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Clinical and Public Health Implications of HIV-1 Genetic Diversity and Drug Resistance Mutations in Angola: A Systematic Review

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Abstract

HIV-1 genetic diversity and drug resistance mutations (DRMs) remain a public health concern mainly in low- and middle-income countries. In this review, we estimated the HIV-1 molecular evolution over the past 40 years (1980-2019) in Angola to help guide affordable strategies for HIV-1 epidemic surveillance. We searched for studies written in English or Portuguese on HIV-1 diversity and DRMs carried out in Angola and published between 1980 and 2019. This review yielded eight studies describing a total of 493 samples. No HIV-1 Group N, O, and P were identified, whereas all non-B subtypes from Group M were identified. About 66% of HIV-1 subtypes were pure subtype and 34% recombinant strains. The frequency of recombinant strains increases from 1980 to 2019 (23.6%-41.4%, p<0.001). The subtypes C, F1, CRF02_AG, and the recombinant U/H were the most frequent. One DRM in the PIs was found (I54 M), 22 in the nucleoside reverse transcriptase inhibitors (NRTIs), and 18 in the non-nucleoside reverse transcriptase inhibitors (NNRTIs). The major DRM in the NRTIs was the M184V, whereas the G190A, K103N, and Y181C were the major DRMs in the NNRTIs. Over the past 40 years, the frequency of the DRM M184V (50-64.3%, p=0.363), G190A (17.2-46.2%, p=0.021), and K103N (34.5-42.3%, p=0.551) increased, while the frequency of Y181C (17.2-7.7%, p=0.289) decreased. The current review shows an increase in HIV-1 genetic complexity and DRMs in Angola. Our findings suggest the need to include PIs or integrase strand transfer inhibitors in the first-line antiretroviral therapy regimens in Angola.* (AIDS Rev. 2020;22:48-56)

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Key words

HIV-1. Genetic diversity. Drug resistance mutation. Antiretroviral therapy failure. Angola.

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Introduction

The discovery of human immunodeficiency virus (HIV) as the cause of the AIDS pandemic was one of the major scientific achievements during the last century[1]. At the end of the year 2019, HIV had caused 37.9 million infections and 770,000 died worldwide[2]. An estimated 220,000 infected and 10,000 deaths related to HIV infection have been reported in Angola in the same period[2]. HIV has been divided into two types (type 1 and type 2)[3]. HIV-1 is responsible for the AIDS pandemic and is further divided into groups (M, N, O, and P), subtypes (A-D, F-H, J, and K), sub-subtypes (A1-A4, A6, F1, and F2), circulating recombinant forms (CRFs), and unique recombinant forms (URFs)[3]. In Angola, all non-B subtypes (nBSs) of Group-M have been identified and the pattern of HIV-1 genetic diversity is closer to that described in the border countries as the Republic of Congo, Democratic Republic of Congo (DRC), Zambia and Namibia[4-6].

In recent years, we have witnessed a significant scaleup in access to antiretroviral therapy (ART) in Africa, which has improved the quality of life and survival of HIV-infected patients[7]. The drug classes of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) have been used as the backbone of ART mainly in low- and middle-income countries (LMICs)[8,9]. In Angola, the ART guidelines recommend a combination of two NRTIs (tenofovir and lamivudine; tenofovir and emtricitabine; zidovudine and lamivudine; abacavir and lamivudine; and didanosine and lamivudine) and one NNRTI (efavirenz or nevirapine) as part of the first-line ART regimens[10,11]. However, one major challenge associated with universal access to ART is the lack of virological and immunological monitoring as well as the rapid spread of HIV-1 variants with drug resistance mutations (DRMs) in LMICs[12-14].

In the past years, numerous epidemiological studies have addressed the important issue of the epidemiology of transmission of HIV drug resistance (HIVDR)[15]. Furthermore, phylogeographical models supported by a firm statistical basis have been usefully applied to the epidemiological reconstruction of the origin and diffusion of viral infectious diseases in spatial and temporal scales[16]. However, conducting phylogeographic studies able to monitor the spread of HIV-1 subtypes as well as identify the dispersion pathway that drives such changes could be crucial to understand the molecular epidemiology of HIV-1 in Angola. In this systematic review, we aimed to estimate the HIV-1 genetic diversity and the frequency of DRMs over the past 40 years (1980-2019) in Angola. This review allowed us to obtain a stronger picture of the molecular epidemiology of HIV-1, evolutionary and transmission dynamics, subtypes dispersion pathway, and the effectiveness of ART regimens and provides affordable strategies to strengthen the management and surveillance of the HIV-1 epidemic in Angola.

Systematic literature review

We performed a systematic review to identify studies written in English or Portuguese published in peer-reviewed journals based on the following inclusion criteria: first, they must be carried out and published between January 1980 and December 2019. Second, the city/state of sampling data must be performed in regions of Angola. Finally, they must investigate the HIV-1 genetic diversity and DRMs in Angola. The search for articles was performed in May 2020. Keywords related to the subject "HIV-1 genetic diversity and DRMs in Angola" were used to search for available articles on PubMed, Google Scholar, MEDLINE, Cochrane, SCIELO, and Web of Science during the years 1980-2019. We include keywords and search terms as follows: search #1: HIV-1 genetic diversity and drug resistance in Angola. Search #2: HIV-1 genetic diversity in Angola. Search #3: HIV-1 drug resistance in Angola. All relevant original research articles that reported HIV-1 genetic diversity and acquired or transmitted DRMs among drug-naïve and experienced adult, child, or infant patients in Angola were included in the analyses.

Study selection and data extraction

A systematic procedure was used to identify articles relevant to this review. First, all titles and abstracts that addressed other topics than HIV-1 genetic diversity and DRMs in Angola were excluded from the study. Second, all duplicate references were excluded. Finally, all studies that evaluated only HIV-1 genetic diversity and did not evaluate DRMs or vice versa were also excluded from the study. For all articles selected and included in this review, we evaluated the number of participants, sampling strategy, HIV-1 genotyping methods, HIV-1 diversity, and DRMs. No minimum sample size per dataset or sequence length of the *pol* gene was specified and all online HIV-1 subtyping tools or algorithms for

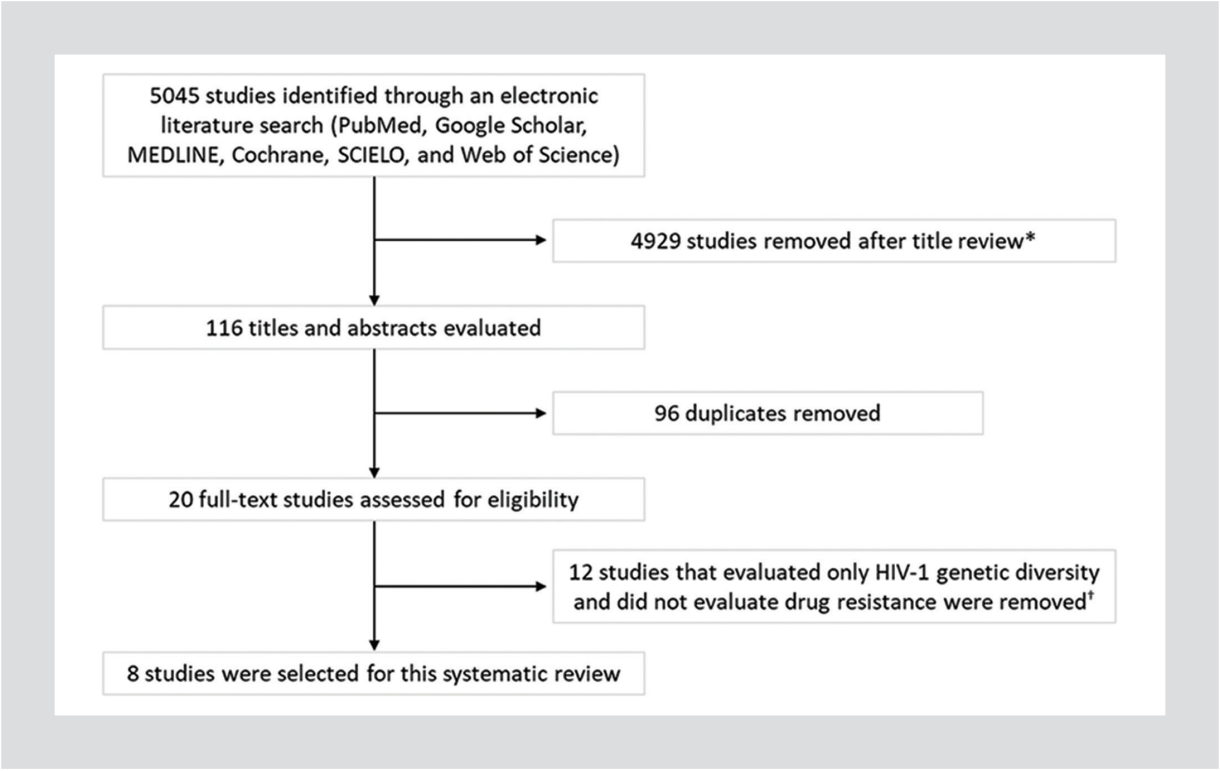

Figure 1. *Flowchart of the selection of studies. All studies were identified through the electronic literature search between 1980 and 2019. The search for articles was performed during May 2020. *For example, antiretroviral therapy for human immunodeficiency virus -2 infection in non-endemic regions. †For example, high genetic diversity of human immunodeficiency virus type 1 in Angola.*

HIVDR evaluation have been accepted. The reviewer (CSS) examined the titles and abstracts, retrieved full-text articles, and assessed articles against eligibility criteria. The reviewer (CSS) extracted the following data from the eligibility articles: city/state of sampling data, the year the studies were conducted and published, population and sampling strategy, HIV-1 genotyping method, genome segment analyzed, results of HIV-1 subtyping, and DRMs. The reviewer (CSS) wrote the original draft. The reviewers (CSS, JM, and MB) performed the review and formal analysis of the data.

Data analysis

The data were analyzed using SPSS version 25 (IBM SPSS Statistics, USA). We evaluated the number of samples designated as HIV-1 subtypes, sub-subtypes, CRFs, and URFs as well as samples presenting any DRM in each data set selected for this review. A Chi-square test was performed to compare proportion and estimate the molecular evolution of HIV-1 and DRMs between the years 1980 and 2019 in Angola. All reported p-values are two tailed and were deemed statistically significant when presented $p<0.05$.

Results

The process of study selection is shown in figure 1. The search found 5045 studies. However, after critical appraisal, a total of eight studies describing a total of 493 samples were found to meet our inclusion criteria and could be included in this review. All selected studies were observational, conducted in Angola, and published in peer-reviewed journals between the years 2000 and 2019. No study was found assessing HIV-1 genetic diversity and DRMs before the year 2000. The summaries of selected studies are shown in table 1.

No HIV-1 Group N, O, and P viruses were identified, whereas all studies identified nBS from Group M. About 66% of HIV-1 subtypes were pure subtype and 34% were recombinant strains. The subtypes A, A1, A2, A3, C, D, F, F1, G, H, J, and K were identified (Fig. 2A). Subtypes C and F1 were the most frequent in almost all studies. Regarding recombinants distribution, CRF02_AG and the recombinant U/H were the most frequent. Furthermore, a vast number of CRFs and URFs have been identified (Fig. 2B). During the years 2000-2019, a significant decrease was observed in the frequency of subtypes A1 (9.9-2.8%, p=0.001), A2

Table 1. HIV-1 molecular epidemiology studies in drug-naïve or treated patients from Angola

Author, year	Location	Population	HIV-1 subtypes	Drug resistance mutations by drug classes
Clemente et al., 2008[20]	Luanda	219 individuals drug-naïve to ART	A, A2, A3, C, D, F, F1, G, H, K, A/C, A/G, A/D, A3/G, CRF01_AE, CRF02_AG, CRF04_cpx, CRF05_DF, CRF11_cpx, G/J, G/U, U/H, and URFs	NRTIs: none NNRTIs: none PIs: none
Garrido et al., 2008[21]	Luanda	294 patients treated	C, F, H, D, G, CRF02_AG, CRF06, CRF01_AE, CRF14_BG, CRF25, CRF19	NRTIs: A62V; D67G; D67N; F116L; K219E; K70R; L74I; M184G; M184V; M41L; T215F; T215I; T215N; T215Y; T69A; T69N; V118D; V118G NNRTIs: A98G; F227V; G190A; K101E; K103N; K103R; V108I; V179D; V179F; Y181C PIs: not evaluated
Ferreira da Silva et al., 2009[27]	Angolan national survey	44 patients	A1, C, D, G, H, and CRF02_AG	NRTIs: M184V; M41L NNRTIs: E138A; V179D; V106I; V90I; Y181H PIs: I54M
Bártolo et al., 2009[22]	Benguela, Cabinda, Cuanza Norte, Cuanza Sul, Luanda, Lunda Norte, Malange and Uíge.	196 individuals drug-naïve to ART	A1, A2, A3, C, D, F1, G, H, J, CRF02_AG, G/H, U/H	NRTIs: D67N; L210W; M184V; M41L; T215F; T215Y NNRTIs: K103N PIs: none
Castelbranco et al., 2010[23]	Luanda	57 individuals drug-naïve to ART	F1, C, A1, D, A/G, G, H, B/D, CRF13_cpx, CRF37_cpx, U/H, and URFs	NRTIs: M184V NNRTIs: G190A PIs: none
Afonso et al., 2012[24]	Central, North and South regions of Angola	101 individuals drug-naïve to ART	C, F1, G, A, D, H, K, CRF02_AG, CRF18_cpx, CRF25_cpx, CRF45_cpx, U/H, and URFs	NRTIs: M184V; M41L; T215F; V75M NNRTIs: G190A; K101E; K103N; M230L; Y106M; Y181C PIs: none
Bártolo et al., 2014[25]	Luanda	139 individuals drug-naïve to ART	HIV-1 subtypes: A, A1, A2, C, D, F1, G, H, J, U/H, U/A, and G/U. HIVDR: 0.7%	NRTIs: none NNRTIs: K103N PIs: none
Sebastião et al., 2019[26]	Luanda	42 individuals drug-naïve to ART	C, F1, A1, G, D, H, CRF02_AG, CRF37_cpx, F1/C, A1/G, and H/G	NRTIs: D67N; M41L; T215S; T69D NNRTIs: G190A; K103N; P225H; Y181I PIs: none

NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; PIs: protease inhibitors.

(5.4-1.0%, p=0.004), F (1.5-0%, p=0.038), and H (7.9-3.8%, p=0.050), while a significant increase in frequencies of the recombinant strains (23.6-41.4%, p<0.001) was observed in the same period (Table 2).

A total of 40 DRMs were detected in the reverse transcriptase (RT) fragment (Fig. 3). Of these were reported a total of 22 (55%) mutations conferring resistance to NRTIs (A62V, D67G, D67N, F116L, K219E,

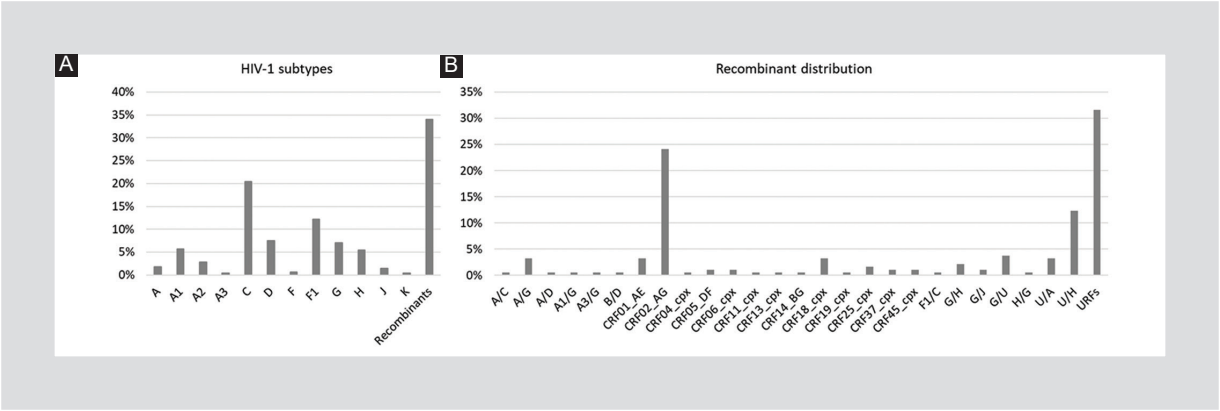

Figure 2. *(**A** and **B**) HIV-1 genetic diversity in Angola, 2000-2019. All reported HIV subtypes belong to the HIV-1 Group M.*

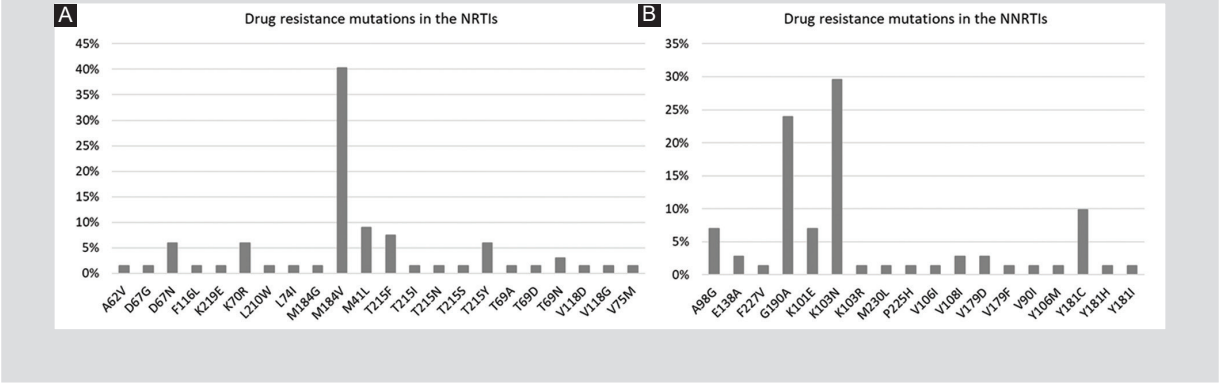

Figure 3. *(**A** and **B**) Prevalence of drug resistance mutations in the reverse transcriptase fragment in Angola, 2000-2019. NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors.*

K70R, L210W, L74I, M184G, M184V, M41L, T215F, T215I, T215N, T215S, T215Y, T69A, T69D, T69N, V118D, V118G, and V75M) and 18 (45%) mutations conferring resistance to NNRTIs (A98G, E138A, F227V, G190A, K101E, K103N, K103R, M230L, P225H, V106I, V108I, V179D, V179F, V90I, Y106M, Y181C, Y181H, and Y181I). The major DRM in NRTIs was the M184V mutation, whereas the G190A, K103N, and Y181C mutations were the major DRMs in the NNRTIs (Fig. 3). One of the studies reported a major DRM (I54 M) in the protease (PR) fragment between the years 2000 and 2009. Between 2000 and 2019, a significant decrease was observed in the frequency of A98G (17.2-0%, p=0.026), while a significant increase was observed in the frequency of G190A (17.2-46.2%, p=0.021) (Table 2). On the other hand, in the same period, the frequencies of DRM M184V, M41L, T215F, and K103N increased, while the frequencies of D67N, K70R, T215Y, A98G, K101E, and Y181C decreased, although not statistically significant (Table 2).

Discussion

Over the past few years, an increase in the proportion of HIV-1 subtypes has been seen and identified globally[17,18]. The previous studies have shown that subtypes A, C, and CRF02_AG are the most prevalent in Africa, subtype B in Europe and Americas, and CRF01_AE in Asia[18,19]. Because pure subtype B was not identified across all selected studies, our results suggest that it is still absent from Angola. The subtypes C, F1, CRF02_AG, and the recombinant U/H were the most frequent in almost all studies revised. However,

Table 2. HIV-1 molecular evolution and drug resistance mutations in Angola, 1980-2019

Independent variable	n (%)	Years; n (%)				p-value
		1980-1989	1990-1999	2000-2009	2010-2019	
HIV-1 subtypes						
A	9 (1.8)	-	-	1 (0.5)	8 (2.8)	0.064
A1	28 (5.7)	-	-	20 (9.9)	8 (2.8)	0.001*
A2	14 (2.8)	-	-	11 (5.4)	3 (1.0)	0.004*
A3	2 (0.4)	-	-	2 (1.0)	0 (0.0)	0.090
C	101 (20.5)	-	-	42 (20.7)	59 (20.3)	0.926
D	37 (7.5)	-	-	19 (9.4)	18 (6.2)	0.191
F	3 (0.6)	-	-	3 (1.5)	0 (0.0)	0.038*
F1	60 (12.2)	-	-	19 (9.4)	41 (14.1)	0.110
G	35 (7.1)	-	-	16 (7.9)	19 (6.6)	0.571
H	27 (5.5)	-	-	16 (7.9)	11 (3.8)	0.050
J	7 (1.4)	-	-	5 (2.5)	2 (0.7)	0.101
K	2 (0.4)	-	-	1 (0.5)	1 (0.3)	0.799
Recombinant	168 (34.1)	-	-	48 (23.6)	120 (41.4)	<0.001*
HIVDR in NRTIs						
D67N	4 (8.0)	-	-	3 (8.3)	1 (7.1)	0.889
K70R	4 (8.0)	-	-	4 (11.1)	0 (0.0)	0.193
M184V	27 (54.0)	-	-	18 (50.0)	9 (64.3)	0.363
M41L	6 (12.0)	-	-	4 (11.1)	2 (14.3)	0.756
T215F	5 (10.0)	-	-	3 (8.3)	2 (14.3)	0.529
T215Y	4 (8.0)	-	-	4 (11.1)	0 (0.0)	0.193
HIVDR in NNRTIs						
A98G	5 (9.1)	-	-	5 (17.2)	0 (0.0)	0.026*
G190A	17 (30.9)	-	-	5 (17.2)	12 (46.2)	0.021*
K101E	5 (9.1)	-	-	4 (13.8)	1 (3.8)	0.200
K103N	21 (38.2)	-	-	10 (34.5)	11 (42.3)	0.551
Y181C	7 (12.7)	-	-	5 (17.2)	2 (7.7)	0.289

HIVDR: HIV drug resistance; NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors.
*The variables were statistically significant for the Chi-square test (p<0.05).

the studies revealed that there is no uniform distribution of HIV-1 subtypes in the different regions (South, North, and Center) of Angola. The southern region of Angola has been dominated by subtype C, the northern region by subtype F1, while the central region by a vast number of CRFs and URFs, particularly the CRF02_AG and the new putative CRF, the recombinant U/H[20-27]. However, further analyses with full-length genome sequences of the recombinant U/H are needed to confirm if this represents a novel HIV-1 CRF in Angola. On the other hand, some HIV-1 variants isolated from Angolan patients not allowing clear clustering within the phylogenetic trees when aligned with the global reference strains[20-26]. Therefore, HIV-1 diversity must be carefully analyzed in some regions of Angola[5]. It is worth mentioning that HIV-2 may be also circulating with low endemicity among HIV patients in Angola, which suggests that differential screening for infection or coinfection by HIV-2 should be always excluded at least once in all HIV seroreactive since superinfection with HIV-2 in people infected with HIV-1 or vice versa can occur mainly in endemic regions with both types of HIV[28,29]. Indeed, other studies have shown that due to sociohistorical ties and intense human migration between the 1970s and 1980s, the HIV-2 frequent in Portugal also prevails in a less extent in its former colonies such as Brazil, India, Mozambique, and Angola[30-32]. On the other hand, this intense migratory flow between Portugal and sub-Saharan African countries as Angola may also have contributed to the introduction of HIV-1 nBS strains in Portugal[33]. At present, the global distribution of HIV-1 nBS strains among Portuguese-born individuals has followed a pattern closer to that described in Angola, characterized mainly by the circulation of all HIV-1 nBS and countless recombinant strains[33-35]. The emergence of nBS strains

in Portuguese population might indicate multiple introductions of HIV-1 African variants in Portugal driven mainly by the immigration or international travel of African patients, especially Angolan patients that have presented all the nBS strains, which reflects the close link between Angola and Portugal and the high degree of HIV-1 genetic diversity in Angola[33]. Furthermore, it is worth mentioning that the increase in the frequency of subtype G in Portugal, associated with the intense human migration between Angola and Portugal, could lead to a continuous introduction of subtype G in Angola and worsen the scenario of the HIV-1 genetic diversity in this African country[33-35]. Thus, multiple migration events to countries in the African, European, American, and Asian continent during the colonial war and the subsequent civil war may have had a decisive contribution to the multiple introductions of HIV-1 subtypes as well as the spread of HIV-1 variants in the different regions of Angola[36]. This hypothesis is strongly supported by the fact that the previous studies reported HIV-1 diversity in Angola similar to that observed in border countries such as the Republic of Congo, DRC, Zambia and Namibia[4-6].

The origin of HIV-1 subtype C in Angola remains uncertain and needs further investigations. However, the previous studies suggested the existence of multiple introductions and several autochthonous transmission networks of subtype C, probably resulting from the mobility of the population between Angola and South African border countries over a long period between the late 1970s and the middle 2000s[37]. These findings are consistent with those observed in this systematic review although we observed a slight decrease in the frequency of subtype C (20.7-20.3%, p=0.926) between the years 2000 and 2019 (Table 2). On the other hand, phylogeographic studies showed that the sub-subtype F1 most probably originated in the DRC/Cameroon in the early 1940s, was exported to South America in the early 1950s, and spread to Angola in 1959 from where it was exported to Romania in about 1962 because of the intense political relations between the two countries[38,39]. Over the years 2000-2019, a statistically significant decrease was observed in the frequency of subtype F (1.5-0%, p=0.038), with no significant variation in sub-subtype F1 (9.4-14.1%, p=0.110) in the same period (Table 2). Besides, the evolutionary dynamics of HIV-1 in Angola has been dominated by a significant decrease in the frequencies of sub-subtypes A1 (9.9-2.8%, p=0.001) and A2 (5.4-1.0%, p=0.004), and an increase in the frequency of subtype A (0.5-2.8%, p=0.064) and recombinant strains (23.6-41.4%, p<0.001). However, the increase in circulation of recombinant strains could seriously affect the diagnosis, monitoring, clinical management, as well as the effectiveness of ART regimens used in Angola. It is also worth mentioning that the subtypes J and K have been present in Angola at low levels since at least 1993, suggesting low biological fitness, low transmission efficiency, or unsuccessful introductions in high-risk populations[40]. It was observed the emergence of numerous recombinant strains belonging to subtypes G and H (Fig. 2B), although we observed a decrease in the frequencies of pure subtypes G (7.9-6.6%, p=0.571) and H (7.9-3.8%, p=0.050) (Table 2). However, virological and immunological changes, as well as the response to ART in patients with recombinant strains belonging to subtypes G and H, deserve further investigation.

Similar to our results, the previous studies showed that the NRTIs and NNRTIs are the drug classes with more HIVDR in East, Central, South, and West Africa and that the major DRM in the NRTIs is the M184V mutation, whereas the G190A, K103N, and Y181C mutations are the major in the NNRTIs[14]. In Angola, the NRTIs have been the major cause of HIVDR compared to NNRTIs (Fig. 3). The frequencies of the M184V (50-64.3%, p=0.363), G190A (17.2-46.2%, p=0.021), and K103N (34.5-42.3%, p=0.551) increased, while Y181C (17.2-7.7%, p=0.289) decreased during the years 2000-2019 (Table 2). The unregulated and unmonitored use of antiretroviral drugs bought in the black market or in an abroad country, as well as the displacement of HIV-infected people to countries that ART is accessible for a long time, are the most likely explanations for the emergence of HIVDR in Angola[15,36]. Another explanation is the extensive use of NRTIs and NNRTIs as the backbone of the first-line ART regimens in Angola[10]. The M184V mutation causes resistance to lamivudine, emtricitabine, didanosine, and abacavir, but increases susceptibility to tenofovir, zidovudine, and stavudine[41,42]. The G190A mutation causes resistance to nevirapine and efavirenz, but increased susceptibility to delavirdine[41,42]. The K103N mutation causes resistance to efavirenz and nevirapine, while the Y181C is often associated with efavirenz, nevirapine, etravirine, and rilpivirine[41,42]. In addition, numerous thymidine analog-associated mutations at positions D67N, K70R, K219E, L210W, M41L, and T215Y/F affecting the susceptibility of zidovudine and stavudine were identified in Angolan patients exposed and unexposed to ART over the past 20 years (2000-2019) (Fig. 3A)[41].

The low frequency of DRMs against the PR fragment could be attributed to the fact that PIs are rarely used in the HIV patients in Angola. This limited use of PIs is explained by the fact the first-line ART regimes used in Angola do not include PIs, which indicates that ART regimens containing PIs might be successfully used in the vast majority of Angolan HIV patients experiencing virological or immunological failure[10,11]. Nevertheless, it is worth mentioning that numerous polymorphisms not related to HIVDR have been detected in PR fragment in several Angolan patients, suggesting that some patients could experience virological failure with second-line ART regimens containing PIs[22-26]. Interestingly, some new polymorphisms not previously described in the Stanford database for untreated patients have been identified in the PR (N37I and H69A) and RT (V35Q, Q174V, V245G, D121F, and A272S) fragments in HIV patients from Angola[22]. However, the clinical and public health implications of these polymorphisms in the serological and molecular diagnosis, as well as the effectiveness of ART regimens, should be subject to further studies.

Based on these findings, we showed that a significant number of HIV patients in Angola are on monotherapy with tenofovir or zidovudine and may be experiencing virological or immunological failure. Therefore, we suggest that the Angolan Ministry of Health should prompt consider the possibility of the implement differential HIV-2 screening, implement the routine use of HIV-1 genotyping in all individuals newly diagnosed with HIV, update currently used ART regimens, and include PIs or moving to generic integrase strand transfer inhibitors (INSTIs) in the first-line ART regimen in Angola[43].

Our systematic review had some limitations. Although the coverage of the review was over the past 40 years (1980-2019), few studies on HIV-1 genetic diversity and DRMs carried out in Angola have been found to meet the defined inclusion criteria. The small number of studies as well as the small number of subjects included in this systematic review diminishes the strength of these findings to support the public health prevention program in Angola. Despite these limitations, our findings highlight some important aspects of the molecular epidemiology of HIV-1 that might pose unprecedented clinical and public health implications, particularly for the vaccine development efforts, serological and molecular diagnosis, virological and immunological monitoring, ART, and clinical management of the AIDS pandemic[44,45]. However, further studies are necessary to obtain a stronger picture of the HIV-1 genetic diversity, evolutionary and transmission dynamics, and the impact on the effectiveness of ART regimens used in Angola.

Conclusion

This systematic review has shown that the HIV-1 epidemic increased in genetic complexity over the past 40 years (1980-2019) in Angola. The superinfection with divergent HIV-1 strains has become more common in Angola. The M184V mutation against the NRTIs and G190A, K103N, and Y181C mutations against the NNRTIs has been the major cause of HIVDR which suggests the need to update currently used ART regimens and included the PIs or INSTIs in the first-line ART regimen in Angola. Furthermore, effective and continued surveillance of the evolutionary dynamics of HIV-1 subtypes on an estimated space temporal scale using a phylogeographical reconstruction should be performed in Angola.

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