VIRAL HEPATITIS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- December 2023

To the CHI Original Clinical Guidance- Issued Viral Hepatitis February 2020

Contents

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Abbreviations

ADV: Adefovir

ALT: Alanine Aminotransferase

CHB: Chronic Hepatitis B

CKD: Chronic Kidney Disease

CTP: Child–Turcotte–Pugh score

DAA: Direct-acting Antivirals

ETV: Entecavir

HBeAg: Hepatitis B e antigen

HBsAg: Hepatitis B surface antigen

HBV: Hepatitis B Virus

HCV: Hepatitis C virus

KDIGO: Kidney Disease Improving Global Outcomes

LAM: Lamivudine

MSM: Men who have sex with men.

NA: Nucleotide Analogs

NAT: Nucleic Acid Testing

NS3/4A, hepatitis C virus nonstructural protein 3–4A; NS5A, hepatitis C virus nonstructural protein 5A.

NS5A: Hepatitis C virus nonstructural protein 5A

PWID: People who inject drugs.

RAS: Resistance-associated substitution.

SASLT: Saudi Association for the Study of Liver diseases and Transplantation

TAF: Tenofovir Alafenamide

TBV: Telbivudine

TDF: Tenofovir disoproxil fumarate

Wk: Week

Executive Summary

The term viral hepatitis can describe either a clinical illness or the histologic findings associated with the disease. Acute infection with a hepatitis virus may result in conditions ranging from subclinical disease to self-limited symptomatic disease to fulminant hepatic failure. Adults with acute hepatitis A or B are usually symptomatic. Persons with acute hepatitis C may be either symptomatic or asymptomatic (i.e., subclinical).[1]

Typical symptoms of acute hepatitis are fatigue, anorexia, nausea, and vomiting. Very high aminotransferase values (>1000 U/L) and hyperbilirubinemia are often observed. Severe cases of acute hepatitis may progress rapidly to acute liver failure, marked by poor hepatic synthetic function. This is often defined as a prothrombin time (PT) of 16 seconds or more and an international normalized ratio (INR) of 1.5 or more in the absence of previous liver disease.[1]

Hepatotropic viruses are by far the most common causes of viral hepatitis. All of them are RNA viruses except for Hepatitis B, which is a DNA virus:[2]

- Hepatitis A and E are transmitted via the fecal-oral route, whereas Hepatitis B, C, and D are primarily blood-borne. Hepatitis A virus (HAV) is typically transmitted by contamination of water and food by the feces of an infected individual. Poor personal hygiene is a risk factor.[2]
- Hepatitis B virus (HBV) is unique in that it can be transmitted vertically. Other modes of transmission include sexual contact via semen and vaginal secretions, through blood via injection drug use or unsafe medical practices, and even via close person-to-person contact.[2]
- Hepatitis C virus (HCV) was a major adverse event associated with blood transfusions before its characterization and the development of blood screening protocols. The main modes of transmission today are through drug use (intravenous or intranasal), contaminated healthcare injections, and through sexual contact. Transfusion-associated transmission does still occur in resource-poor nations.[2]
- Hepatitis D virus (HDV) is similar to HBV and HCV because it is mainly transmitted via blood or sexual contact. However, HDV is unique among the other viruses because it requires the HBV surface antigen (HBsAg) to replicate and is dependent on it. [2]
- Hepatitis E virus (HEV) is also most transmitted by contamination of water and food, and less frequently by the zoonotic route or via transfusion.[2]

The most feared complication of acute viral hepatitis is liver failure. Fulminant hepatitis typically necessitates an immediate liver transplant.

Chronic viral hepatitis can result in cirrhosis and all of the complications associated with cirrhosis, including increased risk for hepatocellular carcinoma.[2]

Historical clues indicating viral hepatitis infection include recent travel to endemic areas, parenteral exposure (intravenous drug use, blood transfusion before 1992), and close or sexual contact with individuals known to have hepatitis or who are suffering from jaundice. Patients should always be asked about immunosuppressive state and organ transplants, as well as exposure to raw meat. Patients may report fever, anorexia, malaise, nausea, vomiting, right upper quadrant fullness or pain, jaundice, dark urine, and pale stools. Some patients are asymptomatic, while others may present with fulminant liver failure. The physical examination may reveal scleral icterus or jaundice, hepatomegaly, and right upper quadrant tenderness.[2]

In 2019, the World Health Organization (WHO) estimated that 354 million people worldwide are living with hepatitis B or C – of which 296 million with hepatitis B – and that 1.1 million deaths occurred that year due to these infections and their effects including liver cancer, cirrhosis, and other conditions caused by chronic viral hepatitis.[3]

In the Kingdom of Saudi Arabia, it is estimated that 636,000 people are carriers of HBV, accounting to 2.24% of the population. For hepatitis C, the estimated prevalence is 0.34% (105,000 carriers).[4] This marks a significant decline as hepatitis B was once considered hyper-endemic in KSA, where infection was acquired mainly through horizontal transmission early in life, and less commonly by vertical transmission similar to what is observed in other HBV-endemic countries. This decline may be attributed to better living conditions, childhood immunization against HBV, universal blood bank screening, and increased awareness of safe clinical and social practices.[5]

The management of hepatitis differs depending on the type:

- HAV is managed supportively and commonly resolves on its own.[2]
- Treatment of acute HBV infection is mainly supportive; however, unique sub-populations require treatment with antiretrovirals. These subpopulations include individuals who are symptomatic, who have elevated bilirubin greater than 3 mg/dl for more than four weeks, who develop coagulopathy, and those who develop acute liver failure. Antiretroviral choices include monotherapy with tenofovir, entecavir (ETV), lamivudine (LAM), or telbivudine (TBV). The decision to treat chronic infection depends on multiple factors which can be reviewed in the HBV specific review topic.[2]

- Direct-acting antivirals (DAAs) are the treatment of choice for HCV infection. However, different genotypes respond better to certain DAA's than others. Furthermore, the decision to treat a patient at the presentation of acute infection versus monitoring to see if the disease becomes chronic and then treating is another issue. This will be explained in the HCV specific review topic.[2]
- The management of acute HDV infection is mainly supportive. Furthermore, though significant data is lacking, pegylated interferon alpha seems to be the treatment of choice in patients requiring treatment for chronic HDV infection.[2]
- HEV is usually self-limited in immunocompetent individuals, with viremia lasting only about three weeks. In the case of acute and self-limiting illness, supportive care with replenishment of vitamins and symptomatic treatment of cholestasis is the mainstay. Ribavirin is used to treat chronic HEV infection, most commonly in solid organ transplant populations.[2]
- Lastly, viral hepatitis infections resulting in fulminant hepatic failure require immediate transfer to a liver transplant center for evaluation of liver transplantation.[2]

CHI issued Viral Hepatitis guidelines in Feb 2020 updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates.

This report functions as an addendum to the prior CHI Viral Hepatitis clinical guidance and seeks to offer guidance for the effective management of **Viral Hepatitis.** It provides an **update on the Viral Hepatitis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the updated guidelines added to the report such as** SASLT practice guidelines for the management of Hepatitis B virus – An update **[2021]**, Hepatitis C Guidance **2023** Update: American Association for the Study of Liver Diseases– Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection and **the new guidelines added to the report such as** Japan Society of Hepatology Guidelines for the Management of Hepatitis B Virus Infection: 2019 update, Hepatitis B Virus Screening and Management for Patients with Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update, Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update, KDIGO 2022 Clinical practice

guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease.

After carefully examining clinical guidelines and reviewing the SFDA drug list, hepatitis B immunoglobulin was added to the CHI formulary, while **removing** DASABUVIR and GRAZOPREVIR, ELBASVIR as they are no longer registered on the SFDA Drug List of December 2023. There have been no new drugs that received FDA approval.

There have been no changes and updates made to the previously listed drugs in terms of drug information and prescribing edits since February 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Viral Hepatitis therapeutic management.

Below is a table summarizing the major changes based on the different Viral Hepatitis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Viral Hepatitis

Management of Viral Hepatitis		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
HEPATITIS C		
Initial Treatment of Hepatitis C Virus–Infected Adults Treatment-naive without cirrhosis or with compensated cirrhosis Glecaprevir/pibrentasvir. Genotype 1–6, duration 8 weeks	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
Sofosbuvir/velpatasvir. Genotype 1–6, *duration* 12 weeks for genotype 3 infection with compensated cirrhosis, NS5A RAS testing is recommended. If baseline NS5A RAS Y93H is present, add weight-based ribavirin or choose another recommended regimen	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of

		American's guidelines, 2023
Ledipasvir/sofosbuvir. Genotype 1, 4, 5, 6 duration 12 wk. Not recommended for genotype 6 infection if subtype is known. • Genotype 1, without cirrhosis, duration 8 weeks (I, B): Applicable to patients without cirrhosis who are not living with human immunodeficiency virus and whose HCV RNA is <6 million IU/mL.	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
Elbasvir/grazoprevir 1b, Genotype 1b, 4, duration 12 wk. • Genotype 1a Alternative duration 12 weeks; For genotype 1a infection, NS5A RAS testing is recommended. If baseline RASs are present (i.e., substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used.	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
Treatment-naive with decompensated cirrhosis		
Sofosbuvir/velpatasvir + weight-based ribavirin. Genotype 1–6, duration 12 weeks. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
Ledipasvir/sofosbuvir + weight-based ribavirin. Genotype 1, 4, 5, 6 duration 12 weeks. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of

		American's guidelines, 2023
Sofosbuvir/velpatasvir. Genotype 1–6 and Ledipasvir/sofosbuvir. Genotypes 1, 4, 5, 6. Duration 24 weeks, applicable to patients who are ribavirin ineligible.	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
<u>Recommendations for Retreatment of Hepatitis C Virus–Infected Adults by Prior Exposure</u>		

• **Sofosbuvir-based treatment failure without cirrhosis or with compensated cirrhosis:**
  ○ **Use Sofosbuvir/velpatasvir/ voxilaprevir.**
  ○ **Genotypes 1–6**
  ○ **Duration 12 weeks.**
  ○ **For genotype 3 infection with compensated cirrhosis, add weight-based ribavirin if there are no contraindications.**
	Recommended, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023

<u>Recommendations for Initial Treatment of Hepatitis C Virus– Infected Pediatric Patients Without Cirrhosis or With Compensated Cirrhosis</u>		
Glecaprevir/pibrentasvir. Genotype 1–6, duration 8 weeks.	*Recommended*, I, B	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
<u>Recurrent HCV post liver transplant without cirrhosis</u> • **Glecaprevir/ pibrentasvir or** • **Sofosbuvir/ velpatasvir.**	*Recommended*, I, B	American Association for the Study of Liver Diseases–Infectious Diseases

• **Genotypes 1–6, duration 12 wk**		Society of American's guidelines, 2023
<u>Recurrent HCV post liver transplant with compensated cirrhosis</u> Ledipasvir/ sofosbuvir. Genotypes 1, 4, 5, 6, duration 12 weeks	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
<u>Recurrent HCV post kidney transplant without cirrhosis or with compensated cirrhosis</u> Ledipasvir/ sofosbuvir. Genotype 1, 4, 5, 6, duration 12 weeks	*Recommended*, I, A	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
<u>HCV-uninfected recipients of liver grafts from HCV-viremic donors</u> • **Glecaprevir/pibrentasvir or** • **Sofosbuvir/velpatasvir.** • **Genotype 1–6*, duration* 12 wk.** • **Timing: initiate treatment within the first 2 weeks posttransplant, preferably within the first week.**	*Recommended*, I, C	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023
<u>HCV-uninfected recipients of non-liver solid organs from HCV-viremic donors</u> • **Glecaprevir/ pibrentasvir, duration (8wk) or** • **Sofosbuvir/ velpatasvir (duration (12wk).** • **Genotype 1–6 Timing: initiate treatment prior to HCV RNA results, immediately pretransplant or day 0 posttransplant, if possible.**	*Recommended. I, C*	American Association for the Study of Liver Diseases–Infectious Diseases Society of American's guidelines, 2023

Otherwise, begin on day 0 to within the first week posttransplant when clinically stable.		
HEPATITIS B		
Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed	Moderate	ASCO Provisional Clinical Opinion Update, 2020
Management of Hepatitis B Virus Infection: Tenofovir disoproxil fumarate (TDF) yields good treatment outcomes for patients not previously treated with nucleotide analogs (NAs)	Level 1b, Grade A	Japan Society of Hepatology Guideline 2019
Tenofovir alafenamide (TAF) yields good treatment outcomes for patients not previously treated with NAs	Level 1b, Grade A	Japan Society of Hepatology Guideline 2019
Switching from TDF to TAF improves renal function and bone density.	Level 2a, Grade A	Japan Society of Hepatology Guideline 2019
Treatment plans for chronic hepatitis and cirrhosis: ETV, TDF, and TAF are the first-line NAs due to their low risk of resistance	Level 2b, Grade A	Japan Society of Hepatology Guideline 2019

NAs are the first-line drugs for cirrhosis	Level 1b, Grade A	Japan Society of Hepatology Guideline 2019

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Viral Hepatitis clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Viral Hepatitis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the February 2020 CHI Viral Hepatitis Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
Section 1.1 Saudi Association for the Study of Liver diseases and Transplantation (SASLT) Practice Guidelines for the Management of Hepatitis B Virus **[2014]**	**Section 1.1.1** SASLT practice guidelines for the management of Hepatitis B virus – An update **[2021]**
Section 1.2 Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Guidance **[2018]**	N/A*
Section 1.3 European Association for the Study of the Liver (EASL) **2017** Clinical Practice Guidelines on the management of hepatitis B virus infection	N/A*
Section 1.4 The Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) Guidelines: Update in Treatment of Hepatitis C Virus Infection [2017] [adopted from the European Association for Study of Liver.	N/A*

EASL Recommendations on Treatment of Hepatitis C] **[updated 2019]**	
Section 1.5 AASLD Hepatitis C Guidance **2019** Update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection	**Section 1.1.2.** Hepatitis C Guidance 2023 Update: American Association for the Study of Liver Diseases– Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection

*: *No updated versions available*

1.1.1 Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) Practice Guidelines for the Management of Hepatitis B Virus (2021)[6,7]

*Please refer to **Section 1.1** of CHI Viral Hepatitis original clinical guidance.*

The Saudi Association for the Study of Liver diseases and Transplantation formed a working group to develop HBV practice guidelines in Saudi Arabia. The methodology used to develop these guidelines was based on reviewing the available evidence, local data, and major international practice guidelines on the management of HBV. The aim of these guidelines is to assist healthcare providers in the management of HBV in Saudi Arabia. These updated guidelines summarize the latest local studies performed on HBV epidemiology, major changes in the prevalence of this virus, and advances in disease management. The 2021 revised edition of **the management of Hepatitis B virus** introduced a set of recommendations with a grading scheme, outlined as follows[6]:

Table 3. SASLT Grading of Recommendations

Strengths of recommendations and levels of evidence	
Grade	**Recommendation**
A	Recommendation based on high-quality evidence: at least one high-quality randomized controlled trial or at least one high-quality meta-analysis.
B	Recommendation based on medium-quality evidence: high-quality cohort study, case-control study, or systematic review
C	Recommendation based on weak evidence: case series or case report.
D	Recommendation based only on expert opinion.

Treatment indications

For patients with acute hepatitis B the main goal of therapy is to prevent the risk of acute or subacute liver failure. Additional goals may consider improving the quality of life by reducing disease-associated symptoms and lowering the risk of chronicity.

Indications for treatment are in general the same for HBeAg-positive and HBeAg-negative patients, and this is based mainly upon the combination of serum HBV DNA levels, serum ALT levels and severity of disease (figure 1).

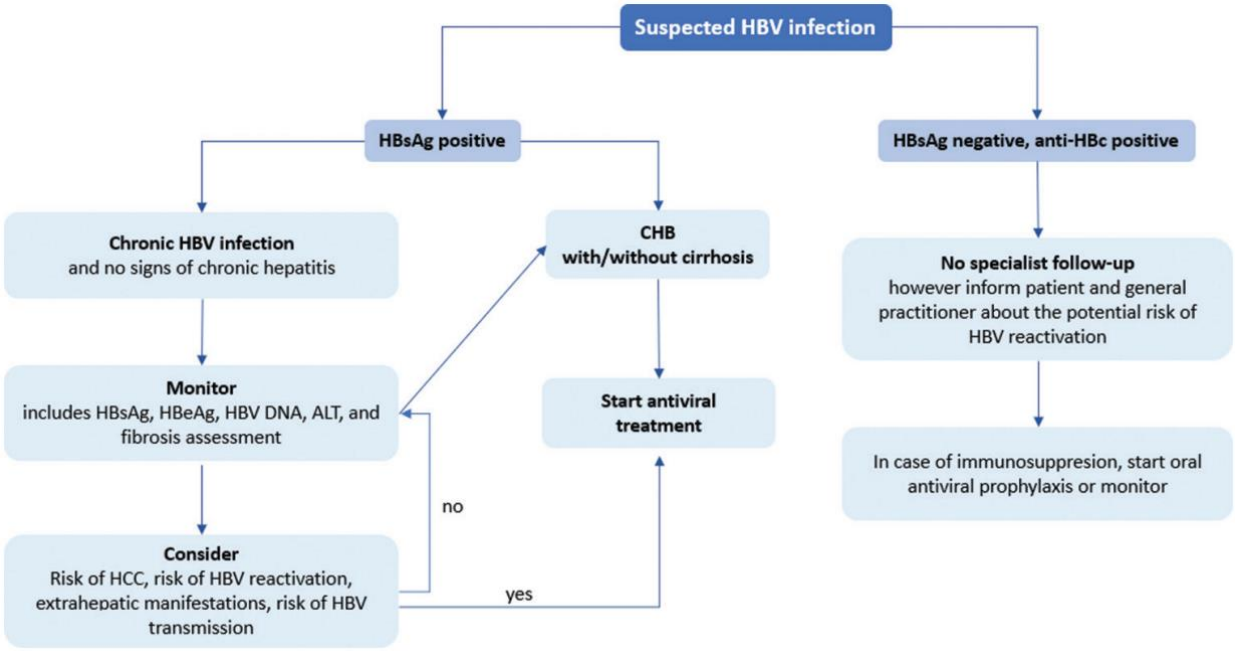

Figure 1. *Algorithm for the management of HBV infection (retrieved from the SASLT 2021 guideline)*

Adapted from SASLT practice guidelines for the management of Hepatitis B virus - An update by Abaalkhail F, Al-Hamoudi W, Khathlan A, et al. Saudi Journal of Gastroenterology. 2021;27(3):115-126. doi: 10.4103/sjg.sjg_539_20

Recommendations for initiation of treatment

- All patients with chronic hepatitis B (HBV DNA > 2,000 IU/mL, ALT > ULN), regardless of HBeAg status, and/or at least moderate liver necroinflammation or fibrosis (Grade A)
- Patients with cirrhosis (compensated or decompensated), with any detectable HBV DNA level and regardless of ALT levels (Grade A)
- Patients with HBV DNA > 20,000 IU/mL and ALT > 2xULN, regardless of the degree of fibrosis (Grade B)

- Patients with HBeAg-positive chronic HBV infection (persistently normal ALT and high HBV DNA levels) may be treated if they are > 30 years, regardless of the severity of liver histological lesions (Grade D)
- Patients with chronic HBV infection (HBV DNA > 2,000 IU/mL, ALT > ULN), regardless of HBeAg status, and a family history of HCC or cirrhosis and extrahepatic manifestations (Grade D)

Recommendations for monitoring of therapy of patients currently not treated

- Patients with HBeAg-positive chronic HBV infection who are younger than 30 years should be followed at least every 3-6 months (Grade B)
- Patients with HBeAg-negative chronic HBV infection and serum HBV DNA

Treatment of chronic hepatitis B (CHB)

Overall, the available NA therapies for HBV can be categorized into medications that have low barrier for resistance, including Lamivudine (LAM), Telbivudine (TBV) and Adefovir (ADV), and medications that have high barrier for resistance, which include Entecavir (ETV), Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF).

- The treatment of choice is the long-term administration of a potent NA with a high barrier to resistance, regardless of the severity of liver disease (Grade A)
- Preferred regimens are **ETV**, **TDF** and **TAF** as **monotherapies** (Grade A)
- LAM, adefovir (ADV) and TBV are not recommended in the treatment of CHB (Grade A)

Treatment of HBV in special populations

<u>HBV-HCV coinfection</u>

- Treatment of HCV through DAAs may lead to reactivation of HBV. Patients who meet the criteria for HBV treatment should be treated concurrently or before initiation of DAA (Grade A)
- HBV DNA and ALT should be monitored every four to eight weeks while on DAA and three months after completion of therapy (Grade D)
- ALT level should be monitored every four weeks while on DAA for patients who are HBsAg-negative but HBcAb-positive. If ALT starts to rise, HBsAg and HBV DNA must be obtained to determine the need to start HBV treatment (Grade D).

HBV-HIV coinfection

- All HIV-positive patients with HBV co-infection should start ART irrespective of CD4 cell count (Grade A)
- HBV-HIV co-infected patients should be treated with TDF- or TAF-based ART regimen (Grade A)

Immunocompromised patients

- Prophylaxis for all patients with positive HBsAg should be done before initiating chemotherapy or other immunosuppressive agents (Grade A)
- HBsAg-negative/anti-HBc-positive patients, should undergo HBV prophylaxis if they are candidates for anti CD20 or are undergoing stem cell transplantation. HBV prophylaxis should continue for at least six months after completion of immunosuppressive treatment and for twelve months if taking anti CD20 (Grade D).

Pregnancy

- All pregnant women must be screened for HBV during the first trimester (Grade A)
- All pregnant women with HBV DNA greater than 100,000 IU/mL in the late second trimester (between 24-28 weeks of gestation) should start antiviral prophylaxis with TDF, or TAF as an alternative (Grade D)
- Switch to TDF or TAF is recommended if the patient is receiving ETV, ADV, or interferon during pregnancy (Grade D)
- Breastfeeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis (Grade B)

1.1.2 American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection (2023)[7]

*Please refer to **Section 1.5** of CHI Viral Hepatitis original clinical guidance.*

The 2023 revised edition of **American Association for the Study of Liver Diseases–Infectious Diseases Society of America recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection** introduced a set of recommendations with a grading scheme, outlined as follows[8]:

Table 4. AASLD/IDSA Recommendations Ratings

Classification of Recommendations and Level of Evidence
Based on scientific evidence and expert opinion, recommendations are rated by the level of evidence (I, II, or III) and the strength of the recommendation (A, B or C) using a system adapted from the American College of Cardiology and American Heart Association. See the original AASLD-IDSA hepatitis C guidance publication or the HCV guidance website for additional details about the processes and methods employed. All recommendations are reviewed and approved by the governing boards of AASLD and IDSA. The HCV guidance panel classifies therapeutic regimens as recommended, alternative, or not recommended based on patient factors (i.e., treatment naive versus experienced, cirrhosis status, and comorbidities) and viral characteristics (i.e., genotype, subtype, resistance-associated substitutions). ➢ Recommended regimens are considered equivalent; alternative regimens are effective but, compared to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data.
Classification Types *Class I:* Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. *Class II:* Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. • IIa: Weight of evidence/opinion is in favor of usefulness/efficacy • IIb: Usefulness/efficacy is less well established by evidence/opinion. *Class III:* Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful. No Benefit- Procedure/Test not helpful or Treatment w/o established proven benefit Harm- Procedure/Test leads to excess cost w/o benefit or is harmful, and or Treatment is harmful
Levels of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses. References used to determine level of evidence must be provided and cited with the recommendation. B: Data derived from a single randomized trial, or nonrandomized studies. References used to determine level of evidence must be provided and cited with the recommendation. C: Consensus opinion of experts, case studies, or standard of care

INITIAL TREATMENT

Initial Treatment of Hepatitis C Virus–Infected Adults

Recommendations are listed by recommended vs alternative and by genotypic activity, evidence level, and alphabetically in table 5:

Table 5. Recommendations for Initial Treatment of Hepatitis C Virus–Infected Adults (Adapted from the AASLD/IDSA 2023 Guideline)

Regimen	Genotype	Classification	Duration (weeks)	Rating	Caveats and Other Considerations
Treatment-naive without cirrhosis or with compensated cirrhosis Glecaprevir/pibrentasvir	1-6	Recommended	8	I, A[a]	
Sofosbuvir/velpatasvir	1-6	Recommended	12	I, A[b]	For genotype 3 infection with compensated cirrhosis, NS5A RAS testing is recommended. If baseline NS5A RAS Y93H is present, add weight-based ribavirin or choose another recommended regimen
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12	I, A[c]	Not recommended for genotype 6e infection if subtype is known.
	1 without cirrhosis	Recommended	8	I, B	Applicable to patients without cirrhosis who are not living with human immunodeficiency virus and whose HCV RNA is
Elbasvir/grazoprevir	1b, 4	Recommended	12	I, A[d]	

	1a	Alternative	12	I, A	For genotype 1a infection, NS5A RAS testing is recommended. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used.
Sofosbuvir/velpatasvir + weight-based ribavirin	3	Alternative	12	IIa, A	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
Sofosbuvir/velpatasvir/ voxilaprevir		Alternative	12	IIa, B	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
Treatment-naive with decompensated cirrhosis					
Sofosbuvir/velpatasvir + weight-based ribavirin	1-6	Recommended	12	I, A[e]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Sofosbuvir/velpatasvir	1-6	Recommended	24	I, A[e]	Applicable to patients who are ribavirin ineligible.
Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	12	I, A[f]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class

					C cirrhosis; increase as tolerated.
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	24	I, A[f]	Applicable to patients who are ribavirin ineligible.

a: The level of evidence rating is I, B for persons with compensated cirrhosis.

b: The level of evidence rating is I, B for persons with genotype 5 or 6 infection.

c: The level of evidence rating is IIa, B for persons with genotype 5 or 6 infection and those with genotype 4 infection and compensated cirrhosis.

d: The level of evidence rating is IIa, B for persons with genotype 4 infection and compensated cirrhosis.

e: Only available data for genotype 6 infection are in persons with compensated cirrhosis.

f: Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.

Figure 2 provides an overview of the simplified HCV treatment algorithm for treatment-naive adults without cirrhosis. Figure 3 reviews the simplified treatment algorithm for HCV treatment-naive adults with compensated cirrhosis.

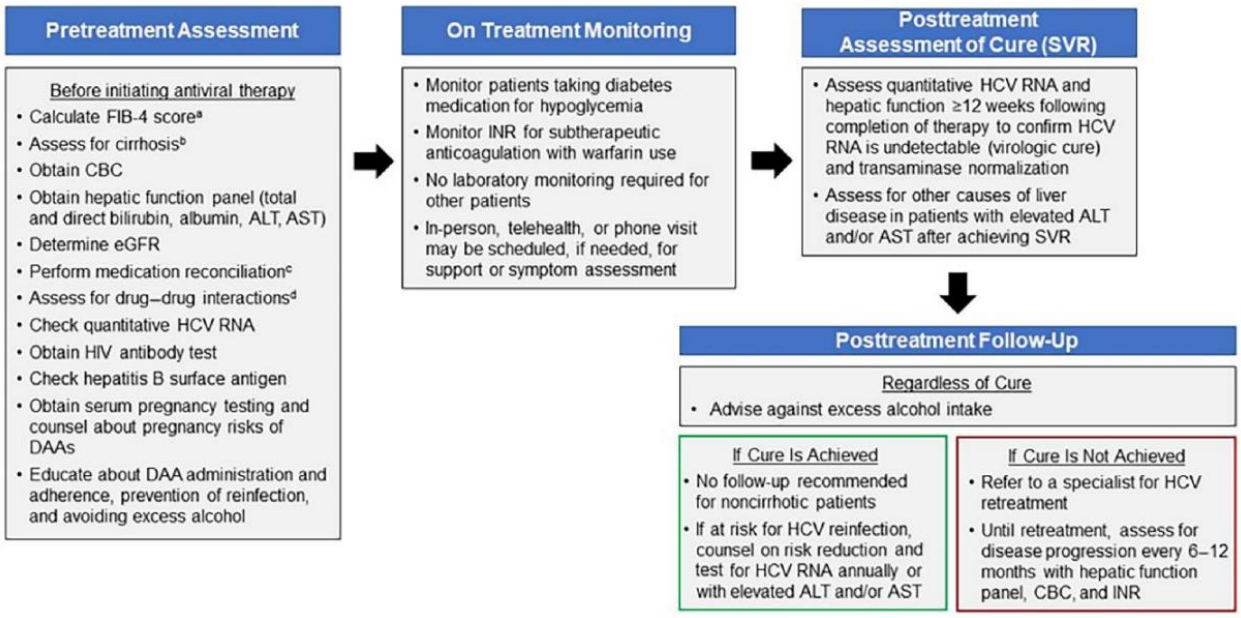

Figure 2. *Simplified algorithm for HCV treatment among HCV treatment-naive adults without cirrhosis (Retrieved from the AASLD/IDSA 2023 guideline)*

Recommended DAA regimens for this simplified treatment approach include either 8 weeks of glecaprevir (300 mg)/pibrentasvir (120 mg) taken with food or 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg). More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment can be found on the HCV guidance website. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index for liver fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; SVR, sustained virologic response. **a** FIB-4 is a noninvasive measure of hepatic fibrosis that is calculated by: (age [years] × AST [U/L]) ÷ (platelet count [109/L] × (ALT1/2 [U/L]). **b** A patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or if they have any of the following from a previously performed test: transient elastography indicating cirrhosis (ie, liver stiffness >12.5 kPa), noninvasive serologic test above the proprietary cutoff indicating cirrhosis (eg, FibroSure, enhanced liver fibrosis test), clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count < 150 000/mm3), or prior liver biopsy showing cirrhosis. **c** Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. **d** Drug–drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker.

Adapted from Hepatitis C Guidance 2023 Update: American Association for the Study of Liver Diseases– Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clinical Infectious Diseases. By Bhattacharya D, Aronsohn A, Price J, et al. doi:10.1093/cid/ciad319

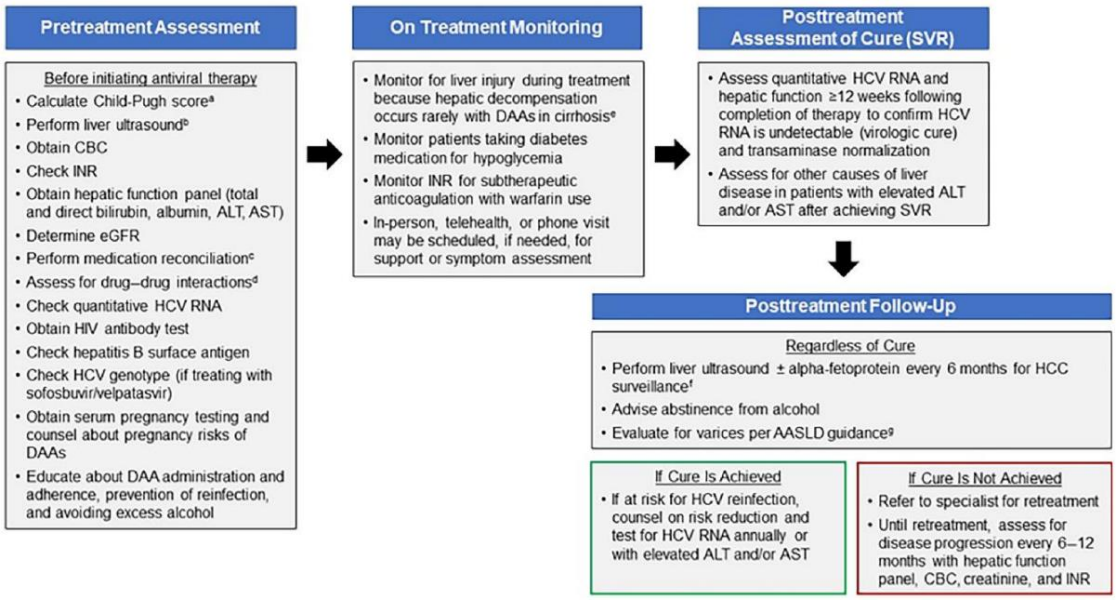

Figure 3. *Simplified algorithm for HCV treatment among HCV treatment-naive adults without cirrhosis (Retrieved from the AASLD/IDSA 2023 guideline)*

Recommended DAA regimens for this simplified treatment approach include either 8 weeks of glecaprevir (300 mg)/pibrentasvir (120) mg taken with food for genotypes 1 through 6 or 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotypes 1, 2, 4, 5, or 6. More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment can be found on the HCV Guidance website. Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; SVR, sustained virologic response. **a** Child–Pugh score based on presence of ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7. Patients with a Child–Pugh score ≥7 (ie, Child–Pugh B or C) have decompensated cirrhosis; this simplified treatment approach is not recommended for patients with decompensated cirrhosis. **b** Obtain liver ultrasound within 6 months prior to initiating antiviral treatment to exclude hepatocellular carcinoma and subclinical ascites. This simplified treatment approach is not recommended for patients with hepatocellular carcinoma and/or decompensated cirrhosis. **c** Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. **d** Drug–drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker. **e** Development of jaundice, ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy may suggest hepatic decompensation. Patients should be referred to a specialist if they develop worsening liver blood tests (eg, total bilirubin, AST, ALT, INR), jaundice, ascites, encephalopathy, or new liver-related symptoms). **f** Ultrasound surveillance for hepatocellular carcinoma (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis, in accordance with AASLD guidance.

Adapted from Hepatitis C Guidance 2023 Update: American Association for the Study of Liver Diseases– Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clinical Infectious Diseases. By Bhattacharya D, Aronsohn A, Price J, et al. doi:10.1093/cid/ciad319

RETREATMENT

Although DAA therapy is curative for most persons [1, 17], the small percentage of those in whom treatment fails to result in SVR12 require retreatment. Updated retreatment recommendations focus on DAA treatment failures, specifically, sofosbuvir-based regimen failure; glecaprevir/pibrentasvir failure; and multiple DAA failure, including sofosbuvir/ velpatasvir/voxilaprevir or sofosbuvir plus glecaprevir/ pibrentasvir (figure 2). Retreatment recommendations for sofosbuvir-based or HCV nonstructural protein 5A (NS5A) inhibitor-based treatment failures in persons with decompensated cirrhosis are also noted in table 6.

Table 6. Recommendations for Retreatment of Hepatitis C Virus–Infected Adults by Prior Exposure (Retrieved from the AASLD/IDSA 2023 Guideline)

Regimen	Genotype	Classification	Duration	Rating	Caveats and Other Considerations
Sofosbuvir-based treatment failure without cirrhosis or with compensated cirrhosis					
Sofosbuvir/velpatasvir/ voxilaprevir	1–6	Recommended	12 wk	I, A	For genotype 3 infection with compensated cirrhosis, add weight-based ribavirin if there are no contraindications.
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Alternative	16 wk	I, A	Not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4A protease inhibitor regimen (eg, elbasvir/grazoprevir).
Glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir + sofosbuvir + weight-based ribavirin	1–6	Recommended	16 wk	IIa, B	
Sofosbuvir/velpatasvir/ voxilaprevir	1–6	Recommended	12 wk	IIa, B	For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended (rating IIa, C).
Sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir + glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir + sofosbuvir + weight-based ribavirin	1–6	Recommended	16 wk	IIa, B	Extension to 24 wk should be considered in extremely difficult cases (eg, genotype 3 infection with compensated cirrhosis) or failure following sofosbuvir + glecaprevir/pibrentasvir therapy.
Sofosbuvir/velpatasvir/ voxilaprevir + weight-based ribavirin	1–6	Recommended	24 wk	IIa, B	
Sofosbuvir- or NS5A inhibitor–based treatment failure with decompensated cirrhosis					
Sofosbuvir/velpatasvir + weight-based ribavirin	1–6	Recommended	24 wk	II, C[a]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	24 wk	II, C[b]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.

Recommendations are listed by recommended vs alternative and by genotypic activity, evidence level, and alphabetically.

Abbreviations: CTP, Child–Turcotte–Pugh score; NS3/4A, hepatitis C virus nonstructural protein 3–4A; NS5A, hepatitis C virus nonstructural protein 5A.

[a]Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.

[b]Only available data for genotype 6 infection are in persons with compensated cirrhosis.

MANAGEMENT OF UNIQUE AND KEY POPULATIONS

The HCV guidance additionally focuses on the special considerations and unmet needs of other unique or key populations, namely, individuals with acute HCV infection, pregnant persons, children and adolescents, and solid organ transplant recipients. Recommendations for these populations aim to maximize the potential benefits of often missed opportunities to reduce hepatitis C infection incidence and prevalence, personal and societal disease burden, and HCV-related morbidity and mortality.

HIV/HCV Coinfection

Treatment-naive persons living with HIV and HCV (without cirrhosis or with compensated cirrhosis) are newly eligible for DAA therapy using a simplified treatment algorithm (figures 2 and 3 above).

Acute HCV Infection

Persons with confirmed acute HCV infection (HCV RNA–positive) should be treated the same as those with chronic HCV infection without awaiting possible spontaneous clearance (i.e., a test-and-treat approach).

The abbreviated course of DAA therapy is not recommended for acute HCV infection.

HCV in Pregnancy

Treatment recommendations during pregnancy are largely unchanged from the previous update. Although there have been no published large-scale clinical trials to evaluate the safety of DAA therapy during pregnancy, smaller studies and case series have not demonstrated any safety concerns. The Guidance Panel suggests that DAA treatment may be considered during pregnancy on a case-by-case basis after a discussion of potential risks and benefits.

HCV in Children

All HCV-infected children and adolescents aged ≥3 years should be treated with an approved DAA regimen regardless of disease severity.

Table 7. Recommendations for Initial Treatment of Hepatitis C Virus– Infected Pediatric Patients Without Cirrhosis or With Compensated Cirrhosis (Adapted from the AASLD/IDSA 2023 Guideline)

Regimen	Genotype	Classification	Duration (weeks)	Rating
Glecaprevir/pibrentasvir	1-6	Recommended	8	I, B
Sofosbuvir/velpatasvir	1-6	Recommended	12	I, B
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12	I, B

Table 8. Recommendations for Retreatment of Hepatitis C Virus–Infected Pediatric Patients by Prior Exposure and Cirrhosis Status (Adapted from the AASLD/IDSA 2023 Guideline)

Regimen	Genotype	Classification	Duration (weeks)	Rating	Cirrhosis status
Interferon-based regimen (±ribavirin) and/or sofosbuvir treatment failure without NS3/4A protease inhibitor or NS5A inhibitor exposure					
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Recommended	8	I, C	No cirrhosis
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Recommended	12	I, C	Compensated cirrhosis
Glecaprevir/pibrentasvir	3	Recommended	16	I, C	Without cirrhosis or with compensated cirrhosis
Sofosbuvir/velpatasvir	1-6	Recommended	12	I, C	Without cirrhosis or with compensated cirrhosis
Sofosbuvir/velpatasvir + weight-based ribavirin	1-6	Recommended	12	I, C	Decompensated cirrhosis
NS3/4A protease inhibitor treatment failure without NS5A inhibitor exposure					
Glecaprevir/pibrentasvir	1-6	Recommended	12	I, C	Without cirrhosis or with compensated cirrhosis
NS5A inhibitor treatment failure without NS3/4A protease inhibitor exposure					
Glecaprevir/pibrentasvir	1-6	Recommended	16	I, C	Without cirrhosis or with compensated cirrhosis
Interferon (± ribavirin) plus a hepatitis C virus protease inhibitor treatment failure					
Ledipasvir/sofosbuvir	4, 5, 6	Recommended	12	I, C	Without cirrhosis or with compensated cirrhosis
Ledipasvir/sofosbuvir	1	Recommended	12	I, C	No cirrhosis
Ledipasvir/sofosbuvir	1	Recommended	24	I, C	Compensated cirrhosis

Management of HCV After Solid Organ Transplantation is shown in the table 9 below:

Table 9. Recommendations for Hepatitis C Virus Treatment Post Transplantation (Retrieved from the AASLD/IDSA 2023 Guideline)

Regimen	Genotypes	Classification	Duration	Rating	Caveats and Other Considerations
Recurrent HCV post liver transplant without cirrhosis					
Glecaprevir/ pibrentasvir	1–6	Recommended	12 wk	I, B	
Sofosbuvir/ velpatasvir	1–6	Recommended	12 wk	I, B	
Ledipasvir/ sofosbuvir	1, 4, 5, 6	Recommended	12 wk	I, B	
Recurrent HCV post liver transplant with compensated cirrhosis					
Sofosbuvir/ velpatasvir	1–6	Recommended	12 wk	I, B	
Glecaprevir/ pibrentasvir	1–6	Recommended	12 wk	I, C	
Ledipasvir/ sofosbuvir	1, 4, 5, 6	Recommended	12 wk	I, A	
Recurrent HCV post kidney transplant without cirrhosis or with compensated cirrhosis					
Glecaprevir/ pibrentasvir	1–6	Recommended	12 wk	I, A[a] IIa, C[b]	
Sofosbuvir/ velpatasvir	1–6	Recommended	12 wk	IIa, C	
Ledipasvir/ sofosbuvir	1, 4, 5, 6	Recommended	12 wk	I, A	
Elbasvir/ grazoprevir	1, 4	Alternative	12 wk	I, B	Limited to patients without baseline NS5A RASs for elbasvir.
HCV-uninfected recipients of liver grafts from HCV-viremic donors					
Glecaprevir/ pibrentasvir	1–6	Recommended	12 wk	I, C	Timing: initiate treatment within the first 2 wk posttransplant, preferably within the first week.
Sofosbuvir/ velpatasvir	1–6	Recommended	12 wk	I, C	Timing: initiate treatment within the first 2 wk posttransplant, preferably within the first week.
HCV-uninfected recipients of non-liver solid organs from HCV-viremic donors					
Glecaprevir/ pibrentasvir	1–6	Recommended	8 wk[c]	I, C	Timing: initiate treatment prior to HCV RNA results, immediately pretransplant or day 0 posttransplant, if possible. Otherwise, begin on day 0 to within the first week posttransplant when clinically stable.
Sofosbuvir/ velpatasvir	1–6	Recommended	12 wk	I, C	Timing: initiate treatment prior to HCV RNA results, immediately pretransplant or day 0 posttransplant, if possible. Otherwise, begin on day 0 to within the first week posttransplant when clinically stable.

Recommendations are listed by genotypic activity, evidence level, and alphabetically.

Abbreviations: HCV, hepatitis C virus; NS5A, hepatitis C virus nonstructural protein 5A; RAS, resistance associated substitution.

[a]Rating is based on evidence for persons without cirrhosis.

[b]Rating is based on evidence for persons with compensated cirrhosis.

[c]If treatment initiation is delayed beyond the first week after transplant, treatment should be extended to 12 weeks.

People Who Inject Drugs

Active or recent drug use or concern for reinfection is not a contraindication to HCV treatment.

At least annual HCV RNA testing is recommended for PWID with recent IDU after they have spontaneously cleared HCV infection or have been successfully treated.

Men Who Have Sex with Men (MSM) Not Living With HIV

Antiviral treatment for HCV-infected MSM should be coupled with ongoing counseling about the risk of HCV reinfection and education about methods to reduce HCV reinfection risk after cure.

At least annual (and risk-based, if indicated) HCV RNA testing is recommended for all high-risk sexually active MSM after successful treatment or spontaneous clearance of HCV infection.

Persons in Correctional Settings

DAA treatment for chronic HCV infection is feasible within jail and prison settings and would aid the HCV elimination effort.

Upon release from a correctional facility, HCV-infected persons with advanced hepatic fibrosis or cirrhosis should be provided linkage to community healthcare for surveillance for HCV-related complications. To prevent HCV reinfection and reduce the risk of progression of HCV-associated liver disease, correctional facilities should provide harm reduction and evidence-based treatment for underlying substance use disorders. Addressing hazardous alcohol use among persons with chronic HCV in a correctional setting may help slow liver disease progression, decrease HCV transmission, and might reduce recidivism.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Viral Hepatitis report, along with their recommendations.

Table 10. List of Additional Guidelines

Additional Guidelines
Section 1.2.1. Japan Society of Hepatology Guidelines for the Management of Hepatitis B Virus Infection: 2019 Update[9]
Section 1.2.2. Hepatitis B Virus Screening and Management for Patients with Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update.[10]
Section 1.2.3 Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update[11]
Section 1.2.4 KDIGO 2022 Clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease[12]

1.2.1 Japan Society of Hepatology Guidelines for the Management of Hepatitis B Virus Infection (2019)[9]

Recommendations from the 2019 guidelines by Japan Society of Hepatology for the management of hepatitis B are summarized below[9]:

Treatment goals

- The treatment goal for antiviral therapy for patients with persistent HBV infection is to prevent liver failure and inhibit hepatocellular carcinogenesis by suppressing hepatitis activity and progression of liver fibrosis, thereby improving the patient's life expectancy and overall quality of life.
- HBsAg is considered the most effective surrogate marker for attaining this treatment goal. The long-term goal of antiviral therapy is to eliminate HBsAg.
- The three short-term goals of antiviral treatment before elimination of HBsAg are persistent normalization of ALT, achievement of negative HBeAg and positive anti-HBe antibody status, and suppression of HBV DNA replication.
- The on-treatment goal is negative HBV DNA; this applies to both chronic hepatitis and cirrhosis.
- Because HBeAg seroconversion and reduction (or elimination) of HBsAg are the expected outcomes of IFN therapy, on-treatment HVB DNA target levels are not used, and the aim is to complete a full course of treatment of 24–48 weeks.
- The off-treatment goals (after IFN therapy and cessation of NA agent) are <2000 IU/mL HBV DNA (chronic hepatitis) and HBV DNA-negative (cirrhosis)

Indications for antiviral therapies

- The three key criteria currently used to determine whether to treat chronic hepatitis B are histological progression, ALT levels, and HBV DNA levels.
- The question of whether HBsAg levels should be added to these criteria requires further study.

Nucleotide analogs

➢ *Tenofovir disoproxil fumarate (TDF)*

- TDF yields good treatment outcomes for patients not previously treated with NAs (level 1b, grade A).
- TDF is also effective for patients resistant or unresponsive to conventional NA therapy (level 1b, grade A). • Patients using TDF long term should be carefully monitored for renal impairment, hypophosphatemia (including Fanconi syndrome), and reduced bone density (level 2b, grade A).
- It is recommended that renal function and serum phosphate during treatment with TDF be monitored periodically (level 2b, grade A).

- TDF is relatively safe for use during pregnancy (level 2b, grade A)

➢ *Tenofovir alafenamide (TAF)*

- TAF yields good treatment outcomes for patients not previously treated with NAs (level 1b, grade A).
- TAF is also effective for patients previously treated with NAs (level 1b, grade A).
- TAF does not reduce renal function or bone density as much as TDF (level 1b, grade A).
- Switching from TDF to TAF improves renal function and bone density (level 2a, grade A).
- There is currently little evidence about the safety of TAF during pregnancy (level 2b, grade A).
- Discontinuation of TAF should be considered for patients whose creatinine clearance drops <15 mL/min (level 6, grade B).

Treatment plans for chronic hepatitis and cirrhosis

- Entecavir, TDF, and TAF are the first-line NAs due to their low risk of resistance (level 2b, grade A).
- The potential teratogenicity of NAs should be discussed with patients who are pregnant or planning to become pregnant. TDF is the only NA with evidence showing it is low risk in pregnancy (level 2b, grade A).
- To minimize adverse events associated with long-term use of NAs, entecavir and TAF are the first-line drugs for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis at treatment initiation (level 1b, grade A).

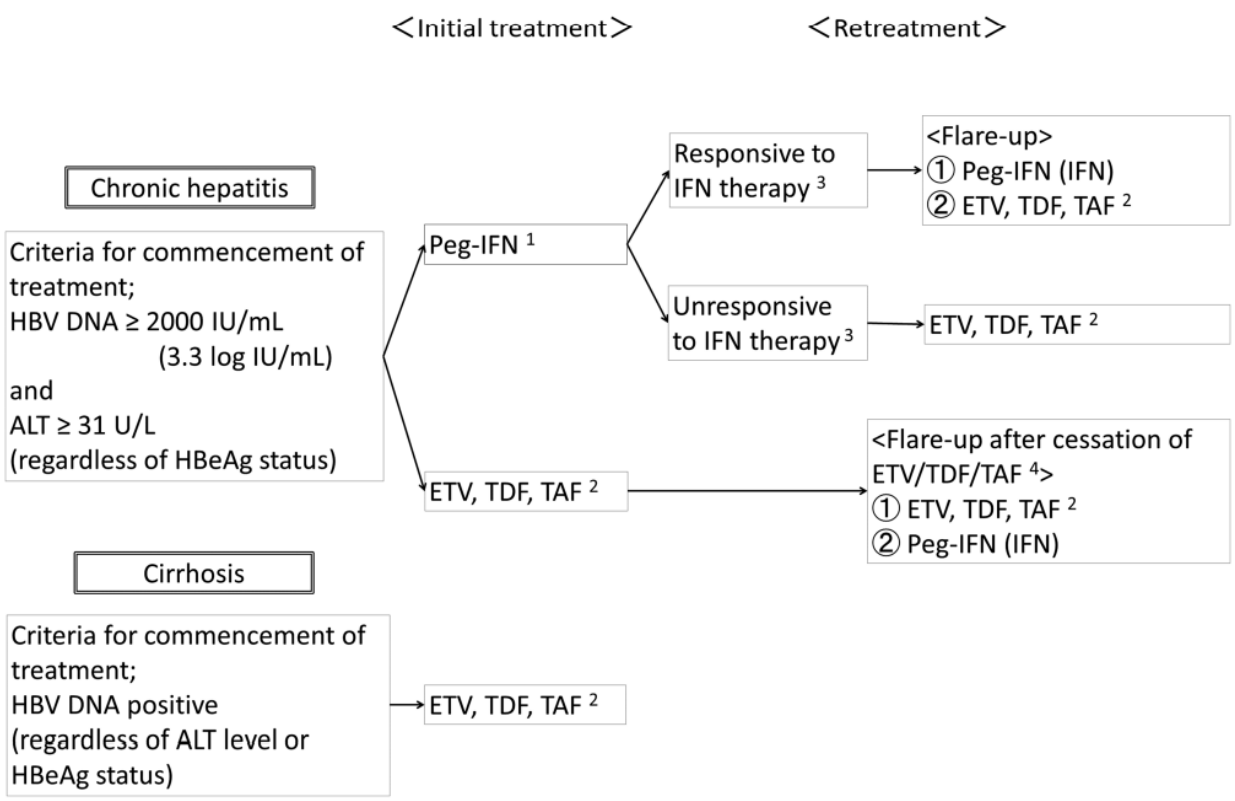

Figure 4. *Basic antiviral treatment protocol for hepatitis B virus (HBV) infection (Retrieved from the Japanese Society of Hepatology 2019 guideline)*

1 Patients should be fully informed of the relatively low rates of hepatitis Be antigen (HBeAg) seroconversion and HBV DNA elimination with this treatment, the difficulty of predicting effectiveness of treatment in advance in individual patients, and anticipated adverse reactions. **2** It should be confirmed that the patient is not planning to become pregnant while on this treatment, and the patient should be fully informed of the need to continue treatment for the long term and the risk of resistance mutations. The properties of each drug should be referenced when selecting the nucleos(t)ide analog to be used. **3** The assessment should be made at 24–48 weeks after completing treatment based on alanine transaminase (ALT) normalization, reduced HBV DNA level (reduced hepatitis B surface antigen [HBsAg level]), and HBeAg elimination in HBeAg-positive patients. **4** Criteria for retreatment of recurrence after cessation of entecavir: HBV DNA ≥100 000 IU/mL (5.0 log IU/ mL) or ALT ≥80 U/L. ETV, entecavir; IFN, interferon; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Adapted from Japan Society of Hepatology Guidelines for the Management of Hepatitis B Virus Infection: 2019 update. Hepatology Research. 2020;50(8):892-923. doi:10.1111/hepr.13504

HBeAg-positive chronic hepatitis

- Treatment is not indicated in HBeAg-positive asymptomatic carriers (level 2b, grade B).
- Treatment is indicated for patients with HBeAg-positive chronic hepatitis B with an HBV DNA level of at least 2000 IU/mL (3.3 log IU/mL) and ALT of at least 31 U/L (level 6, grade B).
- Deferring treatment for approximately 1 year is another option for patients with HBeAg-positive chronic hepatitis B and elevated ALT who show no evidence of advanced fibrosis and are not considered at risk of acute liver failure. However, if spontaneous HBeAg seroconversion does not occur, treatment is necessary to prevent progression of hepatic fibrosis due to persistent hepatitis (level 6, grade B).
- Liver biopsy (or a non-invasive alternative) can be carried out as an optional investigation to determine extent of fibrosis in high-risk patients, even if they do not meet the criteria for treatment initiation, and treatment is indicated if hepatic fibrosis is diagnosed (level 2b, grade B).
- Treatment should be commenced immediately, with no monitoring period, for patients with acute exacerbations of hepatitis associated with jaundice, or if there are concerns about liver failure (level 2b, grade B).

HBeAg-negative chronic hepatitis

- HBeAg-negative patients tend to be older and have more advanced fibrosis than HBeAg-positive patients, so HBeAg-negative chronic hepatitis should be considered a more advanced disease stage (level 4, grade B).
- As for patients with HBeAg-positive chronic hepatitis B, treatment is indicated for patients with HBeAg-negative chronic hepatitis B with an HBV DNA level of at least 2000 IU/mL (3.3 log IU/mL) and ALT of at least 31 U/L (level 2b, grade B).
- Even for patients determined to be inactive carriers, liver biopsy (or a non-invasive alternative) should be carried out to assess the need for treatment when advanced fibrosis is suspected based on imaging studies or platelet counts, or when the patient is at high risk of HCC. Treatment is indicated if hepatic fibrosis is diagnosed by this assessment (level 2b, grade B).
- Even patients determined to be inactive carriers should be monitored every 6–12 months, and treatment is indicated if ALT levels increase (level 2b, grade B)

Cirrhosis

- NAs are the first-line drugs for cirrhosis (level 1b, grade A).
- Long-term NA therapy can reverse fibrosis, even for patients with cirrhosis (level 2b, grade B).
- Relapse after cessation of NA therapy presents a risk of liver failure, so treatment is generally continued for the rest of the patient's life (level 5, grade B).
- Patients treated with NAs for decompensated cirrhosis must be carefully monitored for lactic acidosis, which has been reported to occur in this patient group (level 5, grade B).

Treatment of NA-resistant HBV

- TDF and TAF are effective against lamivudine- and entecavir-resistant HBV, because they are not cross-resistant (level 2b, grade A).
- Adefovir-resistant HBV is slightly less sensitive to TDF and TAF than non-resistant HBV, but both drugs are still clinically effective (level 2b, grade A).
- TDF monotherapy and TDF plus entecavir are equally effective against entecavir-resistant HBV (level 1b, grade A).
- TDF monotherapy and TDF plus entecavir are less effective against adefovir-resistant double-mutant HBV and multidrug-resistant HBV (resistant to adefovir and entecavir; level 1b, grade A).
- Combination therapy with entecavir plus TDF is recommended for poor responders to lamivudine plus adefovir or entecavir plus adefovir (level 2b, grade B).
- Viral resistance to TDF or TAF has never been reported in naive patients (level 2b, grade B).

Treatment strategy in good and poor responders to NA therapy

- When treating a patient with NAs, it is necessary to reconsider the current treatment plan depending on the degree of progress toward the short-term on-treatment goal of undetectable HBV DNA after 12 weeks of treatment (grade B).
- Good responders with undetectable HBV DNA (on monotherapy):It is recommended to switch patients on lamivudine monotherapy to entecavir (level 1b, grade A) or TAF (level 6, grade A).

- Patients on entecavir monotherapy should continue treatment as is. Switching from TDF to TAF is an option for patients on TDF monotherapy, because TDF may cause adverse events with long-term use (level 2a, grade B). Switching to TAF is recommended for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis (level 2a, grade A).
- Good responders with undetectable HBV DNA (on combination therapy): Switching from combination therapy with lamivudine or entecavir plus adefovir or TDF to entecavir plus TAF is an option, because TDF may cause adverse events with long-term use (level 2a, grade B)
- Switching to entecavir plus TAF is recommended for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis (level 2a, grade A).
- Switching from adefovir or TDF to TAF is another option that offers better long-term safety. This is particularly recommended for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis.
- For poor responders in whom HBV DNA remains detectable after 12 months of NA therapy, entecavir, TDF, or TAF monotherapy can be continued as long as the HBV DNA level is decreasing, but drugs should be switched if the HBV DNA level is not decreasing. Treatment switching is particularly warranted if the HBV DNA level is ≥2000 IU/mL (3.3 log IU/mL). Patients with viral breakthrough, defined as an increase in HBV DNA to ≥1.0 log IU/mL during treatment, should be promptly switched to a different regimen. In whichever case, treatment adherence must be confirmed.
- Poor responders with detectable HBV DNA (on monotherapy): It is recommended to switch patients on lamivudine or entecavir to TDF or TAF, which are non-cross-resistant (level 1b, grade A), but entecavir plus TDF (level 1b, grade A) and entecavir plus TAF (level 6, grade C1) are also options.
- It is recommended to switch patients on TDF to entecavir, which is non-cross-resistant, but entecavir plus TDF and entecavir plus TAF are also options (level 6, grade C1).
- Switching to TAF is particularly recommended for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis (level 1b, grade A).
- It is recommended to switch patients on TAF to entecavir, which is non-cross-resistant, but entecavir plus TAF is also an option (level 6, grade C1).
- Poor responders with detectable HBV DNA (on combination therapy): It is recommended to switch patients on lamivudine plus adefovir or entecavir

plus adefovir to entecavir plus TDF (level 4, grade B) or entecavir plus TAF (level 6, grade B). Switching to entecavir plus TAF is particularly recommended for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis (level 6, grade A). Options for patients on lamivudine plus TDF are entecavir plus TDF and entecavir plus TAF (level 6, grade B). Switching to entecavir plus TAF is particularly recommended for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis (level 2a, grade A). Patients on entecavir plus TDF should continue treatment as is. Entecavir plus TAF is another option, because TDF may cause adverse events with long-term use, and switching is particularly recommended for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis (level 2a, grade A).

Cessation of NA therapy

- The following three patient criteria must be met for cessation of NA therapy: (i) both the treating physician and the patient fully understand that after cessation of NA therapy, there is a high incidence of recrudescence of hepatitis, possibly severe; (ii) follow up is possible after treatment cessation, and appropriate treatment is possible even if hepatitis recurs; and (iii) the degree of fibrosis is mild and the hepatic reserve is good, and even if recrudescence of hepatitis occurs, it is unlikely to be severe.
- The three laboratory criteria for cessation of NA therapy are: (i) at least 2 years of administration of NA; (ii) serum HBV DNA level (real-time PCR method) below the limits of detection; and (iii) negative serum HBeAg at the time of treatment cessation.
- When the above criteria are met, it is possible to predict the risk of relapse from HBsAg and HBcrAg levels at the time of cessation of therapy. NA therapy should be continued in the high-risk group.

HBV reactivation

<u>Screening</u>

- Screening for HBV infection should be carried out before treatment in all patients undergoing immunosuppressive therapy or chemotherapy who are at risk of HBV reactivation (level 1b, grade A).
- Screening for HBV infection should be carried out in a systematic fashion, using a highly sensitive test, and include measurement of levels of HBsAg, anti-HBc and anti-HBs antibodies, and HBV DNA (level 1b, grade A).

Basic strategy for prevention and treatment of reactivation

- When immunosuppressive therapy or chemotherapy with the associated risk of HBV reactivation is administered to HBsAg-positive inactive carriers or patients with resolved HBV infection who have an HBV DNA level of ≥20 IU/mL (1.3 log U/mL) on pretreatment screening tests, NA therapy should be commenced without delay (level 1b, grade A).
- Patients with resolved HBV infection and an HBV DNA level of level of level of <20 IU/mL (1.3 log IU/mL) at pretreatment screening tests should undergo regular monitoring of HBV DNA levels during and after their immunosuppressive therapy or chemotherapy. If HBV DNA levels exceed 20 U/mL (1.3 log IU/mL) during monitoring, pre-emptive NA therapy should be commenced (level 2a, grade A).
- Entecavir (level 1b, grade A), TDF, and TAF (level 2b, grade A) are the recommended NAs.
- It is preferable to reduce the viral load before starting immunosuppressive therapy or chemotherapy in HBsAg-positive patients with a high viral load (level 2b, grade A).
- When administering molecular targeted therapy using immunostimulatory drugs in HBsAg-positive patients, it is important to start with NA therapy to reduce the HBV DNA level before therapy whenever possible. Also, because there is currently insufficient evidence about the prevention and treatment of HBV reactivation, and because hepatic dysfunction may still occur during NA therapy, these patients should be carefully monitored (level 5, grade B).
- The criteria for cessation of NA therapy are the same as for cessation of NA therapy in HBsAg-positive patients. For patients with resolved HBV infection, NA therapy should be continued for at least 12 months after completing immunosuppressive therapy or chemotherapy, although cessation of NAs may be considered during this period if ALT remains normal and HBV DNA remains undetectable (level 5, grade B).
- Follow up including HBV DNA monitoring is necessary for at least 12 months after cessation of NA therapy. Treatment should be resumed immediately if the HBV DNA level exceeds 20 IU/mL (1.3 log IU/mL) during the follow-up period (level 5, grade B).

Novel molecular targeted therapies

- Monthly HBV DNA monitoring should be carried out for patients undergoing hematopoietic stem cell transplantation or chemotherapy including rituximab, Obinutuzumab, or fludarabine, during treatment and for at least 12 months after its completion (level 4, grade A).
- HBV DNA monitoring should be carried out every 1– 3 months for patients undergoing non-rituximab-based chemotherapy for hematological malignancies, as well as standard chemotherapy for solid malignancies, although the monitoring duration and intervals can be adjusted in accordance with the nature of the treatment (level 4, grade B).
- Monthly HBV DNA monitoring should be carried out for patients undergoing immunosuppressive therapy for rheumatic or connective tissue diseases, for at least 6 months after commencement or alteration of treatment. After 6 months, the monitoring duration and intervals should be determined in accordance with the nature of the treatment (level 4, grade B).
- It is recommended to continue monitoring HBV DNA at least every 3 months after the first 6 months, but high-sensitivity HBsAg monitoring (sensitivity of 0.005 IU/mL) can be substituted depending on the treatment regimen (level 2a, grade C1).
- If HBV reactivation occurs during chemotherapy or immunosuppressive therapy, it is preferable to consult with a hepatologist and not to immediately stop using the antineoplastic agent with immunosuppressive activity or immunosuppressant agent (level 5, grade C).

Antiviral therapy for hepatitis C

- Only targeting HCV in antiviral therapy for patients with HBV/HCV coinfection or resolved HBV infection can cause reactivation of HBV and severe hepatitis (level 2b, grade A).
- Whether there is coinfection with HBV or resolved HBV infection should be confirmed before starting antiviral therapy for HCV (level 5, grade A).
- Patients with HBV/HCV coinfection must be carefully monitored for HBV reactivation during treatment for HCV. They should be monitored for HBV markers, such as HBV DNA level, before and during treatment for HCV, and should be treated with NAs if the HBV DNA level exceeds 2000 IU/mL before treatment or increases during treatment (level 5, grade B).
- Patients with resolved HBV infection must also be carefully monitored for HBV reactivation during treatment for HCV (level 5, grade B). They should be

tested for HBV as necessary; for example, when an increase in ALT is detected during treatment for HCV and should be treated with NAs if reactivation is confirmed (level 5, grade A).

1.2.2 American Society of Clinical Oncology (ASCO) Provisional Clinical Opinion Update Hepatitis B Virus Screening and Management for Patients with Cancer Prior to Therapy (2020)[10,11]

This Provisional Clinical Opinion update presents a clinically pragmatic approach to hepatitis B virus (HBV) screening and management[10]. The main recommendations are summarized below:

- All patients with cancer anticipating systemic anticancer therapy should be tested for hepatitis B virus (HBV) by 3 tests—hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs)—prior to, or at the beginning of, systemic anticancer therapy. Anticancer therapy should not be delayed for the results of these screening tests. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and anti-HBc–positive with either negative or positive anti-HBs) infection require further action (Type of recommendation: evidence based; benefits outweigh harms; Strength of recommendation: strong).
- Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy. Monitoring recommendations include checking alanine aminotransferase (ALT) and HBV DNA level at baseline prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. Coordination of care with a clinician experienced in HBV management is highly recommended for patients with chronic HBV, especially to monitor for withdrawal flares, determine monitoring and antiviral therapy after the cessation of anticancer therapy, and evaluate for advanced liver disease such as cirrhosis or liver cancer (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).
- Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral

therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed (Type: informal consensus, benefits outweigh harms; Strength of recommendation: moderate).

- Patients with past HBV receiving anticancer therapies associated with an established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months, with immediate antiviral therapy at the earliest sign of HBV reactivation, so long as patients and providers are able to adhere to frequent and consistent follow-up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA is quantifiable but, 1,000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

  Patients with past HBV undergoing anticancer therapies that are not clearly associated with a high risk of HBV reactivation (e.g., regimens that do not include anti-CD20 monoclonal antibodies or stem-cell transplantation) should be followed carefully during cancer treatment, with HBsAg and ALT testing every 3 months (with subsequent HBV DNA testing if a hepatitis flare develops) with initiation of antiviral therapy only if HBsAg becomes positive or HBV DNA exceeds 1,000 IU/mL in the setting of a hepatitis flare. Follow-up testing after the cessation of anticancer therapy is likely not necessary (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).

1.2.3 Japan Society of Hepatology Guidelines for the Management of Hepatitis C Virus Infection (2019)[11]

The Japan Society of Hepatology guidelines for the management of hepatitis C virus infection's recommendations are outlined below[11]:

GOAL OF HEPATITIS C THERAPY

- The goal of hepatitis C therapy is to improve the long-term prognosis for chronic liver disease caused by persistent HCV infection, specifically, to prevent hepatocarcinogenesis and death associated with liver disease. To reach this goal, antiviral therapies are used to achieve HCV clearance (Level 2a, Grade A).
- An increasing number of recent studies have shown HCV clearance through IFN-free DAA therapy to be just as effective as IFN therapy in preventing hepatocarcinogenesis (Level 2b).
- A follow-up for hepatocarcinogenesis needs to be carried out to improve the long-term prognosis even after HCV clearance has been achieved with antiviral therapy. Patients at high risk of hepatocarcinogenesis due to age or advanced fibrosis need to be monitored particularly carefully (Level 2a, Grade A).

ELIGIBILITY FOR TREATMENT

- All patients with hepatitis C, including those with decompensated cirrhosis, are now potentially eligible for antiviral therapy (Level 1b, Grade A).
- This excludes patients who have a poor prognosis due to non-hepatic comorbidities (Grade D).
- The safety of sofosbuvir/velpatasvir has not been established in patients with decompensated cirrhosis with a Child–Pugh score of 13–15 because these patients were not included in Japanese clinical studies (Grade D).

DIRECT-ACTING ANTIVIRALS

➢ *Elbasvir/grazoprevir*

- Twelve-week combination therapy with elbasvir plus grazoprevir yields a high SVR rate for genotype 1 chronic hepatitis C and compensated cirrhosis. Rates reported in Japanese phase III studies range from 96.5% to 97.1% (Level 1b).
- Baseline characteristics such as cirrhosis, prior treatment history, sex, age, and IL28B polymorphism do not affect efficacy (Level 1b).

- Grade 3 or higher increase in AST or ALT was observed in six patients. This increase occurred 8 weeks or later into treatment in five of the six patients (Level 1b).
- The presence of NS3 RAVs at baseline does not affect the efficacy of treatment with elbasvir plus grazoprevir (Level 1b).

➢ *Glecaprevir/pibrentasvir*

- Eight to 12 weeks of treatment with glecaprevir/pibrentasvir yields a high SVR12 rate in genotype 1 and 2 patients with chronic hepatitis C and compensated cirrhosis previously untreated with DAA. Rates reported in Japanese phase III studies range from 98% to 100% (Level 2b).
- Twelve weeks of treatment with glecaprevir/pibrentasvir yields an 83.3% SVR12 rate in genotype 3 patients with chronic hepatitis C and compensated cirrhosis (Level 2b).
- Twelve weeks of treatment with glecaprevir/pibrentasvir also yields a high SVR12 rate of 93.9% in patients previously treated with DAA therapy (Level 2b, Grade B).
- Two patients previously treated with DAA therapy who had NS5A-P32 deletion at baseline (6.3%) both developed treatment failure (Level 2b).

TREATMENT STRATEGY

➢ *Selection of antivirals for treatment of chronic hepatitis*

- First-line regimens for genotype 1 patients are **sofosbuvir/ledipasvir**, **elbasvir plus grazoprevir**, and **glecaprevir/pibrentasvir** (Level 1b, Grade A).
- First-line regimens for genotype 2 patients are **sofosbuvir plus ribavirin**, **glecaprevir/pibrentasvir**, and **sofosbuvir/ledipasvir** (Level 1b, Grade A).
- **Glecaprevir/pibrentasvir** and **sofosbuvir/ledipasvir** are recommended for patients with genotype 1 and 2 mixed infection (Level 5, Grade B).
- Non-responders to previous therapy that did not include DAAs are addressed in these guidelines as treatment-naïve patients because IFN-free DAA therapy can be expected to yield a high SVR rate regardless of responsiveness to the previous therapy (Level 2a, Grade A).

➢ *Selection of antivirals for treatment of compensated cirrhosis*

- In compensated cirrhosis type C, aggressive IFN-free DAA therapy should be used to prevent hepatocarcinogenesis and hepatic failure (Level 1a, Grade A).

- Serious adverse reactions and death were reported in patients with compensated cirrhosis in post marketing studies of IFN-free DAA regimens besides sofosbuvir/velpatasvir. Consequently, patients with compensated cirrhosis who have reduced hepatic functional reserve should be carefully monitored for adverse reactions to antiviral therapy (Level 5, Grade A).
- As in patients with chronic hepatitis, the regimens recommended for initial antiviral therapy and retreatment (of patients not previously treated with DAAs) in patients with compensated cirrhosis are sofosbuvir/ledipasvir, elbasvir plus grazoprevir, and glecaprevir/pibrentasvir for genotype 1, and sofosbuvir plus ribavirin, glecaprevir/pibrentasvir (12 weeks), and sofosbuvir/ledipasvir for genotype 2 (Level 1a, Grade A).
- Regimens with sofosbuvir are contraindicated in patients with severe renal impairment and patients on dialysis (Grade D).

➢ *Selection of antivirals for retreatment of non-responders to DAA therapy*

Selection of antivirals for retreatment of non-responders to IFN-based DAA therapy

- Sofosbuvir/ledipasvir and glecaprevir/pibrentasvir are recommended for retreatment of non-responders to simeprevir, vaniprevir, or three-drug combination therapy with telaprevir, peg-IFN, and ribavirin. Sofosbuvir plus ribavirin is another recommended regimen for genotype 2 patients who do not respond to three-drug combination therapy with telaprevir, peg-IFN, and ribavirin (Level 2a, Grade A)

Retreatment of non-responders to IFN-free DAA therapy

- Non-responders to combination therapy with an NS3 protease inhibitor and NS5A inhibitor (daclatasvir plus asunaprevir, ombitasvir/paritaprevir/ritonavir, or elbasvir plus grazoprevir) acquire various mutations other than L31 and Y93, including P32 deletion and A92 mutation. P32 deletion in particular confers high levels of resistance to NS5A inhibitors, and other variants besides P32 deletion could also reduce efficacy (Level 2a).
- Therefore, it is recommended that a hepatologist carefully select the retreatment regimen for non-responders to previous DAA therapy with consideration of the results of analysis for RAVs in NS3/4A and NS5A, particularly P32 deletion status (Level 6, Grade A).
- A 12-week regimen of glecaprevir/pibrentasvir or 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is the first-line therapy for retreatment of non-responders to previous therapy with a protease inhibitor plus an NS5A inhibitor (daclatasvir plus asunaprevir) (Level 2a, Grade B).

- Use of sofosbuvir/ledipasvir in non-responders to daclatasvir plus asunaprevir is not recommended (Grade D).
- A 12-week regimen of glecaprevir/pibrentasvir or 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is recommended for non-responders to sofosbuvir/ledipasvir (Level 2a, Grade B).
- A 12-week regimen of glecaprevir/pibrentasvir or 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is also recommended for non-responders to sofosbuvir plus ribavirin (Level 2a, Grade B).

Antiviral therapy for decompensated cirrhosis

- A 12-week regimen of sofosbuvir/velpatasvir is an option for patients with decompensated cirrhosis (Level 2a, Grade B).
- For the time being, the decision to use sofosbuvir/velpatasvir in Child–Pugh grade 3 patients with a Child–Pugh score of 13–15 should be made by a hepatologist, and patients who undergo this treatment should be monitored with the utmost care (Level 2a, Grade C1).
- A 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is not covered by Japanese National Health Insuance for patients with decompensated cirrhosis with failed response to DAA therapy, and it should not be used in these patients (Grade D).
- A 12-week regimen of sofosbuvir/velpatasvir can be selected for patients with decompensated cirrhosis with failed response to DAA therapy at the discretion of their hepatologist, but its efficacy in this group is unclear (Level 2a, Grade C1)

HEPATITIS B VIRUS COINFECTION

- Hepatitis B virus/HCV coinfection should be treated more aggressively than infection with HCV alone because fibrosis tends to progress more easily and the likelihood of progression to cirrhosis is higher in coinfected patients (Level 2b, Grade A).
- As in patients infected with HCV alone, IFN-free DAA therapy is recommended for HBV-coinfected patients (Level 2b, Grade A). • Whether the patient has HBV coinfection, or a history of HBV infection should be confirmed before starting antiviral therapy for HCV (Level 5, Grade A).
- Patients with HBV coinfection or who have a history of HBV infection must be carefully monitored for HBV reactivation during treatment for HCV (Level 5, Grade A)

COINFECTION WITH HIV

- Interferon-free DAA therapy is the first-line therapy for HIV-coinfected patients (Level 2a, Grade A).
- The same regimens used to treat HCV infection alone should be used (Level 2a, Grade C1).
- Due care should be taken to avoid drug interactions when selecting DAAs (Level 2a, Grade C1)

GENOTYPES 3–6

- A 12-week regimen of glecaprevir/pibrentasvir is the first-line therapy for chronic hepatitis and compensated cirrhosis in genotype 3 patients (Level 2b, Grade A).
- The decision whether to select a 12-week regimen of glecaprevir/pibrentasvir or a 24-week regimen of sofosbuvir plus ribavirin for patients with genotypes 4 through 6 should be made carefully, taking into consideration the risk of carcinogenesis and potential adverse reactions to each treatment based on factors such as progression of liver disease. Waiting to start treatment should also be considered an option (Level 6, Grade C1)

HEPATITIS C VIRUS INFECTION AND KIDNEY TRANSPLANTATION

- Pretransplant antiviral therapy should be carried out in HCV-infected patients on dialysis scheduled to undergo kidney transplantation because it improves post-transplant renal function, graft survival, and patient survival (Level 2b, Grade A).

Antiviral therapy in patients with renal impairment and patients on dialysis

- Elbasvir plus grazoprevir and glecaprevir/pibrentasvir are recommended for antiviral therapy in genotype 1 patients with hepatitis C who have concurrent severe renal impairment (≥CKD stage 4) (Level 2a, Grade A).
- Neither elbasvir plus grazoprevir nor glecaprevir/pibrentasvir requires dose adjustment in patients with renal impairment (Level 2b, Grade A).
- Glecaprevir/pibrentasvir is recommended for antiviral therapy in genotype 2 patients with hepatitis C who have concurrent severe renal impairment (≥CKD stage 4) (Level 2a, Grade B)

RECURRENCE AFTER LIVER TRANSPLANTATION

- Antiviral therapy is recommended for histologically and serologically proven recurrence of hepatitis C detected by abnormal liver function after liver transplantation in HCV-infected patients, except for those with decompensated cirrhosis after transplantation (Level 2b, Grade A).
- Interferon-free DAA therapy can be safely carried out even in patients with proven or possible rejection, bile duct stenosis, or graft vascular stenosis or occlusion (Level 2b, Grade A).
- Fibrosing cholestatic hepatitis must be promptly treated with antiviral therapy once it is serologically and histologically proven (Level 2b, Grade A).

Treatment of recurrence after liver transplantation

- Treatment of recurrence of hepatitis C after liver transplantation must be carried out by a medical team with extensive knowledge of immunosuppressive therapy after liver transplantation and of the pathology and treatment of hepatitis C (Level 6, Grade A).
- Interferon-free antiviral therapy is preferable for recurrent hepatitis C in patients on immunosuppressive therapy after liver transplantation (Level 2b, Grade A).
- First-line regimens are sofosbuvir/ledipasvir and glecaprevir/pibrentasvir due to their low rate of interactions with immunosuppressants and high SVR rate (Level 2b, Grade A).
- There is little experience with use of glecaprevir/pibrentasvir and sofosbuvir/ledipasvir for non-responders to combination therapy with daclatasvir plus asunaprevir (Level 5, Grade C1).
- Glecaprevir/pibrentasvir is recommended for patients with severe renal impairment because sofosbuvir/ledipasvir is contraindicated in these patients (Level 5, Grade B).

Genotype 2

- Glecaprevir/pibrentasvir is highly likely to become the first-line antiviral therapy for recurrent hepatitis C after liver transplantation in genotype 2 patients with no contraindications, such as decompensated cirrhosis (Level 6, Grade C1).

1.2.4 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease (2022)[12]

KDIGO 2022 Clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease's recommendations are outlined below[12]:

Table 11. KDIGO 2022 Clinical Practice Guideline's Grade for Overall Quality of Evidence and Grading of Recommendations

Grade	Quality of Evidence	Meaning	
A	High	We are confident that the true effect is close to the estimate of the effect	
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	
C	Low	The true effect may be substantially different from the estimate of the effect	
D	Very Low	The estimate of effect is very uncertain, and often will be far from the true effect	
Grade	**Patients**	**Clinicians**	**Policy**
Level 1, strong "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, weak "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

		with her or his values and preferences.	

The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements. They should not be interpreted as being weaker recommendations than Level 1 or 2 recommendation.

Detection and evaluation of HCV in CKD

Screening patients with chronic kidney disease (CKD) for hepatitis C virus (HCV) infection

- We recommend screening all patients for HCV infection at the time of initial evaluation of CKD (1C).
    - We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A).
- We recommend screening all patients for HCV infection upon initiation of in-center hemodialysis or upon transfer from another dialysis facility or modality (1A).
    - We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).
- We suggest screening all patients for HCV infection upon initiation of peritoneal dialysis or home hemodialysis (2D).
- We recommend screening all patients for HCV infection at the time of evaluation for kidney transplantation (1A).

Follow-up HCV screening of in-center hemodialysis patients

- We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients every 6 months (1B).
    - Report any new HCV infection identified in a hemodialysis patient to the appropriate public health authority (Not Graded).
    - In units with a new HCV infection, we recommend that all patients be tested for HCV infection and that the frequency of subsequent HCV testing be increased (1A).

    - We recommend that hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT to detect possible re-infection (1B).
- We suggest that patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer from another facility (2B).
    - We suggest that hemodialysis patients have ALT level checked monthly (2B).

Liver testing in patients with CKD and HCV infection

- We recommend assessing HCV-infected patients with CKD for liver fibrosis (1A).
- We recommend an initial noninvasive evaluation of liver fibrosis (1B).
- When the cause of liver disease is uncertain or noninvasive testing results are discordant, consider liver biopsy (Not Graded).
- We recommend assessment for portal hypertension in CKD patients with suspected advanced fibrosis (F3–4) (1A).

Other testing of patients with HCV infection

- We recommend assessing all patients for kidney disease at the time of HCV infection diagnosis (1A).
    - Screen for kidney disease with urinalysis and estimated glomerular filtration rate (eGFR) (Not Graded).
- If there is no evidence of kidney disease at initial evaluation, patients who remain NAT-positive should undergo repeat screening for kidney disease (Not Graded).
- We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be followed up regularly to assess for progression of kidney disease (1A).
- We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be screened and, if appropriate, vaccinated against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (1A).

Treatment of HCV infection in patients with CKD

- We recommend that all patients with CKD (G1-G5), on dialysis (G5D), and kidney transplant recipients (G1T-G5T) with HCV be evaluated for direct-acting antiviral (DAA)-based therapy as outlined in table 12 (1A).

Table 12. Direct-Acting Antiviral (DAA) Regimens with Evidence of Effectiveness for Various Chronic Kidney Disease (CKD) Populations (Adapted from the KDIGO 2022 Guideline)

CKD populations	Direct-acting antiviral (DAA) regimens[a]	HCV genotypes	Quality of evidence (total N)[b]
G1–G3b, [c] not KTR	Any licensed DAA regimen	All	Not evaluated
G4–G5ND,[d] including KTR[e,f]	Sofosbuvir / Daclatasvir, 12 or 24 wk	All	High (571)
	Glecaprevir / Pibrentasvir, 8 wk	All	High (132)
	Grazoprevir / Elbasvir, 12 wk	1a, 1b, 4	High (857)
	Sofosbuvir / Velpatasvir, 12 wk	All	Low (99)
	Sofosbuvir / Ledipasvir, 12 wk	All	Very low (43)
G5D[g]	Sofosbuvir / Velpatasvir, 12 wk	All	High (405)
	Glecaprevir / Pibrentasvir, 8 wk	All	Moderate (529)
	Sofosbuvir / Daclatasvir, 12 or 24 wk	All	Moderate (278)
	Sofosbuvir / Ledipasvir, 12 wk	All	Moderate (220)
	Grazoprevir / Elbasvir, 12 wk	1a, 1b, 4	Moderate (962)
	PrO ± D, 12 wk	1a, 1b, 4	Moderate (582)
	Daclatasvir / Asunaprevir, 24 wk	1b	Low (341)
KTR,[e] G1–G3b[c]	Sofosbuvir / Ledipasvir, 12 or 24 wk	All	High (300)
	Sofosbuvir / Daclatasvir, 12 or 24 wk	All	High (290)
	PrO ± D, 12 wk	1a, 1b, 4	Very low (33)
	Grazoprevir / Elbasvir, 12 wk	1a, 1b, 4	Very low (21)

[a] The figure includes only regimens that were evaluated by at least 2 studies in the specific CKD population and for which summary sustained virologic response at 12 weeks [wks] (SVR12) was >92%. Sofosbuvir monotherapy is excluded since current DAA regimens incorporate at least 2 agents. Other regimens may be appropriate for the above populations. Readers are encouraged to consult the Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver (EASL) guidelines for the latest information on various regimens. The suggested durations of treatment are those most commonly employed by the relevant studies. Studies commonly extended

treatment for patients with cirrhosis, prior DAA failure, or for some genotypes. Readers should consult the AASLD or EASL guidelines, as needed, to determine optimal treatment duration. [b] The order of hepatitis C virus (HCV) regimens does not indicate a ranking or preferential order of selection. The regimens are presented in order of the quality of evidence, then by HCV genotype, then alphabetically. The differences in quality of evidence primarily relate to the numbers of evaluated patients and small differences in methodological quality of the underlying studies. [c] Estimated glomerular filtration rate (eGFR) ≥ 30 ml/min per 1.73 m^2. [d] eGFR < 30 ml/min per 1.73 m^2, not dialysis dependent. [e] Regimens in kidney transplant recipients (KTRs) should be selected to avoid drug–drug interactions, particularly with calcineurin inhibitors. [f] Strength of evidence for CKD G4T-G5T is very low for all regimens. g Evidence primarily for patients on hemodialysis. Very few patients were on peritoneal dialysis. G, refers to the GFR category with suffix D denoting patients on dialysis and ND denoting patients not on dialysis; PrO±D, ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir.

- We recommend that the choice of specific regimen be based on prior treatment history, drug–drug interactions, GFR, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (1A). If pangenotypic regimens are not available, HCV genotype (and subtype) should guide the choice of treatment.
- Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy (Not Graded).
- We recommend pre-treatment assessment for drug–drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients (1A).
- We recommend that calcineurin inhibitor levels be monitored during and after DAA treatment in kidney transplant recipients (1B).
- All patients with CKD (G1-G5), on dialysis (G5D), and kidney transplant recipients (G1T-G5T) with HCV should undergo testing for hepatitis B virus (HBV) infection prior to DAA therapy (Not Graded).
- All patients with CKD (G1-G5), on dialysis (G5D), and kidney transplant recipients (G1T-G5T) with HCV should undergo testing for hepatitis B virus (HBV) infection prior to DAA therapy (Not Graded).
    - If hepatitis B surface antigen [HBsAg] is present, the patient should undergo assessment for HBV therapy (Not Graded).
    - If HBsAg is absent but markers of prior HBV infection (HBcAb-positive with or without HBsAb) are detected, exclude HBV reactivation with HBV DNA testing if levels of liver function tests rise during DAA therapy (Not Graded)

Preventing HCV transmission in hemodialysis units

- We recommend that hemodialysis facilities adhere to standard infection control procedures including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens (1A).
    - We recommend regular observational audits of infection control procedures in hemodialysis units (1C).
    - We recommend not using dedicated dialysis machines for HCV-infected patients (1D).
    - We suggest not isolating HCV-infected hemodialysis patients (2C).
    - We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection control procedures (2D).
- We recommend that hemodialysis centers examine and track all HCV test results to identify new cases of HCV infections in their patients (1B).
    - We recommend that aggressive measures be taken to improve hand hygiene (and proper glove use), injection safety, and environmental cleaning and disinfection when a new case of HCV is identified that is likely to be dialysis-related (1A).
- Strategies to prevent HCV transmission within hemodialysis units should prioritize adherence to standard infection control practices and should not primarily rely upon the treatment of HCV-infected patients (Not Graded).

Management of HCV-infected patients before and after kidney transplantation

- Evaluation and management of kidney transplant candidates regarding HCV infection
    - We recommend kidney transplantation as the best therapeutic option for patients with CKD G5 irrespective of presence of HCV infection (1A).
    - We suggest that all kidney transplant candidates with HCV be evaluated for severity of liver disease and presence of portal hypertension prior to acceptance for kidney transplantation (2D).
        - We recommend that patients with HCV, compensated cirrhosis, and no portal hypertension undergo isolated kidney transplantation and that patients with decompensated cirrhosis or clinically significant portal hypertension (i.e., hepatic venous pressure gradient ‡10 mm Hg or evidence of portal hypertension on imaging or exam) undergo a simultaneous liver–kidney

transplantation (1B). Treatment of those with mild-to-moderate portal hypertension should be determined on a case-by-case basis.

        - We recommend referring patients with HCV and decompensated cirrhosis for combined liver–kidney transplantation (1B)

    - Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), wait-list times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, and severity of liver fibrosis (Not Graded).

        - We recommend that all kidney transplant candidates with HCV be considered for DAA therapy, either before or after transplantation (1A).

        - We suggest that HCV-infected kidney transplant candidates with a living kidney donor be considered for treatment before or shortly after transplantation depending on the anticipated timing of transplantation (2B)

- Use of kidneys from HCV-infected donors

    - We recommend that all kidney donors be screened for HCV infection with both immunoassay and NAT (if NAT is available) (1A).

    - After assessment of liver fibrosis, HCV-infected potential living kidney donors who do not have cirrhosis should undergo HCV treatment before donation if the recipient is HCV-uninfected; they can be accepted for donation if they achieve sustained virologic response (SVR) and remain otherwise eligible to be a donor (Not Graded).

    - We recommend that kidneys from HCV-infected donors be considered regardless of HCV status of potential kidney transplant recipients (1C).

    - When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers must ensure that patients receive education and are engaged in discussion with sufficient information to provide informed consent. Patients should be informed of the risks and benefits of transplantation with an HCV-infected kidney, including the need for DAA treatment (Not Graded).

    - When transplanting kidneys from HCV-infected donors into HCV-uninfected recipients, transplant centers should confirm availability of DAAs for initiation in the early post-transplant period (Not Graded).

- Use of maintenance immunosuppressive regimens
    - We recommend that kidney transplant recipients being treated with DAAs be evaluated for the need for dose adjustments of concomitant immunosuppressants (1C).
- Management of HCV-related complications in kidney transplant recipients
    - We suggest that patients previously infected with HCV who achieved SVR before transplantation undergo testing by NAT 3 months after transplantation or if liver dysfunction occurs (2D).
    - Kidney transplant recipients with cirrhosis should have the same liver disease follow-up as non-transplant patients, as outlined in the American Association for the Study of Liver Diseases (AASLD) guidelines (Not Graded).
    - HCV-infected kidney transplant recipients should be tested at least every 6 months for proteinuria (Not Graded).
    - We suggest that patients who develop new-onset proteinuria (either urine protein-creatinine ratio > 1 g/g or 24-hour urine protein > 1 g on 2 or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis (2D).
    - We recommend treatment with a DAA regimen in patients with post-transplant HCV-associated glomerulonephritis (1D).

Diagnosis and management of kidney diseases associated with HCV infection

- HCV-infected patients with a typical presentation of immune-complex proliferative glomerulonephritis can be managed without a confirmatory kidney biopsy. However, a biopsy may be indicated in certain clinical circumstances (Not Graded).
- We recommend that patients with HCV-associated glomerulonephritis receive antiviral therapy (1A).
    - We recommend that patients with HCV-associated glomerulonephritis, stable kidney function, and without nephrotic syndrome be treated with DAAs prior to other treatments (1C).
    - We recommend that patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis be treated with both DAAs and immunosuppressive agents with or without plasma exchange (1C). 5.2.2.1: The decision whether to use immunosuppressive agents in

patients with nephrotic syndrome should be individualized (Not Graded).

- We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerulonephritis who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (1B).
    - We recommend rituximab as the first-line immunosuppressive treatment (1C).

Section 2.0 Drug Therapy in Viral Hepatitis

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

2.1.1 Hepatitis B Immunoglobulin

Information on HBIG is detailed in the table below[13]:

Table 13. Hepatitis B Immunoglobulin Drug Information

SCIENTIFIC NAME Hepatitis B Immunoglobulin	
SFDA Classification	Prescription
SFDA Approval	N/A
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	**B16** (acute hepatitis B) **B18.0** (chronic viral hepatitis B with delta agent) **B18.1** (chronic viral hepatitis B without delta agent) **Z20.5** (contact with and (suspected) exposure to viral hepatitis)
Drug Class	Blood Product Derivative
Drug Sub-class	Immune Globulin
ATC Code	J06BB04
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection or infusion
Route of Administration	IV or IM
Dose (Adult) [DDD]	0.06 ml/kg body weight[14]
Maximum Daily Dose Adults	N/A

Dose (pediatrics)	**Perinatal exposure, prophylaxis** (CDC 2005): Infants born to HBsAg-positive mothers: IM: 0.5 mL as a repeat of birth dose if the hepatitis B vaccination series is delayed for as long as 3 months (hepatitis B vaccine should also be administered at the same time/different site) **Postexposure prophylaxis:** *Infants <12 months*: IM: 0.5 mL as soon as possible after exposure (eg, mother or primary caregiver with acute HBV infection); initiate hepatitis B vaccine series *Children ≥12 months and Adolescents*: IM: 0.06 mL/kg as soon as possible after exposure (ie, within 24 hours of needlestick, ocular, or mucosal exposure or within 14 days of sexual exposure); repeat at 28 to 30 days after exposure
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Renal impairment**: Adult and pediatrics: There are no dosage adjustments provided in the manufacturer's labeling **Hepatic Impairment**: Adult and pediatrics There are no dosage adjustments provided in the manufacturer's labeling
Prescribing edits	CU, ST, QL, PE, MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	It can be used simultaneously with hepatitis B vaccine at separate anatomic sites for prevention of transmission after exposure to HBV
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	This medication must be prescribed by or in consultation with a physician who specializes in infectious diseases

PA (Prior Authorization)	N/A
QL (Quantity Limit)	HBIG provides **temporary** (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination.
ST (Step Therapy)	HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as **an adjunct** to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	This medication should be given **as soon as possible** after exposure (ie, **within 24 hours** of needlestick, ocular, or mucosal exposure or **within 14 days** of sexual exposure); **repeat at 28 to 30 days** after exposure in non-responders to hepatitis B vaccine or in patients who refuse vaccination
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common >10%:** **Central nervous system**: Headache **Dermatologic**: Erythema **1% to 10%:** **Cardiovascular**: Hypotension **Central nervous system**: Malaise **Dermatologic**: Ecchymoses **Gastrointestinal**: Nausea, vomiting **Hematologic & oncologic**: Change in WBC count **Hepatic**: Increased serum alkaline phosphatase, increased liver enzymes **Local**: Pain at injection site

	Neuromuscular & skeletal: Myalgia, joint stiffness **Renal**: Increased serum creatinine **<1%, postmarketing, and/or case reports**: Abdominal pain, anaphylactic reaction (rare), angioedema, back pain, chills, diaphoresis, dizziness, dyspnea, fever, flu-like symptoms, hypersensitivity, increased serum lipase, increased serum transaminases, sinus tachycardia, tenderness at injection site, urticaria
Drug Interactions	No interactions of Risk X identified
Special Population	N/A
Pregnancy	Use of HBIG is not contraindicated in pregnant females and may be used for postexposure prophylaxis when indicated (CDC 2001). In addition, use of HBIG has been evaluated to reduce maternal to fetal transmission of hepatis B virus during pregnancy (ACOG 2007)
Lactation	It is not known if immune globulin from these preparations is present in breast milk. The manufacturer recommends that caution be used if administered to breastfeeding females. Endogenous immune globulins are present in breast milk (Agarwal 2011). Infants born to HBsAg-positive mothers (and receive postexposure prophylaxis) or to mothers with unknown HBsAg status may be breastfed (CDC [Schillie 2018]). Use of HBIG is not contraindicated in breastfeeding females (CDC 2001).
Contraindications	HepaGam B: Anaphylactic or severe systemic reaction to human globulin preparations; IgA deficiency;

	postexposure prophylaxis in patients with severe thrombocytopenia or other coagulation disorders which would contraindicate IM injections (administer only if benefit outweighs the risk).
Monitoring Requirements	For liver transplant cases: Serum HBsAg; LFTs; infusion-related adverse events
Precautions	**Anaphylaxis/hypersensitivity reactions**: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1 mg/mL) should be available. Use with caution in patients with isolated immunoglobulin A deficiency or a history of systemic hypersensitivity to human immunoglobulins. **Infusion reactions**: When administered IV, do not exceed recommended infusion rates; may increase risk of adverse events. Patients should be monitored for adverse events during and after the infusion. **Thrombotic events**: Thrombotic events have been reported with administration of intravenous immune globulin; use with caution in patients of advanced age, with a history of atherosclerosis or cardiovascular and/or thrombotic risk factors, patients with impaired cardiac output, coagulation disorders, prolonged immobilization, or patients with known/suspected hyperviscosity. Consider a baseline assessment of blood viscosity in patients at risk for hyperviscosity.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews of Viral Hepatitis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **Below are the HTA recommendations related to HBIG in Viral Hepatitis treatment.**

Table 14. Hepatitis B Immunoglobulin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Hepatitis B Immunoglobulin	NICE	N/A
	CADTH	N/A
	HAS[15]	Hepatitis B immunoprophylaxis indications: • in accidental exposure in non-immunized people (including when vaccination is incomplete or unknown) • in hemodialysis patients pending vaccination being effective • in newborn babies of mothers carrying the hepatitis B virus • in patients who have not developed an immune response after vaccination against the hepatitis B virus (undetectable antibodies against hepatitis B) and who require continued protection against this disease. The committee **recommends** its inclusion. The actual benefit of HUMAN HEPATITIS B IMMUNOGLOBULIN LFB in the Marketing Authorization indications is substantial.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Hepatitis B Immunoglobulin

Hepatitis B Immunoglobulin is indicated for HBV prevention and postexposure prophylaxis. It is given at 0.06 ml/kg body weight. Hepatitis B Immunoglobulin ca be given either intravenously or intramuscularly. Its use is backed up by HAS HTA body in the indications mentioned above. The use of Hepatitis B Immunoglobulin is limited by the anaphylaxis/hypersensitivity reactions, infusion reactions, and thrombotic events.

2.2 Modifications

Modifications made since February 2020: addition of MD as a prescribing edit to all drugs as hepatitis should be treated by a specialist: ID, hepatologists, or gastroenterologist.

2.3 Delisting

The medications below are no longer SFDA registered[16], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs in the disease - section 2*** *of CHI Viral Hepatitis original clinical guidance*

- DASABUVIR
- GRAZOPREVIR, ELBASVIR

Section 3.0 Key Recommendations Synthesis

Hepatitis C

Initial Treatment *of Hepatitis C Virus–Infected Adults (joint)*

- Treatment-naive without cirrhosis or with compensated cirrhosis Glecaprevir/pibrentasvir. Genotype 1–6, ***Recommended***, duration 8 wk I, A
- Sofosbuvir/velpatasvir. Genotype 1–6, ***Recommended*** duration 12 wk I, A For genotype 3 infection with compensated cirrhosis, NS5A RAS testing is recommended. If baseline NS5A RAS Y93H is present, add weight-based ribavirin or choose another recommended regimen.
- Ledipasvir/sofosbuvir. Genotype 1, 4, 5, 6 ***Recommended*** duration 12 wk I, A Not recommended for genotype 6 infection if subtype is known.
    - Genotype 1 without cirrhosis Recommended 8 wk I, B Applicable to patients without cirrhosis who are not living with human immunodeficiency virus and whose HCV RNA is <6 million IU/mL.
- Elbasvir/grazoprevir, Genotype 1b, 4 ***Recommended*** duration 12 wk I, A
    - Genotype 1a Alternative 12 wk I, A For genotype 1a infection, NS5A RAS testing is recommended. If baseline RASs are present (i.e., substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used.
- Sofosbuvir/velpatasvir + weight-based ribavirin 3 ***Alternative*** duration 12 wk IIa, A. Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
- Sofosbuvir/velpatasvir/ voxilaprevir ***Alternative*** 12 wk IIa, B Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.

Treatment-naive *with decompensated cirrhosis*

- Sofosbuvir/velpatasvir + weight-based ribavirin. Genotype, 1–6 **Recommended** duration 12 wk I, A. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
    - Sofosbuvir/velpatasvir. Genotype 1–6 ***Recommended*** duration 24 wk I, A. Applicable to patients who are ribavirin ineligible.
- Ledipasvir/sofosbuvir + weight-based ribavirin. Genotype 1, 4, 5, 6 ***Recommended*** duration 12 wk I, A. Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.

- Ledipasvir/sofosbuvir. Genotype 1, 4, 5, 6 ***Recommended*** duration 24 wk I, A. Applicable to patients who are ribavirin ineligible.

*Recommendations for **Retreatment** of Hepatitis C Virus–Infected Adults by Prior Exposure*

- Sofosbuvir-based treatment failure without cirrhosis or with compensated cirrhosis: Sofosbuvir/velpatasvir/ voxilaprevir. Genotype 1–6 ***Recommended*** duration 12 wk I, A. For genotype 3 infection with compensated cirrhosis, add weight-based ribavirin if there are no contraindications.
- Glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis:
    - Glecaprevir/pibrentasvir + sofosbuvir + weight-based ribavirin 1–6 Recommended duration 16 wk IIa.
    - Sofosbuvir/velpatasvir/ voxilaprevir. Genotype 1–6 ***Recommended*** duration 12 wk IIa, B. For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended (rating IIa, C)
- Sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir + glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis
    - Glecaprevir/pibrentasvir + sofosbuvir + weight-based ribavirin Genotype 1–6 ***Recommended*** duration 16 wk IIa, B Extension to 24 wk should be considered in extremely difficult cases (e.g., genotype 3 infection with compensated cirrhosis) or failure following sofosbuvir + glecaprevir/pibrentasvir therapy.
    - Sofosbuvir/velpatasvir/ voxilaprevir + weight-based ribavirin. Genotype 1–6 ***Recommended*** duration 24 wk IIa, B
- Sofosbuvir- or NS5A inhibitor–based treatment failure with decompensated cirrhosis
    - Sofosbuvir/velpatasvir + weight-based ribavirin. Genotype 1–6 ***Recommended***, duration 24 wk II, C Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
    - Ledipasvir/sofosbuvir + weight-based ribavirin. Genotype 1, 4, 5, 6 ***Recommended***, duration 24 wk II, C Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.

Recommendations for Initial Treatment of Hepatitis C Virus– Infected Pediatric Patients Without Cirrhosis or With Compensated Cirrhosis

- Glecaprevir/pibrentasvir. Genotype 1–6 ***Recommended***, duration 8 wk I, B

*Recommendations for **Retreatment** of Hepatitis C Virus–Infected Pediatric Patients by Prior Exposure and Cirrhosis Status*

- Interferon-based regimen (±ribavirin) and/or sofosbuvir treatment failure without NS3/4A protease inhibitor or NS5A inhibitor exposure
    - Glecaprevir/pibrentasvir 1, 2, 4, 5, 6 ***Recommended*** 8 wk I, C No cirrhosis Glecaprevir/pibrentasvir 1, 2, 4, 5, 6 ***Recommended*** 12 wk I, C Compensated cirrhosis
    - Glecaprevir/pibrentasvir 3 ***Recommended*** 16 wk I, C Without cirrhosis or with compensated cirrhosis.
    - Sofosbuvir/velpatasvir 1–6 ***Recommended*** 12 wk I, C Without cirrhosis or with compensated cirrhosis.
    - Sofosbuvir/velpatasvir + weight-based ribavirin 1–6 ***Recommended*** 12 wk I, C Decompensated cirrhosis.
- NS3/4A protease inhibitor treatment failure without NS5A inhibitor exposure Glecaprevir/pibrentasvir Genotype 1–6 ***Recommended***, duration 12 wk I, C Without cirrhosis or with compensated cirrhosis.
- NS5A inhibitor treatment failure without NS3/4A protease inhibitor exposure Glecaprevir/pibrentasvir Genotype 1–6 ***Recommended*** duration 16 wk I, C Without cirrhosis or with compensated cirrhosis.
- Interferon (± ribavirin) plus a hepatitis C virus protease inhibitor treatment failure
    - Ledipasvir/sofosbuvir, Genotype 4, 5, 6 ***Recommended***, duration 12 wk I, C Without cirrhosis or with compensated cirrhosis
    - Ledipasvir/sofosbuvir, Genotype 1 ***Recommended***, duration 12 wk I, C No cirrhosis.
    - Ledipasvir/sofosbuvir, Genotype 1 ***Recommended***, duration 24 wk I, C Compensated cirrhosis.

Recommendations for Hepatitis C Virus Treatment Post transplantation

Recurrent HCV post liver transplant without cirrhosis

- Glecaprevir/ pibrentasvir and Sofosbuvir/ velpatasvir. Genotype 1–6 ***Recommended***, duration 12 wk I, B
- Ledipasvir/ sofosbuvir. Genotype 1, 4, 5, 6 ***Recommended***, duration 12 wk I, B

Recurrent HCV post liver transplant with compensated cirrhosis

- Ledipasvir/ sofosbuvir. Genotype 1, 4, 5, 6 ***Recommended,*** *duration* 12 wk I, A

Recurrent HCV post kidney transplant without cirrhosis or with compensated cirrhosis

- Ledipasvir/ sofosbuvir. Genotype 1, 4, 5, 6 ***Recommended***, *duration* 12 wk I, A

HCV-uninfected recipients of liver grafts from HCV-viremic donors

- Glecaprevir/ pibrentasvir and Sofosbuvir/ velpatasvir. Genotype 1–6 ***Recommended,*** *duration* 12 wk I, C Timing: initiate treatment within the first 2 wk posttransplant, preferably within the first week.

HCV-uninfected recipients of non-liver solid organs from HCV-viremic donors

- Glecaprevir/ pibrentasvir, duration (8wk) and. Sofosbuvir/ velpatasvir (duration (12wk). Genotype 1–6 ***Recommended***. I, C Timing: initiate treatment prior to HCV RNA results, immediately pretransplant or day 0 posttransplant, if possible. Otherwise, begin on day 0 to within the first week posttransplant when clinically stable.

Hepatitis B

Hepatitis B Virus Screening and Management for Patients with Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update

- Patients with past HBV receiving anticancer therapies associated with an established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months, with immediate antiviral therapy at the earliest sign of HBV reactivation, so long as patients and providers can adhere to frequent and consistent follow-up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA is quantifiable but, 1,000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).[10]
- Patients with past HBV undergoing anticancer therapies that are not clearly associated with a high risk of HBV reactivation (e.g., regimens that do not include

anti-CD20 monoclonal antibodies or stem-cell transplantation) should be followed carefully during cancer treatment, with HBsAg and ALT testing every 3 months (with subsequent HBV DNA testing if a hepatitis flare develops) with initiation of antiviral therapy only if HBsAg becomes positive or HBV DNA exceeds 1,000 IU/mL in the setting of a hepatitis flare. Follow-up testing after the cessation of anticancer therapy is likely not necessary (Type: informal consensus, benefits outweigh harms; Strength of recommendation: strong).[10]

Treatment plans for chronic hepatitis and cirrhosis

- Entecavir, TDF, and TAF are the first-line NAs due to their low risk of resistance (level 2b, grade A).[11]
- The potential teratogenicity of NAs should be discussed with patients who are pregnant or planning to become pregnant. TDF is the only NA with evidence showing it is low risk in pregnancy (level 2b, grade A).[11]
- To minimize adverse events associated with long-term use of NAs, entecavir and TAF are the first-line drugs for patients with renal impairment, hypophosphatemia, or osteopenia/osteoporosis at treatment initiation (level 1b, grade A).[11]

➔ **HBeAg-positive chronic hepatitis:** Treatment is indicated for patients with HBeAg-positive chronic hepatitis B with an HBV DNA level of at least 2000 IU/mL (3.3 log IU/mL) and ALT of at least 31 U/L (level 6, grade B).[11]

➔ **HBeAg-negative chronic hepatitis:** As for patients with HBeAg-positive chronic hepatitis B, treatment is indicated for patients with HBeAg-negative chronic hepatitis B with an HBV DNA level of at least 2000 IU/mL (3.3 log IU/mL) and ALT of at least 31 U/L (level 2b, grade B).[11]

Section 4.0 Conclusion

This report serves as an annex to the previous CHI viral hepatitis report and aims to provide recommendations to aid in the management of viral hepatitis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with viral hepatitis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Viral Hepatitis Scope

Section	Rationale/updates
Section 1.1 Saudi Association for the Study of Liver diseases and Transplantation (SASLT) Practice Guidelines for the Management of Hepatitis B Virus **[2014]**	**Section 1.1.1** SASLT practice guidelines for the management of Hepatitis B virus – An update **[2021]** ➔ These guidelines aim to assist healthcare professionals in the management of HBV in Saudi Arabia. The present update summarizes the latest studies performed on HBV epidemiology in the country, major changes in the prevalence of this virus, and advances in the treatment of the disease. *Recommendations for initiation of treatment* • All patients with chronic hepatitis B (HBV DNA > 2,000 IU/mL, ALT > ULN), regardless of HBeAg status, and/or at least moderate liver necroinflammation or fibrosis (Grade A) • Patients with cirrhosis (compensated or decompensated), with any detectable HBV DNA level and regardless of ALT levels (Grade A) • Patients with HBV DNA > 20,000 IU/mL and ALT > 2xULN, regardless of the degree of fibrosis (Grade B) • Patients with HBeAg-positive chronic HBV infection (persistently normal ALT and high HBV DNA levels) may be treated if they are > 30 years, regardless of the severity of liver histological lesions (Grade D) • Patients with chronic HBV infection (HBV DNA > 2,000 IU/mL, ALT > ULN), regardless of HBeAg status, and a family history of HCC or cirrhosis and extrahepatic manifestations (Grade D) *Recommendations for monitoring of therapy of patients currently not treated* • Patients with HBeAg-positive chronic HBV infection who are younger than 30 years should be followed at least every 3-6 months (Grade B) • Patients with HBeAg-negative chronic HBV infection and serum HBV DNA

	Treatment of CHB: • The treatment of choice is the long-term administration of a potent NA with a high barrier to resistance, regardless of the severity of liver disease (Grade A) • Preferred regimens are ETV, TDF and TAF as monotherapies (Grade A) • LAM, ADV and TBV are not recommended in the treatment of CHB (Grade A) *Treatment of HBV in special populations* • Treatment of HCV through DAAs may lead to reactivation of HBV. Patients who meet the criteria for HBV treatment should be treated concurrently or before initiation of DAA (Grade A) • HBV DNA and ALT should be monitored every four to eight weeks while on DAA and three months after completion of therapy (Grade D) • ALT level should be monitored every four weeks while on DAA for patients who are HBsAg-negative but HBcAb-positive. If ALT starts to rise, HBsAg and HBV DNA must be obtained to determine the need to start HBV treatment (Grade D). *HBV-HIV coinfection* • All HIV-positive patients with HBV co-infection should start ART irrespective of CD4 cell count (Grade A) • HBV-HIV co-infected patients should be treated with TDF- or TAF-based ART regimen (Grade A) *Immunocompromised patients* • Prophylaxis for all patients with positive HBsAg should be done before initiating chemotherapy or other immunosuppressive agents (Grade A) • HBsAg-negative/anti-HBc-positive patients, should undergo HBV prophylaxis if they are candidates for anti CD20 or are undergoing stem cell transplantation. HBV prophylaxis should continue for at least six months after completion of immunosuppressive treatment and for twelve months if taking anti CD20 (Grade D).

	HBV and pregnancy • All pregnant women must be screened for HBV during the first trimester (Grade A) • All pregnant women with HBV DNA greater than 100,000 IU/mL in the late second trimester (between 24-28 weeks of gestation) should start antiviral prophylaxis with TDF, or TAF as an alternative (Grade D) • Switch to TDF or TAF is recommended if the patient is receiving ETV, ADV, or interferon during pregnancy (Grade D) • Breastfeeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis (Grade B)
Section 1.2 Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Guidance **[2018]**	**N/A**
Section 1.3 European Association for the Study of the Liver (EASL) **2017** Clinical Practice Guidelines on the management of hepatitis B virus infection	**N/A**
Section 1.4 The Saudi Association for the Study of Liver Diseases and Transplantation (SASLT)	**N/A**

Guidelines: Update in Treatment of Hepatitis C Virus Infection [2017] [adopted from the European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C] **[updated 2019]**	
Section 1.5 AASLD Hepatitis C Guidance **2019** Update: American Association for the Study of Liver Diseases– Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection	Section 1.1.2. Hepatitis C Guidance 2023 Update: American Association for the Study of Liver Diseases– Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection 1. Recommendations for Initial Treatment of Hepatitis C Virus–Infected Adults. 2. Recommendations for Retreatment of Hepatitis C Virus–Infected Adults by Prior Exposure 3. Recommendations for Initial Treatment of Hepatitis C Virus– Infected Pediatric Patients Without Cirrhosis or With Compensated Cirrhosis 4. Recommendations for Retreatment of Hepatitis C Virus–Infected Pediatric Patients by Prior Exposure and Cirrhosis Status 5. Recommendations for Hepatitis C Virus Treatment Post transplantation ➔ Since the last published update, genotypic activity has been added to the hierarchical ranking of treatment regimens (in addition to recommended or alternative, evidence level, and alphabetical order) ➔ Another significant change is the recommendation that sofosbuvir/velpatasvir/voxilaprevir may be used as an alternative regimen for persons with genotype 3 infection and compensated cirrhosis. ➔ Initial treatment using elbasvir/grazoprevir for genotype 1a infection was changed from a recommended to an alternative regimen because of the need for baseline

	RAS testing. ➔ Additionally, several regimens are no longer recommended because the therapeutics are either no longer available in the United States and/or the regimens have inferior SVR rates compared with currently recommended DAA regimens. These include sofosbuvir and daclatasvir; sofosbuvir and ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir; and sofosbuvir, telaprevir, or boceprevir with pegylated interferon and ribavirin.
N/A	**Section 1.2.1.** Japan Society of Hepatology Guidelines for the Management of Hepatitis B Virus Infection: 2019 update This 2019 version covers: • The nucleotide analogs, tenofovir disoproxil fumarate and tenofovir alafenamide, which were approved in Japan in 2014 and in 2017, respectively, after the first version of the guidelines was published. • Updates to treatment recommendations and management of drug-resistant hepatitis B virus (HBV) that reflect the new availability of these drugs; and • (iii) new information about HBV reactivation with each update. This latest update also contains information about treatment goals, indications for treatment, and cessation of NA therapy, most of which were covered by the first version; other areas have briefer descriptions, because there have been only minor changes since the last version was published.
N/A	**Section 1.2.2.** Hepatitis B Virus Screening and Management for Patients with Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update • All patients with cancer anticipating systemic anticancer therapy should be tested for hepatitis B virus (HBV) by 3 tests—hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs)—prior to, or at the beginning of, systemic anticancer therapy. Anticancer therapy should not be delayed for the results of these screening tests. Findings of chronic HBV (HBsAg-positive) or past HBV

	(HBsAg-negative and anti-HBc–positive with either negative or positive anti-HBs) infection require further action (Type of recommendation: evidence-based, benefits outweigh harms; Strength of recommendation: strong). • Patients with chronic HBV receiving any systemic anticancer therapy should receive antiviral prophylactic therapy for the duration of anticancer therapy, as well as for at least 12 months after receipt of the last anticancer therapy. Monitoring recommendations include checking alanine aminotransferase (ALT) and HBV DNA level at baseline prior to or at the beginning of their anticancer therapy, as well as every 6 months during antiviral therapy. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter. Coordination of care with a clinician experienced in HBV management is highly recommended for patients with chronic HBV, especially to monitor for withdrawal flares, determine monitoring and antiviral therapy after the cessation of anticancer therapy, and evaluate for advanced liver disease such as cirrhosis or liver cancer (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong). • Hormonal therapy without systemic anticancer therapy is unlikely to increase the risk of HBV reactivation in patients with chronic or past HBV. Antiviral therapy and management for these patients should follow national HBV guidelines, independent of cancer therapy, including management by a clinician experienced in HBV management for prevention of liver disease such as cirrhosis or liver cancer. Should their anticancer treatment regimen change beyond hormonal therapy alone, the risk of HBV reactivation based on their new anticancer therapy should be reassessed (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: moderate). • Patients with past HBV receiving anticancer therapies associated with an

	established high risk of HBV reactivation, such as anti-CD20 monoclonal antibodies or stem-cell transplantation, should be started on antiviral prophylaxis at the beginning of anticancer therapy and continued antiviral therapy for at least 12 months after the cessation of anticancer therapy. HBV DNA should be obtained at baseline and followed every 6 months during antiviral therapy. Patients with a negative anti-HBs may be at higher risk of HBV reactivation than patients who have a positive anti-HBs. An alternative pathway is careful monitoring with HBsAg and HBV DNA every 3 months, with immediate antiviral therapy at the earliest sign of HBV reactivation (appearance of HBsAg or HBV DNA. 1,000 IU/mL), so long as patients and providers are able to adhere to frequent and consistent follow-up during anticancer therapy and for up to 12 months after last anticancer therapy (as delayed HBV reactivation may occur years after cessation of anticancer therapy). If HBV DNA is quantifiable but, 1,000 IU/mL, then repeat testing at monthly intervals may be indicated. Hepatitis flares, presenting as elevated ALT levels, can occur after the discontinuation of antiviral therapy. As such, ALT levels should be monitored frequently, at least monthly for the first 3 months after the cessation of antiviral therapy and every 3 months thereafter (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong). • Patients with past HBV undergoing anticancer therapies that are not clearly associated with a high risk of HBV reactivation (e.g., regimens that do not include anti-CD20 monoclonal antibodies or stem-cell transplantation) should be followed carefully during cancer treatment, with HBsAg and ALT testing every 3 months (with subsequent HBV DNA testing if a hepatitis flare develops), with initiation of antiviral therapy only if HBsAg becomes positive or HBV DNA exceeds 1,000 IU/mL in the setting of a hepatitis flare. Follow-up testing after the cessation of anticancer therapy is likely not necessary (Type of recommendation: informal consensus, benefits outweigh harms; Strength of recommendation: strong).
N/A	**Section 1.2.3** Japan Society of Hepatology guidelines for the management of hepatitis

	C virus infection: 2019 update DIRECT-ACTING ANTIVIRALS *Elbasvir/grazoprevir* • Twelve-week combination therapy with elbasvir plus grazoprevir yields a high SVR rate for genotype 1 chronic hepatitis C and compensated cirrhosis. Rates reported in Japanese phase III studies range from 96.5% to 97.1% (Level 1b). • Baseline characteristics such as cirrhosis, prior treatment history, sex, age, and IL28B polymorphism do not affect efficacy (Level 1b). • Grade 3 or higher increase in AST or ALT was observed in six patients. This increase occurred 8 weeks or later into treatment in five of the six patients (Level 1b). • Presence of NS3 RAVs at baseline does not affect the efficacy of treatment with elbasvir plus grazoprevir (Level 1b). *Glecaprevir/pibrentasvir* • Eight to 12 weeks of treatment with glecaprevir/pibrentasvir yields a high SVR12 rate in genotype 1 and 2 patients with chronic hepatitis C and compensated cirrhosis previously untreated with DAA. Rates reported in Japanese phase III studies range from 98% to 100% (Level 2b). • Twelve weeks of treatment with glecaprevir/pibrentasvir yields an 83.3% SVR12 rate in genotype 3 patients with chronic hepatitis C and compensated cirrhosis (Level 2b). • Twelve weeks of treatment with glecaprevir/pibrentasvir also yields a high SVR12 rate of 93.9% in patients previously treated with DAA therapy (Level 2b, Grade B). • Two patients previously treated with DAA therapy who had NS5A-P32 deletion at baseline (6.3%) both developed treatment failure (Level 2b). **TREATMENT STRATEGY** ➢ *Selection of antivirals for treatment of chronic hepatitis*

	• First-line regimens for genotype 1 patients are sofosbuvir/ledipasvir, elbasvir plus grazoprevir, and glecaprevir/pibrentasvir (Level 1b, Grade A). • First-line regimens for genotype 2 patients are sofosbuvir plus ribavirin, glecaprevir/pibrentasvir, and sofosbuvir/ledipasvir (Level 1b, Grade A). · • Glecaprevir/pibrentasvir and sofosbuvir/ledipasvir are recommended for patients with genotype 1 and 2 mixed infection (Level 5, Grade B). • Non-responders to previous therapy that did not include DAAs are addressed in these guidelines as treatment-naïve patients because IFN-free DAA therapy can be expected to yield a high SVR rate regardless of responsiveness to the previous therapy (Level 2a, Grade A). ➢ *Selection of antivirals for treatment of compensated cirrhosis* • In compensated cirrhosis type C, aggressive IFN-free DAA therapy should be used to prevent hepatocarcinogenesis and hepatic failure (Level 1a, Grade A). • Serious adverse reactions and death were reported in patients with compensated cirrhosis in post marketing studies of IFN-free DAA regimens besides sofosbuvir/velpatasvir. Consequently, patients with compensated cirrhosis who have reduced hepatic functional reserve should be carefully monitored for adverse reactions to antiviral therapy (Level 5, Grade A). • As in patients with chronic hepatitis, the regimens recommended for initial antiviral therapy and retreatment (of patients not previously treated with DAAs) in patients with compensated cirrhosis are sofosbuvir/ledipasvir, elbasvir plus grazoprevir, and glecaprevir/pibrentasvir for genotype 1, and sofosbuvir plus ribavirin, glecaprevir/pibrentasvir (12 weeks), and sofosbuvir/ledipasvir for genotype 2 (Level 1a, Grade A). • Regimens with sofosbuvir are contraindicated in patients with severe renal impairment and patients on dialysis (Grade D). • Sofosbuvir/velpatasvir is not covered by Japanese National Health Insurance for the indication of compensated cirrhosis in patients not previously treated with

	DAAs (Grade D) ➢ Selection of antivirals for retreatment of non-responders to DAA therapy <u>Selection of antivirals for retreatment of non-responders to IFN-based DAA therapy</u> • Sofosbuvir/ledipasvir and glecaprevir/pibrentasvir are recommended for retreatment of non-responders to simeprevir, vaniprevir, or three-drug combination therapy with telaprevir, peg-IFN, and ribavirin. Sofosbuvir plus ribavirin is another recommended regimen for genotype 2 patients who do not respond to three-drug combination therapy with telaprevir, peg-IFN, and ribavirin (Level 2a, Grade A) <u>Retreatment of non-responders to IFN-free DAA therapy</u> • Non-responders to combination therapy with an NS3 protease inhibitor and NS5A inhibitor (daclatasvir plus asunaprevir, ombitasvir/paritaprevir/ritonavir, or elbasvir plus grazoprevir) acquire various mutations other than L31 and Y93, including P32 deletion and A92 mutation. P32 deletion in particular confers high levels of resistance to NS5A inhibitors, and other variants besides P32 deletion could also reduce efficacy (Level 2a). • Therefore, it is recommended that a hepatologist carefully select the retreatment regimen for non-responders to previous DAA therapy with consideration of the results of analysis for RAVs in NS3/4A and NS5A, particularly P32 deletion status (Level 6, Grade A). • A 12-week regimen of glecaprevir/pibrentasvir or 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is the first-line therapy for retreatment of non-responders to previous therapy with a protease inhibitor plus an NS5A inhibitor (daclatasvir plus asunaprevir) (Level 2a, Grade B). • Use of sofosbuvir/ledipasvir in non-responders to daclatasvir plus asunaprevir is not recommended (Grade D). • A 12-week regimen of glecaprevir/pibrentasvir or 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is recommended for non-responders to

	sofosbuvir/ledipasvir (Level 2a, Grade B). • A 12-week regimen of glecaprevir/pibrentasvir or 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is also recommended for non-responders to sofosbuvir plus ribavirin (Level 2a, Grade B). **Antiviral therapy for decompensated cirrhosis** • A 12-week regimen of sofosbuvir/velpatasvir is an option for patients with decompensated cirrhosis (Level 2a, Grade B). • For the time being, the decision to use sofosbuvir/velpatasvir in Child–Pugh grade 3 patients with a Child–Pugh score of 13–15 should be made by a hepatologist, and patients who undergo this treatment should be monitored with the utmost care (Level 2a, Grade C1). • A 24-week regimen of sofosbuvir/velpatasvir plus ribavirin is not covered by Japanese National Health Insuance for patients with decompensated cirrhosis with failed response to DAA therapy, and it should not be used in these patients (Grade D). • A 12-week regimen of sofosbuvir/velpatasvir can be selected for patients with decompensated cirrhosis with failed response to DAA therapy at the discretion of their hepatologist, but its efficacy in this group is unclear (Level 2a, Grade C1) *HEPATITIS B VIRUS COINFECTION* • Hepatitis B virus/HCV coinfection should be treated more aggressively than infection with HCV alone because fibrosis tends to progress more easily and the likelihood of progression to cirrhosis is higher in coinfected patients (Level 2b, Grade A). • As in patients infected with HCV alone, IFN-free DAA therapy is recommended for HBV-coinfected patients (Level 2b, Grade A). • Whether the patient has HBV coinfection, or a history of HBV infection should be confirmed before starting antiviral therapy for HCV (Level 5, Grade A). • Patients with HBV coinfection or who have a history of HBV infection must be

	carefully monitored for HBV reactivation during treatment for HCV (Level 5, Grade A) *COINFECTION WITH HIV* • Interferon-free DAA therapy is the first-line therapy for HIV-coinfected patients (Level 2a, Grade A). • The same regimens used to treat HCV infection alone should be used (Level 2a, Grade C1). • Due care should be taken to avoid drug interactions when selecting DAAs (Level 2a, Grade C1) *GENOTYPES 3–6* • A 12-week regimen of glecaprevir/pibrentasvir is the first-line therapy for chronic hepatitis and compensated cirrhosis in genotype 3 patients (Level 2b, Grade A). • The decision whether to select a 12-week regimen of glecaprevir/pibrentasvir or a 24-week regimen of sofosbuvir plus ribavirin for patients with genotypes 4 through 6 should be made carefully, taking into consideration the risk of carcinogenesis and potential adverse reactions to each treatment based on factors such as progression of liver disease. Waiting to start treatment should also be considered an option (Level 6, Grade C1) *Hepatitis C virus infection and kidney transplantation* • Pretransplant antiviral therapy should be carried out in HCV-infected patients on dialysis scheduled to undergo kidney transplantation because it improves post-transplant renal function, graft survival, and patient survival (Level 2b, Grade A). **Antiviral therapy in patients with renal impairment and patients on dialysis** • Elbasvir plus grazoprevir and glecaprevir/pibrentasvir are recommended for antiviral therapy in genotype 1 patients with hepatitis C who have concurrent severe renal impairment (≥CKD stage 4) (Level 2a, Grade A). • Neither elbasvir plus grazoprevir nor glecaprevir/pibrentasvir requires dose

	adjustment in patients with renal impairment (Level 2b, Grade A). • Glecaprevir/pibrentasvir is recommended for antiviral therapy in genotype 2 patients with hepatitis C who have concurrent severe renal impairment (≥CKD stage 4) (Level 2a, Grade B) *RECURRENCE AFTER LIVER TRANSPLANTATION* • Antiviral therapy is recommended for histologically and serologically proven recurrence of hepatitis C detected by abnormal liver function after liver transplantation in HCV-infected patients, except for those with decompensated cirrhosis after transplantation (Level 2b, Grade A). • Interferon-free DAA therapy can be safely carried out even in patients with proven or possible rejection, bile duct stenosis, or graft vascular stenosis or occlusion (Level 2b, Grade A). • Fibrosing cholestatic hepatitis must be promptly treated with antiviral therapy once it is serologically and histologically proven (Level 2b, Grade A). **Treatment of recurrence after liver transplantation** • Treatment of recurrence of hepatitis C after liver transplantation must be carried out by a medical team with extensive knowledge of immunosuppressive therapy after liver transplantation and of the pathology and treatment of hepatitis C (Level 6, Grade A). • Interferon-free antiviral therapy is preferable for recurrent hepatitis C in patients on immunosuppressive therapy after liver transplantation (Level 2b, Grade A). • First-line regimens are sofosbuvir/ledipasvir and glecaprevir/pibrentasvir due to their low rate of interactions with immunosuppressants and high SVR rate (Level 2b, Grade A). • There is little experience with use of glecaprevir/pibrentasvir and sofosbuvir/ledipasvir for non-responders to combination therapy with daclatasvir plus asunaprevir (Level 5, Grade C1).

	• Glecaprevir/pibrentasvir is recommended for patients with severe renal impairment because sofosbuvir/ledipasvir is contraindicated in these patients (Level 5, Grade B). **Genotype 2** • Glecaprevir/pibrentasvir is highly likely to become the first-line antiviral therapy for recurrent hepatitis C after liver transplantation in genotype 2 patients with no contraindications, such as decompensated cirrhosis (Level 6, Grade C1).
N/A	**Section 1.2.4** KDIGO 2022 Clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis c in chronic kidney disease • Chapter 1: Detection and evaluation of HCV in CKD • Chapter 2: Treatment of HCV infection in patients with CKD • Chapter 3: Preventing HCV transmission in hemodialysis units • Chapter 4: Management of HCV-infected patients before and after kidney transplantation • Chapter 5: Diagnosis and management of kidney diseases associated with HCV infection

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Viral Hepatitis:

Query	Filters	Search Details	Results
(((((Hepatitis C[MeSH Terms]) AND (Hepatitis C[Title/Abstract])) OR (Parenterally-Transmitted Non-A, Non-B Hepatitis[Title/Abstract])) OR (Parenterally Transmitted Non A, Non B Hepatitis[Title/Abstract])) OR (PT-NANBH[Title/Abstract])) OR (Hepatitis, Viral, Non-A, Non-B, Parenterally-Transmitted[Title/Abstract])	Guideline, in the last 5 years	((("hepatitis c"[MeSH Terms] OR "hepacivirus"[MeSH Terms]) AND "hepatitis c"[Title/Abstract]) OR "parenterally transmitted non a non b hepatitis"[Title/Abstract] OR "parenterally transmitted non a non b hepatitis"[Title/Abstract] OR "PT-NANBH"[Title/Abstract] OR ((("hepatitis a"[MeSH Terms] OR "hepatitis a"[All Fields] OR ("Hepatitis"[All Fields] AND "viral"[All Fields]) OR "hepatitis viral"[All Fields]) AND "Non-A"[All Fields] AND "Non-B"[All Fields]) AND "Parenterally-Transmitted"[Title/Abstract])) AND	22

		((y_5[Filter]) AND (guideline[Filter]))	
((Hepatitis B[MeSH Terms]) AND (Hepatitis B[Title/Abstract])) OR (Hepatitis B Virus Infection[Title/Abstract])	Guideline, in the last 5 years	(("hepatitis b"[MeSH Terms] AND "hepatitis b"[Title/Abstract]) OR "hepatitis b virus infection"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	21

Appendix D. Treatment Algorithm

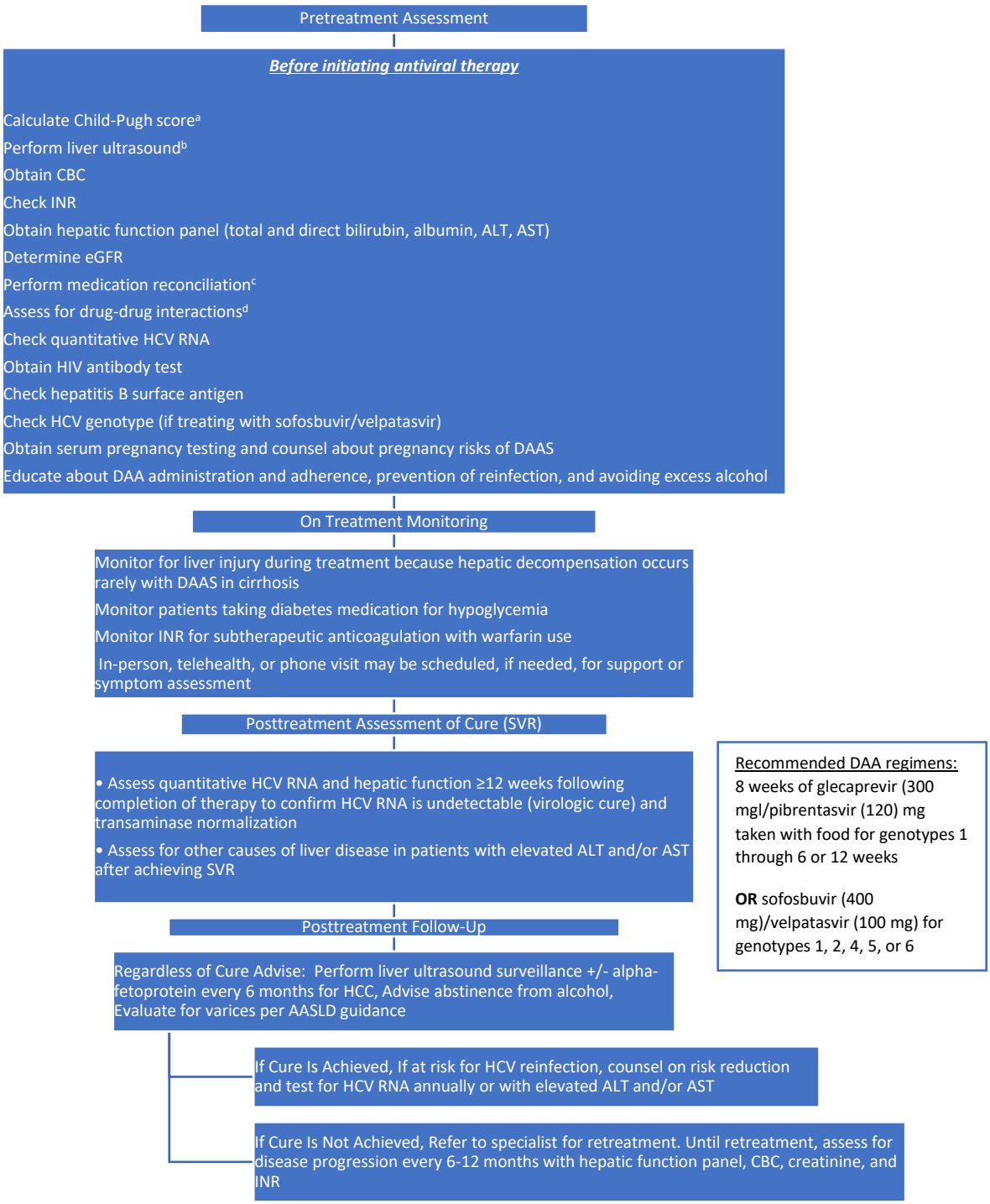

Figure 5. *Simplified algorithm for HCV treatment among HCV treatment-naive adults with compensated cirrhosis*

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; SVR, sustained virologic response.

[a]Child-Pugh score based on presence of ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin <3.5 g/dL, or INR ≥1.7. Patients with a Child-Pugh score ≥7 (ie, Child-Pugh B or C) has decompensated cirrhosis; this simplified treatment approach is not recommended for patients with decompensated cirrhosis. [b]Obtain liver ultrasound within 6 months prior to initiating antiviral treatment to exclude hepatocellular carcinoma and subclinical ascites. This simplified treatment approach is not recommended for patients with hepatocellular carcinoma and/or decompensated cirrhosis. [c]Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. [d]Drug-drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker. [e]Development of jaundice, ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy may suggest hepatic decompensation. Patients should be referred to a specialist if they develop worsening liver blood tests (e.g., total bilirubin, AST, ALT, INR), jaundice, ascites, encephalopathy, or new liver-related symptoms). [f]Ultrasound surveillance for hepatocellular carcinoma (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis, in accordance with AASLD guidance. [g]See AASLD guidance for recommendations regarding the evaluation and management of varices.

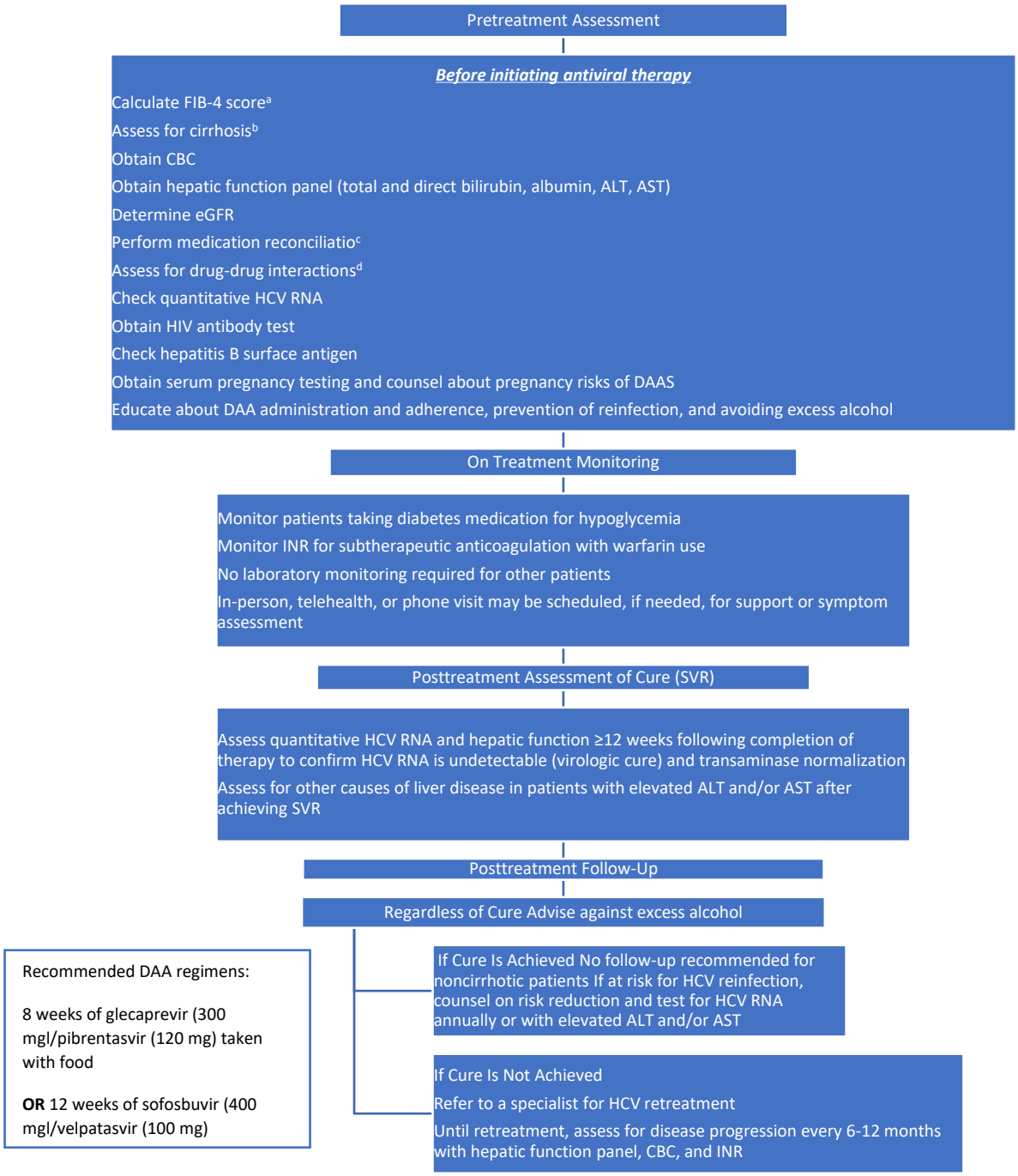

Figure 6. *Simplified algorithm for HCV treatment among HCV treatment-naive adults without cirrhosis.*

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index for liver fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; SVR, sustained virologic response. [a]FIB-4 is a noninvasive measure of hepatic fibrosis that is calculated by: (age [years] x AST [U/L]) (platelet count [109/L) x (ALT1/2 [U/L]). [b]A patient is presumed to

have cirrhosis if they have a FIB-4 score >3.25 or if they have any of the following from a previously performed test: transient elastography indicating cirrhosis (ie, liver stiffness >12.5 kPa), noninvasive serologic test above the pro- prietary cutoff indicating cirrhosis (e.g., FibroSure, enhanced liver fibrosis test), clinical evidence of cirrhosis (e.g., liver nodularity and/or splenomegaly on imaging, platelet count <150 000/mm3), or prior liver biopsy showing cirrhosis. [c]Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. [d]Drug-drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker.

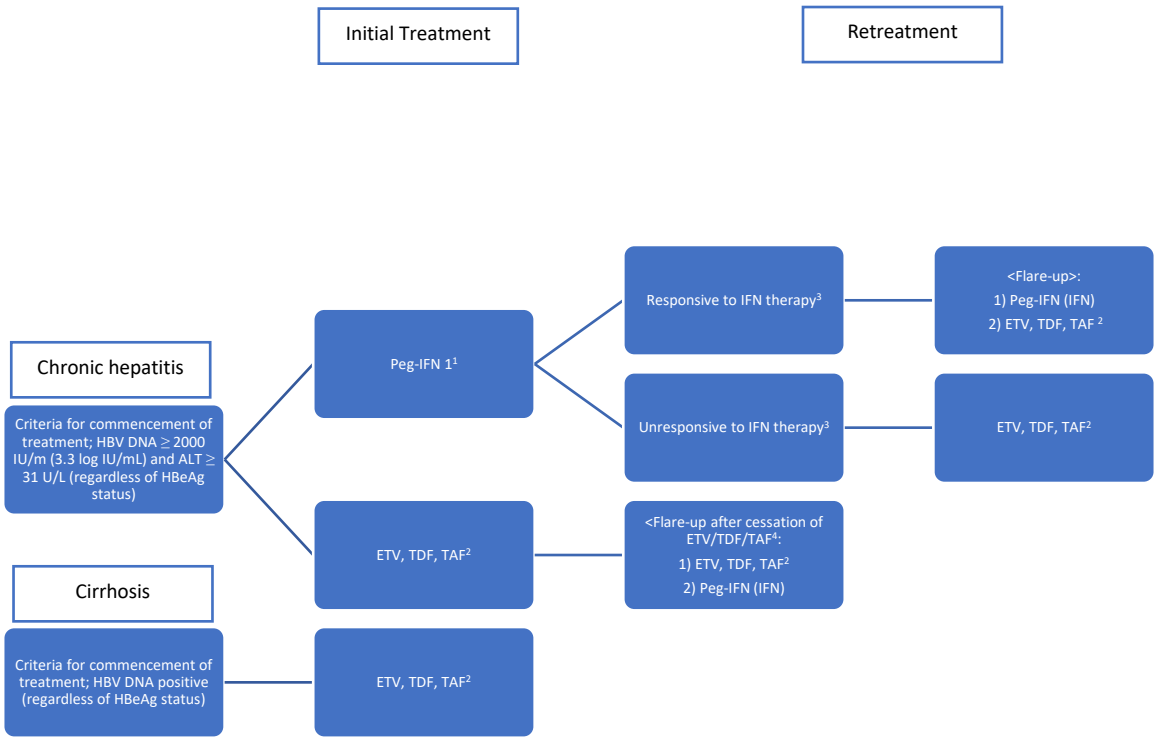

Figure 7. *Basic antiviral treatment protocol for hepatitis B virus (HBV) infection*

[1]Patients should be fully informed of the relatively low rates of hepatitis Be antigen (HBeAg) seroconversion and HBV DNA elimination with this treatment, the difficulty of predicting effectiveness of treatment in advance in individual patients and anticipated adverse reactions. [2]It should be confirmed that the patient is not planning to become pregnant while on this treatment, and the patient should be fully informed of the need to continue treatment for the long term and the risk of resistance mutations. The properties of each drug should be referenced when selecting the nucleos(t)ide analog to be used. [3]The assessment should be made at 24-48 weeks after completing treatment based on alanine transaminase (ALT) normalization, reduced HBV DNA level (reduced hepatitis B surface antigen [HBsAg level]), and HBeAg elimination in HBeAg-positive patients. [4]Criteria for retreatment of recurrence after cessation of entecavir: HBV DNA ≥100 000 IU/mL (5.0 log IU/ mL) or ALT ≥80 U/L. ETV, entecavir; IFN, interferon; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.