

Considerations for Antiretroviral Use in Patients with Coinfections

Hepatitis B/HIV Virus Coinfection (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations

- Before initiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication (**AIII**).
- Because emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have activity against both HIV and HBV, an ART regimen for patients with both HIV and HBV should include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen (**A**).
- If TDF or TAF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (**B**). Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when given to patients with HBV/HIV-coinfection (**AII**). Peginterferon alfa monotherapy may also be considered in certain patients (**CII**).
- Other HBV treatment regimens, including adefovir alone or in combination with 3TC or FTC and telbivudine, **are not recommended** for patients with HBV/HIV coinfection (**CII**).
- Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against stopping these medications and be carefully monitored during interruptions in HBV treatment (**AII**).
- If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression (**AIII**).
- HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment. For that reason, all patients initiating HCV therapy should be tested for HBV. Persons with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes two agents with anti-HBV activity prior to initiating HCV therapy (**AIII**).

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 or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Approximately 5% to 10% of people with HIV in the United States also have chronic hepatitis B virus (HBV) infection.¹ The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in persons with HBV/HIV coinfection than in persons with chronic HBV monoinfection.² Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 T lymphocyte (CD4) cell responses following initiation of antiretroviral therapy (ART).^{3,4} However, antiretroviral (ARV) drug toxicities or several liver-associated complications attributed to flares in HBV activity after initiation or discontinuation of dually active ARV drugs can affect the treatment of HIV in patients with HBV/HIV coinfection.⁵⁻⁷ These complications include the following:

- Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are ARVs approved to treat HIV that are also active against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV.⁸
- The anti-HBV drug entecavir has activity against HIV. However, when entecavir is used to treat HBV in patients with HBV/HIV coinfection who are not on ART, the drug may select for the M184V

mutation that confers HIV resistance to 3TC and FTC. Therefore, when used in patients with HBV/HIV coinfection, entecavir must be used in addition to a fully suppressive ARV regimen (**AII**).⁹

- When 3TC is the only active drug used to treat chronic HBV in patients with HBV/HIV coinfection, 3TC-resistant HBV emerges in approximately 40% and 90% of patients after 2 and 4 years on 3TC, respectively. Therefore, 3TC or FTC, which is similar to 3TC, should be used in combination with other anti-HBV drugs (**AII**).¹⁰
- In patients with HBV/HIV coinfection, immune reconstitution following initiation of treatment for HIV, HBV, or both can be associated with elevated transaminase levels, possibly because HBV-induced liver damage is primarily an immune-mediated disease.¹¹
- Some ARV agents can increase transaminase levels. The rate and magnitude of these increases are higher with HBV/HIV coinfection than with HIV mono-infection.¹²⁻¹⁴ The etiology and consequences of these changes in liver function tests are unclear because the changes may resolve with continued ART. Nevertheless, some experts suspend the suspected agent(s) when the serum alanine transferase (ALT) level increases to 5 to 10 times the upper limit of normal or at a lower threshold if the patient has symptoms of hepatitis. However, increased transaminase levels in persons with HBV/HIV coinfection may indicate hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution; thus, the cause of the elevations should be investigated before discontinuing medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe, as well as HBV DNA levels.

Recommendations for Patients with HBV/HIV Coinfection

- All patients with chronic HBV should be evaluated to assess the severity of HBV infection (see [Hepatitis B Virus Infection](#) in the [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents](#)). Patients with chronic HBV should also be tested for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and, if nonimmune, receive the HAV vaccination. In addition, patients with chronic HBV should be advised to abstain from alcohol and counseled on prevention methods that protect against both HBV and HIV transmission.¹⁵
- Before ART is initiated, all persons who test positive for hepatitis B surface antigen (HBsAg) should be tested for HBV DNA by using a quantitative assay to determine the level of HBV replication (**AIII**), and the test should be repeated every 3 to 6 months to ensure effective HBV suppression. The goal of HBV therapy with nucleoside reverse transcriptase inhibitors (NRTIs) is to prevent liver disease complications by sustained suppression of HBV replication.
- Since HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment,^{16,17} persons with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes agents with anti-HBV activity (such as [TDF or TAF] plus [FTC or 3TC]) prior to initiating HCV therapy (**AIII**). The diagnosis of HBV reactivation should be considered in persons with current HBV infection who experience elevated liver enzymes during or immediately after HCV therapy.

Antiretroviral Drugs with Dual Activities against HBV and HIV

Among the ARV drugs, 3TC, FTC, TAF, and TDF all have activity against HBV. Entecavir is an HBV nucleoside analog which also has weak HIV activity. TAF is a tenofovir prodrug with HBV activity and potentially less renal and bone toxicities than TDF.

The efficacy of TDF versus TAF in patients with HBV mono-infection was evaluated in a randomized controlled trial of HBV treatment-naïve and treatment-experienced HBeAg-negative patients. In this study, TAF was noninferior to TDF based on the percentage of patients with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = .47$).¹⁸ TAF was also noninferior to TDF in HBeAg-

positive patients with chronic HBV monoinfection with a similar percentage of patients achieving HBV DNA levels <29 IU/mL at 48 weeks of therapy (64% for TAF vs. 67% for TDF; $P = .25$).¹⁹ In both studies, patients on TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than patients receiving TDF. The median change in estimated glomerular filtration rate (eGFR) from baseline to 48 weeks also favored TAF.^{18,19}

In patients with HBV/HIV coinfection, (TAF or TDF) plus (3TC or FTC) can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection, whereas 3TC resistance compromises the activity of entecavir against HBV.

Recommended Therapy

The combination of (TAF or TDF) plus (3TC or FTC) should be used as the NRTI backbone of an ARV regimen and for the treatment of both HIV and HBV infection (**AII**).²⁰⁻²² The decision whether to use a TAF- or TDF-containing regimen should be based on an assessment of risk for nephrotoxicity and for acceleration of bone loss. In a switch study in patients with HBV/HIV coinfection, study participants who switched from a primarily TDF-based ART regimen to the fixed-dose combination elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (EVG/c/TAF/FTC) maintained or achieved HBV suppression, with improved eGFR and bone turnover markers.²³ TAF/FTC-containing regimens currently approved for the treatment of HIV infection are not recommended for use in patients with creatinine clearance (CrCl) <30 mL/min. While data on switching from a TDF-based to a TAF-based ART regimen are limited, the data from the EVG/c/TAF/FTC switch study suggest that patients with HBV/HIV coinfection can switch to TAF/FTC-containing regimens with a potential reduction in renal and bone toxicity while maintaining HBV suppression.

Alternative Therapy

If TDF or TAF cannot safely be used, entecavir should be used in addition to a fully suppressive ARV regimen (**AII**); however, entecavir should not be considered as part of the ARV regimen (**BII**).²⁴ Because entecavir and 3TC share a partially overlapping pathway to HBV resistance, it is unknown whether the combination of entecavir plus 3TC or FTC will provide greater virologic or clinical benefit than entecavir alone. In persons with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (approximately every 3 months) of the HBV DNA level to detect viral breakthrough.

Peginterferon alfa monotherapy for up to 48 weeks may also be considered in some patients with HBV/HIV coinfection. However, data on the use of this therapy in persons with HBV/HIV coinfection are limited and, given safety concerns, peginterferon alfa should not be used in persons with HBV/HIV coinfection who have decompensated cirrhosis.

HBV Drugs Not Recommended

Other HBV treatment regimens include telbivudine used in addition to a fully suppressive ARV regimen, or adefovir used in combination with 3TC or FTC and a fully suppressive ARV regimen.^{20,25,26} However, data on these regimens in persons with HBV/HIV coinfection are limited. In addition, these regimens are associated with higher rates of HBV treatment failure and a higher incidence of toxicity when compared to regimens containing TDF, TAF, or entecavir. These toxicities include increased risk of renal disease with adefovir-containing regimens and increased risk of myopathy and neuropathy with telbivudine-containing regimens. Therefore, the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents **does not currently recommend** adefovir or telbivudine for patients with HBV/HIV coinfection.

Changing Antiretroviral Therapy

- **Need to discontinue ARV medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. The use of entecavir to prevent flares can be considered, especially in patients with marginal hepatic reserve such as those with compensated or decompensated cirrhosis.⁸ These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.
- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other ARV agents that effectively suppress HIV (AIII).

References

1. Spradling PR, Richardson JT, Buchacz K, Moorman AC, Brooks JT. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996-2007. *J Viral Hepat.* Feb 11 2010. Available at <https://www.ncbi.nlm.nih.gov/pubmed/20158604>.
2. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.* Dec 14 2002;360(9349):1921-1926. Available at <https://www.ncbi.nlm.nih.gov/pubmed/12493258>.
3. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS.* Mar 24 2005;19(6):593-601. Available at <https://www.ncbi.nlm.nih.gov/pubmed/15802978>.
4. Hoffmann CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfecting HAART recipients. *AIDS.* Sep 10 2009;23(14):1881-1889. Available at <https://www.ncbi.nlm.nih.gov/pubmed/19550291>.
5. Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med.* Jan 2009;10(1):12-18. Available at <https://www.ncbi.nlm.nih.gov/pubmed/18795964>.
6. Law WP, Dore GJ, Duncombe CJ, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. *AIDS.* Oct 17 2003;17(15):2191-2199. Available at <https://www.ncbi.nlm.nih.gov/pubmed/14523276>.
7. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis.* Jul 1 2002;186(1):23-31. Available at <https://www.ncbi.nlm.nih.gov/pubmed/12089658>.
8. Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfecting patients following antiretroviral therapy interruption. *AIDS.* Mar 27 2010;24(6):857-865. Available at <https://www.ncbi.nlm.nih.gov/pubmed/20216301>.
9. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med.* Jun 21 2007;356(25):2614-2621. Available at <https://www.ncbi.nlm.nih.gov/pubmed/17582071>.
10. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology.* Nov 1999;30(5):1302-1306. Available at <https://www.ncbi.nlm.nih.gov/pubmed/10534354>.
11. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis.* Jan 2001;32(1):144-148. Available at <https://www.ncbi.nlm.nih.gov/pubmed/11118394>.
12. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* Jan 5 2000;283(1):74-80. Available at <https://www.ncbi.nlm.nih.gov/pubmed/10632283>.
13. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus coinfection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS.* Dec 22 2000;14(18):2895-2902. Available at <https://www.ncbi.nlm.nih.gov/pubmed/11153671>.
14. Neukam K, Mira JA, Collado A, et al. Liver toxicity of current antiretroviral regimens in HIV-infected patients with

- chronic viral hepatitis in a real-life setting: The HEPAVIR SEG-HEP Cohort. *PLoS One*. 2016;11(2):e0148104. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26848975>.
15. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: 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*. 2016. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
 16. Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *Ann Intern Med*. Jun 06 2017;166(11):792-798. Available at <https://www.ncbi.nlm.nih.gov/pubmed/28437794>.
 17. Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. *Clin Gastroenterol Hepatol*. Jan 2017;15(1):132-136. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27392759>.
 18. Buti M, Gane E, Seto WK, et al. A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-negative, chronic hepatitis B: Week 48 efficacy and safety results. Presented at: EASL International Liver Conference. 2016. Barcelona, Spain.
 19. Chan HLY, Fung S, Seto WK. A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-positive, chronic hepatitis B: Week 48 efficacy and safety results. Presented at: EASL International Liver Conference. 2016. Barcelona, Spain.
 20. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. Nov 2006;44(5):1110-1116. Available at <https://www.ncbi.nlm.nih.gov/pubmed/17058225>.
 21. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfecting individuals. *AIDS*. Aug 24 2009;23(13):1707-1715. Available at <https://www.ncbi.nlm.nih.gov/pubmed/19584701>.
 22. de Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-term therapy with tenofovir is effective for patients co-infected with HIV and HBV. *Gastroenterology*. Aug 26 2010. Available at <https://www.ncbi.nlm.nih.gov/pubmed/20801123>.
 23. Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1/hepatitis B coinfecting adults. *J Acquir Immune Defic Syndr*. May 11 2016. Available at <http://www.ncbi.nlm.nih.gov/pubmed/27171740>.
 24. Pessoa MG, Gazzard B, Huang AK, et al. Efficacy and safety of entecavir for chronic HBV in HIV/HBV coinfecting patients receiving lamivudine as part of antiretroviral therapy. *AIDS*. Sep 12 2008;22(14):1779-1787. Available at <https://www.ncbi.nlm.nih.gov/pubmed/18753861>.
 25. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet*. Sep 1 2001;358(9283):718-723. Available at <https://www.ncbi.nlm.nih.gov/pubmed/11551579>.
 26. Ingiliz P, Valantin MA, Thibault V, et al. Efficacy and safety of adefovir dipivoxil plus pegylated interferon-alpha2a for the treatment of lamivudine-resistant hepatitis B virus infection in HIV-infected patients. *Antivir Ther*. 2008;13(7):895-900. Available at <https://www.ncbi.nlm.nih.gov/pubmed/19043923>.