Global Genetic Variation of HIV-1 Infection

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Abstract: Variability, both at the population (interhost) as well as at the individual (intrahost) level is a key property of HIV that stems mainly from the inherent infidelity of the reverse transcriptase enzyme that the virus uses to transcribe its RNA genome into DNA so that it may be integrated into the human genetic material and propagated along with it. The lack of proofreading mechanisms, high turnover of virions, and propensity for recombination also contribute to the extensive variability of HIV. These parameters provide the virus quasispecies with an impressive capacity to adapt to immunologic, pharmacologic or other selection pressures and have important implications for the diagnosis of new infections, the monitoring of antiretroviral treatment response, and effective vaccine(s) design. Herein, we discuss in detail the global genetic variation of HIV-1 infection.

Keywords: HIV groups, subtypes, clades, classification, epidemiology, origin.

TYPES AND ORIGIN OF HIV

The origin of the two types of the human immunodeficiency virus, HIV-1 [15, 49, 87, 109, 128] and HIV-2 [35], respectively, has been traced to Central Africa. There, they evolved from lentiviruses (i.e. viruses the infection with which evolves slowly) that naturally infected other primate species without causing overt disease, as discussed in the recent reviews by Chakrabarti and Stebbing *et al*. [31, 144]. Separate cross-species (zoonotic) transmission events from simian immunodeficiency virus $(SIV)_{cpz}$-infected chimpanzees (subspecies *Pan troglodytes troglodytes*) [50, 139] and from SIV_{smg}-infected sooty mangabey monkeys (*Cercocebus atys atys*) [63], are currently thought to have introduced HIV-1 and HIV-2 to humans, correspondingly [59]. Infection with either virus type invariably leads to the deadly syndrome that is known as AIDS. However, HIV-2 stains are less pathogenic and have been geographically restricted mainly to West Africa [39, 97]; in contrast, the more virulent HIV-1 strains have spread around the globe, causing the AIDS pandemic (Fig. **1**).

CLASSIFICATION OF HIV-1

The classification of HIV-1 isolates was based on phylogenetic analyses initially of partial nucleotide sequences coding for structural proteins of the virus (*env* and/or *gag*) [92, 137], and later on, of full-length sequences [138]. Such analyses indicated that HIV-1 strains may be broadly classified into three groups: M (for major or main, since it accounts for the vast majority of reported HIV-1 cases worldwide), O (for outlier) and N (for new or non-M, non-O). The few group N isolates that have been identified so far are not clearly distinguished into subtypes. Group O isolates are nevertheless distinguished into three phylogenetic clusters [134], although this distinction is supported rather weakly. In contrast, group M is subdivided into at least nine, associated but distinct, genetic subtypes or clades, A-D, F-H, J, and K, and several circulating recombinant forms (CRFs) [27, 52, 58, 66, 70, 91, 92, 102, 141, 156, 158, 160]. The further phylogenetic structure identified within subtypes A and F led to their further sub-division into two sub-subtypes each, designated as A1 and A2 [54], and F1 and F2 [157, 158], respectively. Genetic similarity throughout the viral genome characterizes the sequences within any one subtype or subsubtype; genomes that are not equidistant from currently defined subtypes over their entire length constitute recombinants of existing subtypes or CRFs, which are designated by a number, with letters indicating the involved subtypes.

The missing letters in the current taxonomic alphabet of group M [132], namely subtypes "E" and "I" [80] were actually found to comprise intersubtype mosaics -although the recombinant origin of subtype E has been disputed [8]-, and they were later designated as CRF01_AE [28, 53, 96, 108] and CRF04_cpx [51, 110, 121], respectively. The "I" designation has thus been dropped from the nomenclature, while the "E" designation has been retained. It should be noted, however, that hitherto pure intact prototype or "parental" clade E strains have not been identified. CRF04_cpx viruses, on the other hand, have been detected only in Cyprus and Greece, yet they must have existed in Africa as early as 1976, since two of the oldest available African isolates, Z321 from 1976 [56, 143] and MAL from 1984 [7], were found to contain short fragments closely related to some domains of this mosaic [51]. In this sense, CRF04_cpx may be more widely dispersed than originally thought.

Characterization of intersubtype recombinant viruses as CRFs entails their identification in at least three epidemiologically unrelated subjects and their genomic sequencing in full-length [122]. According to this definition, sixteen CRFs have been documented until this date, CRF01-CRF16, with the structure of CRF09_cpx [23, 101] still being un-

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1570-162X/06 $50.00+.00

available [2]. CRF05_DF does not formally meet the above criteria to qualify as a CRF at present, since only two full-length sequences, from two Belgian subjects who were presumably infected by partners from the Democratic Republic of Congo (former Zaire) in Central Africa, have been obtained to date [83]. The non-African origin of about half of the described CRFs and the increasing frequency with which they appear as relevant research progresses and better sequence analysis tools become available, highlights their growingly important role in the dynamics of the pandemic [116]. The effects of recombination and superinfection with multiple strains or subtypes of HIV and SIV viruses have been reviewed in detail elsewhere [17].

Group M clades that represent different lineages of the virus are roughly equidistant across their entire genomes in terms of evolutionary distances estimated from their nucleotide sequences [79], with the exception of subtypes B and D that have, nonetheless, been retained as separate subtypes for consistency with previously published work. Of note is that subtype G strains had been suggested not to be "pure" non-recombinants forms since parts of their viral genomes were reported to cluster with subtype A isolates [52]; however, no clear regions of recombination were found by other researchers [27]. At the most diverse envelope gene, which contains five hypervariable regions, V1-V5, and five more conserved sections, C1-C5, group M intersubtype variation approaches 20-30% at the amino acid level, whilst intrasubtype variation in *env* reaches 10-15%.

ORIGIN AND ENDEMICITY OF HIV-1 GROUPS

Each HIV-1 group has presumably arisen from separate chimpanzee-to-human transmission events [36, 50]. The last common ancestor of group M was probably present in a human host, thereby rendering highly improbable the theory that the initial source of HIV were contaminated oral poliovirus vaccines [130, 164, 167]. The date of this last common ancestor was estimated to be towards the first half of the 20th century, around 1931 [78]. The territory within or near the Democratic Republic of Congo, where the first documented HIV seropositive sample was collected in 1959 [109, 173] and where the highest degree of diversity has been detected [108, 162], is thus perceived to constitute the epicenter of group M viruses radiation.

Group O strains, on the other hand, seem to have diverged out of the region of Cameroon [134]. Accordingly, group O strains are endemic, albeit at low frequencies, mainly in Cameroon [11, 58, 112, 123, 160, 161] and in some neighboring countries, such as Gabon [42] and Nigeria [74]. Furthermore, group O infections have been detected in patients of Cameroonian origin living in France [32, 90], Belgium [40], Spain [99], Germany [61], and the United States [135, 147, 148].

Cameroon is also the country where the few infections with group N viruses have been documented [12, 141]. The mosaic pattern, formed by SIVcpzUS- and HIV-1-related sequences, that characterizes their genomic organization is suggestive of an ancestral recombination event in a chimpanzee host [50]. Even though the local HIV prevalence rates are low compared to other African countries [1], the variety of different viral types, groups and subtypes spread in the region apparently introduces the circulating viral populations to new levels of genetic diversity [48, 100], as manifested by the detection of various types of mixed infections between different subtypes of HIV-1 group M, between HIV-1 groups O and M, and even between HIV-1 and HIV-2, in Cameroon [150].

MOLECULAR EPIDEMIOLOGY OF THE MAJOR GROUP M OF HIV-1

The most commonly encountered HIV-1 subtype in Western and Central Europe, North America, and Australia, is the consequently best studied, subtype B, whereas such non-B subtypes as A, C, D and E prevail in the developing world (reviewed in [6, 46, 125]). Furthermore, subtype B is found in the Middle East, Russia, Northern and South Africa, and Southeast Asia. The subtype B strains that caused the initial epidemic among intravenous drug users (IVDUs) in Bangkok, Thailand form a distinct cluster within subtype B on phylogenetic analyses and are termed subtype B′ or Thai B strains [76, 117, 118]. Subtype B′ isolates also circulate in China [57, 165], where they predominate among infected commercial blood donors [33, 145].

Nevertheless, only a small proportion of all HIV-1 infections in the year 2000 (12.3%) was due to subtype B [116]. Immigration and travel have contributed to the observed increase in frequency of non-B HIV-1, and even HIV-2 [113], infections in Europe and the USA [10, 22, 55, 60, 68, 85, 142]. Additionally, evidence of increase in heterogeneity of strains circulating in the West has been presented [14]. Still, most non-B infections are introduced in the West *via* heterosexual transmission from individuals directly associated mostly with sub-Saharan African countries or with other regions of the world where these particular viruses prevail (reviewed in [153]).

Clades that predominate in Africa and Asia, namely C, A (sub-subtype A1) and A/G and A/E recombinants, are particularly significant in the molecular epidemiology of the pandemic. Subtype C has been detected in Eastern and Southern Africa, including Ethiopia especially [67], and Botswana, Zimbabwe, Malawi, Zambia, Namibia, Lesotho and South Africa (reviewed in [70]) as well as in India (reviewed in [21, 165]), Nepal [114] , and China [95, 171, 172]. Subtype C has also been detected in Russia [93] and Brazil [41]. Within subtype C, phylogenetically distinct lineages have been identified: thus, many sequences from India were found to be "C3" (most recently reviewed in [77]), whereas genotypes C′[4] and C′′and recombinants thereof [127] were reported to co-circulate in Ethiopia. Interestingly, the C′-enveloped Ethiopian viruses, which may have a biological advantage over the C′′-enveloped viruses, appear to bear phylogenetic links to the subtype C strains from India and South Africa. Such observations are particularly important given the urgency for the development of an efficacious vaccine. At present, subtype C is the most commonly found subtype, with its strains accounting for approximately half (47.2% in the year 2000) of all HIV-1 infections worldwide; subtype A and CRF02_AG constitute the second leading cause (27% of all infections) of the pandemic [46, 116].

Non-recombinant subtype A viruses are commonly found in Central and East sub-Saharan Africa (Kenya, Uganda, Tanzania, Rwanda) and occasionally in West Africa [16, 26, 44, 72, 75, 111, 124, 129]. Additionally, subtype A viruses

circulate, mainly among IVDUs, in East European countries of the former Soviet Union [19, 20, 93, 94]. A/G recombinants, CRF02_AG [65], on the other hand, dominate in West and parts of West Central Africa [9, 26, 27, 29, 62, 100], although they have been detected in Taiwan [84] as well as in Ecuador, South America more recently [30]. An interesting analysis of AG recombinant lineages circulating in Africa has been presented by Cornelissen *et al.* who in addition discuss their similarities with CRF01_AE strains [37].

Another complex recombinant involving subtypes A, G, J, and K as shown recently [158], CRF06_cpx, has been characterized in Burkina Faso and Mali of West Africa [104, 115]. Originally identified in a Greek patient who had been infected in the Democratic Republic of Congo, CRF11_cpx, is yet another mosaic composed of successive fragments of subtype A, G, J, and CRF01_AE that circulates in Central and West Africa [105, 120, 166]. CRF13_cpx has a similar composition as CRF11_cpx, although the subtype J regions it contains are more related to the subtype J regions of CRF11_cpx rather than the non-recombinant reference strains of subtype J [166].

A recombinant that apparently also originated in Africa, CRF01_AE, caused an explosive epidemic through heterosexual transmission in Thailand [53, 76, 118, 163]. Initially transmitted from Thai prostitutes to their male patrons in the late 1980s, this form spread rapidly among IVDUs and heterosexuals in nearly all countries of Southeast Asia [165]. As a result, CRF01_AE viruses have been found to circulate in the Philippines [119], China [34, 126, 171], Japan [165], and also in Central Africa [70]. A new recombinant form derived from CRF01_AE and subtype B, CRF15_01B, apparently bridged the previously separate epidemics between the the two high-risk populations of heterosexuals and IVDUs in Thailand [156].

Isolated cases of unique viral chimeras of limited epidemiological significance at present, since they have been recognized only in one of a few infected subjects, have been reported in various countries and continents (i.e. in Cameroon [159], the Democratic Republic of Congo [162] , Tanzania [64], India [89] and Cuba [38]). On the contrary, some other CRFs appear to be especially pertinent from an epidemiologic perspective. For instance, CRF03_AB has been detected primarily among IVDUs first in Kaliningrad and then in St. Petersburg and several cities of the former Soviet Union [88, 94]. CRF12_BF and related recombinant viruses are commonly found in Uruguay and Argentina [25], with frequencies reaching 65% of examined cases, according to one report [151, 154]. Interestingly, some circulating viruses are second generation mosaics formed by the recombination of CRF12_BF with subtype B. Similar virologic phenomena that could lead to superinfection of CRFs with different strains, have been observed in Galicia, Spain with CRF14_BG and subtype B viruses [43] as well as in the Yunnan Province of China, with CRF07_BC [133, 146] and strains of other subtypes that are also common in the region [170].

Yunnan is the Province in Southwestern China where the initial HIV-1 outbreak, first with subtype B and then with subtype B′, occurred among IVDUs in 1989 [57, 165, 168]. Later on, in the early 1990s, non-recombinant subtype C variants predominated among IVDUs in the region [95]. Soon in evolutionary time terms, the co-circulating subtypes B′ and C recombined to yield two closely related CRFs that are associated with distinct overland heroin trafficking routes: CRF07_BC in the Xinjiang Province of the Northwest [133, 146] and CRF08_BC in the Guangxi Province of the Southeast [101, 126, 133], respectively. According to latest data, Yunnan constitutes a vital epicenter of the HIV epidemic, with an impressive rate of increase in the number of new infections (30%), the total number of which is expected to reach 10 million by the year 2010 [1].

Evidence that the multiple entries and exchanges of HIV-1 strains with neighboring countries fosters the generation of new recombinant strains, continuously enriching the spectrum of viral subtypes propagated in the region, has been presented [82, 107, 149, 170]. Recently, the evolution of a second generation, inter-CRF recombinant, between CRF07_BC and CRF08_BC, which may represent a new class of CRFs, has even been described in Yunnan [169]. Therefore, the area of Southeast Asia that includes West Yunnan and Central Myanmar (Burma) has rightfully been characterized as a "melting pot" of recombination for HIV-1 [149]. It should be noted that these findings may reflect a selective advantage of new recombinant forms, some of which exhibit "pseudotype" virion structures with the external sections of their envelope glycoproteins exchanged with strains of different lineages over simpler parental strains as observed before [43], hence posing an additional challenge to researchers for the development of effective vaccines and therapies.

The remaining HIV-1 group M clades are present in a more localized pattern. Subtype D has been detected mainly in Eastern and Central Africa, with prevalences reaching more than 40% in Uganda according to one report [131], and to a lesser extent in Southern and Western Africa [16, 42, 70, 73, 155]. Subtype C and D recombinant strains, CRF10_CD, have also been identified in Dar es Salaam, Tanzania (East Africa) [81]. Subtype F was initially defined in the outbreak among institutionalized children who had been infected *via* contaminated blood products and inadequate sterilization techniques in Romania [45]. Several studies since then documented the presence of this subtype, albeit not at a high frequency, in South America [24, 98, 106, 136], Europe [86, 140], and Central Africa [42, 112, 150, 157].

Subtype G has been found to circulate primarily in Western, Eastern and Central Africa [16, 29, 71, 91, 92], being most prevalent in Nigeria [5, 124], and in the Iberian peninsula as recombinant B/G viruses, CRF14_BG [43, 47, 152]. In Russia, subtype G was associated with an epidemic that originated from a male heterosexual who acquired HIV-1 nosocomically while he was living in Mozambique [18]. Subtypes H and J have been identified in Central Africa [16, 70, 71]. Recently, subtype K has been characterized in isolates from Cameroon and the Democratic Republic of Congo [158]. A rare clade recently identified in Congo may represent an additional subtype [103].

This geographic distribution of the HIV-1 subtypes outside Central Africa with one or two clades predominating, could be suggestive of a founder effect of the earliest genetic form that would gain an advantage over forms introduced later in the population [125]. Interestingly, geographically localized subclusters sharing a distinct common ancestry

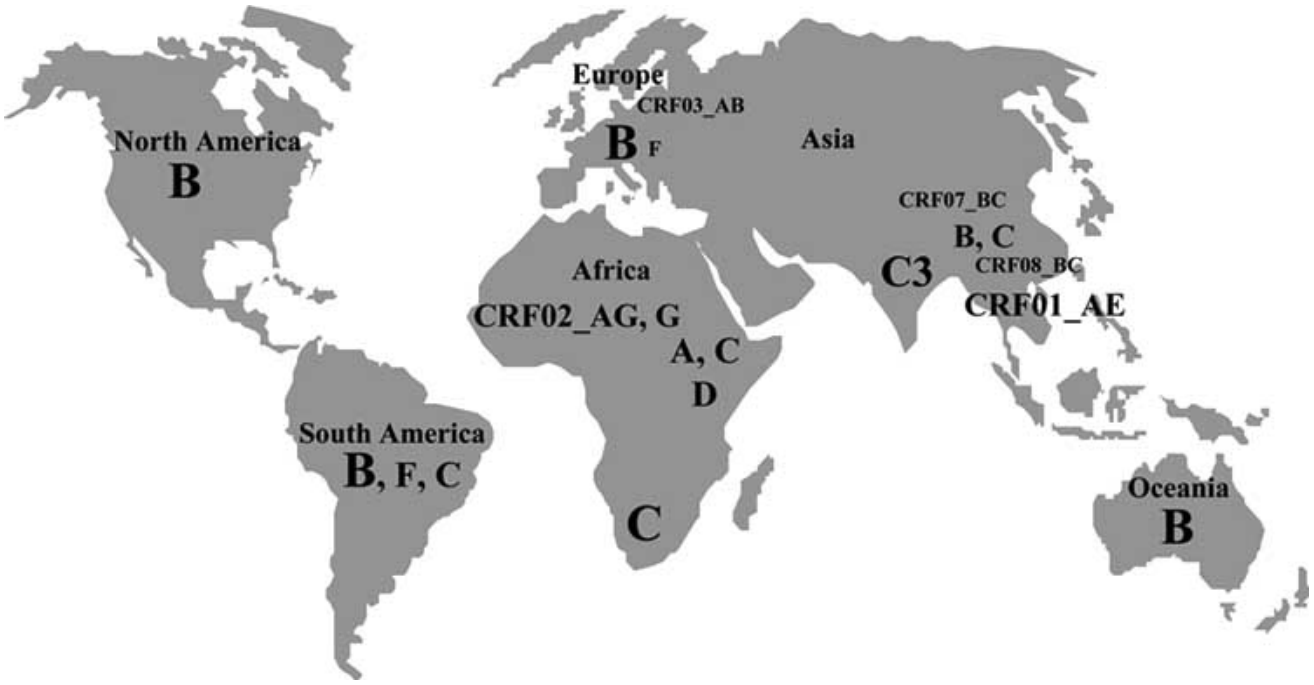

Fig. (1). Global geographic distribution of predominant HIV-1 subtypes and circulating recombinant forms (CRFs).

have been suggested to exist within some subtypes by phylogenetic analyses, including subtype C strains from India and Ethiopia [3, 69], subtype G from Spain and Portugal [43, 47, 152], subtype B viruses from Thailand, and subtype F strains from Romania and a portion of Brazilian F strains that may share a common Central African origin [13, 157].

CONCLUDING REMARKS

Despite the continued extensive research in the field of HIV/AIDS since the discovery of the virus more than two decades ago, the epidemic continues to spread, with HIV-1 strains diversifying rapidly at the population level. The high mutation rates and inherent propensity for recombination of the virus due to its genetic makeup contribute to the remarkable plasticity of its quasispecies. Close molecular epidemiological monitoring of the prevalent subtypes and emerging recombinant forms of the virus on a global scale is rendered necessary, particularly for the development of vaccines that would ideally protect against the entire range of genetic forms of the virus.

ABBREVIATIONS

AIDS	=	Acquired immune deficiency syndrome
CRFs	=	Circulating recombinant forms
Group M	=	Major or main group
Group N	=	New or non-M, non-O group
Group O	=	Outlier group
HIV-1	=	Human immunodeficiency virus type 1
HIV-2	=	Human immunodeficiency virus type 2
IVDUs	=	Intravenous drug users
SIV	=	Simian immunodeficiency virus

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Received: November 29, 2005 **Revised: January 22, 2006** **Accepted: January 25, 2006**