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REVIEW ARTICLE

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Challenges in Managing Hepatitis C in Unique Populations - Pregnant Women, Children, HIV-Co-Infection

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ABSTRACT

Hepatitis C is a critical infection to manage because it is a significant public health issue with substantial morbidity and mortality. Chronic hepatitis C infection can lead to severe liver complications, including cirrhosis, liver failure, and hepatocellular carcinoma.

The treatment of hepatitis C presents unique challenges in certain populations, including pregnant women, children, and individuals co-infected with HIV. The main worry during pregnancy is the possibility of passing the infection from mother to baby, which requires timely screening, careful monitoring, and treatment to ensure both maternal and fetal health. Limited treatment options during pregnancy further complicate management. In children, hepatitis C is often acquired from the mother and often remains undiagnosed. Early diagnosis and intervention are crucial to prevent long-term liver damage, however, treatment options are available for ages 3 years onwards. Treatment protocols are evolving, but limited options for young children and the variability in disease progression pose significant hurdles. For individuals co-infected with HIV, the management of hepatitis C is complicated by accelerated liver disease progression, co-morbidity, compromised immune functions, and potential drug-drug interactions.

This review highlights the challenges in treatment, rapid diagnostic tests, the critical need for tailored approaches, and multidisciplinary care to address the specific needs of these unique populations. Accessible and affordable treatment will ensure better clinical outcomes and advance the global effort to eliminate hepatitis C as a threat to public health.

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Background

Hepatitis C infection is a viral infection that affects the liver and is associated with a high rate of morbidity and mortality. The virus can cause both short-term (acute) and long-term (chronic) infections, which at times can be life-threatening [1]. The hepatitis C virus infection is one of the leading causes of liver infection, cirrhosis, and carcinoma of liver cells [2].

According to the World Health Organization (WHO), approximately 1.0 million hepatitis C infections occur every year [1] The treatment needs antiviral therapy. The development of direct-acting antiviral drugs has revolutionized the management of hepatitis C infections [3]. Despite the efforts to manage and treat this critical health condition, treatment of a unique strata of the population has faced several challenges. The challenges typically occur due to existing co-morbidity such as Immunodeficient conditions, sexually transmitted diseases, age of the patients, pregnancy, drug resistance, and poor virological response [4].

The infection typically spreads through infected blood. People receiving blood transfusion with hepatitis C virus-infected blood, those receiving unsafe medical treatment, people using injection drugs, and individuals having Human Immunodeficiency Virus (HIV) infections fall under the high-risk category of getting the infection [2]. There has also been an increasing load of hepatitis C infections in pregnant and breastfeeding women. The major concern is the perinatal transmission of infection from infected mothers to fetuses. Infections in children occur from mothers during pregnancy or in their youth or adolescence due to high-risk behavior [5,6].

Most developed countries have joined hands with the WHO in the fight to eliminate hepatitis C infection by the year 2030. However, challenges in managing the infection remain in the unique population group. There are limitations in resources that offer care and treatment to infected pregnant women [6]. In children, the prevalence remains underestimated due to the lack of screening in children for hepatitis C infection [5]. The treatment for children is available from the age of 3, hence treating neonates and infants is also extremely challenging with limited treatment options [5]. Treating Hepatitis C infection in HIV patients is also a major challenge due to the accelerated progression of liver damage and drug-drug interaction with anti-retroviral medication used to treat HIV [7].

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The present review presents a summary of the challenges faced during the treatment of Hepatitis C infection in unique population groups such as pregnant women, children, and HIV-infected people. It also highlights the critical need for tailored approaches and multidisciplinary care to address the specific needs of these unique populations, ensuring optimal outcomes and advancing the global effort to eliminate Hepatitis C as a public health threat.

Tracking the Numbers: Hepatitis C Prevalence

Hepatitis C being one of the major causes of severe liver complications, is unevenly distributed around the globe. The recent WHO report states that about 5 million people in the United States have Hepatitis C. Around 50 million people worldwide are affected with a chronic form of hepatitis C infection [1].

Based on information released by the U.S. Centers for Disease Control and Prevention (CDC), chronic hepatitis C infections were reported highest among persons aged 20–39 years, followed by persons aged 50–70 years. Additionally, deaths from hepatitis C were more than 3 times higher in non-Hispanic American Indians and Alaskan Natives, and approximately 1.7 times more in non-Hispanic Black persons than observed non-Hispanic White persons [8]. With an alarming figure of approximately 242000 deaths due to hepatitis C owing to complications such as liver cirrhosis and carcinoma of liver cells, timely diagnosis with sensitive screening methods can help reduce the striking burden of hepatitis C infection [1].

A global strategy put forth by the WHO aims to eliminate the public health threat of hepatitis C infection by 2030 primarily by reducing new infections by 90% and deaths by 65%. Several countries have joined hands with the WHO for the successful implementation of the same [2]. However, gaps still exist in the estimated reduction in the infections and the actual prevalence. Unique population groups such as pregnant women, children, and HIV co-infection in people face several challenges in diagnosis and treatment. With no vaccine available to treat the condition, the elimination of the virus from a person's body solely depends on identifying and eliminating the virus [9].

Challenges in the Management of Hepatitis C in Pregnancy

Globally around 15 million women belonging to the childbearing age of 15 to 49 years have chronic Hepatitis C virus infection and this typically accounts for around 21% of worldwide hepatitis C infections [6]. The increasing rate of hepatitis C infection in women of childbearing age is also a cause of concern. Active hepatitis C infection during pregnancy is often associated with the blockade of bile flow from the liver to the small intestine and has a higher risk of transmission to the fetus from the infected mother. In the U.S., the prevalence of hepatitis C has been well studied by researchers in detail and has been largely linked to injection drug use thereby changing the landscape of the infection and approaches for its diagnosis and treatment. According to the CDC, the rate of hepatitis C infection among women giving birth increased by over four hundred percent from 8 to 41 per ten thousand deliveries during the year 2000 to 2015. One of the adverse outcomes associated with pregnant women with hepatitis C infection is preterm birth and late neonatal death. Hence in the strategy of elimination of hepatitis C by 2030, it is imperative to focus on diagnosing and treating the infection in pregnant women as it will also restrict further transmission to the fetus [10].

The major challenge in hepatitis C infection in pregnant women primarily lies in the early detection of the infection in the women. A systematic review studied research work that included pregnant women with high risks such as repeated miscarriages or abortions, multiple partners, drug abuse, and sexually transmitted coinfection. It was observed that the risk-based screening of pregnant women failed to diagnose cases of hepatitis C virus. The researchers therefore urged to make the screening of pregnant women universal rather than restricting it to a risk-based group [11].

With its unique characteristics and the liver complications that the hepatitis C virus causes, it is necessary to monitor the severity of liver disease in pregnant women and consider the risk of transmission to the fetus. It has been observed that pregnant women having chronic hepatitis C infection have reportedly more severe adverse outcomes during pregnancy. Moreover, the other challenge is the monitoring of the fetus for the infection. The procedure being invasive, the rate of prolonged rupture of the membrane is reported in about 5% of the mother-to-child transmission cases [12].

Treating pregnant women with direct antiviral agents for hepatitis C infection is also one of the many challenges faced while managing the condition. According to the current recommendations, the treatment of pregnant women can be given on a one-to-one basis after the patient-physician discussion regarding the risk-to-benefit ratio in the particular case. An ideal situation would be treating women for hepatitis infection before pregnancy. However, if the condition is diagnosed during pregnancy, then the women should be given proper counseling about the treatment. It was also observed in a study that most pregnant women were ready to take directly acting antiviral agents considering that it would prevent mother-to-fetus transmission [10,13].

In addition to the success of directly acting antiviral agents, currently the pan-genotypic agents have also shown promising results in treating hepatitis C infection. However, the challenge lies in the entire healthcare system and also at the level of individual clinicians providing the treatment and patients. The other challenges faced in managing the treatment in pregnant women include inadequate screening facilities, ill-equipped laboratories for correct diagnosis of the condition before treatment, and restricted access to treatment [14]. Moreover challenges are also being faced at the level of the local health-care agencies working to give the treatment to the pregnant women and socioeconomic challenges [12]. There is a need to change certain treatment provider plans so that there is a reduction in disparities in the ethnic groups and races seeking medical help for Hepatitis C infection in the U.S. Understanding the disparities will be a step forward in the elimination of the virus [15].

The barriers and challenges to the effective management of hepatitis C infection in women during their pregnancy can be overcome with some interventions and different levels such as the treatment provider level, working system level, and patient level. If all three work hand in hand, managing hepatitis Infection will be easier [14]. Including all adults in the screening program and all pregnant women in the screening can help diagnose the

cases in pregnant women. The problem is that almost in every research work anywhere in the world, pregnant women are excluded from the clinical study part and hence diagnosis and treatment become even more difficult. Earlier, pregnant women were excluded from clinical trials to ensure the safety and well-being of both the mother and the unborn child and to avoid potential risks to the fetus. However, recent ethical guidelines emphasize the importance of including pregnant women in research to gather data that is relevant to them. These guidelines ensure that pregnant women are fully informed about the risks and benefits of participating in a trial and that their consent is obtained voluntarily. The goal is to balance the need for scientific knowledge with the protection of vulnerable populations.

There are very limited studies on pregnant women with hepatitis C. One study in Egypt on women of child-bearing age reported accidental consumption of sofosbuvir and daclatasvir around the time they conceive a baby [16]. Seven women stopped the treatment before the 9th week of their pregnancy. Fortunately, there were no adverse outcomes, one baby tested positive for hepatitis C at 18 months but had a low viral load [16]. A study from India included pregnant women (n=15) who had undergone treatment for hepatitis C after completing their first trimester of pregnancy to prevent transmission to their infants [17]. Another example is of a phase I trial in the U.S. in the second trimester of pregnancy of 8 women [18]. It was a pharmacokinetic study that reported the safety of sofosbuvir and ledipasvir in pregnancy. All these are studies with a limited number of participants. For validation of the data obtained, more studies in large populations at multicentre locations are required. Currently, a phase 4 clinical trial (NCT05140941) in pregnant women infected with hepatitis C is undergoing to analyze the safety and efficacy of sofosbuvir and velpatasvir [19].

Improved access to treatment and antenatal monitoring can be made available to these unique patients to avoid the mother-to-fetus transmission of infection which can further reduce the spread of the infection. There is also a paucity of research when it comes to managing this infection during pregnancy. It is necessary to pave a path that stimulates research and treatment in pregnant women as a step toward the elimination of hepatitis C infection worldwide [20].

Complexities of Pediatric Hepatitis C Management

Hepatitis C infection in children presents unique challenges that differ significantly from those in adults. Despite the availability of highly effective antiviral medicines, the management of pediatric hepatitis remains complex [21]. A modeling study published in The Lancet journal has given the prevalence of pediatric hepatitis C patients worldwide as well as in different countries and territories [22]. Around 5 million children are suffering from hepatitis C and the prevalence is higher in low-income countries [22]. Children often acquire infection from their mother during pregnancy which progresses silently, leading to chronic liver disease, cirrhosis, and even hepatocellular carcinoma in adulthood. Older children and teenagers can get infected with hepatitis C if they are given injections with contaminated needles or if there are poor hygiene practices in preventing infections, especially in low to middle-income countries [23].

In 2018, after noticing the effectiveness of antiviral therapeutics in adults, the treatment of sofosbuvir and ledipasvir was approved by the US FDA and European Medicine Agency for children up to three years of age. In 2020, the treatment of sofosbuvir and velpatasvir was approved for adolescents, and in 2021 the treatment was approved for children down to age 3 years [24]. Refer to figure 1 for the new recommendations by WHO for direct-acting antivirals for adolescents and children. These treatments have shown high certainty of evidence in adults (18 years and above).

Direct acting antivirals	Adolescents (12–17 years)	Older children (6–11 years)	Younger children (3–5 years)
	Certainty of evidence		
Sofosbuvir–Daclatasvir* for 12 weeks	High	High	Very low
Sofosbuvir–Velpatasvir for 12 weeks	Low	Low	Very low
Glecaprevir-Pibrentasvir for 8 weeks	Moderate	Moderate	Very low

* The most widely used regimen in adults due to the availability of quality-assured, low-cost generics

Figure 1: New 2022 Recommendations by WHO for the Treatment of Hepatitis C Children of Different Age Groups

Identifying and treating the disease condition at the earliest possible is vital to avoid serious issues later on, but there are many obstacles in the way. Prenatal transmission is a critical source of hepatitis C infection. However, many infected children remain undiagnosed. This is because there is no routine screening program available and also the parents and healthcare providers are not aware [25]. A prospective cohort study showed that vertical transmission was high in the study population, but infection during pregnancy was underdiagnosed [26]. Earlier, a retrospective study has shown that many exposed infants were not tested for diagnosis and also no follow-up was done to monitor their health [27].

Children require tailored treatment regimens and dosages based on their age and other health parameters. Children with active infection need counseling and education to reduce the risk of disease progression and practices to follow to avoid further transmission [28]. These challenges necessitate specialized pediatric care that may not be available in all regions [25].

Until now, efforts to screen and treat hepatitis C worldwide have mostly focused on adults because they suffer the most from the serious chronic effects of liver toxicity. However, not much attention has been given to testing and treating children for this infection indicating the limited awareness towards screening in children and adolescents [29]. Currently the diagnostic screening practices during pregnancy are not enough to identify infection in the child. Additionally, attention should also be given to the testing of siblings of infected pediatric cases as they may be also at risk of mother-to-child or intrafamilial transmission. Many times pediatric hepatitis C infection remains asymptomatic and progresses slowly. The disease may become severe even after 2-3 decades of infection. Therefore, children need long-term monitoring for diagnosis as well as to evaluate the efficacy of treatment and to detect any potential long-term complications, such as liver cirrhosis or liver cancer.

The high cost of the treatment is another challenge, especially in countries with low- and middle-income populations. Affordability and access to generic medicines are important because they make treatments cheaper and more available to people. However, investing in screening and diagnosis is also crucial because it helps identify more people with diseases. When more people are diagnosed, it creates competition among generic medicine manufacturers, which can lower the prices even further [30].

The possibility of comorbidity and additional drug therapies in children with hepatitis C cannot be neglected. Virus-associated dysmetabolism may increase insulin resistance and lower total cholesterol thus complicating the therapeutic response [31]. Therefore, it is recommended that clinicians working with hepatitis C-infected children should also screen their metabolic profile.

Dual Diagnosis Dialemma: Co-Infection of Hepatitis C and HIV

Worldwide, several million people are infected with both viral infections namely HIV and hepatitis C and thus the co-infection prevalence is more than 6% in HIV HIV-infected population [32]. Coinfected individuals often have high viral load, increased risk of developing cirrhosis, faster progression into liver cirrhosis, and finally precipitating into decompensated liver disease [33]. Both the viruses affect liver through immune-mediated mechanisms [34]. The important immune cells of the liver are hepatic stellate cells and kupffer cells. Hepatitis C virus dysregulates functions of natural killer cells causing overexpression of enzymes responsible for fibrosis, whereas HIV decreases the number of kupffer cells and also interacts with stellate cells making them function inappropriately [34]. Earlier this coinfection was considered difficult to treat, however, treatment with interferon-free direct-acting antivirals has shown good efficacy and safety [35]. Despite safe and effective treatments, several challenges complicate the therapy and delay the eradication of the virus (Refer to figure 2).

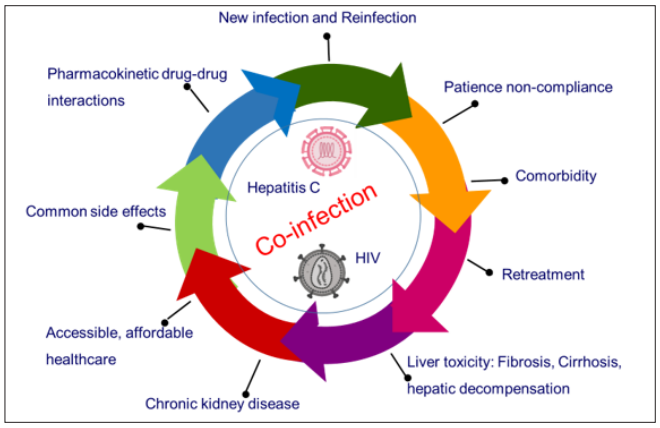

Figure 2: Pictorial Presentation of Several Challenges that are seen in the Management of Hepatitis C Patients Co-Infected with HIV

Pharmacokinetic type of drug interactions between antiretroviral drugs and other medications are common and can lead to either higher or lower levels of the drugs in the body [36]. These changes can sometimes cause more severe side effects or reduce the effectiveness of the drugs. It is important to review all medications with an expert to design a treatment plan that minimizes harmful interactions. The recommendations for managing these interactions can vary depending on whether a new drug is being started or a new medication is being added to an existing therapeutic regimen. Predicting the exact effects of multiple drug interactions can be challenging, especially when the drugs are metabolized by a variety of pathways [36]. examples of such interactions are a combination of grazoprevir and HIV protease inhibitors, dasabuvir and rilpivirine, and efavirenz reducing the drug levels of velpatasvir.

The treatment of HIV and hepatitis C coinfection becomes challenging when the treated patient gets reinfected. Reinfection has been reported in HIV-positive men who have sex with men and those who inject drugs [37]. A meta-analysis of 41 studies conducted in Europe has indicated that longer follow-up after treatment can help reduce the incidence of reinfection [38].

Chronic infection with the hepatitis C virus significantly causes more deaths in adults who are infected with HIV. A meta-analysis of 19 studies conducted in more than 50 nations has shown that in Asian adult patients, liver disease is a leading cause of non-AIDS death in coinfected patients [39]. Coinfection of these two viruses often gives adverse clinical outputs like worsening of HIV infection [40]. However, A long-term study found that having HIV does not reduce the survival rate of cirrhosis patients who have advanced liver fibrosis. For this study, researchers compared patients with advanced liver fibrosis after sustained virological response and with or without coinfection of HIV [41].

Clinical outcomes are determined by measuring CD4 cell counts. Viral load also provides significant information. Additionally, the mortality rate is also used for comparing the therapeutic effectiveness, tolerability, and adverse outcomes. Poor recovery from the illness is often seen as patients often discontinue their antiviral therapy [42]. Slow improvement in CD4 cell counts is an important predictor of poor immune restoration. A meta-analytical study published in Clinical Infectious Diseases analyzed the data of patients having dual viral infections of hepatitis C along with HIV. These patients showed an average rise in their CD4 cell count. It was more than 33 cells/mm^3. However, it was comparatively much less than that for HIV-infected patients without hepatitis C infection [43]. A recent study analyzed the real-world data of over 300 patients suffering from both viral infections. It was a multiple-center experimental analysis. Researchers found that the presence of detectable HIV viral load did not significantly affect the overall risk of death [44]. However, after the hepatitis C cure, the low CD4 cell count (less than 500/mL) showed a strong association with a higher mortality risk. Based on a study in Japanese male coinfected patients (n=12), researchers suggested that instead of CD4, a ratio of CD4/CD8 can serve as a better biomarker [45]. This is because some patients on antiretroviral therapy may restore CD4 count, but will have a low count of circulating CD8 cells. However, this study has a limitation of analysis of small sample size and the study was conducted at one centre. The conclusion needs to be validated in a multicentre study with a large sample size.

Another reason for poor clinical outcomes is hepatotoxicity. The risk for hepatotoxicity is higher in patients with coinfection than in monoinfected patients [46]. Treatment with a combination of highly active antiretroviral drugs often precipitates flares of hepatitis in coinfected patients [34]. It is seen as elevated levels of liver enzymes and changes in replication rates of hepatitis C and the viral load. Sometimes these effects are self-limiting, But if the

patient has cirrhosis, it may turn into hepatic decompensation. Antiretrovirals have successfully reduced disease complications, but long-term therapy often causes metabolic complications. Non-alcoholic fatty liver is one of the complications that progresses into nonalcoholic steatohepatitis. Therefore, researchers proposed fatty liver index as a noninvasive maker to analyze the status of liver toxicity [47]. A long-term clinical trial involving more than 900 co-infected patients demonstrated that a fatty liver index value of ≥60 is a risk factor for all-cause mortality in coinfected patients. It is independent of liver fibrosis and hepatitis cure [47].

Another challenge is the cost and accessibility of therapy for coinfected patients. Although the drugs are highly effective, the overall treatment is expensive. The cost of these medications remains a barrier for many patients, especially in low- and middle-income countries [48]. Even in countries with healthcare coverage, co-infected patients may face high copayments and insurance premiums. In some regions, access to antiviral therapy for HIV is limited due to supply chain issues, lack of healthcare infrastructure, and regulatory barriers [49]. Patients in marginalized communities often face additional barriers to accessing care, including stigma, discrimination, and lack of awareness about available treatments [49].

Conclusion

Managing hepatitis C in unique populations, including pregnant women, children, and HIV co-infected patients, presents distinct challenges that require personalized therapeutic approaches. Pregnant women and children necessitate careful consideration of drug safety and efficacy, as well as the potential impact on development and pregnancy outcomes. HIV co-infected patients face additional complexities due to drug interactions, comorbidity, and the compromised immune system. Despite these challenges, advancements in direct-acting antivirals have significantly improved treatment outcomes. However, ensuring equitable access to these treatments and addressing the specific needs of these populations remain critical. Importance needs to be given to improved screening, access to affordable medications, and targeted public health strategies. Ongoing research and tailored clinical guidelines are essential to optimize care and achieve the goal of hepatitis C elimination.

Additionally, addressing the challenges associated with accessibility and affordability of long-term treatment requires multi-level strategies. This will include modifications in the health policies and reserving more funds for healthcare programs. Additionally, efforts should be directed toward reducing the cost of medications and making generic versions more accessible. Ensuring that patients have access to affordable and effective treatments is crucial for improving the overall health outcomes in these critical populations.

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