AIDS Rev 2000; 2: 190-202

Role of Human Immunodeficiency Virus Type 1 Group O in the AIDS Pandemic

Miguel E. Quiñones-Mateu, Sarah C. Ball, and Eric J. Arts

Division of Infectious Diseases, Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

Abstract

Like other RNA viruses, a high degree of genetic variability and heterogeneity is a hallmark feature of human immunodeficiency virus type 1 (HIV-1) evolution. HIV-1 strains have been divided into three groups: the main (M), the outlier (O), and the non-M, non-O (N) groups. Originally secluded to Cameroon, HIV-1 group O infections have been identified in other West African countries and worldwide. Research in HIV-1 group O is, in part, limited by the availability of samples, but recent molecular epidemiological studies have now mapped a different phylogeny for HIV-1 group O than for group M. Group O isolates appear as diverse as group M, but with fewer clusters that can be classified as defined subtypes or clades. Differences in biological characteristics between groups M and O could explain for reduced spread of HIV-1 group O and ultimately shed light on the factors contributing to the HIV-1 group M epidemic. Finally, better understanding of the origin and diversity of HIV-1 group O viruses is essential for the design of improved diagnostic tests, antiretroviral therapies, and vaccine.

Key words

HIV. Group O. Diversity. Evolution. Subtypes

Origin and distribution of HIV-1

Almost two decades have passed since the acquired immunodeficiency syndrome (AIDS) was first linked to infection by HIV. Unfortunately, most of estimated 33 million HIV infected individuals worldwide suffer through similar disease stages and opportunistic infections. This is remarkable considering the extreme heterogeneity of the etiological agent (http://hiv-web.lanl.gov)[1]. Two distinct types of the human AIDS viruses have been identified, HIV-1 and HIV-2, but HIV-1 is responsible for the vast majority of HIV/AIDS cases throughout the world. Based on phylogenetic analyses, HIV-1 has been subclassified into three distinct virus groups: M (main), O (outlier), and N (non-M, non-O) with the predominant group M consisting of 11 clades designated subtypes A to K[2,3] (Fig. 1A). This classification based solely on sequence identity is supported by at least two different simian immunodeficiency virus (SIV) from non-human primates into the human population (zoonotic, or cross-species), transmission[4]. In the case of HIV-1, at least three zoonotic transmissions from the chimpanzee subspecies, *P. t. troglodytes*, appear to be responsible for the current classification of HIV-1 into the three groups (M, N, and O)[4-6]. Molecular clock analyses have suggested that 1931 (1915-41) is the predicted date for cross-species transmission of the HIV-1 group M predecessor[7]. However, molecular epidemiological data for group N and O was insufficient for a similar time prediction of cross-species transmission.

This review will focus on the rare group O isolates, highlighting their sustained presence in the epi-

Correspondence to:
Eric J. Arts
Division of Infectious Diseases, Department of Medicine
Case Western Reserve University
Biomedical Research Building 10th
2109 Adelbert Rd
Cleveland, OH, 44106-4984
USA

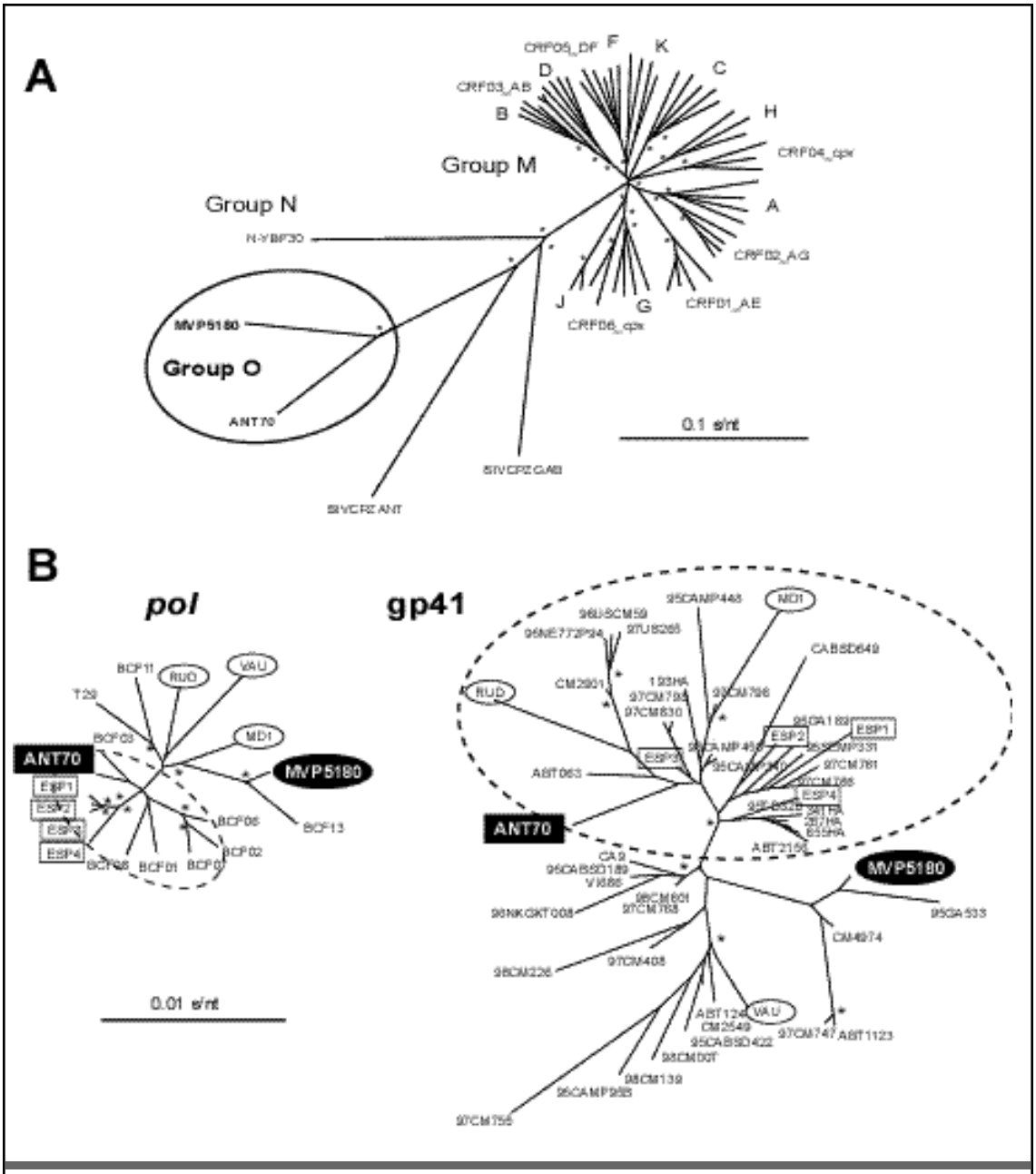

Fig. 1. *(A) Phylogenetic tree analysis of env gene sequences from 56 HIV-1 isolates listed in the HIV Sequence Database (h yperlink http://hiv-web.lanl.gov)[1]. Full-length envelope sequences were utilized to construct a neighbor-joining tree as previously described[28]. Encircled are the sequences corresponding to HIV-1 group O isolates (HIV-1_{ANT70} and HIV-$1_{MVP5180}$). HIV-1 group M (the 11 A to K clades or subtypes and 6 circulating recombinant forms [CRFs]), group N (HIV-1_{YBF30}), and simian immunodeficiency virus (SIV_{CPZANT} and SIV_{CPZGAB}) strains are included in the phylogenetic tree[2,3]. (B) Phylogenetic trees based on HIV-1 group O sequences of two different HIV-1 genomic regions, RT^{pol} and $gp41^{env}$. 18 pol (647 bp) and 51 env (262 bp) sequences were used for this analysis. HIV-1 subtype O:A or ANT70 clade is indicated by the ellipses. HIV-1 group O isolates corresponding to subtype O:A or clustering with HIV-$1_{MVP5180}$ (for the RT^{pol} region) are circled or squared, respectively) in both trees. An asterisk indicates bootstrap resampling values (1000 sets) above 75 %. Distance between two sequences could be obtained by summing the length of the connecting branches, using the scale (in nucleotide substitutions per nucleotide [s/nt]).*

demic, difficulty in detection, and intrinsic resistance to certain antiretroviral drugs. UNAIDS has estimated the current prevalence of genetic subtypes responsible for HIV-1 infections worldwide; 48% subtype M:C, 25% subtype M:A, 16% subtype M:B, 4% subtype M:D, 4% intersubtype recombinant CRF01-AE (previous subtype E), and 3% for the remaining group M subtypes (F, G, H, J, and K) plus, groups N and O. Since the detection of the first group O infection in 1990[8], there is no evidence that prevalence of group O infections has changed especially in the face of an exponential expansion of HIV-1 group M infections.

Worldwide prevalence of HIV-1 group O isolates

In 1990, De Leys *et al*[8] described a highly divergent long terminal repeat (LTR) sequence from a Cameroonian HIV-1 isolate (HIV-1_{ANT70}). Four years later, independent publications reported the complete genome sequence of two HIV-1 strains ob-

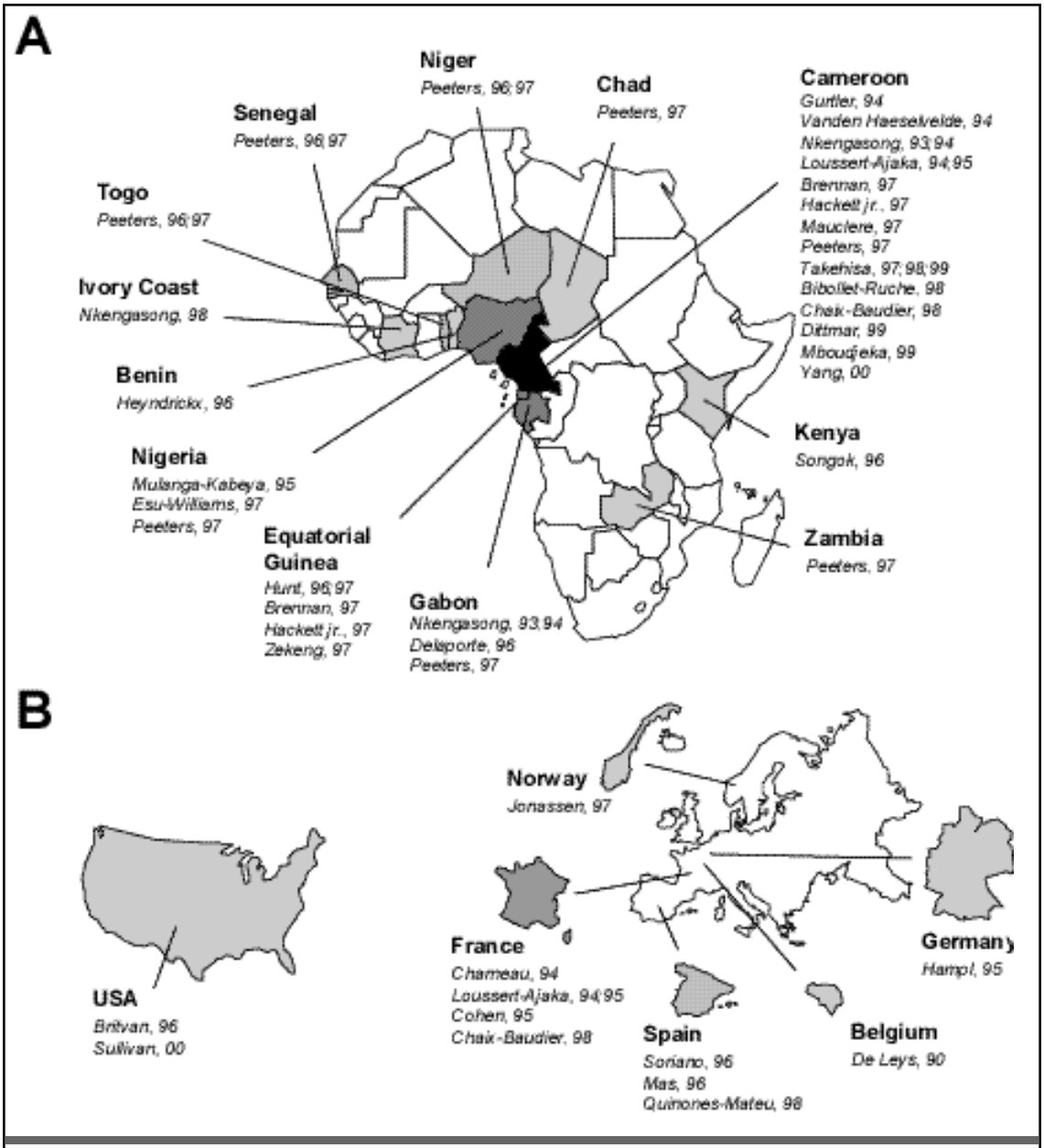

Fig. 2. *Geographical distribution of HIV-1 group O isolates in Africa (A) and worldwide (B). Shade intensity (i.e. black to white) of each region roughly defines the prevalence of HIV-1 group O isolates in these countries. References that contributed to the description of HIV-1 group O isolates from each country are indicated..*

tained from Cameroon: HIV-1_{ANT70}, isolated in 1987[9] and HIV-$1_{MVP5180}$, isolated in 1991[10]. The env gene of these two new strains differed considerably from sequences of other HIV-1 isolates (<50% of nucleotide identity with other group M isolates)[9,10]. Phylogenetic analyses initially classified these two isolates as a new subtype O, but at a genetic distance from other HIV-1 isolates similar to that distance separating HIV-1 and HIV-2[1]. A few months later, Charneau *et al*[11] reported the isolation and *env* sequence of the first HIV-1 subtype O isolate obtained from a patient outside of Africa (HIV-1_{VAU}). Phylogenetic analyses revealed that these three viruses (HIV-1_{ANT70}, HIV-$1_{MVP5180}$, and HIV-1_{VAU}) could be classified into a new viral group, HIV-1 group O (outgroup or outlier)[11]. Following these initial reports, group O infections have been described in several African countries, including Cameroon[9,10,12], Gabon[13], Equatorial Guinea[14,15], Nigeria[16,17], Benin[18], Ivory Coast[19], Togo[17,20], Senegal[17,20], Niger[17,20], Chad[17], Kenya[21], and Zambia[17] (Fig. 2A). The highest prevalence of HIV-1 group O isolates has been documented in West African countries such as Cameroon, Gabon, and Nigeria[17]; with Cameroon at the epicenter[17,22].

A cross-sectional analysis of HIV-1 infections in Cameroon has revealed a high prevalence of group O in the HIV-1 infected populations, ranging from 1% in the northern part of the country, to 6.3% in the capital region[23]. Furthermore, most cases reported outside of Africa have been somehow linked to Cameroon (see below). An extensive serologic

analysis of more than 14,000 sera samples from 12 different African countries showed a relatively low seroprevalence of HIV-1 group O infections[17]. Only 19 sera samples (0.13%), representing eight of the twelve countries, tested positive with group O-specific antibodies. Again, the highest prevalence was observed in Cameroon (2.1%) and neighboring countries, 1.1% in Nigeria and 0.9% in Gabon[17]. However, these serological assays may not be comprehensive and unable to detect divergent group O strains[12,24]. As described below, the diversity in the cluster of group O isolates is similar to that observed amongst group M isolates. Considering only weak intersubtype cross-reactivity with serological assays for group M HIV-1 infections, it is not surprising that a group O serological test could underrepresent the prevalence of group O infections. For example, the first surveillance for HIV-1 group O infections in Cote d'Ivoire, the West African country most severely affected by the AIDS epidemic[25], detected a single group O infection in 3328 sera from HIV-1 infected individuals[19]. Further prospective and retrospective studies using more sensitive group O-specific EIA tests or PCR assays are necessary to monitor the exact prevalence of these viruses in Africa.

Immigration and travel from West Africa have introduced HIV-1 group O isolates to Europe (France[11,12], Germany[26], Belgium[8], Spain[27,28], and Norway[29]) and the United States[30,31] (Fig. 2B). With the exception of an infected French woman[11], all reported group O-infections originate from West Africa. Interestingly, the earliest documented cases of HIV-1 group O infections are also the first known infections with this human retrovirus outside of Africa. A Norwegian sailor traveling along the coast of West Africa had contracted a group O virus between 1961 to 1965. His wife and daughter were subsequently infected with a related group O isolate. HIV DNA was PCR amplified from autopsy material of father and daughter. Phylogenetic analyses of HIV *pol* (635 bp of protease/RT region) and *vif* (818 bp of integrase/*vif*) sequences revealed a clustering of these isolates with the *pol* and *vif* sequences of other HIV-1 group O isolates further corroborating the serological group O classification[29].

Group O infections in Europe are certainly not limited to these initial Norwegian cases. In 1994, nine HIV-1 infected patients living in France were diagnosed as having a group O infection[24], eight of which originated from Cameroon and one from France. The first HIV-1 group O infections in Spain were in a male-female couple, the former had traveled for 10 years in Equatorial Guinea and Cameroon[27,32]. Two other unrelated cases of HIV-1 group O infections were later identified in Spain[28]. In the US, there have only been two reported cases of group O infection[30,31]. Phylogenetic analyses of *gag*, *pol*, and *env* sequences consistently clustered these group O isolates from the Western world, but originating from West Africa, with other HIV-1 group O strains from West African origin[11,12,28,30-34]. To date and since 1961, there is no evidence that direct introduction of HIV-1 group O strains into Europe or the Americas has resulted in transmission beyond the family unit. A summary of all the HIV-1 group O isolates identified is listed in Table 1.

Phylogeny of HIV-1 group O sequences

HIV-1 group O strains constitute a cluster of HIV-1 variants, as genetically diverse as the M group isolates, despite their geographical confinement. A phylogenetic analysis of *env* gene sequences suggests that HIV-1_{ANT70}, HIV-$1_{MVP5180}$, and HIV-1_{VAU} are all separated by a genetic distance similar to that reported for HIV-1 group M subtypes[11]. With the identification of new group O infections, sequence analysis of *gag* (p24) and *env* (C2-V3) regions revealed limited clustering of the group O isolates[12], but failed to define clear phylogenetic branching for the classification of subtypes[12,14,35,36]. Undefined clusters, resulting in an inability to subdivide group O isolates into clades maybe due to (i) limited sample size (to a few sequences available), (ii) insufficient sequence length to reveal phylogenetic associations, and (iii) an evolutionary history of group O distinct from group M.

Although initial sequence analyses of the C2-V3 region could not identify subtypes, the diversity and genetic distances between group O isolates was similar to that between group M isolates within all subtypes[12,14,35,36]. Moreover, group O sequences from all isolates did appear to branch with either HIV-1_{ANT70} or HIV-$1_{MVP5180}$[12,14,28,35-37]. However, in addition to a limited number of group O isolates, the C2-V3 region in *env* may be inappropriate for subtype classification of group O sequences, since the extreme variation and limited sequence length does not support highly structured phylogenies. Phylogenetic analyses of accessory genes *(tat, vif, vpr, and vpu)* from 16 HIV-1 group O isolates identified four loosely defined clusters with branch points below statistically significant bootstrapping values[38]. Recent studies have compared the intra- and intersubtype mutation frequencies and genetic distances in group M and have applied these same parameters to define subtypes in the RT^{pol} and gp41^{env} sequence of group O isolates[28,37,39,40]. Phylogenetic analysis of the RT^{pol} region identified a cluster of 11 HIV-1 group O sequences with HIV-1_{ANT70}, with an intra-cluster nucleotide sequence diversity of 5% or similar to that found in subtypes of HIV-1 group M (average of 4.9% intra-subtype sequence diversity)[28] (Fig. 1B). This group O cluster was designated subtype O:A[28] and was supported by phylogenetic analysis of gp41^{env} sequences (27 group O isolates)[39]. However, analysis of protease sequences from 34 HIV-1 group O isolates failed to identify well-defined clusters with high bootstrap values[37]. Two distinct clusters, observed in RT^{pol} but ill-defined in PR^{pol}, is likely due to increased sequence length used for RT^{pol} analysis. Phylogenetic analysis of the complete gp160 *env* gene revealed that six HIV-1 group O strains branched with HIV-1_{ANT70} strain (100% bootstrapping values) and formed a separate cluster from HIV-$1_{MVP5180}$[40]. Genetic distances within and between the "ANT70"-

Table 1. *Summary of HIV-1 group O isolates*

Isolate [a]	Country	Year of Isolation	Genomic region sequenced [b]				Biotype [c]	References
			gag	*pol*	*env*	*acc*		
T29	Norway	76		PR, RT, IN		vif		29
ANT70	Belgium	87	full	full	full	full	NSI/R5	8,9,40,61
MVP5180	Cameroon	91	full	full	full	full	SI	10,80
CA9	Cameroon	94	p24		full		NSI/R5	13,40,63
CM2549	Cameroon	94	p24		full			36
CA2901	Cameroon	94			gp120		NSI/R5	36,59
CM2902	Cameroon	94			C2V3			36
CA4354	Cameroon	94			C2V3		NSI/R5	36,59
CM6103	Cameroon	94			C2V3			36
CM6104	Cameroon	94			C2V3			36
CA6778	Cameroon	94			C2V3		NSI/R5	36,59
CM7851	Cameroon	94			C2V3			36
CA8161	Cameroon	94			C2V3		SI/X4	36,59
CMR61	Cameroon	94			C2V3			86
CM2171	Cameroon	94					SI/X4	59
DE5267	Germany	95	p24		C2V3			26,36
CA4974	Cameroon	95	p24		full		NSI/R5	26,36
CAMP448	Cameroon	95			gp41-IDR	full		38
CABSD649	Cameroon	95			gp41-IDR			38
CAMP95B	Cameroon	95			gp41-IDR			38
CAMP450	Cameroon	95			gp41-IDR			38
CABSD189	Cameroon	95			gp41-IDR			38
CABSD422	Cameroon	95			gp41-IDR			38
CAMP340	Cameroon	95			gp41-IDR			38
CM8913	Cameroon	95					NSI/R5	59
MVP2171	Cameroon	96	full	full	full	full		36
CAMP539	Cameroon	96				full		38
YBF15	Cameroon	96	p24		C2V3			23
YBF16	Cameroon	96	p24		C2V3			23
YBF17	Cameroon	96	p24		C2V3			23
YBF18	Cameroon	96	p24		C2V3			23
YBF19	Cameroon	96	p24		C2V3			23
YBF20	Cameroon	96	p24		C2V3			23
YBF22	Cameroon	96	p24		C2V3			23
YBF26	Cameroon	96	p24		C2V3			23
YBF28	Cameroon	96	p24		C2V3			23
YBF32	Cameroon	96	p24		C2V3			23
YBF35	Cameroon	96	p24		C2V3			23
YBF37	Cameroon	96	p24		C2V3			23
CM1639	Cameroon	96					NSI/R5	59
CM13127	Cameroon	96					NSI/R5	59
CM13470	Cameroon	96					NSI/R5	59
CM9435	Cameroon	96					NSI/R5	59
CM2274	Cameroon	97					NSI/R5	59
ABT063	Cameroon	97	p24		gp41-IDR			14,35
ABT124	Cameroon	97	p24		gp41-IDR			14,35
ABT325	Cameroon	97	p24					14,35
ABT1066	Cameroon	97		* PR				14
CM408	Cameroon	97		PR	gp41			37
CM830	Cameroon	97		PR	gp41			37
CM755	Cameroon	97		PR	gp41			37
CM747	Cameroon	97		PR	gp41			37
CM768	Cameroon	97		PR	gp41			37
CM766	Cameroon	97		PR	gp41			37
CM798	Cameroon	97		PR	gp41			37
CM761	Cameroon	97		PR	gp41			37
CM139	Cameroon	98		PR	gp41			37
CM226	Cameroon	98			gp41			37
CM601	Cameroon	98		PR	gp41			37
CM00T	Cameroon	98		PR	gp41			37
VAU	France	92		PR	gp41		NSI	11,80
HIV1MAD	France	96			C2V3, gp41			36
DUR / RUD	France	95	p24	PR, RT				80
LT	France	94			C2V3			74
BCF01	France	95	p24	PR, RT	C2V3	full		12,80,38
BCF02	France	95	p24	PR, RT	C2V3	full	NSI	12,80,38,61
BCF03	France	95	p24	PR, RT	C2V3	full		12,80,38
BCF06	France	95	p24	PR, RT	C2V3	full	SI	12,80,38,61

Table 1. *Summary of HIV-1 group O isolates (cont.).*

Isolate [a]	Country	Year of Isolation	Genomic region sequenced [b]				Biotype [c]	References
			gag	*pol*	*env*	*acc*		
BCF07	France	95	p24	PR, RT	C2V3	full	NSI	12,80,38,61
BCF08	France	95	p24	PR, RT	C2V3	full		12,80,38
BCF09	France	95	p24	PR, RT	C2V3	full		38
BCF11	France	95	p24	PR, RT	C2V3	full		12,80,38
BCF12	France	95				full		38
BCF13	France	95		PR, RT		full		38,80
VI686	Gabon	94	p24	PR	full	full	NSI/R5	13,38,43,87
GA533	Gabon	95			gp41-IDR			38
GA189	Gabon	95			gp41-IDR			38
TD320	Chad	95			gp41-IDR			38
NE772P94	Niger	95			gp41-IDR			38
SNMP331	Senegal	95			gp41-IDR	full		38
ESP1	Spain	95		PR	C2V3, gp41		NSI/R5	27,33,32,39,34,29, 76,37
ESP2	Spain	96		PR	C2V3, gp41		NSI/R5	27,33,28,34,39,37
ESP3	Spain	97		PR	C2V3, gp41			28,34,39,37,38
ESP4	Spain	97		PR	C2V3, gp41			28,34,39,37,38
NGKGT008	Nigeria	96			gp41-IDR			
MD1	USA	96		PR	V3, gp41		NSI/R5	30,33,31,37
USCM04	USA	96		PR	gp41-IDR			31,37
ABT2156	E.Guinea	97		PR	gp41-IDR			14,35
ABT1123	E.Guinea	97			gp41-IDR			14
193HA	E.Guinea	97		PR	gp41-IDR			15,35
267HA	E.Guinea	97		PR	gp41-IDR			15,35
341HA	E.Guinea	97		PR	gp41-IDR			15,35
655HA	E.Guinea	97		PR	gp41-IDR			15,35

[a] HIV-1 group O isolate nomenclature. In a few cases, more than one name has been assigned to the same viral isolate in two or more references (i.e. ESP1[32] = 97ES202 {37}, ESP2[28] = 97ES203 {37}, ESP3[28] = 97ES205 {37}, ESP4[28] = 97ES204 {37}, MD1[33] = 97US201 {37}). For the purpose of this review, we have adopted the nomenclature from the first identification.

[b] Genomic regions sequenced for each isolate are listed under group-specific antigen (gag), polymerase (pol), envelope (env), or accessories genes (acc).These regions are further subdivided on the table to indicate the entire sequence or exact region sequenced in *gag* (p24), *pol* (PR, RT, IN), *env* (gp120, C2V3, gp41-IDR), and acc (*tat, vif, vpr,* and *vpu*). An asterisk indicates partial sequences.

[c] Non-syncytium inducing (NSI)/CCR5-tropic (R5) and syncytium inducing (SI)/CXCR4-tropic (X4[54]).

and "MVP5180"-clusters were similar to the intra- and inter-subtype genetic distances in group M[40]. The cluster including the HIV-1_{ANT70} sequence was designated the ANT70 clade or subtype and resembled the previously identified O:A derived from RT*pol* analyses[28]. Recently, a phylogenetic analysis of the largest set of group O isolates (56) confirmed the presence of two clusters[37]. One cluster of gp41*env* sequences contained the HIV-1_{ANT70} isolate and was similar to those clusters previously classified as subtype O:A or subtype ANT70. The other cluster containing the HIV-$1_{MVP5180}$ isolate did not fit the criteria for the group M subtype classification (Fig. 1B).

New HIV-1 group O sequences will be added into the phylogenetic trees with the continued prospective or retrospective identification of group O infections. However, possible differences in transmission or disease progression may contribute to independent and divergent evolutions of group O and M. Although we cannot rule out that new group O sequences will further subdivide the existing phylogenetic trees into more defined clusters, it appears that distinct group M subtypes arising from initial pandemics in Africa may not parallel the spread or evolution of HIV-1 group O.

Differences between HIV-1 groups M and O

a) Diagnostic tests and viral load determination

Diagnostic tests were initially developed for a European and North American population in which subtype M:B strains predominate. However, these tests performed sub-optimally in regions where more divergent HIV-1 strains circulate. HIV infection is primarily diagnosed with serological tests such EIA and Western blot (WB), both of which are insensitive to significant changes in antigenic structure. Although constantly modified to include specific proteins from divergent HIV strains (e.g. HIV-2 isolates), it is impossible to clone, express, and incorporate all HIV genetic variants into these tests. This of course raised concerns about the ability of serological (e.g. EIA and WB) and nucleic acid (e.g. RNA viral load analyses) assays to detect group O viruses. Immediately after the first identification of the rare, highly divergent, group O isolates[8], several studies revealed that serological tests for HIV-1/HIV-2 infections showed poor sensitivity for group O infections[12,24,41]. As described earlier, even the use of serological assays adapted for the new group O isolates resulted in a poor detection of

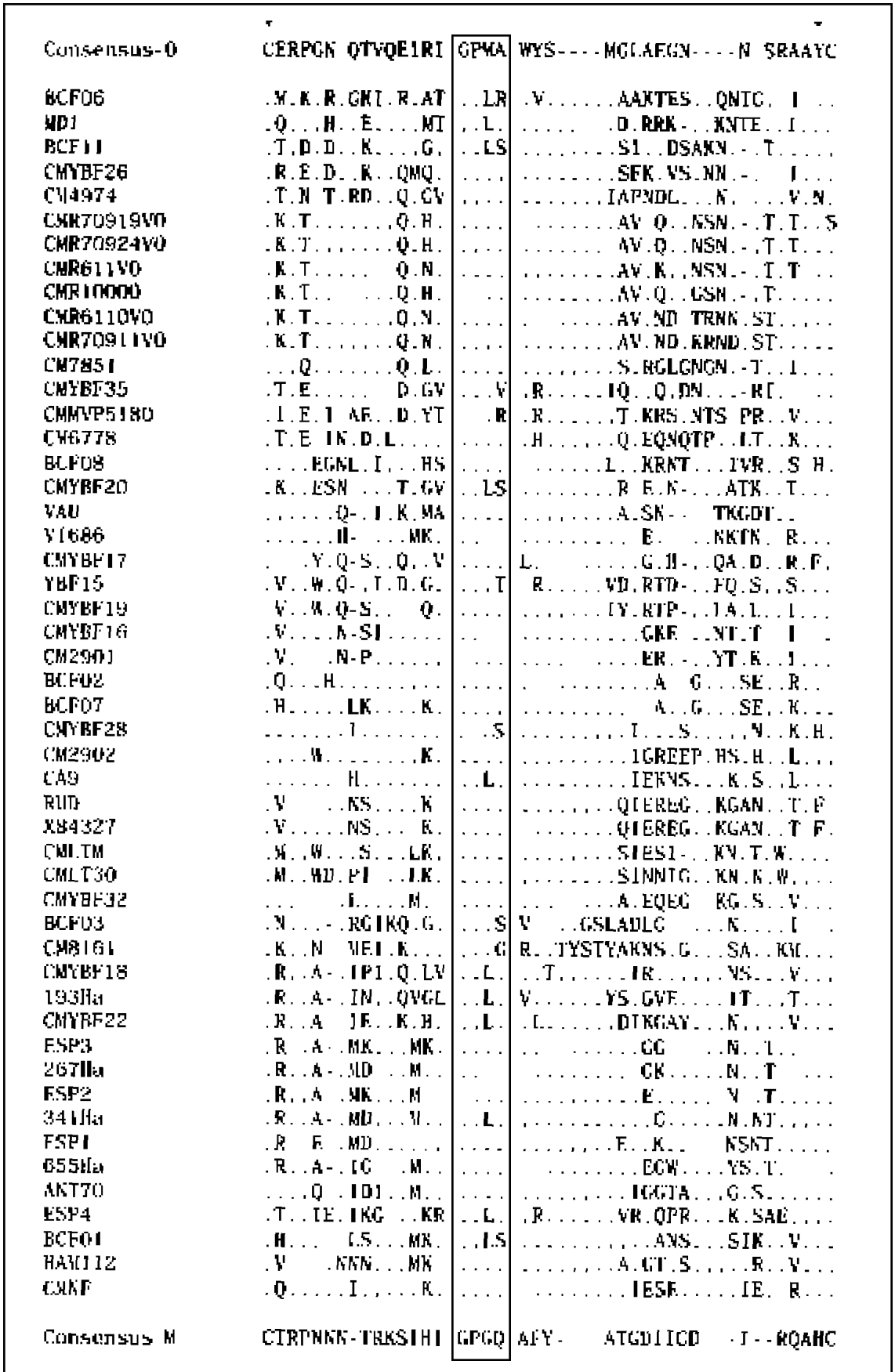

Fig. 3. *Amino acid sequence alignment of gp120^{env} V3-coding region. Fifty-one sequences from HIV-1 group O isolates are compared with consensus sequences of HIV-1 group O and M (h yperlink http://hiv-web.lanl.gov)[1]. Only those amino acids that differed from the group O consensus sequence are shown. The tip or crown of the V3 loop is boxed. Cysteine residues are marked with an asterisk to define the V3 loop. Dots indicate the same amino acid as in the top sequence. Gaps introduced to maintain the alignment are indicated by dashes.*

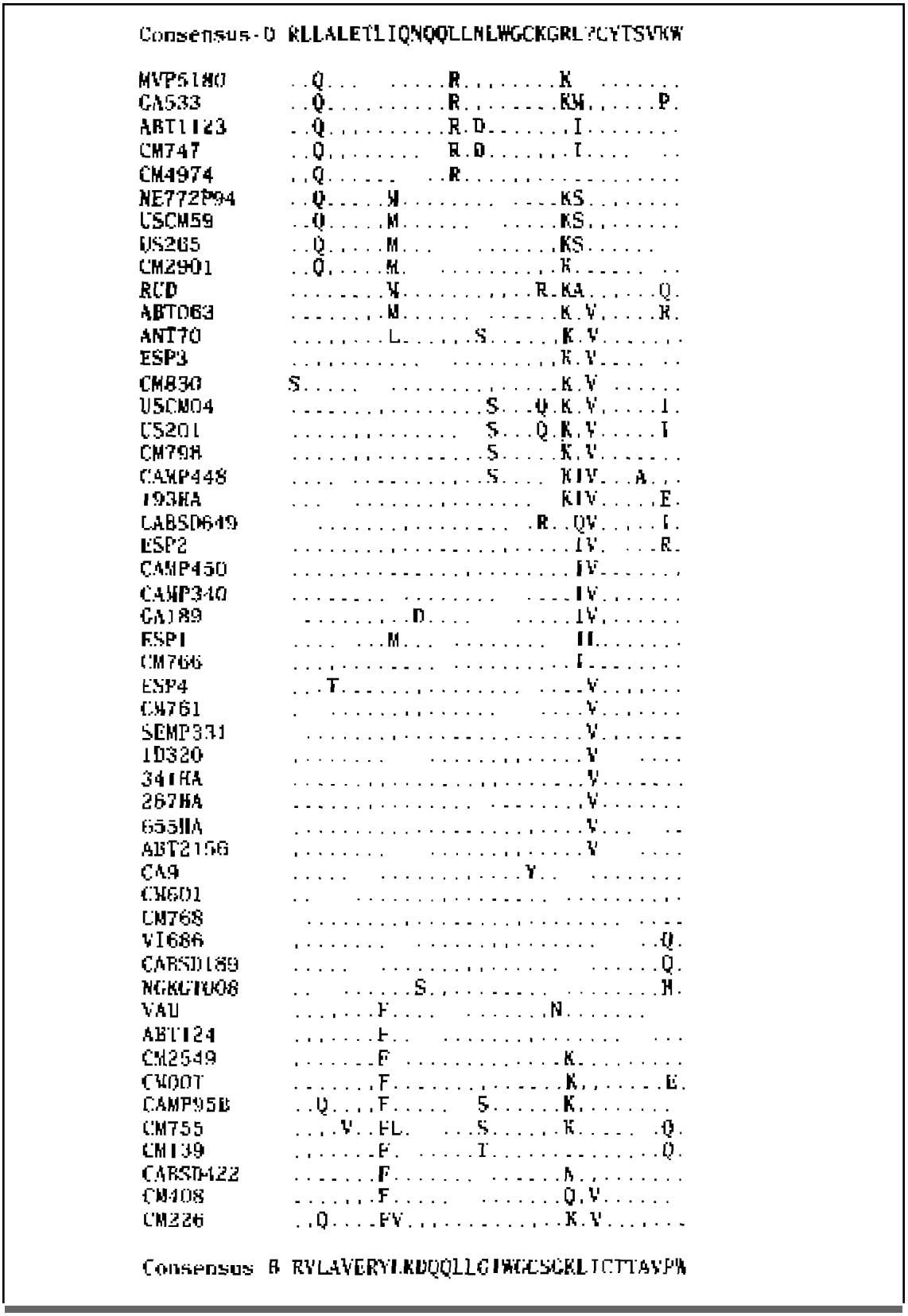

Fig. 4. *Amino acid sequence alignment of gp41^{env} immunodominant region. Forty-nine sequences from HIV-1 group O isolates are compared with consensus sequences of HIV-1 group O and subtype M:B (h yperlink http://hiv-web.lanl.gov)[1]. See legend of Fig. 3 for details.*

group O infections in Western Africa[23,42]. As the number of newly documented infections with HIV-1 group O infections increases, it is apparent that not all HIV-1 group O antibodies react with ANT70 and MVP5180 V3 peptide in a modified ELISA. Alternatively, group O infections can be detected or con-

firmed by different genetic methods including PCR with group O-specific primers[43] or PCR amplification of the *pol* gene followed by *PstI*-restriction analysis[44].

Since both group M and O infected individuals progress to AIDS, antiretroviral therapy with reverse transcriptase and protease inhibitors (RTI and PI, respectively) does benefit patients infected with strains from either groups[28,34,45]. Although HIV-1 viral load is inversely associated with sustained inhibition by antiretroviral drugs and slower disease progression[46], several comparative studies have shown a reduced efficiency of the first viral load assays to quantify plasma HIV-1 RNA in patients infected with non-B subtypes[47-49]. Modified versions of the AMPLICOR HIV-1 test and HIV-1 RNA load NASBA, now involve reverse transcription and PCR amplification of highly conserved regions in RT[50] and long-terminal repeat[51], respectively, and should quantify HIV-1 RNA in both group M and O infected individuals. However, these assays are still dependent on annealing of oligonucleotide primers to conserved regions on a highly divergent virus. Amp-RT (ultrasensitive PCR-based RT activity assay) is another method used to accurately quantify viral load but employs endogenous RT activity to reverse transcribe an exogenous heteropolymeric RNA template[52]. Product from this template, generated with endogenous RT, is PCR amplified and then quantified to estimate viral load. Considering most HIV-1 strains possess RT with similar enzymatic activity, this assay can measure the viral load in any HIV-infected individual, regardless of strain, sequence, subtype, or even group classification. A recent study confirms the accuracy and sensitivity of Amp-RT to measure viral load in group O-infected patients[53].

b) Viral phenotype and coreceptor usage

HIV-1 primary isolates have been further classified according to tropism, cytopathology, and growth kinetics. Most individuals are infected and harbor HIV-1 isolates that do not form syncytium (non syncytium-inducing or NSI) and replicate slowly in macrophages. In contrast, isolates that form syncytium (syncytium-inducing or SI) and show increased rate of replication over NSI isolates in T-cell cultures are only isolated late in disease progression (reviewed in[54]). This difference in phenotype/tropism is now associated with co-receptor usage, that is NSI HIV-1 isolates utilizes CCR5 (R5) chemokine receptor and CD4 for host cell entry while CXCR4 (X4) and CD4 are employed by SI HIV-1 strains. With the exception of subtypes C and D of group M, the distribution of NSI/R5 and SI/X4 isolates in each group M subtype generally corresponds to the frequency of these phenotypes in infected patients[55-58]. Most HIV-1 subtype C isolates are NSI/CCR5-tropic whereas there is a slight increase to CXCR4-tropism amongst subtype D isolates as compared to other subtypes[58]. In the case of HIV-1 group O, there appears to be a predominance of NSI/CCR5-tropic isolates, similar to that observed with group M subtype C isolates. However, it is important to note that this analysis was only performed on 23 isolates[33,40,55,59-61].

c) Genomic sequence and structure

The Gag polyprotein of HIV-1 group M isolates specifically, binds and utilizes cyclophilin A (CyPA) as a chaperone protein during viral assembly[62]. In contrast to HIV-1 group M viruses and the SIV_{CPZGAB} strain, HIV-1 group O isolates encode Gag polyproteins that do not possess the *gag* sequence essential for CyPA binding and packaging into virions[63]. Analyses of the predicted amino acid sequences of Vif, Vpr, the first exon of Tat, and Vpu from 14 HIV-1 group O isolates indicate a significant sequence variation from clade M:B sequences that may result in a phenotypic difference. In subtype M:B, phosphorylation of Vif appears to play a critical role in the regulation of replication and infectivity[64]. The absence of this phosphorylation site in group O Vif proteins may result in altered Vif function in group O isolates or highlight an alternative pathway to accomplish the same function as subtype M:B Vif[38]. Interestingly, Bibollet-Ruche *et al*[38] linked an inability to phosphorylate Vif with the observation that cyclophilin A may not be required for group O replication[63]. In subtype M:B isolates, a ternary complex between p24, CyPA, and phosphorylated Vif may be required for some step in replication[38], providing further evidence for an alternative pathway in group O. Finally, conserved regulatory elements responsible for alternative splicing between the tat exon 2 and its flanking sequences[65] are absent in HIV-1 group O strains[66], suggesting that regulation of splicing may be different in these two HIV-1 groups.

Configuration of the V3 *env* sequence is one of the most striking differences between HIV-1 groups O and M. The tip or crown of the V3 loop, GPGR or GPGQ in most HIV-1 group M isolates, is a highly immunogenic site as well as the target for neutralizing anti-HIV antibodies. These two motifs are not found in group O isolates which contains GPMA as consensus sequence at the V3 crown (Fig. 3). This finding is not surprising considering the extreme genetic variability between HIV-1 group O and M. However, this difference in the V3 crown may hamper efforts to identify conserved, cross-reactive, and immunogenic sites that may induce a neutralizing antibody response.

The immunodominant region (IDR) of gp41 is relatively conserved amongst group M isolates and is the basis for new vaccine approaches[67]. Amongst group O isolates, the gp41 immunodominant region (IDR) is also relatively conserved, but unfortunately quite divergent from the gp41 *env* in subtype M:B isolates (Fig. 4). Variation in the immunodominant regions of group O and M *env* (V3 loop and gp41 IDR) may explain why immunoassays based on subtype M:B reagents are inappropriate for detection of group O infections[14,15,68].

Table 2. *Amino acid sequences in the RT-coding region of group O strains associated with resistance HIV-1 group M isolates.*

HIV-1 group O Isolate	68[a] S→G	98[b] A→G	103[b] K→E/N/Q/R/T	106[b] V→A/I	179[b] V→D/E	181[b] Y→C/I	184[c] M→I/T/V	211[a] R→K	214[a] L→F
Consensus- O	S	***G***	K	V	E	***C***	M	Q	***F***
ANT70	***G***	***G***	K	V	E	***C***	M	Q	***F***
MVP5180	S	***G***	***R***	V	E	Y	***I***	Q	***F***
BCF01	***G***	***G***	***R***	V	E	***C***	M	Q	***F***
BCF02	S	***G***	K	***I***	E	***C***	M	Q	***F***
BCF03	***G***	***G***	K	V	E	***C***	M	Q	***F***
BCF06	***G***	***G***	***R***	V	E	Y	M	Q	***F***
BCF07	S	***G***	K	***I***	E	***C***	M	Q	***F***
BCF08	S	***G***	K	V	E	***C***	M	Q	***F***
BCF11	S	***G***	***R***	V	E	Y	M	Q	***F***
BCF13	S	***G***	***R***	***I***	***K***	***C***	***V***	R	***F***
ESP1	S	***G***	K	V	E	***C***	M	Q	***F***
ESP2	S	***G***	K	V	E	***C***	M	Q	***F***
ESP3	S	***G***	K	V	E	***C***	M	K	***F***
ESP4	S	***G***	K	V	E	***C***	M	Q	***F***
RUD	S	***G***	K	V	E	Y	M	K	***F***
VAU	***G***	***G***	K	V	E	Y	M	K	***F***

Amino acid on bold and italic has been found associated with decreased susceptibility to RT inhibitors in group M isolates.
These amino acid substitutions are associated with resistance to, [a] multiple nucleoside; [b] NNRTI; and [c] 3TC, ddC, and ddI; in group M-subtype B isolates.

d) Transmission and disease progression

The impact of HIV-1 genetic variation on virus replication, transmission, and disease progression is still largely unknown. Aside from epidemiological data showing a low frequency of group O infections in the population, there is no direct evidence suggesting a difference in viral fitness, transmission, or immunogenecity between group O and M. It is still debatable if heterosexual transmission favors certain HIV-1 group M subtypes (A, C, and E) due in part to enhanced infectivity of cells at the mucosal layers (e.g. Langerhan's cells)[69-71]. Furthermore, it is difficult to associate different HIV-1 group M subtypes with specific patterns of disease progression[72,73].

The first case of mother-to-infant transmission with an HIV-1 group O virus was reported in Cameroon[74]. An initial homogeneity of the child's viral population is consistent with the selective transmission of one HIV-1 genotype, as previously described for group M infections[75]. As in subtype M:B-infected children, variability of the HIV-1 group O quasispecies population increased with age. Virological, immunological, and clinical studies have now been performed on two different couples infected with HIV-1 group O strains[34,40,45], i.e. one couple infected with HIV-1_{ANT70A}/HIV-1_{ANT70B} and living in Belgium[8], and the other infected with HIV-1_{ESP1}/HIV-1_{ESP2} and living in Spain[27]. In each case, presumably one individual infected his/her partner with a HIV-1 group O isolate. Interestingly, in both cases, one partner had remained asymptomatic for several years (i.e. stable CD4+ T cells count and isolation of NSI/R5 variants) while his/her partner had progressed to AIDS (i.e. increase of viral load and switch from NSI/R5 to SI/X4). Based on these two limited but independent studies[34,45], it appears that the course of disease does not differ for HIV-1 group O and M infections[77,78]. A detailed analysis of *quasispecies* diversity and intrapatient evolution in the group O-infected couple from Spain provides strong evidence that the mutation frequency of group O isolates was similar to that a group M isolates[28].

e) Antiretroviral response and vaccine development

As with many diagnostic tests, antiretroviral drugs and HIV vaccines are mainly designed and developed in the industrialized countries of Europe and North America. At least in part, the same amino acid substitutions associated with antiretroviral resistance in HIV-1 group M are also emerging in group O isolates exposed to antiretroviral drugs. Previous reports suggest that drug efficacy may vary between different group M subtypes and the same may be more significant between groups[28,79-81]. HIV-1 group O strains are susceptible to NRTI or protease inhibitors but do exhibit high level resistance to NNRTI *in vitro*[28,76,79,80]. Intrinsic resistant to NNRTI is due to the presence of three amino acids (Gly-98, Gln-179, and Cys-181) found in the consensus sequence of group O RT. Substitutions for these residues at positions 98,179, and 181 were initially shown to confer NNRTI resistance in subtype M:B isolates[82] (Table 2).

Several HIV-1 group O-infected individuals have now received antiretroviral treatment[28,80] and have responded with decreases in viral load similar to that observed in group M-infected individuals treated with antiretrovirals. Treatment has also selected for drug-resistant isolates containing the same amino acid substitutions conferring resistance in HIV-1 group M isolates. For example M184V and T215Y in the RT-coding region were selected in

group O-infected patients treated with 3TC and AZT, respectively[28,34]. Recent studies have also described the selection of substitutions in group O protease conferring resistance to protease inhibitors[33,34]. Unfortunately, NNRTI cannot be used for treatment of HIV-1 group O infections due to the intrinsic resistance to this class of drugs. Only efavirenz may prove to be somewhat effective at inhibiting HIV-1 group O replication and could be used in combination therapy of for group O infections.

Finally, neutralization of divergent HIV-1 strains by human sera or killing of infected cells by cytotoxic T lymphocytes shows little clade or group specificity. In other words, clade or group classification based on linear nucleotide sequence has little bearing on initial epitope selection or subsequent cross-isolate neutralization/killing by the immune response. Interestingly, one third of sera obtained from persons infected by group M viruses did neutralize certain group O variants, whereas sera from group O-infected individuals consistently failed to neutralize group M viruses[83,84]. This result may provide some hope in protection against a group O infection afforded by prior vaccination with group M-derived vaccine.

Will HIV-1 group O have an impact on the HIV-1 pandemic?

HIV-1 group O infections are not a new phenomenon. Obviously, group O viruses have not resulted in an epidemic similar in magnitude to the current AIDS pandemic caused by HIV-1 group M viruses. Analyses of stored human samples have shown that HIV-1 group M and O isolates did circulate in West Africa as early as 1959[85] and 1963[29]. Detection of both groups early in the epidemic suggests that HIV-1 group M had a greater fitness in the human population[23]. In future studies, a more comprehensive, molecular epidemiology survey should be conducted to determine the spread of HIV-1 group O throughout the world. Are group O infections confined to West Africa or is there evidence of multiple transmissions outside of this region? Recent identification of HIV-1 group O infections in several countries suggests that HIV-1 group O may not be confined to West Africa. HIV-1 group O infections have still not been reported in Eastern Europe, Central and South America, Asia, or Oceania. Unfortunately, many of these regions still utilize diagnostic tests that may not detect group O infections and many retrospective surveys for group O generally utilizes sera samples from HIV-1 infected cohorts. However, absence of HIV-1 group O may also reflect limited travel/trade between these regions and West Africa.

Other than the sustained and low prevalence of HIV-1 group O in the population for at least five decades, there is little to suggest that HIV-1 group O could not generate a widespread or regional pandemic. The weak detection of group O infections by current diagnostic assays and reduced efficacy of antiretroviral regimens could have significant consequences on even a limited spread of group O viruses. Improvements in diagnostic assays, as well as development of cross-clade/group vaccines or drugs are necessary to control and combat an epidemic caused by these highly diverse pathogens.

Acknowledgments

M.E.Q-M was supported by a research grant from the NIH (K01-HL67610-01). E.J.A. was supported by research grants from the NIH (AI-42645-02, AI-31147, and HL-51636) and from the Commission for Cultural, Educational and Scientific Exchange between the United States of America and Spain, 1999.

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