Chapter 16
Nucleos(t)ide Analogue Based Therapy and Management of Patients

Mauro Viganò, Massimo Puoti, and Pietro Lampertico

Introduction

Antiviral therapy of chronic hepatitis B (CHB) is aimed to improve quality of life and survival by halting progression of liver damage to cirrhosis, end-stage liver disease, liver cancer (HCC), thus preventing anticipated liver-related death [1–3]. These goals are achieved by suppression of hepatitis B virus (HBV) replication either by short-term treatment with pegylated interferon (Peg-IFN) or by long-term therapy with potent nucleos(t)ide analogues (NUCs). According to the most recent international guidelines, Peg-IFN and third generation NUCs such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are the first-line drugs recommended for CHB naïve patients [1–3]. One year of Peg-IFN treatment induces a durable suppression of viral replication in nearly 30 % of patients. However, Peg-IFN requires parenteral administration, has a limited efficacy, causes side effects which are generally mild in nature, and is contraindicated in patients with advanced liver disease due to the risk of decompensation associated with interferon-related hepatitis flares and/or infections. Conversely, management of patients receiving NUCs is very easy and these drugs are the treatment of choice in patients with compensated or decompensated cirrhosis, in patients of advanced age, in pregnant women, and in those not responder, contraindicated or unwilling to Peg-IFN.

M. Viganò
Liver Unit, Ospedale San Giuseppe, Università degli Studi di Milano, Milan, Italy

M. Puoti
Infectious Diseases Division, AO Ospedale Niguarda Ca' Granda, Milan, Italy

P. Lampertico, M.D., Ph.D. (✉)
"A. M. and A. Migliavacca" Center for Liver Disease, Gastroenterology and Hepatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via F. Sforza 35, 20122 Milan, Italy
e-mail: pietro.lampertico@unimi.it

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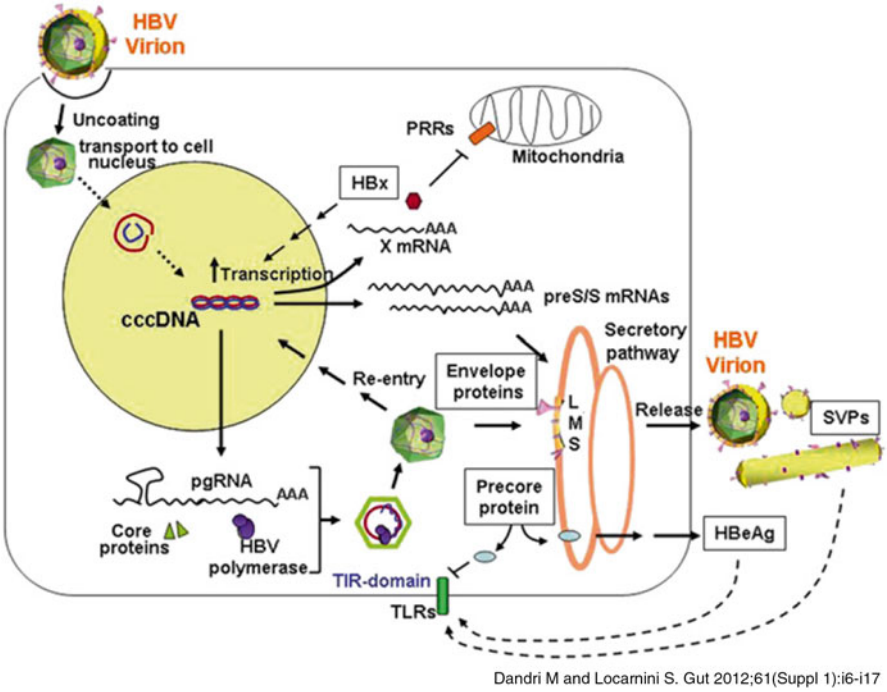

Fig. 16.1 The life cycle of hepatitis B virus (HBV)

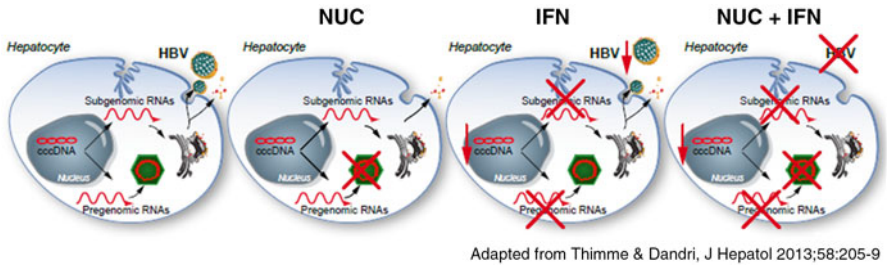

Fig. 16.2 Mechanisms of action of NUC and IFN

All NUCs belong to the same class, i.e., HBV polymerase inhibitors affecting the reverse transcription step of HBV replication (Figs. 16.1 and 16.2). They inhibit the reverse transcription of the pregenomic RNA into HBV DNA but have no direct effect on covalently closed circular DNA (cccDNA), explaining why they have only modest effects on the production of circulating viral antigens, i.e., HBsAg and HBeAg, and why, at variance from interferon-based treatment, immunological control of HBV infection is rarely achieved. However, long-term administration of NUCs is hampered by the selection of drug resistant mutants, leading to loss of efficacy, that differ according to the drug. NUCs can be subdivided into nucleoside

analogues, which include lamivudine (LMV), ETV, telbivudine (LdT) and nucleotide analogues including adefovir dipivoxil (ADV) and TDF. LMV, ADV, and LdT are not any more recommended due to the limited efficacy and moderate to high resistant rates whereas due to the long-term efficacy, the excellent tolerability and the negligible risk of drug-resistance ETV or TDF should be considered as the first-line drugs for CHB patients [3]. Worldwide, these latter drugs have become the preferred option for most patients with CHB, independently on the hepatitis B antigen (HBeAg) status, having the indefinite duration of treatment as the only potential disadvantage. In this chapter, we review the NUCs-based therapy in CHB patients, including HIV-coinfection and pregnant women, mainly focusing on the efficacy and safety of ETV and TDF therapy.

First and Second Generation NUC in Naïve Patients

Lamivudine

LMV was the first nucleoside analogue for the treatment of both HBeAg-positive and -negative patients. One year of LMV treatment achieved virological suppression in 36–44 % of HBeAg-positive patients and in 60–73 % of HBeAg-negative patients while HBeAg seroconversion rate in HBeAg-positive patients was approximately 20 % [4–6]. Notwithstanding, long-term LMV therapy inexorably ends with the selection of specific mutations in the HBV polymerase gene at rates that increase from 20 % after 1 year to peak 70 % after 5 years of therapy [7]. In HBeAg-positive patients, non-Asian ethnicity, high pretreatment serum HBV DNA level, male sex, longer treatment duration, and high body mass index are likely predictors of LMV-resistance (R) [8], whereas factors associated with the development of resistance in HBeAg-negative patients are poorly defined [9, 10]. As a rule, patients with incomplete suppression of HBV replication at week 24 have higher risk of generating mutated strains [11, 12]. The emergence of LMV-R leads to virologic rebound, alanine aminotransferase (ALT) flares, histological worsening, clinical decompensation, and HCC [7, 9, 13]. For those patients developing LMV-R, early add-on ADV or switch to TDF monotherapy is the recommended rescue treatment, whereas switching to another nucleoside analogue such as LdT or ETV is contraindicated as these drugs share a similar resistance profile [7].

Adefovir Dipivoxil

ADV was the first nucleotide analogue approved for use in patients with CHB showing significant HBV DNA reductions and liver histology improvement compared with placebo [14, 15]. In the 48-week registration trials, ADV achieved undetectable serum HBV DNA in 13–21 % of HBeAg-positive, with 12 % of HBeAg seroconversion and in 50–65 % of HBeAg-negative patients [14–16]. In HBeAg-negative

patients, 5-years of ADV treatment achieved a virologic and biochemical response in nearly 70 % of subjects with 5 % of patients achieving hepatitis B surface antigen (HBsAg) seroclearance [17]. Because of the significant rates (29 % after 5-year of treatment) of genotypic resistance (rtN236T and/or rtA181V/T mutations) over long-term administration and the suboptimal rates of virological response, ADV monotherapy is no longer considered in HBV patients [3, 17, 18]. Moreover, treatment with ADV may be limited by renal toxicity. Although none of the patients treated with ADV 10 mg/daily for 48 weeks showed a ≥0.5 mg/dL increase of the serum creatinine [14], this occurrence was reported in up to 9 % of patients after 5 years of ADV treatment [19]. Moreover, several cases of ADV-related Fanconi syndrome have also been reported [19].

Telbivudine

In the phase III GLOBE study, LdT demonstrated superior efficacy in achieving undetectable serum HBV DNA levels compared to LMV [20] and similar results were reported in the second year of the trial, both in HBeAg-positive (56 % vs. 38 %) and HBeAg-negative patients (82 % vs. 57 %) [21]. Among the 596 patients without genotypic resistance to LdT at the end of the 2-year GLOBE trial, two additional years of treatment increased the rates of virological and biochemical response to 76 % and 86 % and to 86 % and 90 % in HBeAg-positive and HBeAg-negative patients, respectively, while the cumulative rate of HBeAg seroconversion increased to 53 % [22]. However, at the second year of treatment the frequency of LdT-R increased to 25 % [21]. LdT was well tolerated even though asymptomatic grade 3/4 increases in creatine kinase levels were more common in LdT than in LMV-treated patients (13 % vs. 4 %, $p<0.001$) [21]. Interestingly enough, long-term LdT therapy was associated with an improvement of renal function particularly among patients with increased risk of renal impairment. Estimated glomerular filtration rate (eGFR) significantly increased by 15 mL/min/1.73 m^2 from baseline to year 4 of treatment [22, 23]. However, because of the significant rates of resistance, current international guidelines do not recommend LdT as a first line therapy for CHB patients.

First and second generation NUCs have been now replaced by third generation NUCs, like ETV and TDF, characterized by high potency and genetic barrier, and low rates of resistance.

Efficacy and Safety of Entecavir in Naïve Patients

ETV in Registration Trials

One year of ETV led to undetectable HBV DNA in 67 % of HBeAg-positive patients with normalization of ALT and HBeAg loss in 68 % and 22 % of patients, respectively [24]. Although ETV showed a continuous viral decline beyond week 48, rates of

HBeAg loss and seroconversion remain relatively low [25, 26]. ETV discontinuation after a 48-week treatment period causes virological and biochemical breakthrough in the majority of patients [27] whereas continuous ETV use for up to the year 5 (0.5 mg/day the first year and then 1 mg/day) resulted in a virological and biochemical response in 94 % and in 80 % of patients, respectively, with HBeAg seroconversion and HBsAg seroclearance of 23 % and 1.4 %, respectively [28]. ETV-R in NUC-naïve CHB patients appears at rates of 1.2 % after 5 years of therapy [29].

In HBeAg-negative patients, 1-year of ETV treatment led to undetectable serum HBV DNA and ALT normalization in 90 % and in 78 % of subjects, respectively. Virological rebound occurred in 2 % of the patients without however emergence of genotypic resistance [30]. ETV discontinuation after the first year of treatment resulted in a virological rebound in the vast majority of patients while patients who continued treatment for up to the third years maintained a virological response [31].

ETV in Cirrhotic Patients

ETV treatment was reported to have good efficacy profile in patients with advanced fibrosis or compensated cirrhosis resulting in undetectable HBV DNA in >90 % and ALT normalization in over 60 % of the patients after 1 year of treatment [32]. Rates of virological response and HBeAg clearance after 1-year of ETV treatment were 89 and 48 % in decompensated patients compared to 78 and 41 % in those with compensated liver disease. Moreover, among patients with decompensated cirrhosis, 65 % achieved a Child-Pugh A score (CPS) and 49 % showed improvement of at least 2 points in the CPS, with a cumulative transplantation-free survival of 87 % [33]. In a randomized, open-label study in 195 CHB patients with decompensated cirrhosis (mean pretreatment MELD score = 16), 1-year treatment with ETV 1 mg daily showed significant greater viral suppression compared to ADV 10 mg daily (57 % vs. 20 %) however with similar HBeAg seroconversion, CPS improvement and survival rates [34].

ETV in Field Practice Studies

In two European field practice studies including 1162 CHB patients (mean age 51 years, 76 % HBeAg-negative, 36 % with cirrhosis) treated with ETV, the 5-year cumulative probability of a virological response was 97 % and 99 %, respectively [35, 36]. One patient only developed ETV-R (L180M, M204V, S202G) at year 3, and was successfully rescued by TDF [36]. The same efficacy results were also reported in Asian studies [37–40] including 1126 treatment-naïve patients. At year 5, 98 % and 95 % of patients achieved undetectable serum HBV DNA and normal ALT, while two patients developed ETV-R within the fourth year of treatment [37]. Rates of long-term virological and serological response in NUC-naïve CHB patients treated with ETV in clinical practice are reported in Fig. 16.3.

HBeAg seroconversion*	15%	38%	58%	55%	67%	33%
HBsAg seroclearance	0.4%	0.2%	4.1%*	3.5%	0.4%	1.5%

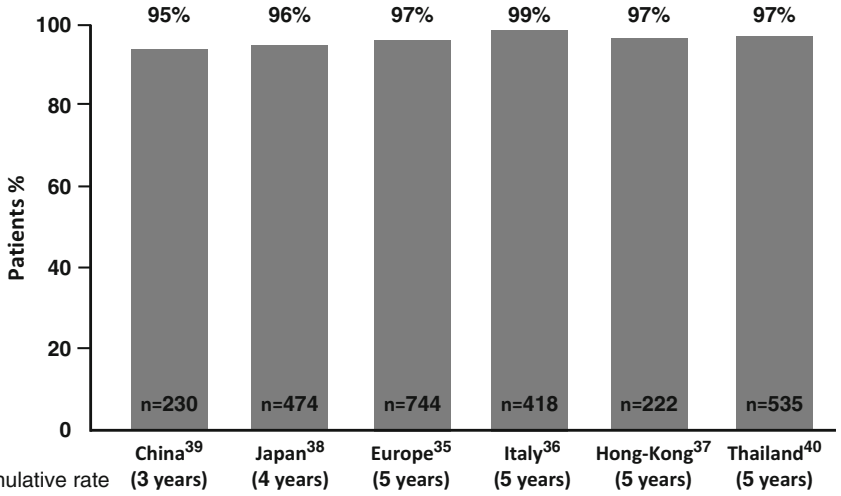

Fig. 16.3 Rates of long-term virological and serological response in NUC-naïve CHB patients treated with ETV in clinical practice

Safety and Tolerability of ETV

Long-term administration of ETV was associated with low rates of severe adverse events (AEs) and drug discontinuation. Analysis from phase III clinical trials showed that after a median of 184 weeks of treatment, 5 % of patients had drug-related grade 3/4 AEs, ultimately leading to treatment discontinuations in 1 % of cases, while 1 % of patients reported a >0.5 mg/dL serum creatinine increase from baseline [41]. Although in 2009 five cases of lactic acidosis were reported in decompensated cirrhotic patients (all with a baseline MELD score >22 points) under ETV treatment [42], this risk was not confirmed in other studies including patients with severe liver disease treated with ETV for 2 years, as only one out of 113 patients developed this AE [34, 43]. Notwithstanding, particular caution should be exercised when administering ETV to patients with severe liver disease and high baseline MELD scores, with ETV treatment to be withdrew in any patient who develops clinical or laboratory findings suggestive of lactic acidosis [44]. The overall favorable safety profile of ETV was also confirmed in a field practice studies. Among 3823 patients exposed to ETV for 12–66 months no major safety issues have been reported [36, 45–48].

Efficacy and Safety of Tenofovir in Naïve Patients

TDF Efficacy in Registration Trials

In two double-blind studies, 1-year treatment with TDF was compared to ADV in HBeAg-positive and HBeAg-negative patients [16]. A significantly higher proportion of patients receiving TDF reached viral suppression compared to those treated with ADV: 76 % vs. 13 % and 93 % vs. 63 % in HBeAg-positive and HBeAg-negative patients, respectively. Significantly more HBeAg-positive patients treated with TDF normalized ALT levels and lost HBsAg compared to those treated with ADV (68 % vs. 54 %; 3 % vs. 0 %). At week 48, no amino acid substitutions within HBV DNA polymerase associated with phenotypic resistance to TDF have developed. The long-term follow-up of the registration trial reported that 98 % of the 146 HBeAg-positive patients and 99 % of the 264 HBeAg-negative patients achieved undetectable HBV DNA after 8 years, without evidence for TDF-R. HBeAg seroclearance was achieved in approximately 30 % of the patients treated for 8 years, while HBsAg loss occurred in 12 % and 1 % of the HBeAg positive and negative patients, respectively [49].

TDF in Patients with Cirrhosis

A phase 2, double-blind study randomized 112 patients with CHB and decompensated liver disease to receive either TDF ($n=45$), combination therapy with Emtricitabine (FTC) plus TDF ($n=45$), or ETV ($n=22$) [50]. After 48 weeks of treatment, virological and biochemical responses were similar among the three treatment arms (71 % vs. 88 % vs. 73 %; 57 % vs. 76 % vs. 55 %). A 2 point median MELD score reduction and a 1 point median CPS reduction were observed in all the three treatment arms.

TDF in Field Practice Studies

Four European field practice studies including 1597 CHB patients (mean age 47 years, 75 % HBeAg-negative, 26 % with cirrhosis) reported that a 3–4 year course of TDF treatment achieved virological response ranging from 92 to 100 % without emergence of TDF-R [51–54]. Rates of long-term virological and serological response in NUC-naïve CHB patients treated with TDF in the registration trial and in clinical practice are reported in Fig. 16.4.

HBeAg seroconversion*	23%	NA	27%	37%	31%
HBsAg seroclearance	5.7%	2.5%	1.6%	17%*	7.5%

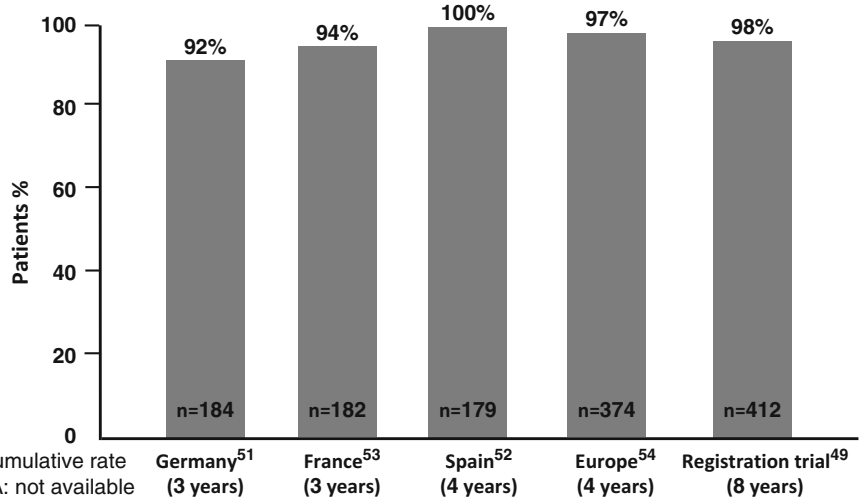

Fig. 16.4 Rates of long-term virological and serological response in NUC-naïve CHB patients treated with TDF in the registration trial and in clinical practice

Safety and Tolerability of TDF

TDF was well tolerated over the 8 years of the long-term follow-up study as only 20 (3.4 %) patients had dose reduction ($n = 18$), temporary treatment interruption ($n = 1$) or drug discontinuation ($n = 1$) for a renal event that consisted of ≥0.5 mg/dL increase in serum creatinine from baseline (2.2 %), phosphorus <2 mg/dL (1.7 %), or eGFR <50 mL/min (1 %) [49]. No significant renal safety difference was observed among decompensated cirrhotics treated with TDF ± FTC or with ETV as the proportion of subjects with a confirmed increase in serum creatinine ≥0.5 mg/dL from baseline or confirmed serum phosphorus <2.0 mg/dL were 9, 7, and 5 % among the three arms of treatment [50]. No major changes of renal function were observed during the 3–4 years of TDF in three European cohort studies [51, 52, 54]. However, in the latter study, enrolling 374 NUC-naıve patients treated with TDF for 4 years, the proportion of patients with eGFR <50 and <60 mL/min increased from 2 to 3 % and from 7 to 11 %, respectively; the rates of patients with serum phosphate <2.3 mg/dL increased from 2 to 5 %, and 1 % of the patients had phosphate <2.0 mg/dL throughout the study period. Overall, the 4-year probability of TDF dose reductions or discontinuations for renal-related AEs was 11 % [54]. An Italian field practice study in 156 NUC-naıve patients treated with TDF for 2 years reported de novo hypophosphatemia (≤2.5 mg/dL) in 6 % of the patients [55]. In a study investigating the

safety of a 2-year course of TDF among patients with mild baseline renal impairment, i.e., eGFR 50–80 mL/min, none of the patients had a ≥0.5 mg/dL increase of serum creatinine, whereas nine patients, all with baseline eGFR <61 mL/min, had eGFR declining <50 mL/min that, however, stabilized after dose adjustment [56]. To date, five cases of TDF-induced Fanconi syndrome have been reported in HBV monoinfected patients [57–59]. To prevent this severe AE, and more in general, chronic tubular damage and phosphate wasting syndrome, TDF dose should be proactively reduced as recently suggested [60].

How Should Patients Be Monitored During NUCs Therapy

Once a NUC is started, viremia should be tested with sensitive PCR assay every 3 months until undetectability (<10–15 IU/mL) is confirmed on two separate occasions, and every 6 months for the following years. Monitoring of HBV DNA is important also to differentiate between treatment failures. Primary non-response, defined as less than 1 $\log_{10}$ IU/mL decrease in HBV DNA levels from baseline to month 3 of therapy, occurs in 2–3 % of the patients only; partial virological response (PVR), i.e., detectable serum HBV DNA at week 48 of treatment in a compliant patient, ranges from 5 to 50 % according to baseline levels of viremia; virological breakthrough, defined as a confirmed increase in HBV DNA level of more than 1 $\log_{10}$ IU/mL compared to the lowest HBV DNA level, is a rare event during long-term ETV or TDF therapy. In HBeAg-positive patients, HBeAg/anti-HBe should be assessed every 6 months whereas HBsAg should be tested every 6–12 months in patients who are HBeAg-negative with persistently undetectable serum HBV DNA to detect HBsAg seroclearance.

As all NUCs are excreted through the kidneys, appropriate dosing adjustments are recommended. All patients should be tested at baseline and during treatment for serum creatinine to calculate the eGFR by MDRD formula to adjust NUC dose if eGFR falls below 50 mL/min, or <60 mL/min for some TDF treated patients [60], or had a rapid decrease during treatment. In addition, the baseline renal risk should be assessed for all patients. High renal risk includes one or more of the following factors: decompensated cirrhosis, creatinine clearance <60 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, solid organ transplantation. All CHB patients receiving TDF should be monitored every 3 months with serum creatinine, eGFR and serum phosphate whereas CHB patients on ETV should be monitored with serum creatinine levels and eGFR only if at high renal risk [3]. Closer renal monitoring is required in those patients with mild, or at risk for, renal impairment. While there is no enough evidence to recommend monitoring of bone density by DEXA scan in all patients receiving TDF-based antiviral regimens, bone mineral density should be assessed in selected patients, i.e., those who have a history of pathologic bone fractures or other risk factors for osteoporosis or bone loss, such as cirrhosis, independently of NUC therapy.

Management of Partial Virological Response to ETV or TDF

Antiviral therapy with ETV or TDF has negligible rates of resistance, though the few cases of ETV-R in NUC-naïve patients occurred in patients with PVR [61]. The optimal management of such patients is currently debatable, it seems reasonable that the HBV DNA levels at week 48 and their kinetics must be taken into account. Patients with residual viremia ≤1000 IU/mL or with continuous decline of serum HBV DNA levels could be maintained on the same drug given the progressive increase of virological responses over time and the negligible risk of resistance. For those with a flat pattern of HBV DNA or with a residual viremia >1000 IU/mL a rescue strategy with a non cross-resistant analogue, i.e., TDF for partial response to ETV and contrariwise, can be recommended [62].

Long-Term Benefits of NUCs Treatment

CHB patients with advanced fibrosis or cirrhosis demonstrated histological improvement and reversal of fibrosis and cirrhosis after long-term treatment with both ETV and TDF. In 57 patients under long-term ETV treatment, a second liver biopsy evaluation after a median of 6 years showed a significant histological improvement (a ≥1 point improvement in the Ishak fibrosis score) in 88 % of patients, including all 10 patients with advanced fibrosis or cirrhosis at baseline [63]. A reduction in Ishak fibrosis score to 4 or less was observed for all four patients who had cirrhosis at baseline [64]. More strong evidence of beneficial effect on fibrosis and cirrhosis regression was reported during 5-year TDF treatment [65]. Of the 348 patients who completed 240 weeks treatment and had biopsy results at baseline and at week 240, 304 (87 %) had histological improvement (≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and 176 (51 %) had regression of fibrosis (≥1 unit decrease in the Ishak staging score). Of the 96 patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74 %) had cirrhosis histologically reversed, whereas 3 (1.2 %) of 252 patients without cirrhosis at baseline progressed to cirrhosis during treatment. Low BMI, absence of diabetes mellitus, normal ALT levels, and mild or absent necroinflammation at year 5 of treatment were associated with a higher likelihood of cirrhosis regression [65]. Clinical decompensation is fully prevented in compensated cirrhotic patients through the 3–5 years of effective ETV and TDF treatment [36, 54, 66–68], whereas among patients with decompensated liver disease survival is significantly improved by antiviral therapy as persistent HBV DNA suppression led to reversal of clinical decompensation in most patients [69]. Recently, several studies evaluated the role of NUC on HCC risk reduction. Annual incidence of HCC among NUC-naïve CHB patients without cirrhosis ranged from 0.6 % to 1.4 % and 0.8 % to 1.4 % in Asian and European patients treated with ETV, respectively [36, 68, 70–73] whereas among TDF-treated

non cirrhotic patients the annual HCC risk ranged from 0.4 to 1 % [54, 73]. In ETV-treated cirrhotic patients, annual incidence of HCC ranged from 2 to 4.1 % in Asian studies [68, 71, 72, 74] and was 2.6 % in European studies [36, 73] while data from European studies in TDF-treated cirrhotics revealed that the risk ranged from 3.7 to 4 % [54, 73]. These HCC rates are very similar to what has been estimated from natural history studies in untreated patients [75].

When Can NUC Treatment Be Stopped?

The best stopping rule for NUC-treated patients is HBsAg loss and anti-HBs seroconversion, the latter is the sole safe stopping rule for cirrhotic patients. This endpoint is however rarely achieved (~1 %) in HBeAg-negative patients and in HBeAg-positive patients infected at birth. By converse, in NUC-treated HBeAg-positive patients with good predictors of response, such as short duration of infection, genotype A, elevated ALT levels and moderate levels of HBV DNA, this stopping rule can be achieved in up to 20 % of the patients after 5 years of treatment. In HBeAg-positive patients without cirrhosis, NUC treatment could be stopped after a confirmed and maintained (≥12 months) anti-HBe seroconversion combined with undetectable HBV DNA, an event that is observed in approximately 40–50 % of the HBeAg-positive treated patients after 5 years of therapy. However, viremia and hepatitis will relapse in up to 50 % of these patients after NUC discontinuation, thus suggesting a very strict monitoring strategy in the post-treatment follow-up to early detect virological rebound and restart therapy. For HBeAg-negative CHB patients there is no consensus between international guidelines about timing of treatment discontinuation. European (EASL) and American (AASLD) guidelines recommend HBsAg seroclearance as NUC stopping rule while Asian-Pacific (APASL) guidelines suggests that NUC cessation could be tempted after at least 2 years of treatment if HBV DNA is undetectable on three separate occasions 6 months apart [1–3]. Two Asian studies evaluated the off-treatment durability of response in HBeAg-negative CHB following ETV discontinuation according to APASL guidelines. Both studies reported high relapse rates (45 % and 91 %, respectively) in the year after treatment discontinuation, suggesting that NUC therapy should be continued indefinitely until the recognized treatment end-point of HBsAg seroclearance [76, 77]. However, this remains a major discussion point as strategies may be country specific [78, 79]. In countries where drug cost is an issue, full reimbursement for therapy and or monitoring is not in place and compliance tends to fade over time, NUC withdrawal might be worth to be carefully explored in selected HBeAg-negative patients. By converse, for patients leaving in countries where oral therapy, and HBV management in general, is fully reimbursed, and/or for those with cirrhosis or poor compliance to off-treatment monitoring, long-term administration till HBsAg clearance might still be the best strategy.

HBV and Pregnancy

Chronic HBV infection in pregnancy is an important global health problem as mother-to-child transmission is the most common mode of acquiring chronic HBV infection in endemic areas [80]. Data on the natural history of CHB during pregnancy are conflicting: some data suggest no worsening of liver disease in the majority of HBV-infected pregnant women while case reports show hepatic exacerbations and fulminant hepatic failures during pregnancy [81–85]. Some additional studies suggest that HBV infection is associated with adverse pregnancy outcomes, including higher rates of preterm birth, gestational diabetes, and antepartum hemorrhage [81–85]. All women should be routinely tested for HBsAg during their first trimester of pregnancy and those resulting positive should be referred for additional assessment and medical management [2, 3]. Without immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and HBV vaccination within 12 h of birth, up to 90 % of infants born to HBeAg-positive mothers become HBV chronically infected [86, 87]. However, up to 28 % risk of perinatal transmission still persist in HBeAg-positive mothers with high HBV DNA levels despite immunoprophylaxis and vaccination [88–91], whereas antiviral prophylaxis in the third trimester of pregnancy has been shown to decrease the risk of HBV transmission [92–98]. Maternal viremia plays a significant role in vertical transmission, with increased risk which starts from HBV DNA levels greater than 6 $\log_{10}$ IU/mL [87, 88, 99]. For this reason, all pregnant women with serum HBV DNA >6 $\log_{10}$ IU/mL in the third trimester, or with HBV perinatal transmission in a prior pregnancy, need to be treated with NUC to initiate between weeks 28–32, with careful discussion of the risks and benefits. In fact, no anti-HBV agent has been approved for use in pregnancy and all NUCs are classified as Food and Drug Administration (FDA) pregnancy risk category C, except for TDF and LdT, which are category B. However, LdT has limited efficacy and moderate to high resistant rates therefore the drug of choice is TDF, due to its potency, leading to a rapid reduction of serum HBV DNA, the null risk of resistance and the excellent safety profile without significant increase in birth defects or adverse outcomes, so far [100–102]. Despite infant plasma TDF concentrations are lower than maternal plasma or breast milk, the label recommends against its use during breastfeeding [103]. However, recent study identified that the exposure to the drug is lower from breastfeeding than from in utero exposure concluding that there is no contraindication to TDF use during breastfeeding [104]. If administered only for prevention of mother-to-child transmission TDF may be discontinued within the first 3 months after delivery whereas in pregnant women who require anti-HBV treatment for their own health, therapy should be maintained. Moreover, pregnant women who need antiviral therapy due to the advanced liver disease may be safely treated with TDF starting from the first trimester while women with advanced liver disease who becomes pregnant under category C NUC need to be immediately switched to TDF, due to the risk of withdrawal flare that could result in reactivation and even decompensation of liver disease.

HIV and HBV Coinfection

Current estimates place the prevalence of CHB among human immunodeficiency virus (HIV)-infected patients between 5 and 20 %. Thus, 2–4 million out of 35 million people living with HIV worldwide have CHB [105, 106]. In some regions in sub-Saharan Africa and Southeast Asia, HBsAg can be found in up to 15–20 % of the HIV population. In Europe, nearly 10 % of HIV-infected individuals have CHB, more than 100-fold the rate in the general population. It is estimated that half of HIV-positive persons have been exposed to HBV and, therefore, exhibit markers of spontaneously self limited HBV infection, i.e., hepatitis B core antibodies (anti-HBc) with or without hepatitis B surface antibodies (anti-HBs) or have current HBsAg [107]. In the case of HIV patients with CHB living in Europe, HBV genotype A is the most prevalent; it is found in approximately three-quarters of HIV–HBV coinfected individuals whereas in Southern Europe, HBV genotype D is equally prevalent to genotype A in this population [107].

Natural History of CHB in Persons Living with HIV

Compared with HBV-monoinfected individuals, HIV–HBV coinfected patients have lower chances for spontaneous HBeAg and HBsAg seroclearance. Serum HBV DNA levels are more elevated, which may in part explain the faster progression to end stage liver disease and HCC characteristically seen in coinfected patients [108]. Following the advent and broader use of highly active antiretroviral therapy (HAART), opportunistic complications have declined dramatically. However, liver-related complications are on the rise in patients coinfected with hepatitis C and B viruses. Current knowledge suggests that treatment of both HIV and HBV may prevent or slow down the development of hepatic complications in such patients [109]. The enhanced risk of liver toxicity of antiviral agents, particularly among cirrhotic HIV–HBV coinfected patients should not preclude prescription of HIV plus HBV therapy, although antiviral with the safest liver profile should be preferred [108]. Patients should be warned against stopping HAART with anti-HBV drugs for any reason because abrupt resumption of HBV replication may lead to a flare in liver enzymes and even fulminant hepatic failure [110].

Diagnosis

All HIV-infected persons must be tested for HBV markers: HBsAg, anti-HBc, and anti-HBs. HBsAg testing must be refreshed yearly in all patients or in case of unexplained ALT elevations, visits or living in endemic areas, new diagnosis of sexually

transmitted diseases. Persons who are anti-HBc-positive and HBsAg-negative, in particular those with elevated ALT, should be screened for HBV DNA in addition to HBsAg, to rule out occult HBV infection. Hepatitis delta antibodies should be screened for in all HBsAg-positive persons [110].

Treatment of Patients with HIV–HBV Coinfection

In patients with HIV–HBV coinfection, HBV therapy is indicated in all individuals with cirrhosis, CD4 counts less than 500 cells/mL, serum HBV DNA >2000 IU/mL, and/or elevated ALT. For most patients, the best option is triple combination of antiretrovirals, including two reverse transcriptase inhibitors with anti-HBV activity, that is, TDF plus LMV or FTC [110]. Some experts strongly believe that any person with HBV infection requiring antiretroviral therapy (ART) should receive TDF plus LMV or FTC unless history of TDF intolerance, particularly with advanced liver fibrosis (METAVIR score: F3/F4). TDF administration should be adapted to eGFR. In persons with no history of treatment with LMV and strict contraindication of TDF, ETV can be used in addition to fully suppressive combination ART without FTC or LMV. In fact ETV displays weak activity against HIV and may select for resistance mutations, thus it should always be administered only in the context of a fully suppressive HIV treatment. ART-naïve Asian, HBeAg-positive, HIV-coinfected persons initiating ART with TDF or TDF + FTC reached unexpectedly high rates of HBe and even anti-HBs seroconversion, strengthening the rationale for early ART. One-year course of Peg-IFN could be considered as therapy for CHB in coinfected patients unwilling to start HAART who have normal CD4 counts, HBeAg-positive, with low HBV DNA, elevated ALT, genotype A, and without advanced liver disease. The addition of anti-HBV NUCs has not been proved to increase Peg-IFN efficacy. In ART treated patients where the nucleoside backbone needs to be changed, anti-HBV therapy may be stopped cautiously in HBeAg-positive persons who have achieved HBeAg-seroconversion for at least 6 months or after confirmed HBs-seroconversion in those who are HBeAg-negative. In persons with liver cirrhosis, stopping of effective anti-HBV treatment is not recommended in order to avoid liver decompensation due to ALT flares. In some cases of TDF intolerance, i.e., renal disease, TDF in doses adjusted to renal clearance in combination with effective ART may be advisable. In persons with no prior LMV exposure, ETV may be used alone. NUCs substitution should only be performed if feasible and appropriate from the perspective of maintaining HIV suppression. Caution is warranted to switch from a TDF-based regimen to drugs with a lower genetic barrier, i.e., FTC or LMV, in particular in LMV-pretreated cirrhotic patients as viral breakthrough due to archived mutated variants is likely to happen. This has also been described in individuals with previous LMV-R who have been switched from TDF to ETV. The addition of ETV to TDF in persons with low persistent HBV replication has not statistically proved to be efficient and should therefore be avoided [110].

Vaccination

The response to the HBV vaccine is influenced by the CD4 cell count and level of HIV loads. In persons with low CD4 cell count (<200 cells/μL) and ongoing HIV replication, ART should be initiated first prior to respective vaccination. Because of the lack of data on the impact of immunization in isolated anti-HBc IgG positive persons (HBsAg negative, anti-HBc positive, and anti-HBs negative profile), vaccination is not presently recommended in this population. In HIV-positive persons vaccinated for HBV with insufficient response (anti-HBs <10 IU/L), re-vaccination should be considered. Double-dose (40 μg) at three to four time points (months 0, 1, 6, and 12) may help to improve response rates to the HBV vaccine. Persons who fail to seroconvert after HBV vaccination and remain at risk for HBV should have annual serological tests for evidence of HBV infection. TDF based cART has been associated with prevention of HBV infection in these persons [110].

Conclusion

The possibility of treatment of CHB patients have evolved fast, several therapeutic options are now available and nowadays hepatitis B is a treatable disease. The most popular and effective anti-HBV therapeutic strategy in CHB patients is the administration of third generation NUC such as ETV and TDF with the aim to maintain HBV DNA to as low a level as possible. Advantages of this strategy include excellent tolerability, long-term viral suppression without emergence of drug-resistance in the majority of patients resulting in biochemical remission, histological improvement, with also cirrhosis regression, and prevention of clinical decompensation while in patients with decompensated liver disease survival is significantly improved though early mortality and HCC do still represent a major clinical challenge. In fact, effective antiviral treatment reduces but does not eliminate the risk of HCC development both in cirrhotics but also in patients with less advanced liver disease. However, long-term administration of ETV or TDF cannot eradicate HBV infection making long-term therapy necessary in most patients with increasing cost and the potential issues of compliance and of unproven safety profiles in lifetime. NUC are the treatment of choice in patients with severe liver disease, in old patients, in those contraindicated or unwilling to Peg-IFN and in patients with concomitant diseases. Moreover, TDF is the first line NUC therapy for pregnant women with serum HBV DNA >6 $\log_{10}$ IU/mL in the third trimester of pregnancy and in pregnant women who need antiviral therapy due to the advanced liver disease. For patients with HIV–HBV coinfection requiring ART and who need anti-HBV treatment the best option is triple combination of antiretrovirals that includes two reverse transcriptase inhibitors with anti-HBV activity such as TDF plus FTC, whereas 48 weeks of Peg-IFN could be considered for HBeAg-positive CHB coinfected patients unwilling to start HAART, having low HBV DNA, elevated ALT, genotype A and without advanced liver disease.

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