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Review Article

HIV-1 Genetic Diversity in the Republic of Congo: Seventeen Years in Review

Laure Stella Ghoma Linguissi[1,2], Nicaise Ndembi[3], Céline Nguefeu Nkenfou[4,5], Pierre Poulain[1,6-9#] and Francine Ntoumi[1,10,11#*]

[1]*Congolese Foundation for Medical Research, Brazzaville, Republic of Congo*
[2]*Département of Biomolecular Research, University of Ouagadougou, Burkina Faso*
[3]*Department of Human Virology, University of Maryland, USA*
[4]*Department of Biological Sciences, University of Yaoundé I, Cameroon*
[5]*Chantal Biya International Reference Centre (CIRCB) for Research on HIV/AIDS Prevention and Management, Cameroon*
[6]*National Institutes of Health and Medical Research, France*
[7]*Department of System Dynamics and Interactions Biological Macromolecules, Université Paris Diderot, France*
[8]*Institut National de la Transfusion Sanguine, DSIMB, France*
[9]*Laboratory of Excellence GR-Ex, France*
[10]*Departments of Sciences and Techniques, Marien Ngouabi University, Republic of Congo*
[11]*Department of Tropical Medicine, University of Tübingen, Germany*
[#]*Both authors contributed equally to the work.*

***Corresponding author**
Francine Ntoumi and Pierre Poulain Fondation Congolaise pour la Recherche Médicale, Cité OMS, villa D6, Djoué, Brazzaville, Republic of Congo, Tel: 242-069-977-980; Email: fntoumi@fcrm-congo.com

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Abstract

Background: The Republic of Congo is at the epicenter of HIV emergence and it is characterized by a high genetic diversity. Previous studies tried to understand the genetic diversity and strain distribution of HIV-1 since 1990, but all of them were based on small sample sizes and limited to urban areas.

Objectives: The main objective of this review was to provide a comprehensive overview and pooled prevalence estimate of different HIV-1 strains circulating in the Republic of Congo between 1999 and 2015.

Methodology: We conducted a literature search using the Pub Med database and retrieved research articles related to the genetic diversity of HIV-1 in the Republic of Congo. The results of these published papers were analyzed and the findings are presented in this review.

Findings: Subtype a remains the most common strain followed by subtypes C, D, E, G, and H. Several circulating recombinants: CRF01_AE, CRF02_AG, CRF11_cpx, CRF37_cpx, CRF18_cpx, unique recombinant forms: A/CRF01_AE, A/H, A/J, A/G, G/H as well as unclassified strains have been documented.

Conclusion: Overall, the high number of HIV-1 subtypes and recombinant viruses in the Republic of Congo suggests the need for a continuous viral surveillance to ensure diagnostic tests and HIV research keep pace with these rapidly evolving viruses.

INTRODUCTION

HIV pandemic originated in Kinshasa in the Democratic Republic of Congo (DRC) in the 1920s [1]. Central Africa was the focus of early transmission and the source of pre-1960 pandemic viruses [2]. As a consequence, the greatest genetic diversity of human immunodeficiency virus type 1 (HIV-1) is observed in Africa [3]. Emergence of HIV-1 in human resulted from at least four cross-species transmissions of simian immunodeficiency viruses (SIVs) from chimpanzees and gorillas [4] and the most recent common ancestor is dated around 1908 [5].

The transmission of SIVs from chimpanzees (SIVcpz) to humans placed the origin of the disease in Central Africa [6]. Congolese SIVcpz genomes are mosaic, probably due to a recombinational event in the recent past, and it provides evidence for a rather recently occurring cross-species transmission between humans and chimpanzees [7]. Former study suggested

that HIV-1 has been introduced into Pygmies through their neighboring Bantu rather than directly from nonhuman primates [8]. Strains from Pygmies and Bantu were similar to those found in the general population.

A viral sequence from 1959 (ZR59) is the oldest HIV-1 infection known so far [9,10]. This viral sequence presented near the ancestral node of subtypes B and D in the major group, indicating that these HIV-1 subtypes, and perhaps all major group viruses, may have evolved from a single introduction into the African population not long before 1959 [9].

In Central Africa, HIV-1 groups M, N, O and P co-circulate in human populations and chimpanzees are infected with genetically closely related viruses [11–19].

HIV-1 group M is divided into nine subtypes (A,B,C,D,F,G,H,J,K) with at least 72 circulating recombinant forms (CRFs) currently identified and thousand unique recombinant forms (URFs) [5,20]. More than 90% of HIV-1 infections worldwide are caused by non-B clades of group M [21].

Epidemiological studies have provided data of HIV-1 distribution and patterns in sub-Saharan Africa [22]. Distribution of HIV-1 subtypes is very heterogeneous [23] and is the result of population migrations [2,24].

The ROC remains a highly endemic area with HIV-1 prevalence at 2.5% [25]. This prevalence is comparable to that of neighboring countries: 1.1% in DRC, 3.9% in Gabon, 2.4% in Angola and 4.3% in Cameroon [26]. The purpose of this review is to provide an overview of published data on HIV-1 genetic diversity, and recombinant forms in the ROC.

METHODOLOGY

Presently, no comprehensive report on the genetic diversity of HIV in the ROC has been done. To collect research data on this topic, research articles on HIV-1 genetic diversity in the ROC have been retrieved from the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM/Pub Med) database. The query was: (Congo* [Title/Abstract]) NOT (democratic republic [Title/Abstract]) AND (HIV [Title/Abstract]) AND ((recombinant* [Title/Abstract]) OR (subtype* [Title/Abstract])).

A total of 277 nucleotide sequences from the ROC were retrieved from the Los Alamos Database (http://www.hiv.lanl.gov) Due to down-sampling, we focused our phylogenetic analysis on HIV-1 *pol* gene sequences (HXB2: 2253-3468), which are typically obtained for HIV drug resistance testing. We included 39 HIV-1 *pol* reference strain and 148 CG sequences in the ClustalW [27] alignment. We performed maximum likelihood phylogenetic reconstruction using PhyML based on General Time-Reversible model with gamma distributed rate variation among nucleotides [28].

RESULTS

Fifteen research articles have been retrieved from the Pub Med database. Seven of them were excluded because their content did not mention any subtype or recombinants of HIV-1. From 1999 to 2015, only 8 HIV molecular characterization studies were conducted in the ROC [29–36].

Study area

Most of the studies were conducted in Brazzaville and Pointe-Noire, mostly for convenience sampling [29–36]. Brazzaville is the capital of the ROC and Pointe-Noire is the largest industrial city. Both cities include about 52 % of the Congolese population. Few studies were also conducted in other cities such as Gamboma and Ouesso [32–34] (See Figure 1 for the geographic catchment of cities and neighboring countries of the ROC).

Epidemiology of HIV-1 in the ROC

In the ROC, HIV-related mortality is high with 37% of the deaths due to AIDS in 2008 [37]. The main route of transmission is almost exclusively through heterosexual vaginal intercourse [35,38]. In 2000, HIV prevalence in Pointe-Noire was 14% and 5% in Brazzaville [39]. In 2009, a marked decrease of the prevalence has been noticed, reaching 6.2% and 3.5% in Pointe-Noire and in Brazzaville, respectively [40]. In 2013, the national prevalence rate dropped to 2.5% [26].

Cohort characteristics

Most published studies have been conducted on small sample sizes including pregnant women (see Table 1 for further details): 29 Congolese AIDS patients enrolled in 1996 and 1997 [29], 32 HIV-1 infected patients living in Brazzaville and Pointe-Noire recruited in 1988 and 1992 [32], 28 HIV-1 strains isolated from Congolese AIDS patients used for the study carried out in 1996 and 1997 [36], 114 HIV-1 positive persons enrolled in 2003 and 2004 [34], 30 seropositive pregnant women in Pointe-Noire in 2005 and 2008 [41], 100 patients in Brazzaville recruited in 2011 [35] and finally 95 HIV-1-positive naïve pregnant women in Pointe-Noire enrolled between 2005 and 2008 [31].

Molecular characterization of HIV-1

HIV-1 sequence diversity varies across genes with a difference of 35% in the envelope glycoprotein's (*env*) and between HIV-1 groups and sub-subtypes [42,43].

Studies done on the HIV subtypes distribution in the ROC were based on: part of the *env* region including the V3 loop [29], part of the 59 *tat–env* (*vpu*) and *env* sequences [36] ; the p24 *gag* region and V3–V5 *env* region [34] ; *env* and *gag* regions and a short segment encoding the *gag* p7/p9 protein have also been successfully used for phylogenetic analysis [32]. Other analyses were based on the *env* C2V3 and/or the *pol* integrase regions [33], *pol* sequences [41], full *protease* and partial *reverse transcriptase* sequencing [31].

In 2006, Niama *et al*. found that 4.8% (from *gag* sequences) and 6.3% (from *env* sequences) of strains could not be classified [34]. Full-length genomic sequences are necessary to identify these unknown strains [44] and to optimally characterize them as potential CRFs, or distinct subtype or sub-subtype [45,46]. In 2012, Pircher *et al* observed 58% of URFs occurred in the Congolese population. The presence of many URFs may be due to a likely high level of multiple infections (super infections or dual infections) [35].

Time and emergence of different HIV-1 genetic variants

Studies have shown that intra-subtype genetic diversity

Table 1: Key elements of HIV studies conducted in the Republic of Congo. U: unclassified subtypes.

	Area of study	Date of data collection	Cohort size	HIV genes studied	Subtypes (%)	Recombinants (%)
Mboudjeka *et al.*, 1999	Cameroon, ROC	1995	57	*env C2V3* and/or the *pol* integrase regions	D, F, G and H	
Candotti *et al.*, 1999	Brazzaville, Pointe-Noire	1988 and 1992	32	350 nucleotides from the C2±V3 region	A (53), G (29), D (3), E (3), F (3)	
Bikandou *et al.*, 2000	Brazzaville, Pointe-Noire	1996 and 1997	29	Part of the *env* region including the V3 loop	A (41), D (3), G (21), H (21), J (7) , U (7)	
Taniguchi *et al.*, 2002	Brazzaville, Pointe-Noire	1996 and 1997	28	part of the 5' *tat-env* (*vpu*) and *env*	*vpu*: A (3.5), D (3.5), G (60), H (17.8), U (14.2) *env:* A (39.2), D (3.5), G (17.8), H (21.4), U (7.1), J (7.1), G (3.5).	
Bikandou *et al.*, 2004	Brazzaville, Pointe-Noire	1998 and 1999	29	*env*	G (20.4)	
Niama *et al.*, 2006)	Pointe-Noire, Gambia, Ouesso	2003 and 2004	114	p24 *gag* and *V3-V5env* region	*gag:* A (36.5), G (30.8), D (12.5) and C, F, H, J, K (15 for all) *env:* A (32.5) and G (21.3), D (12.5) and C, F, H, J, K (15 for all)	CRF_01, CRF_02, CRF_05, CRF_06, CRF_18
Pircher *et al.*, 2013	Brazzaville	2011	100		G, A1, B, D, H, F1, A2, C	CRF02_AG, CRF37_cpx, CRF13_cpx, CRF11_cpx, CRF20_BG, CRF21_A2D, CRF33_01BG, CRF02_AG, CRF37_cpx
Bruzzone *et al.*, 2015	Pointe-Noire	2005 to 2012	95	Full protease and partial reverse transcriptase sequencing	G (8.8), A3 (8.8), D (4.4), B (2.9), H (2.9), A1, C, J, F1, F2 (each 1.45)	URF (35), CRF45_cpx (10.3), CRF37_cpx (7.4), CRF18_cpx (5.9), CRF02_AG (2.9), CRF25_cpx (1.5)

Table 2: Summary of ARVs resistance-associated mutations observed in the ROC Compilation of results from Pircher et al. [35] and Bruzzone et al. [31]. ARVs are categorized into non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).

Patients	Subtypes	Mutations conferring resistance	ARV class
Naive	A1	115F[1]	NRTIs
	URF FU	M184V[2] 101E[1], 103N[1], 190A[1], V90I[2]	NRTIs NNRTIs
	G	90M[1] E138G[2]	PIs NNRTIs
	CRF13_cpx	46L[1]	PIs
	A1	115F, 46L[1]	PIs
	B	V32I, I54M, I84V M41L, M184V, L210W, T215Y[2] K103N[2], E138A[2]	PIs NRTIs NNRTIs
	C	M184V[2] G190A, H221Y[2]	NRTIs NNRTIs
	CRF45_CPX	L210W, T215S[2] D30N, F53Y, G37S[2]	NRTIs PIs
	H	K101E[2]	NNRTIs
	CRF02_AG	K65E[2] V90I[2]	NRTIs NNRTIs
	F2	V179D[2]	NNRTIs
	J	K65E[2]	NRTIs
Treated		184V	NRTIs
		215Y/F, 41L, 67N, 70R, 219Q/E, and 210W 69D/N/S, 74V/I, 44D, 75M/A, 215I/N, and 70E[1]	thymidine-associated mutations (TAMs)
		151M[1]	Nucleotide-associated mutation (NAM)

		103N,181C, 221Y, 98G,190A/S, 179I/T, 106A, 90I, 101E,230L, 138A/G, 101H/R, 98S, 106I, 225H, and 181V[1]	NNRTIs
	F1	46L[1] K70T[2] V106I[2]	PIs (IDV) NRTIs NNRTIs

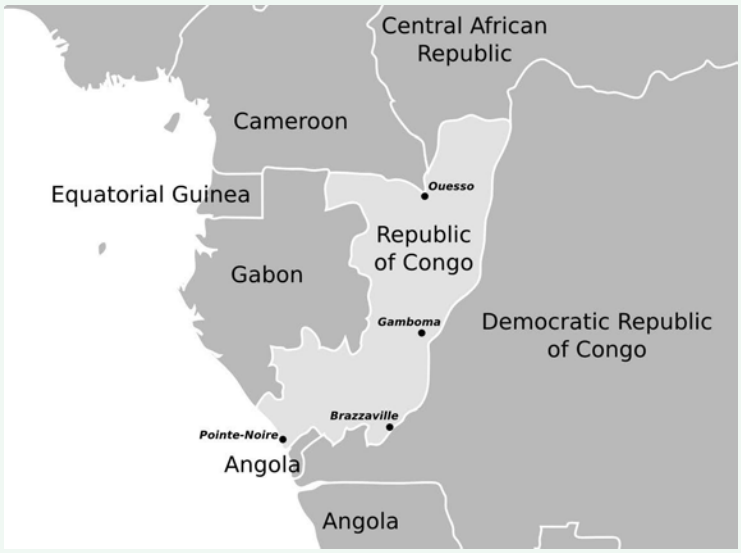

Figure 1 Map of the Republic of Congo with the cities where studies on HIV took place.

increases with time [47,48]. The temporal multiplicity of passages of SIVcpz or VISsmm to humans may be one of the reasons for the existence of these different groups of HIV-1. In this evolutionary process, HIV is extremely fast in its replication, which leads to a large number of variants currently identified in Central Africa, particularly in DRC and in ROC. This high genetic variability of HIV is also due to several causes including transcription errors in the reverse transcriptase [49,50], either by the large number of virions produced that can carry different mutations [51–53], either by selection pressure on the virus that affects the population level [51,52,54,55], either by new genetic recombinants derived from risk behaviors [51,56–59], that increase the likelihood of multiple infections in the same person [60–62]. This last point is very important in Africa, where several studies have observed risk behaviors for HIV infection in the population [63–67].

Subtypes, sub-subtypes and recombinants

Based on the studies listed above, the genotypes observed in the ROC are presented in Table 1. Most HIV infections reported in the ROC are caused by HIV subtypes A, C, D, G, H and inter-subtype recombinants [29–32,34–36,41,44,68]. The emergence of subtypes J and unclassified strains is recent and must be closely monitored [29,31]. Figure 2 represents the phylogenetic tree of HIV sequences reported in the ROC with highlight on major subtypes and recombinants.

High frequencies of CRFs were observed in the ROC such as CRF18, CRF19, CRF02_AG, CRF11_cpx, CRF20_BG, CRF21_A2D, CRF37_cpx, CRF25_cpx and CRF45_cpx (see Table 1 for a comprehensive list) [31,35]. Recombinant CRF37_cpx was also found in Cameroon [69]. Recombinant CRF02_AG is the predominant molecular form of HIV-1 found in Kumasi, Ghana [70]. This CRF was also reported predominant (47% frequency) in Gabon [71] in 2 cross sectional surveys performed in 9 cities in Gabon in 2005 and 2008. Bruzzone *et al.* reported the presence of CRF25_cpx and CRF45_cpx in Pointe-Noire, these recombinants were also found in Angola, the DRC and Gabon [72-74], probably due to the long trading history between these countries.

Studies revealed a high prevalence of URFs: 35% in 2006 [34] and 20% in 2015 [31]. Among all these known recombinants, a study in Pointe-Noire reported a proportion of 57% of putative URFs [75].

The genetic variability of subtype F strains observed in different Central African countries had been studied in depth [71,76]. Phylogenetic analysis of *env* sequences (V3–V5 region and complete gp160) and of partial *gag* sequences revealed that subtype F sequences can be divided into three sub-subtypes: F1, F2, and F3 [31,35,77]. The F3 subgroup was composed of strains originating from several Central African countries [78]. F1 et F2 sub-subtypes were reported in the ROC, with 1.5% frequency each [31,35].

The genetic variability of subtype A strains has been observed in different Central African countries and this subtype A is divided into sub-subtypes A1–A5 [79,80]. The sub-subtypes A1, A2, A4 and A5 were observed in the DRC [81–83]. The sub-subtypes A1, A2 and A3 were also reported in the ROC, at 3, 1 and 8.8% frequency, respectively [31,35]. The sub-subtype A3 was found in Senegal and Guinea-Bissau, as well as in a few neighboring countries in West Africa [84,85]. Bruzzone *et al.* reported the presence of this sub-subtype in the ROC [31].

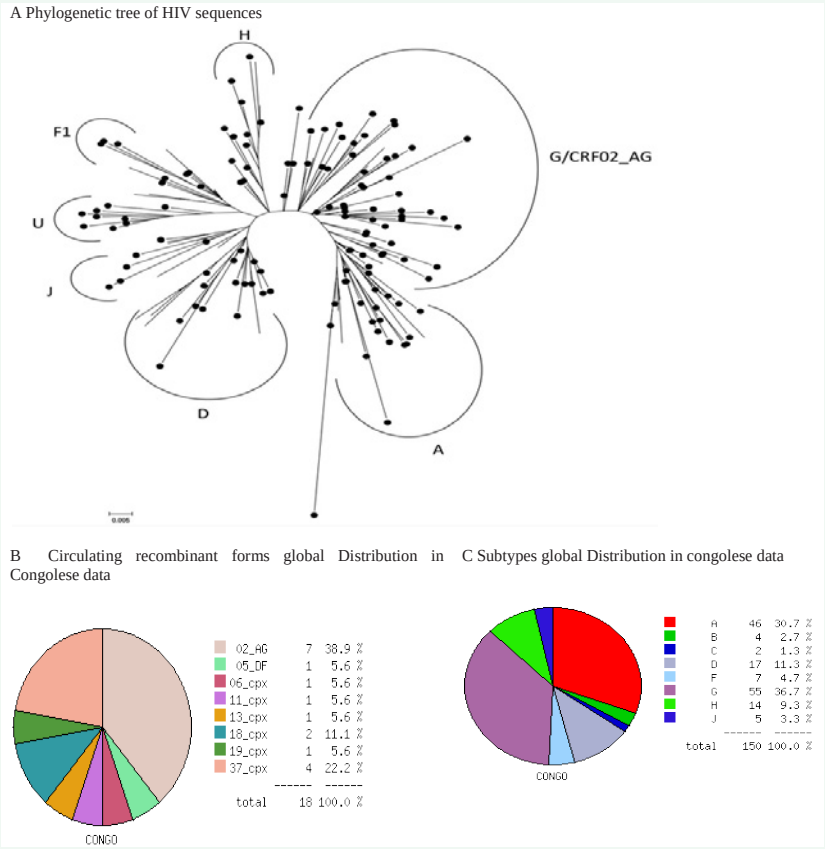

Figure 2 Phylogenetic tree of HIV sequences reported in the ROC and retrieved from the Los Alamos Database.
Panel A shows a phylogenetic analysis of non-B subtype infections in Congolese data.
Panel B and panel C shows the global prevalence of non-B subtypes and circulating recombinant forms in ROC.

In Central Africa, HIV-1 group O (HIV-O) was found in Cameroon and exhibited a very high genetic diversity [86]. HIV-2 was reported in Angola [87,88]. However, HIV-2 and HIV-1 group O were not detected in isolates from Congolese population [32].

HIV-1 detection and diagnosis

Serological diagnosis of HIV-1 infection in sub-Saharan Africa is mostly done with rapid tests such as ImmunoComb HIV-1/2 (Alere / Orgenics Ltd, Yavne, Israël).), Hema-Strip HIV-1/2 (Saliva Diagnostic Systems, (SDS), 11719 NE 95th Street, Vancouver, WA 98682, USA), OraQuick HIV-1 (Orasure Technologies Inc, Bethlelem, USA), Determine HIV-1/2 (Alere Medical Co. Ltd, Chiba, Japan), and UniGold Recombigen HIV(Trinity Biotech plc, IDA Business Park, Bray, Co., Wick low, Ireland) [89]. However some of these assays have shown limitations in detecting HIV-1 subtypes D, F, H, and recombinant CRF02_AG, HIV-1 group O and HIV-2 [90–95]. It has been reported that some fourth-generation assays presented low sensitivity for the detection of p24 antigen from some non-subtype B HIV-1 strains (A, C, F, H, CRF01_AE) and group O [96,97]. Van Heuverswyn *et al*. pointed out that HIV-1 genetic diversity has an impact not only on serological but also on nucleic acid-based diagnostics [98].

In the ROC, similar conclusion could be drawn based on this review. Bruzzone *et al*. reported a 5.5% overestimation of HIV seroprevalence when Determine, instead of Vironostika, was used as second-line test [99]. Studies suggest that HIV-1 genetic diversity may affect the ability of commercially available assays. For instance, the NucliSens Easy Q v.1.2 assay (BioMérieux, Laval, Canada) had difficulty sequencing subtype C, A1, AG, G, and CRF02_AG templates while the Versant HIV-1 RNA 3.0 assay (Siemens Medical Solutions, Mississauga, Canada) had difficulty sequencing B, C, D A1, AG, F1, K, CRF02_AG and non-B subtypes [100,101]. Awareness of any clinical or laboratory differences between the common subtype B of HIV-1 group M and the new HIV-1 strains being seen in practice is therefore increasingly important [102]. For a reliable detection and classification of HIV-1 strains, and in order to minimize the risk of mis-treatment, appropriate reference sequences are needed [41].

HIV-1 and pathologies

HIV-1 diversity may influence the course of HIV infection [103–105]. A number of studies have shown that there is a potential association between HIV-1 subtypes and HIV-1 transmission [106–108]. HIV-1 diversity has an impact on the disease progression through the viral replication and the virus pathogenicity [21,38,109,110]. In a longitudinal study in Uganda, Kiwanuka *et al.* reported that the progression of infection to AIDS disease was shorter in subtype D patients [111]. As this particular subtype is present between 3% and 12.5% in the ROC [29,32,34,36], we can speculate that similar observations

might be done in Congolese patients. In addition, subtype A, predominant in the ROC, could be even more aggressive in terms of disease progression [112,113].

The progression of HIV infection could have an impact on the introduction of anti-retroviral treatment and vaccination strategy [111]. The existence of different HIV-1 subtypes across the globe is also a major challenge for developing a HIV vaccine [114–116]. It is important to know whether a particular vaccine based on one clade may be effective in areas where different clades circulate [115].

Anti-retroviral therapy against HIV delays the onset of AIDS and reduces viral load [117–119] and thus the mortality, morbidity and infection risk [118,120,121].

Anti-retroviral coverage in the ROC although partial becomes a reality. The therapeutic regime recommended for patients with HIV / AIDS is AZT + 3TC + EFV (NVP) or d4T + 3TC + EFV (NVP) or ABC + 3TC + EFV or TDF + FTC + EFV [122].

For HIV positive pregnant women, the prophylactic intervention includes a maternal ARV regimen, perinatal prophylaxis for the mother and child and postnatal support according to feeding choice [123]. Women receive triple Zidovudine (AZT)/Lamivudine (3TC)/nevirapine (NVP) therapy, and if anemia is detected, Zidovudine is replaced by Stavudine (d4T) or Tenofovir (TDF) [124,125]. EFV is prescribed instead of NVP when previous hepatic or skin toxicity to NVP or concomitant tuberculosis (TB) treatment are depicted [125] or during pregnancy [126,127].

HIV and ARV resistance mutations

In the ROC, two studies had been conducted so far on HIV resistance mutations to ARV. Pircher *et al.* showed that the resistance to ARV is the major viral causes of treatment failure [35]. Bruzzone *et al.* reported that Lopinavir-boosted (LPVr) has a very low bio-availability [128]. Table 2 summarizes the results of these studies, which showed a significant resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) [35].

In Gabon and Indonesia, studies also reported natural ARVs resistance-associated mutations [71,129]. The knowledge of these mutations matters particularly for the introduction of new ARVs or switch therapy for HIV-infected patients [71].

In the ROC, administration of poor quality ARVs may increase the risk of mutations conferring resistances to ARVs [128]. We strongly believe a comprehensive study on ARVs resistance-associated mutations should be conducted in this country.

CONCLUSION

These findings suggest a high genetic diversity and extensive heterogeneity in the ROC. The majority of HIV-1 group M subtypes found in the Central Africa was also detected in the ROC, suggesting a local and historical co-circulation of subtypes A, G, B, C, D, E, and F [32]. Based on a limited number of investigations conducted in only two cities, subtype A was reported to be dominant and many recombinants were also observed. Because results were limited to two cities, we may speculate that it is not a picture of the reality, justifying why extensive studies should be carried out in the ROC to accurately depict the representation of HIV-1 diversity.

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