

## HIV/HCV Coinfection: Considerations about Treatment

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### Abstract

Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) Infections are considered public health problems. The coinfection HIV/HCV is common in individuals exposed to parenteral exposure, and HCV has emerged as the leading cause of deaths among HIV-1-seropositive patients. The treatment of HIV/HCV coinfecting people should be able to suppress viral replication for both viruses, with the purpose of to improve the immunological response and include liver damage. These two aspects should be associated with a high safety profile, because the toxicity of antiretroviral drugs used to treat HIV in HIV/HCV coinfecting people, can lead them to death. The management of the treatment of patients is needed to monitor and, if possible, prevent complications related to adverse effects.

**Keywords:** HCV; HIV; Coinfection; Therapy

### Introduction

Infection with Human Immunodeficiency Virus (HIV) currently affects over 33 million people worldwide and is considered a major public health problem worldwide [1,2]. Another important global pandemic is the infection by the hepatitis C virus (HCV), which affects around 3% of world population, approximately 180 million individuals [2-4].

Both HIV and HCV viruses are spread primarily by direct contact with infected blood. The main routes of transmission are blood transfusions not screened for HCV and / or HIV in the past, reuse of syringes, sharing of needles by intravenous drug users (IDUs), instruments for tattooing, piercing and placement used for manicures, sexual transmission and perinatal transmission [2,5,6].

How they divide the same route of transmission, coinfection with these viruses is not an uncommon event, especially among IDUs, where the rate of HCV infection in HIV-seropositive individuals with a history of injection drug use may be between 82 and 93% depending on the group studied. It is believed that about 4 to 5 million people in the world have HIV/HCV coinfection [7].

Analysis involved separate groups of HIV/HCV coinfecting people, IDUs and multi-transfused hemophilia patients showed an increase viral load of HCV after HIV seroconversion. These studies showed a direct influence of coinfection with HIV and HCV on the natural history of HCV [8-10].

Other studies have shown that in HIV/HCV coinfecting groups, liver inflammation is more intense than in patients HCV mono-infected, and the results of this event are the rapid progression of liver fibrosis and progression to liver disease, as cirrhosis and hepatocellular carcinoma in the most serious cases [11,12].

HIV infection has many influences on the progression of HCV in HIV/HCV coinfecting people, but HCV also has influences on the

progression of HCV in these patients. The low count of CD4 + T cells and the high viral load of HIV in HIV/HCV coinfecting people are also associated with increased mortality from liver disease in AIDS patients [3,13-15].

The immune suppression caused by the HIV infection maybe is the main cause for the poor prognosis of HCV disease in coinfecting patients. In acute HCV infection, T cells have an important role in controlling viremia to prevent progression to chronic phase. However, in coinfecting individuals, the response of specific T cells is reduced, which facilitates the HCV replication in the beginning of infection [16,17]. Another essential factor is the functional change of natural killer cells and dendritic cells caused by HIV, because these cells play an important role in innate and adaptive immunity. Perhaps fact contributes to reduce the specific immune response against HCV during the course of HIV/HCV coinfection [18,19].

In chronic hepatitis by HCV, the immune system try to combat the infection by the activation of CD4+ and CD8+ T cells, which also happens during coinfection HIV/HCV, but with a lower level. Unfortunately we know that cellular activation does not increase during the course of coinfection, even with the gain of T cells and immune recovery through to HAART (Highly Active Antiretroviral Therapy) [20]. Liver injury in coinfection may also occur independently of immune suppression as a result of action of these viruses in the liver [7].

Over the past 50 years had a significant progress in developing specific and effective antiviral drugs. The major focus of antiviral research is the chronic infection by viruses such as HIV, Hepatitis B Virus (HBV) and HCV.

Initially, the drugs have been developed principally against viral enzymes. However, more recently the researchers have been developed drugs that inhibit the viral cycle steps and prevent events like virus entry. The current success is new drugs based on structure, function the molecular of viral proteins and mechanisms involved in the interactions between viruses and hosts.

The epidemic caused by HIV, a virus that causes chronic infection for a long period, brought the necessity to control this chronic infection with the development of drugs and new treatment strategies.

The discovery and development of drugs for HCV has progressed significantly in the last decade. Currently, individuals with chronic HCV infection are treated with pegylated interferon (PEG-IFN) and Ribavirin. Nowadays, about 56% of patients have a sustained virological response (SVR) at the end of treatment [3,21]. However, the assertion that the SVR results in viral clearance is controversial because there may be a hidden infection by HCV after SVR in the liver and various types of lymphoid cells (peripheral blood mononuclear cells, B cells and T) [22].

In the same time, developing of new drugs for HIV infection, the knowledge of the viral cycle is bringing new opportunities for therapeutic intervention and the first drugs specifically developed against enzymes of HCV are showing promising results. Despite all the progress in the treatment of HIV and HCV chronic carriers, there are considerable challenges, such as drugs effective against the wild virus and mutants that do not allow the resurgence of viral load, high bioavailability with a long elimination period, low doses that have simple administration (once daily) and all associated with a high safety profile with low toxicity (few adverse effects). Furthermore, the use of drugs combination regimens which not allowed the development of resistance.

After the introduction of HAART, there was a decrease of mortality caused by AIDS among patients with HIV Infection. On the other hand, there was an increase of mortality caused by liver disease in HIV/HCV coinfecting people [7].

The current treatment for chronic monoinfected HCV patients is based on the administration of PEG-IFN and Ribavirin for 24 to 48 weeks. Depending of genotype the SVR rate is 50% [21,23]. Three randomized controlled studies, the APRICOT (AIDS Pegasys Ribavirin International Coinfection Trial), RIBAVIC and ACTG (AIDS Clinical Trial) compared the use of PEG-IFN with Ribavirin treatment with standard interferon with ribavirin in patients coinfecting [24-26]. These three studies demonstrated that the HCV treatment is viable in HIV/HCV coinfecting patients, but the treatment with PEG-IFN is better compared to standard treatment. SVR rates were 14% to 29% in patients with genotype 1 and 44% to 73% with genotypes 2 and 3. These SVR rates are generally lower than those published in studies with HCV monoinfected people, but the dose of ribavirin used in these three studies was lower than the commonly prescribed for monoinfected patients. In another study, the complete dose was prescribed and the response rates were still lower [27].

The kinetics of changes in the level of HCV in serum during treatment based on the INF has been studied. The parameters derived from mathematical models reflect the effectiveness of INF, the elimination rate of the cells and the rate of clearance of free virus [28]. In HIV/HCV coinfecting patients in the first phase of decline (representing effectiveness) and the second phase slope (loss of infected cells) were similar to those HCV monoinfected patients, but clearance was lower [29]. HCV monoinfected people became HCV-RNA negative during treatment late, mainly due to the higher levels found before treatment (baseline). The dynamics of virological response has been used to guide the duration of treatment in these patients [30]. Similarly, studies with HIV/HCV coinfecting patients showed initial virological response, that means HCV RNA-negative or

a decrease of 2 log<sub>10</sub> with respect to baseline at week 12, showing SVR [15,31].

As in HCV monoinfected patients, a SVR is associated with no progression of disease and related to liver histological improvement, which reduces the occurrence of liver decompensation or hepatocarcinoma [32-34]. The HCV genotypes are related to a better SVR after treatment. Individuals infected with genotype 2 and 3 show better response than individuals infected with genotypes 1 and 4.

Although antiviral therapy for HCV is effective in coinfecting patients, this treatment is also associated with an increased risk of complications. The interaction of ribavirin with other nucleoside reverse transcriptase inhibitors can cause mitochondrial toxicity and mortality [35]. This syndrome has been found in patients treated with didanosine (ddI) and can be resolved discontinuing the use of nucleoside reverse transcriptase inhibitor [36].

The hepatic decompensation is another potential complication of treatment with interferon and ribavirin in coinfecting patients. Although relatively rare (1.5% to 2%) is associated with high mortality in patients with cirrhosis, hyperbilirubinemia and to use ddI contributes to these risk factors [37,38].

Probably ribavirin has a synergistic effect with DDI for in vitro inhibition replication. This drug can interact with others antiretrovirals. Ribavirin, in vitro, antagonizes the effect of zidovudine (AZT) in HIV replication, while the use of AZT in patients receiving PEG-INF and ribavirin is associated with a higher rate of anemia [3,9,39,40].

Another important effect is the hepatotoxicity that appeared after the advent of HAART. Mechanisms of hepatotoxicity caused by HAART have not seemed to differ between HCV monoinfected patients and HCV/HIV coinfecting. The development of liver lesion is result of immune reconstitution mediated by aggravation of the hepatocytes infected by HCV [41].

Risk factors for hepatotoxicity in coinfecting patients on antiretroviral therapy include preexisting fibrosis and genotype 3 [42,43]. Any specific combination of medication has been associated with liver injury in patients coinfecting, thus the selection of HAART would be based on other factors. The successful of HCV clearance by treatment with INF plus Ribavirin and SVR is associated with reduced risk of hepatotoxicity induced by HAART [44].

Some studies have shown a new marker for progression of liver fibrosis in HCV monoinfected and HIV/HCV coinfecting patients. There is single nucleotide polymorphisms (SNPs) found in chromosome 19, specifically in the gene that encoded interleukin 28B (IL28B). The IL28B is a cytokine that plays an important role in the adaptive immune response against viral infections [45].

Currently, with the knowledge and development of molecular biology techniques and bioinformatics tools, it becomes clear the importance of the presence of some polymorphisms and different models of gene expression in the human genome, which may be linked to better or poorer response to treatment, a better immune response and other factors. The presence of the polymorphism and differential gene expression may be directly related to different ethnic groups.

In fact, a direct influence on SVR in HCV monoinfected and HIV/HCV coinfecting individuals. It is the presence of a polymorphism in the gene that encodes a protein with interleukin activity of and it was called IL28B or INF lambda. It was demonstrated the presence of

the rs12979860 polymorphism is correlated with the SVR on treatment by INF and ribavirin. The ethnicity is another factor, which Caucasians responded better than Africans [46-49].

These studies showed that the development of new antiviral drugs and new treatment strategies need more studies to evaluate the interactions between host and virus to search genetic markers that can be used as predictors of response to these drugs.

Since the beginning of 2010, it has been shown the influence of treatment on prognosis for HCV monoinfected and HIV/HCV coinfecting individuals, suggesting the use of laboratory marker in clinical practice and the development of a synthetic IL28B by pharmaceutical companies in the future with purpose of use in therapy these patients [46,47].

But in the future has a trend of marker IL28B not be necessary in clinical practice because the use of telaprevir and boceprevir in the treatment. Telaprevir and boceprevir are new protease inhibitors specific to the HCV nonstructural 3/4A serine protease. These new approaches may increase the rate of clearance virus in HCV monoinfected patients [50-53].

Two clinical trials PROVE1 and PROVE2 showed that the therapy duration can be reduced from 48 weeks to 24 weeks for most patients while maintaining an improved SVR with genotype 1 HCV, although with higher rates of discontinuation because of adverse events. In these studies, the rate of SVR was approximately 40% in the standard therapy group (PEG-IFN with ribavirin), 60% in the telaprevir group (PEG-IFN with ribavirin plus telaprevir) treated for 24 weeks and 68% in the telaprevir group treated for 48 weeks. Other important results were an increase in the rate of RVR at week 4 and a low subsequent rate of relapse, with telaprevir-based treatment as compared with standard therapy [50,51].

With these new drug in clinical practice, will be possible a combination therapy with ribavirin, removing the PEG-IFN of standard therapy and perform therapeutic schemes, like in HAART.

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