Determinants of immunological and virological responses to antiretroviral therapy amongst HIV-infected adults in central Argentina: negative influence of hepatitis C infection

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Background: The purpose of this study was to update the epidemiological data on the prevalence of coinfection with hepatitis C virus (HCV) and HIV, and to identify whether specific clinical and epidemiological factors influenced the response of HIV-positive adults to highly active antiretroviral therapy (HAART).

Methods: This retrospective observational cohort study of 238 HIV-infected patients evaluated the effect of different epidemiological and clinical parameters (including HCV coinfection) on therapy response among HIV-infected adults initiating HAART. Multiple logistic regression models were used to identify factors associated with therapy response and estimated risk coefficients.

Results: Seroprevalence of HCV infection in this population was 26% (62/238). We did not observe a significant association between immunological or virological response relating to patient gender or HAART regimen. However, this analysis showed that HCV serological status, age at HIV diagnosis, duration of treatment and WHO clinical stage of AIDS (<200 CD4 cells/ml independently of viral load either < or > to 100 000 copies/ml), were significantly associated with immunological and virological responses to HAART.

Conclusions: These results show further evidence that hepatitis C serostatus is associated with a reduced response to HAART.

Keywords: CD4 cell counts, HAART, HIV/HCV coinfection, response to therapy, viral load

Introduction

Worldwide, hepatitis C virus (HCV) accounts for approximately 130 million chronic infections, with an overall prevalence of 3%. HIV/HCV coinfection affects 4 to 5 million people. It is well established that HIV has an impact on the natural history of HCV, including a higher rate of viral persistence, increased viral load, and more rapid progression to fibrosis, end-stage liver disease, and death. Whether HCV has a negative impact on the disease progression of HIV continues to be debated.[1]

Advances in highly active antiretroviral therapy (HAART) have dramatically reduced morbidity and mortality due to AIDS;[2–4] however, all antiretrovirals have the potential to cause acute and long-term hepatotoxicity and this risk is increased two- to threefold in the presence of chronic liver disease such as that caused by HCV infection.[5] Coinfection with HIV and HCV is, therefore, a substantial medical and public health concern because it complicates patient management and might also decrease the effectiveness of HAART.[6–8]

Other clinical and epidemiological factors and adherence to antiretroviral drugs have also been associated with differences in immunological and virological outcomes in patients taking HAART.[9–11] Although data are conflicting, several studies indicate that women have lower plasma HIV RNA levels than men.[12] Since this measure influences the timing of HAART initiation, it is plausible that women might start treatment later than men, which could contribute to poorer outcomes in female patients compared to male patients.[9,12]

HAART is comprised of complex drug regimens, which require strict adherence to complicated dosing schedules to ensure optimal long-term clinical and survival benefits. At least 95% adherence is required for an adequate virological and immunological response.[13,14] A 2010 study demonstrated that multiple patient-related factors (age, gender, baseline CD4 count and contribution

to household income) have an effect on the adherence to HAART in the first month.[14]

Previous studies in Argentina have documented a general prevalence of HCV infection close to 2%.[15] In addition, a high prevalence of HCV has been reported in studies on small rural communities in Argentina.[16–20] There are also studies on vulnerable populations and coinfected patients.[21–24] In an earlier study we conducted in central Argentina the seroprevalence of HCV/HIV coinfection was 12.3% (38/310).[25] Although HIV-infected patients have been included in the National Public Health program for free access to HIV diagnosis and treatment since the 90s, management of HCV infection was only added to this program in 2010. However, there is limited data regarding factors that predict optimal HAART in our population.

The purpose of this study was to update the epidemiological data on prevalence of HCV/HIV coinfection and to identify whether specific clinical and epidemiological factors (gender, age, HAART scheme, HCV coinfection and disease stage according to the WHO[26]) influence virological and immunological responses to HAART in HIV-positive adults. The knowledge and understanding of such factors is particularly important given the increasing number of patients initiating HAART who need to be maintained on therapy. The findings will be useful in developing tools to assist clinicians in the identification of factors related to poor response prior to initiating therapy. The results can be further used to shape communication and counseling strategies, prior to treatment initiation.

Materials and Methods

Data source and study population

Since 1990, antiretroviral drugs have been centrally distributed in Argentina, at no cost to eligible HIV-infected patients. In 1996 the distribution of antiretroviral drugs became the responsibility of the National AIDS Program and they were distributed among patients through the AIDS Program from the province of Cordoba.

Population and data collection

This was a cohort study of 238 HIV-infected patients who initiated antiretroviral therapy at a national clinical hospital, a public health center in Cordoba (the second most populated inland province of Argentina).

Epidemiological and clinical data were obtained from medical records and collected at baseline, with at least two or three measurements recorded per year thereafter, throughout the 48-month duration of the study.

The patients in this study were recruited from an HIV program in Cordoba, Argentina. All patients included met certain criteria. They all initiated HAART from April 2004 through to December 2007 and had one cell count and plasma HIV RNA level measurement before starting therapy. All patients enrolled in the study had to be at least 18 years old and received a HAART regimen consisting of at least three antiretroviral drugs, including either a nucleoside reverse-transcriptase inhibitor, a non-nucleoside reverse-transcriptase inhibitor, or a protease inhibitor.

Patients were considered eligible for HAART if they were symptomatic (classed as any symptom corresponding to categories B or C of the CDC classification or marker or opportunistic diseases not listed in this classification) or stages 3 and 4 of the WHO clinical staging system, regardless of CD4 count. Asymptomatic patients with CD4 counts <200 or 200–350 cells/ml were also eligible for HAART. The initiation of HAART was considered in those asymptomatic patients with a high RNA HIV level (>100 000 copies/ml).[27] Patients were excluded if they had an ethanol consumption of >50 g/day, hepatitis B coinfection, noninfective liver diseases or HAART adherence <95%. Adherence to HAART was assessed by a pill count taken from each patient when they attended the health center. Any patient with HCV infection received appropriate antiviral treatment.

Variables

The following covariates were considered for inclusion in the multivariate model: gender, age at HIV diagnosis (≥40 years old vs <40 years old), disease stage according to the WHO clinical staging system for HIV/AIDS, HAART regimen and HCV infection.

Outcomes

The clinical outcomes used in the therapy response analyses included immunological response to treatment (defined as a sustained increase in CD4+ cell counts of >350 cells/ml from baseline until the end of follow-up at 48 months) and virological response (defined as a sustained decrease in plasma HIV RNA load of <50 copies/ml from baseline until the end of follow-up).

Study procedures

CD4 counts were performed by using flow cytometry (FacsCount, Becton-Dickinson, NJ, USA). HIV-1 viral loads were obtained using an HIV RNA PCR test [Roche Ultrasensitive HIV RNA Amplicor (Branchburg, NJ, USA) Monitor versión 3.0, detection limit 20–50 copies/ml]. The presence of anti-HCV antibodies was tested in duplicate by Hepatitis C (anti-HCV) ELISA (Wiener Lab., Rosario, Argentina). For sequence analysis, HCV-RNA was extracted from 140 μl of serum with a QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany), reverse transcribed and amplified with conserved primers for 5'-noncoding (5'NCR) as previously described.[28] HCV genotyping was determined by the restriction length polymorphism analysis of the 5'NCR.[28]

Statistical analysis

We calculated mean values and crude rates with 95% exact binomial CIs, after Pearson or Fisher tests for bivariate analysis approach. Statistical significance was established at $p < 0.05$. Odds ratios and 95% CIs were used to quantify the associations between variables and a multiple logistic regression model was used to identify factors associated with, and estimated, risk coefficients. Variables associated with therapy response in univariate analysis ($p < 0.05$) were entered into the model by means of a backward selection method (data not shown). We tested potential confounders before selecting the final model, that is, we entered significant variables into a selected multiple model and estimated their effects on the ORs of the independent variables. The statistical package STATISTICA version 6.0 (2300 EAST 14th street, Tulsa, OK, USA, 2005) for windows from Statsoft was used for the model fitting process.

Results

A total of 238 HIV-infected participants aged 21 years or older were included in this study, 200 males (mean age 39.2 years, range 21–70) and 38 females (mean age 38.8 years, range 23–67). Of these, 62 (26%, 62/238) of whom were HCV seropositive (determined by a positive HCV serological test) and 20.2% were coinfected with HCV (48/238) (nested PCR results). HCV genotype 1 was the most prevalent (62.5%, 30/48). Baseline characteristics of 238 HIV-infected patients are shown in Table 1.

A total of 81% (193/238) of patients achieved a sustained response in the observational period (48 months). Due to the dependence structure between covariates, we fitted multiple logistic regression models in order to obtain the adjusted risk estimates. The variables associated (p < 0.05) with immunological and virological responses (covariate and response variable) are shown in Table 2.

We did not observe a significant association between immunological or virological response and either patient gender or HAART regimen. This analysis showed that HCV serological status, age at HIV diagnosis (>40 years old vs <40 years old), duration of treatment and WHO clinical stage of AIDS (associated with <200 CD4 cells/ml independently of viral load < or > to 100 000 copies/ml), were significantly associated with immunological and virological responses to HAART. In all cases there were no discrepancies between those individuals who were immunological responders and those who were virological responders. Out of the 75 individuals (31.5%, 75/238) with a mean preHAART HIV RNA value <100 000 copies/ml and a CD4 count 200–350 cells/μl, 90.6% (68/75) responded to treatment. In patients who had a mean preHAART HIV RNA value >100 000 copies/ml and a CD4 count 200–350 cells/μl (42.8%, 102/238), responses to HAART were detected in 84.3% (86/102). For the individuals that had a mean preHAART HIV RNA value >100 000 copies/ml and CD4 count <200 cells/μl (24.1%, 57/238), treatment only achieved good outcomes in 64.9% (37/57). The poorest treatment responses were observed in patients who had a mean preHAART HIV RNA value <100 000 copies/ml and CD4 count <200 cells/μl (1.7%, 4/238), with only 50% (2/4) achieving a successful response (p = 0.02) (Table 2).

Discussion

Three main findings can be derived from this study. The prevalence of HCV (principally genotype 1) infection in our region seems to be higher than the ~12% reported in a previous study in the same population.[25] This increase in prevalence is probably because HIV-infected patients were more frequently tested for anti-HCV after 2004. Our data confirm that HCV infection (HCV seropositive) has a negative impact on the immunological and virological recovery experienced by HIV-infected individuals on HAART.

Table 1. Baseline characteristics of 238 HIV-infected patients attending of HIV/SIDA of Clinical National Hospital of Cordoba Province, Argentina

Variables	HIV-infected patients studied (n = 238)
Age, median (range), years	39.2 (21.0–70.0)
Gender, males (%)	200 (84)
Mean preHAART HIV RNA value [<100 000 copies/ml (SD)] and CD4 count <200 cells/μl (%)	57 (23.9)
Mean preHAART HIV RNA value [<100 000 copies/ml (SD)] and CD4 count 200–349 cells/μl (%)	75 (31.5)
Mean preHAART HIV RNA value [>100 000 copies/ml (SD)] and CD4 count 200–349 cells/μl (%)	102 (42.8)
Mean preHAART HIV RNA value [<100 000 copies/ml (SD)] and CD4 count <200 cells/μl (%)	4 (1.7)
Age at HIV diagnosis (≥40 years old) (%)	35 (14.7)
WHO Clinical stage (%)	
1 and 2	174 (73)
3	2 (0.8)
4	62 (26)
HAART Regimen	
NRTI	228 (96)
NNRTI	154 (64.7)
PI	74 (31)
HCV infection (antibody status) (%)	62 (26)
HCV infection (RNA HCV) (%)	48 (20.2)
HCV Genotypes (%)[a]	
HCV-1	30 (62.5)
HCV-2	2 (4.2)
HCV-3	7 (14.6)

NNRTI, non-nucleoside reverse-transcriptase inhibitors; NRTI; nucleoside reverse-transcriptase inhibitors; PI, protease inhibitor.
[a]Nine samples RNA HCV+ had indeterminate genotypes.

Table 2. Multiple logistic regression analysis associated with response post-HAART

Variable	Immunological response (CD4 >0–350 cells/μl)			Virological response (HIV RNA < 50 copies/ml)		
	Adjusted OR	95% CI	p value	Adjusted OR	95% CI	p value
HCV infection (antibody status)[a]	0.34	(0.15–0.82)	0.016	0.33	(0.14–0.77)	0.011
HCV infection male vs female	0.62	(0.27–1.43)	NS	0.87	(0.36–2.07)	NS
Age at HIV diagnosis (<40 years old vs ≥40 years old)[a]	1.04	(1–1.09)	0.030	1.03	(0.99–1.07)	0.041
WHO clinical stage						
3	0.77	(0.37–1.6)	NS	0.24	(0.02–2.85)	NS
4 (<200 CD4 cells/ml)[b]	0.42	(0.21–0.85)	0.016	0.45	(0.22–0.90)	0.024
HAART Regimen						
NNRTI(No N)	0.72	(0.35–1.5)	NS	0.63	(0.3–1.32)	NS
IP	1.13	(0.53–2.40)	NS	1.32	(0.61–2.84)	NS

[a]Association factor: $p < 0.05$.
[b]Viral load was not associated with response.

These data are further evidence of the impact of HCV on the effectiveness of HAART and are consistent with previous reports showing a decrease in response to HAART in coinfected patients.[29–31] In contrast, some initial studies did not recognize any influence of HCV infection on HIV outcome.[32] More recent studies that examined larger cohorts of patients under the benefit of new potent antiretroviral therapies seem to indicate that HCV infection might negatively affect the prognosis of HIV-positive individuals and their response to therapy.[30,33–35]

A new meta-analysis indicates that HCV coinfected patients are not represented in HIV clinical trials, so the cause of the reduced responses to antiretroviral treatment observed in HIV/HCV coinfected patients is unclear.[36]

Not surprisingly, clinical stage according to WHO HIV/AIDS staging system and age at HIV diagnosis were factors associated with response to therapy. Patients classified with disease stage 4 were less likely to respond immunologically and virologically to HAART than patients with disease stage 1. In addition, the baseline CD4 cells absolute value (<200 CD4 cells/ml) was an important predictor of optimal immunological and virological response to HAART, independently of basal viral load. Regarding age, the group of patients aged >40 years at the time of diagnosis were less likely to have a response to HAART, this is probably because older people have a reduced ability to respond to therapy. These results highlight the need for early HIV diagnosis and initiation of treatment.

There is evidence that gender might influence HIV progression and treatment response.[37–39] When HAART first became available, females were less likely to be on therapy and were observed to have diminished therapeutic outcomes.[40] However, in concordance with previous studies, we reported that virological and immunological outcomes did not differ by gender.[9,11]

Several limitations of our study need to be considered. We used serological rather than molecular tests for the multivariate analysis because of the relatively low numbers of patients in the study with positive RNA HCV tests. However, several studies have been made on the basis of HCV serostatus.[29,41] Due to the nature of the medical records of the study population information relating to risk factors was incomplete, therefore, this data was not included in our analysis. Unfortunately, in our region it is not routine to inquire about risk factors; in general priority is given in medical assistance, leaving out medical research. However, according to the limited risk-factor data obtained, the main route of transmission in HCV/HIV coinfected individuals was intravenous drug use. Given that some of the patients in the study were drug users, the impact of HCV infection on the effectiveness of HAART could, therefore, be difficult to distinguish from the impact of using injectable drugs.

To our knowledge, this is the first study of HCV/HIV coinfection that evaluates the real influence of HCV coinfection in response to HAART in the central region of Argentina. This finding encourages us to pay special attention to HCV/HIV coinfection in patients being treated for HIV, in order to improve their prognosis. Although for most coinfected patients, HAART should be initiated before anti-HCV therapy to slow liver progression and increase CD4 counts.[1] If anti-HCV treatment has been started a number of issues need to be taken into account: drug interactions which may lower the circulating levels of antiretroviral drugs, thereby raising concerns of reduced efficacy; drug interactions which may increase the circulating levels of antiretroviral drugs, increasing the risk of toxicity; overlapping toxicity profiles which may cause increased morbidity or mortality and lead to reduced treatment compliance. Some studies have demonstrated the benefits of the treatment of HCV in HIV patients in relation to morbidity and mortality, as well as the growing recognition of the extrahepatic complications associated with HCV infection.[27,42,43]

Our findings have important implications relating to the decision to treat HCV in patients coinfected with HIV and the timing of initiation of HIV therapy in coinfected individuals.

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