

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

Marx PA, Apetrei C, Drucker E. AIDS as a zoonosis? Confusion over the origin of the virus and the origin of the epidemics. J Med Primatol 2004; 33:220–226. © Blackwell Munksgaard, 2004

Preston A. Marx¹, Cristian Apetrei¹, Ernest Drucker²

¹Tulane National Primate Research Center, Covington, LA, and School of Public Health, Tulane University, New Orleans, LA, ²Albert Einstein College of Medicine, Bronx, NY, USA

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.

Key words: cross-species transmission – HIV – pandemic – pathogenesis – primates – SIV

Accepted 24 June 2004.

Prof. Preston A. Marx, Division of Microbiology and Immunology, Tulane National Primate Research Center, 18703 Three Rivers Road, Covington, LA 70433, USA.

Tel: (985) 871 6518; fax: (985) 871 6248; e-mail: pmarxj@tulane.edu

Funding: NIH grant ROI AI44596.

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. amoebiasis 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

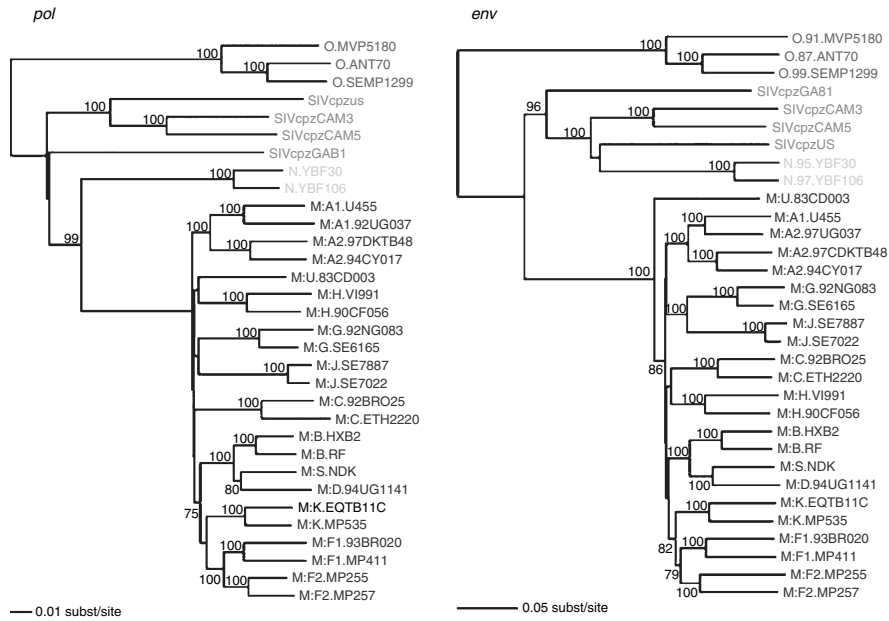


Fig. 1. Phylogenetic analysis showing the relationship between SIVcpz and HIV-1.

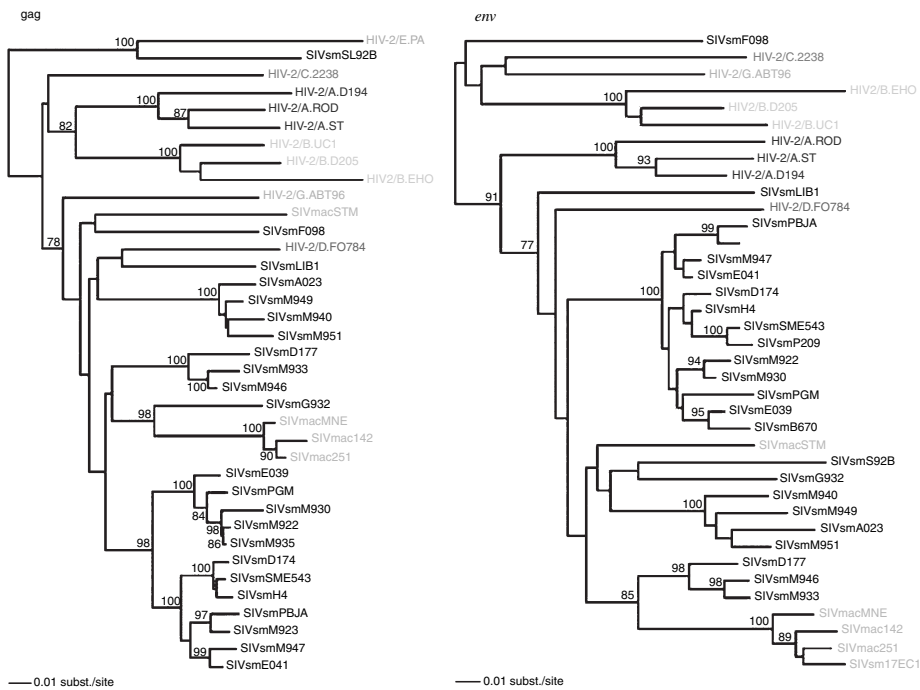


Fig. 2. Phylogenetic analysis showing the relationship between SIVsm and HIV-2.

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. SIV-sm 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 suggests 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.

References

1. AMARA RR, VILLINGER F, ALTMAN JD, LYDY SL, O'NEIL SP, STAPRANS SI, MONTEFIORI DC, XU Y, HERNDON JG, WYATT LS, CANDIDO MA, KOZYR NL, EARL PL, SMITH JM, MA HL, GRIMM BD, HULSEY ML, MILLER J, MCC-LURE HM, MCNICHOLL JM, MOSS B, ROBINSON HL: Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. *Science* 292:69–74, 2001.
2. APETREI C, GORMUS BJ, PANDREA I, METZGER M, TENHAAFT P, MARTIN LN, BOHM R, ALVAREZ X, KOOPMAN G, MURPHEY-CORB M, VEAZEY RS, LACKNER AA, BASKIN G, HEENEY J, MARX PA: Direct inoculation of SIVsm in black mangabey (*Lophocebus aterrimus*). First evidence of AIDS in a heterologous African species and different pathologic outcomes of experimental infection. *J Virol*, in press.
3. AYOUBA A, SOUQUIERES S, NJINKU B, MARTIN PM, MULLER-TRUTWIN MC, ROQUES P, BARRE-SINOUSSE F, MAUCLERE P, SIMON F, NERRIENET E: HIV-1 group N among HIV-1-seropositive individuals in Cameroon. *AIDS* 14:2623–2625, 2000.
4. AYOUBA A, MAUCLERE P, MARTIN PM, CUNIN P, MFOUPOUENDOUN J, NJINKU B, SOUQUIERE S, SIMON F: HIV-1 group O infection in Cameroon, 1986 to 1998. *Emerg Infect Dis* 7:466–467, 2001.
5. BARNETT SW, MURTHY KK, HERNDIER BG, LEVY JA: An AIDS-like condition induced in baboons by HIV-2. *Science* 266:642–646, 1994.
6. BECKERMAN KP: Long-term findings of HIVNET 012: the next steps. *Lancet* 362:842–843, 2003.
7. BEER BE, BAILES E, GOEKEN R, DAPOLITO G, COULIBALY C, NORLEY SG, KURTH R, GAUTIER JP, GAUTIER-HION A, VALLET D, SHARP PM, HIRSCH VM: Simian immunodeficiency virus (SIV) from sun-tailed monkeys (*Cercopithecus solatus*): evidence for host-dependent evolution of SIV within the *C. lhoesti* superspecies. *J Virol* 73:7734–7744, 1999.
8. BODELLE P, MCARTHUR CP, VALLARI A, COFFEY R, YAMAGUCHI J, DEVARE SG, BEYEME MA: Identification and genomic sequence of an HIV-1 group N isolate from Cameroon. *11th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA. Abstr. 145, 2004.
9. BRIDGES CB, LIM W, HU-PRIMMER J, SIMS L, FUKUDA K, MAK KH, ROWE T, THOMPSON WW, CONN L, LU X, COX NJ, KATZ JM: Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997–1998. *J Infect Dis* 185:1005–1010, 2002.
10. BROUSSARD SR, STAPRANS SI, WHITE R, WHITEHEAD EM, FEINBERG MB, ALLAN JS: Simian immunodeficiency virus replicate to high levels in naturally infected African green monkeys without inducing immunologic or neurologic disease. *J Virol* 75:2262–2275, 2001.
11. CAMPBELL GL, MARFIN AA, LANCIOTTI RS, GUBLER DJ: West Nile virus. *Lancet Infect Dis* 2:519–529, 2002.
12. CHAKRABARTI LA, LEWIN SR, ZHANG L, GETTIE A, LUCKAY A, MARTIN LN, SKULSKY E, HO DD, CHENG-MAYER C, MARX PA: Normal T-cell turnover in sooty mangabeys harboring active simian immunodeficiency virus infection. *J Virol* 74:1209–1223, 2000.
13. CHEN Z, TELFER P, GETTIE A, REED P, ZHANG L, HO DD, MARX PA: Genetic characterization of new West African simian immunodeficiency virus SIVsm: geographic clustering of household-derived SIV strains with human immunodeficiency virus type 2 subtypes and genetically diverse viruses from a single feral sooty mangabey troop. *J Virol* 70:3617–3627, 1996.
14. CHEN Z, LUCKAY A, SODORA DL, TELFER P, REED P, GETTIE A, KANU JM, SHADEK RF, YEE JA, HO DD, ZHANG L, MARX PA: Human immunodeficiency virus type 2 (HIV-2) seroprevalence and characterization of a distinct

- HIV-2 genetic subtype from the natural range of simian immunodeficiency virus-infected sooty mangabeys. *J Virol* 71:3953–3960, 1997.
15. CHITNIS A, RAWLS D, MOORE J: Origin of HIV type 1 in Colonial French Equatorial Africa? *AIDS Res Hum Retroviruses* 16:5–8, 2000.
 16. CLAAS EC, DE JONG JC, VAN BEEK R, RIMMELZWAAN GF, OSTERHAUS AD: Human influenza virus A/HongKong/156/97 (H5N1) infection. *Vaccine* 16:977–978, 1998.
 17. CORBET S, MULLER-TRUTWIN MC, VERSMISSE P, DELARUE S, AYOUBA A, LEWIS J, BRUNAK S, MARTIN P, BRUNVEZINET F, SIMON F, BARRE-SINOUSI F, MAUCLERE P: env Sequences of simian immunodeficiency viruses from chimpanzees in Cameroon are strongly related to those of human immunodeficiency virus group N from the same geographic area. *J Virol* 74:529–534, 2000.
 18. COURGNAUD V, SALEMI M, POURRUT X, MPOUDI-NGOLE E, ABELA B, AUZEL P, BIBOLLET-RUCHE F, HAHN B, VANDAMME AM, DELAPORTE E, PEETERS M: Characterization of a novel simian immunodeficiency virus with a vpu gene from greater spot-nosed monkeys (*Cercopithecus nictitans*) provides new insights into simian/human immunodeficiency virus phylogeny. *J Virol* 76:8298–8309, 2002.
 19. DAMOND F, APETREI C, ROBERTSON DL, SOUQUIERE S, LEPRETRE A, MATHERON S, PLANTIER JC, BRUN-VEZINET F, SIMON F: Variability of human immunodeficiency virus type 2 (HIV-2) infection in patients living in France. *Virology* 280:19–30, 2001.
 20. DAMOND F, WOROBEY M, CAMPA P, FARFARA I, COLIN G, MATHERON S, BRUN-VÉZINET F, ROBERTSON DL, SIMON F: Identification of a highly divergent HIV-2 and proposal for a change in HIV-2 classification. *AIDS Res Hum Retroviruses* 20:666–672, 2004.
 21. DESROSIERS RC: Prospects for an AIDS vaccine. *Nat Med* 10:221–223, 2004.
 22. DIOP OM, GUEYE A, DIAS-TAVARES M, KORNFELD C, FAYE A, AVE P, HUERRE M, CORBET S, BARRE-SINOUSI F, MÜLLER-TRUTWIN MC: High levels of viral replication during primary simian immunodeficiency virus SIVagm infection are rapidly and strongly controlled in African green monkeys. *J Virol* 74:7538–7547, 2000.
 23. DIXON B: The origins of AIDS. *Curr Biol* 9:R192, 1999.
 24. *Dorland's Illustrated Medical Dictionary*, 28th edn, Philadelphia, PA: WB Saunders Co., 1994.
 25. DRUCKER E, ALCABES PG, MARX PA: The injection century: massive unsterile injections and the emergence of human pathogens. *Lancet* 358:1989–1992, 2001.
 26. EMAU P, MCCLURE HM, ISAHAKIA M, ELSE JG, FULTZ PN: Isolation from African Sykes' monkeys (*Cercopithecus mitis*) of a lentivirus related to human and simian immunodeficiency viruses. *J Virol* 65:2135–2140, 1991.
 27. GAO F, YUE L, ROBERTSON DL, HILL SC, HUI H, BIGGAR RJ, NEEQUAYE AE, WHELAN TM, HO DD, SHAW GM, SHARP PM, HAHN BH: Genetic diversity of human immunodeficiency virus type 2: evidence for distinct sequence subtypes with differences in virus biology. *J Virol* 68:7433–7447, 1994.
 28. GAO F, BAILES E, ROBERTSON DL, CHEN Y, RODENBURG CM, MICHAEL SF, CUMMINS LB, ARTHUR LO, PEETERS M, SHAW GM, SHARP PM, HAHN BH: Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. *Nature* 397:436–441, 1999.
 29. GOLDSTEIN S, OURMANOV I, BROWN CR, BEER BE, ELKINS WR, PLISHKA R, BUCKLER-WHITE A, HIRSCH VM: Wide range of viral load in healthy African green monkeys naturally infected with simian immunodeficiency virus. *J Virol* 74:11744–11753, 2000.
 30. GRIMM TA, BEER BE, HIRSCH VM, CLOUSE KA: Simian immunodeficiency viruses from multiple lineages infect human macrophages: implications for cross-species transmission. *J Acquir Immune Defic Syndr* 32:362–369, 2003.
 31. HAHN BH, SHAW GM, De COCK KM, SHARP PM: AIDS as a zoonosis: scientific and public health implications. *Science* 287:607–614, 2000.
 32. HIRSCH VM, CAMPBELL BJ, BAILES E, GOEKEN R, BROWN C, ELKINS WR, AXTHELM M, MURPHEY-CORB M, SHARP PM: Characterization of a novel simian immunodeficiency virus (SIV) from L'Hoest monkeys (*Cercopithecus lhoesti*): implications for the origins of SIVmnd and other primate lentiviruses. *J Virol* 73:1036–1045, 1999.
 33. HOCHSCHILD A: *King Leopold's Ghost. A Story of Greed, Terror, and Heroism in Colonial Africa*. Boston, Massachusetts: Houghton Mifflin Comp, 1998.
 34. JACKSON JB, MUSOKE P, FLEMING T, GUAY LA, BAGENDA D, ALLEN M, NAKABIITO C, SHERMAN J, BAKAKI P, OWOR M, DUCAR C, DESEYVE M, MWATHA A, EMEL L, DUEFIELD C, MIROCHNICK M, FOWLER MG, MOFENSON L, MIOTTI P, GIGLIOTTI M, BRAY D, MMIRO F: Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 362:859–868, 2003.
 35. KHABBAZ RF, ROWE T, MURPHEY-CORB M, HENEINE WM, SCHABLE CA, GEORGE JR, PAU CP, PAREKH BS, LAIRMORE MD, CURRAN JW, SCHOCHETMAN G, LAIRMORE MD, MURPHEY-CORB M: Simian immunodeficiency virus needlestick accident in a laboratory worker. *Lancet* 340:271–273, 1992.
 36. KHABBAZ RF, HENEINE W, GEORGE JR, PAREKH B, ROWE T, WOODS T, SWITZER WM, MCCLURE HM, MURPHEY-CORB M, FOLKS TM: Brief report: infection of a laboratory worker with simian immunodeficiency virus. *N Engl J Med* 330:172–177, 1994.
 37. LAVER G, GARMAN E: Pandemic influenza: its origin and control. *Microbes Infect* 4:1309–1316, 2002.
 38. LING B, APETREI C, PANDREA I, VEAZEY RS, LACKNER AA, GORMUS B, MARX PA: Classic AIDS in a sooty mangabey after an 18-year natural infection. *J Virol* 78:8902–8908, 2004.
 39. LOCHER CP, WITT SA, HERNDIER BG, ABBEY NW, TENNER-RACZ K, RACZ P, KIVIAT NB, MURTHY KK, BRASKY K, LELAND M, LEVY JA: Increased virus replication and virulence after serial passage of human immunodeficiency virus type 2 in baboons. *J Virol* 77:77–83, 2003.
 40. MAHY BWJ: *A Dictionary of Virology*, 2nd edn. New York: Academic Press, 1997.
 41. MARX PA, LI Y, LERCHE NW, SUTJIPTO S, GETTIE A, YEE JA, BROTMAN BH, PRINCE AM, HANSON A, WEBSTER RG, DESROSIERS RC: Isolation of a simian immunodeficiency virus related to human immunodeficiency virus type 2 from a west African pet sooty mangabey. *J Virol* 65:4480–4485, 1991.
 42. MARX PA, ALCABES PG, DRUCKER E: Serial human passage of simian immunodeficiency virus by unsterile injections and the emergence of epidemic human immunodeficiency virus in Africa. *Philos Trans R Soc Lond B Biol Sci* 356:911–920, 2001.
 43. ONANGA R, KORNFELD C, PANDREA I, ESTAQUIER J, SOUQUIÈRE S, ROUQUET P, POATY-MAVOUNGOU V,

- M'BOUP S, BARRÉ-SINOUSSE F, SIMON F, APETREI C, ROQUES P, MÜLLER-TRUTWIN MC: High levels of viral replication contrast with only transient changes in CD4⁺ and CD8⁺ cell numbers during the early phase of experimental infection with simian immunodeficiency virus SIVmnd-1 in *Mandrillus sphinx*. *J Virol* 76:10256–10263, 2002.
44. OSTERHAUS AD, PEDERSEN N, van AMERONGEN G, FRANKENHUIS MT, MARTHAS M, REAY E, ROSE TM, PAMUNGKAS J, BOSCH ML: Isolation and partial characterization of a lentivirus from talapoin monkeys (*Myopithecus talapoin*). *Virology* 260:116–124, 1999.
 45. PALELLA FJ, Jr, DELANEY KM, MOORMAN AC, LOVELESS MO, FUHRER J, SATTEN GA, ASCHMAN DJ, HOLMBERG SD: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 338:853–860, 1998.
 46. PANDREA I, ONANGA R, ROUQUET P, BOURRY O, NGARI P, WICKINGS EJ, ROQUES P and APETREI C: Chronic SIV infection ultimately causes immunodeficiency in African non-human primates. *AIDS* 15:2461–2462, 2001.
 47. PEETERS M, COURGNAUD V, ABELA B: Genetic diversity of lentiviruses in non-human primates. *AIDS Rev* 3:3–10, 2001.
 48. PEETERS M, COURGNAUD V, ABELA B, AUZEL P, POURRUT X, BIBOLLET-RUCHE F, LOUL S, LIEGEOIS F, BUTEL C, KOULAGNA D, MPOUDI-NGOLE E, SHAW GM, HAHN BH, DELAPORTE E: Risk to human health from a plethora of simian immunodeficiency viruses in primate bushmeat. *Emerg Infect Dis* 8:451–457, 2002.
 49. RAMSBURG E, ROSE NF, MARX PA, MEFFORD M, NIXON DF, MORETTO WJ, MONTEFIORI D, EARL P, MOSS B, ROSE JK: Highly effective control of an AIDS virus challenge in macaques by using vesicular stomatitis virus and modified vaccinia virus Ankara vaccine vectors in a single-boost protocol. *J Virol* 78:3930–3940, 2004.
 50. REY-CUILLE MA, BERTHIER JL, BOMSEL-DEMONTROY MC, CHADUC Y, MONTAGNIER L, HOVANESSIAN AG, CHAKRABARTI LA: Simian immunodeficiency virus replicates to high levels in sooty mangabeys without inducing disease. *J Virol* 72:3872–3886, 1998.
 51. ROSE NF, MARX PA, LUCKAY A, NIXON DF, MORETTO WJ, DONAHOE SM, MONTEFIORI D, ROBERTS A, BUONOCORE L, ROSE JK: An effective AIDS vaccine based on live attenuated vesicular stomatitis virus recombinants. *Cell* 106:539–549, 2001.
 52. RUPPRECHT CE, HANLON CA, HEMACHUDHA T: Rabies re-examined. *Lancet Infect Dis* 2:327–343, 2002.
 53. SHIVER JW, FU TM, CHEN L, CASIMIRO DR, DAVIES ME, EVANS RK, ZHANG ZQ, SIMON AJ, TRIGONA WL, DUBEY SA, HUANG L, HARRIS VA, LONG RS, LIANG X, HANDT L, SCHLEIF WA, ZHU L, FREED DC, PERSAUD NV, GUAN L, PUNT KS, TANG A, CHEN M, WILSON KA, COLLINS KB, HEIDECKER GJ, FERNANDEZ VR, PERRY HC, JOYCE JG, GRIMM KM, COOK JC, KELLER PM, KRESOCK DS, MACH H, TROUTMAN RD, ISOPI LA, WILLIAMS DM, XU Z, BOHANNON KE, VOLKIN DB, MONTEFIORI DC, MIURA A, KRIVULKA GR, LIFTON MA, KURODA MJ, SCHMITZ JE, LETVIN NL, CAULFIELD MJ, BETT AJ, YUIL R, KASLOW DC, EMINI EA: Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature* 415:331–335, 2002.
 54. SMITH SM, MAKUWA M, LEE F, GETTIE A, RUSSO C, MARX PA: SIVrcm infection of macaques. *J Med Primatol* 27:94–98, 1998.
 55. SOUQUIERE S, BIBOLLET-RUCHE F, ROBERTSON DL, MAKUWA M, APETREI C, ONANGA R, KORNFELD C, PLANTIER JC, GAO F, ABERNETHY K, WHITE LJ, KARESH W, TELFER P, WICKINGS EJ, MAUCLERE P, MARX PA, BARRE-SINOUSSE F, HAHN BH, MULLER-TRUTWIN MC, SIMON F: Wild *Mandrillus sphinx* are carriers of two types of lentivirus. *J Virol* 75:7086–7096, 2001.
 56. *Stedman's Medical Dictionary*, 27th edn, Philadelphia, PA: Lippincott, Williams & Wilkins, 2000.
 57. TAKEHISA J, HARADA Y, NDEMBI N, MBOUDJEKA I, TANIGUCHI Y, NGANSOP C, KUATE S, ZEKENG L, IBUKI K, SHIMADA T, BIKANDOU B, YAMAGUCHI-KABATA Y, MIURA T, IKEDA M, ICHIMURA H, KAPTUE L, HAYAMI M: Natural infection of wild-born mandrills (*Mandrillus sphinx*) with two different types of simian immunodeficiency virus. *AIDS Res Hum Retroviruses* 17:1143–1154, 2001.
 58. TRAINA-DORGE V, BLANCHARD J, MARTIN L, MURPHEY-CORB M: Immunodeficiency and lymphoproliferative disease in an African green monkey dually infected with SIV and STLV-I. *AIDS Res Hum Retroviruses* 8:97–100, 1992.
 59. VILLINGER F, SWITZER WM, PAREKH BS, OTTEN RA, ADAMS D, SHANMUGAM V, BOSTIK P, MAYNE AE, CHIKKALA NF, MCCLURE HM, NOVEMBRE F, YAO Q, HENEINE W, FOLKS TM, ANSARI AA: Induction of long-term protective effects against heterologous challenge in SIVhu-infected macaques. *Virology* 278:194–206, 2000.
 60. WENSING AM, BOUCHER CA: Worldwide transmission of drug-resistant HIV. *AIDS Rev* 5:140–155, 2003.
 61. WHO: *AIDS Epidemic Update: December 2003*. Geneva, Switzerland: UNAIDS. <http://www.who.int/hiv/pub/epidemiology/epi2003/en/>.
 62. YAMAGUKI JY, DEVARE SG, BRENNAN CA: Identification of a new HIV-2 subtype based on phylogenetic analysis of full-length genomic sequence. *AIDS Res Hum Retroviruses* 16:925–930, 2000.