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DEVELOPMENT OF HEPATOTOXICITY IN INDIVIDUALS HARBOURING DIFFERENT HIV SUBTYPES AND DRUG-RESISTANT VARIANTS IN CAMEROON

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ABSTRACT

Objective: **The aim of this study was to determine the effect of HIV-1 genetic variants and drug resistance-associated mutations (DRM) on the development of hepatotoxicity.**

Design and participants: **This was a longitudinal study of 81 newly diagnosed HIV-infected individuals in five HIV Treatment clinics in the Northwest Region (NWR) of Cameroon from February 2016 to November 2016.**

Methodology: **Eighty-one antiretroviral drug-naïve patients were recruited into the study and followed-up for 6 months. Blood samples were collected prior to ART initiation and 180 days (D180) later. Serum levels of aminotransferases were analyzed by enzymatic methods. The HIV-1 protease and reverse transcriptase sequences were obtained using an in-house protocol and DRMs were identified using the Stanford HIVDR interpretation program, and HIV-1 subtypes by phylogeny.**

Results: **The mean age of the study participants was 36.5 years. Of these, 37(45.7%) patients showed hepatotoxicity at D180. There were four pure subtypes and five recombinant types with CRF02_AG (74.1%) being the predominant genetic variants. The prevalence of hepatotoxicity was highest among individuals infected with HIV-1 CRF02_AG (70.3%). The prevalence of DRM was 11.1% (9/81). Hepatotoxicity was significantly (p =0.04) higher 77.8% (7/9) among patients with resistant virus.**

Conclusion: **Data from this study reveals a high level of hepatotoxicity among patients with DRM probably as a result of persistent viral replication. These findings highlight the need to conduct routinely DRM surveillance among patients with hepatotoxicity in order to improve patient management and care.**

INTRODUCTION

In Cameroon, the prevalence of the HIV infection decreased from 5.5% in 2007 to 3.8% in 2016 thus the advent of highly active antiretroviral therapy (HAART) has significantly reduced the morbidity and mortality rates in HIV infected patients[1,2]. However, the use of HAART over different durations of time has shown to induce toxicity on body organs such as the liver hepatocytes and kidney.[2-4] HAART is made up of different categories, namely, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). However, hepatotoxicity has been reported across all families of HAART and is one of the leading causes of morbidity and mortality nowadays.[5-7]

Liver disease is reflected by the elevated serum activity of two commonly used liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). [7] HAART-associated hepatotoxicity occurs in about 1.0% to 54% HIV-infected patients on treatment.[6,8]

Severe hepatotoxicity may lead to discontinuation of HAART among HIV-infected patients.[9] This might lead to treatment failure which eventually leads to DRM and onward transmission of these HIV variants to newly infected patients. This will result to high morbidity and mortality rates.[9-10] Previous studies carried out on hepatotoxicity in Cameroon, Nigeria and Ethiopia dealt mostly with hepatotoxicity prevalence[3, 9] identifying risk factors, [4] the type of HAART class[6, 9] or in co-morbidity infections.[9] Despite this intense research[3-10], no study has reported on the influence of HIV-1 subtypes and DRM on levels of serum transaminases.

Genetic diversity remains one of the major hindrances to the eradication of HIV and has shown to influence disease progression, therapy success and vaccine design. [11, 12] In 2017, over half of all the people harboring HIV (59%) had access to HAART compared to 8 million in 2010. With increased treatment coverage, DRMs are expected to increase.[10] Studies on DRM are mostly prevalence studies in relation to transmitted and acquired resistance mutation[9], response to treatment or in the prevention of transmission.[10,13, 14] However, there is a dearth of data to show if the genetic diversity and DRM has an effect on the development of hepatotoxicity.

Research studies in Cameroon have revealed the circulation of all group M clades (A–D, F–H, J, K), CRFs and URFs[1]. However, it has not been proven if the genetic variation has any impact on the development of hepatotoxicity. Furthermore, Cameroon is one of the countries implementing the current treatment guideline of treating all HIV-infected patients. This has led to the increase scale up of HAART usage. As such, the emergence and transmission of DRMs is a prime importance.

Since new HIV-1 viral variants emerge and DRM is on the rise, it is important to evaluate the influence of HIV-1 genetic diversity and DRM on biochemical markers of hepatotoxicity. We therefore, hypothesize that genetic diversity and DRM has an effect on the development of hepatotoxicity. Thus, the aim of this study is to determine if HIV-1 genetic diversity and DRM has an effect on the development of hepatotoxicity among individuals in the NWR of Cameroon. Findings from this study will provide baseline information on the magnitude of hepatotoxicity in relation to genetic diversity and drug-resistant pattern.

MATERIALS AND METHODS

Study design: This study was a longitudinal study involving newly diagnosed HIV positive individuals visiting public HIV treatment clinics in the NWR. Ethical clearance was obtained from the Cameroon National Ethics Committee (N°2016/01/689/CF/CNERSH/SP). A total of

81 participants aged ≥18 years were recruited into the study. The study population were initiated on treatment and monitored for a period of six months after treatment. Blood samples were collected at baseline prior to ART initiation (D0) and one month (D30) and six months (D180) after treatment (based on the national guidelines for HIV treatment) and used to measure transaminases.

Setting: HIV drug naive patients were recruited during the period of February 2016 to November 2016 from five HIV treatment clinics of; Bafut District Hospital, Santa District Hospital, Bali District Hospital, Ndop District Hospital, and the Bamenda Regional Hospital. The region was first stratified into urban and rural and random picking of sites from each group was done using a random number generation method. The sampled sites better represent the different backgrounds of individuals from the entire NWR of Cameroon. Bafut, Santa, Bali, and Ndop are in rural areas while Bamenda is from urban settings. The participants were followed up for 6 months and blood samples were collected at Day 0, day 30 and day 180.

Study size: The minimum acceptable sample size was calculated to be 91 using the Lorenz formula as stated below

$$N=\frac{(Z_1^{2}{}_{-\alpha})P(1-P)}{i^2}$$

Where, $Z_1 - \alpha$ = the normal distribution value = 1.96, P =Relative prevalence of HIV in the region= 6.3% and ί = precision (sampling error) = 0.05.

Participants: The eligibility criteria were; confirmed HIV newly infected patients and not yet on treatment, acceptance to participate in the study after having signed an informed consent form, male or female ≥ 18 years residing within the study areas and patients negative for hepatitis B and C.

Variables: The participants were initiated on either of the following HAART regimens; Zidovudine (AZT) + Lamivudine (3TC) + Efavirenz (EFV), AZT + 3TC + Nevirapine (NVP) or Tenofovir (TDF) + 3TC + EFV. Socio-demographic and immunological data were obtained from the routine patient record.

Bias: Selection bias occurred during recruitment of the study participants. Drugs were administered by the site physician based on the clinical presentation.

Data sources/ measurement: age, gender, level of education, marital status and $CD4^+$ cell count were obtained from the patient records, while ALT and AST activity were measured using an enzymatic rate method.

Sample collection: Eight millilitres of venous blood was collected in uniquely coded tubes. Of this, three mL and five mL were transferred into dry and ethylene diamine tetra acetic acid (EDTA) tubes respectively. Blood was separated and serum used for the measurement of ALT and AST activity while plasma was used for sequencing the protease-reverse transcriptase (Prot-RT) region of HIV-1.

Measurement of liver function enzymes (ALT, and AST): Measurement of ALT and, AST was done using the SPINREACT commercial kits (Ctra Santa Coloma, Spain) as described by manufactures' manual and guided by the controls (www.spinreact.com) using the Urit 3300 machine (Diamond Diagnostics, USA). Hepatotoxicity was graded based on sex and age according to the criteria set by the AIDS Clinical Trials Group (ACTG) as follows: grade 1 (1.25–2.5 × ULN), grade 2 (2.51–5.0 × ULN), grade 3(5.1–10 × ULN), and grade 4 (>10 × ULN). If the AST and ALT grades were discordant, the higher of the two grades was used for classification.[6]

RNA Extraction, Polymerase Chain Reaction, and Sequencing: Viral RNA was extracted from plasma using the QIAamp Viral RNA Mini kit (QIAGEN, USA) followed by reverse transcription and semi-nested PCR using SuperScript One-Step RT-PCR system and Platinum PCR Supermix (Life Technologies, Carlsbad, CA) respectively, following an in-house protocol. The protease (PR) and reverse transcriptase (RT) regions of the HIV-1 were amplified with sense primer as described by Abongwa *et al*[1].

The genomic sequences of the pol regions analyzed in this study are available in GenBank under the following accession numbers: MK061035-MK061115

Phylogenetic Analysis: The query sequences were aligned with reference sequences of all known HIV-1 group M subtypes, sub-subtypes and circulating recombinant forms (CRFs) from the Los Alamos database. (www.hiv-web.lanl.gov) as describe by Abongwa *et al*.[1]

Drug resistance mutations: The sequences were analyzed for DRMs using the Stanford University HIV database genotypic resistance interpretation algorithms (http://hivdb.stanford.edu/).

Data analysis: The clinical assessment and laboratory results were recorded and double-checked using Microsoft Excel. Participants who failed to meet up with their appointment or who had missing data, were excluded from the analysis. The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23 (Armonk, USA). Categorical variables (age group, gender, level of education, occupation and $CD4^+$ T lymphocyte classification) were expressed as frequencies and proportions and analyzed using chi-square test while continuous variables (age, $CD4^+$ T lymphocyte level, ALT, and AST activity) were expressed as means ± standard error of the mean (SEM). Paired sample T-test was used to compare means of ALT and AST activity at D0 and D180 while Pearson correlation test was used to determine the correlation between ALT and AST at D0 and D180. The level of significance was set at $p<0.05$.

RESULTS

Demographic of patients: The participants were aged between 18-61 years, with a median age of 36.5 years. Majority of these patients were among the age group 30-40years (45.7%), were female (55.5%), attended primary level of education (49.4%), were married (48.1%) and were farmers (32.1%). The mean (range) $CD4^+$ T cell count was 192.7 (8–498) cells/mm^3 and a greater part of the participants had $CD4^+$ T cells count of <200 cells/mm^3 , 59.3 % (48) (Table 1).

Table 1

Socio-demographic and clinical characteristics of study participants (N= 81)

Indicator	Variable	Number (%)
Age (years)	<30	17(21.0)
	30-40	37(45.7)
	>40	27(33.3)
Gender	Male	36(44.4)
	Female	45(55.6
Level of education	None	8(9.9)
	Primary	34(42.0)
	Secondary	30(37.0)
	Tertiary	9(11.1)
Marital status	Divorced	5(6.2)
	Married	39(48.1)
	single	26(32.1)
	Widow/er	11(13.6)
	Civil servant	12(14.8)
Occupation	Farmer	26(32.1)
	Technician	25(30.9)
	Student	8(9.9)
	trader	10(12.3)
$CD4^+$ Classification cells/mm^3	<200	48(59.3)

	200-350	19(23.5)
	350-500	14(17.2)

Prevalence of hepatotoxicity: Using a higher grade of either ALT or AST, a total of 37(45.7%) patients presented with hepatotoxicity at D180. Of these 21(25.9%) patients had mild-to-moderate (grades 1 and 2) hepatotoxicity while 16(19.8%) patients had severe hepatotoxicity (grades 3 and 4). Prevalence of hepatotoxicity was insignificantly (p>0.05) higher among participants in the <30years age group (52.9%), males; (55.6%), those with primary level of education; (47.1%), divorced; (60.0%), technicians; (53.8%) and with $CD4^+$ T cells count of < 200 cells/mm^3 (53.8%). However, none of these differences were statistically significant (p>0.05) as shown on Table 2.

Table 2

Prevalence of hepatotoxicity by Socio-demographic and clinical characteristics

Indicator	Variable	Number (%)	Prevalence	P value*
Age in years	<30	17(21.0)	9(52.9)	0.74
	30-40	37(45.7)	15(41.7)	
	>40	27(33.3)	13(46.4)	
Gender	Male	36(44.4)	20 (55.6)	0.11
	Female	45(55.6)	17(37.8)	
Level of education	None	8(9.9)	3(37.5)	0.97
	Primary	34(42.0)	16(47.1)	
	Secondary	30(37.0)	14(37.8)	
	Tertiary	9(11.1)	4(46.7)	
Marital status	Divorced	5(6.2)	3(60.0)	0.91
	Married	39(48.1)	18(46.2)	
	single	26(32.1)	11(42.3)	
	Widow/er	11(13.6)	5(45.5)	
Occupation	Civil servant	12(14.8)	6(50.0)	0.46
	Farmer	26(32.1)	9(36.0)	
	Technician	25(30.9)	14(53.8)	
	Student	8(9.9)	5(13.5)	
	trader	10(12.3)	3(30.0)	
$CD4^+$ Classification cells/mm^3	<200	48(59.3)	24(50.0)	0.479
	200-350	19(23.5)	6(33.3)	
	350-500	14(17.2)	7(46.7)	

P value for Pearson chi square test

In Table 3, the mean ± SEM of ALT and AST at D180 were significantly (P<0.005) higher compared to mean ± SEM of ALT and AST activity at D0. In addition, Pearson correlation test showed a significant positive correlation (r= 0.65; p=0.000) between ALT and AST activity at D0 and at D180 and although the correlation was weak, it was significant (r= 0.081; p=0.04).

Table 3

Comparison of mean ± SEM of ALT and ASTactivity at D0 and D180

Variable(U/L)	Treatment duration		T	P value	R	P value
	D0	D180				
ALT	25.8 ±1.2	101.5 ±15.9	-4.731	0.000	-0.005	0.96

AST	27.4 ±0.9	121.4±20.4	-4.379	0.000	-0.028	0.81

HIV-1 subtypes: Phylogenetic analysis revealed a high HIV-1 genetic diversity with four subtypes and five circulating recombinant forms (CRFs). The subtypes or sub subtypes were F2 (6: 7.4%), G (3: 3.7%), D (6: 7.4%), and A1 (1: 1.2%), while the circulating recombinant forms (CRFs) were CRF02_AG (60: 74.1%), CRF22_01A1 (2: 2.5%), CRF06_cpx (1: 1.2%), CRF09_cpx (1: 1.2%) and CRF11_cpx (1: 1.2%).

HIV-1 genotypes and hepatotoxicity: Prevalence of hepatotoxicity did not show any significant difference among HIV subtypes (p = 0.52). Of the 37 patients with hepatotoxicity, the prevalence of hepatotoxicity among the different subtypes were A1 (n=1, 2.7%), CRF02_AG (n=26, 70.3%), CRF06_cpx (n=1, 2.7%), CRF11_cpx (n=1, 2.7%), CRF22_01 (n=2, 5.4%), D (n=3, 5.4%), F2 (n=3, 8.1%), G (n=1, 2.7). However, when comparing non-CRF02_AG and CRF02_AG subtypes in figure 1, non-CRF02_AG infected subjects recorded a higher prevalence of 55.0% (11) although the difference was not significant (p= 0.40).

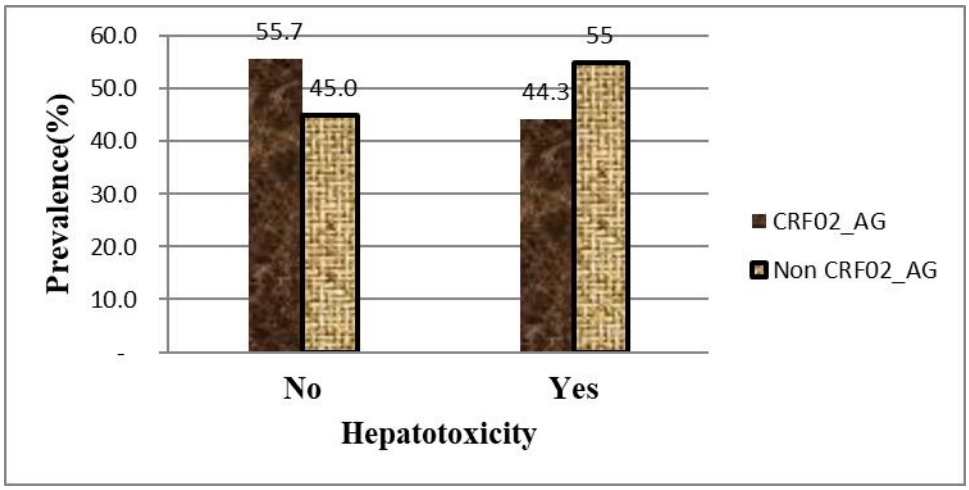

Figure 1: *Hepatotoxicity between CRF02_AG and non-CRF02_AG subtypes*

Prevalence of drug resistance mutation: The prevalence of drug resistance mutation was 11.1% (9/81). Of the resistance mutations observed, 8.6% (7/81) confers resistance to nucleoside reverse transcriptase inhibitor (NRTI), 4.9% (4/81) to non-nucleoside reverse transcriptase inhibitor (NNRTI) and 1.2% (1/81) to protease inhibitors (PI). Dual-class DRM involving both NRTI and NNRTI was observed in three patients (3.7%). One patient was detected with HIV-1 variant harbouring multi DRMs in both NRTI (D67N, K70R, M184V, T215F, K219Q) and NNRTI (V108I, V179E, Y181C) (Table 3).

Table 3

Demographic and immunologic characteristics of patients with DRM

GenBank ID	HIV-1 subtype	HAART at initiation	Drug class resistance mutation			Hepatotoxicity grade
			NRTI	NNRTI	PI	
MK061058	CRF02_AG	TDF+3TC+EFV	K219Q	None	None	0
MK061064	CRF02_AG	TDF+3TC+EFV	T215TA	None	None	2
MK061100	CRF02_AG	TDF+3TC+EFV	M41ML	None	None	3
MK061051	CRF02_AG	3TC+ZDV+NVP	K65E	None	None	4
MK061069	CRF02_AG	TDF+3TC+EFV	None	E138A	None	2
MK061076	CRF02_AG	TDF+3TC+EFV	K70T	E138A	None	1
MK061065	CRF02_AG	3TC+ZDV+NVP	M184MV	K103N	None	4
MK061090	CRF02_AG	TDF+3TC+EFV	D67N, K70R, M184V, T215F, K219Q	V108I, V179E, Y181C	None	0
MK061080	CRF22_01A1	3TC+ZDV+NVP	None	None	I54IFV	3

Legend: *3TC; lamivudine, AZT; zidovudine, EFV; Efavirenz, HAART; Highly active antiretroviral therapy; NNRTI; Non-nucleoside reverse transcriptase inhibitor, NRTI; Nucleoside reverse transcriptase inhibitor, NVP; Nevirapine, PI; protease inhibitors, TDF; tenofovir.*

Assessing Drug Resistance-associated Mutations and hepatotoxicity at D180: At the D180, 77.8% (7/9) of patients with DRM had hepatotoxicity with the following grades: grade 1(n=1), grade 2 (n=2), grade 3 (n=2) and grade 4 (n=2). This difference was significant (P =0.04; Table 4). All the patients harboring NNRTI DRMs presented with hepatotoxicity.

Table 4

Assessing the presence of DRM and prevalence of hepatotoxicity at end of D180

Hepatotoxicity	Drug-resistance mutation	
	No (%)	Yes (%)
No	42(58.3)	2(22.2)
Yes	30(41.7)	7(77.8)

$x^2 = 3.87$ $p= 0.040$

DISCUSSION

Hepatotoxicity linked to HAART is expressed by elevation of liver-associated enzymes such as ALT and AST.[4, 15] Elevations of these enzymes have been associated with all classes of HAART. However, the extent to which each drug of HAART contributes to hepatotoxicity varies.[8, 9, 15]Data from this study showed a significant positive linear relationship between elevated ALT and AST levels with an increase in the duration of treatment irrespective of the treatment regimen. Similar results have been reported elsewhere.[4] There was no significant difference in the use of either ALT or AST in evaluating hepatotoxicity. The liver enzymes elevation is probably associated with mitochondrial damage, direct drug toxicity or hypersensitivity reactions.[4, 6, 7]

Nevertheless, it may also be associated with other factors such as consumption of alcohol, opportunistic infections and concomitant medications.[3] However, since the ratio of AST and ALT activity in this study was less than 2, it indicates that hepatotoxicity in these patients was induced by HAART and not alcohol.[16]

Results from this study like in previous studies in other parts of Cameroon[8, 9] and

elsewhere [6,15] showed a high prevalence of hepatotoxicity in AIDS patients on HAART.[6,8] The high prevalence of hepatotoxicity 37 (45.7%) is evident that hepatotoxicity in AIDS patients is multifactorial[3] and can be attributed to direct drug effect, mitochondrial toxicity, hypersensitivity reaction, or other AIDS-related opportunistic diseases caused by bacteria (*Mycobacterium avium*), fungi (*Candida albicans*, *Coccidioides immitis*), protozoa (*Toxoplasma gondii, Leishmania* species), Helminth (*Strongyloides stercoralis*), viruses (Cytomegalovirus, Herpes simplex virus, Adenovirus) and parasitic infection (Microsporidiosis). It has been reported that opportunistic infections stimulate an immunological response in the hepatic phagocytes, which account for liver enzyme elevation.[2] Moreover, since AIDS patients present with different ailments, there is a high probability that mechanisms of hepatotoxicity may also result from the interaction between HAART and non-antiretroviral drugs.

Various conflicting risk factors for the development of hepatotoxicity have been described in other studies and include HIV , age, gender, race, hepatitis B and C co-infections, increased in $CD4^+$ T cells level after the start of ART, higher baseline levels of ALT and AST, opportunistic infections, cirrhosis, most antiretroviral, anti-tuberculosis and lipid-lowering drugs, alcohol, and metabolic syndrome [4, 6-9]. In this study, there was no statistically significant difference in the prevalence of hepatotoxicity by age group, gender, level of education, occupation and $CD4^+$ T-cells classification. This finding could be because of the small sample size used in this study. However, age group <30 and male gender, recorded the highest hepatotoxicity prevalence. The most probable reason for the high prevalence in these groups can be attributed to their lifestyle that includes high alcohol intake and cigarette smoking. [9] Reason for this gender discrepancy is not clear given that the courses of HAART metabolism in humans are not sex dependent. Thus, this high prevalence could be due to other social habits that are common in males than females since more males than females were found to consume alcohol and cigarettes. The high prevalence of hepatotoxicity in subjects with high $CD4^+$ T-cells may be explained by the fact the use of HAART has shown to increase $CD4^+$ T cells count and body mass index, therefore, there is a high probability that increases in $CD4^+$ T cells count will lead to elevated ALT and AST activity. This result shows that the use of NVP-based regimen associated with high $CD4^+$ T cells count is a risk factor to the development of hepatotoxicity [4, 7].

HIV-1 diversity is one of the greatest challenges among the many challenges in achieving an effective and preventive vaccine.[12,13] Data from this study showed a wide genetic diverse population among HIV-1 group M and these include two pure subtypes, 2 sub subtypes and five CRFs. Similar distributions of HIV-1 genetic variants have also been described in other towns in Cameroon[1 , 10] and elsewhere.[2,12]

The recombinant CRF02_AG which predominates (74.1%) in this study falls within the 48.6-80% range of previous studies conducted in Cameroon and other countries in West Africa, Central Africa, and Europe.[1, 8, 10] The high prevalence of CRF02_AG suggests that this viral strain may be well adapted in the Cameroonian population or may have some biological advantages such as a higher replicative fitness relative to parental subtype A and G which may have modified its propensity to tropism over other co-circulating recombinants strains.[1]

This study was the first study to assess the impact of HIV-1 subtypes on hepatotoxicity. in the North West Region of Cameroon. The result of this study revealed that hepatotoxicity was not significantly higher among patients harbouring the CRF02_AG subtypes. This may be due to the low number of HIV-1 non-CRF02_AG compared to CRF02_AG in the study As such, it is required that such studies be carried with equal HIV-1 subtype populations.

Data from this study revealed a moderate level (11.1%) of DRM as classified by WHO. In Cameroon, this value is higher compared to the 7.3-10.8% range reported from other studies.[10,15] The moderate prevalence can be attributed to poor drug adherence, loss to follow-up, pharmacy stock-outs, lack of proper patient retention in care and the use of ARV drugs to prevent mother-to-child transmission or as pre- and post- exposure prophylaxis.[10] The use of HAART in HIV prevention has led to a high rate of acquired drug resistance and possible onward transmission of the resistant strains to newly infected individuals. More so, it can also be associated with mutations that occur within the HIV-1 genome.[2,10]

Majority of the resistance associated mutations (RAM) were associated with low-level resistance 36.9% (17/46) followed by potential low-level resistance 30.4 % (14/46). Furthermore, DRMs were associated with predicted resistance level to Didanosine followed by Stavudine. This may explain why these drugs are no longer recommended for use in our setting.[17,18]

The high prevalence of 77.8% (7/9) of hepatotoxicity seen in patients with DRM is most probably due to other factors and not HAART. The presence DRM may lead to persistent viral replication since the HAART might be unable to fully suppress its replication. It has been reported that persistent HIV infection causes immune activation and inflammatory processes in Kupffer cells which may stimulate the development of liver fibrosis.[19] Furthermore, persistent viral replication may also lead to mitochondrial toxicity, oxidative stress, or the accumulation of toxic metabolites that leads to intra-hepatic damage.[5] In addition, the mitochondrial toxicity can further induce apoptosis in CD4+ and CD8+ cells and that contributes to fat accumulation in the liver with eventual fibrosis.[19] Nevertheless, it has been shown that the inability of the drug to suppress the growth of the virus will lead to the expression of HIV protein gp120 and co-receptors (CXCR4 and CCR5) on the hepatocyte surface. These proteins have shown to induce cell signalling in the liver that leads to increased expression of pro-collagen alpha-1 that causes advanced fibrosis. [20]

Lastly, since severe hepatotoxicity (grade 3 and 4) was more common in patients (3/4; 75%) with HIV strain with potential NNRTI drug resistance, probably due to the fact that the risk of hepatotoxicity seems to be higher with NNRTI. [4, 9]

CONCLUSIONS

Findings from this study confirmed previous findings that CRF02_AG subtype is still the most predominant subtype and patients harboring CRF02_AG recorded the highest prevalence of hepatotoxicity. In addition, this study revealed moderate levels (11.1%) of drug resistance mutation and 77.9% (7/9) of these patients with DRM presented with hepatotoxicity.

Recommendations

We would like to recommend that given the relatively high prevalence of HAART-related hepatotoxicity, monthly monitoring of transaminases is important for the first 6 months during HAART follow-up. It is important to monitor the evolving HIV diversity and its potential impact on the development of hepatotoxicity. Lastly, AIDS patients with hepatotoxicity should be screened for the presence of variant strains with DRMs.

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