Hepatitis B Coinfection

This is a PDF version of the following document:
Section 1: 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 of these infections occurring in adulthood. Foreign-born individuals, however, are likely to have acquired their HBV infection earlier at birth or in childhood. Genotypes for hepatitis B virus are geographically distributed, with genotype A as the predominant subtype in North America and Europe. In the HIV Outpatient Study (HOPS), investigators examined the prevalence of chronic hepatitis B among persons with HIV infection during the years 1996 to 2007 and found overall that 8.4% of patients tested positive for chronic hepatitis B (either HBsAg-positive or HBV DNA positive), a prevalence 20-fold higher than the 0.42% prevalence in the general population (Figure 1). 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). A separate review estimated an overall 6 to 14% chronic hepatitis B prevalence rate among individuals living with HIV infection in Western Europe and the United States, with prevalence rates of 4-6% of heterosexuals, 7-10% in persons who inject drugs, and 9-17% in men who have sex with men (MSM). 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 hepatitis B infection.

Natural History

When compared to individuals with HBV monoinfection, those with HBV and HIV coinfection tend to have higher baseline HBV DNA levels, lower alanine aminotransferase (ALT) levels, decreased rates of spontaneous HBeAg seroconversion, and more frequent reactivation episodes. Individuals coinfected with HBV and HIV also appear to 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). In one study, investigators reported greater liver-related mortality in persons with HIV and HBV coinfection (14.2 per 1000 person years) than observed in either HIV monoinfection (1.7 per 1000 person years) or HBV monoinfection (0.8 per 1000 person years). Among those coinfected with HIV and HBV, the highest liver-related mortality rates have occurred in individuals with low CD4 cell counts. 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. The widespread use of effective antiretroviral therapy has increased the life expectancy for individuals with HIV infection and has shifted mortality to non-AIDS-related diseases, with an increasing proportion of deaths caused by end-stage liver disease and hepatocellular carcinoma. Several studies have found that liver-related mortality accounts for a significant proportion of non-AIDS-related deaths and viral hepatitis (hepatitis B and C) plays a major role in
these liver-related deaths (Figure 4).\cite{16,17,18,19,20,21} One study noted a higher liver-related mortality in persons coinfected with HIV and HBV when compared with those coinfected with HIV and HCV (Figure 5).\cite{12}

**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.\cite{2,22,23,24} Recommendations and vaccine schedules for hepatitis B 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 antibody (HBsAb), hepatitis B core antibody (anti-HBc), and hepatitis B surface antigen (HBsAg).[1,25] Chronic hepatitis B is defined by the detection of HBsAg on two separate tests that have been obtained at least 6 months apart.[1] Thus, for patients 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. HBV DNA testing should be considered in the following persons with HIV infection who have a negative HBsAg test: those with persistent elevation in ALT in the setting of negative hepatitis B serologic studies (especially those who are not on HBV-active antiretroviral therapy), patients with suspected acute HBV infection who are in the serologic window period (loss of HBsAg without emergence yet of HBsAb), and persons with isolated anti-HBc.[25,26]

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).[24]

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.[27] 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.[28] 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

Up to 20 to 45% of persons with HIV infection, when tested for hepatitis B infection, have isolated hepatitis B core antibody (anti-HBc).[29,30] 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, (3) occult chronic HBV infection with absent HBsAg, or (4) resolving acute HBV infection. 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.[29,31] For persons with HIV and isolated anti-HBc, the Opportunistic Infections Guidelines recommend the following approach.[1] Administer a 1-time dose of hepatitis B vaccine and checking anti-HBs 1-2 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 1-2 months after completing the series.[1]
Evaluating and Counseling Patients with HBV-HIV Coinfection

Patients with HIV infection who are also diagnosed with chronic hepatitis B infection (positive HBsAg on two occasions at least 6 months apart) should undergo further hepatitis B-related evaluation and receive counseling. Laboratory studies, particularly HBeAg and HBV DNA levels, can help determine the phase of the chronic HBV infection; these four phases represent a dynamic interaction between HBV replication and the host immune response (Figure 7).[32] The following information summarizes key recommendations for the initial evaluation of patients with hepatitis B infection in the setting of HIV coinfection:[1]

- **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.[33,34]
- **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 and anti-HBe seroconversion are important benchmarks of therapy.
- **HBV Genotype and Baseline Resistance Assay**: Routine baseline HBV genotyping and resistance testing are not recommended.
- **Serologic Studies for Viral Hepatitis Coinfection**: (1) Assess for hepatitis C coinfection with HCV antibody and (2) determine immunity to hepatitis A virus infection (HAV) with HAV antibody (IgG or total) and vaccinate if not immune to HAV.
- **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. It is worth noting, however, that neither FibroTest nor elastography have been extensively validated for use in clinical decision-making for patients with chronic hepatitis B, with or without HIV infection.
- **Surveillance for Hepatocellular Carcinoma (HCC)**: The Opportunistic Infections Guidelines recommend that 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 20.[1] In addition, the Opportunistic Infections Guidelines note that some experts recommend HCC surveillance in all persons with HIV and HBV coinfection who are older than 40 years of age.[1] The Opportunistic Infections Guidelines and the American Association for the Study of Liver Disease (AASLD) endorse using liver ultrasound every 6 months as the main modality for HCC surveillance.[1,35] Serum alpha-fetoprotein (non-maternal) does not have sufficient specificity to be recommended as a routine screening modality for HCC.[35]
- **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.[36] 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 as well as testing and vaccination of susceptible partners and household members.
Treatment of HBV in Persons Coinfected with HIV

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. 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. Data from patients 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. However, cohort studies with several years of follow-up time suggest that antiviral therapy can readily achieve the short-term goals of virologic suppression and HBeAg seroconversion in patients coinfected with HIV and HBV.

General Approach

The Guidelines for the Use of Antiretroviral Agents Adults and Adolescents Living with HIV 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. 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. Specifically, the regimen should contain at least three antiretroviral medications that have full activity against HIV and 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.

HIV and 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. In addition, tenofovir DF has been shown to suppress HBV DNA levels in patients with lamivudine-resistant HBV. There are, however, less extensive data on HBV treatment efficacy of tenofovir alafenamide. 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. In an open-label, non-comparative switch trial in persons with HIV and 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). Note that in the fixed-dose combination of cobicistat-elvitegravir-tenofovir alafenamide-emtricitabine, the tenofovir alafenamide dose is 10 mg, which is lower than the FDA approved dose of 25 mg for HBV monoinfection, but in the presence of cobicistat, which boosts tenofovir alafenamide, the clinical significance of this difference is uncertain.

Recommended Regimens

When treating patients coinfected with HIV and HBV, the antiretroviral regimen should ideally include a fully suppressive HIV antiretroviral regimen that includes a nucleoside/nucleotide reverse transcriptase inhibitor backbone of either tenofovir DF-emtricitabine, tenofovir alafenamide-
emtricitabine, or tenofovir-DT plus lamivudine as part of a fully suppressive regimen. 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). The Opportunistic Infections Guidelines provide the following recommendations for the summary of treatment of HIV-HBV coinfection with preferred therapies based on creatinine clearance (CrCl) levels:

- **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 (10 or 25 mg) plus emtricitabine 200 mg once daily. Note the 10 mg dose of tenofovir alafenamide is the dose used in the single-tablet regimen elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine.
- **Preferred Therapy with CrCl 30-59 mL/min**: The antiretroviral regimen must include 2 drugs active against HBV, preferably with tenofovir alafenamide (10 or 25 mg) plus emtricitabine 200 mg PO once daily.
- **Preferred Therapy with CrCl Figure 8**: [1,54,55]
- **Use of Entecavir**: If neither tenofovir DF nor tenofovir alafenamide can be used, then entecavir should be added to a fully suppressive HIV antiretroviral regimen to provide a second active agent active against hepatitis B. 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).[1,32,53,56]
- **Use of Adefovir**: Although adefovir has been shown to be effective in the treatment of HBV monoinfection, 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.[1]
- **Use of Telbivudine**: Although telbivudine has been shown to be effective in the treatment of HBV monoinfection, regimens that contain telbivudine are not recommended in persons with HBV and HIV coinfection.[1]

**Caution and Contraindications**

All of the antivirals with activity against HBV can potentially cause lactic acidosis and should be used with caution in patients with impaired hepatic function, especially with a Model for End Stage Liver Disease (MELD) score greater than 18.[57] However, in a phase 2 study comparing tenofovir DF, tenofovir DF-emtricitabine, and entecavir, all regimens were well tolerated in patients with decompensated chronic HBV-associated liver disease, and it is unclear which is the best option for these patients.[58] In addition, interferon (pegylated or standard) is contraindicated for use in patients with decompensated (Child-Trucotte-Pugh class B or C) liver disease.[1] According to the HIV Clinical Practice Guideline for the Management of Chronic Kidney Disease, tenofovir DF is not recommended for use in patients with HIV infection who have a glomerular filtration rate (GFR) or creatinine clearance less than 60 mL/min/1.72m², but some experts use tenofovir DF in HIV-HBV coinfected patients with mild-to-moderate renal insufficiency, adjusting the tenofovir DF dose as indicated, given the high efficacy of tenofovir DF in treating HBV and HIV infection.[59] In this situation, many experts would recommend switching tenofovir DF to tenofovir alafenamide, but if this is not possible, then closely monitor renal function and obtain expert consultation.

**Treatment of HBV Without Treatment of HIV**

Theoretically, a situation could arise where a patient is unwilling or unable to take HIV antiretroviral therapy, but has a more imminent need to treat hepatitis B infection. Treatment of chronic HBV infection is recommended for patients with immune-active chronic hepatitis B as defined by the American Association for the Study of Liver Diseases (AASLD) criteria: (1) elevation of ALT levels
greater than twofold of the upper limit of normal (30 U/L for males and 19 U/L for females) or evidence of significant histologic disease (moderate or greater degree of necroinflammation and/or fibrosis) plus (2) HBV DNA levels greater than 2,000 IU/mL if HBeAg negative or greater than 20,000 IU/mL if HBeAg positive.\[^{32}\] Unfortunately, limited treatment options exist in this setting, primarily because most HBV medications (tenofovir DF, lamivudine, entecavir, adefovir, and probably telbivudine) also have activity against HIV, and can generate drug-resistant HIV if given without a fully suppressive HIV regimen (Figure 9).\[^{1,60}\] Entecavir was originally thought to have minimal activity against HIV, but several reports noted a significant decline in HIV RNA levels and generation of the M184V mutation with entecavir monotherapy.\[^{61,62}\] Thus, when treating HBV in patients coinfected with HIV, entecavir should only be used if the patient is on a fully suppressive HIV antiretroviral regimen. The main first-line option for treatment of HBV alone in persons with HIV coinfection consists of peginterferon-alfa.\[^{1,32}\] Peginterferon is effective in HBV monoinfection, but available data in the setting of coinfection suggest poorer responses and greater toxicity when compared with treatment of patients with HBV monoinfection.\[^{63}\]

**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 significant overlapping anti-hepatitis B activity. Although this type of selection is possible, this approach is not recommended since any regimen constructed that treats HIV alone without HBV will have to exclude tenofovir DF, emtricitabine, and lamivudine and thus will not provide a first-line recommended regimen to treat HIV. We advise expert consultation if this situation arises.
Monitoring Persons with HIV Infection while on HBV Therapy

Monitoring Response to HBV Treatment

Monitoring the virologic response to HBV therapy should consist of checking HBV DNA levels every 3 to 6 months. 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 Opportunistic Infections 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):

- **Primary Virologic Non-Response** *(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 Opportunistic Infections Guidelines also highlight the additional risks conferred by the use of specific anti-HBV medications and recommend the following additional monitoring strategies:

- **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 30-59 mL/min, the Opportunistic Infections Guidelines state that a tenofovir alafenamide-emtricitabine regimen is preferred. Tenofovir alafenamide-emtricitabine is not FDA approved for use when the CrCl is less than 30 mL/min, but the tenofovir alafenamide product specifically for treatment of hepatitis B, which is not combined as a fixed-dose medication, is FDA approved for use in patients with a CrCl of 15 mL/min or greater.
- **Telbivudine**: Telbivudine can cause elevations in creatine phosphokinase (CPK) levels up to 7 times the upper limit of normal, and may induce myopathy. Patients taking telbivudine should have CPK levels checked at baseline, every 3 to 6 months, and if any musculoskeletal symptoms arise. Telbivudine is not recommended for the treatment of HBV in persons coinfected with HIV.
- **Adefovir**: Adefovir can cause renal tubular disease similar to that seen with tenofovir DF, but this is infrequent at the recommended dose (10 mg/day) used to treat HBV infection. Nevertheless, patients taking adefovir should have regular electrolytes and serum creatinine monitoring similar to what is done for tenofovir DF. Adefovir is not recommended for the treatment of HBV in persons coinfected with HIV.
- **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 lymphopenias.[65,66]

- **HIV Antiretroviral Therapy**: Some of the older antiretroviral agents used to treat HIV can potentially cause an increase in aminotransferase levels, with both the rate and magnitude of these increases noted to be greater in patients with HIV-HBV coinfection than in those with HIV monoinfection.[1,67,68] This 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.
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.[1]

Management of Hepatitis B Treatment Failure

For the purposes of management, hepatitis B treatment failure should be categorized as follows: (1) primary nonresponse after 12 weeks of therapy (less than 1 log_{10} decline in HBV DNA levels), or (2) an increase in HBV DNA of greater than 1 log_{10} above nadir.[1] 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.[38,69] These slow kinetics are not necessarily associated with HBV drug resistance,[70,71] but when lamivudine or emtricitabine is used without another active agent against HBV, resistance frequently develops.[1,54,55] The Opportunistic Infections Guidelines recommend the following strategies for the management of HBV treatment failure:[1]

- 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.[1] If a patient has been receiving lamivudine (or emtricitabine) as the sole agent against HBV, then tenofovir DF or tenofovir alafenamide should be added.[1] This strategy should be used even if lamivudine (or emtricitabine) HBV drug resistance is 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),[72] it is reasonable to continue tenofovir DF or tenofovir alafenamide in the setting of slowly declining HBV DNA levels, along with close monitoring.[42,72,73,74] In this setting, some experts would consider adding entecavir to the regimen.[41]
- Because entecavir resistance can emerge rapidly in patients with pre-existing lamivudine resistance, higher-dose entecavir (1.0 mg/day rather than 0.5 mg/day) and more frequent monitoring of HBV DNA levels is recommended in this setting.[1]
- 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).[1]
- If treatment failure occurs on peginterferon, patients can be switched to nucleoside/nucleotide analog therapy (this will require coordination with the existing HIV antiretroviral regimen). Drug resistance is not a concern here. This scenario, while unlikely, may occur in patients who had treatment of HBV with interferon or peginterferon prior to their HIV diagnosis or earlier in the HIV epidemic.
Stopping HBV Treatment and Hepatic Flares

In patients receiving treatment with an antiviral agent for hepatitis B, stopping therapy may result in HBV reactivation and potentially serious hepatic inflammation marked by a rise of serum ALT/AST, commonly referred to as a hepatic flare. In one study involving 255 patients coinfected with HIV and HBV, 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).[75] If a hepatic flare occurs in a patient who stops antiviral therapy, the onset is usually 5 to 16 weeks after the last dose. For patients with chronic hepatitis B infection who stop antiviral therapy, the Opportunistic Infections Guidelines recommend monitoring aminotransferase levels every 6 weeks for 3 months, and then every 3 months thereafter.[1] 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.[76]
HBV-Related Immune Reconstitution Syndrome (HBV-IRIS)

In patients coinfected with HIV and HBV, 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.[77]

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.[1]

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. 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 patients who develop HBV-related IRIS (as indicated by rising ALT levels), 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.[1] With severe IRIS, particularly in a patient with cirrhosis, consultation with a hepatology specialist is recommended. 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.
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 (estimates range from 2 to 15% of patients).[78,79] Risk factors for hepatitis D virus infection remain unclear but infection appears to be more prevalent in persons with HCV coinfection and in certain regions of the world (Africa, South America, Southern Italy, and Russia).[80,81] In the United States, routine screening for hepatitis D virus antibodies is not recommended for persons coinfected with HIV and HBV.[1] Although HIV and hepatitis D virus coinfection has no known adverse impact on clinical, virological, 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.[79,82] There are currently no treatment options specifically FDA-approved for the treatment of the hepatitis D virus, other than suppressing the HBV infection. In the past, peginterferon was the mainstay of therapy but new data is now emerging that antiretroviral therapy containing tenofovir DF can suppress hepatitis D virus RNA levels and modify hepatitis D virus outcomes.[78]
Special Considerations During Pregnancy

Preventing Perinatal Transmission of HBV with HIV Coinfection

The overall rate of transmission of HBV from an HBsAg-positive mother to her neonate during the perinatal period can be as high as 90% in the absence of immunoprophylaxis. The presence of hepatitis B "e" antigen 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%. [24,83] Most vertical transmission of HBV occurs during or shortly before delivery, but can take place less frequently in utero. In a pregnant woman coinfected with HIV and HBV, the strategy for preventing maternal-to-child transmission of HBV and HIV should encompass the following strategies: (1) suppression of maternal HIV and HBV viremia 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 infection; in contrast, mothers who are HBV monoinfected are encouraged to breastfeed. [83] 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. [84,85] Women with HIV-HBV coinfection should receive hepatitis A virus vaccination during pregnancy if not already immune.

Antiviral Regimens for Pregnant HBV-HIV Coinfected Patients

Unfortunately, even with fully suppressed HBV DNA levels, the risk of hepatitis B perinatal transmission is not completely eliminated. [86] Lamivudine, telbivudine, 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. [32] According to the HIV 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. [84] The additional third drug needed for HIV therapy can be determined based on patient preference, ideally using a preferred medication for use during pregnancy. [87] Peginterferon alfa is an abortifacient at high doses and should also not be used in pregnant women. [53]

HBV Prevention Measures for Neonates

Infants weighing greater than 2,000 grams who are born to women with HBV infection, regardless of 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. [1] 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. [83] Post-vaccination testing for both anti-HBs and HBsAg should be performed in all infants after completion of the vaccine series, at age 9 months to 18 months (but not before 9 months of age or earlier than 4 weeks after the last vaccine dose); this regimen is over 95% effective in preventing HBV infection in these infants. [84]
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 patients with HBV monoinfection.\cite{4,88} Data from persons 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.\cite{35} For persons coinfected with HIV and HBV who have evidence of cirrhosis, screening for hepatocellular carcinoma is strongly recommended. In addition, hepatocellular carcinoma surveillance is also recommended in the following four groups with chronic HBV, regardless of the stage of liver disease: Asian men age 40 and older, Asian women age 50 and older, hepatitis B carrier with family history of hepatocellular carcinoma, and African or North American blacks older than age 20.\cite{35} Without evidence of cirrhosis, the benefit of hepatocellular carcinoma surveillance in younger patients (men younger than age 40 or women younger than age 50) is uncertain, other than with black patients. For patients with HBV infection and cirrhosis who have spontaneous or treatment-related clearance of HBV, the risk of developing hepatocellular carcinoma declines over time, but the risk reduction is not immediate. Therefore, these patients should continue to receive hepatocellular carcinoma surveillance.

Method of Hepatocellular Carcinoma Surveillance

The 2011 Guidelines from the American Association for the Study of Liver Disease (AASLD) recommend performing an abdominal ultrasound every 6 months as the screening test for hepatocellular carcinoma surveillance; the use of alpha-fetoprotein for hepatocellular carcinoma surveillance is no longer recommended.\cite{35} 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, patients diagnosed with hepatocellular carcinoma have a poor prognosis, but the best chance for survival occurs when the cancer is detected at a very early stage. In one randomized study in China in patients with chronic HBV monoinfection, hepatocellular carcinoma surveillance was shown to reduce hepatocellular carcinoma-related mortality when compared to no surveillance.\cite{89}
Managing Coinfected Patients with Advanced Liver Disease

The management of HIV-HBV coinfected patients who develop cirrhosis and/or end-stage liver disease is the same as in patients with HBV monoinfection and involves close 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.[90] Persons living with end-stage liver disease and HIV-HBV coinfection should be managed in consultation with a hepatology specialist.[1]
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 HIV-HBV coinfection as for HBV monoinfection: delay progression of liver disease, reduce the risk of hepatocellular carcinoma, and improve survival.
- The Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents recommend initiation of antiretroviral therapy in all persons infected 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 regimen for treating a patient with HIV and HBV coinfection should include three medications that are active against HIV and two medications that are active against HBV. The preferred regimen should include tenofovir DF (or tenofovir alafenamide) plus emtricitabine (or lamivudine) 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 patients with 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 to create a fully suppressive HIV antiretroviral regimen.
- 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 to the infant.
- The management of patients 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


40. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Initiation of antiretroviral therapy. October 17, 2017. [AIDSinfo] -


References


Figures

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


HIV Outpatient 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


HIV Outpatient 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>All-Cause Mortality</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>Liver-Related Mortality</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 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 Risk Factors for Liver Related Deaths in Persons with HIV Infection

Figure 5 Liver Mortality in Persons with HIV Infection: Comparison Based on Coinfection with HBV or HCV


Liver-Related Mortality in Persons with HIV Infection, by Viral Hepatitis Status

- 1997-2001: HBV 14.9, HCV 24.4
- 2002-2010: HBV 8.1, HCV 6.7
# Figure 6 Interpretation Hepatitis B Serology Testing Results


<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBV DNA</th>
<th>HBCab (IgM)</th>
<th>HBCab (IgG)</th>
<th>HbeAg</th>
<th>HBeAb</th>
<th>HBsAb</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<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>✓</td>
<td>−</td>
<td>−</td>
<td>Acute HBV</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>−</td>
<td>✓</td>
<td>+/-</td>
<td>+/-</td>
<td>−</td>
<td>Chronic HBV (&gt; 6 months)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>Immune to HBV (past infection)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>✓</td>
<td>Immune to HBV (vaccinated)</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(^a)</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(^b)</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>

\(^a\) = anti-HIV activity at higher doses; more potent against HBV

\(^b\) = 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 $1 \log_{10} \text{IU/mL}$ 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 24-120. The HBV DNA levels remain undetectable 6 months 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. **HHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents**

**Recommended Regimen Options for Antiretroviral-Naïve Patients**

### Integrase Strand Transfer Inhibitor-Based Regimens:
- Dolutegravir-**abacavir-lamivudine**^; if HLA-B*5701 negative (AI)
- Dolutegravir plus **tenofovir DF-emtricitabine**^ (AI)
- Dolutegravir plus **tenofovir alafenamide-emtricitabine**^ (AII)
- Elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine (AI)
- Elvitegravir-cobicistat-**tenofovir DF-emtricitabine** (AI)
- Raltegravir plus **tenofovir DF-emtricitabine**^ (AI)
- Raltegravir plus **tenofovir alafenamide-emtricitabine**^ (AII)

### Protease Inhibitor-Based Regimens:
- Darunavir plus ritonavir plus **tenofovir DF-emtricitabine**^ (AI)
- Darunavir plus ritonavir plus **tenofovir alafenamide-emtricitabine**^ (AII)

^ Lamivudine may substitute for emtricitabine or vice versa.

^ The evidence supporting this regimen is based on relative bioavailability data coupled with data from randomized, controlled switch trials demonstrating the safety and efficacy of tenofovir alafenamide-containing regimens.

**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:**
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Initiation of antiretroviral therapy. October 17, 2017. [AIDSinfo]