Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

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

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 (CD4) cell count **(AI)**.
- Initial ART regimens 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 regimen should be selected with special consideration for potential drug-drug interactions and overlapping toxicities (see discussion in the text below and in Table 12).
- In patients with lower CD4 counts (e.g., <200 cells/mm^3), ART should be initiated promptly **(AI)** and HCV therapy may be delayed until the patient is stable on HIV treatment **(CIII)**.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy and have their liver fibrosis stage assessed to inform the length of their therapy, ribavirin need (a concern with some regimens), and subsequent risk of hepatocellular carcinoma and liver disease complications.
- 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 interferon-free HCV treatment. 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) rates comparable to those of patients with HCV monoinfection.[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 http://www.hcvguidelines.org/.

Among patients with chronic HCV infection, approximately one-third progress to cirrhosis, at a median time of less than 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 (CD4) 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 continues to exceed that observed in patients without HIV infection.[10,11] Whether HCV infection accelerates HIV progression, as measured by AIDS-related opportunistic infections (OIs) or death,[12] is unclear. Although some older ARV drugs were associated with higher rates of hepatotoxicity in patients with chronic HCV infection,[13,14] the newer ARV agents that are currently in use are less hepatotoxic.

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. 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 guidelines (see http://www.hcvguidelines.org/).

- 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 (HBsAg) should be further evaluated and treated with ART that includes agents with anti-HIV and 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 needs for concurrent HCV treatment with oral DAA regimens and the individual's HBV status.

Antiretroviral Drugs to Start and Avoid

Initial ARV combination regimens recommended for most HIV treatment-naive patients with HCV are the same as those recommended for patients without HCV infection. Special considerations for ARV selection in patients 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 12).
- HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment.[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 [TAF] 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 for consideration of 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 7).

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 monoinfection. 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 if clinically indicated. Mild to moderate fluctuations in ALT and/or AST 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. Patients with significant ALT and/or AST elevation should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute hepatitis A virus [HAV] or HBV infection, hepatobiliary disease, or alcoholic hepatitis).

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found at http://www.hcvguidelines.org/. 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 12 below provides recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection. In patients on modified ART who have suppressed plasma HIV RNA, HIV RNA should be measured within 4 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. After HCV treatment is completed, the modified ART regimen should be continued for at least 2 weeks before reinitiating the original regimen. Continued use of the modified regimen is necessary because of the prolonged half-life of some HCV drugs and the potential risk of drug-drug interactions if a prior HIV regimen is resumed soon after HCV treatment is completed.

Table 12. 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 Food and Drug Administration (FDA)-approved hepatitis C virus (HCV) direct-acting antiviral (DAA) drugs are based on available pharmacokinetic interaction data or 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 HCV guidelines (www.hcvguidelines.org/) for updated information.

Note: Interactions with fosamprenavir, indinavir, nelfinavir, and saquinavir are **not** included in this table. Please refer to the FDA product labels for information regarding drug interactions with these HIV protease inhibitors (PIs). Because the HCV PIs boceprevir and telaprevir are no longer recommended for HCV treatment, these products have been removed from this table.

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-Turcotte 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 12. 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-Turcotte 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	NS3/4A 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									
EFV	✔ ↑ DCV dose to 90 mg/day	✔	✔ If used with TDF, monitor for TDF toxicity.	✘	✘	✘	✘	✘	✘
ETR	✔ ↑ DCV dose to 90 mg/day	✔		✘	✘	✘	✘	✘	✘
NVP	✔ ↑ DCV dose to 90 mg/day	✔		✘	✘	?	✘	✘	✘
RPV	✔	✔		✔	✔	✔	✔	✘	✔

Table 12. 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-Turcotte 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
INSTIs									
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	✔	✔	✔	✔	✔	✔	?	✘	✔

[a] Dasabuvir must be prescribed with ombitasvir/paritaprevir/ritonavir

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

[c] Take ATV 300 mg in the morning at same time as ombitasvir/paritaprevir/ritonavir plus dasabuvir. If taking RTV or COBI, discontinue RTV or COBI in HIV regimen until HCV therapy is completed.

Table 12. 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)

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

[e] Due to increased voxilaprevir exposures when given with pharmacologically boosted DRV or EVG, monitoring patients for hepatotoxicity is recommended until more safety data in clinical settings becomes available.

[f] Due to increased glecaprevir exposures when given with EVG/c, monitoring patients for hepatotoxicity is recommended until more safety data in clinical settings becomes available.

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DAA = direct-acting antiviral agents; DRV = darunavir; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; DSV = dasabuvir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HCV = hepatitis C virus; 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 = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

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