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Management of Chronic Hepatitis B in Patients from Special Populations

Ching-Lung Lai and Man-Fung Yuen

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong 999077, China

Correspondence: hrmelcl@hku.hk; mfyuen@hkucc.hku.hk

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Here we review the management of chronic hepatitis B (CHB) in four special categories of patients: CHB in pregnancy, in patients on immunosuppressive treatments, in patients undergoing liver transplantation, and in patients coinfected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV).

Chronic hepatitis B (CHB) infection poses a major health problem globally. This review discusses the effects and management of CHB in four populations who require special considerations. These include pregnant patients and their offspring, patients requiring immunosuppression, patients requiring liver transplantation, and patients coinfected with the human immunodeficiency virus (HIV) or the hepatitis C virus (HCV).

Reactivation of CHB occurs in up to 45% of HBsAg-positive mothers during the 6 mo after delivery, probably because of restoration of the immune system. The outcome is worse in mothers with cirrhosis. Liver biochemistry and hepatitis B virus (HBV) DNA levels should be closely monitored after delivery. Hepatitis B vaccination together with one dose of hepatitis B immunoglobulin (HBIG) has reduced the perinatal transmission of the hepatitis B virus to infants from >70% to <5%. Recent studies show that the small proportion of infants who still become infected is mainly related to high maternal HBV DNA levels (≥ 6 $\log_{10}$ copies/mL). Treating these mothers with antiviral therapy during the third trimester can further reduce the transmission rate to nearly 0%.

Acute exacerbation of CHB after conventional immunosuppressive therapy has been described mainly in cancer patients, but can also occur in noncancer patients. Such reactivation has also been reported with biological therapy, such as anti-tumor necrosis factor (TNF)-α. With the much more potent anti-CD20 and anti-CD52, reactivation (sometimes fatal) can also occur in patients with occult hepatitis B who are HBsAg negative, up to at least 12 mo after cessation of therapy. HBsAg-positive patients should be given preemptive nucleos(t)ide analog therapy irrespective of HBV DNA levels for at least 12 mo after immunosuppressive therapy. For HBsAg-negative and anti-HBs/anti-HBc-positive patients, if HBV DNA is detectable at baseline, nucleos(t)ide analogs should also be given. If they are HBV DNA negative at baseline, HBV DNA levels should

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be monitored at 1- to 3-mo intervals until 12 mo after the last cycle of therapy. Once HBV DNA is detectable, they should be treated with nucleos(t)ide analogs.

After liver transplantation for CHB patients, HBV recurrence occurs in >80% of patients if no treatment is given. Such recurrence can give rise to rapid development of cirrhosis with 12–23 months, or to fibrosing cholestatic hepatitis. Recurrence can be prevented by the use of low-dose HBIG combined with potent nucleos(t)ide analogs with low-resistance profiles, including entecavir and tenofovir. A recent study shows that entecavir monotherapy, without HBIG, is equally effective.

Five percent to 15% of HBV carriers have coinfection with the HIV. Liver-related mortality is higher in coinfected patients compared with HBV or HIV-monoinfected patients. For patients with quiescent HIV infection not on highly active antiretroviral therapy (HARRT), anti-HBV treatment can be considered when patients fulfill the usual criteria for HBV treatment. In these patients, interferon (IFN) is less effective. Entecavir, with its partial reduction of HIV RNA, may potentially increase the risk of HIV resistance. In HBV/HIV-coinfected patients who require HAARTs, tenofovir combined with lamivudine or emtricitabine is the treatment of choice.

In patients with coinfection of HCV and HBV, HCV usually suppresses HBV replication. So HCV commonly requires more urgent treatment. With the development of direct acting antivirals for HCV with a curative rate of >90%, the main concern is reactivation of HBV after the inhibitory effect of HCV is removed. HBV DNA should, therefore, be closely monitored and patients treated when HBV DNA levels increase.

PATIENTS WITH PREGNANCY

The major concern of pregnancy in mothers with CHB is to prevent the transmission of the virus from the mother to the newborn. However, pregnancy can have some effects on the CHB disease of the mother.

Effects of Pregnancy on Hepatitis B Carrier Mothers

Although some studies suggest that there may be an increase in the complications of pregnancy, such as gestational diabetes, antepartum hemorrhage, and preterm labor in CHB mothers (Tse et al. 2005), this has not been supported by other large-scale studies (To et al. 2003; Lobstein et al. 2011).

Severe reactivation of hepatitis B after delivery was reported in 1991 (Rawal et al. 1991). A more recent study shows that a threefold increase of alanine transaminase (ALT) levels occurred in 45% of mothers within 6 mo after delivery (ter Borg et al. 2008). The rate was, as expected, even higher (62%) in mothers who were treated with lamivudine during the last trimester with the lamivudine being stopped immediately after delivery. During pregnancy, the mother's immune system would be altered to prevent rejection of the fetus, with enhancement of HBV replication. Exacerbation of CHB may occur after delivery with restoration of the immune system.

Liver biochemistry and HBV DNA should be closely monitored in postdelivery women for at least 6 mo. For mothers who are started on antiviral treatment during pregnancy, it is advisable not to stop antiviral therapy abruptly after delivery.

The outcome for cirrhotic pregnant women can be much worse. In a population-based study of 339 cirrhotic women compared with 6625 matched controls, maternal mortality (1.8% vs. 0%) and fetal mortality (5.2% vs. 2.1%) were more frequent ($p < 0.0001$ for both) (Shaheen and Myers 2010). Hepatic decompensation occurred in 15% of patients, with maternal and fetal mortality being 6% and 12%, respectively. Hence, cirrhotic mothers should be treated as well as monitored throughout pregnancy.

Prevention of Maternal to Child Transmission of the Hepatitis B Virus

Many studies, mostly from Taiwan, have documented the risk of maternal to child transmission of HBV before the development of the hep-

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atitis B vaccine in 1981 (Anderson et al. 1975; Stevens et al. 1975). Up to 63% of infants born to HBsAg-positive mothers became HBsAg positive during the first 6 mo of life. Infants born to HBeAg-positive carrier mothers have a higher carrier rate compared with those of HBeAg-negative mothers, showing that transmission is related to high viral load. However, even in infants born of HBeAg-negative mothers, 25%–30% also become chronic carriers, which means that HBeAg-negative mothers can also have high viral loads. The studies also found that 6% of fathers and 67% of siblings were also HBsAg positive. It has subsequently been shown by sequence analysis of HBV mutations that postnatal transmission can also occur from carrier fathers and even aunts (Lin et al. 1990).

There was a marked reduction in the infant infection rate after the availability of both HBIG and HBV (at first plasma derived, and later recombinant) (Beasley et al. 1983; Stevens et al. 1985). In a pioneering study (Wong et al. 1984), the infant carrier state was reduced from 73.2% in the control group to 21.0% in the vaccine alone group, 6.8% in the group receiving vaccine plus one dose of HBIG, and 2.9% in the group receiving vaccine plus multiple doses of HBIG ($p \leq 0.0001$ for all groups).

With more sensitive assays for HBV DNA and better appreciation of the importance of HBV DNA levels, a recent retrospective study of 869 HBsAg-positive mothers and their infants who had received HBIG with three doses of hepatitis B vaccine showed that 27 infants (3.1%) were HBsAg positive at age 7–12 mo (Zou et al. 2012). Maternal HBV DNA levels and detectable HBV DNA in the cord blood were independent risk factors for immunoprophylaxis failure. All failures occurred in infants born to HBeAg-positive mothers with predelivery HBV DNA $\geq 6 \log_{10}$ copies/mL. Two smaller studies (Wiseman et al. 2009; Singh et al. 2011) also confirm that high maternal viral load (in the study of Wiseman et al. [2009], HBV DNA of $> 8 \log_{10}$ copies/mL) is associated with failure of prophylaxis. Because mothers with HBV DNA levels between 6 and 8 $\log_{10}$ copies/mL have been associated with immunoprophylaxis failure in their infants, it is advisable to consider treatment of the mothers with antiviral therapy when their HBV DNA levels are $\geq 6 \log_{10}$ copies/mL.

Choice and Safety of Antiviral Treatment during Pregnancy

Of the five licensed nucleos(t)ide analogs, tenofovir and telbivudine are classified under the U.S. Food and Drug Administration (FDA) pregnancy category B, that is, animal studies do not show any risk to the fetus. Lamivudine, entecavir, and adefovir are under category C, that is, animal studies have shown adverse effects on the fetus.

According to the Antiretroviral Pregnancy Registry (APR) (see www.apregistry.com/forms/interim_report.pdf), set up in 1989 for the evaluation of teratogenic effects of antiretroviral treatment for the human immunodeficiency virus, the birth defect prevalence of tenofovir (as reported up to July 2013) is 46 out of 1982 live births (2.3%), and of lamivudine is 136 out of 4360 (3.1%). The frequencies of birth defects with the other three agents are not as well established because of the paucity of their use in pregnant women. Although the APR cautions that the accuracy of the data is limited by potential under and differential reporting as well as under and differential ascertainment of birth defects, the birth defect frequencies of tenofovir and lamivudine are quite low, and comparable to the birth defect rates of normal pregnancy, estimated to be 2.7% from the Centers for Disease Control and Prevention surveillance (Wang et al. 2013). Both drugs can be used for viral suppression in the third trimester, tenofovir being preferred if the mother requires long-term therapy after delivery because of the high resistance rate associated with lamivudine.

Efficacy of Antiviral Treatment during Pregnancy

There are two controlled studies of lamivudine (Xu et al. 2009) and telbivudine (Han et al. 2011), and one case series study of tenofovir (Pan et al. 2012) given to mothers with high

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Table 1. Summary of the efficacy of nucleos(t)ide analogs treatment in reducing the risk of maternal-to-child transmission of hepatitis B infection

Drug	Number of infants	Maternal HBV DNA before delivery/treatment	Perinatal HBsAg positivity (treated vs. untreated)	*p* Value
Lamivudine versus placebo (Xu et al. 2009)	141	$2.22 \pm 1.6 \times 10^9$ copies/mL versus $2.69 \pm 1.62 \times 10^9$ copies/mL	18% versus 39%	0.014
Telbivudine versus no treatment (Han et al. 2011)	229	8.10 ± 0.58 $\log_{10}$ copies/mL versus 7.98 ± 0.61 $\log_{10}$ copies/mL	0% versus 8%	0.002
Tenofovir (case series) (Pan et al. 2012)	11	8.87 ± 0.45 $\log_{10}$ copies/mL	0%	-

HBV DNA levels in the second to third trimester to reduce the risk of maternal-to-child transmission of HBV. The results of these studies are shown in Table 1. All show the efficacy of viral suppression of the mothers in reducing the risk of transmission to the infants. However, it is worth highlighting that the study with lamivudine (Xu et al. 2009) has an unacceptably high failure rate of 38% in the infants who received placebo plus immunoprophylaxis, probably reflecting inadequate prophylaxis in the study as a whole.

Concerning the duration of treatment, mothers who are in the immune tolerance phase can have the antiviral drug stopped ~4 wk after delivery, with close monitoring of liver biochemistry and HBV DNA for at least 6 mo. Mothers who fulfill the criteria for initiation of antiviral therapy, especially those with preexisting cirrhosis, should be maintained on long-term antiviral treatment (Lai and Yuen 2008). Breast-feeding is not recommended as long as the mothers are receiving antiviral treatment, although this may change with more information from trial data being generated.

PATIENTS REQUIRING IMMUNOSUPPRESSION

In a study of the natural history of 3063 patients with CHB with a median follow-up of 29 mo (range 0.6–291 mo), acute exacerbation (defined as increase in ALT levels to >1.5 times ULN) occurred in 45.5% of subjects. Most of these exacerbations were mild, only 14.6% of patients had hepatitis symptoms, and the mortality was low, 0.7% (Yuen et al. 2003).

Acute Exacerbation of CHB and Immunosuppression

The first report of acute exacerbation of CHB following chemotherapy was by Wands et al. (1975). They followed 25 patients with myeloproliferative and 60 with lymphoproliferative disorders, 17 of whom were HBsAg positive and 40 anti-HBs positive. In three HBsAg-positive patients, bone marrow suppression was associated with an increase in HBsAg titer and ALT levels, signifying hepatocellular damage. Seventeen of the 40 anti-HBs-positive patients had a decrease in anti-HBs titer with HBsAg appearing in five patients (seroreversion).

Following conventional immunosuppressive therapy, and more recently with the biological therapies, such as anti-TNF-α, acute exacerbation has been mainly reported in patients with known CHB (Lau et al. 1989). However, with more recent very potent immunosuppressive agents like rituximab, ofatumumab, and alemtuzumab, severe (sometimes fatal) reactivation has been reported in patients with occult hepatitis B (OHB), that is, patients who are negative for HBsAg pretreatment but positive for other HBV markers, anti-HBc with or without anti-HBs (Yeo et al. 2009).

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Conventional Immunosuppressants

The drugs most commonly reported to give rise to CHB reactivation are prednisolone and the anthracyclines. The reports are mostly in cancer patients, especially in patients with leukemia and lymphomas. These patients have some basic malfunctioning of the immune system.

However, more rarely, cases have been reported in patients with other diseases, in which there is no obvious pretreatment disturbance of the immune system. Early reports included fatal reactivation in two asthma patients and two patients with nephrotic syndrome (Onwubalili 1988; Koga et al. 1992). Two recent reviews have also reported such reactivation in noncancerous patients. The first series was from Singapore, involving 38 CHB patients with rheumatoid arthritis or systemic lupus erythematosus. CHB reactivation occurred in 52.6% of patients, but these attacks were mostly mild (Thong et al. 2007). The second series was from Korea with 198 CHB patients with asthma or chronic obstructive pulmonary disease. Patients who received systemic plus inhalational steroid had a significantly higher incidence of reactivation (11.1%) compared with those who received inhalational steroid only (3.2%, $p = 0.03$) (Kim et al. 2010). The incidence was also higher in patients who received systemic prednisolone for 3 mo or more (15.8%, $p = 0.048$) as well as in patients receiving prednisolone at dosages of 20 mg/d or higher (14.0%, $p = 0.014$). The rarity of reports in noncancer patients is probably related to the usually asymptomatic course of the reactivation, which is still potentially severe.

The mechanism of CHB reactivation with conventional immunosuppressants is likely to be related to immune suppression during therapy with immune rebound on withdrawal of the immunosuppressants. With the use of steroids, there are also two special effects. During steroid therapy, there is enhancement of HBV replication through stimulation of the glucocorticoid responsive element in the HBV (Tur-Kaspa et al. 1986). In addition, high doses of steroids suppress the helper and suppressor T-cell function with increase in primary B-cell function during treatment. On withdrawal of steroid, usually after 4–10 wk, there is rebound of the suppressor T-cell activity, on top of the enhanced HBV viral load. This is the reason why reactivation of CHB is most commonly documented when the chemotherapeutic regimes include a steroid component.

Anti-TNF-α Agents

Because anti-TNF-α agents, including infliximab, etanercept, and adalimumab, are known to reactivate latent infections like tuberculosis, herpesvirus, and histoplasmosis, it is not surprising that it may also reactivate CHB. In a recent systematic review of nine studies involving 122 HBsAg-positive patients, HBV reactivation occurred in 15 cases (12.3%) (Lee et al. 2013a). Only some of the patients received antiviral therapy, but the outcome was said to be satisfactory. Reactivation has also been reported in patients with OHB. In a review of nine studies involving 468 HBsAg-negative and anti-HBc-positive patients, reactivation occurred in eight cases (1.7%) with seven patients having detectable HBV DNA (Lee et al. 2013b). Once again, the outcome was satisfactory.

However, in an earlier review of 35 HBsAg-positive patients on anti-TNF-α agents, there were six cases of symptomatic hepatitis, all associated with infliximab use, with two deaths caused by fulminant hepatic failure and variceal bleed (Carroll and Forgione 2010).

TNF-α and IFN-γ modulate cytotoxic T-lymphocyte-induced suppression of HBV gene expression and replication (Guidotti et al. 1996). Monoclonal antibodies against TNF-α inhibit such activities and, hence, cause CHB reactivation. In the report in which infliximab caused the most severe reactivation (Carroll and Forgione 2010), it has been postulated that this may be because of two factors. First, infliximab is the only TNF-α inhibitor to be given intravenously. With its maximal bioavailability, there may be a "cytokine washout," clearing a large amount of soluble and transmembrane TNF-α. Second, as the only chimeric monoclonal, infliximab may be more potent as an activator of complement-dependent cytotoxicity.

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Anti-CD20 (Rituximab, Ofatumumab) and Anti-CD52 (Alemtuzumab)

These agents are known to reactivate cytomegalovirus, parovirus B19, and adenovirus.

Rituximab was first reported to cause HBV reactivation 7 mo after four weekly courses in a 69-yr-old lymphoma patient who was previously negative for HBsAg and positive for anti-HBs (Dervite et al. 2001). The subsequent reports of reactivation in both CHB and OHB patients are almost all in patients with hematological or lymphoid malignancies.

In a retrospective study of 1087 non-Hodgkin's lymphoma, 5% of the patients were HBsAg positive, 58% were negative for HBV markers or only positive for anti-HBs, and 36% (394 patients) were isolated anti-HBc positive (Targhetta et al. 2008). (These 394 patients were specially studied for the effect of chemotherapy with or without rituximab in OHB patients.) Four patients (1.0%) developed HBV reactivation, two of 245 (0.8%) treated with conventional chemotherapy, and two of 74 (2.7%) treated with chemotherapy and rituximab ($p < 0.05$).

These results were confirmed in another study of 104 patients with diffuse large B-cell lymphoma, of whom 24 were HBsAg positive (Yeo et al. 2009). In the 80 HBsAg-negative patients, no HBV reactivation was detected in the 34 patients who were anti-HBc negative. In the remaining 46 patients who were positive for anti-HBc, no HBV reactivation occurred in the 25 who received only conventional chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone; CHOP), whereas five of the 21 (23.8%) patients who received CHOP plus rituximab (CHOP-R) had HBV reactivation 78–110 days after completion of CHOP-R, with one patient dying of liver failure. The factors associated with HBV reactivation were male sex ($p = 0.0299$), anti-HBc positivity but anti-HBs negative ($p = 0.0025$), as well as the use of rituximab ($p = 0.05$). It should be emphasized that, although this study found an apparent "protective" effect of anti-HBs for OHB reactivation, the first case report was in a patient who was anti-HBs positive. The more recently approved anti-CD20 for the treatment of chronic lymphocytic leukemia, alemtuzumab, has similar effects. The FDA has issued a boxed warning concerning the risk of HBV reactivation with these two agents (Mitka 2013).

Monoclonal anti-CD20 results in profound depletion of B cells, normal and malignant, with decreased humoral immune response persisting for 6–9 mo (van der Kolk et al. 2002). The hepatitis B core antigen (HBcAg) has a unique ability to bind to B cells (Lazdina et al. 2003). HBcAg-binding B cells may act as antigen-presenting cells and prime HBcAg-specific cytotoxic T cells as the B cells recover from the treatment.

Prevention and Management of HBV Reactivation with Immune Suppressive Therapy

There is general agreement on the prevention and management of HBV reactivation for patients receiving immunosuppressive therapy among the major international clinical practice guidelines (Lok and McMahon 2009; EASL 2012; Liaw et al. 2012).

Patients receiving conventional chemotherapy should be screened for HBsAg. If the patient is positive for HBsAg, baseline HBV DNA and standard liver function tests should be checked before treatment. For patients receiving anti-TNF-α, anti-CD20 and anti-CD52, other HBV markers, including anti-HBs and anti-HBc, should be checked. Baseline HBV DNA and standard liver function tests should be performed when any HBV marker is positive.

HBsAg-positive patients should receive preemptive nucleos(t)ide analog therapy irrespective of the HBV DNA levels. The nucles(t)ide analog should be continued for at least 12 mo after the immunosuppressive therapy. Longer periods of treatment should be considered for patients who fulfill the criteria for treatment of CHB at baseline. (These include baseline HBV DNA levels >2000 IU/mL (1U/mL = 5 copies/mL) and ALT levels >ULN (upper limit normal), or when cirrhosis is present.) For patients with low-baseline HBV DNA levels (<2000 IU/mL), who will only receive a finite period of nucleos(t)ide analogs, lamivudine may be used (Loomba et al. 2008). For patients

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with high viral load or who require longer period of treatment, nuclos(t)ide analogs with higher barrier to resistance, entecavir or tenofovir, should be prescribed.

When HBV DNA is detectable in the serum of HBsAg-negative and anti-HBc/anti-HBs-positive patients at baseline, they should be treated as in the HBsAg-positive patients. Those who are negative for HBV DNA at baseline should have HBV DNA and liver function checked at regular intervals of 1–3 mo until at least 12 mo after the last cycle of immunosuppressive therapy. The frequency of monitoring depends on which agent is being used (for example patients on rituximab should be checked more frequently), as well as the presence of significant comorbidities. HBV DNA levels are more sensitive indices of reactivation than liver function because they become detectable before ALT levels start to increase. Once HBV DNA is detectable, the patients should be treated with nucleos(t)ide analogs. It has also been suggested that, for patients who are HBsAg negative and anti-HBc positive, they should be treat preemptively with lamivudine if they are anti-HBs negative or if close follow-up cannot be assured (Marzano et al. 2007).

PATIENTS RECEIVING TRANSPLANTATION

After liver transplantation in patients with chronic CHB infection, the recurrence of HBV infection is very high (>80%) if no treatment is given to reduce the replication of the virus. Such recurrence can give rise to rapid development of cirrhosis with 12–23 mo, or to fibrosing cholestatic hepatitis. Recurrence can be prevented by the use of low-dose HBIG combined with potent nucleos(t)ide analogs with low-resistance profiles, including entecavir and tenofovir. A recent study shows that entecavir monotherapy, without HBIG, is equally effective.

Before the development of antiviral therapy for HBV transplantation, recurrent infection in the liver allograft can lead to rapid development of cirrhosis within 12 to 23 mo (Harrison et al. 1993). This is especially severe and often fatal should the patients develop the histologic picture of fibrosing cholestatic hepatitis (FCH) (Wright 1993). FCH is rapidly progressive, and recurs after retransplantation in the new graft. With immunosuppression, there is excess production of HBsAg in the cytoplasm, and HBcAg in both the cytoplasm and the nucleus of the hepatocytes. It has been postulated that a defect occurs in excretion of surface proteins from the cells, and accumulation of viral proteins within the endoplasmic reticulum is directly toxic to the hepatocytes (Lau et al. 1992).

The first study to report that long-term viral suppression is useful for the prevention of HBV recurrence was performed by Samuel et al. (1993). This study uses passive prophylaxis with HBIG, reducing the risk of HBV recurrence from 75% to 36% at 3 yr for those with no immunoprophylaxis and those receiving long-term HBIG, respectively ($p < 0.001$). There are several reservations about the isolated use of HBIG. It is ineffective in around one-third of the patients even with long-term usage. It is very expensive when used in the large doses that are required for passive prophylaxis. In addition, it is not widely available because it is dependent on plasma from subjects who are positive for anti-HBs.

With the development of nucleos(t)ide analogs, combination of lamivudine, the first available nucleoside analog, and HBIG was shown to be effective in viral suppression up to 1 yr after transplantation (Markowitz et al. 1998). Lamivudine has been shown to reverse FCH in a renal transplant patient who developed acute de novo hepatitis B 8 mo after the renal transplant (Chan et al. 1998).

Until 2012, lamivudine has been used in combination with low-dose HBIG successfully for preventing recurrence of HBV after liver transplantation. The lower dose of HBIG means a lower cost. Resistance to lamivudine, because of the development of the tyrosine methionine aspartate aspartate (YMDD) mutations, is treated with adefovir, high-dose entecavir or, more recently, tenofovir. Studies have shown that just 1 yr of HBIG when combined with lamivudine, is effective and cost-saving, with only 8.9% of patients developing resistance at 5–10 yr of follow-up (Tanaka et al. 2012). All recurrences were treated successfully with additional antiviral therapy.

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With the development of the two current first line nucleos(t)ide analogs, entecavir and tenofovir, with very low rate of resistance (0%–1.2%), combination of entecavir/ tenofovir with HBIG has replaced lamivudine (and adefovir). Even more encouragingly, entecavir monotherapy without HBIG has been shown to be effective in a series of 80 patients (Fung et al. 2011). At 2 yr of follow-up, 91.0% of the patients lost HBsAg with 98.8% achieving undetectable levels of HBV DNA using PCR assay. No studies have been published on tenofovir monotherapy without HBIG to date, but it is to be expected that tenofovir monotherapy is a viable alternative.

PATIENTS WITH COINFECTION WITH HIV AND HCV

HBV and HIV Coinfection

Sharing the common routes of transmission, HBV and HIV coinfection is not an uncommon disease. Of the 40 million world population with HIV infection, 5%–15% are coinfected with HBV (Murphy and Wilcox 2004; Matthews 2007). With the wider use of HAART, morbidity and mortality resulting from coexistent CHB infection has become a more common problem in the HIV-infected population. It has been shown that the chance of hepatitis flares and rate of liver disease progression are higher in patients with HBV/HIV coinfection compared with patients with HBV monoinfection (Colin et al. 1999). Liver-related mortality is higher in HBV/HIV-coinfected patients (14.2/1000 person-years) compared with those of HIV monoinfected patients (1.7/1000 person-years) and HBV monoinfected patients (0.8/1000 person-years) (Thio et al. 2002). Necessity of treatment for HBV in this setting is, therefore, very high. The goal of treatment of CHB in coinfected patients should be the same as for HBV monoinfection, that is, long-term suppression of viral replication to achieve maximal reduction of the rate of development of cirrhosis and/ or hepatocellular carcinoma. Although the treatment initiation criteria for coinfected patients have not been established, it should at least be at the same threshold as for HBV monoinfection. However, because of the more serious outcome of coinfection disease, the treatment criteria may even be less stringent. Concerning the treatment duration, even for HBV monoinfection, it is still controversial among the suggestions of different regional guidelines and experts in the field. It is more generally accepted for HBV/HIV coinfection that treatment for HBV should be indefinite because of the lower response rates and the need of continuous HIV treatment, which may lead to immune reconstitution and provoke immune-mediated attack against the HBV disease.

The status of the HIV infection is very important in the designation of the treatment strategy for HBV in the setting of HBV/HIV coinfection. If the HIV infection is quiescent (e.g., CD4 count >500 cells/mm^3 and low–HIV RNA levels [<100,000 copies/mL]), in which HAART is not required, anti-HBV agents with no anti-HIV effects should be considered for those with HBV DNA >2000 IU/mL and abnormal ALT levels. These include conventional and pegylated IFN, adefovir (at 10 mg daily dose), and telbivudine. This is to avoid the emergence of HIV resistance, which will be problematic for future anti-HIV therapy if needed. However, it seems that by using conventional IFN, the treatment response in HBV/HIV coinfection is poorer compared with HBV monoinfection (Di Martino et al. 2002). The effects of pegylated IFN are mixed according to a few small studies (Wursthorn et al. 2006; Johnson et al. 2007). In addition, it is noteworthy that IFN treatment may lead to bone marrow suppression, which may further deplete CD4 count in these patients. Adefovir at the daily dose of 10 mg has no anti-HIV effect and, hence, may be considered in this scenario. It is, however, limited by only modest HBV DNA suppression and the fairly high rate of HBV-resistance development (20% after 3 yr and 29% after 5 yr for HBeAg-positive and -negative patients, respectively) (Fung et al. 2008). Telbivudine has a more profound HBV DNA suppression, but the rate of resistance is also considerably higher (22.0% and 8.6% after 2 yr of treatment for HBeAg-positive and -negative patients, respectively).

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Although entecavir is proven to be highly effective in HBV monoinfection with negligible rate of development of resistance, its use in HBV/HIV coinfection, which requires HBV suppression without the need of HARRT, is still controversial. A preliminary report has shown that entecavir is associated with a 1 logs copies/mL decline in HIV RNA (McMahon et al. 2007). HIV-1 variants with the lamivudine-resistant mutation, M184V, which has cross resistance profile with entecavir, has been found in one out of three HIV/HBV coinfected patients who have HIV RNA reduction on entecavir monotherapy without HARRT (Sasadeusz et al. 2008). Therefore, it may potentially increase the risk of HIV resistance in patients who are not receiving HARRT.

Tenofovir has been shown to be very potent with an average of 4 logs reduction of HBV DNA in HBV/HIV coinfected patients (Núñez et al. 2002; Ristig et al. 2002; van Bömmel et al. 2002; Benhamou et al. 2003; Nelson et al. 2003). More than 95% of patients have undetectable HBV DNA after 5 yr of tenofovir therapy (de Vries-Sluijs et al. 2010). It has a high genetic barrier for the development of resistance mutations to HBV. Whether the A194T mutation found in patients with suboptimal viral suppression confer actual phenotypic resistance needs further exploration (Amini-Bavil-Olyaee et al. 2009). However, because of its anti-HIV property, it is not recommended in patients who do not need HARRT.

In another scenario, in which treatments for both HBV and HIV infections are required, agents with dual anti-HBV and anti-HIV activities are recommended. Full HARRT regimen with potent anti-HBV activities, for example, tenofovir with lamivudine or with emtricitabine should be considered. Monotherapy using nucleoside analogs, for example, lamivudine and emtricitabine, for HBV is not recommended because of a very high rate of HBV resistance mutations. It has been found that more than 90% of patient will develop lamivudine resistance after 4 yr of therapy (Benhamou et al. 1999). For patients with renal insufficiency, HARRT without tenofovir with addition of entecavir to control HBV infection can be considered.

In patients who are already treated with lamivudine-containing HARRT, continuous and close monitoring of HBV viraemia is necessary. Adefovir or preferably tenofovir should be added in any case of detectable HBV DNA, which is highly suggestive of lamivudine resistance development. It has been shown that 25% and 63% of these patients can achieve undetectable HBV DNA after 144 wk of adefovir and 48 wk of tenofovir, respectively (Benhamou et al. 2006; Cheruvu et al. 2007).

Finally, if only HIV infection is required to be treated and treatment for HBV is not necessarily required, two drugs active against HBV in a fully potent HARRT regimen, for example, tenofovir with lamivudine or with emtricitabine should be considered (Mendes-Corrêa and Núñez 2010; Lacombe and Rockstroh 2012). This is to prevent the risk of HBV viral reactivation caused by immune reconstitution syndrome secondary from the successful HIV treatment.

HBV and HCV Coinfection

Both HBV and HCV share the common route of parenteral transmission. It has been estimated that 5%–10% of CHB patients are anti-HCV positive (Gaeta et al. 2003). Conversely, 2%–10% of CHC patients are positive for HBsAg (Fattovich et al. 1991; Crespo et al. 1994; Dai et al. 2001). High-risk groups of HBV/HCV coinfection include intravenous drug users, patients on haemodialysis and patients with organ transplantation (Pallás et al. 1999; Aroldi et al. 2005; Reddy et al. 2005). Coinfection of both viruses is of prognostic significance as patients with coinfection of HBV and HCV have a significantly higher rate of disease progression and risk of HCC (Kaklamani et al. 1991; Benvegnù et al. 1994; Weltman et al. 1995; Chiaramonte et al. 1999).

As shown by animal and human studies, in the setting of coexistence of two viruses, HCV usually suppresses the HBV replication (Bradley et al. 1983; Brotman et al. 1983; Fong et al. 1991; Crespo et al. 1994) because HCV core protein has inhibitory effects on HBV replication (Shih et al. 1993, 1995; Sheen et al. 1994; Schüttler et

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al. 2002). This may also be the reason for the higher rate of HBsAg seroconversion in coinfected patients (Sheen et al. 1994; Hamzaoui et al. 2013). It is reported that HBsAg seroclearance occurs in 2.1% of HBV/HCV coinfected compared with only and 0.43% in HBV monoinfected patients (Sheen et al. 1994).

It is, therefore, more commonly found that treatment of CHC rather than CHB is more urgently needed, although the viral dominance can change over different periods of time (Pontisso et al. 1996; Potthoff et al. 2010). As far as the treatment response to CHC is concerned, there are no differences in the sustained virological response (SVR) for different genotypes between HBV/HCV-coinfected patients and HCV-monoinfected patients (Liu et al. 2009). The SVRs for genotype 1 are 72.2% and 77.3% and for genotype 2/3 are 82.8% and 84.0% for patients with HBV/HCV coinfection and HCV monoinfection, respectively. At present, pegylated IFN-based therapy is still the main treatment for CHC. As such, there may be some effects on CHB. It has been shown that annual rate of HBsAg seroclearance in this particular group of coinfected patients is as high as 5% (Yeh et al. 2011; Yu et al. 2013).

With the development of direct-acting antivirals (DAA) for CHC, the CHC treatment regimen can now be IFN free. As the curative rate for CHC is more than 90% even for CHC genotype 1 infection, HBV reactivation should be the main concern (after the removal of the inhibitory effects of HBV by HCV). These patients should be monitored very closely by HBV DNA levels during and after HCV antiviral therapy. As high as 36%–62% of coinfected patients with previously undetectable HBV DNA have detectable HBV DNA after successful CHC treatment (Liu et al. 2009; Yu et al. 2010, 2013). If there is HBV reactivation, standard oral nucleoside/nucleotide analogs, for example, entecavir and tenofovir may need to be considered as severe flares of hepatitis have been reported (Weltman et al. 1995; Yalçin et al. 2003), although hepatitis flares have not been observed in other studies (Yu et al. 2013).

For patients with dominant HBV infection, that is, HBV DNA >2000 IU/mL with abnormal ALT levels with undetectable HCV RNA, treatment for HBV is indicated. In a situation where both HBV and HCV viraemia are high, it is recommended to use pegylated IFN and ribavirin, to be followed by entecavir or tenofovir if HBV DNA undetectability is not achieved. However, with the availability of IFN-free DAA treatment for CHC, entecavir or tenofovir may be given concomitantly with the CHC treatment. Given the paucity of the current available data, these approaches need further evaluation.

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