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ORIGINAL RESEARCH

Population mobility and the changing epidemics of HIV-2 in Portugal

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Introduction

Portugal is the European country with the highest frequency of HIV-2 infection, which is mainly concentrated in West Africa. The cumulative number of notified HIV-2 infections in Portugal was 1813 by the end of December 2008. To better characterize the dynamics of HIV-2 infection in the country and to obtain data that may be of use in the prevention of the spread of HIV-2, we evaluated a large pooled sample of patients.

Patients and methods

Five Portuguese hospitals provided data on HIV-2-infected patients from 1984 to the end of 2007. Data concerning demographic characteristics and clinical variables were extracted. Patients were stratified according to date of diagnosis in approximately 5-year categories.

Results

The sample included 442 patients, accounting for 37% of all HIV-2 infections notified in Portugal during that period. HIV-2-infected patients showed clearly different characteristics according to the period of diagnosis. Until 2000, the majority of HIV-2-infected patients were Portuguese-born males living in the north of the country. From 2000 to 2007, most of the patients diagnosed with HIV-2 infection had a West African origin, were predominantly female and were living in the capital, Lisbon. The average age at diagnosis and loss to follow-up significantly increased over time.

Conclusion

HIV-2 infection has been documented in Portugal since the early 1980s and its epidemiology appears to reflect changes in population movement. These include the movements of soldiers and repatriates from African territories during the independence wars and, later, migration and mobility from high-endemicity areas. The findings of this study stress the importance of promoting migrant-sensitive health care.

Keywords: HIV-2, migration, population, mobility, Portugal

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Introduction

There are two types of HIV, HIV-1 and HIV-2, and both entered the human population as a result of zoonotic transmission [1]. However, HIV-2 infection differs from HIV-1 infection in many respects. Although the modes of transmission are the same as for HIV-1, the frequency of transmission is lower; the rates of sexual and vertical transmission are around 5–9 times and 10–20 times lower, respectively, than for HIV-1 [2,3]. HIV-2-infected patients usually exhibit a slower disease progression and a higher proportion are long-term nonprogressors [4–6]. Experience

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with antiretroviral therapy is limited; when to start and which antiretroviral regimen to choose are still poorly defined. The natural resistance of HIV-2 to nonnucleoside reverse transcriptase inhibitors and the absence of a gold standard method for quantification of plasma HIV-2 RNA are other important limitations in the clinical management of HIV-2-infected patients [7–9].

HIV-2 is not considered a global public health problem: while HIV-1 has spread globally, HIV-2 has remained mainly concentrated in West Africa and to a much lesser extent in Europe (primarily Portugal and France) [10,11]. However, HIV-2 infection provides a unique opportunity to study the pathogenesis of HIV infection in humans, and valuable insights can be gained into HIV-1 from studies of HIV-2 [6]. Further, HIV-2 infection is an example of the impact of population mobility on the epidemiology of an infectious disease. In an increasingly globalized world, migration and population mobility will continue to challenge national disease prevention programmes and to demand new approaches as far as health services planning is concerned [12,13].

Portugal has one of the highest estimated incidence levels of HIV infection in Western Europe, with the epidemic having mainly been driven by injecting drug use. During the last decade, however, sexual transmission has been reported as the predominant mode of transmission. Also, recently a clear decline was observed in both the number of reported AIDS cases (new cases halved from 961 in 2003 to 433 in 2009) and AIDS mortality (from 1000 deaths in 2001 to 708 in 2008) [14]. Although >95% of ever-notified HIV cases were HIV-1, Portugal is the European country with the highest prevalence of HIV-2 infection. Further, regions historically linked to Portugal, such as Angola, Mozambique, India and Brazil, have a higher frequency of HIV-2 infection than other countries [10,11]. Since 1989, virus subtyping has been performed routinely in Portugal. HIV (type 1 or 2) diagnoses were reported to a national surveillance department on a voluntary basis until 2005, when notification became mandatory. Nonetheless, delays in reporting are often long and information concerning clinical variables is scarce. The cumulative number of notified HIV-2 infections was 1813 as of December 2008. In the early 1990s, HIV-2 infection accounted for approximately 10% of the annually diagnosed AIDS cases, while it decreased to 2.6% in 2000 and 2.3% in 2008 [14]. The epidemiology of HIV-2 in Portugal has been addressed in three previous studies. The first study, published in 2003, described data for 218 HIV-2-infected patients gathered between 1997 and 2002 at a virology laboratory serving several hospitals in the south of Portugal [15]. Most of the HIV-2-infected people were from Guinea Bissau and Cape Verde. By contrast, in that same year, data from a hospital in the north of Portugal for 132 HIV-2-infected patients obtained from 1985 to 2003 showed that 60% of the patients were male and 95% were Caucasian and born in Portugal, although in 51% of cases direct or indirect relationships with Africa could be established [16]. More recently, data from an infectious disease university hospital in Lisbon for 142 adult patients diagnosed with an HIV-2 infection from 1987 to 2006 were published [17]. Most patients (70%) were female, 83 (68%) were born in West Africa, and heterosexual transmission was documented in 84% of the patients. In the present study, we evaluated a large pooled sample of patients identified in different hospitals located in different regions of the country, using the same protocol. We aimed to better characterize the dynamics of HIV-2 infection in Portugal by overcoming the possible biases of local descriptions.

Patients and methods

Eleven Portuguese hospitals, which together represented two-thirds of all HIV cases ever notified in Portugal, were invited to provide data for HIV-2-infected patients in their respective HIV clinics up to 31 December 2007. By the end of March 2008, five hospitals had contributed to this project: Hospital São João and Hospital Joaquim Urbano, located in the north (Porto region) and Hospital Garcia da Orta, Hospital Santa Maria and Hospital Fernando Fonseca, located in the south (the Lisbon region). All clinical records were manually reviewed and data concerning demographic characteristics (e.g. biological sex and country of origin) and clinical variables such as age at diagnosis, mode of transmission, stage at diagnosis, CD4 cell count at diagnosis, treatment experience, progression to AIDS and final outcome (death) were extracted. Stage at diagnosis was defined as asymptomatic or AIDS, according to the CD4 cell count (defined as <200 cells/μL) or clinical AIDS presentation. Area of residence was extrapolated from the location of the hospital where the patient was followed. Data from 442 patients were obtained. This sample included 37% of all HIV-2 (mono)infections notified in Portugal as of the end of 2007. Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as counts and proportions. Patients were stratified according to date at diagnosis in approximately 5-year categories. Data were analysed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Proportions were compared using the χ^2 test and ages were compared by means of a one-way analysis of variance (ANOVA). *P*-values of <0.05 were considered statistically significant. The ethical committee of Hospital São João approved the study design in 2007. No specific consent was obtained from the patients as the data were used anonymously.

Results

As shown in Table 1, in the sample as a whole there were similar proportions of male and female patients. Patients followed in the southern area of the country represented 59% of the sample population. Dual infections (HIV-1 and HIV-2) accounted for a minority (3.6%) of cases. Around half of the patients were Portuguese citizens (213; 48.2%). Guinea Bissau, Cape Verde and Angola were the countries of origin of 33.5, 7.9 and 2.5% of the patients, respectively.

Table 1 Demographic and clinical characteristics of 442 individuals with HIV-2 infection; Portugal (1985–2007)

	n	%
	442	100
HIV-2 infected patients	426	96.4
HIV-1+2 infected patients	16	3.6
Hospital		
Hospital São João	140	31.7
Hospital Santa Maria	142	32.1
Hospital Fernando Fonseca	64	14.5
Hospital Garcia da Orta	55	12.4
Hospital Joaquim Urbano	41	9.3
Date of diagnosis (years)		
1985–1989	57	12.9
1990–1994	83	18.8
1995–1999	95	21.5
2000–2004	127	28.7
2005–2007	72	16.3
Unknown	8	1.8
Sex		
Female	248	56.1
Male	192	43.4
Unknown	2	0.4
Country of origin		
Portugal	213	48.2
Guinea Bissau	148	33.5
Cape Verde	35	7.9
Angola	11	2.5
Mozambique	2	0.4
Brazil	1	0.2
Unknown	32	7.2
Transmission mode		
Heterosexual	260	58.8
Men who have sex with men	5	1.1
Injecting drug use	10	2.3
Vertical	4	0.9
Transfusional	68	15.4
Not specified	95	21.5
Stage at diagnosis		
AIDS	98	22.2
Asymptomatic	283	64.0
Not specified	61	13.8
Outcome (until Dec 2007)		
Dead	82	18.6
Alive	128	29.0
Unknown	232	52.5

Because of rounding, percentages may add up to over 100.

The mode of transmission was mainly reported as heterosexual (260; 58.8%). Blood transfusions were the route for HIV-2 transmission in 15.4% of cases, but the proportion of cases attributed to blood transfusions has been declining over time. Injecting drug use was the mode of acquisition in 2.3% of patients and men who have sex with men accounted for 1.1%. Vertical transmission was rare (0.9%). The mode of transmission was not specified for 21.5% of the participants.

The majority of the patients were asymptomatic at diagnosis (283; 64.0%). Lymphocyte CD4 cell count at diagnosis was available for 62% of the patients. Of these, 62 (22.6%) had a CD4 count <200 cells/μL. At the last follow-up evaluation, most patients remained treatment-naïve (200; 45.2%). However, 156 (35.3%) were on antiretroviral therapy, 14.5% of whom had experienced at least two different treatment regimens. During follow-up, at least 23.7% developed AIDS. By the end of December 2007, 128 (29%) of the patients were alive; 82 (18.6%) had died. For 232 (52.5%), the outcome was unknown.

HIV-2 infection diagnoses were distributed over time as follows: 1985 to 1989, 57 patients; 1990 to 1994, 83 patients; 1995 to 1999, 95 patients; 2000 to 2004, 127 patients and 2005 to 2007, 73 patients (Table 2). For seven patients, the year of diagnosis was not specified. Before 1989, the majority of patients were male (39; 68.4%), had Portuguese nationality (45; 78.9%) and were living in the north of the country (44; 77.2%). The mean age at diagnosis was 31.0 (±14.7) and 37.8 (±8.9) years for male and female patients, respectively. Most patients were infected through heterosexual intercourse (31; 54.4%), but the proportion of HIV-2 infections attributed to blood transfusions was high (22; 38.6%). Forty-one individuals (71.9%) were asymptomatic at the time of diagnosis.

From 1990 to 1994, the numbers of cases of newly diagnosed HIV-2 infection were nearly equal in men and women (41 men and 42 women). Heterosexual transmission remained the main transmission route (61.4%), followed by blood transfusion (31.3%). More than 70% of cases were diagnosed in the north of the country. From 1995 to 1999, HIV-2 infection was more frequently found in female patients (64; 67.4%). Portugal was the country of birth of 54.7% of individuals. Cases attributed to transfusions declined to 10.5%, while those attributed to heterosexual intercourse increased to 65.3%. Three cases of vertical transmission were diagnosed, while for 17 patients (17.9%) the mode of transmission was not specified. During this period, 63.2% (60) of the diagnoses were made in hospitals located in the south of the country.

From January 2000 to December 2004, 127 additional patients were identified. Most cases were still among

Table 2 Demographic and clinical characteristics of 442* individuals with HIV-2 infection according to period of diagnosis in Portugal (1985–2007)

	1985–1989 *n* (%)	1990–1994 *n* (%)	1995–1999 *n* (%)	2000–2004 *n* (%)	2005–2007 *n* (%)	*P*
HIV-2 diagnosis (sample)*	57 (12.9)	83 (18.8)	95 (21.5)	127 (28.7)	73 (16.5)	
HIV-2 diagnosis† (national notified cases)	123 (10.5)	306 (26.1)	287 (24.5)	315 (26.9)	140 (12.0)	
Sex						
Female	18 (31.6)	41 (49.4)	64 (67.4)	84 (66.1)	39 (53.4)	
Male	39 (68.4)	42 (50.6)	31 (32.6)	43 (33.9)	34 (46.4)	< 0.001
Country of origin						
Portugal	45 (78.9)	60 (72.3)	52 (54.7)	37 (29.1)	17 (23.3)	
West Africa	5 (8.8)	18 (21.7)	32 (33.7)	77 (60.6)	47 (64.4)	
Other	0 (0.0)	1 (1.2)	4 (4.2)	5 (3.9)	4 (5.5)	
Unknown	7 (12.3)	4 (4.8)	7 (7.4)	8 (6.3)	5 (6.8)	< 0.001
Transmission mode						
Heterosexual	31 (54.4)	51 (61.4)	62 (65.3)	75 (59.1)	39 (53.4)	
Men who have sex with men	0 (0.0)	2 (2.4)	0 (0.0)	3 (2.4)	0 (0.0)	
Injecting drug use	1 (1.8)	3 (3.6)	3 (3.2)	2 (1.6)	1 (1.4)	
Vertical	0 (0.0)	0 (0.0)	3 (3.2)	1 (0.8)	0 (0.0)	
Transfusional	22 (38.6)	26 (31.3)	10 (10.5)	6 (4.7)	3 (4.1)	
Not specified	3 (5.3)	1 (1.2)	17 (17.9)	40 (31.5)	30 (41.1)	< 0.001
Stage at diagnosis						
Asymptomatic	41 (71.9)	57 (68.7)	57 (60.0)	80 (63.0)	46 (63.0)	
AIDS	15 (26.3)	19 (22.9)	21 (22.1)	27 (21.2)	15 (20.6)	
Unknown	1 (1.8)	7 (8.4)	17 (17.9)	20 (15.7)	12 (16.4)	0.169
Residence area						
Porto	44 (77.2)	61 (73.5)	35 (36.8)	27 (21.2)	12 (16.4)	
Lisbon	13 (22.8)	22 (26.5)	60 (63.2)	100 (78.7)	61 (83.6)	< 0.001
Outcome (December 2007)						
Death	29 (50.9)	25 (30.1)	21 (22.1)	4 (3.1)	1 (1.4)	
Survival	17 (29.8)	30 (36.1)	23 (24.2)	44 (34.6)	14 (19.2)	
Unknown	11 (19.3)	28 (33.7)	51 (53.7)	79 (62.2)	58 (79.5)	< 0.001

*Date of diagnosis was unknown for seven (1.8%) of the patients in the sample.
†Only mono-infections are included.

female patients (84; 66.1%). The major differences from the previous periods were the patients' country of origin and residence area, with the majority (77; 60.6%) coming from West African countries and being diagnosed in Lisbon (100; 78.7%). Heterosexual intercourse remained the primary mode of HIV-2 acquisition (75; 59.1%) while blood transfusions almost disappeared as a cause of infection (6; 4.7%). In 31.5% of cases the route of transmission was not specified. Most patients had no AIDS-defining illness at diagnosis (80; 63.0%), although the stage at diagnosis was not possible to ascertain for 20 patients (15.7%). In the last three years of the study period (2005–2007), 73 additional patients were diagnosed with HIV-2 infection: 39 women and 34 men. The average age at diagnosis was higher than in the previous periods (43.0 years for women and 48.7 years for men). West African origin was reported for 64.4% of patients (47), while 23.3% (17) were Portuguese. More than 80% of the diagnoses were made at one of the participant hospitals located in Lisbon. Most patients were infected heterosexually (39; 53.4%) and only 4.1% through blood transfusions. No case of vertical transmission was documented. However, the mode of transmission was not specified for 30 patients (41.1%).

Discussion

This sample of 442 HIV-2-infected patients is the largest sample of HIV-2-infected patients ever described. The sample represents 37% of all HIV-2 (mono)infections notified in Portugal as of the end of 2007 and includes patients from hospitals that cover a wide geographical area. The proportion of cases identified over each time period resembles the pattern observed for notified cases and the sample is representative of the transmission dynamics of HIV-2 in the country (Table 2). From 1985 to 2007, HIV-2-infected patients included in the sample presented distinct characteristics according to the period of diagnosis. Until 2000, the majority of HIV-2-infected patients were Portuguese-born men living in the north of the country, but from 2000 to 2007 most patients diagnosed with HIV-2 infection had a West African origin, were predominantly female and

were living in the capital, further south. To understand HIV-2 infection trends, one needs to consider the historical context and the effect of population mobility on virus migration.

HIV-2 infection spread under particular political and social circumstances during the independence wars of former Portuguese territories. In Guinea Bissau, for example, the demographic history of HIV-2 is characterized by a period of low endemicity followed by an exponential increase in the number of infections during the war (1961–1974). Increased commercial sex, unsafe blood transfusions and other events occurring in a socially and economically disrupted country probably facilitated transmission of the virus [11]. The highest prevalence of HIV-2 infection was reported two decades ago in Guinea Bissau: the prevalence was 8% in adults, and reached up to 20% in individuals over 40 years of age [18]. The estimated incidence of HIV-2 infection in Guinea Bissau is now declining: between 1996 and 2006 the incidence rate for HIV-2 infection was 0.24 per 100 person-years (0.5 per 100 person-years for HIV-1) [19]. These historical and socioeconomic circumstances might help to explain why Portugal is the country outside the African continent with the highest number of HIV-2-infected patients. However, studies on HIV-2 epidemiology in Portugal are limited and have provided contradictory descriptions [15–17]. By investigating a larger sample, including patients from five hospitals, we have tried to minimize selection biases.

Important information can be obtained by looking at epidemiological data over time. The independence wars in Portuguese colonies during the period 1960–1974 probably had a role in the introduction of HIV-2 to Portugal. The fact that most HIV-2-infected patients included in our sample who were diagnosed before 1990 were male (39; 68.4%), Portuguese (45; 78.9%) supports this possibility. For more than 10 years, hundreds of thousands of soldiers were sent to Africa. Heterosexual transmission was reported for the majority of cases in the present study, but the importance of blood transfusions and/or surgical procedures performed during the war should not be underestimated. The independence wars were also responsible for a massive influx of repatriates (more than 500 000), including women, into Portugal. From 1990 to 1994, the number of diagnosed infections increased. The similar characteristics in terms of nationality (Portuguese) and area of residence (the north of the country) of most of the persons diagnosed in this period compared to those diagnosed in the previous period may reflect the ongoing transmission of HIV-2 after its introduction into the country. Further, the fact that the proportions of male and female individuals diagnosed were similar supports the hypothesis that transmission from previously infected male patients (many of them probably former soldiers) to their female partners took place. The last 5 years of the 1990s anticipated the change clearly observed from 2000 onwards, probably as a result of increased migration from West Africa, reversing previously described trends.

In 2008, migrants from Guinea Bissau and Cape Verde represented 18% of the total population of migrants in Portugal (6 and 12%, respectively) and in the last few years the number has increased. The geographical distribution of these migrants is heterogeneous, the majority (68.8%) living in southern Portugal [20]. Therefore, it is not surprising to find that native Africans living in the capital (Lisbon) represent the majority of the most recently diagnosed cases of HIV-2 infection. In addition, as two large hospitals located in southern Portugal are not represented in our sample, this epidemiological change is probably underestimated. The general area of residence (north/south) was extrapolated taking into account the hospital where patients were diagnosed and followed, although some patients may not have attended a hospital in their area of residence. Nonetheless, we believe that only a minority would travel more than 300 km to attend another hospital. Data from a Portuguese study addressing this issue revealed that the average distance from a patient's residence to a hospital where HIV-infected patients were admitted was 13 km [21].

Interestingly, there has been over the study period a steeper increase in age at the time of diagnosis, statistically significant for men. However, the proportion of patients presenting with AIDS has not changed substantially. Does this mean that men are being infected later and tested earlier in the course of the infection or, on the contrary, are they being diagnosed at an older age and later but remaining asymptomatic as a result of a slower progression of the disease? Testing for HIV has been performed routinely for blood donations since 1985 and recommendations for screening women before or during pregnancy date back to 1998. Further, there have been campaigns over the last few decades promoting HIV testing of those with a history of injecting drug use, unprotected sexual intercourse or transfusions, particularly in Africa, although information related to the uptake of testing over time, either patient- or provider-initiated, is not available. Studies addressing HIV testing practices and disease progression are needed to answer these and related questions.

Experience with the treatment of HIV-2-infected patients on antiretroviral therapy is limited; when to start and which antiretroviral regimen to choose are still poorly defined. In our sample, we found that, although the majority of patients were treatment-naïve, the proportion of patients who had experienced more than two different treatment regimens (14.5% of those ever treated) highlights

the need to improve the evidence base for decisions on which therapy to initiate.

People living with HIV experienced a major change in survival rates after the introduction of effective treatment regimens. Whether the same applies to the prognosis of HIV-2-infected patients is not known. Also, we cannot infer an effect of the described therapeutic experiences of the study population on the rate of AIDS progression and case fatality. By the end of December 2007, at least 18.6% of the patients had died, 29% were alive and attending scheduled appointments, but most, 52.5%, were lost to follow-up. Surprisingly, the majority of patients for whom no outcome information is available were those diagnosed in more recent years and therefore those that we would expect to be attending consultations at the respective clinics. Moreover, 63.3% of those patients were migrants of African origin. The reasons underlying such a high number of losses to follow-up needs further investigation. Social, economic and cultural factors highlight the need to develop special approaches for migrant populations and to promote migrant-sensitive health care.

As the world's population grows, migration and population mobility are likely to increase [12,13]. The incidence of HIV-2 infection is declining in West Africa but the increasing influx of migrants will probably maintain HIV-2 in Portugal and other countries. For example, in France, between January 2003 and June 2006, 186 HIV-2-infected patients were identified [22]. In Spain, from 1988 to 2006, a total of 146 HIV-2 infections were reported [23]. Up to 2007, 65 patients with HIV-2 (mono)infection were included in the Belgium–Luxembourg database [24]. The majority of HIV-2-infected patients identified in these countries were from a West African country. Also, the number of HIV (including HIV-2) infections acquired in West Africa and diagnosed in England, Wales and Northern Ireland has risen in recent years [25]. The same trend has been observed in the USA, where HIV-2 infection is considered to be rare. From 1985 to 1998, only 79 cases of HIV-2 infection were reported to the Centers for Disease Control and Prevention (CDC). However, data from New York City showed that, between 1 June 2000 and 31 December 2008, 62 more people received a diagnosis of HIV-2 infection. The majority (60 of 62 individuals) were born in Africa [26]. This highlights the need to discuss the impact of migration on national infectious disease epidemiology, of which HIV-2 is just one example.

Conclusions

HIV-2 infection has been documented in Portugal since the early 1980s and its epidemiology appears to reflect changes in population movement. Our study suggests that the introduction of HIV-2 was related to the movements of soldiers and repatriates from African territories during the wars of independence and that migration and mobility of people from high-endemicity areas have, more recently, played a prominent role in the dynamics of HIV-2 infection. The creation of a Portuguese cohort of HIV-2-infected patients would be an important step towards a better understanding of these descriptive findings.

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Conflict of interest: The authors declare that they have no conflict of interest.

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