CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Treatment of Chronic Hepatitis C Virus Infection in Adults

Updates, Authorship, and Related Guidelines

Date of current publication	April 17, 2023
Highlights of changes, additions, and updates in the April 17, 2023 edition	• Recommended DAA Treatment Regimens: The recommendation on how to choose an anti-HCV regimen was revised; choosing a regimen is based on findings from the pretreatment assessment and history of HCV treatment and not HCV genotype. Accordingly, the tables of recommended treatment regimens were revised. • Post-Treatment Care: A recommendation was added for clinicians to refer patients with cirrhosis to a liver disease specialist for continued care. • Note: The NYSDOH AI guideline Treatment of Chronic HCV with Direct-Acting Antivirals (July 2017 through October 2020) was replaced with 3 guidelines: 1) Hepatitis C Virus Screening, Testing and Diagnosis in Adults; 2) Pretreatment Assessment in Adults With Chronic Hepatitis C Virus Infection; and 3) Treatment of Chronic Hepatitis C Virus Infection in Adults
Intended users	Clinicians in New York State who treat adults with chronic HCV
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Writing group	Joshua S. Aron, MD; Christine A. Kerr, MD; Colleen Flanigan, RN, MS; Christopher J. Hoffmann, MD, MPH; Charles J. Gonzalez, MD
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Related NYSDOH AI guidelines	• Hepatitis C Virus Screening, Testing, and Diagnosis in Adults • Pretreatment Assessment in Adults With Chronic Hepatitis C Infection • Substance Use Disorder Treatment in Pregnant Adults

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Contents

Purpose of This Guideline

This guideline for treatment of chronic hepatitis C virus (HCV) infection was developed by the New York State Department of Health AIDS Institute (NYSDOH AI) to guide primary care providers and other practitioners in New York State in treating patients with chronic HCV infection. The guideline aims to achieve the following goals:

- Provide clinicians with current clinical evidence-based recommendations on treating and curing chronic HCV to 1) increase the number of New York State residents treated for and cured of chronic HCV and 2) reduce the growing burden of morbidity and mortality associated with chronic HCV infection.
- Educate clinicians on safely and correctly prescribing anti-HCV medications.
- Educate clinicians on the effects of HCV infection during pregnancy and the risk of vertical HCV transmission during the perinatal period.
- Advise clinicians on the risks associated with HCV treatment in pregnant individuals.
- Provide evidence-based clinical recommendations to support the goals of the New York State Hepatitis C Elimination Plan (NY Cures HepC).

Treatment and cure of chronic HCV: The availability of safe and effective regimens of oral direct-acting antivirals (DAAs) revolutionized HCV care, and DAA regimens are the standard of care for treating and curing chronic HCV. DAAs are molecules that work at different stages of the HCV lifecycle, targeting and inhibiting specific nonstructural proteins of HCV to disrupt

viral replication and infection [UpToDate 2021]. The classes of DAAs are defined by their mechanism of action and therapeutic target.

Current DAAs for treatment of chronic HCV:

- Protease inhibitors (-previrs): glecaprevir, voxilaprevir, grazoprevir
- NS5A inhibitors (-asvirs): ledipasvir, velpatasvir, pibrentasvir, elbasvir
- NS5B nucleoside polymerase inhibitor (-buvir): sofosbuvir

The goal of HCV therapy is a sustained virologic response (SVR), which is defined as the absence of detectable HCV RNA at least 12 weeks after treatment completion. An SVR is the equivalent of a cure. DAA regimens have been associated with an SVR rate of ≥90% and have excellent tolerability in both treatment-naive and treatment-experienced patients with and without cirrhosis [Falade-Nwulia, et al. 2017].

See the tables in the guideline section Recommended DAA Treatment Regimens for options for initial treatment of chronic HCV or retreatment of chronic HCV after treatment failure.

HCV Treatment Goals and Considerations

☑ RECOMMENDATIONS

Considerations in HCV Treatment

- Before initiating antiviral therapy, clinicians should assess CrCl, HIV and HBV status, and the degree of fibrosis, among other factors. (A1)
- Clinicians new to HCV treatment should consult a specialist in treatment of liver disease or viral hepatitis when treating patients who:
  - Have severe renal impairment (CrCl <30 mL/min) and/or are undergoing hemodialysis. (A3)
  - Require retreatment after treatment failure of any DAA regimen. (B3)
- Clinicians should prescribe RBV with caution for patients with a CrCl <50 mL/min. (A1)
  - If prescribed, a reduced dose of 200 mg per day is required.
  - Non-RBV-containing regimens can be prescribed without dose adjustments for patients with CrCl ≥30 mL/min.

Contraindications

- Clinicians should not prescribe RBV for treatment of the following patients:
  - Female or male patients planning conception within 6 months of the last dose of RBV. (A2)
  - Male patients who have pregnant partners. (A2)

Abbreviations: CrCl, creatinine clearance; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; RBV, ribavirin.

Goals

The goal of treatment in patients with chronic HCV infection is to attain a virologic cure, as evidenced by a sustained viral response, in order to reduce all-cause mortality and liver-related complications, including end-stage liver disease, hepatocellular carcinoma, and the morbidity and mortality associated with the extrahepatic manifestation of chronic HCV infection. With the significant advances in treatment, all patients with chronic HCV infection, regardless of fibrosis stage, are considered candidates for antiviral therapy [Simmons, et al. 2015; Smith-Palmer, et al. 2015; van der Meer, et al. 2012].

→ KEY POINTS

- Clinicians can increase their patients' ability to understand treatment-related information and participate in decision-making if they communicate with clear, easily understood, jargon-free, and culturally sensitive language.
- Patient preferences are central to all treatment decisions.

Considerations

This guideline includes recommendations for treating patients with chronic HCV infection, with consideration of individual characteristics such as viral genotype, presence of cirrhosis, and previous treatment history. Concurrent medical conditions, potential drug-drug interactions, and cost/coverage influence are factors in selecting HCV treatment regimens; sex, age, viral load levels, substance use disorders, mental health disorders, and HIV coinfection are not factors in choosing regimens.

The tables in the guideline section Recommended DAA Treatment Regimens present several options for treatment in each category. No regimen is prioritized or recommended over another; regimens are listed alphabetically.

→ KEY POINT

- Cardiac disease and other comorbidities may affect a patient's ability to tolerate RBV-induced anemia and should be considered before initiating an RBV-containing regimen.

Renal impairment: For patients with a CrCl <50 mL/min, RBV should be used with caution; if used, a reduced dose of 200 mg per day is recommended [FDA 2011]. No dose adjustment of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or glecaprevir/pibrentasvir is required in patients with mild, moderate, or severe renal impairment [FDA(a) 2019; FDA(b) 2019; FDA 2017; FDA(a) 2016].

Resistance testing: At present, testing for resistance-associated substitutions (RASs) is not universally recommended. RASs are also referred to as resistance analysis populations and resistance-associated variants. RAS testing is performed when retreatment is considered for patients for whom treatment with a DAA regimen containing an NS5A or NS5B inhibitor has failed (see guideline section Recommended DAA Regimens After PEG-IFN Treatment Failure).

NS5A testing is recommended in patients with HCV genotype 3 who are being considered for 12 weeks of sofosbuvir/velpatasvir and are treatment-naive and have cirrhosis or are treatment-experienced [Hezode, et al. 2018; Foster, et al. 2015]. If the Y93H RAS is present, weight-based RBV should be added to the regimen or another regimen should be selected.

For more information on HCV resistance, see the Infectious Diseases Society of America/American Association for the Study of Liver Disease HCV Resistance Primer.

HCV Testing and Management in Pregnant Adults

☑ RECOMMENDATIONS

HCV Testing and Management in Pregnant Adults

- Clinicians should perform HCV testing in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy (B3).
- Clinicians should advise pregnant patients diagnosed with chronic HCV (a positive HCV antibody test result and detectable HCV RNA) to defer treatment with DAAs until they are no longer pregnant or breastfeeding. (A2)
- If an individual with HCV becomes pregnant during DAA treatment, the clinician should:
  - Advise that the use of DAAs is not currently recommended during pregnancy because of insufficient safety data on the effect on the fetus.
  - Discuss the risks and benefits of continuing treatment.
- Clinicians should refer pregnant patients diagnosed with HCV to a specialist experienced in managing HCV in pregnancy, e.g., hepatologist, gastroenterologist, infectious disease specialist, or high-risk obstetrician. (A3)
- If a pregnant patient with HCV has a substance use disorder, the clinician should provide or refer the patient for substance use treatment, including harm reduction services. (A3)
- Clinicians should advise pregnant and postpartum individuals with HCV monoinfection that HCV is not transmitted through breast milk and breastfeeding is considered safe. (B3)
- Clinicians should advise patients to discontinue breastfeeding if they have or develop cracked or bleeding nipples and to express and discard milk until the bleeding has resolved. (B3)

☑ RECOMMENDATIONS

- Clinicians should refer infants born to mothers with HCV to pediatricians with experience in HCV care. (A3)
  - See CDC: Hepatitis C, Perinatal Infection 2018 Case Definition and IDSA/AASLD: HCV in Pregnancy.

Contraceptive Use With HCV Treatment Containing RBV

- Before initiating RBV as part of an HCV treatment regimen in a patient of childbearing potential, clinicians should confirm a negative pregnancy test and advise patients to use 2 methods of birth control for the duration of DAA therapy and 6 months after completion. (A2)
- If a patient becomes pregnant while taking RBV, the clinician should discontinue the RBV. (A1)
- **Contraindication:** Clinicians should not prescribe RBV for any patient planning pregnancy within 6 months of the last RBV dose or any male patient with a pregnant partner. (A2)

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CDC, Centers for Disease Control and Prevention; DAA, direct-acting antiviral; HCV, hepatitis C virus; IDSA, Infectious Diseases Society of America; RBV, ribavirin.

HCV screening during pregnancy: In New York State, excluding New York City, 2,416 cases of HCV were reported in 2020 among individuals of childbearing age, 15 to 44 years old [NYSDOH 2022]. In New York City, in 2020, 447 cases of HCV were reported among individuals of childbearing age [NYCDOHMH 2021].

These data raise concerns about reaching and treating this population and the potential for perinatal HCV transmission. Data indicate that in areas of high HCV prevalence, 10% to 28% of pregnant individuals with HCV infection are not identified through risk-based screening [Andes, et al. 2021; Koniares, et al. 2020; Fernandez, et al. 2016; Waruingi, et al. 2015; Thomas 2013]. Thus, in alignment with Centers for Disease Control and Prevention [Schillie, et al. 2020] and American College of Obstetricians and Gynecologists (ACOG) [ACOG 2022] recommendations, the NYSDOH and this committee recommend universal testing for HCV infection in individuals who are pregnant or planning to become pregnant and that screening be repeated with each pregnancy. Identifying HCV presents an opportunity to ensure linkage to care and guide obstetric clinicians on the maternal and fetal risks in pregnant patients with HCV. In addition, universal HCV testing during pregnancy appears to be cost-effective [Chaillon, et al. 2021; Tasillo, et al. 2019].

→ KEY POINTS

- All pregnant individuals should be tested for HCV during each pregnancy, along with hepatitis B virus and other suggested prenatal tests.
- If patients engage in ongoing high-risk behaviors during pregnancy, rescreening during pregnancy or the postpartum period is appropriate.

HCV infection during pregnancy: There are no published large-scale studies on DAA treatment for HCV during pregnancy, and treatment of pregnant individuals is not currently recommended. Clinical trials are underway to evaluate the use of DAAs for the treatment of HCV during pregnancy [Chappell, et al. 2020; Yattoo 2018], and the clinician could discuss the possibility of clinical trial participation and refer the patient as appropriate (see Clinical Trials.gov).

If an individual becomes pregnant during DAA treatment, the clinician and patient should discuss the risks (e.g., no information on the effects of the medication on the fetus) and benefits (e.g., probable HCV cure) of continuing treatment and refer the patient to a specialist experienced in managing HCV in pregnancy, such as a hepatologist, gastroenterologist, infectious disease specialist, or high-risk obstetrician. Clinicians with patients who have been exposed to DAA treatment during pregnancy can contact the Treatment in Pregnancy for Hepatitis C Registry.

HCV infection, compared with no HCV infection, is associated with a higher incidence of intrahepatic cholestasis in pregnancy. Intrahepatic cholestasis in pregnancy has significant maternal and fetal morbidity [Wijarnpreecha, et al. 2017], and patients with HCV and this condition should be followed by a liver specialist or an obstetrician experienced in managing high-risk pregnancies [Wijarnpreecha, et al. 2017]. HCV infection during pregnancy has been associated with other adverse maternal and fetal outcomes, including gestational diabetes, low birth weight, small for gestational age, impaired intrauterine fetal growth, preterm delivery, miscarriage, and congenital anomalies [Connell, et al. 2011]. Researchers note that the specific role of HCV in determining these outcomes is unclear because the data may be confounded by comorbid polysubstance use [Connell, et al. 2011]. Patients with HCV and recent or active substance use during pregnancy should be referred to care providers experienced in managing substance use during pregnancy for evaluation, treatment, and harm reduction services.

Perinatal transmission: Approximately 1.0% to 3.6% of pregnant individuals in the United States have HCV infection [Edlin, et al. 2015; Floreani 2013], and the risk of perinatal transmission is estimated at 6% for patients with HCV monoinfection and

>10% for patients with HIV/HCV coinfection [Pawlowska 2015; Arshad, et al. 2011]. Currently, no antiviral treatment is available to reduce HCV transmission during pregnancy.

Intrauterine, intrapartum, and postpartum HCV transmission to the fetus have been reported, but postpartum transmission is believed to be rare [Gibb, et al. 2000]. In utero transmission may occur during all 3 trimesters, and the risk of transmission may be associated with high maternal HCV RNA levels [Elrazek, et al. 2017]. When an individual's immune response is altered during pregnancy, HCV RNA levels usually increase during the second and third trimesters, and there is a synchronous decrease in maternal alanine transaminase levels [Gervais, et al. 2000]. HCV RNA levels decline after delivery; spontaneous postpartum clearance of the HCV infection has been reported and should be considered when evaluating postpartum patients for treatment [Hashem, et al. 2017; Prasad and Honegger 2013].

Data are limited on intrauterine HCV transmission during invasive procedures, such as fetal scalp monitoring, intrauterine pressures, chorionic villi sampling, and amniocentesis. Conditions such as premature rupture of membranes during pregnancy have been associated with increased risk of HCV transmission [Mast, et al. 2005]. However, observational studies have demonstrated that mode of delivery (Cesarean section [C-section] or vaginal) is not associated with the rate of perinatal HCV transmission [Ghamar Chehreh, et al. 2011; Mast, et al. 2005; European Paediatric Hepatitis C Virus Network 2001]. The Society for Maternal-Fetal Medicine/ACOG guidelines recommend against performing a C-section simply to reduce the risk of HCV transmission [Hughes, et al. 2017; Cottrell, et al. 2013].

Breastfeeding: For postpartum individuals with HCV, breastfeeding is an option and is not associated with an increased risk of HCV transmission to the infant [Cottrell, et al. 2013]. However, it should be noted that if the postpartum individual has cracked or bleeding nipples, HCV transmission may occur during breastfeeding through blood or nonintact skin exposure [CDC 2021]. Early discussion with lactation consultants during or after pregnancy may be helpful to minimize difficulties with breastfeeding. For pregnant patients with HIV/HCV coinfection, clinicians should consult ACOG: Labor and Delivery Management of Women With Human Immunodeficiency Virus Infection.

Contraceptive use with HCV treatment containing RBV: For all female and male patients planning conception within 6 months of treatment, use of RBV is contraindicated due to the teratogenic effects of the drug [Sinclair, et al. 2017; FDA 2011]. Before prescribing an RBV-containing regimen for a patient of childbearing potential, a negative pregnancy test is required immediately before initiation of therapy, and using 2 forms of contraception or abstinence is advised during therapy and for 6 months after. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in female patients and female partners of male patients taking RBV.

If an individual with HCV becomes pregnant while taking an HCV treatment regimen containing RBV, RBV should be discontinued.

Recommended DAA Treatment Regimens

☑ RECOMMENDATIONS

Recommended DAA Treatment Regimens

- Clinicians and patients should choose an anti-HCV regimen based on the pretreatment assessment and the patient's previous treatment experience. (A2) See the tables listed below:
  - Table 2: Preferred Regimens for HCV Treatment-Naive Patients
  - Table 3: Alternative Regimens for HCV Treatment-Naive Patients
  - Table 4: Preferred Regimens After PEG-IFN Plus RBV Treatment Failure
  - Table 5: Alternative Regimens After PEG-IFN Plus RBV Treatment Failure
  - Table 6: Recommended Regimens After Sofosbuvir or Elbasvir/Grazoprevir Treatment Failure
  - Table 7: Recommended Regimens After Glecaprevir/Pibrentasvir Treatment Failure
- Clinicians and patients should choose an anti-HCV regimen based on the pretreatment assessment and any previous HCV treatment. (A2)
  - Treatment-naive patients (Tables 2 and 3).
  - Patients previously treated with PEG-IFN (Tables 4 and 5).
  - Patients previously treated with DAAs (Tables 6 and 7).
- If a regimen that includes weight-based RBV is prescribed, clinicians should dose as follows (A1):
  - <75 kg: RBV 400 mg once daily plus 600 mg once daily (total daily dose: 1,000 mg)
  - ≥75 kg: RBV 600 mg twice daily (total daily dose: 1,200 mg)

☑ RECOMMENDATIONS

- In patients with genotype 3 HCV and compensated cirrhosis, clinicians should perform NS5A RAS testing before initiating therapy. (A2)
- Clinicians new to HCV treatment should consult a specialist in treatment of liver disease or viral hepatitis when retreating patients in whom any prior DAA treatment has failed. (B3) Failure is defined as detectable HCV RNA 12 weeks after the conclusion of HCV treatment.

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RAS, resistance-associated substitution; RBV, ribavirin.

All regimens listed in this guideline were available as of October 2022.

These recommendations for treatment of chronic HCV in adults ≥18 years old were developed by the NYSDOH AI HCV Guideline Committee to guide primary care providers and other clinicians in New York State in treating patients with chronic HCV infection. Treatment guidelines for patients ≤17 years old are available at the American Association of the Study of Liver Diseases/Infectious Disease Society of America HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. All available DAA regimens are pangenotypic. As such, these recommendations are based on a patient's treatment experience instead of genotype.

HIV/HCV coinfection: Recommendations for treatment of chronic HCV infection in patients with HIV are the same as those for patients who do not have HIV, but attention to potential drug-drug interactions between DAAs and antiretrovirals is needed (see Box 1, below). Clinicians are encouraged to consult a specialist in the treatment of liver disease or viral hepatitis and an experienced HIV care provider as needed.

→ KEY POINTS

- The choice of regimen should be based on individual pretreatment assessment findings, HCV treatment history, and insurance coverage.
- The recommended regimens within each list are in alphabetical order, not in order of preference; no single regimen is recommended over another within each list of options.

Undetectable or indeterminate genotype: Rarely, laboratories report the results of an HCV genotype test as "undetectable" or "indeterminate" for a patient with detectable HCV viral load [Germer, et al. 2011]. These HCV genotype reports are consistent with active HCV infection. The laboratory may be able to clarify the specific reason for the result. For example, an "undetectable" result may be due to the lower sensitivity of the genotype test compared with the HCV RNA test or a level of HCV RNA that is too low to perform the assay for genotype.

Data on treating patients with HCV who have an undetectable or indeterminate genotype are limited. Patients who have an undetectable or indeterminate HCV genotype can be treated with a pangenotypic regimen such as glecaprevir/pibrentasvir or sofosbuvir/velpatasvir.

Table 1, below, lists recommended oral DAAs. All regimens listed in drug regimen tables for all HCV genotypes refer to oral medications.

Table 1: Recommended Oral Direct-Acting Antiviral Drug Regimens for Adults [a] With Chronic HCV (October 2022)

Drug/Combination	Trade Name
Glecaprevir/pibrentasvir	Mavyret [b]
Ledipasvir/sofosbuvir	Multiple brands [c]
Sofosbuvir/velpatasvir	Multiple brands
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi

Notes:

a. Age ≥18 years old.
b. Glecaprevir/pibrentasvir (GLE/PIB; Mavyret) is indicated for individuals ≥3 years old or weighing ≥45 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6. See prescribing information for full indications, dosing regimens, and information.
c. Ledipasvir/sofosbuvir (LED/SOF; Harvoni; multiple brands) is indicated for individuals ≥3 years old with chronic HCV genotype 1, 4, 5, or 6. See prescribing information for full indications, dosing regimens, and information.

Drug-drug interactions: It is essential to check current resources for potential drug-drug interactions before prescribing direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) treatment.

Box 1: Online Resources for Identifying Drug-Drug Interactions Associated With DAAs

- University of Liverpool HEP Drug Interactions:
  - Provides guidance on managing HCV drug interactions.
  - May not include all medications available in the United States.
- Northeast/Caribbean AETC: HIV and HCV Drug Interactions: Quick Guides for Clinicians

Recommended Treatment Regimens for Treatment-Naive Patients

Recommended regimens: The recommendations are organized by whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens listed below are oral medications.

Treatment interruption and adherence: To achieve HCV cure, strict adherence to the medications as prescribed is essential. Before initiating treatment with a DAA regimen, develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient's DAA treatment is interrupted.

Drug names: A "/" between 2 drug names indicates a co-formulated tablet.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes or validated laboratory endpoints) except where indicated.

Table 2: Preferred Regimens for HCV Treatment-Naive Patients

Genotype	Regimen	Treatment Duration	
		No Cirrhosis	Compensated Cirrhosis
1a, 1b, 2, 4, 5, 6	Glecaprevir 300 mg/pibrentasvir 120 mg once daily	8 weeks [a]	8 weeks [b]
	Sofosbuvir 400 mg/velpatasvir 100 mg once daily	12 weeks [c]	12 weeks [c]
3	Glecaprevir 300 mg/pibrentasvir 120 mg once daily	12 weeks [d]	12 weeks [e]
	Sofosbuvir 400 mg/velpatasvir 100 mg once daily	12 weeks [f]	12 weeks [g,h]

Abbreviations: HCV, hepatitis C virus; RAS, resistance-associated substitution; RBV, ribavirin.

Notes:

a. [Asselah, et al. 2018; Zeuzem, et al. 2018; Kwo, et al. 2017]
b. [Brown, et al. 2019; Forns, et al. 2017]
c. [Feld, et al. 2015; Foster, et al. 2015]
d. [Zeuzem, et al. 2018; Kwo, et al. 2017]
e. [Brown, et al. 2019; Gane(b), et al. 2016]
f. [Foster, et al. 2015]
g. [Esteban, et al. 2018; Foster, et al. 2015]
h. Patients with genotype 3 and compensated cirrhosis require baseline NS5A RAS testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir, and those with the Y93H RAS can be treated with sofosbuvir/velpatasvir plus weight-based RBV [Esteban, et al. 2018].

Table 3: Alternative Regimens for HCV Treatment-Naive Patients			
Genotype/Patient Characteristic	Regimen	Treatment Duration	
		No Cirrhosis	Compensated Cirrhosis
1a or 1b, non-Black, HIV-negative, HCV RNA <6 mil copies/mL (A2)	Ledipasvir 90 mg/sofosbuvir 400 mg once daily	8 weeks [a]	12 weeks [b]
1a or 1b, Black, HIV-positive or HCV RNA ≥6 mil copies/mL (A2)	Ledipasvir 90 mg/sofosbuvir 400 mg once daily	12 weeks [a]	12 weeks [c]
4, 5, 6	Ledipasvir 90 mg/sofosbuvir 400 mg once daily	12 weeks [d]	12 weeks [d]

Abbreviation: HCV, hepatitis C virus.

Notes:

a. [Kowdley, et al. 2017; Terrault, et al. 2016; Kowdley, et al. 2014]
b. [Terrault, et al. 2016; Reddy, et al. 2015]
c. [Terrault, et al. 2016]
d. [Abergel, et al. 2016; Kohli, et al. 2015]

Recommended DAA Regimens After PEG-IFN Treatment Failure

Recommended regimens: The recommendations are organized by whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens listed below are oral medications.

Treatment interruption and adherence: To achieve HCV cure, strict adherence to the medications as prescribed is essential. Before initiating treatment with a DAA regimen, develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient's DAA treatment is interrupted.

Drug names: A "/" between 2 drug names indicates a co-formulated tablet.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes or validated laboratory endpoints) except where indicated.

Table 4: Preferred Regimens After PEG-IFN Plus RBV Treatment Failure			
Genotype	Regimen	Treatment Duration	
		No Cirrhosis	Compensated Cirrhosis
1a, 1b, 2, 4, 5, 6	Glecaprevir 300 mg/pibrentasvir 120 mg once daily	8 weeks [a]	12 weeks [b]
	Sofosbuvir 400 mg/velpatasvir 100 mg once daily	12 weeks [c]	12 weeks [c]
3	Glecaprevir 300 mg/pibrentasvir 120 mg once daily	16 weeks [a]	16 weeks [b]
	Sofosbuvir 400 mg/velpatasvir 100 mg once daily	12 weeks [d]	12 weeks [d,e]

Abbreviations: PEG-IFN, pegylated interferon; RAS, resistance-associated substitution; RBV, ribavirin.

Notes:

a. [Kwo, et al. 2017]
b. [FDA(b) 2019]
c. [Feld, et al. 2015; Foster, et al. 2015]
d. [Foster, et al. 2015]
e. Patients with genotype 3 and compensated cirrhosis require baseline NS5A RAS testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir, and those with the Y93H RAS can be treated with sofosbuvir/velpatasvir plus weight-based RBV [Esteban, et al. 2018].

Table 5: Alternative Regimens After PEG-IFN Plus RBV Treatment Failure			
		Treatment Duration	
Genotype	Regimen	No Cirrhosis	Compensated Cirrhosis
1a, 1b	Ledipasvir 90 mg/sofosbuvir 400 mg once daily	12 weeks [a]	12 weeks [a]
	Ledipasvir 90 mg/sofosbuvir 400 mg once daily plus weight-based RBV twice daily	Not indicated	12 weeks [a]
4, 5, 6	Ledipasvir 90 mg/sofosbuvir 400 mg once daily	12 weeks [b]	12 weeks [b]

Abbreviations: PEG-IFN, pegylated interferon; RBV, ribavirin.

Notes:

a. [Afdhal, et al. 2014; Lawitz, et al. 2014]
b. [Kohli, et al. 2015]

Recommended DAA Retreatment Regimens

Recommended regimens: The recommendations are organized by whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens listed below are oral medications.

Treatment interruption and adherence: To achieve HCV cure, strict adherence to the medications as prescribed is essential. Before initiating treatment with a DAA regimen, develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient's DAA treatment is interrupted.

Drug names: A "/" between 2 drug names indicates a co-formulated tablet.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes or validated laboratory endpoints) except where indicated.

Table 6: Recommended Regimens After Sofosbuvir or Elbasvir/Grazoprevir Treatment Failure			
		Treatment Duration	
Genotype	Regimen	No Cirrhosis	Compensated Cirrhosis
1a, 1b, 2, 4, 5, 6	Glecaprevir 300 mg/pibrentasvir 120 mg once daily	16 weeks [a,b]	16 weeks [b]
	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily	12 weeks [c]	12 weeks [c]
3	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily plus weight-based RBV twice daily	12 weeks [d]	12 weeks [d]

Abbreviations: DAA, direct-acting antiviral; RBV, ribavirin.

Notes:

a. [Lok, et al. 2019; Poordad, et al. 2017]
b. Not recommended for NS3/4 protease inhibitor inclusive combination DAA regimens.
c. [Bourliere, et al. 2018; Bourliere, et al. 2017; Gane(a), et al. 2016]
d. [Bourliere, et al. 2018; Bourliere, et al. 2017]

Table 7: Recommended Regimens After Glecaprevir/Pibrentasvir Treatment Failure			
		Treatment Duration	
Genotype	Regimen	No Cirrhosis	Compensated Cirrhosis
1a, 1b, 2, 3, 4, 5, 6	Glecaprevir 300 mg/pibrentasvir 120 mg plus sofosbuvir 400 mg once daily plus weight-based RBV twice daily	16 weeks [a]	16 weeks [b]
	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily	12 weeks [c]	12 weeks [d,e]

Abbreviation: RBV, ribavirin.

Notes:

a. [Wyles, et al. 2019; Poordad, et al. 2017]
b. [FDA(b) 2019; Wyles, et al. 2019]
c. [Pearlman, et al. 2019; Bourliere, et al. 2017; Gane(a), et al. 2016]
d. [Bourliere, et al. 2017; Gane(a), et al. 2016]
e. Addition of weight-based RBV is recommended.

Monitoring During DAA Treatment

☑ RECOMMENDATIONS

Monitoring of Patients Taking RBV

- While patients are taking RBV, clinicians should perform hemoglobin testing at weeks 2 and 4 of treatment and every 4 weeks thereafter until therapy is complete. (A1)

Monitoring for HBV Reactivation

- In patients who are HBsAg-positive and have no detectable HBV DNA, clinicians should monitor for HBV reactivation by performing AST, ALT, and HBV DNA tests every 4 weeks during HCV treatment. (A3)
- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist for further evaluation of patients who develop detectable HBV DNA. (A3)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; RBV, ribavirin.

The adverse events associated with direct-acting antiviral (DAA) treatment are listed in Table 8, below, and most are manageable. Patients who are taking RBV and experience insomnia may need to adjust the timing of the dose to earlier in the afternoon to avoid any sleep disruption.

→ KEY POINT

- HCV RNA testing is needed only at baseline and at least 12 weeks after treatment is finished; HCV RNA testing is not necessary during or at the completion of treatment.

Transient transaminase and bilirubin elevations may occur during the normal course of DAA therapy. However, severe laboratory value elevations and rare hepatic decompensation have been reported with protease inhibitors during the treatment of patients with cirrhosis [FDA(b) 2019; FDA 2017; FDA(b) 2016; Hayashi, et al. 2016]. Therefore, if the ALT level is elevated above baseline 4 weeks after treatment is initiated, testing should be repeated and levels monitored according to the drug's prescribing information [FDA(b) 2019; FDA 2017; FDA(b) 2016; Hayashi, et al. 2016].

HBV reactivation and HBV-related hepatic flares have occurred both during and after DAA therapy in patients not receiving HBV treatment [Wang, et al. 2017; Sulkowski, et al. 2016; Collins, et al. 2015; Ende, et al. 2015]. The U.S. Food and Drug Administration has issued a drug safety warning regarding these risks.

Table 8: Adverse Events Associated with Direct-Acting Antivirals	
Drug or Combination (brand name)	**Most Common Adverse Reactions (proportion observed)**
Glecaprevir/pibrentasvir (GLE/PIB; Mavyret)	Headache and fatigue (>10%)
Ledipasvir/sofosbuvir (LED/SOF; Harvoni; multiple brands)	Asthenia, headache, and fatigue (≥10%)
Ribavirin (Copegus)	Fatigue/asthenia, pyrexia, myalgia, and headache in adults receiving combination therapy (>40%)
Sofosbuvir/velpatasvir (SOF/VEL; Epclusa; multiple brands)	• With SOF/VEL: headache and fatigue (≥10%, all grades) • With SOF/VEL and ribavirin in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea (≥10%, all grades)
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX; Vosevi)	Headache, fatigue, diarrhea, and nausea (≥10%)
Sources: [FDA(a) 2019; FDA(b) 2019; FDA 2017; FDA(a) 2016; FDA(b) 2016; Hayashi, et al. 2016; FDA 2011]	

Post-Treatment Care

☑ RECOMMENDATIONS

Evaluating the Response to HCV Treatment

- Clinicians should perform HCV RNA testing 12 weeks after treatment is complete to verify that an SVR has been achieved. (A1)
- If SVR is achieved, as established by undetectable HCV RNA at 12 weeks after treatment, clinicians should:
  - Inform their patients that the HCV infection has been cured. (A2)
  - Explain the risk of HCV reinfection and that HCV antibodies are not protective against reinfection. (A1)
- To assess for reinfection in patients with ongoing risk factors, clinicians should perform follow-up screening with HCV RNA testing (not HCV antibody testing) at least annually, even with a history of an SVR. (A1)
- If HCV RNA is detectable at 12 weeks after treatment, clinicians should:
  - Inform patients that treatment has failed. (A1)
  - If new to HCV treatment, consult with a liver disease specialist for retreatment evaluation. (B3)
  - See the guideline section Recommended DAA Retreatment Regimens.

Post-Treatment Monitoring

- For patients taking RBV-containing HCV treatment regimens, clinicians should:
  - Advise female and male patients to take extreme care to avoid pregnancy for 6 months after completion of therapy. (A2)
  - Counsel female and male patients on effective contraceptive use. (A2)
- If an individual becomes pregnant within 6 months of completing an RBV-containing HCV treatment regimen, clinicians should discuss the risks of using DAAs and RBV during pregnancy. (A3)

Patients With Persistent Liver Disease

- Clinicians should evaluate patients with persistent abnormal transaminase levels after SVR for other causes of liver disease and consult with a liver disease specialist. (A3)

☑ RECOMMENDATIONS

- For patients with bridging fibrosis or cirrhosis at the onset of treatment, clinicians should continue screening for HCC with ultrasound and alpha-fetoprotein testing every 6 months indefinitely. (A1)
- Clinicians should refer patients with cirrhosis to a liver disease specialist for continued care. (A3)

Abbreviations: DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RBV, ribavirin; SVR, sustained viral response.

After treatment for chronic HCV infection, follow-up care is based on individual patient factors, including response to recent treatment, previous treatment history, degree of hepatic fibrosis, comorbidities, and cofactors for other sources of liver injury, such as alcohol use or fatty liver disease.

Evaluating the Response to HCV Treatment

All treated individuals should have HCV RNA testing performed 12 weeks after treatment. If there is no detectable HCV RNA at 12 weeks, HCV infection has been cured. In the absence of recurrent risk factors, subsequent HCV testing is not required. However, with late relapse reported in rare (<0.5%) cases, some clinicians may choose to retest at 24 and/or 48 weeks after the end of treatment [Jacobson, et al. 2017].

Successful treatment of chronic HCV infection results in no detectable HCV RNA, but antibodies to HCV are typically retained for life. It is important for treated individuals to understand that they will continue to have antibodies but not active HCV infection. It is also important for patients to understand that, although antibodies to HCV will continue to be present after treatment, HCV antibodies do not offer protection from HCV reinfection. All individuals with no detectable HCV RNA are susceptible to reinfection if re-exposed to HCV. Although the overall rate of reinfection is low, it is elevated among populations at higher risk [Martinello, et al. 2017]. A meta-analysis of 59 studies reporting recurrence after an SVR in 9,049 patients found that the summary 5-year risk of HCV reinfection among high-risk populations was 10.67% [Simmons, et al. 2016]. High risk was defined as having 1 or more risk factors, currently or formerly, for reinfection (injection drug use, imprisonment, and being a man who has sex with other men). Among low-risk populations, defined as those with no known risk factors, the summary 5-year recurrence risk was 0.95% [Simmons, et al. 2016]. For discussion of risk factors, see the NYSDOH AI guideline Hepatitis C Virus Screening, Testing, and Diagnosis in Adults.

Post-Treatment Monitoring

It is important to monitor the resolution of patients' HCV treatment-related adverse events. RBV-containing regimens are teratogenic; patients receiving RBV-containing regimens and their partners should be counseled to avoid pregnancy during treatment and up to 6 months post-treatment. Two forms of effective birth control should be used [FDA 2011].

Table 8: Adverse Events Associated with Direct-Acting Antivirals provides a list of adverse events associated with DAA regimens. During treatment with RBV, patients may experience hemolytic anemia, nausea, cough, shortness of breath, rash, dry skin, pruritus, lactic acidosis, or pancreatitis [FDA 2011]. Patients should be monitored through the follow-up period for resolution of any symptoms.

Hepatitis B virus (HBV) reactivation: HBV-related hepatic flares have been reported during and after DAA therapy in patients who were not receiving concurrent HBV treatment [Wang, et al. 2017; De Monte, et al. 2016; Hayashi, et al. 2016; Sulkowski, et al. 2016; Takayama, et al. 2016; Collins, et al. 2015; Ende, et al. 2015]. The U.S. Food and Drug Administration has issued a drug safety warning regarding these risks. Although data are insufficient to make a definitive recommendation regarding monitoring in patients with isolated hepatitis B core antibody [AASLD/IDSA 2021], it is important to consider HBV reactivation as part of the differential diagnosis for patients with HBV infection who experience unexplained increases in liver enzymes during or after completion of DAA treatment.

Patients With Persistent Liver Disease

Cessation of fibrosis progression and histological improvement are among the benefits of treating chronic HCV infection. However, patients should still be monitored for potential post-treatment decompensation [Jacobson, et al. 2017]. Individuals cured of HCV infection remain at risk of liver disease progression if they have advanced baseline fibrosis, other chronic liver

conditions (e.g., chronic HBV, non-alcoholic fatty liver disease), comorbidities (e.g., metabolic syndrome, alcohol use, uncontrolled coinfection with HIV), or at risk of liver injury from drugs or dietary supplements [Vandenbulcke, et al. 2016].

There is wide individual variation in the time needed for fibrosis progression in patients with chronic liver disease. It is important to maintain an elevated suspicion for progression and the complications associated with hepatic decompensation, particularly in individuals with bridging fibrosis or cirrhosis before the initiation of DAA therapy and HCV cure.

In patients with bridging fibrosis or cirrhosis, an ultrasound and alpha-fetoprotein testing should be performed every 6 months, regardless of SVR, to screen for HCC [Jacobson, et al. 2017]. The risk of HCC for patients with stage 3 or higher fibrosis is 1.5% to 5% per year, but it is not known whether the histologic improvement after successful treatment mitigates this risk [Bruix and Sherman 2011].

All Recommendations

☑ ALL RECOMMENDATIONS: TREATMENT OF CHRONIC HEPATITIS C VIRUS INFECTION IN ADULTS

Considerations in HCV Treatment

- Before initiating antiviral therapy, clinicians should assess CrCl, HIV and HBV status, and the degree of fibrosis, among other factors. (A1)
- Clinicians new to HCV treatment should consult a specialist in treatment of liver disease or viral hepatitis when treating patients who:
  - Have severe renal impairment (CrCl <30 mL/min) and/or are undergoing hemodialysis. (A3)
  - Require retreatment after treatment failure of any DAA regimen. (B3)
- Clinicians should prescribe RBV with caution for patients with a CrCl <50 mL/min. (A1)
  - If prescribed, a reduced dose of 200 mg per day is required.
  - Non-RBV-containing regimens can be prescribed without dose adjustments for patients with CrCl ≥30 mL/min.

Contraindications

- Clinicians should not prescribe RBV for treatment of the following patients:
  - Female or male patients planning conception within 6 months of the last dose of RBV. (A2)
  - Male patients who have pregnant partners. (A2)

HCV Testing and Management in Pregnant Adults

- Clinicians should perform HCV testing in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy (B3).
- Clinicians should advise pregnant patients diagnosed with chronic HCV (a positive HCV antibody test result and detectable HCV RNA) to defer treatment with DAAs until they are no longer pregnant or breastfeeding. (A2)
- If an individual with HCV becomes pregnant during DAA treatment, the clinician should
  - Advise that the use of DAAs is not currently recommended during pregnancy because of insufficient safety data on the effect on the fetus.
  - Discuss the risks and benefits of continuing treatment.
- Clinicians should refer pregnant patients diagnosed with HCV to a specialist experienced in managing HCV in pregnancy, e.g., hepatologist, gastroenterologist, infectious disease specialist, or high-risk obstetrician. (A3)
- If a pregnant patient with HCV has a substance use disorder, the clinician should provide or refer the patient for substance use treatment, including harm reduction services. (A3)
- Clinicians should advise pregnant and postpartum individuals with HCV monoinfection that HCV is not transmitted through breast milk and breastfeeding is considered safe. (B3)
- Clinicians should advise patients to discontinue breastfeeding if they have or develop cracked or bleeding nipples and to express and discard milk until the bleeding has resolved. (B3)
- Clinicians should refer infants born to mothers with HCV to pediatricians with experience in HCV care. (A3)
  - See CDC: Hepatitis C, Perinatal Infection 2018 Case Definition and IDSA/AASLD: HCV in Pregnancy.

Contraceptive Use With HCV Treatment Containing RBV

- Before initiating RBV as part of an HCV treatment regimen in a patient of childbearing potential, clinicians should confirm a negative pregnancy test and advise patients to use 2 methods of birth control for the duration of DAA therapy and 6 months after completion. (A2)
- If a patient becomes pregnant while taking RBV, the clinician should discontinue the RBV. (A1)
- **Contraindication:** Clinicians should not prescribe RBV for any patient planning pregnancy within 6 months of the last RBV dose or any male patient with a pregnant partner. (A2)

Recommended DAA Treatment Regimens

- Clinicians and patients should choose an anti-HCV regimen based on the pretreatment assessment and the patient's previous treatment experience. (A2) See the tables listed below:
  - Table 2: Preferred Regimens for HCV Treatment-Naive Patients
  - Table 3: Alternative Regimens for HCV Treatment-Naive Patients
  - Table 4: Preferred Regimens After PEG-IFN Plus RBV Treatment Failure
  - Table 5: Alternative Regimens After PEG-IFN Plus RBV Treatment Failure
  - Table 6: Recommended Regimens After Sofosbuvir or Elbasvir/Grazoprevir Treatment Failure
  - Table 7: Recommended Regimens After Glecaprevir/Pibrentasvir Treatment Failure

☑ ALL RECOMMENDATIONS: TREATMENT OF CHRONIC HEPATITIS C VIRUS INFECTION IN ADULTS

- Clinicians and patients should choose an anti-HCV regimen based on the pretreatment assessment and any previous HCV treatment. (A2)
  - Treatment-naive patients (Tables 2 and 3).
  - Patients previously treated with PEG-IFN (Tables 4 and 5).
  - Patients previously treated with DAAs (Tables 6 and 7).
- If a regimen that includes weight-based RBV is prescribed, clinicians should dose as follows (A1):
  - <75 kg: RBV 400 mg once daily plus 600 mg once daily (total daily dose: 1,000 mg)
  - ≥75 kg: RBV 600 mg twice daily (total daily dose: 1,200 mg)
- In patients with genotype 3 HCV and compensated cirrhosis, clinicians should perform NS5A RAS testing before initiating therapy. (A2)
- Clinicians new to HCV treatment should consult a specialist in treatment of liver disease or viral hepatitis when retreating patients in whom any prior DAA treatment has failed. (B3) Failure is defined as detectable HCV RNA 12 weeks after the conclusion of HCV treatment.

Monitoring of Patients Taking RBV

- While patients are taking RBV, clinicians should perform hemoglobin testing at weeks 2 and 4 of treatment and every 4 weeks thereafter until therapy is complete. (A1)

Monitoring for HBV Reactivation

- In patients who are HBsAg-positive and have no detectable HBV DNA, clinicians should monitor for HBV reactivation by performing AST, ALT, and HBV DNA tests every 4 weeks during HCV treatment. (A3)
- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist for further evaluation of patients who develop detectable HBV DNA. (A3)

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  - Explain the risk of HCV reinfection and that HCV antibodies are not protective against reinfection. (A1)
- To assess for reinfection in patients with ongoing risk factors, clinicians should perform follow-up screening with HCV RNA testing (not HCV antibody testing) at least annually, even with a history of an SVR. (A1)
- If HCV RNA is detectable at 12 weeks after treatment, clinicians should:
  - Inform patients that treatment has failed. (A1)
  - If new to HCV treatment, consult with a liver disease specialist for retreatment evaluation. (B3)
  - See the guideline section Recommended DAA Retreatment Regimens.

Post-Treatment Monitoring

- For patients taking RBV-containing HCV treatment regimens, clinicians should:
  - Advise female and male patients to take extreme care to avoid pregnancy for 6 months after completion of therapy. (A2)
  - Counsel female and male patients on effective contraceptive use. (A2)
- If an individual becomes pregnant within 6 months of completing an RBV-containing HCV treatment regimen, clinicians should discuss the risks of using DAAs and RBV during pregnancy. (A3)

Patients With Persistent Liver Disease

- Clinicians should evaluate patients with persistent abnormal transaminase levels after SVR for other causes of liver disease and consult with a liver disease specialist. (A3)
- For patients with bridging fibrosis or cirrhosis at the onset of treatment, clinicians should continue screening for HCC with ultrasound and alpha-fetoprotein testing every 6 months indefinitely. (A1)
- Clinicians should refer patients with cirrhosis to a liver disease specialist for continued care. (A3)

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine transaminase; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; DAA, direct-acting antiviral; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDSA, Infectious Diseases Society of America; PEG-IFN, pegylated interferon; RAS, resistance-associated substitution; RBV, ribavirin; SVR, sustained viral response.

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B. Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.