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Efficacy of combined antiretroviral therapy (cART) in Hepatitis B and C associated hepatocellular carcinoma (HCC): a narrative review

Abstract

Introduction: HCC is the 3rd leading cancers in the world. Majority of HCC are due to chronic viral hepatitis including HBV, HCV, and HDV. Progression to cirrhosis and HCC in HBV and HCV infection is linked to level of replication and high serum viral DNA load. The use of antiviral agents is an effective strategy of treating HBV- and HCV- associated HCC.

Aim: To assess the effectiveness of combined antiretroviral therapy on HBV and HCV-associated HCC

Method: A narrative review of literature involving RCT and observational studies was performed. Blinding scores was used to evaluate the quality of the studies. This review was informed by one of the author's experience with hepatitis virus in Africa.

Discussion: The five studies were found to be useful in reducing viral load and improving the pathology of HBV- and HCV- associated cirrhosis, HCC, and decompensated liver disease. The combinations are sofosbuvir plus ledipasvir, declatasvir plus asunaprevir, grazoprevir plus elbasvir with or without ribavirin, ombitasvir, paritaprevir, ritonavir plus ribavirin, sofosbuvir plus ribavirin. However, resistance to either drug or both is a problem that needs to be addressed.

Keywords: hepatocellular carcinoma, cART, hepatitis B virus, hepatitis C virus, efficacy, direct-acting antivirals, cirrhosis, chronic infection, sustained virologic response

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer associated mortality worldwide with an estimated 781,631 death per year. It is the 5th and 9th common cancers in men and women, respectively. About 12% of all oncology cases around the world are due to chronic infections from blood borne cancer causing viral pathogens; including hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis delta virus (HDV).[1] HDV is a satellite virus that depends on HBV for its propagation. Liver cancer cases are among the fastest developing cancers around the world based on incidence and deaths. In general, HCC represent approximately 90% of all liver cancer cases with the risk factors being viral infection of which 54% and 31% of all HCCs are due to HBV and HCV, respectively. Cirrhosis, high alcohol intake, obesity, genetic disorders, and exposure to certain chemicals such as aflatoxins are other risk factors.[2] Viral-associated HCC is ubiquitous health issue; however there are differences in the prevalence around the world. HBV- and HDV- associated HCC are commonly found in the low and middle-income developing countries while HCV-associated HCC are common in high-income developed countries.[3]

HBV infection is a small, partially double-stranded DNA virus that causes acute and chronic hepatitis in humans. It is one of the important human viral pathogens with an estimated 2 billion individual infected with approximately >350 million being chronic carriers, approximately 60 million are co-infected with HDV, and about 2.6 million are co-infected with HCV.[4–6] Despite improvement in the management of chronic HBV infection by antiretroviral therapy and universal vaccine, patients with untreated HBV infection are at a 5- to 100-fold higher risk of developing HCC in comparison to healthy individuals.[7] HBV is endemic in developing countries with HBV-associated incidence of HCC projected to increase over several decades due to high prevalence of chronic HBV infection and prolonged latency to the development of HCC. In Sub Saharan Africa and East Asia, HBV is responsible for approximately 90% of new cases[5] and all HCC among children. HCV on the other hand is a single-stranded, positive-sense RNA which is a major risk factor for liver cirrhosis and HCC. Approximately 71 million people are chronically infected with HCV worldwide. Although direct-acting antivirals (DAAs) eliminate HCV infections in patients, the HCV is still regarded as one of the high risk factors for the development of HCC.[8] Prospective studies have shown significant increase in the incidence of HCC among HCV-infected cohorts in comparison to HCV-negative cohorts.[35] Furthermore, HCV infection is associated with 15- to 20-fold increased risk for HCC development when compared to HCV-negative cohort in cross-sectional and case-control studies.[7] Progression to cirrhosis in HBV and HCV infection is significantly dependent on the level of viral replication while serum viral DNA (DNA load ≥10,000 copies/mL) is strong risks predictor of HCC.[29] HBV and HCV are associated with 54% and 31% of new global HCC, respectively. In addition, co-infection with HBV and HCV is associated with increased risk of developing HCC in comparison to single infection with either HBV or HCV[1].

Chronic HBV and HCV infection causes progressive diseases that involve interplay between the viruses and host inflammatory factors which contribute to the development of advanced liver diseases like HCC through inflammation and liver damage. However, HCC can develop in the absence of inflammation.[35] The effective strategy to avert HCC is the prevention of chronic HBV and HCV infections. Hepatitis B vaccine has led to significant reduction in incidence of HCC in endemic areas. However; currently there are no available

vaccines for HCV. Generally, only 40% of patients are diagnosed early while in those with advanced HCC, their option is palliative treatment which is associated with overall poor survival.[35] This means there is the need for effective treatment options that are tolerable. For chronically HBV- and HCV- infected individuals which are major risk factor for the development of HCC, antiviral therapy such as use of nucleos (t) ide analogs can reduce the risk of developing HCC. It can also play a role in reversing liver damage.[33,34] Antiviral monotherapy is associated with high rates of viral resistance and relapse therefore the optimum strategy is combination of antiviral agents. Other forms of preventing viral-associated HCC include vaccinations at birth and hepatitis B immunoglobulin.

In this narrative review, we discuss the efficacy of combined antiretroviral therapy (cART) in treating and preventing HBV- and HCV - associated HCC.

Method

A systematic review of peer review literature involving randomized controlled trials and observational studies was performed using PubMed from 09/10/2023 to 20/11/2023 and updated on 14/12/2023. The Mesh terms utilized were "hepatocellular carcinoma", "hepatitis B virus", "and hepatitis C virus", "combined antiretroviral therapy". Grey publications were identified from the reviewed articles. Blinding scores was used to assess the quality of RCTs while JBI was used for the quality of the observational studies.[11,30] This systematic review was performed based on the standard set by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)[31] and the search strategy was aimed at identifying relevant publications that evaluated the effect of cART interventions for hepatitis-associated HCC.

Searching other sources

The references of the included publications were scanned for grey literature between 09/10/2023 to 20/11/2023. This was updated on 14/12/2023.

Types of studies included and excluded

A range of study designs were considered in this review including randomized control trials (RCT), case-control studies, prospective and retrospective cohort studies. In addition, only studies that utilized combined antiretroviral drugs were included. Excluded studies include not original study (for e.g. reviews and editorials); thesis, books chapters or conference abstracts; prevalence studies; case report and case series that described only therapeutic interventions. Studies that used monotherapy and other therapeutic interventions such as loco regional therapy or chemoembolization with curative intent were also excluded.

Searches were performed without any limitation such as date of publication, language, and status of the publication. For publication in other language apart from English, Google translate would have been used to translate such publication into English

Data collection and analysis

Selection of studies

Using Covidence software, web-based collaboration software that streamlines the production of systematic and other literature reviews (www.covidence.org), the results of the search methods were screened for eligibility via reading the abstracts. The abstracts were coded as either 'yes', 'no' or 'maybe'. The full text of both 'yes' and 'maybe' were retrieved for further evaluation. In the first instance, duplicates were identified and removed followed by scanning of the titles. Some articles were excluded. In the final phase, articles deemed eligible were retrieved and full- text read for inclusion. The selection processes are outlined in Figure 1 as recommended in PRISM statement.[31] It outlines the number of retrieved records and the number of included as well as excluded studies.

Data extraction and management

Eligible studies were assessed as outlined in the study selection (above). The following were extracted: author, title, source, date of publication, and study design.

Evaluation of risk bias and quality of included studies

The quality of the studies were evaluated using Joanna Brigg Institute (JBI) checklist for case-control studies, JBI checklist for cohort studies, and JBI checklist for case series, respectively. These tools rate the quality of selection, measurement, and comparison of studies (https://jbi.global).

Data synthesis

The result of each study was tabulated. Due to the marked difference in the study designs and reported outcome, a narrative synthesis of data was performed as quantitative meta-analysis was deemed not appropriate.

Results & discussion

Search results

The search resulted in 143 records. Of these, 33 records were removed because they were duplicates. Of the 100 remaining, 65 records were removed as they were not relevant based on scanning the titles which left 35 records. The full-texts of these records were retrieved and evaluated of which 30 records were excluded. 5 records met the inclusion criteria. Figure 1 represents the flow chart used in this review.

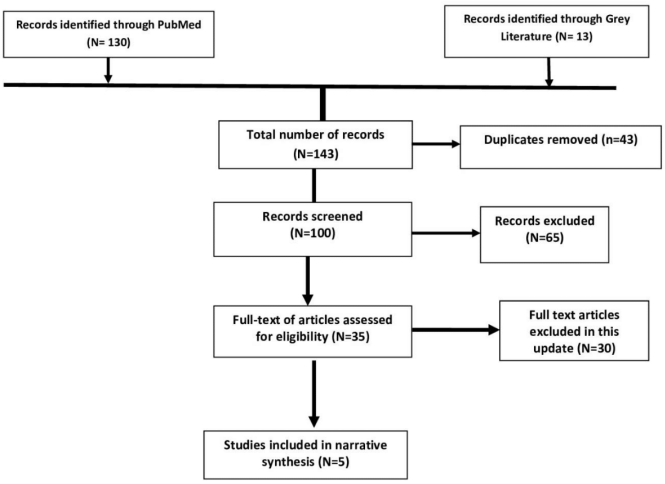

Figure 1 Study flowchart.

Combined antivirals drugs used for HBV- and HCV-associated HCC

Sodosbuvir combined Ledipasvir

Sodosbuvir and ledispasvir (LDV+ SOF) are direct-acting antiviral agents. Sodosbuvir inhibits HCV NS5B RNA-dependent RNA polymerase while ledispasvir is a NS5A inhibitor.[31] The combination of the two antiviral agents was approved for treating HCV genotype 1 infection by the FDA on 10 October, 2014. Sodosbuvir is active against

HCV genotypes 1-4 while ledipasvir is active against HCV genotypes 1a, 1b, 4a, and 5a. It also possesses lower activity against 2a and 3a.[31] The combination of LDV + SOF was evaluated by Kawaoka et al in a case study that involved three patients who attained viral response without any effect on blood concentrations of immunosuppressive agents after sofosbuvir plus ledipasvir treatment. The first patient was a 68 year old female who had HCV-associated liver cirrhosis and failed pegylated-IFN and ribavirin after liver transplant donation. She had been treated with cyclosporine at a dosage of 50mg/day. The second patient was a 63 year old man with HCV-associated liver cirrhosis and HCC who had failed the same combination as the first patient after donor liver transplant. The third patient was a 63 year old female with HCV-associated liver cirrhosis who had been treated with tacrolimus. It was found that alanine aminotransferase level was high after liver transplant while liver biopsy analysis showed active hepatitis or chronic rejection. LDV+SOF were initiated but the treatment was stopped after 4 weeks due to the development of interstitial pneumonia. The serum HCV RNA was negative at the time treatment was discontinued and it remain so 12 weeks after in all the three cases. Combination of SOF + LDV led to remarkable viral response which had little effect on blood levels of immunosuppressive agent for HCV genotype 1 infection after liver transplant.[12] However, the study was stopped due to adverse event. Abaalkhail et al evaluated the safety and efficacy of LDV+SOF in HCV genotype 4 infected patients with cirrhosis or post- liver transplantation involving cohort of patients with cirrhosis before liver transplantation (cohort A) and cohort of post-liver transplantation patients (Cohort B). Patients were given cARTs consisting of (90mg-400mg) once daily for 12-24 weeks with our without ribavirin (RBV). Those with creatinine clearance below 30 were excluded. 111 patients were included consisting of 61 were cirrhotic while 50 were post-liver transplant were treated. 55% of cohort A and 44% of cohort B received RBV. The sustained virologic response (SVR) was 91.8% for cohorts A while cohort B was 86%. No treatment –associated mortality or serious adverse events was reported. RBV dose reduction was observed in 25% without cessation of treatment. The SVR_{12} rates were higher in patients with viral load below 800,000. Data showed that viral load did not have any effect on SVR rate in cohort B while the use of RBV did not have any effect on SVR_{12} and was linked to anemia. LDV+SOF without RBV is an effective and safe treatment approach for patients with HCV genotype 4 infection in pre- and post-liver transplant setting.[13] Barone et al in a prospective observational study compared the SVR at post-treatment week 12 of SOF-LDV in combination with ribavirin for 12 weeks, SOF-LDV alone for 24 weeks. It involved 424 patients of whom 195 were treatment naïve while 229 were treatment-experienced of which 164 were treated for 12 weeks with ribavirin and 260 were administered with SOF-LDV alone for 24 weeks consecutive in HCV genotype 1b-infected patients with cirrhosis. The baseline characteristics of patients who were treated for 12 weeks were significantly different from those treated for 24 weeks based on their age, presence of Child-Pugh class A, lower MELD score and small number of non-responders. In addition, shorter treatment was associated with lower SVR in univariate and multivariate analysis. However, the SVR was not dependent on age, gender, BMI, Child-Pugh class, MELD score or previous ART. Patients who received ribavirin experienced more cases of ascites and headache but less recurrence of HCC and were give more diuretics and cardiopulmonary agents. SOF-LDV plus ribavirin when administered for 12 weeks was less effective than SOF-LDV given alone for 24 weeks.[14] Bourliere et al also reported that LDV-SOF plus ribavirin for 12 weeks and LDV-SOF for 24 weeks provided similar high SVR_{12} rated in previous non-responders with HCV genotype 1 and compensated cirrhosis. This means such short regiment when given with ribavirin could be used to treat treatment-experienced patients with cirrhosis if longer-term treatment is impossible.[15]

Daclatasvir combined Asunaprevir

A novel combination is daclatasvir plus asunaprevir (DCV+ASV). DCV is a NS5A replication complex inhibitor while ASV is a NS3 protease inhibitor. In a phase 3, multicohort study (HALLMARK-DUAL) involving 116 sites in 18 countries between May 11, 2012, and Oct 9, 2013, Manns et al[16] assessed the all-oral therapy with DCV+ASV in patients with genotype 1b infection which included those with unmet needs or cirrhosis, or both. The characteristics of the patients were as follows: adults with chronic HCV genotype 1b infection who were treatment-naïve, previous non-responders to pegylated interferon-α plus ribavirin, and medically ineligible for previously intolerant of or ineligible for and intolerant of pegylated interferon-α plus ribavirin. The treatment-naïve patients were randomly assigned to receive DCV 60 mg once daily plus ASV 100 mg twice daily or given placebo for 12 weeks. Both patients and investigators were blinded to the assigned treatment regimen and HCV RNA results to the end of week 12. The treatment-naïve group was assigned as DVC-ASV arm of the study and continued open-label treatment to the end of week 24 while those assigned to placebo switched to another DSV-ASV study. The non-responders and ineligible, intolerant, or ineligible and intolerant patients were given open-label DSV-ASV for 24 weeks. DSV-ASV arm had SVR in 182 in patients in the treatment-naïve cohort, 162 in the non-responder arm, and 192 in the ineligible, intolerant, or ineligible and intolerant cohort. However, serious adverse events were reported in 12 patients in the treatment-naïve arm, 11 non-responders, and 16 in ineligible, intolerant, or ineligible and intolerant patients. No death was recorded. Grade 3 or 4 laboratory abnormalities were not common. DSV+ASV provided high virological response rate in treatment-naïve, non-responder, and ineligible, intolerant, or ineligible and intolerant patients. It was well tolerated in patients with HCV genotype 1b infection. DSV+ASV can therefore be suggested as an all-oral, IFN-free and ribavirin-free treatment strategy for patients with HCV genotype 1b infection including patients with cirrhosis. Tamori et al assessed the efficacy of DSV+ ASV among 145 patients without resistance-associated substitutions (RASs) at L31 and Y93 in the non-structural protein 5A of HCV genotype 1b. The patients comprised of 49 hepatic cirrhosis and 96 non-cirrhotic patients. They were given 100 mg ASV twice daily plus 60 mg DSV once daily for 24 weeks. SVR_{24} was 96% in the cirrhotic group and 96% in non-cirrhotic group. At the end of treatment, the alanine aminotransferase and AFP levels significantly reduced in cirrhotic patients with SVR. Furthermore, albumin serum level and platelet counts increased significantly. In addition, the rate of HCC recurrence and development was higher in cirrhotic patients than in non-cirrhotic patients. Use of RAS-oriented ASV-DSV therapy can have strong anti-HCV effect in patients with genotype 1b although there is the suggestion that careful management is necessary in patients with cirrhosis.[17] DSV plus twice-daily ASV DUAL therapy is effective for most genotype 1b patients while DSV, ASV plus Pegylated interferon (IFN)/RBV therapy QUAD is effective for nearly all genotype 1a and 1b patients. However neither DUAL nor TRIPLE therapy was effective for genotype 1a patients. Therefore IFN-free regimen including DSV and twice-daily ASV can be tailored for genotype null 1 responders.[18] However, large clinical-epidemiological studies are needed to ascertain association of these combinations with viral hepatitis-associated HCC prevention and treatment.

Grazoprevir combined with elbasvir with /without ribavirin

Grazoprevir is a NS3/4A protease inhibitor while elbasvir is a NS5A inhibitor. In a phase 2, multicentre, randomized controlled trial termed C-WORTHY, these two antiviral agents were assessed for efficacy and safety in patients with HCV mono-infection and HIV/HCV co-infection.[19] The focus of this narrative review is HCV mono-infection. The mono-infection arm consisted of 159 patients who were previously untreated aged 18 years and above with chronic HCV genotype 1 infection and HCV RNA of at least 10 000 IU/mL without evidence of cirrhosis, HCC, or decompensated liver disease. 2 steps were utilized: in the first part, patients were randomly administered grazoprevir (100 mg) combined with elbasvir (20/ 50 mg) with or without ribavirin. 12 weeks post-treatment, SVR_{12} for patients treated with ribavirin was 93% and those without was 98%. Virologic failure was linked with emergence of resistance which was associated with variants to one or both drugs. Grazoprevir when combined with elbasvir with or without ribavirin for 12 weeks in previously untreated HCV-mono-infected patients without cirrhosis achieved SVR12 of 98%. Large observational studies are needed to evaluate this combination in patients with cirrhosis, HCC and decompensated liver disease over long period. Also, prospective interventions for drug resistance for either drug or both are required.

Ombitasvir, Paritaprevir, ritonavir plus ribavirin

AGATE-II part I study was an open-label, partly randomized trial in patients with chronic HCV genotype 4 infection.[20] Patients were either HCV treatment-naïve or treatment-experienced. The study assessed the efficacy and safety of two direct acting antivirals (DAAs) agents: Ombitasvir (an NS5A inhibitor) and paritaprevir (an NS3/4A protease inhibitor) dosed with ritonavir, plus ribavirin for the treatment of chronic HCV infection in Egypt. Ombitasvir, paritaprevir, and ritonavir plus ribavirin for 12 weeks resulted in SVR_{12} in high proportion of patients and were well tolerated among Egyptian patients with HCV genotype 4 infections with or without compensated cirrhosis. Extension of treatment to 24 weeks in patients with cirrhosis was not associated with clinical improvement in patients achieving SVR_{12}. However, some serious adverse events were reported. These included fatigue and headache. Similarly, Sulkowski et al in their study also suggested that shorted duration regimen could be useful in treating HCV genotype 4 patients with compensated cirrhosis. An extended study of AGATE-I included 24 week treatment to fully evaluate treatment duration in patients with chronic HCV genotype 4 infection and compensated cirrhosis reported that extended treatment with ombitasvir/ paritaprevir/ ritonavir and ribavirin to 24 weeks did not have any additional benefit in patients with compensated cirrhosis in terms of treatment efficacy or short-term regression of fibrosis.[28] 93% patients in AGATE-1 part II achieved SVR_{12} which was comparable to patients in AGATE-I where 97% of patients in the 12 week arm and 100% of patients in the 16- week arm achieved SVR12. A subanalysis of AGATE-II study by Waked et al to evaluate the treatment effect in AGATE-II on liver biomarkers in patients with compensated cirrhosis reported that there was a significant improvement in biomarkers of liver injury and liver fibrosis after treatment in the 12-week arm. Similar results were obtained in the 24-week arm. Combinational treatment with ombitasvir, paritaprevir, ritonavir, and ribavirin led to improvement in certain biomarkers of liver synthetic function, injury, and fibrosis which was independent of treatment duration.[30] However, the study design and patient population were limitations of this study therefore large clinical-epidemiological studies are needed which should also evaluate the effect of extended period such as 52 -weeks.

Sofosbuvir combined with ribavirin

Osinusi et al[31] evaluated the safety and efficacy of sofosbuvir as a single DAA administered in combination with weight-based ribavirin (WBR) versus low-dose once daily ribavirin (LDR) for 24 weeks. Efficacy of the treatment was defined by SVR rates 24 weeks post-treatment and viral as well as host factors that are associated with treatment relapse. The study was divided into 2 parts: in the first part, 10 participants with early to moderate liver fibrosis were treated for 24 weeks with 400 mg daily sofosbuvir and WBR of 400 mg qam, 600 mg qpm if < 75 kg or 600 mg bid if > 75 mg. In the second part, 50 eligible participants with all stages of fibrosis which included compensated cirrhosis were randomized via 1:1 allocation ratio to receive 400 mg daily sofosbuvir in combination to either WBR or 600 mg daily LDR in 24 weeks. In the first part, 9 subjects achieved SVR_{24} while in the second part, 7 subjects on WBR and 10 in LDR relapsed leading to SVR_{24} rates of 68% and 48%, respectively. The regimen was well tolerated and safe. Combination of sofosbuvir and WBR was associated with high ratio of sustained virologic response in a population that was considered difficult to treat. Gender (male), advanced liver fibrosis and high baseline HCV RNA are predictors of relapse to this treatment regimen. There were no cases of viral breakthrough in subjects receiving sofosbuvir and ribavirin. A study in New Zealand also reported that sofosbuvir combined with ribavirin for 12 weeks was effective in subjects who were previously not treated and were infected with HCV genotype 1, 2 or 3.[31] However, the overall SVR rates in this study were slightly lower than a study in New Zealand consisting of sofosbuvir plus WBR.[32] In Osinusi et al study, majority of the subjects were of black race with advanced fibrosis while in the New Zealand study, majority were Caucasian, treatment-naïve population.

Discussion and conclusion

The era of DAAs therapy has seen significant improvement in the treatment of chronic hepatitis infection which is associated with the development of HCC and liver damage. DAA has led to increased rates of SVR and excellent safety profile.[34] The following combination was found to be effective in preventing hepatitis-associated HCC: sofosbuvir plus ledipasvir, declatasvir plus asunaprevir, grazoprevir plus elbasvir with or without ribavirin, ombitasvir, paritaprevir, ritonavir plus ribavirin, sofosbuvir plus ribavirin.

Highly effective therapeutic interventions such as cART are associated with suppression of HBV or clearance of HCV which can lead to decreased risk of developing HCC. The effect of DAA for treating viral infections on HVV, tumour recurrence, and progression is inconclusive based on a study in four Spanish referral hospitals that reported an association between DAA treatment and increased risk of *de novo* HCC reoccurrence.[32] This finding was consistent with a study by Conti et al in an Italian retrospective cohort study that consisted of 344 cirrhotic patients without HCC and 59 patients with previous HCC.[33] Several studies did not establish correlation between DAA treatment and increased risk of HCC reoccurrence.[2] Ravi et al in a study reported that after adjusting covariates factors, DAA therapy was not associated with HCC reoccurrence.[34] Of interest are 6 patients developing HCC either during or within 6 months of treatment with DAAs suggesting that DAAs can be associated with HCC occurrence after stopping therapy. This raises question of the duration needed for SVR. Therefore patients on hepatitis-associated HCC receiving DAA regimen should be rigorously monitored and more stringent follow-ups are needed for HCC surveillance because occurrence of liver cancer is not decreased in cirrhotic patients who have been treated

effectively with DAA regimens. In addition, more prospective multi-centre studies are needed to establish strong association between antiviral therapy as well as treatment and prevention of HBV- and HCV- associated HCC. The ultimate aim of antiviral therapy for hepatitis-associated HCC and liver damage should be improving survival thorough preventing liver disease that progress to cirrhosis, liver failure, and HCC. Long-term use of antiviral agents can lead to drug resistant especially when monotherapy is utilized while combination therapy can lead to cross-resistance. Studies are required to elucidate how this can be addressed. Furthermore, more rescue therapy combinations are needed so that patients can be switched to other effective combinations after the development of antiviral resistance. Most of the studies synthesized in this review involved HBV-associated HCC. With an estimated 180 million HCV cases around the globe, chronic HCV patients are underrepresented in clinical studies. Similar, HDV are also associated with HCC and liver damage so future studies should include HDV-associate HCC. More studies should include these populations especially to address the issue of ideal treatment duration in these patients. Period required for utilization of these combinations are inconclusive: should it be 12-weeks or 24-weeks or 52-weeks. AGATE-1 study showed that extended treatment did not add any benefit to patients with compensated cirrhosis. Large cohort studies are needed to evaluate potential benefit or not in other combination. Although single fixed dosed agents are beneficial, fixed dosed combination are the optimum approaches. However, this approach should be able to sustain virologic response that exceeds 95%. Also markers should be used to identify risk factors for HCC development in specific geographical locations since antiviral therapy does not eliminate risk of HCC development in hepatitis-associated HCC. Finally, since antiretroviral agents can prevent the development of HCC, more studies are needed to identify new agents especially for patients with cirrhosis and decompensated liver disease.

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Authors confirm that no aspect of AI and AI-assisted technologies was used while preparing this manuscript.

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Conflicts of interest

The Authors declare that there are no conflicts of interest.

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