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Candidates for therapy: HBV

Geoffrey Dusheiko*

Centre for Hepatology, Royal Free and University College School of Medicine, Pond Street, London NW3 2QG, UK

Hepatitis B may cause liver damage ranging from mild chronic hepatitis to severe active hepatitis, cirrhosis and hepatocellular carcinoma. HIV and HBV co-infection is more likely to lead to lower rates of HBeAg seroconversion, and higher HBV DNA concentrations. Immune restitution may lead to more severe hepatitis. The timing of acquisition of HBV versus HIV will have a bearing on considerations of treatment. Patients may have acquired HIV super-infection of chronic hepatitis B, HBV super-infection of HIV; alternatively, reactivation of hepatitis B may occur in a HIV positive patient, or the patient may be co-infected at diagnosis. The patient may be naïve or experienced or have resistant (HBV) at the time of superinfection. The risk of death is higher in patients with co-infection compared to those with HBV alone. The goals of therapy for hepatitis B are to prevent progression of the disease. If HBV replication can be suppressed, the accompanying reduction in histological activity lessens the risk of progression. Patients may request treatment to reduce infectivity, and this is relevant in co-infected patients. HBV has little effect on HIV or the effect of treatment on HIV; however, HIV, and HIV treatment profoundly affects the natural history of HBV. Therefore, it is usually important to target treatment of HBV to alter the outcome and take into account the impact of HBV treatment on HIV. Special concepts of treatment are applicable in HIV and HBV co-infected patients.

***Keywords*: Antiviral therapy; Hepatitis B; Hepatitis B and HIV co-infection**

1. Introduction

There is a large reservoir of carriers of markers of hepatitis B virus in the human population. Low (less than 2% of the population seropositive for HBsAg), intermediate (2–8%) and high prevalence (more than 8%) areas are recognised. Transmission of hepatitis B can occur by intimate contact and by sexual transmission. Those with frequent changes of sexual partners are at high risk. Viraemic mothers, especially those who are seropositive for HBeAg, almost invariably transmit the infection to their infants, unless hepatitis B vaccination is given. Such perinatal infections lead to a high rate of chronicity. Unsafe injections are an important cause in developed and developed countries [1].

2. Diagnosis and pathology

In chronic hepatitis B with mild activity, only rare piecemeal necrosis is seen. Characteristic hepatocytes with eosinophilic 'ground-glass' cells are relatively common in anti-HBe positive patients with low levels of virus replication. Lobular hepatitis is more common in patients with active virus replication, and raised serum ALT. CD8 positive cells predominate in areas of piecemeal necrosis. HBsAg and HBcAg can be detected by immunoperoxidase staining in routinely fixed liver biopsy sections. Patients with high levels of viraemia may have minimal hepatitis [2].

Hepatitis B is usually diagnosed by the detection of HBsAg in serum. Detection of viral DNA is the optimal method of establishing hepatitis B viraemia and quantitative assays are valuable for monitoring virus loads during antiviral therapy [1,3]. Quantitative tests for HBV DNA are limited by a lack of standardisation of the assays but more recently a WHO standard has been developed [4,5]. HBeAg

* Tel.: +44 2 7 433 2885; fax: +44 2 7 433 2884.
E-mail address: g.dusheiko@medsch.ucl.ac.uk (G. Dusheiko).

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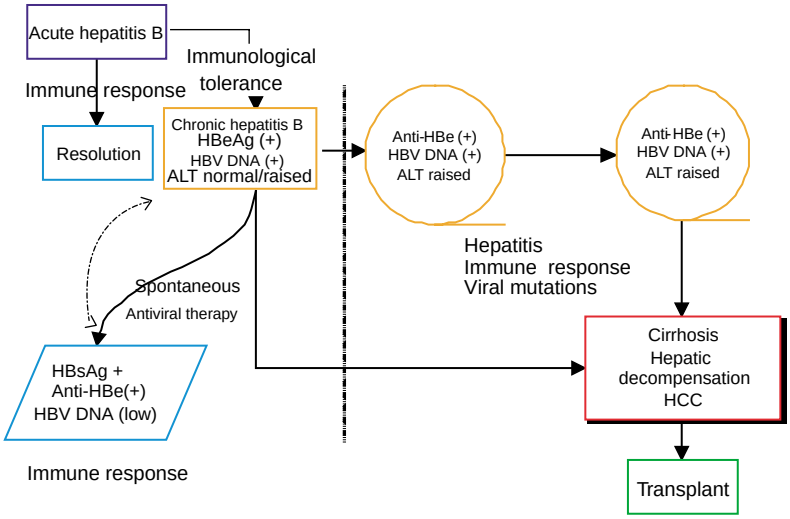

Fig. 1. Serological markers in the natural history of hepatitis B infection. [This figure appears in colour on the web.]

is a marker of viraemia but anti-HBe does not necessarily indicate clearance of virus replication (Figs. 1–3).

Typically, the levels of serum aminotransferases are elevated in patients with HBeAg, HBV DNA-positive chronic hepatitis, but some patients may have normal values. Many patients go on to develop moderate to severe HBeAg positive chronic hepatitis with raised serum ALT after several decades of infection, which can ultimately progress to cirrhosis. The levels of aminotransferases may fluctuate with time. Usually, the levels of alanine aminotransferase (ALT) are higher than those of aspartic aminotransferase (AST). However, with progression of the disease to cirrhosis, the AST/ALT ratio may be reversed. Elevation of these enzymes may be the only abnormality to be found in individuals with asymptomatic and anicteric infections who are tested because of known exposure. A progressive decline in serum albumin concentrations and prolongation of the prothrombin time are characteristically observed after decompensated cirrhosis has developed.

3. Chronic hepatitis B

Chronic hepatitis B is defined as persistence of HBsAg in the circulation for more than 6 months. The disease may cause liver damage varying from mild chronic hepatitis to severe, active hepatitis, cirrhosis and primary liver cancer. Chronic hepatitis B is more frequent in males, more likely to follow infections acquired in childhood than those acquired in adult life, and more likely to occur in patients with natural or acquired immune deficiencies, including HIV infection. In countries where hepatitis B infection is common, the highest prevalence of HBsAg is found in young children, with steadily declining rates among older age groups. HBeAg has been reported to be more common in young than in adult carriers of hepatitis B, whereas the prevalence of anti-HBe seems to increase with age. The management of chronic hepatitis B is complex, with personal, social, and economic implications, and is made more complex with co-infection with HIV

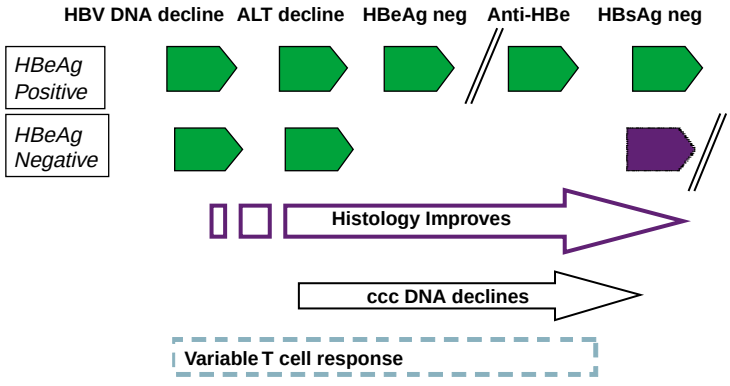

Fig. 2. End points of antiviral response in HBeAg positive and negative patients. [This figure appears in colour on the web.]

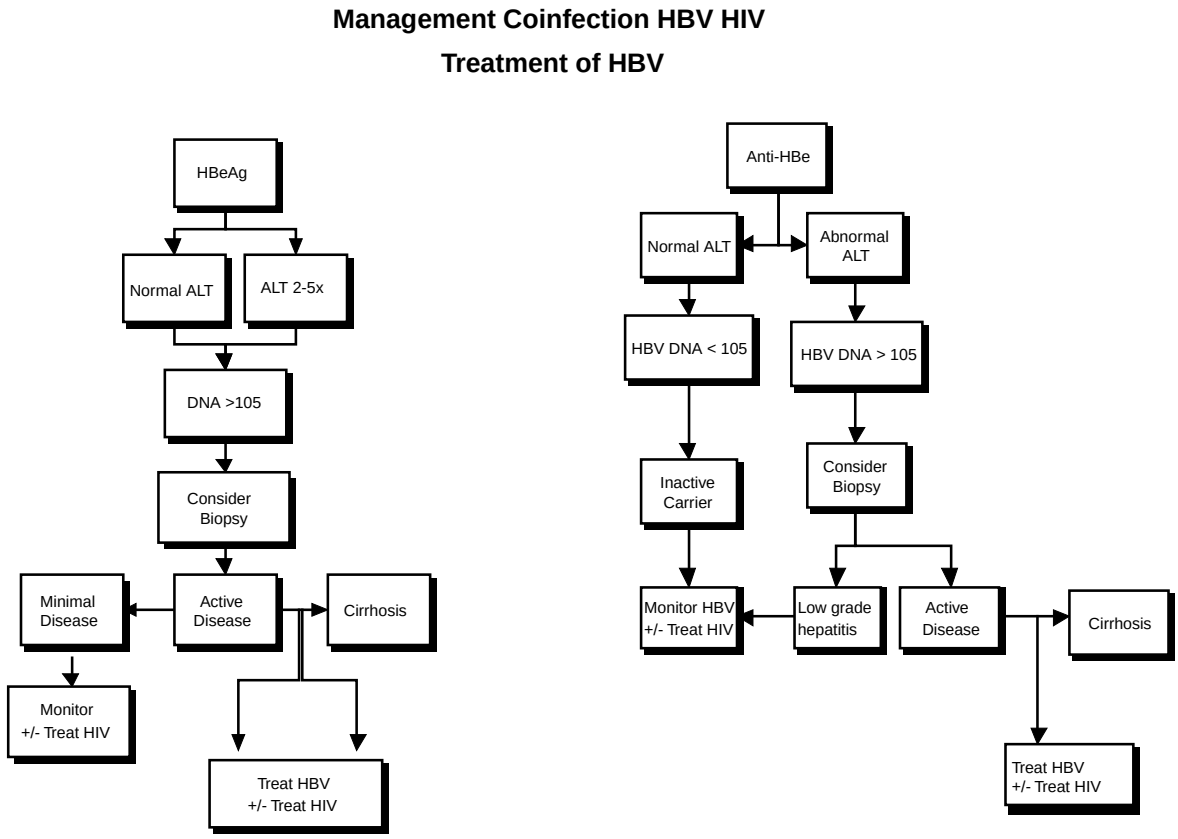

Fig. 3. Treatment of HBeAg positive and negative hepatitis B in HIV-HBV coinfected patients.

4. Natural history

In the immunotolerant phase, HBsAg and HBeAg are detectable; HBV-DNA levels are high (usually $>10^7$ copies/ml) but ALT are normal or minimally elevated. This phase is common in the young and immunosuppressed. The immunotolerant phase may last 10–30 years after perinatal HBV infection. The immunotolerant phase frequently is followed by an 'immunoactive' phase, when serum aminotransferase levels are elevated. Exacerbations in serum aminotransferases may be observed, accompanied by a decrease in serum HBV DNA levels in some HBeAg seroconversion. Seroconversion rates are higher in those with raised serum ALT, and in patients with genotype D and (in Asia) genotype B infection [6]. Seroconversion may occur following a sudden, asymptomatic exacerbation in serum aminotransferases. Once HBeAg is cleared, the disease remits temporarily and serum aminotransferases become normal.

Chronic hepatitis also may be observed in HBeAg-negative patients in whom HBsAg and anti-HBe are present in serum and serum HBV DNA is detectable using PCR based methods; serum aminotransferase levels are elevated and liver biopsy shows necroinflammation. HBeAg is undetectable in these patients because of the predominance of mutant HBV genomes that cannot express HBeAg. Patients with HBeAg-negative (also called pre-core mutant) chronic hepatitis tend to be older, male, and to present with severe necroinflammation and cirrhosis [7]. HBeAg negative chronic hepatitis has a variable course, often with fluctuating serum ALT and serum HBV DNA levels [8]. HBeAg may also become detectable transiently in these patients during acute flares. It is now known that such patients frequently are infected with variants of HBV with mutations in the precore region and which cannot synthesise HBeAg [9] Different patterns of anti-HBe positive disease can be discerned, but typically, patients tend to have recurrent flares.

A spontaneous remission in disease activity may occur in approximately 10–15 per cent of HBeAg positive carriers per year, characterised by disappearance of detectable (by molecular hybridisation) HBV DNA from serum, followed by loss of HBeAg and seroconversion to anti-HBe. The inactive carrier state is characterised by very low serum HBV DNA levels in serum ($<10^5$ copies/ml) and normal serum ALT. The prognosis of these patients, if stable without pre-existing advanced disease, is benign. However, a proportion of patients will develop active viral replication and raised ALT. If low levels of replication persist, serum HBsAg may become undetectable in serum and anti-HBs detectable. HBsAg may be lost in 1–2% of patients per year. However, a proportion of anti-HBe-positive individuals with low levels of HBV DNA may later develop higher

levels of HBV replication and raised ALT and progress to HBeAg negative chronic hepatitis.

Reactivation of hepatitis B may occur with HIV infection [10]. HIV and HBV co-infection is more likely to lead to lower rates of HBeAg seroconversion, and higher HBV DNA concentrations. The risk of death is higher in patients with co-infection compared to those with HBV alone.

HBV genotypes have been reported to correlate with spontaneous and interferon induced HBeAg seroconversion, activity of liver disease, and progression to cirrhosis and HCC, but further study is required. In China and Japan, where genotypes B and C circulate, there is evidence for increased pathogenicity, and likelihood of development of HCC, of genotype C over B.

In HBeAg positive patients, progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year incidence of progression of 8–20%. Progression to cirrhosis generally is faster in HBeAg negative patients, at an annual rate of 8–20%. Recurrent exacerbations and bridging fibrosis with severe necroinflammatory change characterise patients more likely to progress. The reported yearly incidence of hepatic decompensation is about 3%, with a 5-year cumulative incidence of 16%. In a European multicentre longitudinal study to assess the survival of 366 cases of HBsAg-positive compensated cirrhosis, death occurred in 23% of patients, mainly due to liver failure or hepatocellular carcinoma. The cumulative probability of survival in this cohort was 84 and 68% at 5 and 10 years, respectively. The worst survival was in HBeAg and HBV DNA-positive subjects [11]. Chinese patients remaining HBeAg positive were more likely to develop HCC.

Occult hepatitis B is defined as the presence of (usually low) levels of HBV DNA in serum in the absence of detectable HBsAg. Anti-HBc and/or anti-HBs may be present but are undetectable in a significant percentage of cases. Occult infection may occur in HIV infection [12]. There are several reports of HBV genomic sequences from such infections and a variety of mutations have been detected.

5. Antiviral therapy for hepatitis B

5.1. Acute hepatitis B

Most icteric patients with acute hepatitis B resolve their infection and do not require treatment. Fulminant hepatitis B is a severe form of acute infection complicated by encephalopathy and liver failure. Subgroups of fulminant hepatitis B including hyperacute, acute and subacute are defined by the interval between jaundice and encephalopathy. Subacute hepatic necrosis is characterised by a more protracted acute course and transition to chronic hepatitis with ongoing HBV replication. Patients with fulminant hepatitis (including acute and subacute forms) should be considered for liver transplantation, if appropriate. There are no controlled trials of lamivudine or adefovir for patients with acute fulminant or subacute fulminant hepatitis. Anecdotal reports suggest some efficacy of lamivudine in these patients, and carefully administered therapy could be tried, if administered early, and if there is evidence of ongoing HBV replication.

5.2. Chonic hepatitis B: treatment concepts

The timing of acquisition of HBV versus HIV will have a bearing on considerations of treatment. Patients may have acquired HIV super-infection of chronic hepatitis B, HBV super-infection of HIV; alternatively, reactivation of hepatitis B may occur in a HIV positive patient, or the patient may be co-infected at diagnosis. The patient may be naïve or experienced or have resistant (HBV) at the time superinfection. The goals of therapy for hepatitis B are to prevent progression of the disease. If HBV replication can be suppressed, the accompanying reduction in histological activity lessens the risk of progression. Patients may request treatment to reduce infectivity, and this is relevant in co-infected patients. HBV has little effect on HIV or the effect of treatment on HIV; however, HIV, and HIV treatment profoundly effects the natural history of HBV. Therefore, it is usually important to target treatment of HBV to alter the outcome and take into account the impact of HBV treatment on HIV.

If HBV replication can be suppressed, the accompanying reduction in histological chronic active hepatitis lessens the risk of cirrhosis and hepatocellular carcinoma [13]. Patients with mild chronic hepatitis should be monitored carefully at appropriate intervals. Therapy should be considered only if there is evidence of moderate to severe activity. HBeAg positive patients should be followed for a few months to ascertain their status, and antiviral therapy should be considered if there is active HBV replication (HBV DNA above 10^5 copies/mL) and persistent elevation of ALT after 3–6 months of observation. HBeAg negative patients should be considered for antiviral therapy when the serum ALT is raised, and there is active viral replication (HBV DNA above 10^5 copies/mL). Many clinicians would consider a liver biopsy helpful for ascertaining the degree of necroinflammation and fibrosis.

ALT elevations in coinfected patients may be the result of opportunistic infections, HAART hepatotoxicity, mitochondrial toxicity, HBV clearance, immune reconstitution, emergence of drug resistance, reactivation after withdrawal of therapy, or superinfection with HDV, HAV or HCV [14]. Other general causes include alcohol or illegal drugs. HIV and HBV co-infected patients whose immune status is preserved on highly active antiretroviral therapy (HAART) should be considered for anti-HBV therapy, with appropriate therapy for HIV infection to minimise resistance. (Discussed elsewhere). It is helpful to have a full clinical assessment, including assessment of symptoms and signs of hepatic decompensation, biochemical alterations

particularly ALT, virological evaluation including HBeAg, anti-HB and HBV DNA, levels, genotype and mutants.

AFP measurements are required in patients with cirrhosis. Single measures of ALT are not useful in disease as dynamic as hepatitis B, and there is a controversy regarding the level below which HBV DNA concentrations are indicative of 'inactive' disease. Thus, longitudinal measures, over at least a few months or longer may be required. The serum ALT may correlate with histological activity. Conversely, HBV DNA concentrations do not reflect activity. A full staging of the disease includes measures of serum albumin platelet count, prothrombin time, and assessment of cirrhosis, including measures to determine the presence or absence of oesophageal varices. Ultrasonography is usually used to screen patients for HCC, as part of regular surveillance for tumour.

The major goals of therapy for hepatitis B are to prevent progression of the disease to cirrhosis, end stage liver disease or HCC. Occasional patients may request treatment to reduce infectivity, and this is relevant in co-infected patients. HBeAg positive patients with greater disease activity may be more likely to seroconvert to anti-HBe. Patients with chronic HBV and HIV co-infection should be considered for treatment if HBV DNA concentrations are higher than 10^4 or 10^5 copies/ml, with a biopsy showing active hepatitis i.e. inflammation, necrosis or accumulating fibrosis. In many centres, a biopsy would be considered to assess the stage and grade of inflammation, as hepatic morphology can assist the decision to treat. There are several established methods of scoring histology, measuring activity (necroinflammation) separately from stage (fibrosis). There are, however, several limitations of biopsy including sampling error, subjectivity and reproducibility. The activity of hepatitis B can vary over time but ultimately determines the prognosis and response to treatment, particular HBeAg seroconversion. Assessment of fibrosis measures how far the disease has progressed. Progression of disease in hepatitis B is not linear, but is influenced by episodes of activity [15].

Patients with mild disease may not require immediate treatment. Liver biopsy can be helpful. These patients should be monitored carefully at appropriate intervals if is HIV disease is untreated. Treatment of HIV may lead to more severe hepatitis B with immune restitution. Patients with normal ALT are poor responders to interferon and nucleoside analogue monotherapy, and treatment in isolation is seldom indicated in these patients. Response rates in HBeAg positive patients are higher for all currently licensed agents for those patients with higher baseline ALT. Responses may be higher in patients with higher CD4 counts [17,18].

If HAART is indicated for a patient co-infected with HIV lamivudine can be utilised, as lamivudine is active against HIV and HBV. Adefovir also has activity against both viruses although a lower dose is used for HBV. Tenofovir also is active against HBV and HIV, however, the efficacy of tenofovir in hepatitis B infection has not been elucidated in large controlled trials [16].

HBsAg positive patients with extra-hepatic manifestations and active HBV replication may respond to antiviral therapy. Patients with decompensated cirrhosis should be treated in specialist liver units, as the application of antiviral therapy is complex. Prophylactic therapy is recommended for all patients undergoing liver transplantation for end stage hepatitis B, to lower levels of HBV DNA to less than 10^5 copies/ml before transplantation. The optimal timing of transplantation has not been established, but selection of resistant strains before surgery should be avoided. Lamivudine and adefovir are suitable agents. Antiviral therapy for prophylaxis of recurrence post-transplantation probably requires life long continuation of treatment. The most promising prophylaxis, lamivudine together with lifelong HBIG treatment after transplantation results in low rates of reinfection/reactivation after liver transplantation. Shorter courses of HBIG and other forms of prophylaxis, including adefovir in combination with lamivudine, are being studied. The optimal treatments for hepatitis B, including suitable combination therapies, currently are being evaluated.

In summary, HIV affects the natural history of HBV. Patients with active HBV disease should be treated. It may be possible to achieve seroconversion in HBeAg positive disease. Appropriate therapy should be given for HIV infection if indicated, or if treatment of HBV will have an impact on HIV therapy. Anti-HBe positive disease is likely to require long term suppressive therapy. In mild disease, or patients with near normal ALT, liver biopsy can be helpful. These patients should be monitored carefully at appropriate intervals. Response rates in HBeAg positive patients are higher for currently licensed agents for patients with higher baseline ALT but the mechanism is uncertain. Responses may be higher in patients with higher CD4 counts. Long-term suppressive therapy of (HIV) and HBV will be required for HBeAg patients who fail to seroconvert, and for anti-HBe positive patients. This should be factored in before starting therapy. Finally, the clinical care of hepatitis B is rapidly evolving, and is being influenced by the introduction of new nucleoside and nucleotides.

References

[1] Aylward B, Kane M, McNair-Scott R, Hu DH. Model-based estimates of the risk of human immunodeficiency virus and hepatitis B virus transmission through unsafe injections. Int J Epidemiol 1995;24:446–452.

[2] Lefkowitch JH. The liver in AIDS. Semin Liver Dis 1997;17:335–344.

[3] Berger A, Braner J, Doerr HW, Weber B. Quantification of viral load: Clinical relevance for human immunodeficiency virus, hepatitis B virus and hepatitis C virus infection. Intervirology 1998;41:24–34.

[4] Saldanha J, Gerlich W, Lelie N, Dawson P, Heermann K, Heath A. An international collaborative study to establish a World Health Organization international standard for hepatitis B virus DNA nucleic acid amplification techniques. Vox Sang 2001;80:63–71.

[5] Shyamala V, Cottrell J, Arcangel P, Madriaga D, Linnen J, Phelps B, et al. Detection and quantitation of HBV DNA in the WHO International Standard for HIV-1 RNA (NIBSC code: 97/656). J Virol Methods 2004;118:69–72.
[6] Koibuchi T, Hitani A, Nakamura T, Nojiri N, Nakajima K, Jyuji T, et al. Predominance of genotype A HBV in an HBV-HIV-1 dually positive population compared with an HIV-1-negative counterpart in Japan. J Med Virol 2001;64:435–440.
[7] Hadziyannis SJ, Lieberman HM, Karvountzis GG, Shafritz DA. Analysis of liver disease, nuclear HBcAg, viral replication and hepatitis B virus DNA in liver and serum of HBeAg versus anti-HBe positive carriers of hepatitis B virus. Hepatology 1983;3:656–662.
[8] Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology 2001;34:617–624.
[9] Carman WF, Jacyna MR, Hadziyannis S, Karayiannis P, McGarvey MJ, Makris A, et al. Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. Lancet 1989;2:588–591.
[10] Altfeld M, Rockstroh JK, Addo M, Kupfer B, Pult I, Will H, et al. Reactivation of hepatitis B in a long-term anti-HBs-positive patient with AIDS following lamivudine withdrawal. J Hepatol 1998;29:306–309.
[11] Fattovich G, Giustina G, Realdi G, Corrocher R, Schalm SW, Almasio P, et al. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. Hepatology 1997;26:1338–1342.
[12] Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult Hepatitis B in HIV-Infected Patients. J Acquir Immune Defic Syndr 2004;36:869–875.
[13] Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med 1996;334:1422–1427.
[14] Dore GJ, Cooper DA. The impact of HIV therapy on co-infection with hepatitis B and hepatitis C viruses. Curr Opin Infect Dis 2001;14: 749–755.
[15] Hessol NA, Koblin BA, Van Griensven GJP, Bacchetti P, Liu JY, Stevens CE, et al. Progression of human immunodeficiency virus type 1 (HIV- 1) infection among homosexual men in hepatitis B vaccine trial cohorts in Amsterdam, New York City, and San Francisco, 1978–1991. Am J Epidemiol 1994;139:1077–1087.
[16] Van Bommel F, Wunsche T, Mauss S, Reinke P, Bergk A, Schurmann D, et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology 2004;40:1421–1425.
[17] Smit MC, Haverkamp MH, Weersink AJ, Boucher CA, Hoepelman IM. Patients co-infected with HIV and hepatitis-B virus (HBV): the favourable effect of lamivudine, as part of combined antiretroviral therapy, on HBV may be dependent upon the number of CD4-cells. Ned Tijdschr Geneeskd 2004;148:2330–2334.
[18] Bruguera M, Cremades M, Salinas R, Costa J, Grau M, Sans J. Impaired response to recombinant hepatitis B vaccine in HIV-infected persons. J Clin Gastroenterol 1992;14:27–30.