Unsolved Questions over the Origin of HIV and AIDS

Although HIV originated in nonhuman primates, we do not understand how it became a successful pathogen in its human host

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The concept of AIDS as a zoonosis stems from studies that traced HIV origins to two simian species in West and Central Africa—an idea that was reinforced by reports in high-profile journals. Although the simian origin of HIV and other human retroviruses such as human T cell leukemia virus and human foamy viruses is not in dispute, the hypothesis that simian retroviral infections are zoonoses is.

Simply put, a zoonosis is a disease that is acquired from a vertebrate animal. Some microbiologists also consider vector-borne diseases as zoonoses. But the central meaning of zoonosis is that the disease, and not just the infection, is acquired from an animal, not from another human being. In the 2003 edition of Zoonoses: Infectious Diseases Transmissible from Animals to Humans, an ASM publication, HIV is dismissed as a zoonosis on the first page. It contains no chapters on simian retroviral zoonoses because there are none. When we think of zoonosis, we should think of rabies, not AIDS.

Some experts consider this debate semantic and thus of little importance. Thus, because every case of human AIDS is acquired from another human being, it cannot be a zoonosis and the discussion could end here. Yet the underlying question of what launches new diseases among humans, including not only AIDS but also avian flu, Ebola virus, and severe acquired respiratory syndrome (SARS), is critical to address because it so often remains a black box. While we know the origin of HIV and the avian influenza virus and have some leads on the Ebola and SARS viruses, the shocking fact is that we know next to nothing about the factors that launch animal viruses into epidemics, pandemics, or result in dead-end infections. The ecological events that led SIV to become HIV with epidemic potential remain completely unknown.

Looking for SIV

HIV is not one virus but exists as two major viral species, HIV-1 and HIV-2. HIV-1 is further divided into three groups, M, N, and O, with M the “main” group, O the “outlier,” and N filling the alphabetic gap between them. HIV-2 consists of seven subtypes, A through G, with a possible eighth group, H.

HIV types 1 and 2 do not have a single simian species of origin, but two—the chimpanzee and the sooty mangabey. The three HIV-1 groups and eight HIV-2 groups are different enough from one another that they probably arose from 11 separate crossover events, suggesting eight sooty mangabeys and three chimpanzees were responsible for all known HIV infections among humans. After 17 years of field research in West, Equatorial, and East Africa, scientists from several countries have identified at least 40 different monkey species that are infected with 40 different types of SIV.

When I arrived in West Africa in 1988 in search of the source of HIV-2, I believed that AIDS was a zoonosis and that my search for SIV...
would entail many months of camping in African forests, trapping monkeys, and collecting blood samples.

However, it turned out to be a much easier task than I had imagined. Within days of arriving, I learned that monkeys were everywhere because they were being kept as household pets. More importantly, virtually all of them had been born in the wild. In addition, monkeys were and are a valued food animal in much of forested Africa, and monkey carcasses are sold in local game markets. Often hunters will bring motherless baby monkeys home to raise as pets. Our field biologist Paul Telfer and others who were part of the Marx research group in Sierra Leone in the early 1990s later determined that one of those pet monkeys (Fig. 1) was infected with an SIV strain that proved to be an important link to the ancestor of an HIV-2 strain.

Of the 40 known SIVs from 40 different simian species in Africa, almost all were found in former household pets or in bush meat tissue. The discovery of SIV from the red-capped mangabey (RCM) illustrates the importance of pets in the search for SIV. SIVrcm was first discovered in a red-capped mangabey in the town of Lambarene, Gabon.

The setting in which this infected monkey was found tells a story of serendipity and science. Telfer, the field biologist, spent an entire day in Lambarene searching for pet RCMs with no success. This town is located well within the natural range of RCMs, and despite their being endangered, they are fairly common in this area. After a long day, Telfer decided to visit a local bar, where he found an RCM being kept as a pet. This bar monkey was the first known SIVrcm-infected monkey.

SIVrcm proves an interesting virus because it is a key part of the ancestry of SIV from chimpanzees (cpz). SIVcpz is a recombinant between an SIVrcm-like virus and an SIVgsn-like virus from the greater spot-nosed monkeys (Cercopithecus nictitans). SIVcpz, in turn, is most likely the ancestral lineage of HIV-1.

What Do We Really Know about the Origins of HIV and AIDS?

With at least 40 species harboring SIV, where did HIV come from? To answer the question requires characterizing SIVs from the blood or tissue of monkeys and chimpanzees. When blood is not available, as is the case with bush meat, DNA or RNA is extracted directly from the tissue of naturally infected animals. Phylogenetic analyses show that the closest genetic match with HIV type 1 is an SIV from the central African chimpanzee, Pan troglodytes, troglodytes (Fig. 2a, green).

Meanwhile, the closest match for HIV-2 is the SIV found in sooty mangabeys (Fig. 2b, black). The sooty mangabey (Fig. 1) that Telfer found harbored a particularly important SIVsm strain (SIVsm92b [red]). When members of my group sequenced and analyzed the genome of this virus, we learned that its closest phylogenetic match is a version of HIV infecting a man in Los Angeles, Calif. Moreover, this virus, HIV-2 PA, (orange, Fig. 2b) is the only known example of this HIV-2 strain, and that man is the only person known to be infected with that virus.

On the surface, our analyses looked like they resulted from a bad experiment. Was it laboratory contamination? We rejected that explanation because no samples were ever shared between the two groups that conducted the sequence analyses. That part of the mystery was solved when we learned that the Los Angeles man was an immigrant from Sierra Leone who had lived in a village only 50 miles from where the infected SM was found. This study is the most convincing to date that HIV-2 has its direct origins in infected monkeys in forested Africa.
The HIV Epidemic That Wasn’t

With that information, we considered it a relatively simple matter to test persons living in that area of Sierra Leone, searching for small outbreaks of HIV-2. We anticipated finding local cases of AIDS to be an example of a zoonosis.
from local villagers contacting infected sooty mangabeys.

Again, however, our expectations were not met. Although we tested more than 11,000 individuals in Sierra Leone, only 2 were infected with HIV-2. Our hypotheses were further confounded by findings that HIV-2 infections by groups C through G typically are dead-ended, meaning the infected individual does not transmit the virus to other persons. Therefore, outbreaks of AIDS, the disease, could not be traced to contact with sooty mangabeys.

HIV groups A and B (blue, Fig. 2b) are epidemic in about 100,000 persons. But, groups C-G were found only as single-person infections. HIV-2 PA, the virus that matched the SIV-infected household pet, must have infected this man for 20 years because he resided outside Sierra Leone for that long. Yet neither HIV-2 PA nor any other HIV-2 belonging to groups C through G had spread to other persons.

Although the man from Sierra Leone carried HIV-2 antibodies, the virus was never recovered from his blood despite repeated attempts over 4 years. HIV-PA virus is known only from its gag sequence (Fig. 2b), which was amplified from his peripheral blood cells. HIV-2 PA, therefore, appears to be a dead-end infection of extremely low pathogenicity. Indeed, all HIVs except HIV-1 group M are relatively ineffectual pathogens—and epidemiological wimps (Table 1).

We wondered how AIDS could be a zoonosis if the simian virus is not causing AIDS in persons who are in frequent contact with SIV-infected SMs. Thus, we questioned the hypothesis that AIDS is a zoonosis. Although we appear to have identified the animal origins of HIV, nothing is known about the circumstances that led to the AIDS epidemic.

Arguments against AIDS as a Zoonosis

There are several strong arguments against AIDS being a zoonosis. First, SIV commonly infects monkeys, including bush meat and household pets in sub-Saharan Africa, leading to high-frequency exposure of humans. However, researchers have documented only 11 cross-species transmissions to humans from the last 45 years, and only one resulted in a human pandemic, involving HIV-1 group M (Table 1). What is the difference among these viruses? The answer could solve a great riddle as to why the AIDS epidemic emerged in the second half of the 20th century, and not before.

The closest relatives of SIVs are HIV-1 group N (orange, Fig. 1a) and HIV-2 groups C through G (Fig. 2b). Each of these viruses is extremely rare, with only six known HIV-1 group N-infected persons and only single individuals infected by HIV-2 groups C through G. Most SIVs are thus epidemiological failures in humans and not virulent zoonotic agents of disease and epidemics.

Second, in Central and West Africa human exposure to retroviruses through hunting and butchering is ancient, but the AIDS epidemic emerged only in the second half of the 20th century. Anthropologists have documented 50,000 years of human habitation in Central and West Africa. If AIDS were a simple zoonosis that could spread from person to person, it would have emerged there or perhaps in the Americas early during the slave trade. Indeed, slaves were taken to the Americas from the very same regions where SIV-infected sooty mangabeys and chimpanzees were present and hunted for food (Fig. 3). During 300 years of the slave trade, 20 million Africans were landed from coastal Maryland to Rio de Janeiro. A pathogenic SIV among them would have quickly spread to the European colonists in the Americas. Yet it did not. Some factor must have changed in the

<table>
<thead>
<tr>
<th>HIV group or subtype</th>
<th>No. of infections (% of total)</th>
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<tbody>
<tr>
<td>HIV-1</td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>45,000,000,000 (99.6)</td>
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<tr>
<td>Group N</td>
<td>6 (0.000013)</td>
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<tr>
<td>Group O</td>
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<tr>
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*Estimates.
mid-20th century to disrupt the ecology between humans and nonvirulent SIVs.

Third, new species often can clear experimentally or accidentally inoculated SIV, indicating that SIV infections do not always lead to clinical signs of AIDS. In two cases in which SIVsm-derived viruses were accidentally transmitted to humans in laboratories in the United States, one infection was cleared and the second, involving SIVsmB670, caused a persistent but asymptomatic infection. This virus, now called SIVhu, also fails to produce active infections when inoculated into macaques. Thus, SIVsm-related virus infections are of low pathogenicity in humans.

Finally, there is the matter of how readily SIVs replicate in human peripheral blood cells. Most SIVs are known only from their DNA sequences, making it impossible to test whether they can grow in human cells. In fact, only 4 of 13 SIVs were isolated from Cercopithecus monkeys, and only one of those (SIVlhoest) actually grew in human peripheral blood cells. The remaining viruses (SIVsun, SIVsyk, and SIVtal) show very restrictive host-related tropisms.

These arguments suggest that there is a missing link in our understanding of the roots of AIDS. Most HIV groups are only weakly pathogenic and not highly infectious for humans. Despite many opportunities, in only one instance did SIV transform into an infectious, virulent form of HIV during the past 50,000 years of human contact with SIV. If it were not for HIV-1 group M, AIDS and SIV would most likely still be undiscovered.
What Caused the AIDS Epidemic?

We do not know what caused the AIDS epidemic, and this lack of knowledge is profound, extending beyond this particular epidemic. Thus, we do not know why a few new viruses succeed, while most fail to become dangerous to humans. Avian influenza is a good case in point. The flu virus is one of the most readily transmitted viruses that plagues mankind. Avian flu virus is highly lethal, with a mortality rate greater than 50%. Yet outbreaks so far are confined to individuals who have had close contact with infected chickens. Why are some influenza viruses spread easily in epidemics, while others are epidemiological failures? It may be as important to understand the failed viruses as much as the successful ones.

There are a few clues as to how SIV transformed into a dangerous virus, transmissible among humans. One clue is the possibility that a single factor launched the AIDS virus in the last century lies in the finding that HIV broke out in two different African locations. Taking the long view, HIV-1 and HIV-2 did not emerge for 50,000 years, yet appeared at about the same time last century. The range of sooty mangabeys and their ancestral HIV-2 virus is in far western Africa—from Guinea-Bissau east to the Ivory Coast. There is a big geographic gap of almost 1,000 miles before reaching the range of the chimpanzee where HIV-1 emerged. Why did HIV/AIDS not emerge in 50,000 years, but then emerged twice at nearly the same time in two different locations in Africa?

This unlikely coincidence demands a unifying hypothesis, and two are currently being considered. The first concerns unprecedented deforestation in this region during the 20th century and the possibility that particular strains of SIV are much more pathogenic than those that have been identified so far. According to this hypothesis, deforestation and increased hunting significantly increased the odds of exposure for humans to those pathogenic, but formerly sequestered SIV strains. This explanation is the modern equivalent of the “cut hunter hypothesis.”

The second theory is that HIV/AIDS arose from an increase in the use of unsafe injections and transfusions in postcolonial Africa. Moreover, transfusions might have enabled SIV to adapt to humans through serial passage and by other mechanisms such as recombination.

Research Does Not End when HIV Ancestors Are Identified

Uncovering the complete story of the emergence of the AIDS epidemic entails further study. Although identifying HIV’s immediate ancestors proved a successful research venture, that finding does not contribute much to preventing future viral crossovers from animals into humans. If all of Africa were to stop trading in bush meat tomorrow, the AIDS epidemic would continue unabated. Preventing new viruses from plaguing humans will require us to develop an understanding of the nature of pathogenesis of a microbe in a new host species. We lack this important knowledge.

We must come to understand the adaptive processes in potential new hosts that will or will not enable viruses or other potential pathogens to launch emerging diseases. We know much about emerging viruses, but almost nothing about emerging viral diseases.

SUGGESTED READING


