

# Increasing HIV-1 Genetic Diversity in Europe

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(See the article by Paraskevis et al., on pages 1167–76.)

The epidemic spread of HIV-1 in western Europe began in the early 1980s as an extension of the epidemic among homosexual men in the United States. This is inferred from the epidemiological features of the incipient epidemic in western Europe, with most AIDS cases being diagnosed among homosexual men, who frequently referred to traveling to the United States in previous years [1, 2], and from the initial association in this population between HIV-1 seropositivity and recent visits to the United States [3]. Consistent with these epidemiological data, European homosexual men are almost uniformly infected with subtype B [4, 5], first introduced among homosexual men in the United States, with phylogenetic trees supporting multiple introductions in western Europe [6]. The subtype B epidemic subsequently spread to injection drug users (IDUs) in western Europe, either from local epidemics among homosexual men or, in some countries, possibly from a variant originating among North American IDUs [4, 5, 7]. In addition, HIV-1 African clades

were also introduced early in the epidemic in some countries by African immigrants or European natives who had traveled to or lived in sub-Saharan Africa and were infected via heterosexual contact, with most of the earliest cases reported in Belgium and France in patients linked to Central Africa [2, 8–10]. In contrast to subtype B, in most western European countries propagation of African clades has been limited to persons with close epidemiological links to Africa (with some exceptions, discussed below) [11–15].

In the former Soviet Union and in the republics that emerged from its disintegration in 1991, the initial propagation of HIV-1 was much more limited than in western Europe, affecting children in southern Russia (Elista and Rostov-on-Don) who were infected during nosocomial outbreaks caused by a subtype G strain in 1988–1989 [16, 17], homosexual men infected with subtype B viruses [17–19], and individuals infected via heterosexual contact harboring diverse African clades, mainly immigrants from sub-Saharan Africa or individuals epidemiologically linked to this area [16, 18]. The epidemiological picture of the former Soviet Union epidemic started to change dramatically in 1995 with the occurrence of successive outbreaks among IDUs, first in southern Ukraine [20], then in some areas of Russia [21, 22] and Belarus [23], and subsequently in other areas. The HIV-1 epidemic among IDUs in the former So-

viet Union is largely dominated by a subtype A variant of monophyletic origin (variously designated as IDU-A, FSU-A, or A<sub>FSU</sub>) that is distinct from the major African variants [21, 23–26]; it was first introduced in the Ukrainian city of Odessa [27, 28], on the Black Sea, and has spread widely among IDUs to virtually all former Soviet Union countries, with a more recent secondary spread via heterosexual transmission [26, 29, 30].

Therefore, 2 clades dominate the HIV-1 epidemic in Europe, subtype B and the A<sub>FSU</sub> variant, which, according to their geographical spread, divide Europe in 2 major areas: the subtype B area, extending from western Europe to the borders of the former Soviet Union, and the A<sub>FSU</sub> area, comprising former Soviet Union countries. However, there are exceptions to this division (figure 1). Thus, in former Soviet Union countries, subtype B is the major clade among homosexual men [25, 26, 29] and predominates in the Ukrainian city of Nikolayev on the Black Sea [31], where a subtype B variant was introduced among IDUs simultaneously to the A<sub>FSU</sub> variant in Odessa [27]. Circulating recombinant form (CRF) 03\_AB (recombinant between A<sub>FSU</sub> and Nikolayev B variants [32]) dominates the epidemics in the Russian cities of Kaliningrad (22), on the Baltic Sea, and Cherepovets [26], in northwestern Russia. CRF06\_cpx, which circulates mainly in West Africa, has propagated among IDUs in Estonia since 2000, becoming the pre-

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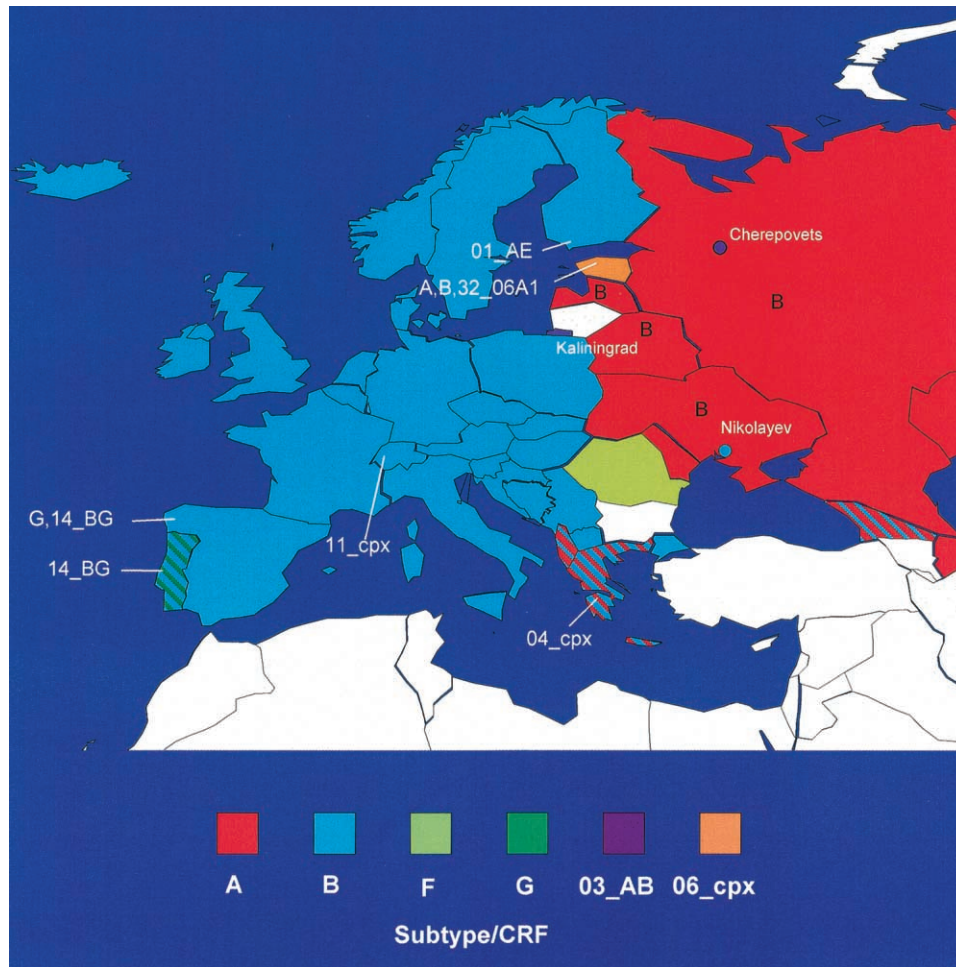
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**Figure 1.** Geographic distribution of the main HIV-1 genetic forms in Europe. The most prevalent genetic forms circulating in each country or city are indicated by color. A hatched pattern indicates that a second genetic form is circulating at a prevalence of  $\geq 20\%$ , with the thinner bars representing the less prevalent clade. Areas of circulation of other genetic forms present at  $< 20\%$  prevalence are specified. Clades found among African immigrants, whose infections are mostly acquired in Africa, are not considered on this map. Areas for which no data on HIV-1 genetic forms were available are shown in white, as are non-European areas. CRF, circulating recombinant form.

dominant variant in this country [33]. Outside the former Soviet Union, in Romania, HIV-1 infections are predominantly of subtype F, among both infections transmitted heterosexually and those acquired during childhood through blood transfusion or unsterile injection [34].

In western Europe, several countries—such as France [35, 36], the United Kingdom [13–15, 37], Belgium [12, 38], and Portugal [39–41]—have large immigrant populations, mostly from sub-Saharan Africa, who were infected via heterosexual contact and harbor diverse HIV-1 clades acquired in their countries of origin. In

these western European countries, recent increases in the proportions of HIV-1 infections among African immigrants are largely responsible for the growth in non-B infections among new diagnoses, reported to be  $> 40\%$  in Britain [14, 37], France [36, 42], and Belgium [38]. Part of these increases may be attributable to infections transmitted within Europe, but in most cases there is an epidemiological link with sub-Saharan Africa [12–14]. An exception to this is Portugal, in which a subtype G variant widely circulates among the native population, is transmitted both heterosexually and among IDUs, and rep-

resents nearly 30% of infections among Portuguese individuals [39, 41]. This variant, which also circulates among a minority of IDUs in northwestern Spain [43, 44], has recombined with subtype B to generate CRF14\_BG [43], which circulates as a minor clade in the western part of the Iberian Peninsula [39, 40, 44]. Other European countries within the “B area” in which non-B clades circulate among the local population are Switzerland, in which CRF11\_cpx, of central African origin, or a related virus is found in approximately half of the IDUs in the western part of the country [45]; Finland, in which a

CRF01\_AE variant of southeast Asian origin caused an outbreak among IDUs in 1998–1999 [46]; and, as recently reported, Albania, in which more than half of HIV-1 infections are caused by a subtype A strain that is transmitted sexually and is distinct from the A<sub>FSU</sub> variant [47].

In this issue of the *Journal*, Paraskevis et al. [48] report the results of a study from Greece, providing one more example of the circulation in a European country of an HIV-1 variant different from the predominant European clades. According to estimates from the Joint United Nations Programme on HIV/AIDS, Greece has an HIV-1 prevalence of 0.2% among adults, with the main transmission mode being sexual (76%), a predominance among homosexual men (46%), and IDUs representing 4% of infections [49]. Until recently, surveys in Greece indicated a large predominance of subtype B (>80% of infections among adults), although various other clades were also detected, with subtype A representing 4%–6% infections, some of them acquired in Greece [50–54]. However, a major shift in the distribution of HIV-1 clades was recently observed among samples collected in 2002–2003, with subtype B decreasing to 49% of infections and subtype A increasing to 33% of infections [55]. In the study in this issue, Paraskevis et al. examined phylogenetic relationships of Greek subtype A viruses, changes in prevalence according to year of diagnosis, epidemiological associations, and the epidemic history. For this, they analyzed protease and partial reverse-transcriptase sequences from 1158 individuals (representing 15% of HIV-1 infections reported in Greece from 1998 through 2005) and found overall proportions of 65.4% for subtype B and 20.6% for subtype A. For 798 patients with a known date of diagnosis, subtype B infections decreased from 94% in 1984 to 33% in 2004, whereas subtype A infections increased from 6% to 42% during the same period, with the largest increases in 2003 and 2004. Subtype A was found in all transmission risk groups except persons

with hemophilia, with lower prevalences among IDUs than among those with sexually transmitted infections, although differences were nonsignificant in multivariate analysis. In a phylogenetic tree, most Greek subtype A sequences formed a cluster (although node support values are not shown), suggesting a single introduction, that branched apart from the A<sub>FSU</sub> clade, with Albanian subtype A viruses forming a subcluster within the Greek cluster, indicating a Greek ancestry of the Albanian variant. By use of a Bayesian method, the origin of the Greek-Albanian variant was dated to approximately 1978. Although the variant is referred to as being of subtype A, this strain, as discussed by the authors, was analyzed in only 1 kb of *pol*, and its genetic characterization will require analysis of full-length genomes.

The rapid expansion of subtype A (or an A-containing recombinant) in Greece is reminiscent of recently reported changes in other established epidemics in which clades circulating at low prevalence became prominent within a few years, such as subtype C in southern Brazil [56], BG recombinant forms in Cuba [57, 58], and CRF33\_01B and related recombinants among IDUs in Malaysia [59, 60]. The expansion of a clade in an epidemic dominated by another previously introduced genetic form could be attributed to a greater transmission efficiency of the expanding variant. In the case of Greece, this would be difficult to reconcile with the relative stability of subtype A prevalence over a decade. An alternative—and perhaps more likely—explanation would be a recent chance introduction into and propagation among a preexisting transmission network of people previously unexposed to HIV-1, an event that could provoke major shifts in clade distribution in areas with relatively low HIV-1 prevalence, such as Greece.

The article by Paraskevis et al., together with other recent reports, lends support to the need for continued HIV-1 molecular epidemiological surveillance to promptly detect changes in the genetic

composition of an epidemic. It also adds to the findings of other studies indicating a trend toward an increasing genetic complexity of HIV-1 epidemics in Europe. Thus, apart from subtype B and the A<sub>FSU</sub> variant, HIV-1 clades reported to be circulating in Europe (excluding infections acquired on or epidemiologically linked to other continents) include subtype G and CRF14\_BG in Portugal and Spain [39, 40, 43, 44], CRF11\_cpx (or a related variant) in Switzerland [45], CRF01\_AE in Finland [46], CRF04\_cpx in Greece [54, 61], subtype F in Romania [34], CRF03\_AB in Russia [22, 26, 29, 62], CRF06\_cpx and CRF32\_06A1 in Estonia [33], a subtype G variant (unrelated to the Iberian strain) in Turin (northwestern Italy) [63], and the newly reported Greek-Albanian subtype A (or A-containing) variant [48], totaling at least 13 different clades. Knowledge of the distribution of HIV-1 genetic forms and of their temporal variations in a population may be of practical importance in view of the correlations between HIV-1 clades and humoral [64] and cellular [65–67] immune responses relevant to vaccines, the development of drug resistance mutations [68], and differing pathogenic potential [69].

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