ABSTRACT

- **Objective:** To review current treatment strategies for the management of chronic hepatitis B (CHB).
- **Methods:** Review of the literature.
- **Results:** There are currently 7 drugs approved by the FDA for the treatment of CHB. Interferon alfa-2a and peginterferon alfa-2a are injectable immunomodulators, while lamivudine, adefovir, telbivudine, entecavir, and tenofovir are direct-acting oral antiviral agents. The goal of treatment in patients with CHB is to reduce the risk of progressive liver damage that leads to development of complications such as cirrhosis and hepatocellular carcinoma. The timing of treatment initiation and duration of antiviral therapy varies among society guidelines and incorporates analysis of liver fibrosis in conjunction with the alanine aminotransferase level.
- **Conclusion:** Hepatitis B is a chronic disease that requires life-long monitoring.

Hepatitis B virus infection (HBV) is a global epidemic with a worldwide burden of more than 400 million chronically infected, a majority of whom reside primarily in the Asia Pacific region [1,2]. The prevalence of chronic hepatitis B (CHB), defined as persistence of HBV surface antigen (HBsAg) for more than 6 months, is estimated to be 1.25 to 2 million in the United States [2–5]. Patients chronically infected with HBV are at increased risk of developing serious sequelae of their underlying liver disease. It is estimated that up to 40% of patients with CHB will develop acute HBV exacerbation, cirrhosis, or hepatocellular carcinoma (HCC) [3,6,7]. Early detection and treatment can reduce the risk of developing these complications, and the American Association for the Study of Liver Diseases (AASLD) has issued formal recommendations for HBV screening among high-risk populations (Table 1) [2].

While early detection of HBV affords patients greater therapeutic options, prevention of HBV is perhaps the best approach towards eventual eradication of this disease. The institution of HBV vaccination programs has translated into dramatic declines in the incidence of HBV infection among vaccinated populations [8]. Among the U.S. population, universal HBV vaccination was implemented in 1991, and data from the National Health and Nutritional Survey (NHANES) demonstrated significant declines in HBV prevalence as a result of this policy. However, the declines in HBV prevalence were seen primarily among children and young adults, while the burden of CHB among the adult populations remained large. This difference likely reflects the disparate epidemiology of HBV in the United States, with nearly 95% of new HBV cases attributed to immigrants from high prevalence countries including China, Vietnam, and the Philippines [9,10]. As such, the implementation of universal vaccination policies has no impact on the burden of disease among patients with preexisting CHB.

The increased risk of liver complications associated with chronic infection with HBV has been well described. A prolonged replicative phase with persistently elevated serum HBV DNA levels is a known risk factor contributing to decompensated disease, cirrhosis, and HCC [11,12]. The goals of treatment with currently available therapies for HBV are aimed at suppressing viral replication and HBV DNA levels, thereby reducing progressive liver inflammation and fibrosis and decreasing the risk of developing serious sequelae. This article will review the currently available therapies for the treatment of CHB. While the management and treatment of CHB is optimized under the guidance of a gastroenterologist/hepatologist, we will aim to provide an overview of the current treatment algorithm with...
specific focus on understanding indications for initiating therapy, an evidenced-based approach to choosing the appropriate antiviral therapy, and managing endpoints of therapy in non-cirrhotic patients monoinfected with hepatitis B.

CASE STUDY

Initial Presentation

A 55-year-old woman from Vietnam is referred to a hepatologist for newly diagnosed HBV infection. She has no significant past medical history and denies any symptoms. Upon routine examination, her primary care physician identified abnormal liver enzymes (alanine aminotransferase [ALT] was more than 3 times the upper limit of normal [ULN]) on laboratory evaluation. Subsequent laboratory tests were notable for hepatitis B surface antigen (HBsAg) positive, hepatitis B surface antibody (anti-HBs) negative, and hepatitis C antibody negative. While she was born in Vietnam, she is not aware of previously being diagnosed with HBV, nor is she aware of HBV among her family members.

- What is the natural history of HBV?
- What are important factors to consider when deciding whether a patient with newly diagnosed HBV warrants antiviral therapy?

**Table 1. High-Risk Populations in Which HBV Screening Is Recommended**

<table>
<thead>
<tr>
<th>Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals from world regions designated as high (HBsAg &gt; 8%) or intermediate (HBsAg 2-7%) prevalence of HBV</td>
</tr>
<tr>
<td>US born individuals not vaccinated at birth whose parents were born in regions designated as high prevalence of HBV</td>
</tr>
<tr>
<td>Household and sexual contacts of HBsAg-positive persons</td>
</tr>
<tr>
<td>Individuals with history of injection drug use or incarceration</td>
</tr>
<tr>
<td>Individuals with multiple sexual partners or history of sexually transmitted diseases</td>
</tr>
<tr>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>Individuals coinfected with HIV or hepatitis C</td>
</tr>
<tr>
<td>Individuals undergoing renal dialysis or needing immunosuppressive therapy</td>
</tr>
<tr>
<td>All pregnant women</td>
</tr>
</tbody>
</table>

Adapted from reference 2.

The immune tolerant stage of CHB is characterized by high levels of viral replication (elevated HBV DNA levels and presence of HBeAg) but no biochemical evidence of active inflammation (normal serum ALT). Histologically, there is minimal or absent inflammation and fibrosis. A liver biopsy is often not required for diagnosis or to guide therapy. This stage of disease is seen primarily in patients infected early in life or at birth and is rarely seen in those infected in adulthood. Treatment is generally not indicated during this stage of disease, and close monitoring is appropriate.

The immune clearance stage of CHB is marked by active attempts by the body to clear infected hepatocytes. This stage is characterized by elevated HBV DNA levels and elevated or fluctuating levels of serum ALT. Active inflammation and variable degrees of fibrosis are often seen on histology. During this phase, seroconversion and development of antibodies to HBeAg (anti-HBe) can occur, and initiating antiviral therapy...
can increase the possibility of achieving seroconversion [15,16]. As such, treatment is usually indicated during this stage of CHB.

Individuals who develop anti-HBe progress to the inactive carrier state also known as the low replicative state. The inactive carrier state is characterized by normal ALT levels and low or undetectable levels of HBV DNA, indicating a non-replicative stage of CHB [17]. Minimal or absent inflammation is seen on histology along with variable degrees of fibrosis. While treatment is usually not indicated during this stage of disease, continued close monitoring is warranted for any evidence of progression to HBV reactivation. Furthermore, despite normal ALT levels and low or undetectable HBV DNA, inactive carriers with persistence of HBsAg continue to have increased risk of HCC [18].

Reactivation of HBV infection can occur at anytime during an individual’s lifetime. This stage of disease is characterized by elevated ALT and high levels of HBV DNA, and can be associated with reappearance of HBeAg, indicating active viral replication. Pathophysiologically, HBV reactivation is associated with development of precore mutants of the hepatitis B virus that facilitate the active viral replication and inflammation that occurs [19,20]. Treatment is indicated during this stage to suppress viral replication in an attempt to achieve a low replicative state.

**Case Continued**

On further evaluation, the patient was found to be HBeAg negative with HBV DNA level of 100,000 IU/mL. Repeat testing of her liver enzymes and liver function tests is notable for persistence of ALT levels greater than 3 times the ULN. Abdominal ultrasound is notable for mild hepatomegaly without mass lesions seen in the liver. After a detailed discussion with the patient, a decision was made to start antiviral therapy.
What are the current treatment algorithms and guidelines for initiating antiviral therapy for CHB?

What are the currently available treatment regimens?

Indications for Therapy

The goal of treatment in patients with CHB is to reduce the risk of progressive liver damage that leads to development of complications such as cirrhosis and HCC.

To achieve this endpoint, antiviral therapy aims to suppress viral replication. The decision to initiate antiviral therapy in CHB is a complex decision that incorporates a detailed evaluation of biochemical data, virus characteristics (ie, serological profile and HBV DNA), and histopathology. Current treatment algorithms begin with determining a patient’s HBeAg status, with some guidelines utilizing development of anti-HBe as a potential endpoint among patients who are HBeAg positive at time of treatment initiation [2]. Furthermore, currently accepted guidelines for the management of HBV vary slightly with regard to their recommendations (Table 3) [2,19,21,22].

Table 2. Serological Patterns in the 4 Stages in Chronic HBV Infection.

<table>
<thead>
<tr>
<th>Stage of Chronic HBV Infection</th>
<th>ALT Elevated?</th>
<th>HBV DNA Elevated?</th>
<th>HBeAg Status?</th>
<th>Treatment Indicated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerant</td>
<td>No</td>
<td>Yes</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Immune clearance</td>
<td>Yes</td>
<td>Yes</td>
<td>Positive/Negative</td>
<td>Yes*</td>
</tr>
<tr>
<td>Inactive carrier</td>
<td>No</td>
<td>No</td>
<td>Negative/Positive</td>
<td>No</td>
</tr>
<tr>
<td>Reactivation</td>
<td>Yes</td>
<td>Yes</td>
<td>Positive</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Current guidelines recommend a period of observation (3–6 months) for patients in the immune clearance phase to monitor for spontaneous HBeAg seroconversion among HBeAg+ patients [2].

Table 3. Indications for Initiating HBV Therapy from 3 Major Guidelines

<table>
<thead>
<tr>
<th>HBeAg-positive CHB</th>
<th>HBeAg-negative CHB</th>
<th>Liver Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keeffe et al [19]</td>
<td>HBV DNA &gt; 20,000 IU/mL and ALT &gt; ULN</td>
<td>Compensated: HBV DNA &gt; 2000 IU/mL (can consider therapy if HBV DNA &lt; 2000 IU/mL)</td>
</tr>
<tr>
<td></td>
<td>Consider liver biopsy if ALT normal and age &gt; 35</td>
<td>Decompensated: any detectable HBV DNA</td>
</tr>
<tr>
<td>EASL [21]</td>
<td>HBV &gt; 2000 IU/mL and/or ALT &gt; ULN</td>
<td>Compensated: any detectable HBV DNA</td>
</tr>
<tr>
<td></td>
<td>Consider liver biopsy and treat if moderate to severe histologic disease present</td>
<td>Decompensated: any detectable HBV DNA</td>
</tr>
<tr>
<td>AASLD [2]</td>
<td>HBV DNA &gt; 20,000 IU/mL and ALT &gt; 2 x ULN (3–6 months of observation with absence of spontaneous HBeAg loss)</td>
<td>Compensated: HBV DNA &gt; 2000 IU/mL; consider therapy if HBV DNA &lt; 2000 IU/mL and ALT &gt; ULN</td>
</tr>
<tr>
<td></td>
<td>Consider liver biopsy if HBV DNA &gt; 20,000 IU/mL and ALT ≤ 2 x ULN, and age &gt; 40 or family history of HCC; treat if significant histologic disease</td>
<td>Decompensated: any detectable HBV DNA</td>
</tr>
</tbody>
</table>

AASLD = American Association for the Study of Liver Diseases; EASL = European Association for the Study of the Liver; HCC = hepatocellular carcinoma. (Adapted from reference 17.)
Current guidelines primarily utilize HBV DNA, serum ALT, and histology data to assess candidacy for antiviral therapy. However, recent studies investigating the natural history of HBV have raised challenges to the current treatment algorithms. Abnormalities in ALT levels is one component in the treatment decision algorithm, and several studies have suggested that currently accepted ranges for normal values may be too wide. For example, one study demonstrated that 20% of individuals over 35 years of age with ALT levels less than 2 times the ULN and elevated HBV DNA can have significant fibrosis on liver biopsy [19]. In addition, a large cohort of Asian patients with CHB were found to have significantly elevated risk of developing long-term complications despite having only mildly elevated ALT levels [23]. While increased HBV DNA is known to be associated with increased risk of HCC, 15% of patients in one study developed HCC with HBV DNA < 10^3 copies/ml [24]. While earlier guidelines have suggested the development of anti-HBe as a potential endpoint of therapy among HBeAg positive patients, several studies have demonstrated that over two-thirds of patients with long-term complications of CHB had previously achieved HBeAg seroconversion [24,25]. Thus, HBV DNA suppression or HbsAg seroconversion may be a more appropriate treatment endpoint.

Currently Available Therapies

There are currently 7 drugs approved by the Food and Drug Administration (FDA) for treatment of CHB: interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. The decision regarding which antiviral therapy to choose incorporates many factors including the efficacy of viral suppression, safety profile, medical comorbidities, and patient preference. All currently approved agents for hepatitis B will need to be renally dosed. Table 4 gives an overview of the main advantages and disadvantages associated with each of the major categories of available therapy.

Interferon-based Therapy

Interferon-based antiviral therapy is one of the earlier treatment regimens utilized for CHB management. The standard interferon alfa-2b has been replaced by peginterferon alfa-2a, which offers patients more convenient administration and dosing while offering comparable or improved antiviral efficacy [22,26]. The advantage of interferon-based therapy is that it remains the treatment regimen with the highest reported rate of off-treatment sustained response. After 48 weeks of interferon therapy, rates of HBeAg seroconversion were reported as high as 27%, with undetectable HBV DNA among 25% of patients. Furthermore, HbsAg loss with subsequent development of anti-HBs developed in 4% to 6% of patients treated with interferon at 6-month follow-up [27–29].

While interferon-based therapy is cautioned and even contraindicated in patients with certain medical comorbidities, a recent comprehensive analysis of 542 patients with CHB who underwent peginterferon therapy developed a HBV interferon treatment index in an attempt to identify patients who would benefit most from interferon therapy by predicting their probability of achieving sustained response [29]. In addition to HBV DNA levels and serum ALT, the model also includes age, gender, and HBV genotype. HBV genotype varies by country and not only impacts the progression of CHB, but also influences response to interferon therapy [29]. Patients with HBV genotype A, B, D, or F commonly clear HBeAg early in life, whereas patients with genotype C clear HBeAg much later in life. HBV genotypes C and F are more likely to experience reappearance of HBeAg positivity after losing HBeAg earlier in their lifetime [30]. HBV among the United States is predominantly genotypes A and C, whereas genotypes B and C are commonly found in Asia and genotypes A and D are seen in Europe and India [31–33]. Based on the interferon treatment index, individuals with HBV genotype A and either ALT > 2 times ULN or HBV DNA < 9log10 copies/mL, or patients with genotype B and C with ALT > 2 times ULN and HBV DNA < 9log10 copies/mL are the most suitable candidates for therapy [29].

Despite the many advantages associated with interferon-based therapy (eg, fixed duration of therapy, high rate of viral suppression of treatment efficacy, absence of selection of resistance mutations), this treatment regimen carries a significant side effect and safety profile compared with newer available oral agents. Current estimates among patients with CHB in the United States indicate that less than 10% of patients are treated with interferon-based therapies, with this number likely continuing to decline with the advancement of the newer oral nucleotide and nucleoside analogs [29,34].

Lamivudine

One of the earlier oral agents approved for treatment of CHB, treatment with lamivudine for 1 year is associ-
ated with HBeAg seroconversion of about 16% to 18%, increasing to 50% seroconversion with 5 years of therapy [35–37]. While treatment with lamivudine has been demonstrated to reduce the rate of fibrosis progression as well as HCC development, even among patients with advanced fibrosis or cirrhosis, the benefit of lamivudine therapy has been well reported [37,38]. However, the durability of response among patients treated with lamivudine therapy is much lower than that of interferon-based therapy. In addition, the high rate of developing resistance with prolonged use makes lamivudine less efficacious than newer oral agents available. Resistance rates as high as 65% to 70% have been reported after 5 years of lamivudine therapy [2,17,39].

**Adefovir**

Approved by the FDA in 2002, adefovir was the first oral nucleotide analog introduced for the treatment of CHB. Available as an alternative treatment regimen for patients with lamivudine failure, 1 year of adefovir therapy has been shown to achieve a 12% rate of HBeAg seroconversion and 53% rate of histologic improvement.

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**Table 4. Advantages and Disadvantages of HBV Treatment Regimens**

<table>
<thead>
<tr>
<th>Class of Therapy</th>
<th>Antiviral Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Immunomodulator  | Interferon-based therapy | • Finite duration of therapy  
• High rate of HBsAg loss  
• Highest rate of SVR  
• Absence of selection for resistance mutations | • Parenteral administration  
• Frequent side effects  
• Contraindicated in: acute live failure, hepatic decompensation, portal hypertension, severe HBV reactivation, psychiatric comorbidities |
| Nucleoside       | Lamivudine        | • Oral administration  
• Good safety profile  
• Relative low cost  
• Abundant studies among patients with end-stage liver disease and pregnant women | • High rate of resistant mutations |
| Nucleoside       | Entecavir         | • Oral administration  
• Most potent nucleoside in lowering HBV DNA  
• Low rate of resistant mutations | • Decreased treatment response and increased resistance in patients with lamivudine resistance |
| Nucleoside       | Telbivudine       | • Oral administration  
• Well tolerated safety profile  
• High potency in lowering HBV DNA  
• Pregnancy category B | • Risk profile includes myopathy and peripheral neuropathy  
• Intermediate resistant mutation |
| Nucleotide       | Adefovir          | • Oral administration  
• Well tolerated safety profile  
• Studied in patients with end-stage liver disease | • Relatively lower potency  
• Relatively higher rate of resistance mutations  
• Nephrotoxicity |
| Nucleotide       | Tenofovir         | • Oral administration  
• More effective than adefovir  
• Low rate of resistance mutations  
• Studied in HIV-coinfection  
• Pregnancy category B | • Risk of nephrotoxicity in HIV-coinfection |

Adapted from reference 17.
among HBeAg-positive patients [40,41]. Unlike lamivudine, adeflovir has good durability of response, with over 90% of patients sustaining HBeAg seroconversion [22,42]. However, development of resistance mutations also complicates adeflovir therapy, with resistance rates of 0%, 3%, 18%, and 29% reported after 1, 2, 4, and 5 years of therapy, respectively [43]. While adeflovir is still available in the treatment armamentarium for CHB patients, its use is declining, and it is gradually being replaced by a newer, more efficacious nucleoside analog, tenofovir.

Entecavir
Entecavir is a potent nucleoside analog that was approved for the treatment of CHB in 2005. Compared with lamivudine, entecavir demonstrated superiority in achieving virologic response, histologic improvement, and normalization of serum ALT. Among patients treated with entecavir, undetectable HBV DNA persisted among 94% of patients treated for 5 years, and high rates of histologic improvement (96%) was seen after 6 years of therapy, even among patients with cirrhosis [44,45].

Compared to adeflovir, entecavir has also demonstrated superiority in achieving viral suppression. After 48 weeks of entecavir therapy compared with adeflovir, patients treated with entecavir demonstrated higher rates of HBV DNA clearance (58% vs. 19%) and ALT normalization (76% vs. 63%), but rates of HBeAg seroconversion were similar (15% vs. 22%) [46]. HBsAg loss, while rare, has been reported in entecavir-treated patients, with 1.7% of patients in one study achieving HBsAg loss after 48 weeks of therapy [47].

Compared with lamivudine and adeflovir, entecavir has a relatively higher genetic barrier to development of resistance. Among nucleoside-naive patients, the rate of resistance remained at 1.2% after 6 years of entecavir therapy [47]. However, among the cohort of lamivudine treatment-refractory patients, the rate of resistance is much higher at 57% after 6 years of therapy [47].

Telbivudine
Telbivudine is a newer oral nucleoside analog that demonstrated superiority when compared with lamivudine. In a randomized phase 3 study comparing telbivudine with lamivudine, the 1-year rate of HBeAg seroconversion associated with telbivudine therapy was 22% and HBV DNA viral suppression was 60%; at 2 years, HBeAg seroconversion was achieved in 30% and viral suppression in 56% [48,49]. The rate of HBsAg loss was comparable to that reported among patients treated with lamivudine therapy [50]. Despite its superior efficacy, telbivudine therapy is also complicated by development of resistance, with resistance rates up to 21.6% after 2 years of therapy among HBeAg-positive patients [26].

Similar to the interferon treatment index, comprehensive analysis of patients undergoing therapy with telbivudine has determined certain baseline pretreatment characteristics to help predict outcomes [50]. Among HBeAg-positive patients, serum HBV DNA < 9log10 copies/mL or ALT > 2 times ULN at baseline along with undetectable HBV DNA at 24 weeks were the strongest predictors of a favorable treatment response. Among HBeAg-negative patients, baseline HBV DNA < 7log10 copies/mL and undetectable HBV DNA at 24 weeks were predictors of favorable treatment response. Adhering to these parameters for selecting ideal telbivudine treatment candidates is associated with significantly lower rates of resistance.

One additional advantage of telbivudine compared with other nucleoside regimens is its more favorable pregnancy category B safety rating. One large study in China included 229 HBeAg+ mothers, comparing 135 women who were started on telbivudine during weeks 22–32 of gestation and continued through 4 weeks postpartum, and 94 controls who did not receive any antiviral therapy [51]. All infants received hepatitis B immune globulin (HBIG) within 12 hours postpartum and HBV vaccinations at 0, 1-, and 6-month intervals. Mothers in the telbivudine treatment arm had higher rates of undetectable HBV DNA at time of delivery (33% vs. 0%) and higher rates of ALT normalization (83% vs. 57%). Furthermore, there were no significant differences in the occurrence of adverse events between the telbivudine group and the control group among both mothers and infants.

Tenofovir
Approved by the FDA in 2008, tenofovir is the most recent oral nucleotide analog introduced for the treatment of CHB. Tenofovir has replaced adeflovir in clinical practice due to its superior efficacy profile along with low reported rates of resistance. Two double-blind randomized phase 3 trials compared 48 weeks of tenofovir therapy with adeflovir. Patients among the tenofovir group demonstrated higher rates of viral suppression (76% vs. 15%), normalization of serum ALT (68% vs. 54%), histologic improvement (67% vs. 12%), and HBsAg loss (3.2% vs. 0%) [52]. Durability of treatment response was also supe-
rior to adeofovir with sustained viral suppression among 99% to 100% of patients after 4 years of therapy [53,54]. Furthermore HBeAg loss was reported among 41% of patients. Patients with HBV genotype A or D, pretreatment HBV DNA > 9log10 copies/mL, and baseline histologic activity index (Knodell score) > 9 had higher likelihood of achieving HBsAg loss [54].

In addition to the superior efficacy in achieving viral suppression, another major advantage of tenofovir is the low rate of resistance. Recent 5-year data presented at the AASLD annual scientific meeting reported no evidence of resistance up to 5 years of therapy [55].

Like telbivudine, tenofovir also holds a pregnancy category B safety rating, and many of the studies evaluating its safety profile include both HIV and HBV patient cohorts. A recent large study utilizing data from the Antiretroviral Pregnancy Registry (APR) included over 13,000 patients that were treated with antiviral therapy during pregnancy. The overall prevalence of birth defects among those treated with antiviral therapy was no different from the rate among population-based controls (2.8% vs. 2.7%). The prevalence of birth defects among patients treated with tenofovir was also similar to population-based controls (2.2% vs. 2.7%) [56].

Case Continued

After reviewing the potential advantages and disadvantages of the different treatment regimens, the patient was started on tenofovir 300 mg orally daily. The importance of close follow-up to monitor her biochemistry profile as well as to ensure she tolerates the medication well was emphasized to the patient.

- What are the endpoints of antiviral therapy for CHB?
- What is the risk of developing drug resistance and how is drug resistance managed?

Endpoints of Therapy

The overall goal of therapy among patients treated for CHB is suppression of HBV DNA and preventing the development of complications associated with the sequelae of CHB. In addition to specific parameters such as HBeAg loss and HBsAg loss, Table 5 defines common terminology utilized in discussing response to therapy.

<table>
<thead>
<tr>
<th>Table 5. Categories of Response to CHB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical response</td>
</tr>
<tr>
<td>Virologic response</td>
</tr>
<tr>
<td>Primary nonresponder</td>
</tr>
<tr>
<td>Histologic response</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
</tbody>
</table>

Adapted from reference 2.

While certain endpoints such as HBsAg loss are rare and difficult to achieve, persistent suppression of viral DNA has been shown to be associated with decreased risk of progression to cirrhosis and HCC [11]. However, the development of resistance is a major barrier to maintaining treatment response. Among the nucleoside and nucleotide analogs, lamivudine has the lowest genetic barrier to resistance, and thus demonstrates the highest rates of HBV drug resistance. Adefovir and telbivudine have intermediate barriers to resistance, while entecavir and tenofovir have higher genetic barriers to resistance. With tenofovir as a notable exception so far, all other remaining non–interferon-based therapies demonstrate incrementally increasing rates of resistance over time (Figure 2).

Management of Drug Resistance

The approach to managing drug resistance in CHB relies on accurate assessment of biochemical profile and virus characteristics. The first manifestation of resistance is the development of virological breakthrough (VBT). VBT is defined as an increase in serum HBV DNA > 1log10 from nadir or re-detection of HBV DNA at levels > 10 times the lower limit of detection after previously achieving undetectable DNA. Persistence of VBT for 1 to 3 months is necessary for confirmation of breakthrough [57]. Biochemical breakthrough (BBT) is defined as elevations in ALT while on therapy in patients that have previously achieved normalization of ALT [22]. Generally VBT precedes development of
BBT, and early detection of VBT is important to help guide changes in antiviral therapy in hopes of preventing HBV flare or other complications. When first evaluating individuals presenting with signs of breakthrough, assessing for medication nonadherence should be performed, as up to 38% of VBT has been attributed to nonadherence [57].

Once drug resistance has been confirmed, the subsequent approach to therapy has been outlined by AASLD and EASL [2,21]. Individuals who have developed resistance while undergoing therapy with lamivudine or telbivudine can be salvaged with the addition of adefovir or tenofovir [2,58-60]. Another approach that has been studied is stopping lamivudine completely and switching to tenofovir/emtricitabine (Truvada) [2]. Entecavir is not currently recommended in lamivudine-refractory patients given the findings of increased rates of resistance to entecavir development among this population.

Adefovir resistance can be salvaged with the addition of lamivudine, telbivudine, or entecavir [2]. AASLD guidelines recommend replacing adefovir with tenofovir monotherapy or combining tenofovir with emtricitabine or lamivudine [2]. EASL guidelines recommend completely stopping adefovir and switching to tenofovir combined with another drug without cross resistance [21]. Among patients with prior lamivudine resistance, Truvada or tenofovir plus entecavir should be utilized [21]. Table 6 highlights the general approach to managing drug resistance according to AASLD and EASL guidelines.

**Case Resolution**

After starting tenofovir therapy, the patient continued to follow up closely with her hepatologist. She tolerated the medication well without any side effects reported. At 24 weeks of therapy, the serum HBV DNA decreased to undetectable range, and her ALT completely normalized. One year after starting tenofovir therapy, the patient continues to do well. Her HBV DNA remains
undetectable and her liver enzymes remain normal. At 1 year, she continues to have positive HBsAg.

SUMMARY

Chronic hepatitis B is a worldwide epidemic associated with significant health consequences including progressive liver damage, cirrhosis, and development of HCC. While the institution of universal screening and vaccination programs in many regions has resulted in dramatic declines in the incidence and prevalence of CHB, the burden of disease among those individuals with pre-existing CHB continues unabated. The goal of therapy is effective viral suppression and prevention of complications that develop as a result of inadequately treated disease. Given the increased rate of HBsAg seroconversion with prolonged use of oral agents such as tenofovir and entecavir, the future will tell whether such seroconversion rate will approach the HBsAg seroconversion rate seen with interferon-based therapy. Our current treatment armamentarium for CHB holds great promise for continued success at viral suppression, with newer drugs on the horizon. Despite the success of current treatment regimens, viral suppression or even HBsAg loss does not eliminate the potential to develop HCC, and patients remain at increased risk of HCC. As such, close monitoring of patients along with HCC screening remains an important part of follow-up care.

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