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Impact of Immigration on HIV-1 Molecular Epidemiology in West Africa, Maghreb and Southern Europe

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Abstract

There is global concern about the relation between international migration and the course of the AIDS epidemic. Maghreb is a North African region, which lies between sub-Saharan Africa and Europe. It has been turned recently into a region of immigration, since there are more and more flows of West African migrants hoping to reach European countries. Here we provide an overview on HIV-1 molecular epidemiology particularly in West African countries, Maghreb (Morocco, Algeria, Tunisia) and southern European countries (Spain, France, and Italy). The studies conducted in several countries of the region revealed different features of HIV-1 molecular epidemiology, especially for the distribution of viral subtypes and for transmitted drug resistance profiles. Furthermore, migration from West Africa to Europe seems to be a potential source of non-B subtype mobility to Maghreb and eventually to southern Europe, where HIV-1 non-B variants significantly increased in the last 10 to 15 years. As genetic differences between subtypes might impact the drug resistance pathways, it is important to provide continuous surveillance programs for the early detection of new variants spreading in the population before they become more prevalent, and to identify resistance profiles in different infected populations, especially migrants. **(AIDS Rev. 2014;16:109-16)**

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Key words

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Introduction

The HIV type-1 pandemic is one of the leading causes of death worldwide and remains a serious challenge to global public health. At the end of 2011, the United Nations Programme on HIV/AIDS (UNAIDS) estimated that there were 34.2 million people living with HIV and that 2.5 million people became newly infected every year[1]. More than 96% of new HIV-1 infections occurred in low- and middle-income countries.

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As the AIDS pandemic progresses, HIV-1 exhibits considerable genetic diversity, which leads to several distinct genetic strains or subtypes within the main group of the virus. With increasing levels of population movement across different regions in the world, the global HIV-1 epidemic is becoming increasingly heterogeneous. While many factors have contributed to the clinical success of antiretroviral therapy, HIV-1 variability remains one of the major obstacles for HIV/AIDS disease control and for the effectiveness of antiretroviral drugs.

The Maghreb is usually defined as the region of North West Africa, including the countries of Morocco, Algeria, and Tunisia. As Maghreb lies between sub-Saharan Africa and Europe, it has been turned recently into a region of immigration[2], since there are flows of West African migrants hoping to reach European countries, with Spain and Italy as the main destinations. From there, migrants often make their way to other European countries, particularly France.

Table 1. HIV-1 estimations in Maghreb, sub-Saharan Africa and Western and Central Europe

Regions and countries	Sub-Saharan Africa*	Western and Central Europe*	Maghreb		
			Morocco	Tunisia	Algeria
Adults living with HIV	23.5 million (22.1-24.8)	900,000 (830,000-1,000,000)	31,000* (20,000-44,000)	1,700* (1,500-1,900)	20,000* (12,000-28,000)
Newly infected adults and children	1.8 million (1.6-2.0)	30,000 (21,000-40,000)	3,600* (2,000-5,000)	39†	684‡
AIDS-related deaths	1.2 million (1.1-1.3)	7,000 (7,600-9,000)	1,600* (< 1,000-2,500)	< 100*	1,100* (< 1,000-1,500)

*UNAIDS estimations (2012)[1]; †Annual average of new cases since 1997[63]; ‡Registered in 2009 from LNR/IPA (Laboratoire National de Reference, Institut Pasteur d'Alger)[64].

The HIV-1 epidemic in sub-Saharan Africa is characterized by genetically diverse viral subtypes. In fact, all known HIV-1 subtypes and groups have been detected in this part of the world. The migration from West Africa to Europe may thus have an influence on the HIV-1 genetic diversity, not only in southern Europe as the destination region, but also in Maghreb as a transit region.

This paper provides an overview of the features of HIV-1 molecular epidemiology by presenting a synthesis of HIV-1 subtype distribution and transmitted drug resistance (TDR) mutations. We focus particularly on the available data from West African countries, Maghreb, and southern European countries (Spain, France, and Italy). We provide an analysis of studies conducted in some European countries about possible connections between major migratory flows from Africa and the course of the HIV-1 epidemic and diversity. The present study employed an initial literature review of peer-reviewed articles in PubMed, UNAIDS, and WHO databases. Original articles written in French and data from institutional reports were included in this extensive review.

Trends in the prevalence of HIV-1 infection in West Africa, Maghreb and southern Europe

The HIV/AIDS epidemic is a major problem in developing countries, especially in sub-Saharan Africa where 69% of the world's infection is harbored. In 2011, there were an estimated 23.5 million people living with HIV in sub-Saharan Africa (Table 1)[1]. Countries with the largest epidemics are in southern Africa. In the countries of West and Central Africa, the prevalence of HIV remains low, with an adult HIV prevalence estimated at 2% or less in 2009 compared to the other sub-Saharan countries. This prevalence is higher in Cameroon (5.3%), Gabon (5.2%), Central African Republic (4.7%), Nigeria (3.6%), and Ivory Coast (3.4%)[3].

The HIV prevalence among the general population of Maghreb countries is very low, generally around 0.1%[4]. In 2011, an estimated 31,000 persons were living with HIV in Morocco compared to 1,700 in Tunisia and 20,000 in Algeria (Table 1). Although the overall HIV prevalence in the region is low, increasing HIV infection is seen in all North African countries, especially in younger age groups. For example in Morocco, most of notified HIV infections (63%) are in young single persons[4,5]. This increased vulnerability of young people to HIV in North Africa is due primarily to their risk behaviors[4,6].

In Western and Central Europe, 900,000 people were living with HIV at the end of 2011, according to UNAIDS estimations (Table 1). The prevalence is higher in Western Europe than in Central Europe. The highest AIDS rates were reported in Portugal, followed by Switzerland, Spain, and France[3]. The groups who are most vulnerable to HIV infection vary between countries, areas, and communities within Western and Central Europe. Populations at higher risk include intravenous drug users and their sexual partners, homosexual men, transgender people, prisoners, sex workers, and migrants[7]. For instance, the spread of HIV in Italy is increasingly concentrated among immigrants. New HIV cases in immigrants rose from 8.8% in 1991 to 30% in 2000[8].

HIV-1 diversity and migration flows

HIV-1 comprises four distinct lineages, termed groups M, N, O, and P, each of which resulted from an independent cross-species transmission event[9]. The HIV-1 group M has been classified into genetically distinct subtypes (A-D, F-H, J-K), sub-subtypes (A1-A3, F1-F2) and circulating recombinant forms (CRF), usually defined

by geographical location. The other lineages of HIV-1 (groups N, O, and P) are highly divergent genetically from the M group and represent a minority of HIV-1 strains that are endemic in Cameroon and neighboring countries in West Central Africa[10].

Molecular epidemiological studies showed that, with the exception of sub-Saharan Africa where most subtypes, CRFs, and several unique recombinant forms (URF) have been detected, there is a specific geographical distribution of HIV-1 subtypes[10]. The global expansion and diversification of the HIV-1 pandemic in the period 2004 to 2007 revealed major epidemics of subtype C that accounted for nearly half (48%) of all global infections and were concentrated mainly in sub-Saharan Africa, India, and parts of Brazil. Subtype A caused 12% of infections and was predominant in Eastern Europe and Northern Asia. Subtype B, which is responsible for 11% of infections worldwide, is predominant in North and Latin America, Europe, Japan, Australia, and North Africa. The CRF02_AG caused 8% of infections and is concentrated in West Africa, with a low prevalence in North Africa. The CRF01_AE caused 5% of infections and is predominant in Southeast Asia, while the G and D subtypes are responsible for 2 and 5% of infections, respectively, and are predominant in Central Africa (Table 2).

Non-B subtype strains are thus responsible for most HIV-1 infections worldwide. More specifically in West Africa, the CRF02_AG, subtypes A and G, are widespread[11]. Today, CRF02_AG strains dominate the epidemic in Ghana (66%), Guinea (89%), Mali (75%)[12], Niger (54.3%)[13], and Senegal (64%)[14].

In Nigeria there was a different distribution of HIV-1 strains belonging to CRF02_AG (range, 39-57%), G subtype (range, 26-58%) and A subtype (range, 49-80%). Cameroon is one country where the most HIV-1 subtypes and groups (M, O, N and P) have been identified[15,16]. The CRF02_AG is however still predominant and ranges from 60 to 68%[11,17].

In Maghreb, patients are mainly infected with HIV subtype B. It is, however, noteworthy that the prevalence of non-B subtypes is increasing, probably as a result of migration, travel, and trade with regions where non-B strains and CRFs are prevalent. Thus in Algeria, different subtypes were identified among HIV-1-infected individuals from various geographic parts of the country[18]. Subtype B was predominant and represented 56% of infections, followed mainly by CRF02_AG and CRF06_cpx with 12.7 and 4.0% of infections, respectively. Other viral recombinants between CRF02_AG and CRF06_cpx have been frequently detected in Algeria (9.7%). Similarly in Tunisia, the distribution of HIV-1 subtypes in the period 2009 to 2010 revealed a predominance of subtype B with 82% of infections, followed by 15% of CRF02_AG, and 1% of subtype C[19].

In Morocco, subtype B accounted for 74% of new infections. However, the prevalence of non-B subtypes has increased in the last years (2004 to 2010) among newly infected subjects[20-23]. The main non-B subtypes detected in drug-naive individuals were CRF02_AG, sub-subtype A1, and CRF01_AE, which represent 15.0, 6.0, and 4.8% of new infections, respectively[22]. A recent phylogenetic study revealed that most of CRF02_AG protease sequences isolated in Morocco fell within a single cluster, which indicates that this cluster is country-specific[21]. All conducted studies clearly indicate that migration potentially contributed to the diffusion of European subtype B as well as to the spread of sub-Saharan African non-B strains in Maghreb countries[21-25] and eventually in southern Europe.

The southern European HIV/AIDS epidemic is dominated by viruses assigned to subtype B (70% across the Europe)[26]. However, the prevalence of non-B subtypes in countries with large immigrant communities, such as Spain, France, and Italy, is rapidly spreading among newly diagnosed individuals[27,28].

According to the European Centre for Disease Prevention and Control (ECDC)[29], migrants from sub-Saharan Africa account for the majority of heterosexually acquired HIV infections diagnosed in European countries in recent years.

Most of HIV infections in people from sub-Saharan Africa are likely to have occurred in the countries of origin. However, migration itself places people in situations of heightened vulnerability to HIV/AIDS[30]. But, there is also evidence that people of sub-Saharan Africa origin are becoming infected by HIV in European countries. In fact, once in the country of destination, migrants could have insufficient access to HIV/AIDS prevention and care services due to, for instance, legal obstacles and cultural and language barriers[31].

Migrant flows from endemic regions represent a significant factor contributing to the spread of circulating non-B subtypes. Several studies suggested that the increase of non-B subtypes in European countries is related to immigration. Infected migrants from sub-Saharan Africa and North Africa showed a higher prevalence of non-B subtypes[32-35].

In France, non-B subtypes among treatment-naive patients with chronic HIV-1 infection increased from 10% in 1998 to 33% in 2001[36]. In a recent study, non-B subtypes were found in all regions of France and

Table 2. Most predominant subtypes and circulating recombinant forms

Subtypes, CRF (%)	C	A	B	CRF02_AG	CRF01_AE	D	G	F	CRF06_cpx	Other groups subtypes CRF and URF
Worldwide (2004-2007)[10]	48	12	11	8	5	5	2	1		8
Italy[47]	1.3 (47/3,670)	1.4 (53/3,670)	88.6 (3,253/3,670)	3.0 (107/3,670)	0.5 (21/3,670)	–	0.6 (23/3,670)	2.7 (99/3,670)	–	1.0 (39/3,670)
Spain[42]	0.5 (12/2,299)	–	92 (2,110/2,299)	3.4 (79/2,299)	0.5 (11/2,299)	0.4 (9/2,299)	1.3 (31/2,299)	0.3 (8/2,299)	–	0.7 (17/2,299)
France[37]	1.06 (12/1,128)	1.6 (18/1,128)	74.7 (843/1,128)	13.8 (156/1,128)	0.7 (8/1,128)	0.8 (9/1,128)	0.9 (11/1,128)	0.8 (10/1,128)	0.7 (8/1,128)	4.7 (53/1,128)
Morocco[22]	2.0 (2/83)	6.0 (5/83)	74.0 (62/83)	15.0 (12/83)	1.2* (2/162)	–	1.2* (2/162)	1.0 (1/83)	–	2.0 (2/83)
Algeria[18]	–	–	56.0 (total of 134)	12.7 (total of 134)	–	–	–	–	4 (total of 134)	> 9 (total of 134)
Tunisia[19]	1 (1/78)	–	82 (64/78)	14 (11/78)	–	–	–	–	–	3 (2/78)
Nigeria[65]	–	3.6 (12/338)	–	45.0 (152/338)	–	–	37.9 (128/338)	–	4.4 (15/338)	9.2 (31/338)
Ghana[66]	0.8 (2/249)	3 (8/234)	–	63 (147/234)	–	–	–	–	–	33‡ (77/234)
Guinea[67]	4.9 (2/41)	4.9 (2/41)	–	53.7 (22/41)	–	–	7.3 (3/41)	2.4 (1/41)	2.4 (1/41)	24.3 (10/41)
Senegal[68]	4 (12/328)	16 (53/328)	3 (10/328)	55 (180/328)	–	4 (11/328)	6 (18/328)	–	7 (24/328)	2 (7/328)
Mali[69]	–	3 (6/198)	–	70 (139/198)	0.5 (1/198)	–	1 (2/198)	1 (2/198)	11 (22/198)	10.6 (21/198)
Burkina Faso[70]	–	3.8 (4/104)	–	37.5 (39/104)	–	–	–	–	44.2 (46/104)	14.3 (15/104)
Cameroon** [15]	2 (1/59)	3 (2/59)	–	52 (31/59)	–	3 (2/59)	–	2 (1/59)	–	37 (22/59)

*Detected in another study[18]; **Treatment-naive Cameroonian subjects with advanced disease; ‡Recombinant CRF02_AG or unclassified subtypes.
CRF: circulating recombinant form.

accounted for 25% of primary HIV-1 infections in the period 1996 to 2010[37]. Several studies indicate that approximately 50% of these HIV-1 non-B infections in France were due to CRF02_AG variants[38], which is the predominant genetic form found in West Africa. In fact, a study carried out among newly diagnosed HIV individuals in France from 2003 to 2005 revealed that individuals from sub-Saharan countries accounted for one-third of all HIV-infected cases (33%). The most frequent origins of these infected cases were Cameroon and Ivory Coast (46%)[39]. However, according to the National Institute of Statistics and Economic Studies (INSEE), the overall migration flows from African countries (other than Maghreb) to France represented only 12.8% of all immigrants in 2009[40]. It still remains far below the flows coming from Maghreb (29.9%) and other European countries (37.7%) where non-B subtypes are also widespread[41].

In Spain, subtype B is predominant, but the prevalence of non-B subtypes increased from 4.4% between 2000 and 2003 to 18.14% in 2010[42,43]. The most prevalent non-B variants in Spain were CRF02_AG (17.48%), subtype A (4.91%), subtype G (4.78%), CRF12_BF (3.14%), and subtype C (3%)[44]. The frequencies of non-B subtypes and CRFs in Spain were supposed to be related to migratory flows[44,45]. De Felipe, et al. showed in their study that 11.1% of newly diagnosed HIV-1-infected patients from southern Spain in 2000-2010 were immigrants. Of these patients, 29% were infected with non-B subtypes and 51.7% with CRF02_AG strains. Most of them were from sub-Saharan Africa[46]. Another study revealed that non-B subtypes were isolated in 15.2% of treatment-naive patients. Only 11% (53/479) of HIV-1-infected Spaniards carried non-B strains, compared to 88.2% (15/17) of sub-Saharan Africans, 58.3% (7/12) of East Europeans, and 50% (8/16) of North Africans[32].

In Italy, the overall proportion of non-B strains increased from 18% in 2000 to 24% in 2010[46]. The most prevalent non-B strains were subtype F1 (23.7% of the total non-B subtypes), followed by subtype A (12.7%), subtype C (11.3%), and subtype G (5.5%). The distribution of these non-B strains varied between patients of European and African origins. Indeed, F1 subtype was present only in one African individual and was the most frequent strain in Europeans with non-B variants (44.3%)[47]. However, the CRF02_AG strain was found in 52.1% of West African subjects living in Italy[47].

The immigration from sub-Saharan Africa to southern Europe increased in the last two decades. Since the Maghreb lies between southern Europe and West Africa, it has been transformed into an area of emigration and also an area of transit migration. For geographic reasons, Spain and Italy are the most common destinies of transit immigrants.

According to different estimates, between 65,000 and 120,000 sub-Saharan Africans enter the Maghreb (Mauritania, Morocco, Tunisia, Algeria, and Libya) every year. About 20-30% was believed to migrate to Europe through Algeria and Morocco. At least 100,000 sub-Saharan migrants now live in Mauritania and Algeria. Tunisia and Morocco host smaller but growing sub-Saharan immigrant communities of several tens of thousands[48]. According to the Association of Friends and Families of the Victims of Clandestine Immigration (AFVIC), Morocco registered 10,000-15,000 irregular migrants from sub-Saharan Africa (40 African states) in 2007. The Moroccan Association for Research & Study on Migration (AMERM) reported that the sub-Saharan migrants transiting from Morocco were from Nigeria (15.7%), Mali (13.1%), Senegal (12.8%), Congo (10.4%), Ivory Coast (9.2%), Guinea (7.3%), and Cameroon (7%)[49]. While most of the migrants consider Morocco as a country of transit, a growing number of them fail to cross to Europe. They were also faced with the restrictive measures of the European policies and were forced to stay in Morocco for a relatively long period rather than returning to their countries of origin, which are more unstable and significantly poorer[49].

Trends of transmitted drug resistance mutations

As the HIV-1 genotypes diverge between West Africa, Maghreb, and southern Europe, it is important to provide an overview of the resistance profiles in these regions (Table 3). Transmitted drug resistance is defined as resistance to one or more antiretroviral drugs found in individuals with no previous drug exposure and is attributed to the direct transmission of resistant strains from treated individuals.

In Africa in general, the prevalence of TDR is different, but remains lower than 5%[50]. In West African countries, TDR prevalence is higher for reverse transcriptase inhibitors and reaches 9%, especially in Cameroon and Mali[51].

In Maghreb, two studies conducted in Morocco identified around 5% of TDR mutations for protease and reverse transcriptase inhibitors[22,23]. One possible explanation for this low prevalence was that the time of infection diagnosis is usually much later than the date of the primary infection. In fact, most individuals who are newly diagnosed with HIV infection in Morocco do

Table 3. The prevalence of transmitted drug resistance mutations

Countries	Spain	Italy	France	Morocco	Mali	Niger	Burkina Faso
Study period	1996-2010	2000-2010	1996-2006	2005-2009	2005-2006	2009	2004-2006
Number of drug-naive patients	732	3,163	415	98	198	96	104
TDR (%)	9.7	14.0	10.9	5.0	11.5	8.3	12.5
TDR in NNRTI (%)	5.0	7.0	4.6	0	9.0	5.2	6.1
TDR in NRTI (%)	6.1	7.0	6.7	1.4	1.5	4.2	10.6
TDR in PI (%)	2.9	3.0	2.9	1.0	1.0	1.0	0
Non-B subtype prevalence (%)	47.7	18.0	25.5	26.0	94.0	100.0	> 87.0
Most predominant non-B subtype	CRF02_AG	F1	CRF02_AG	CRF02_AG	CRF02_AG	CRF02_AG	CRF06_cpx
Studies	Yebra, et al. 2011[44]	Colafigli, et al. 2012[46]	Chaix, et al. 2009[71]	El Annaz, et al. 2011[22]	Derache et al. 2008[69]	Mamadou, et al. 2011[72]	Tebit, et al. 2011[70]

TDR: transmitted drug resistance mutations; PI: protease inhibitors; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: nonnucleoside reverse transcriptase inhibitors.

not know how long they have been infected and were commonly diagnosed at an advanced stage of infection[21,23]. The delay in diagnosis could theoretically decrease detection of TDR due to reversion of the virus to a susceptible genotype[52]. Even so, minor resistance mutations were frequently observed in the protease genes of treatment-naive Moroccan individuals infected with HIV-1 non-B subtypes[21,23].

In southern Europe, where subtype B predominates, TDR rates vary from 9 to 14%[28,54,55]. This high level is likely due to an early and gradual introduction of antiretroviral therapy in these populations. Although baseline resistance increased over time in newly diagnosed cases of non-B infection in Europe, non-B viruses still less frequently carried resistance mutations than did subtype B viruses (4.8 vs. 12.9%)[28].

In France, the proportion of transmitted viruses resistant to at least one antiretroviral drug was estimated at 10.9% in 1996 to 2006[54]. In Spain, a prevalence of 9.7% of TDR was observed in the period 1996 to 2010. Transmitted resistance to reverse transcriptase inhibitors was found to be two or threefold higher than that for protease inhibitors in 2007 to 2010. The TDR was also higher in non-B as compared to the B subtype during this period[44]. In Italy, the prevalence of TDR was 12% (13.2% in subtype B and 9% in non-B subtypes)[38], with a high prevalence of TDR among patients carrying F1 subtype (15.4%)[55].

Since some biological properties differ between the subtypes, the spread of HIV-1 variants should be taken into consideration in the clinical settings. The HIV-1 subtypes have different rates of evolution and their sequence variation may affect antiviral drug resistance development[56-58]. Although it seems that combination antiretroviral regimens are effective against all HIV-1 subtypes, there is emerging evidence that genetic differences between subtypes might impact on drug resistance pathways and the kinetics of drug resistance development. Such diversity may also influence the types of resistance mutations that could eventually emerge upon drug exposure[58]. Specific non-B subtypes showed distinct resistance mutations and subtype-specific polymorphisms that act as minor mutations in subtype B in both protease and reverse transcriptase genes and can affect HIV-1 susceptibility to antiretroviral drugs[60-62]. Natural polymorphisms among non-B subtypes have been reported at protease and reverse transcriptase drug resistance positions, and most of them act as accessory drug resistance mutations in subtype B viruses[62].

Conclusion

There is global concern about the relation between international migration and the course of the AIDS epidemic. A hallmark of the HIV-1 epidemic in Maghreb

and southern Europe is the increase in non-B strain penetration and circulation in the last 10 to 15 years. These changes have taken place as a result of the migration flows from sub-Saharan Africa to Maghreb and Europe, and from Southeast Asia and Central and South America to Western Europe. In addition to migration, trade and tourism in areas with high prevalence of HIV-1 infection is thought to be responsible for the entry of various group M subtypes into previously subtype B-restricted countries.

The studies conducted in several countries of West Africa, Maghreb, and southern Europe revealed different features of HIV-1 molecular epidemiology, especially for the distribution of viral subtypes and for TDR profiles. Nevertheless, further studies concerning TDR in Maghreb are strongly needed among treatment-naive subjects to provide a more accurate picture on drug resistance mutations in the region.

Finally, continuous surveillance programs need to be performed for early detection of new variants spreading in the population before they become more prevalent. Surveillance and prevention measures should not only be directed towards national populations, but also towards migrants, travelers, and tourists who are the major sources and targets of HIV-1 spread.

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