ERADICATING hepatitis C

CE 1.5 CONTACT HOURS

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virus: The APRN's role

Abstract: Chronic hepatitis C virus (HCV) infection is a leading cause of liver disease. The World Health Organization has called for the global elimination of HCV by 2030. NPs can significantly expand the availability of community-based providers and bridge gaps in HCV treatment to assist in eradicating this curable virus.

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The hepatitis C virus (HCV), a major cause of chronic liver disease, is the most commonly reported bloodborne infection in the US.[1] It is estimated that from 2013 to 2016 in the US, approximately 4.1 million people were HCV antibody-positive (indicating past or current infection) and 2.4 million people were HCV RNA-positive (indicating current infection).[2] Annual HCV-related mortality in 2013 was greater than the total combined mortality of 60 other infectious diseases in the US.[3] Although HCV prevalence is highest among people born between 1945 and 1965, reported cases of acute HCV infection have increased, reflecting new infections associated with increasing rates of unsafe injection drug use among younger individuals.[3] However, because of its asymptomatic nature, many acute cases of HCV infection are left undiagnosed, so screening individuals at risk is a public

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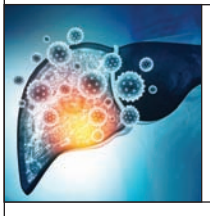
health priority.[4,5] In approximately 15% to 30% of cases of HCV, the virus resolves without treatment after the acute phase of the illness; however, in most individuals, HCV becomes a chronic infection that is lifelong without curative treatment.[6,7]

Chronic HCV infection causes liver inflammation and fibrosis via damage to hepatocytes. HCV generally progresses slowly and is characterized by hepatic inflammation leading to liver fibrosis and cirrhosis. Once established, cirrhosis may progress to hepatic decompensation and hepatocellular carcinoma (HCC).[6] Although the progression of HCV infection is thought to be slow, some individuals have an accelerated course of the disease; in particular those with comorbidities such as nonalcoholic steatohepatitis (NASH), hepatitis B infection, HIV coinfections, and substance use disorder.[6]



NPs educated about HCV can significantly expand the availability of community-based providers and bridge gaps in treatment.

As a result of HCV prevalence and its characteristic pathology, HCV-related cirrhosis has been a leading cause for liver transplantation in the US for decades; however, due to the approval of second-generation direct acting antivirals (DAAs), recent data have demonstrated a decline in HCV-related liver transplantations.[8,9] Newer treatment modalities with DAAs demonstrate improved efficacy and tolerability with shorter durations of therapy, resulting in a major paradigm shift for HCV infection treatment.[10]

The World Health Organization (WHO) has called for elimination of HCV as a major public health threat by 2030.[11] To meet this challenge, clinicians beyond tertiary care referral centers and subspecialty practices must expand HCV testing, prescribe HCV treatment, and eliminate disparities associated with DAA prescribing and access. A priority of the WHO global strategy to eradicate HCV is to address the feasibility and challenges of reducing the number of HCV infection cases through increased public awareness, screening, and diagnosis with linkage to care and access to HCV treatment. Globally, a comprehensive prevention, screening, and treatment strategy could eliminate 15.1 million new infections and 1.5 million cirrhosis and liver cancer deaths with an 81% reduction in incidence and a 61% reduction in mortality compared with 2015 baseline data.[12]

NPs educated about HCV can significantly expand the availability of community-based providers and bridge existing gaps in HCV treatment. With safe, effective, simplified DAA regimens for chronic HCV infections, APRNs are positioned to have increasing roles in assessment, prescribing, and follow-up of patients diagnosed with HCV. These roles continue to emerge across multiple settings, including primary care practices, treatment settings for behavioral health or substance use, and with other high-risk populations, such as incarcerated or homeless individuals. The APRN nonspecialist provider can offer care throughout the diagnosis-linkage-treatment continuum, without the need for hepatology specialist referrals, except in complicated cases such as patients with severe liver or kidney disease, previous HCV treatment failure, or pre- or postliver transplantation.[13-15]

When patients are identified through screening, linkage to care and treatment is vital. Current practice guidelines are aimed at avoiding discriminatory treatment exclusion, which may affect individuals in treatment for substance use disorders, in relapse, or actively using substances. Active substance use is not considered a contraindication to treatment, and NPs should actively work to reduce barriers to care in these individuals.[10] This population represents the largest number of new cases of HCV in the US and should be considered high priority to reduce ongoing viral transmission.[5]

Importance of screening and diagnosis

Testing and linkage to care are the essential first steps in improving health outcomes for people with HCV infection. One-time testing is recommended for any individual born between 1945 and 1965, those currently or previously engaged in high-risk behaviors or those who have been exposed to HCV, immunocompromised individuals, and those with elevated liver enzymes.[10] Annual screening should be considered in any patient at higher risk for HCV infection. These include people who inject drugs (PWID), HIV-infected men who have sex with men (MSM), and any individual with ongoing risk factors for HCV exposure.[16]

Screening for HCV may be done with any FDA-approved assays to detect anti-HCV antibodies.

Fibrosis scoring[23-26]

Ishak definition based on liver pathology	Ishak score	METAVIR score	METAVIR definition based on liver pathology	Fibrosis score based on elastography (cutoff ranges in kPa)
No fibrosis	0	0	No fibrosis	≤7 kPa
Fibrous expansion of *some* portal areas, with or without short fibrous septa	1	1	Fibrous portal expansion	≤7 kPa
Fibrous expansion of *most* portal areas, with or without short fibrous septa	2			
Fibrous expansion of most portal areas with *occasional* portal to portal bridging	3	2	Few bridges or septa	≥7 kPa
Fibrous expansion of portal areas with marked bridging	4	3	Numerous bridges or septa	≥9.5 kPa
Marked bridging with occasional nodules	5			
Cirrhosis, probable or definite	6	4	Cirrhosis	≥12 kPa

If the antibody test is positive, quantitative serum HCV RNA testing by polymerase chain reaction (PCR) for viral load is required for confirmation of current HCV infection. Individuals who screen positive for HCV antibodies and who have detectable levels of HCV in their blood are considered to have active HCV infection.

If a patient's anti-HCV serology is positive but HCV viral load is negative, several explanations exist. Either the patient has completely recovered from a past HCV infection (by spontaneous viral clearance or cured by treatment), the anti-HCV test was a false positive, or the patient is acutely infected with HCV but has not yet generated significant viremia. Testing should be repeated in 3 to 6 months to distinguish acute infection from spontaneous recovery.[10]

The APRN should ensure all antibody-positive patients receive follow-up for confirmatory (HCV viral load) testing in order to avoid missing this opportunity for patient treatment and cure. Methods using alternative rapid testing biomarkers and one-step confirmation tests are currently being studied, which would mitigate this problem by checking HCV antibodies and viral load concurrently.[17] Point-of-care testing may be beneficial to improve uptake in HCV treatment, especially in harder-to-reach populations, such as people who live in rural areas, the homeless, and PWID. Quantitative HCV viral load testing is currently recommended in all cases prior to initiating treatment in order to determine baseline viral load and response to therapy.[10]

Liver disease evaluation

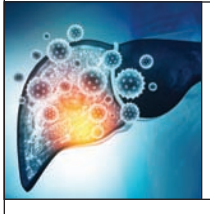
Chronic HCV infection predisposes patients to liver fibrosis and end-stage liver complications through chronic inflammation that leads to scarring, and possibly through the body's immune response to the virus. Liver fibrosis is currently considered a wound-healing response to chronic liver injury. The inflammatory process is classic in nature and drives the fibrogenic response with excessive accumulation of extracellular matrix proteins such as collagen, laminin, and fibronectin.[18,19] Over time, the fibrosis will naturally progress with liver function declining. Typically fibrosis scoring is done with Metavir (F0-F4) or Ishak staging (F0-F6) quantifying the amount of hepatic collagen. Using the Metavir scoring system, fibrosis scores of F0-F1 indicate mild fibrosis, scores of F2 moderate fibrosis, F3 advanced fibrosis, and F4 cirrhosis.[20]

With increasing levels of liver fibrosis and cirrhosis, the risk of HCC rises. Chronic HCV infection is the leading cause of HCC.[21,22] Data continue to emerge about the process and rate of fibrosis reversal after HCV clearance with treatment. Fibrosis reversal occurs after viral eradication with older interferon-based therapy as well as the newer direct-acting antiviral therapies.[20] Therefore, identification of fibrosis stage upon diagnosis of chronic HCV infection is important for treatment planning and long-term management of chronic liver disease. (See *Fibrosis scoring*.)[23-26]

The development of liver fibrosis indicates the onset of progressive disease, which may lead to end-stage

liver complications, such as portal hypertension, ascites, varices, and hepatic encephalopathy. HCV infection may also present with extrahepatic manifestations that are immune-related and inflammatory in nature, such as lymphoma; cryoglobulinemia; and cardiovascular, renal, and neurologic conditions.[27] Patients with absent or mild fibrosis have a relatively low risk of developing cirrhosis over the next 20 years. Patients with portal fibrosis have a progression rate to cirrhosis of 18 to 20 years, and those with septal fibrosis have a progression rate of 8 to 10 years. Early staging of liver fibrosis is critical for HCV management.[28] If more advanced fibrosis or cirrhosis is detected upon diagnosis, additional screening for HCC with imaging and screening for esophageal varices with endoscopy is indicated. The APRN should evaluate the need for lifestyle modifications, such as alcohol and drug abstinence, as well as referrals to psychologists, dietitians, and metabolic clinics for diagnostic and therapeutic interventions.

The liver biopsy, once considered the gold standard for liver fibrosis identification and staging, provides objective data: the amount and pattern of collagen or scar tissue in the liver. The liver sample and the pathologist's experience remain the major determinates of diagnostic accuracy. Because of the increase in availability of noninvasive diagnostic tests, such as direct and indirect biomarkers and elastography, the role of liver biopsy prior to HCV therapy is minimal. Liver biopsy is only indicated in HCV infection for those cases where there are discordant results from two indirect fibrosis markers, where clinicians suspect a secondary cause of liver disease, or when noninvasive methods are unavailable.[29,30] Possibly, more important than the actual stage of fibrosis prior to HCV therapy is the identification of cirrhosis itself.[29]



Counsel patients that treatment for hepatitis C does not provide immunity to other forms of viral hepatitis.

Several direct and indirect serologic markers are commercially available to provide an assessment of liver fibrosis. The noninvasive serum markers available include the AST-to-platelet ratio index score (APRI), the FIB-4 index, FibroMeter, FIBROSpect HCV test, FibroTest (Fibrosure), and Hepascore.[29,31] The APRI calculator is a publicly available tool that uses serum AST and platelet count to estimate liver disease. It is readily available to all clinicians at virtually no cost. It remains one of the most validated noninvasive markers for liver fibrosis and is very useful to exclude significant fibrosis and cirrhosis.[32] The Fibrosis-4 (FIB-4) index is another publicly available tool that uses age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelets to estimate liver fibrosis. It is very inexpensive to administer, simple, and consistently identifies severe fibrosis and cirrhosis, but cases with indeterminate ranges may require further investigation with elastography or biopsy to determine fibrosis level.[31] Combination biomarker panels or indirect markers (Fibrotest, FibroMeter, Hepascore) are validated, blood-based, commercially available algorithms to predict liver fibrosis. The cutoff scores of these general clinical scoring systems vary depending on cause of liver disease, and all have excellent negative predictive values for ruling out advanced liver fibrosis.[29,31] These tests may become part of routine long-term care after cure to assess reversal of fibrosis.

Liver stiffness measurement is a newer noninvasive method to assess liver fibrosis and may be done with transient elastography (TE), magnetic resonance elastography, or several ultrasound-based modalities, such as acoustic radiation force impulse imaging and shear wave elastography, depending on availability. Liver elastography provides instantaneous information regarding liver stiffness and can reliably distinguish patients with a high versus low likelihood of cirrhosis. The test can also estimate the amount of steatosis. Advantages of TE include results immediately available in the clinic, and it is patient- and operator-friendly to use. With obesity, ascites, and limited operator experience, the results are unreliable approximately 15% of the time.[33]

Some state and insurance payer systems require an assessment of liver fibrosis stage prior to approval of HCV medications for treatment, although there is a shift to eliminating this as a criterion for HCV treatment. However, the importance of identification of advanced fibrosis and cirrhosis is critical for patient care. The identification of cirrhosis will influence the HCV treatment regimen, duration of treatment, response to therapy, and long-term screening for HCC, varices, and liver decompensation. A method of liver

Recommended first-line DAA regimens for HCV treatment-naive individuals[38-41]

Name of DAA	Ledipasvir 90 mg/ Sofosbuvir 400 mg (Harvoni)	Grazoprevir 50 mg/ Elbasvir 100 mg (Zepatier)	Velpatasvir 100 mg/ Sofosbuvir 400 mg (Epclusa)	Glecaprevir 100 mg/ Pibrentasvir 40 mg (Mavyret)
Drug classification	NS5A/NS5B	NS3/4A-NS5A	NS5A/NS5B	NS3/4A-NS5A
Genotypes	1, 4, 5, 6	1, 4	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6
Treatment duration	1 tablet daily for 8-12 weeks	1 tablet daily for 12 weeks	1 tablet daily for 12 weeks	3 tablets daily for 8 weeks
FDA approval date	October 2014; Children older than 12: April 2017	January 2016	June 2017	August 2017; Pediatrics: April 2019
Use in compensated cirrhosis	Yes	Yes	Yes	Yes, 12 weeks
Use in severe renal impairment	No	Yes	No	Yes

fibrosis assessment should be used as part of the initial evaluation of chronic liver disease and planning for HCV treatment. If cirrhosis is identified, additional diagnostic evaluations should be done to determine decompensation of liver function and associated complications. Referral to a liver transplant center for evaluation will be needed in these patients as timing of HCV treatment must be carefully planned in these individuals.

HCV treatment regimens

Improvements in noninvasive assessment of liver fibrosis and the development of next-generation pangenotypic DAA medications have simplified the treatment of HCV. Two major pangenotypic DAA treatment regimens were FDA-approved in 2017 and are recommended as the first consideration of treatment-naive, patients without evidence of cirrhosis.[34,35] These newer DAA regimens provide combination therapy in a daily formulation with efficacy rates greater than 95%.[34] The DAA medications for the treatment of chronic HCV infection fall into three distinct classes: nonstructural protein 3/4 (NS3/4A) protease inhibitors, nonstructural protein 5A (NS5A) inhibitors, and nonstructural protein 5B (NS5B) inhibitors.[12] The NS3/4A inhibitors target viral protease, while the NS5A inhibitors destabilize replication complex and viral release. The NS5B inhibitors target polymerase all working together in combination to halt viral replication.[10] Treatment effectiveness with these agents is high and has been studied in treatment-naive and treatment-experienced patients (interferon-based therapy or previous DAA therapy), as well as in patients with compensated and decompensated cirrhosis, renal impairment, and HIV/HCV coinfection.

Practice guidelines from the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) can be found at www.hcvguidelines.org.[36] The website allows users to input variables such as genotype, treatment history, and cirrhosis status to provide HCV regimen treatment recommendations. Efficacy of therapy is measured at 12 weeks posttreatment. If the viral count is undetectable, the patient is considered to have a sustained virologic response (SVR). These positive outcomes and simplification of therapy with once-daily dosing, shorter duration of therapy, and reduced adverse reactions demonstrate that combination DAA therapies are superior to previously used regimens.[34,37] (See *Recommended first-line DAA regimens for HCV treatment-naive individuals.*)[38-41]

Glecaprevir/pibrentasvir (Mavyret) was approved by the FDA in August 2017 as a pangenotypic therapy for treatment of genotypes 1-6.[41] Glecaprevir (100 mg), an NS3/4A protease inhibitor, and pibrentasvir (40 mg), an NS5A inhibitor, are administered in combination as three fixed-dose pills to be taken once daily as an 8-week therapy for treatment-naive, noncirrhotic patients with a 99% SVR rate.[41] Patients with compensated cirrhosis can be treated with this regimen as a 12-week therapy with a 99% SVR rate.[42]

Sofosbuvir/velpatasvir 400 mg/100 mg (Epclusa) was approved by the FDA in June 2016 for genotypes 1-6.[34] This therapy is a combination of an NS5B and

an NS5A inhibitor and is used as a once-daily dose for 12 weeks with a 99% SVR rate.[34,43] This combination can be used for treatment-naive or treatment-experienced patients, with or without compensated cirrhosis.

Sofosbuvir/ledipasvir 400 mg/90 mg (Harvoni), fixed-dose combination approved in 2014, is one of the first FDA-approved DAAs for treatment of patients with genotypes 1, 4, 5, and 6.[44,45] Ledipasvir is a NS5A inhibitor, and sofosbuvir is a NS5B polymerase inhibitor, used as a once-daily fixed dose therapy that has 95% SVR rates in treatment-naive and noncirrhotic patients.[45] A shorter 8-week therapy is recommended only for non-Black patients, without HIV, with HCV RNA levels lower than 6 million copies/mL at baseline. For patients with compensated cirrhosis genotype 1, a 12-week therapy can be considered with SVR rates of 97%.[44] There are limited data regarding cirrhotic patients with genotypes 4, 5, or 6.

Elbasvir/grazoprevir 50 mg/100 mg (Zepatier) was approved January 2016 for genotype 1 and 4. Elbasvir is an NS5A inhibitor and grazoprevir is an NS3/4A protease inhibitor; when used in combination (50 mg/100 mg), as a 12-week therapy, showed SVR rates 92% and above for treatment-naive, noncirrhotic patients.[46] Elbasvir/grazoprevir can be used to treat compensated cirrhotic genotype 1 patients without baseline NS5A resistance associated substitutions.[47]

Treatment recommendations for those patients previously treated with HCV medications will vary depending on HCV regimen used, genotype, and cirrhosis status. APRNs should consult the AASLD treatment guidelines for current recommendations. Glecaprevir/pibrentasvir (Mavyret) is approved for retreatment of genotypes 1-6 interferon experienced noncirrhotic patients as an 8-week therapy with 12 weeks of therapy recommended for compensated cirrhotics.[48] Similarly, sofosbuvir/velpatasvir (Epclusa) is approved for a 12-week therapy for retreatment of peg/interferon failures in genotypes 1-6.[43]

In 2017, the FDA approved a triple combination regimen of sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg Vosevi) as a recommended retreatment option for genotype 1-6 patients who failed therapy with an NS5A inhibitor.[34] Voxilaprevir is a NS3/4 protease inhibitor added to sofosbuvir/velpatasvir NS5B and NS5A combination given as a daily 12-week regimen.[34] An exception should be noted for genotype 3 where weight-based ribavirin therapy should be considered with previous NS5A failure. Efficacy rates for DAA-treatment experienced including NS5A inhibitors, with or without cirrhosis, are over 90% SVR.[49]

When considering HCV treatment in special circumstances such as decompensated cirrhosis, liver transplantation, HIV/HCV coinfection, incarcerated and substance users, and any other special populations, the practice guidelines should be consulted for evidence-based practice guidelines and recommendations for drug regimen choices and duration of therapy as well as any special considerations and patient monitoring. APRNs should consider referral to a specialist for treatment and long-term patient-care needs. Referral may include hepatology, gastroenterology, infectious disease, psychiatry, and addiction specialists, depending on patient needs.

Most major payor systems cover HCV treatment regimens, such as Medicare, Medicaid, and private insurance plans; however, many require a preauthorization process. A checklist for the office staff can be helpful to ensure that all required information is included with the authorization request to facilitate timely access to HCV therapy. While HCV treatment is cost-effective, the regimens can be expensive; however, as generic formulations are available the barrier of cost is reduced.

Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation associated with severe hepatitis flares has been increasingly recognized as a potential adverse event associated with HCV DAA therapy. The highest risk has been observed with HBsAg-positive patients, but HBV reactivation has been reported in patients with isolated anti-HBV core. The FDA previously detailed 24 confirmed cases of HBV infection reactivation during or after HCV DAA therapy and issued a drug safety black box warning in October 2016. Therefore, all patients initiating HCV DAA therapy should be assessed for HBV coinfection through HBsAg, anti-HBsAg, anti-HB core, and anti-HBs prior to the start of medications. People susceptible to HBV infection, shown through low levels of anti-HBs, should receive the hepatitis B vaccine series. A follow-up HB DNA quantitative value should be obtained for all patients who test positive for HBsAg. HBV suppressive therapy should be given before HCV DAA therapy if treatment criteria are met by HBV DNA level. Liver function and HBV DNA levels should be monitored at 4-week intervals during HCV DAA treatment.[10]

Patient considerations and education

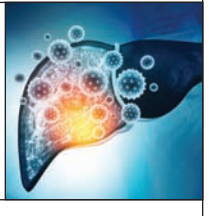
Counsel patients that treatment for hepatitis C does not provide immunity to other forms of viral hepatitis, liver disease, or reinfection with HCV. According to the CDC, immunization for hepatitis A and B should be initiated (although completion is not required) prior to starting HCV.[49]

Education regarding the correct administration of HCV medications including dose frequency, potential drug interactions, food effects, and missed doses is essential before starting therapy. Adverse reactions are minimal with DAAs; however, up to 10% of patients may experience headache, fatigue, and nausea. Drug-drug interactions (DDIs) are important to consider prior to starting treatment. An easy-to-use hepatitis drug interactions website maintained by the University of Liverpool for prescribing clinicians is available at www.hepdruginteractions.org. In particular, sofosbuvir-containing regimens (Harvoni, Epclusa, Vosevi) cannot be coadministered with amiodarone due to their potential to cause serious symptomatic bradycardia; therefore, other antiarrhythmic agents must be used when indicated. Other drugs that may reduce therapeutic efficacy of HCV medication regimens include inducers or inhibitors of the cytochrome P-450 (CYP450) enzyme system. Common agents to be avoided with HCV medications include rifampin, St. John's wort, carbamazepine, azithromycin, and clarithromycin. H2 receptor antagonists (such as famotidine) and proton-pump inhibitors (such as omeprazole) vary by drug recommendation but are best taken 12 hours apart from HCV medications. Ethinyl estradiol containing drugs (such as in combined hormonal contraceptives) may increase the risk of ALT elevations and are generally not used concurrently with DAA therapy. In HIV-infected individuals, the antiretroviral therapies need to be carefully evaluated prior to initiation of certain HCV treatment regimens for the potential of DDIs. Efficacy of the DAA therapies in HIV/HCV coinfected individuals is high and equivalent to individuals with HCV who do not have HIV coinfection.[50]

Given the rise in HCV infection among women of childbearing age, the possibility of using DAAs during pregnancy is being explored.[51] However, limited data currently exist to establish the risk of DAAs on pregnancy outcomes. Pregnant patients with HCV should be referred to a hepatology and obstetrics specialist for management. AASLD-IDSA guidelines currently recommend that treatment of HCV in pregnant women be delayed until after pregnancy completion. Preconception counseling should be performed as needed and nonestrogen-containing contraception should be used to avoid pregnancy while on DAA therapy.[10,51]

Pretreatment assessment of patients' psychosocial history, identification of behavioral risk factors for transmission and reinfection, and the exploration of past or current alcohol and/or substance use disorders are important areas to evaluate in the pretreatment phase as related to adherence. Health literacy, disease knowledge, and the presence of language barriers should also be assessed so that needed education can be provided appropriately. For some patients, discussions regarding values and beliefs, cultural and religious considerations, disclosure and privacy issues, and the stigma associated with HCV infection may be important. The APRN can use motivational interviewing techniques to encourage patients to discuss special concerns they may have and to improve self-efficacy in managing their care. Lifestyle changes related to drug and/or alcohol abuse are best implemented pretreatment with continued follow-up as part of holistic long-term management of care by the APRN.[52] Abstinence from alcohol contributes to optimal therapeutic DAA response. Harm-reduction strategies for individuals with current or recent substance abuse, referral to psychiatry (for medication-assisted treatment), and psychological/behavioral therapy and counseling may also be indicated.[53]

Testing and linkage to care are the essential first steps in improving health outcomes for people with HCV infection.

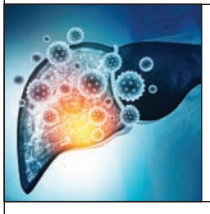


In order to influence HCV transmission and reinfection rates, HCV treatment in PWID or those on opioid replacement therapy is encouraged. Adherence and response rates appear comparable to other HCV-infected populations; however, increased frequency of drug use did correlate with a reduction in HCV treatment efficacy.[54,55] Real-world studies with DAA therapy in this group of patients demonstrate a rate of 93% to 100% treatment completion with an SVR rate of 80%

to 96%. Treatment did not appear to impact opioid replacement therapy or increase drug use.[54] Therefore, HCV treatment in this population is an important public health priority.

Monitoring during and after HCV treatment

Clinic visit scheduling related to an 8- or 12-week treatment course with DAAs should include a baseline visit prior to starting HCV medications, a follow-up visit after 4 weeks of therapy, an end-of-treatment visit (at 8 or 12 weeks), and a posttreatment visit after therapy completion. Patients with adverse drug reactions, complications, or those at risk for nonadherence should be followed more closely as indicated. Quantitative HCV PCR is recommended at baseline, 4 weeks after start of therapy, and at 12 weeks after completion to assess for SVR. Providers may also consider HCV RNA testing at end of treatment, although this is not required.[10] An SVR is defined as an HCV RNA below the limit of detection at 12 weeks posttherapy completion and is a marker for virologic and clinical cure.[10,56]



DAA drug interactions are an important consideration in the posttransplant patient population.

In most cases, HCV RNA will be undetectable at week 4 of treatment. In rare cases where viremia is still present, a week 6 HCV RNA may be repeated. If at that point, the viral load has increased by greater than 10-fold, discontinuation of treatment may be considered after expert consultation. It is important to note that in the small number of patients with low levels of viremia present at week 4, the vast majority will clear the virus with a full course of treatment.

Adherence to the HCV regimen is crucial to achieve viral eradication. Supervision, monitoring, and scheduled lab assessment of HCV RNA during treatment are important components of facilitating adherence. There is recent data to suggest that a more simplified approach to patient monitoring during HCV treatment may be indicated. The SMART-C researchers conducted a multicenter, randomized, open-label study to compare standard monitoring of therapy versus a simplified monitoring that included monitoring visits at week 4 and 8 via phone call from a nurse to assess for adherence and to monitor for adverse reactions. Researchers found a SVR12 rate of 92% in the simplified group compared with a SVR12 rate of 95% in the standard group and concluded that a simplified monitoring schedule may be feasible in patients for whom high adherence is anticipated.[57]

The approach to monitoring patients following completion of HCV therapy is dependent on the pretreatment evaluation and response to therapy. Scenarios include patients who achieved SVR12, patients who completed therapy but did not achieve SVR, and patients who had inadequate treatment because of adherence problems and/or premature discontinuation of treatment. Patients remain at risk for reinfection, non-HCV related liver disease such as fatty liver disease, and alcohol-related liver disease.[57-59] Patients with advanced fibrosis or cirrhosis are at risk for developing HCC regardless of SVR.[60] Practice guidelines recommend follow-up time frames dependent on hepatic fibrosis stage and risk of reinfection. Patients who do not have advanced fibrosis (Metavir F0-F2) do not require special monitoring for HCV or liver care. HCV RNA should be repeated at week 48 posttreatment and if HCV RNA remains undetectable, there is no need for further follow-up. Educate patients that they can become reinfected with HCV. HCV RNA and genotype is recommended to assess for HCV recurrence if reinfection is suspected. Greater than 95% of patients who are treatment-naive, adherent, and have compensated liver disease are likely to achieve SVR.[58,59,61,62]

Special considerations

Decompensated cirrhosis and preliver transplantation. Individuals with decompensated cirrhosis identified by Childs-Turcotte-Pugh Class B and C will need referral to hepatology practitioners for evaluation of end-stage liver disease and the potential for liver transplantation. Decompensated cirrhotic individuals may be successfully treated with DAA regimens; however, the regimens and treatment durations used and timing of DAA therapy is an important decision carefully weighed by considering multiple factors.[60] Some patients will benefit from DAA treatment improving their liver function, fibrosis stage, and quality of life, but it may negatively impact their organ allocation for liver transplantation, or in rare cases, further decompensate liver function.[63] Treatment of HCV with DAA

medications must be individualized with full discussion of the pros and cons of treatment before and after liver transplantation.[64] Liver and kidney transplant patients can be successfully treated with DAAs. DAA drug interactions are an important consideration in the posttransplant patient population. This group requires close follow-up, like the cirrhotic follow-up protocols.[65]

DAA treatment failure and retreatment. Although HCV virologic failures are rare in the DAA era, patients who failed treatment (patients who did not achieve SVR12) should receive reassessment of disease progression every 6 to 12 months.[62] Follow-up would include hepatic function panel, complete blood cell count, international normalized ratio, and fibrosis staging.[62] The outcome of retreatment in these patients will depend on the DAA regimen previously received and the DAA regimen available for retreatment. The first-line regimen in most cases will be the triple combination of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks.[66]

Long-term management and care. All patients who complete HCV DAA therapy should be counseled on risk of HCV reinfection as well as on harm reduction strategies to maintain long-term health and liver optimization. The Health and Liver Optimization program was developed to assist chronic liver disease patients with the development of goals to aid in healthy living and halt further disease progression. Patients with advanced fibrosis or cirrhosis (F3-F4) require ongoing surveillance for progression of chronic liver disease including lab monitoring, imaging for HCC, and variceal screening.[66] Patients with persistently abnormal liver tests who achieved SVR should be evaluated for other causes of liver disease, such as fatty liver disease or alcohol and/or substance use related causes. Annual screening of HCV RNA is recommended for patients at risk for reinfection, such as PWID or other individuals engaged in high-risk behaviors.

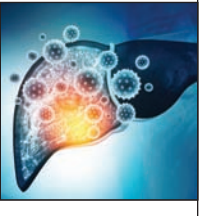
Summary

Individuals receiving DAAs require monitoring in all phases of treatment. Monitoring during therapy involves evaluation of adherence, potential adverse reactions of DAAs, DDIs, and possible HBV reactivation, although these risks are less common with advancement in DAA therapy and education. During treatment, the HCV viral load should be checked at week 4 as a measure of adherence. SVR is confirmed at week 12 posttreatment for confirmation of viral eradication by nondetectable HCV RNA. In patients who do not achieve SVR (<5%), adherence factors should be investigated and other treatment options considered with specialist consultation.

Following treatment and SVR, educational counseling is vital so that high-risk individuals understand the risks of reinfection. Annual HCV RNA testing is recommended for PWID and for those with high-risk sexual practices. Patients with advanced fibrosis (F3-F4) require long-term surveillance for HCC, regardless of whether they achieve SVR. Close follow-up is required in these patients to monitor for HCC using ultrasound and a serum alpha-fetoprotein level every 6 months.[67] Ongoing health-promotion counseling interventions about diet, exercise, and alcohol use is important, especially in patients at risk for NAFLD/NASH, to reduce liver disease progression.

Current screening programs are not yet reaching all potential HCV-infected individuals, and more widespread programs are urgently needed. With recognition of the current disease burden, screening in underserved areas, disparate populations, and in PWID is essential to identify infected individuals and link them to care. Significant disparities exist in access to healthcare for HCV patients and are more prevalent in underserved populations such as the uninsured, those with low socioeconomic status, ethnic minorities, and rural communities. APRNs play a vital role in screening for, diagnosing, treating, and reducing the transmission of HCV to in turn reduce HCV-related morbidity and mortality and eventually achieve eradication of this curable virus.

Annual HCV RNA testing is recommended for PWID and for those with high-risk sexual practices.



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