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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Emerging Challenges in Managing Hepatitis B in HIV Patients

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Abstract Roughly 10 % of HIV-positive individuals worldwide have concomitant chronic hepatitis B virus (HBV) infection, with large differences between geographical regions and/or risk groups. Hepatitis B is a preventable infection with vaccines. However, it cannot be eradicated once acquired, resembling HIV and in contrast with HCV. In developed countries, hepatitis B exhibits particular features in the HIV population. First, HBV infection is less frequently misdiagnosed than in the general population. Second, nucleos(t)ide analogs active against HBV are widely used as part of antiretroviral combinations and are taken by most HIV patients. Lastly, as the HIV population ages given the success of antiretroviral therapy, non-AIDS co-morbidities are becoming a major cause of disease, for which specific drugs are required, increasing the risk of interactions and hepatotoxicity. Furthermore, concern on HBV reactivation is rising as immunosuppressive drug therapies are increasingly been used for cancers and other non-malignant conditions. In this scenario, new challenges are emerging in the management of hepatitis B in HIV-positive individuals. Among them, major interest is focused on failures to suppress HBV replication, HBV breakthroughs and reactivations, the meaning of isolated anti-HBc, screening for liver cancer, and the complexity arising when hepatitis viruses C and/or D are additionally present. This review will focus on these challenges and the major advances in HBV coinfection in HIV.

Key points

Between 5 and 15 % of HIV+ individuals worldwide have chronic hepatitis B, with large differences across geographical regions and/or risk groups.

Hepatitis B is a preventable infection with vaccines. However, if acquired it cannot be eradicated, resembling HIV and in contrast with HCV infection.

Assessment of HBV status is warranted in all HIV+ persons and HBV vaccination should be given to all susceptible individuals.

Coinfection with HCV and HDV must be excluded at least once in all HBsAg+ carriers and ongoing HCV screening recommended for high-risk HIV-positive individuals

Chronic hepatitis B may lead to cirrhosis and liver cancer. HBV-related hepatic disease is accelerated by HIV coinfection. Early use of antivirals improves prognosis.

Treatment of HIV including anti-HBV active agents should be given to all coinfected patients regardless CD4 counts. Tenofovir is the drug of choice due to its dual activity for HIV and HBV. Lamivudine as the only active anti-HBV agent should be discouraged due to high-risk of resistance selection, which decreases sensitivity to entecavir, another first-line HBV nucleoside.

Periodic assessment of liver fibrosis using non-invasive tools (i.e., elastometry) should be performed in HIV-HBV coinfected patients. Screening for hepatocellular carcinoma is warranted in cirrhotics and patients with elevated serum HBV-DNA.

Concerns on HBV reactivation is rising as immunosuppressive drug therapies are increasingly been used for cancers and other non-malignant conditions in an aging HIV population.

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Introduction

Human immunodeficiency virus (HIV) is primarily transmitted by sexual, parenteral, and perinatal exposure, which explains why HIV-HBV coinfection is relatively common [1–4]. Most current estimates of chronic hepatitis B among HIV-infected patients range from 5 to 15 % [1, 5]. Thus, roughly 3 out of the 35 million people living with HIV worldwide have chronic hepatitis B [6•]. In some regions of West Africa and

Southeast Asia, persistent HBsAg+ can be found in up to 15–20 % of the HIV population [7•, 8] whereas in Western Europe, less than 10 % of HIV-infected individuals have chronic hepatitis B [5]. However, this rate is more than 100-fold higher than in the general population [5]. In the USA, half of HIV-positive persons have been exposed to HBV, and exhibit markers of spontaneously self-limited HBV infection (HBV core antibodies [anti-HBc] with/without HBV surface antibodies [anti-HBs]) or have serum HBsAg+ [9].

The prevalence of HBsAg+ after HIV diagnosis has remained relatively stable around 10 % in high-income countries, suggesting a continued need to stress the importance of HBV vaccination in high-risk populations. In low- and middle-income countries, HBV is mainly transmitted in the perinatal period from HBsAg+ mothers, in early childhood from infected peers, or in early youth by heterosexual contacts [6•, 7•, 10]. In high-income countries, HBV vaccination campaigns have halted HBV infection of newborns and infants, with most new infections diagnosed among immigrants or unvaccinated adults with high-risk practices [11]. Lack of protection against HBV acquisition in adults in high-income countries is generally seen in persons who were not vaccinated, did so incompletely, or in subjects that wane protective antibodies such as immunocompromised hosts. Response rates to the HBV vaccine series are almost universal in healthy hosts, and anamnestic immune responses have been shown to protect from infection properly HBV vaccinated individuals despite losing detectable anti-HBs. However, this "recall" protection is reduced in HIV+ persons and patients with end-stage renal disease among other immunocompromised populations.

Given that some nucleos(t)ide analogs (NA) used against HIV as part of most antiretroviral regimens are also active against HBV (namely tenofovir, lamivudine, and emtricitabine), and antiretroviral therapy is currently recommended for the majority of HIV-infected persons [12–14] most patients under care and HIV treatment are also on active therapy for HBV. Thus, challenges other than HBV-related liver disease [1, 15•] have emerged in persons with HIV-HBV coinfection (see Table 1). In this article, we will address them separately.

Table 1 Current challenges managing chronic hepatitis B in HIV patients

- HVB breakthrough
- Failure to suppress HBV replication
- Impaired HBV vaccine response
- Isolated anti-HBc
- Liver cancer screening
- Hepatitis C coinfection
- Hepatitis delta testing

Failure to Suppress HBV Replication

Even in patients with very high baseline serum HBV-DNA, as often seen in HIV-immunosuppressed individuals [1], treatment with potent NAs results in complete viral suppression in most HBV patients, although it may takes years [16, 17•, 18]. Nevertheless, up to 10 % of HIV-HBV coinfected patients may still harbor persistent low-level viremia after 6 years on tenofovir [19•]. Most overt virological and clinical failures with second generation NAs (tenofovir and entecavir) are generally associated with poor drug adherence rather than to selection of drug resistance [20]. Tenofovir is a commonly used NA in HIV/HBV due to the dual antiviral activity. Tenofovir is active in patients with prior failure to and/or selection of lamivudine resistance [21–23]. Moreover, HIV does not seem to compromise the antiviral response to tenofovir in hepatitis B [24].

In a recent study conducted in Ivory Coast, 168 HIV-HBV coinfected individuals initiated therapy containing either lamivudine (n=82) or tenofovir/emtricitabine (n=86) as part of their antiretroviral regimen. After a median of 35 months, undetectable serum HBV-DNA was achieved by 74 % in the lamivudine arm and 94 % in the tenofovir/emtricitabine arm. Only two patients selected lamivudine or emtricitabine resistance-associated mutations, with both occurring in the lamivudine arm [25]. The concern on the selection of lamivudine-resistant HBV in Africa has been significant, as tenofovir has only recently become widely used [26]. In this scenario, lamivudine-resistant HBV has been associated to HBV-related liver disease progression and transmission [27–30].

HBV Breakthroughs

Flares in liver enzymes in persons with HIV and HBV coinfection may result for multiple reasons, as listed in Table 2. They can be grouped into two categories, according to the presence of high or low (suppressed) serum HBV-DNA. In HBV viremic patients, the introduction of potent antiretroviral regimens as treatment for HIV, especially in subjects with low CD4 counts, may precipitate within 1–4 weeks an immune

Table 2 Major causes of liver flares in HIV-HBV coinfected patients

With low HBW-DNA	With high HBV-DNA
• Drug-related hepatotoxicity	• Immune reconstitution syndrome
• HBeAg and/or HBsAg seroconversion	• Discontinuation of antiviral therapy
• Acute hepatitis C	• Selection of drug-resistant HBV
• Hepatitis delta superinfection	• HBV reaction on immunosuppressive drug therapies
	• Spontaneous HBV reactivation

reconstitution response, with destruction of HBV-infected hepatocytes and flares in liver enzymes [31–33]. This phenomenon can occur when anti-HBV active antivirals (i.e., tenofovir +/- emtricitabine) are part of the antiretroviral regimen, in which case the HBV-DNA is lower than baseline.

In HIV-HBV coinfected patients on long-term anti-HBV active antiretroviral therapy and undetectable serum HBV-DNA, the interruption or discontinuation of tenofovir will create the potential for rebound of HBV replication and flares in liver enzymes [34]. This phenomenon has been reported in persons that forget to take their pills while traveling on vacations, or inadvertently by medical staff that tried drug interruptions or switches to avoid drug interactions or toxicities. Occasionally, these episodes of HBV rebound may be accompanied by HBeAg or HBsAg seroconversion, as a result of the abrupt immune dysbalance and can result in significant hepatic injury, especially when not recognized early. Thus, any changes in ARV must be done after considering the HBV status of the patient.

Stopping tenofovir in chronic hepatitis B patients with negative HBeAg and long-term suppression of HBV-DNA has been shown to be safe and accompanied by HBeAg decline with loss of HBsAg in nearly 10 % of patients [35]. This information could be helpful in HIV-HBV coinfected patients experiencing renal and/or bone toxicities on long-term tenofovir therapy [36–40], in whom drug discontinuation is medically indicated. However, due to the high rate of reconversion of HBeAg in the first year off NA, ongoing monitoring of HBeAg, HBV-DNA, and liver enzymes are required. For patients with cirrhosis, NA discontinuation is not recommended due to the risk of fibrosis progression and complications related to liver disease.

HBV Reactivation

The first reactivation of HBV was described in 1975 in 20 patients with lymphoproliferative and myeloproliferative disorders receiving chemotherapy [41]. The rate of HBV reactivation in HBsAg+ patients receiving chemotherapy is approximately 40 %. Among them, the risk of liver failure was 13 % [41]. Reactivation is less likely to develop in HBsAg-negative persons with anti-HBc, who resolved HBV infection but in whom HBV persists in the liver as covalently closed circular DNA (cccDNA) [41]. Less than 5 % experience HBV reactivation with anti-TNF agents but up to 40 % with rituximab. Finally, HBV reactivation in HBcAb+ and HBsAb+ persons as a result of prior HBV resolution is also uncommon, although it may occur occasionally in bone marrow or hematopoietic stem cell transplant recipients and those given B-cell depletion therapy [42•]. Due to the cccDNA integration, anyone previously infected with HBV is at risk of reactivation; a knowledge of the risk for each serologic presentation is important when managing these patients and making recommendations on empiric therapies (see Fig. 1).

Immunosuppressive drug therapies including immunomodulators, immunosuppressants, and biological agents are rapidly expanding their use as treatment for inflammatory bowel disease, rheumatic conditions, some cancers, organ transplantation, and dermatological illnesses. The safety of these drugs in patients with prior exposure to HBV is a challenge, given that HBV reactivation with liver enzyme flares and even life-threatening hepatic decompensation or fulminant hepatitis may occur [43, 44].

HBV reactivation in the HIV setting has been reported in the presence of severe immunodeficiency in persons with isolated anti-HBc [45, 46], although this is a rare situation which can still be seen in very late HIV presenters. As the HIV population ages, thanks to the success and widespread use of antiretroviral therapy, non-AIDS conditions treatable with immunosuppressive drug therapies are on the rise, and prevention of HBV reactivation episodes in this population warrants much attention.

Lamivudine might be considered in certain scenarios, but the risk of drug resistance selection is a drawback using this drug as only anti-HBV agents. Lamivudine is cheap and may be enough as only active anti-HBV agent in patients with relatively low viral load [47]. Entecavir is in HIV-HBV coinfected patients who are not on a fully active antiretroviral regimen, due to a residual anti-HIV activity that is enough to prone selection of drug resistance mutations in HIV [48•].

Most agents used to treat inflammatory diseases are anti-TNF agents (i.e., infliximab, adalimumab, or etanercept). Preemptive therapy with anti-HBV antivirals is recommended in persons with serum HBsAg+ before beginning these therapies in order to prevent and/or ameliorate HBV reactivation. Administration of tenofovir or entecavir for at least 1–3 weeks before beginning immunosuppressive therapies and continuing for 6–12 months after withdrawal is generally recommended [42•].

Similar anti-HBV prophylactic approaches must be followed using other biological agents, such as anti-IL12/23 monoclonal antibodies (i.e., ustekinumab) used in severe refractory psoriasis or inflammatory bowel disease [49]. Finally, the use of corticosteroids at high doses (>20 mg prednisone/day equivalent for more than 2 weeks) has produced similar troubles in HBsAg+ individuals, although at lower rates than using biological agents [50].

In patients with resolved HBV infection exhibiting anti-HBsAb and/or anti-HBc, the risk of HBV reactivation is very low using either anti-TNF or corticosteroids but is significant using anti-CD20 monoclonal antibodies (i.e., rituximab), for which HBV antiviral prophylaxis must also be provided [51].

Finally, it must be noted that HBV rebound along with elevated liver enzymes may occur spontaneously during the natural history of chronic hepatitis B, generally in anti-HBe

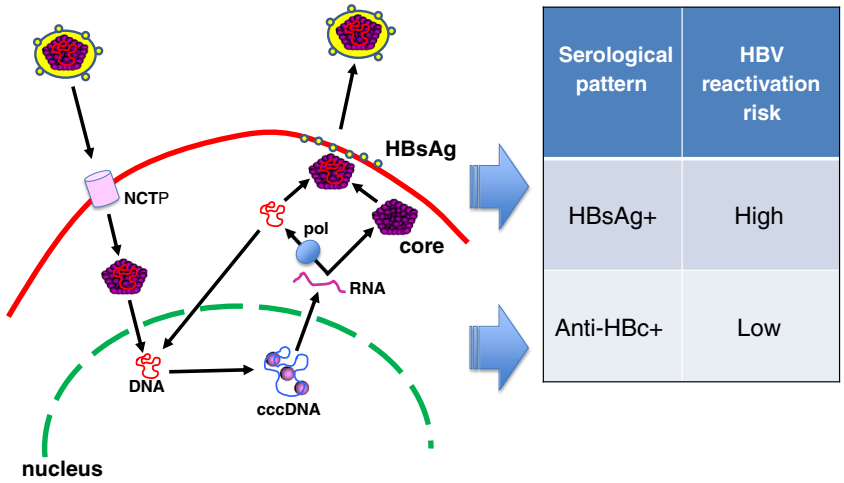

Fig. 1 Hepatitis B replication cycle

patients that select mutant core variants [52]. The risk of progression to cirrhosis and liver cancer is high in this subset of patients, especially in HBV genotype D carriers, for whom treatment is strongly advised [53].

HBV Vaccination

The HBV vaccine is safe and highly effective, offering protection for more than 30 years [54, 55]. Universal infant HBV vaccination was first recommended by WHO in 1992 [54]. However, in most high-income countries, HBV vaccination of target risk populations was only replaced by universal immunization in early childhood in the late nineties, and therefore, some young adults >18 years old may have not been vaccinated. In low- and middle-income countries, the situation is worst; up to 21 % of infants worldwide by 2012 had not received three doses of the HBV vaccine [55]. These data suggest that until HBV vaccine coverage improves globally, we will continue to see disease related to chronic HBV infection.

The response rate and durability of the response to the standard schedule HBV vaccine is poorer in HIV-positive compared to HIV-negative persons [56] and is influenced by both CD4 counts and plasma HIV-RNA. Accordingly, in patients with low CD4 counts (<200 cells/μL) and uncontrolled HIV replication, the success of HBV immunization is negligible. In these individuals, antiretroviral therapy should be prioritized while deferring HBV vaccination. Response rates to HBV vaccine increase substantially after achieving immune-virological recovery in this population, and in one study, the success of the HBV vaccine significantly increased above a threshold of 350 CD4+ T cells/mm^3 [57].

Although some HIV guidelines still recommend a conventional HBV vaccination schedule, the lack of achievement of protective anti-HBsAb titers frequently warrant re-vaccination using double doses and/or additional recall injections (months 0, 1, 6, and 12). Thus, many providers use only the double dose vaccine with either three or four injections [58]. Although some protection from HBV vaccine exists even when anti-HBsAb titers drop below 10 mIU/mL, data in other immunocompromised hosts (for example end-stage liver disease) suggests that there is benefit from boosting HBV immunity when anti-HBsAb titers fall <10 IU/mL [59].

Isolated HBV Core Serology

Exposure to HBV in adults is followed by HBsAg clearance and appearance of anti-HBs and/or anti-HBc antibodies in more than 90 % of cases. Isolated anti-HBc is more commonly seen in HIV-infected individuals [56]. It generally reflects three circumstances, namely (i) clearance of HBsAg following HBV exposure with inability to mount an adequate anti-HBs response or to maintain it over time, (ii) false positive reactions in persons never exposed to HBV, and (iii) interference with HCV, with low HBsAg titers and low-level serum HBV-DNA. Recent data from the Multicenter AIDS Cohort Study favors that isolated HBcAb represents resolved HBV infection with low or undetected HBsAb [60].

At this time, it remains uncertain whether all HIV-infected persons with isolated anti-HBc benefit from vaccination against HBV. Testing must be repeated first. A single vaccine recall injection may distinguish the three possibilities mentioned above (false positivity, prior immunity with undetectable anti-HBs, or low-level HBV infection). If anti-HBs become positive with high titers 1 month after a shot, an anamnestic response should be suspected, and no further vaccine injections are needed [61, 62].

On the other hand, if anti-HBs remain negative after the single HBV vaccine dose, serum HBV-DNA should be tested using a sensitive technique. If low-level HBV-DNA is found, the patient should be considered as HBV infected and therefore does not require any HBV vaccine prophylaxis. In contrast, a negative serum HBV-DNA along with undetectable anti-HBs would suggest that the patient is not infected by

HBV nor has been previously exposed, and vaccination is recommended. Currently four shots using double-doses are generally preferred for HIV persons [58, 63, 64].

HCC Screening

Liver fibrosis as a result of any chronic injury tends to be manifested uniformly by destruction of hepatocytes and replacement by sis matrix deposition. Collagen deposition is not uniform, and areas of cirrhosis are initially scattered. The malignant transformation of hepatocytes is generally seen around scar areas. However, hepatocellular carcinoma in chronic hepatitis B patients may occur in the absence of cirrhosis as result of a direct oncogenic effect of HBV associated to Vpx. In favor of a direct involvement of the virus in cancer is the fact that serum HBV-DNA is one of the best predictors of liver cancer [65•] and that suppression of HBV replication with antiviral therapy reduces the HCC risk [66]. Given that HIV-HBV coinfected patients tend to exhibit greater HBV-DNA levels, dually active antiviral therapy is generally recommended for all these patients, regardless of CD4 counts [1].

In chronic hepatitis B patients on antiviral therapy with suppressed HBV-DNA, hepatic fibrosis tends to improve over time. However, the risk of developing HCC remains increased in those with cirrhosis. This subset of patients must follow periodic screening with abdominal ultrasound at 6-month intervals. In the HIV setting, HCC may develop more frequently with severe immunodeficiency [67] and can be more aggressive, presenting as multicentric tumor and/or with extrahepatic metastases. There are no specific recommendations on HCC screening in chronic hepatitis B patients without cirrhosis and with viral suppression on NAs. In this subset of patients, it seems worth to advice yearly abdominal ultrasound if baseline HBV-DNA was high and suffers from perinatal and/or long-lasting HBV infection.

Hepatitis C Coinfection

Given that HBV and HCV are the most prevalent agents causing chronic viral hepatitis worldwide and that they share transmission routes, coinfection is not uncommon. For the same reason, dual hepatitis infections in persons with HIV infection are not rare. Viral interference occurs in dual active replication of HBV and HCV, generally dominating one virus over the other, although it can fluctuate over time. In HIV-immunosuppressed individuals, poor immune contention results in overt viral replication escape by both HBV and HCV [68]. Thus, HBV-DNA and HCV-RNA should be tested longitudinally more than once in HIV-positive individuals harboring both HBsAg and anti-HCV antibodies.

From a clinical perspective, HBV and HCV dual infections can occur in different scenarios, but HCV superinfection of chronic HBsAg carriers is the most common. It is generally recognized among injecting drug users in HBV highly endemic areas, such as South East Asia [69]. In high-income countries, new HCV epidemics are reported among young white adults living in rural areas in the United States abusing opioids intravenously and among promiscuous homosexual men in Western Europe, North America, and Australia. Occasionally, HCV superinfection of HBsAg carriers has been associated with fulminant hepatitis. On the contrary, HBV superinfection of chronic hepatitis C patients is rare, although it could lead to hepatic decompensation in cirrhotics. Interestingly, HCV may be eradicated following HBV superinfection episodes [70, 71].

Dually viremic patients for HBV and HCV generally represent only a small proportion of HBsAg/anti-HCV+ individuals, but HIV-associated immunodeficiency favors dual replication. Patients replicating both HBV and HCV exhibit an increased risk of developing end-stage liver disease, decompensated cirrhosis, and liver cancer [68, 70, 71].

There are no specific treatment guidelines for HCV-HBV dually infected patients. It is important to determine initially which is the dominant virus before considering any treatment intervention. Then, guidelines for HCV and HBV-monoinfected individuals can be applied correspondingly. In Asia, HBV tends to dominate over HCV replication [69], and subjects with HCV antibodies with repeated negative serum HCV-RNA should be considered as cured from HCV infection, with no concerns on potential HCV relapses if anti-HBV therapy is recommended [72].

In contrast, in patients with chronic hepatitis C having persistent undetectable HBV-DNA despite positive HBsAg (inactive carrier state), the natural history is similar to that of HCV-monoinfected patients [73]. However, if treated for hepatitis C, serum HBV-DNA may increase after achieving sustained virological response [74]. Thus, HBV rebounds when HCV is eradicated with antiviral therapy must be checked periodically in this population and anti-HBV treatment may warrant consideration. In the past, this phenomenon was less manifest given that peginterferon exerted activity against both HCV and HBV, but current oral direct-acting antivirals for HCV may unveil HBV more overtly, as it has been pointed out recently [75•]. At this time, it is unclear the risk of HBV reactivation in HBsAg-negative but anti-HBc+ patients with hepatitis C treated with oral HCV agents.

Hepatitis Delta Misdiagnosis

Hepatitis D virus (HDV) infection only occurs in subjects with hepatitis B, as HDV requires HBsAg to complete its replication cycle in the hepatocyte. Approximately, 5 % of patients with chronic hepatitis B worldwide have HDV coinfection, with large geographical disparities, and peaking at approximately 10 % or higher in some areas of the Mediterranean

basin, Eastern Europe, and Latin America [76]. The prevalence of hepatitis delta among HIV-HBV coinfected patients is around 15 % in Western Europe [77]. It is steadily going down as the number of injecting drug users has declined dramatically and HBV vaccination is broadly ensured in the HIV population [78].

HDV coinfection results in accelerated progression of liver disease in chronic hepatitis B patients [79, 80]. Hepatitis D is the most severe form of chronic viral hepatitis. In our cohort of 1157 HIV-positive persons followed for a median of 7.7 years, the subset of 35 individuals with hepatitis delta had the worst prognosis (see Fig. 2) [81•]. The only approved treatment for HDV infection is peginterferon, although less than 25 % of patients attain and sustain HDV-RNA suppression [82, 83]. Improvement in liver histology has been noticed in patients that achieve sustained viral response after HDV therapy with interferon [84]. The addition of ribavirin, lamivudine, adefovir, or tenofovir to peginterferon does not provide any further benefit to interferon in terms of response rate [85–88]. However, anecdotal reports of resolution of hepatitis delta even with HBsAg clearance have been reported using tenofovir [89, 90]. Moreover, our data suggest that long-term tenofovir therapy could be beneficial in HIV patients with delta hepatitis, particularly in those infected with HBV genotype A [91, 92]. Interestingly, HBsAg clearance does not seem to be followed by HBsAb development, opening the discussion for a potential risk of HBV (and delta) reactivation if NAs are discontinued [90, 93].

Doses and length of peginterferon therapy in hepatitis delta are not well established but the drug should not be given for less than 1 year, considering extension based on initial biochemical/virological responses and tolerance. In patients experiencing a significant serum HDV-RNA drop after 6–12 months of treatment, peginterferon should be maintained until the achievement of complete HDV-RNA suppression. Since HDV relapses are common upon interferon discontinuation, when possible, treatment should be extended until HBsAg loss is attained [94]. This circumstance, however, is rarely achieved. In patients with hepatitis delta and decompensated cirrhosis or HCC, liver transplantation should be strongly considered, especially in the absence of active HCV coinfection, as liver transplant may cure both HBV and HDV infections [95].

Treatment of hepatitis delta remains a major unmeet medical issue, particularly worrisome for HIV-positive individuals, as highlighted above [81]. Following the discovery of NCTP as the major HBV receptor on hepatocytes [96], drug discovery for HBV/HDV is expected to rapidly move steps forward, and clinical trials with new molecules, including entry HBV/HDV inhibitors (i.e., myrcludex) or prenylated inhibitors that block HDV assembly (i.e., lonafarnib) are ongoing [97, 98].

Conclusions

Chronic HBV infection is relatively common in HIV-positive individuals, mainly among those with high-risk sexual behaviors and injection drug users. Although HBV vaccination is mandatory in all HIV-infected persons with negative HBV markers, lower rates of protection due to abnormal immune responses are achieved, especially in subjects with low CD4 counts. HIV accelerates the course of liver disease caused by chronic HBV infection, increasing the risk of end-stage liver disease and hepatocellular carcinoma [15•].

Treatment of HIV including NAs active against HBV improves liver-related outcomes, especially when tenofovir is

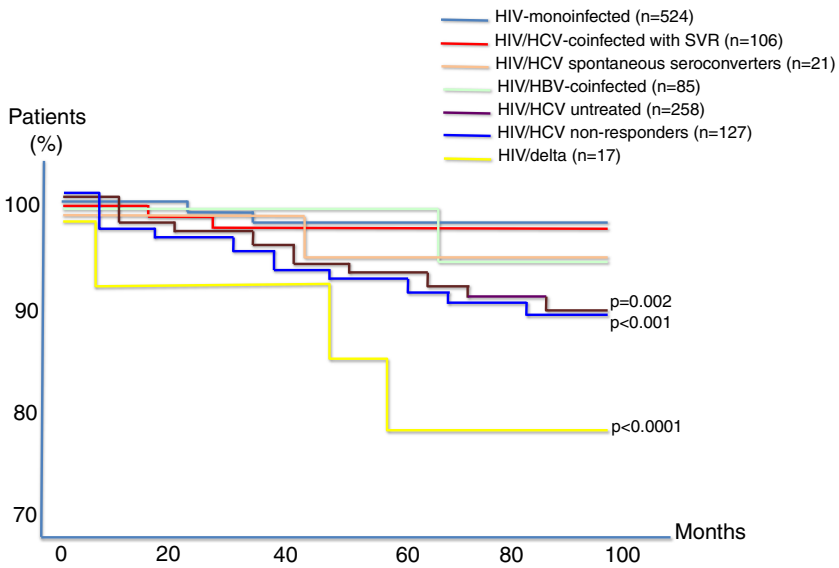

Fig. 2 Time free from liver decompensation events or death in 1147 HIV-infected patients

part of the antiviral regimen. The use of lamivudine as only active anti-HBV agent in HIV-HBV coinfected patients should be discouraged, and if needed, only restricted to individuals with low serum HBV-DNA levels [47]. Otherwise, selection of drug resistance is certain, producing cross-resistance to other antivirals and favoring the emergence of HBV vaccine escape mutants [26, 27, 99, 100].

As the HIV population ages, given the success of antiretroviral therapy, non-AIDS co-morbidities are a major cause of disease, for which specific drugs are required, increasing the risk of interactions and hepatotoxicity. Concerns on HBV reactivation is rising as immunosuppressive drug therapies are increasingly been used for cancers and other non-malignant conditions in an aging HIV population. Attention to HBV infection and risk of HDV coinfection is critically important in the management of HIV-infected patients.

Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. Soriano V, Puoti M, Peters M, et al. Care of HIV patients with chronic hepatitis B: updated recommendations from the HIV-Hepatitis B virus international panel. AIDS. 2008;22:1399–410.
2. Thio C. Hepatitis B, and Human immunodeficiency virus coinfection. Hepatology. 2009;49(suppl):138–45.
3. Soriano V, de Mendoza C, Fernandez-Montero JV, Labarga P, Barreiro P. Management and treatment of chronic hepatitis B in HIV-positive patients. Ann Med. 2014;46:290–6.
4. Kellerman S, Hanson D, McNaghten A, Fleming P. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in HIV-infected participants. J Infect Dis. 2003;188:571–7.
5. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to HAART and increased mortality in the EuroSIDA cohort. AIDS. 2005;19:2117–25.
6. • WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015 (www.who.int) **This document is an updated comprehensive report on the prevention, management and treatment of hepatitis B, with special focus on developing regions. Non-invasive methods for assessing liver fibrosis are overtly recommended instead of liver biopsies whereas tenofovir or entecavir are preferred over lamivudine as HBV therapy**.
7. • Modi A, Feld J. Viral hepatitis and HIV in Africa. AIDS Rev. 2007;9:25–39. **This is one of the most comprehensive reviews on the epidemiology of viral hepatitis in Africa and its overlap with the HIV epidemic**.
8. Geretti AM, Patel M, Sarfo F, et al. Detection of highly prevalent HBV co-infection among HIV-seropositive persons in Ghana. J Clin Microbiol. 2010;48:3223–30.
9. Chun H, Fieberg A, Hullsied K, et al. Epidemiology of Hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. Clin Infect Dis. 2010;50:426–36.
10. Te H, Jensen D. Epidemiology of hepatitis B and C viruses: a global overview. Clin Liver Dis. 2010;14:1–21.
11. Trepo C, Chan H, Lok A. Hepatitis B virus infection. Lancet. 2014;384:2053–63.
12. European AIDS Clinical Society Guidelines. Version 7.0. October 2013. Available at http://www.europeanaidsclinicalsociety.org. Accessed on April 27th 2015.
13. DHHS. Recommendations for use of antiretroviral drugs in HIV-1-infected adults and adolescents. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/.pdf. Accessed on April 27th 2015.
14. Gunthard H, Aberg J, Eron J, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA panel. JAMA. 2014;312:410–25.
15. • Thio C, Seaberg E, Skolasky R, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002;360:1921–6. **This is a pivotal study demonstrating that HIV worsts the natural history of chronic hepatitis B**.
16. Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci (in press).
17. • Martín-Carbonero L, Teixeira T, Poveda E, et al. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. AIDS. 2011;25:73–9. **This study reports HBV outcomes in one of the largest series of HIV-HBV coinfected individuals followed for the longest follow-up on tenofovir-containing regimens**.
18. Koklu S, Tuna Y, Gulsen M, et al. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol. 2013;11:88–94.
19. • Boyd A, Gozlan J, Maylin S, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfected patients undergoing long-term tenofovir: virological and clinical implications. Hepatology. 2014;60:497–507. **This study reported a 10% rate of low-level HBV-DNA in 111 HIV-HBV coinfected patients treated with tenofovir and followed for more than 6 years**.
20. Sheldon J, Camino N, Rodes B, et al. Selection of hepatitis B virus polymerase mutations in HIV coinfected patients treated with tenofovir. Antivir Ther. 2005;10:727–34.
21. Liu Y, Fung S, Gane E, et al. Evaluation of HBV-DNA decay kinetics in patients containing both rtM204V/I mutant and wild-type HBV subpopulations during tenofovir DF (TDF) monotherapy or combination therapy with emtricitabine (FTC)/TDF. J Med Virol. 2014;86:1473–81.
22. Fung S, Kwan P, Fari M, et al. Randomized comparison of tenofovir vs emtricitabine and tenofovir in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology. 2014;146:980–8.
23. Corsa A, Liu Y, Flaherty J, et al. No resistance to tenofovir disoproxil fumarate through 96 weeks of treatment in patients with

lamivudine-resistant chronic hepatitis B. Clin Gastroenterol Hepatol (in press).
24. Plaza Z, Aguilera A, Mena A, et al. Influence of HIV infection on response to tenofovir in patients with chronic hepatitis B. AIDS. 2013;27:2219–24.
25. Boyd A, Moh R, Gabillard D, et al. Low risk of lamivudine-resistant HBV and hepatic flares in treated HIV-HBV co-infected patients from Cote d'Ivoire. Antivir Ther 2015 (in press).
26. Hoffmann C, Charalambous S, Martin D, et al. Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART program. Clin Infect Dis. 2008;47:1479–85.
27. Soriano V, Rivas P, Nuñez M. Risks and benefits of using antiretroviral therapy in HIV-infected patients with chronic hepatitis B in developing regions. Clin Infect Dis. 2008;47:1486–9.
28. Thibault V, Aubron-Olivier C, Agut H, Katlama C. Primary infection with a lamivudine-resistant hepatitis B virus. AIDS. 2002;16:131–3.
29. Tuma P, Pineda J, Labarga P, et al. HBV primary drug resistance in newly diagnosed HIV-HBV-coinfected individuals in Spain. Antivir Ther. 2011;16:585–89.
30. Kouanfack C, Aghokeng A, Mondain A, et al. Lamivudine-resistant HBV infection in HIV-positive patients receiving antiretroviral therapy in a public routine clinic in Cameroon. Antivir Ther. 2012;17:321–6.
31. Velasco M, Morán A, Téllez MJ. Resolution of chronic hepatitis B after ritonavir treatment in an HIV-infected patient. N Engl J Med. 1999;340:1765–6.
32. Crane M, Oliver B, Matthews G, Avihingsanon A, Ubolyam S, Markovska V, et al. Immunopathogenesis of hepatic flare in HIV/HBV-coinfected individuals after the initiation of HBV-active antiretroviral therapy. J Infect Dis. 2009;199:974–81.
33. Soriano V, Puoti M, Garcia-Gascó P, et al. Antiretroviral drugs and liver injury. AIDS. 2008;22:1–13.
34. Dore G, Soriano V, Rockstroh J, Kupfer B, Tedaldi E, Peters L, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. AIDS. 2010;24:857–65.
35. Berg T, Simon K, Mauss S, Schott E, Heyne R, Klass D, et al. Stopping tenofovir treatment after long-term virologic suppression in HBeAg-negative CHB: week 48 interim results from an ongoing randomized, controlled trial (FINITE CHB) [abstract O-119]. J Hepatol. 2015;62(suppl):253.
36. Labarga P, Barreiro P, Martin-Carbonero L, et al. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. AIDS. 2009;23:689–96.
37. Del Palacio M, Romero S, Casado JL. Proximal tubular renal dysfunction or damage in HIV-infected patients. AIDS Rev. 2012;14:179–87.
38. Rifkin B, Perazella M. Tenofovir-associated nephrotoxicity: Fanconi syndrome and renal failure. Am J Med. 2004;117:282–4.
39. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in HIV-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis. 2003;36:1070–3.
40. Bedimo R, Maalouf N, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012;26:825–31.
41. Wands J, Chura C, Roll F, et al. Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. Gastroenterology. 1975;68:105–12.
42.• Perrillo R, Martin P, Lok A. Preventing hepatitis B reactivation due to immunosuppressive drug regimens. JAMA (in press). **This editorial briefly updates which circumstances may prone to hepatitis B reactivation and how to prevent it**.
43. Yeo W, Johnson P. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology. 2006;43:209–20.
44. Seto W, Chan T, Hwang Y, Wong D, Liu K, Gill H, et al. A prospective study of hepatitis B reactivation in patients with prior HBV exposure undergoing hematopoietic stem cell transplantation: reactivation association with graft-versus-host disease [abstract O-009]. J Hepatol. 2015;62(suppl):194.
45. Milazzo L, Ebranati E, Cattaneo D, et al. Recurrence of another hepatitis B virus escape mutant comes back in a patient infected with HIV and low CD4+ count. J Med Virol. 2014;86:97–101.
46. Pei R, Grund S, Verheyen J, Esser S, Chen X, Lu M. Spontaneous reactivation of hepatitis B virus replication in an HIV coinfected patient with isolated anti-hepatitis B core antibodies. Virol J. 2014;11:9.
47. Soriano V, McMahon B. Strategic use of lamivudine in the management of chronic hepatitis B. Antivir Res. 2013;100:435–8.
48.• McMahon B, Jilek B, Brennan T, et al. The HBV drug entecavir—effects on HIV-1 replication and resistance. N Engl J Med. 2007;356:2614–21. **This was the first report of the unexpected weak antiretroviral effect of entecavir and the risk for selection of drug resistance mutations in HIV**.
49. Koskinas J, Tampaki M, Doumba P, Rallis E. Hepatitis B virus reactivation during therapy with ustekinumab for psoriasis in a HBsAg-negative anti-HBs+patient. Br J Dermatol. 2013;168:679–80.
50. López-Serrano P, de la Fuente E, Carrera E, Pérez-Calle J, Fernández C. Hepatitis B and immunosuppressive therapies for chronic inflammatory diseases: when and how to apply prophylaxis, with a special focus on corticosteroid therapy. World J Hepatol. 2015;7:539–47.
51. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, et al. Prospective study of reactivation of HBV in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol. 2011;46:556–64.
52. Lok A, McMahon B. Chronic hepatitis B: update 2009. Hepatology. 2009;50:661–96.
53. Lok A. Personalized treatment of hepatitis B. Clin Mol Hepatol. 2015;21:1–6.
54. Kane M. Global programme for control of hepatitis B infection. Vaccine. 1995;13(suppl):47–9.
55. World Health Organization. Hepatitis B vaccines: WHO position paper. Wkly Epidemiol Rec. 2009;84:405–19.
56. Rivas P, Herrero MD, Puente S, Ramírez-Olivencia G, Soriano V. Immunizations in HIV-infected adults. AIDS Rev. 2007;9:173–87.
57. Fonseca M, Pang L, de Paula-Cavalheiro 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;23:2902–8.
58. Launay O, van der Vliet D, Rosenberg A, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA. 2011;305:1432–40.
59. Roni D, Pathapati R, Kumar A, Nihal L, Sridhar K, Tumkur RS. Safety and efficacy of hepatitis B vaccination in cirrhosis of liver. Adv Virol. 2013;20:196704.
60. Witt M, Lewis R, Rieg G, Seaberg E, Rinaldo C, Thio C. Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the multicenter AIDS cohort study. Clin Infect Dis. 2013;56:606–12.
61. Gandhi R, Wurcel A, Lee H, 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;191:1435–41.

62. Wang Q, Semmo N. T and B cell responses and previous exposure to hepatitis B virus in "anti-HBc alone" patients [abstract O-010]. J Hepatol. 2015;62(suppl):194–5.
63. Locarnini S, Hatzakis A, Chen D, Lok A. Strategies to control hepatitis B: public policy, epidemiology, vaccine and drugs. J Hepatol. 2015;62(suppl):76–86.
64. Whitaker J, Rouphael N, Edupuganti S, Lai L, Mulligan M. Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV-1. Lancet Infect Dis. 2012;12:966–76.
65.• Chen C, Yang H, Su J, et al. Risk of hepatocellular carcinoma across biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65–73. **This manuscript derives from the REVEAL-HBV study and reported for the first time a strong positive direct correlation between baseline serum HBV-DNA and the risk of liver cancer in chronic hepatitis B patients**.
66. Wu C, Lin J, Ho H, Su C, Lee T, Wang S, et al. Association of nucleoside analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B—a nationwide cohort study. Gastroenterology. 2014;147:143–51.
67. Clifford G, Rickenbach M, Polesel J, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. AIDS. 2008;22:2135–41.
68. Fernández-Montero JV, Soriano V. Management of hepatitis C in HIV and/or HBV co-infected patients. Best Pract Res Clin Gastroenterol. 2012;26:517–30.
69. Zhou J, Dore G, Zhang F, Lim P, Chen Y, Asia TREAT, et al. Hepatitis B and C virus coinfection in the TREAT Asia Observational database. J Gastroenterol Hepatol. 2007;22:1510–8.
70. Pontisso P, Ruvoletto M, Fattovich G, Chemello L, Callorini A, Ruol A, et al. Clinical and virological profiles in patients with multiple hepatitis virus infections. Gastroenterology. 1993;105:1529–33.
71. Chu C, Lee S. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. J Gastroenterol Hepatol. 2008;23:512–20.
72. Soriano V, Barreiro P, Martin-Carbonero L, et al. Treatment of chronic hepatitis B or C in HIV-infected patients with dual viral hepatitis. J Infect Dis. 2007;195:1181–3.
73. 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;37:568–76.
74. Liu C, Chuang W, Lee C, et al. Peginterferon alfa-2b plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. Gastroenterology. 2009;136:496–504.
75.• Collins J, Raphael K, Terry C, et al. Hepatitis B reactivation during successful treatment of hepatitis C with sofosbuvir and simeprevir. Clin Infect Dis (in press) **This study records for the first time two cases of HBV reactivation during successful DAA therapy for hepatitis C**.
76. Wedemeyer H, Heidrich B, Manns M. Hepatitis D virus infection – not a vanishing disease in Europe! Hepatology. 2007;45:1331–2.
77. Soriano V, Grint D, d'Arminio-Monforte A, et al. Hepatitis delta in HIV-infected individuals in Europe. AIDS. 2011;25:1987–92.
78. Calle-Serrano B, Manns M, Wedemeyer H. Hepatitis delta and HIV infection. Semin Liver Dis. 2012;32:120–9.
79. Kew M. Hepatitis viruses (other than hepatitis B and C viruses) as causes of hepatocellular carcinoma: an update. J Viral Hepat. 2013;20:149–57.
80. Farci P, Niro G. Clinical features of hepatitis D. Semin Liver Dis. 2012;32:228–36.
81.• Fernández-Montero JV, Vispo E, Barreiro P, Sierra-Enguita R, de Mendoza C, Labarga P, et al. Hepatitis delta is a major determinant of liver decompensation events and death in HIV-infected patients. Clin Infect Dis. 2014;58:1549–53. **This large study highlights the deleterious impact of hepatitis delta on HIV-positive individuals in comparison with coinfection with other hepatitis viruses (B and C)**.
82. Erhardt A, Gerlich W, Starke C, et al. Treatment of chronic hepatitis D with pegylated interferon-alpha 2b. Liver Int. 2006;26:805–10.
83. Yurdaydin C. Treatment of chronic delta hepatitis. Semin Liver Dis. 2012;32:237–44.
84. Farci P, Roskams T, Chessa L, et al. Long-term benefit of interferon as therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. Gastroenterology. 2004;126:1740–9.
85. Niro G, Ciancio A, Gaeta G, et al. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis D. Hepatology. 2006;44:713–20.
86. Yurdaydin C, Bozkaya H, Onder F, et al. Treatment of chronic D hepatitis with lamivudine vs lamivudine+interferon vs interferon. J Viral Hepat. 2008;15:314–21.
87. Wedemeyer H, Yurdaydın C, Dalekos G, HIDIT Study Group, et al. Peginterferon plus adefovir versus either drug alone for hepatitis delta. N Engl J Med. 2011;364:322–31.
88. Wedemeyer H, Port K, Heidrich S, et al. 96 weeks of pegylated interferon alpha-2a plus tenofovir or placebo for the treatment of hepatitis delta: the HIDIT-2 study. Washington DC: AASLD; 2013 [abstract 31].
89. Mansour W, Ducancelle A, Le Gal F, et al. Resolution of chronic hepatitis Delta after 1 year of combined therapy with pegylated interferon, tenofovir and emtricitabine. J Clin Virol. 2010;47:97–9.
90. James G, Sidhu P, Raza M. First report of successful clearance of hepatitis B and D coinfection with tenofovir monotherapy. Hepatology (in press).
91. Sheldon J, Ramos B, Toro C, et al. Does treatment of hepatitis B virus (HBV) infection reduce hepatitis delta virus (HDV) replication in HIV-HBV-HDV-coinfected patients? Antivir Ther. 2008;13:97–102.
92. Soriano V, Vispo E, Sierra-Enguita R, et al. Efficacy of prolonged tenofovir therapy on hepatitis delta in HIV-infected patients. AIDS. 2014;28:2389–94.
93. Soriano V, Barreiro P, de Mendoza C. Tenofovir for hepatitis delta. Hepatology (in press).
94. Farci P. Treatment of chronic hepatitis D: new advances, old challenges. Hepatology. 2006;44:536–9.
95. Roche B, Samuel D. Liver transplantation in delta virus infection. Semin Liver Dis. 2012;32:245–55.
96. Ni Y, Lempp F, Mehrle S, et al. Hepatitis B and D viruses exploit sodium taurocholate co-transporting polypeptide for species-specific entry into hepatocytes. Gastroenterology. 2014;146:1070–83.
97. Zoulim F, Durantel D. Antiviral therapies and prospects for a cure of chronic hepatitis B. Cold Spring Harb Perspect Med. 2015;5:a021501.
98. Yurdaydin C, Idilman R, Choong I, et al. Optimizing the prenylation inhibitor lonafarnib using ritonavir boosting in patients with chronic delta hepatitis. EASL, Vienna, April 2015 [abstract O118]. J Hepatol. 2015;62(suppl):252.
99. Schirmera P, Wintersb M, Holodniy M. HIV-HBV vaccine escape mutant infection with loss of HBV surface antibody and persistent HBV viremia on tenofovir/emtricitabine without antiviral resistance. J Clin Virol. 2011;52:261–4.
100. Pal A, Sarkar N, Saha D, et al. High incidence of lamivudine-resistance associated vaccine-escape HBV mutant among HIV-coinfected patients on prolonged antiretroviral therapy. Antivir Ther (in press).