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The Impact of Human T-Cell Lymphotropic Virus I Infection on Clinical and Immunologic Outcomes in Patients Coinfected With HIV and Hepatitis C Virus

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Abstract

Background—HIV, hepatitis C (HCV), and human T-cell lymphotropic virus I (HTLV-1) are associated with high global burdens of disease, notably in resource-poor locales. They share similar routes of transmission and cause chronic infections with associated morbidity. We performed a cross-sectional study to assess the impact of HTLV-1 infection on clinical outcomes in HIV/HCV-coinfected patients.

Methods—We enrolled 102 (72.3%) with HIV/HCV coinfection (Group 1) and 39 (27.7%) triply infected with HIV, HCV, and HTLV-1 (Group 2). We reviewed medical records of two groups of patients followed in two outpatients services in Salvador, Brazil. We collected and compared demographic, behavioral-related information, immunologic, virologic, and histologic parameters for HIV-1 and HCV infection.

Results—Demographics, virologic, and immunologic characteristics were similar in the two groups; a higher proportion of triply infected patients (Group 2) reported any history of injection drug use compared with dually infected (Group 1) patients (75% vs 45.8%; $P = 0.003$). No differences were seen between groups in HIV clinical outcomes (CD4 count and viral load). Alanine aminotransferase levels were significantly higher in HIV/HCV-coinfected patients ($P = 0.045$). Liver fibrosis damage based on Metavir scores was similar between groups (0.97) but was worse with lower CD4 cell count (under 200 cells/mm³) ($P = 0.01$).

Conclusions—HIV/HTLV-1 and HIV/HCV coinfections may worsen clinical related outcomes, but virologic and immunologic outcomes were similar in both groups. Hepatic measures were worse in patients with more severe immunosuppression.

Keywords

HIV-1 and HCV coinfection; HIV-1; HCV; and HTLV-1 triple infection

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INTRODUCTION

HIV, hepatitis C virus (HCV) and human T-cell lymphotropic virus type 1 (HTLV-1) are viruses that share similar routes of transmission, including parenteral, sexual, and vertical (mother-to-child), although differences do exist with respect to infectivity with each virus. HCV is most efficiently transmitted through percutaneous exposures to infected blood and much less efficiently transmitted by mucosal exposures.¹ The dominant modes of transmission of HTLV-1 in endemic areas like Brazil are from mother to child in breast milk and sexual transmission in adults, but parenteral transmission is not uncommon among injection drug users (IDUs) in this same area. Similarly, HIV transmission, like HTLV-1, occurs through vertical, sexual, and parenteral exposures and coinfection with these other viruses is not uncommon. Populations at high risk of acquiring viral infections sexually or parenterally are likely to have a high prevalence of coinfection with these three viruses.^{2,3} HCV affects over 140 million people worldwide, is a major cause of chronic liver disease and cirrhosis, and the leading indication for liver transplantation in the United States.^{1,4,5} Mortality in association with HCV infection has increased in the last 10 years, rising from 1.09 to 2.57 deaths per 100,000 persons.⁶ Among HIV-infected patients, HCV infection is common, ranging from 15% to 70%,¹ and coinfection has emerged as a major cause of morbidity and mortality in HIV-infected patients.^{7,8} HIV infection is associated with a higher rate of HCV persistence after acute infection,³ severe liver disease,⁹ and increased HCV viral load and accelerated fibrosis.^{10,11} Additionally, HIV/HCV-coinfected patients have poorer sustained viral response (SVR) rates to interferon-based therapies compared with HCV-monoinfected individuals.¹²

HTLV-1 and HTLV-2 are retroviruses that infect T lymphocytes and can cause immunologic abnormalities.¹³ HTLV-1 is endemic in a number of geographic areas such as Japan, Central Africa, the Caribbean, and some Latin America regions, particularly in Brazil.^{14,15} In Brazil, there is a wide geographic diversity in the prevalence of HTLV infection with prevalence ranging from 0.4% to 1.8%.¹⁶ The state of Bahia, in the northeast of the country, is considered the epicenter of HTLV-1 infection, and the city of Salvador, its capital, has the highest reported prevalence in general population.^{2,17} In Brazil and elsewhere, HCV infection is also common in HTLV-1- and 2-infected individuals, principally among IDUs.^{18–20} The influence of HTLV-1 and -2 on HCV infection or HIV/HCV coinfection is not well studied, and its pathogenesis is not well understood. In one study among IDUs, HCV viral load was increased in HIV/HTLV-2-infected patients compared with HCV-monoinfected patients.²¹ A longitudinal study demonstrated accelerated HCV disease progression and hepatocarcinogenesis among HCV/HTLV-1-coinfected patients,²² and, like with HIV, SVR after interferon therapy was lower in patients coinfecting with HTLV-1 and HCV, suggesting that HTLV-1 infection inhibits the elimination of HCV.²³

HIV and HTLV-1 coinfection has been found in Bahia with worse morbidity and survival. A recent review concluded that HIV/HTLV-1-coinfected patients have higher CD4 cell counts compared with HIV-monoinfected patients, although little is known about the overall clinical implications of this.² Infection with all three viruses, HIV, HCV, and HTLV-1/2, has been documented in the southern and southeastern areas of Brazil. HIV and HTLV-1/2 coinfection is more frequent in IDUs and is associated with HCV infection, as HCV seropositivity is independently associated with HTLV and HIV coinfection.^{18,24} HCV infection in HIV-1-infected patients also is associated with seropositivity for anti-HTLV 1/2.²⁵

Few studies have described clinical characteristics in a population triply coinfecting with HIV, HCV, and HTLV-1. Little is known about disease progression and clinical outcomes in these individuals or how these infections may each contribute to changes in the natural history of subsequent disease. Because Salvador has the highest prevalence of HTLV-1 in Brazil, it offers a unique opportunity to study these co-occurring infections. The primary aim of this study was to describe whether HTLV-1 infection modified the clinical outcomes in HIV/HCV-coinfecting patients.

METHODS

Study Population

We conducted a study comparing two groups of patients with data collected retrospectively from outpatient services of two HIV/AIDS care facilities in Salvador, Brazil. Group 1 consisted of patients coinfecting with HIV and HCV and Group 2 of patients triply infected with HIV, HCV, and HTLV-1. Inclusion criteria for both groups were age older than 18 years and serologically confirmed HIV and HCV and/or HTLV-1. Both patient groups were recruited from either of two institutions, the Centro Estadual de Diagnostico, Assistencia e Pesquisa em HIV/Aids (CEDAP), a state center for HIV and AIDS care and research, and the Hospital Universitario Professor Edgard Santos da Universidade Federal da Bahia (HUPES-UFBA), a large hospital affiliated with the Federal University of Bahia. CEDAP has an outpatient population of approximately 8000 HIV-1-infected patients. HUPES-UFBA offers both inpatient and outpatient care; the infectious disease and hepatology units see approximately 1000 patients per month.

We used convenience sampling to recruit patients as they presented for care at the facilities. Physicians and nurses referred patients to investigators, who reviewed medical records (informed consent was waived by the Research Ethics Committee) and with written consent obtained blood samples for immunologic testing (not being reported on in this analysis).

Data Collection

We collected demographic, medical, and some behavioral-related information from patient records and entered it into a database. Data included age, sex, self-reported history of IDU, and sexual behaviors. Men who reported any sex with men were classified as MSM. We recorded CD4 cell count and HIV viral load before and after initiation of antiretroviral treatment (ART); the pre-ART levels were the last ones before ART initiation and the post-ART measures the most recently available. We also compared liver biopsy results (Metavir histologic score²⁶), liver function test results, including alanine transaminase (ALT) and aspartate transaminase, HCV genotype, and whether response to HCV therapy was sustained (SVR) or not.

Laboratory Tests

Laboratory test results were all obtained from medical records. The majority of laboratory testing was conducted in laboratories at the respective clinic or hospital where patients were seen. In brief, testing was done as follows. HIV status was determined using two enzyme immunoassays (HIV-1 QT, Bio Manguinhos, Rapid Check HIV 1 & 2) and confirmed by Western blot (Genelabs, Singapore) and HIV viral load using bDNA kits (Versant HIV-bDNA 3.0 Assay; Siemens, Berkeley, CA). CD4 cell count was determined by flow cytometry (FACSCalibur; Becton Dickinson, San Jose, CA). HTLV-1 was tested by enzyme immunoassay (different manufacturers) and confirmed using Western blot (Genelabs). HCV antibody (anti-HCV) was tested for using enzyme immunoassay (different manufacturers); HCV viral load was measured by quantitative polymerase chain reaction with a lower limit of detection of 600 UI/mL ($\log = 2.78$) and an upper limit of 850,000 UI/

mL (log = 5.93). SVR was determined by qualitative HCV RNA testing (HCV Amplicor 2.0; Roche Diagnostics, Pleasanton, CA) with sensitivity of 50 UI/ml (120 cp/mL), the lower limit of detection; and HCV genotyping was determined by line probe assay. We classified patients as having SVR to therapy if HCV polymerase chain reaction was undetectable 24 weeks after the completion of HCV therapy. We recorded data from liver fibrosis for all patients who underwent percutaneous liver biopsy and used the Metavir histologic score system to determine degree of liver damage. We categorized liver fibrosis in two groups: mild fibrosis F0 and F1 and moderate or advanced fibrosis F2, F3, and F4.

Ethical Review

The study protocol was reviewed and approved by the Research Ethics Committee of the Secretary of Health of the State of Bahia (Comite de Etica em Pesquisa da Secretaria de Saude do Estado da Bahia [CEP-SESAB]).

Statistical Analysis

Analyses are cross-sectional. The principal outcomes of interest were markers of clinical and immune response to HIV and HCV, including HIV viral load, CD4 count, HCV viral load, ALT, aspartate transaminase, and fibrosis score. We calculated prevalence and 95% confidence intervals based on binomial distributions. Summary statistics included frequency tables for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Patients with missing data were excluded from analyses for those factors in which data were missing. We categorized some continuous variables such as age and CD4 count for contingency table analyses. We conducted bivariate analyses examining associations between groups using the chi-square test of association or Fisher exact test where expected cell size was fewer than five and calculated odds ratios and 95% confidence intervals. To further examine associations in subgroups of interest, in particular between CD4 count and liver fibrosis stage, we conducted stratified analyses. We conducted all analyses using STATA Version 9 (Stata Corp, College Station, TX).

RESULTS

Patient Characteristics

A total of 141 subjects were enrolled in the study: 102 (72.3%) with HIV/HCV coinfection (Group 1) and 39 (27.7%) triply infected with HIV, HCV, and HTLV-1 (Group 2). The median age of patients was 46 years (IQR, 42–50) overall, 46 years (IQR, 40–50) in Group 1 and 47.5 years (IQR, 42.8–51.0) in Group 2. Table 1 shows selected demographic and behavioral risk characteristics of both groups. The majority (66%) of patients were male, reported being heterosexual (79.5%), and just over half (54%) had a history of IDU. There were no significant differences between groups with respect to age, sex, or sexual behavior, but the proportion reporting any history of IDU was significantly higher in patients infected with HIV/HCV/HTLV-1 (75%) compared with coinfecting with HIV/HCV (46%). Clinical data were available on all patients, but nine patients were missing data on self-reported exposures (IDU and sexual exposure).

Clinical Characteristics

Table 2 shows HIV and HCV clinical, immunologic, virologic, and histopathologic outcomes in the two groups of patients. Of the 141 patients, 91% (n = 93) of those with HIV/HCV coinfection and 87% (n = 34) with triple infection had initiated ART ($P = 0.48$). No significant differences were seen between measures of HIV viral load and CD4 cell count pre-ART and post-ART between the groups. Pre-ART, 44% of patients had CD4 cell counts above 350 cells/mm³ (42% and 50% in Groups 1 and 2, respectively) and the median

HIV viral load was also comparable. Declines in HIV viral load (to less than 1.69 log₁₀) and increases in CD4 cell count (209 CD4 cells/mm³ and 137 cells/mm³ in Groups 1 and 2, respectively) were seen in both groups ($P < 0.01$ for pre- vs post-ART measures), indicating that both groups responded similarly to ART therapy. The magnitude of the decline in viral load and increase in CD4 did not differ by group ($P = 0.63$ and $P = 0.54$, respectively).

There were no differences between groups with respect to HCV viral load or the distribution of HCV genotype (Table 2). Median ALT was significantly ($P = 0.05$) higher among the HIV/HCV-coinfected group (71 IU/mL; IQR, 39–107) than the HIV/HCV/HTLV-1 triply infected group (48 IU/mL; IQR, 33–90). Of the 58 (41%) patients who received interferon-based therapy, 13 (32%) of HIV/HCV-coinfected and four (44%) of triply infected patients achieved SVR. Overall, 73 (52%) underwent percutaneous liver biopsy; METAVIR histologic scores were similar between groups. However, when fibrosis stage was examined by CD4 cell count stratifying by group (1 and 2), patients with CD4 cell count lower than 200 cells/mm³ had significantly higher fibrosis scores (Mantel-Haenszel $P = 0.01$); however, no difference was found between Groups 1 and 2 (P value for homogeneity of odds ratio between groups = 0.97) (Table 3).

DISCUSSION

In this comparison of HIV/HCV- and HIV/HCV/HTLV-1- infected patients, the principal findings were that both groups demonstrated similar HIV-related outcomes (CD4 count and HIV viral load), but those with HTLV-1 infection demonstrated differences with respect to hepatic-related outcomes, especially in association with more severe HIV-related immunosuppression (CD4 count). Our study found that a significantly higher proportion of patients in both groups with low CD4 cell count (200 cells/mm³ or less) have greater liver fibrosis damage compared with patients with higher CD4- cell count (greater than 200 cells/mm³). Fibrosis levels were higher among those with CD4 cell counts 200 and lower ($P = 0.01$) and did not differ by HIV/HCV versus HIV/HCV/HTLV-1 status ($P = 0.97$). Other evidence of hepatic differences between groups was higher ALT levels in HIV/HCV-coinfected patients compared with HIV/HCV/HTLV-1 triply infected ones; however, ALT was not correlated to HCV RNA viral load or degree of liver fibrosis. This is not unusual, because studies have reported that more than 10% of patients HIV/HCV coinfect show persistently normal ALT even with advanced liver fibrosis.^{27,28} In contrast to our results, another study did find higher HCV viremia in HIV/HCV/HTLV-2-infected patients compared with HIV/HCV-coinfected patients.²¹

There are some conflicting data about immunologic response to ART in patients infected by HIV and HCV. Some authors have found that the CD4 cell increase is smaller after ART in persons with HIV/HCV coinfection, suggesting that HCV may blunt immune recovery, but other studies have failed to confirm this observation.³ In this study, both groups of patients demonstrated similar beneficial responses to ART with significant decreases in HIV viral load and increases in CD4 cell counts after ART initiation. Several reports have demonstrated that coinfection by HTLV-1 or HTLV-2 and HIV increases CD4⁺ cells count, although it does not seem to result in a better immune response. In addition, some published works showed no significant impact of HTLV-2 infection on HIV disease, but this is not true when the involved virus is HTLV-1.¹⁷ These distinct biologic behaviors can promote a different impact on triply infected patients and could explain the different outcomes observed in studies on HTLV-1 coinfection in comparison with others that evaluated coinfection by HTLV-2.^{21–23}

The histologic results from the patient groups compared here confirm the need for careful assessment of liver fibrosis in coinfecting patients, especially those presenting with lower

CD4+ cells count. Although we found no overall differences in liver fibrosis between the groups, immunosuppression, as measured by CD4 cell count, was associated with worse fibrosis scores as found by others.⁹ However, the tendency for the HIV/HCV-infected group with advanced immunosuppression to have more fibrosis than the triply infected group is of interest and deserves more study. Because of the relative small size of our population and some missing data, our findings are limited. Some studies have demonstrated that HIV/HCV-coinfected patients^{9,10,29} and HCV/HTLV-coinfected patients^{22,23} have more severe liver disease than patients with HCV monoinfection. Data from our study suggest that patients triply infected have low liver fibrosis with higher CD4 cell count. These data should encourage early screening for HTLV-1 infection in patients coinfecting by HIV and or HCV, because earlier treatment for HIV and HCV may prevent development of liver fibrosis and potentially achieve better results with chronic hepatitis C therapy.

Our study involved the two major services of AIDS care in Bahia, Brazil, which provide care for approximately 80% of all HIV-infected patients in the state in an area with high HTLV-1 and HCV prevalence. However, there are some limitations to this study. The study data were from clinical chart review, and there are no protocols to standardize the clinical visits between the two institutions. As a result, there are missing data in our sample. Missing data may also be associated with the timeframe in which patients were seen and potentially with socioeconomic status. Bias may also have resulted as a result of numerous potential temporal effects that the cross-sectional analysis cannot address, including by patient (time from infection, time to outcome, and between data points, for instance laboratory and clinical outcome data), and clinical, for example, diagnostic and treatment criteria that may have varied over time. Patients diagnosed earlier with HIV may have been less likely to be diagnosed or treated for HCV infection, and those with fewer resources may also have been less likely to access these services. A larger sample size would facilitate better analysis of these potential effects. As a result, our findings may not be representative of all patients with these co- or triple infections. As protocols for HIV and HCV treatment become more standardized in Brazil, new studies will be needed to further assess outcomes in patients co- and triple infection. Another limitation was that no information about alcohol use was collected. Alcohol exposure could contribute to differences seen in hepatic outcomes or conversely explain why differences were not seen with other outcomes. If alcohol use were differential between groups, these effects could potentially be more complex. Despite these limitations, this study provides new information in an area with where little is known.

Overall, our results suggest that among patients with HIV and HCV coinfection, patients who also have HTLV-1 infection have better outcomes with respect to HCV than their dually infected counterparts. Future research should follow patients for a longer period of time to better delineate the natural history of triple infection. Immunologic studies will also contribute to better understanding of the interactions among these three viruses.

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Demographic Characteristics of HIV/HCV-Coinfected Patients Compared With HIV/HCV/HTLV Triply Infected Patients in Salvador, Brazil

TABLE 1

Variables	Group 1				Group 2			
	Prevalence		HIV/HCV		HIV/HCV/HTLV		p*	
	No.	Percent	No.	Percent	No.	Percent		
Age (years)								
Younger than 30	3	2.1	3	2.9	0	0		
31–39	21	14.9	17	16.7	4	10.2		
40–49	75	53.2	53	52.0	22	56.4		
Older than 50	42	29.8	29	28.4	13	33.3	0.52	
Sex								
Male	93	66.0	68	66.7	25	64.1		
Female	48	34.0	34	33.3	14	35.9	0.77	
IDU (self-reported history) (N = 132) [†]								
Yes	71	53.8	44	45.8	27	75.0		
No	61	46.2	52	54.2	9	25.0	<0.01	
Sex behavior (self-reported history) (N = 132) [†]								
Heterosexual	105	79.5	73	76.0	32	88.9		
MSM	27	20.5	23	24.0	4	11.1	0.10	

* Pearson chi square.

[†] Data on self-reported exposures was missing from nine individuals.

HCV, hepatitis C virus; HTLV, human T-cell lymphotropic virus; IDU, injection drug use; MSM, men who have sex with men.

HIV and HCV Clinical, Immunologic, Virologic, and Histopathologic Outcomes in HIV/HCV-Coinfected Patients Compared With HIV/HCV/HTLV Triply Infected Patients, Salvador, Brazil

TABLE 2

	Group 1 HIV/HCV (N = 102)		Group 2 HIV/HCV/HTLV (N = 39)		P
	No.	Percent	No.	Percent	
Preantiretroviral therapy					
HIV viral load (log10), median (IQR)	4.6 (3.9–5.2)		5.0 (4.1–5.6)		0.15*
CD4 cells/mm ³ , median (IQR)	324 (162–504)		339 (142–665)		0.38*
200 cells/mm ³ or less	27	29.0	14	38.9	
201–349 cells/mm ³	27	29.0	4	11.1	
350 cells/mm ³ or greater	39	41.9	18	50.0	0.10
After antiretroviral therapy initiation					
HIV viral load (log10), median (IQR)	1.7 (1.7–1.7)		1.7 (1.7–2.4)		0.26*
CD4 cells/mm ³ , median (IQR)	540 (338–737)		512 (329–779)		0.73*
HCV viral load (IU/mL)					
Less than 850,000	17	32.1	4	23.5	
850,000 or greater	36	67.9	13	76.5	0.50 [†]
HCV genotype					
1	64	79	20	80	
2	3	3.7	0	0	
3	14	17.3	4	16	
4	0	0	1	4	0.43 ^{†‡}
ALT (IU/mL), median (IQR)	71 (39–107)		48 (33–90)		0.05*
AST (IU/mL), median (IQR)	60 (35–92)		50 (37–82)		0.81*
Fibrosis (Metavir histologic score):					
Fibrosis 0–1	19	31.7	5	38.5	
Fibrosis 2–4	41	68.3	8	61.5	0.64 [‡]
Sustained virologic response	13	31.7	4	44.4	0.47 [‡]

- * Kruskal-Wallis test.
- [†] Fisher exact test.
- [‡] Pearson chi square.

HCV, hepatitis C virus; HTLV, human T-cell lymphotropic virus; IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 3
Fibrosis by CD4 Cell Count and HTLV Status Among Patients Coinfected With HIV and HCV, Salvador, Brazil

	Fibrosis 0–1		Fibrosis 2–4		<i>P</i>
	No.	Percent	No.	Percent	
HIV/HCV					
200 cells/mm ³ or less	2	11.1	14	40.0	
Greater than 201 cells/mm ³	16	88.9	21	60.0	0.06
HIV/HCV/HTLV					
200 cells/mm ³ or less	1	25.0	5	62.5	
Greater than 201 cells/mm ³	3	75.0	3	37.5	0.55
Fibrosis by CD4 cell count					0.01 *

* Mantel-Haenszel *P* adjusting for HTLV status; *P* for homogeneity of odds ratio between HTLV groups = 0.97.
HTLV, human T-cell lymphotropic virus; HCV, hepatitis C virus.