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Predisposing factors of high Lipoprotein(a) in HIV positive patients on HAART at Livingstone General Hospital, Zambia.

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Abstract

Lipoprotein(a) (Lp(a)) is a highly atherogenic independent risk marker for Cardiovascular disease (CVD). Current studies show that Highly Active antiretroviral Therapy (HAART) raises Lp(a) levels in HIV patients, thereby increasing their risk for CVD. However, data on Lp(a) levels in HIV positive patients on HAART in Zambia is limited. This study was conducted to provide Lp(a) distribution, prevalence of high Lp(a) and the factors associated with high Lp(a) levels in HIV patients on HAART. This cross sectional study was conducted between December 2014 and February 2015 at Livingstone General Hospital laboratory were routine fasting serum samples were collected and sent to the University Teaching Hospital Biochemistry laboratory for Lp(a) determination on Beckman coulter AU480 analyzer. Demographic and clinical data from patient files such as age, gender, ART combination and duration on ART were collected. Data was analyzed using STATA v.12 and Statistical Package for Social Sciences (SPSS) v.17. Sample size was 143 comprising of 57 (39.9%) males and 86(60.1) (%) females who had been on HAART for one to ten years. The study participant's age ranged from 18-45 years. Cut off value denoting high Lp(a) concentration used in this study was ≥ 30mg/dL. Lp(a) concentration was normally distributed in the study population with mean 24.17mg/dL ±12.47mg/dL. Prevalence of high Lp(a) was 31.5% . Lp(a) was significantly higher with increasing age (p=0.009) and longer duration on HAART (P<0.001) irrespective of specific ART combination (p=0.086), however, those on AZT+3TC+NVP were 9.02 (AOR) (95%CI [1.41,57.54]) times more likely to have high Lp(a) levels compared to the group receiving TDF+FTC+EFV (p=0.020). The prevalence of high Lp(a) in HIV positive patients on HAART at Livingstone General hospital was high. Age, duration on HAART and AZT+3TC+NVP combination were significant predictors of high Lp(a) levels.

Key words: Lipoprotein(a), Highly Active Antiretroviral Therapy, HIV, Cardiovascular Disease, Zambia

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Introduction

The HIV pandemic over the last decades has been identified as an important contributor to cardiovascular disease (CVD) mortality rates. A recent meta-analysis confirmed a significantly increased risk of CVD in HIV-infected versus uninfected people, and treatment, were associated with elevated risk for CVD [1]. A large body of genetic and epidemiological evidence now suggests a direct association between an elevated plasma lipoprotein(a) (Lp(a)) level and an increased risk for CVD [2].

Lp(a) is a highly atherogenic independent risk marker for CVD and current studies have shown that highly active antiretroviral therapy (HAART) raises the plasma levels of Lp(a) in HIV Positive patients, thereby increasing their risk for CVD [3].

Lp(a) is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B100(Apo-B100) and an additional protein, apolipoprotein(a) (apo (a)), attached via a disulfide bond [4].The plasma concentration of Lp(a) varies over a wide range among individuals. Furthermore, the inter-individual variation in Lp(a) level is 90% genetically determined by the LPA locus on

chromosome 6, although plasma Lp(a) in a particular individual remains stable over a lifetime [5].

Plasma concentrations of Lp(a) vary over a 1000-fold-range, and the distribution of levels is highly skewed, with most whites and Asians having low levels. The distribution of plasma levels in blacks is less skewed, and the median level is 2 to 4 times greater than in whites [6].Although plasma Lp(a) concentration is 90% genetically determined and less modified by other factors, there are some factors known to influence the levels of Lp(a) concentration as briefly mentioned below.

Hypothyroidism is associated with an increase of Lp(a) concentrations, while hyperthyroidism is accompanied by a decrease of Lp(a) [7,8,9]. The chronic consumption of ethanol decreases the Lp(a) concentration and is dose-dependent. However, the Lp(a) concentration rises again after termination or reduction of alcohol consumption [8,10, 11, 12]. Trans-fatty acids found in deep-fried food have also been reported to increase Lp(a) concentration and the increase is particularly marked in individuals with initially elevated Lp(a) concentrations [13,14,15]. Several studies also discuss that mono- or poly-unsaturated fatty acids or fat-modified foods may have a lowering and protective effect on Lp(a) plasma concentrations [14,16,17,18]. Decreased Lp(a) plasma concentrations in smokers compared to non-smokers have been reported [8,19]. The administration of niacin or nicotinic acid may produce a distinct decrease of Lp(a), with simultaneous favorable influence on other parameters of the lipid metabolism [8,20].

Cholestatic liver diseases are associated with reduced Lp(a) concentrations[8]. Elevated Lp(a) plasma concentrations have been reported in patients with diabetic microscopic albuminuria, nephrotic syndrome, nephropathy, kidney failure of different etiology and stages and in type 2 diabetes mellitus [14,21,22].

In a study assessing Lp(a) in patients initiating antiretroviral therapy [23], almost exclusively, patients with high Lp(a) at baseline (median 51.6 mg/dL) showed a profound increase of median 26.7 mg/dL (week 24). This effect was not associated with specific ARVs and was independent of changes in other lipids.

In another study conducted in Burkina Faso [3], among the HIV infected participants, Lp(a) levels were higher in HAART treated group compared to the group that were not treated (p=0.004). Infected subjects on the antiretroviral treatment for 12 months had higher Lp(a) levels than those treated for 6 months (p=0.034). They concluded that adequate management of metabolic abnormalities of HAART-treated HIV-infected patients must include periodic measurement of Lp(a) levels. Another study [24] reported that Lp(a) level higher than 30 mg/dL was observed in 41% of participants receiving Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI).

Most studies with the aim of defining an absolute threshold of Lp(a) serum concentration have reported an approximately two fold increase in cardiovascular risk in patients with Lp(a) ≥30 mg/dL compared with patients with Lp(a) levels <30 mg/dL[25,26].

Materials and Methods

This was a cross sectional laboratory based study conducted at Livingstone General Hospital Laboratory between December, 2014 and February, 2015.

Sampling, specimen collection, storage and analysis

Convenience sampling was employed when selecting HIV seropositive individuals as they reported for routine medical tests at the Laboratory. Convenience sampling was used due to the fact that there were only a few routine fasting lipid profile samples that were usually requested for routine analysis among HIV positive patients at Livingstone General Hospital hence making this type of sampling, the best under these circumstances. A total of 200 samples were collected but only 143 were analyzed successfully due to high cost of reagents. The study participant's age was ranging from 18-45 years consisting of HIV positive patients on HAART (NNRTI and NRTI based regimen only) for at least one year reporting at Livingstone General Hospital Laboratory outpatient department and medical clinic for routine tests. Participants with any record of Withdrawal from combination ART, those on Protease Inhibitors, cigarette smoking, hypertension, diabetes mellitus, Cholestatic liver diseases, kidney failure, nephrotic syndrome, hypothyroidism, hyperthyroidism, chronic consumption of alcohol, administration of niacin or nicotinic acid, Women with repeated abortions, pregnancy, treatment with carbamazepine or sodium valproate were excluded from the study. Clinical and demographic data was collected from patient files and laboratory forms using a data collection form. Routine fasting blood specimens that were requested for lipid profile were conveniently selected, aliqouated and stored at -20^{0}c and transported on dry ice to the University Teaching Hospital Biochemistry Laboratory for analysis. The Randox dedicated Lp(a) reagents were used on Beckman coulter AU480 analyzer. The Randox assay is an immunoturbidimetric (IT) assay for the quantitative in vitro determination of Lp(a) in human serum or plasma. It contains a very high density of isoform-insensitive antibodies and detection reagent – ensuring more Lp(a) bound antibodies are detected and more accurate

measurement. It is Liquid ready-to-use IT assay, excellent stability (open vial stability 30 days on board) and no sample preparation required. Randox produces a 5-point calibrator which takes into account the heterogeneity of the Lp(a) molecule for each of the levels, resulting in excellent commutability of the calibrator with patient samples [28].

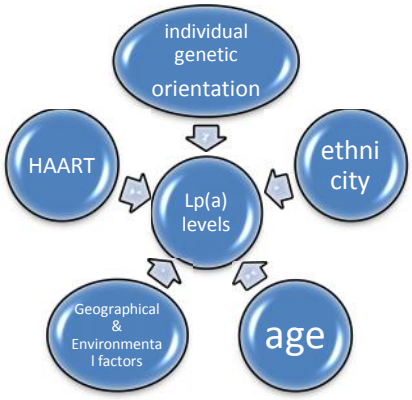
Lp(a) analysis principle: Immunoturbidimetry is the technique that Beckman coulter AU480 analyser uses for Lp(a) analysis. The Lp(a) test measures the rate of increase in light scattered from particles suspended in solution as a result of complexes formed during an antigen-antibody reaction.

Chemical reaction scheme: Lp(a)(sample) + particle bound anti-Lp(a)(antibody) → [Lp(a)(sample)-Antibody complex]

Data analysis: SPSS v.17 and STATA v.12 were used for data analysis. To test whether data in the study population was normally distributed, both graphical and descriptive statistics were used. Shapiro-wilk's test in SPSS was also used to numerically determine further normality of data. For Inference, ANOVA, student's T test, chi-square and Logistic regression were used. At 95% confidence interval, p value less than 0.05 were considered significant.

Ethical considerations: The study was undertaken after ethical approval from the University of Zambia Biomedical Research Ethics Committee. The information obtained in the data collection forms was treated with total confidentiality and was not disclosed to anyone. It was only used for research purposes. No participant identifiers were extracted in the data collection form.

Figure 1: Conceptual framework of factors associated with Lp(a) levels in HIV positive patients



Results

Characteristics of the study population

The total number of participants in the study was 143 and comprised more females, 86 (60.1%) than males, 57(39.9%) with 2:3 male to female ratio. The distribution of Lp(a) in the study population was less skewed and approximately normally distributed. The males had a mean Lp(a) concentrations of 24.6mg/dL ±12.6mg/dL and the females had mean Lp(a) concentrations of 23.9mg/dL± 12.4mg/dL. The participant's mean age was 34±7.6 years. There were 5 groups of different HAART combinations into which the study participants were grouped, with the majority in group 1, as follows; group 1 had 101 (70.6%) participants who were on tenofovir disoproxil fumarate + emtricitabine + efavirenze (TDF+FTC+EFV), group 2 with 18 (12.6%) participants on tenofovir disoproxil fumarate + emtricitabine + nevirapine (TDF+FTC+NVP), group 3 with 10 (7.0%) participants on stavudine + lamivudine + nevirapine (D4T+3TC+NVP), group 4 with 9 (6.3%) participants on zidovudine + lamivudine + nevirapine (AZT+3TC+NVP) and group 5 with 5 (3.5%) participants on stavudine + lamivudine + efavirenz (D4T+3TC+EFV).

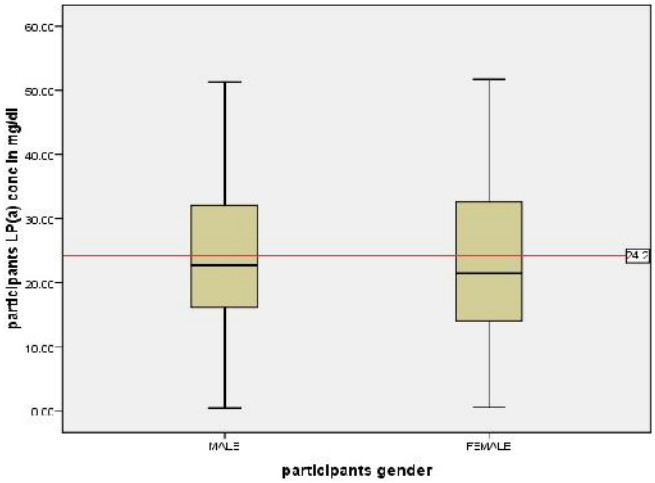


Figure 2: Box plot showing the distribution of Lp(a) concentration levels in males and females

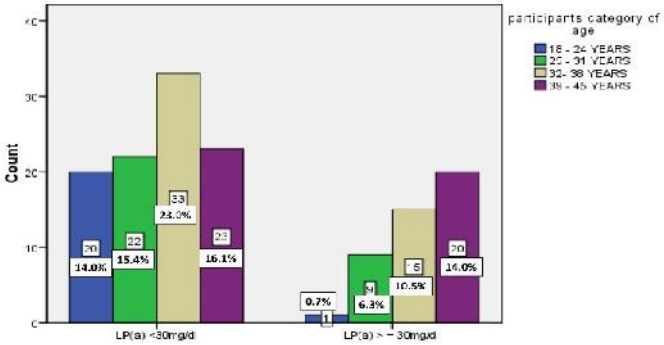


Figure 3: A bar chart showing high and low Lp(a) in different age categories. Out of the 143 participants, 1(0.7%) was in the age category 18-24 years, 9(6.3%) were in the age category 25-31 years, 15(10.5%) in the age category 32-38 years and 20(14.0%) were in the age 39-45 years. As shown in this figure, Lp(a) tended to be raised with increasing age.

As shown in figure 2, Lp(a) was normally distributed in both males and females. Lp(a) tended to be raised with increasing age, p=0.009 (figure 3). As shown in figure 4, Lp(a) tended to be higher with longer duration on HAART, p<0.001. Table 1 shows that there was no difference in the Lp(a) concentration means between males and females, p=0.719 and the type of ART combination p=0.136. Lp(a) increased irrespective of the ART combination. However, there was a difference in the age (p=0.001) and duration on HAART (0<0.001) and mean Lp(a) concentrations.

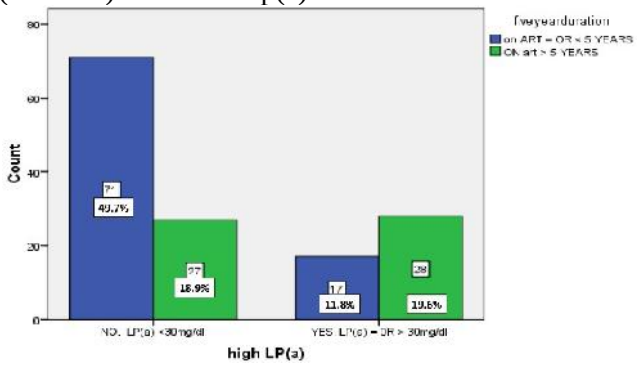


Figure 4: A bar chart showing high and low Lp(a) concentration level in different ART duration category (five year duration).

Characteristic		n (%)	Mean Lp(a) conc. in mg/dL (range)	p-value
ttSex				
	Male	57 (39.9)	24.6 (0.4,51.3)	0.719
	Female	86 (60.1)	23.9 (0.6,51.8)	
Total		143(100)		
aAge category(years)				
	18-24	21 (14.7)	16.1(0.6,41.5)	0.001*
	25-31	31 (21.7)	23.4(0.6,48.5)	
	32-38	48 (33.6)	23.8(0.4,48.9)	
	39-45	43 (30.)	29.1(4.9,51.8)	
aDuration category (years)				
	1-5	88 (61.5)	21.1(0.4,51.3)	<0.001*
	6-10	55 (38.5)	29.2(2.7,51.8)	
aART combination				
TDF/FTC/EFV		101 (70.6)	23.2(0.4,51.8)	0.136
TDF/FTC/NVP		18 (12.6)	28.4(2.7,48.9)	
D4T/3TC/NVP		10 (7.0)	22.4(12.6,39.7)	
AZT/3TC/NVP		9 (6.3)	31.3(11.3,46.3)	
D4T/3TC/EFV		5 (3.5)	18.1(7.0,30.0)	

Table 1: Demographic and clinical characteristics of the study population in comparison with mean Lp(a) concentrations. tt= two sample t test with equal variance was used; a= analysis of variance test was used; *= statistically significant; TDF= tenofovir disoproxil fumarate; FTC= emtricitabine; EFV=efavirenze;NVP=nevirapine; D4T= stavudine; 3TC= lamivudine; AZT= zidovudine

As shown in table 2, there was no association between having high Lp(a) levels and sex (p=0.982) but high Lp(a) levels were more prevalent with age (p=0.009) and increased duration on HAART (p<0.001). Specific ART combination was not associated with increased Lp(a) (p=0.086), all combinations led to high Lp(a) in the long term.

characteristics	high LP(a)level (≥30mg/dl) n (%)	Low Lp(a) level (<30mg) n (%)	p-valuec
n	45(31.5%)	98 (68.5%)	
Sex			
Male	18 (31.6)	39 (68.4)	0.982
Female	27 (31.4)	59 (68.6)	
Age category(in years)			
18-24	1 (4.8)	20 (95.2)	0.009*
25-31	9 (29.0)	22 (71)	
32-38	15 (31.3)	33 (68.8)	
39-45	20 (46.5)	23 (53.5)	
Duration category (in years)			
1-5 years	17 (19.3)	71 (80.7)	<0.001*
6-10 years	28 (50.9)	27 (49.1)	
ART combination			
TDF/FTC/EFV	28 (27.7)	73 (72.3)	0.086
TDF/FTC/NVP	8 (44.4)	10 (55.6)	
D4T/3TC/NVP	2 (20)	8 (80)	
AZT/3TC/NVP	6(66.7)	3(33.3)	
D4T/3TC/EFV	1 (20)	4 (80)	

Table 2: predisposing factors to high Lp(a) concentration. *= statistically significant; C= Chisquared test was used; TDF= tenofovir disoproxil fumarate; FTC= emtricitabine; EFV=efavirenze; NVP=nevirapine; D4T= stavudine; 3TC= lamivudine; AZT= zidovudine. *= statistically significant; C= Chisquared test was used; TDF= tenofovir disoproxil fumarate; FTC= emtricitabine; EFV= efavirenze; NVP = nevirapine; D4T = stavudine; 3TC = lamivudine; AZT = zidovudine

As shown in table 3, the ages 32-45 contributed significantly in predicting high Lp(a) levels with reference to the ages 18-24 years. The odds of having high Lp(a) were about 4 times more in participants on longer duration (6-10 years) compared to the participants on short duration on HAART (1-5 years). The odds of having high Lp(a) in participants on AZT+3TC+NVP, were 9.02 (95% CI[1.41,57.54]) (p=0.020) times more compared to the reference group.

Further statistical tests done: Pearson's correlation in SPSS showed a significant positive relationship between age r(141) = 0.32, p<0.001, duration on HAART r(141) =0.43, p<0.001 and Lp(a) concentration levels.

Variable	Odds Ratio[u] (95% CI)	P value	adjusted Odds[m] Ratio OR (95%CI)	P value
Sex				
Male	1.00		1.00	
Female	0.99 (0.48,2.04)	0.982	0.62 (0.26,1.50)	0.297
Age category(in years)				
18-24	1.00		1.00	
25-31	8.18 (0.95,70.44)	0.056	10.14 (0.89,115.03)	0.062
32-38	9.09 (1.11,74.16)	0.039*	11.47 (1.06,124.04)	0.045*
39-45	17.39 (2.13,141.33)	0.008*	16.32 (1.46,181.98)	0.023*
Duration category (in years)				
1-5 years	1.00		1.00	
6-10 years	4.33 (2.04,9.15)	<0.001*	4.00 (1.66,9.64)	0.002*
ART combination				
TDF/FTC/EFV	1.00		1.00	
TDF/FTC/NVP	2.08 (0.74,5.82)	0.161	1.20 (0.39,3.65)	0.738
D4T/3TC/NVP	0.65 (0.13,3.25)	0.602	0.39 (0.06,2.32)	0.306
AZT/3TC/NVP	5.21 (1.21,22.29)	0.026*	9.02 (1.41,57.54)	0.020*
D4T/3TC/EFV	0.65 (0.06,6.08)	0.707	0.69 (0.05,8.75)	0.780

Table 3: Predictors of High Lipoprotein(a) using univariate and multivariate logistic regression. U= univariate logistic regression was used; m= multivariate logistic regression was used; * = statistically significant ; TDF= tenofovir disoproxil fumarate; FTC= emtricitabine; EFV=efavirenze;NVP=nevirapine; D4T= stavudine; 3TC= lamivudine; AZT= zidovudine

Discussion

Lp(a) concentration was normally distributed in the study population with mean Lp(a) levels of 24.6mg/dL ± 12.6(SD) in males and 23.9mg/dL ± 12.4 in females. The overall mean in the study population was 24.2mg/dL ± 12.5mg/dl. This mean distribution result was different to that reported [3] in Burkina Faso (West Africa) where they reported the mean Lp(a) concentration of 48.3 ± 26.9mg/dL in HAART treated group. The difference was possibly due to their mean age (37.9±10.4 and 41± 7.6 years for participants treated with HAART for six and 12 months respectively) which was higher than the one reported in this study as well as due to genetic, ethnic and geographical variations in Lp(a) concentrations [6,29]. The less skewed distribution of Lp(a) reported in this study is similar to that reported in other studies [29,30] were they reported that Lp(a) distribution is less skewed in black populations.

According to data from prospective studies showing a higher cardiovascular risk in patients with Lp(a) levels ≥30 mg/dL [25,31-33], the same ≥30mg/dL cut off value was used in this study at which Lp(a) concentration level was considered high.

As shown in table 2, the prevalence of high Lp(a) among HIV positive individuals in the study population was 31.5%. The prevalence of high Lp(a) in HIV positive individuals in this study (31.5%) was different, compared to the findings in other studies [24,34] who reported prevalence of 41% and 22%. The differences again may be due to factors such as geographical location, ethnic group, Genetic orientation, Duration on HAART and age of participants.

Age and duration on HAART as predisposing factors to high Lp(a) levels

It was shown from the results that age and duration played an important role in increasing the levels of Lp(a) concentration. The older the participant (p= 0.009) and the longer the duration (p<0.001) the higher the Lp(a) concentration level. Using univariate and multivariate logistic regression (table 3), it was shown that the level of Lp(a) was likely to be higher as age advanced (ages 32-38 AOR 11.47(95% CI[1.06,124.04]) and 38-45 AOR 16.32(95%CI[1.46,181.98]) in comparison with age category 18-24 years. A correlation was done using Pearson's correlation in SPSS and the result showed a significant positive relationship between age r(141) = 0.32, p<0.001, duration on HAART r(141) =0.43, p<0.001 and Lp(a) concentration levels.

As shown in table 2, there was a significant association between age category and having high Lp(a) levels. A logistic regression conducted showed that in comparison to the reference group (18-24 age category) the odds of having high Lp(a) in the ages 32-38 years and 39-45 years were 9.09 (95% CI [1.11,74.16]) and 17.39 (955 CI[2.13,141.33]) respectively and this relationship was significant. Further combined with all the predictors (sex, age, duration on HAART, ART combination), the results showed that the participants aged 32-38 years were 11.47 (95% CI[1.06,124.04]) times more likely to have high Lp(a) serum levels compared to participants aged 18-24 years and the participants aged 39-45 years were 16.32 (95% CI[1.46,181.98]) times more likely to

have high Lp(a) serum levels compared to the participants aged 18-24 years. Another significant finding from the table using the adjusted ratio was that the group that was on ART for six to ten years were 4.00 AOR (95% CI[1.66,9.64]) times more likely to have a Lp(a) ≥ 30mg/dL compared to those participants who were on ART only for one to five years.

The relationship between age, duration on HAART and Lp(a) levels was similar to a study done [3] in west africa were they reported that participants who were on HAART for 12 months had higher Lp(a) levels (54.8mg/dL ± 34.2) compared to the group treated for six months (39.9mg/dL ± 25.6) (p=0.034).They also reported that an increase of Lp(a) with age (p=0.025) was found particularly in the group of 35 to 50 years (58.7 ± 33.5 mg/dL). In a follow up study [28], an absolute change in Lp(a) concentration was reported after six months of ART showing a positive correlation with baseline concentration of Lp(a) (spearman p=0.367, p< 0.01).

Sex as predisposing factor to having high Lp(a)

Sex of the participants had no correlation with Lp(a) levels similar to findings in another study [3], p=0.34.This may be due to the 90% genetic predisposition of Lp(a) levels in individuals [5].

HAART combinations as predisposing factor to having high Lp(a)

In this study, there were more participants (70.6%) on tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and efavirenz (EFV) HAART combinations with regard to other combinations. However, there was no relation between type of ART combination and mean Lp(a) concentration levels (p=0.136) and there was no Specific ART combination associated with raised Lp(a) concentrations (p= 0.086) though the group receiving AZT+3TC+NVP (6.3%) were 9.02 (AOR) (95% CI[1.41,57.54]) times more likely to have high Lp(a) levels compared to the group receiving TDF+FTC+EFV (70.6%) and this was statistically significant. All combinations increased Lp(a) in the long term. In a study conducted in Germany [23], they also reported that no difference was found between patients receiving efavirenz (EFV) and those receiving nevirapine (NVP) (P=0.23) or between those receiving tenofovir (TDF) and those receiving zidovudine (p=0.74).

Conclusion

The prevalence of high Lp(a) serum concentrations in HIV positive patients on HAART at Livingstone General hospital was high (31.5%). We were able to show that Lp(a) concentration was similar in males and females, however, Lp(a) tended to be raised with increasing age (p=0.009) and longer duration on HAART (p <0.001). Even though Lp(a) was raised irrespective of specific ART combination, we were able to show that those on AZT+3TC+NVP were more likely to have high Lp(a) concentration levels. Therefore, age, duration on HAART and AZT+3TC+NVP combination were the significant predisposing factors to high Lp(a) levels in this study. We recommend Periodic serum Lp(a) analysis in HIV positive patients and since Lp(a) levels in the normal population is limited to genetic variations with inter individual variations of 1000, and variations due to ethnicity as well as geographical location, it would be important to conduct a follow-up study to establish what the levels are in the HIV negative and HIV positive treatment naïve population in Zambia as well. Screening of high risk patients and their families for plasma Lp(a) may permit early detection and preventive treatment of CAD (Coronary Artery Disease).

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