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Non-M Variants of Human Immunodeficiency Virus Type 1

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SUMMARY

The AIDS pandemic that started in the early 1980s is due to human immunodeficiency virus type 1 (HIV-1) group M (HIV-M), but apart from this major group, many divergent variants have been described (HIV-1 groups N, O, and P and HIV-2). The four HIV-1 groups arose from independent cross-species transmission of the simian immunodeficiency viruses (SIVs) SIVcpz, infecting chimpanzees, and SIVgor, infecting gorillas. This, together with human adaptation, accounts for their genomic, phylogenetic, and virological specificities. Nevertheless, the natural course of non-M HIV infection seems similar to that of HIV-M. The virological monitoring of infected patients is now possible with commercial kits, but their therapeutic management remains complex. All non-M variants were principally described for patients linked to Cameroon, where HIV-O accounts for 1% of all HIV infections; only 15 cases of HIV-N infection and 2 HIV-P infections have been reported. Despite improvements in our knowledge, many fascinating questions remain concerning the origin, genetic evolution, and slow spread of these variants. Other variants may already exist or may arise in the future, calling for close surveillance. This review provides a comprehensive, up-to-date summary of the current knowledge on these pathogens, including the historical background of their discovery; the latest advances in the comprehension of their origin and spread; and clinical, therapeutic, and laboratory aspects that may be useful for the management and the treatment of patients infected with these divergent viruses.

INTRODUCTION

The first human immunodeficiency virus (HIV) to be isolated, in 1983, was the prototype of what was later designated HIV type 1 (HIV-1) group M (HIV-M) and is the virus responsible for the current pandemic (1). The existence and circulation of other major HIV variants were first suspected in 1985, based on atypical biological profiles of infection among prostitutes in Dakar, Senegal (2). This led to the characterization of a new variant in 1986 (3), designated HIV-2, as it showed marked genetic differences

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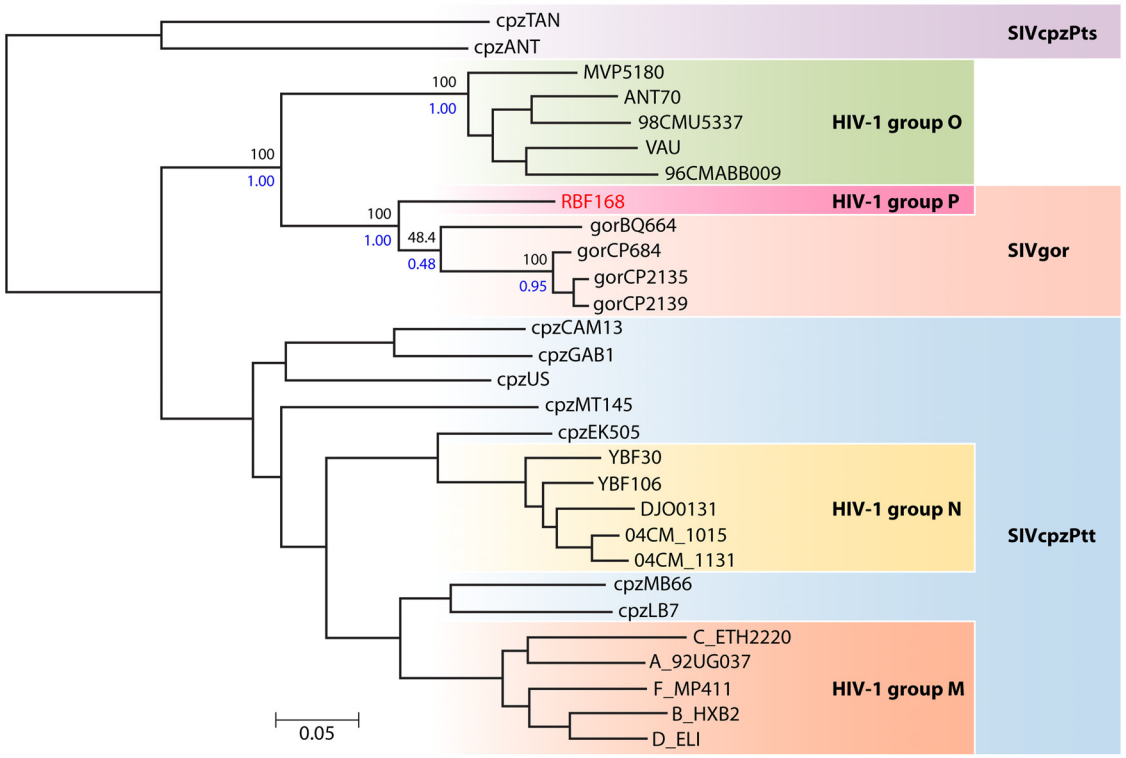


FIG 1 Phylogenetic relationships between the HIV-1, SIVcpz, and SIVgor lineages. (Reprinted from reference 10 with permission of the publisher.)

from HIV-M, including over 50% sequence divergence in the genes encoding the envelope proteins.

Other variants exhibiting less marked genetic divergence from the HIV-M prototype were subsequently identified and are currently divided into three groups based on sequence similarities. Each group arose from independent transmissions of great ape viruses to humans. The first of these variant groups to be identified was HIV-1 group O (HIV-O) in 1990, followed by HIV-1 group N (HIV-N) in 1998, both in patients of Cameroonian origin. In 2009, a new variant was isolated in France, also from a Cameroonian woman, and represented the prototype of a new group, HIV-P.

Although these variants all cause a similar disease in humans, they have specific phylogenetic, virological, and epidemiological characteristics.

DISCOVERY

HIV-O

The prototype strain of HIV-O, ANT70, was isolated in 1990 at the Institute of Tropical Medicine in Antwerp, Belgium, from a Cameroonian couple living in Belgium who presented with generalized lymphadenopathies (4). This virus had particular antigenic and genetic characteristics but was more closely related to HIV-1 than to HIV-2. Subsequent serological studies demonstrated its presence in Cameroon and Gabon (5). In 1994, a new divergent strain (MVP5180), similar to strain ANT70, was isolated in Germany by Gurtler et al. from a Cameroonian man with AIDS (6). In the same year, another variant, VAU, was identified in a French patient with AIDS. The sequence of its *env* gene was similar to those of ANT70 and MVP5180 (7), but phylogenetic analyses showed that these three viruses were as different from one another as the different HIV-M subtypes (7). Nucleotide sequencing showed that the *pol* gene of strains ANT70 and MVP5180 shared 73% homology with HIV-1 variants of European and African origins, whereas the *env* gene shared only 50% homology (8). The overall difference between the genomes was less than 50%, excluding the creation of a new HIV type but requiring HIV-1 to be split into two groups: group M (major) and group O (outlier).

HIV-N

In 1998, a Franco-Cameroonian team identified a new HIV-1 variant strain (YBF30) isolated from a Cameroonian woman who had died of AIDS in 1995 (9), leading to the definition of a new branch in the HIV-1 lineage (Fig. 1). This patient's serum reacted with an envelope antigen from a simian immunodeficiency virus (SIV) isolated from a chimpanzee (SIVcpz), rather than with representative group M and O antigens. Sequence analysis of this strain showed that the phylogenetic position depended on the gene: YBF30 clustered with SIVcpz variants in *env* and between SIVcpz and HIV-M in *gag* and *pol*. A contemporary seroepidemiological study of 700 HIV-positive sera identified 3 that reacted with an antigen representative of the YBF30 prototype strain. Molecular characterization also showed a phylogenetic link between these samples and YBF30, confirming the circulation of these variants in Cameroon. This led to the creation of a new HIV-1 group, group N (HIV-N), for "non-M, non-O."

HIV-P

An atypical variant (RBF168) was first identified in 2009 in a 62-year-old Cameroonian woman who was confirmed to be HIV-1

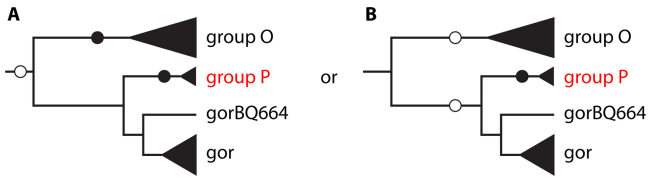


FIG 2 Scenarios for transmission of SIV from chimpanzees and gorillas to humans, explaining the emergence of HIV-O and HIV-P. Empty circles, SIV transmission events from chimpanzees; solid circles, SIV transmission events from gorillas. (A) SIVcpz transmitted to gorillas on one occasion, followed by transmission of SIVgor to humans on two occasions (groups O and P). (B) SIVcpz transmitted to humans on one occasion (group O) and to gorillas on one occasion and then transmission of SIVgor to humans on one occasion (group P). (Modified from reference 10 with permission of the publisher.)

seropositive in 2004, soon after arriving in France (10). HIV-O infection was initially suspected on the basis of negative specific tests for HIV-M along with the patient's origin and the results of a serotyping assay. A high level of viral replication, detected with a technique specific for HIV-O and a group-nonspecific technique, reinforced these suspicions. However, PCR tests specific for group O were negative. Whole-genome sequencing revealed that this virus was clearly distinct from HIV-M, -N, and -O but very similar to a simian immunodeficiency virus (SIVgor) identified in a gorilla population in Cameroon (11) (Fig. 1). This strain was therefore considered the first representative of a new HIV-1 branch, designated group "P" according to the nomenclature. Subsequently, an American team confirmed the presence of this variant in Cameroon after examining a sample taken in 2006 from a 54-year-old Cameroonian man (12).

ORIGIN, ADAPTATION, AND DIVERSIFICATION

Simian Origin

After the discovery in 1989 of an SIV linked to HIV-1, the chimpanzee species *Pan troglodytes troglodytes* (SIVcpz*Ptt*) was suspected of being the original source of HIV-1 (13, 14). The structure of a phylogenetic tree including sequences of SIVcpz*Ptt* and HIV-1 suggested that groups M, N, and O arose from three distinct cross-species transmission events (15, 16). Studies in Cameroon have since demonstrated the strong endemicity and diversity of SIVcpz in wild chimpanzees as well as differences in the geographic distribution of chimpanzees infected by the SIV variants that gave rise to HIV-M and HIV-N (17, 18).

In 2006, the Western lowland gorilla of Cameroon was also shown to carry an SIV (11). The phylogenetic position of SIVgor in the SIVcpz*Ptt* lineage implies the existence of one or several transmission events between chimpanzees and gorillas, without clearly identifying the mode of transmission (19). A phylogenetic link was also established between SIVgor and HIV-O (Fig. 1), but the genetic distance was too large to conclude that HIV-O originated directly from SIVgor. The simian reservoir of HIV-O therefore remains to be identified.

However, the close phylogenetic relationship between HIV-P (represented by the RBF168 prototype strain) and SIVgor makes gorillas the source of this new HIV-1 group (Fig. 2) (10) and suggests that they may be an intermediate host between chimpanzees and humans. This discovery reopens the debate on the origin, evolution, and complex interrelationships between SIV and HIV. A large number of SIV variants, representing potential sources of new HIV variants and also potentially responsible for past transmission events that remain to be determined, probably remain to be identified in African nonhuman primates.

It is difficult to date the initial interspecies transmission event, but molecular-based calculations suggest that the most recent common ancestors (MRCAs) responsible for the current epidemics arose at the beginning of the 20th century (1884 to 1924) for HIV-M (20), in the 1920s (1890 to 1940) for HIV-O (21), and in 1963 (1948 to 1977) for HIV-N (22). Too few HIV-P and SIVgor sequences are available for precise dating of the HIV-P MRCAs, but a recent work estimated the group P MRCA to have arisen in the 1980s and the HIV-P/SIVgor MRCA to have arisen in the second half of the 19th century (23).

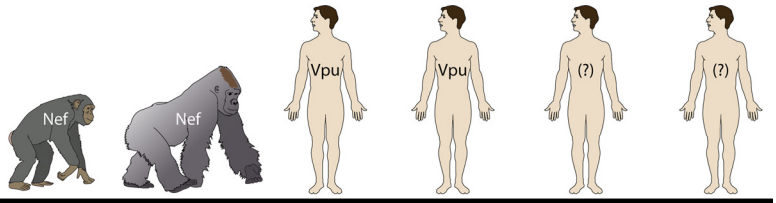
The evolutionary time scale of HIV-O thus appears to be similar to that of HIV-M but with slower growth of the viral population during the 20th century. This would partly explain the lesser dissemination of HIV-O strains (21). The age of the HIV-O epidemic has been confirmed by a study of necropsy specimens from a Norwegian family who died of AIDS in 1976, with up to 10 years of clinical manifestations of HIV infection (24). HIV-O DNA was detected in the father (a sailor who had visited several African countries during the 1960s) and his daughter, while anti-HIV-O antibodies were detected in both the father and the mother. The father represents the oldest documented case of AIDS in Europe. The VAU strain was isolated from a French woman who had never traveled to Africa but who died of AIDS in 1992 (7). This patient was most likely infected before 1980 (her child born in 1980 died in 1981 with clinical features of AIDS). These data suggest that HIV-O was already present in Europe over 40 years ago and that its low prevalence is therefore not due to recent emergence.

Adaptation to Humans

One plausible mode of simian-to-human transmission is human contact with monkey blood during activities with a risk of skin trauma, such as hunting and preparation of bushmeat, or through bites of captive or domesticated monkeys. Once the interspecies barrier was crossed, various biological factors (cellular restriction factors and replicative capacity in the new host) and also environmental, sociological, demographic, behavioral, and medical factors (injections and transfusions, etc.) would have facilitated epidemic spread in human populations. The slow spread of non-M variants could thus be due not only to epidemiological factors but also to poorer human adaptation of these viruses.

Wain et al., upon comparing the entire genomic sequences of HIV-1 and SIVcpz, identified residue 30R (Arg, basic) in the matrix protein p17Gag as an amino acid signature shared by HIV groups M, N, and O (25), whereas all SIVcpz*Ptt* and SIVgor isolates harbor 30M (Met, hydrophobic) (19). The M30R mutation would thus be specific to human adaptation. The HIV-P prototype strain described in France by Plantier et al. carries 30M and is thus more closely related to SIVcpz/SIVgor than to other human viruses (10). This lack of the Gag-30R residue has not prevented human HIV-P transmission but may result in poor adaptation. Paradoxically, the second, recently identified group P strain carries a different adaptive change (Gag-30K) (12).

Among the cellular restriction factors with antiviral activity, tetherin seems to have played a major role in human adaptation of SIV. Tetherin inhibits the release of enveloped viruses by "attaching" them to the cell membrane. In chimpanzees and gorillas, the SIVcpz/SIVgor protein Nef counteracts the action of tetherin



		SIVcpz	SIVgor	HIV-1 M	HIV-1 N	HIV-1 O	HIV-1 P
Nef	CD4	+	+	+	+	+	+
	Tetherin	+	+	−	−	−	−
Vpu	CD4	+	+	+	−	+	+
	Tetherin	−	−	+	+	−	−

FIG 3 Adaptive evolution of the Nef and Vpu viral proteins in primate lentiviruses. The degradation of CD4 receptors by the Nef and Vpu viral proteins and their antagonistic activity against the restriction factor tetherin are represented by +, and the absence of these properties or very low activity is represented by −. The Nef proteins of SIVcpz and SIVgor degrade CD4 receptors and antagonize the factor tetherin in their respective hosts, whereas those of HIV-1 do not have any activity against human tetherin. Only the Vpu protein from HIV-1 group M, through adaptive evolution, possesses antitetherin properties and degrades CD4 receptors. (Reprinted from reference 26 with permission from Elsevier.)

(Fig. 3). In humans, tetherin is resistant to the action of the HIV-M Nef protein, the role of which is replaced by the viral protein Vpu. Furthermore, Vpu degrades CD4 receptors at the surface of infected cells, thus avoiding CD4 interference during virion release. Interestingly, distinct studies recently demonstrated that the HIV-O and HIV-P Vpu proteins do not antagonize tetherin but degrade CD4 receptors (23, 26, 27). HIV-N Vpu proteins gained some modest antitetherin activity (26), except for that of the unique strain recently described outside Cameroon (28) that fully counteracted this antiviral factor as efficiently as the Vpu proteins of pandemic HIV-M strains (29), but none of them can degrade CD4 receptors, thus leading to reinternalization of excreted viruses (26) (Fig. 3). Thus, only HIV-M appears to have evolved a Vpu protein allowing efficient infection of human cells. This may partly explain the success of HIV-M.

Despite these possible adaptive limitations, non-M variants are pathogenic for humans and produce high plasma viral loads, contrary to HIV-2 (derived from another SIV variant [SIVsmm] infecting the sooty mangabey [*Cercocebus atys*]). The genetic proximity between chimpanzees, gorillas, and humans could explain why HIV-1 maintains a high replicative capacity (fitness) in humans. However, Arien et al. reported results of competitive *in vitro* experiments suggesting that the replicative fitness of HIV-O could be inferior to that of HIV-2, which itself had lower replicative fitness than HIV-M (30). Although this "fitness pyramid" matches current differences in the prevalences of these variants, it does not correspond to differences between HIV-2 and HIV-M or HIV-O in terms of viral load, pathogenicity, or transmissibility.

Genetic Diversification in Humans

Following simian-to-human transmission events, HIV evolution has been influenced by biological selective pressure and epidemiological factors.

HIV-O strains show substantial intragroup genetic diversity. Phylogenetic trees constructed from group O genomic sequences show a comet-like symmetry (Fig. 4a), intermediate between the double-star symmetry of HIV-M pandemic strains (Fig. 4b) and the topology of HIV-M sequences from the Democratic Republic of Congo, considered to be among the oldest HIV variants (31). This intragroup diversity has led to HIV-O being divided into clades or clusters that are less closely related to one another than are HIV-M subtypes. Three clades (clades A, B, and C) (32) and five clusters (clusters I to V) (33) have been described, along with numerous divergent unclassified strains (Fig. 4a). These clades and clusters overlap, and a consensus classification is still pending. Among 202 viruses characterized in France and Cameroon, 79% belong to clade A and 4% to 5% belong to clades B and C, while 12% belong to none of these three clades (our unpublished data). This distribution is presumably due to human-to-human transmission in restricted geographic areas, with founder effects of microepidemics represented today by clades A, B, and C, or to a different diversification and evolutionary history of group O relative to those of group M (32).

Data on the genetic diversity of HIV-N are more limited. To date, nine near-complete genomic sequences and five partial sequences have been determined in 14 cases of HIV-N infection confirmed by molecular biology (28, 34). These genomes all have the same profile, including an *env* gene derived from an SIVcpz variant and *gag* and *pol* genes closely related to those of HIV-M. This points to previous dual infection by two SIVcpz variants, probably in a chimpanzee, followed by their recombination (17). Sequence analysis shows a high level of HIV-N intragroup homogeneity (34, 35), which, together with the low prevalence of this group, confirms a relatively recent introduction and very slow spread in the human population.

The two HIV-P strains characterized to date are phylogenetically closely related, yet there is no evidence of any link between the two patients (12). Comparison with SIVs from chimpanzees and gorillas shows no evidence of recombination between these variants and SIV (10). Pending the discovery and characterization of other strains, it is impossible to speculate on the evolution of HIV-P.

NATURAL HISTORY OF INFECTION

The natural history of primate lentivirus infections depends on the virus and its host. Many studies in captive monkeys have indicated that SIV infections were generally considered nonpathogenic in their natural hosts (36). This was particularly demonstrated for sooty mangabey infection by SIVsmm (the original source of HIV-2), characterized by active viral replication but no

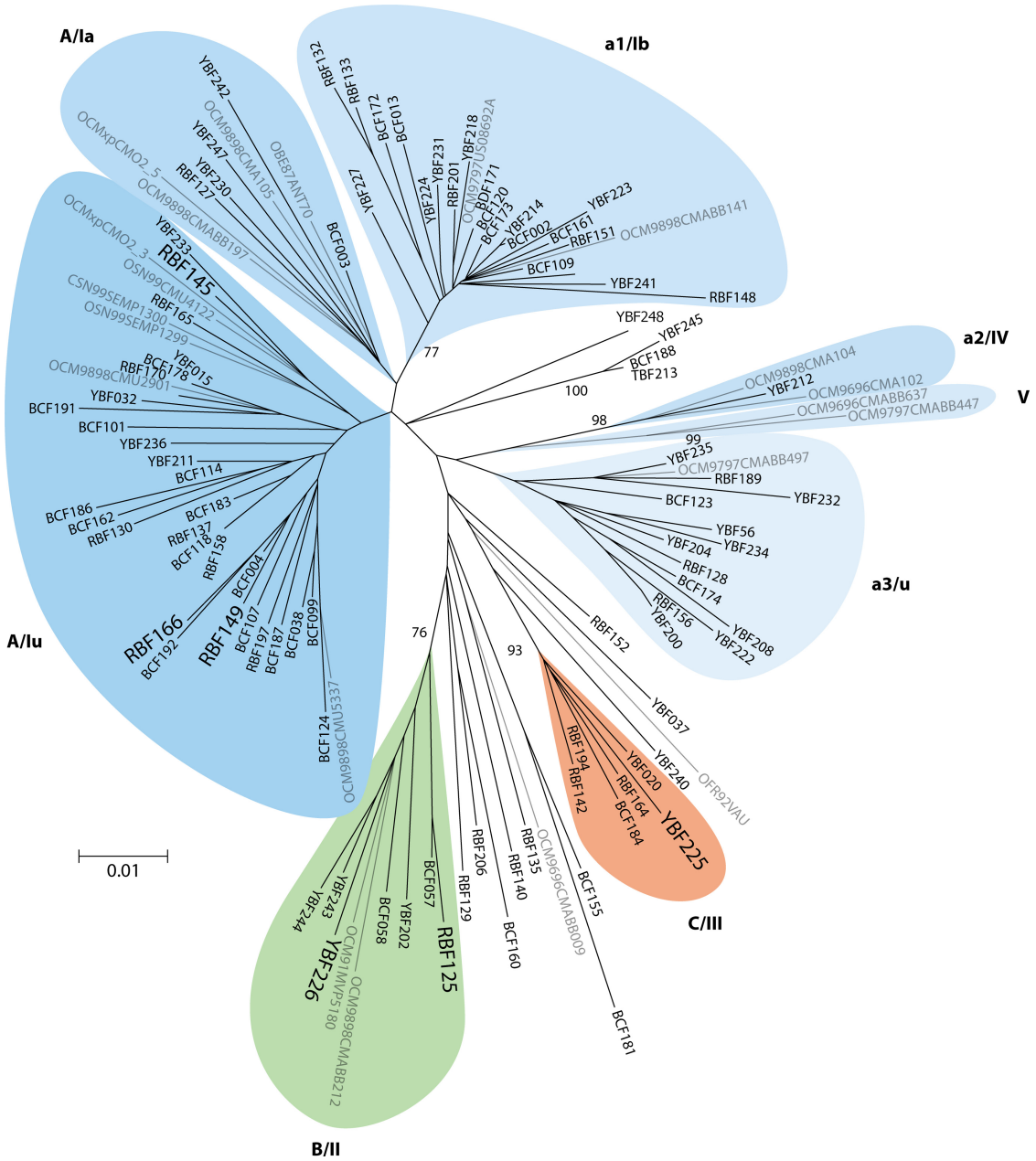


FIG 4 Comparison of phylogenetic trees constructed from 117 HIV-O sequences (a) and 55 HIV-M sequences (b) in the integrase region (603 bp). ACC, GenBank accession number. (Modified from reference 104 with permission of the publisher.)

disease progression (36). However, recently, progression to AIDS has been described in nonhuman primates infected over long periods and having lived long enough, beyond the average life span, to make visible the disease. In particular, infection in chimpanzees by their own SIV (SIVcpz*Ptt* and SIVcpz*Pts*, for the *Pan troglodytes troglodytes* and *Pan troglodytes schweinfurthii* species, respectively) was thought to be harmless until studies demonstrated that SIV infection of *P. troglodytes schweinfurthii* was associated with a 10- to 16-fold increase in age-corrected risk of death (37) and that observations of a naturally SIV-infected *P. troglodytes troglodytes* chimpanzee suggested clinical progression to an AIDS-like disease (38).

In humans, pathogenicity and natural history are largely known for HIV-M pandemic infection, but very few data are available for infections with HIV-1 non-M variants.

HIV-O

Nkengasong et al. described a 10-year follow-up study of a couple infected by strain ANT70 (39). Clinical progression without antiretroviral (ARV) therapy resembled that of HIV-M infection. The woman was still asymptomatic 8 years after seroconversion, and no switch from a non-syncytium-inducing (NSI) to a syncytium-inducing (SI) phenotype had occurred, although her CD4 cell count fell markedly, as in her partner, whose virus switched to an

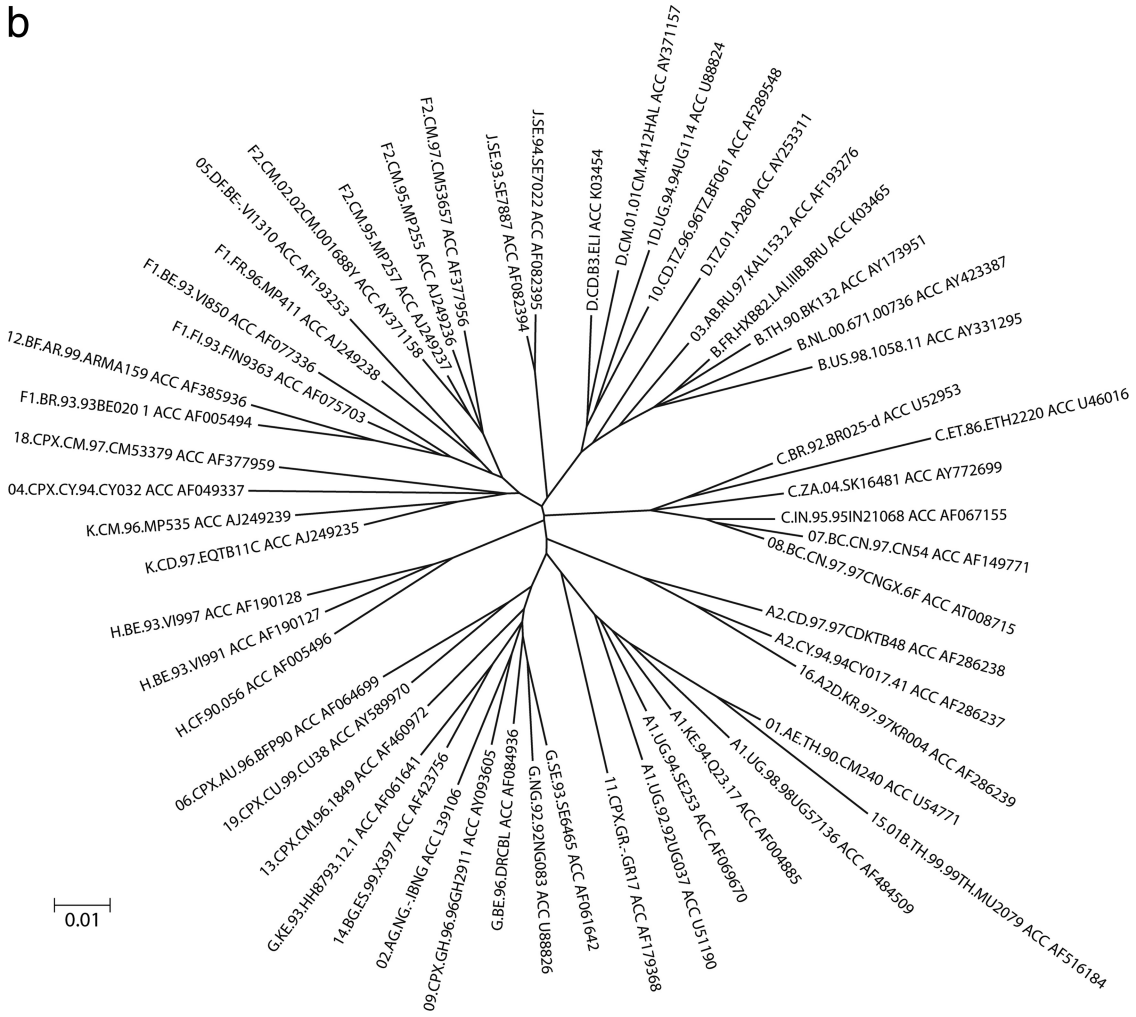


FIG 4 continued

SI phenotype. More recently, serial blood samples collected from an ARV-naive patient during a 7-year period, from diagnosis to symptom onset, were studied retrospectively (40). Clinical progression occurred in the absence of an SI phenotype switch, with viruses using only the CCR5 receptor. A recent *ex vivo* study examined the replicative capacity and cytopathogenicity of eight primary HIV-O isolates and seven HIV-M isolates in models based on peripheral blood mononuclear cells (PBMCs) and excised tonsils. The replicative "fitness" of the HIV-O isolates was five to eight times lower than that of the HIV-M isolates. However, the HIV-O strains showed variable cytopathogenicity in terms of CD4 cell depletion. Two isolates with R5 tropism caused massive depletion, comparable to that caused by X4 isolates and superior to that caused by group M R5 isolates (41).

HIV-O infection thus appears to have a natural history similar to that of HIV-M infection, in keeping with the limited data on *in vivo* replication (42, 43). In the absence of a specific cohort, most data were obtained from evaluations of assay techniques or from follow-up studies of limited numbers of patients and indicated a level of replication similar to that of HIV-M. This was confirmed by a recent study of 18 ARV-naive Cameroonian patients showing a median plasma viral load of 4.1 log copies/ml (42).

Vertical (mother-to-child) transmission of HIV-O has rarely been reported (44, 45), but this may simply be due to the low prevalence of these variants and their difficult detection.

HIV-N

Despite the small number of cases described to date, HIV-N appears to be a pathogenic virus with *in vitro* and *in vivo* replication similar to that of HIV-M (9, 35). Patients develop clinical manifestations similar to those seen in HIV-M infection, even during the acute phase of the primary infection, and progress to AIDS (9, 28, 35, 46, 47). The identification of HIV-N in a 7-year-old orphan suggests that mother-to-child transmission can occur (35, 46), and phylogenetic studies have shown the capacity for human-to-human HIV-N transmission (47, 48).

HIV-P

The HIV-P prototype strain RBF168 was easily isolated from the patient's plasma and cells. Immunological follow-up of this patient, who was ARV naive for 5 years, revealed high plasma viral loads (between 4.5 and 5 log copies/ml) and immunosuppression (mean CD4 cell count, 326 cells/mm^3; nadir, 260 cells/mm^3) characteristic of HIV infection (10). However, without knowledge of

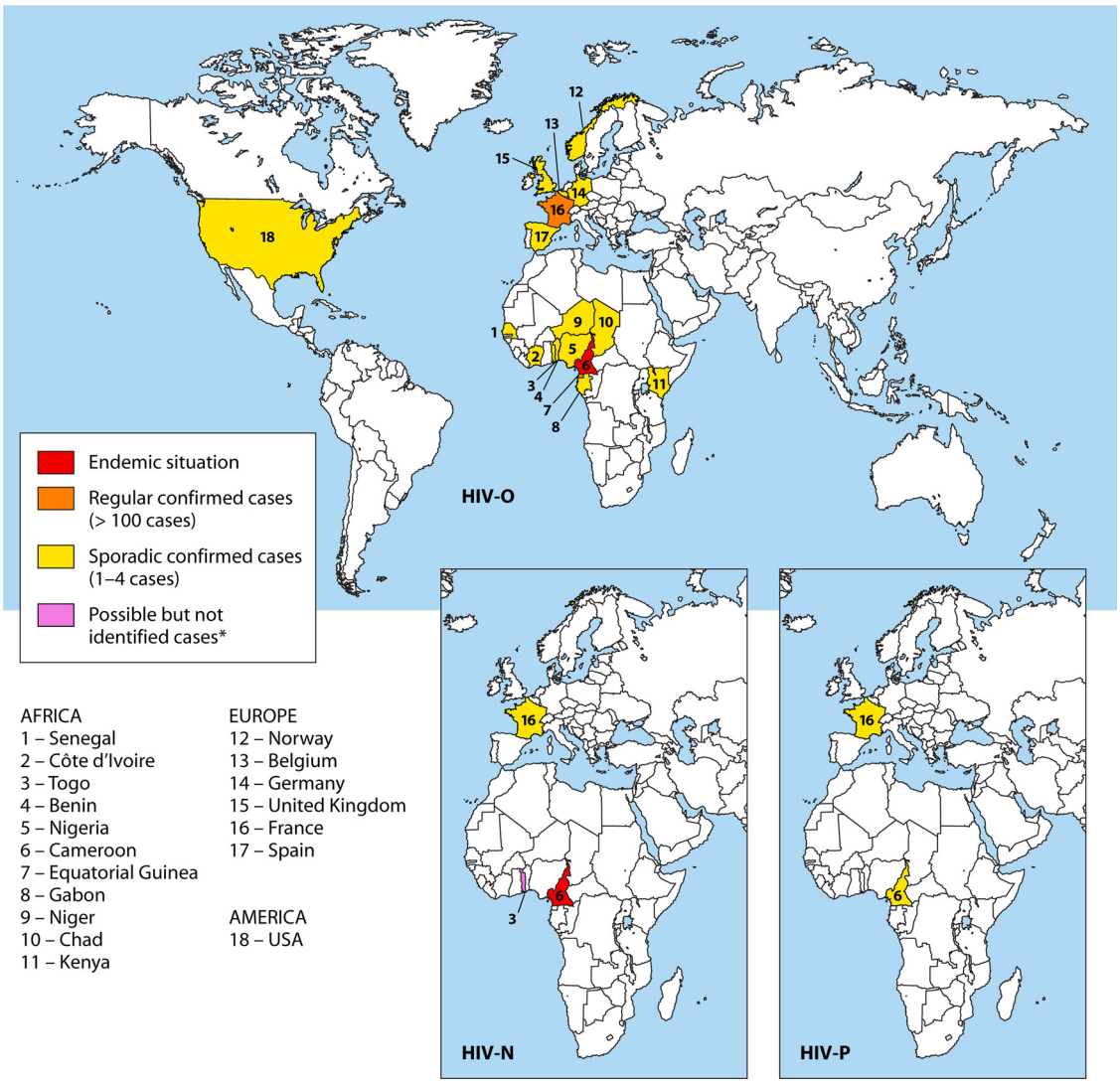


FIG 5 Molecular epidemiology of HIV-1 non-M variants. Shown is a representation of the worldwide distribution of HIV-1 non-M variants according to the number of reported cases published. Three maps are presented for the HIV-O, HIV-N, and HIV-P variants. Only Europe and Africa are represented for the distribution of the variants N and P, as no infection was reported outside these regions. *, Togo is the most likely place of contamination of the HIV-N case reported by Delaugerre et al. (28), but no case was reported from this country.

the date of infection, it is impossible to estimate the kinetics of disease progression. No data on the second case are available (12).

EPIDEMIOLOGY

Situation in Western Central Africa

All group M subtypes and most circulating recombinant forms (CRFs) are present in Central Africa, reflecting the antiquity of the epidemic in this region. However, HIV-1 non-M variants are mainly endemic to Cameroon (and, possibly, bordering regions), suggesting that this region is the origin of all existing HIV-1 groups (Fig. 5). The existence of SIV reservoirs in close proximity to a large human population has undoubtedly contributed to the diversity of the epidemic, through repeated interspecies transmission events.

Sporadic cases of HIV-O were reported in different countries of western Central Africa, such as Chad, Equatorial Guinea, and Gabon (49–52). However, to date, HIV-O is most prevalent in Cameroon, accounting for about 1% of all HIV infections in Cameroon (42). The prevalence has been stable over the last 10 years, while the prevalence of HIV-M has progressed exponentially (53, 54). Cocirculation of groups M and O in Cameroon has resulted in cases of dual M and O (M-O) infections, associated or not with recombinant forms (54–57). The prevalence of dual M-O infection and M/O recombinants is difficult to assess. A seromolecular survey conducted at the Centre Pasteur du Cameroun between 2006 and 2009 suggested that the prevalence of dual infection was about 10% among patients with HIV-O infection (58). This study also identified five unique M/O recombinants, two in patients with no evidence of dual infection, suggesting direct transmission. This confirmed the circulation of M/O recombinants in Cameroon (55–57), despite a low prevalence of M-O dual infection. The complex epidemiological situation in Central Africa, from where M/O CRFs may emerge in the future, must be taken into account when designing therapeutic strategies and future vaccination programs.

To date, only 14 cases of HIV-N infection have been reported in this region, 13 of which have been confirmed by molecular biology, most of them in Cameroon (9, 34, 35, 46–48). Analyses of samples collected between 1997 and 1999 (46) and between 2002 and 2006 (34) in Cameroon showed a very low prevalence of HIV-N infection of 0.1% among all HIV-positive samples.

With only two documented cases of HIV-P infection, both in patients of Cameroonian origin, the prevalence is impossible to estimate. However, a retrospective analysis of 1,736 HIV-positive sera by Vallari et al. suggested a prevalence of 0.06% in Cameroon (12). Regular seroprevalence studies are needed to document the spread of this strain.

Situation outside Western Central Africa

Sporadic cases of HIV-O infection have been described in other regions of West and East Africa, including Senegal, Niger, Benin, Togo, Côte d'Ivoire, Nigeria, and Kenya, (59–64), and in Europe and the United States (4, 65–69) but always in patients or partners of patients originating from or linked to western Central Africa (Fig. 5). In France, little epidemiological information is available, apart from recent data from mandatory notifications, which indicate a prevalence of 0.1% among new diagnoses, representing 35 cases identified since 2003 (according to updated HIV National Reference Center data) (70). This is why a network (RES-O) has been set up by the National HIV Reference Center to monitor these variants. One hundred thirty-six HIV-O-infected patients have been identified since the first case was described in 1992 (43, 71). This is the largest series studied outside Cameroon, including two M-O dual infections (72), one HIV-M superinfection in a patient already infected by HIV-O (73), and one unique M/O recombinant (74).

Regarding HIV-N, it was thought until recently that these variants circulated only in Cameroon. However, in 2011, a primary infection was diagnosed in a Togolese patient living in France after returning from Togo, where he probably became infected. This report indicates that HIV-N is circulating outside Cameroon (28).

All these data, and the discovery of the HIV-P prototype strain in a Cameroonian woman living in France, illustrate the spread and diversity of the HIV pandemic. Regular surveillance of the diversity of strains circulating in Central Africa and also in countries linked to this region is therefore crucial.

LABORATORY TOOLS

Serological Diagnosis

HIV-O. The marked genetic differences between HIV-O and HIV-M are reflected at the antigen level. The poor sensitivity of commercial serological tests for HIV-O variants was first noted in 1994 (75, 76), as all these tests are based on group M antigens. The addition of group O-specific antigens and development of fourth-generation enzyme-linked immunosorbent assay (ELISA) detection tests (combining the detection of p24 antigens and antibodies) have substantially improved the situation (77), but there is still a risk of false-negative HIV-O results (78–84), because test performance is evaluated by using restricted panels that do not cover the broad antigenic diversity of group O and because specific antigens are lacking in some kits.

Western blot profiles of HIV-O infection are variable, ranging from complete profiles to absent or weak reactivity with envelope glycoproteins and stronger reactivity against Gag and Pol proteins

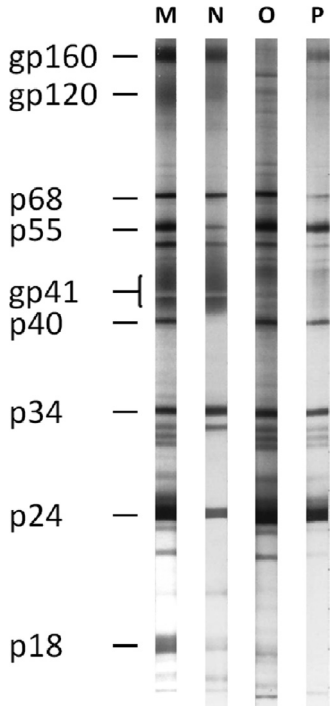


FIG 6 Western blot profiles of HIV-1 groups M, N, O, and P. The figure shows examples of Western blot reactivities with sera positive for the four groups. The group P-positive sample comes from the patient infected by the prototype strain RBF168. Of note, the group N-positive serum does not present a complete profile, due to advanced-stage disease (see reference 35 for complete profiles). The molecular masses of HIV-1 glycoproteins (gp) and proteins (p) are indicated in kDa.

(Fig. 6). Serological confirmation of HIV-O infection requires an ELISA with group-specific peptides derived from the immunodominant region of the transmembrane glycoprotein (Gp41) and the V3 region of the surface glycoprotein (Gp120) (85, 86). No such commercial assays are available, and testing is currently performed only in specialized laboratories and reference centers.

HIV-N. Although derived from SIVcpz, the HIV-N envelope elicits antibodies detectable by commercial tests and gives complete profiles on HIV-1 Western blots (35). The gp41/IDR and gp120/V3 epitopes are well conserved among HIV-N strains (34), theoretically allowing the detection of all such infections. Vallari et al. reported that none of eight HIV-N plasma samples tested with five commercial tests were negative (34). Of note, the primary infection identified in France was well detected by the tests used for routine screening (28).

HIV-P. Although highly divergent from other HIV-1 strains, the two HIV-P strains identified so far raised no problems for serological detection (10, 12). Antibodies directed against the HIV-P prototype strain RBF168 were detected by all six kits tested and gave ratios or intensities (for rapid tests) similar to those of HIV-M strains (10). The Western blot profile (Fig. 6) does not point to a particular variant, while serotyping suggests HIV-O infection. Molecular analyses are thus needed to confirm HIV-P infection.

In conclusion, current screening tests for HIV infection appear to cover non-M variants (except for possible false-negative results with group O), because of the cross-reactivity of

group M antigens or the inclusion of group O antigens, but test performance must be continuously monitored. The failure of screening tests to discriminate among HIV groups may partly explain why the number of non-M cases reported in regions where the disease is endemic is so small and calls for molecular investigations in these countries.

Measurement of Plasma Viral Load

Commercial viral load assays were initially not suitable for quantifying HIV-O variants, until the development by Abbott Molecular (Des Plaines, IL) of assays that can quantify group M and O variants albeit nonspecifically (87–89). Thus, alternative techniques were developed to allow specific molecular diagnosis and quantification of these variants (45, 90, 91). These specific assays are particularly adapted for the management of patients treated with ARV therapies, for the prevention of mother-to-child transmission, and for the proper quantification of HIV-O in patients with dual HIV-M–HIV-O infections or where both HIV-1 groups cocirculate. Comparison of the Abbott RealTime HIV-1 assay with a recent version of an alternative test showed a good correlation, although neither method is perfect (91). The marked genetic diversity of HIV-O means that these methods cannot reliably quantify some strains. Significantly lower values have been observed with the Abbott technique than with the alternative test, due to marked underquantifications for some patients. Particular care is necessary concerning the detection limits of the techniques, with some samples being undetectable with one technique and giving more than 500 copies/ml with another method. This means that residual replication can be overlooked, with a risk of resistance onset.

More recently, Roche Molecular Diagnostics (Rotkreuz, Switzerland) developed a new version of its real-time RT-PCR Cobas TaqMan HIV-1 assay. This v2.0 assay was improved (92), allowing nonspecific quantification of group M and O variants. Initial evaluation with a limited number of samples gave quantitative results for HIV-O equivalent to those of the Abbott assay (93), but these preliminary results need to be confirmed.

Proviral DNA screening for early diagnosis of mother-to-child transmission, especially during ARV therapy of newborns, is possible only with the alternative assays (45, 91).

Few studies are available for groups N and P. The new version of the Roche Cobas v2.0 kit and the Abbott assay can be used to quantify variants belonging to both groups (10, 93, 94), although the results for HIV-N may be underestimated with the latter (28, 94).

Paradoxically, these group-nonspecific assays can be used for virologic follow-up of patients with non-M infection but can no longer be used to detect these viruses. This can lead to delays in appropriate treatment and to a failure to identify dual infection or the presence of recombinant viruses, which cocirculate in regions where the disease is endemic or in countries linked to these regions. Indeed, these viruses were previously detected on the basis of discrepancies between different techniques or between immunologic and virologic results. Now, only genome amplification failure during tests for resistance mutations can suggest the presence of a variant, as current methods are not suited to these strains.

ANTIRETROVIRAL AGENTS

Natural Resistance Based on the Agence Nationale de Recherches sur Le SIDA et Les Hépatites Virales (ANRS) Algorithm

There are no specific recommendations on the therapeutic management of patients infected by non-M variants. However, as the clinical course appears to be similar to that of HIV-M infection, the same criteria for starting treatment are currently used. There is no HIV-O-specific algorithm for the interpretation of genotypic resistance, and results obtained by using algorithms designed for HIV-M are therefore only indicative and must be interpreted with care (95).

Data on HIV-O resistance are far from exhaustive (43, 95). One particularity of most HIV-O strains is their natural resistance to first-generation nonnucleoside reverse transcriptase (RT) inhibitors (NNRTIs) (i.e., nevirapine and efavirenz), due to the natural presence of the Y181C mutation (clade dependent) in the RT region (96, 97). Although 40% of strains possess "wild-type" residue Y181Y, the variable phenotypic sensitivity of these strains to NNRTIs excludes the use of these drugs in all HIV-O-infected patients (98, 99). Etravirine, a second-generation NNRTI, seems to be effective because of its distinct genetic barrier, but the natural presence of the mutations A98G, V106I, E138A, and Y181C described for HIV-M could lead to a lesser sensitivity of a minority of strains (43, 95), although this needs to be confirmed *in vitro*. Concerning nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), there are few polymorphic positions, except for the systematic presence of 210Y, but its influence on drug resistance in HIV-M is not known (43, 95).

The most important polymorphism is found in the protease region. HIV-O does not naturally possess major protease inhibitor (PI) resistance mutations, but the marked polymorphism of these strains is associated with a large number of minor mutations (at least 10) described for group M (42, 43, 95, 100). These mutations lead to possible genotypic resistance to saquinavir and resistance to tipranavir. The phenotypic consequences and impact on the rate of acquisition of PI resistance are not clearly established, owing to the lack of large clinical cohort studies, but these mutations could play a role in the onset of resistance, as suggested for HIV-2 (101–103).

The integrase active site seems to be well conserved; however, marked polymorphism has been noted at known resistance positions *in vitro* (104, 105), but their impact remains to be determined *in vivo*. Recent data on the use of raltegravir combined with other drugs suggest that this class is effective (95, 105–107).

In the Gp41 region, the presence of the N42D mutation in nearly all HIV-O strains, conferring genotypic resistance to enfuvirtide in HIV-M (depending on the algorithms used), seems to rule out the use of this drug (108). However, phenotypic studies and *in vivo* findings in treated patients show that HIV-O strains can be sensitive (95, 108–110).

These limited data therefore suggest that natural polymorphisms in HIV-O have different impacts depending on the target region, with probably little or no consequences for NRTI and integrase strand transfer inhibitor (INSTI) efficacy, uncertainty concerning PIs, and a genotype-phenotype discrepancy for enfuvirtide.

Finally, no resistance data on CCR5 antagonists have yet been published. A recent report on seven HIV-O primary isolates sug-

TABLE 1 Current clinical experience with treatment of non-M infections[a]

Virus group	No. of treated patients	Country(ies) of monitoring	Treatment line(s) used[b]	Reference
HIV-O	22	France	3 NRTI ($n = 2$) 2 NRTI + PI ($n = 18$) 2 NRTI + PI + RAL ($n = 1$) 2 NRTI + RAL ($n = 1$)	43
	12	France	Multiple lines including NRTI ± NNRTI ± PI ± T20 + RAL[c]	106
	9	France	Multiple lines including NRTI ± NNRTI ± PI ± RAL + T20[c]	108
	6	Spain and England	Multiple lines including 2 NRTI + PI[c]	113
	2	Belgium and The Netherlands	Multiple lines including 2 NRTI + PI (d4T + 3TC + IDV[c])	112
	1	Cameroon	Multiple lines including 2 NRTI + PI + RAL (TDF + 3TC + DRV-r + RAL[c])	107
	1	France	2 NRTI + PI (AZT + 3TC + LPV-r[c])	73
	1	Spain	Multiple lines including 2 NRTI + PI + RAL (ddI + FTC + DRV-r + RAL[c])	105
	1	Spain	Multiple lines including NRTI + PI + T20 (d4T + 3TC + TDF + TPV-*r* + T20[c])	110
HIV-N	1	Cameroon	2 NRTI + NNRTI (3TC + d4T + NVP[c])	47
	1	France	2 NRTI + PI + RAL + MVC (TDF + FTC + DRV-r + RAL + MVC[c])	28
HIV-P	1	France	2 NRTI + PI (ABC + 3TC + LPV-r[c])	Our unpublished data

[a] As the clinical course of non-M infections appears to be similar to that of HIV-M infection, the same criteria for starting treatment are currently used. Data on the treatment response *in vivo* are extremely sparse. Presented is a summary of current clinical experiences with treatment of infections with HIV-O, -N, and -P.
[b] The drugs are as follows: 3TC, lamivudine; ABC, abacavir; AZT, zidovudine; d4T, stavudine; ddI, didanosine; DRV, darunavir; FTC, emtricitabine; IDV, indinavir; LPV, lopinavir; MVC, maraviroc; NVP, nevirapine; r, ritonavir; RAL, raltegravir; T20, enfuvirtide; TDF, tenofovir; TPV, tipranavir. The drug classes are as follows: NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.
[c] Late-known treatment at the time of publication.

gests that genotypic tools for determining tropism are poorly predictive (111), but this needs to be confirmed on a larger number of strains.

None of the HIV-N isolates characterized so far has harbored natural polymorphisms leading to resistance to NRTIs, NNRTIs, and PIs (34, 47).

Response to Antiretroviral Therapy and Virologic Failure

Data on the treatment response *in vivo* and on the selection of mutations upon virologic failure are extremely sparse. Table 1 summarizes the current clinical experience with treatment of these non-M HIV-1 infections.

For HIV-O, the data are anecdotal or relatively old, and no cohort follow-up studies are available. In France, limited follow-up of 22 patients with documented treatment (all lines) showed therapeutic success (undetectable viral load) in 13 cases (59%) (43). The paucity of data and the lack of long-term follow-up studies rule out firm conclusions on the efficacy of the different lines of treatment. The same applies to data on virologic failure, which has been linked to mutations described for HIV-M (especially for NRTIs) and also to more specific mutations of HIV-O (112, 113). The impact of the marked protease gene polymorphism on the virologic response has not yet been determined, nor has the predictive value of resistance interpretation algorithms designed for HIV-M been determined, except in a recent study that reported imperfect adaptation (95). However, recent findings showed that even if the management of virological failure in HIV-O-infected patients is difficult, a successful response could be achieved, even for antiretroviral-experienced patients, with combinations using more recent molecules (95, 106).

For HIV-N, data for only two patients treated with ART have been reported. One study reported data for a patient treated with a three-drug regimen (stavudine, lamivudine, and nevirapine) for 18 months, which suggested efficacy of the treatment based on low viral loads and the absence of emergence of resistance mutations in target regions (47). The other study corresponds to the primary infection detected in France, for which the patient was successfully treated by antiretroviral combination therapy with tenofovir, emtricitabine, darunavir-ritonavir, raltegravir, and maraviroc (28).

For HIV-P, only one (RBF168) of the two patients was treated, with a regimen containing abacavir, lamivudine, and lopinavir-ritonavir for 42 months, and this patient presents undetectable viral loads (our unpublished data).

CONCLUSION

The discovery of these HIV-1 non-M variants, as well as HIV-2, and our knowledge of SIV reservoirs show that the HIV pandemic results from multiple transmission events, themselves subject to dynamic processes, including interspecies passages and more or less successful spread in humans. Their emergence is therefore multifactorial, being dependent on specific virological properties of each variant as well as host-related phenomena and factors (biological, historical, epidemiological, and social).

Studies of the molecular mechanisms responsible for the epidemiological differences between these variants and the pandemic group M are needed to better understand the characteristics of replication and transmission of these simian retroviruses to humans. Prospective cohort studies are also necessary to establish the pathophysiology of these infections.

While the emergence of these variants resulted from interspecies transmission in Africa, their circulation has no boundaries, as reflected by the recent detection of HIV-1 group N associated with the initial identification of HIV-1 groups O and P in patients living

in Europe. Although current commercial tests cover most of this genetic diversity, vigilance must be maintained, especially in cases of immunologic-virologic discrepancies or conflicting results of serological diagnosis and virologic follow-up (undetectable viral load or failure to amplify antiretroviral drug target regions). This must be completed by effective global surveillance of genetic diversity, as is currently performed in the United Kingdom, France, and, recently, the United States (114), to ensure the performances of laboratory tests, to dispense the adapted treatment regimens, and to survey the extent of HIV diversity to support the development of effective vaccines.

Despite improvements in our knowledge of these rare variants, many fascinating questions remain regarding their origin and genetic evolution and the reasons for their relatively inefficient spread in the human population.

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