Management of Patients with HIV and Hepatitis B Coinfection

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ABSTRACT

- *Objective*: To review the literature on and provide evidence-based recommendations for management of HIV/ hepatitis B (HBV) coinfection.
- *Methods*: Review of the literature for clinical trials, guidelines, and cohort studies on HIV/HBV disease management.
- *Results*: HIV patients should be evaluated for viral hepatitis. Those who do not have evidence of immunity should be vaccinated and monitored for response. Those who have HIV/HBV should have additional serologies checked to evaluate for hepatitis B e antigen status and level of viremia. All HIV/HBV coinfected patients should be started on antiretroviral therapy with tenofovir-based regimens. Those with HIV/HBV and cirrhosis should be screened for hepatocellular cancer every 6 months.
- *Conclusion*: HIV patients should be vaccinated against hepatitis B; those with coinfection should be treated for both viruses. It is important to monitor for treatment response to both HIV and HBV and liver disease complications.

Key words: *incentives; reinforcement; substance abuse treatment; dissemination; implementation.*

Morbidity and mortality for HIV-infected patients remain high compared to uninfected patients despite effective virologic suppression. Major contributors to illness and death among these patients include cardiovascular disease, non–AIDS-defining malignancies, and chronic liver disease, specifically viral hepatitis [1]. Hepatitis B virus (HBV) infection is one of the main causes of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) globally. Because HIV and HBV can both be acquired through injection drug use and sexual transmission, coinfection occurs frequently. The Joint United Nations Program on HIV/AIDS estimates that 10% of the 33 million HIV-positive patients worldwide have simultaneous chronic HBV infection [2].

HIV/HBV coinfection significantly impacts the natural history, progression, and mortality related to both viruses. HIV infection accelerates HBV-related liver impairment, leading to earlier cirrhosis, end-stage liver disease, and HCC. Conversely, chronic HBV does not have a considerable influence in the progression of HIV; however, antiretroviral treatment (ART) toxicities and/or HBV flares due to immune reconstitution inflammatory syndrome (IRIS) or HBV itself can lead to increased liver-related complications [3,4].

CASE PATIENT 1

Initial Presentation and History

An asymptomatic 38-year-old man diagnosed with HIV infection 1 month ago presents for his initial visit to establish HIV care. The patient is a man who has sex with men (MSM) and is currently sexually active with multiple partners. He reports inconsistent use of condoms. One month ago he underwent routine screening and was found to be HIV-positive. At the time of diagnosis, the patient's baseline CD4 cell count was 328 cells/μL and his viral load was 182,600 copies/mL. The patient wants to discuss the implications of his new diagnosis of HIV and recommendations for further testing and treatment. He is especially interested in HBV screening, since one of his recent partners was known to be positive. The patient has no relevant past medical history. He does not recall the details of his childhood vaccinations. He denies smoking and injection drug use but reports moderate alcohol consumption.

Physical Examination and Laboratory Testing

Physical examination is normal. Laboratory studies

From UT Southwestern Medical Center, Dallas, TX.

Table 1. Interpretation of Hepatitis B Serologic Test Results

Test			
HBsAg	**Anti-HBc**	**Anti-HBs**	**Recommended Management**
Negative	Negative	Negative	Susceptible, no prior exposure
Negative	Negative	Positive	Immune by vaccination
Negative	Positive	Positive	Immune by natural infection
Positive	Positive	Negative	Active infection (IgM anti-HBc can distinguish between acute and chronic)
Negative	Positive	Negative	Isolated anti-HBc due to: • False-positive test • Recovery from acute HBV infection • Distant immunity with loss of anti-HBs • Occult HBV infection

anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M.

Adapted with permission from Koziel MJ, Siddiqui A. Hepatitis B virus and hepatitis delta virus. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 6th ed. Philadelphia: Churchill-Livingstone; 2005: vol. II, 1878.

show normal complete blood count (CBC) and renal and liver function test results, and a baseline HIV genotype does not show resistance. Hepatitis A total antibody (anti-HAV) testing is positive, while tests for hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), and hepatitis C antibody (anti-HCV) are negative.

- **Which screening tests for HBV should be performed in HIV-infected patients?**

Routine screening of all HIV-infected patients for hepatitis A virus, HBV, and hepatitis C virus (HCV) is recommended [5]. Routine HBV screening involves obtaining serologies for HBsAg, anti-HBs, and anti-HBc. With these results, patients can be classified into categories of either active infection, immunity, or no evidence of prior exposure (**Table 1**). The serologic hallmark of active HBV infection is HBsAg, which if persistent for 6 months is diagnostic of chronic HBV infection. Patients with positive HBsAg require a full evaluation, as discussed later in this review. An isolated anti-HBc test usually means past infection with subsequent loss of anti-HBs. Incidence of HBV viremia in HIV-positive patients with isolated positive anti-HBc is variable and ranges from 1% to 36% [5]. All patients without evidence of prior exposure or vaccination as well as individuals with isolated anti-HBc should be offered vaccination against HBV [6].

- **How effective is HBV vaccination in the HIV population?**

Vaccination

Available HBV vaccines in the United States include 2 single-agent vaccines (Recombivax HB [Merck, Whitehouse Station, NJ] and Engerix-B [GlaxoSmithKline, Research Triangle Park, NC]) as well as a combination HAV/HBV vaccine (Twinrix [GlaxoSmithKline]). For adults (age $\geq$ 20 years) with an immunocompromising condition such as HIV infection, current Centers for Disease Control and Prevention guidelines recommend three 40 μg/mL doses of single-agent vaccine administered at 0, 1, and 6 months (Recombivax HB), or four 40 μg/mL doses of single-agent vaccine (2 doses of 20 μg/mL administered simultaneously) at 0, 1, 2, and 6 months (Engerix-B) [7].

The immunogenicity to HBV vaccination in HIV-positive patients is decreased, reflected by lower antibody titers, waning immunity, and seroconversion rates of 18% to 65% [8–11]. Factors associated with poor response include low CD4 cell counts, detectable HIV

RNA, coinfection with HCV, and the general health status of the patient [8]. Ideally, HBV vaccination should occur prior to decline in CD4 cell count below 350 cells/μL. However, guidelines do not recommend deferring vaccination since some patients with advanced HIV disease will seroconvert [6].

Anti-HBs titers should be checked 1 month after completion of the vaccine series to confirm protective antibody titers. For patients with quantitative anti-HBs levels < 10 IU/mL, a second vaccine cycle is recommended. Some specialists may defer revaccination until a sustained increase in CD4 count is achieved on ART.

Two randomized controlled trials have demonstrated that 4 doses of double-dose (40 μg/mL) vaccine generate higher anti-HBs levels than 3 doses of standard-dose (20 μg/mL) vaccine in HIV-infected adults [12,13]. Another study showed that HIV patients with CD4 counts > 350 cells/μL had better responses when immunized with double- dose vaccines on the usual 3-dose series [14]. Currently, the CDC recommends giving a double dose for either a 3-dose schedule or a 4-dose schedule. However, it remains unclear what dosing schedule to use if a patient fails to respond. Likely waiting until the CD4 cell count has increased and HIV viral load is suppressed will be important to seeing a response.

- **What approach for HBV prevention should be taken in this patient?**

The patient's serologies confirm no prior exposure to HBV, and he should be offered HBV vaccination. His CD4 cell count is below 350/μL and he has ongoing HIV viremia, which increases his risk for an inadequate response. However, vaccination should not be delayed, particularly given his high risk of sexual transmission. The patient should be counseled regarding all high-risk behaviors. As discussed above, 3 or 4 doses of the higher dose vaccine (40 μg/mL) should be administered depending on what type of recombinant vaccine is available. An anti-HBs level should be checked 1 month after completion. A full repeat vaccine series using the 40 μg/mL dose should be considered for nonresponders who initially received a standard vaccine series. Experts also recommend checking annual anti-HBs levels to monitor for waning immunity, with a booster dose given if the anti-HBs level drops below the protective range.

- **What vaccination strategy should be used in patients with isolated positive anti-HBc?**

The clinical implications of an isolated positive anti-HBc for vaccination are still uncertain. This serologic pattern may represent a false-positive test, remote HBV infection with loss of anti-HBs, or occult HBV infection with undetectable HBsAg. The latter scenario appears more commonly in HIV-infected patients, particularly with concomitant HCV infection [15].

A recent study suggested that patients with an isolated positive anti-HBc with a negative anamnestic antibody response (anti-HBs titer of < 10 IU/mL 4 weeks after a single 20 μg dose of recombinant HBV vaccine) should be further vaccinated with the double-dose for a 3-dose schedule [6]. Additionally, another study followed HIV/HCV coinfected patients for 9.5 years and found that an isolated positive anti-HBc was not associated with accelerated liver disease progression [16].

Treatment of HIV-1 Infection

Current HIV guidelines recommend initiation of ART for all HIV-infected patients regardless of their CD4 count [17]. ART for a treatment-naïve patient usually consists of 2 nucleotide/nucleoside reverse-transcriptase inhibitors (NRTIs; the "backbone") combined with a third agent (the "anchor"), which can be a nonnucleoside reverse-transcriptase inhibitor (NNRTI), a protease inhibitor (PI) boosted with a boosting agent, or an integrase strand-transfer inhibitor (INSTI) [18,19].

There are numerous studies indicating that incident HBV risk can be reduced by placing those at risk for HBV acquisition on ART containing a combination of tenofovir disoproxil fumarate (TDF), lamivudine, or emtricitabine [20,21]. Another study in MSM found those on ART with HIV viral load < 400 copies/mL were protected from developing HBV compared to those not on ART [22]. Given this patient's higher risk for HBV acquisition, placing him on emtricitabine/TDF backbone as part of ART could be protective against incident HBV [23].

CASE PATIENT 2

Initial Presentation and History

A 32-year-old man diagnosed with HIV infection 8 years ago now on ART presents for follow-up. The patient is an MSM with a history of inconsistent condom use. At the time of HIV diagnosis 8 years ago, the patient had a CD4 cell count of 250 cells/μL and an HIV viral load of 648,000 copies/mL. The patient was initiated on lamivudine/zidovudine and lopinavir/ritonavir, and he achieved complete virologic suppression at 20 weeks, with a CD4 cell count of 455 cells/μL at 1 year. The patient has remained on this regimen without major side effects; however, he reports frequent missed doses over the last 2 years due to "pill fatigue." Previous testing for HBV and HCV at the time of his initial HIV diagnosis was negative, but he failed to complete the HBV vaccine series. He denies alcohol or injection drug use.

Physical Examination and Laboratory Testing

Physical examination is normal. Laboratory studies reveal normal electrolytes and renal function, hemoglobin of 11 g/dL, and platelet count of 235,000/μL. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are 34 U/L and 44 U/L, respectively, with an INR of 1.1 and albumin level of 3.4 g/dL. CD4 cell count is 320 cells/μL with an HIV viral load of 24,500 copies/mL. Viral hepatitis serologies show anti-HAV positive, anti-HCV negative, HBsAg positive, anti-HBc IgG positive, hepatitis Be antigen (HBeAg) negative, and hepatitis B e antibody (anti-HBe) positive. HBV DNA viral load is 685,000 IU/mL.

- **What is the natural history of HIV/HBV coinfection?**

Chronic HBV infection affects about 10% of HIV-infected patients globally. Epidemiologic studies indicate that HIV-infected patients have higher rates of reactivation and progression to chronic HBV infection and chronic liver disease than HIV-negative patients [24–26]. Coinfected patients demonstrate higher serum HBV DNA levels, which lead to more rapid progression of hepatic fibrosis and may increase the risk of cirrhosis and HCC [24,27,28]. HIV infection, however, can mediate the necroinflammatory response through blunting of the immune response that drives pathogenesis in HBV infection. Aminotransferase levels may be only slightly elevated or even normal, particularly in the severely immune suppressed. However, elevation in liver enzymes (hepatitis flare) can occur if a patient stops ART, or if HBV resistance develops. Patients being treated for HIV/HBV coinfection should be counseled that stopping HIV treatment puts them at risk of developing a hepatitis flare.

Large cohort studies of HIV/HBV coinfected patients indicate increased risk of liver-related mortality, most pronounced with lower CD4 cell counts [1,28,29]. Introduction of ART appears to increase rather than attenuate this liver-related mortality, possibly by decreasing AIDS-related mortality and allowing more time for liver disease progression. Finally, a recent meta-analysis including 12,382 patients demonstrated a significant effect of HIV/HBV coinfection on all-cause mortality, with a pooled effect estimate of 1.36 [30].

- **What diagnostic testing should be done in coinfected patients?**

Diagnostic Testing and Evaluation

Persistence of HBsAg for more than 6 months is diagnostic of chronic HBV infection and warrants further serologic evaluation. Patients with chronic HBV infection should be tested for HBeAg, anti-HBe, and HBV DNA levels and have AST and ALT levels measured. Elevation of AST and ALT can be seen with untreated HBV. For those on treatment, a hepatitis flare could be caused by abrupt discontinuation of HBV treatment, development of HBV resistance, or superinfection with another viral pathogen.

HBeAg is a marker of active viral replication and is associated with higher levels of HBV DNA and active liver disease. Seroconversion, or loss of HBeAg and development of anti-HBe, heralds a favorable treatment response for those who were initially HBeAg-positive. However, some HBV variants have precore or core promoter mutations that lead to higher levels of HBV DNA in the absence of HBeAg. This highlights the importance of monitoring HBV DNA levels in all patients with chronic HBV infection. Favorable response to therapy in HBeAg-negative patients is marked by normalization of aminotransferases and HBV DNA suppression.

Hepatitis D virus (HDV) is a defective virus particle that can only replicate in the presence of HBV. Coinfected patients should be tested for anti-HDV if they are injection drug users or are from a high-prevalence region such as the Mediterranean and Amazon basins. Newly acquired HDV infection should also be considered in the context of hepatitis flares.

Although these routine diagnostic tests are essential for management, studies show low adherence rates to HBV testing guidelines by HIV providers [31,32].

- **What is the role of HBV genotype and resistance testing?**

HBV can be classified into 10 different genotypes, A through J, based on genomic sequence variations. Each genotype has a distinct ethnic and geographic distribution, with genotypes A and D predominating in North America. HBV genotyping appears to have important prognostic as well as treatment implications [19]. However, data are still preliminary and the guidelines do not recommend routine genotype testing.

Resistance testing in HBV allows for detection of mutations that decrease effectiveness of antivirals. Exposure to lamivudine can lead to mutations in the YMDD region of the HBV DNA polymerase, resulting in drug resistance. Resistance to lamivudine develops at a rate of approximately 25% after 1 year of drug exposure in HIV/HBV coinfection [33]. On the other hand, studies have shown that entecavir is active against HIV and, most importantly, selects for the M184V mutation in HIV. M184V is associated with lamivudine resistance for HIV treatment, thus limiting treatment options [34,35]. After these findings, the FDA advised against monotherapy with entecavir in patients with HIV/HBV coinfection.

The case patient was on lamivudine during the time of HBV acquisition, and therefore YMDD mutation must be taken into consideration for therapy purposes. He should be switched to a regimen that suppresses both viruses. The development of drug resistance should be assessed in all patients with persistent or breakthrough HBV viremia on ART, particularly the nucleoside analogues. HIV providers treating HIV/HBV coinfection should regularly monitor both HIV and HBV viral load to assess for therapeutic efficacy.

- **What is the role of liver biopsy in this patient?**

Liver biopsy should be considered in all coinfected patients as it remains the gold standard for determining the activity and severity of chronic hepatitis B. However, because it carries inherent risks and is not required prior to treatment in all patients, the decision should be individualized. Liver biopsy can be useful to assess baseline liver histology and may be warranted to rule out significant coexisting genetic or metabolic liver disease. Currently, noninvasive methods to assess liver fibrosis either using elastography or various combinations of serum biomarkers are being evaluated [36] and may be considered in lieu of a liver biopsy [37]. One study compared the accuracy of elastography with liver biopsy in HIV/HBV coinfected patients and demonstrated that the former was proficient in discriminating between absence or mild fibrosis and moderate to severe fibrosis [38]. In general, this test has high accuracy in detecting minimal fibrosis from advanced fibrosis or cirrhosis. For the group in the middle, further investigation with additional methods must be considered [37]. Finally, a recent retrospective study involving 70 HIV/HBV coinfected individuals showed fibrosis regression suggesting beneficial effects of long-term ART on liver stiffness, [39] but further studies are needed to confirm these findings.

CASE 2 CONTINUED

The patient has now been diagnosed with chronic HBV infection. His diagnostic testing is negative for HBeAg and reveals modest HBV viremia with abnormal aminotransferases less than 2 times the upper limit of normal. Drug resistance testing reveals a mutation in the YMDD region indicative of HBV lamivudine resistance. HIV genotype demonstrates a wild-type virus without resistance. The patient asks what treatment options exist.

- **What medications are currently available to treat hepatitis B?**

Treatment

All patients with HIV/HBV coinfection should receive treatment to suppress both viruses, and ART needs to include 2 drugs active against HBV, ideally emtricitabine and TDF. This approach prevents drug resistance, slows progression of HBV infection, and reduces the incidence of IRIS [5]. TDF has been associated with decreased renal function and bone mineral density. Recently, tenofovir alafenamide fumarate (TAF) was approved for the treatment of HIV and HBV. A dose of 10 mg daily is given when coadministered with ritonavir, cobicistat, or protease inhibitors, but a dose of 25 mg should be given when administered with NNRTIs or integrase inhibitors. Compared to TDF, TAF shows less accumulation of tenofovir in kidneys and bones and consequently has reduced renal and bone mineral density effects [40]. All patients should be on a TDF- or TAF-based HIV regimen if they have chronic HBV.

Currently, the following antiviral drugs are FDA-approved for the treatment of HBV infection: interferon alfa-2b, pegylated interferon (peginterferon) alfa-2a, lamivudine and emtricitabine, entecavir, adefovir, TDF, TAF, and telbivudine. Telbivudine and adefovir are no longer recommended due to their association with higher incidence of toxicity and higher rates of HBV treatment failure. A summary of available HBV treatment options is outlined in **Table 2**.

Interferon

Standard interferon alfa-2b blocks HBV replication through interaction with viral proteins and stimulation of host cellular immunity. Peginterferon alfa-2a has proven efficacy in HBV-monoinfected patients, but efficacy data in HIV/HBV coinfected patients is lacking [41,42]. Studies in hepatitis C treatment demonstrate the safety of peginterferon alfa-2a use in HIV-positive patients and indicate that HIV viral suppression occurs with peginterferon without evidence of selection of resistance mutations that affect future ART options [43]. For HIV/HBV coinfected patients not on ART who will receive only therapy for HBV (which is infrequent since all HIV patients should be on ART), pegylated interferon-alfa-2a alone for 48 weeks is the only option that will not cause ART-associated HIV drug resistance [5]. Interferon therapy is contraindicated in patients with decompensated cirrhosis and should be used with caution in patients with active depression, uncontrolled diabetes, and cardiac and pulmonary disease.

Lamivudine and Emtricitabine

Lamivudine is a nucleoside analogue with efficacy against both HIV and HBV. Clinical trials in HIV/HBV-infected patients have shown up to 87% of patients achieve undetectable HBV DNA levels and about 25% achieve HBeAg seroconversion after 1 to 2 years of therapy [44,45]. However, the major issue limiting use of lamivudine is its low genetic barrier to resistance. Mutation of the YMDD motif of the HBV DNA polymerase confers HBV resistance. HIV/HBV coinfected patients develop resistance at rates of up to 94% after 4 years of therapy [33], heralded by rebounds in HBV DNA levels and often hepatitis flares or precipitation of hepatic failure [16]. Because of resistance, lamivudine monotherapy should be avoided; even in patients on ART, abrupt withdrawal of lamivudine or the development of HBV resistance should be closely monitored.

Emtricitabine is another nucleoside analogue with properties and efficacy similar to lamivudine. It is frequently used as a combination pill with TDF (Truvada) in coinfected patients. The same concerns regarding monotherapy and the emergence of resistance that exist for lamivudine apply to emtricitabine.

Tenofovir

TDF, a nucleotide analogue, is one of the preferred first-line agents for HIV treatment and has proven efficacy against both wild-type and lamivudine-resistant HBV. Since it was first used for HIV, TDF has been more extensively studied in coinfected patients compared to most other agents. In a meta-analysis of patients with HIV/HBV coinfection, TDF suppressed HBV viral load to undetectable titers in approximately 90% of patients [46]. Tenofovir is available in 2 preparations: TDF and TAF. TDF has been reported to cause renal impairment as well as bone loss. TAF has shown less renal toxicity and less bone damage [40,47]. In 2016, TAF became available as part as 4 regimens: stand-alone TAF, elvitegravir-cobicistat-emtricitabine-TAF, rilpivirine-emtricitabine-TAF, and TAF-emtricitabine.

TDF and TAF both suppress HIV. Two large randomized trials of HBV monoinfection demonstrate that TAF is noninferior to TDF for the treatment of naïve and treatment-experienced patients [48,49].

Table 2. Medications for the Treatment of HBV/HIV Coinfection

Medication	Dosage	Log HBV Drop at 1 Year	HBeAg Loss at 1 Year, %	Effective Against YMDD Mutant?	Side Effects
Interferon alfa-2b	5 MU daily or 10 MU 3 times per wk for 16 wk	0–27% undetectable HBV DNA	0–8.3	Yes	Flu-like symptoms, cytopenias, thyroid dysfunction, psychiatric
Peginterferon alfa-2a	180 µg/wk	4.5 (32% undetectable HBV DNA)*	32*	Yes	As above
Lamivudine (3TC)	300 mg/day	2.7 (40%–87% undetectable HBV DNA)	22–29	No	Nausea, diarrhea, skin rash, rare lactic acidosis/steatosis
Emtricitabine (FTC)	200 mg/day	3 (50% undetectable HBV DNA)	50	No	Nausea, diarrhea, rash; rare lactic acidosis/steatosis
Tenofovir disoproxil fumarate (TDF)	300 mg/day	4–5.5 (65% undetectable HBV DNA)	0–25	Yes	Rash, nausea/vomiting, diarrhea, headache, rare renal toxicity, Fanconi syndrome, possible osteopenia, lactic acidosis/steatosis
Tenofovir alafenamide fumarate (TAF)	25 mg/day	65% undetectable HBV DNA	14	Yes	Respiratory tract infection, nasopharyngitis, headache, cough, fatigue, diarrhea
Entecavir (ETV)	0.5 mg/day for lamivudine-naïve patients; 1 mg/day for lamivudine-experienced patients	3.6–4.2 (80% undetectable HBV DNA)	2	At higher dose	Headache, fatigue, dizziness, rare lactic acidosis

HBeAg = hepatitis B e antigen; HBV DNA = hepatitis B DNA levels; MU = million units. (Adapted with permission from Kitchell E, Jain MK. Treatment of hepatitis B in HIV-infected persons. In: Sherman KE, editor. HIV and liver disease. New York: Springer; 2012:141–50.)

* Limited data available for HIV-coinfected patients; data shown are from HBV-monoinfected patients.

Entecavir

Entecavir, a guanosine analogue, is a potent HBV DNA polymerase inhibitor that results in greater virologic suppression compared to lamivudine and retains activity against lamivudine-resistant HBV [50]. Importantly, entecavir shares some cross-resistance with lamivudine, so an entecavir dose of 1 mg daily is recommended in lamivudine-experienced patients compared to 0.5 mg daily in lamivudine-naïve patients. Entecavir requires dose reduction for patients with creatinine clearance less than 50 mL/min, although it is not associated with renal toxicity. A 1-log10 reduction in HIV RNA levels as well as emergence of M184V mutations on entecavir monotherapy has been reported [51,52]. M184V confers HIV resistance to lamivudine and emtricitabine. Therefore, entecavir should not be used as monotherapy in HIV-coinfected patients and/or patients with evidence of lamivudine-resistant HBV.

Combination Therapy

Recent updates in the guidelines recommend that since emtricitabine, lamivudine, TDF, and TAF are active against both viruses, patients with coinfection should start ART with a fixed-dose combination of TDF/emtricitabine or TAF/emtricitabine or the individual drug combination TDF plus lamivudine [53]. Most experts recommend the use of combination HBV therapy in patients on ART, particularly with lamivudine given the high rates of resistance.

- **When should HBV treatment be started in patients with coinfection?**

An ART regimen containing TDF (creatinine clearance > 50 mL/min) or TAF (creatinine clearance > 30 mL/min) with lamivudine or emtricitabine should be used in all HIV/HBV patients as soon as the infection is diagnosed. If TDF or TAF cannot be used, the alternate recommended regimen for HBV is entecavir plus a fully suppressive ART. In those with decreased renal function, entecavir should be adjusted to renal function [19].

Although control of viremia is feasible, clearance of infection as marked by loss of HBsAg and development of anti-HBs is unlikely to occur in the majority of patients. Therefore, the goals of treatment focus on prevention of chronic liver disease complications by suppressing viral replication, which can halt disease progression. A suggested algorithm for the management of coinfected patients is provided (**Figure**).

- **What is the duration of therapy for hepatitis B?**

Most patients with HIV/HBV coinfection will require lifelong treatment. All patients on HBV therapy as a part of ART should continue HBV therapy, regardless of seroconversion status. Also, patients should be educated and advised against self-discontinuation as it may trigger hepatitis exacerbations and/or hepatic failure.

CASE PATIENT 3

Initial Presentation and History

Two months after starting treatment for HIV and chronic HBV infection, a 46-year-old Hispanic woman presents to clinic with jaundice and right upper quadrant (RUQ) pain. The patient was recently diagnosed with HIV infection and was naïve to treatment with ART. Her CD4 cell count was 50 cells/μL, and her HIV viral load was 743,000 copies/mL, with no baseline mutations on HIV genotype. The patient was also diagnosed with chronic HBV infection with positive HBsAg and HBeAg and negative HBc IgM serologies, as well as an HBV DNA level of 87 million IU/mL. Routine blood work revealed normal renal function and serum transaminases. The decision was made to start the patient on darunavir/ritonavir and TDF/emtricitabine. The patient was also started on sulfamethoxazole/trimethoprim and azithromycin for opportunistic infection prophylaxis.

Physical Examination and Laboratory Testing

Examination is remarkable for mild tenderness in the RUQ and icteric sclera. Laboratory testing demonstrates the following: AST, 1523 U/L; ALT, 795 U/L; albumin, 2.8 mg/dL; and total bilirubin, 3.5 mg/dL. Her CD4 count has increased to 565 cells/μL, and her HIV viral load is 4320 copies/mL. Results of repeat hepatitis serologies are as follows: HBsAg positive, anti-HBc IgM positive, and an HBV DNA level of 4.2 million IU/mL. Testing for hepatitis A, C, and D is negative, and RUQ sonogram reveals no gallstones.

- **What monitoring should be done for coinfected patients on HBV therapy?**

Monitoring

Providers should routinely monitor patients' response to HIV/HBV therapy. Initially, all coinfected patients should have liver function tests and HBV DNA levels checked every 12 weeks on therapy. Frequent monitoring allows early detection of HBV drug resistance as well as drug-related hepatotoxicity. In HBeAg-positive coinfected patients who achieve HBV DNA suppression, HBeAg and anti-HBe testing should be performed every 6 to 12 months to assess for seroconversion. In HBeAg-negative patients, only HBV DNA and liver function tests are needed. HBV virologic failure is defined as a greater than 1-log10 rise in HBV DNA levels or development of viremia in a patient with a previously suppressed DNA level on therapy.

Typically, virologic failure results from either the development of drug resistance or abrupt withdrawal

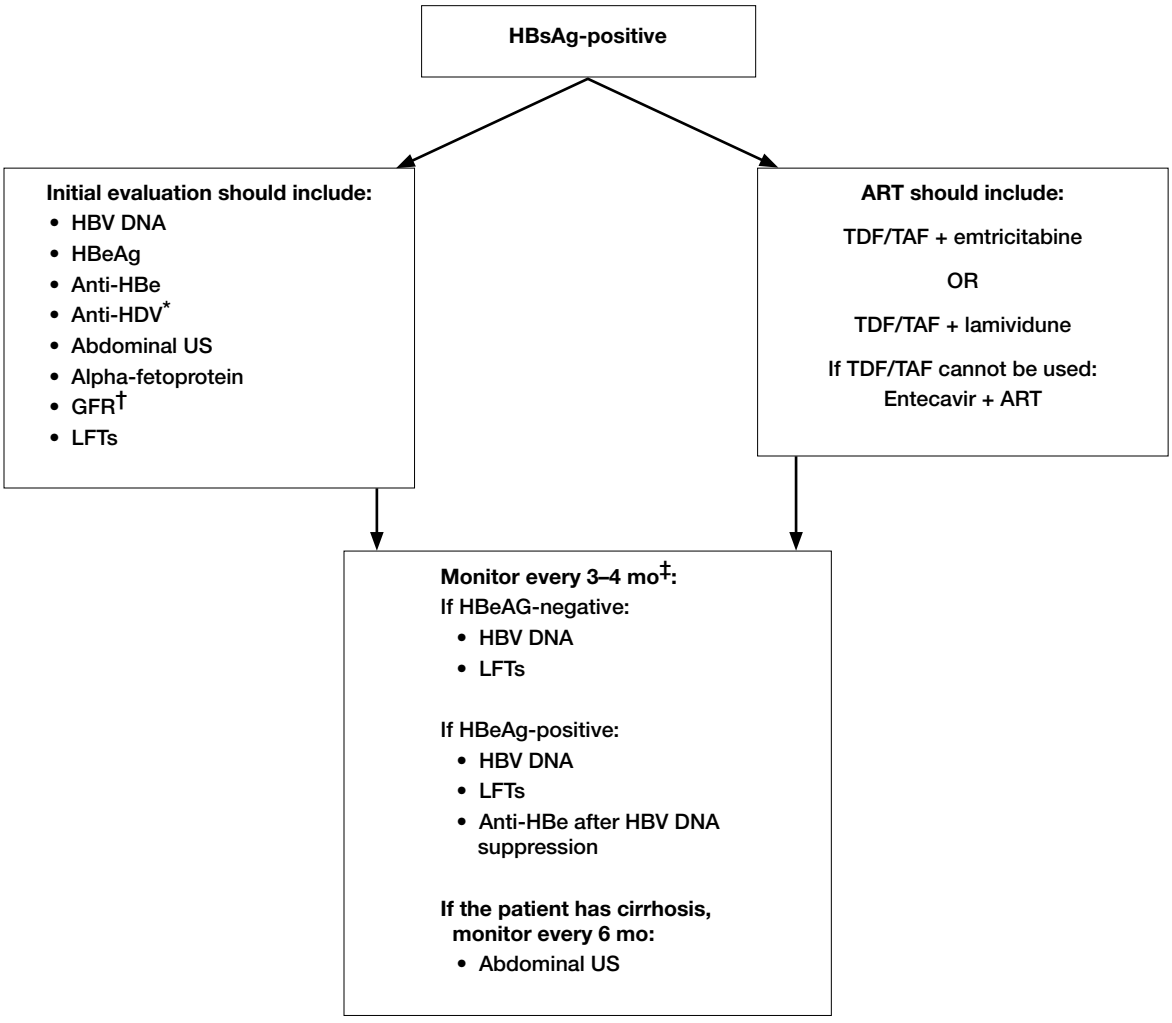

Figure. Evaluation and management of a patient with HIV/HBV coinfection. ART= antiretroviral therapy; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B viral load; HBeAg = hepatitis B e antigen; anti-HBe = hepatitis B e antibody; anti-HDV = hepatitis D antibody; GFR = glomerular filtration rate; LFTs = liver function tests; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide; US = ultrasound. (Adapted with permission from Kitchell E, Jain MK. Treatment of hepatitis B in HIV-infected persons. In: Sherman KE, editor. HIV and liver disease. New York: Springer; 2012:141–150.)

* If injection drug use is a risk factor or patient is from a high prevalence area.

† Some drugs will need to be adjusted for renal dysfunction.

‡ Rise of HBV DNA or LFTs after suppression may indicate viral resistance to HBV therapy.

of active HBV therapy due to patient nonadherence or changes to the ART regimen. Virologic failure can result in a rise in serum aminotransferases as well as decompensation in patients with significant underlying liver disease. Due to this risk, providers must counsel patients about the importance of adherence to therapy and should continue medications active against HBV when making a change in ART regimens, unless HBV drug resistance dictates a change in HBV therapy.

- **What is the likely cause of this patient's hepatitis "flare"?**

Several studies indicate that patients with HIV/HBV coinfection are at increased risk of drug-related hepatotoxicity and grade 4 liver enzyme elevations [54,55]. The first 3 months after initiation of ART is a particularly vulnerable time for liver injury. The differential diagnosis for an acute hepatitis "flare" following the

initiation of ART is broad and includes the following: development of HBV drug resistance [16]; withdrawal of HBV-active medications due to nonadherence [54]; ART-related hepatotoxicity; superimposed infection with HAV, HCV, or HDV; other opportunistic infections including cytomegalovirus and mycobacterium avium complex; or IRIS, resulting in an exaggerated cytotoxic response by the recovering immune system [56,57]. Complete evaluation is critical to distinguish between the possible causes.

In this case, several clues point toward HBV-related IRIS as the most likely cause for the hepatitis "flare." A low pretreatment CD4 cell count with a rapid rise after initiation of ART is associated with a higher rate of IRIS [57]. Serologic testing and imaging excluded superinfection with another hepatotropic virus or biliary tract disease. Appropriate declines in HIV viral load and HBV DNA levels imply patient adherence to therapy and argue against the development of HBV drug resistance. Finally, the emergence of anti-HBc IgM positivity signals HBV reactivation, which is commonly seen in patients with HBV-related IRIS [57]. The preferred treatment for HBV-related IRIS involves continuation of therapy, frequently leading to normalization of aminotransferases and subsequent HBeAg seroconversion. Because IRIS usually manifests within the first 6 to 12 weeks after starting ART, liver enzymes should be monitored closely during this period.

- **What health maintenance should be done for coinfected patients?**

All patients with HIV/HBV coinfection should be monitored for evidence of portal hypertension or cirrhosis and, if these conditions exist, should undergo endoscopic screening for esophageal varices as well as evaluation of ascites and encephalopathy. Patients with HBV are at increased risk for the development of HCC even in the absence of cirrhosis. A recent study showed low rates of HCC screening in HIV/HBV patients by HIV providers [58]. Whether HIV coinfection potentiates HCC risk is uncertain, though coinfected patients present at younger ages and with more symptoms than HIV-negative comparators [59]. Other risk factors for HCC include HCV infection, alcohol abuse, diabetes, obesity, exposure to environmental toxins, and cirrhosis of any etiology (most commonly non-alcoholic fatty liver disease, primary sclerosing cholangitis, primary biliary cirrhosis and hemochromatosis) [60].

The American Association of Liver Diseases (AASLD) guidelines recommend hepatic ultrasound screening every 6 months in all patients with cirrhosis or chronic HBV who are at increased risk (Asian men over the age of 40 years, Asian women over the age of 50 years, African or North American blacks, and patients with family history of HCC) [61]. They should also be referred for an esophagogastroduodenoscopy to evaluate for esophageal varices. In addition, all HIV/HBV coinfected patients with decompensated liver disease should be evaluated for transplantation. HIV infection is not a contraindication for liver transplant with the use of ART. However, since transplantation does not cure HBV infection, post-transplant HBV immune globulin and HBV treatment are required. Contemporary data suggest comparable survival rates after transplant in coinfected patients compared to HBV-monoinfected patients [51].

SUMMARY

Routine screening with HBsAg, anti-HBs, and anti-HBc serologies is recommended for all HIV-positive individuals. Patients without evidence of prior exposure or vaccination and those with isolated anti-HBc should be offered vaccination. HIV-positive adults should receive three or four 40 μg/mL doses of single agent vaccine depending on the recombinant vaccine type available. Anti-HBsAg titers should be checked 1 month after completion of the immunization series. If quantitative anti-HBsAg levels are < 10 IU/mL, patients should receive a second vaccine cycle.

Patients who test positive for HBsAg should be tested for HBeAg, anti-HBe, and HBV DNA levels and have AST and ALT levels checked as well. All patients with HIV/HBV coinfection should start treatment as soon as HIV infection is diagnosed. ART needs to include 2 drugs against HBV, and therefore a fixed-dose combination of TDF/emtricitabine or TAF/emtricitabine or the individual combination of TDF plus lamivudine should be used.

Coinfected patients on treatment should have liver function tests as well as HBV DNA every 12 weeks. In HBeAg-positive coinfected individuals who achieve HBV DNA suppression, HBeAg and anti-HBe testing should be performed every 6 to 12 months to assess for seroconversion. HBV virologic failure is defined as a greater than 1-log10 rise in HBV DNA levels or

development of viremia in a patient with a previously suppressed DNA level on therapy. Those with virologic failure should be tested for HBV resistance thorough HBV genotype. Coinfected patients with cirrhosis should receive ultrasound screening every 6 months for evidence of HCC and esophagogastroduodenoscopy to evaluate for esophageal varices.

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