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# 25 years of Hepatitis C

Parise ER. 25 years of Hepatitis C
**HEADINGS** – Hepacivirus. Liver cirrhosis.

During the decade of 60 and even 70 medical literature recognized only two types of hepatitis: type A, mainly affecting children, spread often at epidemic levels via food or water contaminated with infected feces and never chronic and type B, with parenteral transmission that could eventually evolve into chronicity, leading to the (then called) post-necrotic cirrhosis[15]. After the identification of the Australia antigen (later called surface antigen of hepatitis B, HBsAg) by Blumberg et al.[7] it seemed that the causative agent of parenteral transmission of hepatitis had been found, but it soon became clear that this virus could not be responsible for all cases of post-transfusion hepatitis. When hepatitis A virus was recognized and an antigenic system was developed, it could be associated with the infectious hepatitis. After analysis of many cases of transfusion hepatitis which could not be attributed to the hepatitis virus A or B, cytomegalovirus or Epstein Bar, Alter et al. denominated this disease as non-A non-B hepatitis, and a series of unique epidemiological characteristics were being identified for this hepatitis and its clinical outcomes[3, 4]. Finally in 1989, researchers were able to identify an antibody (Anti-HCV) as a marker for hepatitis C and related to different aspects of the disease[5, 17]. The identification of this antibody and its rapid implementation for blood and derivatives screening by blood banks, associated with the determination of hepatitis B antigenic system determine dramatic reduction in post-transfusion-transmitted disease in the world[17]. However, the damage was already done during the previous years leading up to the discovery of the marker for hepatitis C, millions of people were infected by blood transfusion, use of non-disposable needles and syringes or cutting pierce materials contaminated with hepatitis C.

According to a national study, the prevalence of hepatitis C in Brazil is 1.54% in the adult population (age 20–69 years) and 0.70% in the 10-to-20-year age range[8]. Based on the age distribution data of this survey, the current population infected with the hepatitis C virus (HCV) would be in the order of 2 million of people[19]. Chronic HCV infection follows an asymptomatic or oligosymptomatic course over decades and because of that most infected patients are unaware of their condition and do not look for medical attention. According to DataFolha and Brazilian Society of Hepatology survey performed in 2012 in the main metropolitan areas of the country, only 1/4 of the population of Brazil had already performed the test for hepatitis C[32]. As the majority of patients is not identified and treated of the disease, the hepatitis slowly continues to progress and as late the diagnosis of the infection is made, the more likely the patients will be in advanced stages of the disease[24]. Hepatitis C is now the second leading cause of chronic liver disease in public hospitals and outpatient care facilities only supplanted by alcohol abuse[23] and the leading cause of hepatocellular carcinoma in Brazil[9], accounting for nearly 40% of all cases diagnosed in the country. As an obvious consequence of these facts hepatitis C is now the main cause of liver transplantation, accounting for over half of all cases of cirrhosis and hepatocellular carcinoma leading to transplantation[30].

Official data from Ministry of Health of Brazil, state that 8,216 patients received treatment within the framework of the National Viral Hepatitis Program in 2004, the year of its creation. This number grew from 2009 to 2011, plateauing in the region of 11,000 patients per year in the last years[11]. Even taken in account that 5% to 10% of these cases constitute retreatment of patients that do not responded to previous antiviral therapy, in total, no more than 100,000 patients have already received treatment for hepatitis C in the country. As sustained virological response (SVR) rate could be calculated as no more than 50%, it can be realized that mere 2.5% of the infected population has been cured in Brazil (Figure 1). It bears stressing that, unlike therapy of other viral illnesses, successful treatment of hepatitis C cures the infection, halts disease progression, significantly reduces the risk of developing hepatocellular carcinoma (even in advanced cases) and even reduces non-liver-related mortality, both in patients with HCV infection alone and in the presence of HIV–HCV co-infection[1, 6, 18, 35].

Hepatitis C treatment with interferon was first applied at the time that the disease was called "non A non B hepatitis"[18], and has evolved since them.

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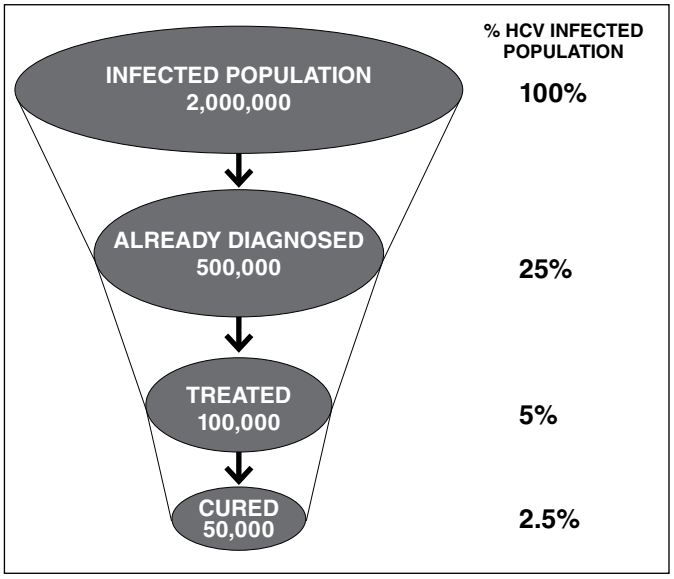


**FIGURE 1**. Efectvity of hepatitis C diagnosis and treatment in Brazil.

The incorporation of ribavirin and, in the last years, of first generation protease inhibitors (telaprevir and boceprevir) have increased significantly the numbers of responders to such antiviral therapy at same time that increased the number and the gravity of the adverse events as demonstrated by Almeida et al. in this issue of ARQA[2]. Despite the limited number of patients studied, which prevents any consideration about the virological response rate, it portrays the higher rate of complications seen with this therapy, with almost 60% of patients with anemia and early discontinuation of treatment in more than 30 % of patients. These numbers were much higher than the observed with dual therapy (peg-interferon and ribavirin), and are in accordance with data from the most important real-life study with triple therapy, the French Cupic Study[16]. The DAA second generation (sofosbuvir, simeprevir and daclatasvir), in the opposite direction, with the possibility of combining themselves and avoiding peguilated interferon are able to significantly reduce the extension and the complexity of the treatment and the incidence of side effects, in parallel with a rate of SVR near 80%-90% for all genotypes[27]. Although extremely important, this achievement is not enough. If the number of patients receiving antiviral therapy stays the same, the expectation for the coming years is of an important increase in the number of chronic hepatitis C complications as cirrhosis and hepatocellular carcinoma, with increase in medical costs for the public and private sector[28]. In order to have a great impact on hepatitis C burden it will be necessary to increase both diagnosis and access to treatment. In the detection of carriers of this virus, it is important to modify the standard used so far to their identification by prioritizing those with parenteral risk factors (blood transfusion, hemodialysis, etc.). About 70% -75% of patients infected by hepatitis C virus in our country is aged more than 40-45 years[13, 24, 31]. Individuals in this age group must be consider at risk and tested for hepatitis C, regardless of whether they have a history of blood transfusions, have made use of disposable syringes and needles, or exposed to other forms of contamination. This strategy proved to be superior to conventional methods in the detection of hepatitis C[10, 29]. In this issue of the Archives of Gastroenterology, Oliveira et al. assessed the prevalence of hepatitis C in Paulista University (UNESP) employee in total more than 3000 people[25]. Despite the low prevalence observed (0.7%) for hepatitis C in such population, they were able to confirm that those older than 40 years of age are at more risk to be contaminated with HCV virus. Additionally the authors call attention to factor overlooked by younger doctors in epidemiological studies, which is the use of non-disposable syringes and needles in the past. It is specially mentioned the application of energetic stimulant (Gluco-energan®) often formerly used by revelers at Carnival or by athletes that is responsible for several cases of hepatitis C in these populations[33]. Increase access to treatment is another important task getting rid of the barriers that prevent the patient to have their treatment[34]. Expedite the diagnosis with rapid serological tests and staging of disease with noninvasive tests in place of liver biopsies, use of more effective drugs with safer treatments, with lower rates of adverse events are important part of this equation. But doctors from other areas beyond the hepatologists and infectious disease specialists will be needed in this fight against hepatitis, and the gastroenterologists are among them. Therapeutic simplicity in the use of new coming drugs (as those to be approved by ANVISA in 2015) in antiviral therapy will allow the gastroenterologist not affect the treatment of hepatitis to join the efforts against hepatitis C.

In this special issue of the Archives of Gastroenterology, we have another interesting article on hepatitis C addressing the beneficial effects of caffeine in the evolution of this liver disease[26]. It has long been aware of the beneficial effects of coffee on serum liver enzymes and the alcoholic liver disease, but since 2009 several studies have shown that caffeine intake, especially in the form of coffee, has a protective effect on the development of hepatitis C virus[12, 14, 21, 22]. In our previously published study[21], we observed a reduction in liver fibrosis in patients taking higher doses of caffeine in univariate and multivariate analysis when compared to patients with lower daily intake of caffeine, but did not observe a relationship between caffeine with inflammatory activity in liver biopsy. We drew attention fact that the amount of caffeine necessary to reduce the degree of fibrosis was significantly lower than in English literature (125 mg or only 4 Brazilian cups of coffee versus 250 mg or 308 mg daily). This difference can be attributed to several factors but interestingly, in our population coffee represented more than 90% of the daily caffeine intake, while in other studies a large contingent of caffeine derived from soft drinks and processed juices[12, 14, 22]. The study of Oliveira et al. confirms our findings of the relationship between lower grade of fibrosis and the ingestion of higher doses of caffeine, although this association was not find in multivariate analysis. The cutoff value for caffeine used was the traditional (250 mg) and although certainly researched, it was not report in the

article the origin of calculated amount of caffeine. It should be remembered that in the South of Brazil there is another form of caffeinated beverage that is the use of mate infusion ("chimarrão"), and it would be interesting to know whether this had any impact in caffeine ingestion in this study. Also like in our study, there was no association between the amount of caffeine and the inflammatory activity in the tissue, suggesting that this protective effect could be relate to the fibrogenic activity of the tissue, but this would be a speculation far beyond the purpose of the studies presented.

Thus, when we complete 25 years of hepatitis C, witnessing one of the fastest and unprecedented advances in the history of medicine in the diagnosis and effective treatment of a disease, is important not to lose focus if we are to make a difference to health policies in this country no impact will be achieve only with excellent medicines. Even with drugs that reach 95% SVR we only effectively will reduce the future impact of the disease if we treat at least 70% of infected patients. It is not yet time to celebrate it's time to roll up our sleeves and go to fight.

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**DESCRITORES** – Hepacivirus. Cirrose hepática.

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