HIV-2 and HTLV-1 Infections in Spain, a Non-Endemic Region

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Abstract

The annual workshop of the Spanish HIV-2/HTLV Study Group was held at the Instituto de Salud Carlos III in Madrid on December 11, 2013. Nearly 100 experts and researchers in retroviruses other than HIV-1, the classical AIDS agent, convened for a one-day meeting devoted to updating knowledge on the epidemiology of HIV-2 and HTLV-1 infections and discussing new diagnostic and therapeutic strategies, with special attention to non-endemic regions such as Spain. The Group was funded 25 years ago and since then has been responsible for the national registry of cases, recording all relevant information for each subject and inviting them to enroll in a prospective cohort and biobank. Up to the end of 2013, a total of 297 individuals with HIV-2 infection were reported in Spain. All but 10 carry HIV-2 subtype A, with the rest being infected with subtype B. Overall, 71% came from sub-Saharan Africa. During the last decade, the incidence of new HIV-2 infections in Spain has remained fairly stable with around 20 cases per year. At the time of diagnosis, plasma HIV-2 RNA was undetectable in 61% of individuals and values in viremic subjects tended to be low (2.8 logs on average). To date, only 26% of HIV-2 individuals have been treated with antiretrovirals. The CD4 counts, however, only increased above 200 cells/mm^3 in 42% of them. On the other hand, 74% of non-treated HIV-2 individuals have > 500 CD4+ T-cells/mm^3. As in HIV-1 infection, X4 tropism in HIV-2 is associated with lower CD4 counts. A total of 253 individuals with HTLV-1 infection were reported in Spain by the end of 2013. Overall, 58% came from Latin America. HTLV-1-associated myelopathy was diagnosed in 29 patients and adult T-cell leukemia/lymphoma in 18. The highest incidence occurred in 2013, with 34 new HTLV-1 diagnoses, largely as result of expanding HTLV screening in blood banks. Attempts to reduce HTLV-1 proviral load in symptomatic or asymptomatic patients with elevated HTLV-1 DNA using antiretrovirals have produced poor results, although integrase inhibitors could be more successful. Although no cases of HTLV-3 or -4 have been identified so far in Spain, 769 individuals have been diagnosed with HTLV-2 infection. Up to 85% of the latest cases are coinfected with HIV-1 and are former intravenous drug users.

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Key words

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Introduction

The annual workshop of the Spanish HIV-2/HTLV Study Group was held at the Instituto de Salud Carlos III in Madrid on December 11, 2013. Nearly 100 experts and researchers working on human retroviruses other than HIV-1, the classical AIDS agent, convened for a one-day meeting devoted to updating knowledge on the epidemiology of HIV-2 and human lymphotropic T virus (HTLV)-1 infections and discussing new diagnostic and therapeutic strategies, with special focus on non-endemic regions such as Spain. The Group was founded 25 years ago and since then it has been responsible for the national registry of cases, recording all relevant information for individual subjects and enrolling most of them in a prospective cohort and biobank. Lastly, the Group has periodically released recommendations on screening and management of HIV-2 and HTLV infections in Spain.

HIV-2

The virus was firstly identified in 1986, examining patients presenting with AIDS and a negative/indeterminate HIV-1 serology[1]. Around 1-2 million people are estimated to be infected with HIV-2 worldwide. The most highly endemic regions are in West Africa and India. France and Portugal are the European countries with the largest number of HIV-2-infected individuals[2]. Up to December 2013, a total of 297 persons with HIV-2 infection have been reported in Spain. Two-thirds (196; 67%) were male and 212 (71%) were immigrants coming from sub-Saharan Africa. Only 51 were native Spaniards, mainly fishermen or persons who admitted sexual contacts with natives from endemic regions. As expected (Fig. 1), most cases were reported in Spanish cities with a large immigrant flow such as Barcelona (n = 72), Madrid (n = 62), Almería (n = 23), the Canary Islands (n = 17), Gerona (n = 15), and Pontevedra (n = 15). In contrast with HIV-1 infection in Spain, most subjects infected with HIV-2 had acquired the virus through heterosexual relationships, although a cluster of older homosexual men has been found in the Basque region. The widely distributed HIV-2 subtype A is also the predominant variant circulating in Spain, although HIV-2 subtype B has been identified in 10 individuals.

During 2013 a total of 18 new cases of HIV-2 infection were reported in Spain. Interestingly, six of them were found in Spanish women, all of whom admitted prior sexual intercourse with African immigrants. Half of them were diagnosed accidentally as part of a routine prenatal screening. Of the remaining 12 newly diagnosed HIV-2 cases in Spain, seven were foreigners coming from West Africa. They were living in Catalonia (n = 8), Madrid (n = 4), the Basque region (n = 2), the Canary Islands (n = 2), and Andalusia (n = 2). The incidence of HIV-2 infections has remained quite stable over the last decade, with an average of 20 new cases reported annually (Fig. 2).

HIV-2 is less pathogenic than HIV-1, doubling the average time to AIDS with 10 to 20 years or more of asymptomatic infection. Thus, epidemiological suspicion must be stressed in persons with high risk of prior exposure, such as immigrants from highly endemic regions or native Spaniards that have traveled to or lived there or admitted sexual intercourse with foreigners from those regions. Given the long asymptomatic period for HIV-2 infections and uncommon classical risk behaviors (i.e. intravenous drug use or homosexual relationships), the pool of HIV-2-infected carriers unaware of their status might be greater than for HIV-1.

The management and treatment of HIV-2 infection has generally followed the rules applied to HIV-1, with a few exceptions. However, the overall efficacy of antiretroviral therapy in HIV-2 is lower than for HIV-1, including both the extent of viral suppression and CD4 count recovery. This has been confirmed in the Spanish cohort as well in a large European study[3]. Thus, there is a need to develop more specific drugs and therapeutic strategies for HIV-2-infected patients. In the Spanish registry, 61% of individuals with HIV-2 infection presented initially with undetectable plasma HIV-2 RNA. Moreover, the median viral load in the subset of viremic patients was 2.8 logs. It should be acknowledged that reliable quantification of HIV-2 RNA is often a challenge and that so far there is no commercial viral load test for HIV-2. Furthermore, accurate measurements are better for subtype A than for other HIV-2 variants[4]. To date only 26% of HIV-2-infected individuals in Spain have received antiretroviral therapy. Despite being treated, 42% of them exhibit < 200 $CD4^+$ T-cells/mm^3, emphasizing that poor immune recovery is frequent in this population. On the other hand, 74% of non-treated HIV-2 individuals have CD4 counts > than 500 cells/mm^3, often after long periods of infection, behaving as long-term nonprogressors. As in HIV-1 infection, X4 tropism in HIV-2 is associated with lower CD4 counts than R5 tropism[5].

No prospective and randomized studies have been conducted to date comparing the effectiveness of

Figure 1. *Geographical distribution of HIV-2 cases in Spain.*

distinct antiretroviral regimens in HIV-2-infected patients. The only available information comes from observational and retrospective studies and always using drugs originally designed for treating HIV-1 infection. We know that HIV-2 is not susceptible to nonnucleoside reverse transcriptase inhibitors such as nevirapine, efavirenz, or rilpivirine. The presence of isoleucine at codon 181 and leucine at codon 188 of the viral reverse transcriptase largely accounts for this. In contrast, the susceptibility to etravirine of HIV-2 is only reduced by 50% compared to HIV-1[6].

While most nucleoside analogues that inhibit the HIV-1 reverse transcriptase are generally active against HIV-2, the presence of several polymorphisms at positions 69, 75, 118, 210, 215, and 219 lead to different degrees of impaired efficacy. Moreover, classical thymidine-associated resistance mutations are rarely selected in HIV-2. Unfortunately, drug resistance in such cases develops as a result of changes that lead to multi-nucleoside resistance, such as K65R and Q151M[6-9].

The HIV-1 protease inhibitors exhibit a wide range of antiviral activity against HIV-2, with saquinavir, lopinavir, and darunavir being the most active[10]. In contrast, HIV-2 is poorly susceptible to fosamprenavir or atazanavir[9]. All marketed HIV-1 integrase inhibitors are active against HIV-2. Moreover, drug resistance mutations to these drugs in HIV-2 are selected at the same positions as in HIV-1. The most frequent change occurs at codon 155, but is less common at positions 92, 143 and 148[11-13].

Dolutegravir is the latest approved HIV-1 integrase inhibitor. It blocks viral replication more potently than raltegravir and elvitegravir. The drug seems to behave similarly against HIV-2, and hypothetically could be tried as salvage therapy for early failures to raltegravir or elvitegravir, especially when there is evidence of lack of codon 148 mutations[14].

Of entry inhibitors, enfuvirtide exhibits 20 to 100 less activity against HIV-2 compared to HIV-1, largely as result of differences in the viral envelope[15]. The CCR5 antagonists, such as maraviroc, display inhibitory activity on HIV-2 replication as long as R5 tropic viruses are present. Several genotypic profiles in the viral envelope have been reported to impair the susceptibility

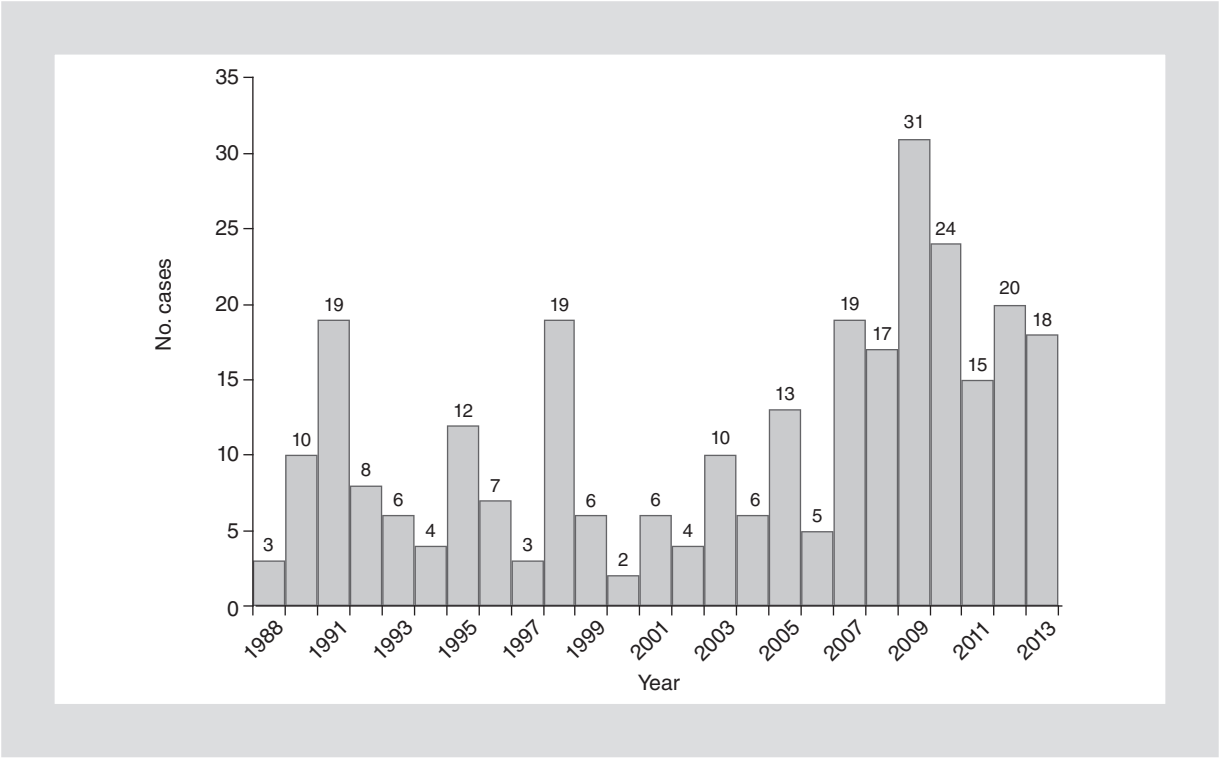

Figure 2. *Trends in HIV-2 incidence in Spain.*

to maraviroc in HIV-2[16]. Some of them reflect the wide coreceptor promiscuity exhibited by a large proportion of HIV-2 isolates[17]. Cenicriviroc is a new coreceptor antagonist in clinical development that interferes with CCR5 and CCR2 binding. It could be more active than maraviroc against HIV-2[18].

HTLV-1

Human lymphotropic T viruses are retroviruses linked genetically to simian T lymphotropic viruses (STLV). Altogether they form the primate T lymphotropic viruses (PTLV), of which there are four phylogroups named from 1 to 4. There have been STLV counterparts identified for all HTLVs except for HTLV-4[19,20]. It is believed that interspecies transmission of PTLV occurred thousands of years ago in Africa and Asia[21], in contrast with retroviruses that are responsible for AIDS, whose effective jump from chimps and gorillas occurred just one century ago[22].

Around 15-20 million people are estimated to be infected with HTLV-1 worldwide[23,24]. Major endemic regions are located in West Africa, South America, the Caribbean basin, and southern Japan[23]. Once a new host is infected, HTLV-1 expansion to new cells within the body mainly occurs throughout viral synapses[25] and clonal expansion of immortalized infected cells. There are no or just a limited number of new cycles of viral replication that involve the HTLV-1 reverse transcriptase. This explains the remarkable lack of genetic variability in HTLV-1 as well as the absence of plasma viremia[26].

Despite most HTLV-1 carriers remaining asymptomatic lifelong, 5% develop clinical complications including subacute myelopathy that affects the legs and sphincters, known as tropical spastic paraparesis or HTLV-1 associated myelopathy (TSP/HAM), and adult T-cell leukemia/lymphoma (ATLL). Several inflammatory conditions (i.e. uveitis, arthritis, myositis and/or thyroiditis) or infectious processes (i.e. infectious dermatitis due to *Staphylococcus aureus* and *Strongyloides stercolaris* infestation) can accompany the characteristic neurological or hematological syndromes[27,28].

Measurement of HTLV-1 proviral load has demonstrated prognostic value, with the risk of developing TSP/HAM or ATLL being significantly higher in HTLV-1 carriers that harbor the virus in more than 20% of their circulating lymphocytes[29,30]. More recently, a few host factors have also been associated with the risk of disease progression, including IL28B polymorphisms and HLA variants (Fig. 3). In this regard, the risk of TSP/HAM is greater in subjects harboring IL28B CC rs12979860 alleles[31] and HLA B*07 and DRB1*01[32].

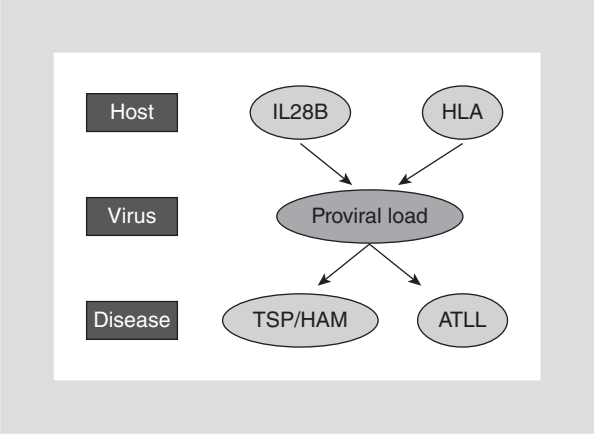

Figure 3. *Major determinants of HTLV-1 disease risk.*

A total of 258 cases of HTLV-1 infection were reported in Spain by the end of 2013. Overall, 58% of individuals came from Latin America, 19% were Spaniards, and 15% African immigrants. TSP/HAM was diagnosed in 29, whereas 18 had ATLL, most of the latter with fatal outcome. Figure 4 shows the geographical distribution of HTLV-1 cases in Spain. Most individuals were diagnosed in the largest urban metropolitan areas such as Madrid (n = 84), Barcelona (n = 78) and A Coruña (n = 21). Regarding their molecular subtype, all but one belonged to the Cosmopolitan subtype a. One Nigerian pregnant woman harbored HTLV-1 subtype b. Within the Cosmopolitan subtype a, two individuals (from Bolivia and Peru) belonged to the Japanese subgroup B, another two (from Senegal and Mauritania) to the North African subgroup D, and the rest to the Transcontinental subgroup A. Recently, we have identified one divergent HTLV-1 strain from an Ethiopian branched off from all five known Cosmopolitan subtype 1a subgroups. Divergent HTLV-1 strains have been introduced into and currently circulate in Spain[33].

During 2013, a total of 34 new cases of HTLV-1 infection were diagnosed in Spain (Fig. 5). This is the largest yearly figure so far. It seems to be associated with the wide introduction of anti-HTLV screening in blood banks across the country to avoid transfusion transmissions. For the first time, a donor with HTLV-1 seroconversion was diagnosed. He came from South America and has been living in Spain for a while. He was negative for anti-HTLV-1 antibodies in a previous donation but became reactive 10 months later. He admitted several heterosexual relationships with immigrants from HTLV-1 endemic regions.

Given the relatively large number of HTLV-1 carriers identified in blood banks in Spain during the last year (22 in total), it seems worthwhile continuing the screening for anti-HTLV antibodies in all Spanish transfusion centers. Screening of pools and/or selective testing of immigrants from endemic regions could maximize the cost/benefit of this intervention[34]. However, in other European countries active anti-HTLV-1 screening policies in blood banks have recently been abandoned[35,36], given the very low prevalence of infection in new donors along with the high efficacy of modern purification procedures such as leukoreduction[37-39].

Two patients with TSP/HAM and one with ATLL were diagnosed in Spain during 2013. All of them had a poor prognosis. A woman with HTLV-1 born in Spain developed TSP/HAM, but the source of the infection was unclear. The second TSP/HAM case was a male from Peru with long-term paraparesis who only recently had been tested for HTLV-1 and found to be positive. This delay in the diagnosis reflects the low clinical suspicion among doctors in Spain. Clearly, more information is needed on HTLV-1 epidemiology and clinical manifestations.

In unique scenarios other than blood transfusion, such as in the setting of organ transplantation or pregnancy, HTLV-1 screening could be restricted to individuals with a high risk of infection rather than being universally recommended. Given the convenience of having results as fast as possible, a rapid test for HTLV-1 antibodies could be worth to develop to be used in organ transplant donors and pregnant women presenting for delivering. Prenatal screening in women coming from HTLV-1 endemic regions could avoid perinatal transmission to the newborn, largely associated with prolonged breastfeeding periods[40]. With respect to organ transplantation, the more frequent and rapid development of neurological symptoms[41,42] or lymphoma[43] in recipients infected at the time of transplantation has encouraged HTLV-1 screening in this setting. However, difficulties in testing donors in a very short time frame along with high rates of false positive results have challenged this policy[44].

There are few and poor therapeutic options for patients with TSP/HAM. In early stages of clinical manifestations, the administration of corticoids may defer or halt the inflammatory injury of the spinal cord[45], with slight improvements in strength and stiffness of the legs. In patients with more severe spasticity and paraparesis, the use of spasmolytics and physiotherapy are crucial for minimizing contractures and osteoarticular deformities. Several studies have examined the role of antiretrovirals, such as zidovudine, lamivudine, or raltegravir,

Figure 4. *Geographical distribution of HTLV-1 cases in Spain.*

overall with poor and controversial results clinically and on proviral load[46,47]. Given its good safety profile, raltegravir is often used in asymptomatic HTLV-1 individuals that harbor high proviral load in an attempt to reduce the risk of disease development. Lamivudine and HIV-1 protease inhibitors do not block HTLV-1 replication *in vitro*[48,49]. In patients with lymphoproliferative disorders associated to HTLV-1 in the setting of immunosuppression, such as in recipients of organ transplants, clinical improvements with reversion of the malignant disease have been reported using corticoids and reducing immunosuppressants[43]. Finally, in patients with overt ATLL, the combination of zidovudine, interferon, and chemotherapy is currently the treatment of choice[50].

Other human retroviruses

Infection with HTLV-2 had been reported in 769 individuals in Spain by the end of 2013. In contrast with HTLV-1 cases, persons infected with HTLV-2 are mostly Spaniards (91%), males (76%), former injecting drug users (77%), and most were coinfected with HIV-1 (85%). The largest numbers of cases were reported in Madrid, Barcelona, Valencia, and Valladolid, with infection being particularly prevalent among persons in jail.

Despite sharing several biological mechanisms with HTLV-1, the target of HTLV-2 is predominantly $CD8^+$ T lymphocytes, which are clonally expanded upon infection[51]. Moreover, very few HTLV-2 carriers develop clinical manifestations potentially attributable to the virus lifelong, although sporadic cases of subacute myelopathy or hematological malignancies have been reported. In Spain, one HTLV-2-infected individual developed a TSP/HAM-like condition[52] and another an inflammatory myopathy[53]. Ten new cases of HTLV-2 infection were reported during 2013 in Spain, all of them asymptomatic.

To date there have been no reports of infection with either HTLV-3 or HTLV-4 in Spain. Specific viral sequences from these retroviruses have been checked in around 10 individuals with seroreactivity to HTLV in enzyme immunoassays but indeterminate Western blot patterns for HTLV-1 and HTLV-2 antibodies. Resembling the situation recently acknowledged in the USA[54], it seems that to date there is no circulation of HTLV-3 and HTLV-4 in Spain.

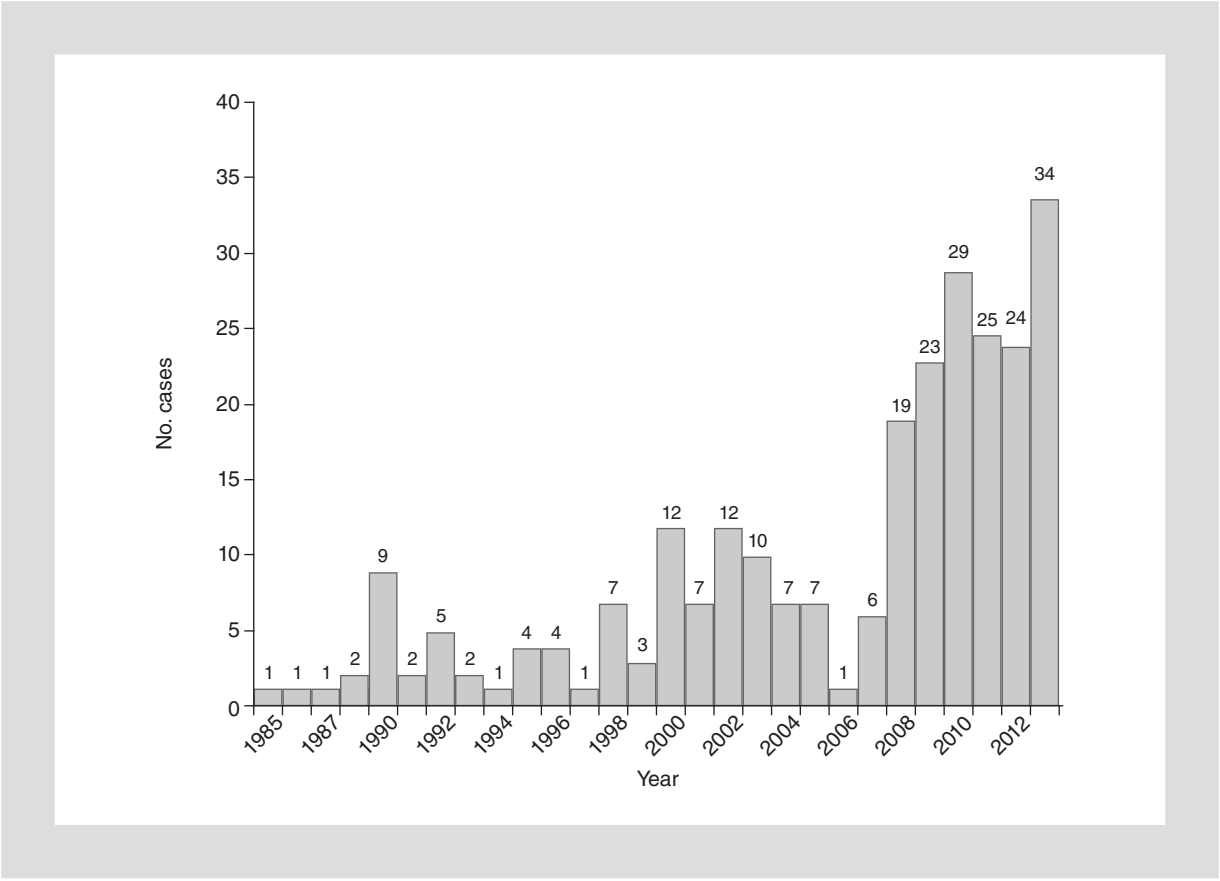

Figure 5. *Trends in HTLV-1 incidence in Spain.*

Conclusions

In light of the current information on retroviral infections other than HIV-1 in Spain, it seems worthwhile to remind health professionals about the increasing circulation of both HIV-2 and HTLV-1 outside endemic regions, and their potential for "silent" transmission from people unaware of their infection. Testing once in the life of asymptomatic immigrants from endemic regions would be desirable to identify asymptomatic carriers that may benefit from adequate monitoring for early recognition of disease or to avoid viral transmission to others. Lastly, it seems crucial to increase the clinical suspicion among medical doctors, who should be alerted to the spectrum of signs/symptoms of conditions associated to either HIV-2 or HTLV-1, and should request testing without unnecessary delays.

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