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Cardiovascular Disease Risk from Protease Inhibitors-ART for HIV: Retrospective Cohort of University Teaching Hospital, Zambia

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Abstract: The burden of Cardiovascular Disease (CVD) in Sub-Saharan Africa is rising amidst a high prevalence of infectious diseases including HIV. While use of certain Antiretroviral Therapy (ART) drugs has been shown to cause dyslipidaemia, little is known about the burden of CVD in the presence of Protease Inhibitors (PIs) in Sub-Saharan Africa. We investigated the incidence and risks associated with the use of PI-containing ART in the development of CVD among HIV seropositive adults at the University Teaching Hospital, Zambia. For this purpose a retrospective cohort study was used to review records of patients on PIs and non PIs between January 2008 and January 2016. The end point of the study was CVD (n=281). Generalized linear models using a log-binomial link were used to assess covariates, while Kaplan Meier method for probability of survival to CVD and time to CVD comorbidity were utilised. The results showed that the incidence of CVD among PIs was 62%, while among the non-PI ART group it was 38%. The risk of CVD was 2.3 times higher ($p<0.001$; 95% CI: 1.86-2.81) in the PIs ART group than non-PI ART group. Risk factors included; Age, CD4 cell count, Type of ART, Years since HIV diagnosis and BMI, with the CVD attributable risk of 56%. The Kaplan-Meier survival estimates for CVD showed a marked difference in survivorship between the two ART groups (Log-rank P=0.003). Based on this therefore, prolonged use of PI-containing ART was significantly associated with a higher incidence of CVD. Addressing the modifiable risk factors could significantly contribute towards reduction of CVD in the HIV population. This study underscores the importance of new screening strategies to be effectively incorporated in ART program. However, many opportunities exist for developing interventions for optimal screening, treatment and prevention of CVD in patients on ART.

Keywords: CVD, HIV Seropositive, Protease Inhibitors, ART

1. Background

Cardiovascular disease (CVD) remains a global health issue and the leading cause of morbidity among the HIV population worldwide. CVD refers to any disease that affects the cardiovascular system, such as cardiac disease, vascular diseases of the brain and kidney and peripheral arterial diseases. The use of Protease Inhibitors form of Antiretroviral Therapy (ART) has been associated with a high risk of lipodystrophy syndrome in HIV patients leading to a CVD. [1, 2] However this link between CVD and PI still remain unclear and therefore require further investigation. A number of variables have been identified as important associated factors for CVD in most cross sectional studies [1, 2, 3]. The proposed mechanism is that CVD may be caused by an interaction between the HIV

infection, immune recovery and antiretroviral medication consequently as well as the sociodemographic and clinical characteristics of the patient [1]. This presents challenges in the management of HIV infections. According to the World Health Organisation (WHO)'s Progress Report of 2015, the number of people living with HIV globally was about 35 million by the end of year 2013 and currently, about 50% of all patients with HIV worldwide die from causes considered unrelated to HIV; 11.7 million were in low- and middle-income countries. The estimated number of people with HIV in poor countries is 32.6 of which 36% are accessing ART. In the same year, 28 million people were eligible for ART and about 1.8 million died due to HIV related complications mostly CVD [2, 3]. This has remained a global problem, but other regions like Sub Saharan Africa is also experiencing an increased burden of CVD. Imperative to mention that most African countries has CVD as the second most common cause of death after infectious disease and it is estimated to account for 11 percent of total deaths [4].

Therefore determining the risk for people on ART is paramount for a successful management of the HIV population.

2. Methods

2.1. Design and Setting

This was a retrospective cohort study conducted at the Adult Infectious Disease Center (AIDC) at the University Teaching Hospital (UTH) in Lusaka, Zambia. There are currently over 12,000 HIV-seropositive adults accessing ART at AIDC. In this study, the cohorts of those who were exposed to PI's were selected from the HIV seropositive population using a systematic random sampling procedure. Those that were unexposed (non PI) group were also selected using the same sampling technique. These two groups were retrospectively followed up from 2008 to 2016, survival analysis was done and CVD was considered a failure in the analysis. The rate of CVD was compared between those exposed to PI's and those not exposed.

AIDC is a research and treatment centre within UTH and has developed numerous HIV protocols in the study of HIV and related comorbidities. The area for the study was chosen because UTH is the highest referral hospital in Zambia and attends to the largest population of HIV seropositive people in the country.

2.2. Selection of Participants and Data Collection

2.2.1. Study Procedures

The records of 281 participants (112 for PI group and 169 for Non PI group) were reviewed and only patients free of CVD prior to the study were enrolled. The data was extracted from the patients' files using a checklist as a tool for variables of interest. Demographic variables included sex, age and area of residence while the presence or absence of CVD was the outcome variable. Clinical variables related to HIV infection were ART exposure, time from HIV diagnosis until CVD development, CD4 cell count and CD4 cell count.

Consent was not obtained from participants as this study involved reviewing of records, however permission was sought from the facility to conduct the study. Ethical clearance was also obtained from the University of Zambia, Biomedical Research Ethics (UNZABREC) with reference number 022-06015.

2.2.2. Statistical Analysis

Stata Version 14 (Stata Corporation, College Station, Texas, USA) was used for the analysis. Descriptive statistics for categorical demographic and clinical variables were compared using Chi-square tests, while the T-test or the Wilcoxon rank sum test were used for continuous variables where appropriate. The Log Binomial model as well as the Cox proportional hazards model was utilized to compare relative CVD risks between the two ART groups when all other variables were controlled for. The Cox model was used to identify the effect of the length of time of ART in developing CVD. Hazard ratios (HRs) and 95% CIs were derived from Cox proportional hazards models. A Kaplan-Meier curve was constructed based on independent factors associated with 7 years survival to CVD. In this study, a P value less than 0.05 was considered statistically significant and all tests were two-sided.

Study entry was defined as date of cohort enrollment in the study (all participants were enrolled in 2008, they were no late entries). End of follow-up was defined as the first occurrence of a CVD as indicated in patients file, death due to any cause, or January 29, 2016. We categorized the age variable, since the dispersion was wide, as well as CD4 cell count (below 350 cells/mm^3 and 350 cells/mm^3 and above) and time since HIV diagnosis (recent HIV means less than three months after positive HIV serology).

3. Results

3.1. Participants' Demographics Characteristics

The demographic characteristics of the study participants are shown in Table 1. Of the patients records reviewed overall female constituted 157 (55.87%) and male were 124 (44.13%) of the study participants. The overall mean age of the respondents in years was 43.12 with a standard deviation of (10.58). Most of the participants were urban based 230 (81.85%) compared to those from rural parts 51 (18.15%).

Table 1. *Characteristics of participants on protease and non-protease inhibitors in a cohort of HIV seropositive adults followed-up from 2008 through 2016 (n=281).*

		Frequencies [n (%)]		
Characteristic Variable	**Overall**	**PI ART group**	**non PI ART group**	**chi-squared p-value**
Standardised age groups				
17-33	56 (19.93)	22 (19.64)	34 (20.12)	0.972|[a]
34-41	52 (18.52)	23 (20.54)	29 (17.16)	
42-46	59 (21.00)	23 (20.54)	36 (21.30)	
47-52	57 (20.28)	22 (19.64)	35 (20.71)	
53-69	57 (20.28)	22 (19.64)	35 (20.71)	
Sex				
Male	124 (44.13)	54 (48.21)	70 (41.42)	0.261|[a]
Female	157 (55.87)	58 (51.79)	99 (58.58)	
Residence				
Urban	230 (81.85)	82 (73.21)	148 (87.57)	0.002|[a]
Rural	51 (18.15)	30 (26.79)	21 (12.43)	
Body Mass Index (kg/m^2)				
<18.5 (underweight)	32 (11.39)	6 (5.36)	26 (15.36)	<0.001|[a]
18.5-24.9(normal weight)	128 (45.55)	41 (36.61)	87 (51.48)	
25-29.9(overweight)	72 (25.62)	33 (29.46)	39 (23.08)	
>30(obese)	49 (17.44)	32 (28.57)	17 (10.10)	
CD4 cell count				
<350	75 (26.69)	29 (25.89)	46 (27.22)	0.006|[a]
>350	206 (73.31)	83 (74.11)	123 (72.78)	
HIV Diagnosis (years) mean(SD)	9.66 (1.88)	9.54 (1.70)	9.73 (1.99)	0.801|[b]
Age mean(SD)	43.12 (10.58)	42.66 (10.52)	43.43 (10.64)	0.726|[b]
SBP mean(SD)	126.63 (14.54)	127.7 (15.59)	125.92 (13.80)	0.156|[b]
DBP mean(SD)	86.44 (22.96)	85.40 (16.22)	87.14 (26.53)	0.732|[b]

a=Chi-squared P-value b=T-test p-value; SBP- Systolic blood pressure; DBP- Diastolic blood pressure

3.2. Cardiovascular Risk for ART Groups

Table 2 shows that the risk of CVD for those on PI was 86.6% while those not on PIs had a risk of 37.9%. The risk of CVD in the PI ART group was 2.3 times higher (95%CI, 1.86, 2.81; p<0.001) than in the non-PI group, with an attributable risk of 56%. This suggests that eliminating risk factors for CVD such as CD4 cell count, age, years since HIV diagnosis and the time to CVD for those on PI would reduce the incidence of CVD by 56%. See table 2.

Table 2. *Contingency table of association between ART and CVD (n=281).*

Frequencies [n (%)]			
	With Cardiovascular Disease	**without Cardiovascular Disease**	**Total**
Protease inhibitor ART group	97(34.51)	15(5.33)	112(39.88)
non protease inhibitor ART group	64(22.77)	105(37.36)	169(60.14)
Total	161(57.29)	120(42.70)	281(100)
	Point	Estimates	95% CI
	Risk Difference	0.49	0.39-0.58
	Risk Ratio	2.28	1.86-2.81
	Attributable Risk	0.56	0.46-0.64
		P<0.001	

3.3. Unadjusted Estimates of Survival Rate of ART Groups to CVD Comorbidity (Kaplan-Meir (K-M)

Unadjusted proportional hazards regression analysis of risk of CVD among HIV seropositive adults by type of ART (PI versus non-PI ART) showed a hazard ratio (HR) of 1.8 (P=0.001 95% CI 1.3, 2.5).

The overall survival, number at risk and events experienced at each time interval in years during the seven-year study period is shown in Figure 1. The Figure also shows that the risk of morbidity in the PI ART group remained higher than in the non-PI ART group regardless of the number of years since recruitment.

The probability of survival from CVD was reduced by 0.5 (50%) in the PI group. Hence the protease ART group had a probability of about 50% of having CVD in a period of 7 years, The probability of survival in the non PI ART group was reduced by 0.7(70%), translating into a probability of about 30% of having CVD. The probability of having CVD is 20% higher in the PI group compared to the non PI group after 7 years of follow-up. Comparing the survival function of the Protease group to that of the non-Protease group, the difference

was statistically significant (Log-rank p value=0.003).

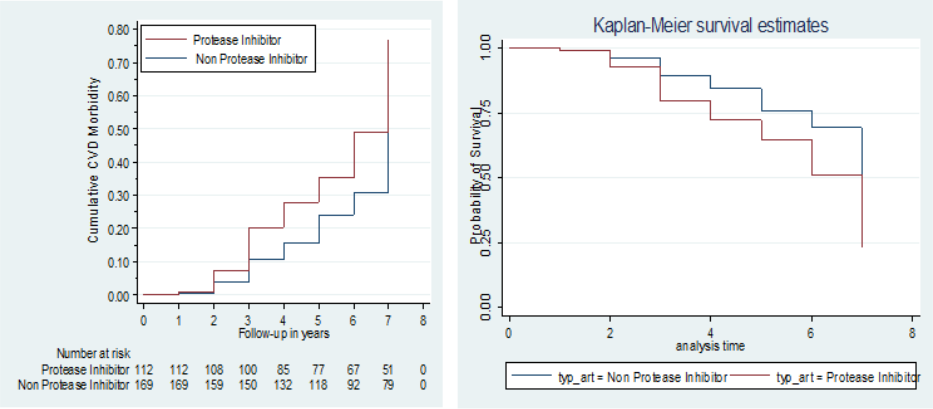

Figure 1. *CVD cumulative morbidity curve and Kaplan-Meier survival estimates for PIs and Non PIs ART groups.*

Notes: In Figure 1 above, time (t) is constant over two years when no CVD are observed and drops abruptly after 2 years for both groups when CVD occur. The time interval is short enough that there is rarely more than one CVD per interval and then the height of the drop at each CVD year indicates the size of the cohort remaining on that year. The accuracy of the survival curve gets less as we move towards the right, as it is based on fewer patients.

3.4. Risk Impact of Type of ART and Related Factors for CVD

Table 3 shows that ART patients on PI with a CD4 cell count of less than 350 cells/mL were 5.10 times more likely to develop CVD after adjusting for age and years since HIV Diagnosis compared to their counterparts (P=0.006). The adjusted risk ratio (that is accounting for the effect of other variables) was 2.60 (CI 2.12-3.30; p= <0.001) times high for those on PI with reference to the non PI group.

It was also found that having lived with HIV for more than 7 years compared to less than 7 years significantly increased the risk for a CVD. Those who had lived with HIV for more than 8 years were 1.78 (p=0.032) times more at risk of developing CVD independent of other variables, while at multivariate there was no statistical difference (RR 2.41; 95% CI 0.12-3.21; p=0.632). The participants' Systolic blood pressure did not seem to predict CVD both at univariate and multivariate.

After carrying out an investigator led stepwise regression, the best fit model predicting the risk of developing CVD among PI patients included age, sex, body mass index, systolic blood pressure, CD4 cell count, years since HIV diagnosis and being exposed to either PI and non PI. Relative rates from this study log binomial regression model are illustrated in Table 3.

The following parameters were assessed and excluded based on non-significance: gender, diastolic blood pressure and age independent of categories. Systolic Blood pressure was retained in the model despite its marginal statistical significance for CVD because of its well-known association with CVD. The model was able to correctly classify by 80.4% which entails that the model is not unreliable. The ROC curve (0.8525) indicated that the results were not due to chance (output results not shown for model classification and ROC curve).

Table 3. *Predictors of CVD among seropositive adults on PIs (univariate and Multivariate Analysis).*

	Univariate	**p-value**	**Adjusted**	**p-value**
Variable	RR(95%CI)		RR(95%CI)	
Standardised age groups				
17-33	1.00	1.00	1.00	1.00
47-52	2.13(0.91-3.12)	0.003*	1.56(1.34-1.72)	0.043
53-69	3.32(0.12-4.13)	0.002*	4.56(3.24-6.21)	0.021
Body Mass Index (kg/m^2)				
<18.5 (underweight)	1.00	1.00	1.00	1.00
18.5-24.9(normal weight)	0.98(0.14-2.21)	0.034*	1.01(0.12-3.21)	0.032
25-29.9(overweight)	1.34(0.03-1.78)	0.032*	1.57(1.21-7.87)	0.004
>30(obese)	1.89(1.12-2.67)	0.002*	1.65(1.12-9.32)	0.003
CD4 cell count				
<350	1.00	1.00	1.00	1.00
>350	4.35(2.31-7.43) 1.86-2.81	0.002*	5.10(3.43-8.43	0.006
Type of ART				
non Protease inhibitors	1.00	1.00	1.00	1.00
Protease inhibitors	2.30(1.86-2.81)	<0.001*	2.60(2.12-3.30)	<0.001
HIV Diagnosis (years)	1.78(1.21-2.32)	0.021*	2.41(0.12-3.21)	0.032

*Univariate significant p values; Abbreviation: RR= Relative Risk

4. Discussion

This study sought to investigate the link between PI-containing ART and the development of CVD in a well-characterized cohort of HIV-infected adults on ART at the University Teaching Hospital in Zambia. It was found that HIV patients taking PIs have a significantly higher burden of CVD compared with the non-PI group.

It was found in this study that the associated risk of CVD was 2.3 times higher in the PI ART group than the non-PI ART group not controlling for any other necessary indicators such as CD4 cell count, Age, Years since HIV diagnosis and the time to CVD. However, after controlling for the effects of the mentioned factors the risk of CVD was 3.51 times higher for those on PI compared to the non-PIs. Before any comparison are made with other studies It is worth mentioning that records of patients reviewed in this study did not have information on smoking and alcohol consumption. These have been found to be important risk factors for CVD among the HIV population [4, 5, 6].

The incidence of CVD for the PI ART group found in this study was lower than a previous study among HIV patients in Dar es Salaam in which the incidence of CVD was 76% [7]. The difference in incidence with the current study could be because the previous study focused on ART naive patients while this study considered both naïve and experienced patients. However, these results are similar to those that were reported from a Latin American HIV cohort of ART patients in which the prevalence of CVD was reported to be 65% [8]. One of the reasons for looking at ART experienced patients for comparison is because it is postulated that CVD is a result of the both the metabolic effects of the HIV virus itself as well as the metabolic effects of ART. Considering this fact, this increases the risk of future cardiovascular events in HIV patients [9].

Our results of the Kaplan Meier shows an increase in CVD comorbidity overtime, also other studies have shown similar finding with respect to this finding that protease inhibitor-based ART is linked with CVD as a result of high lipid levels which begins to show over a period of 2–3 years after initiating ART [10, 11, 12]. Other supporting studies to this effect is the study on the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) which showed evidence of linkage between dyslipidaemia and cardiovascular disease among HIV-infected persons on Non-Reverse Transcriptase Inhibitors and protease inhibitors, the risk is even much higher among older patients; 1.4% of patients in that study had a previous history of cardiovascular disease and 51.5% were cigarette smokers [13]. The mechanisms of how HIV infection and specific forms of ART impose these lipid abnormalities are still unclear and require further investigation. However, the common rationale is that HIV causes immune activation over time. The similar case is that increase in CVD is associated with advance in age, furthermore the HIV immune activation has been reported to persist even after successful treatment with ART [14]. Despite this linkage of ART to CVD development it has been emphasised that ART is crucial in improving life expectancy for the HIV population and in reduction of HIV related morbidities. These patients have longer survival, but bearing in mind that they are more threatened by cardiovascular disease [13, 14].

We found also that the predictors of CVD were ART type and duration, bearing in mind that duration could at the same time translate to increase in age and CD4 cell count over time. The conclusion is that these factors are associated with increased risk for CVD. The risk of CVD is greater in the PI group than in non PI group, and increases with the duration of treatment. Even though there is a probable link of ART to CVD, ART use has revolutionised management of HIV and it has improved the quality of life of the HIV population, also HIV mortality rates remain low [14, 15]. While the use of ART may prolong the life of those taking ART, the increased age in itself may lead to an increase in the risk of CVD, which may confound the results. In this study, age was found to be an independent risk factor for CVD.

With respect to BMI, we found that ART clients who are overweight and obese are likely to have CVD more compared to those with normal and underweights. This finding is consistent with what was reported in a study in Senegal which showed that factors such as higher BMI were associated with a higher risk of CVD [15, 16]. This is an important finding because initiation of ART correlates with rapid weight gain and as such risk reduction strategies for overweight and obese individuals should be of primary focus.

5. Conclusion

Prolonged use of PIs is associated with a higher incidence of cardiovascular disease. The risk factors for CVD include CD4 cell count lower than 350 cells, BMI, length of HIV illness and increase in age. This study underscores the importance of new screening strategies to be effectively incorporated in ART program among Human immune deficiency virus seropositive adults. Cardiovascular disease has emerged as an important cause of morbidity among seropositive adults. Human immune deficiency virus, antiretroviral therapy and host factors contribute to cardiovascular disease. However, many opportunities exist for developing interventions for optimal screening, treatment and prevention of cardiovascular diseases in Zambia.

Declarations

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

Brian Chiluba, Gershom Chongwe and Chola Nakazwe Daka conceived of the study and took part in writing the protocol. Brian Chiluba extracted data, did statistical analyses, and interpreted data. The manuscript was written by Brian Chiluba with significant contributions from Esther Munalula Nkandu, Gershom Chongwe, Chola Nakazwe Daka and Mumbi Chola. All authors made substantial contributions to overall conception and design, drafting the article, or revising it critically for important intellectual content, gave their final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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