Overview of the management of chronic hepatitis C virus infection

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INTRODUCTION

Hepatitis C virus (HCV) can cause both acute and chronic hepatitis. The acute process is self-limited, rarely causes hepatic failure, and usually leads to chronic infection. Chronic HCV infection often follows a progressive course over many years and can ultimately result in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

This topic addresses the general management of patients with chronic HCV infection. Patient selection for treatment and specific treatment regimens are discussed in detail elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection" and "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults" and "Direct-acting antivirals for the treatment of hepatitis C virus infection".)

GUIDELINES

Guidelines for the diagnosis and management of hepatitis C virus (HCV) infection were released jointly by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in 2014, are continuously updated, and can be accessed at

www.hcvguidelines.org [1]. The discussion in this topic is generally consistent with those guidelines.

Other guidelines include treatment recommendations from the European Association for the Study of the Liver (EASL) [2]. World Health Organization (WHO) also released guidelines in 2014 on screening and treatment of HCV, intended primarily for clinicians and policy-makers in low- and middle-income countries [3].

Links to these and other guidelines can be found below. (See 'Society guideline links' below.)

PATIENT EVALUATION

The objectives of the evaluation of patients diagnosed with chronic hepatitis C virus (HCV) include the following:

- Assessment of the extent of liver disease. Specifically, identification of advanced fibrosis or cirrhosis informs the need for additional monitoring and management.
- Assessment of viral and host factors that inform the optimal antiviral selection. These factors may include viral genotype, liver fibrosis stage (and signs of decompensated disease in those with cirrhosis), history of prior antiviral treatment, renal function, and concurrent medication use.
- Identifying comorbidities associated with HCV infection. These include extrahepatic manifestations of chronic HCV infection, such as cryoglobulinemia, HCV-associated renal disease, porphyria cutanea tarda, and autoimmune disorders.

  Additionally, HCV-infected patients should also be tested for human immunodeficiency virus (HIV) and hepatitis B virus (HBV) given the common modes of transmission and the association of these coinfections with more rapid disease progression. HBV reactivation can occur during treatment with a direct-acting antiviral (DAA) and has been rarely associated with liver failure and death. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'HBV coinfection' and 'Monitoring for toxicity' below.)

The evaluation of patients with chronic HCV infection is discussed in detail elsewhere. (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Additional evaluation' and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation'.)

COUNSELING

Psychosocial issues — Although most patients with chronic hepatitis C virus (HCV) infection are asymptomatic at the time of diagnosis, the potential sequelae of chronic HCV infection are significant, and this possibility can have important emotional and physical consequences. Counseling and screening for depression should be a major consideration, both at diagnosis and during subsequent follow-up. Many patients benefit from participation in a support group. (See "Patient education: Hepatitis C (Beyond the Basics)".)

Active injection drug use — Individuals with HCV infection may also have issues with ongoing substance use. Such patients should be counseled on substance use treatment, including psychiatric services or opioid substitution therapy. (See "Continuing care for addiction: Implementation" and "Opioid use disorder: Pharmacologic management".).

Active injection drug use is not a contraindication to antiviral therapy, as long as the patient wishes to be treated and is willing and able to adhere to monitoring during treatment. Patient-centered care tailored to the needs of those who use injection drugs may improve treatment completion rates. In a randomized clinical trial among people who inject drugs, an accessible care model that emphasized low-threshold, flexible HCV management co-located with a syringe service program achieved higher HCV cure rates compared with facilitated referral to local clinicians [4].

Transmission risk — Transmission of HCV is primarily through exposure to infected blood. Counseling should include discussions about the specific routes of HCV transmission and advice on measures to decrease the risk of transmission to other individuals (table 1). Women of childbearing age may also be concerned about the risk of perinatal transmission. These issues are discussed in detail elsewhere. (See "Epidemiology and transmission of hepatitis C virus infection", section on 'Routes of transmission' and "Vertical transmission of hepatitis C virus".)

Diet and behaviors — Patients should be informed about the natural history of HCV infection and counseled on potentially modifiable factors that are associated with accelerated liver disease, including alcohol use, obesity and insulin resistance, and marijuana use. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

Because of the association with more rapid progression of liver disease, we suggest complete avoidance of alcohol for HCV-infected individuals. In addition, we encourage weight loss in patients with obesity and cessation of cigarettes and marijuana. (See "Hepatitis C and alcohol", section on 'How much alcohol is too much?' and "Obesity in adults: Overview of management" and "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment".)

We also advise patients that two to three cups of coffee daily can be beneficial to liver health. Coffee consumption (more than two cups per day) has been associated with a reduced risk of hospitalization and mortality from a number of chronic liver diseases including chronic viral hepatitis, nonalcoholic steatohepatitis (NASH), and alcoholic liver disease [5,6].

GENERAL MANAGEMENT

Antiviral therapy is the cornerstone of treatment of chronic hepatitis C virus (HCV) infection (see 'Antiviral therapy' below). With current antiviral therapies, HCV is relatively easily treated and can be eliminated in almost all patients. Other general measures in the management of patients with chronic HCV include symptom management, dose adjustment of medications, and preventing complications of cirrhosis if present.

Fatigue — Many patients with HCV infection complain of fatigue. The cause is uncertain and may be difficult to ascribe to liver disease alone rather than other comorbidities such as depression. Fatigue and overall quality of life improve in some patients who have a sustained virologic response (SVR) following antiviral therapy, although the improvements may be modest [7,8]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Symptom alleviation'.)

Dose adjustments of medications — Prescription and over-the-counter medications usually do not require a dose adjustment in HCV-infected patients who have normal hepatic function. Many patients voice concern about taking acetaminophen due to its association with liver injury when taken in high doses. Patients do not need to avoid acetaminophen, but we suggest that the dose of acetaminophen not exceed 2 g per 24 hours. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation".)

However, for HCV-infected patients with advanced liver disease or cirrhosis, dose adjustments or avoidance of certain medications may be warranted. In particular, nonsteroidal anti-inflammatory drugs can be hepatotoxic and should be **avoided** in patients with advanced liver disease. These issues are discussed in detail elsewhere. (See "Overview of medication adjustments for adult patients with cirrhosis", section on 'General principles'.)

While statins are frequently withheld from patients with chronic liver disease, available data fail to show an increased risk of adverse effects in patients with compensated chronic liver disease, suggesting that statin use is safe in patients with stable HCV infection [9,10]. In addition, there are some data that suggest statin use is associated with lower fibrosis progression rate and decreased risk of progression to cirrhosis and hepatic decompensation [11-13].

Certain medications, including over-the-counter agents, have interactions with various direct-acting antivirals and may need to be adjusted during therapy. These are discussed in detail elsewhere. (See "Direct-acting antivirals for the treatment of hepatitis C virus infection".)

Vaccination — In addition to standard adult vaccinations, HCV-infected patients who are not immune to hepatitis A or B virus should be vaccinated against these viruses. HCV-infected patients with chronic liver disease should also receive pneumococcal vaccination. Details on these vaccinations are discussed elsewhere (figure 1). (See "Immunizations for adults with chronic liver disease".)

Patients with advanced liver fibrosis or cirrhosis — HCV-infected patients who are found to have advanced fibrosis should be monitored for the development of complications. This includes evaluating for clinical signs of liver failure (including ascites, hepatic encephalopathy, or bleeding from gastroesophageal varices) as well as laboratory testing to identify hepatic dysfunction (hypoalbuminemia, hyperbilirubinemia, or hypoprothrombinemia). Additionally, certain patients with cirrhosis should be screened for the presence of gastroesophageal varices by upper endoscopy. Patients with advanced liver fibrosis or cirrhosis should undergo surveillance for hepatocellular carcinoma (HCC) because HCC occurs at a rate of 1 to 4 percent per year. These issues are discussed in detail elsewhere. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Preventing complications' and "Surveillance for hepatocellular carcinoma in adults".)

Because of reports of hepatic decompensation, including some with fatal outcomes, among patients with cirrhosis who were treated with HV NS3/4A protease inhibitors, we favor additional evaluation in certain patients with cirrhosis prior to treatment with regimens containing protease inhibitors [14,15]. This is discussed in detail elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Direct-acting antivirals'.)

ANTIVIRAL THERAPY

Goals of therapy — The goal of antiviral therapy in patients with chronic hepatitis C virus (HCV) is to eradicate HCV RNA, which is predicted by attainment of a sustained virologic response (SVR), defined as an undetectable RNA level 12 weeks following the completion of therapy.

An SVR is associated with a 97 to 100 percent chance of being HCV RNA negative during long-term follow-up and can therefore be considered cure of the HCV infection [16]. Attaining an SVR (with direct-acting antiviral [DAA] regimens as well as with interferon-based regimens) has been

associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications, even among those patients with advanced liver fibrosis [17-32]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Benefits of treatment'.)

Indications — All patients with virologic evidence of chronic HCV infection (ie, detectable HCV viral level over a six-month period) should be considered for treatment. The introduction of DAAs, drugs that target specific nonstructural proteins of HCV and thus disrupt viral replication and infection (figure 2 and table 2), has revolutionized therapy of HCV infection. Highly effective, well-tolerated, all-oral regimens are now the treatment of choice for the vast majority of HCV-infected patients who have access to these agents. The evaluation and selection of patients for antiviral therapy is discussed in detail elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection".)

In the United States, the high prices of these all-oral antiviral regimens have garnered substantial attention among medical and lay communities. Several studies have suggested that these regimens, even at their introductory high cost, are cost-effective for many populations, including those with genotype 1 infection or advanced fibrosis, because of their superior efficacy in clinical trials [33-37]. Availability of additional agents has made most DAA therapies more affordable to patient and third party payers, and thus more patients have access to them.

Regimen selection — Antiviral therapy of HCV has rapidly evolved following the introduction and proliferation of DAAs that offer the potential for highly effective, interferon-free regimens that are highly active against all genotypes. Regimen selection depends on whether the patient is undergoing initial therapy for chronic HCV infection (algorithm 1) or has relapsed infection following prior antiviral treatment, and it is discussed separately:

- (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults".)
- (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

MONITORING DURING ANTIVIRAL THERAPY

Clinical assessment during treatment with an interferon-free, direct-acting antiviral (DAA) regimen focuses on adherence to the regimen and identification of adverse effects. DAAs are generally well tolerated. Specific side effects are discussed in detail elsewhere. (See "Direct-acting antivirals for the treatment of hepatitis C virus infection".)

Viral monitoring — Monitoring viral levels during treatment with DAA regimens has minimal prognostic value, as almost all patients without cirrhosis in the large DAA trials achieve an undetectable hepatitis C virus (HCV) viral level by four weeks of treatment, and failure to achieve that threshold does not accurately predict failure to achieve a sustained virologic response (SVR) [38,39]. Thus, the main reasons to check viral levels during therapy are to assess adherence to the regimen and to document the treatment course and virologic response in case patients relapse and warrant retreatment. Given the expense of the medicines and the potential risk of viral resistance with inappropriate use, we check HCV RNA quantitative testing at week 4 in clinical practice. The joint guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) additionally recommend rechecking HCV RNA quantitative testing at week 6 if the week 4 level is detectable and discontinuing therapy if the level has increased by >1 log [40]. Although there are no direct clinical data to support this practice, we agree that this is an appropriate approach.

The clinical value of a week 12 (or end of treatment) viral level is uncertain, and most providers do not routinely check it. It is undetectable in the vast majority of treated patients, even among those who have subsequent viral relapse. Furthermore, in one study, all six patients with quantifiable but low level (<65 international units/mL) viremia at the end of DAA-based treatment nevertheless achieved SVR [41]. In the large registration trials of ledipasvir-sofosbuvir, 12 of 22 patients with detectable HCV at the end of treatment still achieved SVR [42].

Virologic response to treatment should be assessed by checking the viral load at 12 weeks following the cessation of therapy. (See 'Follow-up after antiviral therapy' below.)

Monitoring for toxicity — Drug toxicity with interferon-free DAA combinations is uncommon, although intermittent laboratory monitoring during treatment is reasonable.

In the absence of data to suggest otherwise, we agree with the AASLD/IDSA recommendations to check basic laboratory tests (complete blood count, creatinine with estimated glomerular filtration rate (eGFR) calculation, and liver enzyme and bilirubin levels) at week 4 of treatment with any regimen, with more frequent monitoring for concerning results or trends [1].

Adherence counseling — It is important to discuss adherence at each clinic visit. Clinicians should ask patients about medication adherence in a nonjudgmental manner. It is sometimes useful to discuss medication schedules with patients to help them link pill-taking behaviors to other daily activities, such as brushing teeth. If the patient admits acknowledges difficulties with adherence, potential barriers could involve the timing of doses, sizes of pills, and treatment-limiting side effects.

For ribavirin-containing regimens, if insomnia is a problem, the evening dose of ribavirin can be adjusted to earlier in the afternoon.

Additional monitoring for HBV coinfection — Patients with evidence of prior or current HBV infection (ie, those with positive HBV core antibody [HBcAb]) who are not on HBV antiviral therapy warrant specific monitoring because of the risk of HBV reactivation during HCV treatment [1,43]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'HBV coinfection'.)

- For those who are HBV surface antigen (HBsAg)-positive, the following should be performed:
  - Obtain a baseline HBV DNA prior to HCV therapy.
  - For those who meet criteria for antiviral treatment of HBV (table 3), initiate HBV treatment prior to or at the same time as HCV therapy.
  - For those who do not meet criteria for HBV therapy, monitor HBV DNA levels at regular intervals (usually not more frequently than every four weeks) during HCV therapy. Initiate HBV therapy for those whose HBV DNA levels meet criteria for treatment (table 3).
- For those who are HBsAg-negative but HBcAb-positive, there are no data to inform optimal monitoring. We suggest monitoring for HBV reactivation in these patients by checking liver enzymes at four week intervals during HCV therapy. In the event of unexplained increases in liver enzymes and during and/or after completion of HCV therapy, repeat HBsAg testing and HBV DNA should be performed. HBV reactivation is suggested by conversion from an undetectable to a detectable HBV DNA or a rise in HBV DNA level by >2 log international units and may warrant antiviral therapy for HBV infection.

Indications for and regimen selection for HBV antiviral therapy are discussed elsewhere. (See "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy'.)

Following identification of this association between HCV treatment and HBV reactivation, a review of adverse hepatic events associated with DAAs that were reported to the US Food and Drug Administration (FDA) identified 524 cases of liver failure in the course of one year, with an estimated 250,000 individuals treated over a similar time frame [44]. It is unclear what proportion of these represent cases of HBV reactivation or complications in patients with existing advanced liver disease (including inappropriate use of protease inhibitors in patients with decompensated disease), situations in which the risk of liver failure is higher than the

general population. Patients should understand that this risk is overall very low and that further data are needed to more clearly define it.

Additional monitoring for uncommonly used regimens — Additional indications for laboratory testing are regimen specific:

- **Elbasvir-grazoprevir** – Additionally, checking liver enzyme and bilirubin levels at week 8 (and week 12, if treatment duration is 16 weeks) is recommended. If an increase in the alanine aminotransferase exceeds 10-fold the baseline level or is accompanied by symptoms or hyperbilirubinemia, treatment should be discontinued.

- **Paritaprevir-ritonavir-ombitasvir-based regimens** – For those patients who have compensated cirrhosis, close monitoring for hepatic decompensation is warranted during therapy with these regimens. This includes assessment for clinical signs of decompensation (eg, ascites, encephalopathy) throughout the treatment course and testing liver enzyme and bilirubin levels at week 2 in addition to week 4, at weeks 12 and 24 for those who are on a longer duration of therapy, and for any concerning signs or symptoms. Clinical evidence of decompensation or significant increases in these laboratory values should prompt treatment discontinuation.

- **Ribavirin-containing regimens** – We check the complete blood count at weeks 4, 8, and 12 to evaluate for anemia. For those who develop anemia, the dose of ribavirin can be adjusted based on the severity and comorbidities. For patients with no cardiac disease, ribavirin can be reduced to 600 mg daily for hemoglobin levels between 8.5 and 10 g/dL and can be held for levels <8.5 g/dL. For with a history of cardiac disease, ribavirin can be reduced to 600 mg daily for a ≥2 g/dL decrease during any four-week period and can be held for hemoglobin <12 g/dL despite four weeks at a reduced dose. Gradual titration up of the ribavirin dose by 200 mg a day can be attempted if patients have a subsequent increase in the hemoglobin.

  For women of childbearing-age taking a ribavirin-containing regimen, assessment of contraception use and pregnancy testing should be performed during and for six months after treatment. Men taking a ribavirin-containing regimen should be counseled on contraceptive use for sex with a woman of childbearing-age during and for six months after treatment.

FOLLOW-UP AFTER ANTIVIRAL THERAPY

Virologic response to treatment should be assessed by checking the viral load at 12 weeks following the cessation of therapy. Sustained virologic response (SVR) is defined by an undetectable viral level at this time point, which is generally maintained through 24 weeks following the cessation of therapy and beyond. However, a very small proportion of patients (less than 1 percent in studies of direct-acting antivirals) experience virologic relapse between weeks 12 and 24, and some of those cases may be reinfection rather than true relapse [45-47]. Thus, some practitioners also check the viral load at 24 weeks to ensure maintenance of SVR. Although SVR reflects effective cure of hepatitis C virus (HCV) infection, it does not confer immunity to HCV, and patients should be counseled that they are at risk for reinfection with future exposure.

Patients who achieve an SVR and do not have bridging fibrosis or cirrhosis do not require any specific follow-up for their HCV infection, though some will check an HCV viral load one year after the completion of treatment to confirm that the viral load remains undetectable.

Patients who fail to achieve an SVR should continue to be followed for signs of progression of liver disease and assessed for retreatment of HCV infection. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection" and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and 'General management' above.)

Patients with advanced fibrosis or cirrhosis, regardless of whether they attain an SVR, require ongoing monitoring (including liver ultrasonography every six months) because they continue to be at risk of hepatocellular carcinoma and other complications. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'General management'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis C virus infection".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hepatitis C (The Basics)" and "Patient education: Treatment for hepatitis C (The Basics)")
- Beyond the Basics topic (see "Patient education: Hepatitis C (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Initial evaluation** – The evaluation of patients with chronic hepatitis C virus (HCV) infection involves assessing the extent of liver disease, assessing other viral and host factors (including viral genotype, liver fibrosis stage, history of prior antiviral treatment, renal function, and medication use) that inform optimal antiviral selection, and identifying comorbidities associated with HCV infection (including extrahepatic manifestations of HCV infection as well as human immunodeficiency virus [HIV] and hepatitis B virus [HBV] infection). (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Additional evaluation' and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation'.)
- **Counseling on transmission risk and dietary/behavioral modifications** – HCV-infected patients should be counseled on measures to decrease the risk of transmission (table 1) and correcting factors associated with accelerated liver disease, including alcohol use, obesity and insulin resistance, and marijuana use. Substance use treatment is also an important element of care in patients who have ongoing illicit drug use. (See 'Counseling' above.)
- **Additional management issues for advanced fibrosis** – Additional management is warranted for patients who are found to have advanced fibrosis or cirrhosis, including dose modification or avoidance of certain medications (such as nonsteroidal anti-inflammatory drugs) , twice yearly ultrasonography for hepatocellular carcinoma screening, and upper endoscopy screening for esophageal varices. (See "Cirrhosis in

adults: Overview of complications, general management, and prognosis", section on 'General management' and "Overview of medication adjustments for adult patients with cirrhosis".)

- **Goals and benefits of antiviral therapy** – All patients with virologic evidence of chronic HCV infection (ie, detectable HCV viral level over a six-month period) should be considered for antiviral treatment. The goal is to eradicate HCV RNA, which is associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications. (See 'Antiviral therapy' above and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection".)

- **Regimen selection** – Highly effective two- to three-month oral regimens are appropriate options for the majority of individuals with chronic HCV infection. Pan-genotypic regimens are generally first-line options (algorithm 1). Regimen selection depends on treatment history and is discussed elsewhere. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

- **Monitoring during treatment** – It is important to emphasize the importance of adherence at each clinic visit. Intermittent laboratory monitoring may be warranted for patients with evidence of prior or current HBV infection. The purpose of viral level monitoring during treatment is primarily to assess adherence and document the treatment course. We typically check a quantitative HCV RNA test at week 4 of therapy. (See 'Monitoring during antiviral therapy' above.)

- **Assessment of treatment success** – Virologic response to treatment should be assessed by checking the viral load at 12 weeks following the cessation of therapy. Sustained virologic response (SVR) is defined by an undetectable viral level at this time point. (See 'Follow-up after antiviral therapy' above.)

- **Post-treatment management** – Patients who fail to achieve an SVR should continue to be followed for signs of progression of liver disease and assessed for retreatment of HCV infection. Patients with advanced fibrosis or cirrhosis, regardless of whether they attain an SVR, warrant ongoing monitoring because they continue to be at risk of hepatocellular carcinoma and other complications. (See 'Follow-up after antiviral therapy' above.)

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Topic 3673 Version 58.0

GRAPHICS

Counseling to avoid transmission of hepatitis C virus

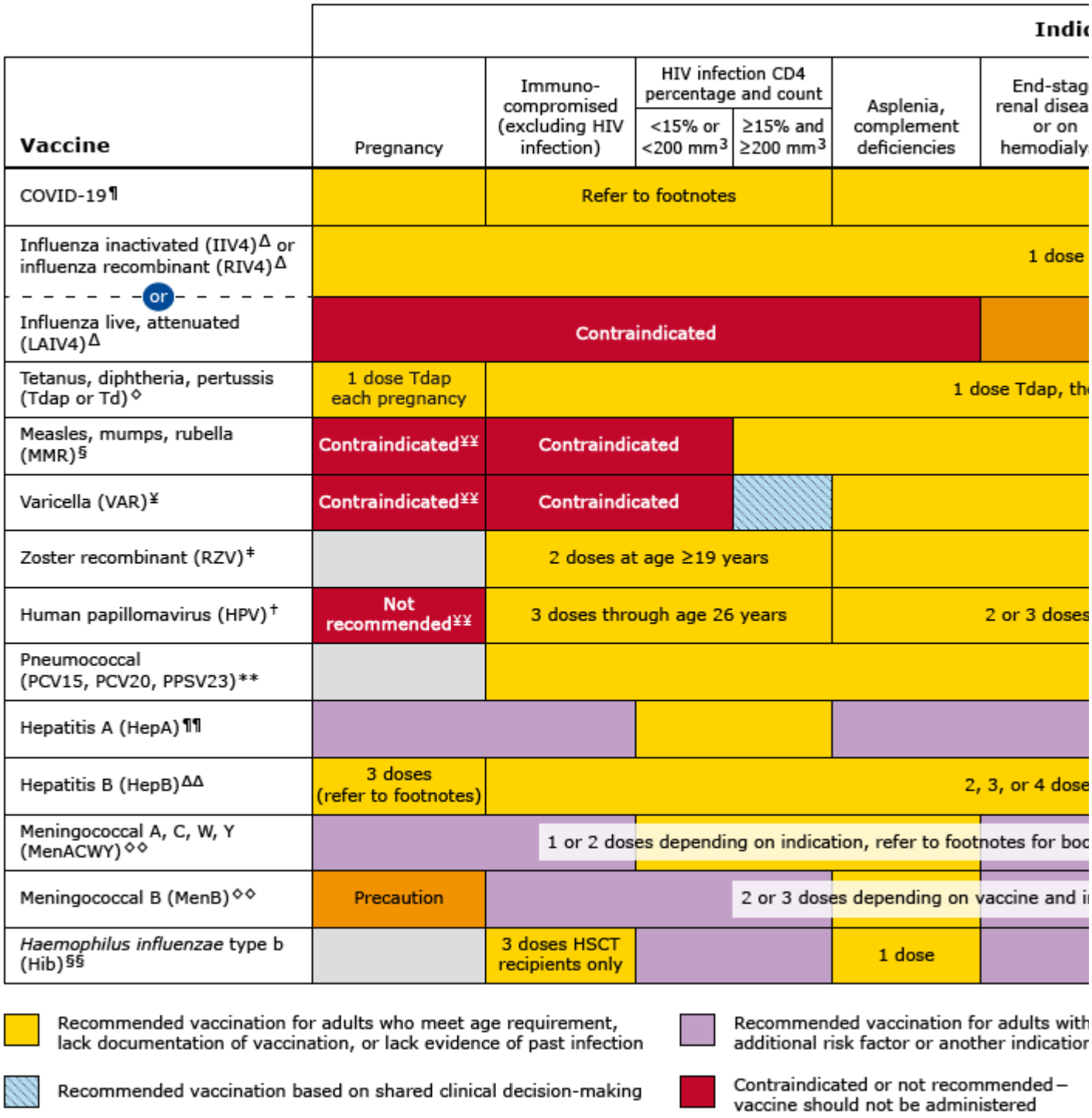
Individuals with HCV infection should be counseled to: ▪ Avoid sharing toothbrushes and dental or shaving equipment ▪ Cover any bleeding wound to prevent others from coming into contact with their blood ▪ Not donate blood ▪ Discuss their HCV status prior to donation of body organs, other tissues, or semen
In general, individuals with HCV infection should be counseled that the risk of sexual transmission is low and that HCV infection itself is not a reason for barrier protection. However, individuals with HCV infection who have HIV co-infection, multiple sexual partners, or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission.
Individuals with HCV infection who use illicit drugs should be counseled to: ▪ Get treated for substance use disorder Those who inject drugs should be counseled to: ▪ Avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment ▪ Use new sterile syringes and filters and disinfected cookers ▪ Clean the injection site with a new alcohol swab ▪ Dispose safely of syringes and needles after one use in a safe, puncture-proof container
Household surfaces or items visibly contaminated with blood from an individual with HCV infection should be cleaned using diluted household bleach (1 part bleach in 9 parts water). Gloves should be worn when cleaning blood spills.

HCV: hepatitis C virus.

Adapted from: AASLD-IDSA. HCV testing and linkage to care. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care (Accessed July 8, 2016).

Graphic 58787 Version 5.0

Recommended adult immunization schedule by medical condition and other in



Administer recommended vaccines if vaccination history is incomplete or unknown. Do not restart or add dc use of trade names is for identification purposes only and does not imply endorsement by the ACIP or CDC.

Polio vaccination

- **Routine vaccination:**
  - Routine poliovirus vaccination of adults residing in the United States is not necessary.
- **Special situations:**

- **Adults at increased risk of exposure to poliovirus with:**
  - **No evidence of a complete polio vaccination series (ie, at least 3 doses):** Administer remain
  - **Evidence of completed polio vaccination series (ie, at least 3 doses):** May administer one life
- For detailed information, refer to www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html.

HSCT: hematopoietic stem cell transplant.

* Precaution for LAIV4 does not apply to alcoholism.

¶ COVID-19 vaccination

- **Routine vaccination:**
  - **Primary series:** 2-dose series at 0, 4 to 8 weeks (Moderna) or 2-dose series at 0, 3 to 8 weeks (Nov
  - **Booster dose:** Refer to www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerati
- **Special situations:**
  - **Persons who are moderately or severely immunocompromised**.
    - **Primary series:**
      - 3-dose series at 0, 4, 8 weeks (Moderna) or 3-dose series at 0, 3, 7 weeks (Pfizer-BioNTech).
      - 2-dose series at 0, 3 weeks (Novavax).
    - **Booster dose:** Refer to www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-conside
    - **Pre-exposure prophylaxis (eg, monoclonal antibodies)** may be considered to complement C considerations/interim-considerations-us.html#immunocompromised.
  - **For Janssen COVID-19 Vaccine recipients** refer to COVID-19 schedule at www.cdc.gov/vaccines/c
  - **NOTE:** Current COVID-19 schedule available at www.cdc.gov/vaccines/covid-19/downloads/COVID- information on Emergency Use Authorization (EUA) indications for COVID-19 vaccines, please visit disease-2019-covid-19/covid-19-vaccines.
- **Contraindications and precautions:**
  - Refer to contraindications and precautions to COVID-19 vaccination.

Δ Influenza vaccination

- **Routine vaccination:**
  - **Age 19 years or older:** 1 dose any influenza vaccine appropriate for age and health status annual
  - **Age 65 years or older:** Any one of quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), adjuvanted inactivated influenza vaccine (aIIV4) is preferred. If none of these three vaccines is ava
  - For the 2022–2023 season, refer to www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm.
  - For the 2023–2024 season, refer to the 2023–2024 ACIP influenza vaccine recommendations.
- **Special situations:**
  - **Egg allergy, hives only:** Any influenza vaccine appropriate for age and health status annually.
  - **Egg allergy–any symptom other than hives** (eg, angioedema, respiratory distress, or required e vaccine appropriate for age and health status may be administered. If using egg-based IIV4 or LA provider who can recognize and manage severe allergic reactions.
  - **Close contacts (eg, caregivers, health care workers) of severely immunosuppressed persons** receive LAIV4. If LAIV4 is given, they should avoid contact with/caring for such immunosuppressed
  - **Severe allergic reaction (eg, anaphylaxis) to a vaccine component or a previous dose of any i** precautions.
  - **History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine:** risks for those at higher risk for severe complications from influenza.
- **Contraindications and precautions:**
  - For contraindications and precautions to influenza vaccination, refer to IIV4 Appendix, LAIV4 Appe

◇ **Tetanus, diphtheria, and pertussis (Tdap) vaccination**

- **Routine vaccination:**
  - **Previously did not receive Tdap at or after age 11 years:** 1 dose Tdap, then Td or Tdap every 10
- **Special situations:**
  - **Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis:** 1 dose of Td or Tdap 6 to 12 months later (Tdap can be substituted for any Td dose, but preferred as
  - **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27 t
  - **Wound management:** Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For cle last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more preferred for persons who have not previously received Tdap or whose Tdap history is unknown. I use Tdap. For detailed information, refer to www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.
- **Contraindications and precautions:**
  - For contraindications and precautions to tetanus, diphtheria, and acellular pertussis (Tdap), refer t

§ **Measles, mumps, and rubella vaccination**

- **Routine vaccination:**
  - **No evidence of immunity to measles, mumps, or rubella:** 1 dose.
    - **Evidence of immunity:** Born before 1957 (health care personnel, refer below), documentation (diagnosis of disease without laboratory confirmation is not evidence of immunity).
- **Special situations:**
  - **Pregnancy with no evidence of immunity to rubella:** MMR contraindicated during pregnancy; a
  - **Nonpregnant women of childbearing age with no evidence of immunity to rubella:** 1 dose.
  - **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 for at least 6 mon** dose series at least 4 weeks apart; MMR contraindicated for HIV infection with CD4 percentage <1
  - **Severe immunocompromising conditions:** MMR contraindicated.
  - **Students in postsecondary educational institutions, international travelers, and household evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart if pre 1 dose MMR.
  - **In mumps outbreak settings**, for information about additional doses of MMR (including 3rd dose
  - **Health care personnel:**
    - **Born before 1957 with no evidence of immunity to measles, mumps, or rubella:** Consider rubella.
    - **Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella:** 2-dose rubella.
- **Contraindications and precautions:**
  - For contraindications and precautions to measles, mumps, rubella (MMR), refer to MMR Appendix

¥ **Varicella vaccination**

- **Routine vaccination:**
  - **No evidence of immunity to varicella:** 2-dose series 4 to 8 weeks apart if previously did not rece varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine, 1 dose at
    - **Evidence of immunity:** US-born before 1980 (except for pregnant women and health care per vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster
- **Special situations:**
  - **Pregnancy with no evidence of immunity to varicella:** VAR contraindicated during pregnancy; a previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series (dose 2: 4 to 8 w regardless of whether US-born before 1980.

- **Health care personnel with no evidence of immunity to varicella:** 1 dose if previously received previously did not receive any varicella-containing vaccine, regardless of whether US-born before
- **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 with no evidence** VAR contraindicated for HIV infection with CD4 percentage <15% or CD4 count <200 cells/mm^3.
- **Severe immunocompromising conditions:** VAR contraindicated.

▪ **Contraindications and precautions:**

- For contraindications and precautions to varicella (VAR), refer to VAR Appendix.

‡ **Zoster vaccination**

▪ **Routine vaccination:**

- **Age 50 years or older** (NOTE: Serologic evidence of prior varicella is not necessary for zoster vacc available, providers should follow ACIP guidelines for varicella vaccination first. RZV is not indicate RZV in persons without a history of varicella or varicella vaccination)**:** 2-dose series recombinant zo weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of zo

▪ **Special situations:**

- **Pregnancy:** There is currently no ACIP recommendation for RZV use in pregnancy. Consider delay
- **Immunocompromising conditions** (including persons with HIV regardless of CD4 count; NOTE: I herpes zoster, providers should refer to the clinical considerations for use of RZV in immunocomp recommendations for further guidance: www.cdc.gov/mmwr/volumes/71/wr/mm7103a2.htm)**:** 2-d (minimum interval: 4 weeks; repeat dose if administered too soon). For detailed information, refer

▪ **Contraindications and precautions:**

- For contraindications and precautions to zoster recombinant vaccine (RZV), refer to RZV Appendix.

† **Human papillomavirus vaccination**

▪ **Routine vaccination:**

- **HPV vaccination recommended for all persons through age 26 years:** 2- or 3-dose series depe
  - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1 to 2 months, 6 months (min dose 1 to dose 3: 5 months; repeat dose if administered too soon).
  - **Age 9 to 14 years at initial vaccination and received 1 dose or 2 doses less than 5 months**
  - **Age 9 to 14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be rest
- **No additional dose recommended when any HPV vaccine series has been completed using tl**

▪ **Shared clinical decision-making:**

- **Some adults age 27 to 45 years:** Based on shared clinical decision-making, 2- or 3-dose series as

▪ **Special situations:**

- **Age ranges recommended above for routine and catch-up vaccination or shared clinical deci**
  - **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those w
  - **Pregnancy:** Pregnancy testing is not needed before vaccination; HPV vaccination is not recom vaccinated while pregnant.

▪ **Contraindications and precautions:**

- For contraindications and precautions to human papillomavirus (HPV) vaccination, refer to HPV Ap

** **Pneumococcal vaccination**

▪ **Routine vaccination:**

- **Age 65 years or older who have:**
  - **Not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccination** this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A min for adults with an immunocompromising condition (NOTE: Immunocompromising conditions

iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Ho transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable gr

- **Previously received only PCV7:** Follow the recommendation above.
- **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR comp www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
- **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PP PPSV23.
- **Previously received both PCV13 and PPSV23 but NO PPSV23 was received at age 65 years** vaccine dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/
- **Previously received both PCV13 and PPSV23, AND PPSV23 was received at age 65 years o** least 5 years after the last pneumococcal vaccine dose.
- For guidance on determining which pneumococcal vaccines a patient needs and when, pleas www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html.

- **Special situations:**
  - **Age 19 to 64 years with certain underlying medical conditions or other risk factors who hav** alcoholism, chronic heart/liver/lung disease, chronic renal failure, cigarette smoking, cochlear im generalized malignancy, HIV, Hodgkin disease, immunodeficiency, iatrogenic immunosuppressio organ transplants, or sickle cell disease, or other hemoglobinopathies**):**
    - **Not previously received a PCV13, PCV15, or PCV20 or whose previous vaccination history** should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A minimu adults with an immunocompromising condition(NOTE: Immunocompromising conditions incl iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Ho transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies
    - **Previously received only PCV7:** Follow the recommendation above.
    - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR comp www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
    - **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PP PPSV23.
    - **Previously received both PCV13 and PPSV23 but have not completed the recommended** dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/vaccines
  - For guidance on determining which pneumococcal vaccines a patient needs and when, please re www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html.
- **Contraindications and precautions:**
  - For contraindications and precautions to Pneumococcal conjugate (PCV15 and PCV20), refer to P PPSV23 Appendix.

¶¶ Hepatitis A vaccination

- **Routine vaccination:**
  - **Not at risk but want protection from hepatitis A (identification of risk factor not required):** apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [mini
- **Special situations:**
  - **At risk for hepatitis A virus infection:** 2-dose series HepA or 3-dose series HepA-HepB as above
    - **Chronic liver disease** (eg, persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, a [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal).
    - **HIV infection**.
    - **Men who have sex with men**.

- **Injection or noninjection drug use**.
- **Persons experiencing homelessness**.
- **Work with hepatitis A virus** in research laboratory or with nonhuman primates with hepatit
- **Travel in countries with high or intermediate endemic hepatitis A** (HepA-HepB [Twinrix] r to 30 days, followed by a booster dose at 12 months).
- **Close, personal contact with international adoptee** (eg, household or regular babysitting) endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks befor
- **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy.
- **Settings for exposure**, including health care settings targeting services to injection or noninj for developmentally disabled persons (individual risk factor screening not required).

- **Contraindications and precautions:**
  - For contraindications and precautions to hepatitis A (HepA) vaccination, refer to HepA Appendix.

ΔΔ **Hepatitis B vaccination**

- **Routine vaccination:**
  - **Age 19 through 59 years:** Complete a 2- or 3-, or 4-dose series.
    - 2-dose series only applies when 2 doses of Heplisav-B (NOTE: Heplisav-B and PreHevbrio are persons) are used at least 4 weeks apart.
    - 3-dose series Engerix-B, PreHevbrio (NOTE: Heplisav-B and PreHevbrio are not recommended Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to d
    - 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 w
    - 4-dose series HepA-HepB (Twinrix) accelerated schedule of 3 doses at 0, 7, and 21 to 30 days,
  - **Age 60 years or older with** known risk factors for hepatitis B virus infection **should** complete a H
  - **Age 60 years or older without** known risk factors for hepatitis B virus infection **may** complete a
    - **Risk factors for hepatitis B virus infection include:**
      - **Chronic liver disease** (eg, persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic aspartate aminotransferase [AST] level greater than twice upper limit of normal).
      - **HIV infection**.
      - **Sexual exposure risk** (eg, sex partners of hepatitis B surface antigen [HBsAg]-positive pe persons seeking evaluation or treatment for a sexually transmitted infection; men who ha
      - **Current or recent injection drug use**.
      - **Percutaneous or mucosal risk for exposure to blood** (eg, household contacts of HBsAg disabled persons; health care and public safety personnel with reasonably anticipated risk maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, a
      - **Incarceration**.
      - **Travel in countries with high or intermediate endemic hepatitis B**.
- **Special situations:**
  - **Patients on dialysis:** complete a 3- or 4-dose series.
    - 3-dose series Recombivax HB at 0, 1, 6 months (NOTE: use Dialysis Formulation 1 mL = 40 mc
    - 4-dose series Engerix-B at 0, 1, 2, and 6 months (NOTE: use 2 mL dose instead of the normal a
- **Contraindications and precautions:**
  - For contraindications and precautions to hepatitis B (HepB) vaccination, refer to HepB Appendix.

◇◇ **Meningococcal vaccination**

- **Special situations for MenACWY:**
  - **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent c eculizumab, ravulizumab) use:** 2-dose series MenACWY-D (Menactra, Menveo, or MenQuadfi) a

- **Travel in countries with hyperendemic or epidemic meningococcal disease, or microbiologi** (Menactra, Menveo, or MenQuadfi) and revaccinate every 5 years if risk remains.
- **First-year college students who live in residential housing (if not previously vaccinated at a** Menveo, or MenQuadfi).
- For MenACWY **booster dose recommendations** for groups listed under "Special situations" and among men who have sex with men) and additional meningococcal vaccination information, refe

- **Shared clinical decision-making for MenB:**
  - **Adolescents and young adults age 16 to 23 years (age 16 to 18 years preferred) not at increa** making, 2-dose series MenB-4C (Bexsero) at least 1 month apart or 2-dose series MenB-FHbp (Tru after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not
- **Special situations for MenB:**
  - **Anatomical or functional asplenia (including sickle cell disease), persistent complement co ravulizumab) use, or microbiologists routinely exposed to *Neisseria meningitidis*** (NOTE: Men if indicated, but at a different anatomic site, if feasible)**:** 2-dose primary series MenB-4C (Bexsero) at 0, 1 to 2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not need dose should be administered at least 4 months after dose 3); MenB-4C and MenB-FHbp are not ir booster 1 year after primary series and revaccinate every 2 to 3 years if risk remains.
  - **Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefits o
  - For MenB **booster dose recommendations** for groups listed under "Special situations" and in ar among men who have sex with men) and additional meningococcal vaccination information, refe
- **Contraindications and precautions:**
  - For contraindications and precautions to meningococcal ACWY (MenACWY) [MenACWY-CRM (Mer MenACWY Appendix.
  - For contraindications and precautions to meningococcal B (MenB) [MenB-4C (Bexsero); MenB-FH

§§ ***Haemophilus influenzae*** **type b vaccination**

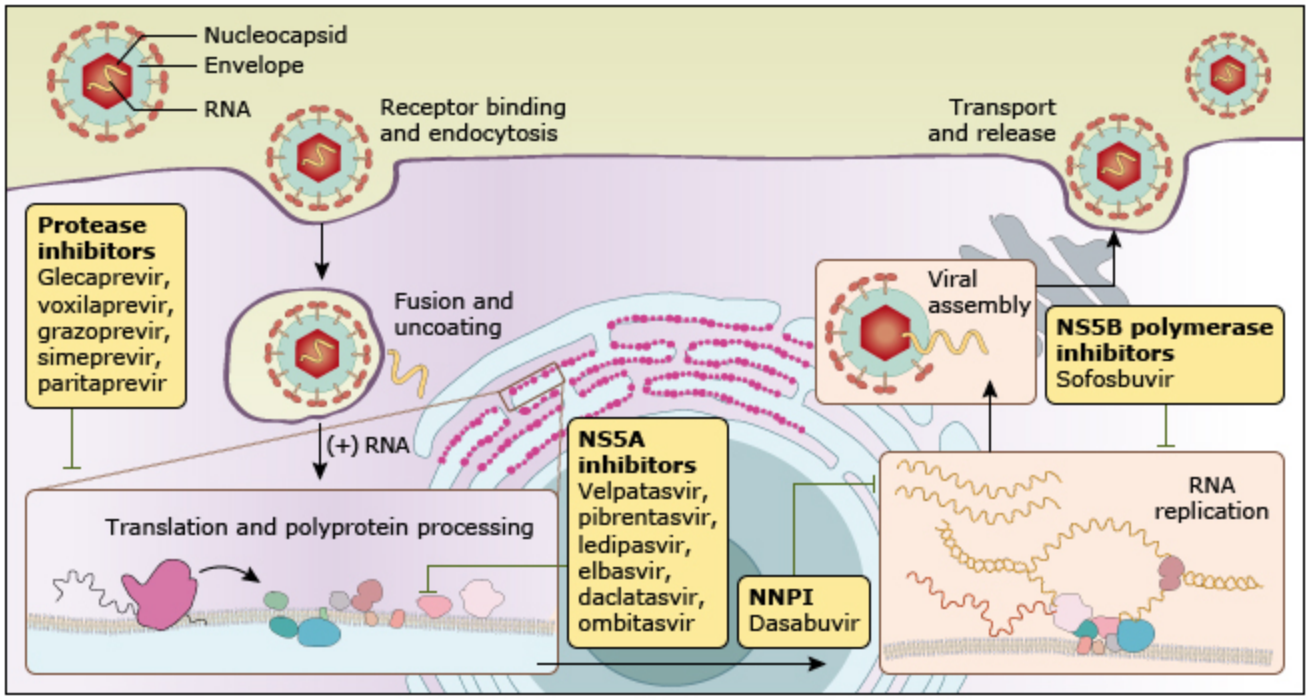
- **Special situations:**
  - **Anatomical or functional asplenia (including sickle cell disease):** 1 dose if previously did not r before splenectomy.
  - **Hematopoietic stem cell transplant (HSCT):** 3-dose series 4 weeks apart starting 6 to 12 month
- **Contraindications and precautions:**
  - For contraindications and precautions to *Haemophilus influenzae* type b (Hib) vaccination, refer to

¥¥ Vaccinate after pregnancy.

Reproduced from: Advisory Committee on Immunization Practices. Recommended Adult Immunization Schedule for ages 19 years or https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html (Accessed on February 15, 2023).

Graphic 62130 Version 23.0

Mechanism of action of direct acting antivirals for hepatitis C virus



NS5A: nonstructural protein 5A; NS5B: nonstructural protein 5B; NNPI: non-nucleoside polymerase inhibitor.

Adapted with permission from Macmillan Publishers Ltd: Clinical Pharmacology & Therapeutics. Au J, Pockros PJ. Novel Therapeutic Approaces for Hepatitis C. Clin Pharmacol Ther 2014; 95:78. Copyright © 2014. www.nature.com/clpt.

Graphic 94365 Version 2.0

Characteristics of direct acting antiviral agents for hepatitis C virus infection

	Protease inhibitors	Nucleos(t)ide polymerase inhibitors	Non-nucleoside polymerase inhibitors	NS5A inhibitors
Potency	High (varies by HCV genotype)	Moderate-to-high (consistent across HCV genotypes and subtypes)	Varies by HCV genotype	High (against multiple HCV genotypes)
Barrier to resistance	Low (1a <1b)	High (1a = 1b)	Very low (1a <1b)	Low (1a <1b)
Potential for drug interactions	High	Low	Variable	Low-to-moderate
Toxicity	Rash, anemia, ↑ bilirubin	Mitochondrial toxicity, interactions with HIV antiretrovirals (nucleoside reverse transcriptase inhibitors) and ribavirin*	Variable	Variable
Dosing	daily to three times daily	daily to twice daily	daily to three times daily	daily
Comments	Later generation protease inhibitors are expected to have higher barriers to resistance and be pan-genotype	Single target for binding at the active site	Many targets for binding at allosteric sites	Multiple antiviral mechanisms of action

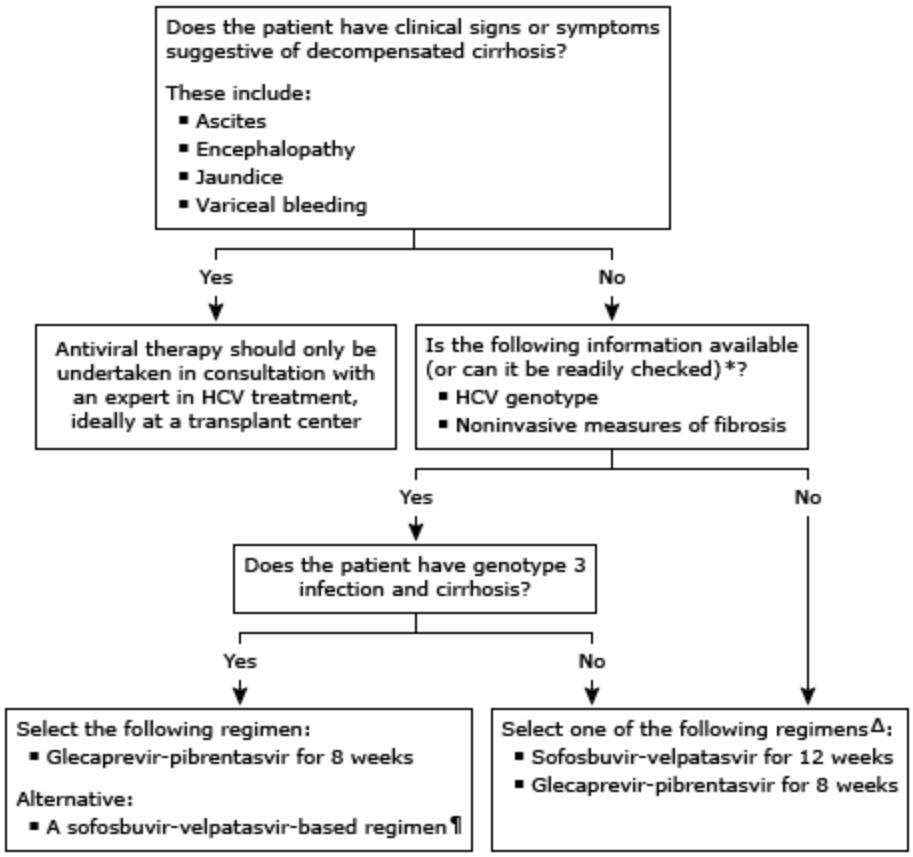
The main targets of the direct acting antiviral agents are the HCV-encoded nonstructural (NS) proteins that are vital to the replication of the virus. Protease inhibitors block the function of the NS3/NS4A serine protease. Nucleoside and nonnucloside inhibitors block the function of the NS5B polymerase. The NS5A protein has a presumptive role in the organization of the replication complex and in regulating replication. It is also involved in assembly of the viral particle that is released from the host cell.

* Such toxicities have plagued the nucleoside inhibitor class as a whole. However, the first available nucleoside polymerase inhibitor, sofosbuvir, has not been associated with serious toxicity.

Adapted from: Schaefer EA, Chung RT. Anti-hepatitis C virus drugs in development. Gastroenterology 2012; 142:1340.

Graphic 93884 Version 1.0

Regimen selection for initial therapy of chronic HCV infection



This algorithm reflects our approach to initial therapy, for which we prioritize simplifying care to reduce barriers to access. The measured outcome of therapy is SVR, which is defined as an undetectable HCV viral level 12 weeks after the completion of therapy and reflects effective cure of infection. For additional details, including the evidence supporting this approach, refer to other UpToDate content on treatment of chronic HCV infection.

SVR: sustained virologic response.

* For initial therapy, knowledge of the HCV genotype and stage of fibrosis is not essential to selecting an antiviral regimen, as the preferred options are highly effective for all patients, regardless of genotype and cirrhosis. However, if these results are already available or if obtaining them does not pose a potential barrier to treatment, the information can be used to tailor regimen selection for a small subset of patients, which may increase their likelihood of SVR by a few percentage points.

¶ In patients with genotype 3 and cirrhosis, testing for the Y93H NS5A resistance-associated substitution is used to guide the optimal

sofosbuvir-velpatasvir-based regimen. Because this testing is not always readily available, we generally favor glecaprevir-pibrentasvir for such patients. Refer to other UpToDate content for more details.

Δ The selection between sofosbuvir-velpatasvir and glecaprevir-pribrentasvir is often dictated by access (eg, payers may only reimburse one of the options). If both are accessible, the choice between them depends on the potential for drug interaction and patient preference regarding practical administration issues.

Graphic 93587 Version 15.0

Recommendations for initial treatment of chronic hepatitis B in nonpregnant adults

HBeAg	HBV DNA (PCR)	ALT	Treatment strategy
Patients without cirrhosis*			
+	>20,000 international units/mL	≤2 x ULN[¶]	Treatment is not recommended, because current treatment has low efficacy in inducing HBeAg seroconversion. Treatment may be considered in older patients (>40 years) and in those with family history of HCC.
			Patients should be monitored[Δ] and treatment considered if ALT becomes elevated >2 x ULN, liver biopsy shows moderate/severe inflammation or fibrosis[◇] (eg, METAVIR score ≥F2), and/or noninvasive testing suggests moderate/severe fibrosis.
+	>20,000 international units/mL	>2 x ULN[¶]	Observe for 3 to 6 months if compensated and treat if no spontaneous HBeAg loss.
			Immediate treatment if severe hepatitis flare (eg, icteric or clinical decompensation).
			ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – Seroconversion from HBeAg to anti-HBe.[‡]
			Duration of therapy:
			▪ PegIFN alfa: 48 weeks.
			▪ ETV, TAF, or TDF: Continue for at least 12 months after HBeAg seroconversion.
–	>2000 international units/mL	>2 x ULN[¶] OR 1 to 2 x ULN[¶] if liver biopsy shows moderate/severe necroinflammation or significant fibrosis[◇] (eg, METAVIR score	ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – HBsAg loss.
			Duration of therapy:
			▪ PegIFN alfa: One year.

		≥F2) or non-invasive testing shows significant fibrosis	
			▪ ETV, TAF, or TDF: Several years or indefinite.[†]
–	≤2000 international units/mL	≤ULN[¶]	Monitor and treat if HBV DNA and ALT increase as described above.
Patients with cirrhosis*			
+/–	Detectable	Any ALT	Compensated:
			▪ HBV DNA >2000 international units/mL – Treat with ETV, TAF, or TDF.[§ ¥] Treatment should be continued indefinitely.**
			▪ HBV DNA <2000 international units/mL – Consider treatment particularly if ALT elevated; close monitoring if treatment is not initiated.
			Decompensated:
			▪ Treat immediately, regardless of ALT or HBV DNA levels. ETV preferred.[§ ¥] TDF may be used with close monitoring of renal function. Refer for liver transplant.
+/–	Undetectable	Any ALT	Compensated: Observe, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis if HBV DNA remains undetectable.
			Decompensated: Refer for liver transplant, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis.

ALT: alanine aminotransferase; anti-HBe: antibody to hepatitis B e antigen; ETV: entecavir; HBeAg: Hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; PegIFN alfa: pegylated interferon alfa; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal.

* Based upon findings on noninvasive testing or liver biopsy performed during the initial evaluation. Patients with advanced fibrosis determined by noninvasive methods should be evaluated using a second method, and if results are concordant, consider managing the same way as patients with cirrhosis.

¶ The American Association for the Study of Liver Diseases (AASLD) recommends using an ALT >35 U/L for men and >25 U/L for women as the upper limit of normal (ULN) rather than local laboratory values.

Δ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of monitoring.

◇ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of indications for biopsy.

§ Adefovir, lamivudine, and telbivudine are not recommended due to a high rate of resistance after the first year and/or weak antiviral activity.

¥ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of which agent to use.

‡ Up to 50% of patients who achieve HBeAg seroconversion can experience a virologic relapse after discontinuing treatment with oral agents. Thus, some providers prefer to treat until HBsAg-loss.

† For most patients, antiviral therapy should be continued indefinitely. However, treatment discontinuation may be considered in persons without cirrhosis who have demonstrated loss of HBsAg and in selected patients who have had undetectable serum HBV DNA for >3 years and agree to close monitoring after stopping treatment. Persons who stop antiviral therapy should be monitored every month for the first six months. Refer to the UpToDate topic on management of hepatitis B virus infection for a detailed discussion of the risks and benefits of stopping antiviral therapy in this setting.

** This includes HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on therapy.

References:

1. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*

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