

Research shows HIV's ancestor millions of years older than believed

Findings open a new avenue in the quest to understand the origins of HIV, which has resulted in millions of deaths

McClatchy newspapers

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An ancient predecessor to the virus that causes Aids evolved in wild primates many millions of years earlier than previously believed, according to research published on Monday from the Stanford University School of Medicine.

The findings open a critical new avenue in the quest to understand the origins of the human immunodeficiency virus, or HIV, which unleashed a pandemic that since 1981 has claimed more than 25 million lives worldwide, and threatens millions more.

The discovery also bolsters scientific hunches that HIV-like viruses may be more broadly distributed among primates and other wildlife than previously thought, posing a potential risk for humans in close contact with these animals. Primates in Africa passed on the two strains of HIV circulating among humans, scientists are convinced.

"It points to the direction for future research, that we need to establish how widespread these viruses are," said Robert Gifford, an infectious disease researcher with Stanford, and lead author of the study.

Gifford and his colleagues studied gray mouse lemurs, squirrel-sized, saucer-eyed primates found on the island nation of Madagascar, off the west coast of Africa.

They found that the lemur genomes they studied carried lentiviruses, which are among a family of viruses that include HIV. Lentiviruses have been intensely studied since the emergence of AIDS in 1981.

While the discovery of lentiviruses in lemurs surprised the researchers, what especially stunned them was the realisation that lemurs must have carried the virus for at least 14m years.

That was the last time a land bridge might have existed between the island and the mainland, providing an opportunity for another species infected with the virus to pass it to the geographically isolated animals, which are native only to Madagascar.

At the outside, lemurs may have carried the virus for as long as 85m years, when the primate family that includes lemurs split from the evolutionary branch that gave rise to monkeys, apes and humans. The only other way lemurs could have acquired lentiviruses over the ages would have required mammals such as infected bats to wing their way across the 250-mile span of ocean between Madagascar and Africa - a scenario the scientists consider unlikely.

The findings upend long-held beliefs about how long primates have carried HIV-like viruses, and how recently these viruses evolved.

"There was a generally accepted maximum of a million years," said Gifford. "But many people thought it might be less than that."

Honing in on how long species carrying lentiviruses have harboured the pathogens helps scientists understand how they spread and evolve in wild populations, and the prevalence of biological defences against them. Certain species of primates, such as mandrills, sooty mangabeys and green monkeys, harbour the viruses without getting ill.

That knowledge, in turn, could be used to protect humans from transmission of other HIV-like viruses still confined to wildlife. It could also help in drug development by pinpointing those features of the virus that remain fixed through its long evolution. These fixed features may prove critical for normal functioning of the virus, and provide a vulnerable target for new Aids drugs.

One strain of HIV, called HIV-2, is widely accepted to have been passed from sooty mangabeys in west Africa to humans, probably bushmeat hunters or those keeping the primates as pets, or both. Scientists believe the other strain, HIV-1, was passed from chimpanzees to humans.

"There's an imperative to try to establish from these findings what the distribution of lentiviruses is, what the routes of transmission are, and the time frame," said Gifford.

Endangered Lemurs Survived Ancient AIDS Epidemic

By Brandon Keim December 16, 2008 | 8:19:39 PM Categories: [Animals](#), [Disease](#)



In the genome of the endangered gray mouse lemur, scientists have found DNA fossils of an ancient version of HIV.

Its exact origins are a mystery, but the clues could help solve a more modern and pressing unknown: how humans can beat AIDS.

Remnants of the ancient retrovirus were found by virologists studying the squirrel-sized primate on its island home of Madagascar. The DNA was deposited when viruses managed to infect sperm or egg cells, writing permanent and heritable copies of themselves into the genetic code.

Virtually every animal's genome contains fragments left by retroviruses over millions of years. (Incredibly, retrovirus genes may [outnumber human genes](#) in our own genome.) To a virologist, every genome is like a Grand Canyon cross-section or piece of [Burgess shale](#).

But deciphering genetic strata is more difficult than dating sedimentary deposits: It's hard to tell exactly when a virus showed up. It's possible that this particular virus — technically known as pSIVgml, or prosimian immunodeficiency virus of the gray mouse lemur — was present when Madagascar split from Africa.

That would make pSIVgml at least 65 million years old — the oldest ancestor of modern HIV yet found. But it's also possible, write Stanford University virologists Robert Gifford and Robert Shafer in the latest *Proceedings of the National Academy of Sciences*, that pSIVgml arrived on the island at some later date, jumping from another species just as HIV jumped from primates to people.

But while HIV destroys human immune systems, leaving bodies vulnerable to ultimately lethal diseases, pSIVgml doesn't affect the lemurs. They may have evolved an immunity to it.

In an accompanying commentary, Harvard Medical School microbiologist Welkin Johnson suggests that scientists compare the ancient virus with its descendant, resurrecting ancient genes and comparing them to modern counterparts. Perhaps we can discover the lemurs' secret.

"The lemurs may present a novel opportunity to glimpse ... a distant mirror of the AIDS epidemic," wrote Johnson.

Unfortunately, there's a catch: Like so many other animals on Madagascar, the gray mouse lemur is in grave danger of going extinct. The few specimens gathered won't be enough.

"One or a few DNA sequences does nothing to capture the diversity represented by an entire species or population," he said in an interview. "It would be virtually impossible to deduce social or behavioral

characteristics, or even complex physical characteristics, by glancing at a single DNA sequence or by testing a biological sample."

In the case of some endangered species, conservationists must appeal to basic sympathies for other living species. Such arguments don't always work: Snail darters and spotted owls are wonderful creatures, but won't be universally missed.

Helping the gray mouse lemur, however, means helping ourselves.

They're a great opportunity: "Hopefully," writes Johnson, "an opportunity gained, not lost."

Image: flickr/[Arthur Chapman](#)

WiSci 2.0: [Brandon Keim's Twitter stream](#) and [Del.icio.us feed](#); [Wired Science on Facebook](#).

Discovery Of Virus In Lemur Could Shed Light On AIDS

ScienceDaily (Dec. 2, 2008) — The genome of a squirrel-sized, saucer-eyed lemur from Madagascar may help scientists understand how HIV-like viruses coevolved with primates, according to new research from the Stanford University School of Medicine. The discovery, to be published online on Dec. 1 in the *Proceedings of the National Academy of Sciences*, could provide insight into why non-human primates don't get AIDS and lead to treatments for humans.

Scientists have long believed that lentiviruses — the family of viruses that includes HIV — started infecting primates within the past million years. In fact, said Rob Gifford, PhD, former postdoctoral researcher in infectious diseases and geographical medicine and lead author of the new study, lentiviruses may have been present in ancestral primates as long as 85 million years ago.

A type of retrovirus, lentiviruses replicate by inserting their RNA into a cell's DNA. Some retroviruses have been known to infect cells that mature into sperm or eggs, incorporating viral DNA into the genome of the host. Until last year, when Gifford discovered Rabbit Endogenous Lentivirus type K among the DNA of the European rabbit, no one knew lentiviruses could be inherited in this way.

"It allows us to put a timeline on the evolution of primate lentiviruses," said Robert Shafer, MD, associate professor (research) of infectious diseases and geographical medicine and senior author of the paper.

Gifford began computer-based screening of the DNA of 21 primates for which at least partial genome sequencing was available. He searched each species for strings of nucleotides that matched the modern lentivirus genome and found one lurking in the DNA of the tiny gray mouse lemur.

Ancestors of the modern lemur colonized Madagascar about 75 million years ago, and since then, lemurs and their lentivirus-carrying African cousins have been evolving separately. Four hundred kilometers of ocean divide the two branches, giving mainland primates limited opportunities to swap germs with lemurs. And the last of the occasional land bridges between the two disappeared beneath the sea 14 million years ago, suggesting that lentiviruses are likely at least that old, say the researchers.

High-end estimates of the age of this lentivirus, called pSIVgml, could range back 85 million years, when the primate family that includes lemurs split from the evolutionary branch that would eventually give rise to monkeys, apes and humans. "Lentiviruses could be very ancient indeed," Gifford said.



The gray mouse lemur. (Credit: Image courtesy of Stanford University Medical Center)

Gifford remains cautious about overestimating the virus's age, warning that the virus could have been spread within the last 14 million years by something that could cross the ocean, such as a bat. But Shafer says that sort of cross-species transmission is unlikely, because bats and primates are very distant relatives. The leap from primate to bat and back would be difficult for a lentivirus to make.

Gifford's find suggests lentiviruses could be discovered in other places they've never been seen, like Asian and New World monkeys. "As far as we're aware, nobody's really looked that hard," said Gifford. He is one of few researchers using genome databases to search for retroviruses.

Finding widespread lentivirus-primate interaction might open doors for HIV/AIDS research. Primates infected with the simian version of HIV are protected from developing AIDS by several genes which code for proteins in the immune system that slow or block retroviral reproduction. Previous research suggests these genes evolved in response to millions of years of retrovirus infection.

Until now, scientists thought lentiviruses were too young to have participated in this evolutionary back-and-forth. But if Gifford and his colleagues find more evidence that lentiviruses and primates have been in each other's genetic business for many millions of years, they could turn that assumption on its head. In the process, they might lead the way to a deeper understanding of the evolution of ancient innate immune defenses against retroviruses, which could have implications for HIV treatments or vaccines.

The research "raises a bunch of interesting questions about how mammals have dealt with these types of viruses over a minimum of 14 million years, what kind of defenses they have developed, and why some mammal species have lost these type of viruses," said Beatrice Hahn, PhD, a professor in the department of medicine at the University of Alabama at Birmingham who studies human retroviruses. She hopes to see more research into the presence of lentiviruses in mammal genomes. "This is molecular archaeology," she said. "There may be a lot of gold in these sequences that hasn't been mined yet."

Gifford and Shafer collaborated on this study with researchers from the Imperial College of London and the Institute for Emergent Infections at the James Martin 21st Century School at Oxford. The research was supported by the National Institute of Allergy and Infectious Diseases and the James Martin 21st Century School.

Adapted from materials provided by [Stanford University Medical Center](#).



The Loom

The Island of Fossil Viruses

By Carl Zimmer | December 17, 2008 1:07 pm



Madagascar has long been famous for its peculiar biodiversity, from its lemurs to its baobob trees. In the mid-1700s, the French naturalist **Philibert Commerson** wrote,

May I announce to you that Madagascar is the naturalist's promised land? Nature seems to have retreated there into a private sanctuary, where she could work on different models from any she has used elsewhere. There you meet bizarre and marvelous forms at every step...

None of the island's land mammal species are found anywhere else on Earth; 95% of the reptile species and 99% of the amphibians are unique as well. Over 15% of all the primate species on Earth live on Madagascar, which makes up only .4% of the Earth's land surface.

It separated from Africa about 120 million years ago, and is now separated by a channel some 250 miles across. Madagascar remained attached to the Indian subcontinent for millions of years more, but eventually they pulled apart as well, with India heading north towards Asia and Madagascar staying put in deep isolation. The species that were on board Madagascar at the separation continued to evolve there. New species arrived later, but only rarely. It's possible that they drifted from Africa on giant rafts of vegetation swept to sea by storms, or lived on islands that existed for a time between Madagascar and the continent. In any case, Madagascar became both a laboratory and a museum. Many new species evolved, adapting to open ecological niches. And while old lineages became extinct elsewhere, they survived on Madagascar. The only primates on Madagascar are the lemurs. They represent the oldest lineage of primates alive today on Earth, having **branched off** from other primates about 70 million years ago.

I guess it was just a matter of time before someone discovered that Madagascar is a museum for viruses as well.

The **discovery**, reported this week, came when a team of American and English scientists perused the genome of the gray mouse lemur. Nestled among its genes were segments of DNA that bore a remarkable resemblance to HIV.

How on Earth could a deadly virus's genes become part of a primate's own genome? Some kinds of viruses, known as retroviruses, replicate by inserting their DNA into host cells, where their DNA can guide the production of new viruses. But many studies indicate that sometimes these viruses infect the cells that will give rise to sperm and eggs. The virus ends up in a fertilized egg and gets passed down to every cell in the developing embryo—including its own sex cells. Now the virus gets passed down through the generations. It may still retain the ability to infect other cells for a while, but mutations typically knock out that ability. Instead, the virus can only insert copies of its DNA back into its own host cell's genome. Over millions of years, this viral DNA spreads through the host genome. **Our own DNA** contains 98,000 stretches of this virus DNA, plus 150,000 tiny viral fragments, making up about 8% of our genome—about five times more DNA than the DNA that encodes proteins.

It wasn't a huge surprise to find one of these so-called endogenous retroviruses in the gray mouse lemur's DNA. What was surprising was that it belonged to the same group of viruses that includes HIV—known as lentiviruses. There is only one other record of a lentivirus going endogenous—**discovered** just last year in rabbits. The scientists who discovered this rare endogenous lentivirus realized they had a rare opportunity on their hands: a chance to infer some of the earliest stages in the evolution of one of the world's worst scourges today: HIV.

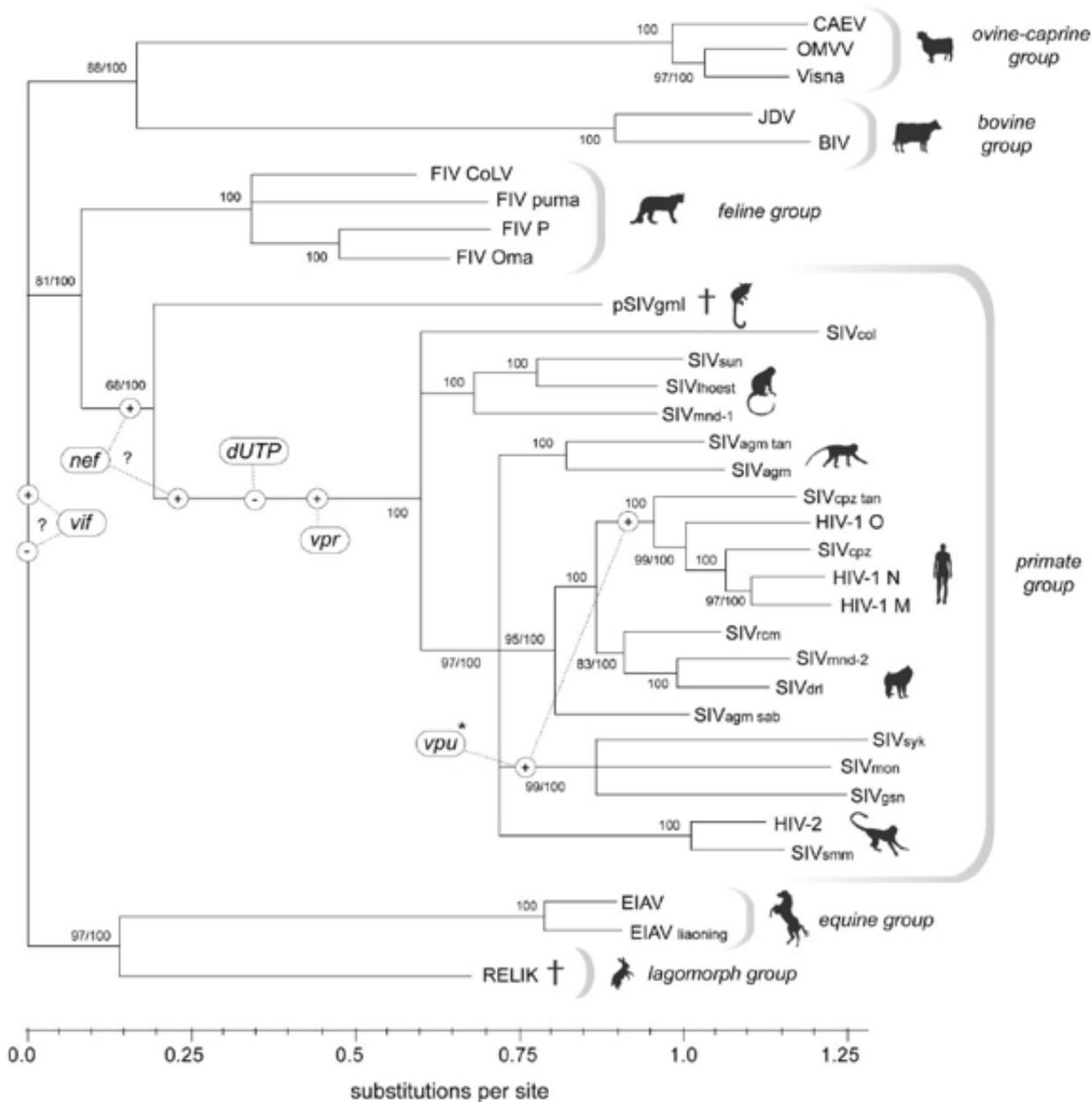
To uncover the history of HIV, scientists build evolutionary trees. They compare strains of the virus that infect humans, and search for related versions in other animals. There's a lot of evidence now that HIV is the result of several viruses that hopped from other primates to humans. There are two main divisions of HIV, HIV-1 and HIV-2. HIV-2 evolved from a virus in monkeys known as sooty mangabeys (SIVsmm for short—the SIV stands for simian immunodeficiency virus, as opposed to human immunodeficiency virus). HIV-1 turns out to be a few different strains, which evolved from chimpanzee viruses known collectively as SIVcpz. The different mutations that have accumulated in HIV strains since these jumps indicates that they took place within the last century.

But there's a lot of evidence scientists can use to trace back the ancestry of HIV further than its jumps into our species. They've found SIV infecting not just chimpanzees and mangabeys, but gorillas and other African monkeys. (Interestingly, primates don't get sick from their strains of SIV, having evolved defenses against them.) Scientists have also found related lentiviruses in cows, horses, sheep, rabbits, and cats. Feline immunodeficiency viruses, in fact, turn out to be the most

These lentiviruses evolved from common ancestors that lived millions of years ago, but the details of that early evolution are hard to tease out of their DNA. Lentiviruses mutate very quickly as they move from host to host, and this rapid mutation eventually erases some of the history chronicled in their DNA. It becomes hard to tell how individual genes in the viruses evolved, for example, and how much viruses moved between species, as opposed to just infecting one host.

The discovery of a relative of SIV in the gray mouse lemur genome was thus exciting for two reasons. One was the fact that it was a lemur carrying the virus DNA. Until now, no one had ever found a SIV-like virus in lemurs. Since lemurs branched off early from other primates, it was possible that SIV first entered primates after that split. This new virus makes the possibility unlikely. The other reason the discovery was exciting was that this virus was endogenous. Once it became part of the lemur's genome, it was protected from mutations by the lemur's sophisticated DNA-repair enzymes. Today its DNA is not the same as when it first entered the lemur genome. But it has changed less than free viruses.

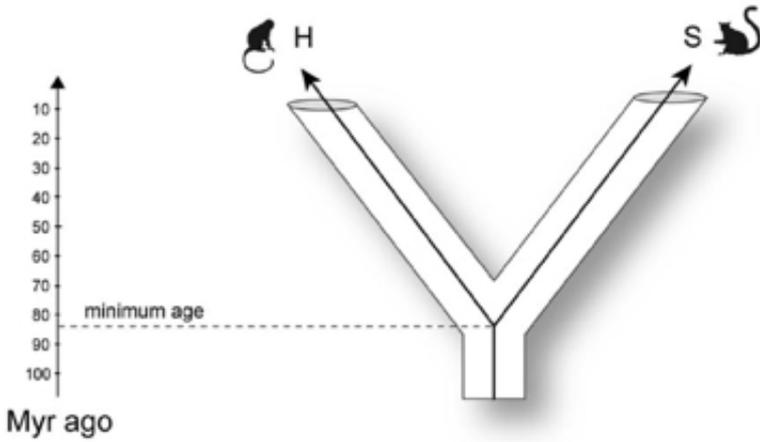
As the scientists scoured the gray mouse lemur more, they discovered ten segments of DNA belonging to the same virus, which they've named pSIVgml (prosimian immunodeficiency virus). Because they were only looking at a rough draft of the gray mouse lemur genome, they predict that this figure may triple when the final read of the genome is finished. To make sure this wasn't just a virus that had infected a lone lemur, they fished for the virus DNA in another gray mouse lemur and found it. They then compared all these pieces of pSIVgml DNA to reconstruct what their common ancestor's genes looked like, and then compared that ancestral virus to viruses in other species. Here's the tree they got:



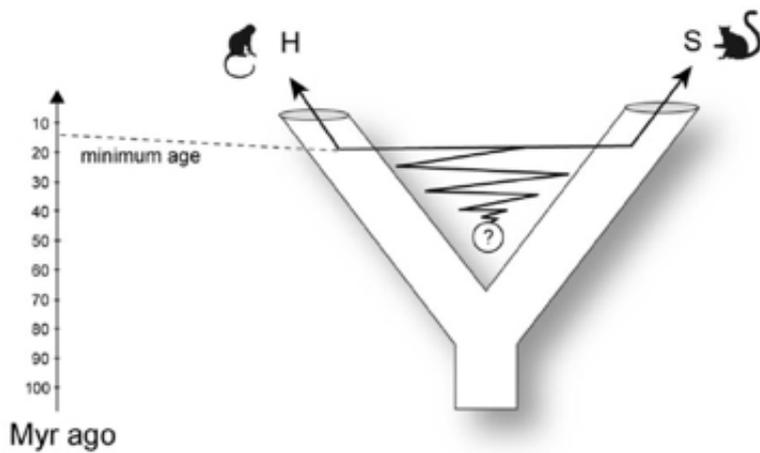
The different versions of the lemur virus appear to share a common ancestor between 1.9 and 3.8 million years old. Before then, pSIVgml’s ancestors must have been free-living, presumably infecting gray mouse lemurs in Madagascar. Exactly when the virus merged with its host isn’t clear, but it has clearly been trapped in lemur genomes for at least a couple million years.

Compared to other lentiviruses, pSIVgml has the same relationship as their lemur hosts do to other hosts. The ancestors of the virus branched off on their own before the evolution of SIV viruses that now infect other primates. This tree indicates that pSIVgml is, in the words of the scientists, a transitional virus. Until now, all the SIV strains scientists had identified were distinct from other lentiviruses in some key ways. They all had two unique genes, for example, called *nef* and *vpr*. But they also lacked a gene found in other lentiviruses, called ~~*vpr*~~-*dUTP*. The gray mouse lemur’s virus has *nef*—which unites it with other SIVs in primates. But it doesn’t have *vpr*. And it still has *dUTP*, which other SIVs have lost. It’s the virus world’s answer to **fish with fingers** or **whales with legs**. The full-blown SIV genome did not evolve all at once, in other words, but in a series of steps, one of which we can now see with the discovery of this extinct virus.

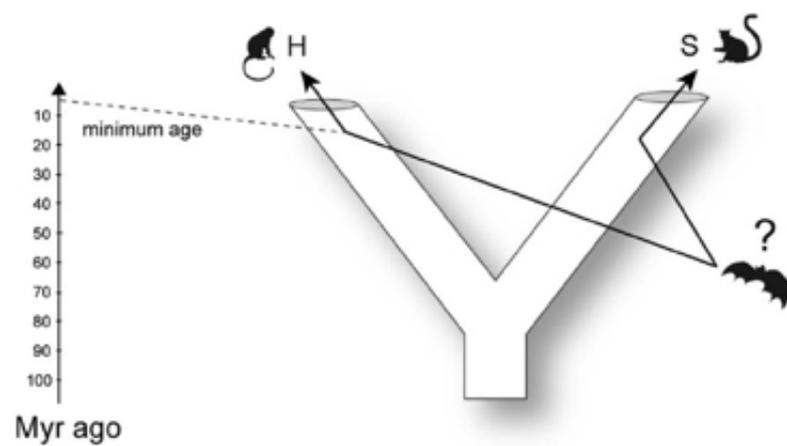
Model 1: ancestral codivergence



Model 2: ancestral transfer via terrestrial route



Model 3: transfer via aerial vector



As with any startling new discovery in evolution, pSIVgml raises some hypotheses that scientists can now test. The virus might have been handed down to mouse gray lemurs today from the viruses that infected the common ancestor of lemurs, monkeys, apes, and humans 85 million years ago. (Model 1 in the picture I've reproduced here.) That fits the pSIVgml tree. But there's a hitch: the monkeys of the New World don't seem to have SIV. So if Model 1 were right, they'd all have to have lost the virus. Possible, but a stretch. Or perhaps one of the rare mammals that came to Madagascar from Africa carried a lentivirus that later hopped the species barrier and infected lemurs. The last time this happened is

14 million years ago (this is model 2). The third possibility is that bats passed lentiviruses to both lemurs in Madagascar and the ancestors of apes and monkeys in Africa (model 3). But no one has found a bat lentivirus.

On the other hand, lentiviruses can be hard to isolate, so perhaps in years to come someone will find a bat lentivirus. Or maybe a howler monkey will turn up with its own strain in Costa Rica, adding support to model 1. Certainly, it would be a good idea to take a closer look at the other 32 species of lemurs on Madagascar, to see if they have freely circulating SIV, or an endogenous virus trapped in their DNA. The museum of Madagascar probably has more secrets for us to find.

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