the ability to achieve high SVR rates with a 12-week course, the recommendation to treat any acute infection has probably to be completely revised, in balance with the high cost and the persisting risk of contagiosity.

In summary, HCV/HIV coinfection is frequent and has to be diagnosed in HIV-infected patients. Acute cases can be efficiently treated questioned mainly by the PR combination, but the combination with first-generation protease inhibitor may allow to reduce the duration of therapy. The rapid development of oral drugs may be the recommendation of treating all acute cases.

Treatments of Chronic Hepatitis C in HIV-HCV-Coinfected Patients

Indication for Treatment

In HIV-HCV-coinfected patients, like in HCV monoinfected, the stage of liver fibrosis is the main factor for treatment decision. The fibrosis stage evaluated by liver biopsy has been prospectively independently associated with liver-related events or death [25]. An abundant literature had also demonstrated the validity of non-invasive markers either biochemical or with elastography for the evaluation of liver fibrosis in coinfected individuals [26–29]. Using invasive or non-invasive procedure, the clinician has to propose an individual-based decision to treat now with the standard of care or to wait for new treatments with better results and less adverse events. Clearly, in patients with extensive fibrosis or cirrhosis (F3 or F4 in METAVIR score), a treatment has to be proposed to the patient. On the contrary for patients with minimal fibrosis (F0 or F1), the development of new drugs encourages to defer the treatment with careful survey [30]. Patients with a Metavir score of $F=2$, the treatment should be considered, especially in those with liver comorbidities. When possible, HCV treatment should be started before antiretroviral treatment (ARV). If HCV therapy cannot be started (or if it is unsuccessful), ARV should be started (even if CD4 levels are above 350/mm^3) to limit the progression of fibrosis. This is because the delay between the date of HIV infection and the beginning of ARV is a factor associated with the progression of liver fibrosis. To reduce the risk of hematotoxicity (anemia and neutropenia for zidovudine), mitochondrial toxicity (didanosine, stavudine), or even an interaction with the

absorption of RBV (abacavir, for example), ARV should be adjusted before beginning anti-HCV combination therapy [9]. Patients with decompensated cirrhosis should be considered as candidates for transplantation, and antiviral treatment should exclude the use of PEG-IFN, given the risk of severe adverse events. Despite the negative impact of HIV on HCV natural history, and even though eradication of HCV modifies the long-term prognosis of these patients, access to HCV treatment in coinfected patients has been limited, but this is also improving [4].

The "Historical" Standard of Care (SOC)

The standard of care for treatment until recently was the association of PEG-IFN and RBV, based on four published randomized studies [31–34], which demonstrated the superiority of this association on standard IFN associated with RBV. The SVR rates reported in theses studies for HIV-HCV-coinfected patients, either for genotype 1 (14–38 %) or for genotype 2 or 3 (44–73 %) were lower than those achieved in HCV monoinfected. In these studies, HIV was controlled in the majority of the patients since 83 to 88 % were on ART, 60 to 70 % had a HIV-RNA undetectable with a median CD4 cell count from 477 to 570 cells/μL [31–34].

Thus, the SVR with the association of PEG-IFN and RBV was at most 44 % in pivotal trials.

The association of PEG-IFN (alpha-2a 180 μg/w or alpha-2b 1.5 μg/kg/w sub-continuously) and weight-based RBV (1000 to 1200 mg/day or 15 mg/kg/day administrated twice daily) was usually the recommended treatment [35]. The optimal duration was adapted to genotypes and to HCV-RNA at weeks 4, 12, and 24. Extended duration of therapy to 72 weeks for genotype 1 or 4 and to 48 weeks for genotype 2 or 3 was drawn from the PRESCO trial [36] and from the ACTG trial [37]. The clinical benefit of the extended therapy to 72 weeks for genotype 1 or 4 proposed to patients without RVR at week 4, with EVR at week 12 and HCV-RNA negative at week 24, remains debated as well as the better dosing of RBV [38] or the impact of RBV concentration measurement on SVR rate [37]. Induction dose of IFN and/or RBV has not demonstrated any benefit [39, 40].

Early viral kinetics are an essential tool for monitoring treatment efficacy and to decide to continue or discontinue unnecessary treatment (stopping or futility rules).

Factors Associated with SVR in "Historical" SOC with PEG-IFN RBV

HCV genotype, HCV-RNA level, liver fibrosis, and IL28B genotype are the major predictors of SVR in both HCV-monoinfected and HIV-HCV-coinfected patients [41]. Other factors like younger age, Caucasian origin, low body mass index, lack of insulin resistance, lack of hepatic steatosis, high CD4 percentage, and lack of previous or current intravenous drug use have been suggested [42]. An optimal adherence is a major concern since a higher dropout rate due to side effects has been prospectively reported in HIV-HCV-coinfected compared to HCV-monoinfected patients [43], and a threshold exposure to both drugs, PEG-IFN, and RBV of 75 % for genotype 1 or 60 % for genotype non-1 was associated with SVR [44].

Toxicity and ARV Interaction

Specific concerns about toxicity and drug interaction with anti-HCV treatment have been described in HIV-HCV-coinfected patients. Among frequent adverse events due to the association of PEG-IFN and RBV, severe weight loss has been described in 29 % of treated patients in the RIBAVIC study [34] which could persist in a minority of the patients after completion of treatment and suggested a role for mitochondrial toxicity [45]. The reduction of around an average of 150 CD4 cells during treatment with a threshold at 200 cells/μL for the inclusion in three pivotal studies [31, 33, 34] is not associated with a significant risk of adverse effects. Zidovudine was independently associated with severe anemia [46], didanosine (with or without stavudine) was associated with an increase risk of symptomatic mitochondrial toxicity and hepatic decompensation [47], and abacavir (due to an interaction with the phosphorylation pathway of RBV) was associated with a lower SVR rate, but this is still debated [48]: these antiretroviral drugs should not be used in patients treated with PEG-IFN- and RBV-including regimen.

The Benefits of Treatment

SVR after HCV therapy corresponds to the eradication of the HCV virus. The consequential reduction in liver necro-inflammation results in stabilization then in an improvement in liver fibrosis and in the absence of comorbidities [49–52]. As in patients with monoinfection, the long-term prognosis changes in patients with SVR, especially those with F3–F4 liver fibrosis. Nevertheless, these patients are still at risk of complications, in particular the development of hepatocellular carcinoma. A benefit is clearly observed in coinfected patients [9] as well as in monoinfected patients [53] with extensive fibrosis or cirrhosis at baseline who achieved SVR (reduction of liver-related morbidity and mortality).

Interestingly, like in HCV monoinfection, SVR has been associated with a reduction of both hepatic and extra-hepatic (including non-AIDS) mortality [54].

Telaprevir- or Boceprevir-Including Regimen in Genotype 1

New anti-HCV molecules and mainly direct-acting agents (DAAs) represent a considerable hope for increasing virologic cure but also a challenge for the management of drug-drug

interactions in HIV-HCV-coinfected patients. The initial strategy consisted in the addition of the two first generation of protease inhibitor (PI) to PEG-IFN and RBV, telaprevir (TVR), or boceprevir (BOC) (Fig. 1). Due to the large number of DAAs in development, future strategies will consist of the combination of DAAs with or without maintaining PEG-IFN and/or RBV:

(a) General results of triple therapy with telaprevir or boceprevir

The first phase 2 randomized study compared triple therapy with telaprevir during 12 weeks followed by bitherapy during 36 weeks to placebo of telaprevir with a similar regimen in 62 genotype 1 HIV-HCV-coinfected naïve patients treated or not with ARV [55]. Higher SVR at 12 weeks post-treatment was observed in telaprevir regimen compared to placebo (74 versus 45 %) with no influence of ART regimen and comparable safety profile than in HIV-negative patients [55]. The second randomized study compared triple therapy with boceprevir during 44 weeks after a 4-week lead in the phase of PEG-IFN and RBV to a similar regimen with placebo in 98 genotype 1 HIV-HCV-coinfected naïve patients [56]. Similarly, higher SVR at 12 weeks post-treatment was observed in boceprevir regimen compared to placebo (61 versus 27 %) with comparable safety profile than in HIV-negative patients [56].

Similar positive results have been recently reported: (1) either in PEG-IFN and RBV (PR)-experienced patients who were given telaprevir- or boceprevir-including regimen allowing to achieve around 85 and 65 % SVR rates, respectively [57, 58] or by combining PR to other first-wave protease inhibitors (faldaprevir, simeprevir…) [59].

The major message is that first-wave first-generation protease inhibitors in combination with PR allow to achieve SVR rates which are similar to those achieved in HCV-monoinfected patients [60].

Trials in HIV-HCV-coinfected patients treated with Quad combination (Asunaprevir, Daclatasvir, PEG-IFN, and RBV) or PEG-IFN-free regimen are still ongoing.

(b) Safety profile and ARV

Similar safety profile has been reported in HIV-HCV-coinfected patients treated with triple therapy compared to HCV monoinfected; however, these results were obtained on limited HIV-HCV-coinfected treated patients, without severe liver disease or significant comorbidities and with limited concomitant ART regimen. Telaprevir and boceprevir are both inhibitors of CYP3A4/5 and P-gp but also a substrate of these two metabolite pathways with a risk of a lot of drug-drug interactions which have been described or suspected. The safety profile of each concomitant treatment has to be carefully evaluated before beginning a triple therapy, and web-accessible database is usually a useful method to check potential interactions (i.e., at www.pharmacoclin.ch or www.hep-druginteractions.org) [61]. Despite the variations of the area under the curve of both ARV and HCV protease inhibitor, the clinical impact in current practice appears limited [56], but drug monitoring may be helpful in managing therapy and also a switch to another antiretroviral therapy for the duration of the new anti-HCV oral combination may be considered.

In summary, the combinations of PEG-IFN-alfa/RBV and the first-generation oral DAAs, telaprevir and boceprevir have demonstrated a high level of antiviral efficacy in HCV-monoinfected patients (75 % of SVR) as well as in HCV/HIV-coinfected patients (60–85 %) with an "acceptable" safety profile. After this first major step, the combination of the second-wave protease inhibitors with PEG-IFN-alfa/RBV (simeprevir,

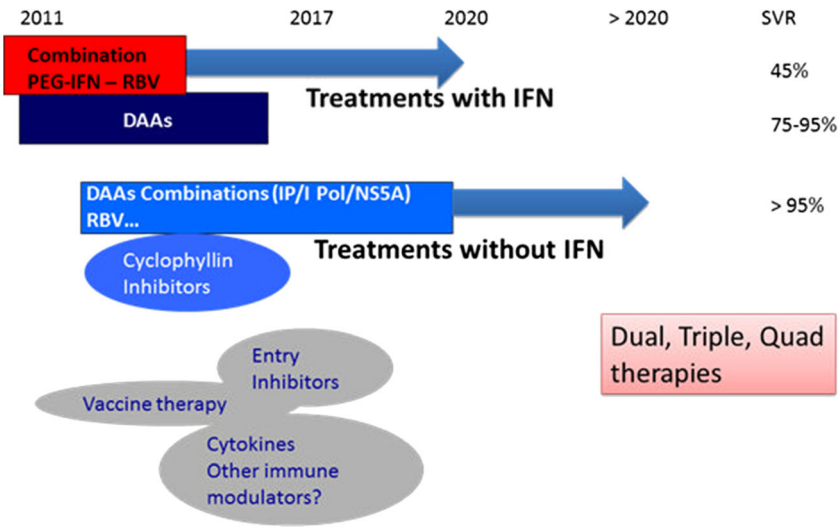

Fig. 1 Therapeutic strategies over time for treating hepatitis C virus (HCV) infection

faldaprevir) have suggested a significant antiviral potency (around 75 % of SVR) with a better tolerance, a lower pill burden, and a reduction in treatment duration, but these combinations should probably have a limited place in the management of patients, given the rapid development of oral direct-acting antiviral drugs (DAAs) combinations.

The Revolution of the Interferon-Free Regimen

A better understanding of the HCV life cycle recently resulted in the development of several second-wave and second-generation specific inhibitor DAAs targeting viral proteins: nucleos(t)idic [62, 63] and non-nucleos(t)idic [64] NS5B polymerase inhibitors, NS5A viral replication complex inhibitors [65], or second-generation protease inhibitors [66, 67]. These new antiviral agents have initially been used in combination with PR, allowing viral cure in 75 to 95 % of patients. This second phase in treatment progress is not only characterized by a wide range of new therapeutic weapons but also by the reduction in treatment duration (12 to 24 weeks) and in pill burden.

The real revolution comes from the development of therapeutic strategies combining direct antiviral agents without interferon (and its own side effects), or even without PR [68–77]. These oral multiple therapies have a better tolerance, a lower pill burden, and shortening treatment duration from 24 to 12 weeks. Above all, these oral combinations give hope for more than 90 % of cure not only in naïve patients but also in experienced treated patients, even those who did not respond to triple therapy with first-generation protease inhibitor, pegylated interferon, and ribavirin.

It is today impossible to summarize all the on-going trials and their efficiency, but these oral 12–24-week multiple therapies will make it possible to cure all the patients in the medium term because (1) they have a pan-genotypic activity, (2) there is no cross resistance between the different classes of direct antiviral agents, and (3) new molecules (third generation) and even new targets (entry inhibitors, release inhibitors) are under study. Other antiviral agents, as cyclophilin inhibitors, antisense RNA, or vaccine therapy, will provide answers to unresolved issues as overcoming an initial non-response to a first-line treatment. These oral combinations of new DAAs are likely to become the SOC for chronic HCV after 2015. The main concern remains the drug-drug interactions especially with ARV: most of the clinical trials have been performed in patients either without antiretroviral treatment or treated with Isentress and tenofovir/emtricitabine. We know that the sofosbuvir regimen does not interact with most of ARV; on the contrary, the standard dosing of daclatasvir (60 mg), a potent and pan-genotypic NS5 inhibitor, has to be increased to 90 mg/day in patients who are treated with a PI boosted by ritonavir or reduced (30 mg/day) in Efavirenz-treated patients. Other issues are adherence, resistance, and availability of these new drugs which cost is prohibitive in most regions for a wide use.

The most recent studies which have been conducted in small numbers of "easy-to-treat" (naïve and non-cirrhotic) HIV-infected patients with short post-treatment period gave outstanding results: in the photon 1 studies combining sofosbuvir and RBV for 12 weeks in GT2-3 patients or 24 weeks in GT1 patients the SVR rate was similar to that reported in HCV monoinfected patients (88, 68 and 75 % respectively) [78].

MK-5172 and MK-8742 are once daily, highly potent inhibitors of the HCV NS3/4A protease and NS5A replication complex, respectively, with a high barrier to resistance and activity against common resistance-associated variants. This 12-week-DAA combination, which can be coadministered with antiretroviral regimens that contain the integrase inhibitor, raltegravir, and dual non-nucleoside reverse transcriptase inhibitors (e.g., tenofovir or abacavir + emtricitabine or lamivudine) without dosage adjustments, resulted in a SVR rate of around 90 % in HCV genotype 1-infected patients with (and without) HIV coinfection in the C-WORTHy trial [79].

Conclusion and Perspectives

Treatment options in HIV-HCV-coinfected patients have been greatly improved in the last few years. The treatment of acute HCV infection in HIV-positive individuals using the association of PEG-IFN/RBV (with a first-generation protease inhibitor in genotype 1-infected patient) will allow a HCV virologic cure in around 80 %. In chronically infected patients, the PEG-IFN/RBV association has demonstrated an efficacy of 20–40 % in genotype 1 and higher in other genotypes, and increasing with optimization of dosing and duration, stopping rules and ART adjustment; the adjunction of telaprevir or boceprevir for genotype 1 increased the chance of HCV cure to around 70 % with drug-drug interactions concerns. Physicians are today, in 2014, in a period of transition between the standard treatment combining PEG-IFN and RBV with or without first-generation HCV protease inhibitors according to HCV genotype and oral combinations of different classes of DAAs with a pan-genotypic antiviral potency and a fair safety which will clearly change the prognosis of HIV/HCV-infected patients. If the second-generation antiretroviral drugs have significantly modified the natural history of HCV infection in HIV-infected patients, the DAA combination removes HIV-infected patients (like cirrhotics or liver transplant recipients) as difficult-to-treat patients.

Compliance with Ethics Guidelines

Conflict of Interest Stanislas Pol declares paid speaking engagements, not related to this article for GSK, BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and Abbvie. Stanislas Pol has received grants, unrelated to this article from BMS, Gilead, Roche, and MSD. Stanislas Pol is also a board member of GSK, BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and Abbvie.

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References

1. Staples Jr CT, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis. 1999;29:150–4.
2. Greub G, Ledergerber B, Battegay M, et al. For the Swiss HIV Cohort Study. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet. 2000;356: 1800–5.
3. Sogni P, Corouge M, Polin S. Emerging therapeutic options for hepatitis C: Unitec House. London: Future Medicine Ltd; 2013. p. 58–71.
4. Naggie S, Sulkowski MS. Management of patients coinfected with HCV and HIV: a close look at the role for direct-acting antivirals. Gastroenterology. 2012;142(6):1324–34.
5. Marcellin P, Pequignot F, Delarocque-Astagneau E, Zarski JP, Ganne N, Hillon P, et al. Mortality related to chronic hepatitis B and chronic hepatitis C in France: evidence for the role of HIV coinfection and alcohol consumption. J Hepatol. 2008;48:200–7.
6. Eslam M, Aparcero R, Kawaguchi T, Del Campo JA, Sata M, Khattab M, et al. Meta-analysis: insulin resistance and sustained virological response in hepatitis C. Aliment Pharmacol Ther. 2011;34:297–305.
7. Mallet V, Vallet-Pichard A, Pol S. The Impact of human immunodeficiency virus on viral hepatitis. Liver Int. 2011;1:1–163.
8. Mallet V, Thiebaut S, Yazdanpanah Y, et al. HCV accelerates non-liver mortality in hiv-infected patients: a nationwide cohort study [CROI abstract 690]. In special issue: abstracts from the 2014 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2014;22(e-1):346.
9. Berenguer J, Alvarez-Pellicer J, Martin PM, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology. 2009;50:407–13.
10. Serpaggi J, Chaix ML, Batisse D, Dupont C, Vallet-Pichard A, Fontaine H, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. AIDS. 2006;20:233–40.
11. Vogel M, Deterding K, Wiegand J, Grüner NH, Baumgarten A, Jung MC, et al. Initial presentation of acute hepatitis C virus (HCV) infection among HIV-negative and HIV-positive individuals-experience from 2 large German networks on the study of acute HCV infection. Clin Infect Dis. 2009;49:317–9.
12. Rockstroh J. Acute hepatitis C in HIV-infected individuals recommendations from the European AIDS Treatment Network (NEAT) consensus conference. AIDS. 2011;25:399–409.
13. Thomson EC, Fleming VM, Main J, Klenerman P, Weber J, Eliahoo J, et al. Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Gut. 2011;60:837–45.
14. Grebely J, Hellard M, Applegate T, Petoumenos K, Yeung B, Feld JJ, et al. Virological responses during treatment for recent hepatitis C virus: potential benefit for RBV use in HCV/HIV co-infection. AIDS. 2012;26:1653–61.
15. Gilleece YC, Browne RE, Asboe D, Atkins M, Mandalia S, Bower M, et al. Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of PEG-IFN and RBV. J Acquir Immune Defic Syndr. 2005;40:41–6.
16. Dominguez S, Ghosn J, Valantin MA, Schruniger A, Simon A, Bonnard P, et al. Efficacy of early treatment of acute hepatitis C infection with PEG-IFN and RBV in HIV-infected patients. AIDS. 2006;20:1157–61.
17. Vogel M, Dominguez S, Bhagani S, Azwa A, Page E, Guiguet M, et al. Treatment of acute HCV infection in HIV-positive patients: experience from a multicentre European cohort. Antivir Ther. 2010;15:267–79.
18. Laguno M, Martínez-Rebollar M, Perez I, Costa J, Larrousse M, Calvo M, et al. Low rate of sustained virological response in an outbreak of acute hepatitis C in HIV-infected patients. AIDS Res Hum Retrovir. 2012;28:1294–300.
19. Piroth L, Larsen C, Binquet C, Alric L, Auperin I, Chaix ML, et al. Treatment of acute hepatitis C in human immunodeficiency virus-infected patients: the HEPAIG study. Hepatology. 2010;52:1915–21.
20. Dorward J, Garrett N, Scott D, Buckland M, Orkin C, Baily G. Successful treatment of acute hepatitis C virus in HIV positive patients using the European AIDS Treatment Network guidelines for treatment duration. J Clin Virol. 2011;52:367–9.
21. Matthews GV, Hellard M, Haber P, Yeung B, Marks P, Baker D, et al. Characteristics and treatment outcomes among HIV-infected individuals in the Australian Trial in Acute Hepatitis C. Clin Infect Dis. 2009;48:650–8.
22. Lambers FA, Brinkman K, Schinkel J, Spijkerman IJ, Molenkamp R, Coutinho RA, et al. Treatment of acute hepatitis C virus infection in HIV-infected MSM: the effect of treatment duration. AIDS. 2011;25: 1333–6.
23. Santantonio T, Fasano M, Sagnelli E, Tundo P, Babudieri S, Fabris P, et al. Acute hepatitis C: A 24-week course of pegylated interferon alpha-2b versus a 12-week course of pegylated interferon alpha-2b alone or with ribavirin. Hepatology. 2014;59:2109.
24. Fierer DS, Dieterich DT, Mullen MP, Branch AD, Uriel AJ, Carriero DC, et al. Telaprevir in the treatment of acute hepatitis C virus infection in HIV-infected men. Clin Infect Dis. 2014;58:873–9.
25. Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA. 2012;308:370–8.
26. Castera L, Winnock M, Pambrun E, Paradis V, Perez P, Loko MA, et al. Comparison of transient elastography (FibroScan), FibroTest, APRI and two algorithms combining these non-invasive tests for liver fibrosis staging in HIV/HCV coinfected patients: ANRS CO13 HEPAVIH and FIBROSTIC collaboration. HIV Med. 2014;15:30–9.
27. Cacoub P, Carrat F, Bédossa P, Lambert J, Pénaranda G, Perronne C, et al. Comparison of non-invasive liver fibrosis biomarkers in HIV/HCV co-infected patients: the fibrovic study—ANRS HC02. J Hepatol. 2008;48:765–73.
28. Calès P, Halfon P, Batisse D, Carrat F, Perré P, Penaranda G, et al. Comparison of liver fibrosis blood tests developed for HCV with new specific tests in HIV/HCV co-infection. J Hepatol. 2010;53:238–44.
29. Calès P, Boursier J, Ducancelle A, Oberti F, Hubert I, Hunault G, et al. Improved fibrosis staging by elastometry and blood test in chronic hepatitis C. Liver Int. 2014;34:907–17.

30. Salmon D, Arvieux C, Bourlière M, Cacoub M, Halfon P, Lacome K, et al. Use of first-generation HCV protease inhibitors in patients coinfected by HIV and HCV genotype 1. Liver Int. 2013. doi:10.1111/liv.12363.
31. Laguno M et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV coinfected patients. AIDS. 2004;18:F27–36.
32. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-García J, Lazzarin A, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004;351:438–50.
33. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004;351:451–9.
34. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. PEG-IFN alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004;292:2839–48.
35. Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, et al. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. HIV Med. 2008;9:82–8.
36. Núñez M, Miralles C, Berdún MA, Losada E, Aguirrebengoa K, Ocampo A, et al. Role of weight-based RBV dosing and extended duration of therapy in chronic hepatitis C in HIV-infected patients: the PRESCO trial. Res Hum Retrovir. 2007;23:972–82.
37. Chung RT, Umbleja T, Chen JY, Andersen JW, Butt AA, Sherman KE. Extended therapy with PEG-IFN and weight-based RBV for HCV-HIV coinfected patients. HIV Clin Trials. 2012;13:70–82.
38. Rodriguez-Torres M, Slim J, Bhatti L, Sterling R, Sulkowski M, Hassanein T, et al. Peginterferon alfa-2a plus ribavirin for HIV-HCV genotype 1 coinfected patients: a randomized international trial. HIV Clin Trials. 2012;13:142–52.
39. Tural C, Solà R, Alvarez NP, Moltó J, Sánchez M, Zamora AM, et al. Effect of an induction period of pegylated interferon-α2a and ribavirin on early virological response in HIV-HCV-coinfected patients: results from the CORAL-2 study. Antivir Ther. 2011;16:833–41.
40. Labarga P, Barreiro P, da Silva A, Guardiola JM, Rubio R, Aguirrebengoa K, et al. Comparison of high ribavirin induction versus standard ribavirin dosing, plus peginterferon-α for the treatment of chronic hepatitis C in HIV-infected patients: the PERICO trial. J Infect Dis. 2012;206:961–8.
41. Medrano J, Neukam K, Rallón N, Rivero A, Resino S, Naggie S, et al. Modeling the probability of sustained virological response to therapy with pegylated interferon plus ribavirin in patients coinfected with hepatitis C virus and HIV. Clin Infect Dis. 2010;51:1209–16.
42. Bhagani S. Current treatment for chronic hepatitis C virus/HIV-infected individuals: the role of pegylated interferon-alpha and ribavirin. Curr Opin HIV AIDS. 2011;6:483–90.
43. Tural C, Galeras JA, Planas R, Coll S, Sirera G, Giménez D, et al. Differences in virological response to pegylated interferon and ribavirin between hepatitis C virus (HCV)-monoinfected and HCV-HIV-coinfected patients. Antivir Ther. 2008;13:1047–55.
44. Opravil M, Rodriguez-Torres M, Rockstroh J, Snoeck E, Chung RT, Tietz A, et al. The dose-response relationship of peginterferon alfa-2a and ribavirin in the treatment of patients coinfected with HIV-HCV. HIV Clin Trials. 2012;13:33–45.
45. Bani-Sadr F, Lapidus N, Bedossa P, De Boever CM, Perronne C, Halfon P, et al. Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors. Clin Infect Dis. 2008;46:768–74.
46. Bani-Sadr F, Goderel I, Penalba C, Billaud E, Doll J, Welker Y, et al. Risk factors for anaemia in human immunodeficiency virus/hepatitis C virus-coinfected patients treated with interferon plus ribavirin. J Viral Hepat. 2007;14:639–44.
47. Bani-Sadr F, Carrat F, Pol S, Hor R, Rosenthal E, Goujard C, et al. Risk factors for symptomatic mitochondrial toxicity in HIV/hepatitis C virus-coinfected patients during interferon plus ribavirin-based therapy. J Acquir Immune Defic Syndr. 2005;40:47–52.
48. Bani-Sadr F, Denoeud L, Morand P, Lunel-Fabiani F, Pol S, Cacoub P, et al. Early virologic failure in HIV-coinfected hepatitis C patients treated with the peginterferon-ribavirin combination: does abacavir play a role? J Acquir Immune Defic Syndr. 2007;45:123–5.
49. Pol S, Soriano V. Management of chronic hepatitis C virus infection in HIV-infected patients. Clin Infect Dis. 2008;47:94–101.
50. Loko MA, Bani-Sadr F, Valantin MA, Lascoux-Combe C, Fontaine H, Bonnard P, et al. Antiretroviral therapy and sustained virological response to HCV therapy are associated with slower liver fibrosis progression in HIV-HCV-coinfected patients: study from the ANRS CO 13 HEPAVIH cohort. Antivir Ther. 2012;17:1335–43.
51. Casado JL, Quereda C, Moreno A, Pérez-Elías MJ, Martí-Belda P, Moreno S. Regression of liver fibrosis is progressive after sustained virological response to HCV therapy in patients with hepatitis C and HIV coinfection. J Viral Hepat. 2013;20:829–37.
52. Labarga P, Fernandez-Montero JV, Barreiro P, Pinilla J, Vispo E, de Mendoza C, et al. Changes in liver fibrosis in HIV/HCV-coinfected patients following different outcomes with peginterferon plus ribavirin therapy. J Viral Hepat. 2014;21:475–9.
53. Mallet V, Gilgenkrantz H, Serpaggi J, Verkarre V, Vallet-Pichard A, Fontaine H, et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med. 2008;149:399–403.
54. Berenguer J, Rodríguez E, Miralles P, Von Watchman MA, López-Aldeguer J, Mallolas J, et al. Sustained virological response to interferon plus ribavirin reduces non-liver-related mortality in patients coinfected with HIV and hepatitis C virus. Clin Infect Dis. 2012;55:728–36.
55. Sulkowski MS, Sherman KE, Dieterich DT, Bsharat M, Mahnke L, Rockstroh JK, et al. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. Ann Intern Med. 2013;159:86–96.
56. Sulkowski M, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infect Dis. 2013;13:597–605.
57. Lacombe K, Valin N, Stitou H, et al. Efficacy and tolerance of telaprevir in HIV-hepatitis C virus genotype 1-coinfected patients failing previous antihepatitis C virus therapy: 24-week results. AIDS. 2013;27:1356–9.
58. Poizot-Martin I, Bellissant E, Colson P, et al. Boceprevir for previously treated HCV-HIV coinfected patients: the ANRS-HC27 BocepreVIH Trial [CROI abstract 659LB]. In special issue: abstracts from the 2014 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2014;22(e-1):326.
59. Dieterich D, Asselah T, Guyader D, Berg T, Schuchmann M, Mauss S, et al. SILEN-C3, a phase 2 randomized trial with faldaprevir plus pegylated interferon α-2a and ribavirin in treatment-naive hepatitis C virus genotype 1-infected patients. Antimicrob Agents Chemother. 2014;58:3429–36.
60. Salmon-Ceron D, Arvieux C, Bourlière M, Cacoub P, Halfon P, Lacombe K, et al. Use of first-generation HCV protease inhibitors in patients coinfected by HIV and HCV genotype 1. Liver Int. 2014;34:869–89.
61. Hulskotte EG et al. Pharmacokinetic interactions between the hepatitis C virus protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, darunavir, and lopinavir. Clin Infect Dis. 2013;56(5):718–26.

62. Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, Demicco M, et al. Sofosbuvir, an NS5 nucleotide polymerase inhibitor, with peginterferon alfa-2a and ribavirin in treatment-naïve patients with hepatitis C genotypes 1, 4, and 6 infection (ATOMIC): an open-label, randomised, multicentre, phase 2 trial. Lancet. 2013. doi:10.1016/S0140-6736(13)60247-0.
63. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368(20):1878–87.
64. Gane EJ, Roberts SK, Stedman CA, Angus PW, Ritchie B, Elston R, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet. 2010;376:1467–75.
65. Pol S, Ghalib RH, Rustgi VK, Martorell C, Everson GT, Tatum HA, et al. Daclatasvir for previously untreated chronic hepatitis C genotype-1 infection: a randomised, parallel-group, double-blind, placebo-controlled, dose-finding, phase 2a trial. Lancet Infect Dis. 2012;12(9):12671–7.
66. Zeuzem S, Asselah T, Angus PW, Zarski JP, Larrey D, Mullhaupt B, et al. Efficacy of the protease inhibitor BI 201335, the polymerase inhibitor BI 207127 and ribavirin in patients with chronic hepatitis C. Gastroenterology. 2011;141(6):2047–55.
67. Lenz O, Vijgen L, Berke JM, Cummings MD, Fevery B, Peeters M, et al. Virologic response and characterisation of HCV genotype 2–6 in patients receiving TMC435 monotherapy (study TMC435-C202). J Hepatol. 2013;58(3):445–51. doi:10.1016/j.jhep.2012.10.028. Epub 2012.
68. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012;366(3):216–24.
69. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013;368(1):34–45.
70. Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med. 2013;368(1):45–5.
71. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370(3):211–21. doi:10.1056/NEJMoa1306218.
72. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med. 2014;370(3):222–32. doi:10.1056/NEJMoa1306227.
73. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370(21):1973–82.
74. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Copper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370(21):1983–92.
75. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889–98.
76. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483–93.
77. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370(20):1879–88.
78. Naggie S, Sulkowski M, Lalezari J, et al. Sofosbuvir plus ribavirin for HCV genotype 1–3 infection in HIV coinfected patients (PHOTON-1) [CROI abstract 26]. In special issue: abstracts from the 2014 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2014;22(e-1):14.
79. Sulkowski et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA. 2014;312(4):353–61.