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Infection of a Yellow Baboon with Simian Immunodeficiency Virus from African Green Monkeys: Evidence for Cross-Species Transmission in the Wild

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Many African primates are known to be naturally infected with simian immunodeficiency viruses (SIVs), but only a fraction of these viruses has been molecularly characterized. One primate species for which only serological evidence of SIV infection has been reported is the yellow baboon (*Papio hamadryas cynocephalus*). Two wild-living baboons with strong SIV_{AGM} seroreactivity were previously identified in a Tanzanian national park where baboons and African green monkeys shared the same habitat (T. Kodama, D. P. Silva, M. D. Daniel, J. E. Phillips-Conroy, C. J. Jolly, J. Rogers, and R. C. Desrosiers, AIDS Res. Hum. Retroviruses 5:337–343, 1989). To determine the genetic identity of the viruses infecting these animals, we used PCR to examine SIV sequences directly in uncultured leukocyte DNA. Targeting two different, nonoverlapping genomic regions, we amplified and sequenced a 673-bp *gag* gene fragment and a 908-bp *env* gene fragment from one of the two baboons. Phylo-genetic analyses revealed that this baboon was infected with an SIV_{AGM} strain of the vervet subtype. These results provide the first direct evidence for simian-to-simian cross-species transmission of SIV in the wild.

As more and more primate lentiviruses are being discovered and molecularly characterized (12–14, 19, 23, 50, 51), there is increasing evidence that cross-species transmission has played a central role in their evolutionary history and has influenced their disease expression and in vivo pathogenicity (8, 24, 29, 38, 39, 47). For example, the two human immunodeficiency viruses, human immunodeficiency virus type 1 (HIV-1) and HIV-2, which are both highly pathogenic in humans (5), are each closely related at the genetic level to nonpathogenic simian immunodeficiency viruses (SIVs) infecting chimpanzees (SIV_{CPZ}) and sooty mangabeys (SIV_{SM}), respectively (21, 22). This, along with other virological and epidemiological data arguing for a simian origin of AIDS (13, 21, 22, 34, 42), supports the conclusion that HIV-1 and HIV-2 are the result of simian-to-human cross-species transmissions and represent zoonotic infections of humans (10, 38, 39, 47). Cross-species transmission has also been responsible for outbreaks of simian AIDS among primates in captivity (7, 25, 40). Inadvertent transmission of SIV_{SM} to four different species of captive macaques has resulted in the generation of SIV_{MAC} and an illness very similar to human AIDS (7, 25, 27, 40). Finally, there is circumstantial evidence for cross-species transmission of primate lentiviruses in the wild. Sequence analysis of SIV_{AGM} from West African green monkeys recently revealed a mosaic virus genome consistent with a recombination event between ancestors of viruses now found in other African green monkey species and sooty mangabeys (23). Taken together, these findings suggest that lentiviruses have crossed between primate species on several occasions in the past. However, direct examples of such cross-species transmissions, particularly between wild-ranging primates in their natural habitat, have not yet been reported.

Our understanding of the origins and evolution of the various primate lentiviruses is certainly incomplete, particularly since there are many more SIV infections than have been molecularly characterized (24). One of the primate species for which there is only serological evidence for SIV infection is the yellow baboon. In 1989, Kodama and coworkers conducted a seroepidemiological survey of 124 free-ranging yellow baboons (*Papio hamadryas cynocephalus*) from Mikumi National Park of central Tanzania and 155 hamadryas baboons (*P. hamadryas hamadryas*) and olive baboons (*P. hamadryas anubis*) from Awash National Park of Ethiopia (28). Using purified SIV_{AGM} (strain 385) and SIV_{MAC} (strain 239) antigens in an enzyme-linked immunosorbent assay (ELISA), these investigators identified two animals from the Mikumi baboon population harboring serum antibodies reactive with SIV_{AGM}, but not with SIV_{MAC}, antigens. Subsequent Western blot (immunoblot) analysis confirmed these results, demonstrating strong reaction of both sera with all major SIV_{AGM} proteins (including external and transmembrane envelope glycoproteins and the major viral core protein; see Fig. 1 in reference 28). No antibody-positive animals were identified in the Ethiopian cohort. Since yellow baboons are know to occasionally prey upon and eat smaller monkeys (16), the question of whether

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TABLE 1. Nested PCR primer pairs used to amplify SIV sequences from uncultured baboon leukocyte DNA[a]

Primer pair[b]	Nucleotide sequence	Location[c]	Fragment size (bp), genomic region
Outer pair			
gag A	5′-AAGTACCAAATTAAACATTTAATATGGGCAGG-3′	513–544	673, *gag* (p17/p28)
gag B	5′-CATTGTCTCTGATATGGCCAAATTTTCCACA-3′	1635–1666	
Inner pair			
gag C	5′-CACCAGGAAAAGAAAGTGAAAGACACAGAGGAAGC-3′	696–730	
gag D	5′-GCATTCTGAATGAGCAAAGATTCTGTCATCCA-3′	1404–1435	
Outer pair			
env A[d]	5′-GAAGCTTGTGATAAAACATATTGGGAT-3′	6415–6441	908, *env* (gp120/gp41)
env B[d]	5′-AGAGCTGTGACGCGGGCATTGAGG-3′	7566–7589	
Inner pair			
env C	5′-GTGCATTGTACAGGGTTAATGAATACAACAG-3′	6544–6574	
env D	5′-TTCTTCTGCTGCTGCAGTATCCCAGCAAG-3′	7474–7502	

[a] Reaction conditions were 40 cycles of 1 min at 94°C, 1 min at 55°C, and 1 min at 72°C.
[b] Primer pairs were designed according to SIV_{AGM} consensus sequences (23).
[c] Sequences are numbered according to the published sequence of SIV_{AGM} TYO-1 (11).
[d] Previously published primer pair (23).

the two seropositive animals had acquired their SIV infection by cross-species transmission from naturally infected African green monkeys living in the same habitat was raised (28). Here, we report attempts to characterize the genetic identities of these baboon viruses.

The two seropositive yellow baboons (termed 2006 and 2010) were adult (parous) females belonging to a single social group. Both appeared healthy at the time of evaluation, and animal 2010 carried a seemingly healthy infant. The animals were trapped in 1985 as described elsewhere (45), and blood was drawn into Vacutainers containing anticoagulant. Within 8 h of collection, blood was centrifuged on-site to separate plasma, erythrocyte, and leukocyte (buffy coat) fractions. These were frozen in liquid nitrogen and transported to the United States (because blood samples were obtained under field conditions, total leukocyte counts and differentials were not determined and cells were not viably frozen for subsequent virus isolation studies). In the fall of 1986, DNA was extracted from the leukocyte preparations for studies of baboon population genetics (45). Importantly, this was done by an investigator (J. Rogers) who had never worked with HIV- or SIV-infected specimens or performed molecular studies on HIV or SIV isolates. In 1994, aliquots of baboon leukocyte DNA (which had been stored at 4°C) were shipped under code to the University of Alabama at Birmingham for PCR amplification of SIV sequences. In addition, plasma samples from the two seropositive baboons were available for reverse transcriptase PCR analyses.

Leukocyte DNA preparations from 10 baboons were analyzed by nested PCR techniques, and primer pairs were designed according to SIV_{AGM} consensus sequences (Table 1). These included samples from the two animals with strong SIV_{AGM} seroreactivity (2006 and 2010 [28]), from two additional animals with borderline SIV_{AGM} seroreactivity (5005 and 5003 [28]), and from six animals with no detectable antibodies (3115, 3133, IK01, 5016, 1006, and 1016). Two vervet isolates from Kenya (termed SIV_{AGM}ver266 and SIV_{AGM}ver385 [32]) served as positive controls (vervet, grivet, tantalus, and sabaeus monkeys represent the four species of African green monkeys, all of which are infected with SIV_{AGM} in the wild [2, 3, 20, 36]). Figure 1 depicts the two genomic regions targeted for PCR amplification: a 908-bp *env* fragment chosen to allow comparison with previously reported SIV_{AGM} strains (23) and a 673-bp *gag* fragment selected to obtain additional sequences for more comprehensive phylogenetic analyses. All amplification reactions were performed in 100 μl containing 10 mM Tris HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.01% (wt/vol) gelatin, 200 μM deoxynucleotide triphosphates, 20 pmol of each primer, and 2.5 U of *Taq* polymerase, as well as 1 to 2 μg of leukocyte DNA. By using primer pairs and conditions outlined in Table 1, viral sequences were amplified only from leukocyte DNA of animal 2010. Gel electrophoresis revealed *gag* and *env* fragments of the expected sizes (according to SIV_{AGM} consensus sequences), although not every DNA aliquot yielded positive results. By contrast, no viral sequences were amplified from leukocyte DNA of animal 2006, despite repeated attempts, redesigned primer pairs, and variation of amplification conditions (amplification products observed under relaxed PCR conditions were found to contain sequences of nonviral origin [data not shown]). Also negative were attempts to amplify sequences from the plasma of 2006 and 2010 by using the same primer pairs and the highly sensitive reverse transcriptase PCR technique (44). Finally, no viral sequences were amplified from leukocyte DNAs of baboons 5003 and 5005 (with low ELISA seroreactivity) or from the six control animals.

gag and *env* amplification products from baboon 2010 were subcloned into pCRII by T/A overhang, and one recombinant clone for each region was sequenced by the dideoxynucleotide chain termination method. This was also done for *env* amplification products from SIV_{AGM}ver266 and SIV_{AGM}ver385. All clones were found to contain uninterrupted open reading frames. The potential translation products of these sequences were aligned with those from other available SIV_{AGM} strains (Fig. 2; *gag* protein sequences from sabaeus viruses were excluded because they are known to be recombinant [23]). In the amplified *env* region, the baboon virus exhibited a distribution of conserved and hypervariable regions that was very

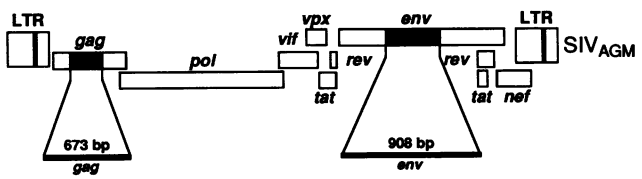

FIG. 1. Genomic regions targeted for PCR amplification of uncultured baboon leukocyte DNA. Primer pairs and PCR conditions are outlined in Table 1. LTR, long terminal repeat.

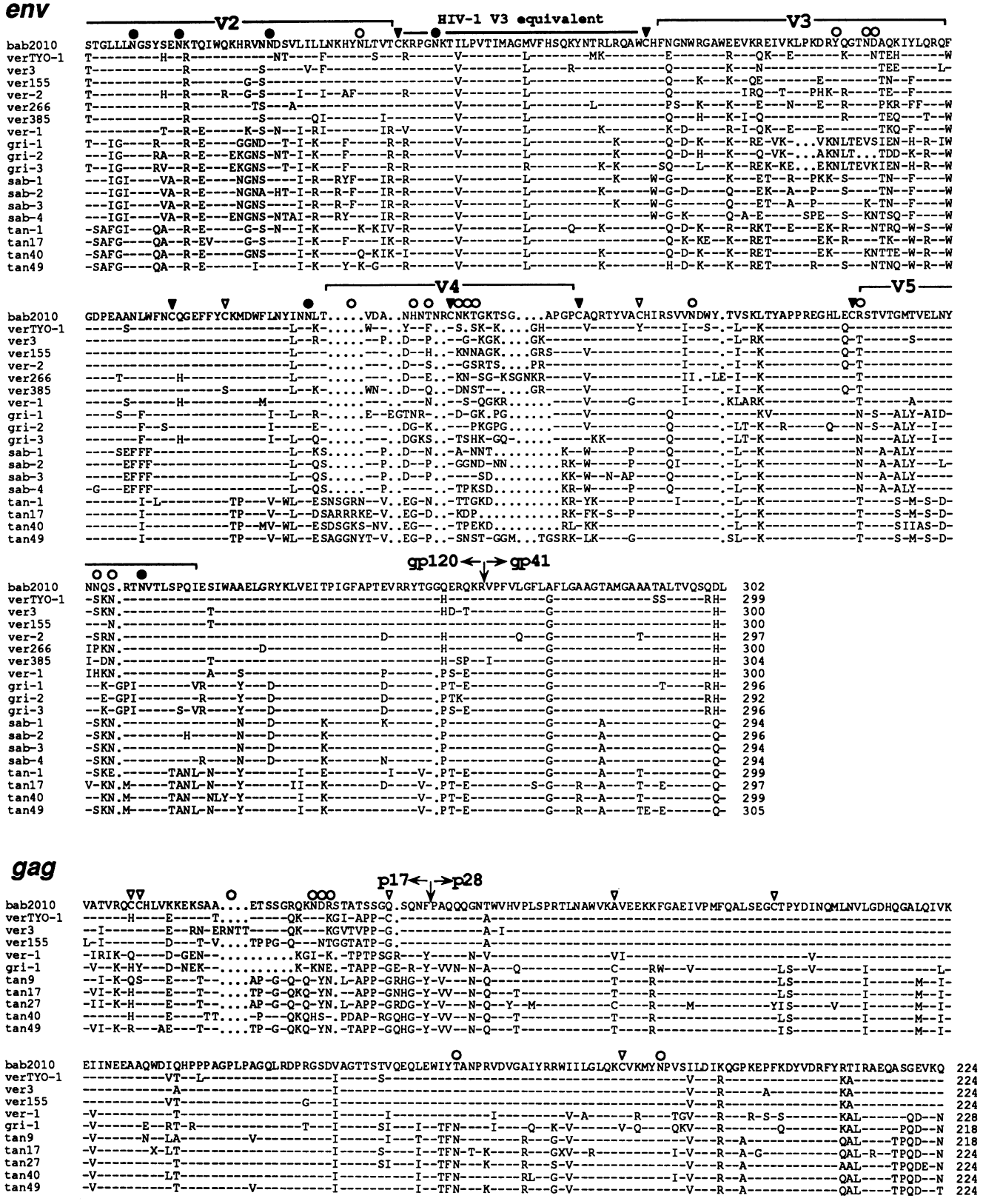
env
V2
HIV-1 V3 equivalent
V3
V4
V5
gp120
gp41
gag
p17
p28
bab2010
verTYO-1
ver3
ver155
ver-2
ver266
ver385
ver-1
gri-1
gri-2
gri-3
sab-1
sab-2
sab-3
sab-4
tan-1
tan17
tan40
tan49
tan9
tan27

FIG. 2. Alignment of partial baboon *env* and *gag* protein sequences with corresponding sequences from multiple SIV_{AGM} isolates. PCR-derived *env* and *gag* nucleotide sequences from baboon 2010 were translated and aligned with previously reported SIV_{AGM} sequences in the same genomic regions (23, 37). Dashes indicate sequence identity with the baboon reference sequences, while dots represent gaps introduced to optimize the alignments. X's indicate in-frame stop codons. Triangles and circles above the baboon sequence indicate cysteine and N-linked glycosylation sites, respectively (solid signs indicate sequence identity, while open signs indicate sequence variation). V2, V3, V4, and V5 designate hypervariable SIV_{AGM} *env* domains as previously described (36). Also indicated are a highly conserved region corresponding to the HIV-1 V3 loop and the putative envelope precursor cleavage site. The p17/p28 *gag* precursor cleavage site was determined by comparison with HIV-1 and HIV-2 (49). All SIV_{AGM} sequences have been published (37) except for envelope sequences for ver266 and ver385.

similar to that previously reported for vervet, grivet, sabaeus, and tantalus viruses (23). All cysteine residues present in SIV_{AGM} strains were also present in the baboon *env* sequence, and very little sequence variability was observed in regions corresponding to HIV-1 *env* and *gag* domains of known function, including the envelope precursor cleavage site, the putative fusion peptide at the N terminus of gp41, and the putative p17/p28 cleavage site in *gag* (35, 49). From the alignments (Fig. 2), it was also evident that the baboon sequences were more similar to those of SIV_{AGM} from vervet monkeys than to those from the other African green monkey species. In pairwise comparisons of the *env* region, the baboon virus differed from vervet viruses at around 18% of amino acid residues but differed from grivet, sabaeus, and tantalus viruses at about 32%; similar values were observed for the *gag* region.

To elucidate the evolutionary relationship of the baboon virus (termed bab2010 in Fig. 2 to 4) to the various SIV_{AGM} subtypes, phylogenetic trees were constructed from the aligned protein sequences depicted in Fig. 2. As reported previously (3, 20, 23, 36), SIV_{AGM} isolates were found to cluster (with very high bootstrap repeatability) in a host species-dependent manner (Fig. 3). From the sequence alignments, we expected the baboon virus to be more closely related to viruses from vervets than to those from other African green monkey species. This, in fact, was the case in both *env* and *gag* trees, in which bab2010 fell within the vervet cluster (Fig. 3). Among the vervet viruses, one isolate (ver-1) clearly diverged before the others, but the radiation of the other isolates was essentially star-like with very short internal branches separating the successive nodes and only small bootstrap values at each node. The results for *env* (Fig. 3A) and *gag* (Fig. 3B) regions were very similar, although there were fewer *gag* sequences available for vervet and grivet viruses. These protein sequence-derived trees were drawn as unrooted, because although the root appears to be near the central node from which the four different SIV_{AGM} subtypes radiate, it is not clear (from analyses using various outgroups) exactly where this most ancestral point lies.

To investigate the relationship of bab2010 to the vervet viruses in greater detail, DNA sequences were compared. The method of Li et al. (30, 31) was used to separately estimate the numbers of synonymous (K_S) and nonsynonymous (K_A) nucleotide substitutions per site in pairwise comparisons. These distance values for silent sites were high: for both genes, K_S estimates involving ver-1 were all greater than 1 synonymous substitution per site, indicating that they are nearing saturation. Therefore, K_A values, which ranged from 0.042 to 0.113

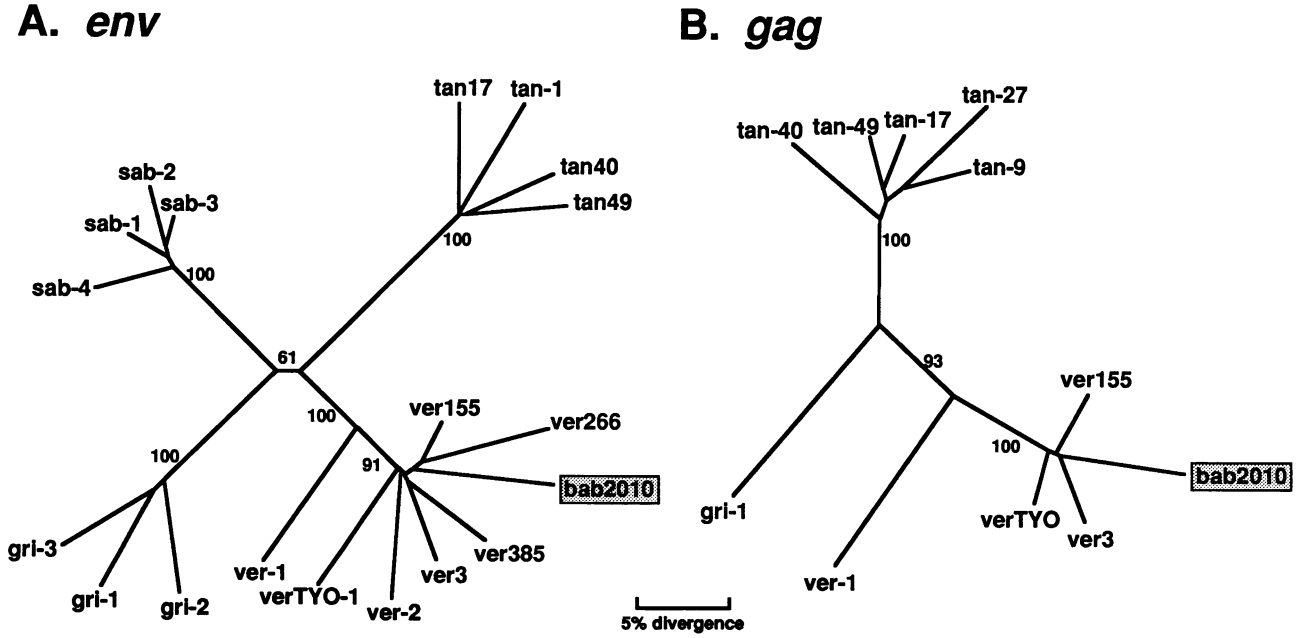

FIG. 3. Phylogenetic relationship of the bab2010 virus to SIV_{AGM}s from vervet, grivet, sabaeus, and tantalus monkeys, based on *env* (A) and *gag* (B) protein sequences (Fig. 2). Branch lengths are drawn to scale (the bar indicates 0.05 amino acid substitutions per site), and the numbers near internal nodes indicate the percentage of bootstraps (out of 1,000) in which various clades were found (values under 60% are omitted). Unrooted trees were constructed by the neighbor-joining method (46) applied to pairwise sequence distances estimated by Kimura's empirical method (26). Sites at which there was a gap in any sequence in the alignment (including the entire V4 loop of the *env* protein) were excluded from the computation; 272 and 212 sites were compared in the *env* and *gag* proteins, respectively. All methods were implemented with CLUSTAL V (18).

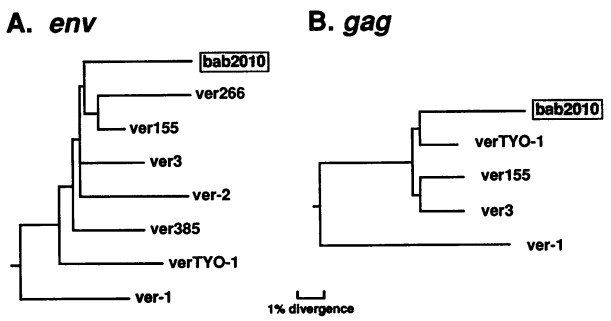

FIG. 4. Phylogenetic relationship of the bab2010 virus to SIV_{AGM} from vervet monkeys, based on *env* (A) and *gag* (B) DNA sequences. Branch lengths are drawn to scale (the bar indicates 0.01 nonsynonymous nucleotide substitutions per site). Unrooted trees were constructed by the neighbor-joining method (46) applied to pairwise sequence distances estimated by the method of Li et al. (30, 31), and the root was then placed on the branch to ver-1 according to the data shown in Fig. 3. Sites at which there was a gap in any sequence in the alignment (including the sequence encoding the central region of the V4 loop in *env*) were excluded from the computation; 287 and 217 codons were compared in *env* and *gag*, respectively.

(for *env*) and 0.034 to 0.159 (for *gag*), were used to derive phylogenetic trees (Fig. 4). These trees were rooted by placing ver-1 as the outgroup, according to the phylogenies in Fig. 3. Even at this more detailed level, little phylogenetic structure was apparent within the major vervet virus clade, and bab2010 was not significantly more closely related to any particular vervet isolate so far characterized (Fig. 4).

The phylogenetic results depicted in Fig. 3 and 4 indicate that baboon 2010 was infected with an SIV_{AGM} of the vervet subtype and thus provide the first direct evidence for simian-to-simian cross-species transmission of SIV in the wild. This is in full agreement with the finding of high-titer SIV_{AGM} (vervet)-specific antibodies in the same animal (1, 28). In the wild, African green monkeys exhibit a high frequency of SIV_{AGM} infection, i.e., seroprevalence rates of 20 to 50% (2, 3, 17, 20, 33, 36, 41, 43). Moreover, African green monkeys are numerous throughout sub-Saharan Africa, and the four different species reside in well-defined and only partially overlapping habitats (3, 36). Vervet monkeys are the most widely distributed and range from East to South Africa. Importantly, they constitute the African green monkey population present in Mikumi National Park. This suggests that transmission of SIV_{AGM} to baboon 2010 may have occurred locally. Indeed, one particular group of vervet monkeys was seen on a regular basis in the vicinity of the baboon social group to which both 2010 and 2006 belonged. Moreover, both vervets and baboons lived close to a small village near the park headquarters and were known to frequently search for food in the vicinity of the ranger station. It is thus possible that some form of physical interaction (most likely biting or predation) occurred in this context and that baboon 2010 itself was the animal involved in the cross-species transmission event.

The rate of evolution of SIV_{AGM} has not been quantified, and so it is not possible to estimate dates for the divergence points in the evolutionary trees. We (2, 3, 23) and others (20, 36) have argued that the species-specific clustering of SIV_{AGM} isolates reflects a long-standing virus-host relationship and that African green monkeys have been infected with SIV_{AGM} for a long period of time, possibly even before their speciation and divergence from a common ancestor (2, 3, 23). This, in turn, implies that the divergence of the four SIV_{AGM} subtypes occurred relatively anciently. However, even if the time of divergence of the lineages leading to bab2010 and the vervet viruses were known, this would still not allow us to discern at what point along the branch to bab2010 the cross-species transmission occurred. It might be anticipated that the rate of sequence evolution would accelerate subsequent to the entrance of the virus into a new host, because the new environment might exert different selection pressures. The bab2010 branch in the *gag* tree (Fig. 4B) is considerably longer than those for the three most closely related vervet viruses, indicating a higher evolutionary rate. However, the same phenomenon is not seen in the *env* tree (Fig. 4A), even though it seems likely that selectively driven sequence changes following cross-species transmission would be more apparent in the *env* gene than in the *gag* gene. In fact, in the *env* tree, there is considerable variation in branch lengths among the vervet viruses in general (e.g., contrast the branch lengths to ver155 and ver266). Therefore, we hesitate to make any inference from the branch lengths in Fig. 4B. If the cross-species transmission had indeed occurred very recently, i.e., if baboon 2010 was the animal infected by a vervet, then there may have been insufficient time for any evolutionary rate change to become apparent.

Although we failed to amplify SIV sequences from baboon 2006, it is likely (on the basis of the serological and epidemiological results discussed above) that this animal was also infected with an SIV_{AGM}-like virus. There are several factors which might account for why these PCR attempts remained unsuccessful, including primer mismatch, infection with a more divergent SIV_{AGM} strain, and suboptimal PCR conditions. The most likely explanation, however, is low virus burden. First, PCR was performed on total leukocyte DNA, which means that the target DNA was diluted by at least a factor of 3 (lymphocytes and monocytes, which are the presumed target cells for SIV infection in the baboon, represent only about 30% of the total leukocyte population [15]). Second, even in the case of baboon 2010, not all DNA aliquots yielded a positive amplification, suggesting limited amounts of SIV DNA and thus limited numbers of infected target cells. Third, reverse transcriptase PCR with plasma samples of both seropositive animals was negative, again suggesting a low viral load. These findings, together with the lack of any signs of disease, are consistent with a low copy number of proviral sequences in the peripheral blood of both animals. At this point, it should also be emphasized that contamination cannot explain the positive PCR results obtained for baboon 2010. All DNA samples were analyzed under code, and only leukocyte DNA from the one seropositive animal yielded a positive amplification product. More importantly, all SIV_{AGM} strains ever analyzed at (or shipped to) the University of Alabama at Birmingham have been sequenced in the same *env* region. Thus, any new virus whose sequences fail to match this collection has to represent an authentic SIV strain.

Despite suggestions of low viral load, the finding of high-titer SIV_{AGM}-specific antibodies and SIV_{AGM}-specific sequences in peripheral blood cells of animal 2010 indicates that this baboon virus was replicating in vivo. In current nomenclature, SIV isolates are given a subscript to denote their species of origin; thus, this virus could be called SIV_{BAB}. However, this might be taken to imply that the virus is spreading in its new host, for which there is currently no evidence. In fact, the low seroprevalence of SIV in the free-ranging baboon populations (28, 41) and the lack of similar SIV infections in captive baboons (1) suggest that transmission between animals is either extremely rare or nonexistent. But even if future studies were to document virus passage among baboons, the name

SIV_{BAB} could still be problematic. Captive baboons can be experimentally infected with a variety of different lentiviruses, including SIV-HIV chimeras (1) and HIV-2 (6). It is thus possible that free-ranging baboons are similarly susceptible to additional lentiviruses, particularly other strains of SIV_{AGM}, like those from grivet monkeys. In this context, it should be mentioned that a recent survey of 45 baboons from Ethiopia identified 16 animals with strong Western blot reactivity to the core protein of SIV_{MNE} (a virus closely related to SIV_{MAC}), which could indicate infection with such viruses (4). If future studies were to find that some baboons harbor additional strains of SIV, such viruses would then also fall under the classification of SIV_{BAB}. This would lead to the confusion of having similarly named viruses of quite different transmission origins and, accordingly, different phylogenetic relationships. Thus, unless more information becomes available concerning the prevalence, transmission patterns, and genetic identity of SIVs naturally infecting baboons, we suggest that the current virus be named SIV_{AGM}bab2010.

In summary, we present here molecular evidence for cross-species transmission of a primate lentivirus in the wild. Although the time points of transmission and the clinical consequences remain unknown, this finding adds to the already complex picture of primate lentiviral evolution. Guenons, including African green monkeys and other members of the genus *Cercopithecus*, are among the most numerous and the most geographically dispersed primates in Africa. They are also the most commonly SIV infected and thus represent the largest natural reservoir for primate lentiviruses (24). Indeed, of the five known major lineages of primate lentiviruses (29, 47), two (SIV_{AGM} and SIV_{SYK}) are naturally infecting with respect to *Cercopithecus* species. The natural hosts of two others, SIV_{CPZ} and SIV_{MND}, are much less clear, primarily because only very few infected chimpanzees and mandrills have been identified in the wild (9, 42). In addition, African green monkeys appear to have been infected with SIV_{AGM} for very long periods of time, and the mosaic genome of SIV_{AGM} from West African sabaeus monkeys provides evidence for an ancient recombination event involving predecessors of viruses currently infecting African green monkeys and sooty mangabeys (23). Finally, SIV_{AGM} has recently been isolated from a captive-born white-crowned mangabey monkey (*Cercocebus torquatus lunulatus*) housed at a Kenyan primate research center, suggesting SIV_{AGM} transmission to still another primate species in captivity (48). Taken together, these findings suggest that monkeys of the genus *Cercopithecus* may have represented a main source of infection for other African primate species in the past (23, 47). Our finding here that baboons can be infected with SIV_{AGM} from vervet monkeys is at the very least consistent with this hypothesis and adds to a growing picture of multiple cross-species transmissions of primate lentiviruses, with monkeys of the genus *Cercopithecus* as a potential central reservoir.

Nucleotide sequence accession numbers. GenBank accession numbers for the baboon virus are U10899 for *gag*2010 and U10897 for *env*2010. Envelope sequences for ver266 and ver385 are available under accession numbers U10896 and U10898, respectively.

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