Reduction of Infectivity in Chronic Hepatitis B Virus Carriers among Healthcare Providers and Pregnant Women by Antiviral Therapy

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Key Words

Hepatitis B · Hepatitis B virus chronic carrier · Hepatitis B virus DNA · Hepatitis B virus infectivity · Healthcare providers · Mother-to-child transmission · Antiviral therapy · Entecavir · Tenofovir · Telbivudine

Abstract

The main purpose of therapy for infectious diseases is restoration or protection of the patient's health, but suppression or elimination of infectious agents is also important. In two well-defined situations, reduction of potential infectivity may be the main reason for therapy in hepatitis B virus (HBV) carriers who do not suffer from significant disease: (1) healthcare providers who perform exposure-prone procedures to prevent transmission of HBV to individuals, and (2) pregnant women in the third trimester to prevent transmission to the fetus. This article describes the necessity to recognize highly viremic HBV-infected individuals in these situations, the methods to estimate the risk of transmission, and the therapeutic possibilities to prevent transmission. With today's methods of monitoring HBV DNA, it is possible to reliably estimate the risk of transmission. The drugs entecavir or tenofovir are able to suppress infectivity of HBV carriers to levels acceptable for healthcare providers performing exposure-prone procedures. According to the CDC, 'chronic HBV

infection in itself should not preclude the practice or study of medicine, surgery, dentistry, or allied health professions.' Treatment of pregnant women with very high levels of HBV DNA prevents the transmission to the fetus and further if the newborn receives immediate active/passive immunization against HBV.

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Hepatitis B virus (HBV) is almost exclusively produced in the liver of the infected host. It is not excreted to the bile and is not actively transported to stools, urine, or secretions. Besides the liver the main reservoir of HBV is the blood or plasma of infected subjects. A not well-defined passive transfer of HBV from serum to saliva, semen, vaginal secretions, or breast milk may occur, but it results in 100- to 1,000-fold lower HBV concentrations than in plasma. Even more restricted than release of the virus is the entry into a new host because the virus has to reach and enter the hepatocytes of the new host before it can replicate and establish infection. This is only possible via the blood-stream after entry to wounds or by a much less efficient passage through mucosa. In view of these restrictions, it is rather surprising that more than 40% of the human population have been infected with HBV, resulting in 240 million chronic HBV carriers and 620,000

HBV-associated deaths annually [1]. Three factors determine the transmissibility of HBV: (1) the duration of viremia, (2) the concentration of infectious HBV particles in the plasma, and (3) the kind and frequency of contacts allowing transfer of HBV from the infected host to another susceptible recipient.

Transmissibility of HBV

Duration of Viremia

Concerning the duration of HBV-productive infection, transmission from mother to child leads in the great majority of cases to quasi-immunotolerance against HBV with very high viremia lasting for decades. This form of transmission generates the majority of highly infectious HBV carriers in East and Southeast Asia. Infection during the first years of life from other sources, e.g. family members, close friends, or inadequate hygiene during injections or invasive medical procedures also leads very often to persistent infection, which happens frequently in Sub-Saharan Africa. Transmission later in life causes in immunocompetent subjects predominantly transient infections with varying degrees of inflammatory liver disease; however, a certain, quite variable proportion of seemingly immunocompetent adult patients develops persistent infection (see Tillmann and Patel [this issue, pp. 181–188]). This is the period of life when most Caucasian HBV carriers in Europe and North America have acquired their chronic infection. The proportion of persistent infection increases when the patients have some degree of mild immune deficiency, e.g. induced by HIV coinfection or hemodialysis, and is 100% when infection occurs during immune ablation required during treatment in certain hematological malignancies.

Efficiency and outcome of transmission also depends on the dose of infectious virus and the mode of inoculation into the new host: intravenous injection is the most efficient and mucocutaneous contact is the least efficient. Viremia during transient resolving infections exists for weeks to months depending on the rapidity of protective immune responses and is highest *before* onset of clinical symptoms or transaminase rise. It may reach peak levels almost as high as in the quasi-immunotolerant HBV carrier for several weeks, but levels are already decreasing and lower during the acute phase. Overall, single unrecognized chronic carriers are much more often the source of transmission than acutely infected subjects, but in certain settings with high exposure, outbreaks may occur via transmission chains from newly infected, still asymptomatic cases.

Level of Viremia

The true level of viremia, i.e. the number of infectious HBV particles within 1 ml of serum or plasma, is difficult to measure in a bioassay. Full susceptibility for HBV is only present in the differentiated hepatocytes from humans and from some not readily available animal species within an intact cellular hepatic architecture, i.e. the liver *in vivo*. Early experiments in humans [2], and later in chimpanzees [3], revealed that dilutions of sera from chronic HBV carriers to 1:10⁷ or 1:10⁸ were able to induce HBV infection when 1 ml was injected intravenously. Typical infectious doses producing an infection in 50% (ID₅₀) of chimpanzees were between 10^{7.5} and 10⁸/ml [3]. Explanted primary hepatocyte cultures from susceptible species are partially useful, but require at least 1,000-fold higher virus doses for detection of any replication [4]. Full susceptibility of explanted human hepatocytes can be restored if they are implanted in livers of immunologically manipulated mouse strains which tolerate foreign tissue [5]. While this animal model is more feasible than chimpanzees, it is still too difficult to be used as a means to measure HBV infectivity routinely in sera from subjects for the monitoring of infectivity.

Surrogate Markers of HBV Infectivity

The first available marker of active HBV infection was a serum protein named Australia antigen. When it had been recognized that it was the surface antigen of HBV, HBsAg, it was used to detect and defer asymptotically infected blood donors [2]. It soon became apparent that the infectivity of HBsAg-positive persons in normal life was highly variable. The explanation is that HBsAg is an essential component of complete infectious HBV, but the infected hepatocyte produces a huge excess of HBsAg which is secreted as a noninfectious 'subviral' particle into the blood. There it may favor high-dose antigen tolerance to HBV and, furthermore, it may be a decoy for neutralizing antibodies (anti-HBs). However, tolerance to HBsAg does not mean tolerance to the entire HBV. Thus, many HBsAg carriers have very low levels of infectious HBV in their blood.

Another HBV marker was detected soon after, the 'e' antigen, HBeAg. HBeAg-positive HBsAg carriers often transmit HBV to recipients during needle stick accidents while HBeAg-negative or HBe-antibody-positive carriers do not [6]. Likewise, HBeAg-positive mothers often transmit HBV to their newborns, e.g. one study showed a rate of 91% [7], whereas HBeAg-negative mothers transmit rarely. HBeAg is, however, a nonessential HBV pro-

tein and acts only as an immune modulator favoring immune tolerance to the closely related core antigen of HBV [8]. Once persistent HBV infection is established, HBeAg may disappear and viremia usually decreases to lower levels, but HBV can in rare cases still replicate at high levels [9] and be transmitted efficiently.

HBV DNA

The best surrogate marker for the presence and number of infectious HBV particles is the number of HBV DNA molecules. Various designations have been used for this marker, like 'copies' (of the viral DNA genome), 'genome equivalents' (GE or geq), or simply 'genomes'. Besides sensitive qualitative methods of nucleic acid amplification techniques (NAT) for screening purposes, today quantitative real-time PCR or related assays are the methods of choice. Before the introduction of this technique, the quantitation of HBV DNA was highly inaccurate. In a WHO trial on the standardization of this assay, participants failed to find consistent results on the GE in the tentative International Standard Preparation (IS) for HBV DNA. Thus, it was decided in 2000 to assign to this IS 10^6 arbitrary IU of HBV DNA per ml [10], which is now available as the 2nd IS [11]. Comparisons with the serum used for preparation of the IS with PCR tests in limiting dilution and with biophysically quantitated cloned HBV DNA suggested that 1 IU corresponds to 5.4 ± 0.6 GE [12]. In this and other articles, the conversion factor from GE or copies to IU is assumed to be 5. However, each test has its own conversion factor between 3 and 7. Recently, the Paul Ehrlich Institute (Langen, Germany) evaluated for the WHO the performance of 14 frequently used tests with 15 reference samples containing approximately $6 \log_{10}$ IU/ml of various HBV subgenotypes from A1 to G in comparison to the 2nd IS which has genotype A2. All quantitative tests were able to detect HBV DNA in the 2nd WHO IS very accurately with an expected mean value of $6.01 \log_{10}$ IU/ml and a relatively small SD of $0.17 \log_{10}$ IU/ml. Some assays did not detect the rare genotypes F and G, but most assays performed very well with all genotypes showing interassay SD between 0.16 and $0.27 \log_{10}$ IU/ml [13]. Thus, levels of HBV DNA can be determined quite accurately provided timely, standardized procedures are applied.

Correlation between ID₅₀ and GE of HBV DNA

For most virus species, the number of physical virus particles is much larger, e.g. 1,000-fold, than the number of fully infectious virions. However, the comparisons of

ID₅₀ and GE in some selected sera from HBeAg-positive chronic carriers suggest that the proportion of infectious virions is relatively high. For example, Hsia et al. [3] report: 'The minimal copy number of HBV DNA in chronic carriers of HBV that can infect the chimpanzee model was estimated to be from 3 to 169 geq based upon the three well-characterized inocula.' In another experiment with two chimpanzees, even 1 GE was sufficient to induce a full HBV infection in both animals [14]. Almost as sensitive as the chimpanzee may be the humanized mouse [5]. This system also allowed detection of infectivity in inocula containing statistically only 1 GE/ml when the serum came from the preacute phase of an experimentally infected chimpanzee; however, the ratio of ID₅₀ to GE decreased 100-fold when virions from the still HBsAg-positive but late phase of the chimpanzee's primary infection were inoculated [15].

Shikata et al. [16] compared the infectivity of HBeAg-positive and anti-HBe-positive serum pools from HBsAg carriers in intravenously inoculated chimpanzees and reported: 'There seemed to be a remarkable difference in infectivity between the HBeAg-positive serum and the anti-HBe-positive serum; the former serum was 10^8 times more infectious than the latter.' In fact, none of the 4 chimpanzees inoculated with 1:10 dilutions of the anti-HBe-positive sample was infected and only 1 was infected with the undiluted sample. Unfortunately, HBV DNA assays were not done in the 1970s, but a later study from Corden et al. [17] showed that 'HBV DNA could be detected and quantified in 64.5% (136 of 211) of carriers whose serum did not contain HBeAg with a median level of $3.6 \log_{10}$ copies/ml (range of $5.7 \log_{10}$ copies)'. Thus, it is probable that the inoculum used by Shikata et al. [16] contained around 1,000 GE/ml, but it was not infectious at 1:10 dilution. The data suggest that HBeAg-negative or late-phase sera contain on average a much lower proportion of infectious virions than HBeAg-positive samples. Also very low is the ratio of infectiousness to physical virus particles in plasmas from blood donors with occult HBV infection (OBI) whose HBV was transmitted to recipients. In these HBV carriers whose HBsAg levels were too low to be detected, 'the 50% minimum infectious dose (ID₅₀) of OBI HBV DNA [was] estimated at 1,049 (117–3,441) copies' [18]. In summary, the GEs give the upper limit of infectious particles present in a sample when inoculated intravenously into a fully susceptible subject, but in HBeAg-negative samples from the post-acute phase of HBV infection, the proportion of infectious particles often may be lower by a factor of 1:1,000 or less.

Transmission of HBV from Healthcare Providers to Patients

Risk of Transmission

Before vaccination was available and widely applied, healthcare providers (HCPs) were at a high risk of acquiring an HBV infection during exposure-prone procedures, including cuts and needle sticks with infectious patient blood. While most infections resolved, about 5–10% of those infected became HBV carriers themselves and thus a potential infection risk for the patients on whom they performed exposure-prone procedures. After some neglect of this problem, medical societies and public health authorities began in the late 1980s to analyze the situation and to request increasingly stringent restrictions for HCPs with chronic HBV infection. Table 1 shows the published evidence for HBV transmission from HBeAg-positive HCPs to patients in the 15 years before 2004 [19]. From these data it is obvious that HBeAg-positive HCPs are a considerable risk for patients during exposure-prone procedures. A transmission rate as high as 24% was found for one physician during cesarean section, but more typical are rates between 5.5 and 13% in high-risk operations like thoracic surgery. In 2003, many countries released restrictions for HBsAg-positive HCPs. Thereafter, only 1 case of an HBV-transmitting HCP (last case in table 1) was published. He had not been identified during the routine testing of HCPs after vaccination and caused 2 proven and 6 possible transmissions through orthopedic operations in 232 patients [20].

Absence of HBeAg does not exclude infectivity as listed in table 2. The transmission rates are 10 times lower during high-risk operations and all 4 physicians for whom viremia was reported had 10^6 GE/ml or more. As an exception, Corden et al. [17] reported that one surgeon who had transmitted HBV had only 64,000 GE/ml. However, the sample for viral load quantification was taken at least 3 months after the transmission event and, furthermore, the calibration of the test may have been too low by a factor of 5 [19]. Thus, this result may not be representative.

Prevention of HBV Transmission from HCP to Patients

Guidelines exist in many countries, e.g. in Germany from the DVV (2005) [21], in the UK from the Department of Health (2007) [22], in the USA from the American College of Surgeons (2004) [23], from the SHEA (2010) [24], and from the CDC (2012) [25]; furthermore, a European consortium provided guidelines in 2003 [26]. All guidelines agree that HCPs should know their HBV

Table 1. HBV transmission rate from HBeAg-positive physicians to patients during surgery

Type of surgery	Patients, n		Study
	followed	infected (%)	
General surgery	514	1 (0.2)	Oliver 1999
General surgery	183	5 (2.8)	Balogun 1999
Thorax surgery	72	5 (7.0)	Haerem 1981
Thorax surgery	279	17 (6.0)	Prentice 1992
Thorax surgery	144	19 (13.0)	Harpaz 1996
Thorax surgery	310	20 (6.0)	Heptonstall 1996
Sternotomy	75	13 (17.0)	
Vascular surgery	159	5 (3.0)	
Gynecology	211	6 (2.8)	Lettau 1986
Gynecology	247	22 (9.0)	Welch 1986
Hysterectomy	42	10 (24.0)	
Cesarean section	51	10 (20.0)	
Other	144	2 (1.4)	
General surgery	1,564	28 (1.8)	Spijkerman 2002
High risk	412	20 (4.8)	
Low risk	1,564	8 (0.7)	
Thorax surgery	1,193	66 (5.5)	Gerlich 2004 [19]
Orthopedic surgery	232	2/8 (0.8/3.4)	Enfield 2013 [20]
Total	4,717	189 (4.0)	
High risk	168	33 (19.6)	
Average risk	2,117	58 (2.7)	

Translated from [19]. Activities with specified high risk are printed bold.

Table 2. HBV transmission rate from HBeAg-negative and -positive physicians to patients during surgery

Type of surgery	Patients, n		HBV DNA GE/ml	Study
	followed	infected (%)		
Gynecology	85	3 (3.5)	4×10^6	Incident Team 1997
Cesarean section	57	3 (5.2)		
Other	28	0 (0)		
Gynecology	110	1 (0.9)	6×10^6	Incident Team 1997
Cesarean section	25	0 (0)		
Other	86	1 (1.2)		
General surgery	21	1 (4.8)	3×10^6	Incident Team 1997
Thorax surgery	123	2 (1.6)	1×10^6	Molyneaux 2000
Orthopedic surgery	118	1 (0.8)	unknown	Sundkvist 1998
Total	527	8 (1.5)		
High risk	195	6 (2.0)		
Average risk	332	2 (0.6)		

Translated from [19]. Activities with specified high risk are printed bold.

status, and if they are not yet immune, they should be vaccinated and the success of the vaccination should be measured some weeks after the last dose of vaccine by determination of the anti-HBs titer. The practice to vaccinate HCPs without prior testing for anti-HBc is mentioned in several of these and other guidelines on HBV vaccination of HCPs. This may create the unfortunate situation that an unrecognized HBV carrier with HBsAg may develop anti-HBs after vaccination but still remain infectious. Even worse, in the case of the transmitting orthopedic surgeon (mentioned above), the assay of HBsAg was completely forgotten, although anti-HBs had remained negative [20]. The German guidelines recommend anti-HBc testing of HCPs prior to vaccination and, if positive, subsequent testing for anti-HBs and HBsAg.

All guidelines request that HCPs who are HBsAg carriers be tested for HBeAg and anti-HBe and for HBV viremia, preferably by a reference laboratory. In contrast, the restrictions for HCPs who are HBeAg- and/or HBV-DNA-positive are quite divergent. In the UK, all HBeAg-positive carriers are excluded from exposure-prone procedures as are all HBsAg carriers without HBeAg if they have >1,000 GE/ml (>200 IU/ml) [22]. This means that more than half of the HBeAg-negative HBV carriers are excluded. The European Consortium allows 10,000 GE/ml, but also requires HBeAg negativity [26]. The German recommendations exclude all HBV carriers with 100,000 GE/ml from exposure-prone procedures (similar to the Dutch recommendations), and request supervision and individual evaluation and recommendation by an expert panel at viremia levels >1,000 GE/ml irrespective of HBeAg status [21]. The 2012 recommendations of the CDC request supervision by an expert panel at viremia levels >1,000 IU/ml (5,000 GE/ml) and exclude exposure-prone procedures, or according to CDC category I: 'Procedures known or likely to pose an increased risk of percutaneous injury to a health-care provider that have resulted in provider-to-patient transmission of hepatitis B virus' [25]. Monitoring of HBV DNA levels is recommended at 3- or 6-month intervals. A more specific description is given in the recommendations from the SHEA [24], which distinguishes three risk categories and only the third category restricts many types of major surgery.

Treatment of HCPs for Reduction of Infectivity

Available Drugs and Resistance

The therapy of patients with chronic hepatitis B is described in the article from van Bömmel [this issue, pp.

171–180]. Here, only the effect of this therapy on viremia is discussed. Antiviral therapy with 1 of the 5 licensed HBV reverse transcriptase-inhibiting nucleoside or nucleotide analogs (NUCs; lamivudine, telbivudine, entecavir, adefovir, and tenofovir) can reduce viremia, but it cannot eliminate the viral DNA from the infected hepatocyte. Thus, drugs have to be taken for many years, possibly even lifelong. Lamivudine, the first available NUC, often leads after an initial success to resistance and recurrence of viremia and inflammation. Telbivudine is more efficient than lamivudine, but is not effective against lamivudine-resistant strains and itself also selects for resistance. Adefovir has a lower inhibitory effect from the beginning and may also lead to resistance. Even more complicated is the situation with entecavir because it is very efficient in treatment-naïve HBV carriers, but resistance often emerges when given to carriers who had already developed lamivudine resistance (see Warner and Locarnini [this issue, pp. 218–224]). The only drug without any known clinical resistance is tenofovir.

Guidelines on Therapy of HBV-Infected HCPs

The relatively low efficacy of the early drugs lamivudine and adefovir and the frequent resistance development may have been the reason why the European consortium [26] and health authorities in the UK do not allow HCPs receiving antiviral therapy to perform exposure-prone procedures. In 2007, an exception was made for HCPs who are HBeAg negative and have baseline viremia levels <100,000 GE/ml [22]. In contrast, Dutch authors recommended in 2003 to treat HCPs who have viremia >10⁵ GE/ml with either NUCs or interferon [27]. Since 2005, the German recommendations [21] have allowed antiviral therapy with the aim to reduce viremia to acceptably low levels (<1,000–100,000 GE/ml depending on the professional activity), but requested continuous monitoring at 3-month intervals. The CDC recommendations from 2012 [25] also allow the reduction of viremia by antiviral therapy to values <1,000 IU/ml (<5,000 GE/ml), requiring 6-month intervals for control.

The current EASL clinical practice guidelines on management of chronic hepatitis B virus infection (from 2012) [28] recommend therapy for healthcare workers with the following: 'In many countries, healthcare workers, including surgeons, gynaecologists and dentists, who are HBsAg-positive with HBV DNA >2,000 IU/ml should be treated with a potent antiviral agent with a high barrier to resistance (i.e. entecavir or tenofovir), to reduce levels of HBV DNA ideally to undetectable or at least to <2,000 IU/ml before resuming exposure-prone proce-

dures (B1). Monitoring for compliance and efficacy in practicing surgeons is required. The long-term safety, efficacy, complications and economic implications of such a policy are unknown.' The last sentence refers to the fact that there is only one published case series on HCPs who otherwise would not need a therapy except for reduction of the viremia. According to the EASL, these are in particular: (1) 'Immunotolerant patients: HBeAg-positive patients under 30 years of age with persistently normal ALT levels and a high HBV DNA level, without any evidence of liver disease and without a family history of HCC or cirrhosis ...' and (2) 'HBeAg-negative patients with persistently normal ALT levels (ALT determinations at least every 3 months for at least 1 year) and HBV DNA levels above 2,000 but below 20,000 IU/ml, without any evidence of liver disease ...'. The Canadian health authorities have adopted these recommendations for their own guidelines on HBV-infected HCP [29].

Reduction of Viremia in HBV-Infected HCPs

Published evidence for the efficacy of antiviral therapy on the transmission rate to patients is limited. A Dutch team reported reduction of viremia to <1,000 copies/ml in 18 HCPs with either interferon- α or various NUCs [30]. There is no reason to believe that the efficacy of NUC therapy is significantly worse in asymptomatic immunotolerant HBV carriers than in highly viremic HBeAg-positive patients with chronic hepatitis B. The licensing studies showed that within 1 year 67% of HBeAg-positive patients treated with entecavir had undetectable HBV DNA levels (<80 IU/ml) and 76% of those were treated with tenofovir. With HBeAg-negative patients the virological response within 1 year is much better with 90 and 93%, respectively [28]. Meanwhile, many additional systematic studies have been published which demonstrate the high safety, efficacy, and low frequency of side effects for both tenofovir [31] and entecavir [32] for periods up to 6 or 5 years, respectively. Entecavir led to undetectable HBV DNA in 97.1% at the end of treatment and to resistance in only 2 of 222 patients [32]. Response to entecavir may be slow initially, but improves over time to satisfactory levels [33, 34]. A switch to tenofovir can induce disappearance of viremia in those few patients who did not achieve a complete virological response with entecavir [35]. Entecavir should be avoided in lamivudine-resistant patients, but tenofovir is fully active in these patients and led to undetectable HBV DNA in 89.4% of the patients within 96 weeks with very mild side effects [36]. The closely related NUC adefovir leaves many patients with a weak response and sometimes with resistance to

adefovir [28]. Tenofovir is slightly less efficient against adefovir-resistant strains in vitro [Glebe and coworkers, unpubl.]. The Dutch guidelines for therapy of chronic hepatitis B from 2012 recommend to switch preferably to entecavir in patients with adefovir resistance [37]. However, tenofovir led in 82–84% of adefovir-experienced patients to <400 GE/ml HBV DNA after 3 years [38]. Resistance to tenofovir was never observed [31, 36, 38]. The combination with emtricitabin (which is used for HIV) was not superior to tenofovir monotherapy [31, 36, 38].

Short-Term Effect of NUCs

Concerning kinetics, acceptable levels of viremia (<1,000 IU/ml for the CDC or <2,000 IU/ml for Europe except UK) are reached more often and much faster in HBeAg-negative carriers because they have lower baseline levels of viremia and possibly a higher turnover of HBV-containing hepatocytes. The immunotolerant HBeAg-positive carriers typically have baseline viremia levels >10⁸ IU/ml [28]. The mean reduction of viremia obtained in HBeAg-positive patients with entecavir within 1 year was reported to be 6.9 log₁₀ copies/ml [39]. A detailed study on the kinetics under tenofovir therapy showed that the mean value in patients with moderately high viremia (80% of the patients) fell from 7.3 to 3.7 log₁₀ copies/ml (the level allowed by the CDC) within approximately 12 weeks, while patients with >9.0 baseline level (20% of the patients) needed roughly 52 weeks [40]. In a direct comparison of tenofovir and entecavir, decreases of -4.0 or -4.5 log₁₀ units/ml, respectively, were found after 3 months of therapy [41], with a slightly better final virological response with tenofovir. In conclusion, viremia can be suppressed in the majority HCPs by 3 months of entecavir or tenofovir therapy to acceptable levels. The approximately 40% of HBeAg carriers with very high viremia >10⁹ GE/ml need longer therapy, but most of them will reach acceptable or even undetectable levels within 1 year. The possibilities to control viremia even in HCPs with very high baseline viremia are so good that there is no justification to permanently exclude them from any type of procedure provided they are compliant and adequately monitored.

Interferon Therapy

Perspectives for a permanent cure by NUCs ultimately with disappearance of HBsAg are less favorable because this requires elimination of HBV-infected hepatocytes. This potentially pathogenic mechanism is not very active in the two asymptomatic groups of HCPs mentioned by the EASL. A sustained virological response after cessation

of therapy can be obtained in a minority of patients with pegylated interferon- α (see Brunetto and Bonino [this issue, pp. 163–170]). In the time before NUCs were available, interferon therapy was the only option. The author learned about two highly viremic surgeons with $>10^9$ GE/ml in whom interferon- α induced a sustained response resulting in viremia $<10^5$ GE/ml. Both had transmitted HBV to many patients before therapy, but no transmissions were found after therapy, although one had operated on $>2,000$ patients. For the dependable suppression of viremia within a shorter time period, a combination therapy with entecavir or tenofovir would be desirable, but there is no data on this type of combination.

Treatment of Pregnant Women with High Viremia

Teratogenicity of Available Drugs

Under normal circumstances, antiviral therapy against HBV should not be initiated during pregnancy and if an unexpected pregnancy occurs under therapy, cessation of the therapy may be considered in women without advanced fibrosis or highly active hepatitis B. If therapy is continued, theoretically the drug with the lowest risk for the unborn should be given. Lamivudine, adefovir, and entecavir are listed by the FDA as pregnancy category C drugs. According to the FDA classification, category C drugs could potentially be used with some reservation: ‘Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.’ Tenofovir and telbivudine are listed as category B: ‘Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.’ Thus, tenofovir is theoretically the drug of choice during the entire pregnancy or if contraception is not applied during the child-bearing age. However, both lamivudine and tenofovir have been used in thousands of HIV-infected pregnant women, not only in the third trimester but also during entire pregnancy. Birth defects were observed with lamivudine in 2.88%, and with tenofovir in 2.17%, both of which were not significantly different from the normal rate of 2.72% in the USA [42]. There is very limited data on the teratogenicity of adefovir, entecavir, and telbivudine during early pregnancy. Interferon is contraindicated during

pregnancy. The problem of chronic hepatitis B in pregnancy and its therapy has been subject of several reviews [42–44] and will not be discussed here in more detail.

Indications for Reduction of Maternal HBV Viremia

Mother-to-child transmission of HBV occurs in the great majority of HBeAg-positive mothers unless the infant is not immediately vaccinated. Many experts believe that transmission occurs during birth, but others – mainly from China – believe that it can also occur in utero. The latter assumption is supported by the fact that amniocentesis may lead to transmission in women with very high viremia [45, 46]. Irrespectively, mother-to-child transmission is in most cases efficiently interrupted by immediate active/passive immunization of the newborn. However, this often fails when the mother has a very high viremia. As an example, Ding et al. [45] found among 167 HBeAg-positive mothers 37 who had viremia $>10^7$ IU/ml, but only 12 infants from these mothers became chronically infected in spite of immediate active/passive immunization. Algorithms have been proposed to recognize increased risks for transmission [47, 48], and a cutoff at $>200,000$ IU/ml maternal HBV DNA was identified as a risk factor [47].

Lamivudine was the first drug to be applied in the third trimester for reduction of viremia and prevention of mother-to-child transmission. In the first case series, van Zonneveld et al. [49] found only 1 chronically infected infant from 8 lamivudine-treated mothers with $>1.2 \times 10^9$ geq/ml baseline viremia, whereas 7 of 25 infants from untreated control mothers were infected. A meta-analysis of 4 more recent controlled studies showed that HBV DNA was detected after 6 months in 25 of 224 immunized infants from lamivudine-treated mothers and in 69 of 191 immunized infants from untreated mothers. This is a residual transmission rate not prevented by lamivudine of 31% [50]. Prevention was less effective when the viremia was $>10^9$ GE/ml before treatment and when treatment started only at week 32 of gestation [51]. In this period from week 32 to 40, the reduction of viremia was only $-2.6 \log_{10}$ and resistant mutants were selected [52]. In another study, lamivudine was used during the entire pregnancy, but the outcome was still suboptimal because 2 of 68 infants became infected in spite of adequate postnatal immunization and one had a resistant mutant [53].

Telbivudine is more effective than lamivudine and is a pregnancy category B drug. Its vulnerability to resistance development is probably less relevant when the drug is used in treatment-naïve patients for not more than 8 months. A meta-analysis of 3 controlled studies performed in China revealed that only 2 of 222 immunized

infants from telbivudine-treated mothers had HBV DNA 6 months after birth compared to 26 of 178 infants from a highly viremic control group of mothers [54]. Telbivudine has also been administered over the entire pregnancy and could prevent transmission to the infants completely [55], although this is not recommended by any guideline.

Tenofovir is not only a category B drug like telbivudine, but it is also highly efficient and does not cause resistance development. Its safety record in pregnancy is very good; potential problems with nephrotoxicity have to be monitored, but are obviously not a frequent obstacle [56]. Tenofovir seems to be the best choice for treatment of HBV infection during any phase of pregnancy and thereafter [28, 29], but data on its efficacy on mother-to-child transmission is very limited. However, a recent publication on a case series is encouraging [57]: 'Eleven Asian mothers received TDF [tenofovir] at the median gestational age of 29 (28–32) weeks and the median duration of TDF use before delivery was 10 (7–12) weeks. A significant reduction in serum HBV-DNA was achieved at delivery compared with baseline (mean 5.25 ± 1.79 vs. $8.87 \pm 0.45 \log_{10}$ copies/ml, respectively; $p < 0.01$). ... All infants were hepatitis B surface antigen negative 28–36 weeks after birth.' Further studies are necessary to extend these findings, but the way to a complete prevention of mother-to-child transmission seems to be open.

Screening for Transmission-Prone HBV Infection

Screening of pregnant women for HBsAg is particularly important for effective prevention of new chronic infections in infants. It is mandatory in many developed countries, but the current practice may be suboptimal. The German guidelines for examination of pregnant women request testing for HBsAg after the 32nd week of gestation [58], which is too late for efficient reduction of viremia by NUCs. An earlier time point would be better, as recommended in the Netherlands [59]. However, identification of HBsAg-positive mothers is not enough because the necessary measures are often not taken. Even in developed countries like the UK [60] or New Zealand [61] viremia is often not determined and an indicated antiviral therapy not initiated. If the current possibilities of diagnosis and therapy would be implemented, mother-to-child transmission of HBV could be prevented completely. Further studies are clearly needed and effective practical guidelines should be developed.

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