# Considerations for Antiretroviral Use in Patients with Coinfections

## Hepatitis B Virus/HIV Coinfection

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| Panel's Recommendations |
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| • 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).<br>• Because emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have activity against both HIV and HBV, an antiretroviral (ARV) 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 ARV regimen (AI).<br>• In people with HBV/HIV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity is not recommended (AII), because HBV resistance to these drugs can emerge.<br>• If TDF or TAF cannot be safely used, the alternative recommended HBV therapy is entecavir, in addition to a fully suppressive ARV regimen (BI). Entecavir has weak 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 also may be considered in certain patients (CII).<br>• 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).<br>• 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 they should be carefully monitored during interruptions of HBV treatment (AII).<br>• When switching "or modifying" an ARV regimen in a person with HBV/HIV coinfection, ARV drugs that are active against HBV should be continued (AII) or specific anti-HBV drugs should be initiated.<br>• HBV reactivation has been observed in people with HBV infection during interferon-free hepatitis C virus (HCV) treatment. For that reason, all patients initiating HCV therapy should be tested for HBV. People 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 = Weak*<br>*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 people with HBV/HIV coinfection than in people 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 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, 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 and HBV 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 liver transaminase levels. The incidence and magnitude of these increases are higher with HBV/HIV coinfection than with HIV monoinfection.[12-14] The etiology and consequences of these changes in transaminases 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 and/or new elevations in bilirubin. However, increased transaminase levels in people 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, which should decrease in the setting of immune reconstitution.

## *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 in the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV). Patients with chronic HBV also should 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 also 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. A recent

large cohort study found that persistent HBV viremia on ART and high HBV DNA levels were associated with a higher risk of hepatocellular carcinoma (HCC), even if HIV was suppressed; whereas sustained HBV DNA suppression for ≥1 year was associated with a 58% reduction in HCC risk.[16]

- Because HBV reactivation has been observed in people with HBV infection during interferon-free hepatitis C virus (HCV) treatment,[17,18] people 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 people 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 that has weak HIV activity. TAF is a tenofovir prodrug with HBV activity and potentially less renal and bone toxicities than TDF, although weight gain does occur more commonly with TAF than TDF.[19,20]

The efficacy of TDF versus TAF in patients with HBV monoinfection was evaluated in a randomized controlled trial of HBV treatment-naive 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; $P = 0.47$).[21] TAF also was 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; $P = 0.25$).[22] 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.[21,22]

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 people 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).**[23-25] 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, and balanced with the potential for weight gain with TAF as compared with TDF. In a switch study in patients with HBV/HIV coinfection, study participants who switched from a primarily TDF-based ARV 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.[26] TAF/FTC-containing regimens currently approved for the treatment of HIV infection **are not recommended** for use in patients with creatinine clearance <30 mL/min (except for patients receiving hemodialysis). Although data on switching from a TDF-based to a TAF-based ARV 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 be safely 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).**[27] 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 people 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 also may be considered in some patients with HBV/HIV coinfection. However, data on the use of this therapy in people with HBV/HIV coinfection are limited and, given safety concerns, peginterferon alfa should not be used in people 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.[23,28,29] However, data on these regimens in people 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 Adults and Adolescents with HIV **does not recommend** adefovir or telbivudine for patients with HBV/HIV coinfection.

## *Changing Antiretroviral Therapy*

- When switching "or modifying" an ARV regimen in a person with HBV/HIV coinfection: ARV drugs that are active against HBV should be continued **(AII)** or specific anti-HBV drugs should be initiated.
- **Need to discontinue ARV medications active against HBV in patients with HBV/HIV coinfection:** Withdrawal of HBV active treatment in a patient with active HBV infection **is not recommended** in patients with HBV/HIV coinfection. If a recommended active HBV drug cannot be continued (tenofovir, entecavir), presumably due to concern for safety, and HBV active therapy must be withdrawn, the patient's clinical course should be monitored with frequent testing of liver transaminases and total bilirubin. The risk of HBV flare in this setting is highest in patients with positive HBeAg and those with active HBV. If no anti-HBV ARV drug can be used, 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] Recommended HBV active drugs should be used in addition to a fully suppressive ARV regimen.

## 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*. 2010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20158604.

2. Thio CL, Seaberg EC, Skolasky RJ, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 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*. 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 coinfected HAART recipients. *AIDS*. 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*. 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*. 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*. 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-coinfected patients following antiretroviral therapy interruption. *AIDS*. 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*. 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*. 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*. 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*. 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 co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. 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 Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection.

16. Kim HN, Newcomb CW, Carbonari DM, et al. Risk of HCC with hepatitis B viremia among HIV/HBV-coinfected persons in North America. *Hepatology*. 2021;74(3):1190-1202. Available at: https://pubmed.ncbi.nlm.nih.gov/33780007.

17. 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*. 2017;166(11):792-798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28437794.

18. 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*. 2017;15(1):132-136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27392759.

19. Wood BR, Huhn GD. Excess weight gain with integrase inhibitors and tenofovir alafenamide: what is the mechanism and does it matter? *Open Forum Infect Dis*. 2021;8(12):ofab542. Available at: https://pubmed.ncbi.nlm.nih.gov/34877366.

20. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin Infect Dis*. 2020;71(6):1379-1389. Available at: https://pubmed.ncbi.nlm.nih.gov/31606734.

21. Buti M, Gane E, Seto WK, et al. GS06 - 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. *Journal of Hepatology*. 2016;64(2, Supplement):S135-S136. Available at: https://www.sciencedirect.com/science/article/pii/S0168827816016378.

22. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-Positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1(3):185-195. Available at: https://pubmed.ncbi.nlm.nih.gov/28404091.

23. 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*. 2006;44(5):1110-1116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17058225.

24. 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 coinfected individuals. *AIDS*. 2009;23(13):1707-1715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19584701.

25. 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*. 2010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20801123.

26. 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 coinfected adults. *J Acquir Immune Defic Syndr*. 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27171740.

27. Pessoa MG, Gazzard B, Huang AK, et al. Efficacy and safety of entecavir for chronic HBV in HIV/HBV coinfected patients receiving lamivudine as part of antiretroviral therapy. *AIDS*. 2008;22(14):1779-1787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18753861.

28. 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*. 2001;358(9283):718-723. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11551579.

29. 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.