Research Article

Comparative *In-silio* Analysis of HIV-1 Pol Gene in Some West African Countries in Relation to its Antiviral Drugs Susceptibility

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Abstract | The evolution of human immunodeficiency virus type 1 (HIV-1) has been shown to be relevant to HIV-1 pathogenesis and disease. HIV-1 genome has nine genes; gag, pol, and env genes are common in all replication-competent retroviruses, and the pol gene is very unique encoding the enzymes for replication. Our objective is to describe the relatedness of these HIV-1 pol genes with each other and its antiviral drug susceptibility which will provide more information on its sensitivity and resistivity to each antiviral drug. Seventeen partial genome sequences of HIV-1 Pol gene from some West African countries were retrieved from NCBI database. Evolutionary relationship was determined by Multiple sequence alignment using Clusta W and the sequences were further analyzed using MEGA 6 for phylogenetic tree. The sensitivity to antiviral drugs was analyzed using the Stanford University HIV Drug Resistance Database. Our results revealed that Kenyan strain (SN-042062), Ugandan strain (DR138-13), Sudanese strain (G-01035) and Nigerian strain (NGA-INF-2016-618) have similar branch length. The susceptibility percentage for each antiviral drug ranged from 82.35% (Tenofovir) to 64.70% (Rilpivirine) while and resistance percentage ranged from 35.29% (Rilpivirine) to 23.52% (Nevirapine). In conclusions, HIV isolates from Nigeria and Sudan have the highest and closest homology. Likewise, it has shown that Tenofovir is the most effective antiviral drug which might be because its nucleoside reverse transcriptase inhibitors.

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Introduction

The evolution of human immunodeficiency virus type 1 (HIV-1) has been shown to be relevant to itspathogenesis (Pineda-Peña et al., 2013). HIV-1 genome has nine genes: *gag*, encoding structural proteins; *env*, encoding for envelope protein; *pol*, encoding for the enzyme of replication (protease, RT, RNase H, integrase); *tat* and *rev*, involved with regulation of gene expression; and *vif*, *vpr, vpu*, and *nef*, and they are accessory genes required for optimal viral replication *in vivo* (Soares et al., 2013). The pol gene encodes two enzymes that define the replicative strategy of retroviruses; reverse transcriptase (RT) copies the viral RNA genome into DNA, and integrase (IN) mediates the insertion of that DNA into the genomic DNA of an infected cell to establish the provirus (persistent infection) (Brass et al., 2008). Primary resistance represents a challenge for the control of HIV-1 because it can reduce the efficacy of antiretroviral therapy and has a direct impact on the clinical outcomes. However, there are some

concerns about the emergence and transmission of drug resistant HIV-1 in developing countries with widespread exposure to ART due to poor adherence and suboptimal ART doses (De Sá Filho et al., 2006). The present study aims for in silico comprehensive investigation and the molecular epidemiology of the HIV-1 subtypes circulating in some African countries based on a large number of clinical samples representing different geographic regions based on the viral pol genes. Also, the phylogenetic analyses of the pol (protease and reverse transcriptase) gene and antiviral drugs susceptibility testing against HIV-1 will be described.

Materials and Methods

Retrieval of sequences containing HIV-1 pol gene

A total of seventeen partial genome sequences containing HIV-1 Pol gene from some West African countries were retrieved from the National Centre for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/nucleotide/). The selected countries were Benin Republic, Nigeria, Mali, Sudan, Uganda, Cameroon and Kenya.

Sequences analysis and determination of sensitivity and resistance to antiviral agents

The HIV-1 Pol gene sequences were analyzed using the Stanford University HIV Drug Resistance Database (https://hivdb.stanford.edu/). Sequences were uploaded into the HIVdb program to determine sensitivity or resistance to different antiviral agents grouped into classes such as nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors and protease inhibitors.

Evolutionary relationship analysis

Thirteen sequences out of the seventeen (13/17) HIV-1 Pol gene sequences were aligned and subjected to Clusta W (Using the Mega 5.2 program) for Multiple sequence alignment. Data analysis was carried out to find their inter-generic variation. The sequences were further analyzed by neighbor-joining method using MEGA 6 for phylogenetic tree construction (Tamura et al., 2013).

Results and Discussion

Distribution of sequences in selected west African countries

The highest numbers of sequences retrieved were obtained from Benin Republic, Nigeria, Sudan and Cameroon having a distribution percentage of 17.65% each. This was closely followed by Uganda with 11.76% and the least number of sequences were obtained from Cote d'Ivoire, Kenya and Mali with 5.88% as shown in Figure 1.

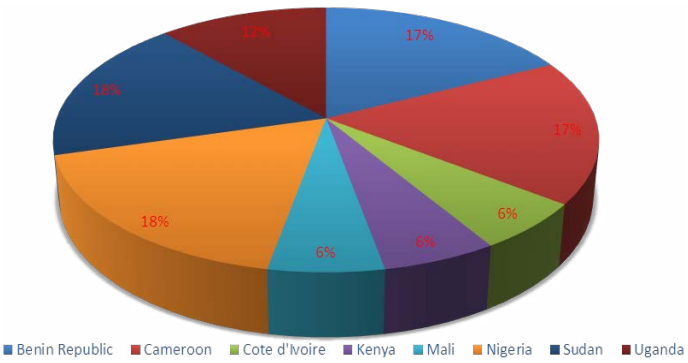

Figure 1: *Distribution of HIV-1 pol gene sequences in relation to geographic location.*

Susceptibility testing in relation to the antiviral agents

The susceptibility test of the HIV-1 pol gene sequences to antiviral agents were described as shown in Table 1. According to the Stanford University HIV Drug Resistance Database, Tenofovir was the most effective antiviral agents on the analyzed sequences, as 14 out of 17 sequences were susceptible (82.35%) and Rilpiviin was the least effective; with11outof17 retrieved sequences showing susceptibility to the drug, that is, 35.29% were resistant) (Figure 2).

On the other hand, the susceptibility rates for Atazanavir, Darunavir, Lopinavir, Abacavir, Zidovudine, Emtricitabine, Lamivudine, Tenofovir, Doravirine, Efavirenz, Etravirine, Nevirapine and Rilpivirine were 12(70.58%), 12(70.58%), 12(70.58%), 12(70.58%), 12(70.58%), 12(70.58%), 12(70.58%), 14(82.35%), 12(70.58%), 12(70.58%), 12(70.58%), 13(76.47%) and 11(64.70%), respectively. The highest resistant rate was observed in Rilpivirine which was 6 (35.29%).

Phylogenetic analysis of HIV -1 pol gene in selected west Africa countries

Phylogenetic analysis revealed that HIV-1 pol gene diversified into two cluster which is termed as Group A and B (Figure 1). Group A represents iAG_10089R isolate from Benin, 20178v01 isolate from Nigeria, C513S-J0 strain from Benin, SGO-90 strain from Mali pol protein, ZZP606 strain from Nigeria, G_01035 strain from Sudan and NGA-INF-2016-618 strain from Nigeria. While Group B has SU272 isolate from Sudan, 92UG024 isolate from Uganda, D375T-J0 isolate from Benin, MR008 isolate

Table 1: *Susceptibility test of HIV-1 pol gene sequences to antiviral agents.*

Class of antiviral agents	Antiviral agents	Number (%) response of organisms to antiviral agents	
		No of susceptible organisms	No of resistant isolates
Protease inhibitors	Atazanavir (ATV)	12(70.58)	5(29.42)
	Darunavir (DRV)	12(70.58)	5(29.42)
	Lopinavir(LPV)	12(70.58)	5(29.42)
Nucleoside reverse transcriptase inhibitors	Abacavir (ABC)	12(70.58)	5(29.42)
	Zidovudine (AZT)	12(70.58)	5(29.42)
	Emtricitabine (FTC)	12(70.58)	5(29.42)
	Lamivudine (3TC)	12(70.58)	5(29.42)
	Tenofovir (TDF)	14(82.35)	3(17.64)
Non-nucleoside reverse transcriptase inhibitors	Doravirine (DOR)	12(70.58)	5(29.42)
	Efavirenz (EFV)	12(70.58)	5(29.42)
	Etravirine (ETR)	12(70.58)	5(29.42)
	Nevirapine (NVP)	13(76.47)	4(23.52)
	Rilpivirine (RPV)	11(64.70)`	6(35.29)

from Cameroon, SN-042062 isolate from Kenya and DR138-13 isolate from Uganda. Cluster A has six clades while cluster B has four clades. Kenyan SN-042062, Ugandan DR138-13 strain; Sudanese G_01035 strain and Nigerian NGA-INF-2016-618 isolate from Nigeria have similar branch length and have close homology relationship (Figure 3).

Figure 2: *Susceptibility test of HIV-1 pol gene sequences to antiviral agents.*

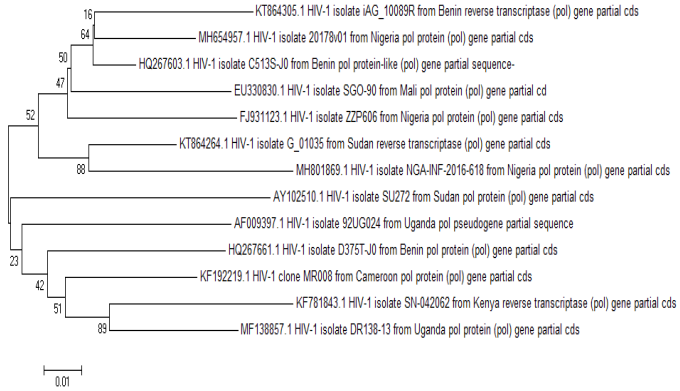

Figure 3: *Phylogeny based on HIV-1 pol gene showed the geographical variation among representative West African countries.*

Antimicrobial resistance in microorganisms have become a global threat and these include viruses such as Human Immunodeficiency Virus (HIV) (Ayukekbong et al., 2017). It has been reported that organisms which show high percentage of similarity in their genes have similar pattern of evolution (Pazo and Valencia, 2001; Joshi and Xu, 2007).

Our results showed that HIV-1 strains from Kenya (SN-042062) and Uganda (DR138-13) have close identity similar pattern of evolution based on the Pol gene analysis (Hein et al., 1996), if observed two sequences identity is more than 70%, it is concluded that such have about 90% probability to share similar biological processes and function. HIV-1 pol gene present in most West Africa countries has a wide range of variance in its homology relationship with one another which is an indication that the strains are in diverse forms. The acquisition of resistance could have important implications in regard to durability of therapy and although responsiveness to first-line therapy should not theoretically be affected by considerations of viral subtype and drug resistance, well-designed long-term longitudinal studies involving patients infected by viruses of different subtypes should be carried out.

Authors Contribution

The article was jointly researched and written by all the authors, our focus was on HIV-1 pol genes associated with selected Africa countries in relation to their susceptibility and resistant to viral drugs which

will assist in the management of the viral infection.

Conflict of interest

The authors have declared no conflict of interest.

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