Treatment of Hepatitis C Virus in Special Populations (HBV Coinfection, Drug Users, and Prisoners)

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6.1 Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) Coinfection, Their Peculiar Interaction, and Treatment

6.1.1 Introduction

HBV and HCV are responsible for most cases of chronic hepatitis, liver cirrhosis, and HCC in all countries although nonalcoholic steatohepatitis (NASH) is becoming the leading cause in the West after the advent of treatment for HCV [1, 2]. Geographical areas, which have intermediate or high HBV and HCV endemicity, favor occurrence of dual infection. In areas like Spain, Italy, Japan, Taiwan, and Iran, 5–40% of patients with HBV are coinfected with HCV whereas 2–25% of patients with HCV are positive for hepatitis B surface antigen (HbsAg) [3–8]. The high-risk population reported to have high likelihood of the coinfection are intravenous drug users (IVDU), hemodialysis patients, patients undergoing organ transplantation, HIV-infected subjects, men having sex with men, and thalassemic patients.

The viruses have a reciprocal inhibition of viral genomes [1, 6, 9–12]. It results in a dynamic fluctuation of HBV and HCV viremia and also spontaneous clearance of one or both viruses as observed in a 1-year longitudinal study [13]. Sheen et al. reported that HBsAg clearance was 2.5 times higher in HBsAg/anti-HCV-positive cases as against HBV-positive/anti-HCV-negative cases [14].

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However, HBV and HCV coinfection is a serious virological condition associated with more severe forms of liver disease and increased incidence of HCC [15–19]. The advent of second-generation DAAs has changed the face of HCV therapy. With eradication rates reaching 95%, the discussion has now shifted to the behavior of HBV when HCV is eradicated [20–25]. HBV reactivation in dual infections where HBV is inactive is infrequent and this was found in a recent study from the USA, which showed that this could be prevented by HBV screening and adequate HBV treatment [25].

6.1.2 Epidemiology

The incidence of HBV/HCV coinfection is primarily calculated from clinical studies with scarce population-based studies. Clinical studies have shown that 2–10% of patients with chronic HCV have circulating HBsAg [26, 27] and 5–20% of patients with chronic hepatitis B are anti-HCV positive [5]. Occult HBV is observed in patients with chronic HCV where there is no measurable S antigen but there is positive HBV DNA so just measuring HBsAg will miss this diagnosis. In a study from India, 16% of chronic HBV-related liver disease patients had HBV and HCV coinfection at a much higher rate than that reported in a retrospective study from Egypt (0.7% of 3300 patients) [28]. This prevalence was 2.6% in 1950 chronic carriers examined in Turkey [29], and ranged from 7 to 15% in studies performed in Spain [3], Italy [4, 30], Japan, Taiwan [31, 32], and Iran [33]. The rate of HBV/HCV coinfection in HCV chronic carriers was 1.4% in two large surveys performed in the USA whereas in a third US study this rate reached 5.8% [8, 34, 35]. In two large Italian surveys the rate of HBV/HCV coinfection was 1.3% in 2001 and 1.2% in 2014 [36–38].

HBV/HCV coinfection is found frequently in several high-risk population such as IVDU/people who inject drugs (PWID), patients on hemodialysis, patients undergoing organ transplantation, HIV-positive individuals, and beta thalassemia patients [4, 34, 39–41]. The same risk factors were found in a US study where younger age, drug abuse, HIV coinfection, male sex, and comorbidities requiring blood transfusion or blood transfusions were independent risk factors for this coinfection [4].

In a study from New York on the incidence and prevalence of HBV and HCV coinfection, of the 1257 subjects with chronic HCV infection, 773 (61.5%; 95% CI, 58.8–64.2%) had evidence of prior exposure to HBV (HBcAb positive), whereas 73 (5.8%; 95% CI, 4.5–7.1%) had dual infection with HBV (HBsAg positive) [8].

All of the HBcAb-positive subjects were positive for total antibody against the HBV core antigen, but none were HBc immunoglobulin M positive. The prevalence of HBV dual infection was significantly higher in patients enrolled at the VA New York Harbor Healthcare System than those subjects seen at Bellevue Hospital Center (6.5% vs. 3.3% [$P = 0.04$]). Among the 73 patients with HBV/HCV dual infection, 54 (74.0%; 95% CI, 63.7–84.3%) were HBeAg positive. The prevalence of HBV infection was strongly associated with injection drug use and increased as

the number of lifetime sexual partners increased. The prevalence of HBV dual infection differed significantly according to age, race/ethnicity, injection drug use, and number of lifetime sexual partners. HBV dual infection was highest in those 40 years of age, whereas it was lowest in those who were 50–59 years of age. Asians had the highest prevalence of HBV dual infection followed by blacks [8].

6.1.3 Viral Interactions

HBV and HCV interactions have been studied in both in vitro studies and clinical scenarios. In vitro studies have demonstrated that liver cells replicating HBV may be infected by HCV [42] and that HBV and HCV can replicate in the same hepatocytes with no evidence of interference [43], observations confirmed by in vitro co-transfectional studies using full-length HBV genomes and HCV replicons [44]. The coexistence of HBV and HCV in the same hepatocytes has also been observed in liver biopsies of patients with HBV/HCV dual infection [45]. Other in vitro studies provided data in favor of a reciprocal suppression or of viral interference [15, 46] and demonstrated that the HCV "core" protein strongly inhibits HBV replication [47].

It has also been shown that the HCV NS5A protein may influence HBV activity. However, due to contrasting data in terms of inhibition or enhancement of HBV replication at present there is no concrete evidence to arrive at that conclusion [48].

The inverse relationship between the replicative levels of the two viruses suggests direct or indirect viral interference, which has been confirmed in clinical studies [49, 50]. Most cross-sectional studies evaluated the viral load of both viruses at a single checkpoint and reported a dominant role of HCV (high HCV-RNA and low or undetectable HBV-DNA levels), whereas reciprocal interference or even a dominant effect of HBV is described less frequently [5, 46, 51, 52].

Patients with HCV predominance have higher serum IFN γ-induced protein 10 (IP-10) levels and lower HBsAg levels than those with HBV predominance, suggesting that in dual-HBV/HCV infection, HCV suppresses both HBV-DNA and HBsAg synthesis by immune mechanisms [53].

Accordingly, in chimpanzees with HBV chronic infection, acute HCV superinfection suppresses HBV replication, resulting in reduced HBsAg serum values [5, 9, 54, 55] and increased IP-10 values [14]. HBV and HCV interact differently in the innate immune system. HCV activates the IFN type I genes, whereas HBV is unable to activate the antiviral innate immune response within infected hepatocytes since it inhibits the signaling pathways inducing IFN production. As HBV is sensitive to the antiviral effect of type I IFN response, drug-induced HCV eradication in patients with dual-HBV/HCV infection may be followed by a transient HBV reactivation.

Cellular and humoral adaptive immune responses play a central role for the control of both viruses. In HBV infection, major histocompatibility complex (MHC) class II-restricted CD4+ helper T cells generate antibodies to clear circulating virus particles and MHC class I-restricted CD8+ T lymphocytes eliminate the infected cells.

Both innate and adaptive immune responses drive the spontaneous clearance of HCV infection. Innate immunity includes the release of antiviral cytokines and the activation of innate immune cells and the adaptive immune response, which play a crucial role in HCV clearance through HCV-specific CD4 and CD8 T-cell responses. Patients who spontaneously resolve acute HCV infection develop long-lived memory T cells, whereas in persistent infection the number of virus-specific T cells tends to decrease and to have an exhausted phenotype [56, 57].

Bellecave et al. analyzed HBV and HCV replication in the same in vitro model and concluded that the reciprocal replicative suppression observed in coinfected patients was not attributable to direct antiviral interference but, as both viruses are susceptible to the effects of innate and/or adaptive immune responses, it was more likely attributable to cytokines produced by infected cells or by infiltrating T cells present in the in vitro model [44].

Ethnic differences have also been suggested as factors influencing the dominant role of one virus over the other [31], a suggestion that still awaits confirmation. In the middle of the last decade, an Italian multicenter study longitudinally examined a large series of HBsAg/anti-HCV-positive patients [58] where the analysis of HBV-DNA in the liver extracts and observing an increase of serological IgM anti-HBc titer at the time of the abrupt elevation of the aminotransferase levels seem to be the most useful tools in revealing HBV activation as a cause of acute hepatitis in chronic HBsAg carriers; overall the phase of viremia is transient, indicating wide fluctuations in the HBV-DNA and HCV-RNA levels.

6.1.4 Clinical Features and Scenarios

6.1.4.1 Hepatitis C Superinfection

In areas of high prevalence of HBV infection, such as Asia Pacific countries, HCV superinfection in individuals with chronic hepatitis B (CHB) infection is the most common scenario of HBV/HCV coinfection [55, 59]. Two studies from Taiwan showed that a significant proportion of instances of fulminant/sub-fulminant hepatitis in those with CHB infection (HBsAg carriers) could be attributed to HCV superinfection [60, 61]. A recent study by Liaw et al. found that acute HCV infection in patients with CHB infection could be associated with more severe symptoms during the acute phase [59, 62]. More importantly, long-term follow-up analyses showed that those with HCV superinfection had higher cumulative rates of liver cirrhosis (48% at 10 years) and hepatocellular carcinoma (HCC) (32% at 20 years). In a prospective study on Taiwanese patients admitted with acute HCV, the occurrence of fulminant hepatic failure was significantly higher among those with underlying HBV infection than those without (23% vs. 3%, $P < 0.01$) [62].

6.1.4.2 Hepatitis B Superinfection

Superinfection with HBV in patients with chronic hepatitis C (CHC) is less common. Previous case reports indicated that HBV superinfection was associated with acute deterioration of liver function resulting in fulminant hepatitis [63, 64]. In one

study they found that anti-HCV can disappear during HBV superinfection. A small study showed that the incidence of hepatic encephalopathy or ascites formation was higher in HCV patients with HBV superinfection as compared to monoinfection with HBV infection alone (29% vs. 0%, $P < 0.05$) [6, 64].

HBV superinfection in patients with chronic HCV infection was responsible for a strong inhibition of HCV replication, which led to the eradication of HCV in a quarter of the patients. In fact, 6 out of 24 patients who were still HCV-RNA negative 3 years after HBV superinfection remained so even at the 4th year, and at the 5th and 6th years for those tested. At the time of HBV superinfection, the differences distinguishing patients who subsequently eradicated HCV infection from those showing only a temporary inhibition of HCV were a higher prevalence of cases with severe acute hepatitis B and a higher level of serum aminotransferases in the first subgroup, differences that were statistically significant and of clinical relevance. Thus, even though extensive acute hepatocellular necrosis can be life threatening, it may lead to a clearance of chronic HCV infection. The inhibition exerted by HBV superinfection on HCV chronic replication was really impressive in one patient who became HCV-RNA negative. In two studies on patients with fulminant and sub-fulminant hepatitis, HBV/HCV coinfection was responsible for nearly 10% of cases [27, 65]. Apart from acute HBV/HCV coinfection, both HCV superinfection in HBsAg chronic carriers [59] and HBV superinfection in HCV chronic carriers [66] may be followed by chronic HBV/HCV dual infection, a complete recovery from one or both infections, or, less frequently, progression to a fulminant or subfulminant form. A self-limiting, benign course with a complete recovery from one or both infections occurs more frequently in the simultaneous acquisition of HBV/HCV dual infection [67] than HBV or HCV superinfections of HCV or HBV chronic carriers, respectively, who, due to preexisting liver damage, frequently develop significant histological injury. If anti-HCV becomes negative, it is a predictor of HCV eradication soon after acute hepatitis B.

6.1.4.3 Occult HBV Infection in Patients with HCV Infection

Occult HBV infection has frequently been identified in patients with CHC infection. The prevalence of "occult" HBV infection among HCV-infected persons is unknown, but has been detected in as many as 50% of patients in some series [68–70]. From the available evidence we can conclude that occult HBV infection might aggravate the clinical outcome of CHC and contribute to the development of liver cirrhosis and HCC [71–73]. The prevalence of anti-HBc is high among HCV-positive individuals. HCV-positive individuals who are anti-HBc positive have (1) a higher prevalence of cirrhosis; (2) lower HCV-RNA levels; and (3) an impaired ability to respond to interferon treatment [73].

AASLD suggests that all HCV patients who are about to initiate DAA therapy should be assessed for HBV coinfection by checking for the presence of HBsAg, anti-HBs, and anti-HBc. In addition, patients with positive HBsAg should be tested for HBV DNA viral load prior to the initiation of DAA therapy [22].

EASL guidelines suggest that patients should be tested for HB antigen, anti-HBc, and anti-HB antibodies before the initiation of DAA therapy [21]. If HB

antigen is present, or if HBV DNA is detectable in HB antigen-negative, anti-HBc antibody-positive patients ("occult" hepatitis B), then concurrent anti-HBV nucleotide therapy is indicated [21].

6.1.4.4 Fibrosis Progression in HBV/HCV Coinfection

Several studies have compared the histological findings between HBV/HCV coinfection with single viral infection. Zarski et al. found that liver injury was more severe in dual infection than in HCV single infection, piecemeal necrosis and fibrosis, and incidence of liver cirrhosis [46]. Several cross-sectional studies found that HBV/HCV coinfection is associated with a higher prevalence of liver cirrhosis and hepatic decompensation as compared with monoinfection alone. This is yet to be proven in longitudinal studies with sequential liver biopsies to evaluate the rate of fibrosis progression in coinfected subjects [3, 5, 46, 67].

The median necro-inflammatory score was significantly higher in HBV/HCV-coinfected patients than in those with HCV monoinfection (8.0 [IQR, 6.0–10.0] vs. 5.0 [IQR, 4.0–7.0]; (P<0.001). Bini and Perumalswami found that HBV/HCV-coinfected patients had more advanced fibrosis than those with HCV monoinfection in their review of 1245 patients with HCV infection. Stage 3 or 4 fibrosis was present in 84.6% of patients with HBV/HCV infection and 29.9% of those with HCV monoinfection (P<0.001) [8].

6.1.4.5 Impact of HBV/HCV Coinfection on Development of HCC

Coinfection with HBV and HCV has been shown in many case–control studies to correlate with an increased risk of developing HCC [16, 74–76]. Benvegnu et al. conducted a prospective study of 290 cirrhotic patients and found that coinfection (detectable anti-HCV and HBsAg) was an independent predictor for development of HCC by both univariate and multivariate analyses. In this longitudinal study, the incidence of HCC (per 100 person years) was 6.4 in coinfected patients, compared to 2.0 in HBV and 3.7 in HCV-monoinfected patients, while the cumulative risk of developing HCC at 10 years was 45% in coinfected patients, compared with 16% and 28% in HBV- and HCV-monoinfected disease controls [77].

A meta-analysis conducted by Donato et al. enrolled 32 case–control studies to investigate the impact of HBV/HCV coinfection on the development of HCC. This study showed that the relative risk of HCC in coinfected patients (odds ratio [OR] = 165) was significantly higher than HBV (OR = 22.5) and HCV (OR = 17.3) infection alone [17].

6.1.4.6 Chronic Hepatitis B Treatment

The treatment strategies include IFN-alpha-based immunomodulation and nucleos(t)ide analog (NUC)-based inhibition of viral replication [21, 78, 79]. IFN-alpha is a cytokine with direct antiviral, immunomodulatory, and antiproliferative effects, while NUCs suppress HBV synthesis by inhibiting DNA elongation and HBV reverse transcription. These treatments, however, do not eradicate HBV infection since the covalently closed circular DNA (cccDNA) persists in infected hepatocytes and seroconversion to anti-HBs is infrequent [80].

Seven drugs are available for the treatment of CHB in Europe and in the USA:

1. Two formulations of alpha-IFN, conventional and pegylated (Peg-IFN)
2. Three NUCs, lamivudine (LAM), adefovir dipivoxil, and telbivudine, which have lost popularity due to their low genetic barrier
3. Two NUCs with a high genetic barrier, entecavir (ETV) and tenofovir disoproxil fumarate (TDF), which are now widely used and provide long-term virological suppression

In addition, a new formulation of TDF, tenofovir alafenamide (TAF), has been approved in Europe and the USA. This formulation is better tolerated than TDF because of a lower frequency of adverse bone and renal reactions in long-term treatment.

PEG-IFN has the advantage of a finite duration of treatment and of a higher rate of seroconversion to e antigen neg and s antigen neg status, but its use is limited in practice to the HBeAg-positive patients with normal immune reactivity. Both ETV and TDF monotherapies have shown great efficacy, since they obtain long-term viral suppression in 95% of patients, with a regression of liver fibrosis and prevention of cirrhosis [16–19]; however, conversion to HBsAg negative is infrequent and the onset of HCC seems to be preventable only for some treated patients [48, 49].

6.1.4.7 Chronic Hepatitis C Therapy

The treatment of chronic HCV infection has undergone significant changes over the past 25 years. Alpha-IFN was the first pan-genotypic option [21, 81–83], used in combination with ribavirin (RBV) from 1998 to improve treatment efficacy. In 2001–2002, Peg-IFN replaced conventional IFN and, in combination with RBV, further raised the HCV-genotype 1 sustained virological response (SVR) rate to 43% [21]. The SVR rate improved to approximately 70% in 2011 by combining Peg-IFN and RBV with a first-generation DAA, an NS3/4A protease inhibitor telaprevir or boceprevir. Subsequently, simeprevir, a potent inhibitor targeting HCV NS3/4A of HCV-genotype 1 or 4, and sofosbuvir, an NS5B polymerase, was the first all-oral regimen.

At present, IFN-free DAA treatment regimen comprises NS3/4A protease inhibitors, NS5A inhibitors (nucleotides and non-nucleotide analogs), and NS5B polymerase inhibitors, acting, respectively, on different strategic points of HCV replication: self-cleavage, viral replication and assembly, and synthesis of RNA polymerase.

The combination regimens ledipasvir/sofosbuvir and the “3D” regimen (ombitasvir/paritaprevir/ritonavir plus dasabuvir) were approved in 2014 and the combinations daclatasvir plus sofosbuvir and elbasvir/grazoprevir in 2015 and 2016, respectively [84]. The combination therapy with sofosbuvir/velpatasvir is a pan-genotypic DAA treatment approved in June 2016; sofosbuvir/velpatasvir/voxilaprevir in June 2017, and glecaprevir and pibrentasvir in August 2017, provides SVR12 rates in 95–100% for all HCV genotypes [85, 86]. Worthy of note, all DAA combination treatments provided SVR12 rates around or over 95% after an 8–12-week administration both for chronic hepatitis and compensated cirrhotic patients.

6.1.4.8 IFN-Based and DAA-Based Therapy of HCV/HBV Dual Infection

The management of patients with HCV/HBV dual infection includes the eradication of HCV, permanent suppression of HBV replication, resolution of hepatic necroinflammation, prevention of cirrhosis and HCC, and ultimately improved survival [87].

The treatment of HCV/HBV dual infection is complex and should be individualized according to the HBV and HCV loads and liver histology or, in the absence of liver biopsy, the ALT serum concentration or with noninvasive surrogate methods to assess liver fibrosis (Fig. 6.1).

A contemporary active replication of HBV DNA and HCV RNA is infrequent in patients with HBV/HCV dual infection, because in most cases reciprocal viral interference leads to a dominant productive virus that should be identified before deciding treatment.

In cases of both HBV and HCV being active, both infections should be treated with a high genetic barrier NUC for the HBV and with a combination of two or more second-generation DAAs for the HCV infection (Fig. 6.1).

This combination therapy should also be used to treat HBV/HCV cirrhotic patients, independently of the extent of viral production. For patients with HBV/HCV dual infection without cirrhosis, HBV treatment should be applied when HBV infection is in a productive phase, whereas in a nonproductive phase only monitoring for HBV reactivation up to 1 year after the end of DAA therapy (Fig. 6.2).

Anti-HCV treatment is a priority for HBV/HCV patients with HCV predominance (high HCV RNA and absent HBV DNA or below the threshold of treatment), but close monitoring of HBV replication is mandatory for an early diagnosis of HBV reactivation, a phenomenon interpreted as an unbalanced HBV replication due to the eradication of HCV with DAA-based treatment [12, 46, 88, 89]. In this

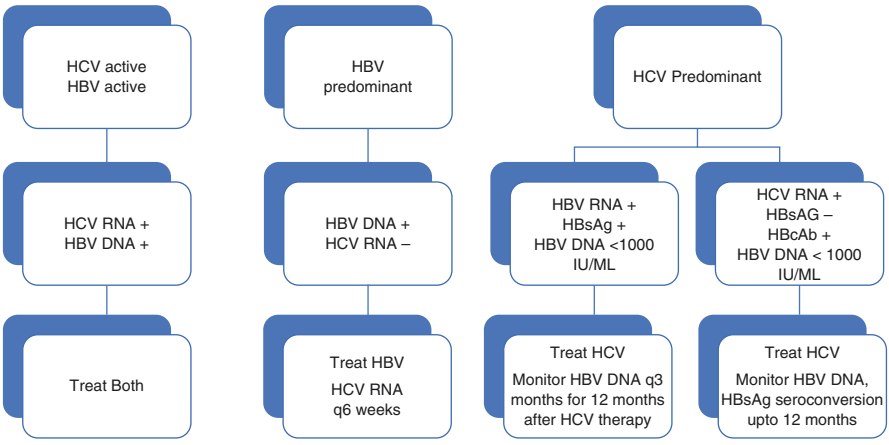

Fig. 6.1 Treatment algorithm based on active HCV and HBV infection and predominance of HCV versus HBV infections

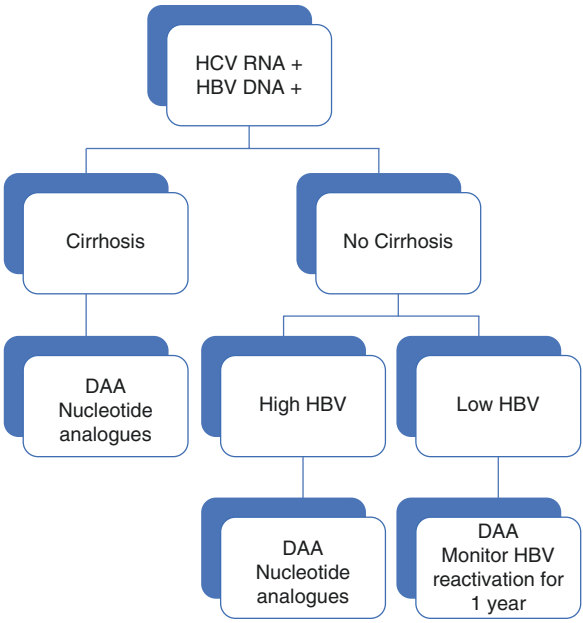

Fig. 6.2 Treatment algorithm for patients who are positive for both HCV RNA and HBV DNA

prospective study, the combination of ledipasvir and sofosbuvir for 12 weeks produced a SVR in 100% of patients with HCV infection who were coinfected with HBV. Most patients had an increase in the level of HBV DNA not associated with signs or symptoms (Fig. 6.3).

Potthoff et al. described HBV reactivation in 31% of 13 HBsAg-positive/HBV DNA-negative patients after anti-HCV treatment with Peg-IFN and RBV observed for up to 48 months [90]. In a study by Liu et al., 36.4% of 77 HBV/HCV patients with undetectable serum HBV DNA at baseline became positive on Peg-IFN/RBV treatment administered to eradicate HCV infection. HBV reactivation was more frequent in patients who achieved SVR (33.3%) than in nonresponders (8.7%) [91].

Belperio et al. retrospectively evaluated 377 HBsAg-positive patients and 7295 with isolated anti-HCV treated with a DAA regimen among 62,920 veterans treated in the USA. An increase in the HBV load of more than 3 log was observed in nine patients, eight known to be HBsAg positive (2.1%) and one with isolated anti-HBc before treatment. An HBV DNA increase of less than 3 log was observed in 12 (3.1%) subjects known to be HBsAg positive before treatment, while a concomitant biochemical reactivation occurred only in three cases [25]. In addition, Chen et al. carried out a systematic review and meta-analysis to compare the rates of HBV reactivation in HBV/HCV-coinfected patients treated with either an IFN-based therapy or a DAA regimen [92]. Of the 779 patients with dual-HBV/HCV infection, the incidence rate of HBV reactivation was similar in those treated with IFN-based treatments (14.5%) or with DAA regimens (12.2%), but it occurred much earlier (within 4–8 weeks of treatment) and was more frequently associated with clinical and/or biochemical abnormalities in those treated with DAAs (12.2% vs. 0%) [26].

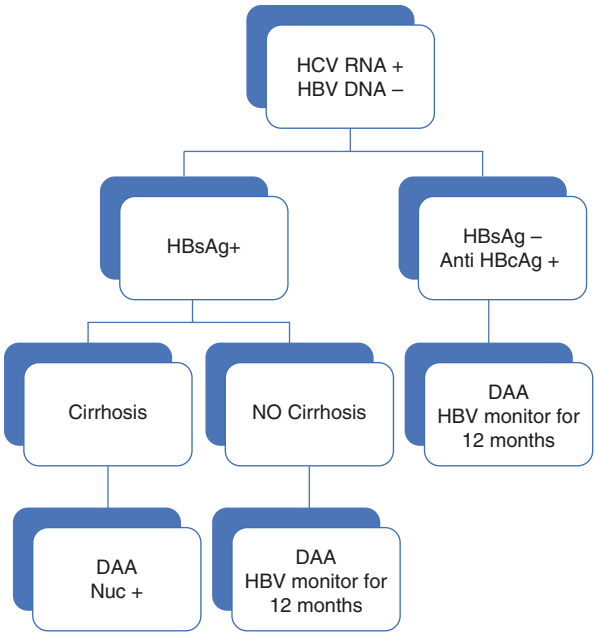

Fig. 6.3 Treatment algorithm for patients with positive hepatitis C RNA but negative HBV DNA

A cohort of 137 consecutive HCV patients treated with IFN-free regimens in routine clinical practice was evaluated. From this cohort, plasma samples of 44 subjects with positive serology for HBV (anti-HBc positive) were tested for HBV DNA levels at baseline and 24 weeks after the end of the treatment. Two of them were HBsAg positive, while the others had signs of a past HBV exposure (HBsAg negative ± HBsAb positive). No reactivation was found in HBcAb-positive and HBsAg-negative subjects. Of the two HBsAg positive, one experienced an increase in HBV DNA levels of ≥2 log10 IU/mL during treatment. However, the reactivation was without clinical impact and, most important, was followed by HBsAg loss [93].

In the US FDA Adverse Event Reporting System (FAERS) on 29 cases of severe HBV reactivation occurring from November 2013 to October 2016 in different countries, predominantly after 4–8 weeks of DAA treatment, the mean age was 60.7 years; 13 were males and 16 females [92]. Of these 29, 2 died of liver failure, 1 underwent liver transplantation, 8 developed clinical symptoms requiring hospitalization in 6, and 10 discontinued DAA treatment. This FAERS report underlines the need to screen for HBsAg, HBsAb, and HBcAb in all patients undergoing treatment for HCV eradication [92].

Eight (28%) of the patients were reported to have a clinical illness that accompanied the increase in HBV DNA levels; of these, 6 (75%) were hospitalized. Reported symptoms included malaise, fatigue, abdominal pain, jaundice, and encephalopathy. Among the 19 patients with minimal information, 5 discontinued DAA treatment because of HBV-R, 2 were hospitalized, and at least 7 were started on

medication to treat HBV infection. More than half of the patients (15 of 29, 52%) eventually received HBV antiviral therapy (tenofovir or entecavir); 8 were specifically noted to have received no treatment for HBV infection. No reports of treatment were found for the remaining 6 patients.

Among the 15 patients who received HBV therapy, treatment was delayed by 7 days or more after diagnosis in at least 7 (47%), 1 of whom died. In addition, a possible delay occurred in at least 7 other patients, 1 of whom required a liver transplant. All patients in the current series were receiving treatment for HCV infection and therefore were presumed to be undergoing monitoring for liver events. Despite provider knowledge of relevant baseline HBV status in these cases, diagnosis and treatment of HBV-R were delayed after an increase in transaminase or HBV DNA levels was noted, with delays ranging from 7 to 60 days to treatment. This indicating close follow-up and initiation of HBV therapy at the earliest can save lives and reduce morbidity [92].

HBsAg-negative/HBcAb-positive patients with HCV infection should also be monitored for HBV reactivation during DAA treatment [82]. In a retrospective study, 5 (5.9%) of 84 patients with a productive HCV infection and previously resolved HBV infection developed HBV reactivation under IFN-free DAA treatment (sofosbuvir/ledipasvir or sofosbuvir/RBV or daclatasvir/asunaprevir) [92], whereas Sulkowski et al. did not find any HBV reactivation in 103 HBsAg-negative/HBcAb-positive patients with HCV infection treated with sofosbuvir/ledipasvir [94].

Patients with HBV predominance (HBV DNA level more than 2000 IU/ml and low or absent HCV RNA) should first be considered for anti-HBV treatment, but monitoring for HCV reactivation consequent to HBV suppression is highly recommended. HBV therapy is highly recommended in patients with cirrhosis regardless of the HBV viral load. HCV reactivation, defined as an increase in viral load to at least 1 log10 IU/mL above the baseline value, is relatively infrequent in NUC treatment for HBV suppression and is usually limited to an asymptomatic virological abnormality associated only in a minority of cases with an abnormal enzymatic profile without.

When tenofovir is the antiviral choice for HBV therapy, the co-administration with ledipasvir/sofosbuvir or with velpatasvir/sofosbuvir should be carefully monitored because of a possible increase in tenofovir serum concentration.

Treatment of anti-HIV-positive patients with chronic hepatitis due to HBV/HCV dual infection is essential to prevent the development of cirrhosis, life-threatening liver failure, and HCC. Early antiretroviral treatment including drugs with anti-HBV and anti-HIV activity is recommended, and tenofovir combined with LAM or emtricitabine should be used to suppress HBV replication.

The DAA-based combination treatments with second- or third-generation DAAs bring about HCV eradication in about 95% of patients both in HCV monoinfection and in dual-HBV/HCV infection, whether anti-HIV positive or anti-HIV negative, with a strong warning to consider the potential drug-to-drug interaction with HIV antiretrovirals.

6.1.5 Conclusions

Treatment of dual-HCV/HBV infection is complex, since it has several aims, such as the eradication of HCV infection, suppression of HBV replication, a reduction in liver damage, and prevention of cirrhosis and HCC. Further complexities come from the numerous virological profiles we can observe in patients with dual-HBV/HCV infection, which reflect alternate phases in viral replication, due in part to the natural course of each infection and in part to reciprocal viral interference.

These complexities oblige us to make individual therapeutic choices based on the HBV and HCV loads and the severity of liver disease, to prevent viral reactivation and disease deterioration.

The favorable news for HBV/HCV-coinfected patients, as well as for HCV-monoinfected patients is that a combination of second-generation DAAs obtains HCV eradication in about 95% of cases and that this treatment is well tolerated and rarely associated with serious adverse reactions. IFN-based treatments are now obsolete as they are inferior to DAA regimens in eradicating HCV infection and have poor tolerability.

HCV eradication, long-term HBV suppression, and consequent prevention of viral reactivation are highly recommended for cirrhotic patients, independently of the viral production, the contemporary administration of a second-generation DAA regimen, and a high genetic barrier NUC being the treatment of choice. The choice of therapy is dictated by careful evaluation of disease progression, HBV and HCV loads, and comorbidities. Several virological profiles can be observed in dual-HBV/HCV chronic infection, which reflect alternate phases in viral replication, due in part to the natural course of each viral infection and in part to the inhibitory effect exerted by one virus on the replication of the other.

A combination therapy with a high genetic barrier NUC and DAA should be administered also to non-cirrhotic patients with both viruses in a productive phase, because treatment of one infection may induce a reactivation of the other.

In cirrhotic patients with HCV predominance, treatment entails the combination of second-generation DAAs associated with high genetic barrier anti-HBV NUCs starting before or together with the DAA regimen regardless of the HBV load because in these cases HBV reactivation may be serious or life threatening even in patients with a low or an absent HBV load. For patients with chronic hepatitis with HCV predominance, treatment with the combination of second-generation DAAs should be associated with close monitoring of the HBV load for an early diagnosis of HBV reactivation. However, in these cases, the range of the rates of HBV reactivation in retrospective or small prospective studies is wide (from 5 to 63%), suggesting the need for multicenter prospective investigations.

How to manage any single case of HBV reactivation is still controversial, since the current international guidelines are of little use in single cases, and as contrasting information comes from case reports [92]. Whatever the clinical presentation of HBV reactivation in patients with dual-HBV/HCV infection treated with DAAs, treatment with high genetic barrier anti-HBV NUCs, close monitoring of the clinical condition, and HBV DNA and ALT serum levels are strongly recommended up

to 1 year after the end of DAA treatment; clinicians should always bear in mind the recent FDA report on the extremely detrimental effect of HBV reactivation in some patients treated with DAAs [92].

Even HBsAg-negative/HBcAb-positive patients with HCV infection may be at risk of HBV reactivation during DAA treatment [82], since ccc DNA persists in the liver after HBsAg clearance and even after seroconversion to anti-HBs. HBV reactivation occurs infrequently in these patients, but monitoring during DAA treatment is advisable with viral loads every 4 weeks during treatment and every 3 months after completion for 1 year [92, 94].

Patients with HBV predominance (HBV DNA serum level more than 2000 IU/ml and low or absent HCV RNA) should be considered for anti-HBV treatment and monitoring for HCV reactivation.

Due to the high potency and high genetic barrier of ETV and tenofovir, they have been used successfully for years to inhibit HBV replication and, consequently, they should be used to impair HBV synthesis in dual-HBV/HCV infection with HBV dominance. Due to the high sensitivity of the modern HCV RNA assays, the possibility that a negative HCV RNA could reflect a previous HCV eradication cannot be excluded and an HBV DNA-positive/HCV RNA-negative pattern might be an HBV monoinfection with serological evidence of a past HCV infection rather than dual-HBV/HCV infection with HBV predominance.

There is little information on HCV reactivation under NUC treatment, an unlikely event that is asymptomatic in most cases; however, monitoring for HCV replication seems appropriate mainly to extend our knowledge in this setting and possibly for treatment decisions to be made.

Combination treatments with two or more second-generation DAAs of different classes achieve HCV eradication in about 95% of patients with HCV monoinfection or dual-HBV/HCV infection; they are well tolerated and rarely responsible for serious adverse effects. Because of reciprocal viral interference, a contemporary HBV and HCV production is infrequent in patients with HBV/HCV dual infection. For patients with both viruses in a productive phase and for patients with cirrhosis, treatment should include a DAA regimen and a high genetic barrier NUC.

In cases with HCV predominance (Fig. 6.3) (HCV RNA positive, HBV DNA negative, or under the treatment threshold), a combination of two or more DAAs should be used to eradicate HCV infection, obtain a reduction in liver damage, and prevent progression to cirrhosis and HCC, unfavorable events more frequent in dual than in single HBV or HCV infection. In patients with a mild or moderate liver disease, close monitoring of the HBV load during DAA treatment is highly recommended for an early diagnosis of HBV reactivation, identifiable by an increase in the HBV load associated with an increase in ALT serum levels in a minority of cases. Instead, in patients with liver cirrhosis, a NUC regimen should be started before or together with DAA treatment because in these cases HBV reactivation may be a serious event.

Overall, close monitoring of the clinical events and the HBV DNA and serum ALT concentration is necessary even in these cases for an early diagnosis of HBV reactivation and to establish the relative therapeutic decisions to be made. Little

information is available on HCV reactivation in HBV/HCV patients with HBV predominance treated with ETV or tenofovir. Fortunately, this reactivation seems to be infrequent and usually limited to an asymptomatic virological abnormality, but monitoring of HCV replication seems appropriate both to extend our knowledge on this point and to intervene without delay. The cost of DAA treatments has limited their use in the past, but the reduction in prices in Western countries, the use of generics, and the sharp decline in prices in developing countries now make a long-term project of global eradication of HCV infection possible.

6.2 HCV Treatment in Injection Drug Users (IDUs)

6.2.1 Introduction

According to the United Nations Office on Drugs and Crime (UNODC), about 275 million people worldwide that is about 5.6% of the global population aged 15–64 years used drugs at least once during 2016 and approximately 450,000 people died as a result of drug used in 2015 [95].

The joint UNODC/WHO/UNAIDS/World Bank estimates the number of IDUs/people who inject drugs (PWID) for 2013 to be 12.19 million (range: 8.48–21.46 million). This corresponds to 0.26% (range 0.18–0.46%) of the adult population aged 15–64. This estimate is based on reports from 93 countries covering 84% of the global population aged 15–64. The highest prevalence of PWID continues to be in Eastern and South-Eastern Europe, where 1.27% of the general population aged 15–64 is estimated to be injecting drugs, which is nearly five times the global average. In terms of actual numbers, the largest proportion resides in East and Southeast Asia, with an estimated 3.15 million PWID. In North America, this number is 2.07 million comprising 17% of the global total number of PWID [95] (Fig. 6.4).

6.2.2 Epidemiology of Hepatitis C in IVDU

Injecting drugs poses the strongest risk for HCV infection in the USA and Europe, with an estimated HCV seroprevalence of 10–70% [96, 97]. While globally about 2.2% of the total population is affected with hepatitis C, this number was remarkably high at 52% in PWID (6.3 million PWID) worldwide in the year 2013 [95]. Countries with large PWID populations have considerably higher number of hepatitis C-infected individuals with 1.93 million PWID in China (2012) and 1.52 million PWID in the USA (2007) [98, 99] (Fig. 6.5).

To add to the woes, a systematic review showed that a high proportion of PWID are unaware of their hepatitis C diagnosis and even among those known to be infected have low chances of getting antiviral treatment. This study reported high level of undiagnosed hepatitis C among PWID with a median of 49% (range: 24–76%) and low proportion of PWID with hepatitis C who started antiviral treatment with a median of 9.5% (range: 1–19%) [100].

Region	Subregion	People who inject drugs					
		Estimated number			Prevalence (percentage)		
		low	best	high	low	best	high
Africa		**330,000**	**1,000,000**	**5,590,000**	**0.05**	**0.16**	**0.91**
America		**2,150,000**	**2,820,000**	**3,970,000**	**0.34**	**0.44**	**0.62**
	North America	1,780,000	2,070,000	2,380,000	0.56	0.65	0.75
	Latin America and the Caribbean	370,000	750,000	1,590,000	0.11	0.23	0.49
Asia		**3,380,000**	**4,560,000**	**6,110,000**	**0.12**	**0.16**	**0.21**
	Central Asia and Transcaucasia	360,000	410,000	470,000	0.66	0.75	0.87
	East and South-East Asia	2,330,000	3,150,000	4,300,000	0.15	0.20	0.27
	South-West Asia	400,000	670,000	940,000	0.22	0.37	0.51
	Near and Middle East	30,000	70,000	130,000	0.03	0.08	0.13
	South Asia	250,000	260,000	260,000	0.03	0.03	0.03
Europe		**2,500,000**	**3,680,000**	**5,630,000**	**0.45**	**0.67**	**1.02**
	Eastern and South-Eastern Europe	1,790,000	2,910,000	4,780,000	0.78	1.27	2.09
	Western and Central Europe	710,000	770,000	850,000	0.22	0.24	0.26
Oceania		**120,000**	**130,000**	**160,000**	**0.49**	**0.53**	**0.66**
GLOBAL		**8,480,000**	**12,190,000**	**21,460,000**	**0.18**	**0.26**	**0.46**

Fig. 6.4 Estimated number and prevalence (percentage) of people who currently inject drugs among the general population aged 15–64, 2013 (source courtesy: www.unodc.org)

6.2.3 Initial Testing in IVDU

Both Centers for Disease Control (CDC) and United States Preventive Services Task Force (USPSTF) recommend a one-time testing in people with a history of injecting drugs and annual HCV testing for persons who inject drugs and following a high-risk episode. These recommendations are also endorsed by American association for the study of liver diseases (AASLD) and European association for the study of the liver (EASL) [21, 22, 101]. An HCV antibody test is recommended for initial HCV testing and if the result is positive active (current) infection should be confirmed by a sensitive HCV RNA test. Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV RNA testing is recommended, as HCV-antibody test will likely be positive. Quantitative HCV RNA testing and HCV genotype testing are recommended before initiation of antiviral regimen. CDC recommends using an FDA-approved quantitative or qualitative nuclear amplification test (NAT) with detection level of 25 IU/mL or lower to detect HCV RNA [22].

It is of utmost importance to educate PWID regarding precautions needed to avoid exposing others to infected blood since persons who use injection drugs are at risk of sharing needles and other contaminated drug injection equipment.

6.2.4 Goal of HCV Treatment in IVDU

The goal of HCV treatment in PWID is similar to general population infected with hepatitis C, which is to reduce all-cause mortality and complications from chronic hepatitis C infection such as end-stage liver disease and hepatocellular carcinoma.

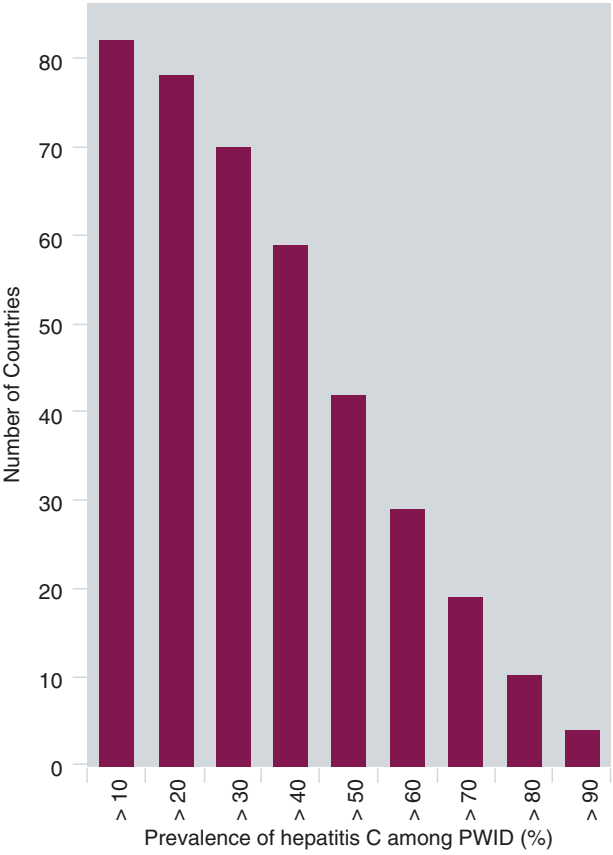

Fig. 6.5 Prevalence of hepatitis C in patients who inject drugs. Courtesy: UNODC. Number of countries, by prevalence of hepatitis C among people who inject drugs. (*Note: Total number of countries with data on hepatitis C prevalence among PWID is 88*)

Treatment is recommended for all with chronic HCV infection, except those with a short life expectancy. The end point of HCV therapy is achieving SVR defined as undetectable viral load at least 12 weeks after completion of therapy. Studies have shown that patients who achieve SVR (cured of HCV) have decrease in liver inflammation and rate of liver fibrosis and necrosis progression [102]. An upward of 70% reduction in the risk of HCC and a 90% reduction in the risk of liver-related mortality and liver transplantation has been reported in patients who achieve SVR [103–105]. In addition, an improvement in portal hypertension and splenomegaly has been reported as well. Apart from liver-related improvements, patients who achieve SVR have several extrahepatic advantages such as reduction in symptoms and mortality from cryoglobulinemic vasculitis, lymphoproliferative disorders, and non-Hodgkin's lymphoma [106–108].

A number of studies have shown that the benefit of SVR is highest when achieved in early stages of fibrosis preferably before Metavir F3. Treatment delay can lead to rapid progression of fibrosis with one study showing survival rate of 92% for those with SVR compared to 88% for those not treated and 82% with failed treatment at 15 years [109]. Another Swiss study showed that there is two and five times higher rates of liver-related mortality for Metavir fibrosis stages F3 and F4, respectively, compared with treating at Metavir stage F2 [110].

6.2.5 Management Strategies

Theoretically, testing and linkage to care combined with treatment of HCV infection in PWID with hepatitis C infection hold great potential in decreasing HCV incidence and prevalence, although there is still lack of strategies to integrate hepatitis C treatment with risk reduction techniques such as opiate substitution therapy, and needle and syringe exchange programs [111].

In an ideal world, treatment of hepatitis C in IVDU should be delivered in a multidisciplinary setting with involvement of social workers and psychotherapist to reduce the risk of reinfection and manage common social and psychiatric comorbidities in this patient population [112–114].

Currently there is strong evidence in support of treating hepatitis C in IVDU by their ability to show adherence to treatment and low rate of reinfection countering arguments that proposed treating IDU with hepatitis C as an absolute contraindication [115–117]. Combining HCV treatment with needle exchange and opioid agonist therapy can help significantly decrease the HCV disease burden [111].

6.2.6 Treatment Strategies

6.2.6.1 Interferon Era

Prior to 2011, pegylated interferon in combination with ribavirin was used for treatment of hepatitis C. Depending on genotype, treatment duration varied from 24 to 48 weeks [118]. The combined treatment of pegylated interferon and ribavirin has been found to be modestly effective in PWID with reported median SVR of 54.3% [119] and ranging from 45 to 70% for genotypes 1 and 4, and 70–80% for genotypes 2 and 3. Unfortunately, it was associated with high rates of adverse effects wherein about half of patients experience flu-like symptoms leading to discontinuation in several patients [118, 120].

A 10-year retrospective study from Ireland showed no significant difference in treatment nonadherence between PWID and nondrug users who were treated with Peg-IFN alpha/RBV (8.4% in PWID vs. 6.8% in non-PWIDs; RR 1.23, CI 0.76–1.99). Additionally, SVR in PWID was similar to non-PWID (64.2% vs. 60.9%, RR 1.05, 95% CI 0.95–1.17) [121]. The multicenter clinical trial (ACTIVATE) assessed adherence and response to directly observed Peg-IFN alpha-2a plus self-administered RBV for 12 (undetectable HCV RNA at 4 weeks) or 24 (detectable HCV RNA at

4 weeks) in patients with genotype 2 and 3 hepatitis C virus infection. Study results showed that overall 76% completed treatment although much higher rate of treatment completion was observed among patients receiving 12 weeks versus 24 weeks of therapy (97% vs. 46%, $P < 0.001$) [122]. These were important findings showing that shortening the duration of therapy can increase treatment completion of PWID. A randomized, open-label, parallel group trial from Canada investigated the efficacy and safety of directly observed Peg-IFN alpha-2a plus self-administered ribavirin for the treatment of hepatitis C virus (HCV) among people with active drug use and found that in patients actively using drugs treated with directly observed therapy SVR is comparable to that seen in clinical trials of nondrug users, and the rate of HCV reinfection is low [123]. A number of other retrospective and prospective studies have now shown comparable adherence of interferon-based regimens and efficacy in persons who inject drugs and those who do not use injected drugs with a meta-analysis of treatment with Peg-IFN, with or without ribavirin showing SVR rates of 37% and 67% for genotypes 1 or 4 and 2 or 3, respectively, in active or recent drug users [115, 119].

6.2.6.2 Follow-Up Studies for Hepatitis C Virus Treated with Peg-IFN/Ribavirin Among IVDU

Traditionally, clinicians have swayed away from treating hepatitis C in active injection drug users. However, as mentioned above several studies have now shown comparable adherence to treatment among PWID and nondrug users. The other concern has been reinfection after successful treatment. In a 5-year follow-up study of 116 patients, 45 patients achieved SVR, of which 27 were IVDU. Of these 27, HCV RNA reappeared in 1 patient compared to 0 of 18 nondrug users ($P = 0.41$) [124]. Aspinall et al. in their systematic review and meta-analysis showed pooled risk of 2.4 (95% CI, 0.9–6.1) per 100 person-years across 5 studies (comprising 131 drug users) examining reinfection [115].

6.2.6.3 DAA Era

With the introduction of direct-acting antivirals (DAAs) in the last few years, the treatment of hepatitis C infection has been revolutionized. Even though DAAs can achieve greater than 90% SVR rates, their efficacy depends primarily on adherence to the treatment raising concerns especially in underprivileged patients such as PWID [125]. Most of our information about the use of DAAs in PWID is based on post hoc analysis of clinical trials on DAAs in the treatment of hepatitis C although data have been conflicting where some studies report poor adherence in active drug users and high rate of reinfection while others show no difference between drug use and adherence.

Petersen et al. found that recent drug abuse was a risk factor for nonadherence [126]. The C-Edge CO-STAR trial estimated the incidence of reinfection after treatment with elbasvir and grazoprevir in patients on opioid substitution therapy and found it to be 10.6 (95% CI 3.42–24.6) per 100 person years from the end of therapy to follow-up week 12 [127]. Other clinical trials have not found the same

association between drug use and nonadherence. Grebely et al. in their post hoc analysis of the phase 3 ION-1 study showed no relation between nonadherence and drug use [128]. In the D3FEAT study, patients with HCV genotype 1 on OST and/or recent injection drug use received a combination of ombitasvir, ritonavir-boosted paritaprevir, and dasabuvir with or without ribavirin for 12 weeks in 87 participants and found that 94% completed 12 weeks of therapy and 91% achieved SVR with no virological failure with no impact of injecting drug use on SVR [129]. The SIMLIFY study that included only IDUs receiving or not receiving OST treated with fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks found adherence of 94% and SVR12 of 94% with one reinfection [130].

More recently there has been few real-world studies that confirmed high treatment completion rates (93–100%) and high SVR rates (80–96%) in patients receiving OST treated with DAAs [131–134]. A retrospective cohort study from 15 hospitals in Belgium consisting of 579 patients (19.9% PWID) found that PWID especially active users are underserved by DAAs. PWID were more infected with genotypes 1a and 3 ($P = 0.001$). There were equal rates of side effects (44.7% vs. 46.6%; $P = 0.847$), similar rates of treatment completion (95.7% vs. 98.1%; $P = 0.244$), and SVR (93.0% vs. 94.8%; $P = 0.430$) between PWID and non-PWID, respectively. Treatment adherence is similar in PWID and the general population, even in patients with active abuse. This study concluded that DAAs were safe and effective in PWID despite the higher prevalence of difficult-to-treat genotypes [135].

A study from Canada in 74 patients on DAAs showed that strong adherence and SVR with DAAs are achievable, with appropriate supports, even in the context of substance use, and complex health/social issues [132]. A recent study by Schitz et al. showed their results of treating 15 IDUs with DAAs under direct observation of a physician or nurse. In this study every patient completed treatment with 100% SVR [136]. The RISE II Study, which evaluated real-world adherence to DAAs among 61 patients receiving OST, found that adherence was comparable to registration trial [137]. Several other prospective studies have shown that DAA treatment of PWID with hepatitis C is safe and effective showing high HCV cure rates regardless of active drug use or opioid agonist therapy [134, 138].

Based on this data, it is recommended that treatment of hepatitis C in drug users with DAAs should be on a case-to-case basis and mere active drug use should not be an absolution contraindication to treatment. These recommendations are also endorsed by EASL guidelines on treatment of hepatitis C [21].

6.2.7 Hepatitis C Prevention Strategies in PWID

Apart from treating hepatitis C in PWID, it is extremely important to prevent transmission of hepatitis C in PWID, which in turn will help decrease the disease burden. Programs such as needle and syringe program and opiate substitution therapy are currently in place to achieve this goal.

6.2.8 Needle and Syringe Program (NSP)

Also known as needle exchange program (NEP) or syringe-exchange program (SEP), this is a service that allows IDUs to obtain hypodermic needles at minimal cost or for free. The primary basis for this is harm reduction that attempts to reduce the risk factors for diseases such as hepatitis and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). An important part of the exchange programs requires users to return used syringes to receive an equal number of new syringes. A study by the WHO found that NSPs substantially reduce the spread of HIV among IDUs in a cost-effective manner [139].

6.2.9 Opiate Substitution Therapy (OST)

Opioid substitution therapy is another program where IDUs who commonly inject an opiate derivative such as heroin are supplied with a replacement drug, a prescribed medicine such as methadone or buprenorphine, which is usually administered orally in a supervised clinical setting. The effectiveness of this therapy is recognized in developed countries although more data is needed from developing countries [139].

The role that NSP and OST play in preventing hepatitis C transmission is controversial. Van der Meer et al. and Turner et al. showed that NSP and OST are key primary interventions that can greatly reduce an individual's HCV risk [104, 140]. However, Vickerman et al. in their model predictions showed that OST and high-coverage NSP are unlikely to achieve meaningful reductions in HCV prevalence among PWID [141]. Model projections have suggested that HCV prevention can be achieved by HCV treatment among PWID. Martin et al. have proposed that it is more cost effective to treat PWID with ongoing transmission risk compared to former PWID [142]. A multicenter UK study that collected data on PWID who were treated and achieved SVR reported that current treatment rates among PWID are unlikely to achieve observable reductions in HCV prevalence over the next 10 years. However, scaling up treatment to 26/1000 PWID annually with IFN-free direct-acting antivirals (DAAs) can achieve an observable absolute reduction in HCV chronic prevalence of at least 15% among PWID [143].

These findings are similar to a previous study by the same author in which mathematical models suggested that upscaling of HCV treatment is required to achieve a reduction in HCV prevalence of more than 40% among PWID over the next decade [111].

Dimova et al. in their systematic review and meta-analysis found that the treatment completion rate among drug users was 83.4% (95% confidence interval [CI], 77.1–88.9%). Among studies that included addiction-treated and -untreated patients during HCV therapy, the higher the proportion of addiction-treated patients, the higher the HCV treatment completion rate ($P < 0.0001$) [144].

6.2.10 Conclusion

Treatment of hepatitis C in IV drug users is a complex phenomenon and best served in a multidisciplinary approach. There is robust data showing evidence in favor of treatment of PWID with comparable rates of adherence and reinfection compared to nondrug users. Even though this data has been for Peg-IFN alpha and ribavirin, there are increasing number of studies showing similar results with newer direct-acting antivirals. DAAs are highly active agents against hepatitis C, which are expected to eradicate hepatitis C in most patients with excellent side effect profile. DAAs in combination with programs such as needle syringe program and opiate substitution therapy will help not only in treatment of affected patients but also in preventing transmission of the virus. PWID during the year preceding treatment should be offered ideally biannual, at least annual testing for reinfection after DAA-induced SVR.

6.3 Treatment of HCV in Prisoners

6.3.1 Epidemiology of HCV in Prisoners

The population of prisoners is growing at a rapid rate compared to general population growth in the world and is currently estimated at about 10.35 million with a large number cycling through this on a yearly basis [145]. There is a high prevalence of viral hepatitis in prisoners compared with the corresponding non-prisoner population particularly among those in prison with a history of injecting drug use with a recent systematic review estimating prevalence of 15.5% for HCV among prisoners in Western Europe and 20.2% in Eastern Europe [146]. Another study from Australia among 253 inmates reported incidence of hepatitis C at 34.2 per 100 person years [147]. An updated study from US prisons reported prevalence of hepatitis C at 17.4% with chronic infection estimated to be between 12 and 35%. A more recent review of hepatitis C infection in prisoners found the prevalence ranging from 3.1 to 38% [148].

6.3.2 Risk Factors for HCV in Prisoners

The high prevalence is likely due to high incidence of psychiatric and social issues, unsafe lifestyle, IVDU, tattooing, promiscuous behavior, violence, and overcrowding that prisoners experience before and during incarceration [149]. The main risk factor in prisoners is IVDU with some studies showing continued use of injection drugs after imprisonment and widespread sharing of infected equipment [150]. The other risk factors for HCV infection were older age and previous incarceration with one study showing HCV prevalence to be 58.5% in inmates over 45 years with an odds ratio of 13.1 [151].

6.3.3 Barriers to Treatment

Unfortunately, there are several barriers in the treatment of hepatitis C in prisoners. Most incarcerated individuals are unaware of their diagnosis. Social taboo, fear of the diagnosis, discrimination, lack of awareness, and lack of medical personal to treat hepatitis C are some of the obstacles that prisoners with hepatitis C face. There is strong evidence now that inmates with chronic hepatitis C can achieve SVR with the same rate as non-incarcerated patients [152]. However, this can only be achieved with collaborative efforts of prison authorities and physicians by implementing strategies for regular screening of prisoners with anti-HCV antibody. According to one study from Australia, approximately 8000 individuals were HCV antibody positive of the 50,000 individuals in custody; however only 313 prisoners received antiviral treatment. This study reported fear of side effects and stigma of being identified to custodial authorities as HCV infected being the common barriers [153].

6.3.4 Treatment

It is highly important to provide HCV testing, treatment, and linkage to care services to people who are incarcerated since over 90% of prisoners will be released back to their communities within a few years of sentencing [154]. Most of the information on treatment of hepatitis C in prisoners comes from cross-sectional studies. A range of 28–69% has been reported regarding SVR with Peg-IFN plus ribavirin combination treatment in prisoners with hepatitis C [155–157]. SVRs were 74% for those not released or transferred, 59% for those transferred and 45% for those released during treatment. This study confirmed that HCV treatment in prison is both feasible and effective with the caveat of poorer outcomes for prisoners who were either released or transferred during therapy [158].

More recently there is highly encouraging data on the use of DAAs in prisoners. This option is attractive for its short duration and possibility of directly observed treatment or supervision. Marco et al. studied all patients treated at the ten prisons of Catalonia and at three public hospitals in the Barcelona area over a 15-month period. Prisoners were significantly younger than non-prisoners, with higher proportions of men drug users. Overall, 98.4% of patients completed treatment with low discontinuation rate although higher in inmates (3.7% vs. 1.2%, $P = 0.003$). SVR was 93.1% in inmates versus 96.5% in noninmates ($P = 0.08$). Virologic failure rates were similar (3.8% vs. 3% in noninmates; $P = 0.60$) [159]. Bartlett et al. recently reported excellent results on their study of 119 patients with chronic HCV infection treated with DAA therapy in an Australian prison with HCV in-prison viremic prevalence declining from 12 to 1% [160]. Apart from high adherence rates and SVR, research has shown that HCV treatment with DAAs is cost effective in prison settings [161].

6.4 Conclusion

Treatment of hepatitis C in prisoners is a multistep approach. Ideally a dedicated team of specialists, diagnostic tests, and treatment procedures should be established at every prison. Due to high effectiveness of DAAs, it should be initiated as early as possible in all eligible patients with the goal of curing and preventing transmission.

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