AIDS Rev 2002;4:27-35

Hepatitis B Virus Co-infection in Human Immunodeficiency Virus-infected Subjects

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Abstract

Shared epidemiological risks have resulted in HIV-infected populations having a high prevalence of hepatitis B virus (HBV) co-infection. Several prospective studies have investigated the impact of HBV co-infection on HIV disease progression; most of them were negative. On the contrary, there is evidence that HIV may modify the natural history of HBV infection. HIV positive subjects have higher rates of HBV chronification, higher HBV replication, lower ALT levels and lower rates of seroconversion to anti-HBe and anti-HBs. The impact of HIV co-infection on the outcome of HBV infection is still controversial, even if some studies have shown an accelerated progression towards decompensated cirrhosis in HIV co-infected subjects. HBV co-infection is a risk factor for severe hepatotoxicity during HAART. Vaccination for HBV is mandatory in non-immune HIV subjects, however its efficacy in immunesuppressed patients is still controversial. HIV co-infection decreases the effectiveness of Interferon in the treatment of HBV infection. Because of its activity against both HBV and HIV, lamivudine is used in HIV-HBV co-infected patients at doses of 300 mg/daily and as part of an antiretroviral regimen, but the rate of sustained response is poor and HBV strains with mutations associated with lamivudine resistance occur at a rate of 20% per year. Trials of new drugs with activity against HBV, some of them with activity also against HIV, and some of them without cross-resistance with lamivudine, are now underway. Highly Active Anti-Hepatitis B Therapy will probably soon come of age.

Key words

HIV. HBV. Cirrhosis. HAART. Lamivudine. Adefovir.

Introduction

The introduction of highly active antiretroviral therapies (HAART) has significantly increased the life expectancy of HIV-infected patients[1]. In the last few years, unfortunately, the consequences of chronic hepatitis have become clearer, either as result of decompensated cirrhosis or as a greater risk for hepatotoxicity of antiretroviral drugs. Chronic liver infections are one of the most important causes of hospital admission and mortality among HIV-positive patients during the HAART era in the developed world[2-4]. Thus, it is becoming important to focus on the management of concurrent hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in order to prevent decompensated cirrhosis, Hepatocellular Carcinoma (HCC) and HAART hepatotoxicity and, thus, to improve survival in HIV-infected subjects.

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Hepatitis B virus

The hepatitis B virus (HBV) is a 42 nm particle belonging to the *Hepadnaviridae*[5]. The virus has been classified by molecular diagnostic techniques into six major genotypes, A-F[6]. It has a 3.2 kb, partially double-stranded, relaxed circular DNA genome that encodes four overlapping ORFs, the envelope gene (preS/S), core gene (preC/C), the X gene and the polymerase gene (P). The HBV genome is translated in overlapping ORFs, which limits the number of mutations that can be tolerated. The HBV genome, after virus attachment to hepatocyte receptors, is released in the hepatocyte nucleus where it is converted to a covalently closed circular DNA (cccDNA) that is the template for the synthesis of m-RNA and of the pre-genomic RNA. The pre-genomic RNA is transported to the cytoplasm, incorporated in the nucleocapsids and retrotranscribed by a reverse transcriptase into minus-strand HBV-DNA and there, with the synthesis of plus strand, HBV genome synthesis is completed[7]. Most antiviral drugs have little or no effect on cccDNA, accounting for the rapid reappearance of HBV-DNA after discontinuation of antiviral therapy. Loss of cccDNA is dependent on loss of hepatocytes, so patients with a higher cell-turnover are likely to deplete the cccDNA pool more rapidly and so need treatment for a shorter time[8]. Several mutations in nucleotide sequences of HBV have important clinical and virological consequences. Mutations in the polymerase gene have been found in patients undergoing antiviral therapy who develop evidence of antiviral resistance[9]. The best-characterized polymerase mutants are found during therapy with lamivudine. These mutants have changes in the conserved YMDD motif of the catalytic domain of the polymerase enzyme that confers resistance to lamivudine[9,10]. The most common mutation conferring resistance to lamivudine occurs at codon 552 (M552V or M552I) and is frequently coupled to additional changes in codon 528 (L528M). These lamivudine-resistant mutant HBV strains are less replication efficient than wild-type[11,12]. Factors that correlated with the development of lamivudine-resistant strains are: Asian ethnicity, higher baseline HBV-DNA levels, male sex, immune suppression and higher body-mass index.

Epidemiology of HBV infection in HIV-infected patients

The distribution of HBV varies widely around the world[13]. In some areas such as Southeast Asia, Africa and China, over 50% of the population become infected with rates of persistent HBV carriage of up of 15%. In Northern Europe and Australia, the HBsAg carrier rate is approximately 0.1%[14]. Carrier rates are highly variable and related to different modes of transmission and age at the time of infection. The number of reported cases of HBV has declined by over 50% since the availability of a specific vaccine[15]. HBV is detected in semen, saliva and nasopharyngeal fluids and can be transmitted both sexually and by exposure to infected blood. Thus HBV and HIV infections share risk factors and HBV-HIV co-infection is quite common. More than 80% of HIV-positive patients have some markers of past or current HBV infection[16] and 8-11% of them are HBsAg carriers[12]. The population groups with the greatest prevalence of co-infection are male homosexuals, intravenous drug users and patients coming from areas with HBV endemia; a lower rate is found among other risk groups[16].

Pathogenesis and natural history of HBV infection

HBV pathogenesis is largely immune mediated and not due to a cytopathic effect, and there is no correlation between viral load and severity of liver disease. The central event in HBV pathogenesis is the recognition of virus-infected hepatocytes by CD8+ cytotoxic T lymphocytes (CLT)[17,18]. In the great majority (>95%) of acute infections with HBV, the CTL response leads to a successful viral clearance[18]. More than 90% of immune-competent persons that become infected with HBV, after an acute self-limited hepatitis, develop a long-lasting protective cellular and humoral immunity with clearance of HBsAg and appearance of anti-HBsAg antibodies, the so called HBsAg seroconversion[19]. In the remaining 10% of infected subjects, this phenomenon could occur never in life or after a long time period. The chronic phase of ineffective but active immune response induces chronic hepatitis, which may eventually lead to cirrhosis. The defect in cell-mediated immunity present in HIV infection, as with exogenous immune-suppression, is known to stimulate HBV replication and is associated with a higher rate of chronicization and a lower rate of HBV immune clearance[20-21].

In rare instances, HBV may exert intrinsic cytopathic effects that are not immune-mediated. These are generally found in states of endogenous immunesuppression.

An important event in the natural history of HBV infection, that usually occurs during a phase of active immune response, is the HBeAg seroconversion: the clearance of HBeAg from serum, followed by the appearance of anti-HBeAg antibodies. HBeAg is a post-translationally modificated product of the precore/core region of HBV genome[19]. HBeAg seroconversion usually represents transition from active chronic hepatitis to an inactive carrier state, with low HBV replication and without liver inflammation, and occurs at a yearly rate of 5-15%[19].

Unfortunately, a proportion of patients remain HBeAg negative but retain high HBV replication and persistent liver inflammation; these patients harbor a variant HBV that does not produce HBeAg, usually because of mutations in the precore and core genome regions[19]. These mutations are selected during HBeAg seroconversion and are more common in HBV genotype B, C, D, which are more frequent in Southern Europe and East Asia. So there are two forms of hepatitis that could be two steps of HBV infection in the same subject: HBeAg positive

and HBeAg negative hepatitis[19]. In Southern Europe, 30-80% of subjects with chronic hepatitis B are in the HBeAg negative phase[19].

Diagnosis of HBV infection

A diagnosis of hepatitis can usually be made on the clinical ground, epidemiological setting and features; however only virus-specific tests can identify the virus. Highly sensitive and specific tests are available for HBsAg, HBeAg and HBeAb and are of great diagnostic use in defining the presence of active infection (HBsAg) or disease phase (HBeAg and HBeAb)[19]. Indeed, measurement of viral nucleic acid serum is important for the management of HBV infection. The lower limit of sensitivity of these routine tests ranges from 10^5 to 10^6 copies/ml[22]. Recently, a quantitative polymerase chain reaction assay has been developed that can detect HBV-DNA at levels as low as 10^2 to 10^3 copies/ml. This assay detects HBV-DNA in a higher proportion of patients with chronic HBV infection and can yield positive results even in HBsAg carriers without apparent disease[23]. An arbitrary value of 10^5 copies/ml was chosen as the threshold indicating chronic hepatitis B at a recent NIH conference[19]. The detection of anti-HBc IgM class reactivity is also a useful test in clinical practice: high titres indicate acute and recent infection, lower titres might indicate chronic ongoing immune response against HBV antigen that is usually related to HBV-induced liver injury. Anti-HBs antibodies are the marker of immunity and protection against HBV.

Impact of HBV co-infection on HIV disease progression

HBV is mainly an hepatotropic virus, but it has also been shown to be a lymphotropic virus so that HIV-1 and HBV "meet" at the cellular level in co-infected patients[24] Extra-chromosomal sequences of HBV-DNA in peripheral mononuclear cells have been reported as more prevalent among AIDS patients than among asymptomatic HIV carriers[24]. This finding suggests a complex interaction between HIV and HBV and some authors have suggested that HBV could alter the course of HIV infection, inducing faster progression to AIDS. Recent studies have been conducted to investigate the molecular relationship between the two viruses. A recent study has demonstrated that HBV-X protein (HBx) super-induces ongoing HIV replication and HIV-1 long-terminal repeat (LTR) transcription[25]. These results obtained *in vitro* support the hypothesis that HBx could contribute to a faster progression to AIDS in HBV-HIV co-infected individuals.

Several cross-sectional and longitudinal studies designed to assess the impact of HBV co-infection on HIV disease progression have been published in the last 15 years. Two longitudinal studies did not show any impact of HBV co-infection on CD4 depletion, progression to full-blown AIDS, or AIDS induced mortality[26,27]. These results have been confirmed in an analysis of data from a cohort of British homosexuals, but this study has not excluded an effect on the development of certain HIV-related complications, such as thrombocytopenia[28].

On the other hand, two studies identified an association between HBV infection and a more severe evolution of HIV disease. In a Scandinavian cohort of homosexual men, the influence of previous or present hepatitis B infection was associated with a more rapid HIV disease progression[29]. Another study revealed that HBV co-infection was associated with reduced survival in patients with full-blown AIDS[30].

These investigations, however, suffer from many limitations. Small sample size, lack of CD4+ baseline cells, incomplete representation of the transmission categories, unknown date of HIV infection and partial knowledge of HBV markers can explain these contrasting results.

Impact of HIV co-infection on HBV disease progression

There are many evidences that co-infection with HIV significantly modifies the natural history of HBV infection. In patients with HBV infection, HIV co-infection is associated with:

- Higher chronicization rate of acute HBV[29,31-34].
- Higher levels of HBV replication, even in the presence of hepatitis Delta virus super-infection[29,31-38].
- Lower rate of spontaneous loss of HBeAg and/or HBsAg and seroconversion to anti-HBe and anti-HBs[29,31].

There are contradictory data on the activity of inflammatory liver disease in co-infected patients. Many studies from northern Europe and USA cohorts of homosexuals showed a significantly less severe necroinflammatory activity in HIV co-infected patients[33,36,39]. This observation seems to be related to the immunological pathogenesis of liver damage in chronic HBV infection. However, immunesuppression related to HIV is associated with reactivation of HBV infection in patients who have lost detectable HBV surface antigen (HBsAg)[20-21,37]. On the contrary, some studies performed in Californian and French cohorts, which included many injection drugs users, showed increased necroinflammatory activity in HIV seropositive subjects[40,41]. Contradictory data have also been published about the impact of HIV on hepatitis B progression towards cirrhosis and hepatocellular carcinoma: some northern European and USA studies did not reveal an unfavorable impact of HIV co-infection on hepatitis B evolution[28,32-33,35,36], while two French studies[37,41] clearly identified a more rapid progression towards cirrhosis in HIV/HBV co-infected subjects.

These discrepancies could be related to differences in the prevalence of infecting HBV genotypes and of mutant HBeAg defective HBV strains, to differences in the degree of immunesuppression, and to the different prevalence of co-factors associated with liver injury (alcohol, HCV, HDV, etc.) in the various cohorts. In the presence of high prevalence of

HCV and HDV co-infections, HBV co-infection has been related with a significantly higher incidence of end stage liver disease related death in HIV-seropositives, independently from other factors[42], with an adjusted OR of 9 (95% Confidence Interval 3.8-21.7). Long-term follow-up prospective studies of HBV-HIV co-infected patients, considering immune status, influence of other potential causes of liver injury, and the genotype of infecting HBV strains, is required to determine if HBV-related liver disease may influence the prognosis of co-infected patients.

Antiretroviral treatment and HBV co-infection

Use of highly active antiretroviral therapy (HAART) may be limited by the development of liver toxicity[43] that occurs in 5-15% of treated patients[44-51]. HBsAg reactivity has independently been associated with a higher incidence of severe hepatic cytolysis during HAART in 3[47-49] out of 8 studies[44-51]. In one study, dual HBV-HCV co-infection has been identified as an independent risk factor for severe hepatotoxicity during HAART[51]. On the other hand, HAART may be associated with recovery of cell-mediated immunity, leading to immune-mediated HBV- and HCV-specific liver damage. The immune restoration could either promote clearance of the virus[52] or lead to an exacerbation of cytolysis, but most of the patients do not clear HBsAg[53]. Consequently, HIV seropositives with chronic hepatitis B should be strictly monitored during antiretroviral treatment.

Hepatic cytolysis in an HIV patient with HBsAg reactivity taking HAART could be related to several factors: drugs toxicities, immune restoration of anti-HBV immune response, HBV flare after lamivudine withdrawal, occurrence of lamivudine HBV resistant strains[52-58] or other co-infections or super-infections by hepatotropic viruses (HAV and/or HCV and/or HDV). A careful definition of the etiology of ALT flares occurring during HAART is mandatory before stopping or changing an effective antiretroviral regimen.

Recently, a higher incidence of nephrolithiasis has been observed in patients co-infected with HIV and HBV or HCV virus, which suggests that underlying multifactorial hepatic damage may limit liver catabolism of indinavir, and, consequently, increase its renal excretion and the risk of nephrolithiasis[59].

Prevention and treatment of HBV co-infection in HIV-infected patients

The impact of HBV on HAART tolerability and on the occurrence of end stage liver disease makes mandatory the search for an effective strategy for HBV prevention and treatment in HIV-seropositive individuals.

Anti-HBV vaccination in HIV-infected subjects

Current HBV vaccines induce protective levels of antibody to HBsAg in 95% of children and 90% of immunecompetent adults[60]. In HIV-infected subjects prior to the HAART era, the HBV vaccine appeared to be less effective than in immunecompetent persons[61,62]. In addition, it is possible that the administration of an inactivated vaccine, by activating T-lymphocytes, temporarily stimulates HIV replication and induces transient increases of HIV-RNA[59-66]. However, because of the higher risk of developing HBV carrier status with prolonged ALT elevation and clinical illness, HBV vaccination is recommended for all HIV-positive subjects, especially in the earlier phases[67]. Given the theoretical concern that increases in HIV-RNA following vaccination during pregnancy might increase the risk of perinatal transmission of HIV, it may be wished to defer vaccination for such patients until after HAART is initiated[66,67].

Treatment of hepatitis B in HIV co-infected subjects

The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease, in order to prevent decompensated cirrhosis and hepatocellular carcinoma[19,67]. The surrogate end points used to assess treatment response include normalization of serum ALT levels, undetectable HBV-DNA by an unamplified serum assay, loss of HBeAg in HBeAg positive patients and improvement in liver histology[19,67]. Current therapy of chronic hepatitis B has limited long-term efficacy. Thus a careful balance of patient's age, severity of liver disease, likelihood of response and potential adverse events and complication, is needed before starting treatment[19,67]. Recently, the American Association for the Study of Liver Diseases has produced guidelines including recommendations for treatment of chronic hepatitis B according to HBeAg status, HBV-DNA levels, ALT levels and liver histology; these recommendations are summarized in table 1[67].

Two drugs have been approved as therapeutic agents for chronic hepatitis B: Interferon alpha (IFNa) and lamivudine. However many nucleosides and nucleotide analogues active *in vitro* against HBV are currently under evaluation as anti-HBV therapeutic agents in phase II and III trials

Interferon alfa

Interferons (IFNs) have antiviral, antiproliferative and immune-modulatory effects. IFNa has been shown to be effective in suppressing HBV replication and in inducing remission of chronic hepatitis, but is associated with many adverse events: flu-like syndrome, fatigue, leukopenia, thrombocytopenia and depression are the most common, but mythocondrial damage and hypertrigliceridemia have also been described[67].

Several controlled trials on the efficacy of IFNa therapy in chronic hepatitis B have been conducted before HIV identification in the first half of the 80's; five of them cumulatively included 55 HIV-HBV co-infected patients[68-73]. Only three out of these five tri-

Table 1. *American Association of the Liver Practice Guidelines: Recommendation for Treatment of Chronic HBV infection*[67]

HBeAg	HBV-DNA	ALT	Treatment Strategy
+	+	<2 x normal	Low efficacy for INF-a and lamivudine. Observe patients; consider treatment when ALT becomes elevated.
+	+	>2 x normal	**INF-a and lamivudine** If INFa non responders or if contraindications to INF-a, prefer lamivudine.
–	+	>2 x normal	**INF-a or lamivudine** Long-term treatment
–	–	<2 x normal	**No treatment required**
+/–	+	Cirrhosis	*Compensated:* **INF-a** (Close monitoring required) or **lamivudine**. *Decompensated:* **lamivudine**. Optimal timing of therapy unknown. Liver transplantation.
+/–	–	Cirrhosis	*Compensated:* Observe *Decompensated:* Liver transplantation

als[70,72,73] reported the proportion of response to treatment stratified according to HIV status. After identification, HIV infection was considered an exclusion criterion in all but four of the studies started after 1985[74-77]. Thus, the results of interferon treatment for chronic hepatitis B in HIV seropositives may be extrapolated from these seven reports[70,72-77] and are summarized in table 1. Putting together the results of the five comparative trials[70,72-75], seven out of 54 treated patients showed virological response versus none of the 46 untreated patients enrolled as controls; thus a pooled significant rate difference of 0.08 (95% C.I., 0.067-0.23) between the proportion of responders in treated and untreated HIV patients can be found. This meta-analysis suggests that IFNa is significantly more effective than no treatment in inducing HBeAg seroconversion, but, summarizing data obtained in controlled trials, at least 10 patients have to be treated in order to obtain one response. The results of long-term follow up of these patients have not been reported in these five studies; at least a case of loss of anti-HBeAg reactivity and of relapse of HBV active replication has been described in an HIV-infected patient who showed anti-e seroconversion lasting six months after IFNa treatment[78]. In these five trials, clinical data and CD4+ cell-counts of HIV positives are not reported, so they are insufficient to identify predictors of response and then to draw the profile of HIV-HBV co-infected ideal candidates for interferon treatment. Two more recent pilot uncontrolled studies[76,77], conducted in French patients with CD4 counts higher than 300, reported higher rates of response (6/31 treated patients: 20%), which have been maintained in the long term and were comparable to those usually obtained in HIV-uninfected patients. In one of these studies, high serum ALT levels have been reported as a good predictor of response in HIV-seropositives[77]. Thus, arbitrarily extrapolating data from these two studies, immune competent patients with elevated ALT levels seem to be the most responsive to IFNa treatment.

A meta-analysis of 16 randomized, controlled trials[68] showed that treatment response rates were significantly lower in HIV-negatives than in HIV-seropositives, with a 0.38 difference between differences in proportion of responders (CI 0.06-0.70; p = 0.02). The lower efficacy of IFNa in HIV co-infected patients with chronic hepatitis B has been confirmed by a more recent prospective study of the same group[74]. These results have led to consider HIV infection as a contraindication for IFNa treatment of chronic hepatitis B[68]. However, in these studies CD4 counts and HCV serostatus have not been reported. HCV co-infection, which is frequent in HIV co-infected patients, has been associated with poor response to interferon in patients with hepatitis B[79]. In addition, in all these studies HIV-infected subjects showed baseline ALT levels significantly lower than HIV-seronegatives[70,72-74]; this has been identified as an independent predictor of poor response to IFNa in two meta-analyses of controlled trials conducted in HIV-uninfected subjects[80,81] and in a study on HIV-infected subjects[77]. Thus, it is not possible to assess if the association between HIV co-infection and lower response rates to Interferon alpha observed in these studies is independent from CD4 counts and ALT levels, or from confounders such as HCV co-infection. In addition, results from the three French studies are comparable to those obtained in HIV-seronegatives (Table 2). Data on the results of IFNa in the treatment of HBeAg-negative hepatitis B in HIV co-infected patients are poor and inconclusive[75].

In conclusion, available data on the effect of IFN therapy on HBV infection in HIV-positive persons are poor; however they suggest that in these patients IFNa seems to be more effective than no treatment; therefore Interferon alpha remains a possible treatment option. The rate of response seems to be lower than that observed in HIV-negative subjects, even though the independent effect of HIV co-infection on this low responsiveness has to be fully demonstrated. Published data are still insufficient to select optimal candidates for IFNa among HIV-infected patients with chronic hepatitis B. However, the best candidates are probably patients with CD4 > 350, with ALT levels greater than two times the

Table 2. *Persistent loss of HBV viral replication in HIV-positive patients treated and untreated with Interferon alpha.*

Authors (year; ref)	Nº Pts	Dose (MIU, Schedule)	Duration (weeks)	Nº Persistent responders
Hoofnagle (1988;70)	8	5-10/tw	16	2
	4	no treatment	–	0
Brook (1989;72)	5	2.5/m² tw	24	0
	5	5/m² tw	24	0
	6	10/m² tw	24	0
	6	no treatment	24	0
Brook (1989;73)	6	10/ m² /day	12	0
	9	no treatment		0
Wong (1995;74)	12	10/tw	12	1
	13	no treatment	12	0
Pol (1992;75)	12	6/tw	24	4
	14	no treatment	24	0
Di Martino (1996;76)	5	5/tw	24	2
Di Martino (2000;77)	26	5/tw	24	4

upper normal limit and not assuming HAART. In fact, IFNa shares toxicities with some antiretrovirals and cumulates its toxicities with others. Moreover, the impact of interferon on survival of HIV co-infected subjects with chronic hepatitis B remains unknown. Thus the advantages of IFNa in the treatment of patients assuming HAART are very questionable.

Nucleoside and nucleotide analogues

Lamivudine is an oral nucleoside analogue, active against both HIV and HBV replication[82]. As is well known by those involved in the treatment of HIV-infected patients, lamivudine is well tolerated. It promptly inhibits HBV replication, leading to a marked decrease in HBV-DNA levels that is usually followed by improvements in ALT levels and liver histology[83], but only 16-18% of patients show sustained loss of HBeAg and less than 1% loose HBsAg[19,67,83]. Histological improvement during treatment has been observed in 49-56% of patients[19,67,83]. The recommended treatment duration for HBeAg-positive chronic hepatitis B is one year[67]. Treatment may be continued in patients who have not developed HBeAg seroconversion[19,67]. The recommended treatment duration for HBeAg-negative chronic hepatitis B is longer than one year, but the optimal duration has not been established[19,67]. In HIV-seropositives, lamivudine should be administered in the context of HAART at 300 mg/day in order to avoid the rapid emergence of HIV mutations (M184V) associated with lamivudine resistance. In HIV-HBV co-infected patients, lamivudine therapy leads to the inhibition of HBV replication in 86.4% (95%CI: 75.7-93.6) of treated subjects, improves liver histology and is able to reverse hepatic decompensation in those with advanced cirrhosis[84,85]. However, HBV resistance occurs in 50 and 90% of HIV-HBV co-infected patients after two and four years[84-88] at rates higher than in HIV-uninfected subjects[19;67] and even during treatment with the usual anti-HIV dose of 300 mg daily[84-88]. In HIV-seropositives, HBV resistance is associated with the duration of lamivudine therapy and not to pre-treatment HBV-DNA serum level, ALT serum level and CD4+ cell-count[84-88].The emergence of HBV-resistant mutants has been associated with ALT flares in a minority of patients[54,55,58,84-88], however a fatal case of liver failure has been described[58]. Treatment may be continued in patients who have breakthrough of HBV infection due to lamivudine-resistant mutants, as along as the benefit to the patient both on HIV and HBV infections is maintained. The evaluation of the benefit on HBV infection should be based on clinical assessment of liver function and liver disease stage and ALT and HBV-DNA levels.

In patients with clinically-significant hepatitis B, prescription of lamivudine as a part of HAART, in which it is the only anti-HBV agent for periods longer than one year, should be carefully evaluated in the absence of advanced fibrosis or decompensated liver disease, with a balance between the benefits on HIV against the risks of occurrence of HBV-resistant mutants. In HIV-HBV co-infected patients with emergence of HIV-resistant mutants, withdrawal of lamivudine should be careful evaluated in the light of activity and stage of hepatitis B infection. In patients with well-controlled and advanced chronic hepatitis B, lamivudine should probably be continued in addition to the new HAART regimen. In the remaining patients, lamivudine, careful monitoring of HBV replication and liver function tests for at least six months, should follow withdrawal.

In conclusion, nowadays lamivudine should be used wisely both as an anti-HIV and anti-HBV drug in patients with chronic hepatitis B and HIV co-infection, in order to spare a precious and still unique therapeutic tool. Probably treatment should be started in the presence of advanced fibrosis or rapidly evolving liver disease. A major focus of future clinical investigation of the therapy will be aimed at means of preventing viral resistance. The lesson that has been learnt by antiretroviral treatment suggests that the use of combinations of anti-

Table 3. *Nucleoside and nucleotide analogues, and drugs active against HBV under development and their anti-HIV efficacy* [92]

Drug	Drug Class	Development Phase	Activity against HIV	Activity against HBV lamivudine resistant mutants
Adefovir	Nucleotide analogue	III	Yes*	Yes
Clevudine	Nucleoside analogue	III	No	Yes
Emtricitabine/ Coviracil	Nucleoside analogue	III	Yes	No
Entecavir	Nucleoside analogue	III	No	Yes
Tenofovir	Nucleotide analogue	III	Yes	Yes
MIV-210	Nucleoside analogue	I	No	No data
DAPD	Nucleotide analogue	II	Yes	Yes
ACH126443	Nucleoside analogue	Ib/II	Yes	No data
MCC 478	Nucleotide analogue	I	No data	No data
Hep B Zyme	Ribozyme	I	No	No data

HBV drugs might prevent or slow the occurrence of HBV-resistant mutants. Most promising is combination therapy using agents that are active against lamivudine-resistance HBV, such as adefovir and entecavir and not famciclovir, the oral prodrug of penciclovir that shows cross-resistance with lamivudine[89].

Adefovir dipivoxil is a nucleoside analogue with activity against a broad range of viruses, including HIV. A recent open-label pilot study has been conducted to assess the safety and efficacy of adefovir dipivoxil (10 mg QD) in co-infected patients with lamivudine resistant HBV strains[90]. The results at 48 weeks have indicated that adefovir dipivoxil is effective against lamivudine resistant strains in HBV-HIV positive individuals.

Tenofovir, another anti-HIV drug, is able to induce an impressive inhibition of HBV replication, even in the presence of mutations associated with lamivudine resistance[91]. Many other anti-HBV drugs are actually under evaluation[92] and are listed in table 3. Some of them have also anti-HIV activity. Thus, in the near future, a combination treatment with two or more drugs, eventually active on both HBV and HIV, will be of use for the treatment of HIV-HBV co-infected patients.

Conclusions

HBV co-infection is common in HIV-seropositives and can cause significant morbidity and mortality, especially in the presence of other concurrent causes of liver injury. Even if there are some *in vitro* data suggesting an adjuvant action of HBV genes on HIV replication, there are not convincing results to support an unfavorable impact of HBV co-infection on HIV disease progression. On the contrary, HIV heavily modifies the course of HBV infection, inducing higher rates of chronicity, viral replication and lower rates of HBeAg and HBsAg clearance. The impact of HIV on Hepatitis B evolution towards cirrhosis is still unclear. HBV co-infection might be associated with severe hepatotoxicity during HAART.

For these reasons, prevention and treatment of HBV infection is mandatory in HIV-seropositives. Vaccination for HBV in non-immune HIV-infected patients is advised, even if there are some doubts about its efficacy. IFNa treatment is largely ineffective and lamivudine should be used wisely in patients without advanced liver disease. New antivirals active on HBV are currently under evaluation in phase I-III trials; some of them show anti-HIV activity. Combinations of anti-HIV and anti-HBV antivirals administered chronically could probably be a potential treatment strategy for hepatitis B in HIV-seropositives. Randomized controlled trials are needed to test this hypothesis.

Acknowledgments

We would like to thank Prof Antonio Craxì, director of the Institute of Gastroenterology of the University of Palermo, Italy, for his suggestions and critical revision of this manuscript.

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