The management of hepatitis C virus (HCV)–infected patients is rapidly evolving. Data suggest that HIV/HCV–coinfected patients treated with new, 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 as they relate to HIV/HCV 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/.

Approximately one-third of patients with chronic HCV infection 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 HIV/HCV–coinfected patients had a three fold greater risk of progression to cirrhosis or decompensated liver disease than HCV-monoinfected patients.\(^5\) This accelerated rate is magnified in HIV/HCV–coinfected patients with low CD4 T lymphocyte (CD4) cell counts. Although antiretroviral therapy...
(ART) appears to slow the rate of HCV disease progression in HIV/HCV-coinfected patients, several studies have demonstrated that the rate continues to exceed that observed in those without HIV infection. Whether HCV infection accelerates HIV progression, as measured by AIDS-related opportunistic infections (OIs) or death, is unclear. Although older antiretroviral (ARV) drugs have been associated with higher rates of hepatotoxicity in patients with chronic HCV infection, 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 HIV/HCV-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. These new agents, when used with or without PegIFN and RBV, have been shown to achieve high SVR rates. The first DAA agents approved for the treatment of HCV infection in combination with PegIFN/RBV were the HCV protease inhibitors (PI), boceprevir and telaprevir. In HCV genotype 1 infected patients, the combined use of either boceprevir or telaprevir with PegIFN/RBV was associated with higher rates of SVR than use of PegIFN/RBV alone; however, combined use of the drugs was associated with a large pill burden, increased dosing frequency, and adverse effects. Subsequently approved DAA agents in the same class (simeprevir) and in newer classes (sofosbuvir, ledipasvir) that are used with or without RBV have high SVR rates, reduced pill burden, less frequent dosing, fewer side effects, and shorter durations of therapy. Accordingly, the combination of boceprevir or telaprevir with PegIFN/RBV is no longer recommended, and has been replaced by newer combination regimens. Additional guidance on the treatment and management of HCV in HIV–infected and uninfected adults can be found at http://www.hcvguidelines.org.

Assessment of HIV/Hepatitis C Virus Coinfection

- All HIV–infected patients should be screened for HCV infection using sensitive immunoassays licensed for detection of antibody to HCV in blood. 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 (http://www.hcvguidelines.org).

- Patients with HIV/HCV coinfection should be counseled to avoid consuming alcohol and to use appropriate precautions to prevent transmission of HIV and/or HCV to others. HIV/HCV–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 HIV/HCV coinfection should be evaluated for HCV therapy.

Antiretroviral Therapy in HIV/Hepatitis C Virus Coinfection

When to Start Antiretroviral Therapy

The rate of liver disease (liver fibrosis) is accelerated in HIV/HCV–coinfected patients, particularly in individuals with low CD4 counts (<550 cells/mm³). Data largely from retrospective cohort studies are inconsistent regarding the effect of ART on the natural history of HCV disease. However, ART may slow the progression of liver disease by preserving or restoring immune function and by reducing HIV–related immune activation and inflammation. Therefore, ART should be initiated in most HIV/HCV–coinfected patients, regardless of CD4 count (BII). However, in HIV treatment–naive patients with CD4 counts >500 cells/mm³, 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/mm³, those with CD4 counts <200 had lower HCV treatment responses and higher toxicity rates to PegIFN/RBV. Data regarding HCV treatment response to combination therapy with DAA agents in those with advanced immunosuppression is lacking. For patients with lower CD4 counts (e.g., <200 cells/mm³), ART should be initiated expeditiously (AI) and HCV therapy may be delayed until the patient is stable on HIV treatment (CIII).

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 HIV/HCV–coinfected patients include the following:

- When both HIV and HCV treatments are indicated, the choice of ARV regimens from among those appropriate for HIV infection should be guided by the HCV treatment regimen selected with special consideration of potential drug–drug interactions (see Table 12) and overlapping toxicities.

Cirrhotic patients should be carefully assessed 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).

**Concurrent Treatment of HIV and Hepatitis C Virus Infection**

Concurrent treatment of HIV and HCV is feasible but 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 thereby inform decision making on when to start HCV. 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, before HCV treatment is initiated the ART regimen may need to be modified 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. If a prior HIV regimen is to be reinitiated after HCV treatment is completed, the modified ART regimen should be continued for at least 2 weeks after completion of HCV treatment. 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).

**Drug–Drug Interaction**

Considerations for the concurrent use of ART and recommended HCV agents (per http://hcvguidelines.org/) are as follows:

- **Simeprevir** (similar to boceprevir and telaprevir) is a HCV NS3/4A PI that has been studied in HIV/HCV–coinfected patients. Simeprevir is a substrate and inhibitor of CYP3A4 and p–glycoprotein (p–gp) enzymes, and therefore may have significant interactions with certain ARVs that are metabolized by the same pathways. Simeprevir is also an inhibitor of the drug transporter OATP1B1/3. On the basis of drug–drug interaction studies in healthy volunteers, simeprevir can be coadministered with ritonavir (RAL), dolasetrione, rilpivirine (RPV), efavirenz (EFV), etravirine, HIV PIs, cobicistat (cobi), or elvitegravir/cobicistat/tenofovir/emtricitabine (EVG/cobi/TDF/FTC) is not recommended (see Table 12 for recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection).

- **Sofosbuvir** is an HCV NS5B nucleotide polymerase inhibitors 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 p–gp. P–gp inducers, such as tipranavir, may decrease sofosbuvir plasma concentrations and should not be co–administered with sofosbuvir. No other clinically significant pharmacokinetic interactions between sofosbuvir and ARVs have been identified. Drug–drug interaction studies in healthy volunteers did not find any significant interaction between sofosbuvir and darunavir/ritonavir, EFV, RPV, RAL, TDF, or FTC (see Table 12 for recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection).
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A fixed drug combination of sofosbuvir and ledipasvir has been approved by the Food and Drug Administration. A fixed drug combination of sofosbuvir and ledipasvir has been approved by the Food and Drug Administration. Ledipasvir is an HCV NS5A inhibitor and, similar to sofosbuvir, is not metabolized by the cytochrome P450 system of enzymes and is a substrate for p-gp. The potential for clinically significant drug–drug interactions is low. However, the coadministration of sofosbuvir/ledipasvir and ARV regimens containing TDF together with an HIV PI boosted with either RTV or cobi is associated with increased exposure to TDF (see Table 12 for recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection). In some patients, alternative HCV or ARV drugs should be considered to avoid increases in TDF exposures. If the drugs are co-administered, the patient should be monitored for potential TDF–associated renal injury by assessing measurements of renal function (i.e., estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein) before HCV treatment initiation and periodically during treatment.

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

Table 12. Recommendations for Concomitant Use of Selected Antiretroviral Drugs and All Food and Drug Administration (FDA)-Approved Drugs for Treatment of Hepatitis C in HIV-Infected Adults

These recommendations for concomitant use of selected HIV drugs with FDA-approved HCV drugs are based on available data on pharmacokinetics interaction or on predictions based on the known metabolic pathway of the agents. In some cases, there are not enough data for any recommendations; these cases are indicated in the table. Whenever HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. Given the rapidly evolving field of HCV therapy, readers should also refer to the latest drug product labels and HCV guidelines (www.hcvguidelines.org/) for updated information on the concurrent use of HIV and HCV drugs.

<table>
<thead>
<tr>
<th>Select ARV Drugs by Drug Class</th>
<th>HCV Drugs</th>
<th>HCV Direct–Acting Antiviral Agents</th>
<th>HCV Non–Direct–Acting Antiviral Agents</th>
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<tr>
<td></td>
<td></td>
<td>NS5B Inhibitor Co-Formulated NSSA/NS5B Inhibitor</td>
<td>HCV Protease Inhibitors</td>
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<tr>
<td></td>
<td></td>
<td>Sofosbuvir Ledipasvir/Sofosbuvir Simeprevir</td>
<td>No Longer Recommended by HCV Guidelines</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Boceprevir Telaprevir (Discontinued from U.S. market in October 2014)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Ribavirin Pegylated interferon alpha</td>
</tr>
</tbody>
</table>

**Nucleoside Reverse Transcriptase Inhibitors**

| FTC   | √     | √     | √     | √     | √     | √     | √     |
| 3TC   | √     | √     | √     | √     | √     | √     | √     |
| ABC   | √     | √     | √     | √     | √     | √     | √     |
| TDF   | √     | √     | √     | √     | √     | √     | √     |

| ZDV   | √     | √     | √     | X     | X     | X     | X     |

**HIV Protease Inhibitors**

| ATV, ATV/r, or ATV/cobi | √     | √     | X     | X     | X     | √     | √     |
| DRV/r or DRV/cobi      | √     | √     | X     | X     | X     | √     | √     |
| FPV or FPV/r           | √     | √     | X     | X     | X     | √     | √     |
| LPV/r                  | √     | √     | X     | X     | X     | √     | √     |

### Non-Nucleoside Reverse Transcriptase Inhibitors

<table>
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<tr>
<th>Drug</th>
<th>√</th>
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<tr>
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<tr>
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#### EFV

- If EFV used with TDF/FTC, monitor for TDF toxicity due to ↑TDF level.
- ↑ teleprevir dose to 1125 mg q8h

#### ETR

- EXCEPTION ETR + boceprevir is not recommended when coadministered with drugs that may further decrease ETR (e.g., TDF, DVR/r, LPV/r, SQV/r).

#### NVP

- Refer to recommendations for specific ritonavir-boosted PI

#### RVP

- Refer to recommendations for specific ritonavir-boosted PI

#### Integrase Strand Transfer Inhibitors

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<tr>
<td>EVG/cobi/TDF/FTC</td>
<td>√</td>
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<td>X</td>
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</table>
| EVG + (PI/r without cobi) | Refer to recommendations for specific ritonavir-boosted PI

#### CCR5 Antagonist

<table>
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### Key to Symbols:
- √ = ARV agent and HCV drug that can be used concomitantly
- ↑ = Increase
- ↓ = Decrease
- X = Concomitant use of the ARV agent and HCV drug is not recommended
- ? = Data limited or not available on PK interactions between the ARV and HCV drugs

### Key to Acronyms:
- 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; ATV/cobi = atazanavir/cobicistat; cobi = cobicistat; DRV/r = darunavir/ritonavir; DRV/cobi = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FDA = Food and Drug Administration; HCV = hepatitis C virus; HIV = human immunodeficiency 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; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

### References

1. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in...


34. Labarga P, Soriano V, Vispo ME, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful


