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# AIDS as a zoonosis? Confusion over the origin of the virus and the origin of the epidemics

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Abstract: Based on findings demonstrating the simian ancestry of HIV, AIDS has been reported to be a zoonosis. However, this theory has never been proved and must seriously be questioned. Several arguments show that HIV-AIDS is not a zoonosis. (i) If AIDS were a zoonosis, there must be evidence of AIDS being directly acquired from an animal species, as is rabies, a disease that is directly acquired from animals. (ii) Despite long-term and frequent human exposure to SIV-infected monkeys in Africa, only 11 cross-species transmission events are known, and only four of these have resulted in significant human-to-human transmission, generating HIV-1 groups M and O and HIV-2 groups A and B. The closest relatives of SIVcpz (HIV-1 group N) and of SIVsm (HIV-2 groups C–H) are extremely rare, with only six HIV-1 group N-infected patients and only single individuals known to be infected by HIV-2 groups C–H. SIV, while capable of cross-species transmission, is thus poorly adapted for disease and epidemic spread. If AIDS were a zoonosis that is capable of significant human-to-human spread, there would be a plethora of founder subtypes and groups. (iii) Human exposure to SIV is thousands of years old, but AIDS emerged only in the 20th century. If AIDS were a zoonosis that spread into the human population, it would have spread to the West during slave trade. (iv) Experimental transmission of SIVs to different species of monkeys is often well controlled by the new host, showing that the virus and not the disease is transmitted. Therefore, we conclude that cross-species transmission of SIV does not in itself constitute the basis for a zoonosis. Transmission *per se* is not the major requirement for the generation of the AIDS epidemic. All HIVs do derive from simian species, but AIDS does not qualify as a zoonosis and this explanation cannot in itself account for the origin of AIDS epidemic. It is important to distinguish AIDS from true zoonoses (e.g. rabies) because research is needed to understand the processes by which animal viruses cause sustained human-to-human transmission, epidemics and even pandemics. Much is known about emerging viruses, but almost nothing is known about emerging viral diseases.

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## Introduction

The emergence of AIDS in the late 1970s in the USA was the first sign of one of the deadliest pandemics in human history. In relatively short time, AIDS became a leading cause of mortality in the world and a cause of serious economic and social problems in of Central and southern Africa. The prevalence of Human Immunodeficiency Virus (HIV) increased rapidly, reaching apocalyptic levels of 30% by the end of the 20th century in southern regions of Africa [61]. Significant economic consequences have resulted from the reduction in life expectancy in some African nations [61]. In addition, the number of orphans in regions most affected by HIV has increased dramatically. A second wave of the epidemic reached Asia, where billions of people are at risk, with tens of millions already infected in India and China [61]. AIDS, therefore, is a major health problem in need of rapid and equitable medical and political solutions. The development of

effective antiretroviral drugs (ARV) has partially controlled the problem in developed countries [45]. However, in developing countries, ARV is not yet available in spite of efforts by UNAIDS and other non-governmental organizations to provide drugs at least to patients in the late stages of infection [http://www.who.int/3by5/en/]. An effective prevention strategy for controlling mother-to-child HIV transmission was implemented in some African countries and has showed promising results [6, 34]. The increased transmission of resistant viruses reported in Western countries is a major concern [60] and the magnitude of this problem may further increase with the advent of ARVs in those regions where treatments are administered without monitoring the virus infection. Effective vaccines are an ideal solution to control in AIDS worldwide, but vaccine development has been too slow to meet the need. Moreover, although moderate optimism was generated by recent reports showing control of SIVmac replication in macaques [1, 49, 51, 53], the mechanism of immune protection in rhesus macaques and their relevance to HIV-AIDS is not known [21].

In this context, debates on the origin of HIV have generated a dispute concerning the fundamental character of AIDS. Based on results showing the simian origin of HIV [14, 17, 28], AIDS was treated as a zoonosis [31]. This hypothesis was based on data showing cross-species transmission of SIV [14, 27]. Supporting data for SIV as the origin of HIV are (i) similarities in viral genome organization; (ii) close phylogenetic relationships between SIV and HIV; (iii) SIV prevalence in the natural host; (iv) geographic coincidence and (v) plausible routes of transmission. Both the SIVsm/HIV-2 and SIVcpz/HIV-1 groups fulfill these criteria [13, 17, 28]. However, although the simian source of HIV is acknowledged, the emergence of the AIDS epidemic is not understood. Moreover, the idea that AIDS is a zoonosis has never been proved and must be seriously questioned.

## Results and Discussion

Why is this question important? Is this simply a semantic argument? It is important to distinguish AIDS from true zoonoses (e.g. rabies) because research is needed to understand the processes by which animal viruses cause epidemics and even pandemics. Although much is known about the origin of HIV, nothing is known about the mechanism of AIDS emergence. This field of AIDS research does not end with the discovery of the source of HIV. We must eventually understand the adaptive process(es) in the new host that will (or perhaps more importantly will not) launch an emerging disease. We know much about emerging viruses, but almost nothing about emerging viral diseases.

A strong rationale for studying the character of AIDS is the social implications that have serious consequences for the ecology of non-human primates. An incorrect assumption concerning the risk of acquiring AIDS from simian bush meat may result in deliberate killing of monkeys to prevent the spread of AIDS, a disastrous consequence for endangered non-human primates (NHPs) that is likely to have little effect on the AIDS epidemic.

An illustration of the confusion caused by misinterpretations of data on the origin of AIDS, the disease, is reaction of the non-scientific press in reports showing that chimpanzees were the source of HIV-1, the virus. 'Chimpanzee meat blamed for AIDS epidemic' [23] was the headline in a front-page article in the *New York Times*. The first paragraph of the article stated that 'Chimpanzees slaughtered for food in west central Africa was the original source of AIDS'. Another was from the *Daily telegraph* which stated that: 'AIDS started by humans eating chimps'. The fact that the original scientific paper suggested that route of human infection with SIVcpz was exposure to blood during hunting and butchering and not the ingestion of meat [28] is incidental to the bigger issue that research only identifies the source of the virus and not the mechanism by which AIDS emerged. The corrected headline would have been, 'Chimpanzees slaughtered for food in west central Africa was the original source of HIV'. The results indicate that humans have been exposed to SIV-infected bush meat for thousands of years, but AIDS only emerged in the 20th century. If AIDS were a simple zoonosis with potential to become a health threat in humans as reported [31], it would have appeared earlier in Africa and would have emerged in the West during the era of slave trade when millions of Africans were brought to North and South America [33].

### Definitions – what are zoonoses?

The definition of a zoonosis is 'a disease of animals that may be transmitted to man under natural conditions (e.g. brucellosis, rabies)' [24] or 'a disease communicated from one kind of animal to another or to a human being; usually restricted to diseases transmitted naturally to man from animals' (Medical Dictionary Online, http://cancerweb.ncl.ac.uk/cgi-bin/omd). Interestingly, in

the Dictionary of Virology it is emphasized that the term zoonosis is frequently misused: 'a zoonosis is a disease or an infection naturally transmitted between vertebrate animals and humans. However, the term has been frequently misunderstood' [40]. The emphasis is on a zoonosis being a naturally acquired disease from an animal source. There is no evidence for AIDS being acquired directly from an animal source.

Stedman's Medical Dictionary [56] provides more details. Zooanthroponosis – a zoonosis normally maintained by humans, but can be transmitted to other vertebrates (e.g. ameobiasis to dogs, tuberculosis); Amphixenosis – a zoonosis maintained in nature by humans and lower animals (e.g. staphylococcoses). Amphixenosis would be the correct term for AIDS if it were a disease maintained in nature by animal to animal transmission and humans to human transmission. But the argument is more than semantics.

### Arguments against AIDS as a zoonosis

The following facts do not support AIDS as a zoonosis.

1. In spite of the large number of exposures to SIV-infected monkeys in Central and West Africa [41, 48], extensive molecular epidemiologic studies have documented only 11 cross-species transmission events during the last 50 years. Only four of these cross-over events resulted in epidemic strains. They are HIV-1 group M, the major group of viruses of the pandemic, group O, which is responsible for perhaps 5% of cases in Cameroon [4] and groups A and B of HIV-2, which are the epidemic forms of HIV-2 [19, 27]. Figure 1 shows some of the closest relatives of SIVcpz (HIV-1 group N) and of SIVsm (HIV-2 groups C–G) (Fig. 2). These viruses are extremely rare in humans, with only six HIV-1 group N-infected patients known [3, 8] and only single individuals infected by HIV-2 groups C–H (Fig. 1) [13, 20, 27, 62]. These findings indicate that cross-species transmission of SIV is not in itself sufficient for spread into new human populations to generate an epidemic.

The concept that viruses transmitted across species are usually weak pathogens unsuited for initiating large-scale epidemics is not unique to SIV. Direct transmission of avian influenza virus has relatively lower epidemic potential compared with recombinant influenza viruses originating from the pig 'mixing vessels'. Only 18 cases of H5N1 influenza infection were recorded in Hong Kong [16]. These cases were severe, with a mortality rate of more than 30%. However, no evidence of human-to-human transmission of H5N1 virus was found [37]. Moreover, serological screening of poultry workers directly exposed to the avian virus has shown that about 10% were seropositive, and that the infection was asymptomatic or mildly symptomatic, with no secondary cases reported [9]. These findings suggest a need for adaptation of animal-origin viruses before they are capable of human-to-human transmission.

2. Experimental cross-species transmissions of SIVs in different species of monkeys have shown that in many cases the virus is relatively non-pathogenic and cleared by the new host [54, 57, C. Apetrei, unpublished]. Moreover, some of the HIV-2 groups show low pathogenic potential in the human host [13, 27]. Although baboons were reported to develop AIDS following infection with HIV-2 [5] it was clearly shown that serial passage of the virus in baboons will result in an increased pathogenicity [39]. We recently had the opportunity to characterize the outcome of cross-species transmission of SIVsm in three black mangabeys [2]. Although AIDS was observed in one animal, the SIVsm infection was cleared in the remaining two. These findings lead to the conclusion that cross-species transmission of a lentivirus is not the only requirement for the selection of a pathogenic virus in the new host and that studies have to be conducted to characterize the mechanisms of virus adaptation to the new host.

3. The SIVs infections in their natural host are generally asymptomatic in spite of high viral loads over long periods of time [10, 12, 22, 29, 43, 50]. Immunodeficiency is extremely rare in African non-human primate hosts [2, 38, 46, 55, 58] and generally occurs after long incubation periods that exceed the normal life span of non-human primate species [46]. This finding reinforces the assumption that a change in the pathological potential of the virus is needed for SIV to become pathogenic in a new primate host [39]. In zoonotic diseases such as rabies or West Nile encephalitis, the animal source is also susceptible to the disease [11, 52].

4. Finally, in Central Africa, humans have been exposed for centuries to SIVs and the epidemic only emerged in the second half of the last century, which suggests the intervention of some factor(s) favoring the emergence of HIV. These factors could be deforestation, increase of urbanization and travel in the 20th century [15]. In addition, it has been postulated that the main factor behind the emergence of HIV in human population may have been an increase in injections, unsterile needles and syringes as well as unsafe transfusion practices. This factor may have significantly promoted viral adaptation through serial passages [25, 42] or favor

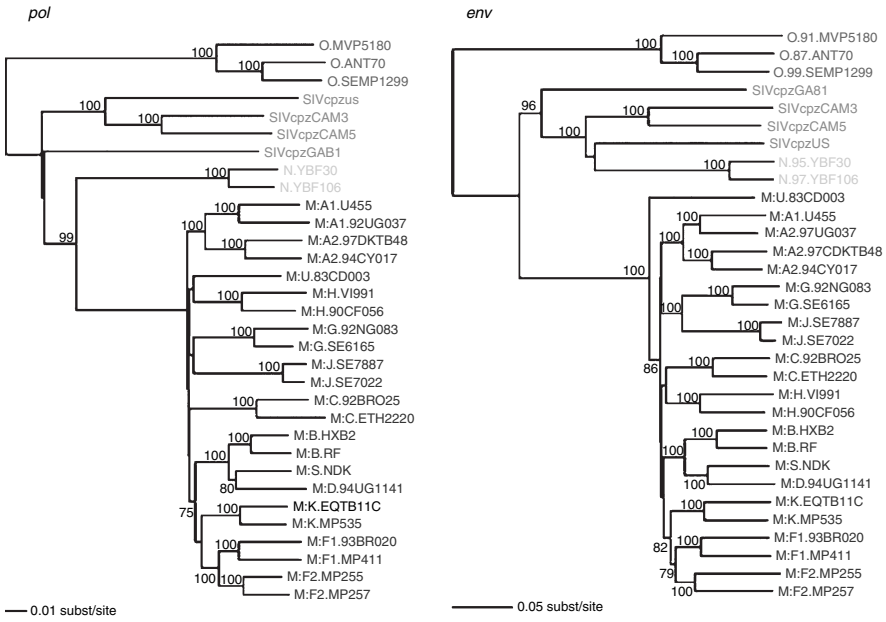


*Fig. 1.* Phylogenetic analysis showing the relationship between SIVcpz and HIV-1.

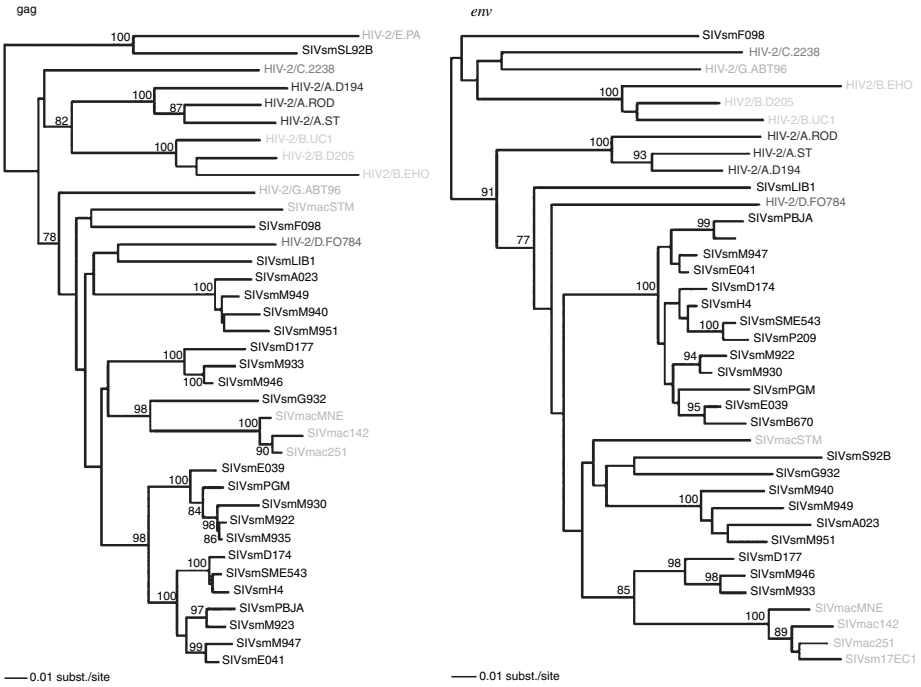


*Fig. 2.* Phylogenetic analysis showing the relationship between SIVsm and HIV-2.

adaptation by other mechanisms such as recombination.

## And what if AIDS was a zoonosis?

If AIDS was a zoonosis, then human exposure to SIV would result in AIDS in the SIV-infected individual. Are there any data to support this assumption? During the study of SIV infections in macaques, cases of human laboratory workers becoming infected with SIV were reported. SIVsm had been accidentally transmitted to humans in laboratories in the US but in one case the infection was cleared [35] whereas in the second

case (a human infection with SIVsmB670), a persistent non-symptomatic infection had been observed [36]. Macaques inoculated with SIVhu failed to develop productive infection due to the occurrence of deletions in different genomic regions [59]. This suggest that (i) SIVsm directly transmitted to humans is of low pathogenicity and (ii) that the cross-transmitted SIVsm must undergo adaptation into the new human host in order to replicate efficiently to generate immune suppression and to initiate an epidemic.

Most of the SIVs found thus far have not been grown *in vitro* and are only known from sequences. However, it has been repeatedly reported that most SIVs will replicate in human peripheral blood mononuclear cells (PBMCs) [18, 31, 48, 47]. This is an overstatement. For example, only four SIVs of 13 reported in *Cercopithecus* monkeys have been isolated and only one of them (SIVlhoest) is known to grow on human PBMCs. Remaining viruses (SIVsun, SIVsyk and SIVtal) have a very restrictive host-related tropism [7, 26, 30, 32, 44].

These arguments indicate that viral cross-species transmission is in itself not the only requirement for the generation of epidemics, and that the ancestry of HIV should not be confused with the origins of AIDS. Other factors must be required for HIV adaptation and epidemic spread of SIV in the new human host. Therefore, AIDS is not a zoonosis [42], but a human infectious disease of zoonotic origin.

## Conclusion

With the advent of AIDS, avian flu, Ebola and SARS, the question of what launches new epidemics and pandemics is extremely important. The somewhat shocking answer is that we actually know nothing about the factors that launch animal viruses into epidemics or pandemics. Equally important is the question as to why most animal viruses fail to reach a sustained human-to-human transmission. These are critically important questions that are being bypassed. When we think zoonosis, we should think of diseases like rabies. There is no evidence that a person can contract AIDS from a monkey or chimpanzee. There is still a missing link.

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