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

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Hepatitis C Virus/HIV Coinfection (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations

- All people with HIV should be screened for hepatitis C virus (HCV) infection **(AIII)**. Patients at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected **(AIII)**.
- Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most persons with HCV/HIV coinfection, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 T lymphocyte cell count **(AI)**.
- Initial ART regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the ART and HCV treatment regimens should be selected with special consideration for potential drug-drug interactions and overlapping toxicities **(AIII)** (see discussion in the text below and in Table 13).
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy, which includes having their liver fibrosis stage assessed to inform the length of their therapy and subsequent risk of hepatocellular carcinoma and liver disease complications **(AIII)**.
- Persons with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and core (HBcAb; total or IgG). Persons who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination **(AIII)**.
- HBV reactivation has been observed in persons with HBV infection during HCV treatment with direct-acting antivirals (DAAs). Accordingly, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) 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*

The treatment of hepatitis C virus (HCV) infection is rapidly evolving. Patients with HCV/HIV coinfection treated with all-oral, direct-acting antiviral (DAA) HCV regimens can achieve sustained virologic response (HCV cure) at rates comparable to those of patients with HCV mono-infection.[1-3] This section of the guidelines focuses on hepatic safety and drug-drug interaction issues related to HCV/HIV coinfection and the concomitant use of antiretroviral (ARV) agents and HCV drugs. For specific guidance on HCV treatment, clinicians should refer to the HCV Guidance from the American Association for the Study of Liver Diseases.

Among patients with chronic HCV infection, approximately one-third progress to cirrhosis, at a median time of <20 years.[4,5] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[6-9] A meta-analysis found that patients with HCV/HIV coinfection had a three-fold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV monoinfection.[8] The risk of progression is even greater in patients with HCV/HIV coinfection who have low CD4 T lymphocyte cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in patients with HCV/HIV coinfection, several studies have demonstrated that the rate of disease progression continues to exceed that observed in patients without HIV infection.[10,11] Whether HCV infection accelerates HIV progression, as measured by the occurrence of AIDS-related opportunistic infections (OIs) or death,[12] is unclear. With older ARV drugs, persons with chronic HCV co-infection experienced higher rates of hepatotoxicity than those seen in persons without HCV.[13,14] These higher rates have not been observed with the newer ARV agents that are currently in use.

Assessment of HCV/HIV Coinfection

- All patients with HIV should be screened for HCV infection using sensitive immunoassays licensed for

the detection of antibodies to HCV in blood.[15] At-risk HCV-seronegative patients should undergo repeat testing annually or as clinically indicated. HCV-seropositive patients should be tested for HCV RNA using a sensitive quantitative assay to confirm the presence of active infection. Patients who test HCV RNA positive should undergo HCV genotyping and liver disease staging as recommended by the HCV Guidance.

- Patients with HCV/HIV coinfection should be counseled to avoid consuming alcohol and to use appropriate precautions to prevent transmission of HIV and/or HCV to others.
- People with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and core (HBcAb; total or IgG).
  - Persons with evidence of active HBV infection (as determined by the presence of HBsAg) should be further evaluated and treated with ART that includes agents with anti-HIV and anti-HBV activities **(AIII)**.
  - Those who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination.
- Patients with HCV/HIV coinfection who are susceptible to hepatitis A virus (HAV) should be vaccinated.
- All patients with HCV/HIV coinfection are candidates for curative HCV treatment.

Antiretroviral Therapy in HCV/HIV Coinfection

When to Start Antiretroviral Therapy

Initiation of ART for persons with HCV/HIV coinfection should follow the recommendations for all persons with HIV infection, taking into account the need for concurrent HCV treatment with oral DAA regimens, drug-drug interaction potentials, and the individual's HBV status.

Considerations When Starting Antiretroviral Therapy

The same regimens that are recommended for initial treatment of HIV in most ART-naive persons are also recommended for persons with HCV/HIV coinfection. Special considerations for ARV selection in persons with HCV/HIV coinfection include the following:

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug-drug interactions with the HCV treatment regimen (see Table 13).
- In persons with HCV/HBV coinfection, HBV reactivation has been observed during HCV treatment with DAAs.[16,17] Therefore, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes agents with anti-HBV activity (such as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide plus emtricitabine or lamivudine) prior to initiating HCV therapy **(AIII)**.
- Cirrhotic patients should be evaluated for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. All patients with Child-Pugh class B or C disease should be evaluated by an expert in advanced liver disease and considered for liver transplantation. Furthermore, hepatically metabolized ARV and HCV DAA drugs may be contraindicated or require dose modification in patients with Child-Pugh class B and C disease (see Appendix B, Table 8).

Hepatotoxicity

Drug-induced liver injury (DILI) following the initiation of ART is more common in patients with HCV/HIV coinfection than in those with HIV mono-infection. Individuals with HCV/HIV coinfection

who have advanced liver disease (e.g., cirrhosis, end-stage liver disease) are at greatest risk for DILI.[18] Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[19] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 4 to 8 weeks after initiation of ART and at least every 6 to 12 months thereafter, and more often if clinically indicated. Mild to moderate fluctuations in ALT and/or AST levels (<5 times upper limit of normal [ULN]) are typical in individuals with chronic HCV infection. In the absence of signs and/or symptoms of liver disease or increases in bilirubin, these fluctuations do not warrant interruption of ART, but do warrant monitoring to ensure a return to baseline. Patients with significant elevations in ALT and/or AST levels (>5 times ULN), concomitant increase in total bilirubin, and/or concomitant symptoms (weakness, nausea, vomiting) should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis). If these signs and symptoms do not resolve, ART should be discontinued.

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found in the HCV Guidance. Several ARV drugs and HCV DAAs have the potential for clinically significant pharmacokinetic drug-drug interactions when used in combination. Prior to starting HCV therapy, the ART regimen may need to be modified to reduce the drug-drug interaction potential. Table 13 below provides recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection. In patients receiving ART that has been modified to accommodate HCV treatment, HIV RNA should be measured within 2 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. Clinicians should wait at least 2 weeks after ART modification before initiating an HCV DAA regimen. Clinicians should also wait for at least 2 weeks before resuming the original ART regimen after a patient completes the HCV DAA regimen. The prolonged half-life of some HIV and HCV drugs poses a potential risk of drug-drug interactions if a regimen is resumed soon after ART modification or HCV treatment completion.

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 1 of 4)

The recommendations in this table for concomitant use of selected HIV drugs with FDA-approved HCV DAA drugs are based on available PK interaction data or are predictions based on the known metabolic pathway of the agents. In some cases, there are not enough data to make any recommendations, and these instances are indicated in the table. In all cases where HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. As the field of HCV therapy is rapidly evolving, readers should also refer to the latest drug product labels and the HCV Guidance for updated information.

Note: Interactions with FPV, IDV, NFV, and SQV are **not** included in this table. Please refer to the FDA product labels for information regarding drug interactions with these HIV PIs.

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)				
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
NRTIs									
3TC	✓	✓	✓	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓ Monitor for TDF toxicity.	✓ Monitor for TDF toxicity.	✓ Monitor for TDF toxicity.	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓	✓	✓	✓
PIs									
Unboosted ATV	✓	✓	✓	✓	✘	✘	✘	✓[b]	✘

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 2 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)				
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
PIs, continued									
ATV/r or ATV/c	✓ ↓ DCV dose to 30 mg/day	✓	✓ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated toxicities.[d]	✓ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated toxicities.[d]	✘	✘	✘	✓[c]	✘
DRV/r or DRV/c	✓	✓			✓ If a PI/r is used with TDF, ↑ TDF concentrations. Monitor for TDF-associated toxicities.[d] Consider monitoring for hepatotoxicity.[e]	✘	✘	✘	✘
LPV/r	✓	✓			✘	✘	✘	✘	✘
TPV/r	?	✘	✘	✘	✘	✘	✘	✘	✘
NNRTIs									
DOR	✓	✓	✓ If used with TDF, monitor for TDF toxicity.	✓	✓	✓	✓	✓	✓
EFV	✓ ↑ DCV dose to 90 mg/day	✓		✘	✘	✘	✘	✘	✘
ETR	✓ ↑ DCV dose to 90 mg/day	✓		✘	✘	✘	✘	✘	✘

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 3 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)				
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
NNRTIs, continued									
NVP	✓ ↑ DCV dose to 90 mg/day	✓	✓ If used with TDF, monitor for TDF toxicity.	✘	✘	✘	✘	✘	✘
RPV	✓	✓		✓	✓	✓	✓	✘	✓
INSTIs									
BIC/TAF/FTC	✓	✓	✓	✓	✓	✓	✓	✓	✓
DTG	✓	✓	✓ If used with TDF, monitor for TDF toxicity.	✓	✓	✓	✓	✓	✓
EVG/c/TDF/ FTC	✓ ↓ DCV dose to 30 mg/day	✓	✘	✓ If used with TDF, monitor for TDF toxicity.	✓ If used with TDF, monitor for TDF toxicity. Consider monitoring for hepatotoxicity.[e]	✓ If used with TDF, monitor for TDF toxicity. Consider monitoring for hepatotoxicity.[f]	✘	✘	✘
EVG/c/TAF/ FTC	✓ ↓ DCV dose to 30 mg/day	✓	✓	✓	✓ Consider monitoring for hepatotoxicity.[e]	✓ Consider monitoring for hepatotoxicity.[f]	✘	✘	✘
RAL	✓	✓	✓	✓	✓	✓	✓	✓	✓
CCR5 Antagonist									
MVC	✓	✓	✓	✓	✓	✓	✓	✘	✓

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 4 of 4)

[a] Dasabuvir must be prescribed with ombitasvir/paritaprevir/RTV.

[b] Reduce ATV dose to 300 mg and instruct the patient to take it in the morning at same time as ombitasvir/paritaprevir/RTV plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.

[c] This HCV regimen contains RTV. If ATV is part of the ARV regimen, prescribe ATV 300 mg without COBI or RTV. It should be taken in the morning at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. Resume RTV or COBI regimen when HCV therapy is completed.

[d] Consider using an alternative HCV treatment or ARV regimen to avoid increases in TDF exposure. If co-administration is necessary, monitor patient for TDF-associated adverse reactions.

[e] Voxilaprevir exposures can increase when it is coadministered with pharmacologically boosted DRV or EVG. Until more safety data in clinical settings becomes available, patients who are receiving voxilaprevir and pharmacologically boosted DRV or EVG should be monitored for hepatotoxicity.

[f] Glecaprevir exposures can increase when it is coadministered with EVG/c. Until more safety data in clinical settings becomes available, patients who are receiving glecaprevir and EVG/c should be monitored for hepatotoxicity.

Key to Symbols:

✓ = ARV agents that can be used concomitantly

✘ = ARV agents not recommended

? = data limited or not available on pharmacokinetic interactions with ARV drug

↑ = increase

↓ = decrease

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; DSV = dasabuvir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDA = Food and Drug Administration; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FTC = emtricitabine; HCV = hepatitis C virus; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

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