AIDS Rev. 2012;14:83-100

Update on HIV-1 Diversity in Africa: A Decade in Review

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Abstract

Background: ***HIV-1 strains have diversified extensively through mutation and recombination since their initial transmission to human beings many decades ago in Central Africa in the first part of the 20th Century (between 1915 and 1941). The upward trend in global HIV-1 diversity has continued unabated, with newer groups, subtypes, and unique and circulating recombinants increasingly being reported, especially in Africa.***

Objective: ***In this review, we focus on the extensive diversity of HIV-1 over a decade (2000-2011), in 51 countries of the three African geographic regions (eastern and southern, western and central, and northern Africa) as per the WHO/UNAIDS 2010 classification.***

Methodology: ***References for this review were identified through searches of PubMed, conference abstracts, Google Scholar, and Springer Online Archives Collection. We retrieved 273 citations, of which 200 reported HIV-1 diversity from Africa from January, 2000 to August, 2011. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English and French were included.***

Findings: ***There has been a high diversity of HIV-1 in its epicenter, west-central Africa. A few subtypes, namely, A (A1, A2, A3, A4, A5), C, CRF02_AG, and D accounted for about 85% of new infections. Subtype A and D have been stable in East Africa; C in southern Africa; A, G, CRF02_AG, and CRF06_cpx in western Africa; and subtype B and CRF02_AG in northern Africa. Recently a new putative group, designated P, was reported to be found in two Cameroonians.***

Conclusion: ***The regional distributions of individual subtypes and recombinants are broadly stable, although unique/circulating recombinant forms may play an increasing role in the HIV pandemic. Understanding the kinetics and directions of this continuing adaptation and its impact on viral fitness, immunogenicity, and pathogenicity are crucial to the successful design of effective HIV vaccines. There is need for regular monitoring and review updates, such as the one presented here, to assist countries to plan and anticipate complex forms that may be introduced with time.*** **(AIDS Rev. 2012;14:83-100)**

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Key words

HIV-1. Genetic diversity. Subtypes. Africa.

Introduction

Globally, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates show that 33.3 million people including children were infected with HIV by the end of 2009. Of this number, 2.6 million were new infections, with another 1.8 million deaths[1]. Sub-Saharan Africa accounted for over 67% of the total population that was living with the virus. Of the 7,000 new infections per day, 97% occurred in middle- and low-income countries[1].

Africa has some of the poorest countries in the world whose populations have been severely affected by HIV. For example, by the end of 2009, nine African countries had more than 10% of their adult population infected with HIV[1]. In some countries the epidemic is even higher, e.g. in Botswana, 24.8% of adults are now

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infected with HIV, while in South Africa, 17.8% are infected. Rates of acquiring new HIV infections are still high in sub-Saharan Africa, with an estimated 1.9 million people becoming infected in 2009[1].

HIV-1 is characterized by an extensive genetic diversity[2-6]. Mutational escape results in a remarkable degree of viral diversity within HIV-1 and its adaptation in response to both immune activity and antiretroviral therapy (ART). However, not all escape mutations are advantageous to the virus since some can severely hinder viral fitness[7,8]. Nevertheless, HIV strains often exhibit specific associations with particular geographic regions and/or modes of transmission[9-11]. Tracking these dynamic associations through surveillance of genetic diversity has facilitated epidemiological investigations and informed public health strategies aimed at preventing viral spread[5]. Several studies have demonstrated that HIV-1 subtypes are not randomly distributed around the globe but show distinct geographical distributions[3,12-16]. The resultant viral diversity has implications for possible differential rates of transmission, disease progression, responses to ART (including the development of resistance), and vaccine development[17,18].

The main objective of this review is to summarize the current available data on HIV-1 subtype diversity in Africa. It provides an update on the genetic diversity of HIV-1 strains in Africa and by region. In particular, it provides an overview of recent epidemiological research findings on multiple infections and geographic distribution of HIV subtypes in 51 of the 54 African countries. The information provided by this review could complement and update available knowledge of HIV-1 diversity in Africa, and provide critical information for diagnostic tools, vaccine development, and possible clues for tracking similar transmission patterns in future.

Origins of HIV

It has been postulated that HIV-1 originated from three independent cross-species transmissions of simian immunodeficiency virus (SIVcpzPtt) infecting chimpanzees (SIVcpz; *Pan troglodytes troglodytes*) in west-central Africa, giving rise to pandemic (group M) and non-pandemic (groups N and O) clades of HIV-1, while the SIV origin of group O (outlier) viruses has not been identified[19-21] (Fig. 1). Recently, one new putative group, designated P, was reported to be found in Cameroonian patients[6,22]. The group P viral sequences, RBF168 and 06CMU14788, form a distinct HIV-1 lineage that includes SIV sequences from western gorillas (SIVgor; *Gorilla gorilla gorilla*), suggesting that group P originated from gorillas[22-24]. On the other hand, HIV-2 is believed to have originated from SIV_{Sm} from the sooty mangabey monkey (*Cercocebus atys*)[25,26]. The sooty mangabey is the only primate species naturally infected with viruses related to HIV-2 and is found in western Africa[27]. The HIV-2 has continuously evolved out of the epicenter in western Africa and formed recombinants[28,29] including a circulating recombinant form (CRF). The first HIV-2 CRF was described among recently isolated genomes from Japanese patients (who were believed to have had links with similarly infected individuals from western Africa) based on three recently isolated genomes from Japan and 1990 isolate 7312A from Cote d'Ivoire.

Evolution of HIV-1 and classification

Subtype designations have been powerful molecular epidemiological tools to track the course of the HIV-1 pandemic. Evolutionary analyses have revealed an origin of pandemic HIV-1 group M in the Congo River basin in the first part of the 20th Century (between 1915 and 1941), but the patterns of historical viral spread in or around its epicenter remain largely unexplored[30-34]. Group M is the predominant circulating HIV-1 group. It has been divided into the current nine subtypes: A-D, F-H, J, and K[2,3]. Within some subtypes, further distinct sequence clusters exist based on genetic variation of 15-20% (variation between subtypes is usually 25-35%), leading to the classification of virus strains into sub-subtypes. For example, subtype A has been subdivided into sub-subtype A1, A2, A3, A4, and A5, and F has been subdivided into F1 and F2. Furthermore, inter-subtype recombinant genomes are common, but many of them are found only in the dually-infected individual patient in which they arose. If an inter-subtype recombinant virus continues to be transmitted from one individual to another, it can be classified as a CRF. The CRF represent recombinant HIV-1 genomes that have infected three or more persons who are not epidemiologically related, so they can be assumed to have an epidemiologically relevant contribution to the HIV-1 M group epidemic. The CRF are labeled with numbers rather than letters, and numbered in the order in which they were first adequately described, e.g. CRF02_AG. At least 51 CRF along with a myriad of unique recombinant forms (URF) have been identified[35].

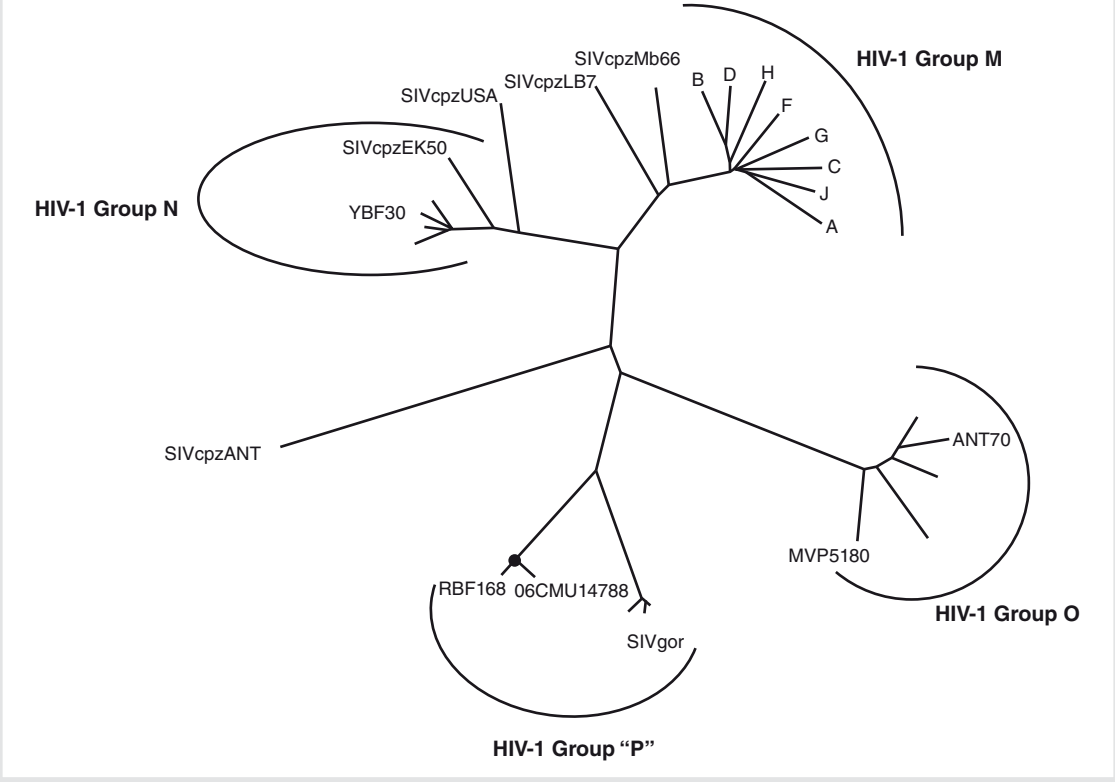

Figure 1. *Phylogenetic tree derived from nucleotide alignment of genome sequences. HIV-1 group M is represented by single sequences for each subtype A through H and J; group N and group O are each represented by five sequences, with isolates YBF30, ANT70, and MVP5180 indicated, and SIVgor is represented by three sequences, CP684, CP2135, and CP2139. The alignment consisted of 7,509 nucleotides after gaps were stripped.*

Group N is a very distinctive form of the virus that has only been identified in a few individuals in Cameroon. Group N is sometimes referred to as Not-M, Not-O, also sometimes as the "new" group, and is also thought to have originated from a chimpanzee transmission. Subtypes within the HIV-1 N group are not yet clearly defined. Very few isolates have been identified and sequenced from humans[36-39].

HIV-1 group O, sometimes referred to as the "outlier" group, is rare and contains very diverse viruses, but is still relatively rarely found. It is thought to have originated in a transmission to humans from wild gorillas[23]. Subtypes within the HIV-1 O group are not yet defined, although the diversity of sequences within the HIV-1 O group is nearly as great as the diversity of sequences in the HIV-1 M group. Unlike group M viruses, phylogenetic analyses of the *gag* and *env* genes do not reveal distinct subtypes in the HIV-1 O group.

Impact of HIV diversity on HIV diagnosis, treatment, and vaccine development

Preliminary data reveal a very heterogeneous distribution and dominance of different genetic subtypes depending on the country analyzed. In Africa, all known HIV-1 genetic subtypes and groups, including groups N, O, and P, are present. This diversity has an impact on serological diagnosis, virologic follow up, and therapeutic monitoring[40-44]. Whether the various groups, subtypes, and recombinant forms of HIV-1 have biological differences (for example, with respect to transmissibility and the course of disease progression) is not known[10,45,46]. A relationship between genetic subtype and natural resistance against antiretroviral drugs has been reported[47,48]. The degree to which vaccines based on one subtype will elicit cross-protection against other subtypes is still poorly understood; hence the need to understand the geographic distribution of

the major HIV-1 subtypes for appropriate interpretation of HIV vaccine trials.

A current area of some controversy is the association of emerging mutations with viral subtype. For instance, preferential emergence of the K65R mutation has been described in subtype C-infected patients failing stavudine/didanosine-based regimens in Botswana[49]. Also, K65R was detected in subtype C viruses after a shorter period of culture *in vitro* compared with subtype B virus, and was attributed to the presence of polymorphisms at positions 64, 65, and 66 in reverse transcriptase of subtype C viruses[50], although this was not confirmed[51]. Subtype C viruses also develop resistance against nonnucleoside reverse transcriptase inhibitors through either the K103N or V106M mutations, whereas subtype B viruses rarely develop V106M mutations[52]. Nelfinavir resistance appears to occur primarily through L90M mutations in subtype G and C and other non-B subtypes, whereas subtype B acquires either D30N or L90M nelfinavir-resistant mutations. Lemey, et al. have shown important differences in the evolutionary rates of different subtypes using Bayesian Markov Chain Monte Carlo relaxed-clock phylogenetic analysis. It was observed that CRF02_AG had a higher mean substitution rate than all other subtypes in both *pol* and *env*, while subtype D had lower rates in *pol* and *env* (along with subtype B in *pol*). Subtype G showed a similar pattern to that for CRF02_AG[53,54]. The differences in mean substitution rates between subtypes can be due to differences in the generation time, mutation rate, or (immune) selective pressure and may suggest less accumulation of mutations in subtype D compared to any other subtype[55].

HIV-1 genetic diversity has long been identified as a key challenge in the development of an effective, preventive HIV vaccine. No one knows if an effective vaccine would be dependent on conserved epitopes or on conformational presentation. Therefore, many strategies are being pursued to confront the issue of high diversity among HIV isolates, including the use of consensus sequences, the deployment of a combination of immunogens from different subtypes, the creation of mosaic immunogens assembled through computational optimization from pieces of natural sequences, and the construction of multi-subtype immunogens derived from conserved regions of the HIV-1 consensus proteome[17,18,56,57]. Though infected individuals mount immune responses, there are reports of mutational escape by viruses from responses by $CD8^+$ cytotoxic T-cells and neutralizing antibodies over time. Peptides based on highly conserved HIV-1 consensus group M sequences, which are phylogenetically closer to most circulating strains, may provide potential alternative vaccine candidates in populations with diverse infections[58].

Epidemiology of HIV

The original cross-species transmission of HIV is believed to have occurred in west-central Africa and has been evolving in humans since at least the early 1900s[59]. Despite high diversity in its origin in west-central Africa, a limited number of viruses have spread, with four subtypes and two CRF being responsible for 90% of infections. Worldwide, it has been shown that 48% of infections are caused by subtype C; 12% by subtype A; 11% by subtype B; 5% by subtype G; 2% by subtype D; and 22% recombinants[4]. We present below a detailed update of the literature of the HIV epidemic in each African country, in alphabetical order, within the three main regions: east and southern Africa; west and central Africa; and north Africa.

East and southern Africa

Countries with the largest epidemics are in southern Africa; in South Africa, Zambia, and Zimbabwe, the subtype C epidemic has continued to predominate and the HIV/AIDS prevalence has either stabilized or has shown a sign of decline according to the UNAIDS 2010 report. In the past 10 years, data on HIV-1 subtypes in southern Africa has significantly increased in seven of the 10 southern African countries. Subtype data has been published from Angola[60-62], Botswana[49,63-67], Malawi[68-71], Mozambique[72-76], South Africa[69,77-90], Zambia[69,90-95], and Zimbabwe[69,96-98]; however, very limited data is available from Lesotho[99,100], Namibia, and Swaziland[99,101], despite reported high HIV prevalence rates.

The heteroduplex mobility assay (HMA) and multiregion hybridization assay (MHA) offered a more affordable option for simple and rapid classification of HIV-1 subtypes, and was used in many areas, such as Tanzania, Uganda, and Ethiopia. However due to cross-reactivity across subtypes, this method could not define specific sequence differences between isolates of the same or different subtypes. In an attempted optimization, we developed and applied these assays to detect inter- and intra-subtype dual infections (both simultaneous coinfection and consecutive superinfection) and determined the prevalence of dual infection within some couples known to have discordant HIV-1

subtypes from 155 participants in a rural clinical cohort in southwestern Uganda. Of these, 45 participants were suspected to be either dually infected with HIV-1 subtypes A and D or to be infected with recombinants viruses. Cloning and DNA sequencing confirmed the evidence of only two dual infections (Ssemwanga and Ndembi, unpublished data). Direct DNA viral sequencing of fragments greater > 1,000 base pairs has been appropriate in characterizing infecting HIV-1 subtypes or CRF/URF and has been used to monitor regional and global HIV-1 spread[4,102-105]. 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[106]. This has been a major drawback in subtype analysis in Africa, though it is proving to be a dependable tool. Nonetheless, in southern Africa, subtypes A, C, and D together with their recombinants are the major subtypes and account for > 50% of infections. In East Africa, HIV subtype diversity is characterized by strains that are further dependent on human migratory patterns. The majority of infections are due to subtype A, with others being due to subtypes C and D and a high proportion of CRF/URF.

Angola

Severe HIV/AIDS epidemic has been recorded in Angola[1], with the adult population shown to have divergent HIV subtypes and recombinants[60-62,107]. Most HIV subtype data in Angola has been derived from sequencing of the *pol* gene[60,62,107] or *pol*, *gag* and *env* genes[61,107]. Early data from HIV-1 *pol* sequences showed that subtype C and F were the most predominant, while subtypes A, D, G, and H were also found[60]. Similarly, unclassified sequences were also found, suggesting they were unknown new subtypes or recombinants from unknown subtypes. Another subsequent study that analyzed 48 samples in the HIV *gag* and *env* genes found a contrasting prevalence of subtype A1 being predominant (38%), followed by C (15%) and several other subtypes: H (10%), J (6%), G (4%), A2 (4%), F1 (2%), and D (2%)[61]. The subtype F1 in Angola is thought to have originated from the Democratic Republic of Congo (DRC)[108] and was introduced into Brazil by emigrants during the late 1970s (1975-1980), coinciding with the beginning of the Angolan civil war in 1975[109,110]. One comprehensive study in Angola analyzed almost 400 sequences from *gag*, *pol,* and *env* genes of 159 HIV-infected patients derived from eight provinces across Angola[107] and found two distinct sub-clusters within the subtype A, which were defined as new A5 and A6 sub-subtypes[107]. In the Angolan population, close to 50% of viruses were recombinants, with predominance of subtype A and CRF02_AG. In another study of transmitted drug resistance among newly diagnosed HIV-infected pregnant women, the same subtype distribution was observed[62].

Botswana

Although subtype data of most studies was derived from small sample sizes using *pol* sequence data, subtype C is the most predominant in Botswana[49,63-67]. Data from a study based on 71 *pol* sequences from 11 representative districts of northern and southern Botswana classified all but one (which exhibited *pol* gene mosaicism) as subtype C[66].

Eritrea

In Eritrea, epidemiological studies on HIV-1 subtypes have been similar to reports in Ethiopia. This is because the two countries were originally one. Prolonged civil war between the two countries led to their separation, but population movements have remained the same. HIV-1 subtypes reported from this region are mainly subtype C[111].

Ethiopia

Subtype C is predominant in Ethiopia; over 80% of all reported subtypes are classified as C[112]. The subtype C found here has its origin in India and is believed to have been introduced from South Africa and, through founder effects, has spread through Djibouti, Eritrea, and Ethiopia[111], although others speculate entry from several sources including neighboring countries like Somalia, Sudan, and Djibouti where subtype C has been detected[113-120].

Furthermore, within subtype C, there are sub-clusters, hence the diversity into C and C'[112,121-125].

Kenya

HIV-1 subtype A was reported as the predominant strain in southern Kenya, with over 30% recombinants[126-128]. All along, studies have shown that subtype A1 is predominant in Kenya, but subtypes A2, D, C, and G together with their recombinants have also been described[126,129-135]. Whereas subtypes A and D are

believed to have been introduced into Kenya from western Africa through Uganda, their recombinations are thought to be as a result of founder effects[128]. This has been shown by the detection of subtypes A, C, and D together with CRF16_A2D recombinants[136]. Kenyan subtype C has two distinct epidemics; one from north Africa, believed to be Ethiopian C, where this has been the major strain with links to India, while another epidemic is from the south, believed to have its origin in southern Africa where subtype C is predominant, as illustrated by the marked increase in prevalence of subtype C in northern Kenya[137]. The southern epidemic is thought to be as a result of direct introduction from southern Africa through Tanzania. As such, Kenya appears to have an array of subtypes that co-circulate courtesy of increased human migration in and around East and central Africa. For instance, in a study among HIV patients in Kilifi, phylogeographic analysis of 153 *pol* sequences compared with those from other regions of Africa showed that while many sequences were closely related to sequences from Kenya, others were most closely related to known sequences from other parts of Africa, including West Africa[128].

Lesotho

The first few known reports showed the dominance of subtype C among migrant mine workers from Lesotho in South Africa[99], and since then, very limited data is available. Subtype A was shown in a subsequent study in a patient from Lesotho in South Africa[100].

Malawi

There has been an increase in the generation of data on the HIV-1 subtype from Malawi over the years[68-71]. The scaling up of ART has increased the *pol* gene sequence data (used in laboratory monitoring of patients and ART success), with one study reporting subtype C as the only subtype in Malawi[68]. Other studies found envelope diversity during vertical transmission of HIV-1 in mother-infant pairs and also reported the predominance of subtype C in Malawi[70]. In a study to determine subtype C diversity in Malawi, Zambia, Zimbabwe, and South Africa in preparation for vaccine trials in southern Africa, no evidence of intersubtype recombination was reported[69] and a recent study also showed the predominance of subtype C in drug-naive HIV-positive individuals in a rural population in Malawi[71].

Mozambique

In the recent past, most of the subtype data from Mozambique has been derived from sequencing the *pol* gene, in studies outlined below, to determine prevalence of drug-resistant mutations among ART-naive HIV-positive individuals. Several studies have reported varying subtype distribution estimates, but with subtype C being predominant[72-76]. A study among treatment-naive individuals showed the predominance of subtype C[72]. In southern Mozambique, a study to determine HIV-1 diversity between 1999 and 2004 found predominance of subtype C, with 2004 sequences showing significantly more genetic diversity than sequences from 1999[73]. In yet another study among 75 HIV-positive drug-naive pregnant women, the majority of sequences were subtype C, with few subtypes A, D, and some recombinants[76]. In addition to subtype C, a few sequences were found that clustered with subtype A, D, and some recombinants[76]. In Maputo, a study to monitor viral loads and drug resistance among individuals taking first-line therapy for at least 12 months showed that among the 15 individuals with viral loads > 1,000 copies/ml, of which 12 were sequenced, eight were infected with subtype C, whereas the other four had CRF08_BC[75]. Another study in Maputo to determine the subtype distribution and level of transmitted drug resistance in a healthcare setting also found predominantly subtype distribution as C (80.8%), G (3.8%), CRF37_cpx (6.7%), unclassified (U) (1.0%), and recombinant strains (7.7%) comprising the A, C, D, F, and U clades[74].

Rwanda

HIV-1 subtypes A and C have been reported to be predominant in Rwanda. Studies among antenatal clinic attendees in Kigali showed that subtype A together with its recombinants accounted for the majority of infections[138,139]. Similarly, another study on samples from urban Kigali documented subtype A as predominant[90]. The limited data on HIV subtypes in Rwanda may be attributed to civil war and the 1994 Rwandan genocide, which coincided with the up-scaling of gene sequencing technologies in this region.

Seychelles and Madagascar

Seychelles and Madagascar are important tourist destinations and offer a good opportunity in studying HIV subtype spread since infections are known to

spread with human migration. In a study of 40 HIV-infected patients in Mahe hospital, Seychelles, it was reported that besides recombinants, CRF01_AE and CRF02_AG, subtype A was the most prevalent[140]. A similar study in Madagascar found in addition the presence of complex HIV-1 strains (CRF02_AG, CRF06_cpx, and CRF10_CD). Most viruses were related to those detected in neighboring mainland countries and from around the world[141].

South Africa

In South Africa, there is rich data from many studies that have documented subtype C as the predominant subtype[69,77-90]. In Kwazulu-Natal, a region with an explosive outbreak of HIV infection, analysis of 72 treatment-naive patients in protease and C2V5 envelope regions showed that all were subtype C that segregated with other C viruses from southern Africa[78]. In Cape Town, a study demonstrated some phylogenetic diversity among treatment-naive HIV-positive patients; among 140 *pol* sequences analyzed, 133 (95%) were subtype C, five (3.6%) subtype B, and one each subtype G and CRF02_AG[81]. Several other studies across South Africa in the Free State[83], Kwazulu-Natal[78,82], Cape Town[69,84,90] and other areas have shown a high prevalence of subtype C and very few representatives of the other subtypes and recombinants[84,86]. The observed increase in non-subtype C strains has been attributed to immigration of people from countries with civil unrest and also immigrant workers into South Africa[86].

Swaziland

Since 1998, when some subtype C data from Swazi migrant workers was reported[99], limited data showing predominance of subtypes C has been documented among patients in Swaziland[101].

Tanzania

In Tanzania, HIV-1 subtypes A and C have been documented as major circulating strains[142-146]. Subtype C is thought to have been introduced from southern Africa, where it is the most common strain in circulation, and through founder effects from Lubumbashi in the DRC[125]. A study conducted among HIV patients in Mbeya region found multiple infections (recombination, dual infections, and triple infection using single genome amplification) to account for 27%[147]. The proportion of HIV subtype recombinants in the country has also been increasing with new sequencing technologies[148-151]. More than 60% of detected recombinants are those of subtype C. This differs from the Kenyan epidemic, which consists of mostly A and D recombinants[128]. Tanzania also leads East Africa with the highest prevalence of reported recombinants[152]. It is here that CRF10_CD was reported among perinatally infected infants, an indication that this CRF has been circulating among the Tanzanian population[148] for some time.

Uganda

As far back as the mid-1980s[153], multiple genetic subtypes of HIV-1 were reported in Uganda, with A and D as the most prevalent and with connections to their cities of origin in central Africa[11,103,105,125,154-159]. The prevalence of HIV-1 decreased from an estimated 14% in the early 1990s to around 8% in 1999 as a result of an aggressive prevention program and open discussions on issues surrounding HIV[160]. Detailed and systematic characterization of the HIV-1 epidemic in Uganda over time showed that the distribution and degree of genetic diversity of the two predominant subtypes, A and D, differed[11,153]. In an eight-year (1994-2002) interval, a significant decrease of 8% in subtype D prevalence was detected[11]. Subtype D was replaced with an increase of subtype A and recombinant strains. It was noted that subtype D is decreasing in Rakai, probably as a consequence of faster disease progression and lower infectivity of this subtype[45,46]. Recent studies have confirmed an increase in prevalence of subtype A1, with consistent detection of A/D recombinants and dual infections[158,159].

Zambia

Several studies in Zambia have reported predominance of subtype C[69,90-95]. Some earlier reports investigating the prevalence of drug resistance mutations among ART-naive Zambians showed that 93% of all infections were of subtype C[91]. In a study among 548 participants, 98% of sequences were found to be subtype C[95]. More recently, in a multicentre study including Entebbe, Kigali, Kilifi, Lusaka, and Cape Town, a significant increase in subtype C transmitted drug resistance in Zambia was reported[90].

Zimbabwe

Over the years, subtype data has been generated from Zimbabwe[69,96-98,161]. Similar to other geographic

regions, available subtype data from Zimbabwe is from *pol* sequence data for estimation of ART resistance. Subtype C was exclusively found in 21 Zimbabwean patients who were failing ART[96]. In a recent study to determine the virologic response to triple nucleoside/nucleotide analogue regimens over 48 weeks among Ugandan and Zimbabwean adults, subtype C was predominantly found in Zimbabwe, whereas A and D were found in Uganda[97]. Based on Bayesian analysis from 177 *pol* subtype C sequences, the origin and evolutionary history of subtype C in Zimbabwe was shown to have been due to regional conflict and migration during the Zimbabwean national independence, following a period of socio-political instability[161].

The observed lack of HIV diversity data from Comoros, Lesotho, Mauritius, Namibia, and Swaziland could not be explained, but it may probably be due to cultural norms and laws that prohibit HIV research as well as the population's lack of knowledge on HIV/AIDS resulting in heightened stigma. It could also be due to lack of both technical and financial capacity of these countries to carry out diversity studies. This therefore highlights the existing gaps in HIV diversity data in some of the sub-Saharan countries.

West and Central Africa

Benin

Subtype data from Benin has not been extensively published[162-164]; earlier reports from Cotonou showed a prevalence of 39% CRF02_AG as determined by the *gag* HMA methodology[162]. Another study that was done in a randomly selected general population and sex workers in Kisumu (Kenya), Ndola (Zambia), Cotonou (Benin), and Yaounde (Cameroon) revealed that 70% of infections in Cotonou were subtype A by *env,* but 50% of the *env* subtype A infections were found to be CRF02_AG when the *gag* gene was analyzed[163]. In Cotonou, CRF02_AG was found at a prevalence of 66%, subtypes G, A3, CRF06_cpx and other URF were found in HIV-1-infected patients receiving ART in routine clinics[164].

Burkina Faso

A study to determine HIV-1 drug resistance among newly diagnosed patients before scaling up ART in Burkina Faso and Cameroon found that among the 97 samples from Burkina Faso, the subtype distribution was CRF02_AG (n = 47; 48.5%), CRF06_cpx (n = 46; 47.4%), A (n = 3; 3.1%), and G (n = 1; 1.0%)[165]. A high predominance of recombinant HIV-1 strains CRF06_cpx 16/29 (55.17%), CRF02_AG 9/29 (31.03%), A1 2/29 (6.89%), G 1/29 (3.44%), and CRF09_cpx 1/29 (3.44%) was shown when 29 samples were sequenced from non-HAART and HAART-treated patients from Burkina Faso[166]. Another study on prevention of mother-to-child transmission of HIV in 227 seropositive women found that 221 were infected with HIV-1, four with HIV-2, and two with mixed HIV infections; all three children infected with HIV-1 had CRF06_cpx[167]. The predominance of CRF02_AG (56.5%) and AGK/K/AK (26.1%) was shown among patients on ART in Burkina Faso and Mali[168]. Several studies have shown the predominance of CRF02_AG and CRF06_ cpx in Burkina Faso[169-171].

Burundi

In Burundi, a study among HIV drug-naive individuals showed that subtype C was the most common strain in Bujumbura[172]. However, a study by Vidal, et al.[273] found 28.6% to be recombinants. HIV-1 subtype data in this country is limited due to conflicts, but is thought to be influenced by prevailing subtypes in the DRC[125].

Cameroon

Cameroon probably has the highest number of HIV-1 subtypes found in any country in the world. HIV-1 group O is endemic to Cameroon and west-central Africa, accounting for only 1-6% of all cases of HIV-1 infection in Cameroon (about 10,000 to 20,000 people)[173-175]. HIV-1 N is extremely rare at present and has only been found in Cameroon[39]. Recently a new putative group, designated P, was reported to be found in two Cameroonians[6,22]. To date only two group P infections have been reported (Fig. 1). Studies conducted in the major cities of Yaoundé and Douala in 1999 and 2002 evaluated the HIV strains present in blood donors, patients with tuberculosis, and those with sexually transmitted infections showed CRF02_AG was the predominant strain, accounting for 60-68% of HIV infections, with an additional 26% classified as URF. Subtypes, D, F2, and G, and CRF, 01, 11, 13, 22, 36, and 37 have been identified in Cameroon. Although there are regional differences in strain prevalence, diversity is high throughout the country in both urban and rural areas[16,43,102,176-183]. Moreover, Brennan, et al. analyzed 676 HIV-infected blood

donations collected from 1997 through 2004 at blood banks in Douala and Yaoundé and found that group M accounted for 97.3% (n = 658) of infections, whereas group O was present in 2.2% (n = 15) and HIV-2 in 0.4% (n = 3). Within the group M infections, 14 subtypes and CRF and URF were identified[33,184]. Overall, CRF02_AG accounted for 58.2% of infections, URF 14.8%, and levels of subtypes, A, B, C, D, F2, and G, and CRF, 01, 06, 09, 11, 13, 22, and 37, varied from 0.2 to 6.1%. Evaluation of HIV strains present in the donor population over a nine-year period showed no substantial changes in the proportion of infections caused by each subtype and CRF, the percentage of intersubtype recombinants, or the strain composition of the URF. Multiple infections (dual and triple infection) and recombination between highly divergent HIV-1 strains have been reported in Cameroon[43,174,185-188].

Cape Verde

HIV subtype data from Cape Verde is very limited; however, there has been a case report of a patient from Cape Verde who was diagnosed with an extremely rare HIV-2 with severe neurological disease in the USA[189].

Central African Republic

The circulation of numerous HIV-1 subtypes have been reported from the Central African Republic (CAR), including subtypes A1, A2, A3, A4, B, C, D, CRF01_AE, F, G, H, CRF06_cpx CRF11_cpx, CRF13_cpx, and CRF19_cpx[102,190,191]. Several full-length CRF01_AE viruses from the CAR have been characterized[192].

Chad

HIV-1 in Chad has been documented, but little information on subtypes exists[193,194]. Lasky, et al. identified the genetic subtypes by *env* HMA of HIV-1 from two individuals who were infected overseas on deployment to Chad as subtype B. In the group of HIV-1-infected individuals that was studied and who were deployed overseas, 63.4% were infected with non-B strains. In addition, subtype A, B, and C viruses in this population were very heterogeneous. Vidal, et al. assessed the molecular epidemiology of HIV-1 *env* and *gag* from 107 samples from patients attending the general hospital in N'Djamena, which revealed that four subtypes (A, D, G, and F) and three CRF were found to co-circulate, and a minor proportion of the strains could not be clearly classified.

Côte d'Ivoire

Several studies from Côte d'Ivoire have reported on the HIV diversity and prevalence of HIV drug resistance[170,195-202]. An earlier study in a cohort of 99 seroconverts in Abidjan revealed that most of the isolates (82/99, 83%) were CRF02 AG, nine strains were HIV-1 subtype A, one was a recombinant between A (*pol*) and F2 (*env*), four clustered with CRF06_cpx, and three isolates formed an isolated cluster[195]. A field evaluation of a *gag*-based HMA in comparison with DNA sequencing on 108 samples in Abidjan showed that (82%) were CRF02_AG, 14 (11%) were subtype A, five (4%) were subtype G, three (2%) were subtype D, one was CRF01_AE, and one was subtype H. Several other studies in Côte d'Ivoire have documented the predominance of CRF02_AG based on drug resistance testing data[170,196,199-202].

Democratic Republic of Congo

Numerous studies have assessed the extent of genetic diversity of HIV-1 group M viruses in the DRC (formerly Zaire). The high number of co-circulating HIV-1 subtypes, high intra-subtype diversity, the high number of possible recombinant viruses and unclassified strains are all consistent with the presence of an old and mature epidemic in the DRC, suggesting that the region is the epicenter of HIV-1 group M[31,203-209]. Several epidemiological surveys in both rural and urban areas of the DRC have confirmed that all known HIV-1 subtypes are co-circulating. The proportion of CRF02_AG among subtype A strains based on *env* sequences decreases from west to central Africa, with an absence of CRF02_AG in the DRC. Kita, et al. found that a high proportion (16/27; 59.3%) of HIV-1 strains in Likasi were intersubtype recombinants[210]. This was higher than that reported in other regions of DRC (29-44%). Interestingly, two HIV-1 strains from Likasi (00CD009 and 01CD208) significantly clustered with CRF02_AG reference strains (with 97.4% bootstrap value). This was the first report of CRF02_AG in the DRC, suggesting that CRF02_AG is spreading into Central Africa. CRF02_AG and subtype A represent 70-80% of circulating HIV-1 strains in west and west-central Africa. Vidal, et al. undertook an epidemiological survey (247 samples) in three regions of the DRC: Kinshasa (the capital city), Bwamanda (north), and Mbuyi-Maya (south). All known subtypes were found to co-circulate, and for 6% of the samples the subtype could not be identified. Subtype A is predominant, with prevalences

decreasing from north to south (69% in the north, 53% in the capital city, and 46% in the south). Subtype C, D, G, and H prevalences ranged from 7-9%, whereas subtype F, J, K, and CRF01-AE strains represented 2-4% of the samples; only one subtype B strain was identified. The highest prevalence (25%) of subtype C was in the south, and CRF01-AE was seen mainly in the north[211]. Yang, et al. looked at HIV-1 subtype distribution among commercial sex workers from Kinshasa during the mid-1980s. The *env* analysis showed that of 24 samples, 37.5% were subtype G, 21% subtype A, 12.5% sub-subtype F1, 8% CRF01_AE, 4% subtype D, and 4% subtype H; 12.5% were unclassified[212].

Equatorial Guinea

Equatorial Guinea borders to the north with Cameroon, where different subtypes of group M and O simultaneously circulate. Analysis of 119 plasma samples from HIV-1 seropositive individuals showed that CRF02_AG accounted for 47%, sub-subtype A3, subtype C, subtype D, subtype F (clustered close to F2), subtype G, CRF06_cpx, CRF09_cpx, CRF11_cpx, CRF22_cpx, and CRF26_A5U have been reported[213-215]. HIV-1 group O has also been identified in Equatorial Guinea[173].

Gabon

Besides HIV-1 group O being documented in Gabon, HIV-1 group M, subtypes A, B, F, G, H, K, CRF01_AE, CRF02_AG, and CRF11_cpx have also been reported in three independent studies[216,217]. Phylogenetic analysis of 31 strains from Gabon found two subtype A, four subtype D, one subtype G, one subtype H, eight CRF02_AG, six CRF MAL-like, six URF and one unclassified[218].

Gambia

After 16 years of HIV surveillance in western Africa (1988-2003), it has been shown that the prevalence of HIV-1 in the Gambia is increasing while HIV-2 is declining[219]. The HIV subtype distribution in the Gambia based on full envelope sequences has shown presence of a novel CRF (named CRF49_cpx) in addition to the predominant CRF02_AG, a few HIV-1 subtypes B, C, and D[220]. Another study among 20 patients showed 12 infections with HIV-2 and eight dual infections with HIV-1 and HIV-2[221].

Ghana

Most studies in Ghana have documented CRF02_AG as the predominant strain[222,223]. Phylogenetic analysis of HIV-1 partial *pol* sequences from 207 Ghanaian individuals revealed that 66% of infections were CRF02_AG, whereas 25% were URF. CRF02_AG was the parental strain in 87% of URF, forming recombinants with genetic forms circulating in minor proportions: CRF06_cpx, sub-subtype A3, CRF09_cpx and subtypes G and D. Two triple recombinants (CRF02_AG/A3/CRF06_cpx and CRF02_AG/A3/CRF09_cpx) were also identified[223]. A study on 25 treatment-naive patients from Ghana showed a predominance of CRF02_AG strain (n = 22), but three (13.6%) of these were recombinants with HIV-1 subtype K and/or A1. Two patients had unclassified/complex strains with D/CRF01_AE and G/CRF02_AG subtypes[222].

Guinea

HIV-1 and HIV-2 have been reported to be prevalent in Guinea[224]. In Conakry, a study on 99 ART-naive patients found that 89% were infected with CRF02_AG recombinant virus.

Guinea-Bissau and Liberia

In Guinea-Bissau, among 711 females, a high prevalence of HIV-1 (9.5%), HIV-2 (1.8%) and dual HIV-1 and HIV-2 (1.1%) was reported among women attending sexual health clinics[225]. In another study to assess the prevalence of HIV-1 and HIV-2 before, during, and after the civil war in Guinea-Bissau, it was found that the prevalence of HIV-1 increased and that of HIV-2 decreased, and the risk of acquiring HIV-1 was more than fourfold compared to HIV-2[226]. There is, however, not much data on HIV diversity in Guinea-Bissau. In Liberia, possibly due to the long civil war in the past couple of years, there is no HIV diversity data that we could include in our review.

Mali and Mauritania

The most prevalent HIV-1 strain in Mali is CRF02_AG; other strains like CRF01_AE, CRF06_cpx, CRF09_cpx, other HIV-1 subtypes and several recombinants between CRF and known subtypes have been reported[227-230]. Similar to other studies, most sequence data from Mali has been generated from routine sequencing of the *pol* gene for surveillance of drug resistance. A study to

determine the prevalence of drug resistance among 98 ART-naive patients in Bamako showed that CRF02-AG constituted 75% of cases, followed by the CRF06-cpx subtype (20%), and intersubtype recombinants between CRF02-AG, CRF01-AE, and CRF06-cpx were also described in 5% of cases[227]. Analysis of the *pol* gene among 198 ART-naive patients diagnosed with HIV-1 between 2005 and 2006 in Bamako and Segou showed the prevalence of CRF02_AG in Bamako (74%; 73/99) and in Segou (70%; 66/94). Distribution of the other subtypes was: 22 CRF06_cpx (11%), six A (3%), five CRF09_cpx (3%), two G (1%), two F2 (1%), one CRF01_AE (0.5%), and one CRF18_cpx (0.5%), with a greater diversity in Bamako than in Segou[228]. Other studies showed similar prevalence of CRF02_AG strain in Mali[229,230]. We did not have sufficient data that described the diversity of HIV in Mauritania.

Niger

The CRF02_AG and CRF06_cpx have been reported to be the most predominant strains in Niger[231,232]. Genetic characterization of 110 HIV-positive samples in the V3-V5 envelope region and p24 *gag* region showed that the majority of the strains were CRF02_AG (54.3%) or CRF06_cpx (18.1%) in *env* and *gag*; more than 9% of the samples were recombinants between CRF02_AG and CRF06_cpx; nine were CRF06_cpx in *env* but CRF02 in *gag*, and for one sample the opposite was seen[231].

Nigeria

Significant data has been published to describe the diversity of HIV in Nigeria, showing the presence of CRF02_AG, HIV-1 subtype G, HIV-1 sub-subtype A3, CRF06_cpx and other recombinants[233-241]. The differences in the geographic distribution of subtype A and G was shown in a study where the overall prevalence of subtype A and G was 61 and 39%, respectively[233]. This study further showed that subtype A was predominant (70%) in the south (Lagos), subtype G was predominant (58%) in the north (Kano), and both subtypes were equally distributed in the northeast (Maiduguri): A (49%) and G (47%)[233]. An earlier evaluation of the protease gene among 10 ART-naive HIV-positive patients in Nigeria showed that 80% of samples were subtype A and the rest were unclassified divergent strains[234]. In Oyo state, analysis of 50 ART-naive patients showed the predominance of CRF02_AG (57%), subtype G (26%), and CRF06_cpx (11%)[235]. Characterization of transmitted resistance among 14 infants infected by their HIV-positive mothers in Jos, Plateau State revealed presence of CRF02_AG (n = 5), HIV-1 subtype G (n = 5), HIV-1 sub-subtype A3 (n = 2), CRF06_cpx (n = 1), and HIV-1 subtype D recombinant (n = 1)[236]. Another study has also shown a prevalence of CRF02_AG (45%) and HIV-1 subtype G (38%) in an evaluation of 338 patients who were failing first-line therapy in Nigeria[238]. Evaluation of 28 HIV-positive patients in the *env* and *gag* genes showed predominance of CRF02_AG at 39% and HIV-1 subtype G at 32%[239]. Recently, the prevalence of CRF02_AG (45%), subtype G (38%) and other CRF and URF has been reported among Nigerian patients failing first-line ART[241].

Republic of Congo

Niama, et al. assessed the HIV molecular epidemiology in the Republic of Congo[242]. Phylogenetic analysis of HIV-1 *gag* p24 sequences showed the predominance of subtypes A and G strains (36.5 and 30.8%, respectively), followed by subtype D strains (12.5%). Subtype H represented 3.85% of the strains, and 4.8% of the samples could not be classified and were identified as U (unclassified). Bikandou, et al. summarized the frequency of the different subtypes (A, C, D, G, H) for the *env* gene in three independent studies[243-245]. The percentage of subtype G in the first three studies was 29.4% for samples collected in 1988-1992, 24.1 and 21.4% for samples collected in 1996-1997, and 20.4% for samples collected in 1998-1999[245] using HMA and direct sequencing.

Senegal

Studies in Senegal have shown the predominance of HIV-1 CRF02_AG, other variants, URF[170,246-249], and HIV-2[250]. Data from studies on both treatment-naive (n = 104) and experienced (n = 94) patients in Senegal showed a predominance of CRF02_AG (64%), with 10 other variants C [14/200 (7%)), B [10/200 (5%)], CRF06-cpx [5/200 (2.5%)], D [4/200 (2%)], CRF11-cpx [4/200 (2%)], A3 [3/200 (1.5%)], G [3/200 (1.5%)], A [2/200 (1%)], A1 [1/200 (0.5%)], and CRF45 [1/200 (0.5%)] and 25 URF[249]. All HIV-1 group M subtypes have earlier been documented to be present in Senegal, with 84.6% of infections with subtype A[251]. In the period between 1988 and 2001, the emergence of sub-subtype A3 was reported among female sex workers in Dakar, Senegal[213,252]. A surprising study

among men who have sex with men in Senegal found that 40% of infections were due to subtype C, CRF02_AG (24.3%), B (18.6%), G (8.6%), CRF09_cpx (4.3%), and URF (4.3%)[253].

Sierra Leone

There is not much data on the diversity of HIV in Sierra Leone, probably due to the past political instability. However, there was a case report of a patient that harbored a CRF02_AG with multi-NRTI-resistance[254]; this report probably indicates that the CRF02_AG may be co-circulating in Sierra Leone. In another case report, the isolation of a new strain of HIV-2 (HIV2-NWK08F) from a Sierra Leone immigrant was identified in the USA[255].

Togo

Togo is also an area where not much work has been reported on HIV diversity; however, there is a study that reported a high genetic diversity and prevalence of drug resistance mutations among ART-naive patients[256]. In this study, phylogenetic analysis of HIV-1 *pol* and *env* showed that CRF02_AG (48.7 and 51.2%) and G (12.8 and 16.2%) were predominant, followed by A3 (6.4 and 6.2%), and CRF06_cpx (3.8 and 12.5%), respectively. One strain was identified as CRF05 in *pol* and *env*. Two divergent subtype A strains in *env* were unclassified (U) in *pol* but clustered with a previously described complex recombinant strain.

Northern Africa

There is paucity of data on HIV subtypes in northern Africa. This is due to constraints, such as cultural norms and laws, the population's lack of knowledge about HIV/AIDS, and the bureaucratic health systems, which hinder the development and implementation of effective surveillance. This leads to possible perennial underreporting of HIV prevalence and almost no reporting on subtype diversity. However, seroprevalence studies among different HIV risk groups have been reported in some countries[257-259].

Algeria

In Algeria, the characterization of HIV-1 has shown high subtype diversity[258]. Subtype B has been reported as the predominant subtype, particularly in the northern part of the country, but there is a high diversity of the virus, including CRF02_AG, CRF06_cpx, and CRF02_AG/CRF06_cpx, which tend to increase in the southern part that borders sub-Saharan African countries[260]. In a recent study among treatment-experienced and treatment-naive patients, a similar trend was observed, with subtypes B, CRF06_cpx, CRF02_AG, G, D, A, F, C, and CRF09_cpx being detected[261].

Djibouti

The earliest study of HIV-1 subtypes in Djibouti among French military personnel on missions abroad showed predominance of subtypes C (48%), B (33%), A (15%), and CRF01_AE (3%)[193]. In a study of HIV-1 *env* isolates from African countries, subtypes A and C were exclusively reported from Djibouti, though the number of isolates was small[115]. It was shown in subsequent studies that the majority of infections were of subtype C, A, D as well as CRF02_AG recombinants, consistent with previous findings[120,262].

Egypt

Besides seroprevalence studies[257,259], very little is known about the distribution of HIV subtypes in Egypt. However, one study has reported HIV-1 subtype B as predominant in Egypt[263].

Libyan Arab Jamahiriya

In an analysis of HIV-1 and hepatitis C viruses among children in Al-Fateh hospital in Benghazi, Libya, HIV-1 CRF02_AG was reported to have been circulating among the Benghazi population, leading to vertical transmission from mothers to their infants[264]. The findings were contrary to the belief that these children were infected by foreign health workers. The CRF02_AG subtype detected among the children showed a single CRF02_AG lineage with links to West African sequences. This emphasized the importance of surveillance and ruled out introduction of the infections by foreign health workers[265].

Morocco

HIV-1 subtype surveillance studies have reported subtype B in Morocco[266,267]. In a study of HIV-1-infected treatment-naive individuals in Casablanca, it was established that subtype B predominated (74.6%),

followed by CRF02_AG (15.5%), CRF01_AE (4.2%), C (1.4%), G (2.8%), and F2 (1.4%)[268]. Among HIV-infected treatment-naive patients from Rabat, it was established that HIV-1 subtype B predominated (74%), followed by CRF02_AG (15%), A1 (6%), C (2%), F1 (1%), CRF09_cpx (1%), and CRF25_cpx (1%)[269].

Somalia

In Somalia, though no visible studies on HIV subtypes have been done, the limited available data has documented subtype A, C and their recombinants as the most common[116,117]. In a study among HIV patients on the border between Kenya and Somalia, it was reported that subtype A was common[270]. A study on genetic diversity of the HIV *env* from isolates of African origin reported presence of subtype C in Somalia[115].

Sudan

In Sudan, subtype D is the most common[119]. However, its introduction here might have been from two fronts; from Central Africa and also from Uganda or Kenya where this subtype is prevalent. Here the two global subtype D lineages, one circulating in East Africa and another in west-central Africa, are believed to mix[119]. Also found in Sudan is subtype C, which probably originated in Ethiopia, Sudan's neighbor to the east. However, little is known about HIV-1 diversity in the greater part of this country due to civil war. Like other Arab countries, northern Sudan is Muslim and therefore abhors reporting on HIV. The south has limited data, which has generally been obtained from refugee camps in Kenya[137]. Southern Sudan became independent on 9th July 2011 after more than 25 years of civil war with northern Sudan. So far it is a country with the poorest health infrastructure. With this independence, Southern Sudan joined the East African community, United Nations, and the African Union. It is hoped that there will be accelerated HIV research and data dissemination for the majority who may have missed out on the expanded treatment access in Africa.

Tunisia

In Tunisia, the first HIV-1 subtype surveillance report showed the presence of subtype B and CRF02_AG[271]. Similarly, Karray-Hakim, et al. reported the same trend[272].

Table 1 and 2, summarize HIV-1 subtype distribution from selected peer-reviewed studies that have documented HIV subtype diversity in eastern, western, southern and northern Africa.

Conclusion

In this review, we examined the trend of HIV-1 subtype diversity in 51 African countries over the last decade. This is also the period in which new technologies in HIV research have been rolled out in middle- and low-income countries, and collaborations with developed countries increased to cope with the increased access to prevention strategies, treatment, and vaccine trials. The increased use of automated sequencing technologies has made it possible for many countries to monitor their HIV spread and prognosis. This is critical for developing country strategies to contain the epidemic. However, the sequence information was not available from several countries (Comoros, Mauritius, and Sao Tome and Principe). Overall, the regional distributions of individual subtypes and recombinants are broadly stable, although URF/CRF may play an increasing role in the HIV pandemic.

Acknowledgments

Nicaise Ndembi and Deogratius Ssemwanga were supported by EDCTP Senior Fellowship award TA.2007.40200.011. Additional funding was by Abbott Research agreement # 7000-9611-1- 2010 to Nicaise Ndembi.

Supplementary data

Supplementary data is available at AIDS Reviews journal online (http://www.aidsreviews.com). This data is provided by the author and published online to benefit the reader. The contents of all supplementary data are the sole responsibility of the authors.

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Update on HIV-1 Diversity in Africa: A Decade in Review

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Table 1. Selected studies that have documented HIV subtype diversity in eastern Africa

Author	Year published	Year of sampling	Population studied	Site	Gene sequenced	Subtypes determined (%)					
						A	C	D	G	B	Recombinants
Kageha, et al.	2011	2008	General patients	Central Kenya	Partial *env*	69.8	11.5	18.7			
Hue, et al.	2011	2009	Newly infected patients	Coastal Kenya	Partial *pol*	74	10	7	1		8
Lihana, et al.	2010	2005	Patients on ART	Nairobi	Partial *pol*, *env*	42.9*		7.1			50
Khamadi, et al.	2009	2005	HIV patients	Coastal Kenya	Partial *env*	86	5	8	1		
Khoja, et al.	2008	2007	General patients	Nairobi	Partial *gag*	56.5	10.1	18.8	2.9		11.6
Kiptoo, et al.	2008	2006	ANC mothers	North Rift, Kenya	Partial *pol*	74.3*	10.3	12.8	2.6		
Khamadi, et al.	2008	2005	General patients	Northern Kenya	Partial, *pol*, *env*	57	27	9			7
Land, et al.	2008	1996	Commercial sex workers	Nairobi	Partial *env*	70	6	9			15
Steain, et al.	2005	2004	ANC Mothers	Western Kenya	Partial *gag*, *env*	40					60†
Khamadi, et al.	2005	2005	General patients	Northern Kenya	Partial, *env*	50	39	11			
Songok, et al.	2003	2000	Antenatal clinic attendees	Western Kenya	Partial *env*	63.3	3.3	6.7	3.3		23.3
Dowling, et al.	2002	2000		Southern Kenya		56	2.4	2.4			39
Mosha, et al.	2011	2004-2005	HIV drug-naive youths	Dar es Salaam, Tanzania	*pol*	27	23	4			46
Nofemela, et al.	2011	2009	HIV patients	Mbeya, Tanzania	Single genome amplification	18.1	41	4.5			36.4
Nyombi, et al.	2008	2005	Drug-naïve ANC attendees	Kagera, and Kilimanjaro	*pol*	34	26	19			21
Somi, et al.	2008	2006		Dar es Salaam, Tanzania		33.3	33.3	10.3			23.1
Nyombi, et al.	2008	2005	ANC mothers	Kagera, Tanzania	Partial *pol*, *env*	27.8	29.6	16.7			25.9
Nyombi, et al.	2008	1985-2005	HIV patients	Northern Tanzania	Partial *env*	29	31	27			13
Herbinger, et al.	2006	2000	ANC, blood donors		MHA	8.5	40.8	3.8			46.9
Arroyo, et al.	2005	2003	General population	Mbeya, Tanzania		18	43	3			36
Arroyo, et al.	2004	2001	Blood donors	Mbeya, Tanzania	Full length	15	55	5			25
Kiwelu, et al.	2003	2002	Bar and hotel workers	Moshi, Tanzania	Partial *gag*, *env*	48	20	8			25
Ndembi, et al	2011	2009-2010	Drug-naive VCT attendees	Kampala Uganda	Partial *pol*	51.4	2.9	32.9			12.9
Kiwanuka, et al.	2010	1997-2002	General cohort	Rakai, Uganda	Near full length	15.7		59.6			24.7
Lyagoba, et al.	2010	2003-2004	Cohort	DART Uganda	Partial *pol*	66	3	30			1
Eshleman, et al.	2009	1993-2003	Drug-naive adults	Rakai, Uganda	Partial *pol*, *env*	25	1	63.5			9.6
Ndembi, et al	2008	2007	Drug-naive HIV patients	Entebbe, Uganda	Partial *pol*	50*	2	39			9
Herbeck, et al.	2007	1989-2000	Antenatal cohort	Uganda	Partial *env*	45	5	41			9
Yirrell, et al.	2004	1990	General cohort	Uganda	Partial *env*, *gag*	25		49			26
Eshleman, et al.	2004	2000	Antenatal cohort	HIVNET, Uganda	Partial *pol*	52.7	2.2	35.1			10
Hu, et al.	2000	1997	General patients	Uganda		49	2.5	48			
Rayfield, et al.	1998	1997	Cross sectional	Uganda	Partial *env*	57.4	0.5	42.1			
Vidal, et al.	2007	2002	Drug-naive	Bujumbura, Burundi	Partial *pol*, *env*	0.8	68.9	1.7			28.6
Koch, et al.	2001	1998	HIV-positive drug-naive	Bujumbura, Burundi	Partial *pol*, *env*	11.1	88.9				
Servais, et al.	2004	2000	ANC	Kigali, Rwanda	Partial *pol*	79	14	4.7			2.3
Kassu, et al.	2007	2003	Treatment-naive	Northwest Ethiopia	Partial *gag*, *pol*, *env*	1.1	97.8	1.1			
Hussein, et al.	2000	1997	Commercial sex workers	Addis Ababa	HMA		98.5	1.5			
Hierholzer, et al.	2002	1998-1999	HIV patients and blood donors	Khartoum, Sudan	Partial *env*	6.7	30	50		3.3	10

ART: antiretroviral therapy; ANC: antenatal clinic; HMA: heteroduplex mobility assay; MHA: multiregional hybridization assay.
*Total A1 and A2. †Including dual infections.

Table 2 A. Selected studies that have documented HIV subtype diversity in southern Africa

Author	Year published	Year of sampling	Population studied	Site	Gene sequenced	Subtypes %								Circulating recombinant forms (CRF) %					Others %	
						A	B	C	D	F	G	H	J	02	08	09	13	37	URF	U
Bartolo, et al.	2005	2001	Patients	Luanda/Kabinda, Angola	Partial *env*, *gag*	42		15	2	2	4	10	6						17	2
Bartolo, et al.	2009	1997, 2001	Patients	Angola	Partial *env*, *gag*, *pol*			80.8			3.8							6.7	7.7	1
Castelbranco, et al.	2010	2008-2009	Pregnant women	Luanda, Angola	Partial *env*	14.2		17.1	8.5	22.8	8.5	5.7		8.5			2.9	2.9	5.7	2.9
Bussmann, et al.	2005	2001	Patients	Botswana	partial *pol*			100												
Petch, et al.	2005	1996-2001	Patients	Malawi	Partial *pol*			100												
Bellocchi, et al.	2005	2003	Patients	Mozambique	Partial *pol*			98.3			1.7									
Lahuerta, et al.	2008	1999-2004	Patients	Southern Mozambique	Partial LTR, *env*, *pol*			100												
Maldonado, et al.	2009	2006	Patients	Maputo, Mozambique	Partial *pol*			66.7							33.3					
Bartolo, et al.	2009	2002-2004	Patients	Maputo, Mozambique	Partial *pol*			80.8			3.8							6.7	7.7	1.0
Gordon, et al.	2003	2001-2002	Patients	KwaZulu-Natal, South Africa	Partial *env*, *pol*			100												
Jacobs, et al.	2008	2002-2004	Patients	Cape Town, South Africa	Partial *pol*		3.6	95			0.7			0.7						
Huang, et al.	2009	2006	Patients	Free State, South Africa	Partial *pol*			100												
Marconi, et al.	2008	2005-2006	Patients	KwaZulu Natal, South Africa	Partial *pol*	0.9	0.9	97.4											0.9	
Jacobs, et al.	2009	2000-2001	Patients	Cape Town, South Africa	Partial *env*	3.1	6.9	89.1		0.3	0.3								0.3	0.3
Fish, et al.	2010	2009	Patients	South Africa	Partial *pol*			97.3											2.7	
Papathanasopoulos, et al.	2010	2004-2007	Patients	South Africa	Partial *pol*			97											3	
Romani, et al.	2009	2002-2004	Patients	South Africa	Partial *vpr*			93											7	
Scriba, et al.	2001	1998	Patients	South Africa	Partial *vif*, *vpr*, *vpu*			100												
Deho, et al.	2008	2002-2003	Patients	Swaziland	Partial *pol*			100												
Hamers, et al.	2010	2007-2008	Patients	Lusaka, Zambia	Partial *pol*	0.5		98	0.2		0.4			0.5		0.4				
Handema, et al.	2003	2000	Patients	Zambia	Partial *env*, *gag*, *pol*			100												
Kantor, et al.	2002	2001	Patients	Zimbabwe	Partial *pol*			100												
Kassaye, et al.	2007	2000-2001	Pregnant women	Zimbabwe	Partial *pol*			100												
Dalai, et al.	2009	1991-2006	Antenatal women	Zimbabwe	Partial *pol*			100												

Table 2 B. Selected studies that have documented HIV subtype diversity in western Africa

Author	Year published	Year of sampling	Study Population	Site	Gene Sequenced	Subtypes %						Circulating recombinant forms (CRF) %								Others %	
						A	B	C	D	F	G	01	02	05	06	09	11	13	45	U	URF
Marjorie Monleau, et al.	2011	2008	Patients	Cotonou, Benin	Partial *pol*	3.1					6.3		65.6		3.1						21.9
Vergne, et al.	2006	2003	Patients	Burkina Faso	Partial *pol*	3.1					1		48.5		47.4						
Nadembega, et al.	2006	2003-2004	Patients	Ouagadougou Burkina Faso	Partial *pol*	6.9					3.4		31		55.2	3.4					
Simpore, et al.	2007	2004-2006	Mother- infant pairs	Burkina Faso	Partial *pol*										100						
Tebit, et al.	2008	2004-2006	Patients	Ouagadougou, Burkina Faso	Partial *pol*	1.3	1.3						40		48	1.3				8	
Tebit, et al.	2009	2004-2006	Patients	Ouagadougou, Burkina Faso	Partial *pol*	3.8							37.5		44.2	1.9				12.5	
Adje-Toure, et al.	2003	1998-2000	Patients	Abidjan, Cote d'Ivoire	Partial *pol*								100								
Chaix, et al.	2005	2000-2003	Children	Abidjan, Cote d'Ivoire.	Partial *pol*								94.7		2.6					2.6	
Toni, et al.	2007	2002-2006	Patients	Abidjan, Cote d'Ivoire	Partial *pol*	7							88		2						6
Delgado, et al.	2008	2002-2004	Patients	Ghana	Partial *pol*	2.4	0.5				1.4		65.7		3.9	1					25.1
Charpentier, et al.	2011	2009	Patients	Conakry, Guinea	Partial *pol*	3			1		1		89			4					1
Derache, et al.	2007	2005	Patients	Bamako, Mali	Partial *pol*								75		20						5
Haidara, et al.	2010	2007-2008	Patients	Mali	Partial *pol*	2	5.9	4			3	2	71.3		7.9	2		1			1
Imamichi, et al.	2009	2003-2005	Patients	Mali	Partial *pol*	13							69.6		8.7	8.7					
Mamadou, et al.	2002	1997-2000	Patients	Niger	Partial *env*, *gag*								54.3		18.1						27.6
Ajoge, et al.	2011	2007	Pregnant women	North-central Nigeria	Partial *env*, *gag*			3.6		3.6	32.1		39.3								21.4
Ajoge, et al.	2011	2007	Pregnant women	North-central Nigeria	Partial *pol*			3.6		3.6	39.9		50								3.6
Chaplin, et al.	2011	2004-2009	Patients	Nigeria	Partial *pol*	3.6					37.9		45		4.4						9.2
Hawkins, et al.	2009	2005	Patients	Nigeria	Partial *pol*	3.6					37.9		44.9		4.4						9.2
Ojesina, et al.	2007	2003-2004	Mother-infant pairs	Nigeria	Partial *pol*	15.4					30.8				38.5	7.7					7.7
Peeters, et al.	2000	1996	FSW, patients, plood donors	Nigeria		61.3		0.4	0.8	2	37.5										
Vicente, et al.	2001	1996	Patients	Nigeria	Partial *pol*	80														20	
Diop-Ndiaye, et al.	2010	1998-2001	Patients	Senegal	Partial *pol*	3	5	7	2		1.5		64		2.5		2		0.5		12.5
Yaotse, et al.	2009	2006-2007	Patients	Lome, Togo	Partial *pol*	6.4					12.8		48.7	1.3	3.8					2.6	24.4

FSW: female sex workers.