Treatment of HCV in Persons with HIV Coinfection

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Module 6: Treatment of Key Populations and Unique Situations
Lesson 1: Treatment of HCV in Persons with HIV Coinfection

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Background of HIV-HCV Coinfection

In the United States, approximately 5% of adults with chronic hepatitis C virus (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] Further, individuals with HIV-HCV coinfection have decreased access to liver transplantation compared with persons who have HCV monoinfection.[12] For all these reasons, treatment of HCV in persons with HIV coinfection remains a high priority.

HCV Treatment Data in Persons with HIV Coinfection

Multiple HCV treatment studies using direct-acting antiviral (DAA)-based therapy have demonstrated sustained virologic response (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.[13] In these trials, most participants did not have cirrhosis and most had CD4 counts well above 200 cells/mm^3.[14,15,16,17,18] Subsequently, 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, showed comparable HCV SVR rates in persons with HIV-HCV coinfection compared with those who have HCV monoinfection.[19,20,21] 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 elbasvir-grazoprevir once daily for 12 weeks.[16] Among those enrolled, 86% had genotype 1a or 1b infection and 16% had compensated cirrhosis. The overall SVR12 rate was 96% (210 of 218) 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.[16]
- **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.[22] 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).[22] All but 10 participants were taking raltegravir, dolutegravir, or rilpivirine as the antiretroviral therapy anchor drug. The overall SVR12 rate was 98% (150 of 153); one individual with HCV genotype 3 and cirrhosis experienced on-treatment HCV virologic breakthrough.[22]
- **Ledipasvir-Sofosbuvir** (ION-4): In this phase 3, open-label, multicenter study, investigators enrolled 335 adults with HCV genotype 1 or 4 who had HIV coinfection to receive a 12-week course of ledipasvir-sofosbuvir.[15] Enrollment included HCV treatment-naïve and HCV treatment-experienced individuals, including 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.[15] 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.[23] 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, and rilpivirine). Overall, 98% (49 of 50) of the participants achieved an SVR12.[23]
- **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.[18] 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.[18] 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% (101 of 106); two viral relapses occurred, both in persons with genotype 1a HCV; no participants experienced HIV viral rebound during HCV treatment.[18] 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.[18]

- **Sofosbuvir-Velpatasvir-Voxilaprevir** (RESOLVE): The RESOLVE study was a single-arm, open-label, phase 2b trial of sofosbuvir-velpatasvir-voxilaprevir for 12 weeks in 77 adults with or without HIV coinfection who had experienced treatment failure with prior DAA therapy.[24] The study had high proportionate enrollment among men (83%), persons of Black race (86%), those with HCV genotype 1a (75%), and persons with prior treatment with ledipasvir-sofosbuvir (89%).[24] Among all study participants, 40% (31 of 77) had compensated cirrhosis and 17 had HIV coinfection; all persons with HIV were taking antiretroviral therapy.[24] Overall, in an intent-to-treat analysis, 91% (70 of 77) achieved an SVR12 and only one of the nonresponders had a viral relapse.[24] Of those with HIV, 82% (14 of 17) achieved an SVR12.[24]

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.[13] 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.[13] 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 due to insufficient data on the efficacy of these 8-week regimens among individuals with coinfection.[13]

- **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 genotypes and compensated cirrhosis, the recommended treatment duration for glecaprevir-pibrentasvir is 8 weeks for those with HCV monoinfection, but 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, but 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 emphasize 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-HCV coinfection, antiretroviral therapy should be initiated to treat HIV, regardless of the CD4 cell count and fibrosis stage.
- Elevations in hepatic aminotransferase levels and hepatotoxicity following initiation of antiretroviral therapy occur more commonly in persons with HIV-HCV coinfection than when treating persons with HIV monoinfection, although most of the supporting data supporting this observation were generated in the era prior to the widespread use of HIV integrase strand transfer inhibitors. The higher risk elevations in hepatic aminotransferase levels after starting antiretroviral therapy in persons with HCV coinfection is at least partially attributable to immune reconstitution inflammatory syndrome.
- If treatment for both HIV and HCV is indicated, the selection of the 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 count 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 Hepatoxicity after Initiating Antiretroviral Therapy

Because of the increased risk of hepatoxicity after initiating antiretroviral therapy in persons with HCV confection, the Adult and Adolescent ARV Guidelines recommend 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 and be 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 acute hepatitis A virus infection, acute hepatitis B virus infection, alcoholic hepatitis, 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[13]
  - Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs-Recommended Regimens
- HHS Adult and Adolescent Antiretroviral Therapy Guidelines: Drug-Drug Interaction[33,34]
  - Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults with HIV
- University of California at San Francisco (UCSF) Center for HIV Information
  - Database of Antiretroviral Drug Interactions
- University of Liverpool, England
  - HEP Drug Interactions
  - HIV Drug Interactions

Drug Interaction Summaries

The following provides key points related to potential drug interactions between HCV medications (DAAs and ribavirin) and HIV antiretroviral medications. The first section will address interactions 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 medications.

Antiretroviral Medication: Key Points

The following summarizes key points with the use of antiretroviral medications with the five recommended AASLD-IDSA HCV regimens: elbasvir-grazoprevir, glecaprevir-pibrentasvir, ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, and sofosbuvir-velpatasvir-voxilaprevir.[13,34,35,36,37]

- **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 plus an NS5A inhibitor (ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, or sofosbuvir-velpatasvir-voxilaprevir); the NS5A inhibitor in these regimens can increase tenofovir DF drug levels.
- **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. The use of efavirenz or etravirine with DAAs can reduce DAA concentrations and may reduce the HCV therapeutic efficacy.
- **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.

- **Entry Inhibitors CCR5 Antagonist**: The entry inhibitors ibalizumab (postattachment inhibitor) maraviroc (CCR5 antagonist), and enfuvirtide (fusion inhibitor) do not have any significant drug interactions with DAA medications. Coadministration of fostemsavir (attachment inhibitor) with either elbasvir-grazoprevir or sofosbuvir-velpatasvir-voxilaprevir may result in an increase of grazoprevir or voxilaprevir levels.

HCV DAAs: Key Points

The following provides key points 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 levels may decrease if given with CYP3A inducers, such as efavirenz and etravirine. Coadministration of elbasvir-grazoprevir is contraindicated with all protease inhibitors; the NNRTIs efavirenz, etravirine, nevirapine, and any cobicistat-containing regimen. The use of elbasvir-grazoprevir with fostemsavir should be avoided, if possible, due to increased grazoprevir levels.
- **Glecaprevir-Pibrentasvir**: Glecaprevir is a substrate of OATP1B1/3, p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), as well as an inhibitor of these transporters. The levels of glecaprevir are increased when used with the HIV protease inhibitors atazanavir, lopinavir, or ritonavir.[38] In addition, use of atazanavir with glecaprevir-pibrentasvir has been associated with increased risk of ALT elevation; 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, lopinavir, 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 BCRP transporters. Ledipasvir increases tenofovir AUC (area under the plasma drug concentration-time curve) 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. The use of elbasvir-grazoprevir with fostemsavir should be avoided, if possible, due to increased voxilaprevir levels.

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 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 a few specific 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.

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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.

Source: Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34:1193-9.

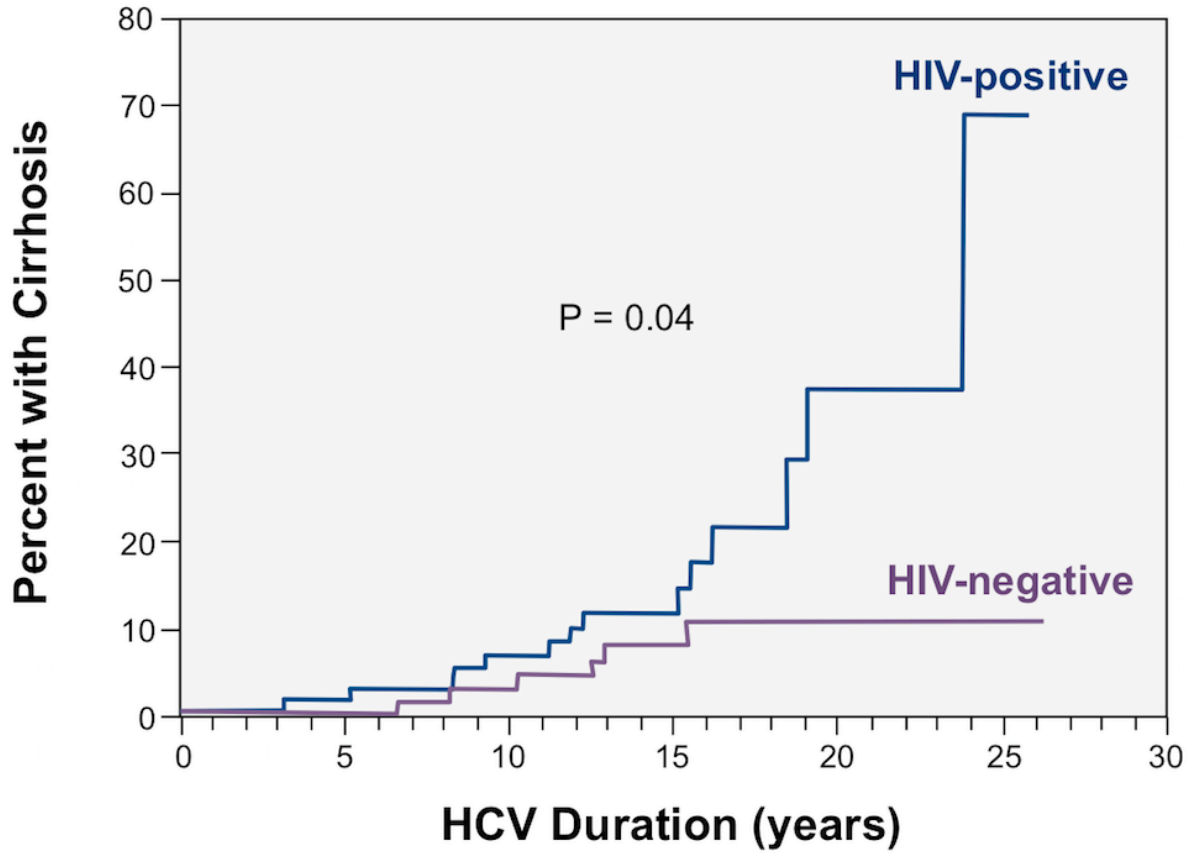

Figure 2 SVR Rates in Treatment-Naïve Adults with HIV-HCV Coinfection versus HCV Monoinfection

SVR Rates with GT 1 HCV-HIV Coinfection and HCV Monoinfection				
Regimen (12 weeks)	Genotype 1			
	HCV-HIV Coinfection		HCV Monoinfection	
	Study	SVR	Study	SVR
Elbasvir-Grazoprevir	C-EDGE Coinfection	95%	C-EDGE TN	95%
Glecaprevir-Pibrentasvir	EXPEDITION-2	98%	ENDURANCE-1	99%
Ledipasvir-Sofosbuvir	ION-4	96%	ION-1	99%
Sofosbuvir-Velpatasvir	ASTRAL-5	95%	ASTRAL-1	98%