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# HTLV infection in HCV-antibody positive patients in Spain

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## Abstract

Since hepatitis C virus (HCV) and human T-lymphotropic virus (HTLV) share transmission routes, dual infection could be frequent. In Spain, HTLV underdiagnosis is highlighted by the high proportion of patients presenting either with tropical spastic paraparesis (TSP) or adult T-cell leukemia (ATL) at first diagnosis. We examined whether the renewed efforts for expanding HCV testing may provide a sentinel population that might selectively be targeted to unveil asymptomatic HTLV carriers. The presence of anti-HTLV antibodies was examined in 3,838 consecutive individuals with reactive HCV serology attended during the last three years at 13 hospitals distributed across the Spanish geography. Overall 71% were male and the median age was 41-years old. Foreigners represented 9% of the study population. A total of 50 individuals (1.3%) were seroreactive for HTLV, being 30 confirmed as HTLV-2 and two as HTLV-1 (0.12%). The remaining 18 had indeterminate Western blot patterns. Most individuals with HTLV-2 and HTLV indeterminate serology were HIV-positive, former injection drug users and native Spaniards. In contrast, the two HTLV-1 infections were found in men coming from Brazil and the Dominican Republic, respectively. In summary, the overall prevalence of HTLV infection in individuals living in Spain seropositive for HCV is 1.3%, more than 10-fold greater than in general outclinics in Spain. However, immigrants from HTLV-1 endemic regions and former injection drug users with HTLV-2 infection are by far the major contributory groups in HCV patients. Therefore, testing for HTLV in newly diagnosed HCV individuals would not contribute much to improve late HTLV diagnosis in Spain.

## Introduction

Human T-lymphotropic virus type 1 (HTLV-1) infection is a neglected disease despite affecting more than 10 million people worldwide.[1,2] Lifelong nearly 10% of HTLV-1 carriers may develop clinical manifestations, including two life-threatening illnesses, namely a subacute invalidating myelopathy known as tropical spastic paraparesis (TSP)[3] and a malignant acute T-cell leukemia/lymphoma (ATL).[4] There are highly endemic regions for HTLV-1 infection in South Japan, Iran, Papua New Guinea, Sub-Saharan Africa, South America and the Caribbean basin.[1,2] HTLV-1 infection is rather rare among native Europeans but in Romania. However, the rate of infection in Europe has been on the rise during the last decades among immigrants from endemic areas, travellers and their sexual contacts.[5,6] In contrast, HTLV-2, which is rarely pathogenic, has been circulating among injection drug users in Europe and North America for long time.[7,8]

As HTLV-1, hepatitis C virus (HCV) is a blood-borne pathogen. Not surprisingly, both HTLV and HCV are more often diagnosed in persons infected with other viruses having overlapping transmission routes, such as human immunodeficiency virus (HIV) or hepatitis B virus (HBV).[9,10] In contrast with retroviruses and HBV, transmission of HCV is uncommon throughout sexual contact,[11,12] although recent outbreaks of acute hepatitis C among homosexual men have changed this view.[13] The natural history of chronic hepatitis C is well known to be accelerated in patients coinfected with HIV and/or hepatitis B, at least in part due to persistent immune activation and chronic inflammation.[14,15] In contrast, there is limited information on the rate of HCV and HTLV coinfection, and particularly on the influence of HTLV on HCV-related liver disease progression or treatment outcomes.[16-22] In Spain, HTLV underdiagnosis is highlighted by the high proportion of first diagnosis presenting with either TSP or ATL.[6]

The recent recommendation for expanding HCV screening,[23] in order to unveil the large number of people unaware of their hepatitis C that could benefit from new antiviral therapies, may provide a unique opportunity for identifying a sentinel group in which HTLV testing might be cost-effective. In this study we assessed the

prevalence of antibodies to HTLV-1/2 in a large and representative group of individuals HCV-seropositive living in Spain.



## PATIENTS AND METHODS

All 45 clinics belonging to the HTLV Spanish network were invited to participate in the survey in year 2012. The study was designed as a cross-sectional blinded analysis of all HCV-antibody positive individuals consecutively attended at the different settings distributed across the Spanish geography. The study obtained approval from the corresponding hospital ethics committees. Along with serum storage, main demographics including age, gender, HIV status, risk behaviour, and country of origin were collected in a case report form specially designed for this study.

Anti-HTLV antibodies were tested using either a commercial enzyme immunoassays (EIA) (Murex HTLV I+II; Diasorin, Madrid, Spain) or a chemiluminescent microparticle immunoassay (Architect, rHTLV-I/II, Abbott, Chicago, IL). EIA testing was carried out in pools of five sera, a step previously shown to preserve sensitivity and improve specificity.[24] Sera from reactive pools were re-tested individually and further confirmed and typed using Western blot (Bioblot HTLV, Genelabs, Singapore). Interpretation was made following the HTLV Blot 2.4 interpretation criteria.[25] Data from medical records were recovered for all subjects HTLV-seropositive.

Anti-HCV antibodies had been tested using distinct commercial EIAs and serum HCV-RNA had been measured using a PCR assay (Roche, Madrid, Spain).

***Statistical analysis.*** All results are given as absolute values or proportions, and mean or median values. Comparisons were made using the chi square test, with Fisher correction when appropriated. Differences were considered to be significant only when p values were lower than 0.05. All analyses were performed using SPSS version 15.0.

## RESULTS

From January 2013 to December 2015, a cross-sectional blinded study was conducted in all HCV-antibody positive individuals consecutively attended at 13 different settings distributed across the Spanish geography. A total of 3,838 HCV-seroreactive individuals were tested for HTLV antibodies. **Table 1** summarizes the most relevant features of the study population. Clinics contributing actively to the survey were distributed across the whole Spanish geography, including the Canary islands. Mean age was 41 years-old and 71% were male. The majority were native Spaniards (91%), being the rest foreigners coming from other European countries (3.2%), Latin America (2%) and Africa (1.8%). The most likely route of HCV acquisition was needle exchange in injection drug users (67%), sex in gay men (17%), heterosexual contact (9%) and transfusions (2.9%).

HCV genotype could be characterized in 955 viremic individuals. By far, genotype 1 was the most frequent (66%), followed by genotype 3 (17.5%), genotype 4 (13.6%) and genotype 2 (2.9%). Finally, coinfection with HIV-1 could be investigated in 1,284 patients, being positive in 345 (26.8%).

Overall 50 individuals (1.3%) were EIA or CMIA reactive for HTLV. Western blot confirmed 2 as HTLV-1 positive and 30 as HTLV-2 positive. The remaining 18 samples repeatedly depicted indeterminate Western blot profiles. Given the blinded nature of the study, a second blood sample could not be obtained for further PCR examination in peripheral blood mononuclear cells. Of note, HTLV-seroreactive cases were widely distributed across the Spanish geography, with no evidence of clusters or links between them.

HTLV-1 infections were found in a 50 years-old male immigrant from the Dominican Republic. Most likely he had acquired the infection in his country of origin through heterosexual contacts. The second HTLV-1 carrier was a 49 years-old male born in Brazil and coinfected with HIV-1. None complained signs or symptoms potentially associated to HTLV-1 infection at the time of diagnosis. In contrast, HTLV-2 and HTLV-indeterminate individuals were mostly native Spaniards, being the only

exceptions from Italy, Portugal and Germany (one each). Most of them were former injection drug users and more than half were HIV-positive (**Table 2**).



## DISCUSSION

The overall prevalence of HTLV infection in HCV-seropositive persons in Spain was 1.3% in our study, more than 10-fold higher than in the general population attended in outclinics.[26] However, it should be highlighted that HTLV-1 only was found among foreigners coming from endemic countries in Latin America whereas HTLV-2 was mostly found in native Spaniards with history of prior injection drug use, being most of them coinfected with HIV-1. Our results suggest that HCV-seroreactivity is a weak surrogate for HTLV-1 infection in Spain and that immigration from highly HTLV-1 endemic areas should be the major alert for unveiling the diagnosis of asymptomatic HTLV-1 carriers. Our data are in agreement with results from prior smaller surveys.[27-29]

Overall 50 individuals (1.3%) were reactive for HTLV in screening assays. Western blot confirmed 2 as HTLV-1 positive and 30 as HTLV-2 positive. The remaining 18 samples repeatedly depicted indeterminate Western blot profiles, as previously reported in HIV-infected injection drug users that were later confirmed mostly as HTLV-2.[30] Overall, 13 of our 18 Western blot indeterminate specimens belonged to former injection drug users, and 10 were HIV-positive. Given the blinded nature of the study, a second blood sample could not be obtained for further PCR examination in peripheral blood mononuclear cells.

Roughly 75% of individuals exposed to HCV develop chronic infection and become at risk for developing liver cirrhosis and occasionally hepatocellular carcinoma. Worldwide 80 million people are estimated to suffer from chronic HCV infection. In most Western countries, chronic hepatitis C is the major cause for liver transplantation.[11] HTLV co-infection may enhance HCV replication and viral load, leading to lower HCV sustained virological response to interferon-α treatment, and influencing HCV liver disease progression.[17-22] On the other hand, no data exist on the potential influence of HCV on HTLV pathogenicity. Hypothetically, immune

activation and chronic inflammation driven by persistent replication of one virus may provide a continuous stimulus for replication of other co-existing viruses, as already being demonstrated in the HIV setting.[31]

A national registry of HTLV-1 and HTLV-2 cases exists in Spain since 1988, when the first individuals with HTLV-1 infection were reported.[6,32] A total of 327 cases of HTLV-1 had been diagnosed until the end of 2016. Overall, 62% were immigrants from Latin America and 13% came from Africa, being only 19% native Spaniards. Males were 39% and mean age at diagnosis was 41 years-old. Symptomatic HTLV-1 infections had been diagnosed in 58 individuals (18%), being TSP in 33 and ATL in 25 patients. New diagnoses of HTLV-1 infection have risen sharply in Spain since 2008, largely as result of broader HTLV screening in blood banks and the growing arrival of immigrants.[33]

On the other hand, a total of 793 cases of HTLV-2 infection had been reported in Spain up to December 2016. In contrast with HTLV-1 persons, HTLV-2 carriers are mostly native Spaniards (91%), males (76%), former injection drug users (78%) and frequently coinfected with HIV-1 (85%). The number of reported cases of HTLV-2 has been steadily declining in Spain since year 2002, mostly reflecting reduced injection drug use behaviors.[34]

In Spain, HTLV underdiagnosis is highlighted by the high proportion of first diagnosis presenting either TSP or ATL.[6] Given that HCV and HTLV share transmission routes, dual infection could be particularly frequent. In the current study, we examined whether the renewed efforts for expanding HCV testing for antiviral curative purposes may provide a unique sentinel population that might selectively be targeted to unveil asymptomatic HTLV carriers. The presence of anti-HTLV antibodies was examined in 3,838 consecutive individuals with reactive HCV serology attended during the last three years. The overall prevalence of HTLV infection was 1.3%, more than 10-fold greater than in the general Spanish outpatient population.[26] However, immigrants from HTLV-1 endemic regions and former injection drug users with HTLV-2 infection were the major contributory risk groups in HCV patients. Therefore, our results suggest that HTLV testing of HTLV newly diagnosed HCV individuals would not contribute much to improve late HTLV diagnosis.

At this time, HTLV screening of first donors in blood banks, pregnant women[35] and donor-recipient transplants[36] seem to be the most cost-effective strategies to identify asymptomatic HTLV-1 carriers in Spain. People coming from HTLV-1 endemic regions, their sexual contacts or children are overrepresented among newly diagnosed HTLV-1 individuals in any of these groups. Since HTLV-1-infected mothers may largely prevent transmission to their newborns avoiding breastfeeding[37] and TSP may develop more frequently and rapidly in transplant recipients,[38-40] it seems worth to recommend universal HTLV screening of at least these two groups in Spain, where there immigrants from endemic regions, mostly Latin America, represents a large population. In blood banks, the introduction of leukoreduction procedures drastically minimizes the risk of HTLV transmission;[41] however, universal HTLV screening of first donors perhaps using pools may still be a cost-effective strategy. From our study, we conclude that HCV is a weak surrogate for HTLV-1 infection and that immigration from highly HTLV-1 endemic areas should be the major target for unveiling asymptomatic carriers. In other words, HTLV testing of newly diagnosed HCV individuals would not contribute much to improve late HTLV diagnosis.

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Table 1. Main characteristics of the HCV study population.

| | |
|---|---|
| No. | 3,838 |
| Male (%) | 71 |
| Median age (IQR), years | 41 (31-57) |
| Origin (%) | |
| Native Spaniards | 91 |
| Latin America | 2 |
| Africa | 1.8 |
| East Europe | 1.3 |
| West Europe | 1.9 |
| Risk group (%) | |
| Injection drug use | 67 |
| Men who have sex with men | 17 |
| Heterosexual contact | 9 |
| Transfusion | 2.9 |
| Others | 3 |
| HCV genotypes (%) | |
| 1 | 66 |
| 2 | 2.9 |
| 3 | 17.5 |
| 4 | 13.6 |

Table 2. Main characteristics of the HTLV population.

| No. | HTLV-1+ (n=2) | HTLV-2+ (n=30) | HTLV indeterminate (n=18) |
|---|---|---|---|
| Male | 1 | 24 | 13 |
| Country of origin | Dominican Republic (1)<br>Brazil (1) | Spain (29)<br>Germany (1) | Spain (14)<br>Italy (1)<br>Portugal (1)<br>Unknown (2) |
| Risk group | Birth in endemic regions (2) | IDU (24) | IDU (12)<br>HTSEX (1) |
| HCV genotype | G2 (1)<br>Unknown (1) | G1 (7)<br>G3 (3)<br>Unknown (20) | G1 (4)<br>Unknown (14) |
| HIV-1 coinfection | 1 | 21 | 10 |

*IDU, injection drug use; HTSEX, heterosexual*