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Coinfection of Hepatitis B and C in HIV Patients: A Review of the State of the Art

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Abstract

Infection with the human immunodeficiency virus (HIV) modifies the course of infection by the virus of hepatitis B (HBV) by several mechanisms: the rate of chronicity, prolonging viremia by HBV, and increase in morbidity related to liver disease. The treatment for both infections should be done in a coordinated manner, to avoid the emergence of resistance in HIV, HBV or both, as well as major alterations in the hepatic enzymes. Monotherapies with lamivudine or emtricitabine select, rapidly, mutant strains of the HBV and HIV. Monotherapy with adefovir has moderate effects in coinfected patients as they already have mutations. If the treatment of HBV can defer until the combination antiretroviral therapy of HIV is necessary, these patients should receive a combination of tenofovir plus lamivudine (or emtricitabine), since this provides a powerful therapy against HBV and establishes a good central axis for antiretroviral therapy. In addition, it would prevent the selection of HBV variant resistance. The influence of HIV in the HCV infection. Increase in load HIV-driven viral hepatitis exacerbates hepatic lesions and influences transmission of the HCV. The risk of sexual transmission increases when HIV is present in the carrier. Coinfection modifies the evolution of fibrosis in patients with HIV, with higher speed in those who have low CD4 counts, so that the onset of cirrhosis occurs before, and the risk of liver decompensation is also more frequent. The consequence of this situation is an increase in liver-related morbidity and mortality.

Keywords: hepatitis B, HIV coinfection, hepatitis C

1. Introduction

The hepatitis B virus is one of the most pathogenic and prevalent in the world. In some places, up to 95% of those infected with HIV have also been infected with hepatitis B, and 10–15% will develop chronic hepatitis B. However, there is a great variation for both infections according to the geographical region and the risk group. In the USA, it is estimated that 100,000 HIV-infected patients suffer from chronic HBV. We do not have data for our country. In patients coinfected with HIV and HBV, HBV is less likely to be eliminated. The infection with primary HBV leads to chronic hepatitis in 2–5% of immunocompetent adults, while patients infected with HIV can become chronic about 5 times more (15–23%). One possible reason is the T-cell defect associated with HIV infection.

HBV and HIV have several characteristics in common even though HBV is a double-stranded DNA virus. After entering the hepatocyte, viral DNA is integrated into the host genome and the viral RNA is translated by the HBV inverse polymerase in new viral DNA and transcribed to viral proteins. The reverse transcription can be inhibited by nucleic acid (t) transcriptase inhibitors reverse. The integration of the virus into the host's genome in hepatocytes and CD4+ T cells prevents its eradication.

Finally, the mechanisms used to develop resistance are very similar in both viruses. All HIV patients should be screened for HBV and HCV. Screening of HIV-infected patients for HBV must start with the HBsAg application, anti-HBs, and anti-HBc. If a positive HBsAg is found, you must complete the study with HBeAg, anti-HBe, and HBV DNA. On the other hand, for all patients diagnosed with HBV infection, you should have an ELISA for HIV to rule out coinfection.

Like patients monoinfected with HBV with chronic hepatitis B, those coinfected with HIV should be evaluated every 6–12 months for hepatocellular carcinoma, by measuring alpha-fetus protein and performing an ultrasound of the liver. This recommendation is regardless of whether the patient has apparent cirrhosis or not.

The improvement of survival in infected patients by the human immunodeficiency virus (HIV), resulting from the introduction of the therapy powerful anti-retroviral ("HAART"), has caused chronic liver infections will become important causes of hospitalization and mortality in patients infected with HIV (HIV+) [1].

Liver diseases and their consequences represent between 30 and 55% of the causes of death in these patients [2]. Frequently, the infection by the viruses of the hepatitis B (HBV) and hepatitis C (HCV) is a cause of chronic liver disease in patients who are HIV+, which can be attributed to the means of transmission and the epidemiological factors among the three viruses [3].

Although the impact of HBV is still not well known in the progression of HIV disease, you have to be very clear about the interference of infection by HIV in the natural history of HBV infection. Coinfected patients have viral loads of HBV that are higher than monoinfected, with a greater risk and a shorter time of evolution to cirrhosis [4].

The presence of HIV modifies the natural history of HCV infection, accelerating the progression of hepatic disease in coinfected people. Of people infected with HCV, between 8 and 24% contract cirrhosis in the first 10–20 years after their HCV infection [5]. The annual incidence of hepatocellular carcinoma of cirrhosis is between 1 and 4% [5].

Works carried out in different countries have shown that the prevalence of HIV/HBV coinfection ranges between 4.8 and 15% [6–8]. In Brazil, according to previous studies in various urban areas, the prevalence of chronic hepatitis B in patients who are HIV+ ranged between 5.3 and 19.2% [9–12]. Studies conducted in several countries reveal that the frequency in the presence of anti-HCV in patients who are HIV+ varies between 0 and 42.5% [6–8].

2. Coinfection with hepatitis B in patients with HIV

Hepatitis B, caused by the hepatitis virus B (HBV), is an important problem of public health and it is the most serious kind of viral hepatitis. It can cause chronic liver disease and carries a high risk of death for cirrhosis and liver cancer. It is estimated that in the world there are 2 billion people infected with HBV and more than 350 million with chronic liver infection [13].

Coinfection of HBV with the human immunodeficiency virus (HIV) is common since they have the same transmission routes.

In Western Europe and in the United States, it has been found that 7–10% of HIV patients have a chronic infection by HBV, with men who have sex with other men being the group with the highest prevalence [14–16]. Patients coinfected with HBV and HIV have an increased risk of liver cirrhosis, terminal liver disease and death by hepatic pathology, especially in patients with low CD4 lymphocyte counts and concomitant use of alcohol [15]. There is a greater risk of hepatocarcinoma and adverse hepatotoxic effects in patients using therapy with highly effective antiretroviral drugs (TARAE) coinfected with hepatitis B [16].

Ninety-five percent of HBV infections in adults who are healthy are self-limiting with an elimination of HBV blood and lasting immunity against the reinfection. Chronic infection happens in less than 5% of patients older than 5 years [14, 17]. Immunosuppressed patients such as patients with HIV, who are in substitution therapy for kidney and diabetics, present a greater risk of chronicity of HBV infection [18–20]. Approximately 15% of patients with chronic infection older than 5 years can evolve into cirrhosis and hepatic cancer, remaining asymptomatic until the appearance of the clinical manifestations of said complications [21]. It is estimated that 20% of HIV-positive patients infected with HBV will develop chronic hepatitis by this agent [18].

The antigens and antibodies associated with the infection of hepatitis B virus are as follows:

A. Surface antigen (HBs Ag): Associated to active infection. Identify patients who are infectious and can be detected from 3 to 5 weeks after the infection. When it remains more than 6 months high, it is related to chronic infection with HBV [22].

B. Antibody against surface antigen (anti-HBs): Its presence indicates in the most of the time, immunity for infection with HBV, natural or acquired, as long as its value is equal or superior to 10 IU/ml (International Units per milliliter) [23].

C. Antibodies against the core of HBV (anti-HBc): The total anti-HBc is considered a marker of the previous infection by HBV. Is composed of two fractions: anticore IgM, appears at the onset of symptoms, up to 30 days after the appearance of HBs Ag, or during the period in which the biochemical tests liver cells are altered in the infection acute and declines between 3 and 12 months after the exhibition; anticore IgG, appears during the acute phase of the disease associated with HBs Ag and persists throughout life of the individual infected with HBV. The presence of anticore IgG can mean: (1) the previous infection with immunity, presence of concomitant antibody to the antigen of serum surface greater than 10 IU/ml. (2) in the previous infection with loss of anti-HBs, these patients have no evidence neither of viral replication nor of antibodies against the surface antigen, because the levels of these antibodies have disappeared over time, but reappear after the application of one or more doses of the vaccine against hepatitis B.

D. HBV infection hidden, are patients with presence of DNA viral serum or liver and absence of HBs Ag and anti-HBs. This situation is not uncommon in patients HIV positive, infection with the virus Hepatitis C and in areas of high prevalence of infection by HBV.

The infection hidden by HBV may be present in 10–45% of HIV-positive patients [24, 25]. Therefore, it is recommended that in all HIV-positive patients the following exams for HBV screening are done: HBs Ag, total anti-HBc or anticore IgG and

anti-HBs. If the patient has an isolated positive IgG anticore, it is a must to perform the viral load of HBV DNA. If a patient has anticore IgG positive in isolation and the viral load for HBV is negative, this patient should be vaccinated against hepatitis B and he or she could have an anamnestic or primary response [26, 27].

In patients infected with HIV, atypical serological patterns may appear. More frequent is the isolated presence of anti-HBc (**Table 1**), indicative of hepatitis B cured with loss of antibodies. Exceptionally, it may be hepatitis hidden B, defined by the presence of HBV DNA in liver and serum (viremia will usually be <103 copies/ml and may be intermittent) in patients with negative HBsAg. In the hidden hepatitis B, the markers usually detected are anti-HBc, anti-HBs, and anti-HBe, although these markers can be negative (hepatitis B hid seronegative) 4 in most patients with hidden hepatitis B, the HbeAg is negative4 (**Table 1**).

2.1 The course of concurrent hepatitis B and HIV infection

In HIV-positive patients, chronic hepatitis B has an unfavorable evolution compared with patients infected only with HBV, and the associated mortality risk with hepatopathy is significantly increased. In the MACS study (multicenter AIDS cohort study), coinfected patients had an associated mortality to liver disease 8 times higher than HIV-positive patients HBsAg negative and 15 times greater than patients negative for both infections. Mortality associated with hepatopathy due to hepatitis B has increased, significantly, since the introduction of the highly active antiretroviral therapy (HAART).

In addition to increased mortality, in coinfected patients, HIV accelerates the progression of hepatitis B and increases the risk of cirrhosis significantly. It is important that the clinician is not fooled by the apparent benign course of hepatitis B in HIV patients since this is due to its cellular immunological compromise. Frequently, these patients have only one slight increase in transaminases. However,

Type infection	Anti-HBS	HBsAg	Anti-HBc (IgM)	Anti-HBc (IgG)	HBeAg	Anti-HBe	AND HBV
Acute infection	—	+	+	−/+	+	—	+
Past infection	+/−	—	—	+	—	—	—
Asymptomatic carrier	—	+	—	+	—	−/+	—
Chronic hepatitis B HBeAg+	—	+	—	+	+	—	+
Chronic hepatitis B mutant pre-core	—	+	—	+	—	−/+	+
Occult viral infection positive	+	—	+/−	+	+/−	−/+	+
Occult viral infection negative	—	—	—	—	—	—	+
History of vaccination	+	—	—	—	—	—	—

Table 1.
Serologic markers of HBV and clinical interpretation.

if HBV-DNA is measured, as a marker of viral replication, this is higher in HIV patients than in patients who are immunocompetent.

There is a direct correlation between the degree of immunosuppression and control of HBV replication in the coinfected patients. Patients with AIDS usually show, more frequently, signs of active viral replication. Even in cases with hepatitis B, apparently resolved, progressive deterioration of the immune system can lead to re-activation of an HBV infection. Most studies on the influence of hepatitis B in the evolution of HIV infection have not demonstrated a shortening in survival. The infection with HBV does not lead to a faster reduction of cells CD4+ or increase the frequency of defining diseases of AIDS. However, some interactions do occur. For example, the hepatotoxicity associated with antiretroviral drugs is three times more in patients with chronic HBV hepatitis.

2.2 Prevention

All HIV-infected patients who are serologically negative for HBV should be vaccinated; this should be done despite the fact that the vaccine may be less effective in them. Approximately 30% of patients who are HIV positive are primarily nonresponsive to the vaccine, against 2.5% of immunocompetent individuals. This is especially true for individuals with minor CD4 of 500 cells/mm³. Therefore, for these patients, a standard vaccination schedule is recommended. If the patient has less than 350 CD4 cells, it is advised to postpone vaccination until after antiretroviral therapy, and patients should be educated in strategies to prevent the progression of liver diseases, such as suppressing consumption of alcohol and tobacco and not using herbal supplement (many of which are hepatotoxic).

Standard vaccination against HBV is less effective in infected patients for HIV. The administration of four doses of 40 μg (months 0, 1, 2, and 6) improves significantly the serological response, and it is the recommended guideline [28].

The consumption of alcohol has an additive effect in terms of progression to fulminant hepatitis, development of aggressive chronic liver disease, and development of hepatocellular carcinoma. Hepatotoxic drugs must be used very carefully and under strict surveillance [29].

2.3 Treatment

HBV-HCV and HBV-HCV-HDV infections are associated with further progression of rapid liver fibrosis [30]. The treatment indications for patients coinfected with HBV-HCV are the 16, same as for each of the infections separately. In patients with multiple infections, there is a predominance of replication (VHD > HCV > HBV) that conditions the detection of viral loads of HBV and HCV lower than in patients without multiple infections [31].

The suppression of HIV replication and immunological improvement secondary to initiation of antiretroviral treatment (ART) is associated with a lower progression of liver disease, even in patients with decompensated cirrhosis [32].

Therefore, ART is a priority in the care of these patients. In those with preserved liver function, any of the drugs recommended in the therapeutic guidelines can be used since the risk of severe hepatotoxicity is low. In child B/C stages, protease inhibitors (PIs) and raltegravir (RAL) are more secure than NEV or EFV [33].

Dolutegravir [34], etravirine [35], and rilpivirine [36] can be used as there is no need to adjust the dose in patients with moderate hepatic insufficiency (child A/B), and in advanced stages, some centers monitor the plasma concentrations of the drugs and adjust their doses. RAL has demonstrated adequate serum levels without the need for dose adjustment and a good tolerance in child [37] stage C patients.

In coinfected patients with HBV/HIV, tenofovir (TDF) suppresses HBV replication in most patients and should be part of the ART, and if there are no contraindications, whenever possible, it will be added as second nucleoside analog (t) gone [33] TC or FTC.

It must be taken into account that simeprevir (SMV) increases TDF levels and, potentially, the risk of nephrotoxicity. In an observational study in patients infected with HIV and coinfected with HBV/HDV, the addition of interferon for 48 weeks to treatment with TDF (n = 4) was associated with a greater decrease in VHD-RNA compared to TDF (n = 13). However, the guideline optimal treatment and response monitoring are not well determined and the clinical relevance of the decrease in VHD-RNA due to IFN is unknown [38].

3. Coinfection with hepatitis C in patients with HIV

The influence of HIV in the HCV infection. Increase in load HIV-driven viral hepatitis exacerbates Hepatic lesions and influences transmission of the HCV. The risk of sexual transmission increases when HIV is present in the carrier. This situation is more evident in the case of homosexual men with multiple sexual contacts without using a preservative [39, 40].

In the case of mother-to-child transmission, the risk of transmission to the fetus in coinfected women for HIV is between 2 and 5 times higher than in mothers monoinfected by HCV and it is between 5 and 25% [41].

Hepatitis C behaves differently in people with HIV, since HIV accelerates the evolution of hepatitis C (even so, many people have lived for many years with a coinfection for HIV and HCV, often without knowing they were coinfected). The risk of significant damage to the liver is greater in people with HIV who have a CD4 count below 200 cells/mm^3. HCV can be treated, regardless of whether the person is or is not infected with HIV. Antiretroviral therapy has reduced notably the number of deaths caused by HIV. Currently, liver disease in the terminal stage produced by coinfection with HCV has become one of the causes of death rates among people living with HIV in certain areas of the United States and Western Europe. In part, this is because HCV infection can go undiagnosed until there has already been serious liver damage.

Coinfection modifies the evolution of fibrosis in patients with HIV, with higher speed in those who have low CD4 counts, so that the onset of cirrhosis occurs before, and the risk of liver decompensation is also more frequent. The consequence of this situation is an increase in liver-related morbidity and mortality [42, 43].

It is confirmed that coinfection by the HIV alters the natural history of HCV, that increases the risk of can become chronic of HCV, accelerates the progression of liver fibrosis associated with VHC [44], increases the risk of decompensation of cirrhosis and decreases survival after the first episode of decompensation. On the contrary, contradictory data have been published about the impact that HCV can have in the natural history of HIV, although does not seem to influence the progression of clinical events defining AIDS or in mortality [45, 46].

The progression of fibrosis is variable and depends on factors related to the causative agent and factors related to the host. Among these factors, consumption of alcohol, age at acquisition of infection, race, viral coinfections like the concomitant infection with HIV, time of infection, body mass index, and various genetic factors have been described [22]. Among these, the studies in animals have identified some determinant genetic progression of fibrosis; as well in humans, we have tried to identify polymorphism genetics to predict the degree of progression in hepatitis C and in steatosis of a nonalcoholic liver [47]. Therefore, there are a number of factors that you can modify to prevent the progression of liver fibrosis, including alcohol

intake and other toxins, the normalization of the index of body mass, and the prevention of infections for other hepatotropic viruses.

Hepatitis C does not make HIV worse, but it can complicate your treatment, since many drugs to treat HIV metabolize in the liver. Coinfected people have more risk of developing hepatotoxicity associated with the antiretroviral treatment than those who only have HIV. In any case, the benefits of HIV treatment outweigh the risk of hepatic toxicity [48].

HCV screening tests are recommended to all people with HIV. Even if you have already been diagnosed with coinfection with HIV and HCV, it is important to know how HCV is diagnosed and controlled. Unlike HIV, a positive result in the HCV antibody test does not always mean that the person has a chronic infection [48].

HCV screening tests consist of two stages. As usual, first, a test for the detection of antibodies against HCV is carried out. If the result is positive, this means that you have been infected by hepatitis C before and possibly still have. People who eliminated hepatitis C spontaneously without treatment still have the antibodies for many years afterwards. On the other hand, in some cases, the results of the antibodies screening tests are negative even when the person has a chronic infection of hepatitis C. This can happen if [48]:

- the CD4 cell count is low (usually less than 200), since it is possible that the immune system is not producing antibodies; or

- the screening test is performed very shortly after having been infected, since antibodies take between 6 and 24 weeks to develop.

An HCV RNA (viral load) screening test is needed to confirm the existence of a chronic infection (by HCV). The test of viral load searches for genetic material of HCV in the same way that HIV viral load test is used to detect this virus. If the quantity of HCV RNA in the bloodstream is detectable, it means that is currently infected with HCV. If on the other hand it is undetectable, a second test must be performed after 6 months. Yes, if the viral load is not detected in two successive tests, it means that the person has eliminated HCV from the body (**Table 2**) [48].

3.1 Prophylaxis

Serology should be performed against HAV and HBV to all adult patients infected with HIV, and even more so if infection coexists with HCV in order to

Diagnosis	Previous infection and eliminated by hepatitis C virus	Acute infection by hepatitis C virus	Chronic infection by hepatitis C virus
Detection of antibodies	Positive	Negative, is positive 6–24 weeks	Positive
Detection of viral load (HCV RNA)	Undetectable in two tests performed, at least 6 months apart	Detectable in 1 or 2 weeks, usually at very high levels	Detectable
ALT test (alanine aminotransferase)	It can be normal, fluctuate, or show a high level of persistent way	It can be between 7 and 10 times higher than the normal level	It can be normal from persistent way, fluctuate, or show a high level of persistent way

Table 2.
Diagnosis of HCV and clinical interpretation.

vaccinate, if appropriate, after having carried out the immunological study. In patients with susceptible HIV, the vaccine against hepatitis A will be administered in a two-dose schedule separated by 6 months at patients presenting figures > 200 CD4/ml. With those who are in a degree of older immunosuppression, you should wait until your CD4 numbers increase above the 200 cells/ml. There are no recommendations about when to perform the revaccination.

The standard vaccination guideline against HBV is three doses intramuscularly in the deltoids at 0, 1, and 6 months, which produce immunity greater than 90%. The answers are worse particularly among those with lower CD4 [49]. It has been postulated that doubling the standard doses or administering another dose could produce more adequate protection titles [50]. Patients with CD4 < 200 will proceed to vaccination when the figure has increased.

Immunization with the vaccine is lost with time, so controls must be carried out later to check the protection. Controls will be carried out between 4 and 12 weeks after finishing the vaccination, and more lately once a year.

3.2 Treatment for genotype 1 of hepatitis C

The evidence supports that the beginning of the antiretroviral therapy and, therefore, controlling early replication of HIV and maintaining a good immunological situation are the first measures to adopt in the coinfected patients. Existing data indicate that antiretroviral treatment can slow down the progression of chronic HCV liver disease in the coinfected patient, even in the carriers of liver disease, increasing their survival [51, 52].

Studies based on liver biopsies have demonstrated a relationship between the management of antiretroviral treatment, immunological improvement, and the presence of lower grades of hepatic fibrosis [53, 54].

3.2.1 Boceprevir or telaprevir + PR

In patients coinfected with HIV and HCV genotype 1 and without previous treatment for HCV SVR after treatment with Boceprevir (BOC) or telaprevir (TVR) was higher (63–74%) than in those treated with PR (29–45%) [55, 56].

Efficacy and side effects with both triple patterns were similar to those observed in monoinfected patients. The dose of RBV was 800 mg/d in almost all patients. Although significant pharmacokinetic interactions have been described, the co-administration of lopinavir/r, atazanavir/r, and darunavir/r, allowed in the study with PR/BOC, did not affect efficacy [55].

The results of the Unite 115 study support the dosage of TVR every 12 h in coinfected patients and ART based on IP/r or raltegravir, as well as the possibility of shortening the duration to 24 weeks (T12 + PR24) in patients without cirrhosis with HCV-RNA undetectable in S4 and S12.

In pretreated coinfected patients, the results of observational studies are similar to those obtained in clinical trials with monoinfected patients. The efficacy of these guidelines is insufficient in cirrhotic patients or patients with previous response to partial or null P/R. Due to its limited efficacy and high toxicity, treatment with BOC and TVR should be considered for exceptional use, in patients with genotype 1, without treatment or with recurrence prior to PR, when the guidelines considered preferred are not available or alternatives:

1. P/R + TVR × 12 s + P/R× 36 s. (AI). If undetectable viral load in s4 and s12, in absence of cirrhosis: P/R× 24 s (BI)

2. P/R× 4 s (lead-in) + P/R + BOC× 44 s (BI)

3.2.2 Sofosbuvir (SOF) + PR

In the study NEUTRINO [57], 291 patients infected with HCV, genotype 1, without prior treatment, received treatment with SOF + PegIFN alpha-2a + RBV (1000–1200 mg/d) during 12 weeks. Overall, 89% of patients with genotype 1 reached RVS12: subtype 1a, 92% (207/225); subtype 1b, 82% (54/66). The RVS12s was lower in cirrhotic patients (80%) than in noncirrhotic patients (92%).

In a multinational observational study (HCV-TARGET) [58], two thousand and sixty-three patients were analyzed treated with guidelines based on SOF, in combination with PR or with SMV±RBV (in patients with genotype 1) or in combination with RBV (in patients with genotypes 2 or 3); 48% were cirrhotic, 52% pretreated, and 18% with failure prior to triple treatment with PR + IP. Overall, 5.7% of patients had serious side effects (12 patients died and 9 of them were cirrhotic).

In this study, 85% (140/164) of patients with genotype 1 (45% pretreated; 27% pretreated with PR + IP) treated for 12 weeks with SOF + PR obtained an RVS4. SVR4 was higher in noncirrhotic patients (90%) than in cirrhotic patients (70%).

In the observational study TRIO [59] (n = 295, with genotype 1), the SVR 12 s global in patients without previous treatment (analysis by an intention of treatment) was 77%, without differences between cirrhotic patients (81%; 112/138) or not (81%, 25/31). In patients with previous failure (RN: 36%), RVS12 was 72% (90/125): 76% in noncirrhotic patients (n = 39) and 62% in cirrhotic patients (n = 85). Based on the previous regimen, RVS12 was 73% in patients with failure prior to IP + PR (n = 40) and 67% in patients with failure prior to PR (n = 36). Two percent of the patients abandoned the treatment because of side effects.

3.2.3 Simeprevir (SMV) + PR

In the QUEST-1 [60] clinical trials and QUEST-2 [61], the efficacy and safety of SMV (150 mg/d) + PR versus placebo + PR for 24 or 48 weeks (according to criteria of TGR) in patients monoinfected by HCV genotype 1 without previous treatment, the RVS24s overall was 80–81% for SMV + PR and 50% for PBO + P/R. SVR in patients infected with HCV subtype 1a with and without the Q80K polymorphism in the protease was 58% and 84%, respectively. The SVR obtained by patients with subtype 1b was 85% (228/267) globally and 90% (172/192) in the subgroup of European patients included in both studies. Depending on the degree of basal fibrosis, they reached SVR 84% (317/378) of the patients with fibrosis F0-F2, 73% (60/82) with F3, and 60% of the patients with cirrhosis.

A remarkable aspect is the predictive value of the response obtained with this guideline in week 4 of treatment. Of the 521 patients who started treatment with SMV in the QUEST studies, 78% (404/521) showed an RVR, and of them, 90% (362/404) reached RVS12.

In the study TMC435-C212 [62], 106 patients coinfected with HIV/HCV were analyzed treated with SMV/PR, with overall RVS12s of 74%; without previous treatment (n = 53): 79%; previous relapse (n = 15): 87%; RP (n = 10): 70%; RN (n = 28): 57%. Eighty-nine percent of patients without previous treatment or with recurrence, he obtained an RVR and of this 89%, he reached RVS12s. Treatment with SMV + PR was generally well tolerated, with a tolerability profile and safety similar to those shown in monoinfected patients.

In the PROMISE [63] study, patients monoinfected by HCV with recurrence were randomized previously after P/R, to treatment with SMV (n = 260) versus placebo (n = 133) during 12 weeks, with P/R (24–48 weeks). The RVS12s was 86% (128/149) in patients with subtype 1b and 70% (78/111) in those with subtype 1a (78% and 47% in patients without and with the Q80K polymorphism, respectively). Ninety-three percent obtained an RVRe and shortened the total duration of treatment at 24 weeks.

In the ATTAIN study [64], the noninferiority of SMV versus TVR was demonstrated, in combination with PR, in infected or monoinfected patients with partial or no response to RP. Based on the previous response, the SVR obtained was: patients with previous RP, 70% (163/234) with SMV versus 68.5% (163/238) with TVR; patients with previous RN, 44% (63/145) with SMV versus 47% (67/146) with TVR10. The risk of anemia was 3 times smaller in those treated with SMV, being also of a milder character than that that occurred in the TVR group.

3.3 Treatment for genotypes 2 and 3 of hepatitis C

3.3.1 PEGIFN + RBV

In patients coinfected with HIV/HCV genotypes 2/3, the probability of reaching an SVR with pegIFN-alpha-2a (180 μg/week) or alpha-2b (1.5 μg g/kg/week) and adjusted RBV weight (800–1200 mg/d) for 48 weeks is 62–71% [65, 66].

Patients without cirrhosis who achieve an RVR can be treated for 24 weeks without reduction of response rates [67, 68]. In patients with genotype 2 or 3, without previous treatment, due to the lower efficacy and toxicity associated with prolonged administration, treatment with PR should be considered for exceptional use, when the guidelines considered are not available preferred or alternative:

PR × 48 s (BI). In patients with RVR, PR × 24 s, in the absence of cirrhosis (BII).

3.3.2 SOF + RBV

In four clinical studies, phase III, with monoinfected patients with genotype 2, treated with SOF/RBV for 12 weeks, the SVR ranged between 86 and 97% [57, 60, 69]. Also, in the PHOTON 1 [70] studio in patients without prior treatment coinfected with genotype 2, the treatment with SOF/RBV for 12 weeks showed an RVS12 of 88% (23/26); in patients pretreated, the SVR after 24 weeks of treatment was 92%.

Although the data are inconclusive, pretreated cirrhotic patients could benefit from a treatment of more than 12 weeks. In the FUSION study, in patients, the SVR was pretreated 60% (6/10) in cirrhotic patients treated for 12 weeks and 78% (7/9) in those treated for 16 weeks [60].

3.3.3 SOF + DCV

In study AI444-040 89% (16/18) of the monoinfected with genotype 3, without treatment previous, non-cirrhotic, treated with SOF (400 mg/d) + DCV (60 mg/d) ± RBV during 24 weeks, he obtained an SVR, with no apparent impact of the inclusion or not of RBV in the effectiveness [70].

In the ALLY 3 study, 152 patients infected with HCV genotype 3 were treated with SOF 400 mg/d + DCV 60 mg/d for 12 weeks. Overall, they obtained an RVS12 on 90% (91/101) of patients without previous treatment: cirrhotic: 58% (11/19);

without cirrhosis: 97% (73/75). Eighty-six percent (44/51) of the pretreated reached RVS12: cirrhotic, 69% (9/13); noncirrhotic, 94% (32/34) [71].

3.4 Treatment for genotype 4 of hepatitis C

3.4.1 PEGIFN ALFA + RBV

Overall, the probability of SVR of patients coinfected with genotype 4 to standard treatment with PR is less than 30% (**Table 1**) 1–5, although it is higher in patients with IL28B CC [32].

3.4.2 SOF + PR

We do not have information with the new direct antivirals in patients coinfected. In patients monoinfected with HCV, the analysis of patients with genotype 4 included in the Neutrino7 study showed an RVS12 of 96% (27/28) after 12 weeks of treatment with SOF + PR (1000–1200 mg/d).

3.4.3 SOF + RBV

In another study [72] in patients of Egyptian descent, the efficacy of SOF 400 mg/day + RBV (1000–1200 mg/day) for 24 weeks was greater than the 12-week schedule, in patients without previous treatment, 100% (14/14) versus 79% (11/14), as in pretreated, 93% (14/15) versus 59% (10/17).

In the Photon 2 [73] study, 84% (26/31) of patients coinfected with genotype 4, without pretreatment, treated with SOF + RBV for 24 weeks obtained an SVR: noncirrhotic 83% (19/23); cirrhotic 88% (7/8).

3.4.4 Interactions between medications

Boceprevir is a potent CYP3A4/5 cytochrome inhibitor. Exposure to medicinal products metabolized by CYP3A4/5 may increase when administered with BOC, which could increase or prolong its therapeutic effects and adverse reactions. BOC is partially metabolized by CYP3A4/5. The joint administration of BOC with drugs that induce or inhibit activity of CYP3A4/5 could increase or decrease exposure to Boceprevir [74]. Boceprevir is contraindicated when co-administered with drugs whose elimination is highly dependent on CYP3A4/5 and in which the elevation of plasma concentrations is associated with serious adverse events or they pose a vital risk. This is the case of midazolam, triazolam, bepridil, pimozide, lumefantrine, halofantrine, lovastatin, quetiapine, alfuzosin, silodosin, and derivatives ergotamines [74].

Telaprevir is partially metabolized by CYP3A and is a substrate of the glycoprotein-P (gp-P). Co-administration of Telaprevir with CYP3A-inducing drugs and/or gp-P can reduce plasma concentrations of TVR. On the contrary, its co-administration with CYP3A inhibitor drugs and/or gp-P may increase plasma concentrations of Telaprevir. On the other hand, Telaprevir is an inhibitor potent of CYP3A4 and gp-P. This inhibition is time dependent and can be intensified during the first 2 weeks of treatment. At the end of the treatment, it may be necessary that approximately 1 week elapses for the inhibitory effect of Telaprevir to disappear. Telaprevir administration can increase the systemic exposure to drugs that are substrates of CYP3A or of gp-P, which may lead to an increase or prolongation of its effects and risk of adverse reactions [75].

Simeprevir is metabolized by CYP3A4. Therefore, the co-administration of Simeprevir with inhibitors of CYP3A4 can increase their plasma concentrations,

and in contrast, co-administration of Simeprevir with CYP3A-inducing drugs can reduce plasma concentrations of Simeprevir [76]. Its use is not recommended combined with other nonanalog reverse transcriptase inhibitor nucleosides [76, 77]. The use of SMV with HIV protease inhibitors enhanced or not with ritonavir [77].

Sofosbuvir is a substrate of the gp-P. Therefore, drugs or products that are powerful inducers of gp-P (rifampicin, S Juan's herb, carbamazepine, and phenytoin) can reduce plasma concentrations of SOF and reduce its therapeutic effect. The interactions of Sofosbuvir with antiretroviral drugs have been investigated in a phase 1 clinical trial conducted in healthy volunteers [78]. Sofosbuvir modified the pharmacokinetics of antiretrovirals evaluated within the limits of the prespecified equivalency interval [79].

The interaction between Sofosbuvir and recent integrase inhibitors has not been evaluated; however, the existence of interactions has not foreseen significant differences between Sofosbuvir and these drugs [78].

Daclatasvir is a substrate of CYP3A4 and gp-P. Inducers of CYP3A4 and of gp-P can reduce plasma levels and the therapeutic effect of DCV. The co-administration with potent inducers of CYP3A4 and gp-P is contraindicated, while it is recommended to adjust your dose when used with moderate inductors. Inhibitors of CYP3A4 can increase plasma levels of DCV, so it is recommended to adjust their dose [80]. Daclatasvir has a scarce influence on cytochrome CYP3A4, so that its administration does not affect relevant to the metabolism of antiretroviral drugs and, therefore, adjustment of these is not required.

The administration of efavirenz induces the metabolism of daclatasvir reducing your AUC by approximately 50%. Therefore, it is necessary to increase the dose of daclatasvir at 90 mg/day in case of concomitant use with efavirenz. On the contrary, atazanavir/ritonavir increases the daclatasvir by 2.1 times and, consequently, it is required to reduce the dose of daclatasvir at 30 mg. Daclatasvir/ritonavir increases to a lesser extent the AUC of daclatasvir, by 40%, so it would not require dose adjustment of daclatasvir [81]. The dosage of daclatasvir is the same for ATV/r or DRV/r that for atazanavir or darunavir powered with cobicistat (COBI); that is, the doses of daclatasvir are 30 mg/day co-administered with atazanavir/cobicistat and 60 mg/day with daclatasvir/cobicistat [81]. No relevant interactions between tenofovir disoproxil fumarate and daclatasvir have been observed [80].

4. Summary of hepatitis C treatment according to the genotype

In **Table 3**, you can see the summary of hepatitis C treatment according to the genotype.

5. Conclusions

The influence of HIV in the HCV infection. Increase in load HIV-driven viral hepatitis exacerbates hepatic lesions and influences transmission of the HCV. The risk of sexual transmission increases when HIV is present in the carrier. This situation is more evident in the case of homosexual men with multiple sexual contacts without using a preservative [39, 40].

In the case of mother-to-child transmission, the risk of transmission to the fetus in coinfected women for HIV is between 2 and 5 times higher than in mothers monoinfected by HCV and it is between 5 and 25% [41].

Coinfection modifies the evolution of fibrosis in patients with HIV, with higher speed in those who have low CD4 counts, so that the onset of cirrhosis occurs

Genotype hepatitis C virus	Treatment	Indications	Contraindications	Doses
Genotype 1 (1a or 1b) and 4, 5 or 6	Ledipasvir + sofosbuvir	Patient with chronic hepatitis C genotype 1 (1a and 1b), 4, 5, or 6, with the following characteristics: • No cirrhosis or compensated cirrhosis (child A) or decompensated (child B and C) and • Without prior treatment or with previous treatment with peg-IFN and RBV or with previous treatment with inhibitors of first-generation proteases (Telaprevir or Boceprevir) • Patient with HIV coinfection and the same characteristics considered, taking into account the drug interactions and dose adjustments according to the antiretroviral	• Patient with genotype 2 or 3 • Patient with chronic renal failure with creatinine clearance <30 ml/min	90 mg LDV + 400 mg SOF
Genotype 1 (1a or 1b) and 2 or 3	Daclatasvir + sofosbuvir	• Patient with chronic hepatitis C genotype 1 (1a and 1b), 2, and 3, with the following characteristics: • No cirrhosis or compensated cirrhosis (child A) or decompensated (child B and C) and without prior treatment or with previous treatment with peg-IFN and RBV or with previous treatment with inhibitors of first-generation proteases (Telaprevir or Boceprevir) • Patient with HIV coinfection and the same mentioned characteristics, taking into account the drug interactions and dose adjustments according to the antiretroviral	Patient with chronic renal failure with creatinine clearance <30 ml/min	60 mg DCV + 400 mg SOF

Genotype hepatitis C virus	Treatment	Indications	Contraindications	Doses
Genotype 1 (1a or 1b)	Panitaprivir+ ombitasvir + ritonavir + dasabuvir	Patient with chronic hepatitis C genotype 1 (1a or 1b) with the following characteristics: • No cirrhosis or compensated cirrhosis (child A) and • Without prior treatment or with previous treatment with peg-IFN and RBV • Patient with HIV coinfection and the same mentioned characteristics, taking into account the drug interactions and dose adjustments according to the antiretroviral. Patient with the same characteristics mentioned, and with advanced chronic renal failure (clearance of creatinine <30 mL/min-80 mL/min) or in therapy renal replacement	• Patient with genotype 2, 3, 5, or 6 Patient with decompensated cirrhosis (child B or C)	150 mg PTV + 25 mg OBV + 100 mg r + 500 mg dasabuvir
Genotype 1b	Daclatasvir + asunaprevir	• Patients with chronic hepatitis C genotype 1b with the following characteristics: • No cirrhosis or compensated cirrhosis (child A) and without prior treatment or with previous treatment with peg-IFN and RBV	• Patient with genotype 1a, 2, 3, 4, 5, or 6 • Patient with polymorphism of the N5SA • Patients previously treated with inhibitors of first-generation proteases (Telaprevir or Boceprevir)	60 mg DVC + 100 mg asunaprevir

Genotype hepatitis C virus	Treatment	Indications	Contraindications	Doses
Genotype 1	Simeprevir + Ribavarina	Patient with chronic hepatitis C genotype 1, with following characteristics: • No cirrhosis or compensated cirrhosis (child A) and • Without previous treatment or with previous treatment with peg-IFN and RBV	Patient with chronic renal failure with creatinine clearance <30 ml/min. Patient with all the following characteristics: • Genotype 1a • Cirrhosis • - Q80K polymorphism	150 mg SMV + 400 mg SOF
Genotype 2	Sofosbuvir + Ribavarina	Patient with chronic hepatitis C genotype 2, with the following characteristics: • No cirrhosis or compensated cirrhosis (child A) and • Without prior treatment or with previous treatment with peg-IFN and RBV	• Patient with chronic renal failure with creatinine clearance <30 ml/min • Patient with anemia • Caution should be exercised with the use of RBV in patients of childbearing age, because if it is teratogenic, you must wait at least 6 months after its use to consider pregnancy	400 mg SOF + 1000 mg RBV (if the patient's weight is less than 75 kg) or 1200 mg of RBV (If the weight of the patient is greater than or equal to 75 kg)
Genotype 3	Sofosbuvir + Ribavarina + Peg-IFN	Patient with chronic hepatitis C genotype 3, with the following characteristics: • No cirrhosis or compensated cirrhosis (child A) and • Without prior treatment or with previous treatment with peg-IFN and RBV or with previous treatment with SOF + RBV	• Patient with chronic renal failure with creatinine clearance <30 ml/min • Patient with previous intolerance or effects secondary to pegylated interferon • Patient with anemia. Caution should be exercised with the use of RBV in patients of childbearing age, because if it is teratogenic, you must wait at least 6 months after its use to consider pregnancy	401 mg SOF + 1000 mg RBV + 180 mcg peg-IFN (if the patient's weight is less than 75 kg) or 1200 mg of RBV (If the weight of the patient is greater than or equal to 75 kg)

Genotype hepatitis C virus	Treatment	Indications	Contraindications	Doses
Genotype 4	Sofosbuvir + Ribavarina	Patient with chronic hepatitis C genotype 4, with the following characteristics: • No cirrhosis or compensated cirrhosis (child A) and • Without prior treatment or with previous treatment with peg-IFN and RBV	• Patient with chronic renal failure with creatinine clearance <30 ml/min • Patient with anemia • Caution should be exercised with the use of RBV in patients of childbearing age, because if it is teratogenic, you must wait at least 6 months after its use to consider pregnancy	400 mg SOF + 1000 mg RBV (if the patient's weight is less than 75 kg) or 1200 mg of RBV (If the weight of the patient is greater than or equal to 75 kg)

Table 3.
Treatment of hepatitis C according to genotype.

before, and the risk of liver decompensation is also more frequent. The consequence of this situation is an increase in liver-related morbidity and mortality [42, 43].

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Conflict of interest

The authors express no conflicts of interest.

Acronyms and abbreviations

BCV	boceprevir
BEC	beclabuvir
DCV	daclatasvir
FVD	faldaprevir
IFN	interferon
Peg-IFN/RBV	peginterferon or pegylated IFN + ribavirina
LDV	ledipasvir
OBV	ombitasvir
Peg-IFN	peginterferon
PTV	paritaprevir
r	ritonavir
RBV	ribavirina
SMV	simeprevir
SOF	sofosbuvir
TDF	tenofovir
TLV	telaprevir

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