Original Research Article

C-Reactive Protein Levels and Hypertension in HIV Infected Children on Highly anti-retroviral Therapy at the University of Abuja Teaching Hospital, Gwagwalada, Nigeria.

Abstract

Aim: To evaluate C-reactive protein levels in stable HIV positive children and adolescents on anti-retroviral therapy overtime in our health facility, and relate the findings to their CD4, viral-load, and blood pressure.
Study design: A cross-sectional hospital-based survey.
Place and Duration of Study: At Paediatric Out-patient Special Treatment Clinic of University of Abuja Teaching Hospital, Gwagwalada over a six-month period.
Methodology: The subjects were consecutively enrolled until the required sample size was met. Data entry and analysis was with SPSS version 23 computer software.
Sample: We included 126 (66 males and 60 females) subjects. Their biodata, weight, length/height, body-mass-index, blood pressure, CD4 cell count, viral-load, and ~~c~~C-reactive proteins were measured.
Results: Their mean age was 14.1±3.1 [7, 18] years, and most 69(54.8%) were 15-18 years. Majority 73(57.9%) had body-mass-index of <18 kg/m, many 99(78.6%) had vertical transmission, 82(65.1%) were from low socio-economic background, while most 104(82.5%) were on 2nd line medications. Their mean duration on anti-retroviral-therapy, CD4-cell-count, viral-load, and C-reactive-protein at enrollment were 7.2±2.9 [1, 16] years, 792.11±37.8 cells/mm^3, 1203.5±155.4 copies/ml, and 9.9±2.7mg/l respectively. ~~One-hundred-and-one~~101 (88.1%) of the recruited subjects had normal/minor elevation of CRP of <10mg/ml, while 15(11.9%) had moderate elevation of 10-100mg/ml. None had marked or severe elevation. The prevalence of hypertension was 10(7.9%) with diastolic form 7(5.6%) being commoner than systolic 3(2.4%). Multivariate analysis showed significant association between C-reactive-protein with CD4-cell-count [OR, 0.11 (CI, 0.008-1.029, *P=.006*)], systolic-blood-pressure [OR, 0.26 (CI, 0.81-2.97, *P=.026*)], and diastolic-blood-pressure [OR, 0.10, (CI, 0.14 (0.35-3.59), *P=.013*)].
Conclusion: There is high prevalence of hypertension among stable HIV positive children and adolescent on highly active antiretroviral therapy overtime in our center. C-reactive protein can be used to monitor risk of development of hypertension in these subjects.

Key words: HIV ~~infected, children, adolescents~~positive children and adolescents, highly active anti-retroviral therapy, C-reactive protein, blood pressure.

Introduction

With increasing access to highly active anti-retroviral therapy (HAART), many vertically infected HIV children and adolescents are predisposed to developing cardiovascular disease (CVD) of which hypertension (HTN) remain a very well-established risk factor from chronic HIV infection, and prolonged use of antiretroviral therapy (ART), [Cruse et al, 2012; Masenga et al, 2019]. HTN prevalence continue to be higher in people living with HIV (PLHIV) despite viral suppression by anti-retroviral therapy (ART), [Freiberg et al, 2013]. A heightened systemic inflammatory process with activation of both innate and adaptive immune systems contributes to the development of HTN in the general population, and animal studies [Donati et al, 2003; Van et al 2014; McMaster et al, 2015]. Inflammation with complex immune interaction in HIV infection is associated with endothelial dysfunction and increases the risk of HTN in both treated and untreated infected

individual [Donati et al, 2003]. Viral proteins and/or ART activates antigen presenting and T cells which infiltrate the vasculature and the kidneys and release cytokines IL-6, IL-17A, and IFN-γ (Fig 1) which promote vascular dysfunction, alteration in sympathetic nervous outflow, retention of sodium, and water, leading to HTN), [Masenga et al, 2019]. Blood pressure (BP), the product of cardiac output and total peripheral vascular resistance is regulated by circulating blood volume, vascular caliber, elasticity, reactivity [Van et al, 2014], humoral mediators, and neural stimulation. HTN defined as systolic blood pressure (SBP) of ≥130 mmHg, and/or diastolic blood pressure (DBP) of ≥80 mmHg is emerging as a growing concern in HIV population [Wilson et al, 2009; Fahme et al, 2018]. This particularly worrisome in sub-Saharan African countries that bears the highest global burden of both HIV and HTN among adult population [WHO, 2022; Ferdinand, **2020].** Information of such is also required in children and adolescents in our sub-region where HIV is also endemic. The prevalence of HTN among PLHIV in adult population has surged from increased life expectancy from use of ART. A study conducted in Kenya, Uganda, Burundi and Zambia reported prevalence of 50% [Dillon et al, 2013], 27% [Migisha et al, 2021], 17.4% [Harimenshi] et al, 2022], and 18.4% [Musekwa et al, 2021] in such population. Its prevalence in children and adolescents living with HIV (CALHIV) ranges from 19.6% by [Chatterton-Kirchmeier et al, 2015] from USA, to 10.9% by [David et al, 2021**]** from Nigeria, and 2.7% by [Sainz et al, 2014] from Spain.

Research into CVD risk factors in general population has identified C reactive protein (CRP) as one of the predictive biomarkers [Ross et al, 2009]. CRP is a homo-pentameric acute-phase inflammatory protein synthesized primarily in liver hepatocytes in response to infection or inflammation [Gabay and Kushner, 1999]. Because CRP levels often go up before appearance of symptoms, and drops at recovery, is especially useful for tracking infections. Studies have also shown that despite the control of HIV replication below the assay threshold (20 to 50 copies/ml), HIV replication persists along with immune activation [Ostrowski et al, 2008]. The ongoing inflammation in spite of treatment with HARRT probably arises from evolving HIV production, co-pathogen load especially of cytomegalovirus (CMV) and herpes viruses, loss of immune-regulatory T cells, translocation of lipopolysaccharide across a damaged gut mucosa, and irreversible fibrosis of the lymphoid infrastructure [Lichtner et al, 2015; Feldman et al, 2003]. HIV is a lifelong infection which requires constant monitoring for ongoing inflammation that can predispose to HTN. We therefore conducted this study to evaluated the CRP concentration in stable CALHIV on HARRT overtime for ongoing inflammatory and HTN.

Material and methods

Study design: A cross-sectional hospital-based survey was carried out at the Paediatric Out-patient Special Treatment Clinic (POSTC) of the University of Abuja Teaching Hospital (UATH) between the months of August to December 2023 to evaluate the level(s) of CRP in stable HIV positive children and adolescents on anti-retroviral-therapy overtime in the facility, and relate the findings to their CD4 cell count, viral load, and blood pressure.

Study setting and population: POSTC is an out-patient clinic service area of the health institution where HIV infected children, adolescents and exposed babies were followed up for treatment and monitoring. It has consulting rooms for the doctors, nurses, and adherence counsellors. Record clerks, pharmacists, nutritionists, and home base-care providers are also at their disposal on week days (Monday-Friday, from 7.30 am to 4 pm.). UATH is a 500-bed capacity referral hospital, sub-serving the people of Federal Capital Territory (FCT) Abuja, and five neighbouring states. It is ~~Is~~

one of the first centres in the country to start offering free HIV/AIDS services through the President Emergency Plan for AIDs Relief (PEPFAR) since 2005, and Federal Government of Nigeria (FGN). The subjects were clinically stable paediatric HIV infected patients ≤18 years, with no clinical evidence of infection such as fever, cough, painful urination, painful swallowing, etc, not having any chronic illness such as diabetics, asthma, heart diseases, and must have been on HARRT for >6 months. Excluded were those unwilling to participate in the study, those with chronic illnesses, and those who has been on HAART for <6months. Consecutive eligible children were enrolled after caregivers has provided written informed consent and children ≥7 years provide inform assent.

Variables: Variables collected included body weight, height, body mass index (BMI), blood pressure, CRP, viral load (VL), and CD4 cell count,

Data collection tool: A structured questionnaire was used to collect their bio-data which included their age, sex, educational status, socio-economic class (SEC) of the parents using Olusanya classification [Olusanya et al, 1985], mode of transmission of HIV, durations of HAART, type of HAART, and parents' survival status.

Data collection: Weight, height was measured, body-mass-index calculated and classified according to WHO (underweight <18.0, normal is 18.5-24.9, overweight is ≥25.0, obesity is ≥30.0). BP was measured twice using (*Accosson Sphygomanometer, Accoson Works, Parkway, CM19 5QP England*) with appropriate cuff for age, and average measurement of the two taken. It was also categorized according to the updated American Academy of Pediatrics definitions of BP for individuals ≥10 years [Flynn et al, 2017]. Accordingly, BP was defined as normal when BP is <120/< 80 mmHg), elevated BP (120/ 80 to 129/>80 mmHg), stage 1 HTN (130/80 to 139/89 mmHg), and stage 2 HTN (≥140/90 mmHg). Subjects with elevated BP (systolic BP ≥ 120 mmHg or diastolic BP ≥ 80 mmHg) were considered to have high BP (HBP), while those with BP (systolic BP <90 mmHg or diastolic BP <60 mmHg) were considered to have low PB (LBP) [Flynn et al, 2017]. Measurement of CD4 cell and VL were done at enrolment, or retrieve from medical record if not recently done. While CD4 cell count was measured using automated Partec Cyflow easy count kit (*Partec code no. 05-8401 Western Germany*), VL was done with (*Roche Smp /prep /cobs Taqman 96, USA)*. Weight and height were measured using Seca weighing scale accurate to 0.1kg, and Seca stadiometer.

CRP was measured using quantitative rapid Fine care test kit catalogue number W201 that employs the sandwich immune detection method. Level <3 mg/l is normal value; 3 to <10 mg/l indicates normal/minor elevation; 10 to <100 mg/l is moderate elevation; >100-<500mg/l mg/dl is marked elevation; while >500 mg/dl represents severe elevation [Nehring et al, 2024]. Or HsCRP levels <1.0 mg/l, 1.0–3.0 mg/l and >3.0 mg/l indicate low, average and high CVD risk, respectively [Pearson et al, 2003].

Sample size: Sample size was calculated using **[**Kish, 1968] sampling method for cross-sectional study with formula, $n= Z^2pq/d^2$, where n=desired sample size (when population is greater than 10,000), Z=standard normal deviate usually set at 1.96, which correspond to 95% confidence interval, p= prevalence of hypertension in Nigerian children and adolescent by [David et al, 2021], q= proportion unknown 1-p, and d=degree of accuracy set at 0.02 for a higher accuracy.

Data analysis: Was carried out using SPSS version 23.0 computer software. This provided frequency tables, mean, standard deviation and ranges. Student t test was used to compare group

means, while chi-square was used to analyze categorical data. Logistic regression was used for the covariates that were significant, and p<0.05 was considered statistically significant.
~~**Ethics clearance**: Was obtained from the ethics committee of the health institution before commencement of the study~~ already given in the end

Results

Socio-demographic analysis: The characteristics of the study population was shown in table 1. Of a total of 126 participants recruited, 66 were males, and 60 females given a male to female ratio of 1.1:1. Their mean age was 14.1±3.1 [7, 18] years with majority 69(54.8%) being between 15-18 years, and least 15(11.9) <10 years. Many 81(64.3%), 91(72.2%), and 82(65.1%) had secondary level of education, were Christians, and from low socio-economic class. They had a mean BMI of 17.6± 3.5 [8.2, 29.6] kg/m2, with majority 73(57.9%) being <18 kg/m2, and least 3(2.4%) between 25-<30kg/m. While majority 99(78.6%) had their HIV infection through vertical transmission, 27(21.4%) had through blood transfusion, sexual, barbering, etc. Most of the participants in this study 90(71.4%) also had both parents alive, however 7(5.6%) and 29(23.0%) has lost both or one parent respectively. Majority of the recruited subjects 104(82.5%) were already on 2nd line HAART, while 22(17.4%) were still on 1st line medication with their mean duration on HARRT being 7.2±2.9[1, 16] years. Their mean CD4 cell count, and VL at enrollment, and CRP into the study were 792.11±37.8 cells/mm^3, 1203.5±155.4 copies/ml, and 9.9±2.7mg/l respectively. The prevalence of HTN was 10(7.9%) with diastolic HTN 7(5.6%) being commoner than systolic 3(2.4%) form. Majority 108(85.7%) had normal SBP with mean of 102.87±11.99 [70, 130] mmHg, while 104(82.5%) had normal DBP with mean of 68.41± 9.6 [50, 90] mmHg. Fifteen (11.9%) had low SBP, and 16(12.7%) had low DBP. There was no statistically significant difference in all the variables studied for the male and the female subjects, their P=0.05.

Descriptive analysis: The levels of CRP of the study population were depicted in Fig 2. It showed that 80 (63.5%) of the subjects had normal CRP of <3mg/ml, 31(24.6%) had normal/slight elevation of 3 to <10mg/l, while 4(3.2%) had 10-<20mg/l, 7(5.6%) had 20-<50mg/l, and 4(3.2%) had >50mg/l ie 15(11.9%) showing moderate elevation of CRP. None had marked or severe elevation.

Bivariate analysis: Table 2 showed the CRP levels of the study participants. More of the subjects with moderate elevation of CRP were females 8(53.3%), those at the age range of 15 to 18 years 7(46.7%), those with BMI of <18kg/m^2 11(73.3%), those from low SEC 10(66.7%), and those with vertical transmission 11(73.3%). Others were those who has lost one 7(53.3%), or both parents 7(46.7%), those with low CD4 count of <200cell/mm^3 8(53.3%), and those with VL >1,000 copies/ml 14(93.3%). Variables with statistically significant relationships with CRP were parental survival status, P=0.001, CD4, P=0.035, and VL, P=0.001, systolic BP, P=.022, and diastolic BP, P=.017. No association was seen with other variables, P >.05.

Multivariate analysis: Table 3 depicts the multivariate analysis of significant variables with bivariate model. Significant relationship was seen between CRP with CD4, [OR 0.11, CI (0.008-1.029, P=0.006)], SBP [OR, 0.26 (0.81-2.97, P=.026)], and DBP [OR, 0.10, CI (0.008-1.029, P=.013)]. No association was seen with the other variables; P >.05.

Table 1: Characteristics of the Study Population based on Gender

Variables	**Male (%), n=66 Mean ± SD**	**Female (%), n=60 Mean ± SD**	**Total (%) [Range], n=126 Mean ± SD**	**P value**
Age (years)	*14.5±2.9	*13.7±3.3	*14.1±3.1 [7, 18]	.150
<10	10(16.7)	5(7.6)	15(11.9)	
10-<15	19(31.7)	23(34.9)	42(33.3)	.290
15-18	31(51.7)	38(57.6)	69(54.8)	
Socio-economic Status				
Upper	6(9.1)	7(11.7)	13(10.3)	
Middle	18(27.3)	13(21.7)	31(24.6)	.723
Low	42(63.3)	40(66.7)	82(65.1)	
Body Mass Index (kg/m^2)				
Mean BMI	*17.3±3.4	*17.9±38	*17.6± 3.5 [8.2, 29.6]	.351
<18	40(60.6)	33(55.0)	73(57.9)	.18
18-24.9	26(39.4)	24(40.0)	50(39.7)	
25-<30	0(0.0)	3(5.0)	3(2.4)	
>30	0(0.0)	0(0.0)	0(0.0)	
Mode of Transmission				
Vertical	48(72.7)	51(85.0)	99(78.6)	

Non-vertical	18(27.3)	9(15.0)	27(21.4)	.598
Parent Survival Status				
Both parents alive	51(77.3)	39(65.0)	90(71.4)	
Both parents dead	5(7.6)	2(3.3)	7(5.6)	.917
One parent dead	12(18.2)	17(28.3)	29(23.0)	
Systolic Blood Pressure(mmHg)				
Mean Systolic BP	103.53±10.89	102.13±13.17	102.87±11.99 [70, 130]	.917
Normal	60(90.1)	55(91.7)	115(91.3)	
High	1(1.5)	2(3.3)	3(2.4)	.282
Low	5(7.6)	3(5.0)	8(6.3)	
Diastolic Blood Pressure(mmHg)				
Mean Diastolic BP	68.18±9.27	68.67±10.16	68.41± 9.6 [50, 90]	.778
Normal	61(92.4)	53(88.3)	113(89.5)	
High	3(4.5)	4(6.7)	7(5.6)	
Low	2(3.0)	3(5.0)	6(4.8)	
1st line HAART	10(15.2)	12(20.0)	22(17.4)	.705
2nd line HAART	53(80.3)	51(85.0)	104(82.5)	.851
Duration of HAART (Years)	*7.1±2.8	*7.3±3.0	*7.2±2.9[1, 16]	.699
CD4 at Study Enrollment (cell/mm^3)	*765.67±401.86	*822.20±344.99	*792.11±37.8	.401
VL at Study Enrollment (copies/ml)	4046.0±199.1	3834.5±224.9	3940.5±255.4	.152
CRP at Enrollment(mg/l)	6.4±1.4	13.7±5.5	9.9±2.7	.183

Table 2: C-Reactive Protein and Study Variables, (n=126).

Variables	**CRP [<3mg/l] n= 80**	**CRP (%) [3-<10mg/l] n=31**	**CRP (%) [10-100mg/l] n=15**	**Total (%) n=126**	**P value**
Sex					
Male	42(52.5)	17(54.8)	7(46.7)	66(52.4)	
Female	38(47.5)	14(45.2)	8(53.3)	60(47.6)	.546
Age (years)					
<10	7(8.8)	5(16.1)	3(20.0)	15(11.9)	
10-<15	28(35.0)	9(29.0)	5(33.3)	42(33.3)	.151
15-18	45(56.2)	17(54.8)	7(46.7)	69(54.8)	
BMI(kg/m^2)					
<18	46(57.5)	16(51.6)	11(73.3)	73(57.9)	
18-24.9	32(40.0)	14(45.2)	4(26.7)	50(39.7)	.574
25->30	2(2.5)	1(3.2)	0(0.0)	3(2.4)	
Socio-economic status					
Upper	8(10.0)	4(12.9)	1(6.6)	13(10.3)	
Middle	16(20.0)	11(35.5)	4(26.7)	31(24.6)	
Low	56(70.0)	16(51.6)	10(66.7)	82(65.1)	.972
Mode of Transmission					
Vertical	71(88.8)	17(54.8)	11(73.3)	99(78.6)	

Non-vertical	9(11.2)	14(45.2)	4(26.7)	28(22.2)	.472
Parents Survival Status					
Both parents alive	72(90.0)	18(58.1)	0(0.0)	90(71.4)	
Both parents dead	0(0.0)	0(0.0)	7(46.7)	7(5.6)	.001
One parent dead	8(10.0)	13(41.9)	8(53.3)	29(23.0)	
Systolic Blood Pressure					
Normal	79(98.8)	27(87.1)	9(60.0)	115(91.3)	
High	0(0.0)	0(0.0)	3(20.0)	3(2.4)	.022
Low	1(1.3)	4(12.9)	3(20.0)	8(6.3)	
Diastolic Blood Pressure					
Normal	76(95.0)	27(87.1)	10(66.7)	113(89.7)	
High	1(1.3)	1(3.2)	5(33.3)	7(5.6)	.017
Low	3(3.8)	3(9.7)	0(0.0)	6(4.8)	
CD4 at enrolment (cells/mm^3)					
<200	0(0.0)	0(0.9)	8(53.3)	8(6.3)	
200- 500	12(15.0)	3(9.7)	3(20.0)	18(14.3)	.035
.>500	68(85.0)	28(90.3)	4(26.7)	100 (79.4)	
VL at enrolment (copies/ml)					
<20	46(57.5)	14(45.2)	0(0.0)	60(47.6)	
20-1000	16(20.0)	13(41.9)	1(6.7)	30(23.8)	.001
>1000	18(22.5.8)	4(12.9)	14(93.3)	36(28.6)	

Table 3: Multivariate logistic regression for CRP with Significant Bivariate Variables.

Variables	**CRP Level**		**OR (95% CI)**	**P value**
	<10mg/l(%)	**>10mg/l (%)**		
Parent survival status				
One parent dead	21(18.9)	8(53.3)	1	
Both parents dead	0(0.0)	7(46.7)	0.65(0.6713-26.785)	
Both parent alive	90(81.1)	0(0.0)	1.35 (0.5231-19.7641)	.48
CD4 cell count (cells/mm3)				
<200	0(0.0)	8(53.3)	1	
200-500	15(13.5)	3(20.0)	0.08(0.061-1.3132)	
>500	96(86.5)	4(27.7)	0.11 (0.008-1.029)	.006
Viral Load (Copies/ml)				
>1000	22(19.8)	14(93.3)	1	
20-1000	29(26.1)	1(6.7)	0.87(0.676-11.3132)	
<20	60(54.1)	0(0.0)	25. (0.0149-4.1723)	.32
Systolic Blood Pressure(mmHg)				
Low	5(4.5)	3(20.0)	1	

High	0(0.0)	3(20.0)	0.26 (0.81-2.97)	
Normal	106(95.5)	9(60.0)	0.18 (0.55-4.89)	.026
Diastolic Blood Pressure (mmHg)				
Low	6(5.4)	0(0.0)	1	
High	2(1.8)	5(33.3)	0.14 (0.35-3.59)	
Normal	103(92.8)	10(66.7)	0.26 (0.81-2.97)	.013

Fig. 1: Conceptual schematic of the effect of HIV infection and treatment can activate the immune system leading to HTN. Viral proteins and/or ART activates antigen presenting and T cells which infiltrate the vasculature and the kidneys and release cytokines IL-6, IL-17A, and IFN-γ which promote vascular dysfunction, retention of sodium, and water, leading to hypertension [Masenga et al, 2019].

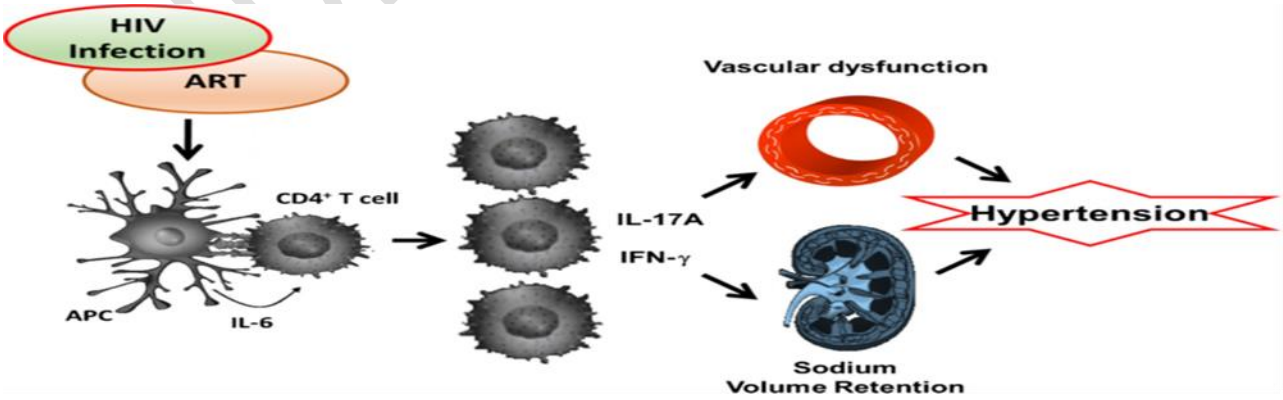
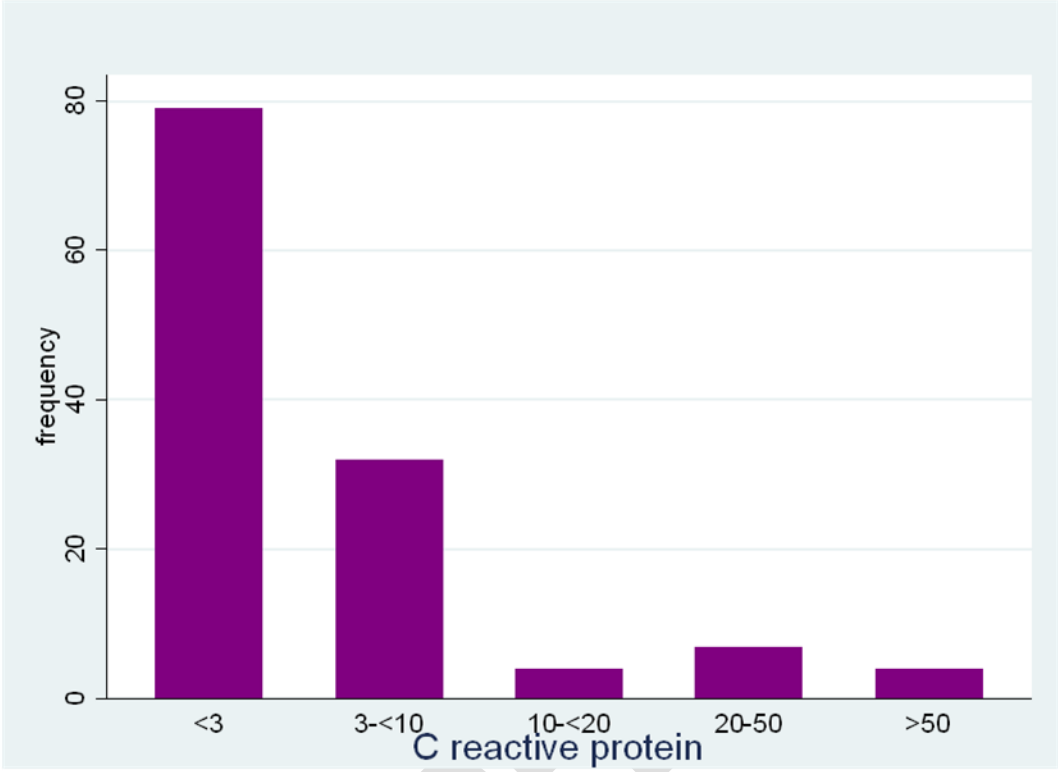


Fig 2: Levels of CRP (mg/l) of the Study Population



Discussion

This study explored the levels of CRP in stable CALHIV on HARRT in our health facility, and relate it to their CD4 celI count, VL, and BP. In this study, the mean CRP in our stable subjects was 9.9±2.7mg/l, in keeping with normal/mild inflammation. This compared favorably to 8.65±10.89 mg/l by [Udoh et al, 2021] among HIV ~~+ve~~positive children on HAART in Nigeria, it also compared to 4.2 (1-13.9) mg/l by same [Udo et al, 2020] among +ve children also from Nigeria, and to 8.1±2.4mg/l and 7.5±12.2mg/l by [Gleason et , 2015] from Ethiopia among +ve adult population, and [Hurwitz et al, 2004**]** also in adults in USA. The finding was however lower than 22.64±12.45mg/l by [Ugwu et al, 2016**]** in adults in Nigeria. The different mean CRP from various studies across the globe might be due to the nature of their study population. While the present study focused on the stable patients on HARRT over time with no clinical evidence of infection, others looked at HARRT naïve patients with opportunistic infections. The study also documented 11.9% of the subjects to have moderate elevation of their CRP. This was also similar to 11.0% elevation in CRP among adults initiated on ART in Uganda by [Chaisson et al, 2019] and much lower than 24% of persistent CRP of >5mg/l also seen in adult patients by [Shivakoti et al, 2016] in their multi-country study. These findings buttress the statement that immune activation continues to occur in PLHIV regardless of the positive outcomes of HAART. [Shivakoti et al,

2016] attributed such persistent increase in CRP to anemia, hypoalbuminemia, concurrent infections, and low-level viremia. Such elevated CRP in this study in spite of clinical stability of the subjects might be from low level viremia, and ongoing inflammation probably from co-infection from other pathogens, as previous report from same center reported CMV [Okechukwu and Thairu, 2020] and hepatitis B and C [Okechukwu et al, 2020] co-infection of 10.6%, and 4.6% among CALHIV on HARRT.

From this study, the prevalence of HTN among CALHIV on ART was 7.9%. This was higher than the pooled prevalence of 4% among the general pediatric population in Nigeria [Ejike, 2017], and globally [Song et al, 2019], probably from effect of their chronic HIV inflammation and prolong use of ART in their cardiovascular system. The prevalence of HTN in PLWH in Sub-Saharan African countries ranged from 2.0 to 50.2% with most cases occurring among those receiving ART [Masenga et al, 2019]. Though the effect of specific ART regimens on BP has not been well established, the low to moderate increase attributed to non-nucleoside reverse transcriptase inhibitors (NNRTI's), and protease inhibitors (PIs) has been reported by some researchers [Bigna et al, 2016; Calò et al, 2013]. Earlier studies have shown patients to become hypertensive in most cases after 2 years of ART, with systolic pressure increasing further after 5 years of ART [Calò et al, 2013]. Aside the traditional risk factors for HTN, and effect of ART on BP, IL-17A, IFN-γ, and CD4+ T cells were among the inflammatory parameters associated with HTN in ART treated PLWH. The prevalence of HTN in PLWH however varies by population, and subgroups even within the same countries. Our findings of 7.9% prevalence of HTN in CALHIV in this study however aligned closer to prevalence of 10.9% by [David et al, 2021] among adolescents with HIV in Nigeria. It was slightly higher than 2.7% from vertically transmitted Caucasian HIV positive adolescents from Spain by [Sainz et al, 2014]. Other studies reported higher prevalence of 19.6%, by [Chatterton-Kirchmeier et al, 2015**]** from USA among positive adolescents, 49% by [Migisha et al, 2023] from CALHIV from Uganda, and 17.4% by [Harimenshi et al, 2022] among positive adults in Burundi. The disparity in the prevalence of HTN from different countries across the globe among both children and adults arises from several reasons; genetic, a well-established risk factor for black population; gender, mostly higher in men than women; socio-economic differences; lifestyle eg tobacco smoking; obesity BMI ≥25 kg/m^2; duration of ART, higher risk with increased duration on ART; clinical stages of HIV infection, higher among ART treated versus ART naive (28.7% vs 5.3%; 17% vs 2%; 30 vs 21.9% and 38% vs 19%, respectively); types of ART, commoner in regimen containing NNRTIs and PIs; and selected study population e.g., hospitalized and outpatients. The prevalence also depends on number of times BP measurement was taken, whether once or twice/three times, because repeated measurements in different occasions are widely recommended for the diagnosis of HTN. While some researchers used single BP measurement for their cohort eg [Chatterton-Kirchmeier et al, 2015] from USA, others such as [Sainz et al, 2014] used 3 BP measurements, while the present study used 2 measurements.

Higher CRP has been associated with lower CD4, and higher VL among infected individuals [Wadgera and Yadhav, 2017]. However, reports from various studies have yielded mixed results [Wadgera and Yadhav, 2017; Drain et al, 2007; Tahir et al, 2004; Grützmeier and Sandström, 1999]**.** While some have reported significant association between increase CRP with faster disease progression; low CD4, and high VL with greater risk of mortality,[40-42] others found elevated CRP to be associated with reduced mortality [Grützmeier and Sandström, 1999; Kiefer et al, 2018]. [Wadgera and Kala-Yadhav, 2017; Tahir et al, 2004], found negative correlation (r=-0.2324, P<0.01), and (r=-0.596 P=0.000) between CRP and CD4 cell count, [Drain et al, 2007] also

observed high CRP to be better than either low CD4 count <200/µl and high VL ≥50,000 copies/ml for predicting disease progression to AIDS. They however stated that while CRP was not better than CD4 or VL in predicting mortality outcomes, it however remained a very strong and almost comparable predictor. Grützmeier and Sandström, 1999, on the other hand reported patients with opportunistic infections with low CD4 cell count to have significantly lower increase in CRP concentration, while Kiefer et al, 2018 reported ART independently of CD4 changes not to be associated with decreases in hsCRP. In the present study, significant association was also documented between CRP and CD4 cell [OR, CI, 0.11 (0.008-1.029, P=0.006)], in keeping with other studies [Drain et al, 2007; Tahir et al, 2004; Grützmeier and Sandström, 1999].

In PLWH, ART does not completely eradicate HIV infection, there is residual virus replicating at low levels over long periods of time that will eventually cause long term micro-inflammation. Impaired immunity, and activate inflammatory pathways induce oxidative stress, leading to endothelial dysfunction, which is a key factor in the pathogenesis of HTN. In the present study, significant association was documented between CRP and SBP [OR, CI, 0.26 (0.81-2.97, P=0.026)], and DBP [OR, 0.10, CI,0.14 (0.35-3.59), P=0.013)]. Similar finding was also recorded by [Ou-Yang et al, 2023]. In their study, ART duration, CD4+ cell counts, HIV-RNA <100 copies/mL, hsCRP, systemic immune- inflammation index (SII), SIRI, were positively associated with hypertensive risk in PLWH. They noted that ART duration of 5 to 9 years and >10 years increased risk of HTN by 7 & 12-folds. **[**Barrow et al, 2019] equally reported strongly association between inflammation and HTN.

Conclusion. There is high prevalence of HTN among HIV positive children and adolescent on HARRT in our center. C reactive protein can be used to monitor risk of development of hypertension in these subjects.

ETHICAL APPROVAL: The study was approved by ethics committee of the health institution please mention the ethical clearance memo number

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

References

1. Cruse B, Cysique LA, Markus R, Brew BJ (2012). Cerebrovascular disease in HIV-infected individuals in the era of highly active antiretroviral therapy. J Neuro-Oncol, 18:264–276. PubMed | Google Scholar.

2. Masenga SK, Hamooya BM, Nzala S, Kwenda G, Heimburger DC, Mutale W, Munsaka SM, et al (2019). Patho-immune mechanisms of hypertension in HIV: A systematic and thematic review. Curr. Hypertens. Rep, 21(7):56. https://doi: 10.1007/s11906-019-0956-5. PubMed | Google Scholar.
3. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al (2013). HIV infection and the risk of acute myocardial infarction. JAMA Intern Med, 173:614–622. https://doi: 10.1001/jamainternmed.2013.3728. PubMed | Google Scholar.
4. de Gaetano DK, Rabagliati R, Tumbarello M, Tacconelli E, Amore C, Cauda R, et al (2003). Increased soluble markers of endothelial dysfunction in HIV-positive patients under highly active antiretroviral therapy. AIDS, 17:765–768. PubMed | Google Scholar.
5. Mian MOR, Paradis P, Schiffrin EL (2014). Innate immunity in hypertension. Curr Hypertens Rep, 16:413. https://doi: 10.1007/s11906-013-0413-9. PubMed | Google Scholar
6. 6. McMaster WG, Kirabo A, Madhur MS, Harrison DG (2015). Inflammation, immunity, and hypertensive end-organ damage. Circ Res, 116:1022–1033. https://doi: 10.1161/CIRCRESAHA.116.303697. PubMed | Google Scholar.
7. Wilson SL, Scullard G, Fidler SJ, Weber JN, Poulter NR (2009). Effects of HIV status and antiretroviral therapy on blood pressure. HIV Med, 10:388–394. PubMed | Google Scholar
8. Fahme SA, Bloomfeld GS, Peck R (2018). Hypertension in HIV-infected adults: novel pathophysiologic mechanisms. Hypertension, 72:44–55. https://doi.org/10.1161/HYPERTENSIONAHA.118.10893. PubMed | Google Scholar.
9. World Health Organization (2022). HIV/AIDS Fact sheet. Accessed 10 July 2022.
10. Ferdinand KC (2020). Uncontrolled hypertension in sub-Saharan Africa: Now is the time to address a looming crisis. J Clin Hypertens, 22(11):2111– 3. https://doi.org/10.1111/jch.14046. PubMed | Google Scholar.
11. Dillon DG, Gurdasani D, Riha J, Ekoru K, Asiki G, Mayanja BN, et al (2013). African partnership for chronic disease research (APCDR) association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis. Int J Epidemiol, 42:1754–71. https:// doi. org/ 10. 1093/ ije/ dyt198. PubMed | Google Scholar.
12. Migisha R, Ario AR, Kadobera D, Bulage L, Katana E, Ndyabakira A, et al (2023). High blood pressure and associated factors among HIV-infected young persons aged 13 to 25 years at selected health facilities in Rwenzori region, western Uganda, September–October 2021. Clinical Hypertension, 29:6. https://doi.org/10.1186/s40885-022-00230-5. PubMed | Google Scholar.
13. Harimenshi D, Niyongabo T, Preux PM, Aboyans V, Desormais I (2022). Hypertensionand associated factors in HIV-infected patients receiving antiretroviral treatment in Burundi: a cross-sectional study. Sci Rep, 12(1):20509. https://doi. org/ 10. 1038/ s41598- 022- 24997-7. PubMed | Google Scholar.
14. Musekwa R, Hamooya BM, Koethe JR, Nzala S, Masenga SK (2021). Prevalence and correlates of hypertension in HIV-positive adults from the Livingstone Central Hospital, Zambia. Pan Afr Med J, 12(39):237. https:// doi. org/ 10. 11604/ pamj. 2021. 39. 237. 29718. PubMed | Google Scholar.

15. Chatterton-Kirchmeier S, Camacho-Gonzalez AF, McCracken CE, Chakraborty R, Batisky DL (2015). Increased prevalence of elevated blood pressures in HIV-infected children, adolescents and young adults. Pediatr Infect Dis J, 34:610–614. PubMed | Google Scholar.
16. David AN, Gbaja-Biamila TA, Odubela OO, Musari- Martins TE, Ezemelue PN, Opaneye BA, et al (2021). Prevalence of hypertension among adolescents living with human immunodeficiency virus in Lagos, Nigeria. Edorium J Pediatr, 5:100009P05DN2021. PubMed | Google Scholar.
17. Sainz T, Álvarez-Fuente M, Navarro ML, Díaz L, Rojo P, Blázquez D, de José MI, Ramos JT, et al (2014). Madrid Cohort of HIV-infected children and adolescents integrated in the Pediatric branch of the Spanish National AIDS Network (CoRISPE). Subclinical atherosclerosis and markers of immune activation in HIV-infected children and adolescents: CaroVIH Study. J Acquir Immune Defic Syndr, 65:42–49. PubMed | Google Scholar.
18. Tungsiripat M, Adell J, McComsey GA (2009). Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy. Clin Infect Dis, 49:1119–1127. PubMed | Google Scholar.
19. Gabay C, Kushner I (1999). Acute-phase proteins and other systemic responses to inflammation. N Engl J Med, 340:448-454. PubMed | Google Scholar.
20. Ostrowski SR, Katzenstein TL, Pedersen BK, Gerstoft J, Ullum H (2008). Residual viraemia in HIV-1-infected patients with plasma viral load < or=20 copies/ml is associated with increased blood levels of soluble immune activation markers. Scand J Immunol, 68:652–60. https://doi:10.1111/j.1365-3083.2008.02184.x. PubMed | Google Scholar.
21. Lichtner M, Cicconi P, Vita S, Cozzi-Lepri A, Galli M, Lo Caputo S, et al (2015). ICONA Foundation Study. Cytomegalovirus coinfection is associated with an increased risk of severe non-AIDS-defining events in a large cohort of HIV-infected patients. J Infect Dis, 211:178–86. https://doi:10.1093/infdis/jiu417. PubMed | Google Scholar.
22. Feldman JG, Goldwasser P, Holman S, DeHovitz J, Minkoff H (2003). C-reactive protein is an independent predictor of mortality in women with HIV-infection. J Acquir Immune Defic Syndr, 32:210-214. PubMed | Google Scholar.
23. Olusanya O, Okpere E, Ezimokhai M (1985). The importance of social class in voluntary fertility control in a developing country. W Afr J Med. 4: 205–12. 33.
24. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al (2017). Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics, 140:e20171904. PubMed | Google Scholar.
25. Rana C, Gareth. Nehring SA, Goyal A, Patel BC (2024). C Reactive Protein. Treasure Island (FL): StatPearls Publishing; 2024 Jan. http://creativecommons.org/licenses/by-nc-nd/4.0/). PMID: 28722873. PubMed | Google Scholar.
26. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M et al (2003). Centers for Disease Control and Prevention, American Heart Association: Markers

of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation, 107:499–511. PubMed | Google Scholar.

27. Udoh OC., Bassey EU, and Dixon-Umo OT (2021). Determinants of raised serum C-reactive protein in HIV infected children on HARRT at University of Uyo Teaching Hospital, Uyo. International Journal of Current Medical and Pharmaceutical Research, 7(4): 5687-5690. PubMed | Google Scholar.
28. Udoh OC, Dixon-Umo OT, Bassey EU (2020). The value of serum C reactive protein in the assessment of severity of HIV infection among children in a resource limited setting. Int J Res Med Sci, 8(8):3007-3012. PubMed | Google Scholar.
29. Gleason RL Jr, Caulk AW, Seifu D, Parker I, Brani Vidakovic B, Getenet H, et al (2015). Current Efavirenz (EFV) or ritonavir-boosted lopinavir (LPV/r) use correlates with elevate markers of atherosclerosis in HIV-infected subjects in Addis Ababa, Ethiopia. PLoS ONE, 10(4): e0117125. PubMed | Google Scholar.
30. Hurwitz BE, Klimas NG, Llabre MM, Maher KJ, Skyler JS, Bilsker MS, Shvawn M, et al (2004). HIV, metabolic syndrome X, inflammation, oxidative stress, and coronary heart disease risk: role of protease inhibitor exposure. Cardiovasc Toxicol, 4(3):303–16. PubMed | Google Scholar.
31. Ugwu MC, Okogun GRA, Okoye CF, Ekebor K., Nwafia CJ, Nnona AE, et al (2016). Human Serum Protein and C-Reactive Protein Levels Among Infected Subjects In Uromi and its Environs in Edo, Nigeria. IJBAIR, 5(3): 74 – 80. PubMed | Google Scholar.
32. Chaisson LH, Semitala FC, Asege L, Mwebe S, Katende J, Nakaye M, et al (2019). Point-of-care C-reactive protein and risk of early mortality among adults initiating antiretroviral therapy. AIDS, 33(5): 895–902. https://doi:10.1097/QAD.0000000000002130. PubMed | Google Scholar.
33. Shivakoti R, Yang W, Berendes S, Mwelase N, Kanyama C, Pillay S, et al (2016). Persistently elevated c-reactive protein level in the first year of antiretroviral therapy, despite virologic suppression, is associated with HIV disease progression in resource-constrained settings. JID, 213(1): 1074- 1078. https://academic.oup.com/jid/article/213/7/1074/2912159. PubMed | Google Scholar.
34. Okechukwu AA, and Thairu Y (2020). Cytomegalovirus co-infection with HIV in children and adolescents on antiretroviral therapy in Abuja, Nigeria. Afr. J. Clin. Exper. Microbiol, 21 (1): 36 – 44. PubMed | Google Scholar.
35. Okechukwu AA, Thairu Y, Dalili MS (2020). HIV Co-Infection with Hepatitis B and C and Liver Function in Children and Adolescents on Antiretroviral Therapy in a Tertiary Health Institution in Abuja. West Afr JNl of Med, 37 (3): 260-267. PubMed | Google Scholar.
36. Ejike CECC (2017). Prevalence of hypertension in Nigerian children and adolescents: A systematic review and trend analysis of data from the past four decades. J Trop Pediatr, 63(3):229–41. PubMed | Google Scholar.

37. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K et al (2019). Global prevalence of hypertension in children: A systematic review and meta-analysis. JAMA Pediatr, 173(12):1–10. PubMed | Google Scholar.
38. Bigna JJR, Nansseu JRN, Um LN, Noumegni SRN, Simé PSD, Aminde LN, et al (2016). Prevalence and incidence of pulmonary hypertension among HIV-infected people in Africa: a systematic review and meta-analysis. BMJ Open, 6:e011921. PubMed | Google Scholar.
39. Calò LA, Caielli P, Maiolino G, Rossi G (2013). Arterial hypertension and cardiovascular risk in HIV-infected patients. J Cardiovas Med, 14:553–8. PubMed | Google Scholar.
40. Wadgera N, and Kala Yadhav ML (2017). C-reactive protein as an early marker of opportunistic infections in HIV. J AIDS Clin Res, 8:(6): 46- https://DOI: 10.4172/2155-6113-C1-017. PubMed | Google Scholar.
41. Drain PK, Kupka R, Msamanga GI, Urassa W, Mugusi F, Fawzi WW (2007). C reactive protein independently predicts HIV related outcomes among women and children in a resource poor setting. AIDS, 21:2067 75. PubMed | Google Scholar.
42. Tahir A, Yusuph H, Bakki B, JibrinYB (2004). Correlation between c-reactive protein and CD4+ cell count in HIV-infected and HIV/PTB co-infected patients at the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Nigeria. Highland Med Res Journal, 2(2): 9-18. PubMed | Google Scholar.
43. Grützmeier S, Sandström E (1999). C reactive protein levels in HIV complicated by opportunistic infections and infections with common bacterial pathogens. Scand J Infect Dis, 31:229 34. PubMed | Google Scholar.
44. Kiefer EM, Hoover DR, Shi Q, Dusingize JC, Sinayobye JD, Anastos K (2018). Longitudinal evaluation of markers of inflammation in HIV-positive and HIV-negative Rw andan women. HIV Medicine, 19:734—744. https://DOI: 10.1111/hiv.12665. PubMed | Google Scholar.
45. Ou-Yang H, Fu H, Luo Y, Xu Z, Liu J, Gao R, et al (2023). Inflammation markers and the risk of hypertension in people living with HIV. Frontiers in Immunology. 10.3389/fimmu.2023.1133640. PubMed | Google Scholar.
46. Barrows IR, Ramezani A, Raj DS (2019). Inflammation, immunity, and oxidative stress in hypertension-partners in crime? Adv Chronic Kidney Dis, 26(2):122–30. https://doi: 10.1053/j.ackd.2019.03.001. PubMed | Google Scholar.

47. Abbreviations

48. AIDS
49. CRP0
50. CMV
51. CDV
52. ART
53. HARRT
54. HTN
55. HIV
56. BMI

57. PLHIV
58. CALHIV
59. SBP
60. DPB
61. HBP
62. LBP
63. POSTC
64. UATH
65. FCT
66. SEC
67. PEPFAR
68. NNRTIs
69. PIs
70. VL
71. SPSS
72. HsCRP
73. SII
74. SIRI
75. SEC