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Evidence for continuing cross-species transmission of SIVsmm to humans: characterization of a new HIV-2 lineage in rural Côte d'Ivoire

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Abstract

HIV types 1 and 2 (HIV-1 and HIV-2) are the result of multiple cross-species transmissions of their simian counterparts (SIVs) to humans. We studied whether new SIVs lineages have been transmitted to humans in rural Côte d'Ivoire and identified a novel HIV-2 variant (HIV-2-07IC-TNP03) not related to any of the previously defined HIV-2 groups. This finding shows that sooty mangabey viruses continue to be transmitted to humans, causing new zoonotic outbreaks.

Simian immunodeficiency viruses (SIVs) from chimpanzees and gorillas from west central Africa have crossed the species barrier on at least four occasions leading to HIV-1 group M, N, O and P. HIV-2 group A–H viruses result from eight independent transmissions of SIVsmm strains naturally infecting sooty mangabeys in West Africa [1]. Exposure to blood or tissues from infected animals, through hunting and butchering of nonhuman primate (NHP) bushmeat or bites and other injuries caused by pets represent the most plausible source for human infection [2]. Recent studies showed ongoing exposure of humans to a wide variety of SIVs, and the description in 2009 of HIV-1 group P in two Cameroonian patients illustrates that our knowledge on HIV diversity and possible cross-species transmissions is still incomplete [3–7]. To explore other transmissions to humans, we examined to what extent SIV infections could be detected in humans in rural villages that border the Tai National Park (TNP) in the southwest of Côte d'Ivoire, where NHP bushmeat is still an important resource [8]. High levels of SIV infections have previously been shown

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Conflicts of interest

There are no conflicts of interest.

GenBank Accession numbers: The nucleotide sequences from the present study were deposited under the accession numbers [GenBank: KC693496 -KC693505].

Author's contributions: A.A. performed all molecular, phylogenetic and diversity analyses with the contribution of A.E. and S.L. F.L. and M.P. designed the study. F.L., C.A. and S.C. initiated, supervised and coordinated studies in Côte d'Ivoire. B.H., H.L. and Y.L. contributed materials and reference sequences for analysis. A.A., B.H., E.D., F.L., S.C., and M.P. wrote the article.

in sooty mangabeys as well as western red and olive colobus in the TNP [9–12] and phylogenetic analyses revealed that some HIV-2 groups clustered with SIVsmm strains from this region [1,12].

We studied blood samples collected between 2006 and 2007 from individuals living in 18 villages bordering the TNP and in which HTLV-1 strains closely related to their local simian counterparts (STLV-1) have been documented [13]. All participants signed informed consent forms and completed a questionnaire on exposure to NHP via activities such as hunting, butchering or meat consumption. Samples ($n = 764$) were screened with a previously described highly sensitive in-house Luminex Multiple Analyte Profiling (xMAP) assay using peptides representing the major HIV and SIV lineages, which has been shown to detect even genetically divergent SIVs [3]. Fifty-five samples reacted with HIV-1/SIVcpz/SIVgor peptides and 50 were confirmed to harbor HIV-1 specific antibodies in the Inno-LIA HIV confirmatory assay. The remaining five were Inno-LIA negative ($n = 2$), indeterminate ($n = 2$) or not tested ($n = 1$; no serum left). Six samples reacted with HIV-2/SIVsmm peptides and were all confirmed to be HIV-2 positive using the same confirmatory assay. Finally, three samples reacted repeatedly and exclusively with SIV peptides representing SIVcol ($n = 1$), SIVmnd2 ($n = 1$) and SIVwrc/SIVmnd2 ($n = 1$).

We attempted molecular characterization of all HIV-2/SIVsmm and SIV antibody reactive samples. HIV-1 samples were not analyzed further because NHP in this area are not infected with HIV-1 related viruses. Both universal and lineage-specific PCR primers [3,14] yielded negative results for the three samples that exclusively reacted with SIV peptides. The universal *pol* primers [14] amplified viral sequences from three HIV-2 samples for which DNA was available. To characterize these new HIV-2 strains further, we amplified partial *gag* (800 bp) and *env* (gp41, 480 bp) fragments for which the highest number of SIVsmm sequences and representatives of all HIV-2 groups are available [12]. Phylogenetic trees derived from Gag (Fig. 1a) and Env (gp41) (Fig. 1b) protein sequences revealed that two strains, 07IC-TNP01 and 06IC-TNP02, clustered with HIV-2 group A and B viruses, respectively. However, the third HIV-2 strain (07IC-TNP03) did not fall into any of the previously defined HIV-2 groups. In both genomic regions, SIVsmm from sooty mangabeys from TNP seemed to represent the closest relatives of 07IC-TNP03. These topologies were observed with maximum likelihood (Fig. 1) and Bayesian (not shown) methods.

We next sequenced the entire proviral genome of 07IC-TNP03 by amplifying overlapping subgenomic fragments. In addition, we also sequenced the genome of a new SIVsmm (SIVsmm753) strain, obtained from a wild-living sooty mangabey found dead in TNP in the course of a long-term wildlife mortality monitoring program [15]. Phylogenetic trees analysis using partial *pol* sequences (RT and integrase) of HIV-2 C, D, E and F and *gp41-nef* sequences for HIV-2 D, confirmed that the new strain was different from these groups (SDC1 A-C, <http://links.lww.com/QAD/A378>). Similarity plots (SDC2 A, <http://links.lww.com/QAD/A379>) and bootscan analyses (data not shown) on full-length nucleotide sequences revealed that HIV-2–07IC-TNP03 was distinct from the epidemic HIV-2 A and B strains over its entire genome. Given the absence of full-length genome sequences for HIV-2 group C, D, E and F and the paucity of full-length SIVsmm sequences for comparison, it is difficult to determine the exact evolutionary history of the new HIV-2 strain. 07IC-TNP03 has a complex genetic structure, with alternating fragments not related to any of the known HIV-2 and SIVsmm lineages [*gag*, half of *pol* (3'end) accessory genes, part of *env* and *nef*], and small regions more closely related to HIV-2 G, H or SIVsmm, although these relationships were not always supported by high bootstrap values. The genetic distance between 07IC-TNP03 and members of HIV-2 groups G and H was higher than HIV-1 groups A and B intragroup distances (SDC2 B, <http://links.lww.com/QAD/A379>). This mirrors observations for partial *gag*, *pol* and *env* regions of HIV-2 groups H and

C, which are considered two independent cross-species transmissions [16]. HIV-2 G and H stains are rare and have only been identified in single individuals from Côte d'Ivoire infected in the early 90 s or before [16], suggesting inefficient spread or dead-end infections, thus limiting the chances to recombine with other HIV-2 strains. In contrast, high-genetic diversity and recombination rates have been observed for SIVsmm strains from wild and captive mangabeys [4,12,17]. Therefore, it is most likely that the new virus, 07IC-TNP03, emerged following an independent transmission event of a recombinant SIVsmm strain.

The new HIV-2 strain was identified in an 8-year-old boy. Consumption of primate bushmeat was reported for the boy. It is thus possible that this boy was exposed through contact with an infected monkey and/or helped with preparing bushmeat. Although vertical transmission of HIV-2 is exceedingly rare, the possibility that the boy acquired his infection from his mother cannot formally be excluded. We do not know whether his mother was amongst the participants due to the anonymous nature of the study. Additional studies are necessary to determine whether this new HIV-2 group represents an isolated case or has spread in the local population. Our study clearly shows that our knowledge on HIV diversity is far from complete. The finding of this ninth HIV-2 lineage emphasizes the need to elucidate the molecular and biological factors associated with the emergence of SIVsmm strains in humans.

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Ethical considerations: Permission for the study was obtained from the Institut Pasteur (Abidjan, Côte d'Ivoire) and the Ministère de la Santé of Côte d'Ivoire, representing the ethics commission (Ref #: 0428/MDCS/CAB-1/kss). The study was performed according to the Declaration of Helsinki, 'Ethical Principles for Medical Research Involving Human Subjects,' as last revised by the World Medical Association. Informed consent forms were signed by all participants after the scope of the study was explained in the local language.

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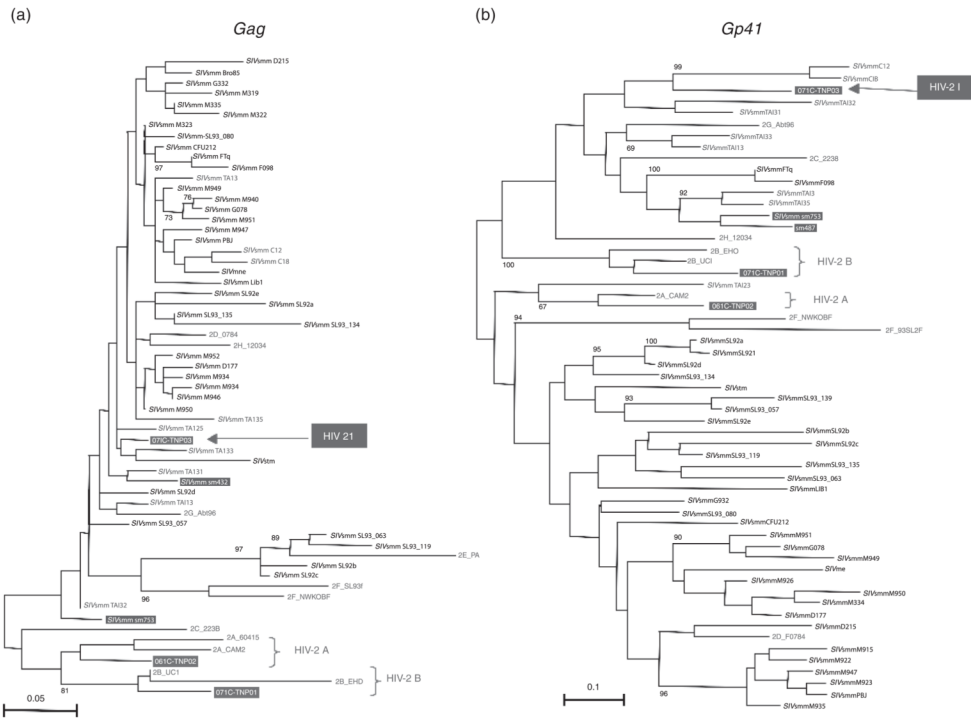


Fig. 1. Phylogenetic relationships of the new HIV-2 strains (HIV-2-06IC-TNP02, HIV-2-07IC-TNP01 and HIV-2-07IC-TNP03) and the new SIVsmm753 to previously characterized SIVsmm and HIV-2 strains in gag (180 amino acids) (a) and env (gp41, 132 amino acids) (b) regions SIVsmm from Côte d’Ivoire is highlighted in black, SIVsmm from Liberia and Sierra Leone in blue and SIVsmm from captive mangabeys in the US in italic font. HIV-2 strains are highlighted in red. The new HIV-2 and SIVsmm strains from this study are boxed in red and blue, respectively. The trees were inferred with maximum likelihood (ML) methods using PHYML [18]. Appropriate amino acids substitution models were selected for each data set using MEGA5. Asterisks on branches represent bootstrap values more than 70% from 1000 pseudo-replicates. Scale bars represent substitutions per site. Trees were also inferred with Bayesian methods and confirmed topologies of maximum likelihood methods (data not shown).