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

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

Panel Recommendations
• All HIV-infected patients should be screened for hepatitis C virus (HCV) infection. Patients at high risk of HCV infection should be screened annually and whenever HCV infection is suspected.
• 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 HCV/HIV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all HCV/HIV-coinfected patients, regardless of CD4 T lymphocyte (CD4) cell count **(AI)**.
• Initial ART regimens recommended for most HCV/HIV-coinfected patients are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the regimen should be selected with special considerations of potential drug-drug interactions and overlapping toxicities with the HCV treatment regimen (see discussion in the text below and in Table 12).
• Combined treatment of HIV and HCV can be complicated by drug-drug interactions, increased pill burden, and toxicities. Although ART should be initiated for all HCV/HIV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm^3 some clinicians may choose to defer ART until HCV treatment is completed **(CIII)**.
• In patients with lower CD4 counts (eg, <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)**.
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. Data suggest that HCV/HIV-coinfected patients treated with all-oral HCV regimens have sustained virologic response rates comparable to those of HCV-monoinfected patients. The purpose of this section is to discuss 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, please 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.[1,2] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[3-6] A meta-analysis found that HCV/HIV-coinfected patients had a three-fold greater risk of progression to cirrhosis or decompensated liver disease than HCV-monoinfected patients.[5] The risk of progression is even greater in HCV/HIV-coinfected patients with low CD4 T lymphocyte (CD4) cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in HCV/HIV-coinfected patients, several studies have demonstrated that the rate continues to exceed that observed in patients without HIV infection.[7,8] Whether HCV infection accelerates HIV progression, as measured by AIDS-related opportunistic infections (OIs) or death,[9] is unclear. Although some older ARV drugs that are no longer commonly used have been associated with higher rates of hepatotoxicity in patients with chronic HCV infection,[10,11] newer ARV agents currently in use appear to be less hepatotoxic.

For more than a decade, the mainstay of treatment for HCV infection was a combination regimen of peginterferon and ribavirin (PegIFN/RBV), but this regimen was associated with a poor rate of sustained virologic response (SVR), especially in HCV/HIV-coinfected patients. Rapid advances in HCV drug development led to the discovery of new classes of direct-acting antiviral (DAA) agents that target the HCV replication cycle. Recently approved DAA agents are used with or without RBV and have higher SVR rates, reduced pill burden, less frequent dosing, fewer side effects, and shorter durations of therapy than earlier approved agents.[12-16] Guidance on the treatment and management of HCV in HIV-infected and HIV-uninfected adults can be found at http://www.hcvguidelines.org/.[17]

Assessment of Hepatitis C Virus/HIV Coinfection

- All HIV-infected patients should be screened for HCV infection using sensitive immunoassays licensed for the detection of antibody to HCV in blood.[18] 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 most updated 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. HCV/HIV-coinfected patients who are susceptible to hepatitis A virus (HAV) or hepatitis B virus (HBV) infection should be vaccinated against these viruses.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy.

Antiretroviral Therapy in Hepatitis C Virus/HIV Coinfection

When to Start Antiretroviral Therapy

The rate of liver disease (liver fibrosis) progression is accelerated in HCV/HIV-coinfected patients, particularly in individuals with low CD4 counts (≤350 cells/mm^3). Data largely from retrospective cohort studies are inconsistent regarding the effect of ART on the natural history of HCV disease;[6,19,20] however, some studies suggest that ART may slow the progression of liver disease by preserving or restoring immune function and by reducing HIV-related immune activation and inflammation.[21-23] Therefore, ART should be initiated in all HCV/HIV-coinfected patients, regardless of CD4 count **(AI)**. However, in HIV treatment-naive patients with CD4 counts >500 cells/mm^3, some clinicians may choose to defer ART until HCV treatment is completed to avoid drug-drug interactions **(CIII)**. Compared to patients with CD4 counts >350 cells/mm^3, those with CD4 counts <200 cells/mm^3 had lower HCV treatment response rates and higher rates of toxicity due to PegIFN/RBV.[24] There is a lack of data regarding HCV treatment response to combination therapy with DAA agents in those with advanced immunosuppression. For patients with lower CD4 counts (eg, <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)**.[25-28]

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 HCV/HIV-coinfected patients include the folllowing:

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug-drug interactions (see Table 12) and overlapping toxicities with the HCV treatment regimen.
- Cirrhotic patients should be carefully evaluated by an expert in advanced liver disease for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. This assessment is necessary because 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 HCV/HIV-coinfected patients than in those with HIV monoinfection. HVC/HIV coinfected individuals with advanced liver disease (eg, cirrhosis, end-stage liver disease) are at greatest risk for DILI.[29] Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[30]

- Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual ARV agents across clinical trials is difficult. The incidence of significant elevations in liver enzyme levels (more than 5 times the upper limit of the normal laboratory reference range) is low with currently recommended ART regimens. Hypersensitivity (or allergic) reactions associated with rash and elevations in liver enzymes can occur with certain ARVs. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 2 to 8 weeks after initiation of ART and every 3 to 6 months thereafter. 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 (eg, acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis). Short-term interruption of the ART regimen or of the specific drug suspected of causing the DILI may be required.[31]

Concurrent Treatment of HIV and Hepatitis C Virus Infection

Concurrent treatment of HIV and HCV is feasible, but treatment may be complicated by pill burden, drug-drug interactions, and toxicities. In this context, the stage of HCV disease should be assessed to determine the medical need for HCV treatment and to inform the decision on when to start treatment. Additional guidance on the treatment and management of HCV in HIV-infected and uninfected adults can be found at http://www.hcvguidelines.org/. If the decision is to treat HCV, the ART regimen may need to be modified before HCV treatment is initiated to reduce the potential for drug-drug interactions and/or toxicities that may develop during the period of concurrent HIV and HCV treatment. See Table 12 for recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection. In patients with suppressed plasma HIV RNA and modified ART, 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.

Antiretroviral and Hepatitis C Virus Drug-Drug Interactions

Considerations for the concurrent use of ART and recommended HCV agents (per http://hcvguidelines.org/) are discussed below. Table 12 provides recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection.

- Sofosbuvir is an HCV NS5B nucleotide polymerase inhibitor that is not metabolized by the cytochrome P450 enzyme system and, therefore, can be used in combination with most ARV drugs. Sofosbuvir is a substrate of p-glycoprotein (P-gp). P-gp inducers, such as tipranavir (TPV), may decrease sofosbuvir plasma concentrations and should not be coadministered with sofosbuvir. No other clinically significant pharmacokinetic interactions between sofosbuvir and ARVs have been identified.
- Ledipasvir is an HCV NS5A inhibitor and is part of a fixed-dose drug combination of sofosbuvir and ledipasvir.[32] Similar to sofosbuvir, ledipasvir is not metabolized by the cytochrome P (CYP) 450 system of enzymes and is a substrate for P-gp. Ledipasvir inhibits the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. The use of P-gp inducers is not recommended with ledipasivir/sofosbuvir. Coadministering ledipasvir/sofosbuvir and ARV regimens containing tenofovir disoproxil fumarate (TDF) is associated with increased exposure to TDF, especially when TDF is taken with an HIV protease inhibitor (PI) boosted with either ritonavir (RTV) or cobicistat (COBI). In some patients, alternative HCV or ARV drugs should be considered to avoid increases in TDF exposures. If the drugs are coadministered, the patient should be monitored for potential TDF-associated renal injury by assessing measurements of renal function (ie, estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein) before HCV treatment initiation and periodically during treatment.

- Daclatasvir is an HCV NS5A inhibitor that is approved for use with sofosbuvir.[33] Daclatasvir is a substrate of CYP3A and an inhibitor of P-gp, OATP1B1/3, and BCRP. Moderate or strong inducers of CYP3A, such as efavirenz (EFV), etravirine (ETR), and nevirapine (NVP), may decrease plasma levels of daclatasvir and reduce the drug's therapeutic effect. In this case, the daclatasvir dosage should be increased from 60 mg once daily to 90 mg once daily. By contrast, strong CYP3A inhibitors may increase plasma levels of daclatasvir, in which case the daclatasvir dosage should be reduced to 30 mg once daily. Clinically relevant interactions between daclatasvir and TDF have not been observed. Because daclatasvir also is an inhibitor of P-gp, OATP1B1/3, and BCRP, administration of daclatasvir may increase systemic exposure to medications that are substrates of these transporters and proteins, which could increase or prolong the therapeutic or adverse effects of that medication.

- Elbasvir (a NS5A inhibitor) and grazoprevir (an HCV PI) are available in combination as a fixed-dose tablet. Both elbasvir and grazoprevir are substrates of CYP3A and P-gp.[34] In addition, grazoprevir is a substrate of OATP1B1/3 transporters. Coadministration of the elbasvir and grazoprevir combination with strong CYP3A inducers, such as EFV, is contraindicated because elbasvir and grazoprevir concentrations may be decreased. Coadministration of strong CYP3A4 inhibitors with elbasvir and grazoprevir is also contraindicated or not recommended bcause elbasvir and grazoprevir concentrations may increase. Elbasvir and grazoprevir are also inhibitors of the drug transporter BCRP and may increase plasma concentrations of coadministered BCRP substrates.

- The fixed-dose drug combination of ombitasvir (a NS5A inhibitor), paritaprevir (an HCV PI), and RTV (a pharmacokinetic [PK] enhancer) is copackaged with or without dasabuvir, an NS5B inhibitor.[35,36]
    - Paritaprevir is a substrate and inhibitor of the CYP3A4 enzymes and therefore may have significant interactions with certain ARVs that are metabolized by, or may induce or inhibit, the same pathways. Paritaprevir is also a substrate and inhibitor of OATP1B1/3.
    - Both ombitasvir and paritaprevir are inhibitors of UGT1A1 and also substrates of P-gp and BCRP.
    - Dasabuvir is primarily metabolized by the CYP2C8 enzymes. It is also an inhibitor of UGT1A1 and a substrate of P-gp and BCRP.
    - Coadministration of ombitasvir/paritaprevir/RTV with drugs that are substrates or inhibitors of the enzymes and drug transporters noted may result in increased plasma concentrations of either the HCV drugs or the coadministered drug. Given that several CYP enzymes and drug transporters are involved in the metabolism of ombitasvir, paritaprevir, and RTV, complex drug-drug interactions are likely. Therefore, clinicians need to consider all coadministered drugs for potential drug-drug interactions.
    - If a patient's ART regimen contains RTV- or COBI-boosted atazanavir (ATV), the boosting agent should be discontinued during therapy with ombitasvir/paritaprevir/RTV and ATV should be taken in the morning at the same time as the HCV therapy. RTV or COBI should be restarted after completion of HCV treatment. HIV-infected patients not on ART should be placed on an alternative HCV regimen because RTV has activity against HIV.

- Simeprevir is an HCV NS3/4A PI that is approved for use with sofosbuvir. Simeprevir is a substrate and inhibitor of CYP3A4 and P gp enzymes, and therefore has significant interactions with ARVs that are metabolized by the same pathways (eg, HIV PIs, EFV, ETR). Simeprevir is also an inhibitor of the drug transporter OATP1B1/3.

Given that the treatment of HCV is rapidly evolving, this section will be updated when new HCV drugs that may impact the treatment of HIV are approved. For guidance on the treatment of HCV infection, refer to http://www.hcvguidelines.org/.

Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 1 of 3)

The recommendations in this table for concomitant use of selected HIV drugs with FDA-approved HCV direct-acting antiviral (DAA) drugs are based on available pharmacokinetics 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.

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[b]	Simeprevir
Nucleoside Reverse Transcriptase Inhibitors						
3TC	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓ Monitor for TDF toxicity.	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓
HIV Protease Inhibitors						
ATV (unboosted)	✓	✓	✓	×	✓ 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.	×

Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 2 of 3)

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir	Simeprevir
HIV Protease Inhibitors, continued						
ATV/r or ATV/c	✓ ↓ DCV dose to 30 mg/day	✓	✓ If PI/r (or ATV/c, DRV/c) is used with TDF, ↑TDF concentrations are expected. If coadministration necessary, monitor for TDF-associated toxicities (see footnote[c]).	×	✓ Take ATV 300 mg in the morning at same time as ombitasvir/ paritaprevir/r plus dasubuvir; discontinue RTV or COBI in HIV regimen until HCV therapy completed.	×
DRV/r or DRV/c	✓	✓		×	×	×
FPV or FPV/r	✓	✓		×	×	×
LPV/r	✓	✓		×	×	×
SQV/r	✓ ↓ DCV dose to 30 mg/day			×	×	×
TPV/r	?	×	×	×	×	×
Non-Nucleoside Reverse Transcriptase Inhibitors						
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 HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 3 of 3)

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir	Simeprevir
Integrase Strand Transfer Inhibitors						
DTG	✓	✓	✓ If used with TDF, monitor for TDF toxicity.	✓	✓	✓
EVG/c/TDF/FTC	✓ ↓ DCV dose to 30 mg/day	✓	×	×	×	×
EVG/c/TAF/FTC	✓ ↓ DCV dose to 30 mg/day	✓	✓	×	×	×
EVG (plus PI/r without COBI)	✓ ↓ DCV dose to 30 mg/day for all PI/r, except TPV/r — do not coadminister	Refer to Recommendations for individual ritonavir-boosted PI.				
RAL	✓	✓	✓	✓	✓	✓
CCR5 Antagonist						
MVC	✓	✓	✓	?	×	✓

[a] Since boceprevir is no longer recommended for HCV treatment and telaprevir is no longer available in the United States, these products have been removed from this table.

[b] Dasabuvir must be prescribed with ombitasvir/paritaprevir/ritonavir.

[c] Consider alternative HCV or ARV therapy to avoid increases in TDF exposure. If coadministration is necessary, monitor for TDF-associated adverse reactions.

Key to Symbols: ✓ = ARV agents that can be used concomitantly

× = ARV agents not recommended

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; c or COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; 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/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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