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Island Biogeography Reveals the Deep History of SIV

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The ubiquity of simian immunodeficiency virus (SIV) in African nonhuman primates and the discovery of ancient endogenous lentiviruses (1) suggest that SIV is very old. Conversely, molecular clock methods calibrated by using modern sequences indicate a time scale of just centuries (2, 3). To resolve this conundrum, we sampled monkeys on Bioko Island, Equatorial Guinea, which was isolated from Africa as sea levels rose 10,000 to 12,000 years before the present (yr B.P.) (fig. S1) (4). Bushmeat specimens were screened by SIV serological tests and reverse transcription polymerase chain reaction (RT-PCR) and sequencing of conserved viral *pol* gene fragments [472 to 633 base pairs (bp)], followed by phylogenetic analyses.

Of 79 individuals from six species, we detected 22 sequence-confirmed SIV positives in four species, with a prevalence of 22 to 33% (table S1). Phylogenetic analyses (Fig. 1 and figs. S2 and S3) revealed previously uncharacterized species-specific SIV lineages in *Cercopithecus erythrotis erythrotis* (SIVreg-Bioko), *Colobus satanas satanas* (SIVbcl-Bioko), and *Cercopithecus preussi insularis* (SIVprg-Bioko). The fourth, the Bioko drill, *Mandrillus leucophaeus poensis*, is infected with SIVdrl-Bioko and has a mainland conspecific

counterpart, *Mandrillus leucophaeus leucophaeus*, infected with SIVdrl (fig. S1). These viruses form a monophyletic group with SIVmnd-2 from the mandrill, the closest relative of the drill (Fig. 1).

Each Bioko SIV lineage shares ancestry with a mainland virus found in a monkey of the same genus (Fig. 1). Barring the possibility that humans introduced multiple species-specific SIV lineages to the wild monkey populations of Bioko, the mainland and island SIVdrl variants must have been evolving independently since Bioko became isolated ~10,000 yr B.P., and perhaps longer given the high levels of genetic diversity seen within local SIV populations. We used the SIVdrl/SIVdrl-Bioko ancestor dated ~10,000 yr B.P. to calibrate our molecular clock phylogenetic analysis. From amino acid sequences, the mean estimate of the time of the most recent common ancestor (TMRCA) of SIV was 76,794 yr B.P. (95% highest probability density from 32,821 to 132,780). This is older than TMRCA estimates from nucleotides [using all three codon positions, 49,129 (29,078 to 71,268); with third positions only, 28,077 (19,184 to 37,305)]. This pattern suggests that the more rapidly evolving the character, the more biased the dating estimate becomes toward the present. Perhaps both the nu-

cleotide and the amino acid analyses run up against stringent evolutionary constraints and saturation problems (fig. S4), which makes correcting for repeated substitutions at the same site difficult.

The four Bioko SIV lineages are genetically diverse and phylogenetically connected with those found across continental Africa, which leaves little doubt that the age of SIV is much greater than previously inferred (3). Molecular clock analyses of RNA viruses produce plausible, often unassailable, inferences over the short term, but our results raise the possibility of fundamental problems at deeper times scales for SIV and perhaps other viruses. Although we accept current estimates of HIV-1 and HIV-2 TMRCA of <100 yr B.P., implying short-term evolutionary rates ~125 times faster than our (conservative) Bioko-calibrated SIV estimate, the possibility of a deeper-than-assumed history for HIV may be worth investigating.

SIVs have been present in African primates for more than 32,000 years, which suggests that humans may have had sporadic encounters with these viruses for millennia. Changes in human behavior or ecology were likely necessary before nascent HIVs could become established (5, 6). Although evidence of codivergence between SIV and its natural hosts is still lacking, our results are suggestive that generally low pathogenicity of SIV is likely a consequence of long-term host-virus coevolution. A similar accommodation between HIV and humans should therefore not be expected to arise soon.

References and Notes

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Supporting Online Material

www.sciencemag.org/cgi/content/full/329/5998/1487/DC1

Materials and Methods

Figs. S1 to S6

Table S1

References

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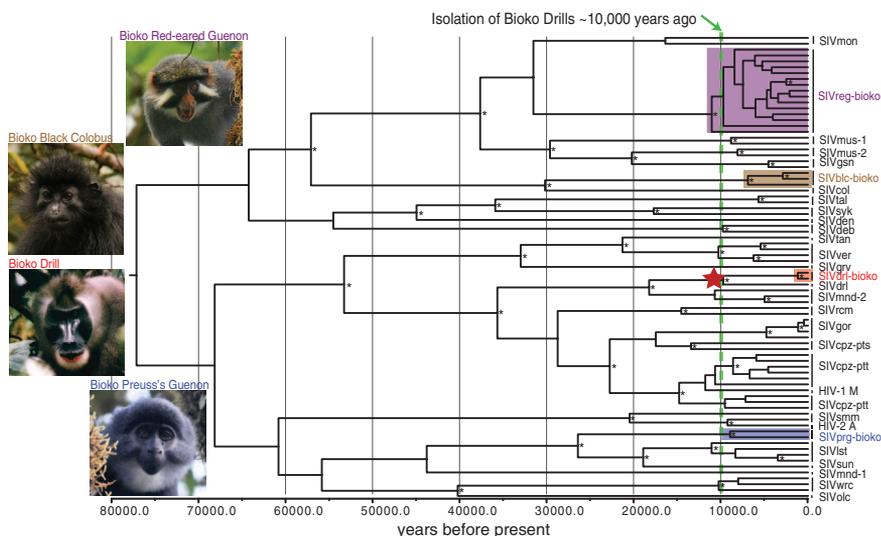


Fig. 1. The biogeographical calibration point: the isolation of Bioko ~10,000 years ago. The dashed green line indicates the most recent time the current mainland and Bioko drill viruses could have shared a common ancestor (red star). This is a maximum clade credibility tree from amino acid sequences, with node heights (yr B.P.) representing the mean value of the posterior sample of the Bayesian analysis. Well-supported nodes (0.95 or greater posterior probability) are marked with asterisks. Viruses from Bioko species are highlighted with colored rectangles. See fig. S3 for species-specific SIV abbreviations and probability distributions of the TMRCA for each node. [Photo credits: for red-eared guenon and black colobus, T. Laman; drill, C. Santiestevan; Preuss's guenon, R. Berg]

ERRATUM

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