



## **Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents**

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## Considerations for Antiretroviral Use in Patients with Coinfections

### Hepatitis B (HBV)/HIV Virus Coinfection (Last updated July 14, 2016; last reviewed July 14, 2016)

#### 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, for patients coinfecting with HIV and HBV, ART should be initiated with the fixed-dose combination of TDF/FTC or TAF/FTC, or the individual drug combinations of TDF plus 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen (**AI**).
- If TDF or TAF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (**BI**). 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 used in HBV/HIV-coinfecting patients (**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 HBV/HIV coinfecting patients (**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 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**).

**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 HIV-infected persons in the United States also have chronic hepatitis B virus (HBV) infection.<sup>1</sup> The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in HBV/HIV-infected persons than in persons with chronic HBV mono-infection.<sup>2</sup> 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).<sup>3,4</sup> 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.<sup>5-7</sup> 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.<sup>8</sup>
- The anti-HBV drug entecavir has activity against HIV. However, when entecavir is used to treat HBV in HBV/HIV-coinfecting patients not on ART, the drug may select for the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, when used in HBV/HIV-coinfecting patients, entecavir must be used in addition to a fully suppressive ARV regimen (**AII**).<sup>9</sup>
- When 3TC is the only active drug used to treat chronic HBV in HBV/HIV coinfecting patients, 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**).<sup>10</sup>

- In HBV/HIV coinfecting patients, immune reconstitution following initiation of treatment for HIV, HBV, or both can be associated with elevated transaminase levels, possibly because HBV is primarily an immune-mediated disease.<sup>11</sup>
- 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.<sup>12-14</sup> 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. However, increased transaminase levels in HBV/HIV-coinfecting persons 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 HBV/HIV-Coinfecting Patients***

- All patients with chronic HBV should be evaluated to assess the severity of HBV infection (see the [HBV](#) section of 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.<sup>15</sup>
- Before ART is initiated, all persons who test positive for 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 NRTIs is to prevent liver disease complications by sustained suppression of HBV replication.

### ***Antiviral 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 HBV-mono-infecting patients 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;  $P = 0.47$ ).<sup>16</sup> TAF was also noninferior to TDF in HBeAg-positive patients with chronic HBV mono-infection with similar percentage of patients achieving HBV DNA levels <29 IU/ml at 48 weeks of therapy (64% for TAF vs. 67% for TDF;  $P = 0.25$ ).<sup>17</sup> In both studies, patients on TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at week 48 than patients receiving TDF. The median change in estimated glomerular filtration rate (eGFR) from baseline to week 48 also favored TAF.<sup>16,17</sup>

In HBV/HIV-coinfecting patients, only TDF (with FTC or 3TC) or **TAF/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.

### ***Recommended Therapy***

The combination of TDF (with FTC or 3TC) or **TAF/FTC** should be used as the NRTI backbone of an ARV regimen and for the treatment of both HIV and HBV infection<sup>18-20</sup> (**AII**). **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 HBV/HIV-coinfecting patients, study participants who switched from a

primarily TDF-based ART regimen to the fixed-dose combination EVG/c/TAF/FTC maintained or achieved HBV suppression, with improved eGFR and bone turnover markers.<sup>21</sup> Currently TAF/FTC-containing regimens 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 HBV/HIV-coinfected patients 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<sup>22</sup> (**BII**). 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 HBV/HIV-coinfected patients. 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 HBV/HIV-coinfected persons with decompensated cirrhosis.

### **Not Recommended Therapy**

Other HBV treatment regimens include adefovir in combination with 3TC or FTC, or telbivudine in addition to a fully suppressive ARV regimen.<sup>18,23,24</sup> However, data on these regimens in persons with HBV/HIV coinfection are limited. In addition, compared to TDF, TAF, or entecavir, these regimens are associated with a higher incidence of toxicity, including renal disease when used with adefovir and myopathy and neuropathy when used with telbivudine, as well as higher rates of HBV treatment failure. Therefore, the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents does not currently recommend ADV or telbivudine for HBV/HIV-coinfected patients.

- **Need to discontinue 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.<sup>8</sup> 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**).

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