

PHYLOGENETIC ANALYSIS OF SIV DERIVED FROM MANDRILL AND DRILL

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Habitat of mandrills and related species
4. SIVmnd-1 infection in southern mandrills
5. SIVmnd-2 infection in northern mandrills
6. Origins of SIVmnd-1, SIVmnd-2 and SIVdrl
7. Possibility of zoonotic transmission of SIV from mandrills to humans
8. Conclusion
9. Acknowledgement
10. References

1. ABSTRACT

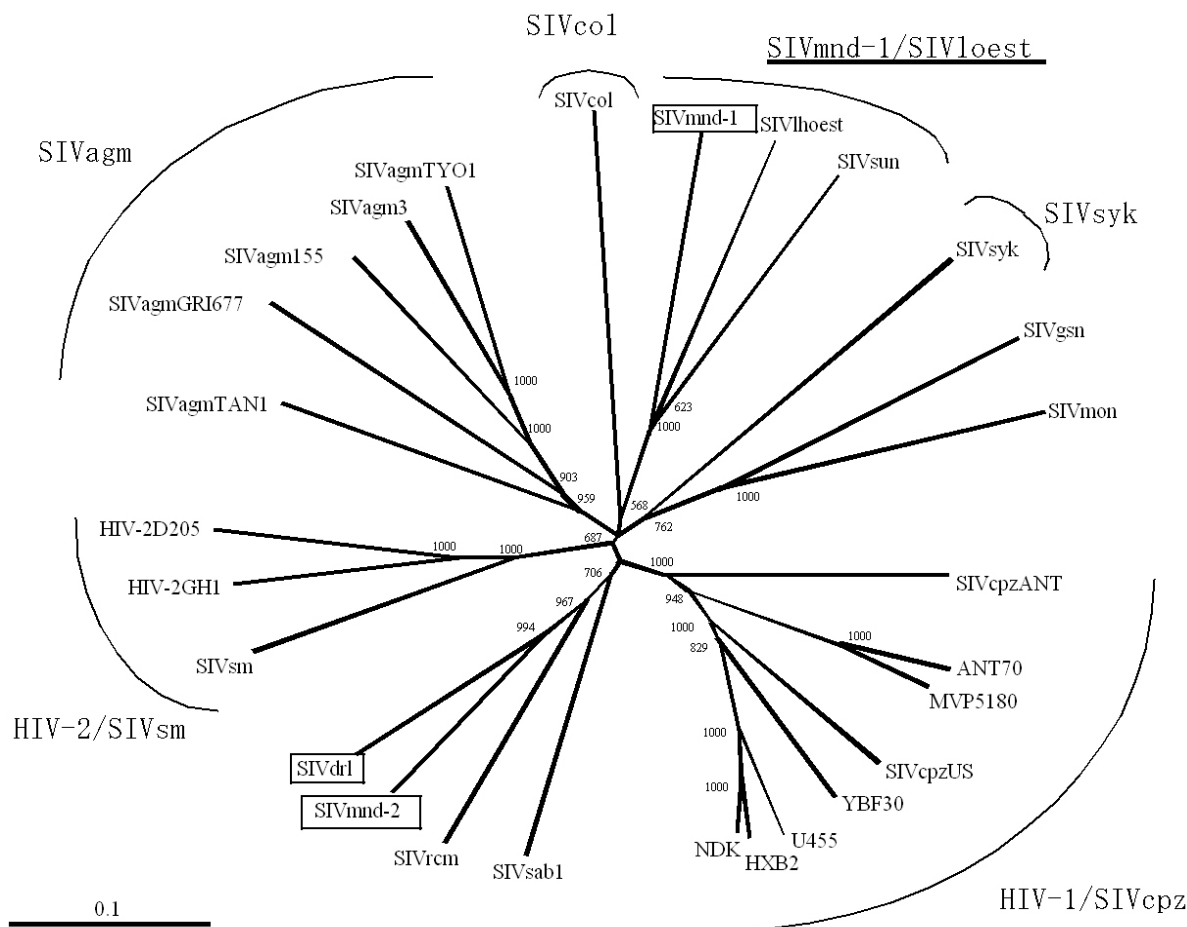
SIVmnd was isolated from mandrills in Gabon in 1989 soon after the existence of simian counterparts of HIV such as SIVmac and SIVagm was known. Since then the SIVmnd has been long considered as an independent SIV lineage and the natural host is the mandrill. However this initial finding turned out to be more complex by the recent finding of new SIV isolated from mandrills living in northern mandrill habitat, and other SIV isolated from drills and other species. One fact which made these findings complicated was the fact that the SIVmnd made a tight cluster with SIVlhoest and SIVsun from genus *Cercopithecus*, which is different from genus *Mandrillus*. A second fact is that the second SIVmnd isolates are different in the genomic structure from the former SIVmnd and almost similar to SIVdrl from drills, and phylogenetically closely related with each other. At present, the former SIVmnd isolate is termed SIVmnd-1 and the second SIVmnd isolate is called SIVmnd-2. Interestingly SIVmnd-2/SIVdrl has the same mosaic structure containing the *vpx* gene which is absent in SIVmnd-1. The mosaic structure was probably due to a recombination between SIVmnd-1 and SIVrcm from red capped mangabey (or similar viruses) having the *vpx* gene. However this recombination event is not recent, and SIVmnd-1, SIVmnd-2 and SIVdrl have been likely maintained for a long period of time in each species. In this article, we speculate on the origin and evolution of these SIVs.

2. INTRODUCTION

Simian immunodeficiency viruses (SIVs) naturally infect a wide range of wild African nonhuman primates. They are members of the lentivirus family along with human immunodeficiency virus type 1 and type 2 (HIV-1 and HIV-2). On the basis of similarity of the genome sequences of these viruses, they are classified into six major, approximately equidistant, phylogenetic lineages (Figure 1) (1-2), namely, (I) SIVcpz in chimpanzees (*Patroglodytes*), which clusters with HIV-1 (3-5); (II) SIVsm in sooty mangabeys (*Cercocebus atys*), which clusters with HIV-2 (6-7); (III) SIVagm in four sub-species of African green monkey (*Cercopithecus aethiops*) (8-10),

(IV) SIVmnd-1 in mandrills (*Mandrillus sphinx*) (11)(12), SIVlhoest in l'Hoest monkeys (*Cercopithecus lhoesti lhoesti*) (13-14) and SIVsun in sun-tailed monkey (*Cercopithecus lhoesti solatus*) (15); (V) SIVsyk in sykes' monkey (*Cercopithecus mitis albogularis*) (16); and (VI) SIVcol in guereza colobus (*Colobus guereza*) (17). Recently four new fully-sequenced SIV isolates not belonging to the above-mentioned lineages have been reported; SIVrcm from red-capped mangabey, (*Cercocebus torquatus*) (18-19), SIVgsn from greater spot-nosed monkeys (*Cercopithecus nictitans*) (20), SIVmnd-2 from mandrill (21-23) and SIVdrl from drill (*Mandrillus leucophaeus*) (24-25). These isolates have not yet been classified but in this article the latter two are described in detail. In addition, several other SIV isolates that have not been fully sequenced have been reported: SIVtal from talapoin (*Miopithecus talapoin*) (26), SIVmus from mustached monkeys (*Cercopithecus cephus*) (26), SIVmon from mona monkeys (*Cercopithecus mona*) (27), and SIVdeb from De Brazza's monkeys (*Cercopithecus neglectus*) (26).

Phylogenetic analyses of these primate lentiviruses revealed that some SIV lineages have evolved simultaneously with their host. For example, SIVagm is in the four African green monkey sub-species, and SIVlhoest and SIVsun are in the *Cercopithecus lhoesti super-species* (9,28). While some viruses have evolved in the host, others have been acquired by cross-species transmission. Primates that naturally acquired the SIVagm group viruses include patas monkeys (29), yellow baboons (30), chacma baboons (31) and white-crowned mangabey (32). In addition, the full-length genome sequences of some SIVs raise the possibility that they are recombinant viruses. These include SIVsab from sabaeus monkeys (10), SIVrcm from red-capped mangabeys (18-19) and SIVgsn from greater spotnosed monkeys (20). These observations indicate that host-dependent evolution, natural cross-species transmission, co-infection and recombination between highly divergent viruses have been existing since the beginning of the evolution of primate lentiviruses, and



3. HABITAT OF MANDRILLS AND RELATED SPECIES

other primates (33). Another species of the genus *Mandrillus*, the drill inhabits the neighboring area of habitat of mandrills. Its habitat is the tropical rain forest between the Cross River in southeastern Nigeria and the Sanaga River in Cameroon, and in Bioko Island of Equatorial Guinea (Figure 2). Drills, like mandrills, are omnivorous (33). Because of habitat loss by destruction and degradation of evergreen forests and indiscriminate hunting for commercial bushmeat, both species have been endangered. They are recognized as the highest-ranked primate species for conservation, and are listed in CITES-I.

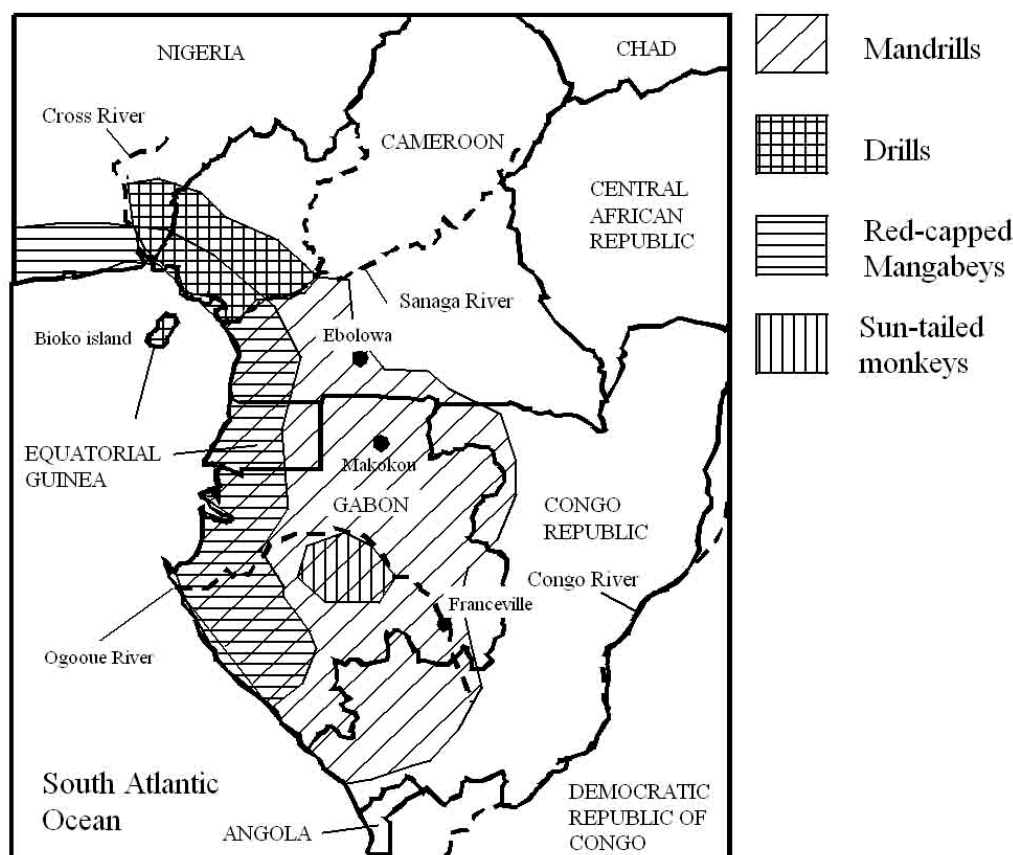


Figure 2. Geographic distributions of referred monkey species related to mandrill in West Central Africa.

in a wide range of sub-Saharan Africa and one of the species, l'Hoest monkey inhabits evergreen forests in eastern Democratic Republic of Congo, western Uganda, Rwanda and Burundi (33). The habitat of l'Hoest monkeys is distant from, and does not overlap with, the habitats of mandrill and drill.

4. SIVmnd-1 INFECTION IN SOUTHERN MANDRILLS

In 1988, Tsujimoto *et al.* in the author's group isolated a novel SIV from mandrill, later designated as SIVmnd-1, in a semi-free-ranging colony in Franceville in Gabon (11-12). An extrachromosomal closed circular DNA clone was obtained from a male mandrill and sequenced. In addition to *gag*, *pol* and *env* genes, open reading frames corresponding to the *vif*, *vpr*, *tat*, *rev* and *nef* genes were found (Figure 3). This virus does not, however, contain open reading frames corresponding to *vpu* which is present in HIV-1, or *vpx* which is present in HIV-2. A phylogenetic analysis revealed that the SIVmnd-1 lineage diverged from a common SIV ancestor at approximately the same time as other SIV lineages (Figure 1). Several SIVmnd-1 strains were isolated from other mandrills within the colony, in which the seropositive frequency was 10% (34), and all of the viruses were found to be highly related, indicating intracolony transmission of the same SIVmnd-1 strain,

possibly by horizontal transmission (35-36). The seropositive frequency is unavailable on SIVmnd-1 in wild-living mandrills inhabiting other areas.

In 1999, a new SIV strain, SIVlhoest, was isolated from l'Hoest monkeys (*Cercopithecus l'hoesti*) in eastern Democratic Republic of Congo by Hirsch *et al.* (13). In spite of the distant genetic relationships between their hosts, SIVmnd-1 and SIVlhoest were clearly more closely related to each other than to any other SIVs (Figure 1). Soon after this finding, SIVsun was isolated from a wild-caught sun-tailed monkey (*Cercopithecus l'hoesti solatus*) in Gabon (15). SIVsun and SIVlhoest made a monophyletic cluster together with SIVmnd-1 (Figure 1). The fact that the same lineage viruses were isolated from different genus hosts indicated that cross-species transmission occurred in their history.

5. SIVmnd-2 INFECTION IN NORTHERN MANDRILLS

Recently, the second type of SIVmnd (SIVmnd-2) was isolated from wild-born mandrills from the northern mandrill habitat by two independent research groups. Souquiere *et al.* isolated the virus from wild-born mandrills captured in northern Gabon (21). Takehisa *et al.* in the author's group also found SIVmnd-2 in wild-born

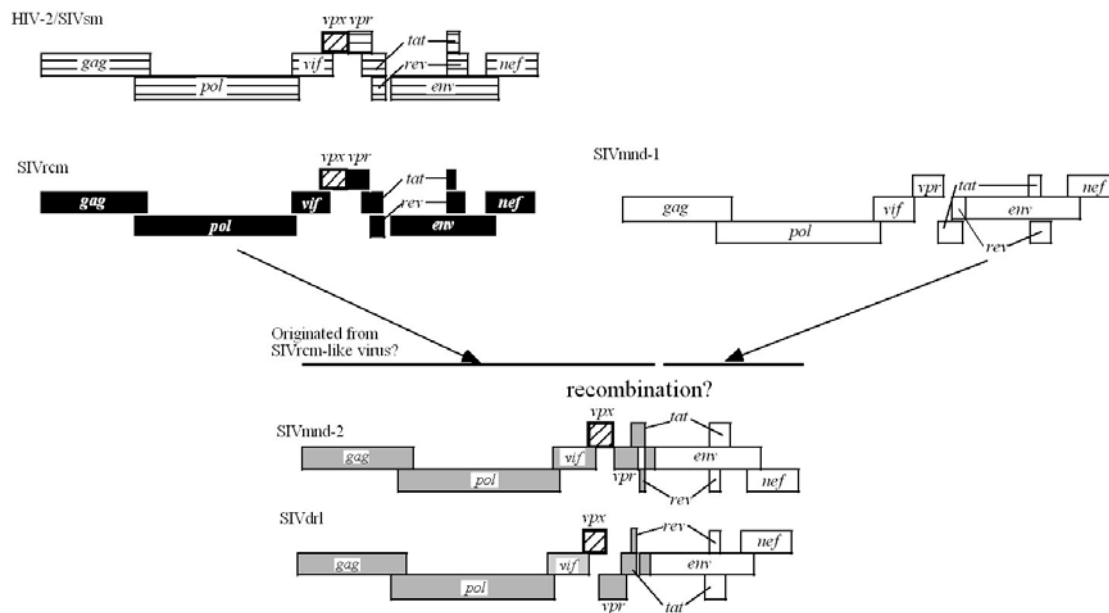


Figure 3. Genomic structures of SIVmnd-1, SIVmnd-2, SIVdrl and related viruses, and possible recombination event.

mandrills housed as pets in villages near Ebolowa town in southern Cameroon (22-23). We screened 30 mandrills in this area and found five (16.7%) of them seropositive. The SIVmnd-2 in these mandrills differed from SIVmnd-1 both structurally and phylogenetically. Both groups proposed that these virus isolates should be considered as different type.

The genomic organization including the position of structural and regulatory genes in SIVmnd-2 was similar to that of HIV-2/SIVsm and SIVrcm (Figure 3) (21,23,19). Each of these viruses encodes *gag*, *pol* and *env*, as well as the accessory genes *vif*, *vpx*, *vpr*, *tat*, *rev* and *nef*, but lacks the *vpu* gene. In contrast to SIVmnd-1, SIVmnd-2 carries the *vpx*, which is present only in HIV-2/SIVsm and SIVrcm.

Interestingly, when the data was utilized to prepare phylogenetic trees based on different genomic regions, SIVmnd-2 made different clusters with other SIVs (21-23). Based on the sequences encoding *gag*, *pol*, *vif*, *vpr* and *tat*, SIVmnd-2 is more closely related to SIVrcm (Figure 4A). On the other hand, based on the sequences encoding *env* and *nef*, it is more closely related to SIVmnd-1 (Figure 4B). In addition to this fact, diversity plotting analysis of SIVmnd-2 compared to SIVmnd-1, SIVdrl and SIVrcm suggest that SIVmnd-2 was derived most likely by recombinational events between SIVmnd-1 and SIVrcm-like viruses (Figure 3).

Recently, SIVdrl isolated from drills, which were wild-born but had been housed at North American or European zoological parks for a long period of time, were fully sequenced (25). SIVdrl is highly related to SIVmnd-2 with respect to genomic structure (Figure 3) and genetic distance (Figure 4A and 4B). The breakpoint of recombination is located at approximately the same

position in SIVmnd-2 and SIVdrl, suggesting that SIVmnd-2 and SIVdrl are descendants of the same recombinant event having the same origin. Because all SIVdrl isolates (from zoos, sanctuaries in Cameroon, the Rehabilitation and Breeding Center in Nigeria) have almost the same sequence, SIVdrl must have been in the drill population in the wild for a long time.

6. ORIGINS OF SIVmnd-1, SIVmnd-2 AND SIVdrl

As described above, SIVmnd-1 and SIVlhoest/SIVsun are highly related and considered to be in the same SIV lineage, however, their hosts belong to phylogenetically distant groups, indicating an ancient cross-species transmission between these two monkey genera. Beers *et al.* suggested that l'Hoeist monkeys are a natural reservoir of this virus lineage (14). The seroprevalence of SIV among the l'Hoeist monkey population in the wild was remarkably high (57%). This seroprevalence rate is similar to that observed in wild African green monkey populations, which are considered to be the natural reservoir of SIVagm. The genetic diversity observed among SIVlhoest isolates is approximately the same as that observed among SIVagm isolates from naturally infected-vervet monkeys, which are one of the sub-species of African green monkeys. Therefore, Beer *et al.* proposed that SIVlhoest is a natural reservoir of this virus lineage of SIVmnd-1/SIVlhoest/SIVsun. However, the habitat of the l'Hoeist monkey does not overlap with that of mandrill, suggesting that direct transmission of SIVlhoest from l'Hoeist monkey to mandrill is unlikely.

In contrast to the above-mentioned SIVlhoest origin, Harada *et al.* suggested the possibility that mandrill is a natural reservoir of this virus lineage for the following reason (23). The *env* gene of SIVmnd-2 is closely related to that of SIVmnd-1 (Figure 4B), indicating that these viruses

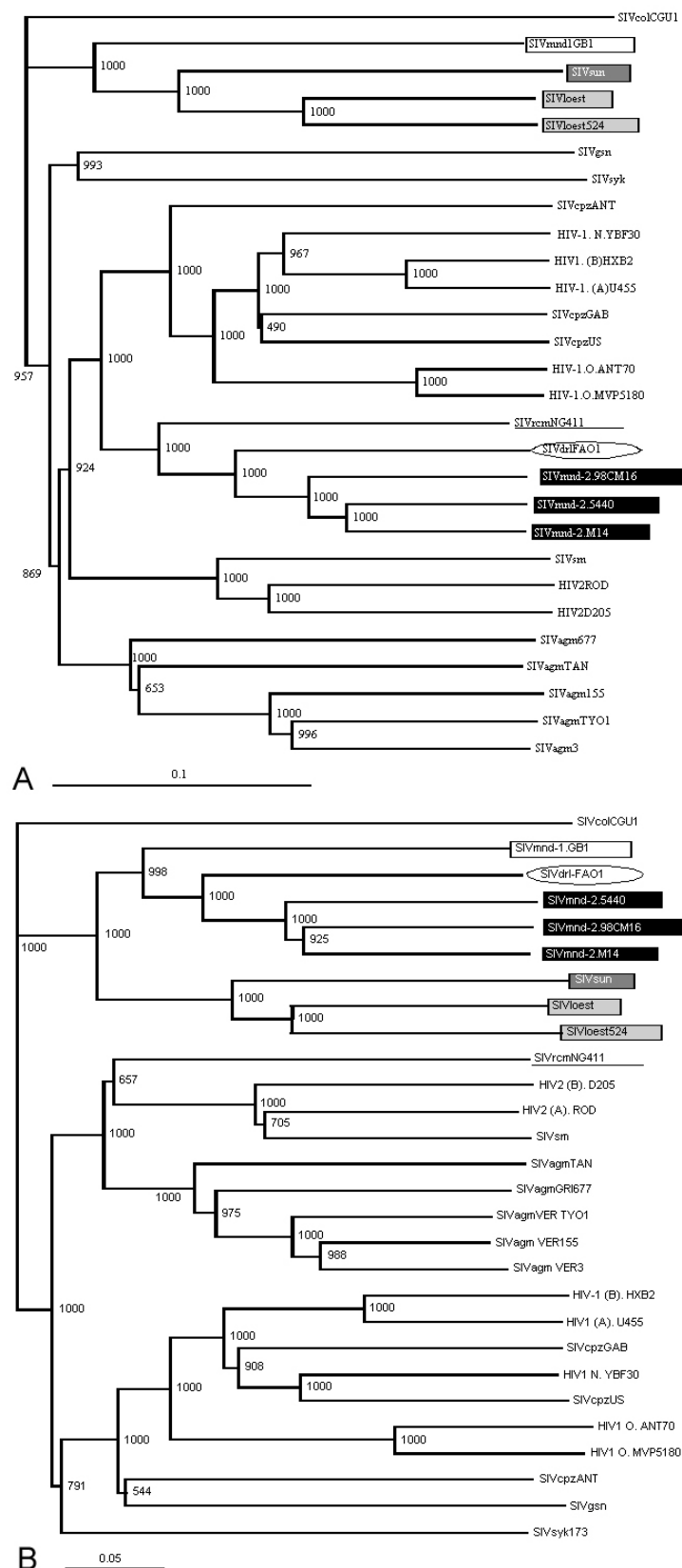


Figure 4. Phylogenetic trees of the primate lentiviruses. (A) constructed from the gag-pol ORFs sequences, and (B) constructed from env ORF sequences. Details are described in Figure 1.

have the same ancestor. However, the genetic diversity between SIVmnd-1 and SIVmnd-2 in the *env* region is greater than that between SIVlhoest and SIVsun, and greater than that among SIVlhoest isolates. In general, a genus having a high genetic diversity of SIV is assumed to be the original host of the virus lineage. Therefore, Harada *et al.* hypothesized that mandrill is an original host of this virus lineage. In both hypotheses, it is still unclear why SIVmnd-1 is found only in mandrills in the southern habitat. In any case, SIVmnd-1 has long been present and has greatly diverged in the mandrill population, even if mandrills acquired the virus from Cercopithecus monkeys.

How did mandrills and drills acquired SIVmnd-2 or SIVdrl? It is unlikely that the ancestors of mandrills and drills were infected with SIVmnd-2 and SIVdrl type virus, because SIVmnd-2 is present only in mandrills in their northern habitat (north of the Ogooue River in Gabon) (25). It seems unlikely that cross-species transmission occurred recently between mandrills and drills because the habitat of mandrills is adjacent to, but does not overlap, that of drills (Figure 1) (33). However, there was a report suggesting the existence of viral transmission between mandrills and drills. Hu *et al.* found one SIVmnd-2 strain that is closely related to SIVdrl, which raises the possibility of viral transmission between mandrills and drills (25).

Harada *et al.* hypothesized the following scenario to explain the evolution of SIVmnd-2 and SIVmnd-1 (23,37). At some time in the past, mandrills were infected with a virus belonging to the SIVmnd-1/SIVlhoest lineage. After this virus spread in the mandrill population, the mandrills carrying this virus in the northern habitat became superinfected with another type of SIV carrying the vpx gene, such as SIVrcm from the red-capped mangabey, whose habitat overlapped with the habitats of mandrills and drills (Figure 1). In this mandrill population, SIVmnd-1 acquired the 5' half of the genome including the vpx gene by recombination and resulted in SIVmnd-2, which remained in the mandrill population residing with northern habitat. The mosaic structure of SIVmnd-2 and SIVdrl probably resulted from recombination between SIVmnd-1 and SIVrcm or a SIVrcm-like virus (Figure 3), as is strongly suggested by the diversity plot analysis of these viruses (21,25). Further studies of wild primates that share the habitats of mandrills and drills are needed in effort to clarify the origin and evolution of SIV from *Mandrillus* genus.

7. POSSIBILITY OF ZOONOTIC TRANSMISSION OF SIV FROM MANDRILLS TO HUMANS

It is widely accepted that HIV-1 and HIV-2 resulted from cross-species transmission to human from chimpanzee and sooty mangabey, respectively (2,6,7,4). The possibility of zoonotic transmission of SIVmnd to humans can not be neglected. Transmission from mandrills to humans of another primate retrovirus, simian T-cell lymphotropic virus type 1 (STLV-1), the simian counterpart of human T-cell lymphotropic virus type 1 (HTLV-1), was suggested by close molecular and phylogenetic relationships between STLV-1 from mandrills

in Gabon and the Central African group of HTLV-1 strains obtained from pygmies in Cameroon and Central African Republic and from healthy carriers in Gabon (38).

High rates of SIV seropositivity among wild-caught mandrills (16.7%) (22) suggests the possible occurrence of direct contact between SIV-infected monkeys and humans. The contact may have occurred during the hunting or butchering of monkeys by humans. Moreover, mandrills are often kept as pet animals. Souquiere *et al.* reported that a Cameroonian HIV-infected patient showed higher serological reactivity to the V3 peptide of SIVmnd-1 than that of the HIV-1 or HIV-2, although SIVmnd-like virus was not detected in the patient (21). Further epidemiological surveillance and characterization of HIV in this area is needed to evaluate the extent of transmission of SIVs to humans.

8. CONCLUSION

SIVmnd from mandrill is now known to consist of two groups, SIVmnd-1 and SIVmnd-2. SIVmnd-1 from mandrills (*Mandrillus* genus) together with SIVlhoest and SIVsun from monkeys of the genus *Cercopithecus*, make one lineage. We now call this lineage the SIVmnd-1/l'hoest/sun lineage, indicating intergenus transmission. SIVmnd-2 and SIVdrl from drill (genus *Mandrillus*) are almost the same in their genomic structure and phylogenetic relationship with other SIVs. They also have a mosaic structure, acquired through recombination between SIVmnd-1 and SIVrcm (or a SIVrcm-like virus) having the vpx gene.

Interspecies (or intergenus) transmission shown in the SIVmnd-1/l'hoest/sun lineage and the recombination shown in SIVmnd-2/SIVdrl are unlikely to be recent events because of the difference in the present habitats of mandrills and drills. Virus diversification in a host species, interspecies transmission and recombination between SIVs have resulted in a highly complex SIV/HIV family. The origin and evolution of groups of SIV discussed in this article remain unclear. Further studies of the origin and evolution of SIVs in Central Africa are needed to clarify these groups and understand the complexity of HIV/SIV evolution. These studies may also help to prevent another virus from jumping from monkeys to humans.

9. ACKNOWLEDGEMENT

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