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**Management of antiviral drug resistance in chronic hepatitis B**

Bang KB*et al*. Management of CHB resistance

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**Abstract**

Rescue antiviral treatment for patients with resistance to preexisting nucleos(t)ide analogues remains a clinical challenge. The correct choice of a first-line treatment of high potency and with a high genetic barrier to achieve sustained long-term suppression of viral replication provides the best chance of preventing treatment failure and the emergence of drug resistance. The management of treatment failure and drug resistance requires a precise and accurate clinical and virologic monitoring. Combination treatment with antiviral drugs that belong to different groups is associated with a lower chance of developing resistance to rescue drugs. To guarantee better control of viral replication in patients with drug resistance, the addition of another drug without a cross resistance profile should be given as early as possible, preferably at the time when genotypic resistance emerges. Long-term surveillance for treatment efficacy and possible emergence of drug resistance should be continued to prevent the emergence of multidrug-resistant strains.

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**Key words:** Chronic hepatitis B; Antiviral resistance; Rescue treatment; Multidrug resistance; Cross resistance

**Core tip:** Proliferation of hepatitis B virus (HBV) is the key driver of liver injury and disease progression, and thus sustained HBV suppression is of paramount importance in the management of chronic hepatitis B. Long-term antiviral treatment is usually required to achieve sustained suppression of HBV. However, antiviral drug resistance is a serious problem of long-term antiviral treatment, and this poses a critical challenge. Prevention and proper management of antiviral drug resistance are decisive to long-term success of treatment.

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**Background to the development of antiviral drug resistance**

Although potent antiviral agents for the treatment of chronic hepatitis B (CHB) are currently available, total eradication of hepatitis B virus (HBV) remains practically impossible. Data on the natural history of CHB and the clinical effectiveness of long-term antiviral treatment emphasize the paramount importance of prolonged viral suppression to very low levels. Though, nucleos(t)ide analogues are associated with good viral suppression, as shown by the reduction of serum HBV-DNA levels, viral resistance still is a problem in long-term treatment.

Replication of HBV DNA occurs via a RNA intermediate. In the nucleus of the hepatocyte, host and viral polymerases repair the partially relaxed circular genome of HBV to a fully double stranded covalently closed circular DNA (cccDNA). The cccDNA serves as a template for the transcription of all the HBV messenger RNA (mRNA). The viral RNAs include the pregenomic RNA, which serves as both the template for reverse transcription and for the core and polymerase synthesis, as well as the 3 subgenomic mRNAs necessary for the translation of the envelop protein and X protein[1,2].

The error-prone HBV reverse transcription (rt)-polymerase causes a high nucleotide substitution rate, generating a population of viral variants or quasispecies capable of rapidly adapting to endogenous (host immune response) and exogenous selection (antiviral treatment) pressures. The spontaneous mutation rate for HBV is estimated to be 1.4 x 10-5-3.2 x 10-5 nucleotide substitutions per site and per cycle[3,4].Concerning the high viral replication rate of more than 1011 virions per day[5], at least 1010 point mutations could occur in a HBV genome every day. Given the whole genome length of 3.2 kb, all possible single base changes can be produced in a day. The error-prone process of HBV replication, in which errors occur due to the absence of a proof-reading mechanism during the intermediate step of viral replication through reverse transcription, is responsible for the frequent incorporation of inaccurate nucleotides. A major obstacle for the generation of a new viral strain in this background of extremely high mutational frequency is the intrinsic frameshift overlapping organization of the four open reading frames of the HBV genome. However, due to the high mutational rate, it is not unusual to observe drug-resistant HBV already present in a viral population that has not yet been exposed to any nucleos(t)ide analogues.

Effective treatments have been developed for CHB that significantly reduce the morbidity and mortality. Treatment efficacy can be affected by factors such as the development of adverse effects, compliance to the drug, previous treatment with suboptimal regimens, infection with drug resistant viral strains, inadequate exposure due to the pharmacological properties of the particular drug(s) and individual genetic variation. Five drugs belonging to the nucleos(t)ide analogues have been approved for treatment of CHB in most parts of the world[6].The nucleos(t)ide analogues directly inhibits the reverse transcriptase activity of the HBV polymerase. The approved nucleos(t)ide analogues include lamivudine (LAM), a synthetic deoxy cytidine analogue with an unnatural L-conformation, and related L-nucleoside, telbivudine (LdT; β-L-thymidine). A second group, the acyclic phosphonates include adefovir dipivoxil (ADV), a prodrug for the acyclic 2’-deoxy adenosine monophosphate analogue adefovir, and the structurally similar tenofovir (TDF). A third group contains a D-cyclopentane sugar moiety and has the most potent anti-HBV drug discovered to date, the deoxy guanosine analogue entecavir.[7] This structural subgroups of the nucleos(t)ide analogues is clinically useful because it helps subgrouping the classifications of drug resistance of nucleos(t)ide analogues and guides rescue antiviral treatment according to the cross-resistance profile (Table 1)[ 8].

Antiviral drug resistance is defined as the decreased susceptibility of a virus to the inhibitory effect of a drug, which results from a series of adaptive mutations under the selection pressure of antiviral treatment. Two types of mutations have been identified: primary resistance mutations, which are directly responsible for the associated drug resistance, and secondary or compensatory mutations, which occur in order for the virus to facilitate replication competence, because the primary resistance mutations may be associated with a reduction in replication fitness[9].Replication fitness refers to the ability of a virus to replicate under the selective forces. Usually, mutant viruses show less replication fitness; however, over time, secondary mutations, such as rt80, rt180, and rt173 develop after the initial primary rtM204I/V mutation, which restores the functional defects of viral polymerase caused by the primary resistance mutations[10-13].

**Factors associated with the emergence of antiviral drug resistance**

The likelihood of the emergence of drug resistance depends on the baseline characteristics of the patients, viral factors, drug properties, and treatment regimens. Male gender, older age, high body mass index (BMI), high alanine aminotransferase (ALT) level, high HBV DNA concentration, high histological score (indicating a higher degree of necroinflammation), and the presence of core promoter mutations are reported to be associated with a higher risk of LAM resistance[14-19].A few studies have shown that the HBV genotypes A and D are associated with higher rates of LAM-resistant and ADV-resistant mutations, respectively[20-23].Some correlations between the genotypes of HBV and the selection of specific mutations might exist; however, most studies have shown that HBV genotypes have no relevance to the treatment response and the rate of emergence of drug resistant mutations[24-27].

Another important factor associated with the emergence of drug resistance is the persistence of viral replication during antiviral treatment. Yuen *et al*[28] found that the rate of emergence of LAM-resistant HBV strain was directly proportional to the HBV DNA concentration at week 24 after treatment (8%, 13%, 32%, and 64% for patients with 24-wk HBV DNA concentration lower than 200 copies/mL, 3 log10 copies/mL, 4 log10 copies/mL, and 4 log10 copies/mL and higher, respectively, at a median follow-up of 29 mo). Fukai *et al*[29] also found that patients with undetectable HBV DNA by PCR at week 24 of LAM treatment had a substantially lower rate of virologic breakthrough. Multivariate analysis including the variables of pretreatment ALT level, pretreatment HBV DNA level, and HBV DNA level at week 24 showed that the HBV DNA level at week 24 was the only independent variable associated with the occurrence of a virologic breakthrough. The GLOBE trial, the phase III multicenter trial of LdT, also showed the importance of HBV DNA suppression at week 24 for the emergence of antiviral resistance. Eighteen of 203 (9%) HBeAg-positive patients and 11 of 177 (6%) HBeAg-negative patients with undetectable HBV DNA at week 24 had LdT resistance at year 2, compared to 46 of 107 (43%) HBeAg-positive patients and 7 of 10 (70%) HBeAg-negative patients with an HBV DNA concentration of more than 4 log10 copies/mL at week 24[30]. Because of the slower and less potent antiviral activity of ADV, the on-treatment HBV DNA concentration was assessed at week 48, instead of week 24. Five of 89 (6%) patients with an HBV DNA concentration of less than 300 copies/mL at week 48 had ADV resistance at 192 wk, compared to 17 of 35 (49%) patients with an HBV DNA concentration of more than 3 log10 copies/mL[31].All of the above-mentioned studies stressed the importance of rapid and profound suppression of viral replication to minimize the emergence of drug resistant HBV during long-term treatment with nucleos(t)ide analogues.

**Management of antiviral drug resistance**

The management of treatment failure has changed significantly in recent years. Actually, treatment failure can be expanded to include a partial virologic response as well as the classic virologic breakthrough with the availability of potent antiviral drugs and precise virologic monitoring tools. Compliance to antiviral drugs in all patients should be closely monitored and reinforced when necessary and antiviral drug resistance should be managed according to the resistance testing profile of the patient’s specific HBV polymerase DNA sequence, in the context of the available cross resistance data (Table 1).

**LAM-resistant HBV**

The treatment strategy for LAM-resistance can also be applicable to LdT-resistance because of the shared drug-resistance profile (rtM204I/V) between LAM and LdT. The rtM204I and rtM204V mutations refer to the substitution of methionine with isoleucine or valine, respectively, at codon 204 of the reverse transcriptase gene. Previously these mutations were called YMDD mutations, but the terminology is no longer recommended[32]. rtM204V mutation emerges during LAM treatment; however, rtM204I can develop during the administration of LAM, LdT, or clevudine[30,33-35]. A rtM204V mutation may commonly be associated with rtL180M, but not with rtM204I mutation[36]. These mutations are sensitive to ADV and TDF, but they exhibit cross-resistance to ETV and show an eight-fold decrease in sensitivity. Kim *et al*[37] have shown that the biochemical response at 12 mo of ADV add-on LAM combination treatment was better in patients with an rtM204I mutation than rtM204V+ rtM204I/V mutations. Additionally, early treatment failure was more common in patients with rtM204V+ rtM204I/V mutations than with an rtM204I mutation. The rtA181T mutation has been detected in 5% of LAM-resistant patients. This mutation exhibits cross resistance to ADV, but remain sensitive to ETV[38].

A pilot study which compared the antiviral efficacy of ADV monotherapy with ADV add-on LAM combination therapy against LAM-resistant HBV infection found a comparable reduction of the viral load (-4.4 log10 copies/mL *vs* -3.59 log10 copies/mL, respectively) and normalization of the serum ALT level (53% *vs* 47%). However, a transient ALT flare was found in 37% of the patients in the ADV monotherapy group[39]. Therefore, switching to ADV monotherapy or short-term (2-3 mo) ADV-LAM combination treatment during rescue ADV treatment to prevent a transient ALT flare was recommended. The rate of ADV resistance in LAM-resistant patients was shown to be as high as 18% at 1 year, compared with 0% in LAM-naïve patients[40]. A study by Yeon *et al*[41] for 67 patients with LAM-resistance who were switched to ADV reported a cumulative ADV resistance rate of 6% and 25% at years 1 and 2, respectively. According to a study from Hong Kong, for 56 patients with LAM-resistance, the cumulative occurrence rate of ADV-resistance at 2 years was 18% for patients who had switched to ADV and 7% for patients who had ADV added to LAM[42]. A recent study of ADV add-on LAM combination treatment for patients with preexisting LAM-resistance showed that the cumulative ADV resistance rates were 1%, 2%, 4%, and 4% for the first 4 years[43]. Therefore, it seems likely that the ADV-resistance rate in patients with preexisting LAM-resistance can be greatly reduced by ADV add-on LAM rather than switching to ADV.

The timing of the ADV add-on for patients with preexisting LAM-resistance is another crucial factor for better viral suppression. A study performed by Lampertico *et al*[44] showed that the addition of ADV at the time when the HBV DNA concentration was 3-6 log10 copies/mL and the serum ALT was normal resulted in 100% of the 74 HBeAg-negative patients with preexisting LAM-resistance achieving an undetectable HBV DNA level at 3 months. This was compared with only 46% of the patients with an HBV DNA concentration of more than 6 log10 copies/mL and a high serum ALT level at the time of the addition of the ADV. Thus, the addition of ADV as early as possible (at the time of the detection of genotypic resistance, if possible) is the best strategy for the rescue treatment of patients with LAM resistance.

ETV has also been evaluated as a rescue treatment option for patients with Lam resistance. A study by Kim *et al*[45] showed that ETV 1.0 mg daily for 24 patients with preexisting LAM resistance had a mean log10 HBV DNA concentration reduction of 2.89, 3.34, and 3.71 at 6, 12, and 24 mo from the baseline. In comparison, ADV add-on LAM combination for 36 patients with preexisting LAM resistance had a mean log10 HBV DNA concentration reduction of 4.17, 4.63, and 4.86 at 6, 12, and 24 mo from the baseline. This result was statistically analyzed and it was concluded that ADV add-on LAM combination therapy significantly suppressed log10 HBV-DNA to a greater extent than ETV monotherapy at 3, 6, and 12 mo after the initiation of rescue antiviral treatment. Additionally, viral breakthrough and genotypic resistance were detected in six (25.0%) patients receiving ETV monotherapy, whereas no case of genotypic resistance was detected in the ADV add-on LAM combination therapy group 24 mo after the initiation of each antiviral treatment. Although the genotypic resistance rate of ETV is as low as 1.2% at year 5 in treatment-naïve patients, it has been reported that the cumulative rates of ETV genotypic resistance in patients with preexisting LAM-resistance are 6%, 15%, 36%, 46%, and 51% from years 1 to 5[46]. ETV is probably inferior to early ADV add-on for the treatment of LAM-resistant HBV.

TDF has shown potent antiviral activity against LAM-resistant HBV as well as against wild type HBV[47,48]. In a study of 53 patients with LAM-resistance and HBV DNA of more than 6 log10 copies/mL who received TDF, there was a reduction in the HBVDNA concentration of more than 5 log10 copies/mL at week 48 compared to 3 log10 copies/mL in those who received ADV[47]. An HBV DNA concentration of less than 400 copies/mL was achieved in all TDF-treated patients compared with only 44% of patients treated with ADV. In a recent study with a longer follow-up period of 23 months, TDF monotherapy resulted in 100% HBV DNA undetectability among LAM-resistant CHB patients[49]. Therefore, treatment strategies which include TDF seems to be more effective than those involving ADV for rescue treatment in patients with LAM-resistance. However, there is a report of TDF resistance in patients with LAM-resistance who received TDF monotherapy, so the efficacy of TDF monotherapy requires further verification[50]. One recent study showed that among 109 LAM-resistant CHB patients, TDF plus LAM combination treatment was more efficacious in reducing the HBV DNA level than TDF monotherapy, ADV monotherapy, and ADV add-on LAM combination therapy[51]. More recently, combination treatment of TDF plus LdT produced a higher rate of virologic response (defined as a HBV DNA reduction of more than 2 log10 copies/mL) than combination therapy of TDF plus LAM after 12 mo of treatment[52].

**ADV-resistant HBV**

Development of resistance to ADV is slower compared to LAM, with the reported rate being 2% at 2 years and 29% at 5 years[31,53]. The primary mutations associated with ADV-resistance are rtN236T and rtI233V in the D domain and rtA181T/V in the B domain[21,31,54-56]. The rtN236T mutant remains sensitive to LAM, LdT, and ETV with less than 3-fold change in the IC50 and has a moderately decreased replication capacity compared to wild type HBV[53,57]. The rtA181T/V mutation is associated with decreased susceptibility to LAM, LdT, and ETV (8- to 16-fold) but is sensitive to TDF (about 2-fold change in IC50)[58,59]. TDF is effective in suppressing HBV replication in patients who exhibiting LAM-resistance who have failed to respond adequately to ADV, and in patients resistant to both LAM and ADV[60]. However, reduced sensitivity to TDF was demonstrated in ADV-resistant HBV, indicating potential cross-resistance[49]. Therefore, adding emtricitabine (FTC) or LAM to TDF could be a more appropriate treatment strategy than TDF monotherapy in patients with ADV resistance. Actually, the addition of FTC led to a further decrease in the serum HBV DNA level in patients with ADV resistance and a suboptimal response to TDF monotherapy[61].

ETV has been demonstrated to be effective in suppressing the replication of HBV in patients with ADV-resistance. ETV is effective against both rtA181T/V and rtN236T mutant HBV strains[62-65] because ETV does not possess cross-resistance with ADV[38]. Combination treatment of ADV plus ETV is considered to be a better treatment option because the selection of LAM-resistant strains during ETV-monotherapy can result in subsequent ETV-resistance[66]. Combination treatment of ETV and TDF can also be a treatment option for multidrug resistant HBV infection which includes ADV resistance (especially rtA181T/V) [67].

**ETV-resistant HBV**

Few clinical studies have investigated the treatment of ETV-resistant HBV. ETV-resistant HBV is still sensitive to ADV, and ADV can be considered to be an initial treatment option in CHB patients with ETV-resistance. Clinical studies indicated that ADV was effective in suppressing the replication of ETV-resistant HBV[68,69].Combination treatment of ADV plus ETV would be a more appropriate treatment option for reducing ADV resistance and improving antiviral efficacy[66]. TDF is reported to be effective in suppressing the replication of ETV-resistant HBV. In most of the CHB patients with ETV-resistant HBV who showed persistent viremia after LAM plus ADV treatment, HBV DNA became undetectable after 6 months treatment of TDF[70].

**TDF-resistant HBV**

There are no data on the management of TDF resistance. An in vitro study showed that replication of the rtA194T mutant was suppressed effectively by ETV and intermediately by LdT[71].

**Multidrug resistance**

Although most HBV strains are resistant to a particular nucleo(t)ide analogue, this resistance can be effectively suppressed by using a nucleo(t)ide analogue from a different structural group. However, multidrug resistance might become a problem in the future. Prolonged and sequential exposure to nucleo(t)ide analogues promotes the formation of clusters of mutations such as rtA181T/I233V/N236T/M250L, all on the one dominant HBV genome, and these clusters are associated with multidrug resistance[72]. To avoid the development of multidrug resistant HBV, efforts should be made to achieve maximal viral suppression with a selection of drugs that have complementary cross-resistance profiles.

**Safety of rescue antiviral treatment**

The frequencies of the occurrence of serious adverse events among the ETV 1.0 mg monotherapy, ADV 10 mg monotherapy, and ADV add-on LAM combination treatment were reported to be similar and most of the adverse events were mild-to moderate in severity[45]. Reported serious adverse events included abdominal, nausea and diarrhea on ETV 1.0 mg monotherapy, and elevation of serum creatinine level in ADV monotherapy and ADV add-on LAM combination treatment. No patients with TDF rescue treatment were reported to develop renal toxicity, defined as a decrease of eGFR more than 20% from baseline. No cases of hypophosphatemia or other adverse events associated with TDF therapy were observed[73].

**Recommendations of guidelines for rescue therapy in patients with antiviral drug resistance**

Guidelines can provide evidence-based framework of judgement for determining the most appropriate rescue therapy in CHB patients with antiviral drug resistance; however, individualized and flexible approaches are needed in each patient, considering the patient’s preference, physician’s experiences, socioeconomic and reimbursement environment of each patient and physician, and progress in knowledge for chronic hepatitis B. Recommendations of guidelines for rescue therapy in CHB patients with antiviral drug resistance are summarized in Table 2.

**Summary of antiviral drug efficacies in rescue settings**

Virologic and serologic responses to various rescue therapies were summarized in Table 3.

**Conclusion**

To prevent and minimize the emergence of drug resistance, nucleo(t)ide analogues that cause rapid viral suppression with a high genetic barrier to resistance should be the treatment of choice. Clinical studies have shown that drugs with a high genetic barrier to resistance, such as ETV and TDF, have significantly lower rates of resistance compared to those with a low genetic barrier to resistance, such as LAM, ADV and LdT. The first choice of an antiviral drug should include a highly potent agent with a high genetic barrier in order to achieve sustained long-term suppression of viral replication, thereby providing the best chance of achieving the primary goal of treatment – the prevention of liver disease progression. Management of treatment failure due to the emergence of antiviral resistance requires precise clinical and virologic monitoring and rescue treatment with the appropriate complementary drug(s), with checking of their cross-resistance profile as early as possible. To achieve a better clinical response in CHB patients with antiviral drug resistance, the addition of another nucleo(t)ide analogue from a different structural group without cross-resistance should be given, preferably at the time when genotypic resistance emerges. Although antiviral drug resistance remains a major clinical concern, continuous virologic monitoring with sensitive and quantitative tools and the development of a new generation of antiviral agents with a better potency and high genetic barrier to resistance have brought major improvements in the management of patients with CHB.

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**Table 1 Classifications and context cross-resistance profiles of antiviral drugs in chronic hepatitis B**[8]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Classification** | **Amino acid substitution in the rt domain** | **LAM** | **LdT** | **ETV** | **ADV** | **TDF** |
|  | Wild-type | S | S | S | S | S |
| LAM + LdT resistance | M204I/V | R | R | I | S | S |
| ADV resistance | N236T | S | S | S | R | I |
| LAM + LdT + ADV (multi-drugs) resistance | A181T/V | R | R | S | R | I |
| ADV + TDF resistance | A181T/V + N236T | R | R | S | R | R |
| ETV resistance | L180M + M204I/V ± I169 ± T184 ± S202 ± M250 | R | R | R | S | S |
| TDF resistance | A194T | R | S | S | NA | R |

Adapted and modified from reference [8]. LAM: Lamivudine; LdT: Telbivudine; ETV: Entecavir; ADV: Adefovir; TDF: Tenofovir; S: Sensitive; I: Intermediate; R: Resistant; NA: Not available.

**Table 2 Recommendations of guidelines for rescue therapy in chronic hepatitis B patients with antiviral drug resistance**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drugs to which antiviral resistance developed** | **AASLD (2009)[74]** | **EASL (2012)[6]** | **APASL (2008)[75]** |
| LAM | Add ADV or TDFStop LAM, switch to Truvada®1 | Switch to TDFAdd ADV, if TDF is not available | Add-on ADV therapySwitching to ETV therapy (1 mg/d) is an optionSwitching to interferon-based therapy is an option |
| LdT | Add ADV or TDFStop LdT, switch to Truvada® | Switch to TDFAdd ADV, if TDF is not available. | Add-on ADV therapySwitching to interferon-based therapy is an option |
| ADV | Add LAM2Stop ADV, switch to Truvada®Switch to or add ETV2 | If nucleoside-naive before ADV then switch to ETV or TDFIf the patient has high viremia then switch toETVIf there is prior LAM resistance then switch toTDF or add a nucleoside analogue | For LAM-naive patients who develop drug resistance while on ADV, add-on or switching to LAM, LdT, or ETV is indicatedSwitching to interferon-based therapy is an option |
| ETV | Switch to TDF or Truvada® | Switch to or add TDFAdd ADV, if TDF is not available |  |

1Truvada® = combination pill with emtricitabine 200 mg and TDF 300 mg; 2Durability of viral suppression unknown, especially in patients with prior LAM resistance. AASLD: American Association for the Study of the Liver Diseases; EASL: European Association for the Study of the Liver Diseases; APASL: Asian-Pacific Assocation for the study of the Liver Diseases; LAM: Lamivudine; LdT: Telbivudine; ETV: Entecavir; ADV: Adefovir; TDF: Tenofovir.

**Table 3 Antiviral drug efficacies in rescue settings**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Virologic, serologic, and biochemical responses**  | **ADV monotherapy[76]** | **ETV monotherapy[45,46]** | **ADV + LAM combination therapy[43]** | **ADV + LdT combination therapy[77]** | **ADV + ETV combination therapy[78,79]** |
| Patients with undetectable HBV-DNA (%)1 yr2 yr3 yr4 yr5 yr | 22.848.956.860.360.3 | 54.550.0 | 61707982 | 70.3 | 88.897.8 |
| Cumulative probability of genotypic resistance (%)1 yr2 yr3 yr4 yr5 yr | 4.418.434.352.365.6 | 615364651 | 0.70.91.3 | 0 | 00 |
| Cumulative probability of HBeAg seroconversion (%)1 yr2 yr3 yr4 yr5 yr | 7.312.715.017.017.0 | 00 | 24 | 9.67 | 15.626.7 |
| Cumulative probability of ALT normalization (%)1 yr2 yr3 yr4 yr5 yr | 80.383.286.788.288.2 | 77.380.0 | 848789 | 64.0 | 100100 |

ADV: Adefovir; ETV: Entecavir; LAM: Lamivudine; LdT: Telbivudine; TDF: Tenofovir; HBV-DNA: Hepatitis B virus deoxynucleic acid; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase.