Since the isolation of HIV, multiple transmissions are thought to have occurred between man and other old-world primates. Assessment of samples from apes and human beings with African equatorial forest ancestry has traced the origin of HIV-1 to chimpanzees, and dated its most recent common ancestor to 1908. The evolution of HIV-1 has been rapid, which has resulted in a complex classification, worldwide spread, and intermixing of strains; at least 48 circulating recombinant forms are currently identified. In addition to posing a nearly insurmountable challenge for diagnosis, treatment, vaccine development, and prevention, this extreme and divergent evolution has led to differences in virulence between HIV-1 groups, subtypes, or both. Coincidental changes in human migration in the Congo river basin also affected spread of disease. Research over the past 25 years and advances in genomic sequencing methods, such as deep DNA sequencing, have greatly improved understanding and analysis of the thousands to millions of full infectious HIV-1 genomes.

**Introduction**

HIV is highly heterogeneous within infected individuals owing to rapid turnover rates, high viral load, and an error-prone reverse transcriptase enzyme that lacks proofreading activity. High variability is also the consequence of recombination, which can shuffle mutations between viral genomes and lead to major antigenic shifts or alterations in virulence. Ultimately, therefore, the continual, divergent evolution of HIV-1 in man to epidemic levels over the past 100 years originates from the swarms of HIV-1 strains (or quasispecies) within each human host.

Since the isolation of HIV-1 in the early 1980s, rapid development and application of various molecular tools, such as nucleic acid isolation and purification techniques in frozen, faecal, and urine samples or paraaffin-fixed tissue samples, have substantially improved understanding of the origins and evolution of HIV-1. In the first two decades of HIV-1 research, sequencing was limited to short HIV-1 genomic regions, which could only provide crude estimates of the geographical distribution of HIV-1 subtypes and gene evolution. Advances in amplification and sequencing of the complete HIV-1 genome, however, have enabled specific classification of HIV-1 subtypes and recombinants. Within infected individuals analyses of quasispecies (ten to 50 clones) typically relied on bacterial cloning or sequencing or on single-genome amplification, but thousands of clones are now being analysed by pyrosequencing methods.

This Review summarises the emergence of new HIV strains in the worldwide pandemic, with emphasis on the circulating recombinant forms (CRFs), discusses the progress made in the methods used to track the global molecular evolution of HIV, and appraises the importance of these new strains and methods in the future control and prevention of HIV.

**Origin and classification**

The likely progenitor of HIV-1, simian immunodeficiency virus (SIV) in chimpanzees (SIVcpz), seems to be a recombinant virus derived from lentiviruses of the red capped mangabey and greater spotted monkey, or a closely related species. Characterisation of SIVcpz has been complicated by the presence of lentiviruses in more than 30 species of non-human primates in sub-Saharan Africa. The SIVs could have crossed to man multiple times over several decades and led to divergence (figure 1). On the basis of phylogenetic analysis HIV has been classified into two types—HIV-1 and HIV-2. The latter is separated into eight groups, of which A and B are the most prominent, and HIV-1 into the groups M (main), N (non-M, non-O), and O (outlier). Group M is further categorised into nine subtypes (A–D, F–H, J, and K), sub-subtypes, and 48 CRFs (table 1, figure 1) that are identified by numbers (ascending in order of discovery) followed by letters of the parental subtypes. The origins of HIV-1 groups M and N have been traced to SIV-infected Pan troglodytes troglodytes (Ptt) chimpanzees inhabiting the eastern equatorial forests of Cameroon, in west central Africa. The same geographical region was probably also the site of origin for group O HIV-1: the closest SIV relative was found in gorillas (Gorilla gorilla: SIVgor), although chimpanzees are likely to have been the original hosts (figure 1). Another HIV-1 group-O-like variant is that more closely related to SIVgor than to group O, has been identified in a Cameroonian living in France and has been designated to a tentative new group, P. HIV-2 originated from SIV in sooty mangabeys (Cercocebus atys; figure 1).

By use of molecular clocks, the estimated times of the most recent common ancestors of HIV-1 groups M, O, and N in central Africa are 1908 (range 1884–1924), 1920 (1890–1940), and 1963 (1948–77), respectively, and for HIV-2 groups A and B the dates are 1932 (1906–55) and 1935 (1907–61), respectively (figure 2). The HIV-2 epidemic probably started in Guinea Bissau (figures 1 and 2), but Santiago and co-workers reported significant clustering of HIV-2 group A and groups with strains of sooty mangabeys SIV in the Tai forest, Côte d’Ivoire. HIV-1 and HIV-2 both spread exponentially early in the epidemic, but the patterns of infection have...
Figure 1: Relations between and genetic diversity in HIV-1 groups M, N, O, and P, HIV-2, and SIVs, and patterns of cross-species transmission

CRF=circulating recombinant form. cpz=chimpanzee. gor=gorilla. cpx=complex. SIV=simian immunodeficiency virus.

Homo sapiens

Pan troglodytes troglodytes (chimpanzee)

Gorilla gorilla

Figure 1: Relations between and genetic diversity in HIV-1 groups M, N, O, and P, HIV-2, and SIVs, and patterns of cross-species transmission

CRF=circulating recombinant form. cpz=chimpanzee. gor=gorilla. cpx=complex. SIV=simian immunodeficiency virus.
HIV-1 group M currently accounts for more than 30 million infections, but HIV-2 presently accounts for fewer than 1 million of all HIV infections;\textsuperscript{14–17} in Guinea Bissau, the epicentre of HIV-2, prevalence has dropped from 8·9% in 1987,\textsuperscript{18–20} to 7·4% in 1996,\textsuperscript{21,22} to 4·4% in 2006, whereas that for HIV-1 has increased from 2·3% in 1996 to 4·6% in 2006.

HIV-1 groups M, N, O, and P are phylogenetically interspersed along SIVcpzPit and SIVgor lineages, which suggests they arose from four independent ape-to-human transmissions.\textsuperscript{23–25} The distributions in human beings differ strikingly: group O infections are most concentrated in Cameroon, with spread being restricted mainly to neighbouring central African countries; groups N and P have been found in a small number of Cameroonian; and group M strains have spread worldwide and multiple subtypes have been identified (figure 2).\textsuperscript{26–28} Group M viruses encode protein sequences in gag, pol, and env that have 14–35% divergence from their closest known SIVcpz relatives.\textsuperscript{29,30} Genetic diversity is frequent but the consequences are unknown, although Wain and colleagues\textsuperscript{31} identified a viral genetic change in the p17 matrix protein encoded by the gag gene that might have facilitated the adaptation of SIVcpz to its human host. In particular, the aminoacid residue 30 of Gag has a conserved Arg or Lys in all HIV-1 groups (except subtype M-C, which has a conserved Met), whereas Met30 is seen in Gag of SIVgor and SIVcpzPit, and Lys30 is seen in SIV-infected Pan troglodytes schweinfurthii.\textsuperscript{32} HIV-1 with Met30Lys Gag has replicated better in human peripheral blood mononuclear cells (PBMCs) than in chimpanzee PBMCs.\textsuperscript{33} The matrix protein could, therefore, modulate virus fitness after cross-species transmission, with primate lentiviruses being subject to host selection pressure.

**Molecular epidemiology**

Group M causes most HIV-1 infections, owing to its high numbers of subtypes and CRFs. These subtypes form phylogenetic clusters with aminoacid differences of 25–30% in env, 20% in gag, and 10% in pol.\textsuperscript{34,35} Some subtypes are linked geographically. Variation within group M is greatest in the Congo river basin, which is probably the site of initial zoonotic jumps and regional diversification (table 2, figure 2).\textsuperscript{36–38} Two HIV-1 sequences—a 1960 sample from the current Democratic Republic of Congo (DRC) and a 1959 sample from the DRC (labelled as being from Zaire)—have helped to root the subtype A and D phylogenetic lineages, respectively, and to age the epidemic in the region (figure 2).\textsuperscript{39,40} Initial subtype distribution indicated dominance of subtype B in the western world and of subtype A in sub-Saharan Africa. Subtype A eventually extended into the former Soviet Union (figure 2). In the past 15 years, however, the rapid emergence of new subtypes and intermixing of strains has altered the geographical distribution of subtypes.\textsuperscript{41–43} In addition, some pre-existing subtypes, such as A and F, have continued to evolve into sub-subtypes—for instance A1–A4 and F1–F2 (figure 1),\textsuperscript{44} that form distinct lineages within a given subtype but that have lesser degrees of genetic divergence.

**Sub-Saharan Africa bears the highest burden of HIV-1 in terms of prevalence and diversity** (figure 3). The epidemics in west and central Africa seem to have stabilised in prevalence, but these regions, along with the Congo river basin, continue to be hot spots for HIV diversity (figure 3). Most, if not all, subtypes, sub-subtypes and CRFs have been reported in the DRC and Cameroon,\textsuperscript{71,77–80} As in the DRC, HIV-1 strains in Angola are highly diverse, and classification into sub-subtypes A5 and A6 might be required.\textsuperscript{81} From Cameroon, moving westwards to Nigeria, HIV-1 diversity decreases, as shown by the dominance of CRF02_AG subtypes A and G (figure 3). This trend continues with western migration to Côte d’Ivoire, Ghana, Senegal, and Mali, where CRF02_AG predominates, with reports of isolated cases of CRF06_cpx (complex subtype).\textsuperscript{82–85} Finally, CRF06_cpx and the second-generation recombinants CRF02_AG/CRF06_cpx dominate the epidemic in Burkina Faso, with subtypes A and G rarely being reported.\textsuperscript{86–88} Although the HIV-1 genetic diversity is high in west and central Africa, HIV-1 prevalence remains surprisingly lower than in most other regions of sub-Saharan Africa (figure 3). The highest prevalence shifted in the late 1990s from east Africa (Uganda, Kenya, and Tanzania) to the southern African region. On average, close to 20% of the human population in South Africa, Lesotho, Botswana, and Zimbabwe are thought to be infected with HIV-1.\textsuperscript{89}

This shift provides strong evidence for the founder-effect theory (a single introduction followed by a rapid spread)
since the southern African epidemic is due almost entirely to the spread of HIV-1 subtype C (figure 3). Independent, rapid spread of subtype C in east Asia has also contributed to this subtype being responsible for more than 51% of all HIV-1 infections worldwide (figure 4). Although initially absent, HIV-1 subtype C now circulates at low levels as a pure (non-recombinant) subtype or a recombinant form in Kenya and Uganda. The overall HIV-1 incidence is, however, decreasing (figures 2 and 3). The HIV epidemic in Asia is dynamic and all subtypes that circulate are due to multiple founder events. Subtype B was the first introduced into Asia in the mid-1980s, and was seen mainly in China, India, and Thailand. This strain has been named B’ (also known as Thai B) because of its divergence from the subtype B that occurs in the Americas (figure 2). Deng and colleagues reported this divergence occurred about 15 years after the B subtype began to spread, which roughly coincides with CRF01_AE being introduced into Thailand (figure 2). CRF01_AE has now gained dominance in Thailand; likewise, subtype C is currently dominant in most east Asian countries. Subtypes B and C have recombined to form CRF07_BC and CRF08_BC in China (figure 4). The northern triangle of Burma seems to have the greatest HIV-1 diversity in Asia, with seeding of CRF01_AE and subtype B’ from Thailand, possibly subtypes A, B, and C from India, and CRF07 and CRF08_B’C, from Yunnan province in China.

Figure 2: Estimated time line of global evolution and spread of HIV types, groups, and subtypes
Enlarged parts of map show the main disease epicentres. The time line indicates the key events in the evolution of HIV-1 groups M, N, and O and of HIV-2. CRF=circulating recombinant form.
A shortage of well organised needle exchange programmes for injecting illicit-drug users in this region could contribute to the complexity of HIV-1 subtype recombination there and further afield.

In eastern Europe the breakdown of the former Soviet Union has coincided with a rise of HIV-1 infections and, most notably, the spread of sub-subtype A1, which has been linked to intravenous drug use, and of subtype B (and to a lesser extent CRF03_AB), mainly through sexual transmission. In western Europe, as in North America and Australia, subtype B predominates. The prevalence of non-B strains has, however, increased owing to the influx of immigrants from Africa and Asia. Portugal has the highest prevalence of HIV-2 and other non-B subtypes in Europe, which might be related to the colonial war in Angola in the mid-1970s.

In South America, prevalence and diversity of HIV-1 are highest in Brazil and Argentina, with substantial circulation of subtypes B, C, and F, and BC and BF recombinants. Two reports showed close relations between the subtype C viruses in South America and those in Kenya, Ethiopia, and Burundi. The subtype C epidemic is estimated to have originated in 1958 (figure 2), and was first reported from Ethiopia in 1990 (figure 2), from where it spread to Israel. The virus also spread from eastern Africa to Brazil, and then to Argentina and Uruguay (figure 2). Subtype C was thought to originally have been introduced into Brazil from Mozambique, but this theory is not supported by phylogenetic analysis. The subtype C epidemic is now the fastest emerging epidemic in South America: in the Rio do Sol region of southern Brazil, subtype C or a BC recombinant accounted for 35% of cases in 1996, 52% in 2002, and nearly 59% in 2008, and the current estimate is nearly 70%.

The HIV-1 epidemic in the Caribbean might be the clearest reflection of different founder events, given notable immigration, travel, and trade. Longstanding links between the DRC and Haiti and between Angola and Cuba might explain the presence and age of certain HIV-1 strains in the Caribbean. Gilbert and co-workers applied a relaxed molecular clock to sequences derived from a 1982 Haitian DNA sample and calculated that subtype B was introduced into Haiti between 1962 and 1970, probably from the DRC, and from Haiti into the USA in 1972 (figure 2). Likewise, the oldest known HIV-1 subtype B infection in the entire epidemic was in a sample from 1982 or 1983, from Haitian immigrants in the USA (figure 2). Unlike the Haitian epidemic, that in Cuba is diversified, with CRF18_cpx and CRF19_cpx subtype C all circulating, but is marked by the CRF20, CRF23, and CRF24, for which subtypes B and G are parental (table 1). Relative to Cuba and Haiti, HIV-1 has more recently arrived through true founder event in other Caribbean islands, such as Trinidad and Tobago and the Dominican Republic.

**Table 2:** Some important milestones in the evolution of HIV

<table>
<thead>
<tr>
<th>Event or finding</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1983</td>
<td>Isolation of HIV-1</td>
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<tr>
<td>1984</td>
<td>CD4 identified as HIV receptor</td>
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<tr>
<td>1985</td>
<td>Sequence of HIV and genetic diversity reported</td>
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<tr>
<td>1986</td>
<td>Isolation of HIV-2</td>
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<tr>
<td>1987</td>
<td>First antiretroviral drug, zidovudine, approved by the FDA</td>
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<tr>
<td>1988</td>
<td>Second HIV drug, didanosine, approved by the FDA</td>
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<tr>
<td>1990</td>
<td>First report of a divergent form of HIV-1 (group O)</td>
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<tr>
<td>1991</td>
<td>Zalcitabine approved by the FDA</td>
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<tr>
<td>1992</td>
<td>Transmission of zidovudine-resistant virus documented</td>
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<tr>
<td>1993</td>
<td>Detailed characterisation of two reference group O viruses</td>
</tr>
<tr>
<td>1994</td>
<td>Discovery of CXCR4 and CCR5 as HIV co-receptors</td>
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<tr>
<td>1995</td>
<td>Introduction of combination highly active antiretroviral therapy</td>
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<tr>
<td>1997</td>
<td>Group O isolated from 1970s frozen Norwegian human samples</td>
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<tr>
<td>1998</td>
<td>Sequencing of a 1959 HIV-1 sample from the DRC</td>
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<tr>
<td>1999</td>
<td>Identification of HIV-1 group N</td>
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<tr>
<td>2000</td>
<td>First detailed proof that HIV-1 originated from SIVcpzPrPe</td>
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<tr>
<td>2002</td>
<td>SIVcpz identified in infected chimpanzees</td>
</tr>
<tr>
<td>2003</td>
<td>Discovery of APOBEC-3G, an anti-HIV host factor</td>
</tr>
<tr>
<td>2004</td>
<td>SIVcpz described as a recombinant between SIVrcm and SIVgsn</td>
</tr>
<tr>
<td>2005</td>
<td>High SIV prevalence in wild-caught chimpanzees in equatorial Africa</td>
</tr>
<tr>
<td>2006</td>
<td>Confirmation that HIV-1 group N and M exist in chimpanzees in equatorial forests of Africa</td>
</tr>
<tr>
<td>2007</td>
<td>HIV-1 group-O-like sequences found among gorillas in southeastern Cameroon</td>
</tr>
<tr>
<td>2008</td>
<td>Sequencing of a 1960 HIV strain from a paraffin-embedded tissue sample from the DRC</td>
</tr>
<tr>
<td>2009</td>
<td>Identification of gorilla-like group O sequences in human beings</td>
</tr>
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</table>

**Recombination**

CRFs and unique recombinant forms (URFs) are created after co-infection with at least two different HIV-1 isolates. Initially, identification of multiple infections was difficult and reports were rare. New technologies, such as the heteroduplex tracking assay and real-time PCR, however, improved detection. URFs comprise more than 30% of infections in regions where several HIV subtypes co-circulate (figure 3). Isolates were initially classified into different subtypes on the basis of clusters of partial gag and env sequences. A shared node in a phylogenetic tree suggested a common ancestry. Sequencing of longer and near-full length of HIV genomes has led to clearer understanding of lineages. CRFs and URFs have genome segments derived from more than one subtype (figure 4), but members of a CRF group share the same mosaic HIV-1 genomic structure and are derived from at least three epidemiologically unlinked ancestors, whereas URFs do not. CRFs currently comprise about 20% of all
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Proportion of HIV-1 subtypes in Africa

Congo River Basin East/central Africa

West Africa

Southern Africa

Ethiopia/Eritrea/Somalia/Djibouti

Figure 3: Evolution of HIV prevalence and genotypes in five regions of sub-Saharan Africa from 1990 to 2007\textsuperscript{37,75,76}

CRF=circulating recombinant form. URF=unique recombinant form.
known HIV infections. However, if CRF02_AG (~2 million infections) and CRF01_AE (~1.6 million infections) are taken to be pure subtypes, on the basis of phylogenetic reclassifications, this proportion drops to around 10%.

The first HIV-1 isolate to be identified as a recombinant was MAL, a strain derived from subtypes A and D that was obtained from a 1976 blood sample from the DRC. Of the 48 CRFs described so far, 16 (25%) have genomic structures incorporating sequences from more than two HIV subtypes (complex recombinants; table 1). For example, CRF06_cpx includes genomic segments with subtypes A, G, J, and K sequences. The origin of this CRF is unknown, but Burkina Faso, where CRF06_cpx is dominant, might have been an HIV-1 epicentre from which this strain spread to neighbouring countries, such as Niger, Mali, Côte d’Ivoire, and Nigeria, and through a founder event in Kaliningrad, Russia (table 1). In south and southeast Asia (except India), CRFs and other recombinants comprise about 88% of circulating strains. Initially, HIV-1 groups and types were thought too diverse to recombine even after potential dual infection, but there have been three reports of M/O recombination. In one case, generation of the M/O recombinant led to the gradual elimination of the parental isolates. The HIV-1 recombination sites selected during dual infection are thought to be more related to the mechanics of strand transfer during reverse transcription and selection of replication-competent chimeric virus than to sequence conservation between the strains. Thus, given sufficient opportunity through multiple dual infections within one or more host species over hundreds of years, recombination between distantly related SIV strains with different target hosts might have been possible. SIVcpz, for which SIV in the greater spot-nosed monkey is one of its parental strains, is a recombinant in the 3’ end of the genome, which includes vpu and env genes. HIV-1 group N arose from recombination between an SIVcpz group-N-like strain and a progenitor of HIV-1 group M, which possibly infected a subspecies of chimpanzees before being transmitted to man. Given cross-species introductions, or possibly jumping, of SIV between non-human primates, a future recombination event between HIV-1 and HIV-2, groups N and O, or even with other SIV strains, cannot be ruled out.
Genetic assessment

The understanding of the worldwide rate and direction of HIV-1 evolution will greatly affect future methods and strategies for diagnosis, therapy, and prevention. Serology by commercially available ELISA or EIA is the most widely used diagnostic method. Improvements in methods to identify new and diverse HIV-1 isolates means that the panel of necessary proteins to test has substantially expanded.46–51 Fourth-generation HIV immunoassays now detect p24 antigen and HIV-specific antibody simultaneously, and can identify most infections with group M and O strains.115 ELISA does, however, lack sensitivity and specificity to identify serotypes.

DNA sequencing is highly effective, but given the initial high costs and the type of equipment and advanced training needed, this approach was not routine in Africa during the 1990s and remains prohibitive in the developing world. The heteroduplex mobility assay offered a more-affordable option for simple and rapid classification of HIV-1 subtypes,116–118 and was used in many areas with the help of workshops provided by WHO. However, although this method has been improved with the use of radiolabelled probes, heteroduplex analyses cannot define specific sequence differences between isolates of the same or different subtypes.

Direct DNA sequencing is appropriate to characterise the infecting HIV-1 subtype or recombinant form and to monitor regional and global HIV-1 spread. Although DNA sequencing of a bulk PCR product remains less expensive and faster to perform than a clonal DNA sequence analysis, minor HIV-1 variants (frequency <20–30%) cannot be detected. The development of technologies able to process massive DNA sequences in parallel has obvious advantages for detecting minor HIV-1 variants. The Solexa sequencing approach by Illumina (San Diego, CA, USA) provides the greatest depth in clonal sequencing with the generation of 1 Gbp DNA sequence per lane of analyses. However, a drawback of this technology is poor subtyping and CRF identification because of short sequence reads (ten to 50 nucleotides) and lack of linkage to reconstruct HIV-1 genes or genomes. The Genome Sequencer FLX Titanium series (454 Life Sciences, Roche Applied Science, Branford, CT, USA) provides longer sequence reads (100–500 nucleotides), but the longest current sequencing platform is the PacBio RS (Pacific Biosciences, Menlo Park, CA, USA), which provides read lengths longer than 1000 nucleotides with low error rates. If appropriately applied and with accurate tags for sequence identification, this technology can be used to reliably estimate HIV-1 population diversity within patients, provide a high-throughput alternative for HIV-1 subtype identification and track disease spread, readily identify dual infection with HIV-1 subtypes or recombinants, and sequence full HIV-1 genomes.

Even with these extreme advances in DNA sequencing technology, limitations still exist in relation to sample collection. To understand the global and historic evolution of primate lentiviruses, samples must be collected from the remaining old-world primate species.20,29,121 Collection from HIV-infected human beings is easy, but non-invasive collection of samples from monkeys in the wild has proven extremely difficult, although sampling techniques, such as the collection of urine and faecal samples from apes, have improved.20 Furthermore, analyses of current samples might not identify the most recent common ancestors of HIV-1 closer to the zoonotic transmission. Generation of lentiviral sequences from stored human tissue samples, such as Bouin-fixed, paraffin-embedded tissue samples from west and central Africa, that predate the rapid expansion of AIDS is crucial. Finally, phylogenetic methods and algorithms have been improved along with sampling and extraction techniques. For example, new Bayesian methods enabled the co-estimation of HIV-1 divergence times under relaxed or strict molecular clock models, and have been essential for dating the introduction of different HIV-1 types, groups, and even some subtypes of HIV-1 group M.25,27,32,119 The development of second-generation DNA sequencing methods has, however, quickly stretched the capabilities of most phylogenetic algorithms.

Phenotypes

The extreme diversity between HIV-1 groups or subtypes has continually raised questions as to whether genotypes are associated with any specific biological or phenotypic traits. Within HIV-1 groups and subtypes, isolates use different co-receptors (CCR5 and CXCR4) in association with CD4 for HIV-1 entry.1,120 In newly infected and asymptomatic individuals most viruses are those that use CCR5, but as the disease progresses, variants that use the CXCR4 co-receptor, or both CCR5 and CXCR4, can emerge and dominate in the HIV-1 population, although the pattern can differ between subtypes. A switch to CXCR4 usage has been associated with acceleration of disease progression. The ability to use either or both of these co-receptors for viral entry is typically conferred by discrete genetic variation in the V3 loop of the HIV-1 envelope glycoprotein. Subtype C strains predominantly use CCR5 and rarely switch to CXCR4 or dual tropic use. By contrast, subtype D strains use CXCR4 receptors earlier and more frequently in infection than other HIV-1 subtypes, which might be why individuals infected with this subtype progress rapidly to AIDS.111,112 Such differences in transmission and disease progression could clearly impact the global distribution and prevalence of these viral strains.

A more general question relates to the possible impact of HIV-1 evolution on disease and global virus distribution. This topic has not been the subject of intense investigation because comparing the natural history of infections by different HIV-1 subtypes could require 5–20 years or longer of intense follow-up and the absence of treatment. Although disease progression in
HIV-1 subtype B infections is at least partly understood, infections with the dominant subtype A, C, and D, as well as CRF02_AG, have been poorly studied, partly because they are highly prevalent in resource-poor settings. As antiretroviral treatment is now widely available, these studies might never be ethically feasible. However, several studies in Uganda and Kenya have suggested progression to AIDS is faster in people with HIV-1 subtype D than in those with subtype A infections. In another study subtype C infections in Zimbabwean women progressed two to three times slower than subtype A and D infections in Ugandan women, on the basis of CD4 cell counts, but these findings require confirmation in follow-up studies. The finding that subtype D led to faster progression than subtype A in this study, though, might lend support to the theory that subtype C infection leads to slow progression.

In other studies the findings related to speed of progression in individuals infected with subtype C vary. Slow progression would support the reduced virulence of HIV-1 subtype C purported on the basis of in-vitro fitness studies, which indicate subtype C isolates from human PBMCs had the lowest replicative fitness when compared directly with other group M isolates. Direct correlations have been reported between replicative fitness of an HIV-1 isolate and its virulence in patients. For instance, patients infected with HIV-1 harbouring a deletion in the nef gene and, therefore, with severely impaired replication, had sustained non-progression of disease. Defective viruses with reduced cell-entry efficiency have been identified in patients with elite suppression, who maintain undetectable viral loads without antiretroviral treatment. In-vivo virulence is also related to several host factors, such as immune response and genetic variations in host-derived HIV-1 co-receptors (eg, CCR5). Thus, correlations of disease progression and in-vitro HIV-1 fitness might not be comparable across patients. However, at the population level, low-frequency differences in host polymorphisms related to HIV-1 progression are probably negated. As a consequence, clear distinctions in HIV-1 subtype fitness could be the best correlate of differences in disease progression.

Spread of HIV-1 in the human population is determined by virus virulence and host-to-host transmission. For example, prevalence of HIV-2 has been decreasing in west Africa over the past three decades, from 8-9% in 1987 to less than 4-4% by 2006, owing to an apparent decline in virulence. These effects could be related to reduced replicative fitness of certain HIV-2 strains in PBMCs. Poor HIV-2 fitness has been noted in ex-vivo dendritic cell cultures, which is a possible model of HIV transmission fitness. By contrast, subtype C HIV-1 isolates are still readily transmitted between human hosts, and compete with other HIV-1 group M isolates in various in-vitro models of transmission, such as in penile, vaginal, or rectal tissue, and even Langerhans cell and human skin explants. This observation was in contrast to the pathogenic fitness model where subtype C HIV-1 isolates replicated with poor efficiency in PBMCs. Some host-pathogen models suggest that pathogen spread is associated with duration of infection, transmissibility, and opportunity for transmission. For example, as well as being the dominant strain in the initial founder events, subtype C causes disease with a long asymptomatic period, which increases opportunity for transmission compared with that of other group M subtypes. If increased opportunity for transmission remains during chronic disease (5–15 years), it could counteract high transmissibility of other subtypes soon after infection (~1–3 months). Ultimately, HIV could evolve to an attenuated state similar to the persistently non-progressive SIVcpz infections noted in chimpanzees, but the time required for this attenuation might be hundreds to millions of years and is still the subject of debate.

Conclusion

Of the past century of HIV, the latter 25 years have yielded the greatest number of lessons in evolution and epidemiology, which could be beneficial in the study of other viruses. Tracing the origin of HIV has confirmed that viruses can jump from one species to another after a very long period of no transmission and adapt rapidly. The spread of HIV-1 to large urban centres occurred during preindependent and postcolonial times in Africa, when massive human emigration out of small villages in the dense tropical forests of Congo river basin occurred, for example to Kinshasa (formerly Leopoldville) in the DRC, which is near the origin of HIV and has notable diversity in HIV subtypes. Constant and increasingly easy worldwide travel is a major contributor to HIV diversification. New URFs and CRFs will continue to emerge and will definitely have major roles in the development of prevention and control strategies for HIV. Improvements in sampling and monitoring techniques might facilitate the ability to use old archival samples to knit together the complex evolutionary past of the HIV epidemic. Finally, these advanced evolutionary studies on primate lentiviruses must be coupled with phenotypic analyses on the actual viruses and advances in understanding of spread in the population over time, changes in virulence, and transmissibility.

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed, with the search terms “HIV subtypes”, “HIV origin”, “HIV evolution”, “HIV fitness”, “HIV and recombination”, “HIV diagnosis”, “HIV molecular epidemiology”, and “SIV diversity”. The references of identified articles were manually searched for further relevant papers and we also searched our own reference databases. We only included full-text English-language papers.
Review

Contributors

EJA and DMT agreed on the structure and content of the Review. DMT did the initial search for published articles and wrote the first draft. EJA and DMT revised the first and subsequent drafts and approved the final version for submission.

Conflicts of interest

EJA has received speaker’s fees from the University of Washington, the University of Massachusetts, and Merck, has a patent under review, and has received royalties from Diagnostic Hybrids/Quidel for HIV-1 yeast-based cloning and on an oligonucleotide ligation assay. DMT declares that he has no conflicts of interest.

Acknowledgments

EJA and DMT are supported by grant R01 from the National Institutes of Health.

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