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REVIEW

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The slowdown of new infections by human retroviruses has reached a plateau in Spain

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Abstract

The 2022 annual meeting of the HTLV & HIV-2 Spanish Network was held in Madrid on December 14. We summarize here the main information presented and discussed at the workshop and review time trends for human retroviral infections in Spain. As transmissible agents, infections by human retroviruses are of obligatory declaration. Until the end of 2022, the Spanish national registry had recorded 451 cases of HTLV-1, 821 of HTLV-2, and 416 of HIV-2. For HIV-1, estimates are of 150 000 people currently living with HIV-1 and 60 000 cumulative deaths due to AIDS. During year 2022, new diagnoses in Spain were of 22 for HTLV-1, 6 for HTLV-2, and 7 for HIV-2. The last updated figures for HIV-1 are from 2021 and counted 2786 new diagnoses. The slowdown in yearly infections for HIV-1 in Spain points out that new strategies are needed to achieve the United Nations 95-95-95 targets by 2025.

For the remaining neglected human retroviral infections, their control might be pushed throughout four interventions: (1) expanding testing; (2) improving education and interventions aimed to reduce risk behaviors; (3) facilitating access to antiretrovirals as treatment and prevention, including further development of long-acting formulations; and (4) increasing vaccine research efforts. Spain is a 47 million population country in South Europe with strong migration flows from HTLV-1 endemic regions in Latin America and Sub-Saharan Africa. At this time universal HTLV screening has been implemented only in the transplantation setting, following the report of 5 cases of HTLV-associated myelopathy shortly after transplantation of organs from HTLV-1 positive donors. There are four target populations for expanding testing and unveiling asymptomatic carriers responsible for silent HTLV-1 transmissions: (1) migrants; (2) individuals with sexually transmitted infections; (3) pregnant women; and (4) blood donors.

KEYWORDS

blood donors, epidemiology, HIV-1, HIV-2, HTLV-1, HTLV-2, human retroviruses, intervention, pregnant women, prevention, sexually transmitted infections, surveillance, transfusion, transplantation

1 | INTRODUCTION

Retroviruses are infectious particles that contain a unique enzyme, the reverse transcriptase, that converts the viral RNA into complementary DNA that then integrates into the host cell DNA. Viral progeny is produced from this proviral DNA. During the late 70s, Robert Gallo and his team at the National Cancer Institute (Bethesda, MD) isolated the first human retroviruses, known as HTLV-1, HTLV-2, and HTLV-3 (later renamed as HIV-1). The discovery was largely facilitated by the advent of interleukin-2 as growth factor for T cells.[1]

To date, four human retroviruses have been identified as cause of lifelong infections, severe illnesses and global epidemics (Table 1). Rare cases of another two human retroviruses (HTLV-3 and HTLV-4) have been described in West Africa.[2,3] HIV-1 is by far the most prevalent and currently infects 40 million people. Since its recognition in 1981, AIDS has produced more than 40 million deaths.[4] Global estimates for HIV-2 infections are of 1–2 million people.[5] HTLV-1 infects 10 million and produces subacute myelopathy or T-cell leukemia/lymphomas in 10% of carriers.[6] Lastly, HTLV-2 infects 1 million people and may produce neurological symptoms very rarely.[7]

In Europe, infection with distinct human retroviruses is well documented. Whereas a disproportionate number of HTLV-1 and HIV-2 infections in European countries are diagnosed in migrants from the respective endemic regions,[6,8–11] infections with HIV-1 and HTLV-2 are preferentially diagnosed in European natives, being

TABLE 1 Main epidemiological features of global human retroviral epidemics.

	Estimated infected population (millions)	High endemic regions	High risk populations
HTLV-1	10	– South & Central America – Caribbean islands – West & Central Africa – South Japan – Iran, Southwest India	– Australian aborigins – Amerindians – Black Africans – Okinawa's descendants
HTLV-2	1	– West & Central Africa – Amazon basin	– Injection drug users – African pygmees – Amerindians
HIV-1	40	– Sub-Saharan Africa – Caribbean basin	– Men having sex with men – Injection drug users – Heterosexuals with multiple partners
HIV-2	1–2	– West Africa	– Heterosexuals with multiple partners

mostly men who have sex with men for HIV-1, and persons who inject drugs (PWID) for HTLV-2.[12,13]

A nationwide HTLV & HIV-2 register was created in Spain in 1989. Main demographics, clinical symptoms/signs, and laboratory findings are collected at baseline and longitudinally using a standardized case report form. Notification of HTLV-1, HTLV-2, and HIV-2 cases to the national register is voluntary. Members of the Spanish HTLV & HIV-2 Network cover most of the lab facilities where these viruses can be diagnosed and characterized. In addition, from the coordination team, other clinics are contacted when new cases are identified at the National Hospital Discharge database and have not been previously reported at the register. Further details have been specified elsewhere for HTLV-1[14] and are similarly applied to HIV-2.

The Spanish HTLV & HIV-2 network updates on a yearly basis the national figures for these viral infections and produces recommendations for screening and/or medical management. The 2022 annual meeting of the HTLV & HIV-2 Spanish Network was held in Madrid on December 14. National trends for HIV-1 were reported alike. We summarize here the main information presented and discussed at the workshop.

2 | HTLV-1 EPIDEMICS

Current estimated for HTLV-1 infection worldwide are of 8–10 million people. However, a large proportion of infected individuals who are asymptomatic must be unaware of their infection. Large endemic areas exist as hot spots indigenous populations in Sub-Saharan Africa, Latin America, and Australia.[15–17] Infection with HTLV-1 in Spain has generally been noticed following the clinical presentation of patients with either tropical spastic paraparesis/HTLV-associated myelopathy (TSP/HAM) or adult T-cell leukemia/lymphomas (ATL). Less frequently, HTLV-1 has been found testing migrants with *Strongyloides stercoralis* infection. The first case of TSP/HAM was reported in 1990 in a Spanish nun that had been working at a religious initiative in Peru for decades. There she had received transfusions for managing episodes of malaria. She developed paraparesis years later and returned to Spain, where she was diagnosed as positive for HTLV-1.[18]

Since then, a total of 451 individuals have been reported as infected with HTLV-1 in Spain. All cases have been confirmed by immunoblot and/or PCR. Nearly two thirds were female. Median age at diagnosis was 41 years. Most had acquired the infection throughout sexual contact, although vertical transmission was suspected for 10%. Late presentation was relatively frequent due to poor clinical suspicion and testing.[19] Overall, 22% of patients first appeared with clinical manifestations, mostly subacute myelopathy or T-cell leukemias/lymphomas.[20] More than two thirds of HTLV-1 cases in Spain have been diagnosed in persons coming from Latin America and only 16% are native Spaniards (Table 2). Persons in the latest group frequently reported having had sex partners from HTLV-1 endemic regions. Most individuals with HTLV-1 in Spain are living at the largest urban cities of Madrid (n = 140) and Barcelona (n = 126).

Hospitalizations in HTLV-1 carriers are low in Spain and have remained stable during the last two decades.[14] Besides admissions due to typical clinical complications of HTLV-1, such as leukemia or myelopathy, there is evidence supporting that persistent immune activation and chronic inflammation in HTLV-1 carriers might contribute as well to an increased morbidity with higher rates of cardiovascular disease, neurodegenerative illnesses, and frailty.[21]

Compared to the older period, cases of HTLV-1 increased since 2008, when HTLV universal screening of blood donors begun in some—but not all—blood banks. The yearly incidence of HTLV-1 infections in Spain has remained relatively stable around 20 cases per year during the last decade, after peaking in 2013 with 33 new diagnoses (Figure 1). In year 2022, a total of 22 new individuals with HTLV-1 were diagnosed in Spain. Six of them first presented with clinical manifestations, such as TSP/HAM

TABLE 2 Main characteristics at the time of diagnosis of human retroviral infections in Spain.

	HTLV-1	HTLV-2	HIV-1	HIV-2
Infected population	451	821	150 000[a]	416
Male (%)	35	76	86	63
Mean age (years)	41	35	36	42
Major transmission routes	Heterosexual, vertical	IDU, heterosexual	MSM, heterosexual, IDU	heterosexual
Disease (%)	22	3 cases	24	16
Foreigners (%)	82	10	39	86
New infections 2022	22	6	2786[b]	7

Abbreviations: IDU, injection drug use; MSM, men having sex with men.

[a]Real estimates are of 150 000, as 15% remain undiagnosed.

[b]Figures for 2021 instead of 2022

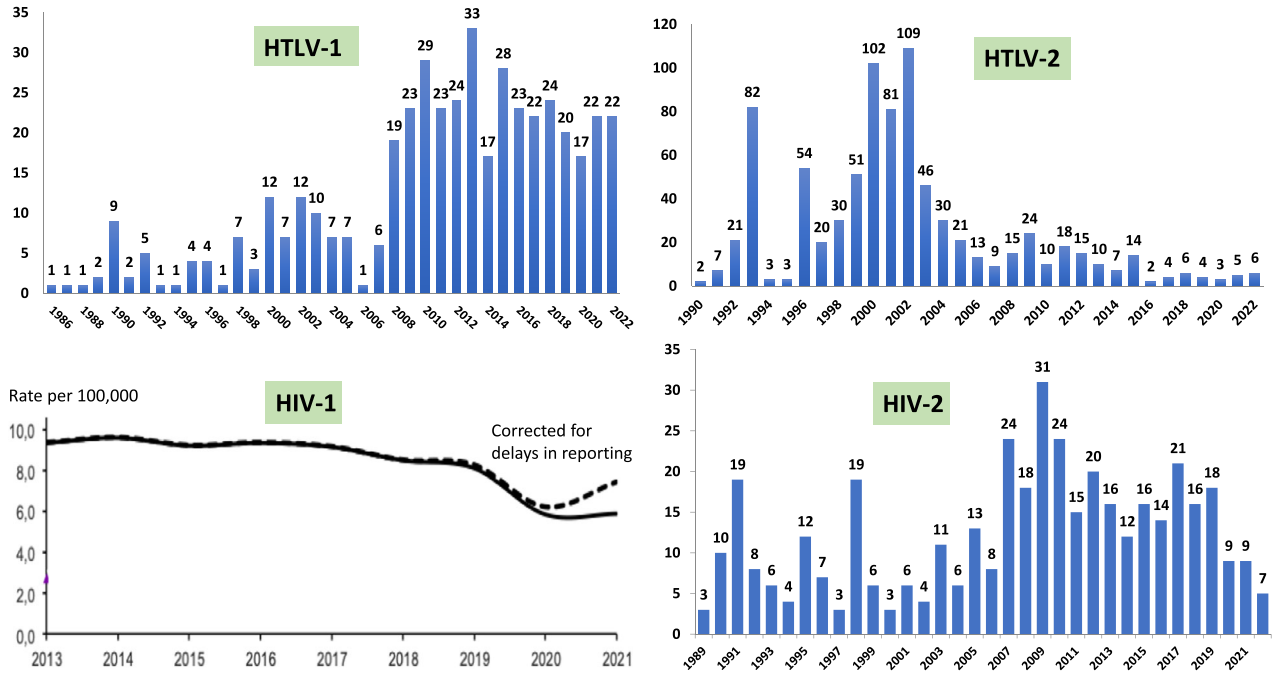

FIGURE 1 Yearly report of new infections with human retroviruses in Spain.

(*n* = 3) or ATL (*n* = 2). Sixteen were from Latin America and two from West Africa. One was from Iran. Only two were native Spaniards.

2.1 | Transplantation

Six individuals at the HTLV Spanish register had been infected with HTLV-1 following solid organ transplantation, of whom 5 developed myelopathy within a short timeframe.[22,23] The large viral inoculum size and posttransplant immunosuppression most likely contributed to that unusually frequent and rapid disease progression. Based on these findings, universal HTLV screening of organ and stem cell donors has become mandatory in Spain since 2019. Since then no HTLV-1-positive organ donors have been identified. Unfortunately, the relatively high rate of false positive results for HTLV serology has forced to rule out organs thereafter found to be from noninfected individuals. The advent of sensitive, more specific and faster molecular diagnostic tests for HTLV-1 is eagerly awaited.

2.2 | Transfusion & blood donors

During 2022, 8 out of 21 new reported cases of HTLV-1 were blood donors identified at two large transfusion centers in Madrid and Barcelona. At this time, the rate of HTLV in blood donors in Spain seems to be higher than for other agents whose screening is mandatory, such as HIV (3.4/100 000) or hepatitis C (4.34/100 000).[24]

HTLV screening of blood donors is currently not mandatory in Spain (law RD1088/2005), there is concern for potential transmission in blood banks. Although leukoreduction of blood donations significantly reduces the chances of transmission of HTLV-1, an intracellular virus, the efficacy of the procedure is not 100%. Since 2008, HTLV screening of Latin Americans along with Chagas disease testing begun in some blood banks, such as the regional transfusion center in Barcelona. Given the relatively high number of diagnoses, universal HTLV testing using pools was decided thereafter. A total of 51 donors had been diagnosed with HTLV-1 during the next 10 years. Although many were Latin Americans, one quarter were Europeans, including Spaniards. Furthermore, two seroconversions were identified among Latin Americans. Fortunately, none of the earlier recipients were infected.[25] Since 2018, another 17 donors have been identified with HTLV-1 along with three seroconversions.

2.3 | Sexually transmitted infections (STI)

In 2022, a nationwide study begun to assess the HTLV seroprevalence in people at high risk for STI in Spain. From 1652 individuals attending STI clinics, 4 cases of HTLV-1 and another 4 of HTLV-2 were identified. All HTLV-1 cases but 1 were young Latin American men. The only female was an older Spaniard. An interesting observation refers to the recognition of HIV-1 coinfection in 2 of the HTLV-1 positive men. Both referred multiple sex partners, some of whom used pre-exposure prophylaxis (PrEP). The possibility of antiretrovirals to protect from both HIV and HTLV infections will be examined in this population.

2.4 | Pregnant women

Testing of 6331 pregnant women in Spain during 2022 identified 2 cases of HTLV-1 infection. Both were Latin American women. Although the overall rate of HTLV-1 among pregnant women in Spain remains stable and low around 0.03%, the rate among Latin American pregnant women is 0.4%.

2.5 | Migrants

A retrospective study conducted during the last decade identified 83 (0.5%) cases of HTLV-1 following testing of 17 007 migrants to Spain. The majority were female (77%), median age 42 years and median time from arrival to Spain until diagnosis was 10 years. Most cases were from Latin America and Sub-Saharan Africa. Roughly 15% had clinical manifestations linked to HTLV-1, being the rest asymptomatic.[26] The molecular epidemiology of HTLV-1 in Spain has been examined in 94 samples. Subtype A is present in all but two Africans that carry subtype B. These results support the predominant circulation of HTLV-1a worldwide whereas a wider virus heterogeneity is mostly restricted to Sub-Saharan Africa.[27]

3 | HTLV-2 EPIDEMICS

The first isolates of HTLV-2 were obtained in 1982 from primary T lymphocytes cultured with IL-2 from a patient with hairy cell T cell leukemia.[28] Although this discovery followed the earlier identification of HTLV-1 as the first human retrovirus,[29] phylogenetic evolutionary studies have concluded that HTLV-2 should be considered as the first of retroviruses that infected humans, nearly 400 000 years ago.[30] The corresponding primate counterpart, named STLV-2, was first described in bonobos.

The high prevalence of HTLV-2 infection among some Amerindian tribes (i.e., Kayapo) in the Brazilian Amazon,[31] and in pygmies in Central-West Africa[32] is remarkable. Given the lack of firm association between HTLV-2 and any human illness, and the possibility to infect and integrate into human sperm cells, some authors have suggested that HTLV-2 could be in the process of becoming endogenous, as it seems to have occurred with 8% of the human genome.[33]

Besides primitive native indigenous populations, HTLV-2 is characteristically prevalent among PWID worldwide, from North America and Europe to Vietnam.[34] As expected, sexual partners of HTLV-2 infected PWID are at high risk of infection.[35] For this reason, coinfection between HTLV-2 and HIV-1 is quite frequent. In this regard, HIV testing functions as a "*proxi*" for HTLV-2 infection, limiting unnoticed spreading of the virus.

In contrast with the rest of human retroviruses, the pathogenicity of HTLV-2 is very low. Neurological symptoms, occasionally resembling TSP/HAM have been reported occasionally. In Spain, two individuals with clinical manifestations potentially linked to HTLV-2 have been reported to date. Both were coinfected with HIV-1. One presented a myopathy with histological confirmation[36] and another developed paraparesis following initiation of antiretroviral therapy to treat HIV-1, resembling an immune reconstitution inflammatory syndrome.[37] It is noteworthy that clinical manifestations potentially associated to HTLV-2 does not develop in the transplantation setting, where large inoculum size and immunosuppression might potentiate viral pathogenicity.[38]

During 2022, six new cases of HTLV-2 were reported in Spain. Four were coinfected with HIV-1 and all acknowledged prior injection drug use. All HTLV-2 cases were Spaniards but one who originated in Nigeria. The yearly incidence of HTLV-2 has been declining in Spain during the last two decades, following a peak reached in 2002, when 109 cases were diagnosed (Figure 1). Indeed, during the last couple of years, a median of 5 cases have been reported annually.

4 | HIV-1 EPIDEMICS

In Spain, current estimates are of 150 000 persons living with HIV-1. However, around 15% have not been diagnosed and remain unaware of their infection.[39] This subset of individuals is considered as an important source of new infections. For the last decade, new infections have been steadily declining to be around 3000 new diagnosis per year (Figure 1). The drop seen during 2020 was consequence of misreporting due to the COVID-19 pandemic along with transient reductions in risk exposures due to social isolation mandates. However, new HIV-1 diagnoses rebounded in 2021 to 2786 individuals. During the COVID-19 pandemic, clinical presentation with advanced HIV disease and AIDS run in parallel with lower new HIV diagnosis of asymptomatic individuals, most likely due to suboptimal care in this population.[40]

New HIV-1 infections in Spain are mainly occurring in male (86%), being men having sex with men 56% of all cases. Their median age is 36 years. More than 38% are foreigners, mostly migrants from Latin America and Sub-Saharan Africa. The overall incidence rate of HIV-1 in Spain is one of the highest in Europe, approaching 8 per 100 000 population per year. In comparison to other neighbor countries, such as France, United Kingdom, or Germany, the extent of PrEP use in Spain is scaling up slowly. However, the benefit of information and education on sexual risk behaviors and access to PrEP seems to have attained a plateau.

5 | HIV-2 EPIDEMICS

A total of 416 individuals infected with HIV-2 had been diagnosed in Spain until the end of 2022. Male represented 63%. Mean age at diagnosis was 42 years. Roughly 77% were migrants from Sub-Saharan Africa. Spaniards represented 14% of cases, most of whom acknowledged having had sex partners from West Africa.

Most persons with HIV-2 in Spain are living in the major cities—Barcelona (n = 85) and Madrid (n = 76)—and regions with large African migrant population—Basque country (n = 47) and Almeria (n = 45). Up to 9% of HIV-2 individuals are coinfected with HIV-1. Finally, HIV-2 subtype A is by far the predominant variant, although 10% of patients carry HIV-2 subtype B.

During 2022, seven new cases of HIV-2 were reported in Spain. One presented with advanced immunodeficiency and AIDS clinical conditions. Heterosexual contacts were the most likely mode of contagion. All new HIV-2 cases were Africans but one, who was an older Spanish woman.

The yearly incidence of HIV-2 has been declining in Spain during the last decade, following a peak reached in 2009, when 31 cases were diagnosed (Figure 1). Indeed, during the last couple of years, less than 10 cases have been reported per year. It should be noted, however, that the impact of the COVID-19 pandemic, reducing migration flows, might have contributed to this lower rate of HIV-2 diagnoses.[41]

6 | INTERVENTIONS TOWARD THE ELIMINATION OF HUMAN RETROVIRAL EPIDEMICS

The slowdown in reduced yearly infections for HIV-1 in Spain points out that new strategies are needed to achieve the United Nations 95-95-95 targets by 2025.[42] The elimination of HIV-1 and the remaining neglected human retroviruses may be pushed forward by four interventions: (1) expanding testing; (2) improving education and interventions aimed to reduce risk behaviors[43]; (3) facilitating access to antiretrovirals as treatment and prevention, and pushing further development of long-acting formulations[44,45]; and (4) increasing vaccine research efforts, especially for HIV-1 and HTLV-1.

Spain is a 47 million population country in South Europe with strong migration flows from HTLV-1 endemic regions in Latin America and Sub-Saharan Africa. Likewise, Spain is a major entrance in Europe for Sub-Saharan migrants coming from HIV-2 African endemic regions (Figure 2). Accordingly, target populations for expanding testing and unveil asymptomatic carriers responsible for silent retroviral transmissions, are four groups: (1) blood donors; (2) individuals with STI; (3) pregnant women; and (4) migrants.

Recognition of HIV-2 is facilitated by wide HIV screening programs. However, at this time universal HTLV screening only has been implemented in the transplantation setting,[46,47] following the report of 5 cases of TSP/HAM in recipients of HTLV-1 positive organs.[22,23] There is a window of opportunity for major intervention expanding HTLV testing to all pregnant women as part of antenatal screening (along with HIV, hepatitis, and syphilis) and in persons attending STI clinics, as HTLV-1 is largely transmitted by sexual contact. Preliminary data from two studies on HTLV-1 conducted in 2022 in these sentinel populations were presented.

The results of HTLV-1 testing of pregnant women in Spain during 2022 showed that prevalence rate has remained stable for two decades.[48,49] However, among Latin American pregnant women was 0.4%, a rate higher than that observed for other infections such as HIV (0.1%–0.26%)[50] or syphilis (0.11%),[51] for which screening is mandatory during pregnancy. In the last 10 years, the number of Latin American women of childbearing age in Spain has risen from 40 385 to 109 479, which represents a 2.7-fold increase. Women from Sub-Saharan Africa have increased from 4091 to 5347, which represents a 1.3-fold increase.[52] Finally, around 25% of pregnant women attended in Spain during the last 5 years are foreigners and 80% come from endemic countries for HTLV-1. Given that vertical transmission is

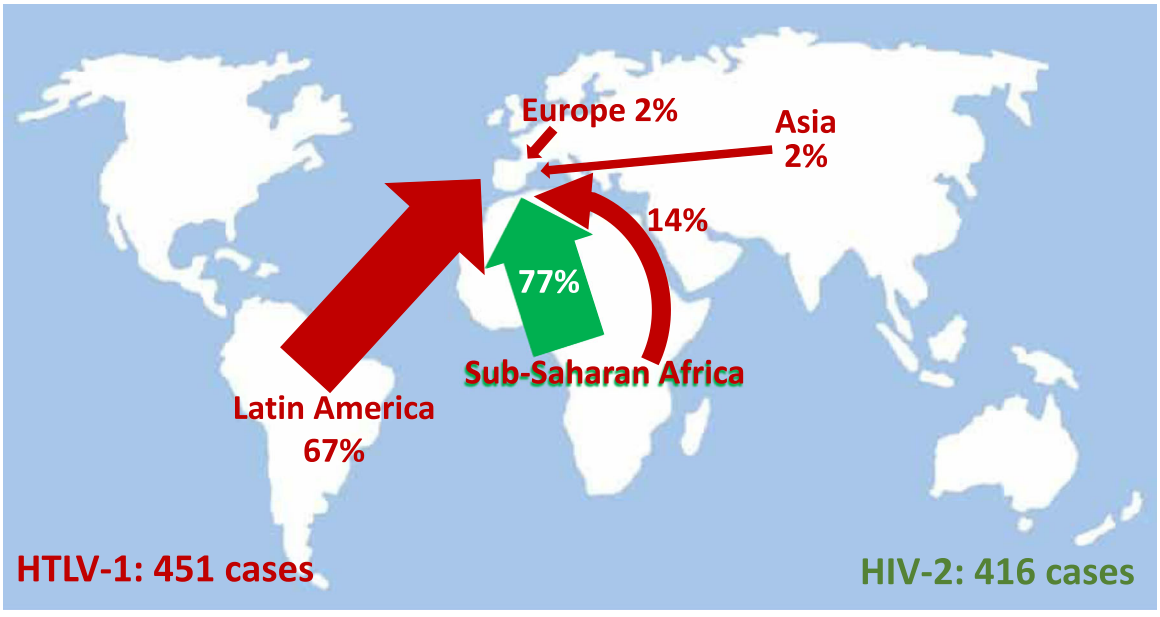

FIGURE 2 Major geographical sources for HTLV-1 and HIV-2 in Spain.

almost fully stopped avoiding breastfeeding,[53] universal HTLV screening of pregnant women in Spain seems to be justified.

With respect to STI patients, data from an ongoing study conducted in Spain were reported during the workshop for 2022. Preliminary results were recorded above. HTLV-1 was mostly found among Latin American male, mostly men who had sex with men. At this time, it is unclear in what extent the use of antiretrovirals to treat or prevent HIV-1 contagion as PrEP might protect from sexual transmission of HTLV-1 infection.[54] In vitro data support that cabotegravir may halt HTLV-1 transmission[55] and long-acting formulations of this drug are increasingly being used by persons engaged in high-risk sexual behaviors. It should be noted that the extent of PrEP use in this population is still low in Spain compared to other Western European countries. In the meantime, our preliminary findings highlight the convenience of adding anti-HTLV testing for individuals presenting or at risk for any STI.[56]

The consideration of introducing universal HTLV screening of blood donors in Spain is under debate, as current data suggest that it will unveil a significant number of asymptomatic HTLV carriers. During 2022, 8 out of 21 new reported cases of HTLV-1 were blood donors identified at two large transfusion centers in Madrid and Barcelona. At this time, the rate of HTLV in blood donors in Spain is higher than for other agents whose screening is mandatory, such as HIV or hepatitis C. Although leukoreduction of blood donations significantly reduces the chances of transmission of HTLV-1, an intracellular virus, the efficacy of the procedure is not 100%.[57] On the other hand, a significant proportion of new HTLV-1 diagnoses are found in native Spaniards, suggesting that selective testing of donors coming from endemic regions will not avoid completely the risk of HTLV-1 transmission. Thus, at this time universal HTLV screening might be considered worthy in Spain, at least for a while, allowing to collect updated information and make reliable recommendations.

AUTHOR CONTRIBUTIONS

Vicente Soriano and Carmen de Mendoza designed the study. Vicente Soriano and Carmen de Mendoza wrote the first draft. All authors contributed providing local information and revised the manuscript draft. All authors approved the final submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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