Current Hepatology Reports (2019) 18:363–369
https://doi.org/10.1007/s11901-019-00483-z

HEPATITIS B (JK LIM, SECTION EDITOR)

Management of Virologic Failure in Patients with Chronic Hepatitis B Treated with Nucleos(t)ide Analogues

Zaid H. Tafesh[1] · Robert S. Brown Jr[1]

Published online: 22 July 2019

Abstract

Purpose of the Review Poorly controlled hepatitis B increases the risk for liver-related morbidity. Although there are now six approved nucleos(t)ide analogues (NA) for the treatment of chronic hepatitis B (CHB), drug resistance and thus virologic breakthrough still exist. This review outlines a systematic approach to the management of virologic failure in patients with CHB treated with NAs.

Recent Findings Current NAs can be divided into older generation and newer generation agents, with newer generation agents associated with lower rates of virologic breakthrough. Both tenofovir dipovoxil fumarate (TDF) and tenofovir alafenamide (TAF) are equally as effective in addressing virologic breakthrough while on all other NAs. Entecavir is an effective treatment option for NA naïve patients only, with high rates of resistance to entecavir in those exposed to older NAs.

Summary The management of virologic breakthroughs should focus on identifying risk factors for future drug resistance and escalation to appropriate newer generation drug options to avoid long-term liver-related morbidity.

Keywords Chronic hepatitis B · Nucleos(t)ide analogues · Virologic breakthrough · Hepatitis B viremia · Cirrhosis · Viral hepatitis

Introduction

Hepatitis B virus (HBV) infection is a global health concern that has persisted despite decades of progress in vaccination and antiviral therapy. Although a highly effective HBV vaccine was introduced in 1982, there remain nearly 257 million people infected with the virus worldwide. [1] The estimated prevalence of HBV infection within the USA has varied based on the population of interest. A 7-year population survey from 1999 to 2006 found that 0.27% of individuals were Hepatitis B surface antigen (HBsAg) positive, which suggested that around 750,000 people were chronically infected with the virus during that time period. [2] This number increases considerably to 2.2 million individuals when foreign-born residents of the USA are taken into consideration [3], emphasizing the national impact of HBV and the importance of offering effective treatment when clinically appropriate.

While the majority of adults who develop acute HBV will recover with supportive care, develop immunity, and not require long-term therapy, those who do develop chronic hepatitis B (CHB) infection are at risk for long-term complications including cirrhosis and hepatocellular carcinoma (HCC). [4] Consequently, the decision to treat CHB has focused primarily on identifying signs of disease activity and progression, including serum levels of alanine aminotransferase (ALT) and HBV DNA, while taking into consideration any evidence of advanced fibrosis. [4–6] This approach has permitted the timely introduction of antiviral drugs before the risk of liver disease progression related to CHB begins to increase.

Prior to the introduction of nucleos(t)ide analogues (NA), pegylated and standard interferon-α was the most commonly used drug for adult patients infected with HBV with indications for treatment. However, its variable level of effectiveness and significant side-effect profile has limited its role to those who desire a finite treatment course, especially in the era of more effective and tolerable oral antiviral therapy options. [5] Currently, there are six approved NAs for the treatment of HBV infection. They can be further divided into preferred and non-preferred first-line agents based primarily on the

This article is part of the Topical Collection on *Hepatitis B*

✉ Zaid H. Tafesh
zat2003@nyp.org

[1] Division of Gastroenterology & Hepatology, Weill Cornell Medicine, 1305 York Avenue, 4th Floor, New York, NY 10021, USA

barrier to resistance of each particular agent. The preferred NAs are the newer generation options and include entecavir, tenofovir dipovoxil fumarate (TDF), and tenofovir alafenamide (TAF), while the non-preferred options include lamivudine, adefovir, and telbivudine. [4, 7] Ideally, all patients would be started on one of the three preferred options, which share both high potency and a high barrier to resistance. However, factors including cost and accessibility (especially in resource-poor countries) may limit access to newer generation NAs. Under these circumstances, virologic failure is more likely and requires a swift modification in therapy to address the uncontrolled HBV infection. Moreover, despite the low likelihood of ongoing viremia on entecavir, TDF, or TAF, it remains a possibility [8] and introduces an even more challenging problem, as alternative drugs do not yet exist and combination therapy increases cost.

This review outlines a systematic approach to the management of virologic failure in patients with CHB treated with NAs. The definition of treatment failure in CHB is delineated and the approach to inadequate HBV control while on each of the six approved nucleos(t)ide analogues is outlined. An additional commentary on how to address low-level viremia while on appropriate therapy is also presented.

Treatment Duration, Goals, and Defining Failure

The thresholds to initiate antiviral therapy in individuals who are HBsAg positive differ depending on the e-antigen status at the time of assessment. [4, 5, 7] This approach stems from identifying immune-active phases of CHB that represent higher levels of disease of activity not controlled by effective immune surveillance. High-level viremia alone without evidence of elevated liver enzymes or advanced fibrosis (immune-tolerant HBV) does not currently establish an immediate need for therapy. However, once the agreed upon thresholds are met, one of the approved NAs for the treatment of HBV can be initiated.

The overall goal of therapy is to decrease morbidity and mortality by reducing inflammation and the risk of fibrosis. Biochemically, providers should aim towards durable HBV DNA suppression, Hepatitis B e-antigen (HBeAg) loss and seroconversion (if positive at the start of treatment), and HBsAg loss and seroconversion. These three goals are each respectively more difficult to achieve, with HBV DNA suppression with normalization of ALT the most commonly encountered scenario. [6] Fortunately, virologic suppression with NAs has consistently been shown to improve long-term outcomes by reducing the risk of hepatocellular carcinoma and complications of cirrhosis. [9, 10] Therefore, precisely defining virologic response, persistent viremia, and virologic breakthrough is an important first step to tackling overall virologic failure in patients with CHB on treatment.

Virologic Response

The American Association for the Study of Liver Disease (AASLD) defines virologic response as achieving an undetectable HBV DNA at 96 weeks of treatment. [6] The European Association for the Study of Liver Disease (EASL) goes further to define partial virologic response when HBV DNA remains detectable but has decreased by 1 $\log_{10}$ IU/ml [5], an important group to distinguish from those who are deemed non-responders to therapy. The move from considering failure to achieve virologic response from 48 weeks to 96 weeks of treatment has mostly been driven by newer generation NAs with incremental efficacy even after 48 weeks of antiviral therapy in patients who are HBeAg positive and < 1% rates of antiviral resistance with long-term (3 or more years) use. [11]

Persistent Viremia

To remain consistent with the definition of virologic response, persistent viremia can be viewed as detectable HBV DNA after 96 weeks of treatment and/or a plateau in the decline of HBV DNA. Low-level viremia on the other hand is defined as < 2000 IU/mL of HBV DNA but detectable on serum PCR. [6, 12]

Virologic Breakthrough

Virologic breakthrough can occur in one of two circumstances, either when there is partial response to initial NA therapy or a complete response with undetectable levels of HBV DNA. In the former scenario, a breakthrough event is defined by an increase in HBV DNA by > 1 log compared with the lowest previously measured level, while in the latter situation, a detectable HBV DNA greater than or equal to 100 IU/mL is the commonly used cutoff value. [5, 6]. In both circumstances, this should be confirmed with a second measurement prior to changes in management.

Management of Virologic Failure on Nucleos(t)ide Analogues

As previously mentioned, it is preferable that individuals who require HBV treatment be started on newer generation NAs, given the high barrier to resistance. However, all approved NAs have shown effectiveness over placebo in individuals with HBV infection, and therefore remain potential options for initial treatment. [7] When considering the best approach to virologic failure while on any of the selected NAs, providers must first

assess for adherence to therapy (Fig. 1). Non-adherence may provide a plausible explanation for persistent viremia or even virologic breakthrough [13], and can be easily missed if a patient does not openly offer this information. In fact, a recently published 10-year longitudinal observational study evaluating the consequences of poor adherence to entecavir in patients with CHB revealed that those with less than 90% adherence had increased liver-related and overall mortality, as well as a higher incidence of liver-related complications and HCC. [14] Hence, confirming adherence is an important step in improving long-term outcomes. Once adherence is confirmed, countering virologic failure depends on a host of factors, which includes the current choice of NA therapy. Virologic breakthrough establishes a need to rethink an individual's management plan. Conversely, the approach taken towards addressing persistent viremia on NAs is somewhat more nuanced. This is mainly related to the fact that persistent viremia, unlike virologic breakthrough, is less likely to be associated with HBV resistance. [15]

When to Consider Resistance Testing

NA resistance testing is based on molecular identification of drug-resistant HBV. The available diagnostic methods include hybridization, restriction fragment polymorphism analysis, and sequencing. [16] The development of drug resistance while on NAs for CHB is almost exclusively associated with virologic breakthrough. [4–6, 15]. Current diagnostic techniques to detect drug-resistant HBV strains are limited to circulating HBV DNA of at least 1000 IU/mL, [4] making it unfeasible to determine whether NA resistance is responsible for ongoing low-level viremia. Luckily, drug resistance to the preferred initial NA therapies is uncommon even in slow virologic responders, and current guidelines do not recommend routine drug-resistance testing in this patient population, as it is unlikely to change management. Alternatively, if available, determining the specific mutation associated with a virologic breakthrough event can be helpful in future treatment planning, especially if there is ongoing viremia with entecavir therapy and the patient had any prior lamivudine exposure. In most cases, however, persistent viremia as detected by HBV DNA testing does not necessarily reflect viral resistance, especially when non-compliance to therapy is suspected. As detailed later, delineating the resistance mutations that a provider is facing when managing a virologic breakthrough event is helpful in determining what future therapy options are unlikely to be effective. Currently, sequencing-based methods using polymerase chain reaction (PCR) are limited by their ability to detect a particular mutation only if it is present in over 20% of the tested sample, limiting its sensitivity. Alternatively, if pyrosequencing is available, it is a much faster and more sensitive method to detect HBV resistance, and is the preferred test of choice. [17]

Virologic Breakthrough on Older Generation Nucleos(t)ide Analogues

Positive drug-resistance testing is most common in patients receiving lamivudine and telbivudine as compared with other

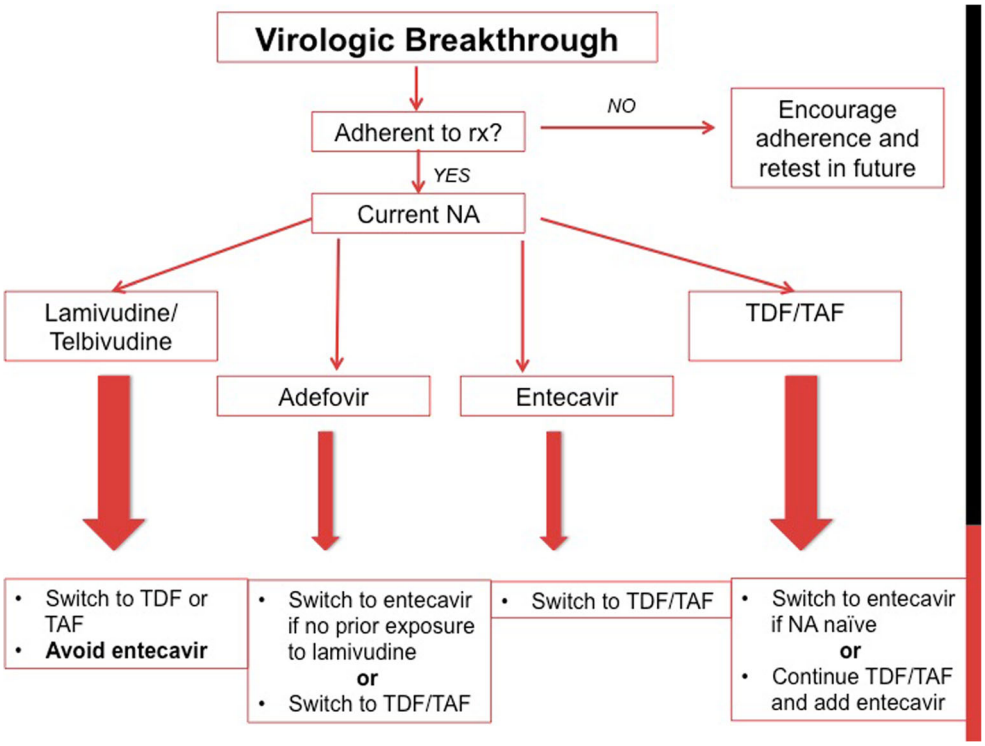

Fig. 1 Algorithm for management of virologic breakthrough on nucleos(t)ide analogues

NAs. [15] The most common HBV mutation variants resulting in lamivudine resistance include *M204V*, *M204I*, and *L180M + M204V*. [5, 6] Unfortunately, lamivudine use has demonstrated an incremental increase in HBV resistance overtime, with around a quarter of patients at 1 year harboring a lamivudine-resistant strain of HBV. This number dramatically increases at 5 years with some data suggesting drug-resistance rates as high as 65–70%. [18, 19] The majority of virologic breakthroughs on lamivudine ultimately will result in a biochemical breakthrough with a rise in ALT levels, and therefore necessitates early alteration in the treatment approach. [20]

Fortunately, there have been a number of trials analyzing several different rescue therapies for lamivudine-resistant HBV, including combination therapy with older generation NAs and monotherapy with newer generation options. Entecavir is a poor salvage therapy option when treatment with lamivudine fails to achieve an adequate result. This is primarily related to the fact that at a molecular level, entecavir resistance relies on the presence of substitutions including M204I/V ± L180M that confer resistance to lamivudine. These substitutions predispose to the development of T184, S202, or M250 reverse transcriptase substitutions [21], which allow circulating HBV to evade the effects of entecavir, in stark contrast to NA naïve patients. These findings have been substantiated in a number of clinical and observational studies. Kim et al. presented data on one hundred and four Korean patients with CHB with documented lamivudine resistance that were treated either with the addition of adefovir, a switch to adefovir monotherapy, or a switch to entecavir monotherapy. Adding adefovir to lamivudine was superior in HBV DNA suppression and resulted in the least number of virologic breakthroughs while on rescue therapy, arguably the most important indicator of success. [22] A large meta-analysis that included over 600 patients with lamivudine-resistant HBV reinforced that the major difference in meaningful clinical outcomes between individuals switched to entecavir as compared with the addition of adefovir was the higher rate of virologic breakthrough in the entecavir group [23], with some studies reporting no virologic breakthroughs on adefovir-lamivudine combination therapy. [24] However, at 5 years, adefovir-lamivudine combination treatment showed only modest rates of HBV DNA undetectability (74%) with a 5-year resistance rate to adefovir of 10.2%. [25] Given these long-term results, tenofovir-based rescue treatment regimens are the preferred option in the setting of lamivudine resistance resulting in virologic breakthrough. Under these circumstances, tenofovir monotherapy has been compared with both tenofovir-lamivudine and tenofovir-emtricitabine combination treatment, and has consistently shown to be effective at achieving virologic response alone both in individuals who were first tried on lamivudine-adefovir rescue treatment and in general in the setting of lamivudine resistance. [18, 26] Moreover, tenofovir resistance is rare, and therefore makes it the ideal drug of choice when faced with virologic failure while on lamivudine. [4] At the 5-year treatment mark, tenofovir alone was equally as effective as tenofovir-emtricitabine in successfully achieving a virologic response after failing lamivudine. [27]

Management of virologic failure/breakthrough while receiving telbivudine should be approached in a similar fashion to lamivudine resistance. Tenofovir-based monotherapy is preferred over combination therapy with tenofovir, and entecavir again should be avoided given the high rate of subsequent entecavir resistance and virologic failure. [4–6]

Similar to lamivudine, virologic breakthrough on adefovir is more likely to occur when drug resistance develops. Though less common than in patients on lamivudine, adefovir resistance at 4–5 years on treatment occurred in roughly one-fifth of patients, regardless of HBeAg status. [28, 29] However, unlike lamivudine, pure resistance to adefovir is not as predictive of future entecavir failure. Consequently, both the AASLD and EASL recommend a switch to entecavir monotherapy as one option for the treatment of virologic failure on adefovir, but only when there is no concern for potential lamivudine-associated mutations. [4–6] However, a large portion of patients are started on adefovir after a period of lamivudine exposure, either as salvage therapy (alone or in combination with another NA) or as an alternative new option after FDA approval. When rates of drug resistance were compared between lamivudine-resistant and treatment-naïve patients, the incidence of rtA1818V/T and rtN236T adefovir-associated mutations were more common in the former group. [30] Cumulative virologic breakthrough rates on entecavir in the presence of both adefovir and lamivudine resistance is as high as 75% at 36 months, even more prominent than in patients with resistance to lamivudine alone. [31, 32] Therefore, providers need to take special caution to rule out any potential lamivudine resistance either by direct molecular testing or history suggesting exposure to lamivudine. If lamivudine resistance is confirmed or suspected, then a tenofovir-based salvage regimen is the preferred route. TDF alone is effective in suppressing HBV DNA in the setting of a previous history of adefovir monotherapy or in combination with lamivudine, with the majority of patients achieving HBV DNA suppression at a mean treatment duration of 23 months. [33] Studies in patients with confirmed HBV resistance to adefovir reinforced the usefulness of tenofovir monotherapy in management of virologic breakthrough in this patient population, with long-term viral suppression rates above 80% at 168 weeks regardless of whether an additional antiviral agent was used. [26, 34, 35]

Virologic Breakthrough on Entecavir and Tenofovir-Based (TDF, TAF) Therapies

Entecavir is a highly effective NA for the treatment of CHB. Suppression of HBV DNA is durable on entecavir when patients are NA naïve. The cumulative probability of entecavir

resistance over 5 years in NA naïve individuals is 1.2%, with 0.8% suffering from virologic breakthrough. These numbers are substantially higher in patients that failed lamivudine, with a virologic breakthrough rate of 43%. [21] Unfortunately, many HBV-infected individuals receiving entecavir have seen multiple older generation NAs, contributing to the development of multidrug-resistant (MDR) strains of HBV. [36] This ultimately increases the probability of yet another treatment failure and need for escalation of therapy. Fortunately, tenofovir-based regimens provide a reliable solution to virologic failure on entecavir. While the AASLD advocates for either a switch to tenofovir monotherapy (TDF or TAF) or combination entecavir-tenofovir when faced with this scenario, the European guidelines take a more conservative approach and recommend an immediate switch to tenofovir alone. [4–6] In patients exposed to various lines of NAs and harboring both MDR and entecavir resistance profiles, combination therapy with entecavir and tenofovir was both effective and safe in inducing complete HBV DNA suppression at 4.5–6 months on average. [36, 37] In a randomized control trial comparing TDF monotherapy with TDF + entecavir as rescue therapy in the setting of documented entecavir resistance with elevated HBV DNA levels, TDF monotherapy was able to mount a favorable virologic response similar to combination treatment. Only one case of virologic breakthrough on TDF monotherapy was reported in a non-adherent individual. [38] Consequently, tenofovir-based monotherapy has strong evidence to support its use in the setting of virologic failure on entecavir. This includes monotherapy with TAF, which has shown susceptibility to drug-resistant HBV isolates in vitro, [39] has a non-inferior efficacy profile to TDF at 48 weeks, and carries a more favorable safety profile in terms of bone and renal outcomes. [40]

In contrast to other NAs used for the treatment of CHB, true resistance to TDF and TAF in HBV-monoinfected individuals is rare. Both drugs are highly effective and rarely result in virologic breakthrough, with 8-year and 2-year follow-up data available for TDF and TAF, respectively. [4, 11, 38–41] There have been at least two reports of potential TDF resistance in the literature, both confirming by molecular testing, the high genetic barrier to resistance on this NA. [42, 43] When this scenario is encountered in practice, if HBV DNA levels remain detectable but low, then continuing TDF and TAF with close monitoring is an appropriate first step. However, if HBV DNA levels continue to rise or a true virologic breakthrough event occurs, then options include stopping tenofovir and switching to entecavir in individuals previously NA naïve, or continuing tenofovir with the addition of entecavir in everyone else. [4, 44]

Persistent Viremia

The clinical significance of persistent viremia outside of meeting criteria for virologic breakthrough remains controversial. In general, in the setting of low-level viremia, resistance testing is difficult and therefore further complicates a provider's ability to determine whether this finding is meaningful. An earlier study by Kim et al. compared the effect of virological response with entecavir on the development of HCC after 1 year of treatment in patients with compensated and decompensated cirrhosis. No virologic response (defined as HBV DNA < 20 IU/mL) at 1 year was an independent risk factor for developing HCC (HR 2.10), although in a subgroup analysis, this effect was only seen in patients with decompensated cirrhosis. [45] In a more recent analysis of 875 HBV-monoinfected patients receiving entecavir, an increased risk of HCC was observed in all patients with cirrhosis (compensated and decompensated) with low-level viremia (detectable HBV DNA but < 2000 IU/mL). [46] In a recent Korean study looking at individuals with only decompensated HBV cirrhosis, early viral response at 6 months to entecavir or lamivudine was not associated with any short-term mortality benefit. However, a maintained virologic response (undetectable HBV DNA while on therapy) did result in higher long-term transplant-free survival, although rates of HCC did not differ between those who did and did not achieve persistent undetectable HBV DNA. [47] Taken together, the results of these different studies suggests that addressing persistent viremia while on NAs should be tailored to each patient's specific risks for developing complications of advanced liver disease including decompensated cirrhosis and HCC. If further HBV DNA suppression is desired based on a patient's risk profile, then individuals on older generation NAs or entecavir should be switched to a tenofovir-based treatment regimen.

Conclusion

It is undeniable that the introduction of NAs has transformed the landscape of CHB management. When indicated, treatment of CHB primarily targets patients at the highest risk of developing complications of active HBV infection and consequently, meeting the appropriate treatment goals carries considerable value. While newer generations of NAs, including entecavir, TDF, and TAF, are highly effective with low rates of resistance; many individuals harboring the infection began treatment in the era of older generation NAs or come from resource-poor countries that do not offer preferred NAs as a first-line option. As a result, virologic breakthrough events continue to occur in these individuals and should be managed in a systematic fashion. The mainstay of addressing NA failure is to identify risk factors for non-adherence and subsequent NA resistance. Prior NA exposures and HBV resistance testing can best predict future therapy failures and provide valuable guidance in terms of the most appropriate next drug of choice. Ultimately, tenofovir-based regimens (TDF or TAF) are the most convenient salvage therapy options when faced

with virologic breakthrough on older NAs. However, cost and side-effect profiles are important considerations, and therefore, our approach has the benefit of allowing the provider to choose among different management strategies, when clinically appropriate. Ultimately, although NAs have redefined our ability to control CHB infection, a curative therapy is the hope for the future.

Compliance with Ethical Standards

Conflict of Interest Dr. Brown reports grants and personal fees from Gilead, personal fees from BMS, outside the submitted work. Dr. Tafesh declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. World Health Organization. *Hepatitis B* 2018, July 18 [cited 2019 April 21, 2019]; Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.
2. Wasley A, Kruszon-Moran D, Kuhnert W, Simard EP, Finelli L, McQuillan G, et al. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. J Infect Dis. 2010;202(2):192–201.
3. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. Hepatology. 2012;56(2):422–33.
4. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–99.
5. European Association for the Study of the Liver. Electronic address, e.e.e. and L. European Association for the Study of the, EASL. Clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol, 2017. 2017;67(2):370–98.
6. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261–83.
7. Lok AS, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. Hepatology. 2016;63(1):284–306.
8. Lee S, Ahn SH, Jung KS, Kim DY, Kim BK, Kim SU, et al. Tenofovir versus tenofovir plus entecavir for chronic hepatitis B with lamivudine resistance and entecavir resistance. J Viral Hepat. 2017;24(2):141–7.
9. Papatheodoridis GV, Chan HLY, Hansen BE, Janssen HLA, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol. 2015;62(4):956–67.
10. Su TH, Hu TH, Chen CY, Huang YH, Chuang WL, Lin CC, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int. 2016;36(12):1755–64.
11. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68(4):672–81.
12. Terrault N. Is low level viremia acceptable during antiviral therapy of patients with HBV infection and decompensated cirrhosis? Clin Gastroenterol Hepatol. 2018;16(12):1876–8.
13. Sheppard-Law S, Zablotska-Manos I, Kermeen M, Holdaway S, Lee A, Zekry A, et al. Factors associated with HBV virological breakthrough. Antivir Ther. 2017;22(1):53–60.
14. Shin JW, Jung SW, Lee SB, Lee BU, Park BR, Park EJ, et al. Medication nonadherence increases hepatocellular carcinoma, cirrhotic complications, and mortality in chronic hepatitis B patients treated with entecavir. Am J Gastroenterol. 2018;113(7):998–1008.
15. Salpini R, Alteri C, Cento V, Pollicita M, Micheli V, Gubertini G, et al. Snapshot on drug-resistance rate and profiles in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. J Med Virol. 2013;85(6):996–1004.
16. Kim JH, et al. Molecular diagnosis and treatment of drug-resistant hepatitis B virus. World J Gastroenterol. 2014;20(19):5708–20.
17. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. Gastroenterology. 2009;137(5):1593–608 e1–2.
18. Fung S, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, et al. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology. 2014;146(4):980–8.
19. Lok AS, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology. 2003;125(6):1714–22.
20. Papatheodoridis GV, Dimou E, Laras A, Papadimitropoulos V, Hadziyannis SJ. Course of virologic breakthroughs under long-term lamivudine in HBeAg-negative precore mutant HBV liver disease. Hepatology. 2002;36(1):219–26.
21. Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology. 2009;49(5):1503–14.
22. Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, Jeon WK, et al. Rescue therapy for lamivudine-resistant chronic hepatitis B: comparison between entecavir 1.0 mg monotherapy, adefovir monotherapy and adefovir add-on lamivudine combination therapy. J Gastroenterol Hepatol. 2010;25(8):1374–80.
23. Huang ZB, Zhao SS, Huang Y, Dai XH, Zhou RR, Yi PP, et al. Comparison of the efficacy of lamivudine plus adefovir versus entecavir in the treatment of lamivudine-resistant chronic hepatitis B: a systematic review and meta-analysis. Clin Ther. 2013;35(12):1997–2006.
24. Chung GE, Kim W, Lee KL, Hwang SY, Lee JH, Kim HY, et al. Add-on adefovir is superior to a switch to entecavir as rescue therapy for lamivudine-resistant chronic hepatitis B. Dig Dis Sci. 2011;56(7):2130–6.
25. Seto WK, Liu K, Fung J, Wong DKH, Yuen JCH, Hung IFN, et al. Outcome of lamivudine-resistant chronic hepatitis B after up to 5 years of combination therapy with adefovir. Antivir Ther. 2012;17(7):1255–62.
26. Park JH, Jung SW, Park NH, Park BR, Kim MH, Kim CJ, et al. Efficacy of tenofovir-based rescue therapy in lamivudine-resistant chronic hepatitis B patients with failure of lamivudine and adefovir combination. Clin Ther. 2015;37(7):1433–42.
27. Fung S, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, et al. Tenofovir disoproxil fumarate (TDF) vs. emtricitabine (FTC)/TDF in lamivudine resistant hepatitis B: a 5-year randomised study. J Hepatol. 2017;66(1):11–8.
28. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang T–T, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology. 2006;131(6):1743–51.
29. Marcellin P, Chang TT, Lim SGL, Sievert W, Tong M, Arterburn S, et al. Long-term efficacy and safety of adefovir dipivoxil for the

treatment of hepatitis B e antigen-positive chronic hepatitis B. Hepatology. 2008;48(3):750–8.
30. Lee YS, Suh DJ, Lim YS, Jung SW, Kim KM, Lee HC, et al. Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. Hepatology. 2006;43(6):1385–91.
31. Park JW, Kim HS, Seo DD, Jang JS, Shin WG, Kim KH, et al. Long-term efficacy of entecavir in adefovir-refractory chronic hepatitis B patients with prior lamivudine resistance. J Viral Hepat. 2011;18(10):e475–81.
32. Shim JH, Suh DJ, Kim KM, Lim YS, Lee HC, Chung YH, et al. Efficacy of entecavir in patients with chronic hepatitis B resistant to both lamivudine and adefovir or to lamivudine alone. Hepatology. 2009;50(4):1064–71.
33. van Bommel F, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology. 2010;51(1):73–80.
34. Berg T, Zoulim F, Moeller B, Trinh H, Marcellin P, Chan S, et al. Long-term efficacy and safety of emtricitabine plus tenofovir DF vs. tenofovir DF monotherapy in adefovir-experienced chronic hepatitis B patients. J Hepatol. 2014;60(4):715–22.
35. Lim YS, Yoo BC, Byun KS, Kwon SY, Kim YJ, An J, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in adefovir-resistant chronic hepatitis B patients with multiple drug failure: results of a randomised trial. Gut. 2016;65(6):1042–51.
36. Lee YB, Lee JH, Lee DH, Cho H, Ahn H, Choi WM, et al. Efficacy of entecavir-tenofovir combination therapy for chronic hepatitis B patients with multidrug-resistant strains. Antimicrob Agents Chemother. 2014;58(11):6710–6.
37. Petersen J, Ratziu V, Buti M, Janssen HLA, Brown A, Lampertico P, et al. Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: an international multicenter cohort study. J Hepatol. 2012;56(3):520–6.
38. Lim YS, Byun KS, Yoo BC, Kwon SY, Kim YJ, An J, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in patients with entecavir-resistant chronic hepatitis B with multiple drug failure: results of a randomised trial. Gut. 2016;65(5):852–60.
39. Liu Y, Miller MD, Kitrinos KM. Tenofovir alafenamide demonstrates broad cross-genotype activity against wild-type HBV clinical isolates and maintains susceptibility to drug-resistant HBV isolates in vitro. Antivir Res. 2017;139:25–31.
40. Chan HL, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):185–95.
41. Koklu S, et al. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol. 2013;11(1):88–94.
42. Cho WH, Lee HJ, Bang KB, Kim SB, Song IH. Development of tenofovir disoproxil fumarate resistance after complete viral suppression in a patient with treatment-naive chronic hepatitis B: a case report and review of the literature. World J Gastroenterol. 2018;24(17):1919–24.
43. Park ES, Lee AR, Kim DH, Lee JH, Yoo JJ, Ahn SH, et al. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. J Hepatol. 2019;70(6):1093–102.
44. Kwon H, Lok AS. Hepatitis B therapy. Nat Rev Gastroenterol Hepatol. 2011;8(5):275–84.
45. Kim SS, Hwang JC, Lim SG, Ahn SJ, Cheong JY, Cho SW. Effect of virological response to entecavir on the development of hepatocellular carcinoma in hepatitis B viral cirrhotic patients: comparison between compensated and decompensated cirrhosis. Am J Gastroenterol. 2014;109(8):1223–33.
46. Kim JH, Sinn DH, Kang W, Gwak GY, Paik YH, Choi MS, et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. Hepatology. 2017;66(2):335–43.
47. Jang JW, Choi JY, Kim YS, Yoo JJ, Woo HY, Choi SK, et al. Effects of virologic response to treatment on short- and long-term outcomes of patients with chronic hepatitis B virus infection and decompensated cirrhosis. Clin Gastroenterol Hepatol. 2018;16(12):1954–63 **e3**.