DIAGNOSTIC AND THERAPEUTIC ADVANCES IN HEPATOLOGY

Drug Therapy: Tenofovir

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Patient Scenario

A 52-year-old woman who is in otherwise excellent health is evaluated for liver test abnormalities. Her aspartate aminotransferase and alanine aminotransferase levels are 130 U/L and 142 U/L, respectively, and her alkaline phosphatase, bilirubin, albumin, and creatinine levels are normal. Her body mass index is 25.5 kg/m^2, and physical examination is unremarkable. Serological test results are as follows: hepatitis B surface antigen–positive, immunoglobulin G hepatitis B core antibody–positive, hepatitis B surface antibody–negative, hepatitis B e antigen–negative, anti–hepatitis B e antibody–positive, and a hepatitis B virus DNA count of 2.4 million IU/mL. Test results for hepatitis C, human immunodeficiency virus, and delta hepatitis are negative. Although a liver biopsy was not performed, there is no clinical, laboratory, or radiographical evidence of cirrhosis. **What is the role of tenofovir in this patient?**

The Problem: Antiviral Therapy for Hepatitis B. When to Start? Which Drugs?

An increased number of efficacious and safe treatment options has broadened the indications for the treatment of hepatitis B. Treatment is clearly indicated in patients with life-threatening liver disease (such as acute liver failure, decompensated cirrhosis, or severe flare of hepatitis) and in those with compensated cirrhosis and high levels of serum hepatitis B virus (HBV) DNA. For patients with precirrhotic liver disease, the decision to start treatment is usually based on biochemical or histological evidence of active or advanced liver disease: elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) or moderate-severe inflammation (Metavir activity score $\geq$A2 or histological activity index $\geq$7) or fibrosis (Metavir fibrosis score $\geq$F2 or Ishak fibrosis score $\geq$3), in the presence of high levels of serum HBV DNA. Because liver biopsies are not performed on all patients in clinical practice, indications for hepatitis B treatment have relied primarily on ALT and HBV DNA levels.

Antiviral therapy is recommended for hepatitis B e antigen (HBeAg)-positive patients who have ALT levels that fluctuate or are persistently >2 times the upper limit of normal and who remain HBeAg-positive after 3-6 months of observation (to determine if they might undergo spontaneous HBeAg seroconversion).[1-3] A threshold serum HBV DNA level has not been included in some guidelines because the vast majority of HBeAg-positive patients have very high HBV DNA levels (>9 log IU/mL). Antiviral therapy is also recommended for patients with normal or slightly elevated ALT levels if there is histological evidence of significant liver disease, or if the patient remains HBeAg-positive beyond the age of 40 years. Although large population-based studies have shown that high serum HBV DNA is associated with adverse outcomes, antiviral therapy is not recommended for young HBeAg-positive patients with persistently normal ALT (immune tolerance phase) because response rates are lower in these patients,[4,5] and it is possible that some of them will undergo spontaneous HBeAg seroconversion in the ensuing years.

Antiviral therapy is recommended for HBeAg-negative patients who have ALT levels that fluctuate or are persistently >2 times the upper limit of normal and have a serum HBV DNA count of >20,000 IU/mL.[1-3] Lower ALT and HBV DNA cutoffs should be used in older patients and in patients with histological evidence of significant liver disease. Fluctuations in ALT and HBV DNA are common in HBeAg-negative patients; therefore, patients who have normal ALT and low or undetectable HBV DNA at presentation should be closely monitored for at least 12 months to determine if they are in an inactive carrier state or if they have HBeAg-negative hepatitis.

The key decision regarding choice of treatment is whether to use interferon (IFN) or a nucleos(t)ide

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IFN, interferon.

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analog. The advantages of IFN include a finite duration of treatment, a higher rate of hepatitis B surface antigen (HBsAg) loss, and lack of drug resistance mutations. The disadvantages of IFN include need for parenteral administration and frequent adverse effects. It should be emphasized that although IFN is administered for a finite duration, only 25%-35% of HBeAg-positive patients have sustained HBeAg seroconversion[6] and 13%-18% of HBeAg-negative patients have sustained viral suppression during posttreatment follow-up of up to 3-5 years.[7] Furthermore, a higher rate of HBsAg loss is observed mainly in HBeAg-positive patients with genotype A infection.[6] The advantages of nucleos(t)ide analogs include oral administration and infrequent adverse effects. A major advantage of nucleos(t)ide analogs is that they can be administered safely in patients with decompensated liver disease, although a recent case report found that lactic acidosis can occur in patients with severe liver failure.[8] The main disadvantage of nucleos(t)ide analogs is the need for long duration and often lifelong treatment to maintain viral suppression. Unlike IFN, nucleos(t)ide analogs lack immune modulatory activities and have no direct effect on clearance of infected hepatocytes or covalently closed circular DNA. This accounts for the high rate of viral relapse when treatment is stopped. Another disadvantage of nucleos(t)ide analogs is drug resistance, although this problem has been greatly diminished with the availability of newer drugs such as entecavir and tenofovir, which have high genetic barriers to resistance.

The choice of antiviral therapy should be made jointly between the physician and the patient. Young patients with precirrhotic liver disease who are reluctant to commit to many years of treatment and have no contraindications to IFN treatment should be encouraged to try IFN, particularly if they are HBeAg-positive with high ALT and low HBV DNA levels or have genotype A infection.[9] IFN should also be considered in young women who plan to start a family in the next few years. Older patients, those with decompensated liver disease, and those with contraindications to IFN therapy should receive nucleos(t)ide analog therapy. Of the five approved nucleos(t)ide analogs, only entecavir and tenofovir meet the criteria for an ideal first-line drug owing to their potent antiviral activity, low risk of antiviral resistance, and good safety profile.

The choice between entecavir and tenofovir depends on patient characteristics and safety profile (Table 1). Tenofovir is active against lamivudine-, telbivudine-, and entecavir- resistant HBV, and is partially active against adefovir-resistant HBV. Entecavir is active against adefovir- and tenofovir- resistant HBV. It is also active against lamivudine- and telbivudine- resistant HBV, but a higher dose is required and the risk of subsequent entecavir resistance is high (51% after 5 years).[10] Tenofovir is a class B drug regarding safety in pregnancy, and data on approximately 800 infants born to women with human immunodeficiency virus (HIV) and HBV coinfection did not reveal any increased risk of birth defects.[11] Entecavir, on the other hand, is a class C drug, and safety data in human pregnancies are limited. Tenofovir is associated with a small risk of nephrotoxicity ranging from decrease renal clearance to renal tubular defects, including Fanconi anemia.[12,13] Tenofovir has also been reported to be associated with decreased bone mineral density in patients with HIV and HBV coinfection.[14] Entecavir in doses severalfold higher than that used in humans was associated with higher rates of tumors in the brain, lungs, and liver in rodents.[15] To date, there is no evidence that entecavir increases the risk of neoplasms in humans. Tenofovir may be administered with or without food, whereas entecavir should be administered on an empty stomach.

Although tenofovir and entecavir are both ideal first-line drugs, tenofovir is preferred in patients who have received lamivudine previously, in young women

Table 1. Comparison of Entecavir and Tenofovir

	Entecavir	Tenofovir
Antiviral activity		
Wild-type HBV	Yes	Yes
Lamivudine/telbivudine-resistant HBV	Decreased activity	Yes
Entecavir-resistant HBV	–	Yes
Adefovir-resistant HBV	Yes	Decreased activity
Tenofovir-resistant HBV	Yes	–
Virological response, week 48-52		
HBeAg+ patients		
Log decrease in HBV DNA	6.9	6.2
HBeAg seroconversion	21%	21%
HBsAg loss	2%	3%
HBeAg– patients		
Log decrease in HBV DNA	5.0	4.6
HBsAg loss	<1%	0%
Genotypic resistance		
Nucleoside-naïve patients	1.2% (year 5)	0% (year 3)
Lamivudine-experienced patients	51% (year 5)	Not available
Adverse effects	None	Nephrotoxicity, decreased bone mineral density
Safety in pregnancy	Class C	Class B
Dosage		
Nucleoside-naïve patients	0.5 mg/day	300 mg/day
Nucleos(t)ide-experienced patients	1.0 mg/day	300 mg/day

who plan to start a family in the next few years, and in patients who want more flexibility with regard to the time of day at which they take their medicine; entecavir is preferred in older patients and in patients with other medical conditions that increase the risk of renal failure.

Tenofovir

Tenofovir is administered as the prodrug tenofovir disoproxil fumarate (9-[(R)-2-(phosphonomethoxy)-prophy]adenin, or PMPA), a nucleotide that is phosphorylated to PMPApp. PMPApp works as a chain terminator if incorporated into the DNA chain and is a competitive inhibitor of natural deoxyadenosine 5′-triphosphate. After oral administration, tenofovir disoproxil fumarate is converted to tenofovir by plasma esterases. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion.

A dose ranging study in HIV-1–infected patients revealed that a 300-mg dose of tenofovir was optimal. Dose ranging studies have not been performed in patients with HBV infection. The dosage approved for treatment of both nucleos(t)ide-naïve and nucleos (t)ide-experienced HBV patients is 300 mg/day. Dose adjustments should be made in patients with renal impairment to achieve optimal plasma exposure (Table 2); however, data on the efficacy of these dose regimens in suppressing HBV replication are not available.

In vitro studies have shown that tenofovir and adefovir have similar antiviral activity on a molar basis. This finding explains why tenofovir administered in 300-mg doses is more effective in suppressing HBV replication than 10-mg doses of adefovir in clinical practice. The mutations associated with primary resistance to tenofovir have not been clearly defined. No confirmed tenofovir resistance after up to 3 years of treatment has been reported in phase III trials,[16] but it should be emphasized that the study design in these trials allowed for the addition of emtricitabine at week 72 in patients who still had detectable serum HBV DNA. Therefore, the rate of resistance during tenofovir monotherapy beyond week 72 is unknown. An alanine to threonine substitution at position 194 (rtA194T) has been reported to be associated with tenofovir resistance.[17] HBV variants with rtA194T mutation remain susceptible to entecavir.[18] *In vitro* studies have found that susceptibility of HBV isolates with adefovir resistance mutations, alanine to valine or alanine substitution at position 181 (rtA181V/T) or asparagine to threonine substitution at position 236 (rtN236T), to tenofovir is decreased by three- to four-fold.[19] Clinical studies have confirmed that tenofovir is less effective in suppressing HBV replication in patients with adefovir resistance than in nucleos(t)ide-naïve patients.[20]

Table 2. Dose Adjustment of Tenofovir in Patients With Altered Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended 300-mg Dosing Interval
≥50	Every 24 hours
30-49	Every 48 hours
10-29	Every 72-96 hours
<10 and not on dialysis	Not available
Hemodialysis patients	Every 7 days or after a total of 12 hours of dialysis

Tenofovir is more efficacious than adefovir in patients with lamivudine or telbivudine resistance. Whereas "add-on" therapy was recommended when adefovir was used as rescue therapy, preliminary data suggest that "switch-to" therapy may suffice when tenofovir is used as rescue therapy.[20] Patients with suboptimal viral suppression during adefovir therapy and no confirmed drug resistance will also benefit from switching to tenofovir, but tenofovir is not an optimal rescue therapy for those with confirmed adefovir resistance. In vitro data suggest that tenofovir is effective in the management of patients with entecavir resistance, but clinical data are limited. It is unclear whether tenofovir should be added to or substituted for entecavir. For patients with prior lamivudine resistance and subsequent entecavir resistance, it might be more appropriate to add tenofovir.

Tenofovir is available as a monotherapeutic agent (Viread) or in combination with emtricitabine (Truvada). The combination pill makes it more convenient for patients who require tenofovir plus a nucleoside, as in the case of patients who have acquired resistance to sequential monotherapy with lamivudine and then adefovir.

Monitoring for Response and Drug-Related Adverse Effects

Patients receiving tenofovir should be tested for serum HBV DNA every 3 months to assess virological response and to detect virological breakthrough. Frequency of HBV DNA testing may be decreased to every 6 months after serum HBV DNA has become undetectable. Patients with virological breakthrough should be counseled regarding the importance of medication adherence. Confirmation of genotypic resistance should be performed whenever possible before treatment is modified. Because signature resistance

mutations have not been established, interpretation of the sequencing result can be problematic when pretreatment sequences are not available for comparison and *in vitro* susceptibility assays are not feasible.

In patients who were HBeAg-positive at the start of treatment, HBeAg and HBe antibody should be tested every 6 months to document HBeAg seroconversion. In patients who were HBeAg-negative at the start of treatment, HBsAg should be tested annually to document HBsAg loss. Treatment may be discontinued in HBeAg-positive patients who have confirmed HBeAg seroconversion and who have completed 12 months of consolidation therapy as well as in HBeAg-negative patients who have confirmed HBsAg loss.

Serum chemistries including creatinine and phosphorus should be monitored every 6 months. Monitoring may be more frequent in patients with impaired baseline renal function or other medical conditions that increase the risk of renal failure.

Areas of Uncertainty

Since the approval of tenofovir for the treatment of hepatitis B in 2008, much has been learned about its efficacy in various settings; however, there are still areas of uncertainty. Would combination therapy of tenofovir and IFN or a nucleoside be superior to tenofovir monotherapy? Available data suggest that combination therapy is unlikely to improve viral suppression or to decrease drug resistance for nucleoside-naïve patients. It is also unclear whether addition of IFN will improve immune control and increase the rate of HBsAg loss. Case series suggest that tenofovir monotherapy may suffice in patients with lamivudine-, telbivudine-, or entecavir- resistance, but longer follow-up is needed to determine the risk of subsequent tenofovir resistance. Data from the Antiretroviral Registry suggest that tenofovir is safe even when administered during the first trimester of pregnancy, but it remains unclear whether tenofovir increases the risk of miscarriage and whether tenofovir in lactating mothers will have any adverse effect on the growth and development of the infant. Given the potential for nephrotoxicity, the long-term safety of tenofovir needs to be clarified, particularly for transplant recipients receiving concomitant calcineurin inhibitors. Furthermore, the recent report of entecavir-associated lactic acidosis in patients with severe liver failure may be a class effect, and further study is needed to clarify the safety of tenofovir in liver transplant recipients and in patients with acute liver failure or decompensated cirrhosis.

Recommendations

The patient described in this scenario should be started on antiviral treatment. It is likely that she has been infected with HBV for more than five decades, and her serum HBV DNA level is very high. Furthermore, her elevated AST and ALT levels indicate that she has HBeAg-negative hepatitis. Because she is in otherwise excellent health and has no evidence of cirrhosis, she is a candidate for pegylated IFN, entecavir, or tenofovir. Any of these first-line therapies would be appropriate depending on the patient's preference. If the patient opts for IFN, treatment will be administered for 1 year. Recent data suggest that monitoring serum HBsAg titer may be more accurate than monitoring serum HBV DNA in predicting long-term viral suppression and may be considered if this test is available. If the patient chooses entecavir or tenofovir, treatment will be administered until she becomes HBsAg-negative, which will likely take many years if it were to occur. Regardless of the choice of treatment, this patient should be monitored for virological response and adverse events, and HCC surveillance should also be performed.

Note: Tenofovir is marketed in the United States as Viread (Gilead Sciences). The combination of emtricitabine (200 mg) and tenofovir (300 mg) is marketed as Truvada (Gilead Sciences). Entacavir is marketed as Baraclude (Bristol-Myers Squibb) and comes in 0.5 mg and 1 mg tablets. The costs for a 30-day supply are: Viread (300 mg), US $853; Truvada, US $1,319; and Baraclude (0.5 mg and 1 mg), US $941. The Baraclude tablets are triangular in shape and are not scored, making it difficult to split them without the use of a pill cutter.

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