Recent Advances in the Treatment of HIV/HBV and HIV/HCV Co-Infection

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Abstract: Concurrent infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) in patients positive for human immunodeficiency virus (HIV) is relatively common. The treatment of co-infected individuals is rather complex because the anti-viral therapy may be associated with drug-resistance, hepatotoxicity and lack of response. Herein, we present a summary of the available compounds and the recent recommendations concerning the therapeutic management of HIV/HBV and HIV/HCV co-infections.

Keywords: HIV, HBV, HCV, co-infection, treatment, drugs.

INTRODUCTION

Persistent infection with hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) is associated globally with significant morbidity and mortality [1, 2]. Because these viral pathogens share similar routes of transmission, the concomitant presence of HBV and/or HCV in patients infected with HIV is unfortunately a relatively common scenario. Co-infections have many adverse health effects and comprise currently an important clinical challenge [1, 3].

HBV is transmitted by percutaneous or mucous membrane exposure to infectious body fluids, by sexual contact with an infected person, and perinatally from an infected mother to her infant [4]. The endemicity of HBV infection is affected by the age at which most infections occur. In many parts around the globe (sub-Saharan Africa and Southeast Asia), HBV is transmitted early in life and, consequently, a significant fraction of the population is chronically infected with HBV (>8%). On the other hand, the problem is relatively limited in the developed world (<1%) in which the majority of infections occur during adulthood [4]. However, in the setting of HIV disease in western countries, the prevalence of chronic HBV infection is substantially larger and approximates 6–14% overall. This figure varies markedly by risk group ranging from 4–6% in heterosexuals to 9–17% among men who have sex with men (MSM) [4].

Percutaneous exposure to blood is the leading route of HCV transmission [4]. Prior to the systematic blood screening for HCV, most cases of HCV infection were attributed to the transfusion of contaminated blood units. Nowadays, post-transfusion infections have been virtually eliminated and HCV is mainly observed in persons with past history of injecting illegal substances. Worldwide, the prevalence of HCV infection is around 2% [2, 4]. In the field of HIV/HCV co-infection, however, 20–30% of HIV seropositive individuals are concurrently infected with HCV [4]. Among the sub-population of intravenous drug users, the prevalence of HCV infection is even larger (>60%) [4, 5].

In the case of co-infections, the research focuses on the combined pathogenesis of the co-existing viruses. Substantial lines of evidence have accumulated so far, which support the negative effect of HIV on the progression of hepatitis B [6]. Although controversial results had been reported concerning the characteristics of the opposite virological interaction, in other words the impact of HBV infection on the natural history of HIV disease [7, 8], a recent meta-analysis revealed the increased all-cause mortality of HIV/HBV co-infected patients compared with HIV mono-infected individuals [1]. With respect to HIV/HCV co-infection, previous research has demonstrated the more rapid progression of liver disease and the poorer overall prognosis of HCV patients in the context of HIV disease. On the other hand, the effect of HCV on the course of HIV disease still remains unclear [7, 9-11].

The introduction of highly active antiretroviral therapy (HAART) has reduced considerably the incidence of acquired immune deficiency syndrome (AIDS) and mortality in HIV-infected individuals. However, with the increased longetivity, other co-morbidities including liver-associated disease have emerged as a major cause of death among HIV-infected persons. Consequently, the proper management of chronic viral hepatitis in these patients is of great importance.

The aims of this review include the presentation of the recent recommendations concerning the therapeutic management of HIV/HBV and HIV/HCV co-infections and

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the description of the arsenal of currently available drugs from a more chemical and molecular perspective.

TREATMENT OF HBV INFECTION IN PATIENTS WITH CONCURRENT HIV INFECTION

As mentioned previously, concurrent HBV infection is an important cause of mortality among HIV patients in the HAART era [1, 12]. At the same time, HIV interferes with all phases of the natural history of hepatitis B leading to higher levels of serum HBV deoxyribonucleic acid (DNA), prolonged period of HBV infectivity, increased incidence of cirrhosis, and a higher risk of hepatocellular carcinoma [13-18]. Quite fortunately, the number of anti-HBV drugs has increased in the last years and many agents with dual activity against HBV and HIV are currently available. However, the therapeutic management of co-infection is far from simple and demands the proper attention of the clinician [17]. According to the recent guidelines, the antiretroviral therapy should be initiated in HIV patients with HBV co-infection, regardless of the number of cluster of differentiation (CD) 4 T-cells, when treatment of hepatitis B is indicated [18]. The decision to treat HBV depends on many factors including the severity of liver disease, the likelihood of therapeutic response, the potential of adverse events and the careful evaluation of determinants of liver disease [19]. Generally, if serum HBV DNA levels exceed 2,000 international units (IU)/mL and the aminotransferases are elevated, anti-HBV therapy should be advised [19]. Since the optimal goal of anti-HBV treatment to achieve HBV-surface antigen (HBsAg) clearance occurs infrequently, a more realistic therapeutic target includes the prolonged suppression of HBV replication, the HBV early antigen (HBeAg) seroconversion, the alanine aminotransferase (ALT) normalization, improvements in liver histology, and the prevention of complications of chronic HBV infection such as cirrhosis and hepatocellular carcinoma [19-21].

DRUGS USED FOR THE TREATMENT OF HBV INFECTION IN PATIENTS WITH HIV/HBV CO-INFECTION

In total, seven therapeutic agents are used for the treatment of HBV infection: interferon (IFN)-a, pegylated-interferon (peg-IFN), lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Emtricitabine has anti-HBV activity and is used only in the setting of co-infection (Table **1**) [19, 22].

Interferon alfa-2b was the first drug approved for chronic hepatitis B [23]. The family of interferons-alfa consists of naturally occurring small molecules produced and secreted to circulation in response to viruses. IFNs-a exhibit pleiotropic and profound effects including the inhibition of viral replication, the restriction of cell proliferation and immunomodulatory activities. Rather interestingly, IFNs-a mount the first line of defence against viral infections exploiting a pathway, which involves the Janus family of tyrosine kinase enzymes and the protein group of signal transducers and activators of transcription (JAK/STAT). Ultimately, the signalling process induces IFN-stimulated genes (ISGs) creating a non-virus specific antiviral state within the human cell [24]. Upon binding of circulating IFN-a to the extracellular domains of specific membrane receptors on the cell surface [IFN-a receptor complex (IFNAR) composed of two subunits, IFNAR1 and IFNAR2], the receptor-associated Janus-activated kinase 1 and tyrosine kinase (Tyk) 2 are activated and, in turn, phosphorylate STAT1 on tyrosine 701 and STAT2 on tyrosine 690, respectively. The activated STATs interact strongly with each other by recognizing Src homology (SH) 2 domains and associate with IFN-regulatory factor (IRF) 9 forming a heterotrimer called IFN-stimulated gene factor (ISGF) 3. In the nucleus, the ISGF3 interacts with cellular DNA upregulating the expression of ISGs [24] and, as a result, a wide variety of gene products with antiviral properties are synthesized. Interferon alfa-2a ($C_{860}H_{1353}N_{227}O_{255}S_9$) and -2b ($C_{860}H_{1353}N_{229}O_{255}S_9$) are biosynthetic forms of interferon alfa and consist of 165 amino acids. Interferons alfa-2a and -2b differ at amino acid position 23; alfa-2a has a lysine in this position, whereas -2b has an arginine at the same location [25]. Their molecular weight is approximately 19 kilodaltons (kDa). Exogenously provided interferon alpha interacts with cellular receptors causing the same response cascades observed in endogenous synthesis. The greater effectiveness of exogenous intereferon is attributed to the higher concentrations achieved.

Interferon alfa-2b is administrated to adult HBV patients by the subcutaneous injection of 5 million IU daily or 10 million IU, three times a week. The interferon treatment is particularly effective against HBeAg+ chronic hepatitis B [19, 23]. The results of studies concerning treatment with standard IFN in HIV/HBV infection are conflicting. Some evidence suggests a similar response regardless of HIV co-infection [26], whereas a poorer response to IFN-alfa therapy and more frequent HBV reactivation in HIV co-infected patients was documented by others [19, 27]. Frequent side effects of standard IFN such as flu-like symptoms, psychiatric complications, and bone marrow toxicity have considerably limited the use of this drug [19]. Moreover, and although the etiology remains unknown, flares of hepatic enzymes during IFN treatment are more commonly observed in co-infected patients than in individuals without HIV infection [19].

Pegylated interferon has become the standard therapy for patients with HBV infection. Pegylated interferon alfa-2a is a covalent conjugate of recombinant interferon alfa-2a with a large, branched 40 kDa bis-monomethoxy polyethylene glycol (PEG) linked to the lysine residues of interferon alfa-2a through stable amino bonds resistant to hydrolysis. Therefore, the pegylated IFN alpha-2a circulates as an intact molecule [25, 28]. On the other hand, pegylated interferon alfa-2b has a small, linear 12 kDa PEG moiety covalently attached primarily to histidine (His) 34 of recombinantly produced IFN alpha-2b. The chemical attachment is achieved via unstable urethane bonds susceptible to hydrolysis once the drug is injected releasing thus native interferon. Additional pegylation sites involve lysine and cysteine residues [28]. The site and size of pegylation influence the pharmacokinetic and pharmacodynamic parameters of the pegylated biomolecules. Consequently, pegylated interferon alpha-2a has a very restricted volume of distribution, longer half-life and reduced

Table 1. Drugs Currently Used for the Treatment of HBV Infection in Patients with Concurrent HIV Infection

Generic name	Class	Chemical formula	Molecular Weight	Dose	Adverse reactions
Interferon alfa-2b (IFN)	Protein	$C_{860}H_{1353}N_{229}O_{255}S_9$	19,271 daltons	30-35 million IU/week	Flu like syndrome, psychiatric conditions, bone marrow toxicity
Pegylated Interferon (Peg-IFN) alfa-2a	Protein	Conjugate of IFN alfa-2a ($C_{860}H_{1353}N_{227}O_{255}S_9$) with bis-monomethoxy polyethylene glycol	~60,000 daltons	180mcg once weekly	Psychiatric reactions, bone marrow suppression, fatigue, headache
Lamivudine (3TC)*	Nucleoside analogue	$C_8H_{11}N_3O_3S$	229.26	300mg/day	Exacerbation of hepatitis after discontinuation, pancreatitis, fatigue, headache, nausea, diarrhea, anemia
Adefovir dipivoxil (ADV)**	Nucleotide analogue	$C_{20}H_{32}N_5O_8P$	501.47	10mg/day	Exacerbation of hepatitis after discontinuation, nephrotoxicity, asthenia, headache, nausea, diarrhea
Entecavir (ETV)***	Nucleoside analogue	$C_{12}H_{15}N_5O_3 \times H_2O$	295.29	0.5mg/day†	Exacerbation of hepatitis after discontinuation, headache, nausea, dizziness, tiredness
Telbivudine (LdT)	Nucleoside analogue	$C_{10}H_{14}N_2O_5$	242.23	600mg/day	Exacerbation of hepatitis after discontinuation, myopathy, fatigue, headache, diarrhea, nausea
Tenofovir disoproxil fumarate (TDF) *	Nucleotide analogue	$C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$	635.52	300mg/day	Renal insufficiency, decrease in bone mineral density, exacerbation of hepatitis after discontinuation, asthenia, headache, diarrhea, nausea, vomiting
Emtricitabine (FTC) *	Nucleoside analogue	$C_8H_{10}FN_3O_3S$	247.24	200mg/day	Exacerbation of hepatitis after discontinuation, headache, diarrhea, fatigue, insomnia, abnormal dreams, cough, hyperpigmentation

HBV, hepatitis B virus; HIV, human immunodeficiency virus; IU, international unit; mcg, microgram; mg, milligram; *Active also against HIV; **May also be active against HIV at substantially high doses, which cause nephrotoxicity; ***Weak activity against HIV; †The dose increases to 1mg/day in patients with lamivudine refractory or known lamivudine or telbivudine resistance mutations.

clearance compared with native interferon alpha-2a, and can be given once weekly independently of bodyweight. Pegylated interferon alpha-2b has a shorter half-life in serum than pegylated interferon alpha-2a and requires bodyweight-based dosing [28]. Generally, the PEG conjugated therapeutics are associated with substantially extended half-lives, stable serum concentrations, and improved potency compared with conventional IFN [19]. Peg-IFN alpha-2a has demonstrated its efficacy in HBeAg+ individuals resulting in HBeAg loss and normalization of liver enzymes in almost one-third of patients [19, 29, 30]. In HIV/HBV co-infected patients, IFN-based therapies are less effective and may be used only in compensated cirrhotic patients who do not need antiretroviral therapy and have favourable indicators of IFN response [19]. Combined treatments with nucles(t)ide analogues such as adefovir and lamivudine have not yielded greater rates of sustained response compared with peg-IFN alpha monotherapy [19, 31-33].

Lamivudine (3TC) [2(1H)-Pyrimidinone,4-amino-1-((2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-] is an effective compound with dual activity against both HIV and HBV but at different therapeutic doses [HBV, 100milligram (mg) daily, HIV, 300mg daily] [19, 34]. The molecular formula of lamivudine is $C_8H_{11}N_3O_3S$ and the molecular weight is 229.26 [34]. Lamivudine resembles chemically zalcitabine (2',3'-dideoxycytidine). However, in 3TC, the 3'-carbon of the ribose ring is replaced with sulfur, forming an oxathiolane ring [34]. 3TC is structurally similar to the naturally occurring deoxycytidine triphosphate and competes with the latter molecule for incorporation in the elongating DNA chain. Lamivudine converts in the pharmacologically active 5'-triphosphate metabolite by intracellular phosphrylation. After the removal of the diphospate group and the insertion in the newly synthesized DNA strand, lamivudine interrupts the addition of further nucleotides

because it lacks a free 3'-hydroxyl group on the oxathiolane ring that is needed for 5' to 3' phosphodiester linkages [34].

In HBV mono-infected patients, the administration of 3TC is associated with markedly reduced serum HBV DNA levels, an approximately 20% HBeAg seroconversion rate after one-year therapy and substantial histological improvements in many patients [35-37]. In HIV/HBV co-infected individuals, 3TC is given at a dose of 300mg per day and in combination with at least two other anti-HIV drugs [19]. Despite its effectiveness and the satisfactory safety profile, extended 3TC therapy for HBV is limited by the high frequency of resistance [35, 38], which is usually associated with a rebound in HBV viral load and often with an exacerbation of hepatitis. The most common mutation involves the replacement of the methionine residue of the tyrosine-methionine-aspartate-aspartate (YMDD) locus of the HBV DNA polymerase by valin or isoleucine**.** The oral administration of 3TC, its good tolerability and the once-daily dose has facilitated the administration of lamivudine as an anti-HBV agent in HIV seropositive patients resulting, however, in the development of 3TC-resistant mutations in almost 90% of co-infected patients after prolonged therapy [19, 39, 40].

Adefovir dipivoxil (Propanoic acid, 2,2-dimethyl-, ([(2-[6-amino-9H-purin-9-yl]ethoxy) methyl]phosphinylidene) bis(oxymethylene) ester) is the diester prodrug of adefovir. The molecular formula of Adefovir dipivoxil (ADV) is $C_{20}H_{32}N_5O_8P$ and the molecular weight is 501.47 [41]. After oral administration, adefovir dipivoxil is rapidly converted by esterases to the active moiety adefovir. Even though it was initially used for HIV, achieving activity at relatively high doses (60mg or 120mg), the development of adefovir as an anti-HIV agent was discontinued due to the associated increased risk of nephrotoxicity [19, 41]. However, adefovir proved safe and effective against HBV at the lower dose of 10mg per day. After intracellular phosphorylation to the active form, adefovir diphosphate, the drug competes with the natural substrate, deoxyadenosine triphosphate, and prevents HBV reverse transcriptase from completing the DNA synthesis [41]. Despite being less potent than lamivudine, adefovir has a higher genetic barrier to resistance and is indicated as treatment for lamivudine-resistant chronic hepatitis B [35, 42-44]**.** Resistance to adefovir evolves slowly but it increases progressively exceeding 20% at 2 years of therapy [35, 45]. Adevovir perfoms well in the field of co-infection but the therapeutic improvement has been observed in fewer patients compared with HBV mono-infection [19, 46, 47].

Entecavir (**ETV**) [6H-Purin-6-one, 2-amino-1, 9-dihydro-9-[(1S,3R,4S)-4-hydroxy-3- (hydroxymethyl)-2-methylenecyclopentyl]-monohydrate] is a guanosine analogue with potent, selective activity against HBV [48]. The molecular formula of ETV is $C_{12}H_{15}N_5O_3$ x H_2O and the molecular weight is 295.29. Entecavir is efficiently phosphorylated to the active triphosphate form which, by competing with the natural substrate deoxyguanosine triphosphate, functionally blocks the replication process of HBV at three different phases: Base priming, reverse transcription of the negative strand from the pregenomic messenger ribonucleic acid (RNA) and positive strand HBV DNA synthesis [19, 48]. Entecavir has been found superior to lamivudine in terms of virological, histological and biochemical improvements, while, at the same time, it has a similar safety profile [19, 35, 49]. ETV is effective against wild-type and 3TC- and ADV- resistant HBV mutants [19]. Prolonged ETV therapy resulted in continued clinical benefits in patients with chronic hepatitis B [50]. The incidence of resistance to ETV in treatment-naive patients is low over the course of ETV therapy and remains <1% for up to 4 years [35]. However, in pre-existing 3TC resistance mutations, entecavir resistance occurred at higher rates reaching 43% at the end of fourth year [35, 51]. For this reason, ETV doses of 0.5mg/day are recommended in lamivudine-naïve patients, but 1 mg/day is advised for lamivudine-experienced individuals [19]. Although the drug was not initially considered to inhibit replication of HIV at clinically relevant concentrations, findings from later studies indicated that ETV shows minimal antiretroviral activity and selects for HIV strains bearing the M184V mutation (amino acid exchange of methionine with valine at position 184 of the viral reverse transcriptase) in persons with HIV and HBV co-infection [52-54]. Thus, ETV is not recommended for co-infected patients not receiving HAART, because the risk of developing resistant HIV mutants cannot be excluded [19, 48].

Telbivudine (LdT) [2'-Deoxy-L-thymidine, or 1-((2S,4R,5S)-4-hydroxy-5-hydroxymethyltetrahydrofuran-2y1)-5-methyl-1H-pyrimidine-2,4-dione, or 1-(2-deoxy-β-L-ribofuranosyl)-5methyluracil] belongs to beta-L-nucleosides that are potent, specific and selective inhibitors of HBV replication *in vitro* [55, 56]. It has a molecular formula of $C_{10}H_{14}N_2O_5$ and a molecular weight of 242.23 [55]. Telbivudine is efficiently converted intracellularly into active phosphate metabolites, which block the viral replication by competing with and replacing the natural substrate, thymidine 5'-triphosphate, causing premature DNA chain termination [55, 56]. LdT inhibits the synthesis of both HBV first and second strands [55]. LdT has exhibited greater responses than lamivudine or adefovir and was less likely to cause resistance [57-59]. There is evidence, however, for cross-resistance between telbivudine and lamivudine. Therefore, LdT is not recommended following lamivudine failure and vice versa [19]. The primary signature change responsible for LdT failure, which causes cross-resistance to lamivudine, is the amino acid exchange of methionine with valine or isoleucine at position 204 [19].

Tenofovir disoproxil fumarate (TDF) [Bis(hydroxymethyl) [[(R)-2(6-Amino-9H-purin-9-yl)-1-methylethoxy] methyl]phosphonate,bis(isopropyl carbonate) (ester), fumarate (1:1)] is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of the active agent tenofovir [60]. The molecular formula of TDF is $C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ and the corresponding molecular weight is 635.52. After oral administration, TDF is metabolized by ester hydrolysis to tenofovir, which subsequently is phosphorylized to the pharmacologically active ingredient, tenofovir diphosphate. The latter inhibits the viral process of reverse transcription by competing with the naturally occuring deoxyadenosine 5'-triphosphate, causing early DNA chain termination [60]. Tenofovir is a

weak blocker of mammalian and mitochondrial polymerases. Initially, this agent was approved in combination with other antiretroviral drugs for the treatment of HIV infection but since 2008, TDF is also indicated for the therapeutic management of chronic hepatitis B in adults [35]. Apart from its long-term safety, TDF has clearly exhibited anti-HBV virological efficacy, both in mono-infected individuals and in patients co-infected with HIV and HBV [35, 61, 62]. The potent activity of TDF against HBV has been also observed in patients who have developed lamivudine resistance [19, 62, 63]. TDF shows a very favourable resistance profile and the development of clinical or virological HBV breakthrough during TDF therapy is considered an unlikely event during the first year of treatment. However, in an HIV/HBV co-infected population with 3TC resistance mutations, the selection of a novel, additional amino-acid change (alanine to threonine at position 194), located distal to the catalytic site of the HBV polymerase, was associated *in vitro* with more than a 10-fold loss of TDF susceptibility [19, 64].

Emtricitabine (**FTC**) [(2R-cis)-4-Amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone] belongs to the drug family of nucleoside reverse transcriptase inhibitors. FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 [65]. Emtricitabine is a negative enantiomer of a thio analogue of cytidine but, in contrast to other synthetic cytidine analogues, it has a fluorine in the 5 position. Within the cells, emtricitabine undergoes phosphorylation to a 5'-triphosphate metabolite, which interferes with viral DNA synthesis by competing with deoxycytidine 5'-triphosphate for incorporation into nascent viral DNA. Emtricitabine has been approved on July 2003 for the treatment of HIV infection in combination with other antiretroviral agents (it is also marketed in a fixed-dose combination with tenofovir under the brand name Truvada and as single pill alongside tenofovir and efavirenz with the brand name Atripla) [65]. Emtricitabine results also in significant histological, virological and biochemical improvements in patients with chronic hepatitis B [19, 66]. The beneficial influence of emtricitabine on HIV/HBV coinfection has been extensively evaluated due to the frequent administration of Truvada formulation, which comprises the recommended first option for treating chronic hepatitis B in co-infected individuals [18, 19]. FTC must not be used as monotherapy for HIV/HBV infection because of the high risk for selecting emtricitabine-resistant isolates of HIV. The analysis of these strains has shown that the reduced susceptibility to emtricitabine was related with a substitution in the HIV-1 reverse transcriptase gene, which causes an amino acid exchange of methionine with valine or isoleucine at position 184 [19].

WHAT THERAPY TO START IN HIV+ PATIENTS WITH CHRONIC HEPATITIS B

Patients who were not anticipated to require an HIV regimen in the near future but were in need for HBV treatment were advised to receive agents without dual anti-viral activity, such as peg-IFN, adefovir, or telbivudine, avoiding thus the high risk of developing early HIV resistance [17, 19]. Among these three options, telbivudine was the most potent drug [17] but, as observed in all nucleoside analogues, HBV-resistant strains could appear. A one-year course of peg-IFN was also considered for HBeAg+ patients with elevated liver enzymes, low HBV DNA load and minimal liver fibrosis who could also endure the injections and the associated-side effects [17, 19]. A possible combination of these drugs is an attractive approach but its impact still needs to be evaluated. Entecavir is not recommended to individuals who do not receive concurrent HAART therapy because of its residual activity against HIV replication and the potential for selecting the M184V resistance mutation [19]. Since all the above-mentioned options have suboptimal results and given the established negative influence of HIV on liver disease, an earlier start of HAART including drugs active against both viruses is a reasonable therapeutic alternative for co-infected individuals, which is suggested in current HIV treatment guidelines [18]. The recommended management of HBV/HIV co-infected patients is presented in Tables **2** and **3**. In terms of regimens, if HIV or HBV therapy is needed, the preferred fully suppressive antiretroviral combination should include tenofovir and emtricitabine (Truvada) or tenofovir and lamivudine [18]. If HBV therapy is needed and tenofovir cannot be safely used as part of an HIV therapy, the alternative option for HBV treatment includes entecavir in addition to a fully suppressive combination of anti-HIV drugs [18]. The available data on other HBV regimens are limited in persons with HIV/HBV co-infection. Of note, discontinuation of TDF, 3TC or FTC may potentially cause severe liver damage resulting from reactivation of HBV. Therefore, interruptions in HBV therapy should be carefully monitored [18].

Table 2. Recommendations for HBV/HIV co-Infected Patients [18]

Steps
• All HIV-infected patients with chronic HBV should be advised to abstain from alcohol, assessed for immunity to HAV infection (anti-HAV antibody total) and vaccinated if non-immune, tested for evidence of HCV infection, counseled about preventing HBV transmission and evaluated for the severity of HBV infection
• Prior to initiation of antiretroviral treatment, all persons who test positive for HBsAg should be tested for HBV DNA using a quantitative assay to determine the level of HBV replication
• Regular quantitative testing for serum HBV DNA (every 6-12 months) of persons with chronic HBV infection already receiving ARV active against HBV to determine the effectiveness of therapy in suppressing HBV replication is recommended
• The medication compliance in patients with virological breakthrough should be checked
• The antiviral resistance should be confirmed with genotyping testing
• The patient's clinical course should be monitored with frequent liver function tests

HBV, hepatitis B virus; HIV, human immunodeficiency virus; HAV, hepatitis A virus; HCV, hepatitis C virus; HBsAg, HBV surface antigen; HBV DNA, HBV deoxyribonucleic acid; ARV, antiretroviral treatment.

Table 3. Recommended Regimens for HBV/HIV co-Infected Patients if HBV or HIV Therapy is Needed [18]

	Preferred Regimen	Preferred Regimen	Alternative Regimen	Other HBV Treatment Regimens
Combinations	TDF + 3TC (as the NRTI backbone of a fully suppressive ARV regimen)	TDF + FTC (as the NRTI backbone of a fully suppressive ARV regimen)	ETV + fully suppressive ARV regimen (if HBV treatment is needed and TDF cannot be safely used)	Peg-IFN alfa monotherapy or ADV in combination with 3TC or FTC or LdT in addition to a fully suppressive ARV regimen; however, data on these regimens in persons with HIV/HBV co-infection are limited

HBV, hepatitis B virus; HIV, human immunodeficiency virus; TDF, tenofovir; 3TC, lamivudine; NRTI, nucleoside reverse transcriptase inhibitor; ARV, antiretroviral treatment; FTC, emtricitabine; ETV, entecavir; Peg-IFN, pegylated interferon alpha-2a; ADV, adefovir; LdT: telbivudine.

TREATMENT OF HCV INFECTION IN PATIENTS WITH CONCURRENT HIV INFECTION

HCV is not efficiently transmitted by perinatal or sexual exposures as observed in HBV or HIV. The prevalence of HCV is high in persons who had received unscreened blood or untreated clotting factor products and in injecting drug users [4]. Recently, however, a rapidly increasing number of HCV outbreaks among MSM has been reported [67-70] indicating that HIV homosexuals who practice unsafe sex are at increased risk for sexually acquired HCV. Accumulated research evidence has demonstrated the unfavourable course of HCV infection in HIV co-infected patients. In particular, HIV contributes to the chronicity of HCV infection and the acceleration of the progression of liver fibrosis increasing, consequently, the incidence of cirrhosis, liver failure, and hepatocellular carcinoma [19, 71-77]. Moreover, HIV/HCV co-infected individuals may present poor immunological responses to antiretroviral treatment and experience higher rates of HAART-associated liver toxicity [74, 78, 79].

Host parameters including the extent of liver fibrosis, CD4 T cell counts, and patient's motivation are the most important factors that should determine who is a good candidate for HCV treatment [19]. The performance of liver biopsy for guiding treatment decisions in chronic HCV infection can be avoided because other non-invasive tools such as elastometry (Fibroscan) and serum biochemical indexes have been developed [19, 80, 81]. Transient elastography, which measures liver stiffness, seems to be the most promising non-invasive method for evaluating fibrosis in HIV/HCV co-infected patients [19, 80].

The administration of antiretroviral treatment may slow the progression of liver disease by preserving or restoring the immune mechanisms and decreasing HIV-associated immune activation and inflammation. For the majority of HIV/HCV co-infected individuals, including those with cirrhosis, the benefits of antiretroviral treatment outweigh cautions regarding drug-induced liver damage. Therefore, HAART should be considered for HIV/HCV-coinfected persons, regardless of CD4 T-cell count (18). Although HAART should be started in most HIV/HCV co-infected patients irrespective of the number of CD4 T-cells, in HAART-naive patients with CD4 counts greater than 500 cells per cubic millimeter (mm^3), some clinicians may select to delay HAART until the completion of HCV treatment (18).

Strong preference should be given to initiate HCV treatment in patients with higher CD4 T-cell counts. HCV therapy in HIV patients with less than 200 CD4 T-cells/mm^3 may be deferred because drug-related toxicities and poor responses occur more frequently in immunologically compromised patients. Therefore, treatment-naive co-infected individuals with severe immune deficiency could initiate antiretroviral therapy prior to the administration of anti-HCV treatment, which should be considered after the restoration of CD4 T-cell counts and the significant control of HIV replication [18, 19, 82-84].

Combined treatment of HIV and HCV can be complicated by the large pill burden, potential drug interactions, and overlapping toxicities.

DRUGS USED FOR THE TREATMENT OF HCV INFECTION IN PATIENTS WITH HIV/HCV CO-INFECTION

Combination treatment with pegylated interferon alfa (described above) and ribavirin (RBV) has been established as the standard therapy for chronic HCV infection (Table **4**). Results from numerous studies have demonstrated superior virological outcomes of this combination over non-modified IFN-alpha plus ribavirin both in HCV mono-infected and in HIV co-infected patients. [85-91]**.** The primary aim of anti-HCV treatment is the sustained virological response (SVR) defined as an undetectable serum HCV RNA 6 months after the end of therapy, evaluated using ultrasensitive assays [90]. The length of HCV therapy depends on HCV genotype and on host's response. Generally, the combination of peg-IFN alpha and RBV is given for a period of 24 or 48 weeks [87], in contrast to the long-term therapy against HBV infection.

Ribavirin (1-beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) is a synthetic nucleoside agent with broad antiviral activity. It is structurally related to pyrazofurin (pyrazomycin), guanosine, and xanthosine [92]. The chemical formula of ribavirin is $C_8H_{12}N_4O_5$ and the molecular weight is 244.20 [92]. Ribavirin is converted intracellularly to the monophosphate (RMP), the diphosphate (RDP) and the triphosphate form (RTP) with the latter being the predominant metabolite in all cell types [93, 94]. Adenosine kinase is the cellular enzyme responsible for the initial production of RMP, whose subsequent phosphorylations produce the other two substrates [93]. Phosphorylation is a rapid process with half-maximal values of metabolites being reached within a few hours [93, 94].

Table 4. Drugs Currently Used for the Treatment of HCV Infection in Patients with Concurrent HIV Infection

Generic name	Class	Chemical formula	Molecular Weight	Dose	Adverse Reactions
Pegylated Interferon (Peg-IFN) alfa-2a	Protein	Conjugate of IFN alfa-2a ($C_{860}H_{1353}N_{227}O_{255}S_9$) with bis-monomethoxy polyethylene glycol	~60,000 daltons	180mcg once weekly	Psychiatric reactions, bone marrow suppression, fatigue, headache
Pegylated Interferon (Peg-IFN) alfa-2b	Protein	Conjugate of IFN alfa-2b ($C_{860}H_{1353}N_{229}O_{255}S_9$) with bis-monomethoxy polyethylene glycol	~31,000 daltons	1.5 mcg/kg/per week	Psychiatric reactions, fatigue, headache, nausea
Ribavirin (RBV)	Nucleoside analogue	$C_8H_{12}N_4O_5$	244.20	800mg-1200mg* daily based on body weight and genotype; for HIV patients 800mg daily	Hemolytic anemia, skin reactions, fatigue, pyrexia, myalgia, headache
Telaprevir	HCV NS3-4A protease inhibitor	$C_{36}H_{53}N_7O_6$	679.85	750mg three times daily	Skin reactions, anemia, nausea, diarrhea, fatigue
Boceprevir	HCV NS3-4A protease inhibitor	$C_{27}H_{45}N_5O_5$	519.70	800mg three times daily	Anemia, fatigue, nausea, headache, dysgeusia

HCV, hepatitis C virus; HIV, human immunodeficiency virus; mcg, microgram; mg, milligram; kg, kilogram; NS, non-structural; *Dosage range 800mg-1400mg when administered with peg-IFN alpha-2b.

Various mechanisms by which ribavirin enhances response rates during interferon-based anti-HCV therapies have been proposed [93, 95, 96]. As shown before, many nucleoside analogue triphosphates act as substrate mimics for misincorporation by viral polymerases, an event that causes the death of the progeny strand. Thus, in the case of ribavirin as well, the use of the triphosphorylated metabolite by nucleic acid polymerases could inhibit RNA synthesis and lead, at least theoretically if being incorporated, to premature termination of nascent viral RNA [96]. RTP has been found to inhibit weakly the polymerase of bovine diarrhoeal virus, which is closely related to HCV, and to cause a substantial impediment to RNA elongation after being incorporated into the newly synthesized RNA, opposite cytidine and uridine, in a process catalyzed by an HCV RNA-dependent RNA-polymerase derivative [96-98]. However, this direct effect of RBV on HCV mediated by the viral polymerase was achieved at remarkably higher doses compared with the effective concentrations needed in clinical practice, an observation that suggests a different main mechanism of action [96].

The second proposed mechanism of RBV action refers to the inhibition of inosine monophosphate dehydrogenase (IMPDH), a rate-limiting enzyme that catalyzes the first unique step in the purine metabolic pathway: the conversion of inosine monophosphate (IMP) to xanthosine monophosphate (XMP) [93, 95, 96]. In subsequent steps in this biosynthetic process, XMP is aminated by guanosine monophosphate (GMP) synthase to GMP, which finally converts to guanosine triphosphate (GTP), an important substrate for the synthesis of nucleic acids [93]. RMP is a potent competitive inhibitor of type I and type II isoforms of IMPDH [93]. Studies have shown that RMP interacts with the active substrate pocket of IMPDH and is an excellent mimic of IMP [93]. The inhibition of IMPDH by RMP causes a significant depletion of the competing GTP pools in ribavirin-treated cells interfering thus with the production of an essential molecule for important integral viral processes such as the transcription, the translation and the replication of nucleic acids. Since the reduction of GTPs is non-specific, the blockage of IMPDH could explain the broad-spectrum activity of RBV [93]. However, although IMPDH inhibition contributes significantly to the antiviral activity of ribavirin, there are many instances in which this mechanism alone was insufficient to explain the observed benefits [93, 95, 96].

According to the third proposed mechanism of action, ribavirin is considered a RNA virus mutagen [93, 95, 96]. Because of the poor accuracy and the lack of proofreading repair mechanisms in viral RNA polymerases, HCV and other RNA viruses have an extraordinary mutation frequency and circulate in serum as a swarm of distinct but closely related genomes, termed quasispecies [99]. This genetic heterogeneity is beneficial for the viral population, allowing for rapid evolution and adaption to changes of environmental conditions including immune response and antiviral therapy [95]. However, one theoretical characteristic of quasispecies is the existence of an error threshold relationship, which connects viral fitness and the copying fidelity during replication [95]. In other words, genomic diversity provides a selective advantage for RNA viruses, which, on the other hand, need to achieve a high degree of conservation of specific genomic sequences for the interaction with cell proteins. Since RNA viruses live at the edge of maximal variability, exceeding the tolerable error generation rate is likely to be deleterious to viral viability. Therefore, drug-induced increase of the mutational frequency beyond the upper limit of tolerable genome variability has large effects on viral lethality (lethal mutagenesis) and it could be used as

a therapeutic strategy [100]. As discussed before, RTP incorporates into RNA molecules during replication [101]. Of interest, ribavirin mimics either of the natural purines (guanosine and adenosine) and non-specifically templates incorporation of cytidine or uridine with equal efficiency [101]. This ambiguous base-pairing property of ribavirin is attributed to the rotation of the carboxamide moiety of the pseudobase, which creates hydrogen bond acceptor/donor sites favorable for interaction with either of the pyrimidine molecules [93, 101]. The fact that ribavirin is an ambiguous pourine analogue can support its potential to disproportionally accumulate mutations in the newly synthesized RNA. Several findings so far support the mutagenic role of RBV using model poliovirus polymerase, hantaan virus and GB virus B, a close relative of HCV [101-103]. Moreover, several lines of evidence, both *in vitro* and *in vivo*, suggest that ribavirin is able to act as mutagen during HCV treatment [95, 104, 105].

Ribavirin seems to have also immunomodulatory properties, an important characteristic in terms of therapeutic effectiveness since the antiviral immunity is predominantly mediated by cytotoxic T-cells and antiviral cytokines. The potential immunomodulatory activity of RBV stemmed from observations in HCV-infected patients in whom ribavirin reduced and normalized alanine aminotranferase levels but proved less effective in decreasing or eliminating circulating HCV RNA levels [106]. The balance of T-helper type 1 and T-helper type 2 responses has been found to be relevant to HCV infection; an early T-helper type 1 response, which is associated with cellular immunity and the expression of interleukin (IL)-2, gamma-interferon, and tumor necrosis factor-alpha, is connected with viral clearance [93, 96]. On the other hand, the T-helper type 2 response, which promotes humoral immunity and is linked with the expression of IL-4, IL-5, and IL-10, leads to HCV chronicity [93, 96, 107]. The immunomodulatory effects of ribavirin are supported by many previous studies. More specifically, RBV has been found to change the T-cell balance in the immune system [108]. An *in vitro* study has also shown that ribavirin induced type 1 while suppressed type 2 cytokine production by activated human T-cells [109]. Moreover, patients treated with a combination regimen including IFN-a and ribavirin presented stronger HCV-specific T-cell responses [110].

In conclusion, ribavirin is an old, broad-spectrum antiviral compound that is highly effective in combination with peg IFN-alpha for the treatment of HCV infection. Although ribavirin has been created more than 35 years ago, the exact mechanism of action has not been elucidated.

There are also two new agents that have been recently approved for the treatment of HCV: telaprevir and boceprevir.

Telaprevir is chemically described as (1S,3aR,6aS)-2-[(2S)-2-({(2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino] acetyl}amino)-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-1-carboxamide. Its molecular formula is $C_{36}H_{53}N_7O_6$ and its molecular weight is 679.85 [111].

The HCV RNA genome encodes a single polyprotein precursor of approximately 3,000 amino acids, which is processed proteolytically by both cellular and viral proteases to generate at least 10 individual polypeptides, including four structural proteins (core protein, envelope glycoproteins E1 and E2, and the small membrane polytopic protein with ion channel activity p7) and six nonstructural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [112]. The NS3 protein is a multi-functional protein, with a N-terminal serine protease domain and a C-terminal helicase domain [112]. The NS3-4A membrane-targeted serine protease is a non-covalent, heterodimer complex formed by the N-terminal serine protease domain of NS3 (catalytic subunit) and the NS4A cofactor (activation subunit) [112-114]. The protease activity of NS3 is enhanced by the NS4A cofactor. As a matter of fact, NS4A contributes one beta-strand to the N-terminal protease domain and thus allows its complete folding. Moreover, it causes a conformational change that results in a repositioning of the catalytic triad. NS3 by itself has no transmembrane domain, but it associates non-covalently with the central domain of NS4A, which is a membrane protein [112]. The NS3-4A protease is responsible for the cleavage at four sites of the HCV polyprotein precursor to create the mature NS3, NS4A, NS4B, NS5A, and NS5B [112, 113]. The polyprotein cleavage by NS3-4A in the region downstream of NS3 is important for the creation of components of the viral RNA replication complex and thereby it is not surprising that this protease has been the target for the development of new anti-HCV compounds [112-114]. The discovery of small-molecule, orally available, and potent drug candidates has been partially hampered by the shallow substrate-binding pocket of the HCV NS3-4A serine protease. Moreover, the absence of a robust small animal model for HCV infection has generally forced scientific groups to focus on a combination of anti-HCV activity in cell culture and animal pharmacokinetics as surrogate indicators of efficacy before human clinical trials [114]. However, significant progress has been made and telaprevir was the first, reversible, selective, orally bioavailable inhibitor of HCV NS3-4A serine protease that received approval from the United States Food and Drug Administration in 2011 [111].

The drug, in combination with peg-IFN alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously received IFN-based treatment [111]. Telaprevir is administered for the first 12 weeks of standard HCV combination treatment, followed by a response-guided regimen of either 12 or 36 additional weeks of pegylated interferon alfa and ribavirin [111]. Telaprevir should not be used as monotherapy. Moreover, if peg-IFN alfa and/or ribavirin is discontinued for any reason, telaprevir must also be discontinued [111].

Boceprevir is a linear peptidomimetic ketoamide serine protease inhibitor that binds reversibly to the HCV NS3 active site. It has the following chemical name: (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-

carboxamide. Boceprevir has a molecular formula of $C_{27}H_{45}N_5O_5$ and a molecular weight of 519.70 [115]. It has also been recently approved for the treatment of chronic hepatitis C genotype 1 infection, along with peg-IFN alfa and ribavirin, in adult persons with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous combination therapy [115]. After 4 weeks of peg-IFN/RBV administration, boceprevir is added to the regimen for 24, 32, or 44 additional weeks of HCV therapy.

Other investigational drugs of this class are in advanced stages of clinical research and the first findings are promising. Daclatasvir is a NS5A replication complex inhibitor, which in combination with asunaprevir, an NS3 protease inhibitor, was tested in patients with chronic genotype 1 hepatitis C who failed to response to standard therapy [116]. This was an open-label phase 2a study, and the authors found that treatment for 24 weeks with peg-IFN alpha and ribavirin in combination with the above-mentioned direct-acting agents resulted in high SVR rate. Moreover, it was shown that sustained virological response can be achieved with two direct-acting antiviral agents only [116].

WHAT THERAPY TO START IN HIV+ PATIENTS WITH CHRONIC HEPATITIS C

As mentioned above, the combination of pegylated interferons with standard weigh-based dose of ribavirin is the mainstay of HCV therapy with 40-50% rate of sustained virological response in patients infected with HCV genotype 1 and treated for 48 weeks. The SVR rate is higher (70-80%) in HCV-infected individuals with genotype 2 or 3 after taking peg-IFN alpha and ribavirin at a reduced dose for a period of 24 weeks [117]. There is some evidence that peg-INF alpha-2a is more effective than peg-INF alpha-2b [118-120] but the research findings are not consistent [117, 121]. In contrast, all studies support similar safety profiles of the two pegylated forms of IFN-alpha used in HCV therapy [117, 119, 121]. The addition of HCV NS3-4A inhibitors in the standard combination regimens has yielded high SVR rates. More specifically, in the Protease Inhibition for Viral Evaluation 2 trial, which examined patients with chronic genotype 1 HCV infection not treated previously, the combination of telaprevir with peg-IFN alfa-2a and ribavirin for 12 weeks followed by an additional 12-week course of pegylated interferon-ribavirin, resulted in an SVR of 69% [117, 122]. Two subsequent phase 3 trials involving HCV genotype 1-infected treatment-naive participants and persons with HCV genotype 1 infection who had null or partial response to previous therapy or who had a relapse after an initial response, respectively, confirmed the significant increase in the SVR rates among individuals receiving telaprevir-based therapy in addition to peg-IFN alfa-2a/ribavirin [123, 124]. Remarkably increased proportions of patients with undetectable HCV RNA 24 weeks after the last planned dose of study treatment were also observed in studies on boceprevir use both in untreated [125, 126] and in treatment-experienced subjects infected with HCV genotype 1 [127], when the drug was added, after a 4-week lead-in, to regimens combining peg-IFN alfa-2b/ribavirin.

The standard regimen of peg-IFN alpha and ribavirin is also effective against HCV in the field of HIV/HCV co-infection although the response is suboptimal compared with the HCV mono-infection case [88-91]. In dually infected patients, the two available pegylated interferons have similar

Table 5. Preliminary Recommendations for the Use of Telaprevir or Boceprevir in Patients with Concomitant HCV (Genotype 1) / HIV Infection [18]

	Recommendation
Patients not on ARV	Use either boceprevir or telaprevir
Patients receiving RAL + 2-NRTIs	Use either boceprevir or telaprevir
Patients receiving ATV/r + 2-NRTIs	Use telaprevir at standard dose. Do not use boceprevir
Patients receiving EFV + 2-NRTIs	Use telaprevir at increased dose of 1,125mg every 7–9 hours. Do not use boceprevir
Patients receiving other ARV regimens	• If HCV disease is minimal (i.e., no or mild portal fibrosis), consider deferring HCV treatment given rapidly evolving HCV drug development • If good prognostic factors for HCV treatment response are present—e.g. low HCV RNA level—consider use of Peg-IFN/RBV without HCV NS3-4A protease inhibitor • On the basis of ARV history and HIV genotype testing results, if possible, consider switching to the ARV regimens listed above to allow the use of boceprevir or telaprevir • For patients with complex ARV history or resistance to multiple classes of antiretrovirals, consultation with experts regarding the optimal strategy to minimize the risk of HIV breakthrough may be needed. In such patients, telaprevir may be the preferred HCV NS3-4A protease inhibitor because its duration of use (12 weeks) is shorter than that of boceprevir (24 to 44 weeks)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; ARV, antiretroviral treatment; RAL, raltegravir; NRTI, nucleoside reverse transcriptase inhibitor; ATV/r, atazanavir/ritonavir (booster); EFV, efavirenz; mg, milligram; RNA, ribonucleic acid; Peg-IFN, pegylated interferon; RBV, ribavirin; NS, non-structural.

efficacy and safety properties [128]. When both HIV and HCV treatments are indicated, the choice of the antiretroviral regimen should be directed by the HCV treatment regimen selected taking into consideration the potential drug-drug interactions and overlapping toxicities [18].

Clinical trials of HCV protease inhibitors in combination with peg-IFN/RBV for the treatment of HCV genotype 1 infection in HIV+ patients are in process. Preliminary results from two small studies suggest a more favorable response in HIV/HCV co-infected patients taking boceprevir or telaprevir plus peg-INF alpha/RBV than peg-INF alpha/RBV only [18]. Both boceprevir and telaprevir are substrates and inhibitors of cytochrome P 3A4, although boceprevir is mainly metabolized by aldo-keto reductase. Therefore, the currently approved HCV protease inhibitors may impact HIV treatment containing certain antiretrovirals that are metabolized by the same pathways. Consequently, the antiretroviral regimen may need to be modified to decrease the potential for drug-drug interactions and/or drug toxicities. The preliminary recommendations for the use of telaprevir or boceprevir in patients with concomitant HIV/HCV infection are presented in Table **5**.

TREATMENT OF HIV/HBV/HCV CO-INFECTED PATIENTS

The prevalence of multiple viral hepatitis in HIV patients is 3-5% in developed countries, much higher than in the general population. Regardless of the HIV status, in patients with concomitant HBV/HCV infection, there is a reciprocal inhibitory interaction with one hepatitis virus predominating over the other [19, 129, 130]. Studies however have shown phenomena of alternative dominant replication over time and the existence of various viral patterns including the simultaneous replication of all hepatitis viruses in the presence of HIV disease [19, 131-133].

With the advent of potent therapies against HBV and HCV, the knowledge of whether suppression of one virus with its specific therapy will permit the other virus to reactivate is necessary. This information is particularly useful in patients with HIV infection, in whom the prevalence of viral hepatitis is higher and more severe liver disease and its complications are seen [19, 134]. However, the available research data on the treatment of multiple viral hepatitis and HIV are limited. Therefore, the optimal timing for treatment of these three infections is not clear. Generally, all replicating viruses should be treated, mainly in patients with advanced liver fibrosis. During therapy of one virus, the replication of the other should be carefully monitored [19, 135].

CONCLUSION

Since the identification of HIV and viral hepatitis B and C, great strides have been made in the development of potent therapies. The higher rates of morbidity and mortality in HIV/HBV and HIV/HCV co-infected patients clearly highlight the importance of therapeutical options for this group. Despite the current availability of potent drugs, further research is still needed on the production of new agents and on the efficacy of combinational therapeutic strategies. Data from ongoing trials are expected with great interest hoping that will improve the management and the well being of this patient group.

CONFLICT OF INTEREST

None declared.

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None declared.

ABBREVIATIONS

HBV	=	hepatitis B virus
HCV	=	hepatitis C virus
HIV	=	human immunodeficiency virus
MSM	=	men who have sex with men
HAART	=	highly active antiretroviral therapy
AIDS	=	acquired immune deficiency syndrome
DNA	=	deoxyribonucleic acid
CD	=	cluster of differentiation
IU	=	international unit
HBsAg	=	HBV-surface antigen
HBeAg	=	HBV-early antigen
ALT	=	alanine aminotransferase
IFN	=	interferon
Peg-IFN	=	pegylated interferon
Jak	=	Janus-activated kinase
STAT	=	signal transducer and activator of transcription
ISGs	=	IFN-stimulated genes
IFNAR	=	IFN-a receptor complex
Tyk	=	tyrosine kinase
SH	=	Src homology
IRF	=	IFN-regulatory factor
ISGF	=	IFN-stimulated gene factor
kDa	=	kilodalton
PEG	=	polyethylene glycol
His	=	histidine
3TC	=	lamivudine
mg	=	milligram
YMDD	=	tyrosine-methionine-aspartate-aspartate
ADV	=	adefovir dipivoxil
ETV	=	entecavir
RNA	=	ribonucleic acid
M184V	=	Methionine184Valine

LdT	=	telbivudine
TDF	=	tenofovir disoproxil fumarate
FTC	=	emtricitabine
mm^3	=	cubic millimeter
RBV	=	ribavirin
SVR	=	sustained virological response
RMP	=	ribavirin monophosphate
RDP	=	ribavirin diphosphate
RTP	=	ribavirin triphosphate
IMPDH	=	inosine monophosphate dehydrogenase
IMP	=	inosine monophosphate
XMP	=	xanthosine monophosphate
GMP	=	guanosine monophosphate
GTP	=	guanosine triphosphate
IL	=	interleukin
NS	=	non-structural

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