



Editorials

Hepatitis C and hepatocellular carcinoma in Latin America: Elimination as a path to cancer prevention



1. Hepatitis C

Hepatitis C virus (HCV) is a major cause of global morbidity and mortality [1]. The global prevalence of HCV was estimated at 0.75% in 2019, representing approximately 57.8 million infections [2]. Moreover, cirrhosis and other chronic liver diseases due to HCV infection were associated with 12.2 million disease-adjusted life-years in 2019 (26.3% of cirrhosis disease-adjusted life-years) [3]. In Latin America alone, there are ~3.8 million individuals living with HCV and approximately half of them are estimated to have advanced fibrosis or cirrhosis [4]. HCV is also one of the most common global causes of hepatocellular carcinoma (HCC), and it is associated with a 15- to 20-fold increase in risk and is responsible for 10–25% of all cases of HCC [5,6].

While the advent of direct acting antivirals (DAAs) has revolutionized the management of chronic HCV, challenges in identifying those infected across the globe and providing them with access to care impose a significant barrier to universal cure rates [7–9]. As a result, HCV remains common with approximately 1.5 million annual new infections [7,10]. HCV is frequently asymptomatic until cirrhosis or HCC develops and 25–70% of patients with HCC have advanced, incurable disease at the time of diagnosis, which contributes in large part to the 200,000 to 400,000 annual deaths that can be attributed to HCV [8,10,11].

2. Epidemiology of hepatitis C in Latin America

HCV infections represent an important cause of morbidity in low- and lower middle-income countries [8,12]. In Latin America, there seems to be a variation in prevalence according to the different regions of the continent: with 0.5% prevalence in the Andean and Central regions, 0.6% in the Southern regions, and 0.9% in the Tropical regions [13]. A multicenter cross-sectional study that included 817 patients with HCV from 30 Latin American sites showed that the most common genotypes in the continent are genotype 1 (79.5% of the total; 1a – 29.9%, 1b – 41.6%, mixed 1a/1b – 1.5%, unspecified – 6.5%) and genotype 3 (11.3%) [4]. The most important sources of HCV transmission are the use of injectable drugs, contaminated blood transfusion and to a lesser extent, high-risk sexual behavior [12]. A recent meta-analysis of 23 studies (11,419 patients) has demonstrated a stunning prevalence of HCV infection in 57% of people who inject drugs (PWID) in Latin America [14]. There was considerable heterogeneity among studies though, and the prevalence ranged from 12% in Brazil to 96% in Mexico [14]. It is noteworthy that the prevalence of HCV infection among PWID seems to be decreasing

over time (59% between 1991 and 2000, 63% between 2001 and 2010, and 48% between 2011 and 2020), likely associated with damage-control policies and more effective treatments [14]. A similar meta-analysis evaluating patients with end-stage renal disease undergoing hemodialysis in Latin America, including 20 studies (17 of which were included), found a pooled prevalence of HCV of 11.3% in this population [15]. This is higher than that reported in high-income countries, such as Belgium (4.1%), Canada (4.2%), Germany (4.5%), the United Kingdom (5.4%) or the United States (6.9%) for instance, suggesting that Latin American countries should improve infection control measures in dialysis centers [16]. Again, there was substantial heterogeneity among studies, and HCV prevalence ranged from 2.7% in Brazil to 56.7% in Cuba [15].

Treatment of HCV with DAAs is increasing worldwide and particularly in middle-income countries [12]. The Latin American scenario, however, is quite heterogeneous in this regard. For instance, countries such as Brazil, Argentina, Colombia and Mexico provide all HCV-infected patients with free access to DAA therapy [4]. However, even among these countries, some differences in access to treatment can be noticed. In Brazil, sofosbuvir-velpatasvir and glecaprevir-pibrentasvir are dispensed by the strategic component of the public pharmaceutical assistance, which means that patients can be provided with these drugs the same day they were prescribed. In Argentina, on the other hand, sofosbuvir-velpatasvir and grazoprevir-elbasvir are available, but it can take between 1 and 6 months to receive the prescribed treatment depending on insurance. More recently, countries such as Peru started offering free treatment (sofosbuvir-velpatasvir) for the majority of the population as long as patients present with significant liver fibrosis. Yet, other countries such as Ecuador still cannot offer interferon-free treatments for HCV-infected patients (personal communications from SALRN investigators, www.SALRN.org). These differences highlight some of the challenges of a unified front for treatment and elimination of HCV in the region.

3. Hepatitis C and hepatocellular carcinoma in Latin America

In total, there are approximately 38,000 annual cases diagnosed and 36,000 annual deaths from HCC in Latin America, which speaks to the high mortality of this cancer in the region [17]. These numbers, however, represent only reported cases, with the real numbers likely to be higher. HCV was previously the most common cause of HCC in Latin America, with studies from the years 2005–2017 estimating it as the cause of HCC in 23–48% of cases [18–22]. While a rapid increase in the rate of Metabolic-associated steatotic liver disease (MAFLD) in Latin America has recently surpassed HCV as the most

common cause of HCC, HCV remains an important risk factor now noted in 21% of HCC cases, still unacceptably high for a curable disease [23].

The similarities between the incidence and mortality of HCC in Latin America emphasize the poor prognosis of the condition. While our group previously found that survival was better in HCC secondary to HCV compared to other etiologies, the overall prognosis remained exceedingly poor [18]. Moreover, a recent study of individuals under HCC surveillance in Brazil found a median survival time of 18 months [24]. Outcomes have been shown to be even worse in those who are diagnosed outside of surveillance programs, which is over half of all patients diagnosed with HCC [18]. Unfortunately, the limited options for treatment of HCC, particularly in the 20–41% of Latin Americans who present with advanced disease, has further delayed substantial progress in improving outcomes [11,17]. This has resulted in the mortality of HCC secondary to HCV staying relatively stable in Latin America over the past two decades [25]. All of this speaks to the indisputable need to tackle HCV in the region before patients progress to cirrhosis or HCC, proposing a stronger argument to move away from “target treating” and focus on elimination.

4. Hepatitis C elimination

The highly effective all oral DAA therapies with minimal side effects and short treatment duration have prompted the World Health Organization (WHO) to approve the global strategy for eliminating HCV infection [26]. The ambitious goals set for 2030 were to achieve a 90% HCV diagnosis rate, a 90% reduction in the incidence of new infections, and a 65% reduction in liver-related mortality compared to 2015 [26]. Liver-related mortality due to HCV showed a declining trend, from 400,000 in 2015 to 287,000 (95% CI; 226.1–575.2) in 2019, driven by the number of people treated with DAAs which increased by ten times [2]. Moreover, treatment at the early stages of the disease has proved to be cost-effective by reducing the risk of cirrhosis, HCC, liver transplantation, and mortality [27]. The continuous scale up of treatment with DAAs is crucial to decrease the HCV mortality [28]. However, 79% of HCV infections remain undiagnosed, and 87% have not been treated [2].

All countries should promote tailored policies to increase treatment coverage, develop guidelines, and improve surveillance. Expanding access to HCV treatment should be a public health priority, largely because the achievement of cure results in substantial reductions in liver-related mortality, including HCC [29,30]. In Latin America, however, less than half of the countries have good quality HCV prevalence studies, and/or have not yet developed clinical guidelines for the diagnosis and treatment of HCV [31]. Moreover, some countries still cannot afford the cost of DAAs for elimination of HCV [31]. In the region, Brazil has led the way regarding HCV elimination efforts by launching in 2018 the viral hepatitis control program which included a scale-up of diagnosis and treatment with free access to DAA regimens. However, due to the COVID-19 pandemic, the actions of surveillance and control programs for HCV have been severely affected [32]. In order to be on track to achieve WHO elimination goals, countries from Latin America should perform well-designed prevalence studies, apply HCV universal screening and invest in the treatment of viral hepatitis to prevent future deaths [33]. Nevertheless, the risk of hepatic decompensation and HCC is not entirely eradicated after cure of HCV infection in those with cirrhosis [29,30]. Different tools for estimating HCC risk after achieving cure have been proposed and there are multiple ongoing studies aiming at proper risk stratification of these patients, but we still have an incomplete understanding of this problem [34]. Thus, eradication efforts should be aimed at individuals with chronic HCV at earlier stages, before the onset of cirrhosis and liver-related events.

5. Conclusions

It is clear that the arrival of DAAs for the treatment of HCV has established an important landmark in the trajectory of liver disease with a unique opportunity to cure one of the most lethal chronic viral infections known to men. However, this arrival has impacted Latin America differently, as challenges to broadly implement treatment as a mean of eradication and cancer prevention remain. Advances have been made, but there is an urgent need for public health policies strategically tailored to Latin America and with the potential to be shared across countries in the region to treat as many individuals as possible for HCV so to dramatically decrease cirrhosis and HCC-related mortality.

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Declaration of interests

None.

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