

Care of HIV patients with chronic hepatitis B: updated recommendations from the HIV-Hepatitis B Virus International Panel

Vincent Soriano^a, Massimo Puoti^b, Marion Peters^c, Yves Benhamou^d, Mark Sulkowski^e, Fabien Zoulim^f, Stefan Mauss^g and Juergen Rockstroh^h

Nearly 10% of the estimated 36 million people having HIV worldwide suffer from chronic hepatitis B virus (HBV) infection. The advent of new antiviral agents against HBV and the recent availability of improved molecular diagnostic tools have revolutionized the management of HIV/HBV coinfecting patients. The present study represents an update of the current knowledge about HBV/HIV coinfection and an intent to provide practical advice about how to give the best care to HIV-infected persons with chronic hepatitis B.

© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

AIDS 2008, **22**:1399–1410

Keywords: drug resistance, hepatitis B, hepatitis B virus, HIV, liver, tenofovir

Liver disease is currently one of the leading causes of morbidity and mortality in HIV-infected individuals [1]. Chronic hepatitis B and hepatitis C are the major causes of hepatic disease in this population. Guidelines for managing hepatitis C in HIV-infected patients have recently been released [2,3]. Because new and relevant information regarding hepatitis B has emerged, it is necessary to update guidelines from 2005 for managing chronic hepatitis B (CHB) in HIV persons [2,4]. Nine areas have been identified for which new recommendations are particularly needed. Important topics in hepatitis B virus (HBV)/HIV coinfection are listed below:

- (1) the changing epidemiology and natural history of HBV/HIV coinfection;
- (2) new diagnostic tools;

- (3) treatment of hepatitis B in HIV patients;
- (4) antiviral drug resistance in HBV;
- (5) delta (hepatitis delta virus, HDV) hepatitis;
- (6) multiple viral hepatitis;
- (7) hepatotoxicity of antiretroviral drugs in HBV/HIV patients;
- (8) HBV vaccination in HIV patients;
- (9) liver transplantation in HBV/HIV patients.

Changing epidemiology and natural history

Among the estimated 36 million persons living with HIV worldwide, nearly 4 million (~10%) are chronically infected with HBV [5]. The prevalence of coinfection

^aDepartment of Infectious Diseases, Hospital Carlos III, Madrid, Spain, ^bDepartment of Infectious Diseases, University Hospital, Brescia, Italy, ^cHepatology Unit, University of California, San Francisco, California, USA, ^dDepartment of Hepatology, Hôpital Pitié-Salpêtrière, Paris, France, ^eViral Hepatitis Center, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA, ^fINSERM U871, Université Lyon 1, Hospices Civils de Lyon, Lyon, France, ^gCenter for HIV and Hepatogastroenterology, Duesseldorf, and ^hDepartment of Medicine I, University Hospital, Bonn, Germany.

Correspondence to Dr Vincent Soriano, Department of Infectious Diseases, Hospital Carlos III, Calle Sinesio Delgado 10, Madrid 28029, Spain.

E-mail: vsoriano@dragon.es

Received: 2 September 2007; revised: 23 November 2007; accepted: 26 November 2007.

demonstrates geographical variations, largely due to differences in the predominant routes of transmission. In North America and Europe, more than half of HIV homosexual men have evidence of past HBV infection, and 5–10% suffer from CHB [6], which is defined as the persistence of hepatitis B surface antigen (HBsAg) in serum for over 6 months. Overall, rates of coinfection are slightly lower among injection drug users (IDUs) and persons infected through heterosexual contact [7]. In endemic regions of Africa and Asia, the majority of HBV infections occur perinatally (vertical transmission) or during infancy through close contact within households (horizontal transmission), medical procedures and traditional scarifications [8]. The relative low rate of vertical transmission in Africa compared with Asia is due to a lower prevalence of serum hepatitis B e antigen (HBeAg) in African women with CHB, which is a major determinant of perinatal HBV transmission [9]. Despite availability of HBV vaccines for 25 years, recommended immunization of risk groups, and universal vaccination of infants, the rate of CHB has kept relatively stable in western countries due to the counteracting effect of immigration from HBV endemic regions.

The natural history of hepatitis B is deleteriously influenced by HIV. Increased HBV carriage rates, greater levels of HBV viremia, more rapid decline in hepatitis B surface antibody (anti-HBs), increased reactivation episodes, and faster progression to liver cirrhosis are all characteristic of HBV/HIV-coinfecting patients [4,10]. Moreover, hepatocellular carcinoma may develop at a younger age and is more aggressive in this population [11,12]. In the Multicentre AIDS Cohort Study (MACS) cohort, an eight-fold increased risk of liver-related mortality was seen among HBV/HIV-coinfecting compared with HIV-monoinfected individuals, particularly in patients with low CD4 nadir counts [13]. The effect of HBsAg+ on progression to AIDS, death from all causes, liver-related deaths and response to highly active antiretroviral therapy (HAART) was also examined in EuroSIDA [6]. Among 5728 HIV-infected individuals tested for HBsAg, 498 (8.7%) were positive; there was a 3.6-fold higher risk of liver-related deaths in them compared with HBsAg-negative individuals. The availability of antiretrovirals with potent anti-HBV activity, in particular tenofovir (TDF), appears to have modified this poor outcome in recent years. A halt or even a regression in liver fibrosis has been reported among HIV-infected patients with CHB who have shown prolonged complete suppression of HBV replication with anti-HBV-active antiretroviral drugs [14,15].

New diagnostic tools

In addition, aminotransferases and serological markers (e.g., HBeAg), serum HBV-DNA and HBV genotyping have gained importance for predicting HBV disease

progression and treatment monitoring [16,17]. Pivotal studies conducted in Taiwan, where HBV infection is endemic, have shown that viral load is the major determinant of the risk of liver cirrhosis [18], hepatocellular carcinoma [19] and death [20] in patients with CHB. Moreover, baseline HBV load largely influences the risk of selecting drug resistance to nucleos(t)ide analogues once on therapy [21].

HBV strains can be classified into eight genotypes, designed A–H based on a minimum 8% sequence divergence. HBV genotypes have a distinct geographical distribution, being genotype A predominant in northern Europe, America and some African regions. This genotype may be subdivided into three subgenotypes that also show a distinct geographical distribution [22] and susceptibility to antiviral agents. For instance, adefovir (ADV) may be less efficacious against A2, which is the predominant A variant in Europe. Genotypes B and C are commonly found in east Asia, and the latter has been associated with an increased risk of hepatocellular carcinoma [23]. 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 the USA, and genotype H in North and Central America. More severe forms of CHB have been reported in patients with genotype G [24] and in HBeAg-negative infections due to genotype D. Varying susceptibility to antiviral agents has been reported for distinct HBV genotypes [23,25]; for example, genotype A tends to respond better to interferon than genotype D [26]. Coinfection with several HBV genotypes seems to be rare, below 5%.

Assessment of liver fibrosis has prognostic value and is important for making therapeutic decisions in HBV disease. Liver biopsy was the only method to stage fibrosis until recently. However, new noninvasive tools to measure liver fibrosis have begun to replace or complement histology. They can be divided into two major categories, imaging techniques, such as elastometry (FibroScan) [27], and serum biochemical indexes [i.e., Fibrotest, aspartate aminotransferase to platelet ratio index (APRI), etc.] [28,29]. 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 cirrhosis. These methods, however, have been tested and validated mainly in chronic hepatitis C, with still limited information regarding CHB [30]. Moreover, serum fibrosis markers are generally less reliable in HIV-infected patients, given the inflammatory nature of HIV disease and the frequent prescription of drugs, which may interfere with some serum fibrosis markers [31,32], as it is the case for bilirubin elevations due to atazanavir, gamma glutamyl transpeptidase (GGT) abnormalities with nonnucleoside reverse transcriptase inhibitors (NNRTIs), or cholesterol elevations with

some protease inhibitors. In contrast, fibrosis staging using elastometry seems to be more reliable in this setting, avoiding such interactions [33]. Elastometric measurements can be performed rapidly (10 min), be repeated periodically, are inexpensive, and have more than 90% positive predictive value for advanced fibrosis. However, more information has to be generated to use this technique confidently in HBV/HIV-coinfected patients.

The current work-up for managing CHB and evaluation of HIV patients with CHB are summarized below:

- (1) serum HBeAg, anti-HBe;
- (2) serum delta antibodies;
- (3) serum HBV-DNA load;
- (4) HBV genotype (if detectable viremia);
- (5) liver fibrosis staging (using either liver biopsy or noninvasive tools);
- (6) in cirrhotics: serum albumin, prothrombin time, alfafetoprotein, abdominal ultrasound, and esophageal endoscopy.

Cirrhotic patients require particular attention given the risk of hepatic flares, decompensation and hepatocellular carcinoma. A particular situation is the recognition of serum HBV-DNA in the absence of HBsAg in the circulation, known as occult HBV infection. The prevalence and clinical significance of this condition have been subject to controversy. Although it has not been seen in some studies [34], others have claimed it could be more common in HIV-immunosuppressed individuals or in hepatitis C virus (HCV)-coinfected patients, causing silent liver disease, flares in liver enzymes or impaired response to hepatitis C therapy [35]. Differences in methodology and definitions could explain discordant results [10]. Using strict criteria, occult HBV infection seems to be a rare event and does not account for significant liver damage in most instances. It is more frequent in patients with isolated hepatitis B core antibody (anti-HBc) [36]. Using very sensitive PCR techniques, examining more than one HBV genomic region, and testing hepatic tissue in addition to serum, may increase the chances of recognizing occult HBV infections.

Treatment of hepatitis B in HIV-infected patients

When to treat?

The decision to treat CHB in HIV-infected individuals must be based on careful consideration of the need for antiretroviral therapy for HIV infection, the severity of liver disease, the likelihood of response to anti-HBV agents and potential adverse events. Coinfected individuals with active HBV replication and elevated aminotransferases should be considered for anti-HBV therapy.

In the context of HIV infection, CHB progresses more rapidly to cirrhosis and the response to HBV therapy is lower as immunodeficiency progresses. HBV treatment objectives are the same for individuals with and without HIV coinfection: alanine aminotransferase (ALT) normalization, HBeAg seroconversion, improvement in liver histology and sustained suppression of serum HBV-DNA [37–42].

As liver fibrosis is often accompanied by less hepatic inflammation and liver enzyme elevations in HBV/HIV-coinfected patients [43], monitoring of HBV viremia is pivotal for therapeutic decisions in this population. Recent data from the Risk Evaluation and Education for Alzheimer's disease (REVEAL) studies have highlighted the benefits of low-level HBV replication [18–20], regardless HBeAg status or liver enzyme elevations, or both. Accordingly, the most recent guidelines for CHB recommend starting anti-HBV treatment in HBeAg+ individuals when serum HBV-DNA is greater than 2×10^4 IU/ml. In contrast, in HBeAg-negative patients, the threshold above which therapy is recommended is 2×10^3 IU/ml [39–41]. In view of the suppressive, rather than curative, nature of HBV drugs in most cases, the medication has to be maintained for long periods, even indefinitely, to provide persistent HBV suppression. Patient's characteristics that contribute to treatment success include low-serum HBV-DNA, HBeAg positivity and elevated liver enzymes [39–44], all uncommon in HIV/HBV-coinfected patients.

Given the accelerated course of CHB in HIV-infected individuals [13], treatment should be considered earlier than in HIV-negative counterparts. Figure 1 depicts an algorithm for anti-HBV treatment in HIV-infected patients, which is based on three parameters, by order of importance: serum HBV-DNA, ALT and liver fibrosis staging. When viremia is above 2000 IU/ml or ALT are elevated or both, significant liver damage must be expected, and therefore treatment advised. On the

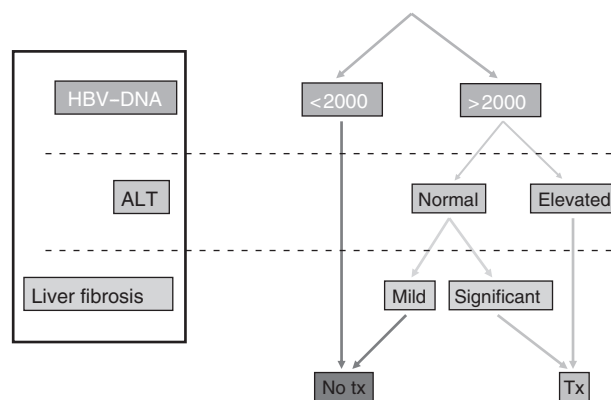


Fig. 1. Therapeutic algorithm for chronic hepatitis B in HIV. HBV-DNA is expressed in IU/ml. ALT, alanine aminotransferase; HBV, hepatitis B virus; Tx, treatment.

contrary, advanced liver fibrosis can sporadically be seen in patients either with low-serum HBV-DNA or normal ALT or both; and these patients will also benefit from antiviral treatment.

Antihepatitis B virus drugs

Seven drugs have been approved for the treatment of CHB and others already used as antiretroviral agents show anti-HBV activity and most likely will soon be approved as therapy for hepatitis B.

Interferon

Interferon (IFN) was the first drug approved for treating CHB. Standard IFN has been replaced by pegylated IFN (pegIFN) in most instances. Weekly pegIFN is prescribed using the same doses recommended for chronic hepatitis C. IFN (or pegIFN) is particularly effective for HBeAg+ individuals with high ALT levels and low-serum HBV-DNA [39–44]. Frequent side effects have limited IFN (pegIFN) use and it is contraindicated in decompensated cirrhotic patients, as it may exacerbate decompensation.

In monoinfected HBeAg+ patients, nearly one-third may lose serum HBeAg and normalize ALT upon 12 months of therapy [45]. Trials comparing pegIFN and lamivudine (LAM) have shown that rates of HBeAg seroconversion, serum HBV-DNA suppression and ALT normalization are significantly higher using pegIFN than LAM, but interestingly there is no further viral suppression using both drugs in combination [46,47].

In HBV/HIV coinfection, IFN (pegIFN) therapy is associated with lower rates of therapeutic success and increased toxicity [48,49]. Therefore, the drug has been used only in compensated cirrhotic patients who do not need antiretroviral therapy and have good predictors of IFN response.

Lamivudine

Lamivudine is an oral cytosine analogue with both anti-HIV and anti-HBV activities. The effectiveness of LAM in the treatment of CHB is very well documented. However, a major problem with the long-term use of LAM is the selection of resistance (25% per year), which is inherently associated with rebound in serum HBV-DNA and subsequent liver enzymes flares [50]. In treating HBV/HIV coinfection, the recommended dose of LAM is 300 mg/day and the drug should always be given with at least two other anti-HIV agents. Given its excellent tolerability, LAM has been widely used as anti-HBV agent in patients coinfecting with HIV, many of whom unfortunately currently harbour LAM-resistant HBV [51,52]. Overall, HBV resistance mutations can be recognized in 94% of HBV viremic patients with HIV infection who have received LAM for over 4 years [53].

Adefovir

Adefovir was the first nucleotide analogue approved for the treatment of HBV. ADV inhibits HIV at doses greater

than approved for treating HBV, but with high risk of nephrotoxicity. At doses of 10 mg/day, ADV suppresses HBV replication, and interestingly is associated with a low rate of resistance compared with LAM [54–56].

In HBV/HIV-coinfecting individuals, ADV was examined in 35 patients with ongoing antiretroviral therapy, including LAM. After 144 weeks of adding ADV, a decrease in serum HBV-DNA was observed in 45% of patients, slightly lower than the 56% observed in HBV mono-infection [57]. Selection of K65R in HIV using ADV monotherapy in coinfecting patients not taking antiretroviral therapy has been a matter of concern, but has not yet been shown even after checking minor virus populations [58].

It is noteworthy that 5–10% of CHB patients do not respond to ADV [59–61]. Several reasons may explain this failure and include pharmacokinetic/pharmacodynamic limitations of the low ADV dosing, genetic polymorphisms (I233V and L217R) [59–61], and cross-resistance with LAM upon selection of changes at codon 181 (A→STV) [53,62].

Entecavir

Entecavir (ETV) is a guanosine analogue that inhibits HBV replication at three different steps (priming, reverse transcriptase and positive strand synthesis) [63]. It is more potent in suppressing serum HBV-DNA than LAM and ADV and is effective against wild type and LAM-resistant and ADV-resistant HBV [64–66]. ETV resistance results from the accumulation of multiple changes in the HBV polymerase in patients with LAM resistance mutations [67]. For this reason, ETV doses of 0.5 mg/day are recommended for LAM-naïve patients, but 1 mg/day is advised for patients with LAM-resistant HBV.

While ETV was originally not thought to be active against HIV [68], recent reports have highlighted that it can reduce plasma HIV-RNA and select M184V in HIV [69,70]. However, the drug seems to exert only a minimal antiretroviral activity [71], although unfortunately enough to select for M184V in HIV [72]. As a result of these findings, a warning from the FDA has alerted against the use of ETV in HIV-infected patients in the absence of antiretroviral therapy. There are also concerns about potential interactions of ETV with some antiretrovirals, for example abacavir, which is another guanosine analogue which might be subject to inhibitory competition [72,73].

Telbivudine

Telbivudine (LdT) is a thymidine L-analogue with no activity against HIV. It has greater anti-HBV efficacy than either LAM or ADV and selects for resistance mutations at intermediate rates [74]. In registration studies, up to 60% of HBeAg+ CHB individuals achieved undetectable HBV-DNA after 12 months of LdT compared with 40% treated with LAM. In the second year of treatment, this

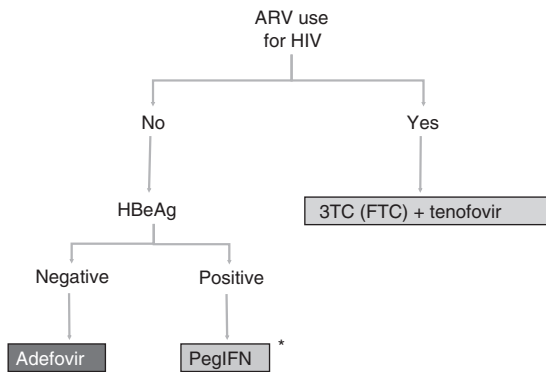


Fig. 2. Treatment of choice for chronic hepatitis B in HIV. Asterisk denotes contraindicated in decompensated cirrhosis. ARV, antiretroviral drug; HBeAg, hepatitis B e antigen; FTC, emtricitabine; pegIFN, pegylated interferon.

rate decreased to 54% due to selection of LdT resistance [74–77]. Characteristically, LdT selects for mutation M204I, with cross-resistance to LAM; therefore, LdT cannot be used following LAM failure, and vice versa. Interestingly, there is no evidence of cross-resistance between LdT and ADV. Finally, no studies have been conducted as yet to test the activity and safety of LdT in HBV/HIV coinfection, nor potential pharmacodynamic interactions with other thymidine analogues, such as zidovudine and stavudine.

Emtricitabine

Like LAM, emtricitabine (FTC) is a cytosine analogue with antiviral activity against both HBV and HIV. It has a longer half-life than LAM and similarly induces a rapid and sharp reduction in 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 [78,79]. No data are available on the use of FTC alone in HBV/HIV coinfection, although wide experience already exists derived from using the drug in combination with TDF in a single pill formulation (Truvada). In fact, Truvada is the preferred choice for treating CHB in HIV-infected patients with a need for antiretroviral therapy, as shown in Fig. 2 [4]. This combination provides potent anti-HBV activity along with a solid backbone for a triple antiretroviral regimen. Like LAM, FTC should not be used as monotherapy in HBV/HIV-coinfected persons due to high risk for selecting M184V in HIV. As FTC and LAM show almost total cross-resistance, FTC should not be prescribed after LAM failure.

Tenofovir

Tenofovir is an adenosine nucleotide analogue, already approved for the treatment of HIV infection. It shows potent activity against HBV in patients with and without LAM resistance [80–85]. HBV resistance to TDF has been occasionally described in HBV/HIV-coinfected patients with LAM resistance mutations. Selection of one additional change, A194T, resulted in more than 10-fold

loss of susceptibility to TDF [86]. Other studies, however, have not confirmed the involvement of this change as cause of TDF resistance. Large clinical trials are currently ongoing to prove the safety and efficacy of TDF in HBV-monoinfected patients. The ACTG A5127 trial was interrupted prematurely after showing that TDF was noninferior to ADV, with evidence that in fact TDF was superior [87]. More recently, a trial has shown superiority of TDF over ADV in drug-naïve CHB-monoinfected patients [88]. In a multicentre European study, TDF–LAM was as potent as TDF after LAM failure, which reflects the lack of cross-resistance between TDF and LAM, and the high potency of TDF, able to overcome any extra benefit of LAM [89].

Preferred drug choice

When HBV infection requires treatment but HIV does not, treatment options for HBV should include agents with no clinical activity against HIV, such as pegIFN, ADV or LdT (Fig. 2). A 12-month course of pegIFN may be advisable for patients with 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 HBV-DNA upon stopping therapy, a benefit which cannot be achieved with any other drug. The limitation of pegIFN is its poor tolerability and lower efficacy in the HIV setting. Moreover, the drug is contraindicated in decompensated cirrhosis, although it can be used with caution in individuals with compensated cirrhosis [7].

For the rest of HBV/HIV-coinfected patients who do not require antiretroviral therapy, long-term nucleos(t)ide therapy is the only option. ADV and LdT may be good alternatives given alone or as combination because of the risk of selecting drug resistance (Fig. 3). If a single agent is used, then patients who do not reach undetectable serum HBV-DNA at week 24 of therapy should have ‘add on’ therapy with the other nucleos(t)ide [76,77]. Adding a drug rather than replacing it is advised, because of reduced risk of HBV resistance with combination. Drugs

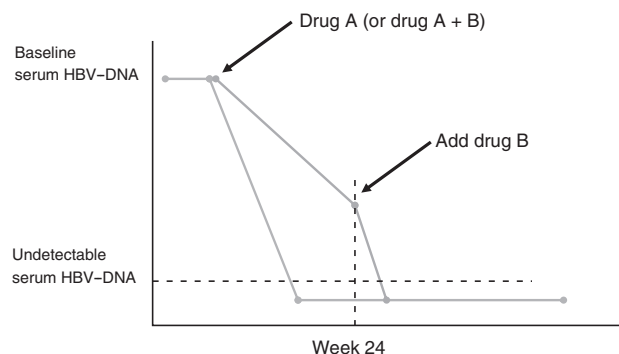


Fig. 3. Initial treatment approach for hepatitis B virus. The principle of ‘very early add-on therapy’. HBV, hepatitis B virus.

with dual HIV and HBV antiviral effect, such as LAM, FTC or TDF should never be used as single agents, given the risk for selecting HIV resistance.

An alternative option is to advance the introduction of antiretroviral therapy, and then include the combination of TDF–FTC (or LAM) as nucleos(t)ide backbone as part of a triple antiretroviral regimen [90]. This option may be particularly reasonable for patients with high plasma HIV-RNA and/or with active risk behaviours, for whom the risk of progression and/or transmission to others, respectively, is increased. Recent HIV treatment guidelines have encouraged this attitude [91].

When both HIV and HBV meet criteria for treatment, the combination TDF–FTC (or LAM) is the preferred choice. Prior exposure to LAM selects for resistance mutations to LdT and occasionally ADV [92]. For individuals with prior LAM exposure and uncontrolled HBV replication, LAM 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, and viral load monitored periodically (every 3 months) to ensure that undetectable viremia is achieved relatively shortly; otherwise drug pressure will drive selection of resistance. With respect to TDF, several studies [80–85] have clearly established its activity in the face of LAM-resistant HBV, with an average reduction of four logs in serum HBV-DNA.

Drug resistance in hepatitis B virus

Failure of anti-HBV therapy can be primary or secondary. Primary antiviral failure is defined as less than one log reduction in serum HBV-DNA within the first 3 months of anti-HBV therapy, generally owing to poor pharmacology with lack of drug potency [53,93]. Transmission of drug-resistant strains might also produce primary failure, but in contrast with the HIV epidemic, this event is still very rare in HBV [94]. Secondary failure generally results either from poor drug adherence or drug resistance or both, and is defined by an increase of greater than one log in HBV-DNA from nadir in patients who initially responded to therapy. HBV-associated drug resistance mutations can be divided into primary and secondary changes. The first ones are directly responsible for lack of susceptibility while the secondary changes tend to be compensatory, which improve the impaired fitness of mutant viruses [53,95]. Figure 4 summarizes the main drug resistance mutations so far described in HBV.

The rate of emergence of HBV resistance mutations can be graded: LAM > FTC > LdT > ADV > ETV > TDF (Fig. 5). While one single mutation may annul the activity of some drugs (e.g., M204I for LAM, FTC and LdT), several changes are required to compromise the activity of others (e.g., L180M+M204V+T250V for ETV). Once

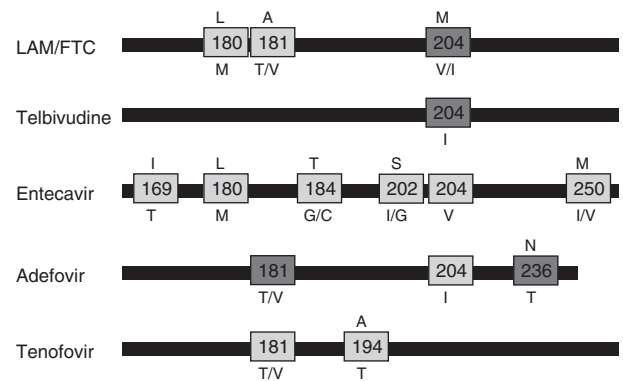


Fig. 4. Hepatitis B virus drug resistance mutations. FTC, emtricitabine; LAM, lamivudine.

resistance has developed to one agent, cross-resistance may reduce or completely hamper the activity of other drugs. This is particularly true for LAM resistance mutations, which annul the activity of FTC and LdT, to a lesser extent of ETV, and occasionally of ADV, while TDF remains active in most instances.

Viral particles in HBV infection are subject to a very rapid turnover, even more pronounced than for HIV [96]. The HBV polymerase cannot correct errors during the replication process and therefore HBV exists as a quasispecies population of close but distinct genomes in a continuous dynamic flow, with preexistence of all changes that may cause drug resistance. Given that the half-life of HBV-infected hepatocytes is longer than most HIV-infected lymphocytes, selection and accumulation of HBV-associated drug resistance mutations takes longer than HIV-associated resistance changes. Figure 6 shows the steady process accompanying HBV resistance, in which initial genotypic changes precedes by weeks or months viral rebounds, with liver enzyme elevations occurring with a variable delay in time. As in HIV, the best way to

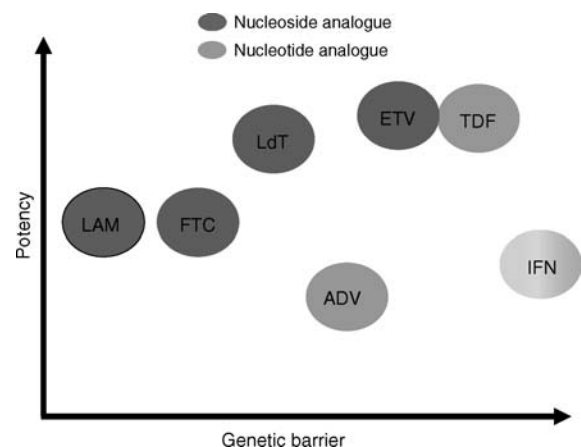


Fig. 5. Potency and genetic barrier for resistance of anti-hepatitis B virus drugs. ADV, adefovir; ETV, entecavir; FTC, emtricitabine; IFN, interferon; LAM, lamivudine; LdT, telbivudine; TDF, tenofovir.

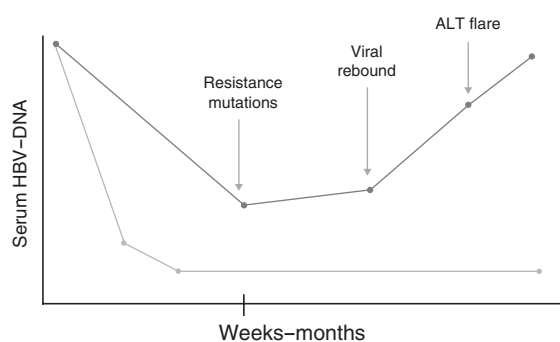


Fig. 6. Changes in hepatitis B virus failure. ALT, alanine aminotransferase; HBV, hepatitis B virus.

avoid or delay selection of HBV drug resistance is to achieve complete suppression of HBV replication. If so, the risk of accumulating further resistance changes is lowered, decreasing the risk of cross-resistance [97]. Although intriguingly anti-HBV combination therapy has not proven to enhance viral suppression, it reduces the risk of selecting drug resistance.

A phenomenon that has recently attracted much attention is that LAM resistance mutations may result in changes in HBV antigenicity. The HBV polymerase and envelope genes overlap and drug resistance mutations in the polymerase may alter HBsAg, causing diminished HBs antigen-antibody binding. This may result in failure of either diagnostic tests or vaccine escape, or both [53,98–100]. These mutations are more frequently found in patients infected by HBV genotype A, which is the most prevalent in European and North American HBV/HIV-coinfected individuals, particularly in homosexual men [101,102].

Delta hepatitis

HDV is a subviral satellite of HBV that depends on the HBsAg for the encapsidation of its own genome, a circular single-stranded RNA molecule of 1700 bp. As HDV shares the same routes of infection as HIV, HBV and HCV, coinfection with some or all these viruses is relatively frequent, especially among IDUs [103]. Therefore, delta superinfection should always be investigated in all HBsAg carriers. Screening for delta antibodies is sufficient for diagnosis.

Almost all individuals with antidelta antibodies are HDV viremic, and prone to develop the most severe form of chronic viral hepatitis [104]. HIV coinfection may further accelerate progression of delta-associated liver disease [104,105]. Thus, HIV-infected patients with delta hepatitis should always be considered candidates for treatment, although therapeutic options are very limited at this time and data on the potential efficacy of drugs other than interferon is scarce [106]. Preliminary findings suggest a benefit using the new potent nucleos(t)ide

analogues (e.g., TDF); however, improvement in liver enzymes, serum delta viremia and liver histology may be recognized only after several months or years of complete suppression of HBV replication [107]. In patients with a preserved immune function and compensated cirrhosis, treatment with pegIFN for 18 months or longer has proven to be efficacious in HIV-uninfected persons with delta hepatitis [108].

Multiple viral hepatitis

The prevalence of multiple viral hepatitis (HBV/HCV, HBV/HDV, HCV/HBV/HDV) in HIV-infected patients is below 3%, but much higher than in the general population [109]. Patients carrying HBV/HCV infections present a reciprocal inhibition of viral replication, with one virus predominating over the other [110]. This predominance may fluctuate over time [111]. However, in patients with severe immunosuppression, replication of all viruses may occur simultaneously [104]. In most HIV-infected patients with relatively good immune status, viral interference seems to favour HCV over HBV replication rather than vice versa [112]. However, the proportion of patients with HCV-antibody having negative serum HCV-RNA is much higher in HBsAg+ patients [113].

Progression of liver disease seems to be further accelerated in HIV-infected patients dually coinfecting with HBV and HCV [114]. Moreover, these individuals are more prone to develop hepatocellular carcinoma [11]. Overall, liver-related mortality is increased in this population as compared with HIV patients with either HBV or HCV [115]. This higher fatality is maintained even when antiretrovirals with anti-HBV activity, such as LAM, are used [116].

A few studies have examined the efficacy and safety of IFN-ribavirin in patients with dual HBV/HCV infections. While one study found a lower response for HCV in HBsAg+ patients compared with HCV-monoinfected individuals (43 versus 60%) [117], most studies have concluded that results are similar [118]. 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, as reactivation of latent infections may occur [119,120]. These usually reflect HBV rebounds following clearance of HCV during or after pegIFN-ribavirin therapy [121,122]; in contrast, HCV rebounds in patients receiving nucleoside analogues active against HBV are rare [122].

Hepatotoxicity of antiretroviral drugs

As for chronic hepatitis C, underlying CHB may enhance the toxicity of antiretroviral agents [123,124]. However,

the vast majority of patients with CHB tolerate HAART well, and the clinician should not delay initiating antiretroviral therapy when necessary [125]. In addition to drug injury, flares in transaminases in patients with CHB can be related to multiple different factors, including immune reconstitution phenomena, HBV rebound after withdrawal of effective anti-HBV therapy, breakthrough with drug-resistant HBV strains, or spontaneous flares of HBV viremia [126–128]. Aetiologies of liver enzyme elevations in HIV/HBV-coinfected patients following initiation of antiretroviral therapy are listed below:

- (1) direct drug-related liver injury;
- (2) immune reconstitution in HBsAg+ patients;
- (3) seroconversion from HBeAg+ and/or HBsAg+ patients;
- (4) HBV reactivation in inactive carriers and occasionally in those with resolved HBV infection;
- (5) selection of drug resistance to HBV;
- (6) development of other viral hepatitis [acute hepatitis A virus (HAV), HCV, HDV].

Seroconversion for either HBeAg or HBsAg may be accompanied by transient flare-ups in aminotransferases [129]. Clinicians must bear all these possibilities in mind before misinterpreting hepatic flares as drug injury.

Hepatitis B virus vaccination in HIV-infected patients

No distinctive adverse clinical reactions to HBV vaccination have been described in the HIV population. Transient elevations in plasma HIV-RNA lasting for several days or a few weeks have been sporadically reported. No prolonged viral load rise, CD4+ cell count decline accelerated HIV disease progression following HBV immunization have been seen [130].

Primary HBV vaccination consists of three intramuscular doses of the hepatitis B vaccine at 0, 1 and 6 months. It produces a protective antibody response in 30–55% of healthy adults aged less than 40 years after the first dose, 75% after the second dose, and greater than 90% after the third dose. Less than 10% of healthy immunocompetent individuals do not mount an appropriate anti-HBs response. Nonresponse is defined as an anti-HBs level less than 10 mIU/ml measured 1–6 months after the last immunization dose. After the age of 40 years, the proportion of persons who mount a protective antibody response declines (75% of vaccinated persons older than 60 years) [131,132]. The immunogenicity of hepatitis B vaccines is impaired in patients with HIV infection. The lack of response to hepatitis B vaccines is more common than for hepatitis A vaccines, because HBV immunogenicity is much more sensitive to CD4 cell counts [130]. Studies [133–138] conducted among HIV-infected

patients have demonstrated response rates of 17–56%, being the response largely influenced by CD4 cell counts. In HIV-infected patients experiencing good responses, protective antibody titres may be lower than in HIV-negative counterparts. In addition, after achieving an adequate HBV antibody response following vaccination, HIV-infected individuals are less likely to maintain sustained high and protective anti-HBs titres [139].

Immunocompetent persons who achieve anti-HBs levels greater than 10 mIU/ml after vaccination have nearly complete protection against HBV infection [131]. Even when anti-HBs titres decline to less than 10 mIU/ml, nearly all immunocompetent vaccinated persons remain protected against HBV infection [131]. The mechanism for continued vaccine-induced protection is thought to be the preservation of immune memory. In contrast, breakthrough HBV infections have been reported in HIV-infected patients when a decline in anti-HBs concentrations to less than 10 mIU/ml has occurred.

Several reimmunization schedules for nonresponders have been examined doubling the standard antigen dose or administering additional doses [140]. In the absence of HAART, a single additional dose of hepatitis B vaccine generally has no beneficial impact on seroconversion [134,141]. However, doubling the HBV vaccine dose may improve responses, at least in patients with higher CD4 cell counts [135,137]. These results, however, have not been confirmed by others [138].

A special situation is that of patients positive for anti-HBc but negative for both HBsAg and anti-HBs. They are infrequently seen in the general population but are common either in the HIV population or in those with chronic hepatitis C or both [142]. One study assessed whether HIV-infected patients with isolated anti-HBc could exhibit an anamnestic response following HBV vaccine, and concluded that only a minority did so [142]. Therefore, the presence of isolated anti-HBc in HIV-infected patients should not be interpreted as a surrogate marker of protection against HBV. Accordingly, these patients should be vaccinated [143].

Liver transplantation

Estimates of liver cirrhosis in HIV-infected patients living in western Europe and North America are of 3–4%, with 18 000/540 000 and 33 000/1 125 000 individuals, respectively [144,145]. These figures might be higher, as suggested by assessing the prevalence of cirrhosis using noninvasive tools, which are more sensitive for identifying mild compensated cirrhosis [146].

The management of HBV/HIV-coinfected persons with advanced liver cirrhosis is complex. Liver-related

complications such as portal hypertension, encephalopathy, ascites and hepatocellular carcinoma, should be managed as with HBV-monoinfected patients. Owing to an increased risk of life-threatening complications, persons with hepatic decompensation are not candidates for IFN or pegIFN therapy, unless orthotopic liver transplantation (OLT) is available. Antiretroviral therapy significantly improves short-term and mid-term outcomes in HIV-infected patients with hepatic decompensation [147] and therefore HAART, with anti-HBV agents in combination, should be given to all HBV viremic patients with decompensated cirrhosis. On the contrary, effective treatment of HIV in advanced cirrhosis may be challenging due to alterations in hepatic metabolism of antiretrovirals and risk of drug-induced liver injury [148–151].

At this time, OLT is the primary treatment option for eligible coinfecting patients with Child-Pugh stage B/C. Of note, mortality in the waiting list is increased in HIV-infected patients who, when possible, should be prioritized [152]. A large study [153] has shown that the cumulative survival in 24 HIV liver transplant recipients is similar to that of HIV-negative controls, being at 3 years of 73 and 78%, respectively. Factors independently associated with poor survival were posttransplant intolerance to HAART, CD4 cell counts less than 200 cells/ μ l, detectable plasma HIV-RNA, and HCV infection. Therefore, HIV infection should no longer be considered a contraindication for OLT. In contrast with HCV, which universally relapses following transplantation [154,155], HBV reinfection is rare (<10%) using prophylactic antihepatitis B immunoglobulin and nucleos(t)ide analogues. However, these patients may face complex drug interactions in the posttransplant period, mainly between immunosuppressors and protease inhibitors that require close monitoring and expertise. Accordingly, OLT in this population should be limited to transplant centres in which a multidisciplinary team including surgeons, hepatologists, pharmacologists and infectious diseases physicians work in concert.

Acknowledgement

This work was supported in part by unrestricted grants from Fundación Investigación y Educación en SIDA (IES), Gilead Sciences and Bristol-Myers-Squibb.

References

- Weber R, Sabin C, Friis-Moller N, Reiss P, El-Sadr W, Kirk O, et al. **Liver-related deaths in persons infected with the HIV: the D:A:D study.** *Arch Intern Med* 2006; **166**:1632–1641.
- Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, et al. **Care of patients coinfecting with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel.** *AIDS* 2007; **21**:1073–1089.
- Alberti A, Clumeck N, Collins S. **Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients.** *J Hepatol* 2005; **42**:615–624.
- Soriano V, Puoti M, Bonacini M. **Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel.** *AIDS* 2005; **19**:221–240.
- Alter M. **Epidemiology of viral hepatitis and HIV co-infection.** *J Hepatol* 2006; **44**:6–9.
- Konopnicki D, Mocroft A, de Wit S. **Hepatitis B and HIV: prevalence, AIDS progression, response to HAART and increased mortality in the EuroSIDA cohort.** *AIDS* 2005; **19**:2117–2125.
- Núñez M, Soriano V. **Management of patients co-infected with hepatitis B virus and HIV.** *Lancet Infect Dis* 2005; **5**:374–382.
- Modi A, Feld J. **Viral hepatitis and HIV in Africa.** *AIDS Rev* 2007; **9**:25–39.
- Hoffmann C, Thio C. **Clinical implications of HIV and hepatitis B co-infection in Asia and Africa.** *Lancet Infect Dis* 2007; **7**:402–409.
- Puoti M, Torti C, Bruno R. **Natural history of chronic hepatitis B in co-infected patients.** *J Hepatol* 2006; **44**:65–70.
- Puoti M, Bruno R, Soriano V, Donato F, Gaeta G, Quinzan G, et al. **Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome.** *AIDS* 2004; **18**:2285–2293.
- Brau N, Fox R, Xiao P, Marks K, Naqvi Z, Taylor L, et al. **Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a US-Canadian multicenter study.** *J Hepatol* 2007; **47**:527–537.
- Thio C, Seaberg E, Skolasky R. **HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter AIDS Cohort Study (MACS).** *Lancet* 2002; **360**:1921–1926.
- Maida I, Soriano V, Castellares C, Ramos B, Sotgiu G, Martin-Carbonero L, et al. **Liver fibrosis in HIV-infected patients with chronic hepatitis B extensively exposed to antiretroviral therapy with anti-HBV activity.** *HIV Clin Trials* 2006; **7**:246–250.
- Mallet V, Dhalluin-Venier V, Verkarre V, Correas J, Chaix ML, Viard J, et al. **Reversibility of cirrhosis in HIV/HBV coinfection.** *Antivir Ther* 2007; **12**:279–283.
- Soriano V, Sheldon J, Ramos B, Nunez M. **Confronting chronic hepatitis B virus infection in HIV: new diagnostic tools and more weapons.** *AIDS* 2006; **20**:451–453.
- Keeffe E, Zeuzem S, Koff R, Dieterich D, Esteban-Mur R, Gane E, et al. **Report of an international workshop: roadmap for management of patients receiving oral therapy for chronic hepatitis B.** *Clin Gastroenterol Hepatol* 2007; **5**:890–897.
- Iloeje U, Yang H, Su J. **Predicting cirrhosis risk based on the level of circulating hepatitis B virus viral load.** *Gastroenterology* 2006; **130**:678–686.
- Chen C, Yang H, Su J. **Risk of hepatocellular carcinoma across biological gradient of serum hepatitis B virus DNA level.** *JAMA* 2006; **295**:65–73.
- Iloeje U, Yang H, Jen C, Su J, Wang L, You S, et al. **Risk and predictors of mortality associated with chronic hepatitis B infection.** *Clin Gastroenterol Hepatol* 2007; **5**:921–931.
- Tillmann H. **Antiviral therapy and resistance with hepatitis B virus infection.** *World J Gastroenterol* 2007; **13**:125–140.
- Schaefer S. **Hepatitis B virus taxonomy and hepatitis B virus genotypes.** *World J Gastroenterol* 2007; **13**:14–21.
- Kao J. **Hepatitis B viral genotypes: clinical relevance and molecular characteristics.** *J Gastroenterol Hepatol* 2002; **17**:643–650.
- Lacombe K, Massari V, Girard P, Serfaty L, Gozlan J, Pialoux G, et al. **Major role of hepatitis B genotypes in liver fibrosis during coinfection with HIV.** *AIDS* 2006; **20**:419–427.
- Gunther S. **Genetic variation in HBV infection: genotypes and mutants.** *J Clin Virol* 2006; **36**:3–11.
- Janssen H, van Zonneveld M, Senturk H, Zeuzem S, Akarca U, Cakaloglu Y, et al. **Pegylated interferon alpha-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomized trial.** *Lancet* 2005; **365**:123–129.
- Zioli M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. **Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C.** *Hepatology* 2005; **4**:48–54.

28. Myers R, Tainturier M, Ratziu V, Piton A, Thibault V, Imbert-Bismut F, *et al.* **Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B.** *J Hepatol* 2003; **39**:222–230.
29. Kim B, Kim S, Park Y, Cheong Y, Kim H, Park J, *et al.* **Non-invasive models to predict liver cirrhosis in patients with chronic hepatitis B.** *Liver Int* 2007; **27**:969–976.
30. Ogawa E, Furusyo N, Toyoda K, Takeoka H, Otaguro S, Hamada M, *et al.* **Transient elastography for patients with chronic hepatitis B and C virus infection: non-invasive, quantitative assessment of liver fibrosis.** *Hepatol Res* 2007; **37**:1002–1010.
31. Macias J, Giron-Gonzalez JA, Gonzalez-Serrano M, Merino D, Cano P, Mira JA, *et al.* **Prediction of liver fibrosis in HIV/hepatitis C virus coinfecting patients by simple noninvasive indexes.** *Gut* 2006; **55**:409–414.
32. Nunes D, Fleming C, Offner G, O'Brien M, Tumilty S, Fix O, *et al.* **HIV infection does not affect the performance of non-invasive markers of fibrosis for the diagnosis of hepatitis C virus-related liver disease.** *J Acquir Immune Defic Syndr* 2005; **40**:538–544.
33. De Ledinghen V, Douvin C, Kettaneh A, Ziol M, Roulot D, Marcellin P, *et al.* **Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfecting patients.** *J Acquir Immune Defic Syndr* 2006; **41**:175–179.
34. Rodríguez-Torres M, Gonzalez-García J, Brau N, Sola R, Moreno S, Rockstroh J, *et al.* **Occult hepatitis B virus infection in the setting of hepatitis C virus (HCV) and HIV co-infection: clinically relevant or a diagnostic problem?** *J Med Virol* 2007; **79**:694–700.
35. Mrani S, Chemin I, Menouar K, Guillaud O, Pradat P, Borghi G, *et al.* **Occult HBV infection may represent a major risk factor of nonresponse to antiviral therapy of chronic hepatitis C.** *J Med Virol* 2007; **79**:1075–1081.
36. Tsui J, French A, Seaberg E, Augenbraun M, Nowicki M, Peters M, *et al.* **Prevalence and long-term effects of occult hepatitis B virus infection in HIV-infected women.** *Clin Infect Dis* 2007; **45**:736–740.
37. Núñez M, Puoti M, Camino N, Soriano V. **Treatment of chronic hepatitis B in HIV-infected patients: present and future.** *Clin Infect Dis* 2003; **37**:1678–1685.
38. Levy V, Grant R. **Antiretroviral therapy for hepatitis B virus-HIV coinfecting patients: promises and pitfalls.** *Clin Infect Dis* 2006; **43**:904–910.
39. Lok A, McMahon B. **Chronic hepatitis B. AASLD Practice Guidelines.** *Hepatology* 2007; **45**:507–539.
40. Keeffe E, Dieterich D, Han S-H. **A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update.** *Clin Gastroenterol Hepatol* 2006; **24**:1003–1016.
41. Hoofnagle J, Doo E, Liang J. **Management of hepatitis B: summary of a clinical research workshop.** *Hepatology* 2007; **45**:1056–1075.
42. Thomas H. **Best practice in the treatment of chronic hepatitis B: a summary of the European Viral Hepatitis Educational Initiative.** *J Hepatol* 2007; **47**:588–597.
43. Perrillo R, Schiff E, Davis G. **A randomized, controlled trial of interferon alfa 2-b alone and after prednisone withdrawal for the treatment of chronic hepatitis B.** *N Engl J Med* 1990; **323**:295–301.
44. Colin J, Cazals-Hatem D, Lioriot M. **Influence of HIV infection on chronic hepatitis B in homosexual men.** *Hepatology* 1999; **29**:1306–1310.
45. Cooksley W. **Treatment with interferons (including pegylated interferons) in patients with chronic hepatitis B.** *Semin Liver Dis* 2004; **24**:45–53.
46. Marcellin P, Lau G, Bonino F. **Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B.** *N Engl J Med* 2004; **351**:1206–1217.
47. Lau G, Piratvisuth T, Luo K. **Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B.** *N Engl J Med* 2005; **352**:2682–2695.
48. Di Martino V, Thevenot T, Colin J. **Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B.** *Gastroenterology* 2002; **123**:1812–1822.
49. Garcia-Gasco P, Sheldon J, Soriano V. **Treatment of chronic hepatitis B in HIV-infected patients in the year 2007.** *J HIV Ther* 2007; **12**:19–23.
50. Suzuki F, Tsubota A, Arase Y. **Efficacy of lamivudine therapy and factors associated with emergence of resistance in chronic hepatitis B virus infection in Japan.** *Intervirology* 2003; **46**:182–189.
51. Matthews G, Bartholomeusz A, Locarnini S. **Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV-infected individuals on extended lamivudine therapy.** *AIDS* 2006; **20**:863–870.
52. Ramos B, Nuñez M, Martin-Carbonero L. **Hepatitis B virus genotypes and lamivudine resistance mutations in HIV/hepatitis B virus-coinfecting patients.** *J Acquir Immune Defic Syndr* 2007; **44**:557–561.
53. Thio C, Locarnini S. **Treatment of HIV-HBV co-infection: clinical and virological issues.** *AIDS Rev* 2007; **9**:40–53.
54. Marcellin P, Chang T, Lim S. **Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B.** *N Engl J Med* 2003; **348**:808–816.
55. Hadziyannis S, Tassopoulos N, Heathcote E. **Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B.** *N Engl J Med* 2005; **352**:2673–2681.
56. Buti M, Elefsiniotis I, Jardi R, Vargas V, Rodríguez-Frias F, Schapper M, *et al.* **Viral genotype and baseline load predict the response to adefovir treatment in lamivudine-resistant chronic hepatitis B patients.** *J Hepatol* 2007; **47**:366–372.
57. Benhamou Y. **Treatment algorithm for chronic hepatitis B in HIV-infected patients.** *J Hepatol* 2006; **44**:90–94.
58. Sheldon J, Corral A, Rodes B, Soriano V. **Risk of selecting K65R in antiretroviral-naïve HIV-infected individuals with chronic hepatitis B treated with adefovir.** *AIDS* 2005; **19**:2036–2038.
59. Schildgen O, Schewe C, Vogel M, Rockstroh J. **Successful therapy of hepatitis B with tenofovir in HIV-infected patients failing previous adefovir and lamivudine treatment.** *AIDS* 2004; **18**:2325–2327.
60. Chang T, Lai C. **Hepatitis B virus with primary resistance to adefovir.** *N Engl J Med* 2006; **355**:322–323.
61. Schildgen O, Sirma H, Funk A. **Variant of hepatitis B virus with primary resistance to adefovir.** *N Engl J Med* 2006; **354**:1807–1812.
62. Karatayli E, Karayalcin S, Karaaslan H. **A novel mutation pattern emerging during lamivudine treatment shows cross-resistance to adefovir dipivoxil treatment.** *Antivir Ther* 2007; **12**:761–768.
63. Seifer M, Hamatake R, Colonno R. **In vitro inhibition of hepadnavirus polymerase by triphosphates of BMS-200475 and lobucavir.** *Antimicrob Agents Chemother* 1998; **42**:3200–3208.
64. Chang T, Gish R, De Man R. **A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B.** *N Engl J Med* 2006; **354**:1001–1010.
65. Lai C, Shouval D, Lok A. **Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B.** *N Engl J Med* 2006; **354**:1011–1020.
66. Yao G. **Entecavir is a potent anti-HBV drug superior to lamivudine: experience from clinical trials in China.** *J Antimicrob Chemother* 2007; **60**:201–205.
67. Tenney D, Levine S, Rose R. **Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to lamivudine.** *Antimicrob Agents Chemother* 2004; **48**:3498–3507.
68. Innaimo S, Seifer M, Bisacchi G, Standing D, Zahler R, Colonno R. **Identification of BMS-200475 as a potent and selective inhibitor of HBV.** *Antimicrob Agents Chemother* 1997; **41**:1444–1448.
69. McMahon M, Jilek B, Brennan T, Thio C. **The HBV drug entecavir: effects on HIV-1 replication and resistance.** *N Engl J Med* 2007; **356**:2614–2621.
70. Jain M, Zoellner C. **Entecavir can select for M184V of HIV-1: a case of an HIV/hepatitis B (HBV) naïve patient treated for chronic HBV.** *AIDS* 2007; **21**:2365–2366.
71. Soriano V, Sheldon J, Garcia-Gasco P, Vispo E. **Lack of anti-HIV activity of entecavir in an HIV patients coinfecting with hepatitis B and delta viruses.** *AIDS* 2007; **21**:2253–2254.
72. Soriano V, Vispo E, Labarga P, Barreiro P. **A low antiretroviral activity of the antihepatitis B drug entecavir may be enough to select for M184V in HIV-1.** *AIDS* 2008; **22**:911–912.

73. Barreiro P, Garcia-Benayas T, Rendon AL, Rodriguez-Novoa S, Soriano V. **Combinations of nucleoside/nucleotide analogues for HIV therapy.** *AIDS Rev* 2004; **6**:234–243.
74. Ruiz-Sancho A, Sheldon J, Soriano V. **Telbivudine: a new option for the treatment of chronic hepatitis B.** *Expert Opin Biol Ther* 2007; **7**:751–761.
75. Lai C, Leung N, Teo E. **A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B.** *Gastroenterology* 2005; **129**:528–536.
76. Lai C, Gane E, Liaw Y, Hsu C, Thongsawat S, Wang Y, *et al.* **Telbivudine versus lamivudine in patients with chronic hepatitis B.** *N Engl J Med* 2007; **357**:2576–2588.
77. Chan H, Heathcote J, Marcellin P, Lai C, Cho M, Moon Y, *et al.* **Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial.** *Ann Intern Med* 2007; **147**:745–754.
78. Bang L, Scott L. **Emtricitabine.** *Drugs* 2003; **63**:2413–2424.
79. Lim S, Ng T, Kung N. **A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B.** *Arch Intern Med* 2006; **166**:49–56.
80. Núñez M, Pérez-Olmeda M, Díaz B, Ríos P, González-Lahoz J, Soriano V. **Activity of tenofovir on hepatitis B virus replication in HIV-co-infected patients failing or partially responding to lamivudine.** *AIDS* 2002; **16**:2352–2354.
81. Nelson M, Portsmouth S, Stebbing J. **An open-label study of tenofovir in HIV-1 and hepatitis B virus co-infected individuals.** *AIDS* 2003; **17**:F7–F10.
82. Dore G, Cooper D, Pozniak A. **Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naïve and experienced patients coinfecting with HIV-1 and hepatitis B virus.** *J Infect Dis* 2004; **189**:1185–1192.
83. Van Bommel F, Wunsche T, Mauss S. **Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection.** *Hepatology* 2004; **40**:1421–1425.
84. Ristig M, Crippin J, Aberg J. **Tenofovir disoproxil fumarate for chronic hepatitis B in HIV-coinfected individuals for whom interferon alpha and lamivudine therapy have failed.** *J Infect Dis* 2002; **186**:1844–1847.
85. Benhamou Y, Fleury H, Trimoulet P. **Antihepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients.** *Hepatology* 2006; **43**:548–555.
86. Sheldon J, Camino N, Rodes B, Soriano V. **Selection of hepatitis B virus polymerase mutations in HIV coinfecting patients treated with tenofovir.** *Antivir Ther* 2005; **10**:727–734.
87. Peters M, Andersen J, Lynch P. **Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127.** *Hepatology* 2006; **44**:1110–1116.
88. Marcellin P, Buti M, Krastev Z, Germanidis G, Kaita K, Kotzev I, *et al.* **A randomized double blind comparison of tenofovir versus adefovir for the treatment of HBeAg-negative chronic hepatitis B: study GS-US-174-0102.** *Hepatology* 2007; **46** (Suppl 1):290A.
89. Schmutz G, Nelson M, Lutz T, Sheldon J, Bruno R, von Boemmel F, *et al.* **Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection.** *AIDS* 2006; **20**:1951–1954.
90. Thio C, Sulkowski M, Thomas D. **Treatment of chronic hepatitis B in HIV-infected persons: thinking outside the black box.** *Clin Infect Dis* 2005; **41**:1035–1040.
91. DHHS. **Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.** <http://AIDSinfo.nih.gov> [Updated 1 December 2007]
92. Osborn M, Lok A. **Antiviral options for the treatment of chronic hepatitis B.** *J Antimicrob Chemother* 2006; **57**:1030–1034.
93. Locarnini S, Hatzakis A, Heathcote J, Zoulim F. **Management of antiviral resistance in patients with chronic hepatitis B.** *Antivir Ther* 2004; **9**:679–693.
94. Thibault V, Aubron-Olivier C, Agut H, Katlama C. **Primary infection with a lamivudine-resistant hepatitis B virus.** *AIDS* 2002; **16**:131–133.
95. Sheldon J, Rodes B, Zoulim F, Bartholomeusz A, Soriano V. **Mutations affecting the replication capacity of the hepatitis B virus.** *J Viral Hepat* 2006; **13**:427–434.
96. Nowack M, Bonhoeffer S, Hill A, Boehme R, Thomas H, McDade H. **Viral dynamics in hepatitis B virus infection.** *Proc Natl Acad Sci U S A* 1996; **93**:4398–4402.
97. Nafa S, Ahmed S, Tavan D, Pichoud C, Berby F, Stuyver L, *et al.* **Early detection of viral resistance by determination of hepatitis B virus polymerase mutations in patients treated by lamivudine for chronic hepatitis B.** *Hepatology* 2000; **32**:1078–1088.
98. Cooley L, Ayres A, Bartholomeusz A, Lewin S, Crowe S, Mijch A, *et al.* **Prevalence and characterization of lamivudine-resistant hepatitis B virus mutations in HIV-HBV co-infected individuals.** *AIDS* 2003; **17**:1649–1657.
99. Sheldon J, Ramos B, Garcia-Samaniego J, Rios P, Bartholomeusz A, Romero M, *et al.* **Selection of hepatitis B virus (HBV) vaccine escape mutants in HBV-infected and HBV/HIV-coinfecting patients failing antiretroviral therapies with anti-HBV activity.** *J Acquir Immune Defic Syndr* 2007; **46**:279–282.
100. Sheldon J, Soriano V. **Hepatitis B virus escape mutants induced by antiviral therapy.** *J Antimicrob Agents* 2008; **61**:766–768.
101. Perez-Olmeda M, Nuñez M, Garcia-Samaniego J, Rios P, Gonzalez-Lahoz J, Soriano V. **Distribution of hepatitis B virus genotypes in HIV-infected patients with chronic hepatitis B: therapeutic implications.** *AIDS Res Human Retroviruses* 2003; **19**:657–659.
102. Halfon P, Bourliere, Pol S, Benhamou Y, Ouzan D, Rotily M, *et al.* **Multicentre study of hepatitis B virus genotypes in France: correlation with liver fibrosis and hepatitis B e antigen status.** *J Viral Hepat* 2006; **13**:329–335.
103. Farci P. **Delta hepatitis: an update.** *J Hepatol* 2003; **39**:212–219.
104. De Pouplana M, Soriano V, Garcia-Samaniego J, *et al.* **More severe course of delta hepatitis in HIV-infected patients.** *Genitourin Med* 1995; **71**:132–133.
105. Sheng W, Hung C, Kao J, Chang S, Chen M, Hsieh S, *et al.* **Impact of hepatitis D virus infection on the long-term outcomes of patients with hepatitis B virus and HIV coinfection in the era of HAART: a matched cohort study.** *Clin Infect Dis* 2007; **44**:988–995.
106. Manesis E, Schina M, Le Gal F, Agelopoulos O, Papaionnaou C, Kalligeros C, *et al.* **Quantitative analysis of hepatitis D virus RNA and hepatitis B surface antigen serum levels in chronic delta hepatitis improves treatment monitoring.** *Antivir Ther* 2007; **12**:381–388.
107. Sheldon J, Ramos B, Toro C, Rios P, Martinez-Alarcon J, Bottecchia M, *et al.* **Does treatment of hepatitis B virus (HBV) infection reduce hepatitis delta virus (HDV) replication in HIV/HBV/HDV co-infected patients?** *Antivir Ther* 2008; **13**:97–102.
108. Niro G, Ciancio A, Gaeta G, Marrone A, Olivero A, Stanzone M, *et al.* **Pegylated interferon alpha-2b monotherapy and in combination with ribavirin in chronic hepatitis delta.** *J Hepatol* 2006; **44** (Suppl 2):188.
109. Arribas J, Gonzalez J, Lorenzo A, Montero D, Ladron D, Montes M, *et al.* **Single (B or C), dual (BC or BD) and triple (BCD) viral hepatitis in HIV-infected patients in Madrid, Spain.** *AIDS* 2005; **19**:1361–1365.
110. Jardi R, Rodriguez F, Buti M, Costa X, Cortina M, Galimany R, *et al.* **Role of hepatitis B, C, and D viruses in dual and triple infection: influence of viral genotypes and hepatitis B precore and basal core promoter mutations on viral replicative interference.** *Hepatology* 2001; **34**:404–410.
111. Raimondo G, Brunetto M, Pontisso P, Smedile A, Maina A, Saitta C, *et al.* **Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfecting patients.** *Hepatology* 2006; **43**:100–107.
112. Martin-Carbonero L, Barreiro P, Jimenez-Galan G, Garcia-Berriguete R, Nuñez M, Rios P, *et al.* **Spontaneous clearance of hepatitis C virus in HIV-infected patients with multiple chronic viral hepatitis.** *J Viral Hepat* 2007; **14**:392–395.
113. Nuñez M, Maida I, Babudieri S, Fedu L, Camino N, Gonzalez-Lahoz J, *et al.* **Hepatitis C viremia in HIV/HCV-coinfecting patients: lower levels in presence of chronic hepatitis B.** *HIV Clin Trials* 2005; **6**:103–106.
114. Sagnelli E, Pasquale G, Coppola N, Scarano F, Marrocco C, Scolastico C, *et al.* **Influence of chronic coinfection with hepatitis B and C virus on liver histology.** *Infection* 2004; **32**:144–148.
115. Bonacini M, Louie S, Bzowej N, Wohl A. **Survival in patients with HIV infection and viral hepatitis B or C: a cohort study.** *AIDS* 2004; **18**:2039–2045.

116. Puoti M, Cozzi-Lepri A, Friis-Moller N, Arici C, Lundgren J, Ledergerber B, *et al.* **Impact of lamivudine on the risk of liver-related death in 2041 HBsAg- and HIV-positive individuals: results from an inter-cohort analysis.** *Antivir Ther* 2006; **11**:567–574.
117. Liu C, Chen P, Lai M, Kao J, Jeng Y, Chen D. **Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients.** *Hepatology* 2003; **37**:568–576.
118. Hung C, Lee C, Lu S, Wang J, Tung H, Chen C, *et al.* **Combination therapy with interferon-alpha and ribavirin in patients with dual hepatitis B and hepatitis C virus infection.** *J Gastroenterol Hepatol* 2005; **20**:727–732.
119. Chuang W, Dai C, Chang W, Lee L, Lin Z, Chen S, *et al.* **Viral interaction and responses in chronic hepatitis C and B coinfecting patients with interferon-alpha plus ribavirin combination therapy.** *Antivir Ther* 2005; **10**:125–133.
120. Yalcin K, Degertekin H, Yildiz F, Kilinc N. **A severe hepatitis flare in an HBV-HCV coinfecting patient during combination therapy with alpha-interferon and ribavirin.** *J Gastroenterol* 2003; **38**:796–800.
121. Chakvetadze C, Bani-Sadr F, Le Pendeven C, Lamontagne F, Vincensini J, Pialoux G. **Reactivation of hepatitis B virus replication during peginterferon-ribavirin therapy in an HIV/hepatitis C virus-co-infected patient with isolated anti-hepatitis B core antibodies.** *AIDS* 2007; **21**:393–394.
122. Soriano V, Barreiro P, Castellares C, Ruiz-Sancho A, Labarga P, Ramos B, *et al.* **Treatment of chronic hepatitis B and/or C in HIV-infected patients with multiple viral hepatitis infections.** *J Infect Dis* 2007; **195**:1181–1183.
123. Sulkowski M, Thomas D, Chaisson R, Moore R. **Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection.** *JAMA* 2000; **283**:74–80.
124. Aceti A, Pasquazzi C, Zechini B, De Bac C, The LIVERHAART Group. **Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection.** *J Acquir Immune Defic Syndr* 2002; **29**:41–48.
125. Cicconi P, Cozzi-Lepri A, Phillips A. **Is the raised risk of liver enzyme elevation in hepatitis co-infected patients any greater in those on antiretroviral therapy than in naïve patients?** *AIDS* 2007; **21**:599–606.
126. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman K. **Chronic active hepatitis B exacerbations in HIV-infected patients following development of resistance to or withdrawal of lamivudine.** *Clin Infect Dis* 1999; **28**:1032–1035.
127. Honkoop P, De Man R, Niesters H, Zondervan P, Schalm S. **Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy.** *Hepatology* 2000; **32**:635–639.
128. McGovern B. **What drives hepatitis B virus-related hepatic flares? Virus, T cells: or a bit of both?** *Clin Infect Dis* 2004; **39**:133–135.
129. Velasco M, Moran A, Tellez MJ. **Resolution of chronic hepatitis B after ritonavir treatment in an HIV-infected patient.** *N Engl J Med* 1999; **340**:1765–1766.
130. Laurence J. **Hepatitis A and B immunizations of individuals infected with HIV.** *Am J Med* 2005; **118** (Suppl 10A):75–83.
131. Mast E, Weinbaum C, Fiore A, Alter M, Bell B, Finelli L, *et al.* **A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults.** *MMWR Recomm Rep* 2006; **55**:1–33.
132. Yu A, Cheung R, Keeffe E. **Hepatitis B vaccines.** *Infect Dis Clin North Am* 2006; **20**:27–45.
133. Collier A, Corey L, Murphy V, Handsfield H. **Antibody to HIV and suboptimal response to hepatitis B vaccination.** *Ann Intern Med* 1988; **109**:101–105.
134. Keet I, van Doornum G, Safary A, Coutinho R. **Insufficient response to hepatitis B vaccination in HIV-positive homosexual men.** *AIDS* 1992; **6**:509–510.
135. Rey D, Krantz V, Partisani M, Schmitt M, Meyer P, Libbrecht E, *et al.* **Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load.** *Vaccine* 2000; **18**:1161–1165.
136. Overton E, Sungkanuparph S, Powderly W, Seyfried W, Groger R, Aberg J. **Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons.** *Clin Infect Dis* 2005; **41**:1045–1048.
137. Fonseca M, Pang L, de Paula-Cavalleiro N, Barone A, Heloisa-Lopes M. **Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose.** *Vaccine* 2005; **23**:2902–2908.
138. Cornejo P, Volkow P, Escobedo K, Vilar D, Ruiz G, Soto-Ramirez L. **Randomized controlled trial of hepatitis B virus vaccine in HIV-1-infected patients comparing two different doses.** *AIDS Res Ther* 2006; **3**:9.
139. Veiga A, Cassej J, Duarte A. **Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naïve) and CD45RO+ (memory) subsets in HIV-1-infected subjects.** *Vaccine* 2006; **24**:7124–7128.
140. Sjogren M. **Prevention of hepatitis B in nonresponders to initial hepatitis B virus vaccination.** *Am J Med* 2005; **118** (Suppl 10A):34–39.
141. Brook G. **Prevention of viral hepatitis in HIV co-infection.** *J Hepatol* 2006; **44** (Suppl 1):104–107.
142. Gandhi R, Wurcel A, Lee H, McGovern B, Shopis J, Geary M, *et al.* **Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies.** *J Infect Dis* 2005; **191**:1435–1441.
143. Rivas P, Herrero MD, Puente S, Ramirez-Olivencia G, Soriano V. **Immunizations in HIV-infected adults.** *AIDS Rev* 2007; **9**:173–187.
144. Hamers F, Downs A. **The changing face of the HIV epidemic in western Europe: what are the implications for public health policies?** *Lancet* 2004; **364**:83–94.
145. Fung J, Eghtesad B, Patel-Tom K, de Vera M, Chapman H, Ragni M. **Liver transplantation in patients with HIV infection.** *Liver Transpl* 2004; **10** (Suppl 2):39–53.
146. Castellares C, Barreiro P, Martin-Carbonero L, Labarga P, Vispo E, Casado R, *et al.* **Liver cirrhosis in HIV-infected patients: prevalence, aetiology and clinical outcome.** *J Viral Hepat* 2008; **15**:165–172.
147. Merchante N, Giron-Gonzalez JA, Gonzalez-Serrano M, Torre-Cisneros J, Garcia-Garcia JA, Arizcorreta A, *et al.* **Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease.** *AIDS* 2006; **20**:49–57.
148. Wyles D, Gerber J. **Antiretroviral drug pharmacokinetics in hepatitis with hepatic dysfunction.** *Clin Infect Dis* 2005; **40**:174–181.
149. Barreiro P, Rodriguez-Novoa S, Labarga P, Ruiz A, Jimenez-Nacher I, Martin-Carbonero L, *et al.* **Influence of liver fibrosis stage on plasma levels of antiretroviral drugs in HIV-infected patients with chronic hepatitis C.** *J Infect Dis* 2007; **195**:973–979.
150. Aranzabal L, Casado JL, Moya J, Moreno S. **Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection.** *Clin Infect Dis* 2005; **40**:588–593.
151. Soriano V, Puoti M, Garcia-Gasco P, Rockstroh J, Benhamou Y, Barreiro P, *et al.* **Antiretroviral drugs and liver injury.** *AIDS* 2008; **22**:1–13.
152. Maida I, Nunez M, Gonzalez-Lahoz J, Soriano V. **Liver transplantation in HIV-HCV coinfecting candidates: what is the most appropriate time for evaluation?** *AIDS Res Hum Retroviruses* 2005; **21**:599–601.
153. Ragni M, Belle S, Im K, Neff G, Roland M, Stock P, *et al.* **Survival of HIV-infected liver transplant recipients.** *J Infect Dis* 2003; **188**:1412–1420.
154. Vennarecci G, Ettore G, Antonini M, Santoro R, Perracchio L, Visco G, Santoro E. **Liver transplantation in HIV-positive patients.** *Transplant Proc* 2007; **39**:1936–1938.
155. Miro JM, Aguero F, Laguno M, Tuset M, Cervera C, Moreno A, *et al.* **Liver transplantation in HIV/hepatitis co-infection.** *J HIV Ther* 2007; **12**:24–35.