

Hepatitis B Coinfection

This is a PDF version of the following document:
Section 4: Co-Occurring Conditions
Topic 5: Hepatitis B Coinfection

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Background

Epidemiology

Hepatitis B virus (HBV) is a significant cause of liver disease among persons living with HIV infection. Among persons with HIV infection born in the United States, acquisition of HBV occurs primarily through sexual contact and injection drug use, with most HBV infections occurring in adulthood. Foreign-born individuals, however, are likely to have acquired HBV infection earlier at birth or in childhood. Genotypes A-H for HBV are geographically distributed, with genotype A as the predominant subtype in the United States among non-Asians and genotype B or C among Asians.[1]

In the HIV Outpatient Study (HOPS), investigators examined the prevalence of chronic HBV among persons with HIV during the years 1996 through 2007 and found overall that 8.4% of patients tested positive for chronic HBV (either HBsAg-positive or HBV DNA positive), a prevalence 20-fold higher than the 0.42% prevalence in the general population (Figure 1).[2] In this same study, analysis of chronic HBV prevalence rates based on HIV acquisition risk factors showed the highest rate was among men who have sex with men (Figure 2).[2] A separate review estimated an overall HBV prevalence of 6 to 14% among individuals living with HIV infection in Western Europe and the United States, with prevalence rates of 4 to 6% in heterosexuals, 7 to 10% in persons who inject drugs, and 9 to 17% in men who have sex with men (MSM).[3] In addition, in North America and Europe, more than half of men with HIV infection who have sex with men have serologic evidence of past HBV infection.[4]

Impact of HIV on Natural History of HBV

When compared to individuals with HBV monoinfection, those with HBV and HIV coinfection have higher baseline HBV DNA levels, lower alanine aminotransferase (ALT) levels, and decreased rates of spontaneous HBeAg seroconversion.[5] Individuals coinfected with HBV and HIV have an accelerated progression of liver disease, as well as an increased risk of hepatocellular carcinoma, all-cause mortality, and liver-related mortality compared to persons with HIV monoinfection (Figure 3).[6,7,8,9,10] In one study, investigators reported greater liver-related mortality in persons with HIV and HBV coinfection (14.2 per 1,000 person-years) than observed in either HIV monoinfection (1.7 per 1000 person-years) or HBV monoinfection (0.8 per 1,000 person-years).[11] Among those with HIV-HBV coinfection, the highest liver-related mortality rates have occurred in individuals with low CD4 cell counts.[12]

Impact of HBV on Natural History of HIV

Analysis of data from three different time periods of the Multicenter AIDS Cohort Study (MACS) study noted a
higher liver-related mortality in persons with HIV-HBV coinfection than with HIV and hepatitis C virus (HCV) coinfection (Figure 4).[12] Multiple other studies have reported HIV-HBV coinfection and HIV-HCV coinfection both have played a major role in liver-related deaths in persons with HIV.[13,14,15,16,17,18] The impact of HBV on HIV natural history remains less clear, with some studies demonstrating no significant effect of HBV coinfection on HIV-related outcomes and others suggesting an adverse impact.[19,20,21] A recent large observational cohort study from the United Kingdom reported higher all-cause mortality and liver-related mortality in persons with HIV if they had coinfection with HBV and/or HCV coinfection, but no increase in AIDS-related mortality (Figure 5).[22]

**Immunization to Prevent Hepatitis B Infection**

Although HBV vaccination has been recommended since the 1980s for men who have sex with men (as well as for persons who inject drugs and for heterosexuals with multiple sex partners), and since 2006 for all individuals with HIV infection, HBV vaccination rates for persons with HIV infection remain low.[2,23,24,25] Indeed, recent surveillance data from the Centers for Disease Control and Prevention (CDC) suggest that over a third of the persons living with HIV who were receiving medical care in the United States did not have documentation of HBV infection, immunity, or vaccination.[26] Recommendations and vaccine schedules for HBV are addressed in detail in the [Immunizations in Adults Topic Review](#) in the Basic Primary Care Module.
Screening for HBV in Persons with HIV Infection

Recommendations for Testing

All persons with HIV infection should undergo screening for HBV infection upon entry into medical care with a panel that includes hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (anti-HBc total).[27] Chronic HBV infection is defined by the detection of HBsAg on two separate tests that have been obtained at least 6 months apart.[27] Thus, for persons who test positive for HBsAg, a repeat HBsAg test should be performed 6 months following this initial positive HBsAg to confirm that chronic HBV infection is present.

Individuals with confirmed chronic HBV should have further testing that includes HBV e-antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA.[27] In addition, for persons with HIV who have negative HBsAg testing, HBV DNA testing should be considered if they have persistent elevation in alanine aminotransferase levels (ALT) or they have suspected acute HBV infection and are in the serologic window period (loss of HBsAg without emergence yet of HBsAb).[28,29] In addition, some experts recommend checking HBV DNA in persons with HIV who have isolated core antibody, since HBV viremia is present in 1 to 36% of persons with HIV and isolated core antibody.[27,30,31]

Interpretation of Hepatitis B Serologic Studies

Serologic testing for the diagnosis of HBV infection involves measurement of the full panel of distinct HBV-specific antigens and antibodies outlined above. Results of this serologic panel can help determine whether a patient is susceptible to infection, immune as a result of resolved infection, immune as a result of vaccination, acutely infected, or chronically infected (Figure 6).[25,32]

Laboratory Markers Following Acute HBV Infection

In patients with acute HBV infection, the first serologic marker to appear is hepatitis B surface antigen (HBsAg), which is the hallmark of HBV infection and can be detected in serum 4 to 10 weeks after HBV acquisition.[33] HBV DNA is usually detectable 10 to 20 days before the appearance of HBsAg, but HBV DNA testing is not generally used for screening purposes. Shortly after the appearance of HBsAg, hepatitis B e antigen (HBeAg) becomes evident; HBeAg is a marker of active viral replication and patients with positive HBeAg typically have high levels of circulating serum HBV DNA.[34]

Concurrent with the onset of clinical symptoms, antibody to hepatitis B core antigen (anti-HBc) appears, primarily detectable as the IgM class (IgM anti-HBc). Although IgM anti-HBc antibodies typically decline to undetectable levels within 6 months, the IgG class (IgG anti-HBc) persists indefinitely as a marker of past HBV infection. Resolution of infection is marked by the loss of HBsAg and the appearance of hepatitis B surface antibody (HBsAb). Patients who go on to resolve their infection also lose the presence of HBeAg and develop antibodies to hepatitis B e antigen (anti-HBe).

Isolated Hepatitis B Core Antibody

Among persons with HIV who undergo serologic testing for HBV, an estimated 17 to 41% have isolated hepatitis B core antibody (anti-HBc).[30,35] There are four possible interpretations of this finding: (1) resolved HBV infection with waning surface antibody (HBsAb) titers (most common), (2) a false-positive core antibody test (person is susceptible to HBV infection), (3) occult "low-level" chronic HBV infection, or (4) resolving acute HBV infection.[32] Several studies have shown that patients with HIV infection, particularly those with coexisting hepatitis C infection, have a higher frequency of isolated core antibody results.[30,36]

For persons with HIV and isolated anti-HBc, the Adult and Adolescent Opportunistic Infection Guidelines recommend the following approach.[27] Administer a one-time dose of hepatitis B vaccine and check anti-HBs
1 to 2 months later. If the anti-HBs titer is greater than 100 IU/mL, then no further vaccination is required. If, however, the titer is less than 100 IU/mL, then a complete series of HBV vaccine (single-dose or double-dose) should be administered, followed by anti-HBs testing 1 to 2 months after completing the series.\[27\] In addition, since 1 to 36% of persons with HIV and isolated core antibody have viremia with HBV, some experts would first check an HBV DNA prior to administering the dose of HBV vaccine.
Evaluating and Counseling Patients with HBV-HIV Coinfection

Individuals with HIV infection who are also diagnosed with chronic HBV (positive HBsAg on two occasions at least 6 months apart) should undergo further HBV-related evaluation and receive counseling. Laboratory studies, particularly HBeAg, anti-HBe, and HBV DNA levels, can help determine the phase of the chronic HBV infection; these phases represent a dynamic interaction between HBV replication and the host immune response (Figure 7).[37] The following information summarizes key recommendations for the initial evaluation of persons diagnosed with HBV in the setting of HIV coinfection:[27]

- **Baseline HBV DNA Level**: HBV DNA quantitation, in conjunction with serum ALT, provides key information that can help determine whether the patient has immune active infection. The baseline HBV DNA level has also been shown in HBV monoinfected patients to be predictive of subsequent risk for cirrhosis and liver cancer.[38,39] Note that if persons are already receiving HIV antiretroviral therapy with agents that have activity against HBV (e.g. tenofovir DF, tenofovir alafenamide, emtricitabine, and lamivudine), the HBV DNA level may be undetectable.
- **HBeAg and anti-HBe**: Baseline testing should include HBeAg and anti-HBe. HBeAg status helps determine the stage (phase) of HBV infection; loss of HBeAg associated with anti-HBe seroconversion is an important benchmark of therapy.
- **HBV Genotype and Baseline Resistance Assay**: Routine baseline HBV genotyping and resistance testing are not recommended.
- **Serologic Studies for Hepatitis A Virus (HAV) and HCV**: (1) Assess for HCV coinfection with HCV antibody and (2) determine immunity to HAV with HAV antibody (IgG or total). Persons without immunity to HAV should receive the HAV vaccine series.
- **Basic Evaluation and Monitoring of Liver Activity and Function**: Evaluate the patient’s liver disease severity with platelet count, albumin, bilirubin, alkaline phosphatase, and prothrombin time and hepatitis activity with ALT, aspartate aminotransferase (AST) at baseline and every 6 months.
- **Staging of Liver Fibrosis**: Consider liver biopsy or noninvasive methods of staging, such as Aspartate aminotransferase-to-Platelet Ratio Index (APRI), Fibrosis-4 (Fib-4) Index, FibroTest (FibroSURE), and transient elastography (FibroScan) to assess for liver fibrosis.[40] It is worth noting, however, that neither FibroTest nor transient elastography have been extensively validated for use in clinical decision-making for patients with chronic HBV, with or without HIV infection.
- **Surveillance for Hepatocellular Carcinoma (HCC)**: Individuals with chronic HIV and HBV coinfection should undergo HCC surveillance every 6 months if they have cirrhosis, or if they are in any of the following groups with increased risk for HCC—Asian men older than age 40, Asian women older than age 50, and males from Sub-Saharan Africa older than age 40.[41] In addition, some experts recommend HCC surveillance in all persons with HIV and HBV coinfection who are older than 40 years of age.[27] The recommended modality for HCC surveillance is abdominal ultrasound every 6 months, with or without serum alpha-fetoprotein.[27,42]
- **Screening for Gastroesophageal Varices**: Patients with HBV and cirrhosis should undergo baseline screening with an esophagogastroduodenoscopy (EGD) to determine whether they have gastroesophageal varices large enough to warrant variceal bleed prophylactic therapy.[43] Patients with varices should undergo evaluation by a medical provider or specialist experienced with management of cirrhosis and prevention of variceal bleeding. If no substantial varices are observed, then EGD should be repeated every 2 years, or when liver decompensation occurs (progression from Child-Turcotte-Pugh Class A to Child-Turcotte-Pugh Class B/C cirrhosis).
- **Counseling**: Initial counseling should include the recommendation to (1) abstain from alcohol and (2) use effective methods to prevent secondary HBV transmission. These include the use of consistent barrier protection with sex partners, as well as testing and vaccination of susceptible partners and household members.
Treatment of HBV and HIV in Persons with HIV-HBV Coinfection

Goals for Treatment of HBV in Persons Coinfected with HIV

The short-term goals for treating HBV in patients with HIV coinfection are the same as in patients with HBV monoinfection: normalize ALT levels, obtain HBeAg seroconversion (if HBe-antigen positive at baseline), and maintain suppression of HBV replication.[37] The long-term goals of HBV treatment are to halt or reverse fibrosis progression, reduce the risk of hepatic decompensation, prevent the development of hepatocellular carcinoma, and decrease HBV-associated mortality.[4,9,37] Data from persons with HBV monoinfection suggest HBV therapy can achieve these goals, but similar long-term studies in persons coinfected with HIV and HBV have not been published.[9,44] Nevertheless, cohort studies with at least a few years of follow-up time suggest that antiviral therapy can readily achieve the shorter-term goals of virologic suppression, HBeAg seroconversion, and even HBsAg seroconversion in persons coinfected with HIV and HBV [45,46,47].

General Approach

The Adult and Adolescent ARV Guidelines recommend initiation of HIV antiretroviral therapy in all persons with HIV infection (regardless of CD4 cell count) to reduce the risk of disease progression and to prevent transmission of HIV.[48] For persons with HIV and HBV coinfection, the treatment should consist of a regimen that provides maximum suppression of both HIV and HBV, regardless of baseline CD4 cell count or HBV DNA levels.[49] Specifically, the antiretroviral regimen should include two agents that have full activity against HBV. Among the HIV antiretroviral medications, four nucleoside/nucleotide reverse transcriptase inhibitors—tenofovir DF, tenofovir alafenamide, emtricitabine, and lamivudine—also have antiviral activity against HBV. Although emtricitabine and lamivudine can be used interchangeably, they should not be used together. Tenofovir DF and tenofovir alafenamide are both highly active against HBV, have high genetic barrier for development of HBV drug resistance, and are active against lamivudine- or emtricitabine-resistant HBV variants.[49,50]

HIV-HBV Coinfection Treatment Data

Antiretroviral regimens that include dual combination of tenofovir DF-emtricitabine or tenofovir DF plus lamivudine have been shown to be highly efficacious in suppressing HBV DNA levels in persons coinfected with HIV and HBV.[46,51,52,53,54] In addition, tenofovir DF has been shown to suppress HBV DNA levels in patients with lamivudine-resistant HBV.[55,56,57] There are, however, less extensive data on HBV treatment efficacy of tenofovir alafenamide in persons with HIV coinfection. Two phase 3 trials in patients with chronic HBV monoinfection have demonstrated comparable efficacy of a 25 mg once-daily dose of tenofovir alafenamide (compared with tenofovir DF) for the treatment of HBV monoinfection, including one study in HBeAg-negative patients and one in HBeAg-positive patients.[58,59] Another trial involving participants with HBV monoinfection demonstrated that a switch from tenofovir DF to tenofovir AF did not result in a reduction in efficacy.[60] In an open-label, non-comparative switch trial in persons with HIV-HBV coinfection, investigators evaluated the efficacy of switching patients to elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine and after 48 weeks, 66 (92%) of patients maintained or achieved virologic suppression (HIV RNA level less than 50 copies/mL and HBV DNA less than 29 IU/mL).[61]

Recommended Regimens

When treating patients coinfected with HIV and HBV, the Adult and Adolescent ARV Guidelines recommend using an antiretroviral regimen that includes a nucleoside/nucleotide reverse transcriptase inhibitor backbone of either tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine, or tenofovir-DF plus lamivudine as part of a fully suppressive regimen.[27,49] Since tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine are the backbone NRTIs in all but one of the recommended HIV antiretroviral regimens for initial therapy, concomitant treatment of HIV and HBV can be achieved in nearly all circumstances without having to make special adjustments in the antiretroviral regimen (Table 1).[27,48,49]
• **Preferred Therapy with CrCl ≥60 mL/min**: The antiretroviral regimen must include two drugs active against HBV, preferably with one of the following oral regimens: (1) tenofovir DF 300 mg plus emtricitabine 200 mg, (2) tenofovir DF 300 mg plus lamivudine 300 mg, or (3) tenofovir alafenamide 25 mg plus emtricitabine 200 mg once daily. Note the dose of tenofovir alafenamide is 10 mg when used as a component of a single-tablet regimen that also contains cobicistat (elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine and darunavir-cobicistat-tenofovir alafenamide-emtricitabine).

• **Alternative Therapy**: If neither tenofovir DF nor tenofovir alafenamide can be used, then entecavir should be added to a fully suppressive HIV antiretroviral regimen that includes lamivudine or emtricitabine to provide a second agent active against HBV.[27,49] For patients with known or suspected lamivudine-resistant HBV, the once-daily oral dose of entecavir should be increased from 0.5 mg to 1.0 mg with normal renal function; entecavir requires dose reduction if the CrCl is less than 50 mL/min).[27,37,49,62]

• **Therapies Not Recommended**: For individuals with HIV and HBV coinfection, the use of lamivudine or emtricitabine without tenofovir DF, tenofovir alafenamide, or entecavir should be avoided since monotherapy of HBV with lamivudine or emtricitabine is associated with high cumulative rates of HBV virologic failure and emergence of resistance (Figure 8).[27,63,64] Regimens that contain adefovir are not recommended in persons with HBV and HIV coinfection due to limited potency and inferiority to tenofovir DF or tenofovir alafenamide.[27]

**Recommended Regimens with Reduced Renal Function**

• **Preferred Therapy with CrCl 30 to 59 mL/min**: Since the antiretroviral regimen should include two drugs active against HBV, the best option with mild renal impairment is tenofovir alafenamide 25 mg plus emtricitabine 200 mg PO once daily. Note the dose of tenofovir alafenamide is 10 mg when used as a component of a single-tablet regimen that also contains cobicistat (elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine and darunavir-cobicistat-tenofovir alafenamide-emtricitabine).

• **Preferred Therapy with CrCl Figure 9).**[27,67,68,69] The recommended first-line option for treatment of HBV alone in persons with HIV coinfection is peginterferon-alfa, but available data with peginterferon-alfa in the setting of coinfection suggest poorer responses and greater toxicity when compared with treatment of individuals with HBV monoinfection.[27,37,70]

**Treatment of HIV Without Treatment of HBV**

In the highly unusual situation where HIV antiretroviral therapy is indicated, but a decision is made not to initiate therapy for hepatitis B, options exist for treatment of HIV alone. This scenario could arise if significant concerns existed regarding the patient's adherence, with inconsistent therapy potentially causing hepatitis flares. If the decision is made to proceed with HIV therapy only, the clinician must carefully select a regimen that does not have overlapping anti-hepatitis B activity, such as dolutegravir-rilpivirine. Although this type of selection may be possible, this approach is highly restrictive and prohibits the use of preferred antiretroviral regimens for initial therapy.[49,71] In addition, data suggest that concurrent treatment of HBV and HIV is indicated to reduce the risk of liver disease progression, a benefit that usually outweighs the risk of HBV-associated flares with treatment interruption. Further, individuals with HIV and HBV and HCV coinfection should be on a fully suppressive antiretroviral therapy and an HBV active regimen if they are to receive direct-acting antiviral treatment for their HCV, due to the potential risk of HBV reactivation during treatment for HCV.[72,73,74]
Monitoring HBV Treatment Response in Persons with HIV Coinfection

Monitoring Response to HBV Treatment

Monitoring the virologic response to HBV therapy should consist of checking HBV DNA levels every 3 to 6 months.[27] The HBV DNA levels accurately predict response to therapy and regular monitoring during therapy is recommended to prevent or minimize the development of drug-resistant variants. In addition, for those patients who are HBeAg-positive at baseline, testing for HBeAg every 6 months is recommended after the patient achieves HBV viral suppression. The decline to an undetectable HBV DNA level typically takes longer than the time to undetectable HIV RNA response to antiretroviral therapy; an incompletely suppressed HBV DNA level after 24 weeks often occurs with HBV therapy, particularly if the baseline level exceeds 100,000 IU/mL. Once the HBV levels become undetectable, the frequency of monitoring HBV DNA levels can change to every 6 months. The Adult and Adolescent Opportunistic Infection Guidelines provide the following definitions for the different virologic responses, based on those generated by the European Association for the Study of the Liver (EASL):[27]

- **Primary Virologic Nonresponse** ([Figure 10](#)): less than 1 log$_{10}$ IU/mL decline in HBV DNA levels 12 weeks after starting therapy
- **Partial Virologic Response** ([Figure 11](#)): greater than or equal to 1 log$_{10}$ IU/mL decline in HBV DNA levels at 24 weeks, but HBV DNA remains detectable
- **Complete Virologic Response** ([Figure 12](#)): undetectable HBV DNA levels at 24 to 48 weeks using a real-time HBV DNA assay
- **Maintained Virologic Response** ([Figure 13](#)): complete virologic response that continues while the patient is on therapy for HBV
- **Sustained Virologic Response** ([Figure 14](#)): a virologic response that is still present 6 months after discontinuing therapy

Monitoring for Medication-Related Toxicity

The Adult and Adolescent Opportunistic Infection Guidelines also highlight the additional risks conferred by the use of specific anti-HBV medications and recommend the following additional monitoring strategies:[27]

- **Tenofovir DF and Tenofovir Alafenamide**: Similar to patients with HIV monoinfection who take tenofovir DF, patients with HIV and HBV coinfection should have electrolytes and serum creatinine checked every 3 to 6 months and urinalysis every 6 months. For patients with GFR less of 30 to 59 mL/min, tenofovir alafenamide-emtricitabine regimen is preferred.[27] Tenofovir alafenamide-emtricitabine is not FDA-approved for use when the CrCl is less than 30 mL/min, but tenofovir alafenamide alone, which is FDA-approved for the treatment of HBV, is approved for use in patients with a CrCl of 15 mL/min or greater.[75]
- **Peginterferon alfa**: Use of peginterferon alfa-2a or peginterferon alfa-2b carries significant risks and toxicities, including neuropsychiatric changes, activation of autoimmune and thyroid disorders, ischemic events related to drug-induced anemia (including myocardial infarction and stroke), bone marrow suppression (especially neutropenia), hepatic decompensation, and hypersensitivity reactions.[9] Secondary infections have also been reported in association with peginterferon-induced leukopenia and lymphopenia.[76, 77]
- **HIV Antiretroviral Therapy**: Some of the older antiretroviral agents used to treat HIV can potentially cause an increase in aminotransferase levels, and the rate and magnitude of hepatic injury may be greater in persons with HIV-HBV coinfection than in those with HIV monoinfection.[27, 78, 79] The hepatic injury has not been observed to occur with the same frequency with current combination regimens, many of which include integrase strand transfer inhibitors. When increases in aminotransferase levels occur in a patient with HBV coinfection who recently started on HIV antiretroviral therapy, it may be difficult to distinguish direct antiretroviral hepatotoxicity from immune reconstitution-related inflammation.[80]
Management of HIV or HBV Virologic Failure

Management of HIV Virologic Failure

If an individual with HIV-HBV coinfection experiences HIV virologic failure, but continues to have adequate HBV suppression on the regimen, then the antiretroviral medications that are active against HBV should be continued (assuming the patient is tolerating these medications) and given in combination with additional antiretroviral medications that are chosen based on HIV drug resistance genotypic testing.[27]

Management of Hepatitis B Treatment Failure

For the purposes of management, HBV treatment failure should be categorized as follows: (1) primary nonresponse after 12 weeks of therapy (less than 1 log\textsubscript{10} decline in HBV DNA levels), or (2) an increase in HBV DNA of greater than 1 log\textsubscript{10} above nadir.[27] It is important to recognize that HBV DNA levels may decline very slowly, especially in the setting of high pretreatment DNA levels and low CD4 cell counts, with some patients taking a few years or more to completely suppress HBV DNA.[46,81] These slow kinetics are not necessarily associated with HBV drug resistance,[82,83] but when lamivudine or emtricitabine is used without another active agent against HBV, resistance frequently develops.[27,63,64] The Adult and Adolescent Opportunistic Infection Guidelines recommend the following strategies for the management of HBV treatment failure in persons with HIV coinfection:[27]

- Because of the high rates of resistance with lamivudine (or emtricitabine) monotherapy to treat hepatitis B, these agents should not be used as the only agent active against HBV.[27] If a patient has been receiving lamivudine (or emtricitabine) as the sole agent against HBV, then tenofovir DF or tenofovir alafenamide should be added.[27] This strategy should be used even if lamivudine (or emtricitabine) HBV drug resistance is not suspected or documented.
- Because tenofovir has a high genetic barrier to HBV resistance compared with most other nucleoside/nucleotide analogs used to treat HIV (and in vivo resistance to tenofovir DF or tenofovir alafenamide is unlikely to develop),[84] it is reasonable to continue tenofovir DF or tenofovir alafenamide in the setting of slowly declining HBV DNA levels, along with close monitoring.[50,84,85,86] In this setting, some experts would consider adding entecavir to the regimen.[49]
- Because entecavir resistance can emerge more readily in persons with pre-existing lamivudine resistance, entecavir is not generally recommended as the mainstay of HBV therapy in such patients. If it is necessary to use entecavir in that setting, higher-dose entecavir (1.0 mg/day rather than 0.5 mg/day) and more frequent monitoring of HBV DNA levels is recommended.[27]
- If treatment failure occurs on entecavir, then the best alternative is to use tenofovir DF with or without emtricitabine (since entecavir resistance confers cross resistance with emtricitabine, lamivudine, and telbivudine).[27]
- Drug resistance is not generally encountered with interferon-based therapy. If, however, treatment failure occurs on peginterferon, the HBV treatment regimen can be switched to oral nucleoside/nucleotide analog therapy; this change will require coordination with the existing HIV antiretroviral regimen.
Stopping HBV Treatment and Hepatic Flares

In persons receiving treatment with one or more antiviral agent(s) active against HBV, stopping therapy may result in HBV reactivation and potentially serious hepatic inflammation, which is marked by a rise of serum hepatic aminotransferase levels and commonly referred to as a hepatic flare—defined as an ALT increase to at least 3 times greater than the baseline level or ALT greater than 100 U/L.[41] In one study involving 255 individuals with HIV and HBV coinfection, when lamivudine was discontinued, approximately 30% of the patients had increases in ALT levels, 5% had grade 3 or grade 4 elevations, and approximately 1% developed fulminant hepatitis and hepatic decompensation (Figure 15).[87]

If a hepatic flare occurs in a patient who stops antiviral therapy, the onset is typically within 6 months after cessation of therapy.[88] For individuals with HIV chronic HBV who stop antiviral therapy, the Adult and Adolescent Opportunistic Infection Guidelines recommend monitoring aminotransferase levels every 6 weeks for 3 months, and then every 3 months thereafter.[27] If a flare develops after stopping HBV therapy, the appropriate course of management is to restart antiviral therapy using a regimen that is fully suppressive for both HIV and HBV. It is also important to note that persons with HIV infection who abruptly stop antiretroviral therapy can have an abrupt marked increase in HIV RNA levels and develop a clinical illness similar to that observed in persons with acute HIV infection.[89]
HBV-Related Immune Reconstitution Syndrome (HBV-IRIS)

In persons with HIV and HBV coinfection, hepatic inflammation can occur after immune recovery in response to effective HIV antiretroviral therapy. This clinical scenario is commonly referred to as immune reconstitution inflammatory syndrome (IRIS).

Risk Factors for Developing HBV-Related IRIS

Although the risk of HBV-related IRIS is highest if HIV is treated without effective therapy against HBV, it can occur even with regimens that are fully active against both HIV and HBV. Baseline risk factors (prior to initiation of antiretroviral therapy) associated with HBV-related IRIS include low CD4 cell count, high HBV DNA level, and elevated baseline ALT level.[92]

Timing and Differential Diagnosis with HBV-Related IRIS

The hepatitis flare is first detected as an increase in ALT levels, typically within 6 to 12 weeks after starting antiretroviral therapy. The differential diagnosis includes direct drug or alcohol hepatotoxicity, a new viral hepatitis infection (acute hepatitis A or C), or an opportunistic infection. To help distinguish between these conditions, a review of the medication history, prior hepatitis A immunization, and history of recent HCV exposure, as well as measurement of serum HBV DNA, HIV RNA, and CD4 cell count.[27]

Monitoring for HBV-Related IRIS

Recommended monitoring for HBV-related IRIS consists of checking ALT levels monthly for 3 to 6 months after initiating antiretroviral therapy, then every 3 months thereafter.[27] If, at 12 months after starting antiretroviral therapy, IRIS has not developed, it is reasonable to return to routine laboratory monitoring.

Management of HBV-Related IRIS

For individuals who develop HBV-related IRIS (as indicated by rising ALT levels in the setting of immune recovery), existing guidelines recommend continuing therapy for HIV and HBV, unless the patient develops hypersensitivity (fever, rash, lymphadenopathy), symptomatic hepatitis (nausea, vomiting, abdominal pain, or jaundice), or the ALT increases to greater than 10 times the upper limit of normal.[27] With severe IRIS, particularly in a patient with cirrhosis, consultation with a hepatologist is recommended.[27] Although corticosteroids are used to manage some IRIS-related disorders, there are insufficient data to recommend for or against the use of corticosteroids in an individual with HIV infection who has hepatitis B-related IRIS.[27]
Hepatitis Delta Virus (Hepatitis D Virus)

Hepatitis delta virus (hepatitis D virus) is a defective satellite RNA virus that depends on the HBsAg for the encapsulation of the hepatitis D genome—it cannot exist or infect individuals in the absence of productive HBV infection. The rate of triple infection with HIV, HBV, and hepatitis D virus is not well defined, but is estimated to occur in less than 15% of persons with HIV-HBV coinfection.\cite{93,94} Risk factors for hepatitis D virus infection remain unclear but infection appears to be more prevalent in persons with a history of injection drug use, and in certain regions of the world (e.g. Africa, South America, Southern Italy, and Russia).\cite{95,96} In the United States, routine screening for hepatitis D virus antibodies is not currently recommended for persons with HIV-HBV coinfection.\cite{27} Although HIV and hepatitis D virus coinfection has no known adverse impact on clinical, virologic, or immunologic responses to antiretroviral therapy, it may increase the risk of hepatic complications, including hepatitis flares, cirrhosis, hepatic decompensation, and death in patients with HIV-HBV coinfection.\cite{94,97}

Treatment of HDV

There are currently no treatment options specifically FDA-approved for the treatment of the hepatitis D virus, other than suppressing the HBV infection. Although peginterferon has been recommended the mainstay of therapy for HDV, some data suggest that tenofovir DF can lower hepatitis D virus RNA levels in a subset of patients with HDV infection.\cite{93,98} The suppression of HDV RNA levels with tenofovir DF results is not reliably sustained and further data are necessary before this is recommended as the main treatment for HDV.\cite{99}
Preventing HBV Perinatal Transmission in Women with HIV Coinfection

Risk of HBV Perinatal Transmission

The overall rate of transmission of HBV from an HBsAg-positive woman to her neonate during the perinatal period can be as high as 90% in the absence of immunoprophylaxis. The presence of HBeAg and the associated higher HBV DNA levels mediate this risk: mothers with a positive HBeAg test have a perinatal transmission rate of 70 to 90% whereas those with a negative HBeAg test have a rate of transmission less than 10%. [25, 32] Most perinatal transmission of HBV occurs during or shortly before delivery, but can take place less frequently in utero. The exact rate of perinatal HBV transmission among mothers with HIV-HBV coinfection is not well established. Most perinatal transmission of HBV occurs during or shortly before delivery, but can take place less frequently in utero.

Strategy for Preventing HBV Maternal-to-Child Transmission

In a pregnant woman with HIV-HBV coinfection, the following strategies should be used to effectively prevent the maternal-to-child transmission of HBV and HIV: (1) suppression of maternal HIV RNA and HBV DNA to undetectable levels during pregnancy and delivery, (2) administration of prophylaxis to the infant after birth (antiretroviral medication for HIV and immunoglobulin and HBV vaccine for HBV), and (3) avoidance of breastfeeding. The breastfeeding recommendation applies in the United States, where safe feeding alternatives are available, and is specific to HIV; in contrast, mothers who are HBV monoinfected are encouraged to breastfeed, since breastfeeding is not thought to confer additional HBV risk in an infant who has received appropriate immune prophylaxis.[32, 100] The mode of delivery in HIV-HBV coinfected pregnant women should be based on standard obstetrical and HIV-related indications alone as there is no indication that caesarian section impacts the risk of vertical HBV transmission.[101, 102] Women with HIV-HBV coinfection should receive hepatitis A virus vaccination during pregnancy if not already immune.

Antiviral Regimens for Pregnant Women with HBV-HIV Coinfection

Unfortunately, even with fully suppressed HBV DNA levels, the risk of HBV perinatal transmission is not completely eliminated.[103] Lamivudine and tenofovir DF have all been studied in pregnancy and can be used safely; there are insufficient data to recommend use of tenofovir alafenamide in pregnancy.[37] According to the Perinatal Guidelines, tenofovir DF plus either lamivudine or emtricitabine is the preferred dual NRTI backbone of antepartum antiretroviral therapy in HIV-HBV coinfected pregnant women.[101] There are inadequate data to recommend use of tenofovir alafenamide. The additional third drug needed for HIV therapy can be determined based on patient preference, ideally using a preferred medication for use during pregnancy.[104] Peginterferon alfa is an abortifacient at high doses and should also not be used in pregnant women.[49]

HBV Prevention Measures for Neonates

Infants weighing greater than 2,000 grams who are born to women with HBV infection, regardless of HBV treatment status during pregnancy, should receive one dose of hepatitis B immune globulin and the first dose of the HBV vaccine series within 12 hours of birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively.[27] Management of infants weighing less than 2,000 grams is the same except that the initial vaccine dose (at birth) should not be counted as part of the vaccine series due to potentially lower immunogenicity in these infants; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning at age 1 month.[32] Postvaccination testing for both anti-HBs and HBsAg should be performed in all infants after completion of the vaccine series, at age 9 to 18 months (but not before 9 months of age or earlier than 4 weeks after the last vaccine dose); this regimen is greater than 95% effective in preventing HBV infection in these infants.[101]
Surveillance for Hepatocellular Carcinoma

Indications for Hepatocellular Carcinoma Surveillance

In persons with HIV-HBV coinfection, hepatocellular carcinoma usually develops at an earlier age and progresses faster than in persons with HBV monoinfection.\[4,105\] Data from populations with HBV monoinfection demonstrate an incidence of hepatocellular carcinoma in chronic HBV of about 0.5% of persons per year and this rate increases to 2.5% per year in patients with cirrhosis.\[106\] For persons who have evidence of cirrhosis, including those with HIV and HBV coinfection, screening for hepatocellular carcinoma is strongly recommended.\[27,42\] For persons living with HIV and HBV coinfection, hepatocellular carcinoma surveillance is indicated in the following groups.\[41\]

- All persons with cirrhosis
- Asian men older than age 40 years
- Asian women older than age 50 years
- Black men older than 40 years of age

For persons with chronic HBV infection who experience spontaneous or treatment-related clearance of HBsAg, the risk of developing liver disease progression declines considerably as does the risk of hepatocellular carcinoma. The risk of hepatocellular carcinoma, however, is thought to persist, particularly in those who are older than 50 years of age and/or have cirrhosis.\[107\] There are limited data on the natural history of persons HIV who experience HBsAg clearance. Therefore, these individuals should continue to receive hepatocellular carcinoma surveillance.

Method of Hepatocellular Carcinoma Surveillance

The American Association for the Study of Liver Diseases (AASLD) 2018 Guidelines for the Treatment of Hepatocellular Carcinoma recommend performing hepatic ultrasound, with or without serum alpha-fetoprotein, every 6 months for hepatocellular carcinoma surveillance.\[42\] The criteria for performing hepatocellular carcinoma surveillance and the surveillance method are the same for persons with HIV-HBV coinfection as with HBV monoinfection. In general, persons diagnosed with hepatocellular carcinoma have a poor prognosis, but survival may be improved if the cancer is detected at a very early stage. There is one randomized, controlled trial as well as observational data to support HCC screening in people with chronic HBV infection, and while the evidence is not methodologically strong, HCC screening is now the standard of care.\[108,109\] Currently, however, the optimal screening practice for patients with HIV-HBV coinfection remains unclear.
Managing Coinfected Patients with Advanced Liver Disease

The management of persons with HIV-HBV coinfection who develop cirrhosis and/or end-stage liver disease is the same as in patients with HBV monoinfection and involves close clinical monitoring of serologic markers, surveillance for hepatocellular carcinoma with serial abdominal ultrasounds, screening endoscopy, and management of any cirrhosis-related complications that develop. Liver transplantation is not readily available for many patients with HIV infection, but has been shown to have favorable outcomes in patients with HIV-HBV coinfection.[110] The management of decompensated cirrhosis or end-stage liver disease in a person with HIV-HBV coinfection should be done by or under the guidance of a hepatologist.[27]
Summary Points

- In the United States, up to 10% of persons living with HIV infection are coinfected with HBV; these patients have a higher risk of liver-related morbidity and mortality when compared with those with HBV monoinfection.
- The long-term treatment goals are the same for persons with HIV-HBV coinfection as for those with HBV monoinfection: delay progression of liver disease, reduce the risk of hepatocellular carcinoma, and improve survival.
- Antiretroviral therapy is recommended in all persons with HIV (regardless of CD4 cell count) to reduce the risk of disease progression and to prevent transmission of HIV; this recommendation encompasses individuals with HIV and HBV coinfection.
- The recommended antiretroviral regimens for treating persons with HIV and HBV coinfection should include three medications that are active against HIV and two medications that are active against HBV. The preferred regimens include tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine as part of a fully suppressive antiretroviral regimen.
- Use of emtricitabine or lamivudine as the only HBV-active agent in an antiretroviral regimen should be avoided whenever possible given the high rates of HBV resistance that develop with these medications.
- For persons with HIV an HBV coinfection and mild renal dysfunction, tenofovir alafenamide can be used as a substitute for tenofovir DF. If neither tenofovir DF nor tenofovir alafenamide can be used, then entecavir should be added as an additional agent as part of a regimen that will fully suppress HBV.
- Management of pregnant women with HIV-HBV coinfection requires antepartum, intrapartum, and postpartum interventions to reduce the risk of maternal-to-child transmission of both HIV and HBV.
- The management of individuals with HIV and HBV coinfection who develop cirrhosis and/or end-stage liver disease is generally the same as patients with HBV monoinfection and involves close clinical monitoring and the assistance of a hepatology specialist when indicated.
Citations


27. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Hepatitis B virus infection. Last Updated: November 13, 2018.


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[PubMed Abstract]

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[PubMed Abstract] -

[PubMed Abstract] -


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Figures

Figure 1 Prevalence of Chronic Hepatitis B in Persons with HIV Infection—HIV Outpatient Study, 1996-2007

These data are from the HIV Out-Patient Study (HOPS), 1996-2007


Chronic HBV Infection = HBsAg+ or detectable HBV DNA
Figure 2 Prevalence of Chronic Hepatitis B in Persons with HIV Infection—HIV Outpatient Study, by HIV Risk Groups, 1996-2007

These data are from the HIV Out-Patient Study (HOPS), 1996-2007


Chronic HBV Infection = HBsAg+ or detectable HBV DNA
Figure 3 Impact of Chronic HBV on Mortality in Persons with HIV Infection


<table>
<thead>
<tr>
<th>Event</th>
<th>HBsAg-positive</th>
<th>HBsAg-negative</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate/100 Person-Years (95% CI)</td>
<td>3.7</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Incidence Rate Ratio (IRR)</td>
<td>1.53</td>
<td>1.0</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Liver-Related Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate/100 Person-Years (95% CI)</td>
<td>0.7</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Incidence Rate Ratio (IRR)</td>
<td>3.58</td>
<td>1.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*The multivariate model was adjusted for latest CD4 cell count and starting highly active antiretroviral therapy as time-updated variables, risk group, gender, ethnic origin, region of Europe, date of enrollment, age, hepatitis C and diagnosis of AIDS. Not adjusted for viral load.
Figure 4 Liver Mortality in Persons with HIV Infection: Comparison Based on Coinfection with HBV or HCV

Figure 5 Mortality in Persons with HIV Infection Based on HBV and HCV Coinfection Status, 2004-2012

These data are from 25,486 individuals enrolled in the UK Collaborative HIV Cohort (UK CHIC) study during the years 2004-2012. This graph shows higher all-cause and liver-related mortality among coinfected individuals than among those with HIV monoinfection. The highest risk was among those triple-infected with HIV, HBV, and HCV.

**Figure 6 Interpretation Hepatitis B Serologic Test Results**


<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBc</th>
<th>IgM Anti-HBc</th>
<th>Anti-HBs</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Susceptible to HBV infection</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>Immune due to natural hepatitis B infection</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Acute HBV</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Chronic hepatitis B infection</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection</td>
</tr>
</tbody>
</table>
Figure 7 Phases of Chronic HBV Infection


<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>Liver Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Tolerant</td>
<td>Normal</td>
<td>Elevated Typically &gt;1 million IU/mL</td>
<td>Positive</td>
<td>Minimal inflammation and fibrosis</td>
</tr>
<tr>
<td>HBeAg-Positive Immune Active</td>
<td>Elevated</td>
<td>Elevated ≥20,000 IU/mL</td>
<td>Positive</td>
<td>Moderate-to-severe inflammation or fibrosis</td>
</tr>
<tr>
<td>Inactive Chronic Hepatitis B</td>
<td>Normal</td>
<td>Low or undetectable &lt;2,000 IU/mL</td>
<td>Negative</td>
<td>Minimal necroinflammation but variable fibrosis</td>
</tr>
<tr>
<td>HBeAg-Negative Immune Reactivation</td>
<td>Elevated</td>
<td>Elevated ≥2,000 IU/mL</td>
<td>Negative</td>
<td>Moderate-to-severe inflammation or fibrosis</td>
</tr>
</tbody>
</table>
Figure 8 HBV Drug Resistance in Persons with HIV Infection and Prolonged Lamivudine Use

The graphic shows the prevalence of HBV lamivudine-resistant mutations increased with longer duration of lamivudine therapy.

## Figure 9 Antiviral Agents with Activity Against HBV and HIV

Note: in this table tenofovir includes tenofovir DF and tenofovir alafenamide.


<table>
<thead>
<tr>
<th>Medication</th>
<th>HBV Activity</th>
<th>HIV Activity</th>
<th>Selection of HIV Resistance Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Yes</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Yes</td>
<td>Partial</td>
<td>Yes</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Yes</td>
<td>Partial&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Tenofovir alafenamide</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<sup>a</sup> = anti-HIV activity at higher doses; more potent against HBV

<sup>b</sup> = No in vitro activity observed against HIV, but HIV RNA decline reported
Figure 10 HBV Therapy: Primary Virologic Nonresponse

This graphic shows a less than 1 log_{10} IU/mL decline in HBV DNA levels 12 weeks after starting therapy.
**Figure 11 HBV Therapy: Partial Virologic Response**

This graphic shows a greater than or equal to $1 \log_{10}$ IU/mL decline in HBV DNA levels at 24 weeks, but HBV DNA remains detectable.
Figure 12 HBV Therapy: Complete Virologic Response

This graphic shows undetectable HBV DNA levels at 24 to 48 weeks using a real-time HBV DNA assay.
Figure 13 HBV Therapy: Maintained Virologic Response

This graphic shows a virologic response that continues while the patient is maintained on therapy for HBV.
**Figure 14 HBV Therapy: Sustained Virologic Response**

In this example, HBV therapy is given for 120 weeks and the HBV DNA is maintained at undetectable levels for weeks 24 to 120. The HBV DNA levels remain undetectable for 48 weeks after discontinuing therapy.
Figure 15 Liver Enzyme Elevation after Lamivudine Discontinuation in Patients with HIV and HBV Coinfection

This graph shows HIV-HBV coinfected persons enrolled in the Swiss HIV Cohort with liver enzyme elevations following withdrawal of lamivudine. The graph shows the hepatotoxicity by grade severity (I-IV).

Table 1. **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV**

**Recommended Initial Regimens for Most People with HIV**

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use (listed in alphabetical order).

### Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors:

**Note:** For individuals of childbearing potential, see the table Considerations Before Initiating one of these regimens.

- Bictegravir-tenofovir alafenamide-emtricitabine (AI)
- Dolutegravir-abacavir-lamivudine\(^a\) (AI)—if HLA-B*5701 negative and without chronic hepatitis B coinfection
- Dolutegravir plus tenofovir alafenamide\(^b\)-emtricitabine (AI)
- Dolutegravir plus tenofovir DF\(^b\)-emtricitabine\(^a\) (AI)
- Raltegravir\(^c\) plus tenofovir DF\(^b\)-emtricitabine\(^a\) (BI)
- Raltegravir\(^c\) plus tenofovir alafenamide\(^b\)-emtricitabine (BII)

### Integrase Strand Transfer Inhibitor + 1 Nucleoside Reverse Transcriptase Inhibitor

- Dolutegravir-lamivudine (AI)—except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom antiretroviral therapy is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

\(^a\) Lamivudine may substitute for emtricitabine or vice versa, if a non-fixed dose NRTI combination is desired.

\(^b\) Tenofovir alafenamide and tenofovir DF are two forms of tenofovir approved by the FDA. Tenofovir alafenamide has fewer bone and kidney toxicities than tenofovir DF, while tenofovir DF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

\(^c\) Raltegravir can be given as 400 mg twice daily or 1200 mg (two 600-mg tablets) once daily.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

**Source:**
