Antiviral Research 85 (2010) 303–315

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

Viral hepatitis and HIV co-infection

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ARTICLE INFO

Article history:
Received 11 September 2009
Received in revised form 20 October 2009
Accepted 23 October 2009

Keywords:
Hepatitis B
Hepatitis C
Hepatitis delta
HIV
Co-infection
Liver
Interferon
Ribavirin
Entecavir
Adefovir
Lamivudine
Tenofovir
Antiviral drugs

ABSTRACT

Chronic hepatitis B virus (HBV) infection is overall recognised in 10% of HIV+ persons worldwide, with large differences according to geographical region. Chronic hepatitis C virus (HCV) infection affects 25% of HIV+ individuals, with greater rates (~75%) in intravenous drug users and persons infected through contaminated blood or blood products. HIV-hepatitis co-infected individuals show an accelerated course of liver disease, with faster progression to cirrhosis. The number of anti-HBV drugs has increased in the last few years, and some agents (e.g. lamivudine, emtricitabine, tenofovir) also exert significant activity against HIV. Emergence of drug resistance challenges the long-term benefit of anti-HBV monotherapy, mainly with lamivudine. The results using new more potent anti-HBV drugs (e.g. tenofovir) are very promising, with prospects for stopping or even revert HBV-related liver damage in most cases. With respect to chronic hepatitis C, the combination of pegylated interferon plus ribavirin given for 1 year permits to achieve sustained HCV clearance in no more than 40% of HIV–HCV co-infected patients. Thus, new direct anti-HCV drugs are eagerly awaited for this population. Although being a minority, HIV+ patients with delta hepatitis and those with multiple hepatitis show the worst prognosis. Appropriate diagnosis and monitoring of chronic viral hepatitis, including the use of non-invasive tools for assessing liver fibrosis and measurement of viral load, may allow to confront adequately chronic viral hepatitis in HIV+ patients, preventing the development of end-stage liver disease, for which the only option available is liver transplantation. This article forms part of a special issue of Antiviral Research marking the 25th anniversary of antiretroviral drug discovery and development, *Vol 85, issue 1, 2010*.

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doi:10.1016/j.antiviral.2009.10.021

1. Introduction

Due to similar routes of transmission, co-infection of HIV with other sexual and blood-borne viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV) and/or hepatitis delta virus (HDV) is relatively common. Of the 35 million people living with HIV worldwide, around 20% (~7 million) had chronic hepatitis C. This population is mainly represented by individuals with past history of intravenous drug use, hemophiliacs and recipients of contaminated blood. With respect to HBV, the situation is slightly different, with rates of chronicity in HIV+ patients ranging from 5% in Western countries to 20% in some HBV endemic regions in Sub-Saharan Africa and South East Asia. Around 15% of HBV–HIV co-infected patients worldwide are superinfected by the delta virus. Individuals with multiple viral hepatitis are a minority, with complex viral interference phenomena and generally poor clinical outcome. Fig. 1 records the overlap of HIV, HBV and HCV epidemics.

2. Hepatitis B and HIV

Among the estimated 35 million persons currently living with HIV worldwide, approximately 3 million are chronically infected with HBV (Soriano et al., 2008). The prevalence of HBV–HIV co-infection demonstrates geographical variations, largely due to differences in the predominant routes of transmission. Studies focused on the natural history of chronic hepatitis B in the HIV setting have demonstrated an increased risk of liver disease progression and death in co-infected individuals (Thio et al., 2002). In North America and Europe more than half of HIV+ men who have sex with men have evidence of past HBV infection, and 5–10% suffer from chronic hepatitis B (Konopnicki et al., 2005), which is defined as the persistence of the HBV surface antigen (HBsAg) in the serum for over 6 months. Rates of HBV–HIV co-infection are slightly lower among intravenous drug users and much lower among people infected through heterosexual contact (Nuñez and Soriano, 2005).

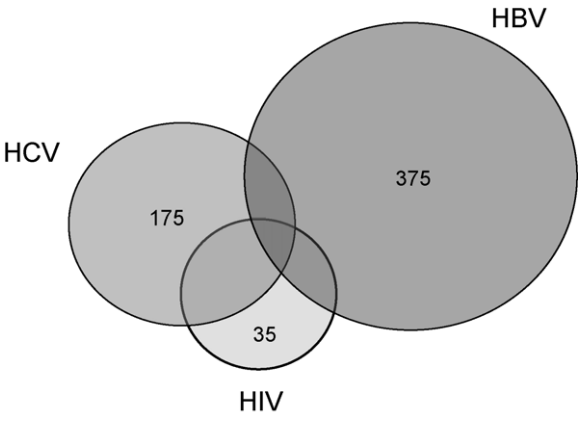

Fig. 1. Estimated number of individuals with HIV, HBV and HCV worldwide.

HBV strains can be classified into 8 genotypes, designed A to H based on a minimum sequence divergence of 8% of the entire genome. HBV genotypes have a distinct geographical distribution, being genotype A predominant in Northern Europe, North and South America, and some African regions. This genotype may be subdivided into 3 subgenotypes which differ at least by 4% in their nucleotide sequence and show also a distinct geographical distribution (Schaefer, 2007). Genotypes B and C are commonly found in East Asia and the latest have been associated with an increased risk of hepatocellular carcinoma (HCC). Genotype D is more frequent in the Mediterranean basin, genotype E in Africa, genotype F in Central and South America, genotype G in France and USA, and genotype H in North and Central America. The geographic distribution of HBV genotypes should be viewed as a dynamic phenomenon due to increased population migrations. A different susceptibility to antiviral agents has been reported for distinct HBV genotypes; for example, genotypes A and B tend to respond better to pegylated interferon than genotypes C and D (Lok and McMahon, 2009). However, information on the role of HBV genotypes in the setting of HIV infection is scarce and needs further research.

2.1. Mandatory HBV screening in HIV+ patients

Several studies have pointed out that one of the main reasons for inadequate HBV care in HIV+ persons is the lack of prior knowledge of the chronic HBV status (Soriano et al., 2008). Given the shared routes of transmission, investigation of HBV serological markers as HBV surface antigen (HBsAg), antibodies against HBsAg (anti-HBs) and anti-core antibodies (anti-HBc), should be made in all HIV+ patients. In those with serum HBsAg+, doctors in charge should further request serum HBV antigen e (HBeAg), HBV–DNA and anti-delta antibodies. A small subset of HIV+ patients with isolated anti-HBc antibodies may show detectable serum HBV–DNA. These occult HBV infections may account for HBV reactivations as immunodeficiency progresses or following removal of anti-HBV nucleoside analogues used as part of antiretroviral regimens. Therefore HBV viremia should be requested in all subjects with isolated anti-HBc (Soriano et al., 2008).

Besides baseline HBV evaluation, HIV+ patients with chronic hepatitis B should be monitored periodically for serum HBV–DNA and the chance of HBeAg seroconversion in those previously positive for HBeAg. Intervals for examinations should ideally not exceed

12 months if not on anti-HBV therapy and 6 months if under anti-HBV therapy. Recent studies in HBV-monoinfected patients have suggested that monitoring serum HBsAg titres every 3–6 months may be helpful in patients under anti-HBV therapy since large HBsAg reductions may predict seroconversion (Andersson and Chung, 2009). In HIV/HBV cirrhotic patients, shorter intervals may be more adequate, and alphafetoprotein and abdominal ultrasonography exams must be requested at 6 months intervals. Furthermore, an upper endoscopy should be made to exclude the presence of oesophageal varices, and if present therapy with beta-blockers must be considered (Soriano et al., 2008).

2.2. When to treat chronic hepatitis B in HIV+ persons?

The decision to treat chronic hepatitis B in HIV–HBV co-infected individuals must be based on a careful consideration of the prognostic factors for liver disease progression, the current severity of liver disease, the likelihood of response to anti-HBV agents and risks of adverse events, and finally the need for antiretroviral therapy against HIV (Soriano et al., 2008; Alberti et al., 2005). HBV–HIV co-infected individuals with active HBV replication and elevated aminotransferases should generally be considered for anti-HBV therapy, since they generally show liver damage. In the context of HIV infection, chronic hepatitis B progresses more rapidly to cirrhosis and the response to anti-HBV therapy may diminishes as immunodeficiency progresses (Soriano et al., 2008). HBV treatment objectives are the same for individuals with and without HIV co-infection: HBeAg seroconversion in HBeAg+ patients, ALT normalisation, improvement in liver histology, sustained suppression of serum HBV–DNA, reduction of hepatic decompensation events in patients with advanced cirrhosis, and reduction of the risk of HCC development (Lok and McMahon, 2007; Keeffe et al., 2006; Hoofnagle et al., 2007).

The benefits of inhibiting HBV replication have been well established; with demonstration of a direct association between serum HBV–DNA levels and the risk for developing liver cirrhosis and HCC, regardless HBeAg status and/or liver enzyme elevations (Chen et al., 2006; Iloeje et al., 2006; Iloeje et al., 2007). The most recent HBV guidelines recommend starting anti-HBV treatment in individuals positive for the hepatitis B e antigen (HBeAg) when serum HBV–DNA is $>2 \times 10^4$ IU/ml. In contrast, in patients with negative serum HBeAg, the threshold above which therapy should be recommended is 2×10^3 IU/ml (Lok and McMahon, 2007; Keeffe et al., 2006; Hoofnagle et al., 2007). In view of the suppressive, rather than curative, nature of HBV therapeutics in most cases, the medication has to be provided for long periods and even indefinitely to maintain its benefit through persistent HBV suppression. Treatment is most beneficial and efficacious when patients are in the immunoactive phase of HBV chronic disease (Lok and McMahon, 2007). Patient's characteristics that contribute to treatment success have been identified, and include low serum HBV–DNA levels, HBeAg positivity and elevated ALT levels (Lok and McMahon, 2007; Keeffe et al., 2006; Hoofnagle et al., 2007).

Given the accelerated course of chronic hepatitis B in HIV+ persons, treatment should be considered more openly than in HIV-negative counterparts (Soriano et al., 2008; Alberti et al., 2005). Fig. 2 records an algorithm for anti-HBV treatment in HIV+ patients, which is based on three parameters, which by order of importance are the following: serum HBV–DNA, ALT and liver fibrosis staging. When viremia is above 2000 IU/ml and/or ALT are elevated, significant liver damage must be expected, and therefore anti-HBV treatment should be advised. On the other hand, advanced liver fibrosis or cirrhosis can sporadically be recognised in patients with low serum HBV–DNA and/or normal ALT; and accordingly these patients may also benefit from antiviral treatment.

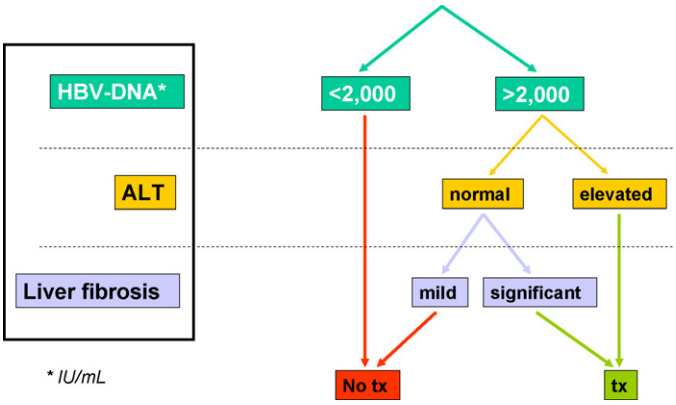

Fig. 2. Management of chronic hepatitis B in HIV/HBV co-infected patients. When to treat.

2.3. Antiviral drugs for chronic hepatitis B in HIV+ patients

Seven drugs have been approved so far for the treatment of chronic hepatitis B, and another, emtricitabine, in combination with tenofovir, is under final evaluation.

2.3.1. Interferon α-2b

It was the first drug approved for treating chronic hepatitis B. Standard interferon alpha (IFNα), however, has been replaced by pegylated IFNα in most instances. IFNα (or pegylated IFNα) is particularly effective for HBeAg+ chronic hepatitis B individuals with elevated ALT, low serum HBV–DNA and HBV genotypes A and B (Lok and McMahon, 2007; Keeffe et al., 2006; Hoofnagle et al., 2007). Frequent side effects of the drug (flu-like symptoms, psychiatric effects, bone marrow suppression, thyroid dysfunction, etc.) and the need for subcutaneous administration have limited its use. Moreover, it is contraindicated in decompensated cirrhotic patients, since it may exacerbate decompensation events. Liver enzyme flares during IFNα treatment are more common in HIV+ persons than in HIV-negative counterparts for unclear reasons. Finally, the efficacy of IFNα is lower in HBV/HIV co-infection regardless CD4 count most likely as result of underlying immune abnormalities (Di Martino et al., 2002). The recommended duration of therapy is 12 months.

2.3.2. Pegylated interferon α-2a

Pegylated forms of IFNα have a longer half-life and higher potency than standard IFNα. In individuals with HBV monoinfection, pegylated IFNα is more effective than standard IFNα. In HBeAg+ patients, nearly one-third may lose serum HBeAg and normalise ALT upon 12 months of therapy (Cooksley, 2004). Trials comparing pegylated IFNα and lamivudine have shown that rates of HBeAg seroconversion, serum HBV–DNA suppression and ALT normalisation are significantly higher using pegylated IFNα than lamivudine, but interestingly there is no further benefit using both drugs in combination.

In HBV/HIV co-infection, IFN-based therapies are associated with lower rates of therapeutic success and increased toxicity (Di Martino et al., 2002; Cooksley, 2004). Therefore, the drug may only be prescribed in non-decompensated cirrhotic patients with no need for antiretroviral therapy and having good chances of IFNα response, such as in those with HBeAg+, elevated ALT and low serum HBV–DNA (Soriano et al., 2008). Treatment is generally provided for 12 months. Fig. 3 summarises the preferred antiviral agents to treat chronic hepatitis B in HIV/HBV co-infected patients, according to the need for antiretroviral therapy and HBeAg status.

When markers of response to either IFNα or pegylated IFNα are not achieved after 12 months of therapy (e.g. HBeAg seroconver-

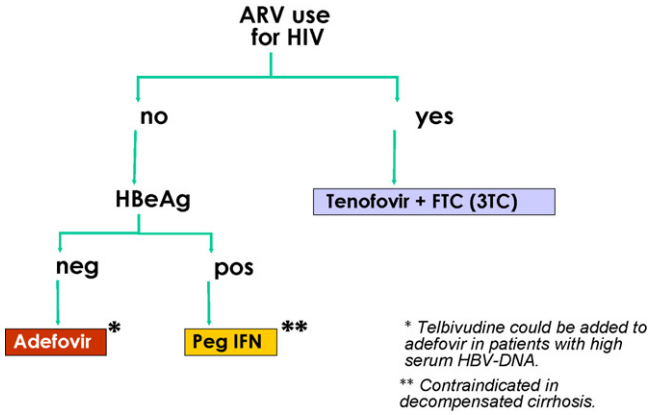

Fig. 3. Management of chronic hepatitis B in HIV/HBV co-infected patients. Which drugs to use.

sion, ALT normalisation or serum HBV–DNA decline), a therapeutic switch to nucleoside analogues must be considered. Given that these drugs are generally better tolerated, therapy is often planned to be given for indefinite periods of time.

The combination of pegIFNα and oral nucleoside analogues has been assessed with lamivudine and adefovir in HBV-monoinfected individuals. No significant benefits in terms of greater antiviral potency compared to pegIFNα monotherapy have been recognised in most studies. However, selection of resistance to lamivudine is delayed in patients exposed to combination therapy (Lok and McMahon, 2009).

2.3.3. Lamivudine (3TC)

It is an oral cytosine nucleoside analogue with both anti-HIV and anti-HBV activities, although the doses needed to suppress HBV (100 mg/day) are much lower than those required for suppressing HIV (300 mg/day). The effectiveness of 3TC in the treatment of chronic hepatitis B is very well documented, providing significant reductions in serum HBV–DNA and ALT levels, improvement in liver histology, and enhanced rate of serum HBeAg loss. However, a major problem with the long-term use of 3TC is selection of viral resistance, which is inherently associated with rebounds in serum HBV–DNA and liver enzyme flare-ups. For treating HBV/HIV co-infection, the recommended dose of 3TC is 300 mg/day and the drug should always be given with at least two other anti-HIV agents; otherwise, HIV resistance mutations would rapidly emerge.

Given its oral administration, excellent tolerability and posology (one pill once daily), 3TC has been widely used as anti-HBV agent, including patients co-infected with HIV, many of whom have received long-term 3TC therapy and unfortunately currently harbour 3TC-resistant HBV (Matthews et al., 2006; Ramos et al., 2007). Overall, HBV resistance mutations can be recognised in more than 90% of viremic patients with HIV infection who have received antiretroviral therapy including 3TC for over 4 years (Tillmann, 2007).

2.3.4. Adefovir (ADV)

It was the first nucleotide analogue approved for the treatment of HBV infection. The drug may also inhibit HIV at doses greater than approved for treating HBV, but then is associated with an increased risk of nephrotoxicity. At doses of 10 mg/day, ADV suppress HBV replication and interestingly is associated with a relatively low rate of resistance (~30% at 5 years) (Tillmann, 2007).

In HBV–HIV co-infected individuals, the performance of ADV was examined in 35 patients with ongoing antiretroviral therapy, including 3TC. After 144 weeks of adding ADV, a decrease in serum HBV–DNA levels was observed in 45% of subjects, which is lower than the 56% observed in HBV monoinfection (Benhamou, 2006). Selection of mutation K65R in HIV using ADV monotherapy in HBV/HIV co-infected patients not taking antiretroviral therapy has been a matter of concern, but at least one study failed to demonstrate this possibility, even after examining minor virus populations using endpoint dilutions (Sheldon et al., 2005).

It is noteworthy that around 10% of chronic hepatitis B patients do not respond to ADV. Several reasons may explain this failure, and include pharmacokinetic/pharmacodynamic limitations of the low ADV dosing, presence of genetic polymorphisms (I233 V and L217R), and cross-resistance with 3TC upon selection of changes at codon 181 (A→STV) (Thio and Locarnini, 2007). It is noteworthy that HBV genotype A2 could be particularly less susceptible to ADV due to natural polymorphisms, and this genotype is quite frequent among HIV/HBV co-infected men who have sex with men in Europe (Ramos et al., 2007).

2.3.5. Entecavir (ETV)

It is a guanosine analogue that inhibits HBV replication at three different steps (priming, reverse transcriptase and positive strand synthesis). ETV shows more potency in suppressing serum HBV–DNA than 3TC and ADV, and is effective against wild-type and 3TC- and ADV-resistant HBV. ETV resistance generally results from the accumulation of multiple changes in the HBV polymerase, including 3TC resistance mutations (Tenney et al., 2004). For this reason, ETV doses of 0.5 mg/day are recommended for 3TC-naïve patients, but 1 mg/day is advised for patients with 3TC-resistant HBV.

While the drug was originally not thought to be active against HIV, a report in early 2007 highlighted that it might produce significant reductions in plasma HIV–RNA and occasionally select for mutation M184 V in HIV (McMahon et al., 2007). Similar cases were soon reported by others, suggesting that while the antiretroviral activity of ETV might be only residual, it is enough for selecting resistance changes in HIV. Recent in vitro findings have confirmed these results (Tchesnokov et al., 2008). Therefore, a warning from the FDA has alerted against the use of ETV in the absence of antiretroviral therapy in HBV/HIV co-infected patients.

2.3.6. Telbivudine (LdT)

It is a thymidine L-analogue with no activity against HIV. LdT has significantly greater antiviral efficacy than either 3TC or ADV in patients with chronic hepatitis B, and selects for resistance mutations at intermediate rates. In studies used for the registration of the drug, up to 60% of HBeAg+ chronic hepatitis B individuals achieved undetectable serum HBV–DNA after 12 months of LdT treatment compared to 40% treated with 3TC (Lai et al., 2005). In the second year of treatment this rate lowered to 54% due selection of LdT resistance. Characteristically, LdT selects for mutation M204I, which causes cross-resistance to 3TC; therefore, LdT should not be used following 3TC failure, and vice versa. Interestingly, there is no evidence so far of cross-resistance between LdT and ADV. Although no experimental evidence exists supporting any anti-HIV activity of LdT, a recent clinical report has alerted about it. Thus, it seems worth to use LdT with great caution in HIV/HBV co-infected patients.

2.3.7. Emtricitabine (FTC)

Like 3TC, FTC is a cytosine analogue with antiviral activity against both HBV and HIV. It has a longer half-life than 3TC and similarly induces a rapid and sharp reduction in serum HBV–DNA at doses of 200 mg/day. Suppression of HBV replication is maintained over 48 weeks of treatment in more than half of patients (Lim et al., 2006). No data are available on FTC monotherapy in HBV/HIV co-infection, although large experience already exists derived from using the drug in combination with tenofovir as a single pill

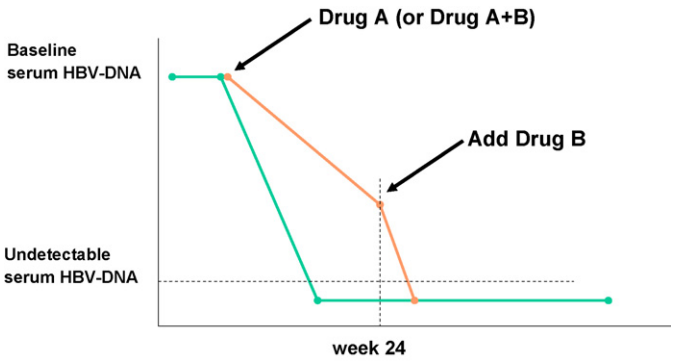

Fig. 4. Treatment approach for HBV. Combination therapy from the beginning or "early add-on therapy".

formulation (Truvada®). In fact, Truvada® is the preferred and recommended choice for treating CHB in HBV/HIV co-infected patients on need for antiretroviral therapy, as shown in Fig. 3 (Soriano et al., 2008). This combination provides potent anti-HBV activity along with a solid backbone for a triple combination antiretroviral regimen. Like 3TC, FTC should not be used as monotherapy in HBV/HIV co-infected persons due to high risk of selection of the M184V resistance mutation in HIV. Since FTC and 3TC show almost total cross-resistance, FTC should not be prescribed after 3TC failure.

2.3.8. Tenofovir (TDF)

It is an adenosine nucleotide analogue, already approved for the treatment of HIV infection. It also shows potent activity against HBV in patients with and without 3TC resistance (Núñez et al., 2002). HBV resistance to TDF has occasionally been described in HBV/HIV co-infected patients with 3TC resistance mutations. In this subset of patients, selection of one additional change, A194T, resulted in more than 10-fold loss of susceptibility to TDF (Sheldon et al., 2005). Large clinical trials have proven the safety and efficacy of the drug in HBV-monoinfected patients, as well as it more potent activity than ADV (Peters et al., 2006).

2.4. Treatment choice for chronic hepatitis B in HIV+ patients

When HBV infection requires treatment but HIV infection does not, generally based on elevated CD4 counts (>350 cells/mm^3), treatment options for HBV should include agents with no clinical activity against HIV, such as pegylated IFNα, ADV or LdT (Fig. 3). ETV should not be used given its residual activity against HIV and potential for selection of the M184V resistance mutation. A 12-month course of pegylated IFNα may be advisable for patients with high CD4 counts and HBeAg+, elevated ALT, low serum HBV–DNA and minimal liver fibrosis, particularly when infected by HBV genotype A. Up to one-third of these patients may show sustained suppression of serum HBV–DNA upon stopping therapy, a benefit which can not be achieved with any other drug. The limitation of pegylated IFNα is its poor tolerability and lower efficacy in the HIV setting (Di Martino et al., 2002). Moreover, the drug is contraindicated in decompensated cirrhosis, although it can be used with caution in individuals with compensated cirrhosis (Nuñez and Soriano, 2005).

For the rest of HBV/HIV co-infected patients who do not need antiretroviral therapy, long-term nucleos(t)ide therapy is the only available option. At the moment, either ADV or LdT might be good alternatives; however, given the risk of selecting drug resistance, an "early add-on" strategy should be considered for patients who do not reach undetectable serum HBV–DNA at week 24 of therapy (Fig. 4). Adding a drug rather than replacing it should be advised, because there is evidence for a protective activity against selection of resistance and less for a synergistic or additive antiviral activity with drug combination. In subjects with very high serum HBV–DNA, ADV and LdT could be given in combination from the beginning, but authors defending this strategy are so far confronted with the lack of data to support it. Finally, drugs with dual antiviral effect, such as 3TC, FTC or TDF should never be used as single agents in HIV/HBV co-infected persons, given the high risk for selection of drug resistance in HIV.

An alternative option in this subset of HBV/HIV co-infected patients on need for anti-HBV therapy but with a relatively well preserved immune status is to advance the time to initiate antiretroviral therapy, and then include the combination of TDF plus FTC (or 3TC) as nucleos(t)ide backbone being part of a triple regimen. This option may be particularly reasonable for patients with a high plasma HIV–RNA and/or with active risk behaviours, for whom the risk of progression and/or transmission to others, respectively, is enhanced. Recent HIV guidelines support this strategy, and favour to advance antiretroviral therapy initiation in patients with hepatitis B and/or C co-infections (Hammer et al., 2008; DHHS, 2009), given the accelerated progression of liver disease as CD4 counts decline. In HBV/HIV co-infected individuals, this decision brings the opportunity to use antivirals with dual activity.

When both HIV and HBV fit criteria to be treated, the main caveat is whether prior exposure to 3TC has occurred. In drug-naïve patients, following what has been advised in HIV-negative individuals, 3TC (or FTC) should no longer be prescribed as only anti-HBV agent, given the risk for selecting HBV resistance mutations that may compromise future therapeutic options, such as ETV, LdT and occasionally ADV. At the moment, the combination of TDF plus FTC (or 3TC) is by far the preferred choice for this subset of patients (Fig. 3).

For individuals with prior exposure to 3TC and uncontrolled HBV replication, 3TC resistance is almost always present and therefore the only available options are rescue interventions based on TDF or ETV. The latest should be used at doses of 1 mg/day in this subset of patients, and viral load monitored periodically in order to assure that undetectable HBV viremia is achieved relatively shortly; otherwise drug pressure will drive selection of resistance. With respect to TDF, several studies have clearly established its activity in the face of 3TC-resistant HBV (Núñez et al., 2002). Of note, although serum HBV–DNA may decline on average 4 logs in this population, it may takes long time (several months or even more than a year) to reach undetectable serum HBV–DNA.

An aspect that merits special attention in HIV/HBV co-infected patients is the need to keep in mind that nucleoside analogue active anti-HBV drugs should not be removed when a change in the antiretroviral regimen is required. Otherwise, unexpected and severe flares in liver enzymes may occur as result of HBV rebounds. Moreover, in HBeAg+ co-infected patients it is worth to keep active anti-HBV drugs for at least 6 months following HBeAg seroconversion before considering the removal of these drugs; otherwise, re-appearance of HBeAg may occur.

2.5. Selection of HBV escape mutants by antiviral drugs

An intriguing phenomenon which recently has attracted much attention is that 3TC resistance mutations may result in changes in HBV antigenicity. The reason for this observation is that the polymerase and envelope genes of HBV overlap and drug resistance mutations in the polymerase may simultaneously alter the HBsAg, causing a diminished HBs antigen–antibody binding. This may result in failure using diagnostic tests or vaccine escape (Thio and Locarnini, 2007; Sheldon and Soriano, 2008). These mutations have been more frequently found in individuals exposed to 3TC and infected with HBV genotype A, which is the most prevalent among European and North American HBV/HIV co-infected patients (Sheldon et al., 2007).

3. Hepatitis C and HIV

Of the 35 million people currently living with HIV worldwide around 20% (~7 million) has chronic hepatitis C (Fig. 1). This population is mainly represented by individuals with past history of intravenous drug use, hemophiliacs and recipients of contaminated blood.

3.1. Outbreaks of acute hepatitis C in HIV+ patients

Outbreaks of hepatitis C among homosexual men have been reported in several large European and North American cities since year 2000 (Danta et al., 2007; van de Laar et al., 2007; Low et al., 2008). This observation is striking since HCV was not thought in the past to be efficiently transmitted by sexual contact, as HBV or HIV. High levels of sexual promiscuity, certain particularly traumatic sex practices, and concomitant ulcerative sexually transmitted diseases (e.g. syphilis), have all been associated with these HCV outbreaks. The increased level of HCV viremia characteristically seen in HIV+ persons might further contribute to this enhanced infectivity.

In contrast to HIV-negative individuals, in whom acute HCV infection may show spontaneous viral clearance in 30% of cases within the first 12 weeks following initial exposure, HIV+ patients experience chronicity in more than 80% of cases (Thomas et al., 2000). Therefore, early therapeutic intervention in acute hepatitis C is particularly indicated in HIV+ individuals, although treatment should not be instituted before 12 weeks of estimated exposure, in order to discard spontaneous HCV clearance. Too long delays, however, should be discouraged since may reduce treatment responses. Treatment of acute hepatitis C in HIV+ patients seems to provide a lower rate of cure than in HIV-negatives (60% vs 80%, respectively). Since the antiviral activity of IFN may be mediated through the cytokine network, immunological abnormalities in the HIV setting could negatively influence interferon efficacy. On the other hand, the rates of HCV clearance obtained in HIV+ patients treated during the acute phase are much higher than in chronic hepatitis C (Low et al., 2008). HCV genotypes 2–3 respond better than genotypes 1–4. More elevated ALT levels during the acute episode and rapid viral clearance on therapy predict better chances of sustained virological response (SVR). In contrast, patient's age, CD4 count, HIV or HCV load and having symptomatic infection do not seem to influence treatment response. At this time it is unclear whether adding RBV to pegIFN would offer any advantage when treating acute hepatitis C in HIV+ individuals. However, given the worse prognosis of HCV infection in HIV+ persons, it seems worthwhile to provide RBV to maximally ensure the attainment of HCV clearance. Following what is advised in HIV-negative persons, 24 weeks of therapy is the recommended duration of treatment of acute hepatitis C in HIV+ patients regardless HCV genotype (Soriano et al., 2007).

3.2. Natural history of HCV-related liver disease in HIV+ patients

Besides experiencing an increased risk of chronification following initial HCV infection, HIV+ individuals with chronic hepatitis C show a faster progression of liver fibrosis (Benhamou et al., 1999; Martin-Carbonero et al., 2004). On average, nearly half of patients have developed liver cirrhosis after 25 years of HCV infection. Low CD4 counts enhance the hepatic fibrogenesis process in co-infected patients, and therefore early introduction of HAART in these patients is warranted (Hammer et al., 2008; DHHS, 2009).

3.3. Treatment of chronic hepatitis C in HIV+ patients

It has become a priority for at least two reasons. Firstly, progression to end-stage liver disease occurs more rapidly in this population (Benhamou et al., 1999; Martin-Carbonero et al., 2004).

Table 1
Factors associated with sustained virological response to HCV therapy in HIV patients.

Host	Virus	Treatment
• Genetic (White ethnicity)	• Genotypes 2/3	• Adequate peginterferon dose
• Younger age	• Low baseline HCV RNA	• Weight-based ribavirin dose
• Minimal liver fibrosis	• Undetectable HCV–RNA at week 4	• Good adherence
• Low body mass index		• No concurrent didanosine or zidovudine
• Lack of insulin resistance		• Use of hematopoietic growth factors when needed
• Lack of hepatic steatosis		
• Higher CD4 count		
• No polysubstance abuse		
• No psychiatric disease		

Secondly, the tolerance of antiretroviral agents is much poor in the presence of underlying chronic hepatitis C, with a greater risk of hepatotoxicity (Sulkowski et al., 2000; Núñez et al., 2001). Successful treatment of chronic hepatitis C can revert these drawbacks. Indeed, clearance of HCV has been associated with a regression of liver fibrosis (Barreiro et al., 2006; Soriano et al., 2006) and with a reduced risk of antiretroviral-related hepatotoxicity (Labarga et al., 2007).

3.4. Selection of HIV+ candidates for HCV therapy

Virological features such as HCV genotype and HCV load largely influence the response to HCV therapy. However, viral factors rarely determine who should be considered as good candidate for HCV therapy. Host factors, including extent of liver fibrosis, CD4 counts, and patient's motivation are the most important parameters that should determine who should receive HCV therapy (see Table 1). More recently, specific host genetic factors have also demonstrated to largely influence treatment outcomes. Of note, a genetic polymorphism near the interleukin 28B gene, encoding interferon gamma 3, has been associated with a two-fold chance in response to pegIFN+RBV. The susceptibility allele is more common in Caucasians than blacks, contributing to explain at least in part the differences in response rates seen between these ethnic groups (Ge et al., 2009; Sakai et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009; Thomas et al., 2009).

3.4.1. Liver fibrosis

The extent of hepatic fibrosis is the best prognostic factor of disease progression in patients with chronic hepatitis C, and therefore its consideration is worth before indicating HCV therapy. Liver biopsy has been for many years the only tool to assess hepatic fibrosis. However, its invasive nature with occasional serious and even life-threatening complications, sampling error and inherent heterogeneity of hepatic fibrosis, low acceptance by most patients, and relatively elevated cost, have prompted the development of non-invasive tools for staging hepatic fibrosis. These are currently split into two major categories, ultrasound techniques, such as elastometry (FibroScan), and serum biochemical indexes (i.e. Fibrotest, APRI, SHASTA, FIB-4, hyaluronic acid, etc.). These tools are generally accurate to discriminate between lack of fibrosis and advanced fibrosis, and less precise to distinguish between intermediate fibrosis stages. Their predictive value is particularly good for advanced hepatic fibrosis and cirrhosis. However, serum fibrosis markers are generally less reliable in co-infected patients, given the inflammatory nature of HIV disease and/or the frequent prescription of drugs

in this population which may interfere with some fibrosis markers in the blood. This is the case for bilirubin elevations due to atazanavir, gamma-glutamyl-transpeptidase (GGT) abnormalities with non-nucleoside reverse transcriptase inhibitors, or cholesterol elevations using most ritonavir-boosted protease inhibitors. In contrast, liver fibrosis staging using elastometry seems to be more reliable in this setting, avoiding such interference (De Ledinghen et al., 2006). Elastometric measurements can be made in 10 min, be repeated periodically, are inexpensive, and had more than 90% positive predictive value for advanced liver fibrosis.

When the diagnosis of any hepatic disease is clear by other means, as occurs with chronic hepatitis C testing positive for serum HCV–RNA, the need for a liver biopsy to stage hepatic fibrosis and guide treatment decisions, is currently no longer justified in most instances. The higher response to pegIFN–RBV with respect to standard interferon, the faster progression of HCV-related liver disease in the HIV population, and the opportunity for assessing viral response at earlier time-points and identify who will and who will not respond to therapy, all favour the prescription of anti-HCV therapy avoiding a liver biopsy in most cases (Soriano et al., 2003).

Patients with repeatedly *normal liver enzymes* might benefit from HCV therapy. Few studies have been conducted so far in co-infected patients with normal ALT. Less than 10% of this population show persistently normal liver enzymes (Maida et al., 2007). Exposure to antiretroviral drugs, alcohol abuse and other conditions explain the lower rate of normal ALT in HIV patients with chronic hepatitis C. On the other hand, significant liver fibrosis has been reported in up to 25–40% of co-infected patients with normal ALT and "silent" cirrhosis in nearly 15% of them (Sanchez-Conde et al., 2006).

HIV/HCV co-infected patients with *liver decompensation* (ascites, gastrointestinal bleeding, hepatic encephalopathy, etc.) should not be treated with pegIFN, given their higher risk for developing serious side effects. These patients should be assessed for liver transplantation. However, patients with compensated cirrhosis (Child-Pugh class A) must be treated with pegIFN plus RBV, because their chance of response is currently relatively high (~25%) and ultimately these patients will benefit more than any other from HCV clearance. In contrast with HIV disease, chronic hepatitis C can be cured and there is conclusive data supporting that undetectable serum HCV–RNA 6 months after completion of treatment really reflects eradication of HCV infection (Soriano et al., 2004).

3.4.2. CD4 count

Old therapeutic trials using IFN monotherapy concluded that the efficacy of HCV therapy depended of baseline CD4 cell counts (Soriano et al., 1996). More recently, a subanalysis of the APRICOT trial has shown that treatment responses are less as lower is the baseline CD4 percentage. Candidates to receive HCV therapy ideally should have more than 200–350 CD4+ T cells/mm^3, a feasible threshold for most patients if antiretroviral therapy is used appropriately.

In patients with CD4 counts below 200 cells/mm^3 and already under HAART, the decision to treat HCV infection must be made taking into account other factors, such as the estimated length of HCV infection, the severity of liver disease, the extent of HIV suppression, and classical predictors of response to HCV therapy such as HCV genotype and viral load (Table 1). It should be kept in mind that toxicities of pegIFN and/or RBV as well as poorer responses may be more frequent in severely immune deficient patients. In general, HCV therapy should be deferred in individuals with less than 200 CD4+ T cells/mm^3, mainly because concerns on toxicity and since the response might be much poor. Moreover, IFN generally causes a decline in the CD4 count, which may put these patients at further risk for developing opportunistic infections. Therefore, in drug-naïve co-infected patients with low CD4 counts, antiretroviral therapy should be considered at front. Once CD4 cells have raised and plasma HIV–RNA is under control, the prescription of HCV therapy should be reassessed (Soriano et al., 2007). Conversely, in antiretroviral-naïve individuals with good CD4 counts, hepatitis C should be treated first. These patients will further benefit from an improved tolerance of antiretroviral drugs (Labarga et al., 2007).

3.4.3. Patient's motivation

Individuals with prior history of serious *neuropsychiatric disorders* should not be treated, because IFN can exacerbate these conditions. Patients currently engaged in heavy alcohol intake and/or illegal drug addiction practices should delay anti-HCV treatment, whereas all efforts should be devoted to put them into detoxification programs.

Patients on methadone are acceptable candidates for HCV therapy. However, up to one-third of them may need adjustments in methadone dosage. This is generally due to psychological demands rather than to pharmacological interactions between anti-HCV drugs and methadone. Ideally, a multidisciplinary team, including experts in addiction medicine and psychologists/psychiatrics, should take care of these patients.

In summary, all HIV persons with chronic HCV infection should be considered at front as potential candidates for HCV therapy, given their higher risk of progression to end-stage liver disease compared to HIV-negative patients and their increased risk of liver toxicity after beginning antiretroviral therapy. The timing for HCV treatment should be decided on an individual basis. Severe neuropsychiatric disorders, alcohol and drug abuse generally contraindicate HCV treatment. However, methadone use and non-decompensated cirrhosis are not contraindications for therapy. Treatment of patients with CD4 counts below 200 cells/mm^3 or low CD4 percentages is less effective and potentially risky; therefore, it should generally not be advised.

3.5. Predictors of response to HCV therapy in HIV+ patients

3.5.1. Baseline variables

Serum HCV–RNA and HCV genotype are the main baseline predictors of SVR to pegIFN–RBV in co-infected as in HCV-monoinfected patients. Several other variables, however, may influence treatment responses, although generally in less extent. As shown in Table 1, they can be grouped in three categories. Especial attention has recently been paid to the negative impact of insulin resistance on HCV treatment response (Romero-Gomez et al., 2005). Insulin resistance is quite prevalent in co-infected patients at least in part due to the use of certain antiretrovirals, as ritonavir-boosted protease inhibitors. Therefore, prevention of insulin resistance and/or its adequate management (even considering treatment with insulin-sensitiser agents when indicated) might improve HCV treatment outcomes in co-infected patients.

3.5.2. Treatment compliance

As in HCV-monoinfected patients, treatment adherence should be encouraged as much as possible. The "80/80/80" rule is equally valid in co-infected patients, meaning that subjects who take more than 80% of pegIFN and of RBV doses during at least 80% of planned period of therapy respond significantly better than the rest. Therefore, adequate selection of treatment candidates, psychological and/or psychiatric support, and use of growth factors to avoid dose reductions of either pegIFN and/or RBV, all must be encouraged in order to keep on adequate doses of anti-HCV medications the majority of patients. Since depressive symptoms are a major obstacle for completion of a full course of therapy in a significant proportion of patients it is worthy to familiarise doctors taking care of co-infected patients with their appropriate use. Management of mild–moderate depression will result in improved SVR

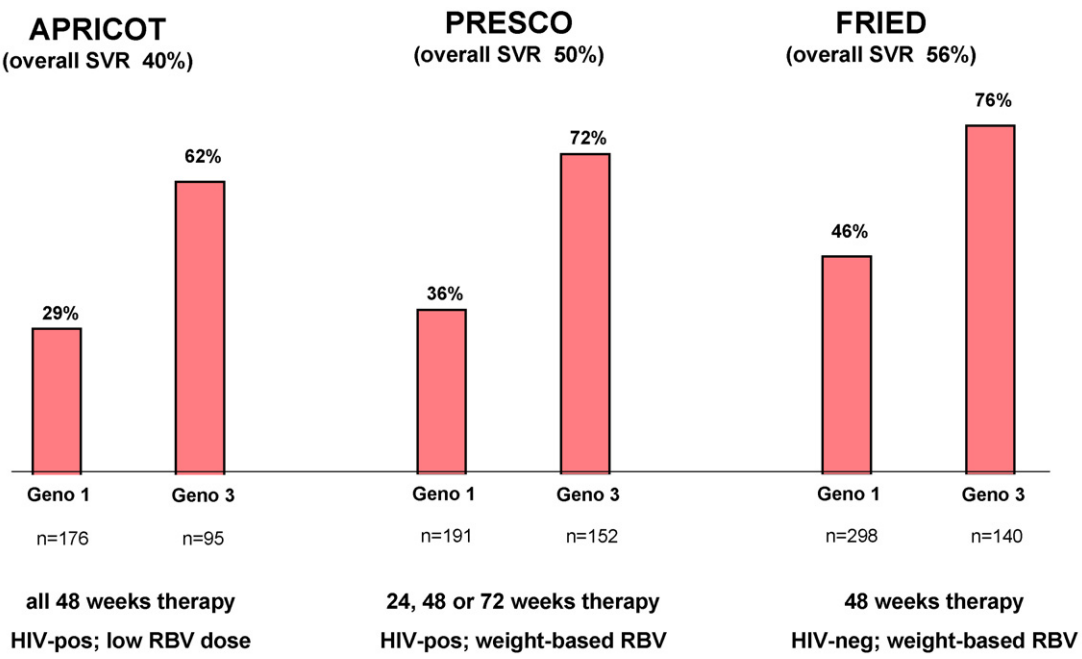

Fig. 5. Proportion of patients with sustained virological response in three different large trials in HIV-positive and HIV-negative patients using low or weight-based ribavirin (RBV) doses (intent-to-treat analysis).

rates. Recognition of major depressive symptoms, however, should prompt to refer patients to a psychiatrist and stop HCV therapy.

3.5.3. HCV kinetics

Changes in serum HCV–RNA in response to pegIFN–RBV is a reliable indicator of treatment efficacy. The availability of sensitive quantitative tools to closely monitor HCV decays under treatment has allowed recognition of early time-points with high predictive value of SVR. Overall, the early virological response to HCV therapy splits patients into those sensitive and those refractory to therapy. Nearly 20% of HCV-monoinfected subjects do not show a significant reduction in HCV viremia (defined as a decline >1 log) during the first month of pegIFN–RBV, and this figure increases up to 30% in co-infected patients (Ramos et al., 2007). In virological responders, the best positive predictive value for SVR is achieved when a negative serum HCV–RNA is attained at week 4 of therapy (rapid virological response, RVR), while the best negative predictive value for SVR is seen when HCV–RNA drops <2 logs at week 12 (Carrat et al., 2004; Torriani et al., 2004; Soriano et al., 2004). Higher baseline HCV–RNA levels in co-infected patients with respect to HCV-monoinfected individuals may explain why they achieve less frequently undetectable HCV viremia at week 4 and therefore less often SVR (Sherman et al., 2005). Alternatively, co-infected patients might show slower HCV decays on HCV therapy (Torriani et al., 2003). Interestingly, the latter could be overcome at least partially using higher RBV doses (Lindahl et al., 2005).

The so-called "2-log stopping rule" refers to the strong predictive value of non-response assessing week 12 virological response. The lack of achieving HCV–RNA declines >2 logs (early virological response, EVR) permits the premature discontinuation of HCV therapy, avoiding side effects and costs, when there is no chance of eradicating HCV infection. Fortunately, this rule works in co-infected as well as in HCV-monoinfected patients (Carrat et al., 2004; Torriani et al., 2004; Soriano et al., 2004). On the other hand, a negative serum HCV–RNA 6 months after completing anti-HCV therapy, which defines SVR, correlates with the long-term clearance of serum HCV as well as with histological and clinical improvements in most patients (Barreiro et al., 2006; Soriano et al., 2006; Maida et al., 2007).

3.6. Optimal pegylated interferon and ribavirin dosing

Adequate exposure to RBV is crucial to maximise responses to HCV therapy (Lindahl et al., 2005), particularly in HIV-co-infected patients (Nuñez et al., 2005; Dixit et al., 2004). Weight-based dosing seems to well balance the highest efficacy and the lowest limiting toxicities of the drug, namely anaemia. Pharmacokinetic studies have shown a good correlation between RBV plasma levels and HCV–RNA responses (Rendon et al., 2005). Thus, the use of fixed low doses of RBV (800 mg per day) in the old trials conducted in co-infected patients could explain their low SVR (Carrat et al., 2004; Torriani et al., 2004). The use of higher RBV doses (1000–1200 mg/day) in the PRESCO trial has confirmed this assumption, since the overall SVR in this trial (50%) is the highest reported so far for co-infected patients (Nuñez et al., 2007). Fig. 5 shows the proportion of patients achieving SVR in pivotal trials as a function of distinct RBV doses and HIV status.

The benefits of adequate RBV exposure seems to be particularly important in co-infected patients and is not limited to those infected with HCV-1/4, and expand to genotype 3 (Núñez et al., 2005). In HCV-monoinfected individuals a flat RBV dose of 800 mg/day seems to be enough for genotype 3, as long as therapy is provided for at least 24 weeks. However, shorter periods of therapy seem to require greater RBV doses in order to minimise relapses (Mangia et al., 2005; von Wagner et al., 2005).

The efficacy of higher doses of pegIFN in co-infected patients has been explored in a few studies. In the CORAL-1 trial, the administration of 270 μg/week of pegIFN alpha-2a for the first 4 weeks did not improve the early virological response, either considering the proportion of patients with undetectable HCV load at week 4 or with >2 log reductions in HCV–RNA at week 12, as compared with the administration of standard doses (180 μg weekly) (Tural et al., 2007). However, the size of the study population in that study was relatively small and nearly half of patients carried non-1 HCV genotypes. In contrast, data from some studies conducted in HCV-monoinfected individuals have suggested that there is a subset of patients who may benefit from exposure to higher pegIFN doses (Marcellin et al., 2006) and therefore this issue still warrants further investigation.

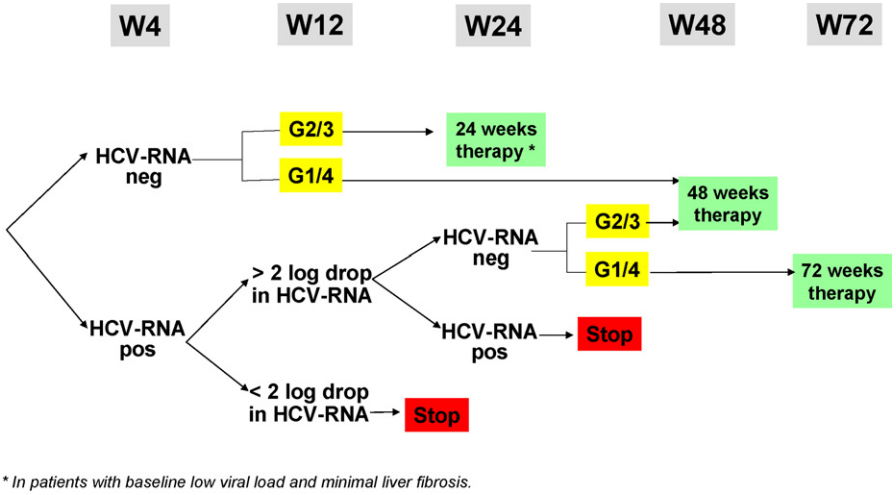

Fig. 6. Proposed optimal duration of HCV therapy in HCV/HIV-co-infected patients.

3.7. Optimal duration of HCV therapy

Studies conducted in HCV-monoinfected patients have shown that RVR, defined as undetectable HCV load at week 4, in patients treated with pegIFN–RBV is the best predictor of SVR and may allow a safety shorten therapy. Accordingly, treatment for only 12-16 weeks in patients with HCV genotype 3 (Mangia et al., 2005; von Wagner et al., 2005) or for only 24 weeks in HCV genotype 1 (Ferenci et al., 2006; Zeuzem et al., 2006) have been proposed for patients with RVR. The picture seems to be slightly different in co-infected patients, in whom, however, this high predictive value of SVR in subjects experiencing RVR has also been reproduced (Martin-Carbonero et al., 2008). First, HCV load is generally higher in this population, which could explain why a lower proportion of them reach undetectable viremia at week 4 (Soriano et al., 2004; Sherman et al., 2005). Second, HCV clearance driven by interferon could be delayed in the HIV setting (Soriano et al., 2004; Torriani et al., 2003). Third, the relapse rate upon completion of treatment might be increased in co-infected patients. This was the case for 24 weeks of therapy in HCV-2/3 in earlier trials (Soriano et al., 2004). For all these reasons, older guidelines recommended that duration of treatment in co-infected patients should be of 48 weeks regardless HCV genotype (Alberti et al., 2005).

Recent studies, however, have questioned these simple views. In a retrospective study conducted in co-infected patients with HCV-2/3, the subset of them who reached undetectable HCV–RNA at week 4 could safely stop therapy at week 24, with minimal risk of relapse (Crespo et al., 2007). On the other hand, a retrospective substudy of the APRICOT trial has shown that patients with HCV genotype 1 with low baseline HCV–RNA and RVR obtained high rates of SVR (61%) and did not relapse (Dieterich et al., 2006), suggesting that shorten periods of therapy could have been enough for those patients. Overall, all these data support shorter periods of therapy on the basis of viral response at week 4 in HCV-2/3 co-infected patients.

In some patients with slow virological response, extended periods of treatment may permit to achieve SVR (Buti et al., 2003). Recognition of detectable viremia at week 4 seems to identify a subset of patients with HCV-1/4 which may benefit from longer duration of therapy as long as it proves to be effective (>2 log drop in HCV–RNA at week 12 followed by undetectable viremia at week 24) (Berg et al., 2006; Sánchez-Tapias et al., 2006). However, the main problem with extended periods of therapy is compliance (Nuñez et al., 2007; Berg et al., 2006). This concern can be particularly problematic in co-infected individuals, given that a poor tolerance of the medication has largely impacted negatively on outcomes (Carrat et al., 2004).

The 2007 guidelines from the HCV–HIV International Panel (Sulkowski et al., 2000) recommend the therapeutic algorithm recorded in Fig. 6. This algorithm has been later endorsed by the European AIDS Clinical Society guidelines (Rockstroh et al., 2008). Shorter periods of therapy (24 weeks) could be advised in patients with HCV-2/3 with RVR, as long as HCV load is low, there is good adherence, no advanced hepatic fibrosis exists, and weight-based RBV dosing is provided. For the rest of HCV-2/3 patients, 48 weeks of therapy could still be advisable. In patients with HCV-1/4, extension of treatment beyond 48 weeks could be recommended in the absence of RVR if the medication is well tolerated. However, as previously noted, high drop-out rates might limit the benefit of this strategy (Nuñez et al., 2007).

3.8. Antiretroviral drugs during HCV therapy

Nucleoside reverse transcriptase inhibitors are the backbone of most current antiretroviral regimens. These compounds mimic physiological nucleosides and enter phosphorylation pathways within the cells causing inhibitory competition and chain termination when incorporated into the nascent viral nucleic acid synthesis. Interactions between antiretrovirals and RBV, which is a guanosine analogue, have been a matter of concern for a while, since in most trials conducted so far more than 75% of HIV/HCV-co-infected patients have received pegIFN–RBV along with antiretroviral medications. In earlier studies, only the enhanced risk of anaemia using concomitantly zidovudine (AZT) was the main focus of attention. Use of recombinant erythropoietin has been recommended to counterbalance this deleterious additive hematological side effect, which otherwise may force to reduce RBV doses in a substantial proportion of patients. On the other hand, RBV enhances the intracellular phosphorylated metabolites of didanosine, increasing the risk of mitochondrial toxicities, including pancreatitis, lactic acidosis and hepatic decompensation (Mauss et al., 2004; Bani-Sadr et al., 2005). The loss of subcutaneous fat typically linked to stavudine may be exacerbated during pegIFN–RBV therapy, mimicking rapidly progressive lipoatrophy (Garcia-Benayas et al., 2002). Rather than RBV, it seems to be pegIFN the main agent responsible for this deleterious effect, although an enhanced synergistic mitochondrial toxicity of RBV and stavudine over the subcutaneous fat tissue has not been ruled out.

Table 2
Classification of and interventions for HCV/HIV-co-infected patients non-responders/relapsers to prior interferon-based therapies.

Category	Recommended intervention
Suboptimal prior treatment schedules: • *Interferon (monotherapy or with ribavirin)* • *Low ribavirin dosing* • *Short length of therapy*	Re-treatment using combination therapy with peginterferon plus weight-based ribavirin doses
Limiting toxicities and poor adherence	Optimal support (psychiatric, pharmacists, use of hematopoietic growth factors)
Virological failure	Wait until new antivirals come to the market

Recent reports have underlined that abacavir may compromise the activity of RBV and therefore might reduce the efficacy of hepatitis C therapy (Bani-Sadr et al., 2007; Vispo et al., 2008). Both drugs are guanosine analogues and may compete in their phosphorylation pathways within the cells. This observation has important therapeutic considerations; moreover, it provides further insights about the mechanism of action of RBV. Although still a matter of controversy, these data indirectly but strongly support that RBV is acting as a true antiviral agent against HCV, rather than exerting immune mediated effects. In this regard, the antiviral effect of RBV against HCV may follows the pattern already well demonstrated against other RNA viruses. With respect to tenofovir, it has no deleterious interactions with RBV, since no interference with the antiviral activity of RBV or an increased risk of nephrotoxicity has been shown (Sanchez-Conde et al., 2005).

3.9. Management of non-responders and relapsers

As result of a wide prescription of pegIFN+RBV in chronic hepatitis C patients, there is a growing pool of patients who did not respond or relapsed to a prior course of treatment. This circumstance is also recognised in co-infected patients, especially in places where hepatitis C therapy has been actively provided for the last decade. Non-responders and relapsers can be classified into three groups (see Table 2) (Soriano et al., 2007). Those exposed to suboptimal therapies in the past and show advanced liver fibrosis should be re-assessed and optimal pegIFN plus RBV regimens must be offered again for at least 1 year. In patients who discontinued the medication due to limiting toxicities (e.g. severe anaemia or depression), adequate support with haematopoietic growth factors or antidepressants must be encouraged. Finally, for the growing number of patients who showed virological failure treated with adequate drug dosing and regimens, the only good advise is to avoid potential hepatotoxic factors (e.g. alcohol) and wait for the new antivirals against HCV.

3.10. Prospects of new HCV drugs for HIV/HCV co-infected patients

The advent of new antiviral drugs against HCV is eagerly awaited by many HIV+ patients with chronic hepatitis C. Many of them are relatively young, show significant liver fibrosis and have already failed a course of pegIFN–RBV. A few considerations merit attention before a widely introduction of HCV specifically targeted antiviral therapies (STAT-C) in the co-infected population (Table 3). Baseline characteristics of hepatitis C in HIV+ patients differ from HIV-negative persons. Higher viral load, greater prevalence of HCV genotypes 3 and 4, more frequent HCV-1a than -1b, and concomitant use of antiretroviral agents may largely influence the performance of STAT-C drugs in the co-infected population. Many of these drugs are less or not effective against HCV genotypes other than HCV-1 (Soriano et al., 2009). Moreover, in the case of HCV protease inhibitors, natural polymorphisms may account for a lower proportion of susceptibility in HCV-1a than -1b variants (Kuntzen et al., 2008). This observation coupled with the greater baseline HCV viremia and the potential for drug interactions, have discouraged the use of STAT-C drugs in co-infected patients until now. However, studies with close monitoring of early viral response have already been initiated.

Table 3
Considerations for the use of new HCV antivirals in HIV/HCV-co-infected patients.

1. Higher HCV load.
2. Higher rate of HCV-1a than -1b.
3. Greater proportion of HCV genotypes 3 and 4.
4. Potential drug interactions with antiretroviral agents.

Table 4
New antivirals against HCV.

Protease inhibitors	Polymerase inhibitors	
	Nucleoside analogues	Non-nucleoside analogues
• Ciluprevir* • ITMN-191/R-7227 • Telaprevir • Boceprevir • GS-9132/ACH-806* • BI-1335 • TMC-435 • MK-7009 • SCH-900518	• Valopicitabine* • R-1626/R-1479* • R-7128/PSI-6130 • MK-0608 • IDX-184 • VHC-759 • BI-127 • MK-3281	•HCV-796* • VHC-916 • XTL-2125* • ANA-598 • GS-9190* • Filibuvir (PF-554)

Table 4 summarises the main STAT-C molecules in clinical development and Table 5 records the main characteristics of the main different drug families. Telaprevir and boceprevir are the two HCV protease inhibitors in more advanced stages of clinical development. Approval is expected for 2011 (Nelson, 2009). In co-infected patients, trials have been initiated with caution and drug development will move slowly following each of the steps in HCV-monoinfected individuals. Moreover, it must be kept in mind that at least initially each of the new antivirals against HCV will be given along with pegIFN+RBV. Moreover, combinations with first-generation HCV protease inhibitors and non-nucleoside analogues will only be active against HCV genotype 1, leaving few options for other HCV variants (exclusively with polymerase inhibitors).

4. Delta hepatitis and HIV

HDV is a defective agent that only infects HBsAg+ carriers. Hepatitis delta is the most aggressive form of chronic viral hepatitis,

Table 5
Main differential features of new direct anti-HCV drugs.

Protease inhibitors	Nucleoside	Non-nucleoside inhibitors
• Interact with the catalytic triad • Genotype-dependent activity for some drugs	• Analogues of natural substrates • Need to be phosphorylated	• 5 distinct target sites at the polymerase • Allosteric inhibition
• Rapid selection of resistance	• Inhibitory competition • Chain terminators • Similar activity against all genotypes • High genetic barrier to resistance	• Genotype-dependent activity • Rapid selection of resistance • Polymorphisms may influence susceptibility

with even further faster progression to liver cirrhosis when associated to HBV or HCV infections. This poor prognosis is even more pronounced in HIV+ patients. The prevalence of anti-delta antibodies in HIV+ patients with HBsAg+ ranges from 15% to 50%, depending on geographical region and risk group category. In Western countries, hepatitis delta is more frequent in intravenous drug users than persons sexually infected with HIV. Most HIV+ patients seropositive for HDV are viremic (HDV-RNA+) and generally reflect superinfections rather than co-infections with HBV (Soriano et al., 2009).

Treatment of chronic hepatitis delta in HIV+ patients with interferon is rarely effective, although no studies have examined the safety and efficacy of pegIFN for longer than 18 months, which has shown to be relatively effective in HIV-uninfected persons (Niro et al., 2006). Recent reports have suggested that the use of potent anti-HBV drugs, such as tenofovir, could indirectly be beneficial against delta hepatitis, producing reductions in HDV replication and halting progression of liver fibrosis (Sheldon et al., 2008).

5. Multiple viral hepatitis and HIV

The prevalence of multiple viral hepatitis (HBV/HCV, HBV/HDV, HCV/HBV/HDV) in HIV patients is below 5% in developed countries, but higher than in the general population. In patients with HDVAb+, replication of this virus uniformly predominates over others, with low or undetectable HBV and/or HCV viremia, and rapid progression to cirrhosis (Mathurin et al., 2000). Patients carrying HBV/HCV infections seem to present a reciprocal inhibition of virus replication, predominating one virus over the other. Moreover, this predominance may occasionally fluctuate over time, with one virus taking over the other intermittently. However, in patients with severe immunosuppression, replication of all hepatitis viruses may occur simultaneously. In most HIV+ patients with relatively good immune status, viral interference seems to favour HCV over HBV replication rather than vice versa (Martín-Carbonero et al., 2007). However, it is noteworthy that the proportion of subjects with HCV-Ab showing negative serum HCV–RNA is much higher in patients carrying HBsAg (Nuñez et al., 2005).

Progression of liver disease seems to be further accelerated in HIV+ patients dually co-infected with HBV and HCV (Sagnelli et al., 2004). Moreover, these individuals are more prone to develop HCC (Puoti et al., 2004). Liver-related mortality is increased in HIV+ patients with multiple viral hepatitis as compared with those with HBV or HCV monoinfection (Bonacini et al., 2004). A few studies have examined the efficacy and safety of IFN–RBV in patients with dual HBV/HCV infections. Overall, most studies have concluded that results are similar. There is little information of the efficacy of pegIFN–RBV in HIV+ patients co-infected with HBV/HCV. Moreover, few data exist regarding the influence of anti-HBV medications on HCV replication in HBV/HCV dually infected patients. The treatment of all replicating viruses should be pursued, mainly in patients with advanced liver fibrosis. During therapy of one virus, replication of the other should be actively monitored since reactivations of latent infections may occur (Soriano et al., 2007).

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