JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Antiretroviral therapy does not affect response to chronic hepatitis C therapy in HIV-coinfected patients

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Abstract

Introduction: Many patients coinfected with the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are using highly active antiretroviral therapy (HAART) and HCV therapy with peginterferon (PEG-IFN) and ribavirina (RBV) because the use of direct-acting antivirals is not a reality in some countries. To know the impact of such medications in the sustained virological response (SVR) during HCV treatment is of great importance.

Methodology: This was a retrospective cohort study of 215 coinfected HIV/HCV patients. The patients were treated with PEG-IFN and RBV between 2007 and 2013 and analyzed by intention to treat. Treatment-experienced patients to HCV and carriers of hepatitis B were excluded. Demographic data (gender, age), mode of infection, HCV genotype, HCV viral load, hepatic fibrosis, HIV status, and type of PEG were evaluated. One hundred eighty-eight (87.4%) patients were using HAART.

Results: SVR was achieved in 55 (29.3%) patients using HAART and in 9 (33.3%) patients not using HAART (p = 0.86). There was no difference in SVR between different HAART medications and regimens using two reverse transcriptase inhibitor nucleosides (NRTIs) or the use of protease inhibitors and non-NRTIs (27.1% versus 31.5%; p = 0.61). The predictive factors for obtaining SVR were low HCV viral load, non-1 genotype, and the use of peginterferon-α2a.

Conclusions: The use of HAART does not influence the SVR of HCV under PEG-IFN and RBV therapy in HIV/HCV coinfected patients.

Key words: HIV; HCV; peginterferon; HAART; therapy.

J Infect Dev Ctries 2016; 10(7):762-769. doi:10.3855/jidc.7452

(Received 13 August 2015 – Accepted 12 October 2015)

Introduction

Around 15% to 30% of patients with human immunodeficiency virus (HIV) are also infected with hepatitis C virus (HCV) [1,2]. The proportion is higher among intravenous drug users (IDUs), reaching 85% to 90% of this population, while the rate among people with high-risk sexual behavior can reach 10% to 14% [3]. In Brazil, a study to assess the prevalence of hepatitis C in 343 HIV patients observed the occurrence of HIV/HCV coinfection in 38.2%, with IDUs being the main exposure category (75.3%) [4].

Chronic liver disease caused by HCV has become a major cause of morbidity and mortality in HIV-infected patients since the introduction of highly active antiretroviral therapy (HAART) in 1996 [5-7]. It has been reported that the progression of chronic hepatitis to cirrhosis, liver failure, and the development of hepatocellular carcinoma could be accelerated in coinfected HIV/HCV patients [8-10], since HIV can adversely affect all stages of the natural history of HCV infection [11]. On the other hand, other authors have demonstrated that the progression of liver disease in HIV/HCV coinfected patients occurs primarily when the HIV infection is inadequately managed [12,13]. Confirming this hypothesis, Tovo *et al.* assessed 385 HIV/HCV coinfected patients, and observed a similar fibrosis progression rate to that of HCV or HIV mono-infected patients [14].

The role of HCV in HIV infection in the HAART era is still controversial. Some authors claim that HCV is related to the progression of HIV disease in that it increases immune activation, with more apoptosis of CD4 lymphocytes [15,16]. However, other studies did not observe a worse HIV progression in coinfected patients [17-22].

The treatment of chronic hepatitis C in HIV/HCV coinfected patients has been evaluated in recent decades, given that the cure of hepatitis C improves survival in these patients [23]. It should be noted that the use of HAART is an independent factor for the

reduction of HCV-related complications, including progression to cirrhosis, hepatocellular carcinoma, and death [7].

Some studies did not show an influence from HAART use and different treatment regimens in the sustained virological response (SVR) of HIV/HCV coinfected patients treated with peginterferon (PEG-IFN) and ribavirin (RBV) [24-26]. Others, however, found differences when medications were analyzed individually and in combination [18,27]. The present study aimed to assess the influence of the use of HAART on the SVR of HIV/HCV coinfected patients treated with PEG-IFN and RBV.

Methodology

This was a retrospective, observational, and non-probabilistic sampling study that evaluated the SVR in HIV/HCV-coinfected patients receiving therapy with PEG-IFN and RBV with respect to the use of HAART.

The patients were all over 18 years of age, treated with PEG-IFN and RBV between 2007 and 2013 through the public health system in two specialized clinics in southern Brazil; the patients were consecutively included in the study.

Treatment-experienced patients and carriers of hepatitis B (HBsAg positive) were excluded from this study.

HIV diagnosis was carried out by enzyme-linked immunosorbent assay (ELISA) and confirmatory test (indirect immunofluorescence, immunoblot, or western blot), as recommended by the Brazilian Public Health Protocols [28,29].

For the diagnosis of HCV, anti-HCV was performed through third-generation ELISA, followed by polymerase chain reaction (PCR) to confirm viremia.

The recommendation for hepatitis C treatment was based on the guidelines of the Brazilian Health Ministry, with treatment recommended for 48 or 72 weeks, depending on the type of response obtained at week 12 of treatment. Patients with any degree of hepatic fibrosis could receive treatment according to this guideline [30,31].

Demographic data (gender, age), mode of infection, HCV genotype, HCV viral load (HCV-RNA), hepatic fibrosis, HIV status (CD4 and HIV-RNA count), PEG type, and HAART regimen used were evaluated.

All patients underwent HCV-RNA testing (viral load or qualitative RNA test) at the beginning of treatment, at week 12, at the end of treatment, and 24 weeks after the end of treatment in order to assess SVR.

Patients were analyzed by intention to treat. Non-responders were defined as those who showed a decrease in HCV-RNA levels of less than 2 logs at week 12, or no viral load below the lower limit of detection at week 24 (for those who showed a decrease in HCV-RNA levels of more than 2 logs at week 12) or at the end of treatment, and those who abandoned or suspended treatment due to side effects. Relapsers were those with negative HCV-RNA at the end of treatment and positive HCV-RNA at week 24 after the end of treatment. SVR was defined as undetectable HCV-RNA at 24 weeks after the completion of treatment. The HCV viral load was considered low when it was less than 600,000 UI/mL [32].

The degree of fibrosis was classified according to the METAVIR scoring system [33] as absent (F0), portal fibrosis without septa (F1), portal fibrosis with rare septa (F2), numerous septa without cirrhosis (F3), and cirrhosis (F4). Patients with a diagnosis of cirrhosis established through clinical, laboratory, imaging, or endoscopy methods and who did not undergo hepatic biopsy were considered to be F4.

The HAART regimens most frequently recommended by the guidelines of the Brazilian Health Ministry contain two analog reverse transcriptase inhibitor nucleosides (NRTIs) and one protease inhibitor (PI) or two NRTIs and one non-nucleoside reverse transcriptase inhibitors (NNRTIs). For the statistical analysis, the medications were grouped according to their class, into PIs (atazanavir, lopinavir/ritonavir, indinavir, fosamprenavir, and saquinavir) or NNRTIs (nevirapine and efavifenz). The most frequently used regimens containing two NRTIs, namely zidovudine (AZT) + lamivudine (3TC), tenofovir (TDF) + 3TC, and stavudine (d4T) + 3TC, were analyzed. Thereby, the difference between these most frequently used NRTI regimens was evaluated. The other NRTI regimens were analyzed together due to their lower frequency of use.

Statistical analysis was performed using SPPS version 18.0 (SPSS, Chicago, USA), and categorical variables were expressed as absolute (n) and relative (%) frequencies. The mean and standard deviation were calculated for the numerical variables. The significance of the relationship between the categorical variables was obtained through Chi-square test or Fisher's exact test. For the comparison between the quantitative variables between the two categories, student's t-test for independent samples or the analysis of variance (ANOVA) were used. Logistic regression analysis was used to adjust for confounders in assessing SVR-related factors. Variables with statistical significance in the

univariate analysis were included in the logistic regression analysis. The significance level adopted was 0.05.

The study was submitted and approved by the local ethics committee.

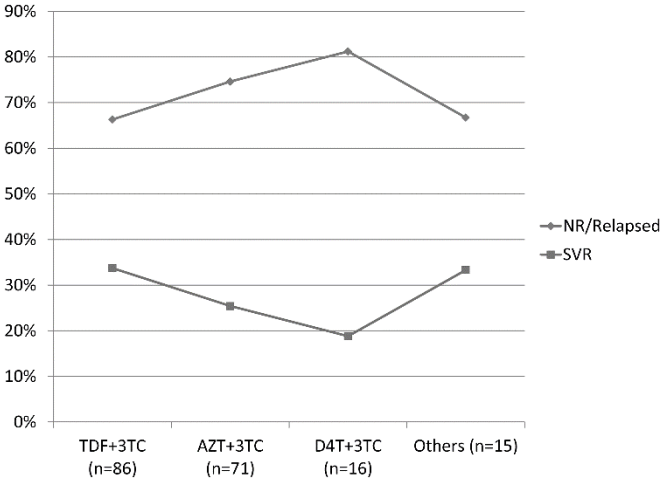
Results

A total of 215 coinfected HIV/HCV patients were evaluated, 188 of whom (87.4%) were taking HAART. Besides a more prevalent undetectable HIV-RNA in patients on HAART and higher CD4 cell count in the group not on HAART, no other significant differences between the groups were observed. The baseline characteristics of both groups are shown in Table 1.

SVR was obtained in 55 (29.3%) individuals in the group of patients on HAART, and in 9 (33.3%) individuals in the group not on HAART, with no significant statistical difference (p = 0.86).

No difference was observed in SVR when comparing the use of PI (26/96; 27.1%) and NNRTI (29/92; 31.5%) (p = 0.61). Among the NRTI group, the most used medication was 3TC (185/188; 98.4%),

Figure 1. Rate of SVR in patients with a three-drug regimen including a PI or an NNRTI according to the N(t)RTI backbone.



NR: non-responders; SVR: sustained virological response; TDF: tenofovir; AZT: zidovudine; 3TC: lamivudine; d4T: stavudine; p = 0.51.

Table 1. Baseline characteristics of patients based on use of highly active antiretroviral therapy (HAART).

	With HAART (n = 188)	Without HAART (n = 27)	p
Age; years (mean ± SD) (n = 215)	44.0 ± 8.9	42.0 ± 9.1	0.28
Gender; n (%) (n = 215)			
Men	136 (72.3)	24 (88.9)	0.11
Women	52 (27.7)	3 (11.1)	
Mode of infection; n (%) (n = 107)			
IDU	40 (43.5)	8 (53.3)	0.77
Transfusion	14 (15.2)	2 (13.3)	
Other or unknown	38 (41.3)	5 (33.3)	
HCV genotype; n (%) (n = 212)			
1	156 (84.3)	24 (88.9)	0.77
2–3	29 (15.7)	3 (11.1)	
HCV-RNA; UI/mL (n = 214)			
< 600,000	32 (17.1)	3 (11.1)	0.58
≥ 600,000	155 (82.9)	24 (88.9)	
Fibrosis (METAVIR); n (%)			
0–1	44 (23.4)	9 (33.3)	0.49
2	60 (31.9)	7 (25.9)	
3–4	64 (34.0)	10 (37.0)	
Not assessed	20 (10.6)	1 (3.7)	
CD4; cells/mm^3 (n = 181)			
< 350	38 (23.2)	1 (5.9)	0.04
351–500	52 (31.7)	3 (17.6)	
> 500	74 (45.1)	13 (76.5)	
HIV-RNA; copies/mL(n = 177)			
≤ 50	140 (87.5)	2 (11.8)	< 0.01
> 50	20 (12.5)	15 (88.2)	
Peginterferon; n (%) (n = 215)			
α2a	91 (48.4)	11 (40.7)	0.59
α2b	97 (51.6)	16 (59.3)	

IDU: intravenous drug users.

followed by TDF (87/188; 46.3%) and AZT (72/188; 38.3%). When assessing the most frequently used regimens, all containing two NRTIs, there was no significant difference in SVR (Figure 1).

A total of 14 (6.5%) patients did not complete treatment; of these, 11 abandoned the treatment and 3 discontinued due to serious adverse events; all 3 of these patients were taking AZT + 3TC. In the abandoned group, 10 (90.9%) were on HAART (p = 0.99).

As showed in Table 2, when evaluating SVR-related factors, an increased SVR in patients with genotypes 2 or 3 was shown in relation to those with genotype 1 (46.9% versus 26.1% p = 0.03). A low HCV viral load was also associated with a higher SVR rate (51.4% versus 25.1%; p = 0.01). Moreover, the group of patients on PEG-α2a showed a better response than those on PEG-α2b (37.3% versus 23.0%, respectively; p = 0.001).

In the multivariate analysis, only variables with statistical significance in the univariate analysis were included in the logistic regression analysis. It was observed that patients with non-1 genotype showed a 2.3 higher chance of SVR and patients with a lower HCV-RNA showed a 3.5 higher chance of achieving SVR when compared to patients with elevated HCV-

Table 2. Sustained virological response based on different variables.

	NR	Relapser	SVR	p
Age; years (mean ± SD) (n = 215)	44.8 ± 8.5	42.1 ± 7.5	42.2 ± 9.9	0.11
Gender; n (%) (n = 215)				
Men	100 (62.5)	14 (8.8)	46 (28.7)	0.52
Women	30 (54.5)	7 (12.7)	18 (32.7)	
Mode of infection; n (%) (n = 107)				
IDU	11 (68.8)	2 (12.5)	3 (18.8)	0.63
Transfusion	32 (66.7)	4 (8.3)	12 (25.0)	
Other or unknown	31 (72.1)	1 (2.3)	11 (25.6)	
HCV genotype; n (%) (n = 212)				
1	116 (64.4)	17 (9.4)	47 (26.1)	0.03
2–3	13 (40.6)	4 (12.5)	15 (46.9)	
HCV-RNA (UI/mL) (n = 214)				
< 600,000	16 (45.7)	1 (2.9)	18 (51.4)	0.01
≥ 600,000	114 (63.7)	20 (11.2)	45 (25.1)	
Fibrosis; n (%)				
0–1	26 (49.1)	08 (15.1)	19 (35.8)	0.38
2	42 (62.7)	7 (10.4)	18 (26.9)	
3–4	50 (67.6)	5 (6.8)	19 (25.7)	
Not assessed	12 (57.1)	1 (4.8)	8 (38.1)	
CD4; cells/mm^3 (n = 181)				
< 350	26 (66.7)	1 (2.6)	12 (30.8)	0.15
351–500	36 (65.5)	7 (12.7)	12 (21.8)	
> 500	45 (51.7)	10 (11.5)	32 (36.8)	
HIV-RNA; n (%) (n = 177)				
≤ 50 copies/mL	84 (59.2)	15 (10.6)	43 (30.3)	0.98
> 50 copies/mL	20 (57.1)	4 (11.4)	11 (31.4)	
Peginterferon; n (%) (n = 215)				
α2a	49 (48.0)	15 (14.7)	38 (37.3)	< 0.001
α2b	81 (71.7)	6 (5.3)	26 (23.0)	

NR: non-responders; IDU: intravenous drug users.

Table 3. Multivariate analysis of factors associated with sustained virological response.

	OR adjusted	95% CI	p
Genotype			
2-3	2.3	1.0–5.3	0.04
HCV-RNA (UI/mL)			
< 600.000	3.5	1.6–7.6	0.01
Peginterferon			
α2a	2.2	1.2–4.2	0.01

Only variables with statistical significance in the univariate analysis were included in the logistic regression analysis; OR: odds ratio; CI: confidence interval.

RNA. Also, those who used PEG- α2a had a 2.2 higher chance of SVR those in the group using PEG- α2b (Table 3).

Discussion

The current guidelines for HIV treatment in many countries, including Brazil, recommend starting HAART as soon as possible, regardless of CD4 count. This recommendation is emphasized in some special populations, such as HIV/HCV-coinfected patients, due the possibility of a higher rate of progression to cirrhosis and liver dysfunction [9,23,34]. However, in the new era of direct-acting antivirals (DAAs), a main issue in these patients will be drug-drug interaction, with fewer options for HAART regimens based on the DAAs used to treat HCV infection, making assessing the presence of HAART on the SVR of patients undergoing treatment for hepatitis C a very important issue.

The results of this study show that the use of HAART did not influence the SVR (29.3% versus 33.3%, respectively). However, there was a small number of patients in the group not using HAART. This could have been due to the guidelines of the Brazilian Health Ministry; even in previous versions, the guidelines recommended starting HAART in HIV/HCV coinfected patients with higher CD4 counts, which made it difficult to find patients who had not received HAART in this population. This finding of no difference between patients with or without HAART was supported by a previous study [24] and another retrospective cohort study evaluating HIV/HCV coinfected patients who underwent treatment for HCV, which showed an SVR of 37% versus 44% on HAART and not on HAART, respectively, with no significant difference [35].

Vogel *et al.* [24] obtained an SVR of 57% in the group using HAART, and 52% in the group not using HAART (p = 0.708). These elevated SVR rates can be explained by the smaller proportion of genotype 1 patients (about 50%), while in the present study, this genotype represented more than 80% of the patients, which is in accordance with epidemiological data in our region [36].

In the present study, there was no relationship between SVR and the different regimens containing two NRTIs. Berenguer *et al.* [35], assessing the use of TDF and 3TC with other medications, observed that the NRTI exerted little effect on SVR, except in regimens containing AZT, which presented a lower SVR probably because of the need to reduce the dose of RBV. In our study, the only finding correlated with this is that three patients who discontinued treatments due to serious adverse events were taking AZT+3TC.

On the other hand, Pineda *et al.* [27] showed, in a retrospective multicenter study with 310 patients, that the group not taking HAART or receiving a combination of TDF or d4T associated with 3TC and one PI or NNRTI showed higher SVR (44% in both) than did those using other HAART regimens (29%).

The effect of medications on SVR, when evaluated individually, has also been a point of discussion, having been related by some studies to an adverse influence on SVR [25,37]. However, such findings have not been confirmed by other authors [24,26-38]. In the present study, we also found no significant difference in SVR between patients who used PI or NNRTI, or even when NRTIs were individually evaluated.

It is known that the SVR in coinfected patients is lower when compared to HCV-monoinfected individuals treated with PEG and RBV [39-43]. In the present study, the difference among SVR according to genotypes was shown, with a SVR of 23.1% for genotype 1 and 46.9% for genotypes 2 and 3 (p = 0.03), very similar to what was found by Ferreira *et al.* (25.9% and 48.2%, respectively) [44].

The low HCV viral load was also a predictive factor for higher SVR (51.4% versus 25.1%; p = 0.01), corroborating the results found in other studies [43,45,46]. On the other hand, we found no association between CD4 and HIV-RNA count and the SVR rate. This is a controversial finding in the literature, since some authors found no relationship between CD4 cell count [47,48] or HIV-RNA viral load and SVR. However, Pineda *et al.* [27] observed that CD4 cell count above 300 cell/mm^3 was an independent factor of better SVR.

The type of PEG used was also a significant factor in the multivariate analysis, with a higher SVR observed in the group using PEG-α2a when compared to the group using PEG-α2b (37.3% versus 23.0% p = 0.001), which was not demonstrated by others authors [43]. This intriguing finding could not be explained easily because even in metanalyses, the difference in SVR between PEG-α2a and PEG-α2b was controversial [49]. Others factors, such as polymorphism of the *IL28B* gene, which could had affected these results, were not evaluated here.

Due to its retrospective nature, this study has some limitations, such as the small number patients who had not used HAART and the lack of control over the treatment indication and monitoring of patient adherence. Another limiting factor is the potential for the existence of unmeasured confounding variables,

which are characteristic of retrospective studies. However, as this was an uncontrolled study, it represents an important source of real-life information, unlike controlled studies, where there is usually a strict selection of study participants.

One of the main concerns in HIV/HCV-coinfected patients in the interferon-free era will be drug-drug interaction, making the choice of a HAART regimen very hard, especially with some of the DAAs used to treat HCV infection. One possible strategy for co-infected HIV/HCV could be a "test-and-treat" approach, with HCV infection treatment taking place before HAART is started, minimizing interaction between HAART and DAAs. In this hypothetical scenario, to know that the absence of HAART will not diminish SRV is of great importance.

Conclusions

SVR in HIV/HCV patients under therapy with PEG and RBV was low and independent of taking HAART. Low HCV-RNA, non-1 genotype, and the PEG-α2a are the only predictive factors of SVR found in our cohort.

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Conflict of interests: No conflict of interests is declared.