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The Burden of Neglected HIV-2 and HTLV-1 Infections in Spain

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Abstract

HIV-2 and HTLV-1 infections are globally less frequent than those produced by HIV-1, the classical AIDS agent. In Spain and up to the end of 2014, a total of 310 cases of HIV-2, 274 of HTLV-1, and 776 of HTLV-2 infections had been reported. No cases of HTLV-3 or HTLV-4 infections have been identified so far in Spain. Most persons infected with HIV-2 or HTLV-1 acknowledge epidemiological risk factors for contagion, such as originating from or living in endemic regions and/or having had sexual partners from those areas. However, risk factors could not be recognized in up to 20-25% of carriers in Spain. Thus, it seems worth keeping a high level of clinical suspicion in order to identify earlier these neglected human retroviral infections, since diagnostic procedures and antiviral treatment are specific for each of these agents. In this article we summarize the major contributions reported at the meeting of the Spanish Group for HIV-2/HTLV held in Madrid in December 2014. **(AIDS Rev. 2015;17:212-9)**

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Key words

HIV-2. HTLV. HIV-1. Epidemiology. Spain. Neglected infections.

Introduction

The Spanish group for the study of human retroviruses other than HIV-1 was founded in 1989. More than one hundred clinicians, epidemiologists, and researchers currently belong to this national network that involves 45 medical centers and blood banks. Although the major focus of attention is on HIV type 2 (HIV-2) and human T-lymphotropic virus type 1 (HTLV-1), other retroviruses are periodically under surveillance. The group promotes distinct epidemiological studies in risk populations and is in charge of a national registry of these viral infections. Based on yearly updated data, recommendations on testing are periodically released. Furthermore, studies on the pathogenesis of associated diseases and antiviral treatment for either HIV-2 or HTLV-1 have been undertaken.

On December 18th, 2014 the annual meeting was held at Puerta de Hierro University Hospital in Madrid. As it was the 25th anniversary of the group, an expert from the Centers for Disease Control (CDC) was invited to speak on the emergence of new human retroviruses. Briefly, more than 75% of new human emerging diseases are due to zoonosis, most being produced by RNA viruses and by far the most being retroviruses.

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Of 1,413,000 species of organisms already known worldwide, viruses only represent around 1,000. It is believed that this figure is an underestimation and that 99% of viral species are not yet identified. Therefore, the risk for human zoonosis should be regarded as a great treat for the coming years. Among circumstances that may favor jumping of viruses from animal reservoirs to humans are hunting of wild animals, consumption of uncooked bushmeat, both relatively frequent in many sub-Saharan regions. On the other hand, people with exposure to non-human primates, such as those working at zoos, wild reserves, slaughter houses, veterinaries, etc., are most prone to acquire new retroviral infections.

The most important retroviruses are simian immunodeficiency viruses (SIV) that infect distinct African primates, with more than nine lineages, and that generally do not lead to clinical manifestations. A second group is represented by simian foamy viruses (SFV), which are widely prevalent, infecting distinct primates and without producing any disease in natural reservoirs. A third group are simian T-lymphotropic viruses (STLV) that infect several primates in Asia and Africa, and are responsible for distinct lymphoproliferative disorders in natural hosts. As expected, all these retroviruses do not recognize borders, and continuously explore if they can move from one region to another far away, or from one host to colonize a new species if opportunities are given. This is why identification of natural hosts and mechanisms of transmission have become crucial to understand, and when possible prevent, the risk of new viral epidemics[1-3].

HIV-2

HIV type 2 comes from interspecies jumps of SIV infecting *sooty mangabey* monkeys that inhabit West African forests. The virus was isolated in 1986 from a few individuals from Cape Verde islands presenting with AIDS; all depicted an indeterminate serological pattern for HIV-1 antibodies[4]. Soon thereafter, HIV-2 epicenters were proposed for Ivory Coast and Guinea-Bissau, where more than one million people were estimated to be infected, although the HIV-2 epidemics there have been declining during the last decade[6]. In Europe, most HIV-2 cases have been reported in Portugal and France, largely in association with strong historical links with their former African colonies.

The first cases of HIV-2 infection in Spain were reported in 1988 among West African immigrants living in Barcelona. Since then, a total of 310 cases have been registered, only twelve of them in the year 2014. Figure 1 records the annual incidence of new HIV-2 diagnoses in Spain. Most HIV-2 carriers in Spain are male (202; 65%), coming from sub-Saharan Africa (223; 74%), although 52 are native Spaniards. As shown in table 1, individuals diagnosed in recent years tend to be older and more frequently asymptomatic. Based on this fact, it seems necessary to always exclude HIV-2 at least once in any new diagnosis of HIV infection, even in the absence of clear epidemiological suspicion. For example, a 57-year old woman was diagnosed in 2014 with HIV-2 infection after presenting with clinical symptoms in the absence of risk behaviors that only became apparent after in-depth questioning thereafter.

In contrast with most HIV-1-positive individuals in Western countries that become infected following homosexual contact or intravenous drug use, most HIV-2 carriers have acquired the infection following heterosexual relationships. HIV-2 group A is by far the most predominant worldwide[7] and the most frequent variant circulating in Spain, although HIV-2 group B has been recognized in 10 subjects. As expected, the geographic distribution of HIV-2 cases in Spain reflects the areas of major immigrant populations from African endemic regions as follows: Barcelona (77), Madrid (63), Almeria (23), the Canary islands (17), Gerona (15), and Pontevedra (15).

Compared to HIV-1 infection, the timeframe between exposure and the beginning of clinical signs/symptoms is generally longer in HIV-2 carriers. During the asymptomatic period, CD4 counts decline slowly in parallel with low-level viral replication that only bursts when immunodeficiency becomes severe. In the Spanish HIV-2 register, 61% of patients examined had undetectable plasma HIV-2 RNA at diagnosis. Moreover, median plasma viral load in the subset of viremic individuals was low, around 2.8 log HIV-2 RNA copies/ml. It must be highlighted that HIV-2 RNA quantitation is not commercially available and heterogeneity for distinct HIV-2 subtypes is a challenge in terms of reliability.

Antiretroviral therapy for HIV-2 still remains steps far behind HIV-1 therapeutics. HIV-2 displays natural resistance to non-nucleoside reverse transcriptase inhibitors such as nevirapine or efavirenz. This is due to the presence of an isoleucine at codon 181 and leucine at codon 188 of the gene coding for the viral polymerase enzyme. Although etravirine and rilpivirine may depict some residual antiviral activity *in vitro*, the susceptibility for HIV-2 remains nearly 1,000-fold lower

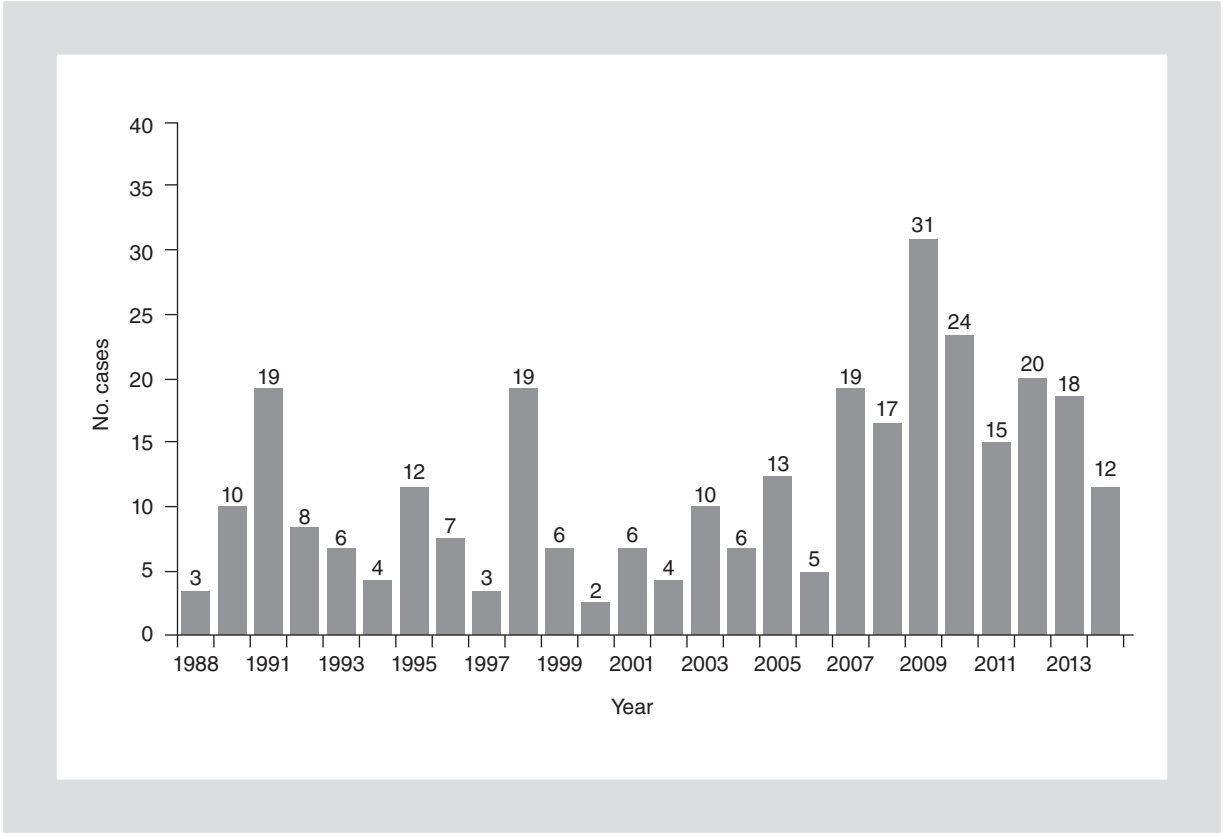

Figure 1. *Incidence of HIV-2 in Spain.*

than for HIV-1, and accordingly their use is discouraged[8]. On the contrary, most nucleos(t)ide analogues active against HIV-1 are also active against HIV-2. Moreover, the selection of drug resistance mutations follows similar mechanistic pathways in both viruses, although HIV-2 tends to select more frequently changes at the polymerase that more often result in multidrug resistance to nucleos(t)ide analogues such as K65R and Q151M[9,10]. Protease inhibitors used against HIV-1 exhibit a wide extent of activity against HIV-2, with the most active inhibitors being saquinavir, lopinavir, and darunavir. In contrast, HIV-2 is poorly susceptible to fosamprenavir, atazanavir, and tipranavir[10-12].

All integrase inhibitors approved for the treatment of HIV-1 are similarly active against HIV-2. Moreover, drug resistance mutations in patients failing on these drugs tend to be selected at the same positions in both viruses. Dolutegravir is the latest approved agent within this class, and is more potent than raltegravir or elvitegravir. Preliminary data suggest that dolutegravir could be similarly the strongest against HIV-2, and hypothetically could be considered for rescue interventions in patients with early failures on raltegravir or elvitegravir, especially when lacking codon 148 mutations[13,14].

Of HIV-1 entry inhibitors, enfuvirtide exhibits 20- to 100-fold less activity against HIV-2 isolates as a result of differences in viral envelope[15]. Maraviroc, a CCR5 antagonist, displays some antiviral activity against HIV-2 isolates with preferential R5 tropism. Certain genotypic profiles at the V3 envelope region of HIV-2 may help to predict in advance which viruses are more likely susceptible to maraviroc[16,17]. However, HIV-2 is known to be able to use a much broader range of coreceptors than HIV-1. In this regard, cenicriviroc, a new CCR5 and CCR2 antagonist in clinical development, could be more active than maraviroc against HIV-2[17].

In summary, all antiretrovirals currently available to treat HIV-2 patients are taken from the HIV-1 armamentarium, with lack of or just residual activity for some agents, which substantially limits the therapeutic options for HIV-2 patients. More specific and stronger antivirals are needed for the growing subset of HIV-2-infected individuals with advanced immunodeficiency, most of whom have already failed and selected resistance to older antiretroviral drugs.

Table 1. Main characteristics of HIV-2 infections in Spain. Comparison of two periods

	1988-2011	2012-2014	p
No.	260	50	
Mean age at diagnosis (mean + SD)	41.9 (12.4)	45.8 (8.8)	0.036*
Male gender (n, %)	173 (67%)	27 (56%)	0.12
Native Spaniards (n, %)	44 (17%)	8 (19%)	0.82
Sub-Saharan origin (n, %)	191 (74%)	32 (74%)	0.98
AIDS (n, %)	44 (17%)	2 (4%)	0.01*
Sexual transmission (n, %)	186 (95%)	28 (96%)	0.9
HIV-1 coinfection (n, %)	27 (10%)	4 (8%)	0.62

*significant statistical value.

HTLV-1

Human T-lymphotropic viruses (HTLVs) come from STLVs that infect monkeys as natural reservoir. Altogether, HTLV and STV constitute the primate T-lymphotropic virus (PTLV) family that includes four phylogroups named from 1 to 4. Interspecies jumps, at least between HTLV-1 and -2, occurred thousands of years ago[18], a remarkable difference from HIV-1 and -2, whose effective jumps from simians to humans occurred just one century ago[19]. This is in agreement with the lower pathogenicity of HTLVs compared to HIVs. Very recently, the last PTLV reservoir still hidden was unveiled; it is the source of HTLV-4, which is now known to be STLV-4 in gorillas[20].

Recent estimates propose that between five and 10 million people are infected with HTLV-1 worldwide[21-23]. The most important endemic regions are in the south of Japan, West Africa, some parts of Central/South America and the Caribbean basin, and certain islands in the South Pacific[21,23,24]. The etiologic role of HTLV-1 has been clearly established for two conditions: a subacute myelopathy that primarily affects the legs called tropical spastic paraparesis or HTLV-associated myelopathy (TSP/HAM), and a lymphoproliferative disorder of $CD4^+$ T-lymphocytes called adult T-cell leukemia/lymphoma (ATLL). Any of these illnesses can be accompanied or preceded by some chronic inflammatory conditions such as uveitis, arthritis, myositis, thyroiditis, or sicca syndrome. In certain geographical regions, HTLV-1 carriers are typically affected by some infectious conditions, such as infective dermatitis in children caused by *Staphylococcus aureus*, or hyperinfestation with *Strongyloides stercoralis*[25].

Factors triggering the development of disease in HTLV-1 carriers are not well characterized. Overall, no more than 10% of infected individuals develop clinical manifestations during their lifetime. Moreover, typically HTLV-1 diseases develop in 40-50-year-old women with TSP/HAM and in 50-60-year-old males with ATLL. As exception, persons infected following transplantation may develop TSP/HAM or ATLL within three years[26-28]. Most likely, HTLV-1-associated diseases result from interactions between viral determinants and multiple host genetic and immunologic factors. In this regard, the role of viral Tax gene and protein in ATLL[29] and of some HLA allelic variants[30] and IL28B polymorphisms[31] in TSP/HAM has been recently highlighted. Age at the time of infection has been proposed to be crucial for developing ATLL, as most cases have been reported in persons infected perinatally, generally from infected mothers. This explains the efforts made to prevent breastfeeding by HTLV-1 mothers. On the other hand, the acquisition of HTLV-1 through parenteral routes (i.e., blood transfusion) has been correlated with the development of TSP/HAM. Interestingly, the risk of neurologic complications can be predicted by testing HTLV-1 proviral load in the bloodstream, the risk of disease being mainly seen in those with more than 5% of peripheral blood mononuclear cells harboring the HTLV-1 provirus[32-34].

In Spain, and up to the end of year 2014, a total of 274 cases of HTLV-1 infection had been reported to the national registry. Individuals from Latin America represented 59% of cases, 18% were native Spaniards, and 15% were African immigrants. So far, 30 have developed TSP/HAM and 20 ATLL, most of the latter with fatal outcome. No significant differences in major

Table 2. Main characteristics of HTLV-1 infections in Spain. Comparison of two periods

	1985-2011	2012-2014	p
No.	199	75	
Mean age at diagnosis (mean + SD)	42.2 (13.5)	44 (11.8)	0.3
Male gender (n, %)	75 (38%)	25 (39%)	0.84
Native Spaniards (n, %)	43 (22%)	8 (12%)	0.1
Latin American origin (n, %)	114 (58%)	42 (66%)	0.19
HAM/TSP (n, %)	25 (12%)	5 (7%)	0.14
ATL (n, %)	14 (7%)	6 (8%)	0.78
Sexual transmission (n, %)	79 (67%)	21 (80%)	0.16
Vertical transmission (n, %)	17 (14%)	3 (11%)	0.7
Transfusion infection (n, %)	7 (3.5%)	0	0.12
HIV-1 coinfection (n, %)	21 (10%)	3 (4%)	0.43

features have occurred in recent times compared to prior years (Table 2). As expected, most cases concentrate around cities with the largest immigration flow such as Madrid (90 cases), Barcelona (83 cases) and Coruña (23 cases).

The number of new reported cases of HTLV-1 infection has been on the rise in Spain since 2008 (Fig. 2). A total of 171 cases have been reported within the last seven years, which represents 62% of the total. In 2014 alone, a total of 17 cases were identified. This trend is largely a result of the recent implementation of anti-HTLV testing in most transfusion centers along with the increase in the immigrant population from HTLV-1 endemic regions, mainly persons coming from Latin America. It must be noted, however, that there are significant differences in the way HTLV is excluded in distinct blood banks across the country. Some centers discharge anti-HTLV testing pools, which already have shown to preserve enough sensitivity. Testing at other centers is limited to first-time donors coming from endemic regions. This trend towards expanding anti-HTLV testing in Spain runs in parallel with the removal of universal testing in neighboring European countries, such as France or Germany, based on current low rates of infection among donors and cost-effectiveness policies, along with universal implementation of leukoreduction[35]. This procedure further reduces the residual risk of transmission of cell-associated agents, and HTLV-1 is known to be propagated mainly by cell-to-cell contact rather than through plasma-free particles[36,37].

In other scenarios, such as in pregnant women or solid organ transplant recipients, anti-HTLV screening might be considered only for persons with high likelihood of infection. Antenatal screening could prevent perinatal transmission as it generally occurs only after prolonged breastfeeding[38]. During the national meeting, the case of a pregnant woman coming from Ghana who was diagnosed with HTLV-1 infection at the time of antenatal screening was reported. This case clearly highlights the benefit of HTLV-1 screening of pregnant women coming from endemic regions. With respect to solid organ transplant recipients, the current recommendation is testing only for donors coming from endemic regions or their sexual partners. However, the high rate and rapid speed of symptoms, either neurologic[26,27] or lymphoproliferative[28], that may follow HTLV-1 acquisition after transplantation, along with the difficulties inherent to characterize the donor's origin in a short timeframe, has encouraged anti-HTLV testing of all transplant donors. This policy, however, is now challenged by the poor specificity of screening assays in low-risk populations causing false positives and the need for confirmation, which often jeopardize times for adequate organ transplantation[39].

Given the dramatic switch to hepatitis C virus (HCV) as result of the introduction of direct-acting antivirals that cure most infected patients, during years 2013 and 2014 the group undertook a survey to know the prevalence of HTLV infection among HCV patients in Spain. Both HTLV-1 and HCV share similar transmission routes (vertical, sexual, and parenteral), which might support

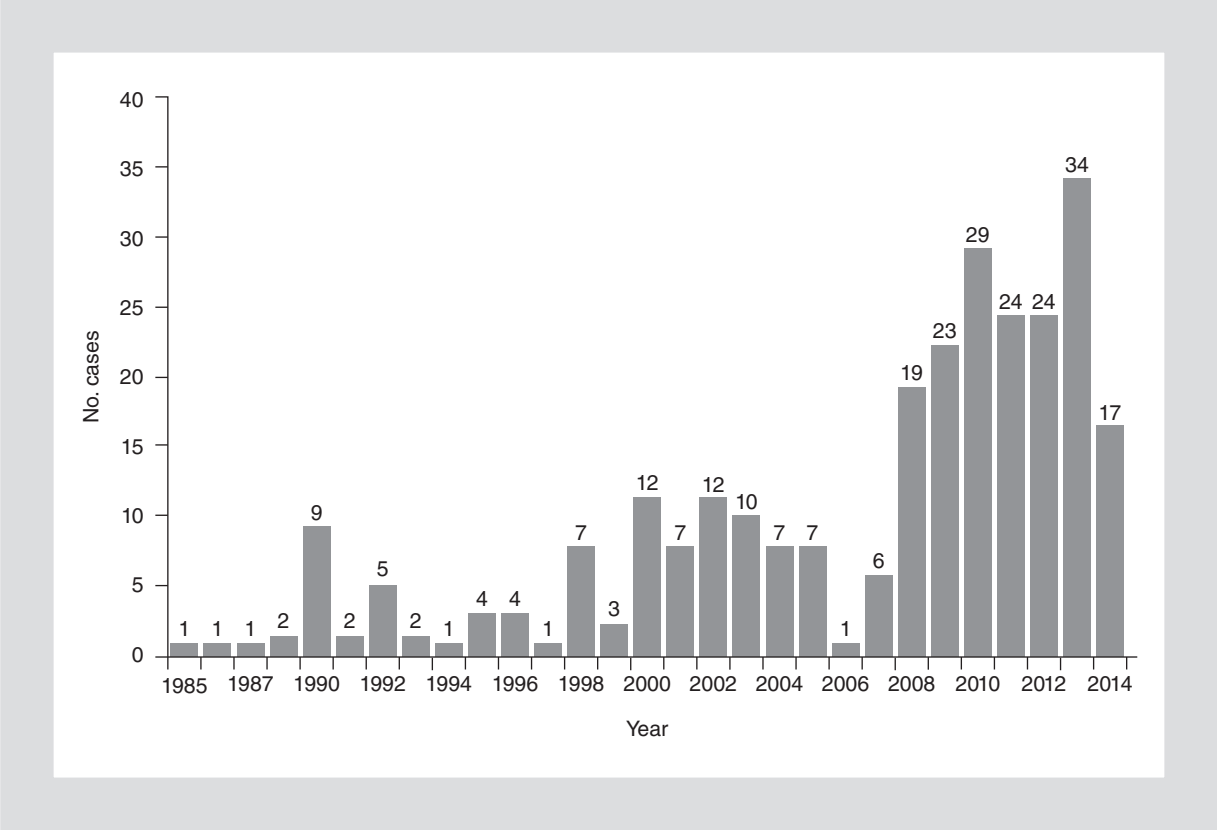

Figure 2. *Incidence of HTLV-1 in Spain.*

that coinfections could be common. The recent claim for expanding anti-HCV screening in the general population, in order to unveil the large pool of persons with hepatitis C unaware of their infection, may provide an unique opportunity for checking whether the HCV population may serve as indirect sentinel for HTLV-1 infections. To date, 12 centers distributed across Spain have participated in the study testing 2,999 samples from HCV-reactive patients. A total of 29 were infected with HTLV-2, one with HTLV-1, and 18 samples EIA-reactive displayed indeterminate *western blot* patterns. Interestingly, most cases of HTLV-2 and/or of indeterminate patterns were native Spaniards, but three were from other European Union countries. All had been injection drug users, which most likely was the source of infection for both HCV and HTLV. The only patient with HCV and HTLV-1 originated in the Dominican Republic. Based on these results, the overall prevalence of HTLV (mostly HTLV-2) would be around 1% in chronic hepatitis C patients in Spain. No further insights on HTLV-1 spreading would derive from testing hepatitis C populations.

HTLV-2, HTLV-3 and HTLV-4

A total of 776 cases of HTLV-2 infection had been reported in Spain up to December 2014. In contrast with HTLV-1 persons, HTLV-2 carriers are mostly native Spaniards (91%) male (76%), injections drug users (78%) and frequently coinfected with HIV-1 (85%). Most cases were reported in large cities, such as Madrid, Barcelona, Valencia, Valladolid, and Zaragoza, being particularly prevalent among persons in jail. Despite exhibiting similar mechanisms of clonal expansion with HTLV-1, $CD8^+$ instead of $CD4^+$ T-cells are the major target of HTLV-2[40]. Perhaps this could contribute to its lower pathogenicity.

To date, only two patients infected with HTLV-2 in Spain have been diagnosed with clinical manifestations potentially linked to their infection. One developed a subacute inflammatory myelopathy resembling TSP/HAM[41] and another developed a severe inflammatory myopathy[42]. During 2014 a total of seven new cases of HTLV-2 were reported to the national registry, all of them asymptomatic.

Neither HTLV-3 nor HTLV-4 cases have been identified so far in Spain, despite specific gene sequences of these retroviruses being examined in more than 100 specimens collected from individuals with indeterminate western blot patterns. As in North America[43], none of the Spanish samples was positive for either HTLV-3 or HTLV-4. Altogether, our data support the notion that infection with these retroviruses so far has not gone beyond Africa.

In the light of all the information available on retroviral infections other than HIV-1 in Spain, it seems worthwhile to emphasize the growing circulation nationwide of both HIV-2 and HTLV-1. Healthcare professionals must be aware and constantly keep in mind that these agents can be silently transmitted and only produce clinical manifestations after many years of infection. Infection must be excluded in persons with epidemiological links and/or clinical manifestations. Early interventions may prevent disease progression and halt transmission. Given that there is no vaccine or effective antiviral treatment for HTLV-1, increasing screening procedures and prevention programs in blood banks, organ transplant settings, and antenatal clinics should be encouraged.

Declaration of interest

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HIV-2 & HTLV Spanish Study Group

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