

World Journal of *Gastroenterology*

World J Gastroenterol 2021 October 28; 27(40): 6737-7004



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INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; Production Department Director: *Yu-Jie Ma*; Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

October 28, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Management of hepatitis B and C in special population

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Author contributions: Kulkarni AV and Duvvuru NR made the study concept; Kulkarni AV did the initial drafting and DNR critically assessed and edited the manuscript; all authors approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: India

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Abstract

Chronic viral hepatitis is one of the leading causes of cirrhosis worldwide. Chronic hepatitis B is more common in the Asia-Pacific region due to the larger population and lower screening availability. Hepatitis C predominates in the west due to injection drug abuse. The discovery of (oral) direct-acting antiviral agents (DAAs) has changed the landscape of chronic hepatitis C (CHC) management. Nucleos(t)ide analogs (NUCs) have also changed the approach to the treatment of chronic hepatitis B (CHB). Oral NUCs and DAAs have excellent efficacy and patient acceptance as well as a lower risk of resistance. However, certain populations have no robust data and safety and efficacy of such oral drugs is still evolving. In this review, we provide an overview of the management of CHB and CHC in special populations, such as those with chronic kidney disease, pregnant women, healthcare workers, and those undergoing chemo- or immunosuppressive therapy.

Key Words: Chronic kidney disease; Pregnancy; Hepatitis B; Hepatitis C; Health care professionals; Tenofovir

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Core Tip: Hepatitis B and hepatitis C are leading causes of liver disease and pose significant burdens on healthcare and the economy, especially in developing countries. The management of chronic hepatitis B and C in special populations is less known. In this review, we discuss the indications, timing of treatment, and safety of drugs in special populations infected with hepatitis B or C. The special populations discussed herein are those with chronic kidney disease, pregnant women, coinfecting patients, healthcare workers, and patients undergoing chemotherapy.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
 Grade B (Very good): B
 Grade C (Good): 0
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: February 22, 2021

Peer-review started: February 22, 2021

First decision: May 13, 2021

Revised: May 30, 2021

Accepted: September 14, 2021

Article in press: September 14, 2021

Published online: October 28, 2021

P-Reviewer: Ikegami T

S-Editor: Wu YXJ

L-Editor: A

P-Editor: Wu RR



Citation: Kulkarni AV, Duvvuru NR. Management of hepatitis B and C in special population. *World J Gastroenterol* 2021; 27(40): 6861-6873

URL: <https://www.wjgnet.com/1007-9327/full/v27/i40/6861.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i40.6861>

INTRODUCTION

Hepatitis B and C together constitute a major etiology of cirrhosis of the liver, especially in the Asia-Pacific region[1-3]. Nucleos(t)ide analogs and direct-acting antivirals (DAAs) are breakthrough treatments for chronic hepatitis B (CHB) and chronic hepatitis C (CHC), respectively. The management of Hepatitis B and C in an adult population without comorbidities is well known. Special population groups are those who are less often studied, and the drugs cannot be tested in such populations due to ethical reasons. The data on management strategies are still evolving for special populations. Such populations include patients with chronic kidney disease (CKD), patients on hemodialysis (HD), pregnant women, coinfecting patients, healthcare workers, and patients undergoing chemotherapy[4]. In this review, we discuss the indications and safety of antiviral agents in special populations.

CHRONIC KIDNEY DISEASE AND HEMODIALYSIS

Hepatitis B and CKD

Hepatitis B is associated with proteinuria and a higher risk of CKD[5,6]. Hepatitis B virus (HBV)-infected treatment naïve patients have a higher incidence of hematuria, glycosuria, and leukocyturia[7]. Nearly 28%-40% of CHB patients have a glomerular filtration rate (GFR) < 90 mL/min/1.73 m²[7,8]. The prevalence of CKD in CHB patients is 3%-8%, with increasing prevalence with age[9]. This translates into an enormous burden of CKD due to the higher prevalence of CHB in the Asia-Pacific region. The presence of hypertension, diabetes mellitus, and cirrhosis further increases the risk of CKD in CHB[9]. Smoking and physical inactivity can also increase the risk of CKD[10]. The presence of CKD can also increase the risk of HBV infection due to immuno-suppression (rising the risk of viral infections), frequent requirements of blood transfusions (for anemia of chronic disease), and HD. The ideal endpoints of CHB treatment are HBsAg loss and anti-HBs seroconversion, which are challenging to attain. Long-term DNA suppression, normalization of alanine transaminase (ALT), and HBeAg loss (in those who are HBe-positive with or without anti-HBe seroconversion) remain the primary achievable endpoints in the treatment of CHB[4]. The data on the management of CHB in CKD are limited. Since ALT levels are suppressed in CKD (and those on HD), initiating treatment in individuals with HBV DNA > 2000 IU/mL (irrespective of ALT levels) is recommended, especially if > F1 fibrosis is documented either by biopsy or noninvasively[11]. Vaccination remains the best preventive strategy for CKD and HD patients. One milliliter each (containing 20 mcg) should be given intramuscularly (in deltoid muscle) four times at 0, 1 mo, 2 mo and 6 mo. The initial anti-HBs titer should be done two months after the first schedule and then annually thereafter. A booster dose is recommended if the anti-HBs is < 10 IU/mL in CKD patients[12]. Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), and entecavir (ETV) have a low risk of resistance and high efficacy in CKD patients[11,13]. Lamivudine, telbivudine, and adefovir are less effective, nephrotoxic, and are associated with risk of resistance. Interferon- α therapy is less tolerated and is not preferred over NUCs, although the advantage of IFN- α of limited duration therapy cannot be ignored. IFN- α can be used in young patients without cirrhosis, psychosis, or autoimmune disease and GFR > 30 mL/min/1.73 m²[13] (Table 1).

Hepatitis C and CKD

Extrahepatic manifestations are more common in hepatitis C virus (HCV) than HBV [14]. CHC patients may have renal failure even in the absence of liver disease[15]. HCV-infected individuals have a 23% higher risk of developing CKD than non-HCV-infected individuals[16]. Hepatitis C is a leading cause of liver disease among patients with CKD, particularly those on dialysis. The seroprevalence of HCV in the Asian population in patients on dialysis ranges between 1%-18%, with higher a prevalence in

Table 1 Hepatitis B in chronic kidney disease

HBV and CKD	
Prevalence of CKD in HBV patients	8%
Pathogenesis	Direct cytopathic effect of the HBV on cells of the kidney; Glomerular deposition of immune complexes; Virus-induced specific immunological effector mechanisms (specific T lymphocyte or antibody); CHB induced cytokine toxicity on renal tissue
Risk factors	Smoking, diabetes mellitus, hypertension, cirrhosis.
Common type of renal injury	Membranous GN; Membranoproliferative GN; Polyarteritis nodosa; IgA nephropathy
Treatment indication	HBV DNA 2000 IU/mL with or without elevated ALT; Liver biopsy-chronic hepatitis with > F1 fibrosis; If planned for renal transplant, initiate NUCs 2 wk before transplant even if DNA ≤ 2000 IU/mL
Safe drugs	TAF (no dose adjustment till eGFR < 15 mL); ETV and TDF (If GFR > 50: ETV 0.5 mg/d or TDF 300 mg/d; GFR 30-49: ETV 0.5 mg alternate day or TDF 300 mg alternate day; GFR 10-29: ETV 0.5 mg once in 3 d and TDF 300 mg once in 3 d; on HD-ETV 0.5 mg or TDF 300 mg after every dialysis or every 7 d)
Prevention	Regular screening; Vaccination (double dose); Serology should be performed every year, and a booster dose should be given if antibody titers are below 10 mIU/mL.

HBV: Hepatitis B virus; CKD: Chronic kidney disease; CHB: Chronic hepatitis B; NUC: Nucleos(t)ide analogues; TDF: Tenofovir disoproxil fumarate; TAF: Tenofovir alafenamide fumarate; ETV: Entecavir; GFR: Glomerular filtration rate; GN: Glomerulonephritis; ALT: Alanine transaminase.

those on HD than in those on peritoneal dialysis, *i.e.*, $8 \pm 5.5\%$ [17]. Due to a higher number of adverse effects, the use of pegylated IFN plus ribavirin is not recommended [18]. Glecaprevir and pibrentasvir are NS3/4A protease and NS5A inhibitors, respectively, which have pangenotypic activity. Glecaprevir 300 mg and pibrentasvir 120 mg in a fixed-dose combination are the treatments of choice for patients with chronic hepatitis C and stage 4 or 5 CKD (including those on HD) [19,20]. In patients with stage 1-3 CKD, similar dosing of DAA without dose adjustments is recommended. However, glecaprevir and pibrentasvir are not available in all countries. Another option for genotype 1b CHC is grazoprevir, 100 mg and elbasvir, 50 mg for 12 wk, which is still unavailable in many countries [21]. Sofosbuvir-based regimens are also safe in patients with renal impairment and cirrhosis (both decompensated and compensated) [22]. Sofosbuvir 400 mg and velpatasvir 100 mg fixed-dose combination is safe and effective for renal impairment patients (even HD patients) with CHC [23]. In patients with CHC and compensated cirrhosis, the recommended duration is 12 wk, while it is 24 wk for decompensated cirrhosis [20]. Sofosbuvir (400 mg) + ledipasvir (90 mg) also has proven efficacy for Genotype 1b with renal impairment but not on HD [24]. Ribavirin may be added for decompensated cirrhosis patients in combination with sofosbuvir-ledipasvir or in persons with HCV genotype 1a who are receiving treatment with elbasvir-grazoprevir and who have baseline NS5A resistance-associated variants for elbasvir. The dose of ribavirin is 200 mg/d for patients with creatinine clearance < 30 mL/min and 200/400 mg alternate day for patients with creatinine clearance between 30 mL/min and 50 mL/min. American Association for the study of Liver Disease (AASLD)/Infectious Disease Society of America (IDSA) has approved the use of sofosbuvir-velpatasvir; however, in some countries, it is still used as an off-label indication in patients with renal impairment [25]. Strict adherence to infection control protocols during dialysis is the only way to prevent HCV spread [26]. To date, no vaccines have succeeded in preventing chronic HCV infection [27]. Anti-HCV antibodies should be tested before initiation of dialysis and then biannually [28]. Monthly ALT estimation is also recommended for those on dialysis (Table 2).

Pregnancy

Pregnancy is an opportunity to diagnose chronic viral hepatitis. Screening for hepatitis B and C is recommended for all individuals to prevent mother-to-child transmission (MTCT) and prevent transmission to health care professionals [29].

HBV and pregnancy: Nearly 10% of childbearing women in the Asia-Pacific region are infected with HBV [30]. There can be four situations in pregnancy: (1) First time incidentally diagnosed CVH during pregnancy; (2) Individuals are infected and are already on treatment with antiviral therapy; (3) Individuals are under surveillance for CVH and are contemplating pregnancy; and (4) Cirrhosis due to viral hepatitis.

Table 2 Hepatitis C in chronic kidney disease

HCV and CKD	
Prevalence of HCV in CKD patients	10%-14%
Pathogenesis	Pronounced leucocyte infiltration of glomerular capillaries and the precipitation of immunoglobulins, immune complexes/cryoglobulins; Glomerular deposition of HCV protein
Risk factors	Age, male gender, lack of HCV treatment, concomitant HAV/HBV infection; Diabetes mellitus
Common types of renal injury	Membranous GN; Membranoproliferative GN; Essential mixed cryoglobulinemia (type II); IgA nephropathy; Polyarteritis nodosa
Treatment indication	Viremia
Safe drugs	Glecapravir + Pibrentasvir; Sofosbuvir + Velpatasvir; Sofosbuvir + Ledipasvir; Grazoprevir + Elbasvir
Prevention	Regular screening and strict infection control procedures; Effective dialysis machine decontamination

HCV: Hepatitis C virus; CKD: Chronic kidney disease; HAV: Hepatitis A virus; GN: Glomerulonephritis.

The risk of transmission to the newborn is as high as 90% if the mother is HBeAg (e antigen)-positive and 10%-12% if the mother is HBeAg-negative and HBeAb (e antibody)-positive[31]. The risk of transmission is also directly proportional to viral load. The risk of progression to chronicity is nearly 90% if the newborn becomes infected[30]. Hence, preventing MTCT is of utmost importance. Screening for HBsAg is mandatory for all pregnant individuals in the first trimester. It is prudent to test HBeAg, HBeAb, and DNA levels by the end of the second trimester. Treatment is indicated if HBV DNA > 200000 IU/mL or HBsAg levels > 4 Log₁₀ IU/mL. TDF can be started at 24-32 wk of gestation and must be continued for up to 12 wk after delivery[4]. Currently, TAF has no data to support its use during pregnancy. However, an initial review of data on TAF in pregnancy is encouraging[32]. If a woman is infected and is already on treatment with antivirals, the treatment must be continued. TDF is the recommended drug of choice during pregnancy, and if the individual is on ETV or any other antivirals, she should be switched to TDF[29]. If the individual is infected and is contemplating pregnancy, it is advised to postpone the treatment until childbirth unless the woman fulfills CHB treatment criteria (presence of advanced fibrosis or high viral load)[29]. Cirrhosis patients who wish to become pregnant should be counseled about the risk of decompensations during pregnancy. Pregnancy-induced volume disturbances are similar to cirrhosis, *i.e.*, reduction in systemic vascular resistance and rise in blood volume and splanchnic vasodilation, which may exacerbate pre-existing portal hypertension[29]. Newborns of HBV-positive mothers should receive active and passive immunization. The newborn should be tested for HBsAb 3 mo after complete immunization (*i.e.*, > 9 mo of age)[33]. Chronic HBV infection may not influence pregnancy outcomes; however, postpregnancy, there may be a flare of HBV due to immune restoration[29,30]. Breastfeeding is not contraindicated, and cesarean section is not indicated for HBV-infected mothers.

HCV and pregnancy: The prevalence of HCV infection is high in Western countries due to injection drug abuse; however, the Asia-Pacific region has a lower prevalence than the west. Due to the large population, the incidence of HCV is considered high in the Asia-Pacific region. The prevalence of HCV in the Asia-Pacific region is 0.1%-5% [34]. The lack of sensitive universal testing in developing countries is a major hindrance to diagnose HCV infection. Further transient elastography is not recommended in pregnant individuals to stage fibrosis.

HCV can affect pregnancy outcomes. HCV, a cytopathic virus, has been linked to intrahepatic cholestasis of pregnancy[35]. HCV can also downregulate multidrug resistance protein 2 (MRP2), which would induce a failure to transport toxic substances and subsequent defects in bile transport; high estrogen and progesterone levels would further compound this effect on MRP2 during pregnancy[35,36]. HCV-infected women also have a higher risk of preterm birth[37]. In contrast, pregnancy being immunosuppressed does not affect HCV. However, in the postpartum period, women may clear the virus spontaneously due to immune reconstitution and HCV-specific T-cell response development[36]. The pooled incidence of MTCT is 6%[38]. Concomitant human immunodeficiency virus (HIV) infection, high HCV viral load, and injection drug abusers (due to acute hepatitis) are at higher risk of transmitting the infection to the newborn[38,39]. MTCT occurs most often in late stages, either during

intrauterine or intrapartum transmission[29]. There is no added benefit of cesarean section and hence is not indicated for patients with HCV infection to prevent transmission. Breastfeeding is not contraindicated[40]. Prolonged rupture of membranes (> 6 h) and invasive tests such as internal fetal monitoring, amniocentesis, and chorionic villous sampling have the potential risk of transmission[41]. Episiotomy should also be avoided, if possible, in HCV-infected pregnant individuals[41]. None of the DAAs have been approved to be used in pregnancy yet. DAAs are category B drugs in pregnancy. Sofosbuvir with ledipasvir has been shown to be effective and safe in pregnancy[42]. The drug was initiated in the 2nd or early third trimester. There are two trials underway assessing DAAs in pregnancy. The first trial evaluating sofosbuvir plus ledipasvir initiated at 24 wk of gestation (ClinicalTrials.gov Identifier: NCT02683005). Another trial assessing sofosbuvir plus velpatasvir commenced six months postpartum (ClinicalTrials.gov Identifier: NCT03570112). The results of these trials are expected soon. Differences in HBV and HCV management are shown in Table 3.

HEALTHCARE WORKERS

Healthcare workers (HCWs) are attending clinicians, surgeons, employees, students, contractors, public-safety workers, or volunteers whose activities involve contact with patients or with blood or other body fluids from patients in healthcare, laboratory, or public-safety settings[43]. HCWs are at risk of becoming infected and can also be a potential source of transmission to patients. The risk of transmission is, although rare from providers to patients, it is recommended to treat HCWs even with a low viral load (HBV DNA < 1000 IU/mL)[44]. Prior to universal vaccination, the risk of transmission was 5%-13% from HBeAg-positive HCWs to patients and 0.8%-3.5% from HBeAg-negative HCWs to patients[45]. The prevalence of HBV among HCWs ranges between 5%-7% in developing countries[46,47]. The presence of HBV infection does not preclude the HCWs from practicing medicine (dentistry or surgery, or any allied health care work) as per the Centers for Disease control and Prevention (CDC) [44]. The European Association for the Study of the Liver recommends treating HCWs if DNA levels are more than 200 IU/mL[4]. The CDC recommends treating HCWs if DNA >1000 IU/mL and prohibits HCWs from performing exposure-prone procedures if DNA >1000 IU/mL[44]. In contrast, transmission of HCV from HCWs to patients is rare. HCWs are at higher risk of becoming infected by patients. A meta-analysis reported higher odds of infection among HCWs than controls[48]. HCWs with viremia should be treated.

COINFECTION

HBV with HIV: The prevalence of HBV HIV coinfection ranges between 5%-20%, with a higher prevalence among injection drug abusers[49]. The risk of liver-related mortality is twice as high in patients with coinfection as in those with HIV monoinfection[50]. HBV also increases overall mortality and hepatocellular carcinoma in HIV-infected patients[51,52]. Coinfected patients have higher levels of HBV viremia and lower rates of HBeAg clearance[53]. HIV-infected patients are prone to drug-induced liver injuries (especially from nevirapine-based regimens) and hepatitis flares[54]. HBV is reported to increase the risk of acquired immunodeficiency syndrome development, but this report was contraindicated in later studies[55]. All coinfecting patients should be treated with ART (antiretroviral therapy) irrespective of the CD4 count[4,56]. ART should contain tenofovir as a part of the regimen. Lamivudine + emtricitabine and tenofovir (TDF or TAF) should be used for treating coinfecting patients. TDF + lamivudine+ efavirenz or nevirapine combination has a lower attrition rate and is associated with lower mortality in HIV/HBV infected patients[57]. A fixed drug combination of elvitegravir, cobicistat, emtricitabine, and TAF has excellent efficacy in HIV/HBV coinfecting patients[58]. Dolutegravir, emtricitabine and TDF/TAF fixed dose combinations may also be considered for patients with HIV/HBV coinfection[59]. All HBsAg patients should be screened for HIV infection prior to initiating tenofovir-based therapy (to prevent resistance), and HIV-infected patients should be screened for HBsAg prior to initiation of ART[56]. If negative, it is recommended to vaccinate the individual to achieve an anti-HBs of ≥ 10 mIU/mL.

Table 3 Hepatitis B and Hepatitis C in pregnancy

	HBV	HCV
MTCT	90% if HBeAg+; 10% if HBeAg-; Directly proportional to viral load	6%; Higher risk with concomitant HIV infection, higher viral load, IV drug abuse; Higher risk with PROM and CVS
Treatment	TDF is safe; Can be initiated in third trimester	DAAs are not approved; Treat prior to pregnancy or 6 mo postpartum
Effect on pregnancy outcome	None	Preterm birth, ICP
Effect of pregnancy on virus	None	None
Effect of postpartum (immune restoration) on virus	Risk of HBV flares	Higher chance of viral clearance
Timing of transmission	Intrapartum > intrauterine	Intrapartum > intrauterine
C-section for all	Not indicated	Not indicated
Breastfeeding	Not contraindicated	Not contraindicated
Prevention	Active and passive immunization to child prevents 90% of transmission; Failure is nearly 15% if the viral load in mother is > log ₆	None
Confirming the perinatal transmission	Persistence of HBsAg in newborn for > 6 mo	Anti-HCV positive at 18 mo of age HCV RNA positive after 2 mo on 2 different samples
Confirming the protection	Anti-HBs titers at 9 mo	Negative Anti-HCV at 18 mo

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IV: Intravenous; MTCT: Mother-to-child transmission; PROM: Prolonged rupture of membranes; CVS: Chorionic villous sampling; Ag: Antigen; ICP: Intrahepatic cholestasis of pregnancy; C-section: Cesarean section.

HCV and HIV coinfection is common in injection drug abusers. HCV does not alter the natural history of HIV; however, HIV infection significantly alters the natural history of HCV. HIV leads to a rapid worsening of liver disease, shortens survival, and increases the risk of decompensations in HCV-related cirrhosis patients[60]. HIV also hastens fibrosis progression in CHC patients. Spontaneous clearance of HCV is noted in 5%-10% of patients with HIV infection, whereas nearly 15%-30% of HIV noninfected patients clear HCV spontaneously[61]. The indication for treating HCV and HIV is similar to those infected with either alone. However, it is recommended to avoid HCV treatment until the CD4 count > 200/μL in coinfecting patients[62]. Sofosbuvir (400 mg) plus velpatasvir (100 mg) is the recommended drug of choice for HCV for 12 wk in cirrhosis and noncirrhosis[63]. Glecapravir and pibrentasvir are other options for HIV and HCV coinfecting patients for 8 wk (no cirrhosis) or 12 wk (cirrhosis)[20] (Figure 1).

HBV with HCV coinfection: The prevalence of HBV/HCV coinfection varies across the globe. The prevalence of HBV coinfection in HCV-positive individuals ranges from 0.7%-5.8%, and the prevalence of HCV coinfection in HBsAg-positive individuals is between 3.4%-23.0%[64,65]. The presence of HCV coinfection leads to rapid progression of liver disease, fibrosis and accelerates the development of hepatocellular carcinoma (HCC)[65]. Patients with HCV viremia should be treated with DAAs, and those satisfying criteria for treatment for HBV should be treated with NUCs. However, if the patient is HBsAg-positive (not satisfying the treatment criteria for HBV) but requires DAA therapy for HCV, NUCs should be initiated[4]. NUCs should be continued for 12 wk post DAA to prevent reactivation of HBV[4]. HCV core protein strongly inhibits HBV replication, and post DAA lack of HCV core poses a risk for HBV reactivation. The incidence of HBV reactivation is around 12%-14% after HCV treatment[66].

CHEMOTHERAPY AND HEMATOLOGICAL MALIGNANCIES

Patients planned for chemotherapy or immunosuppression should be evaluated for HBV and HCV infection[4]. HBV and HCV are strongly associated with non-Hodgkin's lymphoma[67-69]. Approximately 7%-23% of NHL patients have HBV infection, and 3%-10% harbor HCV infection[69-71]. The risk of HBV reactivation in HBsAg-positive patients undergoing chemotherapy ranges from 26%-53%[72]. HCV

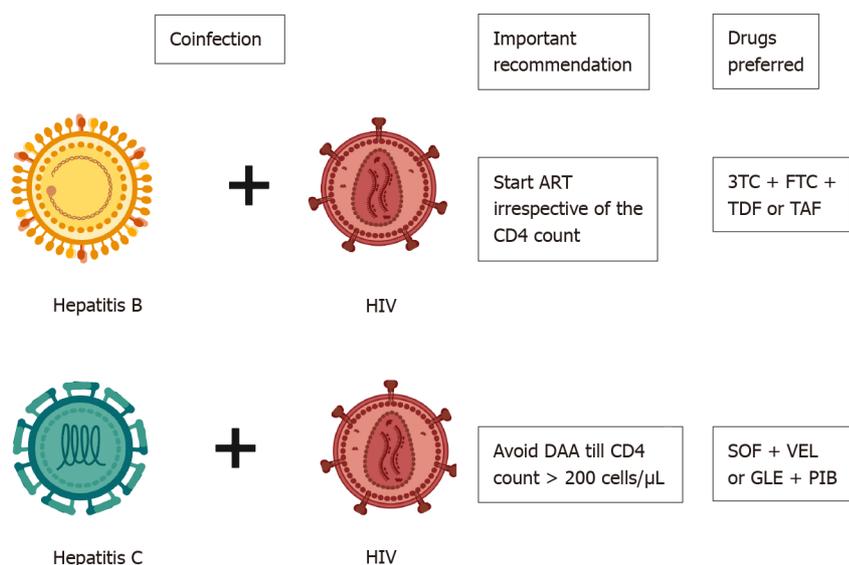


Figure 1 Management of coinfection. Created with biorender.com. HIV: Human immunodeficiency virus; ART: Antiretroviral therapy; 3TC: Lamivudine; FTC: Emtricitabine; TDF: Tenofovir disoproxil fumarate; TAF: Tenofovir alafenamide fumarate; DAA: Directly acting antiviral agents; SOF: Sofosbuvir; VEL: Velpatasvir; GLE: Glecaprevir; PIB: Pibrentasvir.

reactivation is noted in 11% of patients undergoing chemotherapy[73]. If the surface antigen is positive (irrespective of viremia), it is recommended to start NUCs (TDF, TAF, or ETV)[4,72]. Therapy should be continued for 12 mo (18 mo for those on rituximab) after the cessation of immunosuppressive therapy. The stopping rules for those satisfying the standard treatment criteria are the same as those not on immunosuppression.

Patients with HCV viremia should be treated with DAA therapy; however, the timing of therapy is still controversial. If malignancy treatment is deemed urgent, then DAA can be initiated six months after malignancy remission. However, the patient should be monitored for flares. If the malignancy is suspected to be related to the virus itself, then DAAs should be initiated, and viral suppression should be documented prior to chemotherapy initiation[74].

CHILDREN

HBV and children

Chronicity in children is common and depends on the age of acquisition of infection. Perinatally infected patients have a 90% chance of progression to chronicity, while patients infected before 5 years of age have a 25%-50% chance of progression to chronicity. Data on the treatment of the pediatric population are limited. The global prevalence of HBsAg positivity of among children < 5 years of age is 1.3%[75]. The indication for treatment is slightly different from that in the adult population. The presence of cirrhosis (regardless of decompensation status) requires treatment[56]. However, it is recommended to assess the inflammation and stage of fibrosis *via* liver biopsy in all patients prior to therapy. Children with persistently elevated ALT levels (> 1.5 times the upper limit) for ≥ 6 mo who are HBeAg-positive (or ≥ 1 year for HBeAg-negative) with a DNA > 2000 IU/mL and biopsy evidence of moderate to severe necroinflammation or fibrosis require treatment[76]. For patients with a family history of HCC treatment should be initiated even if necroinflammation/fibrosis is mild or absent provided that DNA is > 2000 IU/mL and the ALT levels are elevated [56,76]. TAF (25 mg/d) and ETV (0.015 mg/kg; maximum of 0.5 mg/d) are drugs with high genetic barriers to resistance that are approved for patients aged ≥ 12 years and ≥ 2 years, respectively[75,77]. Last, interferon α -2b (6 million IU/m² thrice weekly) is also approved for children aged ≥ 1 year[75]. For HBeAg-positive children, the drug can be stopped 1 year after HBeAg seroconversion[77]. However, the duration of therapy for HBeAg-negative patients is unknown.

HCV and Children: Nearly 0.15% of the global population aged < 18 years has HCV viremia, which corresponds to 3.26 million (2.07-3.9) children. The seropositivity ranges between 0.2% and 0.4% of the population aged < 18 years[78,79]. Interestingly,

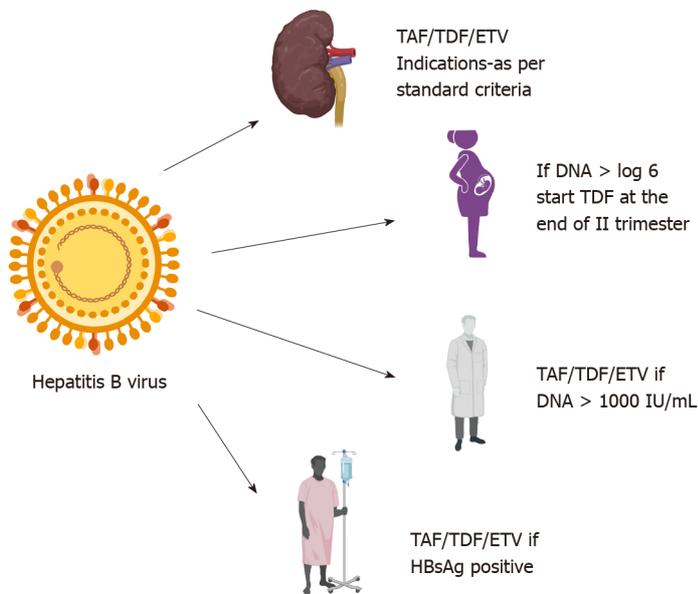


Figure 2 Indications and safety of drugs in special circumstances for hepatitis B. Created with biorender.com. TAF: Tenofovir alafenamide fumarate; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir.

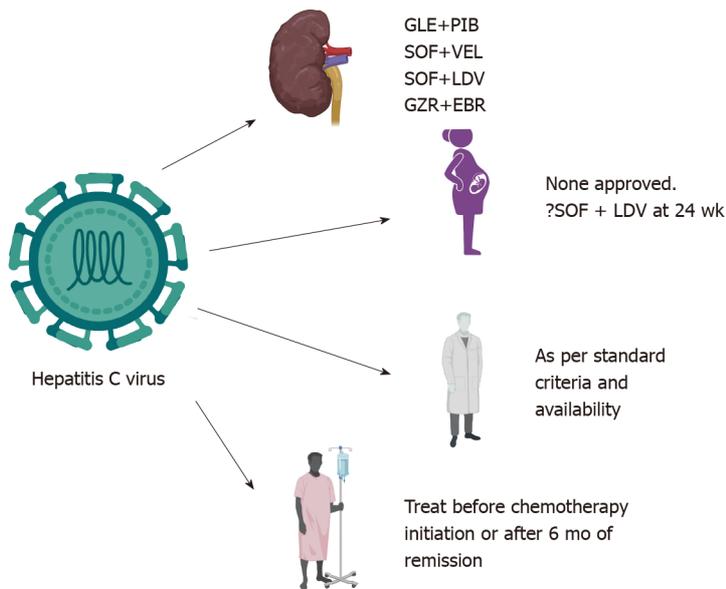


Figure 3 Indications and safety of drugs in special circumstances for hepatitis C. Created with biorender.com. GLE: Glecaprevir; PIB: Pibrentasvir; SOF: Sofosbuvir; VEL: Velpatasvir; LDV: Ledipasvir; GZR: Grazoprevir; EBR: Elbasvir.

25%-40% of children with perinatal transmission spontaneously achieve viral clearance, usually by age 2, and an additional 6%-12% of those with chronic hepatitis C infection may clear the virus before adulthood[80]. Hence, children born to HCV-positive mothers should undergo antibody testing after 18 mo of age[36]. If they are antibody-positive, then their HCV RNA should be assessed after the age of 3 years to confirm the chronicity of infection. The AASLD/IDSA approved drugs widely available are sofosbuvir/Ledipasvir for children aged ≥ 3 years and sofosbuvir/velpatasvir for children aged ≥ 6 years. The doses of these drugs are weight based (sofosbuvir/ledipasvir: < 17 kg: 150 mg/33.75 mg; 17-35 kg: 200 mg/45 mg; ≥ 35 kg: 400 mg/90 mg and sofosbuvir/velpatasvir: 17-30 kg: 200 mg/50 mg; ≥ 30 kg: 400 mg/100 mg) (<https://www.hcvguidelines.org/node/2376/summary>).

CONCLUSION

Although there are recommendations for each of the above conditions described, further research is required in many areas. The role of TAF in pregnancy is unknown. Since newborns have a higher risk of progression to chronicity if infected, is it prudent to treat all the pregnant mothers' pre-emptively needs to be assessed. Furthermore, in countries in which vertical transmission is the most common mode of infection and testing resources (or ability to provide passive immunization to newborns) are limited, is it beneficial to treat all pregnant women infected with HBV needs to be evaluated. There are some data on the safety of concomitant DAA therapy in patients undergoing chemotherapy without any adverse drug-drug interactions[81]. However, prospective trials are still lacking. The most important aspects of managing HBV and HCV in CKD, pregnant patients, HCWs, and immunosuppressed patients are depicted in Figure 2 and 3.

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