Reactivation of Hepatitis B Virus Associated with Chemotherapy and Immunosuppressive Agent

Indra Wijaya, Irsan Hasan

Department of Internal Medicine. Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta Pusat 10430, Indonesia. Correspondence mail: leon_natan@yahoo.com.

ABSTRAK

Reaktivasi virus hepatitis B (HBV) setelah dilakukan kemoterapi dan terapi imunosupresi merupakan akibat serius yang menimbulkan mortalitas dan morbiditas yang berkaitan dengan penyakit hati. Mekanisme reaktivasi HBV masih belum jelas, tetapi para ahli meyakini bahwa mekanismenya melalui penekanan respons imum sehingga dapat meningkatkan beban virus (viral load). Hingga kini, belum ada kriteria diagnostik yang disepakati, namun reaktivasi HBV dapat dipastikan oleh adanya peningkatan kadar HBV-DNA dalam serum. Berbagai konsensus telah membahas hal ini yang meliputi pembahasan tentang jenis dan lamanya terapi analog nukleosida sebagaimana telah diketahui tidak semua pasien dengan hepatitis B kronik akan mengalami reaktivasi. Saat ini, kesadaran akan reaktivasi virus hepatitis B yang samar kini semakin meningkat, khususnya di daerah endemis virus hepatitis B, termasuk Indonesia yang merupakan bagian dari wilayah Asia Pasifik. Terapi antivirus profilaksis (preempative antiviral therapy) merupakan pendekatan terbaik untuk mencegah reaktivasi HBV.

Kata kunci: *reaktivasi virus Hepatitis B, kemoterapi, imunosupresif.*

ABSTRACT

Hepatitis B virus (HBV) reactivation after chemotherapy or immunosuppressive therapy is a serious cause of liver-related morbidity and mortality. The mechanism of HBV reactivation is still unclear, but it is believed due to the suppression of immune response hence increasing the viral load. No uniform diagnostic criteria are available, HBV reactivation can be confirmed by an increase in serum HBV-DNA level. There are many consensus regarding this issue, including the type and duration of nucleoside analogue therapy which need to be understood as not all chronic hepatitis B patients will lead to HBV reactivation. Recently, there has been an increased awareness of reactivation of occult hepatitis B virus, especially in hepatitis B virus endemic area, including Indonesia as part of Asia Pacific region. Preempative antiviral therapy was the best approach to prevent the HBV reactivation.

Key words: *hepatitis B virus reactivation, chemotherapy, immunosuppressive.*

INTRODUCTION

Hepatitis B virus (HBV) reactivation can occur in chronic hepatitis B patient. This issue should be put into account due to serious condition that can lead to fulminant hepatitis, liver failure, and eventually death.[1]

The incidence is unclear, but this condition can be predicted and preventable through evaluation of risk factors, including patient with malignancy who need chemotherapy and imunosuppresant agent.[1]

Complete HBV serology profile should be screened in patient who will undergo cytotoxic chemotherapy and immunosuppressive therapy. It has been known that preempative antiviral therapy is more effective than treatment of HBV reactivation.[1]

HEPATITIS B VIRUS

Hepatitis B virus is a double-stranded DNA virus in Hepadnaviridae family. HBV virion are double-shelled particles, 40 to 42 nm in diameter, with an outer lipoprotein envelope that contains three related envelope glycoproteins (surface antigens). The core contains the viral genome and a polymerase for the viral DNA synthesis in infected cells.[1]

PATHOGENESIS OF HEPATITIS B

Host immune responses to viral antigens on infected hepatocytes are the main mechanism of hepatocellular injury.[2] These responses involve both major-histocompatibility-complex (MHC) class II–restricted, CD4+ helper T cells and MHC class I–restricted, CD8+ cytotoxic T lymphocytes. Recognition reaction of antigen and antigen presenting cell (APC) can lead to either direct lysis of the infected hepatocyte or the release of interferon-γ (IFN-γ) and TNF-α, which can down-regulate viral replication in surrounding hepatocytes without direct cell killing.[3]

Natural histroy of chronic hepatitis B infection depends on the age at the time of infection and the immune response between host immunity and viral replication. Patient who failed to recover from acute infection will lead to chronic infection through 4 phase: immune tolerance, immune clearance, non-replicative, and reactivation phase.[1]

HBV reactivation is related to serologic profile and intensity of immunosuppressive agent.[7] The pathogenesis of HBV reactivation is still unclear, for those receiving high dose or long term of corticosteroids, it maybe due to a glucocorticoid responsive element in the HBV genome that stimulates viral replication and transcriptional activity.[15] The use of chemotherapy will markedly suppress the immune response hence increasing the viral load.[8]

EPIDEMIOLOGY

Approximately 2 billion people worldwide have been infected with HBV during their lifetime, with >350 million remaining chronically infected, leading to terminal liver disease or hepatocellular carcinoma which accounts for 1 million of death annualy. Approximately 45% of population are in HBV endemic area.[5]

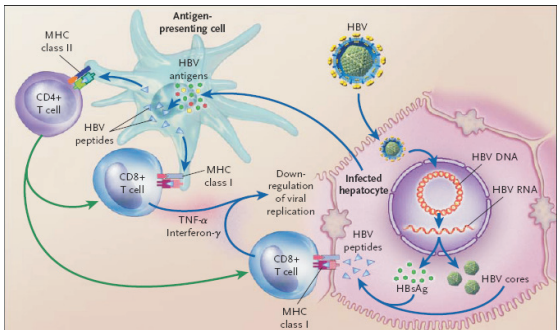

Figure 1. Cellular immune responses to hepatitis B virus[3]

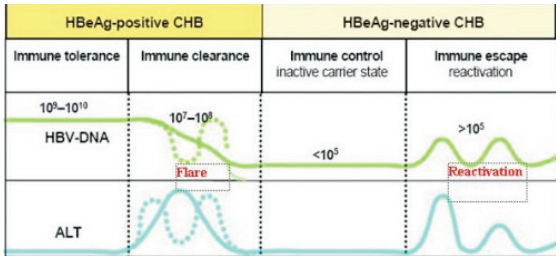

Figure 2. Natural history of chronic hepatitis B[4]

HEPATITIS B VIRUS REACTIVATION

HBV reactivation is a liver necroinflammation in inactive carrier or resulation phase patient. Clinical symptoms are variable from asymptomatic to liver decompensated and death.[6] HBV reactivation is related to serologic profile and intensity of immunosuppressive agent.[7] The pathogenesis of HBV reactivation is still unclear. The use of chemotherapy and highly immunosuppressive agent will markedly suppress the immune response hence increasing the viral load and if the agent was ceased, there will be a fast recovery of immune response and massive cytolitic of infected hepatocytes.[8]

HBV Reactivation Related to Chemotherapy Agent

Currently, there are many reports about HBV reactivation related to chemotherapy and the risk of reactivation is increasing.[9]

Patient with HBsAg (+). Lymphoma patients who are HbsAg (+) are noted to have a higher risk of HBV reactivation after chemotherapy, this may be related to the relatively more immunosuppressive drugs used for lymphoma and also possibly the intrinsic immunosuppressive effect of lymphoma.[10] A prospective study found that ≥60% HBV reactivation occurs in HBsAg (+) patient receiving cytotoxic therapy.[11] Intrahepatic covalently closed circular DNA (cccDNA) is

Table 1. Chemotherapy agent related to HBV reactivation[1]

Class	Agents associated with HBV reactivation	Potential hepatotoxicity
Alkylators	Cyclophosphamide	VOD, hepatocellular injury
	Ifosfamide	Hepatocellular injury, cholestasis
	Chlorambucil	Hepatocellular injury
	Carboplatin, cisplatin	Hepatocellular injury, cholestasis, steatosis, peliosis
Antimetabolites	Cytarabine	VOD, hepatocellular injury
	Fluorouraril	Hepatocellular injury
	Gemcitabine	Hepatocellular injury, cholestasis
	Mercaptopurine	Hepatocellular injury, cholestasis
	Methotrexate	Hepatocellular injury, steatosis, fibrosis, hepatic neoplasm
	Thioguanine	VOD, hepatocellular injury, NRH, peliosis
Antitumor antibiotics	Anthracyclines	Hepatocellular injury, VOD
	Bleomycin	Steatosis
	Mitomycin C	VOD, steatosis
	Actinomycin D	VOD, steatosis
Corticosteroides	Prednisone/Dexamethasone, etc	Hepatomegaly (rare association)
Immunotherapy	Rituximab (anti-CD20)	Hepatocellular injury
	Alemtuzumab (anti-CD52)	Hepatocellular injury
	Infliximab (anti-TNF)	Hepatocellular injury, steatosis
Plant Alkaloids	Vincristine	VOD, hepatocellular injury
	Vinblastine	Hepatocellular injury
Others	Asparginase	Hepatocellular injury, steatosis
	Procarbazine	VOD
	Docetaxel	Hepatocellular injury
	Etoposide	Hepatocellular injury
	Fludarabine	Hepatocellular injury
	Imatinib mesylate	Hepatocellular injury, cholestasis
	Interferon alpha	Hepatocellular injury

the key of viral replication and can be used for predicting HBV reactivation in HBsAg (+) patient receiving chemotherapy.[12]

Patient with HBsAg (-). Patient with HBsAg (-), anti-HBc (+) and undetectable HBV-DNA, ALT and HBV-DNA must be evaluated and treated with nucleoside analog despite of ALT level.[13] HBV reactivation in patient with HBsAg (-) but anti-HBc & anti-HBs (+) and in patient with occult anti-HBc is an uncommon condition therefore it is not recommended for routine antiviral prophylaxis. This patient should be evaluated and treated if HBV-DNA is detectable.[6]

A separate study in Taiwan by Chen et al. has shown that 6% of their HbsAg (-) patients with B-cell lymphoma had occult HBV infection.[13] In a cohort study by Hui et al. of HBsAg (-) hematopoietic stem cell transplant donors in Hong Kong, the prevalence of occult HBV infection was 15.3%.[14]

HBV Reactivation Related to Immunosuppressive Agent

Corticosteroid. HBV replication increases in the presence of corticosteroids. The peak rise in aminotransferases typically occurs 4-6 weeks after withdrawal. The mechanisms are unclear, maybe due to a glucocorticoid responsive element in the HBV genome that stimulates viral replication and transcriptional activity.[15] Study by Cheng et al. found that a steroid-free

chemotherapy regimen reduced the risk of HBV reactivation in patients with lymphoma.[16]

Monoclonal Antibody. Lymphoid malignancies and immunologic conditions often includes the use of monoclonal antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52) which are highly immunosuppressive.[1] Rituximab plus CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) is now a standard treatment of diffuse large B-cell lymphoma (DLBCL).[15] Before preemptive anti-HBV therapy is widely used, treatment of HBsAg (+) lymphoma with CHOP chemotherapy alone is associated with an approximately 50% risk of HBV reactivation, the risks are greater by adding Rituximab.[17]

Anti-TNF-α. Flares of hepatitis have been described during treatment with anti-TNF-α agents in chronic HBV patients with rheumatoid arthritis. Severe flares have also been described in association with methotrexate, particularly following its withdrawal.[18]

Bone Marrow Transplantation. Patient with HBsAg (+) who undergo allogenic bone marrow transplant is in highly immunosuppresive condition and has higher risk of HBV reactivation (14%-50%). Known risk factors are steroid used, anti-HBs (-) donor, and graft-versus-host disease.[1] In graft-versus-host disease, high dose steroid or antithymocyte globulin (ATG) are needed which suppress the immune system.[19] Immunization of HBV is recommended for donor and recipient who has never been infected by HBV.[20]

Renal Transplantation. There has been a report about declining of renal graft function in patient receiving adefovir. Entecavir is drug of choice in patient urdergoing renal transplant.

DIAGNOSIS

Currently, no uniform diagnostic criteria are available for HBV reactivation. HBV reactivation can be confirmed by an increase in serum HBV-DNA level to more than 1 log higher than that of the baseline, an absolute increase exceeding 6 log10 copies/mL, or serum HBV-DNA turning from negative to positive. Serologic evidence of chronic HBV infection would be useful. Commonly, elevation of HBV-DNA happens prior to elevation of transaminase. As reactivation may be transient, more frequent HBV-DNA and ALT monitoring will lead to a higher rate of diagnosis.[10]

TREATMENT

When a clinical diagnosis is made, chemotherapy and potential hepatotoxic agent must be ceased and treatment is based on antiviral and supportive care.[1] Lamivudine, a nucleoside analog, is an effective treatment of chronic HBV infection. The drug is active in controlling viral replication and is therefore potentially useful for the treatment of HBV reactivation. Good prognosis can be estimated if lamivudine is given at the time of HBV-DNA elevation.[21] There is a report about the successful of emergency liver transplantation in heterologous bone marrow transplantation patient with fulminant HBV reactivation.[22]

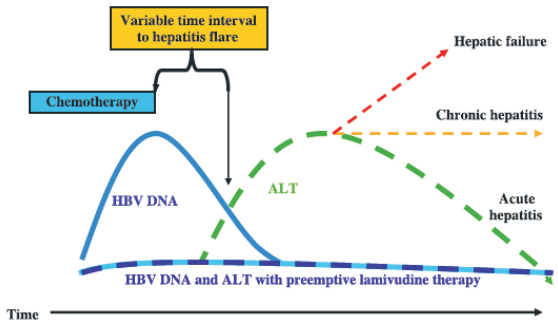

Figure 3. Dynamics of viral load and transaminase in HBV reactivation[1]

PROGNOSIS

HBV reactivation is related to long-term declining of liver function. Eventhough some patients can have spontaneous recovery, mortality rate occurs in about 5% - 40%. Patient with anti-HBc (+) has lower risk of reactivation compared to patient with HBsAg (+), but mortality rate is higher in patient with anti-HBc (+). Mortality rate is still high alhough already been treated with antiviral because usually the viral load is already high and massive immune-mediated hepatocytes injury has already occured.[23]

PROPHYLACTIC

All chemotherapy and immunosuppressive candidates should be screened for HBsAg and anti-HBc before receiving the treatment.[1] There are currently two approaches in management

of patients at risk, namely treatment of HBV reactivation when it is diagnosed, and prevention through preempative treatment prior to or upon initiation of chemotherapy.[6] Preempative antiviral therapy was the best approach to prevent the reactivation.[11]

American Association for the Study of Liver Diseases (AASLD) 2009 consensus recommend prophylactic antiviral therapy for HBV carriers at the onset of chemotherapy or of a finite course of immunosuppressive therapy.[24]

European Association for the Study of the Liver (EASL) 2009 consensus also recommend about HBV vaccination in seronegative patient and evaluate HBV-DNA level before starting chemotherapy and receiving preempative therapy along and continue to at least 12 months after chemotherapy.[25]

Asia Pacific Association for The Study of the Liver (APASL) 2008 consensus recommend lamivudine as preempative therapy for chemotherapy candidates, starting 1 week prior to and continue to at least 12 week after chemotherapy.[26]

Perhimpunan Peneliti Hepatologi Indonesia (PPHI) 2006 consensus also recommend lamivudine therapy before administer chemotherapy or immunosuppresive agent and should be continue at least 6 weeks after treatment.[27]

Metaanalysis study by Ziakas et al. reveales that in 9 trials, cumulative prevalence for HBV reactivation in prophylaxis group was 8.6% compared to 50.6% in control group. The incidence for those who did not receive prophylaxis therapy are 54.5%-100%.[28]

For patient receiving monoclonal antibody treatment, antiviral therapy should be given for at least 12 months because of slow immune recovery.[29]

HBV reactivation can be happened in those who already received lamivudine, this maybe due to drug resistency because of YMDD (tirosin-metionin-aspartat) mutant.[30] Others nucleoside analog like adefovir, entecavir, telbivudine, and tenofovir, can be given to those with lamivudine-resistant.[31]

CONCLUSION

HBV reactivation is a common complication in patient receiving chemotherapy and immunosuppressive agent, therefore we should be aware regarding its serious implication. Patient

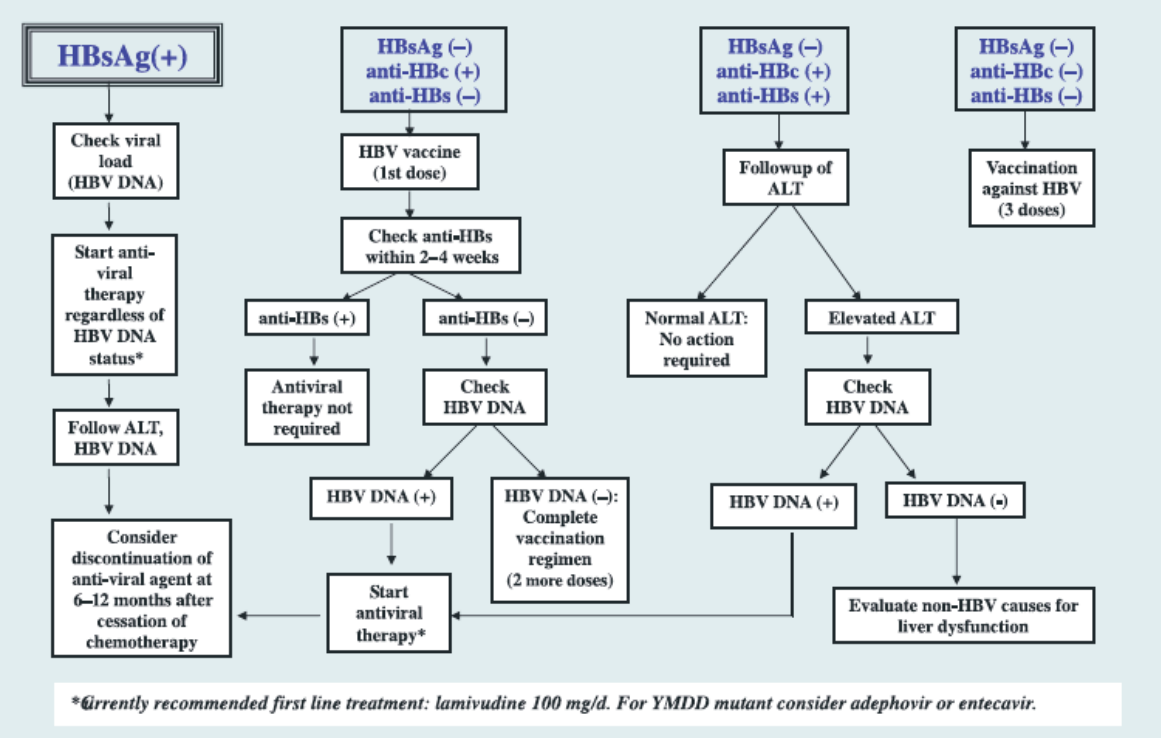

Figure 4. Screening algorithm and prophylaxis of HBV reactivation[1]

with malignancy in HBV endemic area should be screened routinely for hepatitis B status before receiving cytotoxic chemotherapy. Preempative therapy with nucleoside analog had significantly reduced the incidence, morbidity, and mortality of HBV reactivation.

REFERENCES

1. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol. 2007;136:699–712.
2. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measure. J Viral Hepatitis. 2004;11:97–107.
3. Ganem D, Prince AM. Hepatitis B virus infection: natural history and clinical consequences. N Engl J Med. 2004;350:1118-29.
4. Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatol. 2006;43:173–81.
5. Weinbaum CM, Williams I, Mast EE. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep. 2008;57:1-28.
6. Hoofnagle JH. Reactivation of hepatitis B. Hepatol. 2009;49:158-65.
7. Post A, Nagendra S. Reactivation of hepatitis B: pathogenesis and clinical implications. Curr Infect Dis Report. 2009;11:113-9.
8. Kohrt HE, Ouyang DL, Keeffe EB. Lamivudine prophylaxis for chemotherapy-induced reactivation ofchronic hepatitis B virus infection. Aliment Pharmacol Ther. 2006;24(7):1003-16.
9. Hui CK, Cheung WWW, Zhang HY, et al. Rituximab increases the risk of de novo hepatitis B infection in hepatitis B surface antigen negative patients undergoing cytotoxic chemotherapy. J Gastroenterol Hepatol. 2006;21:73-4.
10. Wang F, Xu RH, Han B. High incidence of hepatitis B infection in B-cell subtype non- Hodgkin's lymphoma compared with other cancers. Cancer. 2007;109:1360-4.
11. Kohrt HE, Ouyang DL, Keeffe EB. Systematic review: lamivudine prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. Aliment Pharmacol Ther. 2006;24:1003-16.
12. Hui CK, Bowden S, Jackson K. Clinical significance of intrahepatic hepatitis virus covalently closed circular DNA in chromic hepatitis B patients who received cytotoxic chemotherapy. Blood. 2005;105:2616-7.
13. Chen MH, Hsiao LT, Chiou TJ. High prevalence of occult hepatitis B infection in patients with B-cell non-Hodgkin's lymphoma. Ann Hematol. 2008;87:475-80.
14. Hui CK, Sun J, Au WY. Occult hepatitis B virus infection in hematopoietic stem cell donors in a hepatitis B virus endemic area. J Hepatol. 2005;42:813-9.
15. Yeo W, Chan TC, Leung NW. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol. 2009;27:605.
16. Cheng AL, Hsiung CA, Su IJ. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. Hepatol. 2003;37:1320.
17. Iannitto E, Minardi V, Calvaruso G. Hepatitis B virus reactivation and alemtuzumab. Eur J Haematol. 2005;74:254-8.
18. Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. Ann Rheum Dis. 2006;65:983-9.
19. Ma SY, Au WY, Ng IO. Hepatic graft versus host disease after hematopoietic stem cell transplantation: clinicopathologic features and prognostic implication. Transplantation. 2004;27:1252-9.
20. Piekarska A, Zaucha JM, Hellman A. Prevention of hepatitis B virus transmission from an infected stem cell donor. Bone Marrow Transplant. 2007;40:299-400.
21. Yeo W, Steinberg JL, Tam JS. Lamivudin in the treatment of Hepatitis B virus reactivation during cytotoxic chemotherapy. J Med Virol. 1999;59:263-9.
22. Au WY, Lau GK, Lie A. Emergency living related liver transplantation for fulminant reactivation of Hepatitis B virus after unrelated transplantation. Clin Transplant. 2003;17:121-5.
23. Su WP, Wen CC, Hsiung CA. Long term hepatic consequences of chemotherapy related HBV reactivation in lymphoma patients. World J Gastroenterol. 2005;11:5283-8.
24. Lok AS, McMahon BJ. Chronic hepatitis B: Update 2009. AASLD Practice guideline. Hepatol. 2009;50:1-35.
25. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 2009;50:227-42.
26. Liaw YF, Leung N, Kao JH, et al. Asian-Pasific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int. 2008;2:263-83.
27. Konsensus Perhimpunan Peneliti Hati Indonesia. Panduan Tata Laksana Infeksi hepatitis B kronik. 2006.
28. Ziakas PD, Karsaliakos P, Mylonakis E. Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance. Haematol. 2009;94:998-1005.
29. Hsiao LT, Chiou TJ, Liu JM. Extended lamivudine therapy against hepatitis B virus infection in hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant. 2006;12:84-94.
30. Gauthier J, Bourne EJ, Lutz MW. Quantitation of hepatitis B viraemia and emergence of YMDD variants in patients with chronic hepatitis B treated with lamivudine. J Infect Dis. 1999;180:1757-62.
31. Peters MG, Han Hw H, Martin P. Adevovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterol. 2004;126:91-101.