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The incidence of HIV-2 infection in Spain is declining – a registry data analysis

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ABSTRACT

Objectives: HIV-2 infection is a neglected disease caused by a human retrovirus that causes AIDS more slowly than HIV-1. Infection with HIV-2 is endemic in West Africa. Given its differential features, guidelines recommend ruling out HIV-2 infection in all newly diagnosed HIV-seropositive individuals.

Methods: A national registry of HIV-2 cases was created in Spain in 1989, following the first report of three HIV-2+ individuals in Barcelona. The main demographics, clinical, and virological data are reported up to December 2023.

Results: A total of 424 individuals with HIV-2 infection were recorded in the Spanish registry. After a peak in 2009 when 31 cases were reported, new HIV-2 diagnoses steadily decreased. Less than 10 cases/year have been notified since the COVID-19 pandemic. In 2023, only eight cases were reported.

Mean age at HIV-2 diagnosis was 44 years old, ranging from birth to 83 years. A total of 265 (62.5%) were male. Migrants predominated, being 322 (76%) Sub-Saharan Africans; however, 60 (14.2%) were native Spaniards. Heterosexual exposure was the most likely route of infection in at least 287 (67.7%) cases. A few cases could be traced to transfusions (n = 4), vertical infection (n = 2), or injection drug use (n = 7). In addition, 15 individuals (3.5%) were men who had sex with men. Coinfection with HIV-1 was recognized in 39 (9.2%) individuals. Molecular characterization of HIV-2 subtypes was performed in 139 individuals, 121 being infected with subtype A and 18 with subtype B.

Conclusion: The annual incidence of HIV-2 infection in Spain has decreased after peaking 15 years ago, being the current number of cases below 10 per year. Three-quarters are African migrants, and two-thirds are male. Circulation of HIV-2 in Spain is limited and steadily decreasing.

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Introduction

HIV-2 was isolated in 1986 in African migrants with AIDS attended in Portugal and France [1,2]. The first cases in Spain were identified in 1988 among Sub-Saharan Africans recently arrived in Catalonia [3]. Since then, it has been well established that infection with HIV-2 is endemic in West Africa [4], being found in Europe mostly among migrants and/or natives that had traveled to endemic countries and/or had sex partners from these regions [5].

HIV-2 is less pathogenic than HIV-1 [6,7], causing AIDS only after an average of 15-20 years [8]. Plasma viremia is lower than for HIV-1 [9], which correlates with lower HIV-2 transmissibility either sexual or vertical [4,10]. The susceptibility of HIV-2 to antiretroviral drugs partially differs from HIV-1, being non-nucleoside reverse transcriptase inhibitors typically non-active [11,12].

Given their close ties with former colonies in West Africa, the European countries with the largest number of HIV-2-infected persons are France [13] and Portugal [14]. However, HIV-2 cases have been reported in Belgium, the United Kingdom, and others [15–17]. Herein, we report the main features of the HIV-2 population living in Spain.

Methods

A nationwide HIV-2 registry was created in Spain in 1989. Main demographics, clinical symptoms/signs, and laboratory findings are collected for each new HIV-2-identified individual at baseline and longitudinally using standardized case report forms. Members of the Spanish HIV-2 Network belong to more than 40 centers that cover nationwide most of the lab facilities where this virus can be diagnosed, including public or private microbiology labs or blood banks [18]. From the coordination center, all members of the network were invited to participate in the current study.

Notification of HIV-2 positives to the national registry is voluntary. However, from the coordination team, clinics are contacted when new cases are identified in the public National Hospital Discharge database and there is no previous recording at the HIV-2 national registry. Provision of free access to diagnostic tools including plasma HIV-2 ribonucleic acid (RNA) load and subtyping, facilitates and ensures that almost all HIV-2 cases diagnosed in the country are recorded within the registry within 1-2 years upon first identification.

However, some HIV-2 cases can go undiagnosed. Some of the reasons could be because asymptomatic individuals are frequently not tested, given the lower pathogenicity of HIV-2 compared to HIV-1. On the other hand, migrants have less access to testing, and many HIV-2 carriers are West African migrants. Finally, a large proportion of migrants reside temporarily while traveling through the country to seek asylum in other European countries.

HIV diagnosis had been made following initial screening using antigen-antibody tests. All initially seroreactive samples were subsequently tested using an HIV-1/2 differentiation serological assay, as recommended by the CDC HIV diagnosis algorithm [19]. To discriminate between serological cross-reactivity or dual infection, all samples with double reactivity were retested after serial serum dilution. Truly HIV-1 and HIV-2 dual infections keep antibody reactivity using the confirmatory test, whereas cross-reactivity is recognized because reactivity is lost for specific HIV-1 or HIV-2 antibodies on serial dilutions, as shown previously [20]. In addition, all these samples were tested using HIV-1 RNA and HIV-2 RNA-specific assays, as described below. Given the low viral load values of HIV-2, even in untreated individuals, when cell DNA was available, all initially dually reactive samples on serological tests were tested for specific HIV-1 and HIV-2 proviral gene sequences.

Plasma HIV-1 viremia was examined using the commercial viral load tests available at each of the participating clinics (COBAS 5800/6800/8800 System HIV-1 (Roche), Abbott Real Time HIV-1 (Abbott), VERSANT HIV-1 RNA (kinetic polymerase chain reaction) (Siemens), or Aptima HIV-1 Quant Dx Assay (Hologic). For plasma HIV-2 RNA measurement we used a non-commercial quantitative polymerase chain reaction assay, as described elsewhere [21]. The lower threshold for HIV-2 RNA detection using this assay is 50 copies/mL. Briefly, the region amplified was the Long Terminal Repeat with specific primers and probes. Both HIV-2 group A and B are reliably detected with this assay. For each run, a standard curve was generated using a stock of HIV-2 strain NIHZ, which was counted by electron microscopy and was used as the standard (Advanced Biotechnology Inc, Columbia, Maryland). Before lysis, the stock solution contained 7.2×10^{10} virus particles/mL. The HIV-2 NIHZ stock solution was diluted to obtain 5,000,000; 500,000; 50,000; 5,000; 500 and 50 copies/mL to generate the standard curve. The HIV-2 copy number in each clinical sample was estimated by interpolation from the regression curve. The results were expressed as HIV-2 RNA copies/mL.

HIV-2 subtyping was carried out using *pol* sequences and phylogenetic analyses, as described elsewhere [22]. For the purpose of this study, data collected included year of diagnosis, gender, country of origin, risk group, baseline viremia, CD4 counts, HIV subtype, and antiretroviral therapy.

Statistical analysis

Main variables were recorded as number and percentages, mean plus standard deviation, or median and interquartile ranges (IQR) between 25% and 75%. Mann-Whitney U test was performed for abnormally distributed variables. A Student *t* test was used for variables displaying a normal distribution. Bivariate comparisons of quantitative variables were performed using the chi-square test.

All statistical analyses were performed using the IBM SPSS package for Windows v25.0 (IBM Corp, Armonk, New York). All tests were two-tailed and only *P*-values <0.05 were considered as significant.

Ethical approval

The study was designed as a multicenter and retrospective collection of anonymized and consecutive clinical data associated with serum HIV-2 antibodies. It was approved by the International University of La Rioja (UNIR) ethics committee (ref. 031/2024) and ethics committee (CEIm) Hospital Universitario Puerta de Hierro (ref. PI52-20).

Results

Since the first cases of HIV-2 were identified in 1988 in Spain and up to December 2023, a total of 424 individuals with HIV-2 had been reported at the Spanish HIV-2 registry. After a peak in 2009 when 31 cases were notified, new yearly diagnoses of HIV-2 have steadily decreased nationwide. Less than 10 cases have been reported annually since the beginning of the COVID-19 pandemic (Figure 1). In 2023, only eight cases were notified, all in Africans but one Spaniard.

A total of 265 (62.5%) out of 424 HIV-2 cases were male. HIV-1 and HIV-2 coinfections were included in these figures. Migrants predominated, being 322 (76%) Sub-Saharan Africans; however, 60 (14.2%) were native Spaniards. Mean age at HIV-2 diagnosis was 44.2 years old, ranging from birth to 83 years. Table 1 summarizes the main features of the study population, comparing Sub-Saharan Africans with Spaniards. At HIV-2 diagnosis, Africans were significantly younger than native Spaniards (42.5 vs 51.8 years old, respectively). There were no significant changes in mean age at HIV-2 diagnosis over time.

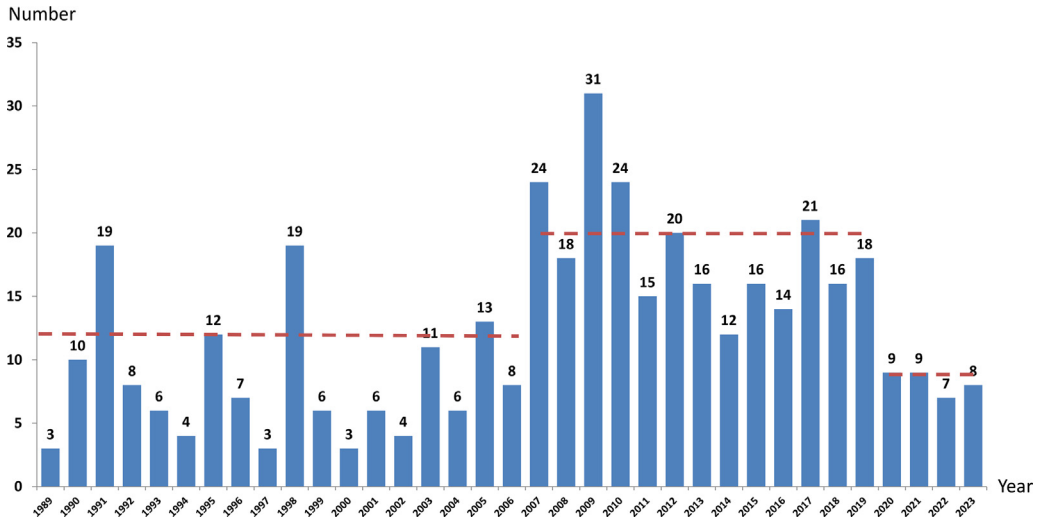

Figure 1. Annual reporting of HIV-2 cases in Spain from 1989 to 2023. Data reported over 34 years can be divided into three periods. Before 2006, the average incidence was 11 cases per year. Between 2007 and 2019 it rose to an average of 20 cases annually. The migrant crisis of Africans that arrived in the Canary Islands in small boats during that period largely accounted for such an HIV-2 increase. Since the beginning of the COVID-19 pandemic in 2020, a mean of only nine cases of HIV-2 per year have been reported in Spain. Dotted lines represent the mean number of HIV-2 cases for each period.

Table 1
Main features of the HIV-2 study population.

	Total[c]	African migrants	Native Spaniards	*P*
Number	424	322 (76%)	60 (14%)	*0.012*
Mean age at diagnosis (years old; standard deviation)	44.2 (12.4)	42.5 (11.3)	51.8 (15.5)	<0.001
Male sex	265	216 (66.8%)	33 (55%)	0.07
Heterosexual contagion	288	235 (72%)	39 (65%)	0.2
HIV-1 coinfection	39	32 (9.9%)	6 (10%)	0.99
HIV-2 subtype A[a]	121	88/100 (88%)	23/29 (79.3%)	0.23
AIDS at diagnosis	69	44 (13.7%)	22 (36.7%)	<0.001
Detectable plasma HIV-2 RNA at diagnosis[b]	50	47/86 (54.6%)	2/11 (18%)	0.023

[a] HIV-2 subtype was available for 139 patients.
[b] HIV-2 RNA was measured at the time of diagnosis and before introducing antiretroviral therapy for 108 patients. Lower limit of detection: 50 copies/mL.
[c] In addition to Africans (n = 322) and native Spaniards (n = 60), another 42 cases of HIV-2 in the Spanish registry are from other regions (other European countries, Brazil, etc.).

Heterosexual exposure was the most likely route of infection for at least 287 (67.7%) cases of HIV-2 infection, with no significant differences comparing Africans and Spaniards. In addition, a few could be traced to transfusions (n = 4), vertical transmission (n = 2), or injection drug use (n = 7). Furthermore, 15 individuals (3.5%) were men who had sex with men, eight of them belonging to a cluster of native older men who had sex with men, all infected in the Basque region of northern Spain [22]. HIV-1 coinfection with HIV-2 was recognized in 39 (9.2%) patients.

The proportion of individuals presenting with advanced HIV infection was significantly greater among natives than among African migrants, along with an older age of the former (52 vs 42 years old; P <0.001).

Molecular characterization of HIV-2 subtypes could be performed in 139 individuals. Up to 121 carried subtype A whereas 18 had subtype B. There were no significant differences when comparing Africans and Spaniards.

The country of origin of Africans is depicted in Figure 2. Up to three-quarters came from only five countries: Guinea-Bissau, Senegal, Gambia, Ivory Coast, and Equatorial Guinea, the latter a former Spanish colony.

Most diagnoses of HIV-2 were made in Spanish regions with the largest African migrant flow, including Catalonia (n = 127), Madrid (n = 78), and Almería (n = 49), as shown in Figure 3. The first cases reported in Almería date back to 2008. Since then, a significant number of newly diagnosed HIV-2 cases has been made in Almería, where a large group of recently arrived Sub-Saharan migrants moved to work at greenhouse facilities.

Discussion

HIV-2 is a human retrovirus that may cause AIDS but more slowly than HIV-1 [6,7]. Infection with HIV-2 is endemic in West Africa [4]. Given its differential features with respect to HIV-1 infection in terms of diagnosis, prognosis, monitoring, and treatment, guidelines recommend excluding HIV-2 in all newly diagnosed HIV-seropositive individuals [23].

The annual incidence of HIV-2 in Spain has decreased after a peak 15 years ago, being the current number of incident cases below 10 per year. We can recognize three periods in the reporting of HIV-2 in Spain during the last 35 years. Before 2006, the average incidence was 11 cases per year. Between 2007 and 2019 it rose to an average of 20 cases annually. The migrant crisis of Africans that arrived in the Canary Islands in small boats during that period largely accounted for such an HIV-2 increase. Since the beginning of the COVID-19 pandemic, a mean of only nine cases per year have been reported in Spain, with no new rebound since then. We postulate that both the early identification of HIV-2 cases upon arrival to Spain coupled with the lower transmissibility of HIV-2 compared to HIV-1 largely accounts for the current declining incidence of HIV-2 in Spain. Other contributors to this decrease could include a much broader use of antiretrovirals coupled with

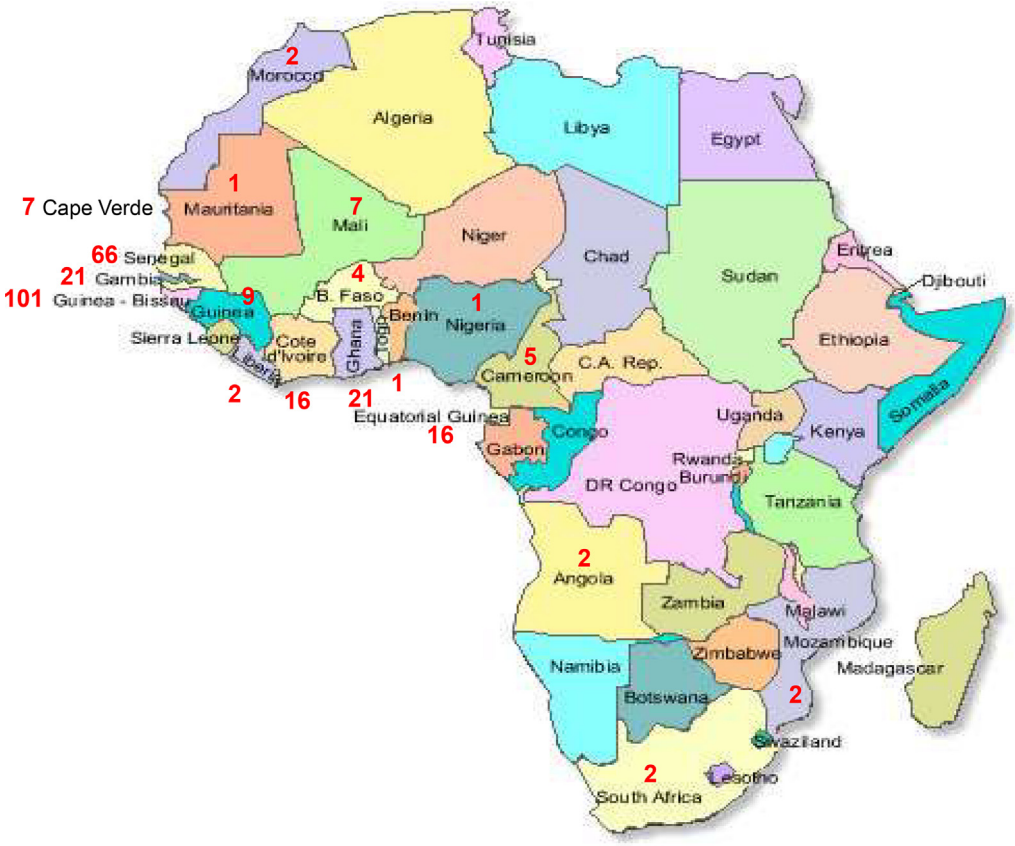

Figure 2. African country of origin of HIV-2 infected individuals living in Spain. Of the 424 individuals with HIV-2 recorded in the Spanish registry, 322 (76%) were Africans and 60 (14.1%) were native Spaniards. The remaining 42 (9.9%) came from other regions (Brazil, Portugal, France, etc.)

Figure 3. Geographic distribution of HIV-2 infected persons identified in Spain. Each number corresponds to HIV-2 cases in distinct geographical regions. In circles are highlighted regions with singular features. Madrid is the largest urban area and capital of Spain, a major focus of concentration for migrants. The four provinces of Catalonia are a major focus of attraction for migrant workers and people planning to move to other European countries. Finally, the Almeria regions have concentrated since 2007 large groups of recently arrived Sub-Saharan migrants working at greenhouse facilities.

lower viremia and lower transmissibility and increased access to HIV testing perhaps only compromised during the COVID-19 pandemic [24]. However, no rebound in HIV-2 reports has been noticed since then.

Of all 424 cumulative cases of HIV-2 reported up to December 2023, three-quarters are African migrants. Spain is a country of 48.5 million people nowadays. Foreigners represent 6.5 million (17%). Roughly 250,000 are Sub-Saharan Africans, being West Africans the largest group by far. Migrants from this region are mostly from Senegal (75,000), Nigeria (35,000), Mali (30,000), Ghana (20,000), and Equatorial Guinea (10,000) [25]; the latter is a former Spanish colony. Based on these data and our findings, we have inferred an overall prevalence of HIV-2 of 0.13% among West Africans living in Spain. This estimate, however, has several limitations. Firstly, most HIV-2 cases in Spain originated from Guinea-Bissau, where HIV-2 is more prevalent than in other West African countries. Second, a subset of migrants living in Spain with HIV-2 should not have been diagnosed yet, since they remain asymptomatic and have not been tested before. However, during the last 2 decades, HIV testing has been performed on all migrants arriving in Spain, as part of a first health checkout.

In an epidemiological survey conducted until 1995, a total of 56 cases of HIV-2 in Spain were described [26]. Only 12 (21.4%) were native Spaniards. The first cases of HIV-2 infection in Spanish natives were reported in Galicia in 1991, in two seamen who had worked for a long time near the African coasts. In contrast, eight cases of HIV-2 in natives belonged to a cluster of older men who had sex with men, all infected in the Basque region of Spain [27].

HIV-2 comprises eight different groups (A-H). Two major HIV-2 groups A and B, were generated by two independent transmission events involving sooty mangabeys infected with SIV_{sm} in the Taï Forest of Ivory Coast, which appear to be linked with the vast majority of cases identified so far. HIV-2 subtype A has an epicenter in Guinea-Bissau and is by far the predominant worldwide. In contrast, subtype B has an epicenter in the Ivory Coast and mostly affects the neighborhoods of Burkina Faso, Mali, and Ghana [28].

The proportion of individuals presenting with advanced HIV infection was significantly greater among natives than among African migrants, along with an older age of the former. A longer time of infection for HIV-2-positive Spaniards compared to Africans could hypothetically be presumed. However, since migrants are regularly tested upon arrival and most of them are young, this could affect the age at diagnosis. Native Spaniards, especially heterosexuals, are generally not tested if asymptomatic. Of note, HIV-1 coinfection was noticed in 10% of each group.

In the Spanish HIV-2 registry, coinfection with HIV-1 was recognized in 39 (9.2%) individuals. Interestingly, the rate was roughly 10% in both Africans and native Spaniards. We already showed a case of HIV-1 superinfection in a prostitute with HIV-2 not taking antiretrovirals [29]. In individuals on antiretroviral therapy, the medication could act as pre-exposure prophylaxis for superinfection with the other HIV variant. On the other hand, the management of this population can be challenging, as previously highlighted especially with respect to antiretroviral therapy [30].

A decrease in HIV-2 prevalence has been noticed globally and especially in endemic regions [31]. In Guinea-Bissau, one of the epicenters of the HIV-2 pandemic, HIV-1 has overtaken HIV-2 over time, given its higher transmissibility [32]. A model has predicted a complete extinction of HIV-2 infection in the endemic Caio region by 2068 [33]. Most likely, broader access to integrase inhibitor-based antiretroviral treatment combinations in African countries has largely contributed to account for the huge decrease in new HIV-2 infections. However, to ensure reaching this goal, further efforts must be focused on improving the management of HIV-2-infected patients [34]. In addition, the gap produced by misdiagnosis should be addressed properly, as good care can only benefit those individuals properly identified. HIV-2 infection alone or as a coinfection with HIV-1 should be excluded at least once in all HIV-seroreactive individuals [35]. Ideally at first diagnosis and otherwise as soon as possible thereafter. With this proactive behavior, HIV-2 misdiagnosis would disappear and wrongly managed clinical cases would be avoided.

In summary, the annual incidence of HIV-2 infection in Spain is declining after peaking 15 years ago, being the current number of cases below 10 per year. Although the circulation of HIV-2 in Spain is limited and steadily going down, a plateau rather than extinction would occur unless efforts to increase earlier recognition and avoidance of misdiagnosis are not implemented.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors have completed the information regarding conflicts of interest in the requested documentation and have no conflicts of interest to disclose.

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Ethical approval

UNIR ethics committee ref. 031/2024 and CEIm HUPHM ref. PI52-20.

Author contributions

VS and CdM conceptualized the work, CdM, VS wrote the first draft. All authors contributed with epidemiological and clinical data, and reviewed and edited the draft.

Appendix

Members of the Spanish HIV-2 Network

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