HIV and sexually transmitted disease

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Historical background to the AIDS epidemic, 1981–1984

In June 1981, the Morbidity and Mortality Weekly Report\(^1\) carried a report of five deaths due to overwhelming *Pneumocystis carinii* pneumonia in Los Angeles, California. *P. carinii* has been recognised for many years as a human opportunistic infection, infrequently causing life-threatening pneumonia in patients with naturally occurring or iatrogenic immunosuppression. Since the development of immunosuppressive regimens for overcoming transplantation rejection, *Pneumocystis* has been seen in patients with compromised cellular immunity. All of the five patients reported\(^1\) had been homosexual men with no prior illness or history of congenital immunodeficiency, and none had taken known immunosuppressive drugs. In December 1981, three reports in the *New England Journal of Medicine* described the medical presentation and laboratory characterisation of a further 20 homosexual men who had died of unexplained immunodeficiency. In every case, previously healthy young men (mean age 35 years) had developed overwhelming opportunistic infections associated with profound cellular immunodeficiency, or Kaposi's sarcoma, a tumour previously associated with immunosuppression. All the patients had an absolute decrease in the number and proportion of CD4+ve T-lymphocytes, and a specific loss of T-cell immunity. The syndrome was initially termed 'gay-related immune deficiency' (GRID), but by the end of 1982, cases of this acquired immunodeficiency had been reported in intravenous drug users, female sexual partners of index cases, children of affected women and in heterosexual men and women from Haiti resident in the US\(^2\). As this disease was clearly not linked exclusively to homosexuality, the term acquired immune deficiency syndrome (AIDS) was adopted\(^2\).

Following the description of AIDS in the US, the disease was described in homosexual men and in intravenous drug users throughout Europe, South Africa and Australia by the end of 1982\(^2\). Subsequently, in 1984, it was reported that heterosexual cases of AIDS were occurring in large numbers in West, Central and Eastern Africa, involving minimally the...
countries of Zaire, Uganda and Rwanda. The global distribution of cases and the occurrence of disease in identical risk groups in different countries suggested strongly that an infectious agent was responsible for the epidemic and, as blood-borne transmission was common, it was most likely to be a virus. Two distinct patterns of transmission were observed:\(^3\): pattern 1 was that of a blood-borne agent which was transmitted in a similar manner to the hepatitis B virus, and was prevalent in homosexual men, i.v. drug users, their sexual partners, and in recipients of blood and blood products. Pattern 1 transmission was occurring throughout the western world, and had turned the US cases into a pandemic over a very short period. Pattern 2 transmission was more similar to a classical sexually transmitted disease, and approximately equal numbers of male and female cases were found; pattern 2 transmission predominated in the developing world, in particular in sub-Saharan Africa\(^3\).

From early 1982 onwards, efforts to identify the causative agent intensified and, in May 1983, a group from the Institut Pasteur, Paris, reported the isolation and propagation of a T-lymphotropic retrovirus, lymphadenopathy associated virus, LAV, from the lymph node of a patient with persistent lymphadenopathy, a syndrome known to be associated with, and preceding the development of, AIDS\(^4\). This virus had been fully characterised by 1984, and formally termed the human immunodeficiency virus type 1 (HIV-1) in 1986. Serological assays for antibodies to HIV-1 were widely commercially available by 1985, allowing large-scale sero-epidemiology and screening to be undertaken. Examination of stored sera revealed that HIV-1 had been introduced into homosexual men in the US during 1978, and had not existed in the US prior to that time. Subsequently, a serological variant, HIV-2, was identified in West Africa\(^5\). HIV-2 leads to persistent life-long infection, and is also associated with the clinical development of AIDS, many years after infection. However, there are reproducible data which show that the likelihood of AIDS developing after HIV-2 infection are lower at 10 years post-infection than with HIV-1, and that HIV-2 is generally less pathogenic, and less transmissible, than HIV-1\(^6\). These epidemiological observations are matched by an apparent lower HIV-2 viral load in peripheral blood than seen in the corresponding time from infection in HIV-1 infected subjects\(^7\).

The full-length sequencing of HIV-1 and HIV-2 isolates revealed that these viruses were lentiviruses, of the retrovirus family, and that all isolates shared a common tropism for T-lymphocytes, through the use of the CD4 receptor\(^8\). The emergence of a new infectious agent in a human population can have only a limited range of explanation; either the infection was previously in an isolated human population from which it had been exported though some societal change, or else it might
have been a zoonosis, newly exposed to human transmission. A third line of explanation, that of an extra-terrestrial or even a man-made origin, has been popular with conspiracy theorists, but will not be further discussed.

The natural history of HIV-1 infection is marked by the long period of time between infection and disease. Following infection across a genital surface, involving infection of CD4/CCR5 bearing cells in the mucosa or submucosa, the virus presumably migrates to a regional lymph node, where viral replication occurs\(^{10}\). A number of rounds of viral replication then occur within the bounds of the regional lymph node, as no detectable virus or immune response occurs for up to 42 days post infection. When the quantity of infected cells exceeds a threshold, viraemia occurs, and the symptoms of an acute non-specific viral illness with tender adenopathy, sore throat, diffuse macular rash, arthralgia and fever. Following the acute viraemia, when up to \(10^7\) viral particles/ml plasma can be found, a primary immune response develops with antibodies to viral proteins and a cytotoxic T-cell response, which limit viral replication and clear viral particles from the plasma. The reduction in viral load in plasma is not matched by a clearance of provirus from peripheral blood mononuclear cells, and cellular viraemia continues in the face of a persistent and sustained cellular and humoral immune response for the duration of the infection. Even while plasma viral load is suppressed by the immune response, CD4+ve T-lymphocyte numbers fall in a linear manner over time (see Fig. 1). The most plausible explanation for the pathogenesis of AIDS over time is the sustained loss of CD4 cells by ongoing HIV viral replication in mature peripheral blood T cells, and by a slight failure of production to match peripheral destruction of HIV+ve CD4+ve cells\(^{11,12}\). However, recent controversy over the pathogenic mechanisms and homeostasis of T-cells...
Resurgent/emergent infectious diseases has revealed that simple viral cytopathic effect on CD4+ve cells may be overly simplistic a model\textsuperscript{13}.

During the course of HIV infection, CD4+ve cells continue to decline in peripheral blood, and plasma viral load slowly rises; on average, CD4+ve cells are lost at a rate of 70 cells/\mu l/year. Over a period of 10–12 years, CD4 cell number declines from a median of 800 to 200/\mu l; at this level, the probability of the cellular immune system containing latent or environmental infections such as \textit{P. carinii} falls, and clinical opportunistic infection becomes increasingly possible. As the viral load rises, HIV isolates with altered co-receptor usage appear, which can use the CXCR4 chemokine receptor rather than CCR5; these isolates are more cytopathic \textit{in vitro}, and may lead to wider tissue distribution of HIV in later disease. AIDS is, therefore, the clinical condition of an immune system which is sufficiently compromised by HIV infection that there is an inability to protect against the growth of low grade pathogens or viral induced tumours.

The application of viral gene sequencing to the study of HIV-1 infection has been particularly informative. It was noted as early as 1985 that no two sequences of HIV-1 isolates were genetically identical\textsuperscript{14}. HIV-1 isolates from patients in the US and in Zaire could differ by as much as 35% in their viral envelope (SU) amino-acid sequences. Even within an individual patient, multiple viral sequences could be obtained, and the swarm of related but separate viral genomes within a single host is termed a quasi-species. The SU protein of viruses within one individual may vary by up to 5% in amino acid sequence, although in phylogenetic analysis, these variants can be shown to be clearly related to a common ancestor viral sequence\textsuperscript{15}. The causes of this extreme viral variability are the lack of proof reading in viral reverse transcription (RT), the error-prone RT enzyme which mis-incorporates at a rate of 1:10\textsuperscript{4} bases, and immune and receptor pressure exerted by the host, which allows for variants to compete for fitness\textsuperscript{16}. On a population level, this potential for viral variability leads to the selection of viral variants upon transmission, resulting in global diversity of HIV strains. However, global sequence analyses reveal that the diversity can be grouped into related sequences, or viral subtypes. At least ten genetic subtypes of HIV-1 have now been described, termed HIV-1 subtypes A–J\textsuperscript{17}, see Figure 2. Of these groups, subtype B has been responsible for the pandemic of infection in homosexual men and i.v. drug users world-wide. All subtypes have been described in sub-Saharan Africa, but more limited subtypes account for new epidemic infections; for example, the heterosexual epidemic in south east Asia and Thailand is almost exclusively E subtype, and the C subtype accounts for most infections in southern Africa. As multiple infection can occur in one subject, at least prior to sero-conversion, recombination between subtypes is possible,
and many chimaeric or recombinant viruses are now described. There are no convincing data at this time of any significant biological differences between the viral genetic subtypes, and they are not viral serotypes in the conventional use of the term. However, it is possible that variants will emerge which are more pathogenic or transmissible over time.

**Animal lentiviruses**

It is now clear that lentiviruses are common causes of exogenous infections of mammalian hosts, generally maintained within the

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**Fig. 2** HIV phylogenetic tree. The viral genetic subtypes of HIV-1, by weighted analysis in the env gene, of subtypes A–H, and the outlier subtype O. The position of SIVcpz, the only non-human isolate to fall within the HIV-1 tree, is also noted.
population at high levels of infection through vertical transmission. All lentiviruses lead to life-long persistent infection, in which the virus is persistently replicating throughout the course of infection, independently of whether the virus is pathogenic within its host. Table 1 shows the lentiviruses identified in a range of mammals; infection is either clinically silent, such as BIV infection of cattle or SIV infection of chimpanzees, or is associated with lymphocytic inflammatory disease of the central nervous system (as in CAEV and MVV). The only species to develop an AIDS-like syndrome in the context of natural infection is the cat, in which horizontally or vertically acquired FIV infection can lead to feline AIDS; the development of AIDS in simian species infected with SIV does not appear to occur following natural infection, but may be induced following experimental infection of Asian old world monkeys, such as rhesus macaques, with SIV isolates derived from naturally infected African old world monkeys, such as the SIV<sub>sm</sub> derived from the West African Sooty Mangabey<sup>19</sup>. Thus, there is a model for the development of human AIDS whereby a virus which is endemic and non-pathogenic in its ‘natural’ host (SIV<sub>sm</sub>) may acquire a pathogenic phenotype on transmission to a non-natural host, the rhesus macaque. A non-pathogenic simian lentivirus might be anticipated to have a new phenotype if transmitted to man.

Lentivirus infection can be extremely widespread within a single animal genus. For example, FIV infection can be identified by serological screening, and appears to infect up to 20% of domestic and household pet cats in the UK, US and Australia<sup>20</sup>. Similar rates of FIV infection have been reported in lions and cheetahs in the Serengeti reserve in Kenya/Tanzania, East Africa. This would imply that FIV infection of felines predates their speciation, approximately 20 million years ago. SIV<sub>agm</sub> infection of African green monkeys (AGM) is found at very high levels in wild caught populations, with population rates of up to 50% by serology. Unlike FIV infection, there is no evidence that SIV<sub>agm</sub> infection leads to any discernible disease or immunosuppression in AGMs. There are three discrete sub-populations of African green monkeys in sub-Saharan Africa, termed vervet, grivet and sebaeus

### Table 1 Mammalian lentiviruses

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<th>Virus</th>
<th>Host</th>
<th>Disease</th>
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<td>Human immunodeficiency virus</td>
<td>HIV</td>
<td>AIDS</td>
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<tr>
<td>Simian immunodeficiency virus</td>
<td>SIV</td>
<td>AIDS or apathogenic</td>
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<td>Bovine immunodeficiency virus</td>
<td>BIV</td>
<td>Lymphadenopathy</td>
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<td>Maedi-Visna virus</td>
<td>MVV</td>
<td>Encephalitis/pneumonitis</td>
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<td>Caprine arthritis-encephalitis virus</td>
<td>CAEV</td>
<td>Arthritis/encephalitis</td>
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<td>Equine infectious anaemia virus</td>
<td>EIAV</td>
<td>Aplastic anaemia</td>
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<td>Feline immunodeficiency virus</td>
<td>FIV</td>
<td>AIDS</td>
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monkeys. Phylogenetic analysis of SIV<sub>agm</sub> sequences shows that SIV<sub>agm</sub> subtypes can be identified, which correspond to the sub-populations; thus, SIV<sub>agm</sub> is also likely to be an old infection preceding their geographical distribution throughout Africa\textsuperscript{19}.

Transmission of FIV appears to occur horizontally through biting and scratching between adults cats, with little evidence of sexual transmission, and by vertical transmission through breast milk predominantly. Similarly, natural transmission of SIV appears to be non-sexual between adults, and SIV appears to be maintained in the population largely through vertical transmission.

Table 2 shows the grouping of primate lentiviruses into five subgroups: human isolates appear in two of these groups; the SIV<sub>sm</sub> group also contains the HIV-2 isolates, and the SIV<sub>cpp</sub> group contains the HIV-1 isolates. The remaining three subgroups, representing SIV isolates from the mandrill (SIV<sub>mdn</sub>), the Sykes' monkey (SIV<sub>syk</sub>) and the African green monkey (SIV<sub>agm</sub>), do not appear to have any corresponding human isolates yet identified.

Few animal lentiviruses currently have defined cell surface virus receptors, with the notable exception of the SIV/HIV groups. All SIV and HIV isolates of all five groups bind primarily with high affinity to the CD4 molecule, and subsequently require a lower affinity interaction between the viral surface glycoprotein (SU) and a 7-transmembrane co-receptor molecule, the chemokine receptor CCR5 or CXCR4\textsuperscript{21}. All primary human HIV infections appear to involve viruses which are CD4/CCR5 tropic, and the SIV<sub>sm</sub> isolates which can infect rhesus macaques appear to use the identical CD4/CCR5 receptor/co-receptors also. The FIV receptor is not feline CD4, but probably feline CD9; however, FIV appears to also use the CXCR4 co-receptor for entry. McClure has previously shown that the CD4 molecule is well conserved in humans, apes and monkeys, and this common receptor and co-receptor

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<th>Group</th>
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<tr>
<td>I</td>
<td>HIV-1</td>
<td>Human</td>
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<td></td>
<td>HIV-2</td>
<td>Human</td>
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<tr>
<td>II</td>
<td>SIV&lt;sub&gt;agm&lt;/sub&gt; sebaeus</td>
<td>African green monkey</td>
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<td></td>
<td>SIV&lt;sub&gt;agm&lt;/sub&gt; grivet</td>
<td>African green monkey</td>
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<td>African green monkey</td>
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<td>III</td>
<td>SIV&lt;sub&gt;agm&lt;/sub&gt;</td>
<td>Mandrill</td>
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<td>IV</td>
<td>SIV&lt;sub&gt;agm&lt;/sub&gt;</td>
<td>Sykes' monkey</td>
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usage has allowed the entry of HIV-like viruses into human populations.$^{22}$

**Zoonotic origin of HIV**

Of the five groups of primate lentiviruses, defined by phylogenetic analyses of viral gene sequences, shown in Table 2, two groups contain viruses which can be found in both human and natural simian infections. This association of related viral sequences in both primate and man immediately lead to the likelihood of a zoonotic origin to the human infection. The potential zoonotic origins of HIV-1 and HIV-2 need to considered separately, and the information is considerably more partial for HIV-1 than HIV-2.

**Origin of HIV-2**

The most compelling data on the origins of HIV-2 come from the work of Hahn and colleagues (University of Alabama), in studying HIV-2 infections and SIV$_{sm}$ in Liberia. Through phylogenetic analyses on the SIV$_{sm}$ sequences from multiple unrelated wild caught animals, they were able to demonstrate a number of related but independent strains of SIV.$^{23}$ A similar phylogenetic analysis of human HIV-2 infections from a region overlapping the origin of the SIV strains revealed a similar distribution of strains, genetically related to the diversity of the SIV strains. From these data, Hahn argued for the interpretation of multiple entry of SIV$_{sm}$ into the human population as HIV-2, rather than a point source epidemic, and speculated that many human infections may have occurred relatively over a long period of time. The near genetic identity of SIV$_{sm}$ and HIV-2 and the similar sub-type organisation of the two groups of viruses would support this hypothesis. The relatively low transmissibility of HIV-2, and its lower pathogenicity, have been responsible for the failure of HIV-2 to become epidemic in Africa, or pandemic. Indeed, although HIV-2 infection has been reported in India, South Africa, China, Europe and the US, there is little evidence of epidemic spread of HIV-2 from index cases in any of those countries.

**Origins of HIV-1**

The data on the possible zoonotic origins of HIV-1 are far less convincing than for HIV-2 and, to date, it has not been possible to identify a species convincingly infected in the wild with an HIV-1-like
HIV and AIDS

SIV virus. However, there have now been four independent isolations of an HIV-1 related SIV\textsuperscript{cpz} from wild caught chimpanzees, in the West Africa state of Gabon\textsuperscript{24}. Despite these wholly plausible and reproducible isolations, serological surveys of chimpanzees have not revealed widespread infection of this species by SIV\textsuperscript{cpz}, and the possibility of acquisition of infection in the chimpanzee through predation of another as yet unidentified species cannot be ruled out. By phylogenetic analysis, the SIV\textsuperscript{cpz} is more closely related to HIV-1 than to HIV-2 or other SIV isolates; however, there is still a significant evolutionary distance between HIV-1 and the chimp SIV\textsuperscript{cpz} sequences, suggesting that these SIVs cannot be the immediate origin of the human epidemic.

Additional insight into the evolutionary origins of HIV-1 have come from the global HIV genotyping initiative undertaken under the direction of the World Health Organization HIV Isolation and Characterisation Network. Phylogenetic analysis of sequences of HIV-1 isolates from diverse geographical locations have allowed the genetic subtypes of HIV-1 to be defined, into groups A–J; each subgroup contains viruses which may differ in up to 12–15% in amino-acid sequence, but the sequence differences between the subtypes exceed 25–30% (see Fig. 2). Each subtype seems to be equidistant from the others, in a star phylogeny in the rooted trees. There has been considerable investigation of the distribution of the genetic subtypes internationally. As noted above, the homosexual and IVDU epidemic from 1981 onwards was exclusively of subtype B, in the US, Europe, South Africa, Thailand and Australia. Subsequent heterosexual epidemics from 1990 onwards in South Africa and Thailand have been exclusively of subtypes C and E, respectively, representing new incoming subtypes rather than transmission from the previously infected endogenous groups. This implies that there was little sexual mixing between the earliest groups to be infected in these countries, for example homosexual white middle class men in South Africa infected in early 1980s with B subtype, and the subsequent epidemic of subtype C infection in black heterosexuals in the townships, mines and homelands. While groups have argued that subtypes C or E might be biologically advantageous to heterosexual transmission, through tropism for Langerhans cells in the vagina, for example, there is little consensus on the reproducibility of these findings, and it is equally plausible that the emergence of mono-subtype epidemics represents a founder effect rather than a biological tropism.

In sub-Saharan Africa, the finding of multiple HIV-1 genetic subtypes within a single risk group and geographical location is the norm. In Uganda, population based studies reveal HIV-1 subtypes A and D predominate, and co-exist within all parts of the country. In similar studies in Gabon and Cameroun, it is possible to identify all subtypes
A–J through examination of randomly selected HIV-1+ve subjects attending clinics, and it appears that all subtypes are currently circulating and being transmitted in these countries. The countries with the greatest prevalence of diverse subtypes are Gabon, Cameroun, Central African Republic and Zaire, and the frequency of subtypes diminishes with distance from these countries, with the epidemic showing the greatest homogeneity in South Africa\textsuperscript{18}. The current interpretation of these data is that the countries with the greatest genetic diversity are those in which the HIV-1 epidemic is oldest. There is a remarkable overlap between the distribution of the SIV\textsubscript{cpz} isolates, from Gabon, and those countries with the greatest frequency of divergent sequences, which include Gabon. Finally, in the course of a serological survey of sera from Cameroun from 1956, a partial HIV-1 viral sequence has been amplified by PCR; this ancestral HIV-1 sits close to the centre of the phylogenetic tree shown in Figure 2, and is related to the B and D subtypes. Analysis of the divergence of sequence all suggest an origin of HIV-1 in human populations of approximately 50 years\textsuperscript{26}.

**Origins of the HIV-1 pandemic**

The evidence outlined above points to an origin of HIV-1 as a new human infection in the past 50 years, most likely as a zoonosis from a simian host in west central Africa. There is no documented clinical, serological or virological evidence of HIV-1 occurring in human populations before the 1950s. The great diversity of HIV-1 sequences within the human population are compatible with a recent origin, although none of these pieces of evidence are conclusive. Nonetheless, it is worthwhile considering the rise of the HIV epidemic in the context of population movements and social change in sub-Saharan Africa since the second World War. This period has been marked by migration of large populations from low density rural environments to high density urban and peri-urban townships, shanties and towns. It is reasonable to hypothesise that HIV-1 infection, arising in humans from a zoonotic origin, may have occurred intermittently in rural areas in Gabon, where infected animals and humans may have frequently encountered one another. Infection of adults in areas of low social mobility might have lead to some horizontal transmission through sexual intercourse, but the infection would have required substantial vertical transmission from mother to child in order to be sustained within the population. In the case of HIV-2, low pathogenic potential leads to a long period of infectious carriage; however, the pathogenic nature of HIV-1 would lead to high mortality in infected adults. The low expectation of children infected at birth to survive to maturity would not allow significant
vertically acquired infection to contribute to adult horizontal transmission. Only with the movement of populations to a peri-urban or urban environment, with greater potential from horizontal sexual transmission, could HIV-1 infection become epidemic.

**Impact of sexually transmitted diseases**

This movement of small numbers of HIV-1 infected adults to a more densely populated peri-urban area would allow for rapid dissemination of a sexually transmitted agent through the more extended sexual networks associated with urban life. The impact of untreated sexually transmitted diseases, such as syphilis, gonorrhoea and chancroid, in causing genital ulceration and facilitating the spread of HIV-1 is considerably higher in sub-Saharan Africa than elsewhere. Several studies have demonstrated the facilitating effect of genital ulcer disease on HIV transmission, presumably both by increasing HIV load in genital secretions through the presence of inflammatory cells including CD4+ve T-cells, and by facilitating transmission across a disrupted mucosal surface\(^2\). While there had been considerable opportunity for STDs to be controlled in Africa through population based diagnosis and treatment, even up to the present day there has been little investment in health care services for STDs. The failure to control STDs was not due to antibiotic resistance, nor to any emergent or resurgent organisms, but simply through lack of political will to invest in control measures.

**Non-infectious factors in HIV transmission**

The great social changes since 1945 do not only involve movement of populations from the rural to the urban environment, but also include technological changes of great impact. Parenteral access to the body via the use of re-useable and subsequently disposable hypodermic needles and syringes, the ability to undertake blood transfusion and widespread immunisation have had a major impact on the delivery of health care, and for the control of infectious disease. However, contamination of needles or blood has also acted to transit viral infection, and this mode of transmission has undoubtedly exacerbated the dissemination of HIV through populations. While there has been speculation that widespread immunisation may have directly lead to HIV transmission, and indeed might have been the cause of the epidemic, there are no data to suggest direct contamination of vaccine stocks in the 1950s, nor of any transmission of SIV via the African green monkey kidney cells used to propagate polio vaccine strains.
Comparison with endemic human retroviruses

The HIV epidemic must be compared and contrasted to the epidemiology of the other human retrovirus, the human T-cell leukaemia/lymphoma virus, HTLV-I and HTLV-II. These oncornaviruses are endemic in old human populations, and are found in 2–5% of the population in West Africa, and in migrants from this region to North, Central and South America; in Japan and the eastern seaboard of Asia, in Melanesia and in Australian Aboriginals, and in Amerindians. This distribution suggests human infection at least for 50,000 years. There is a related simian virus, STLV, which is found in both Asian and African old world monkeys, and presumably HTLV was initially a zoonosis, although the infection has been maintained in human populations through horizontal and vertical transmission. The infection is persistent and lifelong, but mortality is low, and morbidity uncommon until after the reproductive years, allowing a stable endemic infection to be established. However, population movements and social changes since 1945 are also leading to new epidemic dissemination of HTLV-I as a sexually transmitted infection in Europe, and to a global epidemic of HTLV-II in IVDUs. It is not yet clear whether the movement of HTLV into new populations will affect the clinical manifestations or frequency of pathology, as it is likely that the pathogenesis of the HTLV associated diseases have an immunogenetic basis. Thus new epidemic spread may not only lead to global distribution of a previously localised endemic disease, but may also affect disease manifestations.

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