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HEPATITIS B (J LIM, SECTION EDITOR)

HIV/HBV Coinfection

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Abstract Hepatitis B and human immunodeficiency virus (HIV) infections share transmission patterns and risk factors, which explains high prevalence of chronic hepatitis B virus (HBV) infection in HIV-infected patients. Furthermore, thanks to combination of antiretroviral therapies, natural history of HIV infection has changed, and liver diseases became one of the top three primary causes of "non-AIDS (acquired immune deficiency syndrome)-related deaths" in people living with HIV (PLWHIV). Progress has also been achieved in the management of HBV infection with the use of nucleotide analogues having dual activity against HBV and HIV, allowing HBV viral suppression. Thus, HIV infection no longer affects the course of HBV infection. Treatment recommendations are applicated, and HIV-HBV-coinfected patients are mainly screened for HBV, assessed for liver fibrosis, and screened for hepatocellular carcinoma, even if other liver diseases can be associated (particularly hepatitis C or hepatitis D infection, alcohol abuse, non-alcoholic steatohepatitis).

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Introduction

The prevalence of HBV (hepatitis B virus)-HIV (human immunodeficiency virus) coinfection is high: serological markers of HBV show that signs of past or present infection (anti-HBsAg, the HBV surface antigen, and anti-HBc antibodies) are found in three quarters of HIV patients; chronic HBV infection, as defined by the presence of HBsAg and usually HBV DNA detection for more than 6 months, is found in 7–9 % of HIV-infected patients [1, 2]. Two thirds of patients are infected with a "wild-type" HBV coinfection, exporting HBeAg (HBV e antigen). Around 6 to 12 % of HIV-HBV-coinfected patients have a delta co- or superinfection.

The impact and the perception of HBV-HIV coinfection has evolved over time, from a negligible problem overshadowed by the AIDS (acquired immune deficiency syndrome)-related illness towards a genuine risk factor for morbidity and mortality [3, 4]. As well as anti-HBV treatments, recommendations have evolved, most often leading to a convergence between HIV-positive and HIV-negative patients, particularly about the need for and the modalities of chronic hepatitis B assessment and follow-up, but with minimal differences regarding treatment indications and the treatment schedule [5].

The increase in sexually transmitted diseases and acute hepatitis A, B, D, and C in patients with HIV infection emphasizes the risk of HBV infection in this population: this suggests that systematic and regular screening of HBV infection is imperative in people living with HIV, with regular monitoring of anti-HB antibodies and an active preventive

vaccination campaign in this high-risk population against HAV (hepatitis A virus) and HBV [6].

Impact of HBV on the Natural History of HIV Infection

HBV chronic infection does not seem to have an impact on HIV immunovirological evolution or response to combined antiretroviral therapy [1, 4, 7, 8]. Nevertheless, the SMART study showed that the decrease of CD4 count and the increase of HIV viral load were more important during antiretroviral treatment interruption periods in HIV-HBV-coinfected patients than in HIV mono-infected patients [9].

Impact of HIV on the Natural History of HBV Infection

The natural history of HBV is known to be complicated by HIV coinfection with a higher rate of chronic hepatitis; progression to chronic infection is more frequent in patients with HIV and acute HBV infection than in those without HIV: 20 versus 5 % and probably depends on the CD4 count. Moreover, the incidence of cirrhosis and mortality attributable to liver disease were known to be significantly increased in case of HBV-HIV coinfection: HIV infection worsened the course of chronic HBV resulting in faster progression of fibrosis, faster development of cirrhosis and hepatocellular carcinoma, a lower rate of spontaneous HBe or HBs seroconversion, and a greater risk of HBV reactivation in inactive carriers [6, 10••]. Age, high levels of HBV replication, low CD4 count, persistence of HBeAg, and the absence of an antiretroviral treatment active against HIV were poor prognosis factors [11].

Early antiretroviral therapies which restored normal immune function initially resulted in the worsening of liver lesions (due to an immune restoration hepatitis) in the absence of control of HBV replication. As antiretrovirals with a dual antiviral activity (active against both HIV and HBV which share a reverse transcription in their replication cycle) have been used more extensively, the natural history of liver disease has markedly changed this last decade with a reduced incidence of cirrhosis and stabilization or even improvement in the liver severity of the HBV-related disease. Indeed, morbidity and mortality decreased in treated patients in comparison with untreated patients [11, 12], as shown by the diminution of decompensated cirrhosis under antiretroviral therapies including tenofovir [13]. As detailed further in the EPIB 2012 study, one could even suggest that HIV coinfection, unlike HCV or HDV coinfection, no longer seems to worsen HBV-induced fibrosis in highly active antiretroviral therapy (HAART)-treated patients. The reduced severity of HBV-related liver disease in HIV-infected patients is likely a consequence of the long-term treatment with anti-HBV drugs, more often used in HIV/HBV-coinfected than in mono-infected patients [14••]. In the same study, hepatocellular carcinoma was directly correlated with age, gender, and cirrhosis but inversely with HIV coinfection. There is indeed some evidence that lower CD4+ T cell counts are associated with higher risk of hepatocellular carcinoma in HIV-HBV-coinfected individuals [10••, 15]. By analyzing a large hospital database of HIV-infected patients, we recently reported that the historical harmful impact of HBV infection in HIV-infected patients as compared to HIV mono-infected patients had been removed; on the contrary, in HIV/HCV-coinfected patients, overmortality is still present as compared to HIV mono-infected or HIV/HBV-coinfected patients: we do suggest that the difference between HBV- and HCV-coinfected patients is mainly associated with the high rate of viral suppression in HBV patients which contrasts with a low rate in HCV-coinfected patients [15].

This underscores the need for initial and regular fibrosis assessments in HBV-HIV-coinfected patients, since all the coinfected patients should be treated for both infections regardless of biochemical, virological, or histological criteria, if recent recommendations are followed. The initial liver fibrosis assessment allows a clinician to adapt the hepatocellular carcinoma and portal hypertension screening.

Acute liver enzyme elevations are frequent in HIV-HBV-coinfected patients with an annual incidence of 13 % [16]. Most were related to drug-induced liver toxicity; however, two causes are HBV specific: occurrence of anti-HBV analog-resistant mutants which almost disappeared with second-generation drugs (Tenofovir) and HBV reactivation (spontaneously or more frequently after HIV treatment modification including switch to antiretrovirals without anti-HBV activity or discontinuation of a non-adherent patient).

Management of Hepatitis B Infection in HIV-Coinfected Patients

Screening and Evaluation of HBV Infection

Diagnosis and initial evaluation should be the same as in HBV mono-infected patients, even though recommendations are not quite properly followed in coinfected patients [5, 14••]. Concerning histological evaluation for HBV mono-infected patients, the EASL (European Association for the Study of the Liver) guidelines recommend liver biopsy to determine the degree of necroinflammation and fibrosis since hepatic histology can assist the decision to start treatment and also to evaluate other possible causes of liver disease. On the contrary, liver biopsy is not required when cirrhosis diagnosis is obvious or when treatment indication does not depend on histological evaluation [17]. With regard to non-invasive

methods of fibrosis evaluation, there is no clear position, especially regarding transient elastography, except for insisting on the absence of optimal cutoff to confidently evaluate the liver fibrosis.

Nevertheless, in coinfected patients, indication of treatment does not depend on histological evaluation. Given the risk of hepatocellular carcinoma linked to HBV, cirrhosis, and other possible associated liver disease (HCV infection, HDV infection, alcohol abuse, non alcoholic steatohepatitis and even if antiretroviral treatment should be initiated in all HBV-HIVcoinfected patients, the interest of the fibrosis assessment at baseline may be questioned but must not be forgotten: cut-offs for biochemical non-invasive tests and transient elastography have been specifically proposed in HBV-HIV-coinfected patients [18–20].

Treatment: Indications and Modalities

According to the 2012 EASL guidelines, and in agreement with HIV guidelines published in 2008, most coinfected patients should be simultaneously treated for HIV and HBV de novo [21]. In a small number of patients with CD4 count >500/ml, it was suggested that HBV could be treated before the institution of an anti-HIV therapy. However, HIV treatment indications have also evolved since 2012, and it is now recommended that all HIV-positive patients should be treated [8, 22].

Tenofovir combined with emtricitabine or lamivudine plus a third agent active against HIV is indicated [17]. The strong rationale for early dual anti-HIV and anti-HBV therapy has simplified the recommendations for widening the use of tenofovir and emtricitabine or lamivudine in HBV-HIV-coinfected patients, irrespective of immunological, virological, or histological data [5, 17]. Nevertheless, combination of tenofovir and emtricitabine or lamivudine has not been proven to be more virologically efficient than tenofovir alone [5, 23••]. Thus, given the potency and the high genetic barrier of tenofovir, its use as a unique anti-HBV drug may be considered [17], keeping in mind that alone or in association, it will always be part of an efficient HIV antiretroviral treatment. If antiretroviral treatment must be changed, a regiment that is active against HBV must be absolutely maintained.

After 5 years of treatment, HBV replication is controlled in 95 to 99 % of the patients treated by tenofovir [13, 24]. Entecavir can be used in tenofovir-intolerant patients (particularly if renal contraindication or coprescription of potentially nephrotoxic agents). Its efficiency may be limited in long-term lamivudine experienced patients, and even more if they have a viral resistant strain with the YMDD mutation [18].

HBeAg loss is associated with a better histological evolution but is rare in HIV-HBV-coinfected patients [2]. Thus, add-on of pegylated interferon during 48 weeks to a combined antiretroviral therapy including tenofovir was assessed in HBeAg-positive patients but did not significantly increase the HBe seroconversion rate, despite an HBeAg loss in 20 % of the patients [25].

Regarding the patients only treated for HBV (who should be scarce), given the anti-HIV activity of lamivudine, entecavir, or tenofovir, PEG-IFN, adefovir, and telbivudine should be preferred. But, in the absence of HBV virosuppression, treatment of HIV infection should be considered [17]. This underlines the need for HIV screening in all HBsAg-positive patients, especially in those who have an indication for HBV treatment, because of the risk of HIV resistance if using lamivudine, entecavir, or tenofovir as single agents.

Management of Hepatitis B in HIV-Positive Patients in Real Life

Four French studies have retrospectively described characteristics of HBV infection in HIV-infected patients, HBV treatments used (and eventually their conformity with concomitant guidelines), and their virological, serological, and clinical impact [2, 5, 13, 26•]. The 2005 EPIB study reported that the 261 HIV-HBV-coinfected patients underwent fewer serological, virological, and histological evaluations concerning HBV, than the 216 HBV mono-infected patients [2]. HIV-HBV-coinfected patients were more frequently HBeAg positive, had more often cirrhosis on the initial liver biopsy, and less often HBeAg loss or HBe seroconversion after a mean follow-up of 5 years. The 2008 EPIB study showed an improvement in the assessment of HBV chronic infection in HIV-positive patients (but still insufficient: evaluation of liver fibrosis increased from 33 % in 65 % of coinfected patients), as in the efficacy of HBV therapy [5]. Moreover, HIV infection did not have a negative impact on the likelihood of HBV therapeutic success, with even a trend towards a higher rate of HBs seroconversion in HIV-positive patients. This could be related not only to restoration of the immune system achieved on HAART but also to the time spent on effective HIV/HBV therapy, independently of the drug(s) used. On the other hand, it has to be kept in mind that withdrawal of anti-HBV treatment may expose patients to HBV reactivation, even after HBsAg loss or seroconversion [5]. Probably because of the immunovirological impact of HAART and the more frequent and longer use of HBV therapy, the negative impact of HIV on the virological, histological, and clinical evolution of HBV chronic infection seemed to be disappearing in the 2012 survey [14••]. Still, among the 299 HIV-HBV-coinfected patients, hepatitis B was less often assessed than in the 410 mono-infected one. As in the 2008 study, cirrhosis

was not associated with HIV infection (in 2008, this association disappeared after excluding HCV-infected patients, and in 2012, it was associated with age, male gender, Asian origin, alcoholism, HCV, and HDV). Finally, in 2008, the match between the real-life therapeutic management of chronic HBV infection in HIV-infected patients and the recommendations at that time [27] was assessed [26•]. Results confirm a global improvement in the management of HBV-HIV-coinfected patients, but a still often insufficient baseline HBV evaluation. Thus, the recent guidelines recommending treating all HIV patients, and therefore, all coinfected HIV-HBV patients, regardless of their liver disease status, raise hope that concordance between recommendations and real life will further increase. That being said, the systematic indication for early dual anti-HIV and anti-HBV therapy might make it difficult to underline the need for liver fibrosis assessment and follow-up.

Preventive Measures

HIV-infected patients who have no serological markers against HBV should be offered vaccination with a reinforced schedule with a dosage of anti-HBs antibodies 1 to 2 months after the end of the complete schema. Indeed, the efficacy of the standard vaccine schedule (3 intra-deltoid doses at 0, 1 and 6 months) is impaired in HIV-infected patients compared to healthy persons. A four double dose hepatitis B vaccine regimen (40 μg given at 0, 1, 2, and 6 months) has shown improved serological response (anti-HBs antibodies above 10 UI/ml) in HIV subjects [28].

Thus, preventive measures must include not only the expansion of HCV and HBV prevention campaigns to drug users and men who have sex with men, and a systematic testing for HCV and HDV infection when HBV-HIV coinfection is diagnosed and at least once a year in non-infected patients with high risk of exposure, but also vaccination of non-immunized patients against hepatitis B in an accelerated vaccination schedule and against HAV in the absence of HAV immunization.

In patients with HIV infection, hepatocellular carcinoma is an important cause of death due to liver disease. This can occur in patients with cirrhosis, even if viral replication has stopped. Regular screening of hepatocellular carcinoma should be performed by a liver ultrasonography every 6 months following the same indications and modalities as in HBV mono-infected patients. Finally in this regard, and as said above, given that all HIV-HBV-coinfected patients are to be treated regardless of liver evaluation, liver fibrosis should be assessed regularly, even more since HIV-infected patients are also exposed to other liver diseases. However, we must keep in mind that the liver fibrosis assessment using non-invasive tools (biochemical tests or elastometry) in treated patients who have biochemical and virological response is often under-estimated. The initial estimation is strongly recommended to define the suitable follow-up in these patients.

Conclusion

Despite initial differences in prognosis because of the harmful impact of HIV on the natural history of HBV, care of patients is similar for HIV-HBV-coinfected and HBV mono-infected patients. Progress in achieving more potent and safer immune restoration and an effective HBV viral suppression has dramatically modified the prognosis of HBV infection in PLWH IV. Nevertheless, three issues are now priorities: improvement of preventive measures including vaccination and risk reduction, evaluation of liver fibrosis and screening of hepatocellular carcinoma in case of extensive fibrosis or cirrhosis, and implementation of the now simplified treatment recommendations.

Compliance with Ethics Guidelines

Conflict of Interest Stanislas Pol has been a speaker for GSK, BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and AbbVie; has been a board member for GSK, BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and AbbVie; and received grants from BMS, Gilead, Roche, and MSD.

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Human and Animal Rights and Informed Consent Among cited articles where one of the authors of the current report was an author, local institutional review board approval was obtained and maintained for studies where human (or animal) subject research was performed.

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- • Of importance
- •• Of major importance

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