Background of HCV-HIV Coinfection

Impact of HIV Coinfection

In the United States, approximately 5% of adults with chronic hepatitis C (HCV) infection have coinfection with HIV.[1] Among persons living with HIV in the United States, an estimated 15 to 30% have HCV coinfection, but these rates vary significantly based on the individual's risk factor for acquiring HIV.[2,3,4,5] Coinfection with HIV accelerates the progression of hepatic fibrosis and results in a more aggressive course of liver disease (Figure 1).[6,7,8] Cirrhosis has been observed to occur 12 to 16 years earlier in persons coinfected with HCV and HIV compared with those who have HCV monoinfection.[9] For persons living with HIV who have HCV coinfection, liver-related morbidity and mortality is a prominent non-AIDS-related complication—up to 80 to 90% of liver-related deaths in persons living with HIV are attributable to HCV infection.[10,11] Unfortunately, individuals with HCV and HIV coinfection have decreased access to liver transplantation compared with persons with HCV monoinfection.[12] For all these reasons, treatment of HCV in persons with HIV coinfection should have a high priority. Historically, in the interferon era, treatment of HCV in persons with HIV-HCV coinfection had limited uptake, due to a low response rate with interferon-based therapy, a high rate of adverse effects, concerns for interactions with antiretroviral medications, and high prevalence of comorbidities.[13] The availability of highly effective all-oral direct-acting antiviral (DAA) regimens has completely changed the landscape of treating HCV in persons with HIV-HCV coinfection.
HCV Treatment Data in Persons with HIV Coinfection

Multiple studies using DAA-based therapy have demonstrated HCV treatment SVR rates in individuals with HIV-HCV coinfection that are comparable to those with HCV monoinfection (Figure 2), providing convincing evidence that persons with HIV-HCV coinfection should no longer be considered as a “treatment refractory” population.\[14\] In these trials, most participants did not have cirrhosis and most had a CD4 counts well above 200 cells/mm\(^3\).\[15,16,17,18,19\] More recently, however, a variety of observational cohort studies with heterogeneous cohorts of persons with HIV-HCV coinfection, including those with more advanced liver disease and lower CD4 cell counts, have shown comparable HCV SVR rates with HIV-HCV coinfection and HCV monoinfection.\[20,21,22\] The following provides a summary of key clinical trials (in alphabetical order) involving DAA treatment of HCV infection in persons with HIV coinfection.

- **Elbasvir-Grazoprevir (C-EDGE Coinfection):** In this prospective single-arm, open-label clinical trial, investigators enrolled 218 adults with chronic HCV genotype 1, 4, or 6 and HIV coinfection to receive treatment with a 12-week course of elbasvir-grazoprevir once daily for 12 weeks.\[17\] Among those enrolled, 86% had genotype 1a or 1b infection and 16% had compensated cirrhosis. The overall SVR12 rate was 96% by primary analysis, with the breakdown by genotype showing 96.5% for those with genotype 1a, 95.5% for genotype 1b, and 96.4% for genotype 4. All study participants with cirrhosis achieved an SVR12.\[17\]

- **Glecaprevir-Pibrentasvir (EXPEDITION-2):** This open-label, dual-arm, phase 3 trial enrolled adults with HCV (genotype 1, 2, 3, 4, 5, or 6) and HIV coinfection to receive HCV treatment with glecaprevir-pibrentasvir. The 137 participants without cirrhosis were assigned 8 weeks of HCV treatment and the 16 individuals with compensated cirrhosis received 12 weeks.\[23\] The majority (63%) of participants had HCV genotype 1 and 18% were treatment-experienced (16% previously treated with an interferon-based regimen and 2% with a sofosbuvir-based regimen).\[23\] All but 10 participants were taking raltegravir, dolutegravir, or rilpivirine as the antiretroviral therapy anchor drug. The overall SVR12 rate was 98%; one individual with HCV genotype 3 and cirrhosis experienced on-treatment HCV virologic breakthrough.\[23\]

- **Ledipasvir-Sofosbuvir (ION-4):** In this phase 3, open-label, multicenter study, investigators enrolled 335 adults with HCV genotype 1 or 4 who were coinfected with HIV to receive a 12-week course of ledipasvir-sofosbuvir.\[16\] Enrollment included HCV treatment-naïve and HCV treatment-experienced individuals and those without cirrhosis and those with compensated cirrhosis. The HIV enrollment criteria required an HIV RNA level less than 50 copies/mL and a CD4 count greater than 100 cells/mm\(^3\); antiretroviral regimens could include tenofovir DF-emtricitabine plus either efavirenz, rilpivirine, or raltegravir. Overall, 96% (321 of 335) of the study participants who received HCV treatment achieved an SVR12.\[16\] The results were similar regardless of prior treatment status or presence of cirrhosis.

- **Ledipasvir-Sofosbuvir (NIAID ERADICATE):** This phase 2 trial investigated the open-label use of ledipasvir-sofosbuvir for 12 weeks in 50 treatment-naïve adults with HCV (genotype 1) and HIV coinfection.\[24\] Among the 50 participants enrolled, 13 were not taking antiretroviral therapy and 37 were receiving antiretroviral therapy (the antiretroviral medications that were allowed included tenofovir DF-emtricitabine, efavirenz, rilpivirine). Overall, 98% (49 of 50) of the participants achieved an SVR12.\[24\]

- **Sofosbuvir-Velpatasvir (ASTRAL-5):** The ASTRAL-5 study was a single-arm, open-label, phase 3 trial of sofosbuvir-velpatasvir for 12 weeks in adults with HCV and HIV coinfection.\[19\] The study enrolled 106 individuals with HCV genotype 1, 2, 3, 4, or 6; among those enrolled, 18% had compensated cirrhosis and 29% were treatment-experienced.\[19\] The mean CD4 count was 583 cells/mm\(^3\) and all participants had suppressed HIV RNA levels. A variety of antiretroviral regimens, including regimens that contained tenofovir DF and/or boosting agents (cobicistat or ritonavir), were permitted. The overall SVR12 rate was 95%; two viral relapses occurred, both in persons with genotype 1a HCV; no participants experienced HIV viral rebound during HCV treatment.\[19\] The presence of cirrhosis or treatment experience did not appear to influence treatment response. Creatinine clearance was lower among participants taking both tenofovir DF and a boosting agent, but the creatinine clearance...
remained relatively stable over time in all groups.[19]
Recommended HCV Treatment in Persons with HIV Coinfection

AASLD-IDSA HCV Guidance

The AASLD-IDSA HCV Guidance addresses treatment of persons with HCV and HIV coinfection in detail.[14] The AASLD-IDSA HCV Guidance recommends using the same general approach for treating HCV in persons with HCV-HIV coinfection as with HCV monoinfection, but notes the importance of recognizing and managing potential drug interactions between HCV medications and HIV antiretroviral medications.[14] In most instances, the AASLD-IDSA HCV Guidance recommends using the same HCV treatment regimens and duration for persons with HCV-HIV coinfection as for those with HCV monoinfection, with several exceptions, as outlined below, that require a longer treatment duration for persons with HCV-HIV coinfection than those with HCV monoinfection.[14]

- **Treatment-Naïve, Genotypes 1a and 1b; without Cirrhosis**: The recommended treatment duration for ledipasvir-sofosbuvir regimen is 8 weeks for persons with HCV monoinfection (and baseline HCV RNA less than 6 million IU/mL), but the duration should be 12 weeks for persons with HCV-HIV coinfection, regardless of their baseline HCV RNA level.[25,26]
- **Treatment-Naïve, Genotypes 1a, 1b, 2, 3, and 4; with Compensated Cirrhosis**: For persons with these genotype and compensated cirrhosis, the recommended treatment duration for glecaprevir-pibrentasvir is 8 weeks for those with HCV monoinfection and 12 weeks for those with HCV-HIV coinfection.[27,28,29,30,31]
- **Treatment-Naïve, Genotypes 5 or 6; with and without Compensated Cirrhosis**: The recommended treatment duration for glecaprevir-pibrentasvir is 8 weeks for persons with HCV monoinfection and 12 weeks for those with HCV-HIV coinfection.[32]
Treatment of HIV in Persons with HCV Coinfection

General Recommendations

The Adult and Adolescent ARV Guidelines emphasizes the following key points on treating HIV with antiretroviral therapy for persons with HIV and HCV coinfection:[33]

- Antiretroviral therapy is recommended for all persons with HIV.
- Antiretroviral treatment for HIV may slow the progression of HCV-related liver disease and reduce the risk of liver-related morbidity.
- For all persons with HIV and HCV coinfection, antiretroviral therapy should be initiated, regardless of the CD4 cell count and fibrosis stage.
- Following initiation of antiretroviral therapy, elevations in hepatic aminotransferase levels and hepatotoxicity occurs more commonly in persons with HIV and HCV coinfection than in persons with HIV monoinfection. Monitoring after starting antiretroviral therapy should include some of these events attributable to immune reconstitution inflammatory syndrome.
- If treatment for both HIV and HCV is indicated, the selected treatment regimens should consider potential drug interactions and whether the recommended duration for persons with HCV monoinfection should be given for a longer duration because of the confection with HIV.
- For individuals living with HIV who have a CD4 counts less than 200 cells/mm$^3$, it may be advisable to first initiate antiretroviral therapy and defer HCV therapy until the person is stable on antiretroviral therapy with suppressed HIV RNA levels. Most clinical trials evaluating the efficacy of HCV therapy in persons with HIV have enrolled those with suppressed HIV RNA levels and CD4 counts greater than 200 cells/mm$^3$.

Monitoring for Hepatotoxicity after Initiating Antiretroviral Therapy

Because of the increased risk of hepatotoxicity after initiating antiretroviral therapy in persons with HCV coinfection, the Adult and Adolescent ARV Guidelines recommends the following monitoring after initiating antiretroviral therapy in persons with HCV-HIV coinfection.[33]

- Evaluation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should take place 4 to 8 weeks after starting antiretroviral therapy repeated 6 to 12 months later. If the values are elevated, more frequent monitoring will be needed. If HCV remains untreated and not cured, then ALT and AST levels should continue to be monitored every 6 to 12 months.
- Typically, after initiating antiretroviral therapy, persons with untreated chronic HCV will have some increases in ALT and/or AST levels up to 5 times the upper limit of normal; the increases in ALT and/or AST may fluctuate significantly.
- If the individual does not have concomitant symptoms that would suggest liver disease (weakness, nausea, vomiting) and the bilirubin remains normal, then antiretroviral therapy can be continued, but close monitoring of ALT and AST should occur.
- If the individual has ALT and/or AST level elevations greater than 5 times the upper limit of normal, an increase in total bilirubin, and/or concomitant symptoms (weakness, nausea, vomiting), they should undergo careful evaluation for signs and symptoms of liver insufficiency and for alternative causes of liver injury, such as alcoholic hepatitis, acute HAV or HBV infection, or hepatobiliary disease. Antiretroviral therapy should be discontinued if these signs and symptoms do not quickly resolve. Expert consultation may be warranted in this situation.
Drug Interactions with HIV-HCV Coinfection Treatment

Resources for Drug Interaction

Most persons with HIV infection are taking multidrug antiretroviral therapy, which may pose a problem with drug interactions when initiating HCV treatment. For resources on drug interactions that may occur with HIV antiretroviral medications and HCV treatment medications, access the following sites:

- AASLD-IDSA HCV Guidance: Patients with HIV/HCV Coinfection[14]
  - Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs-Recommended Regimens
- HHS Adult and Adolescent Antiretroviral Therapy Guidelines: Drug-Drug Interaction[33,34,35,36,37]
  - Drug Interactions between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs
  - Drug Interactions between Nonnucleoside Reverse Transcriptase Inhibitors and Other Drugs
  - Drug Interactions between Integrase Inhibitors and Other Drugs
  - Drug Interactions between Protease Inhibitors with Other Drugs
- UCSF Center for HIV Information
  - Database of Antiretroviral Drug Interactions
- University of Liverpool
  - HEP Drug Interactions
  - HIV Drug Interactions

Drug Interaction Summaries

The following provides key points related to potential drug interactions for between HCV medications (DAAs and ribavirin) and HIV antiretroviral medications. The first section will address from the perspective of the antiretroviral medication classes with the recommended DAA regimens and the second section addresses interactions from the perspective of the DAA medication.

Antiretroviral Medication: Key Points

The following summarizes key points with the use of antiretroviral medications with the five recommended AASLD HCV regimens: elbasvir-grazoprevir, glecaprevir-pibrentasvir, ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, and sofosbuvir-velpatasvir-voxilaprevir.[14,34,35,36,37]

- **NRTIs**: Abacavir, emtricitabine, lamivudine, and tenofovir alafenamide can be used safely with all recommended HCV regimens. Caution should be used with tenofovir DF in combination with any regimen that includes sofosbuvir (ledipasvir-sofosbuvir, sofovir-velpatasvir, or sofosbuvir-velpatasvir-voxilaprevir).
- **NNRTIs**: Doravirine and rilpivirine can be used safely with all recommended HCV regimens. Efavirenz and etravirine should not be used with any of the recommended HCV treatment regimens, except for ledipasvir-sofosbuvir. For all NNRTIs that are used with tenofovir DF and ledipasvir-sofosbuvir, monitoring should occur for tenofovir DF-associated toxicity should occurs during treatment.
- **INSTIs**: Bictegravir, dolutegravir, and raltegravir; can be used safely with all recommended HCV regimens, with the exception that if dolutegravir is used with tenofovir DF and ledipasvir-sofosbuvir, then monitoring for tenofovir toxicity is recommended. Cobicistat-boosted elvitegravir should not be administered with elbasvir-grazoprevir or the combination of tenofovir DF with ledipasvir-sofosbuvir. Caution should be used if using cobicistat-boosted elvitegravir with glecaprevir-pibrentasvir, sofosbuvir-velpatasvir, or sofosbuvir-velpatasvir-voxilaprevir, especially if concomitantly given with tenofovir DF.
- **PIs**: All ritonavir- or cobicistat-boosted protease inhibitors should be used with caution with all recommended HCV treatment regimens. In addition, boosted atazanavir, boosted darunavir, and boosted lopinavir should not be used with elbasvir-grazoprevir or glecaprevir-pibrentasvir. Further,
boosted atazanavir and boosted lopinavir should not be used with sofosbuvir-velpatasvir-voxilaprevir. Unboosted atazanavir could be used with ledipasvir-sofosbuvir or sofosbuvir-velpatasvir.

- **CCR5 Antagonist**: Maraviroc can safely be used with any of the recommended HCV treatment regimens.

**HCV DAAs: Key Points**

The following provide key point regarding the use of DAAs used to treat HCV in persons with HIV coinfection.

- **Elbasvir-Grazoprevir**: Grazoprevir is a substrate of the OATP1B1/3 transporters and therefore contraindicated for use with OATP1B1/3 inhibitors such as the HIV protease inhibitors or cobicistat-containing regimens that can increase grazoprevir drug levels and the risk of hepatotoxicity. Both elbasvir and grazoprevir are metabolized by the CYP3A levels and thus levels may decrease if given with CYP3A inducers, such as efavirenz and etravirine. Coadministration of elbasvir-grazoprevir is contraindicated with all protease inhibitors, efavirenz, etravirine, nevirapine, or any cobicistat-containing regimen.

- **Glecaprevir-Pibrentasvir**: Glecaprevir is a substrate of OATP1B1/3, P-gp and BRCP and inhibitors of these transporters, specifically the HIV protease inhibitors atazanavir, lopinavir or ritonavir can increase levels of glecaprevir.[38] In addition, use of atazanavir with glecaprevir-pibrentasvir has been associated with increased risk of ALT elevation and therefore these medications should not be used together. Cobicistat-containing regimens may also increase ALT levels, but to a lesser extent; monitoring for hepatotoxicity is advised. Coadministration of glecaprevir-pibrentasvir with inducers of CYP3A, such as efavirenz or etravirine may result in lower plasma concentrations of glecaprevir and pibrentasvir. Glecaprevir-pibrentasvir is contraindicated for use with atazanavir (with or without ritonavir or cobicistat). In addition, glecaprevir-pibrentasvir is not recommended for coadministration with darunavir, ledipasvir, tipranavir, ritonavir, efavirenz, etravirine, or nevirapine.

- **Ledipasvir-Sofosbuvir**: The NS5A inhibitor ledipasvir is not metabolized by the cytochrome p450 system, but is both a substrate and an inhibitor of p-glycoprotein and BRCP transporters. Ledipasvir increases tenofovir AUC levels by 40 to 98% when concomitantly given with tenofovir DF and either rilpivirine or efavirenz. Concurrent use of ledipasvir with tenofovir DF and an HIV protease inhibitor (or cobicistat) has not been adequately studied, but there is concern that tenofovir levels may increase substantially with this combination. Because of this concern and lack of data, the use of ledipasvir with the combination of tenofovir DF and cobicistat- or ritonavir-boosted HIV protease inhibitors should, if possible, be avoided. For similar reasons, ledipasvir-sofosbuvir should not be used with cobicistat, elvitegravir, or tipranavir. Monitoring for tenofovir DF nephrotoxicity or switching to tenofovir alafenamide should be considered. Ledipasvir-sofosbuvir should not be used in persons with HIV infection on tenofovir DF if the baseline creatinine clearance is less than 60 mL/min. Ledipasvir does not have significant drug interactions with tenofovir alafenamide.

- **Ribavirin**: Significant and serious toxicities can occur with the simultaneous use of ribavirin and certain HIV nucleoside reverse transcriptase inhibitors. The use of ribavirin with didanosine is strictly contraindicated due to a marked increase in intracellular didanosine levels, which may cause hepatic failure, pancreatitis, and lactic acidosis. This can also occur with stavudine or zidovudine. Thus, simultaneous use of ribavirin with either didanosine, stavudine, or zidovudine should be avoided. In addition, concurrent use of ribavirin and zidovudine should also be avoided because of additive hematologic toxicity and increased risk of severe anemia with this combination.

- **Sofosbuvir**: This NS5B polymerase inhibitor is rapidly converted to a dominant circulating metabolite (GS-331007). Sofosbuvir is not metabolized by the cytochrome p450 system, but is a substrate of p-glycoprotein. The only significant interaction with antiretroviral medications occurs with the p-glycoprotein inducer tipranavir, which may decrease levels of sofosbuvir and the GS-331007 metabolite. Accordingly, sofosbuvir should not be used concomitantly with tipranavir, but it can be used with all other antiretrovirals.

- **Sofosbuvir-Velpatasvir**: Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 have the potential to decrease plasma concentrations of sofosbuvir and/or velpatasvir. For this reason, efavirenz and etravirine, as well as tipranavir, are contraindicated.
for concurrent use. Velpatasvir, when given with tenofovir DF can increase tenofovir levels so caution is advised when using this combination, especially in persons taking additional medications that may increase tenofovir levels or in persons who have an increased risk for nephrotoxicity. An increase in tenofovir levels can occur with coadministration of sofosbuvir-velpatasvir and tenofovir alafenamide, although to a lesser extent than with tenofovir DF.

- **Sofosbuvir-Velpatasvir-Voxilaprevir**: Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 have the potential to decrease plasma concentrations of sofosbuvir and/or velpatasvir. Therefore, efavirenz, etravirine, and tipranavir are not recommended for concurrent use with sofosbuvir-velpatasvir-voxilaprevir. In addition, atazanavir and lopinavir are not recommended for use with sofosbuvir-velpatasvir-voxilaprevir. The same concerns related to tenofovir DF and velpatasvir discussed above should be considered when using this combination.
Summary Points

- In persons with chronic HCV, coinfection with HIV accelerates the progression of hepatic fibrosis. Therefore, treatment of both HIV and HCV should have high priority in persons with HIV-HCV coinfection.
- The availability of highly effective, convenient, and safe DAA regimens has changed the HCV treatment landscape for persons with HIV-HCV coinfection. Multiple studies using DAA HCV treatment regimens have demonstrated comparable SVR12 rates in persons with HIV-HCV coinfection as in those with HCV monoinfection.
- The AASLD-IDSA HCV Guidance recommends using the same HCV treatment approach for persons with HIV-HCV coinfection as with HCV monoinfection, except the 8-week treatment regimens should be extended to 12-week regimens in several situations.
- Special consideration should be given to monitoring and managing HIV antiretroviral and HCV DAA drug interactions.
- Antiretroviral therapy is recommended for all persons with HIV, including those with HIV-HCV coinfection. Treatment of HIV may slow liver disease progression in persons with HIV-HCV coinfection.
- For persons with HIV-HCV coinfection who are not on antiretroviral therapy and have a CD4 cell count less than 200 cells/mm$^3$, it may be advisable to initiate HIV antiretroviral therapy first and defer HCV treatment until undetectable HIV RNA levels have been obtained.
Citations


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Figures

Figure 1 Progression to Cirrhosis in Patients with HCV Monoinfection and HIV-HCV Coinfection

This graph shows accelerated progression to cirrhosis in patients with HIV-HCV coinfection when compared with those with HCV monoinfection.

### SVR Rates with GT 1 HCV-HIV Coinfection and HCV Monoinfection

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