HIV and Hepatitis B Virus Coinfection: Approach to Management

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Abstract

• **Objective:** To review diagnosis and treatment in patients with HIV and hepatitis B virus (HBV) coinfection.
• **Methods:** Review of the literature in the context of a clinical case.
• **Results:** All patients with HIV should be screened for the presence of coinfection with HBV. Following diagnosis with HBV infection, the level of HBV activity should be assessed with testing for HBeAg, HBV DNA, and potentially a biopsy for staging the degree of fibrosis present. Based on the results of this workup, a decision regarding the role of anti-hepatitis treatment should be made. According to the latest chronic hepatitis B and HIV treatment guidelines, coinfected patients who require treatment for chronic hepatitis B should be started on a regimen that is fully active against both HIV and HBV. A first-line regimen for coinfected patients is generally composed of tenofovir and emtricitabine, plus one other agent active against HIV. In coinfected patients, durable responses are rare, and therefore patients are usually required to remain on therapy indefinitely.
• **Conclusion:** Intensification of surveillance techniques and education programs should be developed to help prevent transmission of infection and integrate coinfected patients into the health care system. Once engaged in care, coinfected patients should receive treatment for both HIV and chronic hepatitis B with the goal of a decrease in liver failure, cirrhosis, hepatocellular carcinoma, and chronic hepatitis B–related mortality.

CASE STUDY

Initial Presentation

A 37-year-old Hispanic man with HIV presents to his new physician for evaluation of his chronic hepatitis B virus (HBV) infection.

History

The patient has been on antiretroviral therapy (ART) for 6 months, which consists of tenofovir, emtricitabine, and efavirenz. He has a CD4 lymphocyte count of 277 (19%) cells/mm³ and an HIV viral load of 66 copies/mL. HIV was diagnosed 19 years ago, with a risk factor of intravenous drug use. He had last used IV heroin 3 months prior to this visit despite completion of a 28-day inpatient drug rehabilitation program 2 years ago. He is originally from Puerto Rico and moved to the United States 3 years ago. He denies any current alcohol intake or tobacco use. The patient’s self-reported nadir CD4 is 110 cells/mm³ and there is no history of any opportunistic infections. Per patient report, the only ART prior to his current regimen was zidovudine for 2 weeks when first diagnosed.

It is unclear when the patient was diagnosed with HBV infection; per patient report, he never received anti-HBV active therapy until 6 months prior when HIV medication was started. Hepatitis B surface antigen (HBsAg) is positive, hepatitis B surface antibody (HBsAb) is negative, hepatitis B core antibody (HBCab) is positive, hepatitis B e antigen (HBeAg) is positive. Laboratory findings are consistent with chronic HBV infection (Table 1).

The patient was hospitalized 2 weeks prior to this visit for abdominal pain and anasarca. The patient was diagnosed at that time with mild portal-systemic encephalopathy (PSE) but had no history of spontaneous bacterial peritonitis. An esophagogastroduodenoscopy (EGD) had been completed during this hospitalization and he was found to have grade 1 esophageal varices, fundic varices, portal hypertensive gastropathy and duodenitis; the patient was placed on nadolol. A paracentesis was not performed secondary to minimal fluid. At this time the patient also began taking lactulose for PSE, as well as furosemide and spironolactone for ascites and edema.

The patient’s past medical history is significant for hepatitis C viral infection with spontaneous clearance of viremia. His most recent review of systems was positive for epistaxis,
cough, nasal congestion, right upper quadrant abdominal pain, nausea, lower extremity and scrotal pain and swelling; he denied hematemesis, melena, hematochezia, increased abdominal girth, back pain, vomiting, and diarrhea.

Physical Examination
On examination, the patient is somewhat disheveled but pleasant, alert, and oriented. He is in no distress and his vital signs are within normal limits. His sclera are anicteric and his skin is not jaundiced. The heart has a regular rate and rhythm, and lungs are clear to auscultation bilaterally. He has normal bowel sounds, his abdomen is diffusely tender but worse in the right upper quadrant, with guarding but no rebound and no Murphy’s sign; he has minimal ascites. He has 3+ bilateral lower extremity pitting edema; there are no spider angiomas, no palmar erythema, and no asterixis.

Initial Treatment
The patient is continued on his ART. He is also counseled on adherence to therapy given the risk of HIV and HBV virologic rebound as well as hepatic decompensation and failure if he were to discontinue chronic HBV medications.

- What factors placed the patient at risk for hepatitis B infection?
- What is the relationship between his HIV-positive status and chronic hepatitis B?

Epidemiology
HBV chronically infects 350 million people worldwide [1], including over 1 million Americans [2]. HBV is primarily transmitted perinatally, through sexual activity, and via percutaneous contact with infected blood [3]. The virus exhibits wide geographic variability based on the regional dominant mode of transmission: the risk of developing chronic hepatitis B after exposure ranges from 90% in infants infected via vertical transmission to less than 5% in immunocompetent adults [4]. Therefore, in areas where vertical transmission predominates the prevalence of chronic disease is significantly greater than in areas in which HBV is transmitted among adults primarily through sex and intravenous drug use. In the United States, where vaccination rates are high, important high-risk groups are immigrants from endemic countries with high prevalence rates of HBV, such as Asia and Africa, and the immunosuppressed. The HIV-positive population is thus at particular risk of chronic infection, and an estimated 6% to 14% of persons infected with HIV are coinfected with chronic HBV in Western Europe and the United States [5]. Given the high prevalence of coinfection in HIV-infected persons, all patients with HIV should be screened for hepatitis B and vaccinated if they are neither infected nor immune.

An estimated 1.25 million people in the United States meet the definition of hepatitis B carrier state: these patients remain positive for HBsAg for greater than 6 months [6]. The majority of HBV carriers do not progress to complicated liver disease as a result of infection; however, approximately 15% to 40% will develop sequelae of the disease, including cirrhosis, liver decompensation, and hepatocellular carcinoma [6]. Complications are more frequent in those who are coinfected with HIV [7].

HIV and Hepatitis B Coinfection
Due to the shared risk factors for transmission, HBV commonly infects HIV-positive patients and results in an increased risk of progressive liver disease in the immunosuppressed. In the United States, approximately 60,000 people are coinfected with HIV and HBV [8], with the highest rates of coinfection found in intravenous drug users and men who have sex with men, especially those older and not previously vaccinated. The presence of HIV infection places patients at increased risk for development of chronic HBV when acutely infected; approximately 20% of HIV-positive
adults develop chronic HBV following horizontal exposure to the virus [9] versus approximately 4% of immunocompetent persons [10]. HIV-positive patients are less likely to spontaneously convert from HBsAg positive to negative and HBeAg positive to anti-HBeAg, both serologic markers of resolving infection [7]. Finally, chronic HIV-HBV coinfected patients tend to sustain higher levels of HBV DNA in the serum and are at higher risk of complications of chronic liver disease, including cirrhosis and death [11].

- What is known regarding the natural history of chronic hepatitis B?

**Definitions**

In order to understand the pathophysiology and treatment of chronic HBV, certain definitions and features of the virus should be outlined. Hepatitis B is a DNA virus containing several viral proteins that are clinically significant: the envelope protein (hepatitis B surface antigen), a nucleocapsid core protein (hepatitis B core antigen), and a soluble nucleocapsid protein (hepatitis B e antigen) [4]. Chronic HBV infection is currently defined by the American Association for the Study of Liver Diseases (AASLD) as the process of chronic necroinflammatory hepatic disease caused by persistent infection with HBV [6]. Chronic HBV is further divided into hepatitis B e antigen–positive and e antigen–negative chronic HBV. Following the initial development of chronic HBV infection, serum HBV DNA levels rise and HBeAg is present. This is usually followed by loss of HBeAg and the development of antibody to HBeAg (anti-HBe) in those who become inactive carriers [6]. The absence of HBeAg is also exhibited by a subset of patients with active chronic infection, described in detail below (Figure 1).

The AASLD [6] uses the following diagnostic criteria to distinguish chronic hepatitis B from an inactive HBsAg carrier state: (1) the persistence of HBsAg for greater than 6 months; (2) the presence of HBV DNA > 20,000 IU/mL (10⁵ copies/mL), though lower values can be seen in HBeAg-negative patients; (3) persistent or intermittent elevations in aminotransferase levels; and (4) liver biopsy demonstrating pathology consistent with moderate or severe necroinflammation. In contrast, patients who are in the inactive carrier state remain HBsAg-positive for greater than 6 months but maintain serum DNA levels of virus < 2000 IU/mL with normal ALT/AST and liver biopsy confirmation of no significant inflammation [6]. Of note, the AASLD's use of 20,000 IU/mL DNA is controversial, as some experts believe lower levels of DNA might suggest chronic active infection.

There are 8 known genotypes, A to H, of viral hepatitis B, distinguished by an 8% viral sequence divergence [12] (Figure 2). Genotype A is the predominant strain in Northern Europe, the United States, and parts of Africa and can be
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Further subdivided into A1, A2, and A3. Genotypes B and C are found most frequently in East Asia, and genotype C has been associated with an increased risk of hepatocellular carcinoma [13]. Genotype D is more common in the Mediterranean, and in Africa, genotype E is frequently found. Finally, genotype F is found in Central and South America, genotype G in France and the United States, and genotype H in North and Central America [12]. Recognition of these varying viral genotypes is clinically significant in that a range of susceptibility to antiviral agents has been cited based on genotype (see “Treatment Modalities”) [12].

The role of HBV genotypes in the course of infection and response to treatment in patients coinfected with HIV is still unclear and the subject of ongoing study.

Natural History

The natural history of chronic hepatitis B can be simplified through division into 5 phases, as described by the European Association for the Study of the Liver (EASL) in recently updated practice guidelines: immune tolerant, immune reactive, inactive hepatitis B carrier state, HBeAg-negative chronic hepatitis B, and HBsAg-negative [14]. Following infection with HBV, HBeAg is positive, reflecting high levels of HBV replication and HBV DNA. During this period of “immune tolerance,” little or no necroinflammation occurs and therefore ALT and AST remain normal (Figure 3). This period is characteristic of those perinatally infected or during early childhood and is a highly infectious period. In contrast, during the “immune reactive” phase of infection, liver enzymes rise and/or fluctuate, while hepatic inflammation and fibrosis occur and the level of replication falls. This period may last from weeks to years, and is more frequently associated with those infected as adults. Notably, during the period of immune reactivity the rate of spontaneous HBeAg loss increases [14].

The “inactive carrier” state is characterized by low levels of HBV DNA, and normal liver enzymes and may include seroconversion of HBeAg to anti-HBe (or HBeAb). This clinical picture is associated with a favorable prognosis, and in about 1% to 3% of cases per year it is accompanied by HBsAg loss and conversion to anti-HBs (or HBsAb) [14]. “HBeAg-negative” chronic hepatitis B refers to chronic infection following seroconversion or loss of HBeAg (sometimes with development of anti-HBe) and is characterized by periodic reactivation with a rise in HBV DNA levels, liver enzymes and hepatic inflammation. Patients with HBeAg-negative chronic hepatitis B are infected with an HBV variant with nucleotide substitution in the precore and/or basal core promoter region of the virus and are thus unable to express HBeAg (“precore mutant chronic hepatitis B”). It is crucial to separate these patients from those who are true “inactive carriers” (ie, patients who express hepatitis B surface antigen but never experience rises in HBV DNA beyond a low level nor exhibit abnormal liver enzymes); in contrast, HBeAg-negative chronic hepatitis B patients are at high risk of progression to fibrosis and advanced liver disease [14].
Finally, true loss of the HBsAg leads to the “HBsAg-negative” phase, during which HBV DNA is generally not detectable, anti-HBc is present, and ultimate development of HBsAb occurs. In occult HBV infection, HBsAg is lost, while low levels of HBV DNA persist in the serum; research into the clinical significance of this scenario is ongoing, and the prognosis is unclear, particularly among HIV-positive patients and other immunosuppressed populations [14].

- What should be included in the initial workup for chronic hepatitis B in the HIV coinfected patient?

Given the high prevalence of HBV coinfection among HIV-positive patients and the higher rates of advanced disease and mortality in coinfected patients, screening for HBV and vaccination if they are neither infected nor immune is imperative. A recent report released by the Institute of Medicine found that as many as 65% of patients infected with hepatitis B are unaware of their status, and many patients do not present to care until they develop symptoms of cirrhosis, liver failure, or cancer [2]. Therefore, the emphasis must be placed on the providers of at-risk populations to screen for HBV in order to diagnose it as early as possible. The tests used to screen for HBV include HBsAg and HBsAb, as previously mentioned; the presence of positive HBsAb indicates prior vaccination with associated immunity, or clearance of infection, while the presence of positive HBsAg indicates infection. A core antibody can also be used as screening, but if positive when sent alone must prompt an HBsAg and HBsAb to distinguish infection from clearance [6].

HBV DNA levels may also be sent to evaluate for occult HBV infection. Management of the isolated core antibody is the subject of ongoing investigation.

Once patients are diagnosed with HBV infection, the following tests should be performed: serum HBsAg, anti-HBc, serum hepatitis D antibodies (see below for further detail), and serum HBV DNA viral load [12] (Table 2).

Table 2. Evaluation of Patients with Chronic Hepatitis B Infection

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<td>Tests to screen for HCC</td>
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<td>AFP at baseline and, in high-risk patients, ultrasound</td>
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<tr>
<td>Consider biopsy to grade and stage liver disease in patients with chronic hepatitis</td>
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<td>HAV antibody to assess need for vaccination</td>
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Suggested follow-up for patients not considered for treatment

If HBeAg positive, HBV DNA > 20,000 IU/mL with normal ALT
  Check ALT q 3–6 mos; increase frequency if becomes elevated
  If ALT 1–2 x ULN: recheck q 1–3 mos; consider liver biopsy if age > 40, ALT borderline or minimally elevated on serial tests. Consider treatment if biopsy shows moderate/severe inflammation or significant fibrosis.
  If ALT < 1 x ULN for 3–6 mos, consider biopsy and treatment.
  Consider screening for HCC

Inactive HBsAg carrier state
  Check ALT q 3 mos for 1 year; if normal persistently check q 6–12 mos thereafter
  If ALT > 1–2 x ULN check serum HBV DNA and exclude other causes of liver disease
  Consider biopsy if ALT borderline or minimally elevated on serial measurements or HBV DNA persistently < 20,000 IU/mL
  Consider treatment if biopsy shows moderate/severe inflammation or significant fibrosis
  Consider screening for HCC

ALF = alpha fetoprotein; HCC = hepatocellular carcinoma; IVDU = intravenous drug use; ULN = upper limit of normal. (Adapted from reference 1.)

Hepatitis delta virus (HDV) is a defective virus, structurally similar to plant viruses, that is reliant on the HBsAg of HBV in order to infect humans and cause liver disease [18]. The virus can be contracted through coinfection with HBV or as a superinfection of HBV. Clinically, HDV results in an acute hepatitis, ranging from mild to fulminant, which is then usually cleared if contracted simultaneously with HBV or persists as a progressive hepatitis when contracted as a superinfection of chronic HBV [18]. It is important to note that although the virus needs the HBsAg to infect, it does not need the hepatitis B virus to remain pathogenic. Thus, in “inactive carriers” with no detectable HBV DNA and no necroinflammation, if coinfected with HDV, there can be progressive fibrosis. Although HDV is predominately found in the intravenous drug using population in the West, the CDC recommendation is to screen for HDV in all patients who are HBsAg-positive [19]. The most effective method of preventing HDV infection is HBV vaccination, as patients with anti-HBs are immune to the disease [18].

New noninvasive methods of testing have recently emerged as tools to help guide prognosis and therapy decisions. These include imaging, using elastometry, FibroScan, as well as biomarkers of fibrosis, such as AST-to-platelet ratio and the age-spleen-platelet ratio index [17]. These techniques are limited in the lack of data on their utility in HIV-HBV coinfected patients and their relative imprecision compared with biopsy to detect intermediate levels of fibrosis [12].

Other Coexisting Viral Infections

Hepatitis delta virus (HDV) is a defective virus, structurally similar to plant viruses, that is reliant on the HBsAg of HBV in order to infect humans and cause liver disease [18]. The virus can be contracted through coinfection with HBV or as a superinfection of HBV. Clinically, HDV results in an acute hepatitis, ranging from mild to fulminant, which is then usually cleared if contracted simultaneously with HBV or persists as a progressive hepatitis when contracted as a superinfection of chronic HBV [18]. It is important to note that although the virus needs the HBsAg to infect, it does not need the hepatitis B virus to remain pathogenic. Thus, in “inactive carriers” with no detectable HBV DNA and no necroinflammation, if coinfected with HDV, there can be progressive fibrosis. Although HDV is predominately found in the intravenous drug using population in the West, the CDC recommendation is to screen for HDV in all patients who are HBsAg-positive [19]. The most effective method of preventing HDV infection is HBV vaccination, as patients with anti-HBs are immune to the disease [18]. Current treatment options for chronic HDV, primarily interferon, have not been shown to be particularly effective and other modalities are under investigation.

Patient Workup

Initial workup for chronic hepatitis B in the patient included an HBV DNA of 2,900,000 IU/mL and an elevated alpha fetoprotein of 779 ng/mL. Significant laboratory abnormalities included platelets of 63 x 10^9/mL, a sodium level of 131 mEq/L, total bilirubin 1.6 mg/dL, direct bilirubin 0.7 mg/dL, AST 269 U/L, ALT 133 U/L, albumin 1.8 g/dL, INR 1.4 IU and creatinine 0.6 mg/dL. He was classified as Child-Pugh B (9 points) and his calculated MELD (model of end-stage liver disease) was 10 points. Hepatitis A and C antibodies were both reactive, and hepatitis C RNA was < 600 IU/mL, on several occasions. Hepatitis delta

If there is detectable HBV DNA, a genotype can be sent. Notably, these serologic and virologic tests are not available in resource-limited countries, unless they are sent as part of research. Patients should subsequently undergo testing to stage their level of fibrosis, via either invasive testing with a biopsy or noninvasively [12]. A liver biopsy is somewhat controversial and is recommended in a variety of clinical scenarios (see “Treatment Initiation”) but not universally.

Recommended indications for liver biopsy include staging the degree of fibrosis in patients with elevated ALT or HBV DNA > 20,000 IU/mL to help decide when to initiate treatment [1], in patients not responding to therapy, and in patients in whom other causes of liver disease need to be evaluated, such as steatosis or drug-induced hepatitis [16].

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antibody was negative. Schistosoma serology was negative; urinalysis was positive for trace protein, but spot urine protein-to-creatinine ratio revealed less than 0.25 grams.

Further chronic hepatitis B workup included a dual phase CT scan that showed a cirrhotic liver, along with mild to moderate central intrahepatic and extrahepatic biliary dilatation, without any obstructing lesion. Also found were ascites and splenomegaly. There was no mass.

A magnetic resonance cholangiogram was done to investigate the biliary dilatation and abdominal pain. The study showed moderate central intrahepatic and mild extrahepatic biliary ductal dilatation without any obstructing stone or mass.

- **Is the patient at risk for hepatocellular carcinoma, and what screening will he need in the future?**

Chronic infection with hepatitis B places our patient at risk for the development of hepatocellular carcinoma. This risk is higher in patients with prolonged periods of the “immune active” phase of infection, rather than those who remain “immune tolerant” or become inactive carriers [20]. Interestingly, patients with chronic hepatitis B may develop hepatocellular carcinoma without progression to cirrhosis, a more frequent phenomenon in younger patients [20]. The incidence of hepatocellular carcinoma among patients with chronic hepatitis B is variable, but the following are considered risk factors: infection with genotype C, family history of hepatocellular carcinoma, male sex, and older age [20]. Additionally, the risk for development of hepatocellular carcinoma remains high in Asian patients despite inactive viral replication and even loss of HBsAg [21]. Therefore, the AASLD recommends screening for hepatocellular carcinoma in HBV carriers with the following risks: Asian men over age 40, Asian women over age 50, persons with cirrhosis, Africans over age 20, and any HBV carrier over age 40 with persistent or intermittent ALT elevation and/or elevated HBV DNA > 2000 IU/mL [1].

- **Should this patient be treated for chronic hepatitis B?**

**Treatment Initiation: Chronic HBV**

The decision to initiate treatment in chronic hepatitis B can be complex and is based on an evolving body of clinical data. The goal of treatment is to suppress HBV replication in order to prevent the progression of chronic hepatitis to cirrhosis and decrease the risk of hepatocellular carcinoma and death [4, 22].

Updated recommendations on when to initiate therapy in chronic hepatitis B patients were published by the AASLD in 2007 [6]. The AASLD recommends that patients who remain HBeAg-positive with HBV DNA levels > 20,000 IU/mL after 3 to 6 months, with ALT 1 to 2 times the upper limit of normal (ULN) or with an age > 40 years should be biopsied and treatment considered if the biopsy shows moderate to severe inflammation or significant fibrosis. If the ALT levels are greater than twice the ULN in these patients, treatment should be considered regardless of biopsy [6]. In HBeAg-negative patients, ALT and HBV DNA should be followed closely, and if ALT is greater than twice the ULN with HBV DNA > 20,000 IU/ml persistently, these patients should be treated, with an optional biopsy beforehand. In HBeAg-negative patients, as in those HBeAg-positive, if the ALT is 1 to 2 times the ULN with HBV DNA levels 2 to 20,000 IU/mL, biopsy should be considered and then treatment decisions made based on biopsy results. HBeAg-negative patients in whom ALT levels remain < 1 time the ULN with HBV DNA < 2000 IU/mL should be monitored with ALT levels every 3 months times 3 then every 6 to 12 months [6] (Figure 4A and Figure 4B).

A notable exception to the treatment initiation algorithm outlined above is that of patients with chronic HBV who receive immunosuppression or chemotherapy. Patients with chronic hepatitis B, including those in the “inactive carrier” phase, are at risk for hepatitis flares and liver decompensation with therapy that suppresses the immune system [20]. These patients should therefore be initiated on antiviral treatment prior to immunosuppression and continued on it throughout the duration of immunosuppression [20]. The CDC recommends that all patients who are to receive immunosuppressive or cytotoxic therapy undergo screening for hepatitis B and identify those who will benefit from prophylactic antiviral therapy [19].

It has been noted that HIV-HBV coinfected patients tend to exhibit less elevation in aminotransferase levels, and therefore monitoring of HBV DNA levels is critical for these patients [12]. Recently there has been a shift toward emphasis on the importance of detectable HBV DNA levels rather than on abnormalities in aminotransferases for all patients with chronic hepatitis B. Many clinicians and investigators have advocated for treatment decisions based on HBV DNA rather than ALT and AST because the transaminases can demonstrate significant variability in chronic HBV and normal values can exist even in patients at substantial risk for cirrhosis and hepatocellular carcinoma [23]. Furthermore, transaminases reflect liver damage from a variety of conditions, and thus do not necessarily indicate damage specifically from HBV. Finally, clinicians argue that describing a cut-off point above which to begin treatment for chronic hepatitis B implies that low levels of HBV DNA
Hiv/Hbv Coinfection may be considered “safe” [23]. However, emerging data demonstrate that even low levels of HBV DNA lead to significant hepatocellular carcinoma risk: data presented at the 2008 EASL meeting showed that patients with HBV levels of 300 to 9999 copies/mL and ALT levels of 16 to 44 U/L were at significantly higher risk than the general population for hepatocellular carcinoma [24]. Recent research also supports treatment of patients with chronic hepatitis B in reducing the risk of hepatocellular carcinoma. Another study presented in abstract form at the EASL meeting in 2008 demonstrated that treatment with a nucleos(t)ide analogue or interferon, compared with controls, resulted in a significant decrease in development of hepatocellular carcinoma in patients with chronic HBV [24].

**Initiation of Treatment in HIV/HBV Coinfection**

In patients coinfected with HIV and HBV, the decision needs to be made regarding whether or not treatment is indicated for HIV, HBV, or both while considering the degree of liver disease present and potential adverse effects of therapy [12].

Figure 4. Management of chronic HBV infection in (A) HBeAg-positive patients and (B) HBeAg-negative patients. ULN = upper limit of normal. (Adapted from reference 1.)
In coinfected patients, chronic hepatitis B progresses more quickly to cirrhosis and end-stage liver disease, and the response to anti-HBV treatment is weakened by more severe immunodeficiency. For these reasons, all coinfected patients with evidence of viral HBV replication and elevated aminotransferases should be considered for treatment. Further, according to the recent U.S. Department of Health and Human Services guidelines on antiretroviral therapy, patients who require treatment for hepatitis B should be started on a regimen that is fully active against both HIV and HBV [25]. The use of a regimen containing only 1 anti-HBV agent (lamivudine, tenofovir, or emtricitabine) should be avoided given the risk of developing resistance. In the situation in which neither HIV nor chronic hepatitis B infection requires treatment, both infections should be monitored closely for progression [25]. If the situation arises in which the patient or provider cannot or does not wish to treat the HIV infection, HBV must be treated with an agent without activity against HIV to prevent monotherapy against HBV. In this scenario the safest drug to use would be pegylated interferon-alfa, which does not cause HIV or HBV resistance [25]. Of the available agents, lamivudine, tenofovir, and emtricitabine all have activity against HIV, and adefovir and entecavir may promote HIV resistance mutations [4]. Therefore, if anti-HBV treatment is indicated without HIV treatment, interferon is the drug of choice, though simultaneous anti-HBV and anti-HIV treatment is ideal [25]. This option is becoming less common as HIV treatment guidelines increasingly advocate for initiation of ART at higher CD4 levels: current U.S. Department of Health and Human Services guidelines [25] recommend considering ART initiation at up to 500 cells/mm³, especially if coinfected with HBV or HCV; the WHO ART guidelines [26] are now recommending ART once a patient has a CD4 ≤ 350 cells/mm³.

- What is the optimal treatment for our patient?

**Treatment Modalities**

According to the most recent guidelines for hepatitis B [1] and HIV [25], the recommendation in coinfected patients is to treat both chronic hepatitis B and HIV together, using 2 components of an ART regimen as agents with activity against both diseases and a third medication to complete the HIV regimen. Detailed descriptions of the medications with anti-HBV activity and their utility in co-infected patients will be discussed below. If one is treating both HBV and HIV, a first-line regimen is generally composed of tenofovir and emtricitabine plus another agent active against HIV, with a goal of having ≥ 3 active agents in an HIV regimen [14]. In the minority of patients in whom chronic hepatitis B is treated without treatment of the HIV, one must be careful to use only drugs that have no activity against HIV, namely interferon. Interferon must be used cautiously in patients with cirrhosis, as therapy can precipitate decompensation, and results in patients coinfected with HIV and HBV have not been as promising as in HBV-monoinfected patients [7]. Drugs with activity against HIV or that can promote HIV resistance, including lamivudine, entecavir, and tenofovir, cannot be used as monotherapy or even dual therapy for chronic hepatitis B as they may confer HIV resistance in coinfected patients if they are not used properly for HIV. In the case of adefovir, the risk of generating HIV resistance is largely theoretical and based on in vitro data [27]; however, this is considered a lower potency agent and therefore may not be selected as first-line therapy.

Drugs with antiviral activity that are currently approved to treat chronic hepatitis B include pegylated-interferon (pegIFN), lamivudine, adefovir, entecavir, telbivudine, emtricitabine (used in combination tablet), and tenofovir. Interferon was the first drug approved for the treatment of chronic hepatitis B and is administered now as pegIFN, which can be given less frequently. Evidence comparing these treatment modalities is continuously evolving, and the decision regarding which medication makes the most sense for a given patient must be made by the patient and provider [20].

**Interferon**

Interferon is effective through a combination of nonspecific antiviral, immunomodulatory and antiproliferative activities [6]. Interferon is particularly useful in patients with high ALT levels and low HBV DNA levels and is contraindicated in patients with advanced or decompensated cirrhosis [12]. Interferon has been associated with better responses in HBV genotype A and B patients than in C and D [14]. The drug is fairly effective in HBV mono-infected patients, with studies demonstrating normalization of transaminases and histologic improvement in about 40% of HBeAg-positive patients and similar rates of HBeAg-negative patients treated with weekly pegIFN after 48 weeks [6]. However, use of pegIFN in coinfected patients is limited by several factors: as IFN has very limited activity against HIV, it should be used only in patients who do not need antiretroviral therapy, or in addition to a fully suppressive HIV regimen or when the patient is HCV coinfected. Additionally, interferon has been associated with lower success rates and higher incidences of toxicity in coinfected patients [12].

The side effect profiles of standard and pegylated IFN are similar. The most common side effects are influenza-like symptoms, including fever, chills, malaise and myalgias, fatigue, anorexia, and weight loss. More serious side effects include depression, emotional lability, which can be severe,
myelosuppression, and thyroid disease, including both hyperthyroidism and hypothyroidism. Interferon therapy can cause hepatitis flares that, in patients with underlying cirrhosis, can precipitate hepatic decompensation [6].

**Lamivudine**

An oral cytosine analogue that is active against HBV and HIV, lamivudine (Epivir, 3TC) causes chain termination when incorporated into the DNA chain and thus inhibits DNA synthesis [6]. Though lamivudine has proven quite effective in the treatment of chronic hepatitis B, with ALT normalization in about 41% to 75% of HBeAg-positive patients and 60% to 79% of HBeAg-negative patients after 48 to 52 weeks [6], its use is limited by high rates of resistance. Genotypic resistance can be detected in 14% to 32% of patients after 1 year of lamivudine treatment and as high as 60% to 70% in patients after 5 years of treatment [6]. In contrast to interferon, studies of lamivudine in persons with decompensated cirrhosis have demonstrated that lamivudine is well tolerated in these patients, and can stabilize or improve their liver function, delaying the need for transplant [28]. Factors that have predicted good response to lamivudine and other nucleos(t)ide analogues are low HBV DNA levels, high pretreatment ALT levels, and high rates of activity on liver biopsy [14]. Lamivudine is generally well tolerated, with few reported adverse effects. In the treatment of HIV/HBV coinfection, it should be administered with 2 other active anti-HIV medications, including one other anti-HBV medication.

**Adefovir**

Adefovir is an oral nucleotide analogue of adenosine monophosphate that is effective against wild-type as well as lamivudine-resistant HBV. Adefovir inhibits reverse transcriptase and DNA polymerase and causes chain termination when incorporated into the HBV DNA [6]. Adefovir has activity against HIV at high doses; however, these doses carry a high risk of nephrotoxicity and adefovir is no longer used for HIV [12]. Adefovir is effective against HBV at a dose of 10 mg/day (a much lower dose than that previously used in HIV), and is associated with less resistance than lamivudine [12] though resistance to adefovir can increase to as high as 30% by the end of 4 years of treatment [4]. The main drawback to adefovir is that it is the least potent of the drugs available to treat HBV; adefovir is slow to suppress HBV DNA levels and patients are most likely to exhibit a primary failure or nonresponse (< 2-log decrease in HBV DNA) with adefovir compared with other treatment modalities [4]. Like the other oral agents, adefovir is generally well tolerated, but because of possible nephrotoxicity, periodic monitoring of renal function is recommended. Adefovir has not been evaluated for first line use in patients with decompensated cirrhosis [6].

**Entecavir**

Entecavir is a guanosine analogue that is considered a potent suppressor of HBV replication, effective against wild-type, lamivudine- and adefovir-resistant HBV [12]. Entecavir inhibits HBV replication at 3 sites: priming of the HBV DNA polymerase, reverse transcription of the negative strand HBV DNA from RNA, and synthesis of positive strand HBV DNA [6]. Patients with lamivudine resistance can develop resistance to entecavir through changes in the HBV polymerase, and therefore patients with lamivudine resistance should be on a higher dose of entecavir (1 mg/day) compared with lamivudine-naive patients (0.5 mg/day). Although not initially thought to be active against HIV, entecavir now appears to decrease HIV RNA by approximately 0.5 log₁₀ and can select for HIV resistance mutations [12]. Therefore, entecavir should not be used in coinfected patients without an already appropriate ART regimen. Entecavir is not part of any ART regimen and would be an additional agent in coinfected patients. Recent guidelines do not yet advocate the use of entecavir in patients with decompensated cirrhosis. Entecavir is generally well-tolerated, with limited adverse effects. In rodents exposed to extremely high doses of entecavir, studies have shown an increased rate of lung and brain tumors as well as hepato cellular carcinoma. However, no human data has shown an increased rate of hepatocellular carcinoma or other cancers in patients on entecavir [6].

**Tebivudine**

Tebivudine is a thymidine analogue with no reported activity against HIV, and is considered more effective against HBV than lamivudine or adefovir [12]. Tebivudine is generally well tolerated, though elevations in creatine phosphokinase levels have been observed in patients treated with tebivudine compared with lamivudine and peripheral neuropathy has also been associated with this medication [4]. Like lamivudine, tebivudine is a drug that confers high rates of resistance [4]. Additionally, tebivudine resistance mutations are cross-resistant with lamivudine, limiting the clinical utility of this agent. Limited data on the efficacy of tebivudine in coinfect ed patients exists; therefore, further studies would be required to elucidate the role of this drug in the HIV-HBV coinfected population [7].

**Tenofovir**

A nucleotide analogue that is structurally similar to adefovir but less nephrotoxic in the dose used for HIV [6]. Tenofovir is approved for the treatment of HIV and it is also manufactured as combination therapy with emtricitabine (Truvada). Clinical trials have demonstrated the efficacy of tenofovir in HBV to be noninferior (in fact superior) to adefovir [29] and it is considered a high potency agent against chronic hepatitis B [4]. Further, efficacy of tenofovir has been shown in patients...
with and without lamivudine resistance, though cases of HBV resistance to tenofovir have been described in coinfected patients with lamivudine resistance [12]. Tenofovir is generally well tolerated but has been associated with Fanconi’s syndrome and renal toxicity; renal function should therefore be monitored in patients on tenofovir.

Emtricitabine
A potent cytosine analogue with efficacy against both HIV and HBV, it is used for HIV in combination with tenofovir as the coformulated tablet. Emtricitabine is similar structurally to lamivudine and therefore confers the same resistance mutations [6]. The main advantage of emtricitabine is the convenience of combination with tenofovir in coinfected patients as Truvada, making it first-line therapy in coinfected patients requiring treatment of both HIV and HBV [12]. Because emtricitabine and lamivudine exhibit cross-resistance, it should not be used in cases of lamivudine failure [12].

In patients monoinfected with chronic hepatitis B, there is at present insufficient data to recommend initial therapy with a combination of antivirals [4] despite the potential benefit of preventing resistance. The current recommendation for first-line treatment is to use a potent drug with the least potential for resistance (ie, entecavir or tenofovir) as monotherapy [14]. In patients in whom the risk of resistance may be catastrophic, or those with a high likelihood of developing resistance due to a high viral load, an alternative approach is the combination of tenofovir with lamivudine or tenofovir plus emtricitabine [14].

- What kind of results should our patient expect from treatment for his hepatitis B?

Management and Goals of Treatment
Because it would require many years of follow-up as well as serial liver biopsies to monitor the progression of chronic hepatitis B to end-stage liver disease, surrogate end points are used to determine the efficacy of hepatitis B treatment modalities during clinical trials. These end points are continually evolving and include conversion to HBeAb in HBeAg-positive patients, conversion to HBsAb, log10 reductions in HBV DNA level or suppression of HBV DNA to an undetectable level (< 10 to 100 IU/mL), normalization of ALT levels, and/or histologic improvement based on a decrease in necrosis and fibrosis seen on biopsy [4].

While on treatment, patients with chronic HBV should have liver chemistries monitored every 3 months and HBV DNA levels every 3 to 6 months. Anti-HBe and HBeAg should be tested after 1 year of treatment and every 3 to 6 months following the first year [6]. Although it may be possible for monoinfected patients to discontinue treatment once they have confirmed HBeAg seroconversion (loss of HBeAg and positive anti-HBe on 2 occasions 1 to 3 months apart) followed by 6 additional months of treatment [6], the durability of response is variable with different treatment regimens and generally much lower in HBeAg-negative patients. For example, interferon responses in HBeAg-positive patients have been sustained in as many as 80% of patients after 1 year but in as few as 10% to 20% of HBeAg-negative patients [4]. Similarly, one study of lamivudine showed sustained response in 77% of treated HBeAg-positive patients with HBeAg seroconversion after a median follow-up of 37 months [6]. However, among HBeAg-negative patients the durability quoted beyond 1 year is under 10% [4]. Theoretically, as long as covalently closed circular DNA (cccDNA) exists in hepatocytes, or replicating DNA, therapy may need to be continued; long-term studies are necessary. Of note, wide variability exists among these studies in the duration of time used to assess durability, as well as the length of consolidation therapy (an extended period of therapy administered following seroconversion).

Treatment Management in HIV/HBV Coinfection
In coinfected patients durable responses are rare, and therefore patients are usually required to remain on therapy indefinitely [4]. It is also uncommon for coinfected patients to lose HBeAg and HBsAg or to seroconvert to anti-HBe and anti-HBs [9]. Because HIV and HBV resistance to monotherapy with the available medications can emerge rapidly, coinfected patients should be on 2 active anti-HBV agents and fully active HIV therapy, as outlined above.

It is important for providers to continue to administer agents with anti-HBV activity when changing or initiating ART regimens because of the risk of immune reconstitution as CD4 counts recover causing a flare of chronic hepatitis B [9]. If in the management of a coinfected patient the need arises to discontinue a dually active agent such as emtricitabine, lamivudine, or tenofovir, the use of an anti-HBV agent such as interferon should be considered to prevent a flare [25].

Data on treatment outcomes in coinfected patients is limited; however, one recent study followed coinfected patients on treatment with lamivudine for a median duration of 5 years. In this cohort, seroconversion occurred in only 10% (17%) of HBeAg-positive patients and was significantly correlated with a sustained HIV response on HAART (with an undetectable HIV RNA for at least 80% of therapy) [30].

Patient Follow-up
On outpatient follow-up 3 months later (9 months after initiation of the HIV and HBV medications),
the patient is found to have a HBV DNA of 31,800,000 IU/mL. Because the patient’s HBV viral load is increasing despite therapy, entecavir is added to his existing regimen of emtricitabine and tenofovir and HBV resistance testing is sent.

- Why is our patient not responding to treatment?

Treatment Resistance

A serious issue in treatment of chronic hepatitis B is the development of resistance mutations associated with extended use of nucleos(t)ide analogues. Higher rates of resistance are associated with higher pretreatment serum HBV DNA levels, length of treatment, high levels of detectable virus following treatment initiation and a history of exposure to nucleos(t)ide analogue medications [6]. In nucleos(t)ide-naive patients, lamivudine is associated with the highest, and entecavir with the lowest, rates of resistance. Resistance initially manifests as virologic breakthrough, defined as a $> 1 \log_{50}$ increase in HBV DNA in a patient on treatment following an initial response [6]. This increase in HBV DNA levels may occur as a result of medication noncompliance; thus adherence must be stringently assessed in this setting. Virologic breakthrough generally leads to a biochemical breakthrough, or elevation in aminotransferases in a patient who had previously exhibited a decline in response to treatment. This may be accompanied by a flare in hepatitis or frank decompensation [6].

Interferon therapy does not appear to be associated with the development of resistance. Lamivudine and telbivudine are associated with mutations in the YMDD motif—tyrosine, methionine, aspartate, aspartate—of the HBV DNA polymerase domain C, involving the substitution of methionine for isoleucine or valine [6]. This may be accompanied by another mutation upstream, involving polymerase domains A and B [4]. Resistance to these agents occurs most frequently among the existing medications used to treat HBV in as many as 60% to 70% of patients after 5 years of treatment with lamivudine [6]. Resistance to adefovir and tenofovir involves mutations in the polymerase domains B and D [4]. Rates of adefovir and tenofovir resistance are lower than that of lamivudine and telbivudine, but may be seen in approximately 20% of patients after 2 years of treatment [6]. In contrast, entecavir and tenofovir are considered agents with low levels of resistance, or a high barrier to the same. Resistance to entecavir is substantially higher among patients who are lamivudine-resistant: while only 3% of nucleoside-naive patients exhibited virologic breakthrough after 96 weeks of entecavir, virologic breakthrough was found in 16% of lamivudine-refractory patients after 96 weeks [6]. This resistance thus seems to require 2 hits: a lamivudine resistance mutation, followed by another amino acid substitution [6].

Additional Patient Follow-up

The patient is found to have HBV genotype A and no resistance mutations are noted. His physician continues the regimen and intensifies discussions with the patient regarding medication adherence. The patient has had multiple inpatient and outpatient visits for abdominal pain, lower extremity pain, and edema and unfortunately has relapsed with his IV heroin use. He has been deemed to not be a liver transplant candidate secondary to his multiple relapses with IV heroin.

- What barriers to care exist in the management of hepatitis B?

Barriers to Care and Future Directions

Chronic HBV is highly prevalent in the HIV-positive population; however, a wide degree of variability in caring for these patients has been demonstrated among providers [31] and substantial barriers to effective care continue to prevent infected patients from receiving treatment. Both health care providers and high-risk populations exhibit a significant deficit in knowledge regarding viral hepatitis that continues to hinder effective care [32]. Additionally, a lack of appropriate screening leads to continued disease transmission and the frequent missed opportunity to treat [2]. In recent recommendations for a national strategy on viral hepatitis, the IOM advocates for enhanced surveillance techniques to accurately quantify the incidence and prevalence of hepatitis B infection, and the development of new outreach and education programs to target both the high-risk and general populations. Additionally, the IOM delineates the need for expansion of immunization programs and coverage for hepatitis B immunization. Finally, these recommendations support the extension of federal funds toward community programs to include hepatitis B screening, vaccination and management services in the care of vulnerable populations [2].

SUMMARY

Despite a decline in the incidence of new acute cases of HBV infection in the United States due to vaccination implementation, chronic hepatitis B remains highly prevalent due to the prolonged duration of infection and immigration from endemic areas [20]. Chronic hepatitis B is common among HIV-infected persons due to shared modes of transmission and because patients with HIV are more likely to develop
chronic disease following infection [9]. All patients with HIV should therefore be screened for the presence of coinfection with HBV.

Following diagnosis with hepatitis B infection, the level of HBV activity should be assessed with testing for HBsAg, HBV DNA and potentially a biopsy for staging the degree of fibrosis present. Based on the results of this workup, a decision regarding the role of anti-hepatitis treatment should be made. According to the latest chronic hepatitis B and HIV treatment guidelines, coinfected patients who require treatment for chronic hepatitis B should be started on a regimen that is fully active against both HIV and HBV [25]. A first-line regimen for coinfected patients is generally composed of tenofovir and emtricitabine, plus one other agent active against HIV [14].

Studies evaluating the impact of chronic hepatitis B treatment on morbidity and mortality are lacking; therefore, surrogate end points such as reduction in HBV DNA are used to assess response to treatment. In coinfected patients, durable responses are rare, and therefore patients are usually required to remain on therapy indefinitely [4].

Further research is necessary to evaluate the natural history of coinfected patients and treatment outcomes. Additionally, intensification of surveillance techniques and education programs should be developed to help prevent transmission of infection and integrate coinfected patients into the health care system. Once engaged in care, coinfected patients should receive treatment for both HIV and chronic hepatitis B with the goal of a decrease in liver failure, cirrhosis, hepatocellular carcinoma, and chronic hepatitis B–related mortality.

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