Original Article

HAART and liver: is it safe?

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Abstract

Introduction: Liver disease caused by hepatitis C virus (HCV) is a major cause of morbidity in HIV patients. This study investigates the possibility that chronic HCV increases the risk of hepatotoxicity after highly active antiretroviral therapy (HAART) initiation.

Methodology: The data from 30 coinfected HIV/HCV and 35 HIV monoinfected patients between August 2008 and August 2010, since the start of HAART, were analyzed along with data from every three months, with clinical/laboratory evaluation until the end of twelve months. The aim of this study was to assess risk and incidence of hepatotoxicity in both groups.

Results: Before the introduction of HAART, coinfected patients had higher average levels of transaminases than did the monoinfected group ($p < 0.001$). After initiation of HAART, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were higher in coinfected patients, regardless of type of HAART they received. Twenty-two (73%) of the coinfected patients had some degree of hepatotoxicity versus only seven (20%) of the monoinfected patients. No patient had severe hepatotoxicity. Risk of hepatotoxicity after HAART in a coinfected patient was 3.7 times higher than in a monoinfected patient (RR 3.7 [1.8–7.4], $p < 0.001$).

Conclusions: This study demonstrates that coinfected patients are at an increased risk for developing hepatotoxicity, but the clinical and immunological benefits of HAART are higher than the risk of hepatotoxicity and rarely justify discontinuation of therapy.

Key words: hepatotoxicity; HIV; hepatitis C; HAART

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Introduction

The epidemiologic pattern of human immunodeficiency virus (HIV) infection and its treatment approaches have changed significantly since this disease, currently considered chronic, was first acknowledged in 1981 [1].

In recent years, a further issue in the antiretroviral treatment scenario has been highlighted – coinfection with hepatitis C virus (HCV) and HIV. The increase in patient survival numbers following the introduction of highly active antiretroviral therapy (HAART) has seen the emergence of HCV infection and chronic hepatic diseases as important morbidity and mortality causes together with HIV [2,3]. Similar transmission routes for HIV and HCV mean that coinfection is currently common, especially in injecting drug users and patients who have undergone blood transfusions, differing slightly from risk groups with isolated HIV or HCV [2,4,5]. It is estimated that 30% to 35% of HIV-infected patients in the United States of America are coinfected with HCV [2,6].

Coinfected HIV/HCV patients progress in many cases to chronic hepatic disease and cirrhosis. Two authors, in different studies, demonstrated that 15% to 25% of cases of coinfected patients evolved to cirrhosis within 10 to 15 years, compared to 3% to 6% of HCV-monoinfected patients in the same time period [2,7]. However, these studies were conducted before the development of HAART. HIV seems to accelerate HCV hepatic disease, especially when related to immunodeficiency progression [2]. Risk factors related to higher progression rates for hepatic fibrosis include alcohol consumption, advanced age, and a T-CD4 lymphocyte count lower than 200 cells/mm3 [7,8].

The role of HAART in the natural history of HCV has been widely discussed. Antiretroviral therapy can initially increase hepatic necroinflammatory activity and accelerate chronic hepatitis C progression [2].

Therefore, many studies propose that HIV/HCV coinfection may increase the risk of developing hepatic disease after antiretroviral therapy is started, and that chronic hepatitis C acts as an independent risk factor for the progression of hepatic disease and hepatotoxicity in coinfected patients during HAART [2,3]. Nevertheless, there are beneficial long-term effects on the course of HCV infection in coinfected patients. This suggests that the use of HAART and the achievement of viral load suppression in these patients reverses the unfavorable course of HCV hepatic disease by the immunological response mechanism, especially in patients with low T-CD4 lymphocyte levels, with a decrease in necroinflammatory activity [9,10]. Additionally, some authors have shown that HAART use leads to a decrease in mortality by hepatic disease and to a decrease in fibrosis progression rates. This indicates that the absence of HAART treatment in coinfected patients will, in most cases, lead to hepatic disease progression and death [11-13].

The aim of this study was to evaluate the occurrence of hepatotoxicity and its related factors in HIV/HCV coinfected patients compared to HIV monoinfected patients.

Methodology

An observational prospective study was adopted involving HIV-diagnosed patients attending the Department of Infectious Diseases, Hospital Nossa Senhora da Conceição, in Porto Alegre, Rio Grande do Sul, Brazil. The hospital is a reference center for the treatment of individuals with HIV. All study participants were HIV positive with no prior history of treatment for the disease and were beginning HAART, regardless of their HCV coinfection status.

The exclusion criteria included diagnosis of the hepatitis B virus, current or previous history of treatment for hepatitis C, and active alcohol or drug use. Patients who failed to return for a second visit were also excluded, together with those with poor HAART treatment adherence or with virologic failure, defined by the lack of a 2-log reduction in HIV viral load within three months and continued detectability within six months.

The participants were categorized into two subgroups to facilitate analysis: HIV monoinfected and HIV/HCV coinfected. Demographic and laboratory data were assessed before initiation of the antiretroviral treatment and again every three months for the next year, resulting in five sets of evaluations. Patients attended the outpatient clinic on these occasions, where they received guidance and clinical/laboratory evaluation. The laboratory tests included measures of transaminases (AST and ALT), platelets, albumin and prothrombin time, along with T-CD4 and T-CD8 lymphocyte counts and HIV viral load measurement. The antiretroviral therapy used was also recorded and assessed, and a comparison was made between groups. Hepatic fibrosis was evaluated through biopsy using the METAVIR score [14]. The use of hepatotoxic medications such as tuberculostatic agents, sulfonamides, and antifungal drugs was recorded for evaluation and comparison between the groups for the occurrence of hepatotoxicity. The data was collected between August 2008 and August 2010.

Hepatotoxicity, defined by the increase of ALT or AST, was classified according to criteria set by the AIDS Clinical Trials Group (ACTG) and Sulkowski *et al*., relative to the upper limit of normal (ULN) [15,16] as follows: grade 1 (1.25–2.5 × ULN); grade 2 (2.51–5.0 × ULN); grade 3 (5.1–10 × ULN); and grade 4 (>10 × ULN). Hepatotoxicity was considered light for grades 1 and 2 and severe for grades 3 and 4, in accordance with the ACTG criteria [16,17]. To avoid confounding factors, patients with levels of AST and/or ALT higher than the ULN before beginning HAART were classified based on alterations relative to this base value rather than the pre-established ULN: grade 1 (1.25–2.5 × base value); grade 2 (2.6–3.5 × base value); grade 3 (3.6–5 × base value); and grade 4 (>5 × base value).

Statistical analyses

For the statistical analyses, continuous variables were presented as mean ± standard deviation and categorical variables as frequency and percentages. The Student's t-test was used to compare the group means and a Chi-square test was used for analysis of the frequencies. A generalized equations test was used with the corresponding Wald chi-squared distribution for significance, given that the variables had normal distribution. The delta values in relation to the baseline figures were also considered, controlling for the baseline value. The Bonferroni test was used for multiple comparisons.

Poisson regression analysis with robust variance was used to assess the risk of hepatotoxicity development in patients with and without coinfection. Variables included in the model were those that related to hepatotoxicity in the bivariate analysis with a statistical significance below 0.05.

A database was created using Microsoft Excel and the data analyzed using the Windows software

Statistical Package for Social Sciences (SPSS Inc., Chicago, USA).

Ethics

All participants were informed of the research aims and signed an informed consent form. This study was approved by the Research Ethics Committee of the Hospital Nossa Senhora da Conceição under protocol No. 136/08, dated 8/04/2008.

Results

From August 2008 to August 2010, a total of 97 HIV patients with no previous history of treatment were recruited and began antiretroviral treatment. Of these, 32 (33%) were excluded in line with the established criteria (virological failure, not returning to consultation, or death), reducing the group to 65 patients (67%). The baseline characteristics of these participants prior to the commencement of HAART are presented in Table 1. Two treatment regimens were adopted: 51 (78%) patients were prescribed nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (all using efavirenz), and 14 (22%) began treatment with NRTIs and ritonavir-boosted protease inhibitors (PI) (10 used lopinavir/ritonavir and 4 used atazanavir/ritonavir).

PCR testing confirmed the HCV status of the participants, with 30 (46%) testing positive and 35 (54%) testing negative. The use of injectable drugs (UID) was the main route of HCV infection, reported by 20 (66%) of the patients from the HIV/HCV coinfected group. A comparison of the HIV/HCV coinfected group with the HIV monoinfected, prior to beginning HAART, showed no differences in relation to gender, age, ethnicity, body mass index (BMI), T-CD4 and CD8 lymphocyte counts and HIV viral load, as presented in Table 1. None of the coinfected patients presented a clinical or histopathological diagnosis of hepatic cirrhosis. There was no segment loss among the patients included in the study.

Of the 30 patients from the coinfected group, 22 (73.3%) were HCV genotype 1, 6 (20%) were genotype 3, and 2 (6.6%) were genotype 2. A total of 16 patients (53%) underwent a hepatic biopsy. The METAVIR scoring system [14] was applied to grade the hepatic fibrosis of the 16 patients from the histopathological evaluations, with 2 (12%) being grade 1, 8 (50%) being grade 2, 1 (6%) being grade 3, and 5 (32%) not having hepatic fibrosis (F0). None of the patients presented grade 4 fibrosis.

The T-CD4 and T-CD8 lymphocyte counts carried out before the start of HAART and subsequently every three months thereafter showed no statistical difference between the groups during the trial. Likewise, the behavior of the T-CD4 and T-CD8 lymphocyte count curves according to the generalized estimating equations test was similar between the groups for all visits.

Transaminase levels before and after HAART

Higher mean AST and ALT levels before the initiation of HAART were presented by the coinfected patients in comparison to the monoinfected group ($p < 0.001$), as shown in Tables 2 and 3. Fourteen (46%) of the coinfected patients had increased AST or ALT levels before HAART initiation, versus two (6%) from the monoinfected group. After the beginning of HAART, serum AST and ALT values significantly increased in the HIV/HCV coinfected group, whereas no significant variations in AST and ALT levels were seen in the monoinfected patients during the 48 weeks of follow-up. The use of a PI or NNRTI did not act as a risk factor for transaminase increases in either of the studied groups. The increase in magnitude of the AST and ALT levels was higher in the HCV coinfected group, regardless of the type of HAART used.

Using the generalized estimating equations test, the behavior of the curves was shown to be different between the groups for AST and ALT, as presented in Figures 1 and 2, considering the deltas in relation to the baseline values and controlling for the baseline value, with $p = 0.012$ for both the AST and ALT.

The variables of age, gender, type of HAART, BMI, and T-CD4 lymphocytes were not found to influence the AST or ALT variations.

Hepatotoxicity prevalence

Twenty-two (73%) of the coinfected patients presented some degree of hepatotoxicity with AST or ALT elevation after HAART initiation, whereas only seven (20%) monoinfected patients were affected in the same way, with statistically significant differences between the groups.

An evaluation of AST in the coinfected group found that grade 1 hepatotoxicity occurred in fifteen (50%) patients and grade 2 occurred in two (7%) patients, with grades 3 and 4 hepatotoxicity not reported in this group. Only three (9%) patients in the monoinfected group displayed grade 1 hepatotoxicity; the remaining grades 2, 3 and 4 were not observed.

Table 1. Basal characteristics of patients before HAART introduction

	Coinfected HIV/HCV (n = 30)	Monoinfected HIV (n = 35)	P
Male, n (%)	22 (73%)	23 (66%)	> 0.05
Female, n (%)	8 (27%)	12 (34%)	> 0.05
Age (years)	41.8 ± 7.9	38.8 ± 10.1	0.09
UID in the past	20 (66%)	2 (6%)	< 0.05
Caucasians	18 (60%)	24 (68%)	> 0.05
BMI	23.6 ± 2.1	24.3 ± 3.6	0.68
CD4+, cells/ mm^3	116.3 ± 87.7	117 ± 101.6	0.98
CD8+, cells/ mm^3	593 ± 466.98	583 ± 373.79	0.68
HIV RNA (copies/mL)	182,000	207,000	0.56
AST (U/l)	41.4 ± 20.1	28.5 ± 11.1	< 0.01
ALT (U/l)	38.1 ± 17.3	26 ± 12.4	< 0.01

UID: use of injectable drugs; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table 2. Mean variation of AST during 48 weeks of follow-up

	Coinfected HIV/HCV (n = 30)	Monoinfected HIV (n = 35)	P
AST (week 0)	41.4 ± 20.1	28.5 ± 11.1	< 0.01
AST (week 12)	46 ± 24.8	28.7 ± 17.5	< 0.01
AST (week 24)	54.6 ± 27.1	25.4 ± 10.7	< 0.01
AST (week 36)	43.9 ± 10.5	22.9 ± 8.7	< 0.01
AST (week 48)	51.5 ± 22.6	22.5 ± 8.7	< 0.01

AST: aspartate aminotransferase

Table 3. Mean variation of ALT during 48 weeks of follow-up

	Coinfected HIV/HCV (n = 30)	Monoinfected HIV (n = 35)	P
ALT (week 0)	38.1 ± 17.3	26 ± 12.4	< 0.01
ALT (week 12)	47.4 ± 29.9	32.4 ± 29.8	< 0.01
ALT (week 24)	61.9 ± 33.9	25.3 ± 15.1	< 0.01
ALT (week 36)	50.7 ± 15.4	24.8 ± 22.2	< 0.01
ALT (week 48)	62.1 ± 38.5	25.2 ± 15.9	< 0.01

ALT: alanine aminotransferase

Figure 1. Variation of ALT during 48 weeks of follow-up

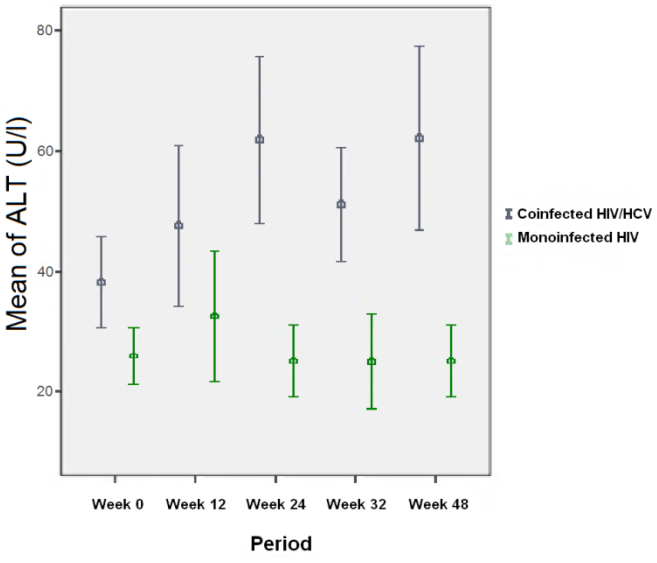
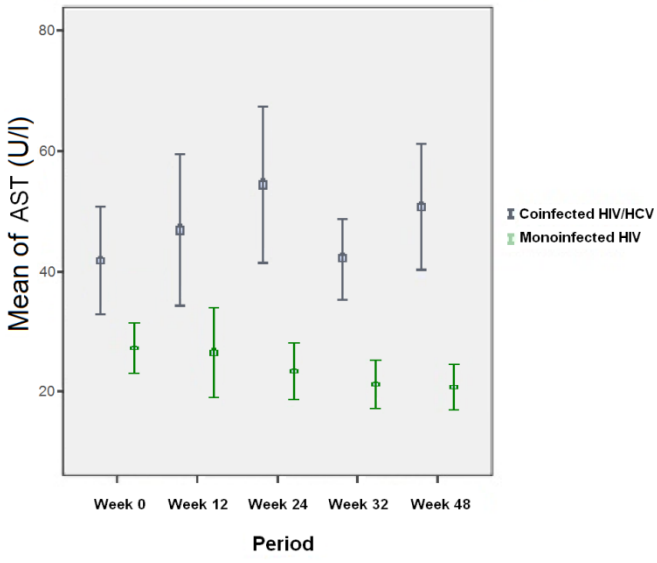


Figure 2. Variation of AST during 48 weeks of follow-up



An evaluation of ALT levels in the coinfected group revealed that grade 1 hepatotoxicity occurred in 14 patients (47%) and grade 2 occurred in 6 (20%) patients, while in the monoinfected group, 5 (14%) patients had grade 1 hepatotoxicity and 2 (6%) had grade 2 hepatotoxicity. No patients developed severe hepatotoxicity, defined as grade 3 or 4. The type of HAART administered was not found to be associated with the risk of hepatotoxicity; however, a history of injectable drug use was shown to be associated.

An analysis of the period in which hepatotoxicity was verified showed it occurred in 18 (62%) patients until the sixth evaluation month, with recovery and further improvement in transaminase levels in the following months (14 patients were coinfected and 4 were monoinfected).

The occurrence of hepatotoxicity was found not to be related to gender, type of HAART, and previous use of alcohol or hepatotoxic drugs other than antiretrovirals (Table 4).

Furthermore, hepatotoxicity was not related to patient age, T-CD4 lymphocyte variation, or HCV genotype 3.

The risk of a patient developing hepatotoxicity was 3.7 times higher in the coinfected group than in the monoinfected (RR 3.7; 95% CI, 1.8–7.4; $p < 0.001$). When this relation was adjusted for UID, the risk was 3.3 times higher (RR 3.3, 95% CI, 1.2–9.5; $p < 0.001$).

Clinical outcomes and adverse effects

Following a 48-week period of evaluation, only three (10%) patients from the coinfected group and three (8.6%) from the monoinfected group failed to attend the final follow-up visit. Two patients stopped therapy due to intolerance of the antiretroviral medications and a further four stopped for unexplained reasons. Data for these patients were included until virologic confirmation of HAART treatment abandonment. No patient had the antiretroviral therapy suspended due to hepatotoxicity.

Discussion

Hepatotoxicity, characterized by the increase in hepatocellular cytolysis rates and significant increases in serum transaminase levels, is a common complication in HIV-positive patients receiving HAART [2,17,18]. An increase in hepatic enzymes can be observed in about 6% to 30% of patients receiving antiretroviral therapy [16,19]. However, severe hepatotoxicity (defined as an increase in transaminase levels five times greater than the normal limit) leading to treatment discontinuation has been reported in less than 10% of patients receiving treatment [2,16]. In the present study, 29 (45%) patients presented some degree of hepatotoxicity, with the percentage being higher in the coinfected group, which is in accordance with the literature. However, no patient presented severe hepatotoxicity or required the suspension of HAART as a result.

Studies suggest that chronic hepatitis C increases the risk of hepatotoxicity by antiretroviral therapy [16,19-22]. Some authors have postulated that hepatitis C is linked to an increased risk of hepatotoxicity for all antiretroviral regimens [23,24], while others have found an increased risk related to only a few antiretroviral agents, such as ritonavir or nevirapine [21,25]. In the present study, grade 1 and 2 hepatotoxicity was found in 22 patients (73%) in the coinfected group; however, the type of HAART was not associated with hepatotoxicity risk. The data shown herein are close to that of some authors who described the incidence of hepatotoxicity in HIV/HCV

Table 4. Association between hepatotoxicity and demographic variables in the groups

	Hepatotoxicity	P	RR (IC 95%)
Coinfected HIV/HCV	22 (77.3%)	< 0.001	3.3 (1.2–9.5)
Monoinfected HIV	7 (20%)		
Male gender	22 (48.9%)	0.442	-
Female gender	7 (35%)		
HAART 1	23 (45.1%)	0.999	-
HAART 2	6 (42.9%)		
Alcohol abuse in the past	11 (57.9%)	0.129	-
No alcohol abuse in the past	11 (32.4%)		
UID in the past	16 (72.7%)	0.001	1.3 (0.6–2.9)
No UID in the past	8 (25%)		
Use of hepatotoxic drug (non-HAART)	14 (48.3%)	0.778	-
No use of hepatotoxic drug (non-HAART)	15 (41.7%)		

HAART 1: 2 NRTI and 1 NNRTI; HAART 2: 2 NRTI and 1 IP with ritonavir boosting; UID: use of injectable drugs

coinfected patients as varying from 25% to 75% [16,18,26,27]. However, it is worth highlighting that unlike the present research, most of these studies had patients with T-CD4 lymphocyte counts equal to or higher than 200 cells/mm3, a situation that may underestimate the occurrence of hepatotoxicity.

The risk of developing hepatotoxicity was 3.7 times higher in the coinfected group than in the monoinfected group (RR 3.7; 95% CI, 1.8–7.4; $p < 0.001$), a similar finding to that described by den Brinker *et al*. and Sulkowski *et al*. [16,20]. Evaluation of the concomitant use of HAART and hepatotoxic drugs, other than the antiretrovirals, showed no difference between the groups; concomitant use, therefore, was found not to be a confounding factor for hepatotoxicity.

It was further observed in this study that hepatotoxicity occurred until the sixth evaluation month in 18 patients (62%). Data showed the earlier occurrence of hepatotoxicity linked to HIV/HCV coinfection, with the immune-mediated mechanism dependent on the initial T-CD4 lymphocyte counts, as describe by some authors [18,28,29]. A further hypothesis for the increase of transaminases in coinfected patients, besides hepatotoxicity, could be the activation of the hepatitis C virus with an increase in the HCV RNA levels after the beginning of HAART, a condition resulting from the immune reconstitution inflammatory syndrome mechanism. Factors related to this condition include young age and low T-CD4 lymphocyte counts [30,31].

The data presented herein demonstrates that HIV patients are at considerable risk of secondary hepatotoxicity following the use of HAART. This risk is greater for HIV/HCV coinfected patients, suggesting the development of cumulative hepatotoxicity and/or immune reconstitution inflammatory syndrome after the beginning of antiretroviral therapy, with no relationship to the type of HAART used. These patients must be subject to a rigorous and periodic follow-up program to evaluate enzyme and hepatic function. We believe that an extended patient follow-up period with the performance of fibrosis evaluations (invasive or non-invasive) may bring valuable information, adding to knowledge on this important subject. Possible limitations of the present study are the small sample size of individuals evaluated and the short time of follow-up of the patients (one year).

Conclusions

Although hepatotoxicity may be more common in patients with HCV, studies have shown the positive impact of antiretroviral treatment on hepatic fibrosis progression in coinfected patients [10,12]. The present study demonstrated that the benefits outweighed the increased risk of hepatotoxicity that coinfected individuals exhibit, as the patients presented an excellent immunological response, similar to HIV-monoinfected patients. Severe hepatotoxicity was very uncommon, thus rarely justifying therapy discontinuation.

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