Expert Review of Anti-infective Therapy

ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: http://www.tandfonline.com/loi/ierz20

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To cite this article: Martine Peeters, Matthieu Jung & Ahidjo Ayouba (2013) The origin and molecular epidemiology of HIV, Expert Review of Anti-infective Therapy, 11:9, 885-896, DOI: 10.1586/14787210.2013.825443

To link to this article: https://doi.org/10.1586/14787210.2013.825443

Published online: 10 Jan 2014.

EXPERT REVIEWS

The origin and molecular epidemiology of HIV

Expert Rev. Anti Infect. Ther. 11(9), 885–896 (2013)

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HIV-1 in humans resulted from at least four cross-species transmissions of simian immunodeficiency viruses (SIVs) from chimpanzees and gorillas in West Central Africa, while HIV-2 viruses resulted from at least eight independent transmissions of SIVs infecting sooty mangabeys in West Africa only, where one of these transmissions (HIV-1 group M) is responsible for the global epidemic. HIV-1 M is subdivided into nine subtypes and a wide diversity of circulating recombinant forms (CRFs) and unique recombinant forms. The heterogenic HIV-1 M subtype/CRF distribution is the result of founder effects. The genetic diversity of HIV-1 continues to increase overtime due to demographic factors such as travel and migration and frequent co/superinfections. In addition, the expanded access to antiretrovirals leads to an increasing number of drug-resistant strains, especially in resource limited countries.

KEYWORDS: cross-species transmission • drug resistance • evolution • HIV-1 • HIV-2 • molecular epidemiology • recombinant • SIV • subtype

AIDS was first recognized around 1980 and today 32 million individuals are estimated to be infected with the HIV, of which 70% live in sub-Saharan Africa. With more than 25 million people who died already, HIV/AIDS continues to be one of the most serious public health threats in the 21st century [101]. Highly active antiretroviral treatment (HAART) regimens are able to reduce and control viral replication, but there is currently no cure to eradicate the virus and there is no vaccine for AIDS in the near future. One of the major characteristics of HIV viruses is their extensive genetic variability. On the basis of phylogenetic analysis of numerous isolates obtained from patients living in different geographic regions, HIV is subdivided into types, groups, subtypes, circulating recombinants forms (CRFs) and unique recombinants forms (URFs) [1].

In this review, we will describe, more in detail, the origin of HIV, its genetic diversity and molecular epidemiology in the current and future epidemic.

Simian origin of HIV: how, where

In 1983, the etiologic agent of AIDS, HIV-1 was identified. Soon after this discovery, a simian origin of AIDS in humans was suspected. The first simian immunodeficiency virus (SIV), SIVmac, was isolated from a rhesus macaque (*Macaca mulatta*) with immune deficiency and clinical symptoms similar to AIDS at the New England Regional Primate Research Center (NERPRC) [2,3]. Moreover, in 1985 a survey among residents from Senegal, West Africa, showed that certain individuals had antibodies to SIV, suggesting the presence of another human retrovirus [4]. In 1986, this observation was confirmed, and a new virus close to HIV-1, called HIV-2, was isolated and characterized in patients living in France, but native from West Africa [5].

Today, it is clearly established that multiple transmissions of SIVs from nonhuman primates (NHPs) to humans are at the origin of HIV [6]. To date, SIVs have been identified in at least 45 different NHP species from Africa and in general each species is infected with a species-specific lineage. HIV-1 is most closely related to SIVcpz and SIVgor, which are isolated from chimpanzees (*Pan troglodytes troglodytes*) and gorillas (*Gorilla gorilla*) respectively. SIVsmm from sooty mangabeys (*Cercocebus atys*) are the closest relatives to HIV-2 [7–10]. The initial genetic diversity of HIV is associated with multiple introductions of genetically diverse simian viruses into humans, and the different groups of HIV-1 (M, N, O and P) and HIV-2 (A-H) are the results of independent cross-species transmission events [6]. The most plausible routes of cross-species transmissions are the exposure to infected blood or tissues, when

 10.1586/14787210.2013.825443 ISSN 1478-7210

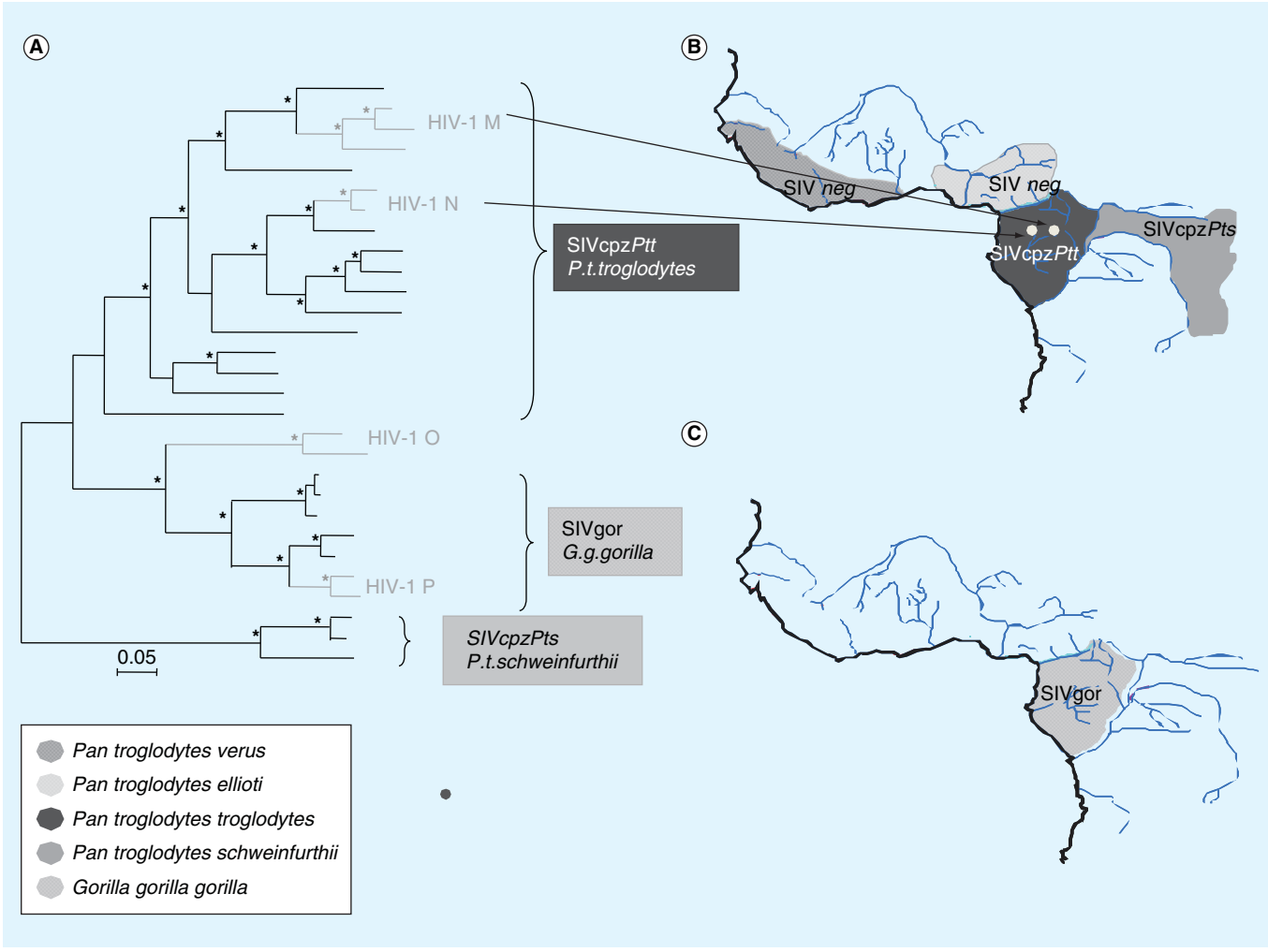

Figure 1. Schematic representation of the geographic distribution of HIV-1 M subtypes and CRFs circulating in 2007. (A) Evolutionary relationship of SIVcpz*Pts* infecting eastern chimpanzees (*Pan troglodytes schweinfurthii*), SIVcpz*Ptt* infecting central chimpanzees (*Pan troglodytes troglodytes*) and SIVgor infecting western lowland gorillas (*Gorilla gorilla gorilla*) in black, and HIV-1 group M, N, O and P strains in humans (in gray) based on maximum likelihood phylogenetic analysis of partial *env* (gp41) sequences. Horizontal branch lengths are drawn to scale (the scale bar indicates 0.05 substitutions per site). Stars indicate bootstrap values >80%. **(B)** The geographical range of the four chimpanzee (*Pan troglodytes spp*) subspecies are shown. No naturally occurring SIV has been identified yet in the upper Guinea chimpanzee (*P.t.verus*) and the Gulf of Guinea chimpanzee (*P.t. elliotti*). **(C)** The geographical range of western lowland gorillas (*Gorilla gorilla gorilla*). The geographic areas where wild chimpanzee populations infected with the ancestors of HIV-1 group M and N have been identified are shown with white circles.
SIV: Simian immunodeficiency viruses.

hunting or butchering NHPs for bushmeat, but bites or other injuries from pet NHPs are also possible [11–13].

The origin of HIV-1

More than 20 years ago, the first SIVcpz strains were identified in two captive wild-born chimpanzees in Gabon, SIVcpzGab1 and SIVcpzGab2 [14]. Characterization of a third SIVcpz, SIVcpz*ANT*, in an animal that originated from the Democratic Republic of Congo (DRC, former Zaire), showed an unexpected high degree of genetic diversity among chimpanzee viruses [15,16]. Subsequent studies showed that this was related to the fact that they were derived from two different chimpanzee subspecies [7]. These initial observations also showed that all HIV-1 strains were more closely related to SIVcpz*Ptt* from the Central chimpanzees (*P. t. troglodytes*) in West Central Africa than to SIVcpz*Pts* from Eastern chimpanzees (*P. t. schweinfurtii)* in East Central Africa (Figure 1). However, all initial data on SIVs from chimpanzees were obtained on a handful of wild-caught animals, captured as infants and does not reflect the SIVcpz diversity and prevalence in the wild. In order to define the extent of the SIVcpz reservoirs, which are at the origin of HIV-1 in humans, studies in wild living apes were needed. The major difficulty in the study of SIVcpz infection in the wild is the endangered status of chimpanzees and the fact that they live in isolated forest areas. Non-invasive methods for the detection and characterization of SIV in fecal and urine

samples developed in 2002, allowed large scale molecular epidemiological studies in wild ape populations [17,18]. Today, >6,000 fecal samples have been collected from the four different subspecies across Africa. These studies showed that only two subspecies from the Central Africa are infected with SIVcpz. Genetic characterization of numerous new SIVcpz*Ptt* from *P. t. troglodytes* and SIVcpz*Pts* isolates from *P. t. schweinfurthii*, confirmed that their hosts are each infected with a subspecies-specific lineage and all HIV-1 groups are most closely related to SIVcpz*Ptt* from West Central Africa (Figure 1) [8,9,19–21]. In both chimpanzee subspecies, SIVcpz prevalences are heterogeneous and can range from absence of infection to intermediate (5–15%) or high rates (30–50%) in certain communities. Within the SIVcpz*Ptt* and SIVcpz*Pts* lineages significant geographic clustering was observed, and the ancestors of the HIV-1 group M and N strains have been identified in distinct chimpanzee communities in south-east and south-central Cameroon (Figure 1) [8].

Chimpanzees and gorillas are sympatric species and share the same habitats in certain areas of Central Africa. This non-invasive method allowed to study also SIV infection in wild gorilla populations. In 2006, SIV infection was described for the first time in wild western lowland gorillas (*Gorilla gorilla gorilla*) in Cameroon. SIVgor formed a monophyletic group within the HIV-1/SIVcpz radiation, and was more closely related to HIV-1 groups O and P (Figure 1) [9,22]. Today, >4,000 fecal samples from gorillas, mainly western lowland gorillas from Cameroon, have been tested. Compared to SIVcpz in chimpanzees, SIVgor is less widespread and prevalence is lower, although it can reach up to 20% in certain gorilla groups [20,23]. The close phylogenetic relationship of the recently discovered HIV-1 group P and SIVgor, suggested that group P is derived from a gorilla lentivirus [24]. The reservoir of this group is most likely in gorilla populations in south-west Cameroon [25]. However, no SIVgor strains sufficiently close to group O has been identified to be the direct ancestor of HIV-1 O in humans and more studies are needed to clarify the exact origin of group O (Figure 1).

The four HIV-1 groups are thus clearly the result of four independent cross-species transmissions from chimpanzees and gorillas, in West Central Africa, to humans, but only one, HIV-1 group M (discovered in 1983), has spread across Africa and all the other continents. Group O, described in 1990, remained restricted to West Central Africa, and the highest prevalence is seen in Cameroon where it represents currently 1% of HIV-1 infections [26–28]. Group N and P, described in 1998 and 2009 respectively, have only been observed in a handful of Cameroonian patients, <20 for HIV-1 N and two for HIV-1 P [24,29–31].

The geographic areas where HIV-1 O, N and P have been documented correspond to the areas where their ancestors or closely related SIVs have been identified. Concerning HIV-1 group M, molecular epidemiological studies showed that the epicenter of this pandemic lineage is located in the western part of the Democratic Republic of Congo (DRC) at 1,000 km distance where the ancestors have been identified in Cameroon [8,19,32,33]. To date, no data are available on SIV infection in wild chimpanzee and gorilla populations living between southern Cameroon and Kinshasa, the capital city of DRC, and it cannot be excluded that in this area other chimpanzee populations exist that are infected with viruses also closely related to HIV-1 M. It is also possible that the virus arrived in Kinshasa, due to commercial activities and exchanges with southern Cameroon at the end of the 19th and beginning of 20th century [34].

Retrospective studies showed that about 20 years before the first AIDS cases were observed in the USA, HIV-1 M strains circulated already among humans in Kinshasa (former Leopoldville). HIV-1 strains were identified in a serum from 1959 and in a biopsy from 1960 [35,36]. Both strains exhibited already a high genetic diversity. Molecular clock analyses showed that HIV-1 group M started to diverge in the human population at the beginning of the 20th century, around 1908 (confidence interval of 1884–1924). The time of the HIV-1 group O radiation is estimated around 1920 (1890–1940) [37]. The low numbers of HIV-1 N infections and the lower intragroup genetic diversity suggest a more recent introduction of the HIV-1 N lineage into the human population around 1963 (1948–1977) [37]. Today, only two strains are available for HIV-1 P and estimates on dates are uncertain, but probably between 1845 and 1989 [38].

The origin of HIV-2

The closest simian counterpart for HIV-2 is SIVsmm infecting sooty mangabeys (*Cercocebus atys*) in West Africa [10,39]. HIV-2 remained restricted to West Africa and today HIV-2 prevalences are even decreasing because HIV-1 becomes predominant [40,41]. This is most likely due to the fact that as compared to HIV-1, HIV-2 is less pathogenic, less transmissible with almost absence of mother to child transmission and less efficient sexual transmission most likely related to lower viral loads [42,43]. In West Africa, the highest HIV-2 prevalences have been observed in Guinea-Bissau and southern Senegal (Casamance area). At least eight cross-species transmissions have been observed, leading to HIV-2 groups A–H [44]. A recent study identified a HIV-2 variant which is distinct from all other HIV-2 groups and could represent a 9th cross-species transmission event [45]. Only groups A and B are represented in the HIV-2 epidemic. Overall, HIV-2 group A predominates and the epicenter is located in Guinea Bissau, HIV-2 group B is less prevalent and circulates mainly in Ivory Coast and Ghana [46]. Recombinants between HIV-2 groups A and B have also been reported, and the first HIV-2 A/B intergroup recombinant was described in 2008 from a Cameroonian patient [47]. Subsequently, the first circulating recombinant form of HIV-2 (CRF01_AB) was observed in 2010 in three patients living in Japan, and this CRF was related to a HIV-2 isolated in 1990 from a patient living in Ivory Coast [48]. The other HIV-2 groups have been documented in one or two individuals only and are assumed to represent dead end

infections or infections associated with very low spread. Except for groups G and H, groups C, D, E and F were isolated in rural areas where people are frequently in contact with SIV infected mangabeys (via bushmeat or pets) [6]. The ancestors of the epidemic HIV-2 group A and B viruses, as well as for group C, G and H, were identified in wild sooty mangabey populations from the Taï forest in Ivory Coast, close to the border with Liberia [49] which correspond to the eastern part of the sooty mangabey range. Molecular clock analyses traced the origin of the HIV-2 group A and B epidemics to be around 1932 (1906–1955) and 1935 (1907–1961) respectively [37,50].

Genetic diversity & molecular epidemiology of HIV-1 group M, the pandemic strain

Classification of HIV-1 M

The genetic variability of HIV is the result of the high error rate and recombinogenic properties of the reverse transcriptase enzyme during viral replication together with the high turnover of viral particles [51,52]. Today, based on phylogenetic analysis, HIV-1 group M can be further subdivided into nine subtypes (A-D, F-H, J, K), denoted with letters, and subtypes A and F can be further subdivided into sub-subtypes, A1 to A4 and F1 and F2. Initially, based on envelope sequences only, subtype E and I have been described, but subsequent analysis of the full-length genomes of these viruses, revealed that they had a mosaic structure. Subtype E corresponds today to CRF01_AE and subtype I to CRF04_cpx [1,102]. Threshold of genetic variation within subtype is set from 8–17%, and between subtypes from 17% and 35%, depending on the subtypes and genomic regions examined [53]. The highest genetic diversity is seen in the *env* gene, and as a consequence subtypes for which only few strains have been identified, have often the lowest intra-subtype diversity. With our current knowledge, subtypes B and D would be better considered as sub-subtypes of a single subtype, however, for historical reasons it is difficult to change these designations. Inter-subtype recombinant viruses are observed in many instances. In case of further spread of such recombinant viruses within the human population, they become a CRF when documented in at least three individuals without any evident epidemiologic link. They are called URF, if they remain restricted to a limited number of individuals. Currently, there are 58 CRFs and numerous URFs have been reported [102]. Figure 2 illustrates the HIV-1 genetic diversity. Whereas subtypes are annotated with letters, each CRF is indicated with a number reflecting the order in which they are described. In addition to the number, a two-letter code is added that indicates the subtypes present in the mosaic structure, for example, CRF02_AG indicates a recombination between subtypes A and G. When three or more subtypes are involved, cpx is used to refer to a complex mosaic structure. When CRFs recombine, the viruses are called second generation CRFs and the number of the first generation CRF is used instead of a letter; ex. CRF48_01B indicates a recombination between CRF01_AE and subtype B. Certain CRFs, like CRF01_AE and CRF02_AG, were already present early in the epidemic but many other CRFs emerged more recently. The classification of HIV-1 strains evolves when new subtypes and/or CRFs are observed over time. The genetic diversity within subtypes and CRFs also increases over time [33]. HIV subtypes and CRFs are annotated in the order in which they are described and therefore the HIV classification does not always reflect their evolutionary history or order of appearance in the epidemic [54]. This is especially the case in areas where the HIV epidemic is older and where various variants co-circulate. This is illustrated by a study which performed a detailed reanalysis of HIV-1 subtypes and a subset of CRFs, which suggests that CRF02_AG is a pure subtype A variant and that subtype G has a recombinant structure [54].

Geographic distribution of different HIV-1 M variants

The classification of HIV strains has helped in tracking the course of the HIV pandemic. The genetic characterization of a large number of HIV-1 strains from diverse geographic areas, showed a heterogeneous geographic distribution of the different subtypes and CRFs worldwide (Figure 3). Overall, subtype C predominates in the global epidemic and represented 48% of HIV-1 infections between 2004 and 2007 [55]. In the same period, subtypes A and B represented 12% and 11% respectively, followed by CRF02_AG (8%), CRF01_AE (5%), subtype G (5%) and subtype D (2%) [55]. Subtypes F, H, J and K represented <1% and other CRFs represented 4% of infections in the world. The total proportion of recombinant HIV-1 strains, CRFs and URFs combined, represent 20% of HIV-1 infections worldwide [55].

The highest genetic diversity in terms of number of co-circulating subtypes, intra-subtype diversity and recombinant strains have been observed in the western part of the Democratic Republic of Congo (DRC) [32,33]. This high genetic diversity together with the fact that HIV-1 subtype A and D strains circulated already in Kinshasa, the capital city of DRC, 20 years before the recognition of the first AIDS cases, around 1980, suggest that the epidemic is ancient in DRC [35,36]. Therefore, this part of Africa is considered as the epicenter where the initial diversification of the HIV-1 group M strains occurred and from where the different HIV-1 M variants started to spread across Africa and subsequently to other continents in the world. The heterogeneous geographic distribution of HIV-1 variants is the result of different founder effects, related to demographic factors, as well as travel and migrations of human populations [56]. To what extent biological factors, specific for certain subtypes and/or CRFs, played a role in the more or less efficient spread of certain variants is not yet established today.

Because the reservoirs and the epicenter of the HIV-1 M are located in West Central Africa, the highest genetic diversity is seen in DRC and the surrounding countries like Cameroon, Angola, Central African Republic, Gabon and Equatorial Guinea. In the other parts of sub-Saharan Africa, subtypes and CRFs are unevenly distributed [57]. The epidemic in southern Africa is almost exclusively due to subtype C which represents almost 100% of HIV-1 infections in South Africa, Zimbabwe, Mozambique, Malawi, Swaziland and Botswana. Subtype C

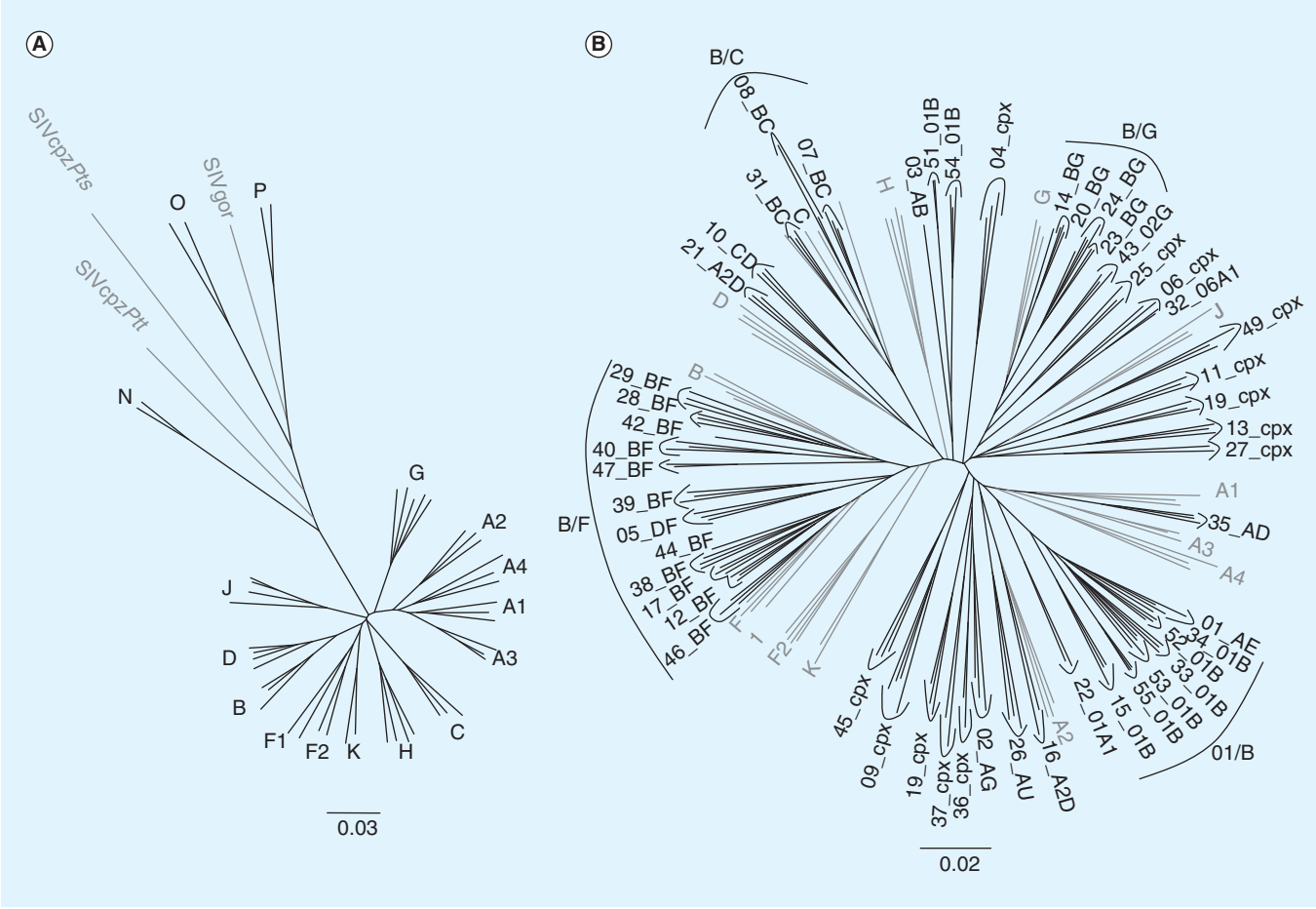

Figure 2. (A) Phylogenetic tree of near full-length genome sequences representing the genetic diversity of the pure HIV-1 group M subtypes and sub-subtypes within the HIV-1/SIVcpz/SIVgor lineage. Representative HIV-1 isolates from groups M, N, O and P were used to perform the phylogenetic analysis (Neighbor-Joining method). HIV-1 strains are highlighted in black and SIV strains in gray and dotted lines. **(B)** Phylogenetic tree (Neighbor-Joining method) of near full-length genome sequences representing the genetic diversity of the pure HIV-1 group M (in gray and dotted lines) and CRFs in black. Branch lengths are drawn to scale (the bar indicates divergence in percentage).
CRFs: Circulating recombinant forms.

predominates also in certain countries from East Africa, like Burundi, and in Horn of Africa. In other East African countries like Kenya, Tanzania or Rwanda, subtype A predominates but subtypes C and D co-circulate in different proportions according to the different countries and numerous unique recombinants involving subtypes A, C and D have also been described. In West Africa, 50–80% of infections are caused by CRF02_AG. CRF06_cpx also plays a role in the HIV-1 epidemics in Togo, Burkina Faso, Niger and Nigeria, where it can represent 20–50% of circulating strains.

In North America and Western Europe, subtype B predominates [55]. Molecular epidemiologic studies and molecular clock analysis showed that the ancestors of the current subtype B strains originated from Central Africa [58]. Subtype B strains most probably arrived in Haiti in the middle of the 1960s before they started to spread in the USA and Europe among men having sex with men (MSM), intravenous drug users (IDU) and hemophilia patients. In Eastern Europe, subtype A and CRF03_AB are widely present among IDUs. In South America, subtypes B and F predominate. In Southeast Asia, CRF01_AE and subtype B co-circulate. In India, subtype C predominates, but subtype A co-circulates in certain regions. In China, CRF07_BC and CRF08_BC predominate in IDUs and CRF01_AE is frequently observed among heterosexually acquired infections. Subtype B is widely present in Australia, but subtype C predominates in other parts of Oceania [55]. The increasing mobility and migration of human lead to introduction of new HIV-1 variants and intermixing with existing strains in different parts of the world. Therefore the geographic distribution of HIV-1 variants is thus a dynamic process.

Changing patterns of HIV-1 subtype & CRF distribution over time

Analysis of the global distribution of HIV-1 subtypes and recombinants indicated a stable distribution of HIV-1 subtypes worldwide between 2004 and 2007, with a slight increase

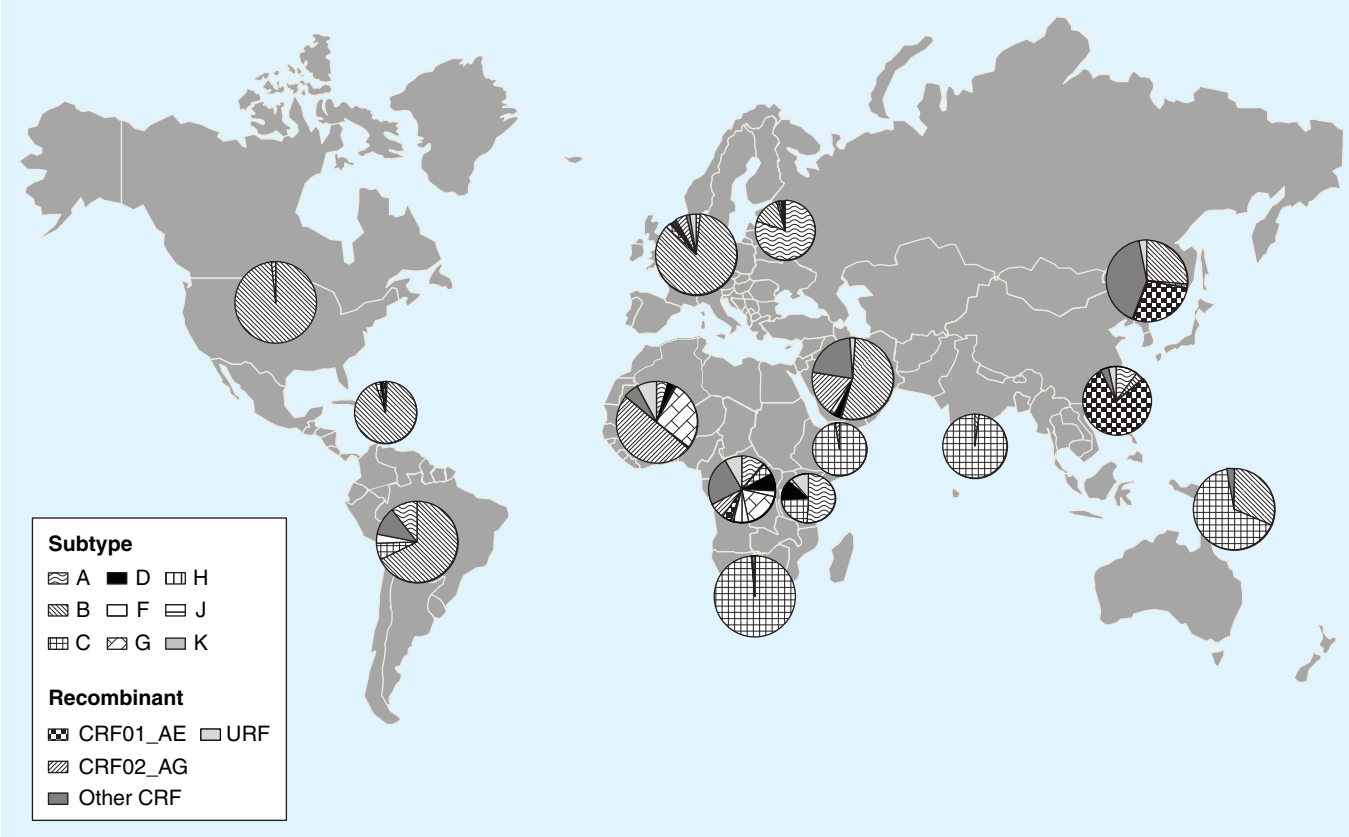

Figure 3. The geographic distribution of HIV-1 M subtypes and CRFs circulating in 2007 In Latin America CRFs and URFs are derived from subtypes B and F or B and C. In Southeast Asia CRFs and URFs are derived from CRF01_AE and subtype B. In China, CRFs are derived from subtypes B and C. In sub-Saharan Africa, CRFs and URFs have complex mosaic structures involving numerous co-circulating subtypes and CRFs.
CRFs: Circulating recombinant forms; URFs: Unique recombinant forms.
Data taken from [55].

(1.4%) of recombinant strains [55]. However, more detailed analysis showed significant differences over time in certain geographic areas. Initially, only subtypes B and F were introduced in South America, but today a wide diversity of B/F recombinants circulate including at least 11 CRFs and numerous URFs [102]. Subtype C has been introduced in Brazil between 1960 and 1980 and represents today between 30% and 60% of HIV-1 infections in southern Brazil. Subtype C has also spread to other regions of Brazil and other countries of South America [59–61]. In addition numerous unique B/C recombinants and CRF31_BC co-circulate today. A similar scenario has been observed in Southeast Asia where subtype B predominated in the IDU population and CRF01_AE among heterosexually transmitted infections. Today, CRF01_AE is the predominant strain in both population groups and 10 CRFs and numerous URFs involving subtype B and CRF01_AE have been described [102].

Subtype B predominates in Western Europe, but more and more non-B subtypes and CRFs are identified overtime. The origin of these non-B subtypes and CRFs is often associated with immigration. Today, non-B strains are still being imported into Europe and some remain largely limited to migrant populations, such as CRF02_AG in France [62]. However, some non-B variants are now also established in the native European population, like subtype G in Portugal [63] or subtype A in Greece which predominates today among newly diagnosed HIV-1 infected individuals [64].

With the introduction of new HIV-1 variants, new recombinants can emerge and can spread widely, especially in populations with high risk behavior and where HIV prevalences are high. For example, in France, recent molecular epidemiological studies have shown that subtype B viruses still predominate, but the proportion of non-B variants is increasing over time, from 10% between 1999–2000 to 28% between 2004–2010 among recently infected patients [65,66]. Fifty percent of non-B variants in France are CRF02_AG due to close links with West Africa, where this form is prevalent. Although, subtype B was initially associated with the MSM and heterosexual population native from France, and CRF02_AG with heterosexual migrants from sub-Saharan Africa. Clusters of CRF02_AG viruses have now been identified in the MSM population and B/CRF02_AG recombinants have been documented [67]. A similar scenario has recently been observed in

the United Kingdom with the emergence of CRF50_A1/D in the MSM population [68].

Another example of a sub-epidemic in a high risk population group is the MSM population in Senegal, 40% of MSM were infected with subtype C vs 4% only of the general population [69]. Evolutionary reconstructions suggest that multiple subtype C viruses entered Senegal but only one, which most likely resulted from a single introduction, did efficiently spread in the MSM population underlining the importance of high risk behavior in the efficient spread of viruses [70].

Overall, with the intermixing of subtypes and CRFs, new recombinant viruses are generated and their numbers and complexity will increase since recombination involving viruses that are already recombinant, will occur. Moreover, even distantly related viruses can recombine, as illustrated by the reports that describe inter-group recombinants between HIV-1 group O and M in Cameroon and now also in France [28,71,72]. Inter-group recombinants are also described between HIV-2 groups A and B, as already mentioned above. HIV-1 and HIV-2 dual infections have been observed in areas where both viruses co-circulate, but today no HIV-1/HIV-2 recombinant has been reported yet.

Dual infections with different HIV-1 subtypes/CRFs

Concomitant (co-infection) or sequential (super-infection) infection by different HIV-1 strains result into recombinants viruses. The fact that numerous recombinant viruses have been discovered clearly implies that co-infection with divergent HIV-1 strains is more frequently than previously thought. Persons co-infected or super-infected with strains from the same or from different subtypes, but also with different HIV-1 groups (M and O), have been documented [28,73,74]. Depending on the population groups studied (high vs low risk), the regional HIV-1 prevalence and the different methodologies used, rates of dual infection between 0% and 20% have been reported [73]. High HIV-1 genetic diversity, populations with high risk behavior and high HIV prevalences are main determinant of the frequency of dual infections with different subtypes/CRFs. As evidenced by the growing number of CRFs and URFs of HIV-1, dual and super-infections of individuals contribute to the increasing overall diversity of HIV, representing additional challenge toward a development of AIDS and preventive strategies.

Transmission of HIV-1 strains with drug resistance mutations

Antiretroviral treatment (ART) has significantly improved survival among patients infected with HIV. However during ART, drug resistant strains can emerge and can be transmitted. In high-income countries, patients are monitored on a regular basis for plasma viral load and genotypic resistance testing, to allow a rapid switch to alternative efficient drugs and to reduce the risk of transmission of drug resistant strains. North America and Europe have the longest experience with ART and 16–25% and 9–14% of new HIV-1 infections in the USA and Western Europe, respectively, are with drug resistant strains [75]. Given these high rates, a genotypic drug resistance test is recommended prior to treatment. With the use of more potent drug combinations, the prevalence of transmitted resistance in the developed world seems to be stable or even declines in certain areas [65,76].

Due to the efforts of many international organizations, the number of people receiving ART in resource limited countries has now significantly increased over the last years, most notably in sub-Saharan Africa [103]. However, the high costs of viral load tests and the corresponding equipment as well as the need for highly qualified personnel, limits the access to viral load tests in resource limited countries. Similarly, access to genotypic drug resistance testing at the patient level is almost absent today. Therefore, these countries are using the WHO public health approach to ART delivery, which proposes standard first-line and second-line therapy with treatment initiation and switch guided by clinical disease progression and where possible also with CD4 cell counts monitoring. One major consequence of this strategy is the emergence of high-level resistances during first-line therapy, since many people will stay on a virologically failing regimen for longer periods. In addition, other factors such as the limited number of trained health workers, irregular drug supplies and non-adherence related to financial cost of clinical visits and transport to clinic, family pressure or traditional medicine contribute also to the emergence of drug resistances. Rapid or uncontrolled emergence of drug resistance at the population level is thus feared as a potential consequence of ART scale-up in resource-limited countries. Indeed, the increasing expansion of ART in sub-Saharan Africa showed high rates of treatment failure; in some countries, up to 20% of patients harbored drug resistant strains after 12 or 24 months of ART [77,78,104]. The two most frequently selected mutations are M184V and K103N associated with resistance to 3TC and non-nucleoside reverse transcriptase inhibitors(NNRTIs) respectively [104]. Most studies on transmitted drug resistance reported that <5% of new infections in resource limited countries are caused by resistant viruses [104]. But prevalence as high as 10% have been reported in localized areas. Recent meta-analysis suggest that transmitted drug resistance increased gradually over time and was associated with duration of rollout of ART [75,79]. This is especially the case in East and Southern Africa. The emergence and spread of resistant strains compromise the effectiveness of national HIV treatment guidelines, especially in resource-poor countries where the choice of alternative drugs at affordable costs is limited. Figure 4 shows the frequency of strains resistant to NNRTIs in patients recently infected (since 2007) or diagnosed in Africa, Asia and Latin America.

Drug resistant HIV can also be transmitted from the mother to her child following failing interventions for the prevention of mother-to-child transmission (pMTCT). In Western Europe and North America, HIV pMTCT using combined ART starting early in the pregnancy has virtually eliminated pediatric HIV infections. In resource limited countries, especially in sub-Saharan Africa, several factors including usage of less complete

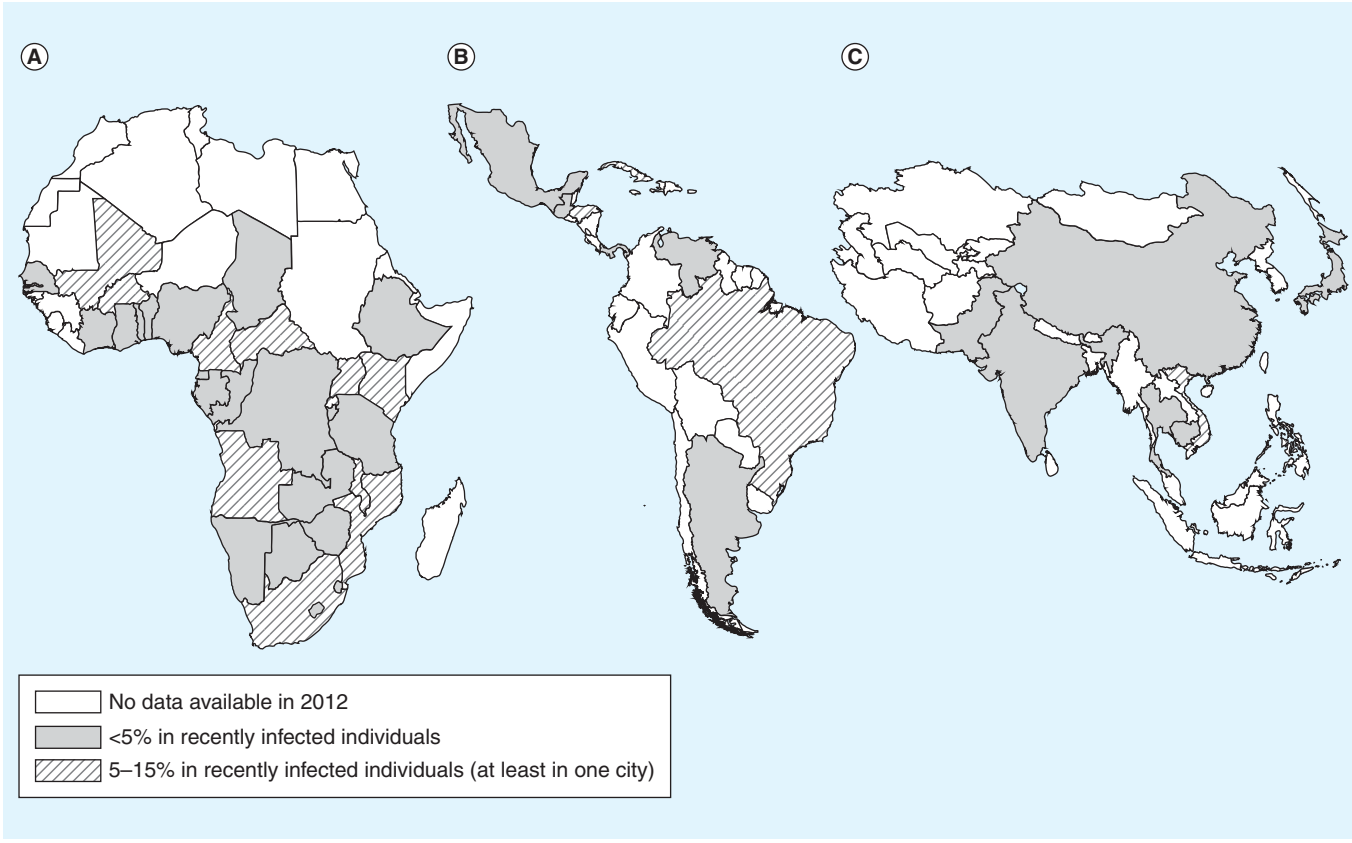

Figure 4. Frequency of transmitted NNRTI drug resistance in recently infected and/or diagnosed HIV-1 infected patients. Africa **(A)**, Asia **(B)** and Latin America **(C)**. Data are compiled from studies reporting on patients included between 2007 and 2012. NNRTI: Non-nucleoside reverse transcriptase inhibitors.

ART prophylaxis did not allow the control of HIV-1 vertical transmission. Hence, single dose Nevirapine to the mother at the labor onset and to her child in the first 72 h of life, although halving the rate of HIV-1 MTCT, has been rapidly abandoned because of rapid selection and transmission of drug resistant viruses [80,81]. Indeed, 10–75% of mothers [82] and 4–87% of children [83], depending on the study site, developed resistance to nevirapine after a single dose, thus compromising the efficacy of first line regimen that contain nevirapine and efavirenz. These pMTCT programs contributed also to the wide presence of NNRTI resistance in sub-Saharan Africa and are now replaced by other strategies.

Expert commentary & five-year view

The current HIV-1 M epidemic illustrates the impact of a single cross-species transmission. The first AIDS cases with HIV-1 M were observed in 1981, but the virus circulated already in the human population, especially in Central Africa since the beginning of the 20th century. Already 12 transmissions from ape to human have been documented, four for HIV-1 and eight for HIV-2 (recently a 9th transmission is documented). However, it is very likely that others occurred in the past but remained undetected, because the virus could not adapt to his new host or was not introduced into an environment where conditions for efficient and rapid spread were present. Several studies showed that humans are still exposed to a wide diversity of SIVs through hunting and butchering NHPs for bushmeat. Cross-species transmission of other SIVs from mangabeys, chimpanzees, gorillas or other NHP species has to be considered given the high prevalence of SIVs in some primate species (>50%), the increasing presence of humans in tropical forest areas (logging and mining industries) and subsequent increasing contact and exposure to SIV infected primates through hunting and bushmeat preparation together with the socio-economic and demographic factors predisposing global expansion of viral infections [12]. The discovery of HIV-1 P in 2009 in two Cameroonian patients, and a possible new group of HIV-2 in 2012 in Ivory Coast, clearly illustrate that our knowledge of genetic diversity and cross-species transmissions are still incomplete. One major public health implication of additional cross-species transmission with new SIV strains, is the fact that they are not always recognized by commercial HIV-1/HIV-2 screening assays. As a consequence, due to the long incubation period, human infection with such variants can go unrecognized for several years, especially in areas with poor health systems, and lead to another epidemic until broadly cross-reacting or more specific assays are available.

Today it is clear that the genetic diversity of the global HIV-1 M epidemic continues to increase over time. This concerns the intra-subtype diversity and the number of recombinant strains and their complexity. Today, the number of CRFs is significantly higher than the number of subtypes, and their number will continue to increase. However, some of these CRF remain restricted to few individuals. Future reports on new CRFs should therefore focus on CRFs which play a major role in the global epidemic.

The geographical distribution of different subtypes or CRF is also a dynamic process. The genetic diversity of HIV has implications on diagnosis, treatments, viral pathogenicity, transmission and vaccine development [84]. The increasing complexity of HIV-1 strains and changing patterns of their geographic distribution over time continue to be a challenge for efficient diagnosis, patient care and prevention strategies. For all these reasons, it is important to continue to characterize the viruses circulating in different populations around the world. Finally, with the significant increase in the number of people receiving ART, the number of resistant strains that are transmitted may increase, especially in resource limited countries. Continuous global surveillance for drug resistance is needed to ensure that the treatment regimens are still adapted.

Financial & competing interest disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was used in the production of this manuscript.

Key issues

- Simian immunodeficiency virus (SIV) from chimpanzees and gorillas from West Central Africa have crossed the species barrier on at least four occasions leading to HIV-1 in humans and HIV-2 viruses result from at least eight independent transmissions of SIVs infecting sooty mangabeys in West Africa.
- Only one of these zoonotic transmissions is responsible for the global epidemic which is caused by HIV-1 group M.
- HIV-1 group M is subdivided into nine subtypes and a wide diversity of circulating recombinant forms (CRFs) and unique recombinant forms (URFs). Today 58 CRFs have been described.
- The epicenter of the HIV-1 M epidemic is located in the western part of the Democratic Republic of Congo from where the different HIV-1 M variants started to spread across Africa and subsequently to other continents in the world.
- The heterogenic HIV-1 M subtype/CRF distribution is the result of founder effects related to demographic factors such as travel and migration, and co/superinfections.
- The genetic diversity of the global HIV-1 M epidemic continues to increase over time. This concerns the intra-subtype diversity and the number of recombinant strains and their complexity.
- The expanded access to antiretrovirals leads to an increasing number of drug-resistant strains, especially in resource limited countries.
- Humans are still exposed to a wide diversity of SIVs through hunting and butchering non-human primates for bushmeat and cross-species transmission of other SIVs has to be considered. Due to the long incubation period, human infection with such variants can go unrecognized for several years and lead to another epidemic, especially in areas with poor health systems.

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