Hepatitis B and human immunodeficiency virus co-infection

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Abstract

Hepatitis B and human immunodeficiency virus (HBV and HIV) infection share transmission patterns and risk factors, which explains high prevalence of chronic HBV infection in HIV infected patients. The natural course of HBV disease is altered by the HIV infection with less chance to clear acute HBV infection, faster progression to cirrhosis and higher risk of liver-related death in HIV-HBV co-infected patients than in HBV mono-infected ones. HIV infected patients with chronic hepatitis B should be counseled for liver damage and surveillance of chronic hepatitis B should be performed to screen early hepatocellular carcinoma. Noninvasive tools are now available to evaluate liver fibrosis. Isolated hepatitis B core antibodies (anti-HBc) are a good predictive marker of occult HBV infection. Still the prevalence and significance of occult HBV infection is controversial, but its screening may be important in the management of antiretroviral therapy. Vaccination against HBV infection is recommended in non-immune HIV patients. The optimal treatment for almost all HIV-HBV co-infected patients should contain tenofovir plus lamivudine or emtricitabine and treatment should not be stopped to avoid HBV reactivation. Long term tenofovir therapy may lead to significant decline in hepatitis B surface Antigen. The emergence of resistant HBV strains may compromise the HBV therapy and vaccine therapy.

Core tip: Hepatitis B and human immunodeficiency virus (HBV and HIV) infection share transmission patterns and risk factors, which explains high prevalence of chronic HBV infection in HIV infected patients. The natural course of HBV disease is altered by the HIV infection with less chance to clear acute HBV infection, faster progression to cirrhosis and higher risk of liver-related death in HIV-HBV co-infected patients than in HBV mono-infected ones. The management of HBV co-infection in HIV infected persons remains a challenge. This review provides update on epidemiology, natural history, diagnosis, prevention and treatment of hepatitis B infection in HIV infected patients.

INTRODUCTION

Since the advent of highly active antiretroviral treatment (HAART), human immunodeficiency virus (HIV)-associated morbidity and mortality has substantially decline. Liver diseases mainly due to hepatitis virus have emerged as a major cause of non-AIDS-related death[1,2]. As HIV and hepatitis B virus (HBV) share the same routes of

transmission through sexual and percutaneous contact[3], co-infection is common. Care of hepatitis B among HIV infected individuals is a major challenge in the management of HIV infection. This review will summarize the last data on epidemiology, natural history, diagnosis, prevention and treatment of chronic hepatitis B in HIV infected patients.

EPIDEMIOLOGY

As HIV and HBV infection share common routes of transmission, the prevalence of hepatitis B markers [anti hepatitis B core antibodies (anti-HBc) and/or hepatitis B surface antigen (HBs-Ag)] is very high among HIV infected persons: up to 90%[4]. Among the estimated 40 million persons infected with HIV worldwide, approximately 2-4 million (up to 10%) are chronically infected with HBV. This prevalence varies with geographic region.

In regions as Sub-Saharan Africa and east Asia, with high HBV prevalence, the majority of HBV infections occurs perinatally or during early childhood through household close contact, medical or cultural procedures like scarification or tattoo[5]; thus HBV infections are more likely to progress to chronic infections, resulting in high prevalence of chronic HBV infection among youth population at risk for sexually-acquired HIV[4]. Of note, the risk of chronicity without HBV immunization is greater (> 90%) in infants born from mothers with high viral load indirectly represented by the positivity of hepatitis B e antigen (HBe-Ag)[6]. This explains the relative low rate of vertical transmission in Africa compared with Asia due to lower prevalence of serum HBe-Ag in African women with chronic hepatitis B[7].

In low HBV prevalence areas such as North America, Western Europe and Australia, HBV infection is mainly acquired in adulthood in high-risk groups, *i.e.* injection drug users (IDU) persons with multiple heterosexual partners, and men who have sex with men (MSM)[4]. Chronic HBV infection occurs in 6% to 14% of HIV-infected persons[8-10]. The highest prevalence of co-infection in western countries is among MSM[4,10].

NATURAL HISTORY

HIV infection deleteriously affects the natural history of adult acquired HBV infection by impairing the innate and adaptive humoral and cellular immunity[6]. In immunocompromised patients, rates of chronicity after acute hepatitis B are higher, while rates of spontaneous loss of HBe-Ag and/or HBs-Ag and seroconversion to anti-HBe and anti-HBs are low[11-13]. Of note, acute hepatitis B resolves in 90% to 95% of immunocompetent individuals who acquire their infection in adulthood[14]. Bodsworth et al. found six fold more risks to develop chronic hepatitis B after HBV infection in HIV-infected individuals than in HIV-negative persons; the rate of HBe-Ag clearance in this study was up to five fold decreased in the HIV-infected patients[11]. It has been shown that higher CD4

cells count is correlated with higher clearance rates of HBV viremia during acute infection[6]. Nevertheless, HIV-infected persons with protective antibody to hepatitis B antigen (anti-HBs) remain at risk for loss of anti-HBs antibodies and for reactivation of HBV termed reverse seroconversion[15,16]. Hepatitis reverse seroconversion is rare (from 0.019 to 0.2 cases/100 patient-years) and occurred more frequently in the setting of HIV virologic failure[17]. Other characteristics in patients with HBV infection were reported: HIV co-infection are higher levels of HBV viremia, more frequent reactivation episodes and more rapid progression of liver fibrosis[12,18]. Several studies have also showed that HIV related immune suppression worsens the natural course of HBV infection by hastening progression to cirrhosis and liver related death[8,19]. The Swiss HIV cohort study first reported a direct effect of HIV related immunodeficiency on HBV-related hepatocellular carcinoma (HCC): 26 HCC patients were identified and matched with 251 controls and a significant association was observed between latest CD4 cell count (odd ratio per 100 cell/μL decrease= 1.33) and HCC risk[20].

As the influence of HIV infection on the course of HBV co-infection has been showed, the effects of HBV on the progression of HIV disease are controversial. In a retrospective cohort study in Greece among 1729 HIV-infected patients, no significant impact of HBV co-infection was suggested on progression to AIDS, and the meta-analysis (including 12382 patients from 11 studies) from the same study confirmed the absence of any effect by HBV infection on AIDS development[21]. This meta-analysis revealed increased rate of overall mortality among HIV-HBV co-infection. A higher risk for liver-related mortality in HIV-HBV co-infected individuals was found in the Multicenter Cohort Study, especially when CD4 cell nadir counts were low[8]. Data from the Euro-SIDA cohort showed no impact of HBV co-infection on the occurrence of new AIDS diagnosis or AIDS defining illness but there were also increased liver-related mortality: among patients who died, mortality increased from 8% in HBs-Ag negative to 18% in HBs-Ag positive patients[10]. These findings were reinforced by data from a Thai cohort that showed no impact of hepatitis co-infection on response to combine antiretroviral therapy (cART) and on progression of HIV disease[22]. A recent study including participants from all over the world (11 countries) showed association between HBV co-infection and lower CD4 cell count at the time of HAART initiation compared with HIV mono-infected patients, especially those with high HBV DNA[23]. In a long term analysis questioning the impact of HBV on HIV outcomes while on HAART, the absence of HBV influence on HIV suppression and CD4 cell increase was found but mortality was higher in the HBV co-infected group[24].

In the French mortality survey collecting causes of death among HIV infected patients: liver related disease mostly due to hepatitis C virus (HCV) co-infection was the 3rd underlying cause of death after AIDS defining ill-

ness and cancer[25-27].

DIAGNOSIS OF HBV INFECTION IN HIV-INFECTED PATIENTS

HIV-infected persons have to be tested for HBV infection. Initial testing for HBs-Ag, anti-HBs and anti-HBc (hepatitis B core) should be performed because these will identify the majority of patients with chronic hepatitis B. Some specialists would test for HBs-Ag and anti-HBs only, excluding anti-HBc, as its presence or absence does not usually affect clinical practice[28]. In practical routine, the presence of anti-HBc alone may lead to hepatitis B vaccination after occult hepatitis has been excluded (see below). Those who are diagnosed with chronic hepatitis B (presence of Hbs-Ag twice during more than 6 mo) should have an initial assessment with testing for HBV DNA and hepatitis D virus (HDV) status and HCV status. Classical HBe serology testing have now little interest comparing with HBV DNA in term of risk of transmission and of treatment efficiency[29].

HBV genotyping may be part of the diagnostic tools and may be useful for predicting HBV disease progression and treatment monitoring[30]. The most prevalent HBV genotype found among HIV infected patients is type A in Europe and North America[30-32]. Association has been described between advanced liver fibrosis and genotype G[31], or between higher HBV DNA and genotypes C, D, F[23]. From the EuroSIDA cohort, higher HBV DNA levels have been associated with HBV genotype A[33]. However, HBV genotyping is not well defined in the scheme of HBV management and is not performed in practical routine.

Until now the need for HBV drug resistance testing prior to starting HBV treatment has not been demonstrated[23]. HBV resistance testing should be performed in case of detectable HBV viremia in patients who have already received lamivudine. Nevertheless, no impact of lamivudine resistance has been showed on long-term efficacy of tenofovir[34].

Occult HBV infection is defined by the presence of HBV in plasma and/or in liver tissue of patients without detectable HBs-Ag. Conflicting results have been reported on its prevalence ranging from very low (less than 0.1%) to higher prevalence, 5.4% reported in a French cohort of HIV-HCV co-infected patients[35]. An early study reported up to 90% prevalence of occult hepatitis B[36], while most studies found prevalence around 10% to 20 %[37-40]. This wide range may be explained by the heterogeneity of study populations and the usage of different sensitivity and specificity of HBV DNA assays[39,41]. Isolated anti-HBc is good predictive marker of occult HBV, and HBV DNA should be tested in the pattern of anti-HBc alone when patients exhibit serum transaminases abnormalities or liver failure[42]. Still the contribution of occult HBV on liver damage remains unclear[43]. But screening of occult HBV infection may have implications in terms of antiretroviral therapy and risk of immune re-

constitution[42].

Liver fibrosis has to be assessed because it will establish a prognostic value and will be part of the therapeutic decisions. Noninvasive tools such as transient elastography (FibroScan) or serum biochemical indexes (Fibrotest) are now available to evaluate liver fibrosis[44-46]; though these tools are not accurate to discriminate intermediate stages of fibrosis[47], the combined use of fibroscan and fibrotest can improve the diagnostic accuracy and reduce the need for liver biopsy which stays the current gold standard[48,49].

HEPATITIS B PREVENTION

Current guidelines recommend that HIV-infected patients who have no serological markers against HBV (HBs-Ag, anti-HBs and anti-HBc negative) should be offered vaccination with a dosage of anti-Hbs 1 to 2 mo after the end of the complete scheme[28,50,51]. The standard vaccine schedule (3 doses at 0, 1 and 6 mo) is impaired in HIV-infected subjects compared to healthy persons[52]. A four double doses of hepatitis B vaccine regimen (40 μg given at 0, 1, 2 and 6 mo) has showed improved serological response (*i.e.*, anti-HBs antibodies above 10 UI/mL) in HIV infected subjects[53] and has been recently recommended in French guidelines. This scheme is also of interest regarding the high rate of patients achieving anti-HBs titers above 100 IU/L (Table 1)

In the absence of seroprotection (anti-HBs antibodies < 10 IU/L) at the end of vaccination, one to three additional doses of HBV vaccine should be administered. For patients with seroconversion, anti-HBs levels should rechecked every year in order to administer booster vaccine dose when anti-HBs levels decline < 10 IU/L.

The management of patients with isolated anti-HBc is not clear. This serological pattern might reflect exposure in the past following which anti-HBs did not develop or have fallen below the detection level[54] or more rarely occult HBV infection[42]. The CDC guidelines recommend to administer one dose of hepatitis B vaccine and determine the serological response 2-4 wk later[28]. If an adequate protective antibody level is revealed, immunization is complete. If not, HBV DNA should be tested to assess occult HBV infection[29]. If no HBV DNA is detected, some recommend a complete scheme of HBV vaccination[55].

In case of failure of repeat immunization, serological markers of HBV should be monitored annually, and including tenofovir in the cART can be considered.

MANAGEMENT OF CHRONIC HEPATITIS B IN HIV INFECTED PATIENTS

HIV-infected subjects should be counseled regarding prevention of liver damage: limitation of alcohol consumption[56], avoiding hepatotoxic drugs (common use of paracetamol). They also should be vaccinated against hepatitis A virus (HAV) if not immune: HAV superinfec-

n = 426	IM 20 µg x 3	IM 40 µg x 4	ID 4 µg x 4
	n = 141	*n* = 145	*n* = 140
Response rates	65%	82%	77%
At week 28	95%CI: 56%-72%	95%CI: 77%-88%	95%CI: 69%-84%
(Anti-HBs > 10 mIU/mL)		*P* < 0.001 *vs* IM 20 × 3	*P* = 0.02 *vs* IM 20 × 3
High responders rates	41%	74%	53%
(Anti-HBs > 100 mIU/mL)	95%CI: 33%-50%	95%CI: 66%-81%	95%CI: 44%-61%
		P < 0.001 *vs* IM 20 × 3	*P* = 0.06 *vs* IM 20 × 3

Anti-HBs: Antibody to hepatitis B antigen.

tion has been associated with high risk of liver failure and death in patients with underlying chronic liver disease[57,58].

Surveillance of chronic hepatitis B infection using abdominal ultrasound every 6 mo should be performed to detect early HCC in patients at risk: that is to say cirrhotic patients, but also non-cirrhotic HBV carriers with active hepatitis or family history of HCC, and non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3[59]. Serum alpha-fetoprotein (AFP) has a suboptimal performance but can be associated in the surveillance of chronic hepatitis B[59].

Cirrhotic patients should be monitored for the presence of esophageal varices using upper-gastrointestinal endoscopy every 1-2 year.

TREATMENT OF CHRONIC HEPATITIS B IN HIV INFECTED PATIENTS

The indication of chronic hepatitis B treatment in HIV infected individuals is based on a list of several considerations: the indication of cART for HIV infection, the stage of the liver disease and its risk to progression to clinically significant liver complications[60]. The goal of HBV treatment is in the best case to achieve HBs-Ag clearance with anti-HBs seroconversion, but this objective is rarely reached (less than 10% of HBV mono-infected patients under interferon treatment and probably even less in HIV-HBV co-infected patients)[29]. In practical routines the objectives for HBV treatment are: normalization of alanine aminotransferase (ALT), HBe-Ag seroconversion as HBe-Ag loss was associated with better histological liver evolution[61], and mainly sustained suppression of HBV replication to reduce liver inflammation and to stop or delay progression of fibrosis, to avoid development of cirrhosis, decompensation, HCC and liver related death[29].

Drugs that have been approved in Europe for the treatment of HBV include standard interferon (IFN) replaced by pegylated interferon (pegIFN), lamivudine, adefovir, entecavir and telbivudine. Tenofovir and emtricitabine are approved for HIV and are also active against HBV. It is essential in the management of HBV treatment to avoid the development of HBV associated drug resistance, which has already emerged under lamivudine

monotherapy (occurring in more than 80% of patients after 5 years of treatment)[51]. Furthermore a subset of lamivudine-resistant HBV isolates may behave as vaccine escapes mutants. The incidence of mutants selected by nucleos(t)ide analogues seem to be increasing and thus problematic especially in limited resources settings where there is restrained access to powerful anti-HBV drugs[62]. Entecavir monotherapy showed low rates (1.2%) of resistance in nucleosive-naïve patients treated for up to 5 years, but this rate increases to 51% in patients with lamivudine resistance[63]. Tenofovir offers the benefit of no evidence of developing tenofovir-resistance mutations after monitoring up to 7 years, with no effect of lamivudine prior exposure and/or resistance[64,65].

When HIV infection does not require treatment, which should be a less frequent situation as European and United States guidelines, recommend early HIV treatment initiation, algorithm for HBV treatment is based on serum HBV DNA, ALT and liver fibrosis staging. Treatment is advised when viremia is above 2000 IU/mL or ALT are elevated, or both, but also when advanced liver fibrosis is seen (with or without HBV DNA/ALT abnormalities)[60]. Treatment options for HBV infection should include agents without HIV antiviral activity to reduce risk of viral resistance[60]. PegIFN based therapy for a finite course of 12 mo is an option with possible benefit of sustained response in particular when HBe-Ag positive, elevated ALT and low serum HBV DNA. But the rate of such response is low[66], and the frequent side effects with bad impact on the quality of life of pegIFN limit its use[67,68]. Monotherapy of adefovir is an alternative but given the risk of selecting drug resistance, an early "add-on" strategy should be considered when criteria of undetectable HBV viremia is not met at week 24 of therapy[69].

When both HIV and HBV infections meet criteria to be treated, which will turn to be the most frequent situation regarding recent guidelines for HIV treatment, the combination of tenofovir and emtricitabine (or lamivudine) is the preferred choice[50,70]. In case of prior exposure to lamivudine with selected resistance to lamivudine, tenofovir is recommended because it has demonstrated its activity toward lamivudine-resistant HBV[71]. A recent meta-analysis confirmed the durable suppression of HBV viremia with no impact of previous lamivudine

exposure[64]. Combine therapy is recommended but until now no significant benefit of combine therapy over tenofovir alone has been demonstrated[32,64].

Seroclearance of HBs-Ag is a rare outcome during long term HBV therapy with potent nucleos(t)ide analogues. Dutch study investigated long term HBs-Ag level kinetics in HIV-HBV co-infected patients treated with tenofovir[72], and showed that the decline in HBs-Ag was essentially found among HBe-Ag positive HIV-HBV co-infected patients. It also showed that long term tenofovir therapy leads to significant decline in HBs-Ag, that there was a correlation between CD4 cells count and HBs-Ag level kinetics and that HBs-Ag kinetics early during treatment were predictive of HBs-Ag seroclearance[72].

HDV has a unique replication progress that requires co-infection with HBV. It suppresses HBV replication but it causes severe liver disease with rapid progression to cirrhosis (10%-15% of patients within 2 years)[73,74]. The prevalence of anti-HDV in HBV-HIV co-infected patients in EuroSIDA cohort is 14.5%[75]. Delta hepatitis increases the risk of liver related death and overall mortality in HIV infected patients[75]. Interferon therapy is the only evidence-based treatment for HDV, still a small study has pointed out the potential benefit of potent anti-HBV nucleos(t)ide analogues therapy in chronic delta hepatitis[76].

Patients under treatment should be monitored to assess response. A durable anti-HBe seroconversion in HBe-Ag positive patients is a marker of clinical relevant response. When using nucleot(s)ide analogues initial response is defined as at least 1 log10 drop in HBV DNA levels within 3 mo. HBV DNA should then be measured every 3 mo.

Treatment efficacy is measured by the HBV DNA negativation below the lower limit of detection, ideally after 6-12 mo of treatment[28].

Resistance should be suspected in compliant patients if HBV DNA levels increase by 1 log10 or more, if available resistance testing should be performed[29]. Non or poor adherence to treatment remains the first diagnostic in case of failure[77,78].

Discontinuation of anti-HBV treatment can result in potentially fatal hepatitis flares[79] and should be avoid when possible.

Add-on pegIFN in HBe-Ag HIV co-infected patients under treatment with tenofovir and undetectable HBV DNA did not seem to increase rates of HBe-Ag seroconversion[80].

CONCLUSION

What should not be forgotten is that HBV persists in the liver even after successful immunological control of the infection, therefore HBV infected patients are at risk of HBV reactivation. As HIV infection worsens the course of HBV infection with more severe outcome of the liver disease and higher rates of mortality, HBV status should be assessed in HIV-infected patients. Patients with nega-

tive HBs-Ag and negative anti-HBs and anti-HBc should be offered vaccination and HBV co-infected patients should be treated regardless of the CD4 count. Tenofovir plus lamivudine or emtricitabine with a third agent should the recommended first line therapy for almost all HIV-infected HBs-Ag patients. HBV treatment should not be stopped because long-term therapy can possibly lead to HBs-Ag loss and because of the risk HBV reactivation. Besides, the initiation of cART can also lead to an immune restoration disease with immune mediated injury. Periodic liver fibrosis assessment is warranted in HBV-HIV co-infected patients using non-invasive tools. Some challenges remain as optimizing the assessment of HBV infection in the context of HIV, the emergence and spreading of resistant HBV strains compromising HBV therapy and vaccine strategy (vaccine escape mutants).

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