

Barriers to treatment of hepatitis C in HIV/HCV coinfecting adults in Brazil

ABSTRACT

The objective of this study was to assess the prevalence of barriers to interferon treatment in a population of HIV/HCV coinfecting patients. A cross-sectional study was conducted at two AIDS Outpatient Clinics in Brazil. The study included all HIV infected patients followed at these institutions from January 2005 to November 2007. Medical records of 2,024 HIV-infected patients were evaluated. The prevalence of anti-HCV positive patients among them was 16.7%. Medical records of HCV/HIV coinfecting patients were analyzed. 189 patients with the following characteristics were included in our study: mean age 43 years; male gender 65%; former IDUs (52%); HCV genotype 1 (66.4%); HCV genotype 3 (30.5%); median CD4+ T cell count was 340 cells/mm³. Among 189 patients included in the analyses, only 75 (39.6%) were considered eligible for HCV treatment. The most frequent reasons for non-treatment were: non-compliance during clinical follow-up (31.4%), advanced HIV disease (21.9%), excessive alcohol consumption or active drug use (18.7%), and psychiatric disorders (10.1%). **Conclusions:** In Brazil, as in elsewhere, more than half of HIV/HCV coinfecting patients (60.4%) have been considered not candidates to received anti-HCV treatment. The main reasons may be deemed questionable: non-adherence, drug abuse, and psychiatric disease. Our results highlight the importance of multidisciplinary teams to optimize the access of coinfecting patients to HCV treatment.

Keywords: hepatitis C, HIV, coinfecting, treatment.

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INTRODUCTION

Liver disease associated with hepatitis C (HCV) is a major problem among HIV-positive individuals. Different studies in North America and Europe have shown that 30% of HIV-infected patients are coinfecting with hepatitis C virus. In Brazil this prevalence ranges from 4.1% to 53.8% according to different studies.¹⁻¹⁰

In Brazil, the AIDS treatment program guarantees free access to highly active antiretroviral therapy (HAART) for all people living with HIV/AIDS in need of treatment. According to recent data, in Brazil around 600,000 individuals might be HIV infected.¹¹ Therefore, it would be reasonable to think that about 200,000 of these patients might be HCV coinfecting.

HIV significantly worsens liver disease in HCV-positive patients and appears to accelerate progression to cirrhosis. Liver-related mortality is higher in patients infected by both HCV and HIV compared to those with HCV alone.¹²

Successful treatment of HCV with interferon-based therapy reduces the morbidity and mortality of patients. Therefore, in HIV coinfecting patients, treatment of hepatitis C should be a priority. Unfortunately, reports from different parts of the world have demonstrated that only 30% of coinfecting HIV/HCV patients are considered eligible for interferon therapy.¹³⁻¹⁹

In Brazil, there is no data regarding this eligibility on coinfecting population. In Brazil, HIV population is insured by a government-sponsored health care system that covers treatment for HIV and viral hepatitis coinfections. Lack of access to treatment will result in an increase in end-stage liver disease with its high socioeconomic impact in the future. Strategies aimed at improving the eligibility of interferon-based treatment in this population are urgently needed.

The objective of our study was to analyze the rate of treatment among HIV/HCV patients

Authors

Maria Cássia Mendes-Corrêa¹
Martins LG²
Ferreira PA³
Tenore S³
Leite OH¹
Leite AG^{1,2}
Cavalcante AJW¹
Shimose M²
Silva MH²
Uip DE¹
Abrão Ferreira PR³

¹Infectious Diseases Research Unit, Fundação e Faculdade de Medicina do ABC, Santo André, São Paulo, Brazil.

²AIDS Outpatient Clinic, São Bernardo do Campo, São Paulo, Brazil.

³AIDS Outpatient Clinic, Faculdade de Medicina da Universidade Federal de São Paulo, São Paulo, Brazil.

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Correspondence to:

Maria Cássia Mendes-Corrêa
Rua Capote Valente, 432, cj. 145
São Paulo – SP – Brazil
CEP: 05409-001
Phone: +55-11-30820427
Email: cassiamc@uol.com.br

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followed in two AIDS Outpatient Clinics in Brazil, in order to determine the reasons for non-treatment in this group. Our goal was to identify specific factors that could limit the availability of HCV treatment in the coinfecting population, in order to determine potential opportunities for improving the treatment rate in this group.

MATERIAL AND METHODS

Study design

A cross-sectional study was conducted at two AIDS Outpatient Clinics in Brazil. The study included all HIV infected patients followed at these institutions from January 2005 to November 2007.

Patients and methods

Patient population

All HIV-infected patients followed at these institutions were initially included.

From January 2005 to November 2007, medical records were reviewed to identify anti-HCV reactive patients.

Data collection

A standard collection form was created by the authors of this article, in order to optimize the type and means of data collection. The forms were prospectively filled out by trained physicians who were also responsible for medical care in the units. Medical records from these patients were reviewed to analyse the demographic and clinical characteristics necessary to fill out the collection forms. Data were obtained on: age, sex, use of antiretroviral therapy, CD4+ T cell count (current), history of exposure to HCV therapy.

According to the standardized data collection form used in the present study, the reasons related to non-treatment were as follows: non-compliance during clinical follow-up, psychiatric disorders, active drug use, excessive alcohol ingestion, other comorbidities (not HIV-related), advanced HIV disease, CD4+ T cell count < 200 cells/mm³, advanced liver disease, unfavorable socioeconomic conditions, patient refusal to treatment, patient refusal to liver biopsy, and others.

Eligibility study

In the present study, eligible patients to therapy were defined as patients who had indication for HCV therapy and were currently on therapy for HCV or had received it in the past. Non-eligible patients were defined as patients without indication for HCV therapy according to clinical practice guidelines and patients that despite no absolute contraindication for therapy did not receive it for different reasons (according to the standardized data collection form).

In order to better analyze eligibility to treatment, patients with undetectable HCV-RNA or with no histological indication for therapy were not included in the eligibility

study. We also excluded individuals with missing information regarding clinical contraindications for HCV therapy. Criteria for treatment were defined based upon current clinical practice guidelines.

Analyses

A descriptive analysis was performed to tabulate the primary and contributing factors accounting for why patients did not initiate HCV therapy.

RESULTS

The study was conducted at two AIDS Outpatient Clinics in Brazil: AIDS Outpatient Clinic, São Bernardo do Campo, São Paulo, Brazil (SBC) and AIDS Outpatient Clinic of Faculdade de Medicina da Universidade Federal de São Paulo (UNIFESP). 2024 HIV-infected patients were evaluated from January 2005 to November 2007. The prevalence of anti-HCV positive patients among them was 16.7 % (Table 1). Plasma HCV RNA levels were measured in anti-HCV antibody positive patients. Spontaneous HCV clearance had occurred in 69 (36.5%) anti-HCV antibody positive patients.

A total of 340 coinfecting patients were identified. One hundred eighty-nine patients were included in our study. One hundred fifty-one patients were excluded in our study

Table 1. Characteristics of patients (189) in a retrospective study of patients with hepatitis C virus (HCV) and HIV coinfection

Age, years, mean (range)	43 (22-75)
Male	121 (65%)
CD4+ cell count, cells/mm ³ Median	394 (20-1490)
Antiretroviral therapy history yes	166 (88%)
Risk category for HCV transmission UDI	98 (%)
HCV Genotype	
Genotype 1	113 (66.4%)
Genotype 2	04 (2.3%)
Genotype 3	52 (30.5%)
Genotype 4	01 (0.5%)
Genotype - Data not available	19/189 (10%)
RNA-VHC Non-reactant	69 (36.5%)
Liver biopsy available	95 (50.3%)
HIV-HBV-HCV coinfection	13 (6.8%)

*Genotype available for 170 patients.

for the following reasons: missing clinical data (n = 49), absence of histological criteria for HCV treatment (n = 22), RNA-HCV non-reagent (n = 69), sudden death of unknown cause (n = 03), transference of medical unit (n = 8) (Table 3).

Table 1 summarizes demographic and clinical characteristics of included patients. The mean age was 43 years (range 22–75). Most patients were male (65%) and former IDUs (52%). Of the total group, 95 (50.3%) patients underwent liver biopsy. HCV genotype 1 was the most prevalent genotype (66.4%), followed by genotype 3 (30.5%), genotype 2 (2.3%), and genotype 4 (0.5%).

With regard to HIV infection status, the median CD4+ T cell count was 340 cells/mm³ (20-1490). HAART was being taken by 88% of patients.

Among 189 patients included in the analyses, only 75 (39.6%) of HCV/HIV coinfecting patients were considered eligible for HCV treatment. They had already been exposed to interferon (IFN)-based therapies or were currently under treatment. One hundred fourteen patients (72.7%) were considered not eligible for HCV therapy (Table 2). The reasons for non-treatment of this infection were as follows: unfavourable socioeconomic conditions (0.5%), waiting for liver biopsy (0.5%), patient refusal to liver biopsy (2.2%), patient refusal to treatment (2.2%), other comorbidity (5.5%), decompensate cirrhosis (6%), psychiatric disorder (10.1%), excessive alcohol consumption or active drug use (18.7%), advanced HIV disease or CD4 < 200 cells/mm³ (21.9%), non-compliance during clinical follow-up (31.4%). There were 1.5 reasons for non-treatment per patient (Table 4).

Table 2. Eligible and non-eligible patients among 189 HIV/HCV coinfecting patients

	SBC	UNIFESP	Total
Eligible patients	43 (43.4%)	32 (35.5%)	75 (39.6%)
Non-eligible patients	56 (56.6%)	58 (64.5%)	114 (72.7%)
Total	99	90	189

Table 3. Reasons for non-inclusion in the eligibility study (151 HIV/HCV coinfecting patients)

	SBC (n) %	UNIFESP (n) %	Total (n) %
Missing clinical data	4	45	49 (32.4)
RNA-VHC non-reagent	63	6	69 (45.7)
Minimal hepatic lesions	10	12	22 (14.5)
Sudden death	2	1	03 (02)
Medical unit transference	8	-	08 (5.3)
Total	87	64	151 (100)

Table 4. Reasons for the non-treatment of HCV infection in 114 HIV/HCV coinfecting patients

Reasons for non-treatment	SBC	UNIFESP	TOTAL	
	n	n	n	%
Unfavorable socioeconomic conditions	1	-	1	0.5
Waiting for liver biopsy	1	-	1	0.5
Liver biopsy refusal	4	-	4	2.2
Patient refusal to treatment	3	1	4	2.2
Other comorbidity (endocrinologic, neurologic, vascular etc.)	7	3	10	5.5
Decompensated cirrhosis	5	6	11	6.0
Psychiatric disorder	16	4	20	10.1
Excessive alcohol consumption or active drug use	22	12	34	18.7
Advanced HIV disease or CD4 < 200 cells/mm ³	20	20	40	21.9
Non-compliance during clinical follow-up	45	12	57	31.4
Total	124	58	182	100

DISCUSSION

According to our data, only 39.6% of the HIV/HCV coinfecting patients followed in two Brazilian institutions were considered eligible for HCV treatment. The reasons for non-treatment of this infection were numerous, with 1.5 reasons per patient. The most frequent reasons were: non-compliance during clinical follow-up (31.4%), advanced HIV disease or $CD4 < 200$ cells/mm³ (21.9%), excessive alcohol consumption or active drug use (18.7%), and psychiatric disorders (10.1%). Patient refusal to treatment or patient refusal to biopsy was occurred in only a minority of cases (4.4%).

Several studies have demonstrated comparably low rates of treatment uptake in the setting of HIV/HCV coinfection in different parts of the world.¹³⁻¹⁹ Results regarding specific barriers to treatment were quite similar among those studies. Psychiatric disorders, excessive alcohol consumption and active drug use have frequently been mentioned as important barriers to treatment among HIV/HCV coinfecting patients, as well as among HCV mono-infected patient.²⁰⁻²⁴ Depression is one of the most frequent diagnoses among all psychiatric disorders in HCV mono and coinfecting patients. In the HIV coinfecting population, it has been associated with decreased adherence to medical therapy²⁵ and increased mortality.^{26,27} Our study is consistent with these data. Among our group of coinfecting patients, severe psychiatric disorders, mainly severe depression, non-compliance to therapy, and advanced HIV disease were strongly associated with non-eligibility to HCV treatment.

Considering that HIV coinfection is currently an exclusion criteria at almost all transplant centers, there may be more than an urgency to treat these patients. Efforts to improve the rate of treatment in the coinfection group must accompany the improvements being realized in available treatment of chronic hepatitis C. Recognition that HIV-infected patients who also have hepatitis C may be prone to more depressive symptoms has important management implications. Institution of antidepressant therapy may enhance medical adherence, which is the key to successful antiretroviral management and patient's ability to tolerate treatment for HCV infection.

Individuals who are not currently eligible to receive HCV treatment should be referred to management of comorbid conditions and re-evaluated at regular intervals to determine if these barriers have been overcome (e.g., successful treatment of depression). Ideally, a multidisciplinary team including experts in addiction medicine, psychologists, and psychiatrists should take care of these patients. Physicians must carefully weigh the potential benefits and risks of therapy for each individual, taking into account the best predictor of treatment response.

It would be important to emphasize that in our opinion not all HCV/HIV coinfecting patients are adequate candidates

for HCV therapy. The need for treatment mainly relies on the severity of liver damage, the virological characteristics of HCV infection (genotype, viral load), and the HIV status. Different contraindications for HCV therapy, however, may discourage its use (i.e., severe neuropsychiatric conditions etc.).

In patients with CD4 counts below 200 cells/mm³, the decision to treat HCV infection must be made cautiously. In this group of patients, HCV therapy should be deferred, mainly due to concerns on toxicity since the response may be much poorer. Individuals with prior history of serious neuropsychiatric disorders should not be treated, because interferon can exacerbate these conditions. Patients currently engaged in heavy alcohol intake or illegal drug addiction practices should delay treatment, whereas all efforts should be devoted to put them into detoxification programs.

Successful treatment and virus eradication with interferon-based therapy can potentially reduce the morbidity and mortality associated with the development of cirrhosis from hepatitis C. Solving the problems of poor adherence to medical visits, and active alcohol and drug abuse, could ultimately result in the treatment of HCV in many coinfecting patients.

Our study had some limitations. First, the information about reasons for non-treatment was collected from medical charts that may vary in completeness and be more vulnerable to bias. An attempt was made to minimize completeness bias by applying the same standardized questionnaire to all cases included. Second, this study was largely derived from two urban centers. Therefore it may be less generalized to other populations in Brazil. Third, treatment eligibility is likely to vary over time so that treatment-ineligible persons may become eligible as their clinical and social circumstances change. Re-evaluations at regular intervals of the same patient population could better determine these barriers. Fourth, unfavorable socioeconomic conditions may not have been fully evaluated, since all information came from medical charts. In order to minimize this kind of bias, the physician in charge of each patient was invited to complete the standardized collection form to all cases included.

Despite these limitations, we believe that our results demonstrate that coinfection treatment requires expertise in managing addictions, psychiatric illness, and poverty. Like many other services in the world, Brazil's AIDS and hepatitis treatment programs have very limited access to these services.

According to our data, 31.4% of the subjects involved in our study were not referred to treatment because they were non-adherent to HIV treatment and were non-compliant during clinical follow-up. We understand that one way to achieve a more significant number of coinfecting patients under HCV treatment is to optimize adherence in HIV programs. To achieve success with currently available therapies, a multidisciplinary clinical care model is necessary.

A multidisciplinary model of care could address the social and psychiatric issues frequently encountered in this population, reduce the loss of patients to follow-up, effectively educate and prepare patients, and treat a larger proportion of the HIV/HCV coinfecting population.

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Erratum

In the published article, one of the author name was missing. The corrected author group is provided below:

Maria Cássia Mendes-Corrêa¹, Martins LG², Ferreira PA³, Tenore S³, Leite OH¹, Leite AG^{1,2}, Cavalcante AJW¹, Shimose M², Silva MH², Uip DE¹, Abrão Ferreira PR³

¹ Infectious Diseases Research Unit, Fundação e Faculdade de Medicina do ABC, Santo André, São Paulo, Brazil.

² AIDS Outpatient Clinic, São Bernardo do Campo, São Paulo, Brazil.

³ AIDS Outpatient Clinic, Faculdade de Medicina da Universidade Federal de São Paulo, São Paulo, Brazil.