 doi:10.20944/preprints202208.0370.v1

Article

Medium-Long Term Impacts of Antiretroviral Drugs on Arterial Blood Pressure in People Living with HIV in Malawi

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Abstract

Introduction: We aimed to explore the medium-long term impacts of Anti-Retroviral Treatment (ART) on Hypertension in a sample of HIV-positive in Malawi. **Methodology**: This was a retrospective case control study carried out at DREAM health Centre in Blantyre/Malawi on patients who were enrolled from **2005 to 2019,** Information about age, gender, blood pressure, ART regimen, BMI, CD4 count, Viral load, Biochemistry, hemoglobine, marital status, education level, survival and period on ARVs were retrieved from data base from 01/01/2006 to 31/12/2015.. In total, we enreolled (alive and on HAART)1350 patients > 18 years (mean age: 43.4 and the SD was ±10.7 with 1031 (65.9%) females and 534 (34.1%) males who were taking (or have taken) ARVs for more than 6 months at the date of enrollment and who were not affected by hypertension or potentially related diseases like Renal failure at the enrollment. The mean observation time, from the HAART initiation was 77 months per person (SD±40). **Results**: The sample was made up by two groups of patients, 675 who developed hypertension and 675 who did not, with similar age and gender composition. Among patients with hypertension, 30/675 (4.4%) developed a stage 3 hypertension, 154 a stage 2 (22.8%) and 491 a stage 1 (72.8%). Hypertension stages were not associated to statistic significant differences of age and/or gender(p=0.422, p=0.281 respectively). At baseline, patients who developed hypertension showed higher hemoglobin, higher CD4 count and lower VL(P<0.001). Patients on AZT-based regimen and TDF based regimen were at high risk to develop hypertension while PI-based regimen was protective to hypertension(P<0.001). In a multivariate analysis, factors independently associated to Hypertension were higher CD4 count and Body Mass Index at the visit date, while Baseline Viral Load and PI-Including regimes were protective factors. Education level was inversely associated with risk of hypertension, while being married was associated of risk of hypertension (p<0.001). Mortality rate

 doi:10.20944/preprints202208.0370.v1

among hypertensive patients was 1.6% for those traited for hypertension against the 3.6% for those not treated.

Conclusion: this study shows a protective action of PI-including regimens compared with AZT based regimen that is associated to an increased risk of hypertension. Factors related to a better general health status are associated to an higher risk of hypertension as well as lower education, older age and male gender. Treatment should be started as soon as Hypertension stages 2-3 are reached and control by behavioral factors is no longer effective.

Keywords: Hypertension; HIV; ARVs

INTRODUCTION

Globally, 37 million people are living with the HIV virus. [1] Since the year 2000, the number of individuals with access to antiretroviral therapy (ART) has significantly increased from 700 000 to >16 million. [1, 2] Widespread ART use has halved the HIV-related mortality rate, from an estimated 2 million deaths in 2005 to 1 million in 2016 [1, 2]. However, during the same time period cardiovascular disease mortality rates more than doubled in people living with HIV [3]. Hypertension is the leading risk factor for mortality worldwide and it is a growing problem in HIV-infected adults [4]. HIV-infected adults on ART have a higher prevalence of hypertension when compared with HIV-uninfected individuals [4–6].

Globally, hypertension caused approximately 12.8% of all deaths in 2012. This accounted for 3.7% disability adjusted life years (DALYS) in the same year [7]. Across the WHO regions, the prevalence of raised blood pressure was highest in Africa, where it was 46% for both sexes combined. Both men and women have high rates of raised blood pressure in the Africa region. The lowest prevalence of raised blood pressure was in the WHO Region of the Americas at 35% for both sexes. Men in this region had higher prevalence than women (39% for men and 32% for women). In all WHO regions, men have slightly higher prevalence of raised blood pressure than women. This difference was only statistically significant in the Americas and Europe. An interesting meta-analysis published by Okechukwu S Ogah and all in recent advances in hypertension in sub-Saharan Africa took into consideration 38 publications from SSA partly carried out in urban areas and partly in rural ones-. This studies found a Prevalence of hypertension among the general population at 47% in Niger, 44.9% in Malawi, 44.2% in Seychelles,

44% in Sierra Leone. It was projected from these studies that Hypertension prevalence in Africa will reach 66 % in 2025 in the general population.

Fig 1-Recent estimated prevalence of raised blood pressure in Africa according to countries by the WHO

The values for urban studies ranged from 15.2% in the Democratic Republic of Congo to as high as 47.5% in Cameroon.

Table 1-Prevalence of hypertension in some selected African countries

No	Country	Population 2010	Men	Women	All
1	Niger	155111953	52.5	42.8	47.8
2	Sao Tome and Principe	168397	46	43.2	44.5
3	Ivory Coast	19737800	44.1	38.6	41.5
4	Mozambique	23390765	46.7	43.3	44.4
5	Seychelles	86518	46.6	41.8	44.2
6	Namibia	2283289	45.1	41.8	43.4
7	Malawi	14900841	45.6	41.4	43.4
8	Cape verde	455999	46.8	41.9	44.1
9	Zambia	13088570	41.3	39	40.1

Source WHO, NCD Country profile 2011.

In addition, HIV-infected adults with hypertension have a higher risk of cardiovascular events and all-cause mortality than HIV-uninfected adults with hypertension or HIV-infected adults with normal blood pressure. A prospective cohort study of >80 000 HIV-infected and uninfected American veterans followed 6 years on average, for example, found that HIV-infected adults with hypertension had a 2-fold higher risk of incident acute myocardial infarction as compared with HIV-uninfected adults with hypertension [1-2].

 doi:10.20944/preprints202208.0370.v1

Sub Saharan Africa (SSA) has the highest burden of HIV/AIDS, with an estimated 25.8 million people living with HIV and about 1.4 million new infections in 2014 [7]. Antiretroviral Therapy (ART) has improved the quality of life of People Living With HIV (PLWH) and has improved life expectancy substantially [9-10]. By June 2015, 15.8 million PLWH were receiving ART globally, of which 10.7 million were in SSA [7]. As people on ART live longer, challenges of long-term HIV infection, lifestyle changes, aging and the toxic effects of ART, are emerging. Risk factors for Cardiovascular Disease (CVD) among PLWH may be similar to the general population and include family history, age, male gender, hypertension, smoking, obesity, diabetes mellitus and hyperlipidemia [10]. PLWH on ART have an estimated 10-year risk of developing CVD greater than 20% of people who are HIV positive but not on ART [11]. The expected deaths attributable to CVD are projected to double to 2.4 million in 2030 relative to reports from 2000 [12]. Mortality due to CVD in SSA including Uganda is estimated to be threefold higher than in Western Europe [13]. In industrialized countries where ART has been provided for longer periods, ART agents, particularly Protease Inhibitors (PI), have been associated with cardio metabolic risk factors, including impaired glucose metabolism, dyslipidemia, obesity and hypertension [14] but this has not been demonstrated in African settings where most of the HIV patients start HAART without knowing their baseline parameters like BMI, Viral load, creatinine, Heamoglobine... There is evidence to suggest that baseline metabolic profiles and associations between HIV, ART and cardio metabolic risk factors may differ between populations; in fact baseline glycaemia, blood pressure, LDL, BMI, total triglyceride was associated with cardiovascular risk with $p<0.001$, the causes of differences between different populations remains unclear, the African Americans and the black Africans has got high risk of developing

hypertension due to lack of awareness, early treatment and prevention of hypertension Several studies among young adults have reported higher hypertension incidence rates for blacks compared with whites. In the Bogalusa Heart Study, blacks had an increased risk of hypertension compared with whites after 15 years of follow-up from childhood to young adulthood.27 In the Coronary Artery Risk Development in Young Adults Study, a prospective cohort study of adults age 18 to 30 years at baseline, blacks had a higher incidence of hypertension compared with whites over a 10-year follow-up period.6 In addition, in the National Health and Nutrition Examination Survey I Epidemiological Follow-Up Study, blacks had a higher incidence of hypertension than whites over 9.5 years of follow-up, with differences by age.7 At ages 25 to 34 years, the incidences of hypertension among black men and women (27.3% and 23.6%, respectively) were 2 times higher than white men and women (11.9% and 8.1%, respectively).

Similar differences were also noted for the 35- to 54-year age group; however, hypertension incidence rates were similar among blacks and whites at ages >55 years. In a secondary analysis of clinical trial participants ages 30 to 54 years at baseline who were followed for 7 years, the incidence of hypertension was similar for blacks and whites. The previous study was a secondary analysis of clinical trial participants identified through an employer screening program in a single community, whereas the current study participants were from a population-based sample of multiple communities across the United States. In the Atherosclerosis Risk in Communities Study, a prospective cohort study of adults ages 45 to 64 years at baseline, blacks had a higher overall incidence of hypertension compared with whites over 3 years of follow-up.9 The Atherosclerosis Risk in Communities Study used the same definition of hypertension as applied in the current study, and the higher incidence of hypertension for blacks compared with whites was present overall and within age strata (50 years and >50 years) after 6 years of follow-up[15].

1-The link between hypertension and HIV treatment

Hypertension and Human Immunodeficiency Virus (HIV) infection are chronic conditions which are asymptomatic and manageable in early stage [16]. The interaction between hypertension and HIV is complex. Renal insufficiency due to HIV infection contributes to secondary hypertension [17–19]. The HIV infected patients on ART live longer and gain weight. Weight gain is a risk factor of hypertension [16].

Weight gain can also be a side effect of ART medicines. ART medicines such as ritonavir-boosted lopinavir (protease inhibitors), efavirenz and tenofovir are associated with hypertension [18]. This is mediated through their side effects. Studies show that insulin resistance precedes lipodystrophy that is connected to weight gains. The antiretroviral medication, especially protease inhibitors, can increase insulin resistance and cause lipotoxocity and HIV-associated lipodystrophy leading to cardiovascular pathology. This includes the ability of PIs to directly and/or indirectly alter body fat composition [6,7], lipid profiles [8], adipocytokine levels [9], and mediators of inflammation [10]. In addition, the potential for nucleoside reverse transcriptase inhibitor (NRTI)-induced changes in mitochondrial function to also influence insulin sensitivity has recently gained greater attention [11]. The complexity of antiretroviral regimens employed in clinical practice, including frequent changes in therapies, have hindered efforts to identify the direct effects of individual PIs on tissue whole-body glucose homeostasis. However, in the search for safer anti-retroviral agents, increased understanding of the direct molecular targets of PIs, offers great potential in ongoing efforts to design and test for newer generations of drugs that in addition to overcoming the problem of viral resistance also have improved safety profiles. This is particularly important given the expectations for long-term PI exposure in aging HIV infected populations. The clinical use of HIV protease inhibitors in HIV positive humans is clearly associated with the development of measurable changes in insulin sensitivity [12]. In many patients, when combined with underlying genetic risk, environmental factors, and other components of highly [20-21]. This results in metabolic syndrome and eventually hypertension. Tenofovir causes renal tubular toxicity resulting in renal dysfunction and eventually hypertension especially when there is pre-existing renal disease [22–24].

Although all hypertensive patients are at risk of uncontrolled hypertension, those who are HIV positive and on ART have higher risk [17-18].

2-The link between HIV infection and cardiovascular diseases

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Cardiac abnormalities in HIV-positive persons were noted as early as 1989 [25-26] (pre-HAART era) and included dilated cardiomyopathy, endo-, myo- and peri-carditis, and pulmonary hypertension [25-28].

In Ethiopia, Maya Korem and coll in 2017 found obesity, family history, advanced age, diabetes, and metabolic syndrome to be associated with hypertension. These are the known risk factors for Hypertension, closely related to insulin resistance in the general population.

One of the largest studies on Hypertension done in the world showed that Patients with HIV have a higher prevalence of hypertension than closely matched HIV-negative controls, as investigators from the Netherlands report in the online edition of Clinical Infectious Diseases. Moreover, hypertension in patients with HIV was associated with changes in body composition, including both abdominal obesity and fat wasting associated with stavudine, an older Nucleoside Reverse Transcriptase Inhibitor (NRTI), which although now little used in richer countries was until recently a mainstay of antiretroviral regimens in resource-limited settings (87).

However, Feinstein MJ and coll [3] found that the overall prevalence of hypertension was 31% and was similar among those receiving and not receiving HAART (32% vs. 29%, p = 0.47). Factors associated with hypertension in the multivariate model included increasing age, longer duration of HIV, higher body mass index, and diabetes, with a trend for African American ethnicity.

. Chronic immune activation presents a challenge to the myocardium and some studies emphasized its role as a crucial factor in HIV-mediated onset of heart diseases. For example, Becker et al. [29] found that HIV infected HAART naïve patients with acute coronary syndrome (ACS) exhibited less traditional CVD risk factors than their HIV-negative counterparts (with ACS). Moreover, such individuals displayed a significantly higher thrombotic burden and distinct angiographic characteristics.

Similar results were reported by other studies [30-31] and the data point towards a distinct pathogenesis of cardiovascular abnormalities in HIV-infected compared to healthy individuals. HIV-positive patients with Acute Cardiovascular Syndrome (ACS) were compared to HIV-negative and diabetic non-ACS counterparts, and although the extent of multi-vessel disease in all three groups was similar; HIV-positive individuals were much younger and exhibited less complex lesions than matched controls [29]. Furthermore, the degree of subclinical coronary atherosclerosis was elevated within the HIV-infected population [31]. Therefore the nature of HIV itself allows for viral-mediated activation of pathways

(especially inflammatory) that contribute to the development of thrombotic and atherosclerotic disease progression in addition to the traditional risk factor pathways.

ARVs inhibit the viral lifecycle at key stages and the combination of different drug classes (as HAART) constitutes critical weaponry in the fight against HIV/AIDS (Fig2). PIs act by inhibiting HIV aspartyl protease leading to the production of immature and non-infectious viral particles [32]. Several HIV-PI-type drugs were developed since the advent of HAART in 1995 [33], with Lopinavir/Ritonavir widely used globally and currently the only available PI in South African clinics. Focusing on the Lopinavir/Ritonavir, both are heterocyclic compounds with the liver a major site for Lopinavir metabolism. After uptake, Lopinavir is released into circulation where most of it binds to plasma proteins [34] Where after it can be taken up, to varying degrees, by most tissues including the heart (based on study in animal model) [49]. Lopinavir is metabolized to a number of oxidative metabolites; although the parent compound is the major circulating drug with only a small percentage of metabolites present [34-35], PIs are implicated in the development of cardiovascular complications with greater risk for Acute Myocardial Infarction (AMI) and coronary syndromes. One of the largest clinical studies assessing the risk for AMI with HAART—the Data Collection for Adverse events of Anti- HIV Drugs (DAD) Study Group—recruited 23, 468 HIV-positive patients on ART [39-41] and established that cumulative HAART exposure was linked to a robust increase for AMI (26% relative change). Here the HIV PIs contributed the most significant risk to AMI onset. Although the absolute risk for AMI was low when adjusted for confounding parameters, HAART and PIs exacerbated traditional CVD risk factors such as cholesterol, lipid abnormalities, and diabetes.

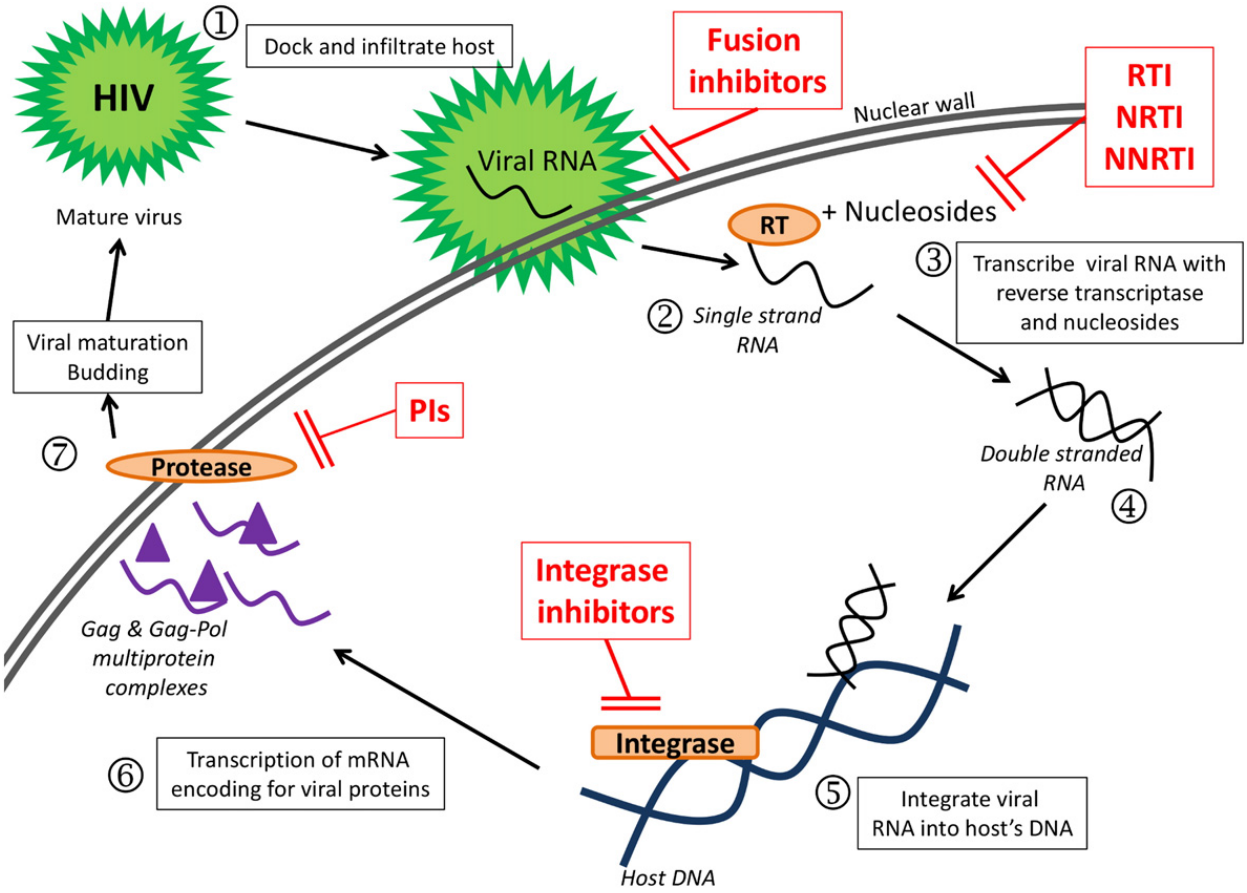

Fig. 2. HIV lifecycle and antiretroviral drug targets. 1. The virus docks and infiltrates the cell membrane of the host cell; 2. Single-strand viral RNA enters the host nucleus; 3. Viral reverse transcriptase transcribes single-stranded RNA; 4. Production of double-stranded RNA; 5. RNA enters the nucleus and integrates itself within the host's DNA with integrase; 6. The host's transcription system allows viral mRNA production for viral proteins; and 7. Gag and Gag-pol multi-protein complexes assemble and bud at the host's cell wall where proteases cleave proteins and mature viral particles. HAART can inhibit key viral enzymes at various stages of the viral life cycle—fusion inhibitors, reverse transcriptase (RTI), nucleosides and nonnucleoside reverse transcriptase inhibitors (NRTI, NNRTI), integrase inhibitors and protease inhibitors (PI). HIV—human immunodeficiency virus.

High burden of undiagnosed and untreated hypertension in people living with HIV in Malawi.

There is high and increasing burden of hypertension in Malawi in the general population and specifically among people living with HIV.[42, 43]

In Malawi, the prevalence of Hypertension varies from one group to another, in 2009, according to the WHO STEPS survey (by definition, STEPS State Tobacco Education Prevention. STEPS is a WHO-developed, standardized but flexible framework for countries to monitor the main NCD risk factors through questionnaire, assessment and physical and biochemical measurements. It is coordinated by national authorities of the implementing country) done by the ministry of health, the hypertension prevalence was 35% among adults, which is lower than the result found by the WHO/NCD result in 2011 which found 43.4% among adults; we note that the prevalence of hypertension is increasing from year to year; 94% of these patients are unaware and therefore untreated [44-46]. In a small HIV-infected

cohort in Blantyre, 46% of patients were found to have elevated blood pressure [45]. The lack of a well-organized and funded national hypertension screening and treatment programme leaves hypertension in patients poorly managed [47-49].

There exists a high burden of undiagnosed and untreated hypertension within Malawi's HIV infected population. Africa is facing a growing double burden of communicable and non-communicable diseases. It is projected that by 2025 nearly three-quarters of people with hypertension will be living in developing countries. Hypertension is expected to lead to more deaths in Africa than infectious diseases in the next 20-30 years.[47,48] Malawi is facing a high prevalence of hypertension in the general population. Whilst only limited data exists, the burden of hypertension in Malawi in people living with HIV appears to be at least as common as in the general population.

Research Question:

We Aim to find medium-long term impacts of ARVs on blood pressure.

Methodology

This is a case control study carried out at DREAM health Centre Blantyre/Malawi under the DREAM 2.0 program.

Information about age, sex, blood pressure, ART regimen, BMI, CD4 count, Viral load, Biochemistry, full blood count, marital status, education level, survival and period on ARVs were retrieved from the DREAM program data base. Informed consent from the patients is collected at the beginning of care to analyze the data gathered on a routine basis by the program.

The study involved all the Electronic Medical Records of the DREAM data base at 10/10/2015

Exclusion criteria

1. Patients who were not taking arvs or the ones who were taking arvs from less than 6 months.
2. Patients younger than 18 years at the time they started arvs,
3. Patients who were affected by hypertension or related disease at the time when they started ARVs

The study involved **1350** patients aged over 18 years (mean age: 43.4 and the SD was ±10.7 with 1031 (65.9%) females and 534(34.1%) males who were taking ARVs for more than 6 months at the date of enrollment and who were not affected by hypertension or related diseases like Renal failure.

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Table 3. gender

	Frequency	%	% value	Cumulative %
F	1031	65,9	65,9	65,9
M	534	34,1	34,1	100,0
Total	1565	100,0	100,0	

The patients have been divided in subgroups according to the ARV drugs taken (PI based, d4Tbased, AZT based and TDF based regimens).

The analysis was carried out keeping into account two main end-points:

1. Having developed Hypertension

2. Death

The second end point was achieved by a prospective cohort analysis approach starting from the enrollment visit in advance until the end of February 2019.

Hypertension was defined according the following criteria:

1. Prehypertension/no hypertension was defined as normal blood pressure with Systolic Blood Pressure (SBP) 120–139 mmHg or Diastolic Blood Pressure (DBP) 80–89 mmHg.

2. Stage 1 Hypertension was defined as SBP > 139 mmHg<159 or DBP >90 and <99 mmHg measured at least two times

3. Stage 2. Hypertension was defined as SBP> 160 and DBP>100

4- Stage 3/Severe hypertension was defined as SBP<180 and/or DBP>110

Use of protease inhibitors (PIs) was defined as being prescribed any of the locally available PIs which include lopinavir, ritonavir or darunavir and Atazanavir

BMI was defined and categorized according to standard international definitions: Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m2). More than 25…was category 1 and less that 25 was category 0.

Creatinine measurements in micromoles per liter were converted to milligrams per deciliter and dichotomized in two categories according to the threshold of 1.20

Glomerular filtration rate was estimated using the abbreviated Modified Diet in Renal Disease equation formula Cochroft [20]. CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72).

 doi:10.20944/preprints202208.0370.v1

Blood sample was collected at base line (before ART initiation) and the first viral load control and cd4 count at 6 months and then routine Viral load control every year while. Routine biochemistry and full blood count were controlled every 6 months.

Descriptive analyses were performed to display the overall distribution of the cardiovascular, clinical and HIV-related risk factors for men and women. Continuous variables are displayed as mean and SD or as median and interquartile range. For our descriptive analyses, Categorical variables are expressed as proportions.

Categorical variables have been compared by the Pearson CHI-Square test, while continuous ones by T-TEST. Multivariate Analyses have been performed to establish the inference of the different risk factors on the outcomes. All these analysis have been carried out using SPSS 25.0 statistical package. The analysis is designed to describe the relation between several risk factor for hypertension with the two end-points reported above.

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RESULTS

In total, we analyzed 1350 patients from January 2006 to December 2016, 675 of participants developed hypertension during this period and 675 did not develop hypertension representing 50% each group.

The analysis is designed to describe the relation between several risk factor for hypertension with the two end-points reported above. The mean age was 43.2026 for the non-hypertensive patients and 42.5783 for hypertensive patient, p=0.281, the mean difference was not significant and the p value shows that age is similar in the two group. Gender was equally distributed too, between the two samples

Table 4 distribution of the sample according to hypertension

		frequency	%	% cumulative
values	Non hypertension	675	50,0	50,0
	hypertension	675	50,0	100,0
	Total	1350	100,0	100

Table 5. Mean age according to diagnosis of hypertension

	hypertension	N	Mean	std. deviation	Standard mean error
age	Non-Hypertension	675	43,2026	10,97274	0.42234
	Hypertension	675	42,5783	10,30152	0.39651

Table 6. Hypertension by gender

	Hypertension	Total	

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			Non Hypertension	Hypertension		CHI-SQUARE
Sex	F	N	451	437	888	p=0.422
		%	50,8%	49,2%	100,0%	
	M	N	224	238	462	
		%	48,5%	51,5%	100,0%	
Total		N	675	675	1350	
		%	50,0%	50,0%	100,0%	

Gender…M=Male, F=female

Table 7. Stage of hypertension

		Frequency	%	% cumulative
value	prehypertension	675	50,0	50,0
	Stage 1	491	36,4	86,4
	Stage 2	154	11,4	97,8
	severe	30	2,2	100,0
	Total	1350	100,0	

Table 8. Description of age according to hypertension stage

	N	mean	std. deviation	95% CI of mean		p
				lower limit	upper limit	
Pre hypertension	675					
Stage 1	491	43,2026	10,97274	42,3734	44,0319	0.115
Stage 2	154	42,2969	9,49939	41,4546	43,1393	
severe	30	42,6799	11,80284	40,8009	44,5588	
Total	1350	46,6620	13,71411	41,5411	51,7829	

From the above table, the mean age according to level of hypertension is similar in the three levels of hypertension and at 95% of CI the p>0.05 shows that there is no statistic significant differences among the groups (Anova Test)

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Table 9. CREAT BL HEMO BL BMI BL VL BL CD BL by hypertension
(Baseline parameters)

hypertension		CREAT BL	HEMO BL	BMI BL	VL BL	CD4 BL
Non	Mean	0.9949	11.244	21.4392	97418.388	222.43
hypertension	N	603	671	666	675	675
	SD	2.88428	5.9574	4.63046	141749.925	192.067
Hypertension	Mean	0.7443	12.038	23.2317	19330.240	383.88
	N	209	629	671	611	627
	SD	0.24251	2.0729	4.46985	68813.336	220.688
Total	Mean	0.9304	11.628	22.3388	60317.409	300.18
	N	812	1300	1337	1286	1302
	SD	2.49045	4.5321	4.63638	119619.375	221.491

According to the baseline parameters, we noticed that the mean creat was high among non-hypertensive patients compare to hypertensive patients (0.99 vs 0.74), also the mean HB was low among non-hypertensive patients compare to hypertensive patients (11.2 vs 12.03)

For the Viral load, the mean was higher in non-hypertensive patients compare to hypertensive patients (97418 copies vs 19330), the mean of viral load for non-hypertensive patients was 5 times higher than hypertensive patients;

For the CD4 count Baseline, we noticed the mean for non-hypertensive patients was half of the mean for hypertensive patients(222.43 cells vs 418 cells) with total mean of 300 cells. Taking into consideration the BMI, again higher values correlate with the development of hypertension since non hypertensive patients had a mean of BMI=21,43, while the mean BMI for hypertensive patients was 23.15, meaning the hypertensive patients had about 1.8 point higher BMI compare to non-hypertensive patients. All this explains that most of our patients who developed hypertension during the period of the study came for the first time at the clinic in better health (good BMI, good CD4 count, good HB, good creatinine) than the ones who did not develop hypertension.

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Table 10. CREAT BL HEMO BL BMI BL VL BL CD BL * level_hypert						
level_hypert		CREAT BL	HEMO BL	BMI BL	VL BL	CD BL
prehypertension	Mean	0.9949	11.244	21.4392	97418.38815	222.43
	N	603	671	666	675	675
	SD	2.88428	5.9574	4.63046	141749.925054	192.067
Stage 1	Mean	0.7385	12.055	23.1540	21132.55955	371.87
	N	148	459	489	445	460
	SD	0.24630	2.1470	4.41300	69204.919744	220.450
Stage 2	Mean	0.7682	11.992	23.4562	16025.31206	418.36
	N	55	145	153	141	140
	SD	0.23502	1.8662	4.64454	73219.215874	221.307
severe	Mean	0.6667	11.980	23.3569	5888.76000	409.63
	N	6	25	29	25	27
	SD	0.22792	1.8837	4.60071	12925.203855	207.843
Total	Mean	0.9304	11.628	22.3388	60317.40980	300.18
	N	812	1300	1337	1286	1302
	SD	2.49045	4.5321	4.63638	119619.375892	221.491
Mann-Whitney U test	p	<0.001	<.001	<.001	<.001	<.001

According to the level of hypertension and baseline parameters, we found that the mean creat base line was very similar for hypertension stage 1, 2, and severe(0.73, 0.76 and 0.66 respectively). The same similarity was noticed for HB baseline regarding hypertension level, 12 for stage 1, 11.99 for stage 2 and 11.98 for severe hypertension with $p<0.001$; for the VL base line regarding to level of hypertension, we found that only pre-hypertensive patients had high VL at baseline with 97418, while for stage 1 hypertension, the mean for viral load was 21132 copies/ml; for stage 2 hypertension, we found 16025 copies/ml and for sever hypertension, we found mean viral load at 5888 copies /ml.The p value is less than 0.001 which shows there is an relationship between viral load baseline and risk of developing hypertension. Mean CD4 count baseline regarding the level of hypertension shows baseline cd4 count mean low in non-hypertensive patients compare to hypertensive patients ($p<0.001$), statistically significant; the same for the BMI, at the three levels of hypertension, the BMI was higher compare to non- hypertensive patients(23vs21) $p<0.001$

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Table 11. Association of hypertension according to baseline creatinine

creatinine			hypertension		Total	CHI-Square
			Non	with		p
	<1	N	555	653	1208	p<0.001
		%	45.9%	54.1%	100.0%	
	>1	N	120	22	142	
		%	84.5%	15.5%	100.0%	
Total		N	675	675	1350	
		%	50.0%	50.0%	100.0%	

Among our participants, patients with hypertension and creatinine baseline over 1 represented 54.1%; while for non- hypertensive, patient's creat over 1 represented 84.5%.

The Chi Square test shows p<0.001 which means that hypertension is more likely to happen in people with low creatinine.

Table 12. Incidence of hypertension according to BMI baseline

			hypertension		Total	CHI-SQUARE
			No	With		
BMI BL2	<25	N	547	491	1038	p<0.001
		%	52.7%	47.3%	100.0%	
	>25	N	128	184	312	
		%	41.0%	59.0%	100.0%	
Total		N	675	675	1350	
		%	50.0%	50.0%	100.0%	

BMI baseline: among patients with hypertension, 184/312 had hypertension with BMI over 25 at the base line representing 59%, while patients without hypertension, 52.7 % had BMI<25, the P value is less than 0.001 meaning that patient with high BMI at base line are more likely to develop hypertension

Table 13. Viral load base line

			hypertension		Total	CHI SQUARE
			N0	With		
VL BL2	<1000	N	91	475	566	p<0.001
		%	16.1%	83.9%	100.0%	
	>1000	N	584	200	784	
		%	74.5%	25.5%	100.0%	
Total		N	675	675	1350	
		%	50.0%	50.0%	100.0%	

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Viral load Baseline: In our cohort, patients who had viral load less than 1000 copies/ml, 475/566 developed hypertension representing 83.9%, for patients who had Viral load baseline over 1000 copies/ml, 584/784 did not develop hypertension representing 74.5%, p<0.001, meaning people with high viral load are at less risk to develop hypertension.

Table 14. hypertension according to CD4 Baseline

			hypertension			
			No	With	Total	CHI SQUARE
CD4 BL	<350	N	534	356	890	p<0.001
		%	60.0%	40.0%	100.0%	
	>350	N	141	315	456	
		%	30.9%	69.1%	100.0%	
Total		N	675	671	1346	
		%	50.1%	49.9%	100.0%	

CD4 Count Baseline: in Total, 890 patients had CD4 count baseline < 350 cells/ml and among this group, 356 patients developed hypertension representing 40%, for those with CD4 count over 350 cell/ml, we had a total of 456 and among this group, 69.1% developed hypertension with p<0.001, which means, patients with CD4 count over 350 cells/ml are more likely to developed hypertension.

Table 15. Mean Creat Hemo BMI VL CD4 * hypertension FUP

hypertension		Creat	Hemo	BMI	VL	CD4
Non	Mean	0.8998	12.361	21.9687	11856.77630	436.30
	N	473	672	661	675	675
	SD.	0.33175	2.0962	4.52700	59954.514091	243.213
With	Mean	0.9045	12.817	23.6887	3455.50815	438.66
	N	436	671	671	675	675
	SD	0.41070	1.9020	4.88142	17857.862185	204.618
Total	Mean	0.9021	12.589	22.8351	7656.14222	437.48
	N	909	1343	1332	1350	1350
	SD	0.37152	2.0137	4.78509	44417.692517	224.665

Hypertension according to the follow up parameters.

From the table above, we noticed that the mean creatinine is very similar from hypertensive to non-hypertensive clients, (0.904 vs 0.899) this tells us that the health conditions of our clients have been improved by the ART treatment, high creat is related to kidney damage but ART treatment had improved

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the health conditions of these patients; this is why the mean creat for hypertensive patients and non hypertensive patients is very similar. The same scenario is found with heomoglobine follow up, we found that the mean hemoglobin is similar for non-hypertensive and hypertensive patients (12.36 vs 12.81)

CD4 count: we found the follow up CD4 count mean was 436 cells/ for non-hypertensive patients vs 438 cells/ml for hypertensive patients, this also shows that the follow up CD4 count is almost the same for non-hypertensive patients vs hypertensive patients, the difference is very slim, while at the base line, the CD4 count for non hypertensive patients was half of hypertensive patients, this is the good effect of the ART. After being on ART the immunologic conditions are improved.

Viral load follow up: we noticed also the reduction of the gap between non hypertensive and hypertensive, the difference is 8401, the mean VL follow up is 11856 copies/ml while the mean for the hypertensive patients is 3455 copies/ml, the difference at baseline between hypertension and non-hypertension was 78,088 copies/ml, this shows again the impact of the ART treatment, we notice a very good improvement in term of VL and in doing so, patients also improve their health conditions

Table 16. Creat Hemo BMI VL CD4 * level_hypert FUP

Level of hypertension		Creat	Hemo	BMI	VL	CD4
Pre-hypertension	Mean	0.8998	12.361	21.9687	11856.77630	436.30
	N	473	672	661	675	675
	SD.	0.33175	2.0962	4.52700	59954.51409	243.213
Stage 1	Mean	0.9163	12.860	23.8023	2990.07943	436.54
	N	328	489	487	491	491
	SD	0.45766	1.8796	4.90303	16777.96629	209.232
Stage2	Mean	0.8480	12.725	23.3159	4790.51299	456.64
	N	88	153	154	154	154
	SD	0.19826	1.7630	4.81155	21864.04645	192.472
severe	Media	0.9585	12.576	23.7583	4220.00000	381.10
	N	20	29	30	30	30
	SD	0.23813	2.8235	4.95396	10935.17110	180.878
Total	Mean	0.9021	12.589	22.8351	7656.14222	437.48
	N	909	1343	1332	1350	1350
	SD	0.37152	2.0137	4.78509	44417.69251	224.665
Kruskal wallis test		p<0.001	P<0.001	P>0.1	P>0.1	P>0.1

Hypertension level according to the follow up parameters.

Ceatinine follow up: We noticed as mentioned before that there is a reduction of gap between hypertensive patients and non-hypertensive patients, we see that the creatinine level is very similar for

non-hypertensive patients across the three level of hypertension(0.8998, 0.916, 0.8480, 0.9585 respectively)

Hemoglobin follow up vs level of hypertension: similar situation is also noticed with hemoglobin and hypertension levels, since all of the hypertensive patients, irrespective their level, have got around 12 g/dl as hemoglobin very similar to those with non-hypertension (p<0.001)

BMI follow up: for the BMI follow up, the situation resemble to the previous one, the BMI for the hypertensive patients is still high compare to non-hypertensive patients but with a reduction of the difference, we noticed an improvement in term of BMI for the non-hypertensive patients from 21.43 to 21.96; for hypertensive patients, we also noticed an increase of BMI from 23.23 at base line to 23.67 for the follow up.

Table 17. Incidence of hypertension according to first and second line ARV treatment.

			hypertension			CHI SQUARE before
			No	With	Total	
First line regimen	ABC-based	N	7	0	7	p<0.001
		%	100.0%	0.0%	100.0%	
	Azt-based	N	43	28	71	
		%	60.6%	39.4%	100.0%	
	d4t-based	No	587	644	1231	
		%	47.7%	52.3%	100.0%	
	Tdf-based	N	28	3	31	
		%	90.3%	9.7%	100.0%	
	PI-including	N	10	0	10	
		%	100.0%	0.0%	100.0%	
Total		N	675	675	1350	
		%	50.0%	50.0%	100.0%	

The previous ART line was the regimen that our patients were taking before changing to a new regimen due to change of policy, side effect or treatment failure. In most of the cases, this the first regimen was started after Knowing to be HIV positive.

According to the first line ART regimen and the presence of hypertension, we found that majority of our patients were on Stavudine based regimen (91.8%). Those are also the patients who were more likely developing hypertension (p=0.001). However, we should take into account that the majority of

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these patients shifted to different ARV regimens because of several causes, and this shift should be taken into account in order to assess the factors associated to hypertension.

Table 18. Hypertension according to the ART regimen at the enrollment

			hypertension		Total	CHI square
			No	With		
ARV regimen	PIbased	N	55	45	100	p<0.001
		%	55.0%	45.0%	100.0%	
	aztbased	N	84	94	178	
		%	47.2%	52.8%	100.0%	
	d4tbased	N	197	1	198	
		%	99.5%	0.5%	100.0%	
	tdfbased	N	339	535	874	
		%	38.8%	61.2%	100.0%	
Totale		N	675	675	1350	
		%	50.0%	50.0%	100.0%	

The current ART line is the ART regimen each participant is taking during the enrolment.

The Table above(18) shows that 535/874 clients who were on Tenofovir based regimen during the enrollment developed hypertension representing 61.2%, while 45/100 patients on Protease inhibitors (45%), and 94/178 receiving AZT based regimen, (52.8%)

Table 19. Incidence of hypertension according to education level

			hypertension		Total	CHI SQUARE
			No	With		
Education	No education	N	53	117	170	p<0.001
		%	31.2%	68.8%	100.0%	
	primary	N	324	276	600	
		%	54.0%	46.0%	100.0%	
	secondary	N	265	248	513	
		%	51.7%	48.3%	100.0%	
	Tertiary/university	N	33	34	67	

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		%	49.3%	50.7%	100.0%	
Total		N	675	675	1350	
		%	50.0%	50.0%	100.0%	

The Incidence of hypertension according to the education level: in our cohort, we found that 117/170 hypertensive patients had no education meaning did not go to school, representing 68.8% of the total number of patients who did not go to school and we can say that being low educated was related to the presence of hypertension and statistically significant with p<0.001, while 34/67 among the university patients representing 50.7% had hypertension.

Table 20. Hypertension level according to education

			level_hypert					CHI Square
			prehypertension	Stage 1	Stage 2	severe	Total	
Education	No education	N	53	84	27	6	170	p<0.001
		%	31.2%	49.4%	15.9%	3.5%	100.0%	
	primary	N	324	197	68	11	600	
		%	54.0%	32.8%	11.3%	1.8%	100.0%	
	secondary	N	265	183	53	12	513	
		%	51.7%	35.7%	10.3%	2.3%	100.0%	
	tertiary	N	33	27	6	1	67	
		%	49.3%	40.3%	9.0%	1.5%	100.0%	
Total		N	675	491	154	30	1350	
		%	50.0%	36.4%	11.4%	2.2%	100.0%	

When we did the Chi-square test to find out the interaction of education level and the hypertension level, we found:

For non-educated patients, stage 1 hypertension dominated with almost half of the patients 84/170 representing 49.45% followed by pre-hypertensive patients with 53/170 representing 31.2%, this means that with the stage of hypertension, the stage 1 was 71.79% of the non-educated patients, with p<0.001, statistically significant.

Among the primary level patients, we noticed that 324/600 had prehypertension representing 54%, with p<0.001.

For secondary level patients, we also noticed that over half (51.7%) 0265/513 of them had prehypertension with p<0.001 meaning that being at secondary level is not related to a risk of hypertension

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For the university level, we noticed that 40.3% had hypertension stage 1(27/67)

Table 21. Incidence of hypertension according to marital status

			hypertension		Total	
			Non	yes		
M.Status	divorced	N	71	68	139	p=0.001
		%	51.1%	48.9%	100.0%	
	single	N	75	37	112	
		%	67.0%	33.0%	100.0%	
	Married	N	395	473	868	
		%	45.5%	54.5%	100.0%	
	widow	N	134	97	231	
		%	58.0%	42.0%	100.0%	
Total		N	675	675	1350	
		%	50.0%	50.0%	100.0%	

According to the marital status, in total we had 868/1350(64.29%) married patients men and women followed by widow 231/1350(17.11%) , we found that being married represented 54.5% of hypertension against 45.5% for non hypertension with P<0.001; while being single, the hypertension rate was 33%(37/112), the single patients had got less risk of developing hypertension. For divorced or separated patient, the rate was closer for hypertension and non-hypertension (48.9% and 51.1% respectively, for those who were widow, we noticed that over half had no hypertension58% vs 42% for non- hypertension with p<0.001,

Table 22. Incidence of hypertension according to marital status

			level_hypert				Total	CHI-SQUARE
			Pre-hypertension	Stage 1	Stage 2	severe		
M.Status	separated	N	71	49	17	2	139	P=0.001
		%	51.1%	35.3%	12.2%	1.4%	100.0%	
	single	N	75	28	9	0	112	
		%	67.0%	25.0%	8.0%	0.0%	100.0%	
	married	N	395	341	107	25	868	
		%	45.5%	39.3%	12.3%	2.9%	100.0%	
	widow	N	134	73	21	3	231	
		%	58.0%	31.6%	9.1%	1.3%	100.0%	
Total		N	675	491	154	30	1350	

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	%	50.0%	36.4%	11.4%	2.2%	100.0%	

After doing the CHI-Square test to see the interaction between hypertension level and marital status; we found that among the divorced, 71/139 had no hypertension, but 49/139 had hypertension stage 1 representing 35.3%, for patients who were not married(singles), we found 67% (75/112) had no hypertension.

Among those with hypertension, hypertension level1 was the highest with 28/37(75.67%), for those married, we noticed a predominance of pre-hypertension with 45.5% followed by hypertension stage 1(39.3%), then stage 2 (12.3%) and stage 3 with 2.9%. But overall, the hypertensive patients represented 54.5% with p=0.001, while for the widow, we noted a predominance of prehypertension with 58%, followed by hypertension stage 1, 2 and 3 (31.6% 9.15% 1.3%) respectively

Overall, among those with hypertension, we noticed that hypertension stage one was the most common representing 491/675(72.74%)

After doing the logistic regression test, we found that the risk of developing hypertension is related to lower Education level, current ART regimen (regimen : AZT and TDF based regimen), lower base line Viral load, higher base line BMI and BMI after follow up with p<0.05.

Table 24. Multi variable Logistic Regression

dependent variable: Hypertension

Model		Coefficient		Standard Coefficient		
		B	Errore standard	Beta	T	Sign.
1	(Costante)	0.748	0.047		15.982	<0.001
	Education	-0.047	0.014	-0.071	-3.260	0.001
	Marital .Status	-0.006	0.014	-0.009	-0.433	0.665
	current ART Line	0.052	0.011	0.100	4.558	<0.001
	Viral load	-0.039	0.030	-0.029	-1.296	0.195
	BMI	0.084	0.027	0.073	3.112	0.002
	Viral Load Base line	-0.566	0.022	-0.558	-25.356	<0.001
	BMI Base line	0.073	0.028	0.062	2.631	0.009

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Table 25. Mean time on ART according to regimens

Current line		Current ART days	Previous ART days	Total ARV days
PI-including	mean	593.3500	2027.6400	2620.9900
	N	100	100	100
	SD.	936.06924	741.76189	1200.76662
Azt based	mean	1578.3315	1163.5730	2741.9045
	N	178	178	178
	SD.	920.12162	717.72352	1050.06434
d4t based	mean	970.3687	98.0859	1068.4545
	N	198	198	198
	SD.	879.72214	208.80238	863.12975
Tdf based	mean	581.8410	1908.6876	2490.5286
	N	874	874	874
	SD	967.84949	614.13547	1103.48013
Total	mean	771.0667	1553.6993	2324.7659
	N	1350	1350	1350
	SD	1005.96557	887.57021	1194.24323

According to days on HAART, we noticed that patients on PI based regimen had got less days on HAART with mean days of 2620, but most of these patients were on other regimen either on D4T or AZT based regime; During the current Art days, we found a mean time of administration of 593 days for PI based patients, while for the previous HAART, regimen the mean was 2027 days with SD±741.76. Patient on AZT based regimen experienced 2741.90 days on first line HAART, but when we consider days on current HAART, we found 1578.33, which is three times for the PI based ; most of these patients had been on AZT for long time ago, because after changing the policy in Malawi in 2011, AZT remained still one of the first choice drugs in the country; For D4T based regimen, we noticed a particularity, the mean days on first line ART(previous ART) were 98 and for the current HAART the mean days were 970. This is understandable because in 2011, D4T was withdrawn from the ART

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regimen in the country and most of patients who are still recorded as on D4T regimen for the current ART line are those who died, or transferred out or abandoned. At the beginning of the ART program in MALAWI, many patients were in stage 3 or 4 and many of them died or changed the drugs to TDF in 2011 when TDF began the main first line ART recommended. The mean days on TDF current line was= 581.84 and mean days on previous line was=1908.68, in total the mean days on ART was=2490.52

This is due to protocol change, in 2011, TDF was introduced to replace D4T due to its side effects like lipodystrophy and lactic acidosis

Table 26. Incidence of hypertension according to ARV regimen at the enrollment adjusted for education at baseline and BMI. CD4 count and Viral load at visit date.

	B	Sign.	OR	95.0% CI Inferior	Superior
Azt-based		0.001	1		
PI-based	-0.468	0.036	0.627	0.405	0.969
TDF-based	-0.457	0.000	0.633	0.500	0.801
Education	-0.285	0.000	0.752	0.659	0.859
BMI	0.330	0.008	1.391	1.092	1.773
CD4	-0.219	0.044	0.803	0.648	0.994
VL Base line	0.827	0.000	2.286	1.842	2.838

Taking out D4T because many patients who started ARVs with stavudine died.

We noticed that the incidence of hypertension was related to AZT based current line with p=0.001; PI based regimen with p=0.036 but protective with 95% CI(lower 0.405 and upper 0.969) meaning patients who were on PIs based regimen had less risk of developing hypertension, also TDF based regimen (OR=0.633; CL95% 0.500-0.833; p<0.001) therefore both regimens (TDF and PIs) showed a protective effect on the development of hypertension compared with the AZT-based regimen. Most of our clients who were on Stavudine based regimen at the beginning of the ART were substituted to Tenofovir based regimen after the protocol was changed in the country in 2011 due to side effects related to Stavudine. Education level was associated to the development hypertension with p<0.001 with low education related to the presence of hypertension, higher BMI base line and follow up were associated to an increased risk of developing hypertension p=0.008, as well as higher base line CD4 count even if p=0.044 is very close to 0.05. Finally low baseline Viral load was related to a risk of hypertension with p<0.001 with low baseline viral load related to the onset of hypertension.

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Table 27 Descriptive table highlighting association between ART regimens and period of ART days

ART DAYS		N	Mean	SD .	Error std.	95% CI of mean		minimum	Maximum	p
						lower	upper			
From ART-initiation to second line -initiation	PI-based	100	2027.6400	741.76189	74.17619	1880.4583	2174.8217	0.00	3788.00	<0.001
	Tdf-based	782	1957.6049	599.38883	21.43410	1915.5296	1999.6801	7.00	4003.00	
	Azt-based	270	1275.7852	691.56806	42.08749	1192.9224	1358.6480	-14.00	3891.00	
	Total	1152	1803.8828	699.07304	20.59664	1763.4717	1844.2940	-14.00	4003.00	
From second line initiation to enrollment date	PI-based	100	593.3500	936.06924	93.60692	407.6136	779.0864	-2073.00	2406.00	0.318
	Tdf-based	782	743.6547	868.56022	31.05965	682.6844	804.6250	-2099.00	3124.00	
	Azt-based	270	770.1259	1397.21095	85.03155	602.7139	937.5379	-1827.00	3331.00	
	Total	1152	736.8116	1022.53754	30.12680	677.7020	795.9212	-2099.00	3331.00	
From enrollment date to censor date (28.02.2019)	PI-based	100	1178.1300	856.77592	85.67759	1008.1271	1348.1329	28.00	3472.00	<0.001
	Tdf-based	782	1282.3696	790.64010	28.27323	1226.8690	1337.8701	5.00	3276.00	
	Azt-based	270	1507.6037	1062.74769	64.67676	1380.2667	1634.9407	2.00	3748.00	
	Total	1152	1326.1102	873.03551	25.72206	1275.6429	1376.5776	2.00	3748.00	

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The first line treatment at country level was stavudine-based regimen for all HIV positive patients. The protocols run by the DREAM program before 2012 encompassed the use of AZT-based regimen during pregnancies because of their effectiveness already showed in other countries. Many HIV positive women, at the end of the pregnancy, remained in that regimen. This is the possible explanation of the longer time on AZT based regimen in our cohort. However, patients who died before changing treatment have been excluded from the analysis, because their mean observation time was clearly lower than the others and this showed they were in worse condition at baseline.

Taking into consideration the time on ART, we noted that according to previous ART taken by patients. the mean days on PI-based regimens was 2027 days (SD±741.76189) this number is also taking into account those who were on Stavudine because PIs are not an indication for first line ART regimen in Malawi, so patients switched to PIs because of treatment failure and hardly because of side effect (and this is considered as non -standard regimen); for the Tenofovir based regimen, we noted that majority of patients 782/1152 representing 67.88%, with mean of days on HAART=1957.6049 SD=599.38883 were on tenofovir based regimen, for the same reason mentioned above, most of these patients who were on Stavudine before but some they started straight on tenofovir based regimen in 2011 when the policy was changed.

After doing the Anova test; we see that the risk of developing hypertension is related to the previous line which the patient was taking and this can be explained by the long period on ART ($p<0.001$), but for the current ART regimen, the $P=0.318$($p>0.05$) so no relation between ART current line and risk of hypertension, after taking into consideration the total time on ART, we also see clearly the relation between the time on HAART and the risk of developing hypertension with $p<0.001$. After doing the multivariable regression test, we notice that when PIs are combined with AZT, patients are more likely to develop hypertension with $p<0.001$, the same when AZT

Table 29. Hypertension according to ARV regimen adjusted for education at baseline and BMI. CD4 count and Viral load at visit date. Logistic Regression Variable: hypertension = 1 vs no hypertension = 0

	B	Sign.	OR	95% C.I.	
				Lower	Upper
AZT-Based		0.060	1.000		
PI-based	-0.232	0.490	0.793	0.411	1.532

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TDF-based	0.352	0.082	1.422	0.957	2.114
Education	-0.268	0.014	0.765	0.617	0.948
Age	-0.007	0.434	0.993	0.977	1.010
Baseline Haemoglobin (less than 10.0 gm/100ml vs more than 10.0)	0.147	0.465	1.158	0.782	1.715
Baseline BMI (less than 25.0 vs more than 25.0)	0.453	0.017	1.573	1.083	2.284
Baseline Viral Load (less than 1000 c/ml vs more than 1000)	-2.817	0.000	0.060	0.041	0.086
Baseline CD4 count (less than 350 cells/ηL vs less than 350)	0.214	0.221	1.239	0.879	1.746
Total Time on HAART (less than 1500 days, 1500-2500, 2501-3600, more than 3600)	-1.153	0.000	0.316	0.265	0.377

Risk of developing hypertension.

The multivariable analysis (Tab 29) shows the statistic significant association of higher time on HAART are also associated with the Risk of developing hypertension.

For education level, we noticed that the B=-0.268 and p=0.014, OR=0.765(95% CI: 0.617-0.948) meaning that the more you increase your education level the more you are protected to hypertension.

For Age we found the B=-0.007, p=0.34 statistically no significant, the OR=0.99 at 95% CI (0.911-1.010) meaning that the impact of age on developing hypertension in this sample is minimum if any.

For Hemoglobine base line we noticed B=0.14 and p=0.465 and OR=1.15 at 95% CI (0.782-1.715)this shows that there is an increase risk related to an increase of HB, this correlate to our first statement that patients in better health is at high risk of developing hypertension

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Baseline BMI, in this parameter we found that B=0453, p=0.017 and OR=1.573 at 95% (1.083-2.284) statistically significant.

Baseline VL, in this parameter we found a negative B with -02817 and p=0.000, OR=0.060 at 95% CI (0.041-0.086) which is statistically significant, this means that patient with VL less than 1000 copies at baseline had an increased risk of developing hypertension

CD4 count baseline, the situation is the opposite, patients with CD4 count over 350 had an increased risk of 1.239 to develop hypertension though statistically not significant

For Total time on ART, we notice that patients who had long period on HAART increased their hypertension risk by 0.36, with p=0.000 and B=-1,153

. Table 30. mean

Total time on ARVs (Days) according to Hypertension and Hypertensive treatment

	Mean	N	SD
No Hypertensive Patients	3112,4854	478	1036,18549
Hypertensive patients not on Hypertension treatment	1935,0000	545	
Hypertensive patients on Hypertension treatment	2980,9070	129	631,68832
Total	2540,6944	1152	1107,19305

When comparing the time on HAART, we found that the mean of patient not hypertensive is 3112 days while the mean for hypertensive patients not on BP drugs was 1980, the mean days for hypertensive patients on BP drugs was 2980 days, almost double for the hypertensive patient not on BP drugs; this explain that hypertensive patient on BP drugs live more than patient with hypertension without BP drugs

Table 31. correlation

		Total Time on BP drugs
Total time on ARVs	Pearson Correlation	0.435
	Two tales stat. Significant	<0.001
	N	128

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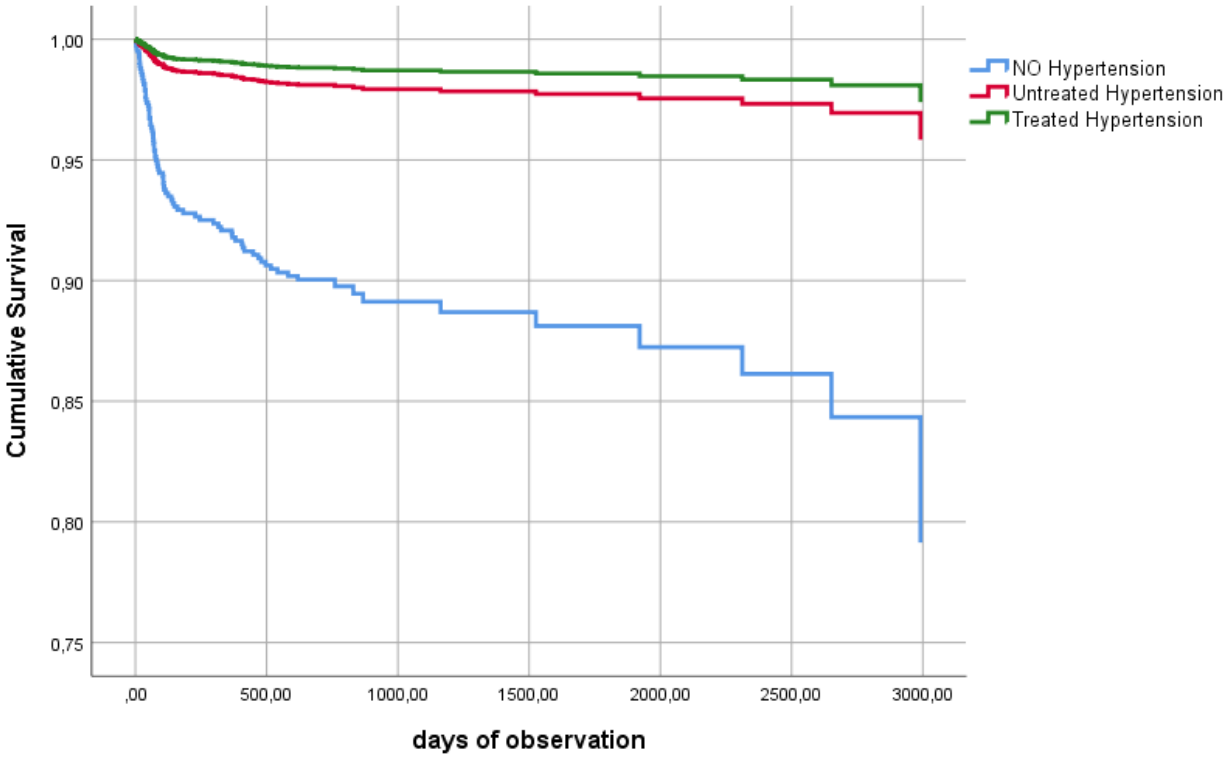

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Fig 32. Cumulative survival according to Hypertension and Hypertensive treatment adjusted for Age, Gender, Education, BMI, CD4 count, Viral load and ARV regimen – (Cox Proportional Hazard Risk)

	B	Sign.	RR	95,0% CI	
				Lower	Upper
Age (continuous variable)	-0.007	0.481	0.993	0.972	1.013
Gender (Male vs Female)	-0.230	0.336	0.794	0.497	1.270
Education (no education/ primary education/ secondary education/degree – continuous variable)	-0.208	0.187	0.812	0.597	1.106
Viral Load (<1000 c/ml vs ≥ 1000 c/ml)	-0.557	0.041	0.573	0.336	0.978
CD4 Count (<350/ηL vs 350-500 vs >500)	-0.567	0.000	0.567	0.426	0.756
BMI (<18 vs 18-20 vs >20)	-0.552	0.000	0.576	0.437	0.759
AZT based (point of reference)			1.000		
PI based	**-0.735**	0.043	0.479	0.235	0.979
TDF based	**-0.859**	0.001	0.424	0.261	0.689
Hypertension and Treatment			1.000		
No treatment Hypertension	2.181	0.003	8.854	2.130	36.799
Treated Hypertension	0.476	0.529	1.609	0.366	7.069

The graph above shows that the survival is lower in patients without hypertension, and most of this patients are those who were on stavudine and started HAART with very bad health conditions, while for hypertensive patient, we notice a longer period of survival in patients with hypertension and treated with BP drugs compare to patients with hypertension without BP treatment

In this sample we cannot find a clear impact of kind of ARV treatment on development of hypertension. Most important seems to be life style and BMI and Education. Longer time on arvs seems to be associated to the development of hypertension, but this evidence could be biased by the baseline condition of the different subsamples. In the comparison among the different kinds of treatment age and gender did not seem to play a major role.

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DISCUSSIONS

Impact of different ARV regimens on Hypertension

Infection with human immunodeficiency virus (HIV) and treatment with antiretroviral may affect the Heart functions and its structures. Endothelial dysfunction is followed by clinical manifestations of atherosclerosis [55, Celermajer 1997]. The Mechanism of HIV related endothelial dysfunction is not clear, the atherogenic profile is likely to increase the cardiovascular risks including infarction and premature atherosclerosis [56 Metha and Reilly in 2005]. The suspicion that the use of HAART increases the cardiovascular risk and its complication is still under dispute by some researchers based on the fact that atherosclerosis of the heart may take 10-15 years and the use of HAART 2-3 years cannot develop hypertension[57 Martin and all in 1999].

In this study, the development of hypertension in HIV positive patients on HAART was related to days on HAART.

NRTI: Stavudine (D4T) based regimen: Certain nucleoside reverse transcriptase inhibitors may also play some role in the pathophysiology of hypertension in HIV-infected adults, although data are conflicting. One prospective cohort study of 444 HIV-infected adults without hypertension at baseline, found that combination therapy with lamivudine and tenofovir as compared with lamivudine and zidovudine was associated with an increased risk of hypertension (OR, 2.3; 95% CI, 1.0–5.2; *P*=0.046) [58]. Similarly, a sub analysis of a prospective cohort study of 527 HIV-infected and 517 HIV-uninfected adults found that prior stavudine exposure was independently associated with hypertension (OR, 1.54; 95% CI, 1.04–2.30). Other studies, including our own, have shown no relationship between nucleoside reverse transcriptase inhibitor use and hypertension [59]

There have been fewer studies exploring the association between non-nucleoside reverse transcriptase inhibitors and hypertension. However, a prospective open-label clinical trial that evaluated the cardiometabolic outcomes after HIV-infected participants, were switched from an older generation (nevirapine) to a newer generation non-nucleoside reverse

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transcriptase inhibitors (rilpivirine) demonstrated a mean systolic blood pressure decrease of 6.0 mm Hg (95% CI, −1.7 to −10.3; *P*=0.007) after 24 weeks of therapy [60]

For D4T based regimen we noticed a particularity, the mean days on first line ART (previous ART) were 98 and for the current HAART, the mean days were 970, this is understandable because in 2011, D4T was withdrawn from the ART regimen in the country and most of patients who are still recorded as on D4T regimen for the current ART line are those who died, or transferred out or abandoned. At the beginning of the ART program in MALAWI, many patients were in stage 3 or 4 and many of them died or changed the drugs to TDF in 2011 when TDF became the main first line ART recommended in the country. According to the first line ART regimen and the presence of hypertension, we found that majority of our patient were on Stavudine based regimen (91.8%). Those are also the patients who were more likely developing hypertension (p=0.001). However we should take into account that the majority of these patients shifted to different ARV regimens because of several causes, and this shift should be taken into account in order to assess the factors associated to hypertension, similar result was fund by [61] Micheal Carter who found in 2016 a relationship between Stavudine and risk of hypertension with p<0.002.

For the Tenofovir based regimen, we note the highest number of patients 782/1152 representing 67.88%, with mean of days on HAART=1957.60, SD±599.38., For the same reason most of this patients were on Stavudine before but some they started straight on tenofovir based regimen in 2011 when the policy was changed. After doing the Anova test we see that the risk of developing hypertension is related to the previous line that the patient was taking and this can be explained by the long period on ART with p<0.001, but for the current ART regimen the p-value=0.318 showed that no relation between ART current line and risk of hypertension can be observed. We also see clearly the relation between the total time on HAART and the risk of developing hypertension with p<0.001, as other Authors like [62] Robert A Ngala and Flutse Fianko found a significant cardiovascular risk among patient who used NRTIs.

For patients who were on Zudovidine (AZT) based regimen, Patient on AZT based regimen experienced 2741.90 days on first line HAART, but when we consider days on current HAART we found 1578.33, which is three times for the PI based ; most of these patients had been on AZT for long time ago, because after changing the policy in Malawi in 2011, AZT remained still one of the first choice drugs in the country. The use of AZT was significantly associated to the development of hypertension in our cohort with p<0.001, probably due to the long period on AZT, as already explained, though the policy changed in 2011 . Robert A Ngala and Flutse[62] found the same correlation between AZT use and hypertension, they also found a correlation between the time on AZT and hypertension with p<0.001, in their result, they found the risk of developing systolic and diastolic hypertension for HAART-experienced group was about 5 times compared to the HAART- naive group. Also 11.6% (18/164) diastolic hypertensive HAART-experienced participants used d4T/3TC/NVP and 3.9% (6/164), 5.2% (8/164) and 1.9% (3/164) diastolic hypertensive patients used d4T/3TC/EFV, AZT/3TC/NVP and AZT/3TC/EFV, respectively.

According to days on HAART; we notice that patients on PI based regimen had got less days on HAART with mean days of 2620, but most of these patients were on other regimen either on D4T or AZT based regime

For the current ART days, we found a mean time of administration of 593 days for PI based patients, while for the previous HAART regimen the mean was 2027 days with SD=741.76189, this is understandable from the fact that less than 5% of our patients on HAART had got treatment failure as PIs are used for second intension for treatment failure, we found that Patients on PIs had less risk to develop hypertension mainly when PIs are associated with TDF p=0.299 but when PIs are associated with zudovidine, we noticed statistic significant regarding hypertension with p=0.001, there was a strong associated between TDF use based regimen and AZT used as previous line with p<0.001 for the development of hypertension, all these results are seen in the above table 28, we also found that being in good health was a risk of developing hypertension and the baseline parameters showed this relation, those who had high CD4 count,

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low viral load, good hemoglobin, high BMI had high risk of developing hypertension with p<0.001, our result is in line with the results found by Crane and all[63] in 2006 who found Lopinavir/ritonavir was significantly associated with an increased incidence of new-onset hypertension (OR, 2.5; P=0.03)

PIs have been implicated in the pathophysiology of hypertension in HIV-infected adults through numerous mechanisms including RAAS(renin–angiotensin–aldosterone system) activation, endothelial dysfunction, arterial stiffness, lipodystrophy, and dyslipidemia.[64]. The use of PIs is associated with RAAS activation. Acting on adipocytes directly, the PI combinations ritonavir/lopinavir and ritonavir/atazanavir were shown to activate adipokine-mediated inflammatory pathways that led to activation of adipose RAAS. An in vitro study of human and murine adipocytes demonstrated ≤4-fold increase of angiotensin receptor protein expression after only 5 days of exposure to lopinavir/ritonavir or atazanavir/ritonavir. This effect was prevented by the use of RAAS antagonists[65].

BMI(Body mass index) at baseline. Good Weight before starting HAART was a risk factor to develop hypertension in our cohort. Among patients with hypertension, 184/312 representing 59%, had BMI over 25 at baseline while patients without hypertension, 52.7 % had BMI<25, the P value is less than 0.001 meaning that patients with high BMI at base line are more likely to develop hypertension in our cohort. Taking into consideration the BMI, again higher values correlate with the development of hypertension since non hypertensive patients had a mean of BMI=21,43, while the mean BMI for hypertensive patients was 23.15, hypertensive patients had about 1.8 times higher BMI compare to non-hypertensive patients. All this explains that most of our patients who developed hypertension during the period of the study came for the first time at the clinic in better health (good BMI, good CD4 count, good HB, good creatinine) than the ones who did not develop hypertension. Our result is in correlation with the results found by Michael Carter [61] in her publication in 2016 found that Infection with HIV remained significantly associated with increased prevalence of hypertension after controlling for age, gender and ethnicity (OR = 1.52; 95% CI, 1.17-1.98; p = 0.002), and also after

adjustment for common risk factors for hypertension such as smoking, alcohol use, BMI and physical activity ($p < 0.001$). Baekken and all [66] found statistically significant predictors of new-onset hypertension: older age, higher BMI, higher total cholesterol, longer duration of ART, and micro-albuminuria. P<0.001.

CD4 count: a lot of studies concerning the relation between CD4 count level and hypertension in HIV positive patients have been carried out, but no consensus have been found, in this study we analyzed CD4 count of patients before start HAART and measured the CD4 count the time they developed hypertension. In Total, 890 patients had CD4 count baseline < 350 cells/ml and among this group 356 patients developed hypertension representing 40%, for those with CD4 count over 350 cell/ml, we had a total of 456 and among this group 69.1% developed hypertension with p<0.001, which means, patients with CD4 count over 350 cells/ml are more likely to develop hypertension, again as mentioned already in the table 28, patients who started HAART with good health(good Cd4 count, good BMI, good Viral load) had an increased risk to develop hypertension during the cascades of the HIV treatment, our result is in line with the results found by Leite LHM, Sampaio ABMM [66] who found a significant relation between hypertension and high CD4 count in a cohort in Brasil and the advanced age, longest time on HAART, BMI> 25, Peck [67] in 2014 found similar results with hypertension related to Age, alcohol use, BMI, microalbuminuria, low eGFR, and higher current CD4 T-cell count wich were independently associated with hypertension. Another similar result was found by Christian Akem Dimala and al [68] an Association between high CD4 Cell Count and Blood Pressure and Its Variation with Body Mass Index Categories in HIV-Infected Patients. In their study, they found that there was

a statistically significant association between BMI as a categorical variable and both hypertension (Fisher's exact, $p = 0.010$) and CD4 cell count (Fisher's exact, $p = 0.012$). The observed trend was an increasing prevalence of hypertension across increasing BMI and a higher BMI with higher CD4 cell count. Factors found to be associated with hypertension were age above 40, male gender, BMI-defined overweight/obesity, they particularly noticed that participants with CD4

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cell counts ≥ 350 cells/μL were three times more likely to have hypertension than those with CD4 cell counts < 350 cells/μL (OR: 3.07; 95% CI: 1.32–7.16; p = 0.006). During the follow up, the same scenario was different regarding CD4 count, we noticed For the CD4 count we found that the follow up CD4 count mean was 436 cells/ for non-hypertensive patients vs 438 cells/ml, this also shows that the follow up cd4 count is almost the same for non-hypertensive patients vs hypertensive patients, the difference is very slim, while at the base line, the mean CD4 count was the double for patient without hypertension the difference was almost half for the hypertensive patients, here we also see the good effect of the ART treatment. P=0.044, meaning when the immunity improved the risk of having hypertension remain the same for both everyone.

Viral Load: Viral load Baseline: Among patients who have viral load less than 1000 copies/ml, 475/566 developed hypertension representing 83.9%, (see table 13). For patients who had Viral load baseline over 1000 copies/ml, 584/784 did not develop hypertension representing 74.5%, p<0.001, meaning people with high viral load are at less risk to develop hypertension, and people with low Viral load were those in good health and high Viral load is a sign of advance HIV disease. For the Viral load follow up, we noticed the same scenario, also the reduction of the gap between non hypertensive and hypertensive, the difference is 8,401, the mean VL follow up is 11,856 copies/ml while the mean for the hypertensive patients is 3,455 copies/ml, the difference at baseline between hypertension and non-hypertension was 78,088 copies/ml, this shows again the impact of the ART treatment, with a very good improvement in term of VL and in doing so, patients also improve their health conditions.

Hemoglobine level:

Hemoglobin level at baseline: Hemoglobin level is also a sign of HIV disease level, when the hemoglobin level is low at baseline, it means advanced HIV disease and vice versa, in our study according to the baseline parameters, we noticed that the mean HB was low among non-hypertensive patients compare to hypertensive patients (11.2 vs 12.03); though

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the difference is slim but still more, we noticed that patients who started HAART with good HB had 1 time more changes to develop hypertension compare to those with low hemoglobin, as the patients were on HAART, we also noticed the same difference during the follow up, the mean hemoglobin is similar for non-hypertensive and hypertensive patients(12.36 vs 12.81) so still there is a very slim difference between the hypertensive and non-hypertensive patients in term of hemoglobin, and this shows that the treatment has improved the health conditions of patients. Our result is in correlation with the result found by - Femke Atsma , Ingrid Veldhuizen [69] Between subjects, the mean SBP increased with increasing Hb level. For men, the SBP increased by 1.3 mm Hg (95% CI, 1.1–1.4 mm Hg) per millimole per liter increase in Hb level. For women, the SBP increased by 1.8 mm Hg (95% CI, 1.6–2.0 mm Hg) for each millimole per liter increase in Hb level. We observed comparable patterns for DBP DBP rose 1.4 mm Hg (95% CI, 1.3–1.5 mm Hg) per millimole per liter increase in Hb level in men and 1.5 mm Hg (95% CI, 1.4–1.6 mm Hg) per millimole per liter Hb in women.

The mechanisms that might lead to an elevated blood pressure in individuals with an increased Hb level are not entirely known. In the past, several biological mechanisms for the Hb-blood pressure association have been proposed. It has been reported that Hb is strongly related to arterial stiffness, as measured by pulse wave velocity, which, in turn, increases SBP and DBP. Furthermore, free Hb may be a scavenger of Nitric oxide(NO). Nitric oxide, produced in the endothelial cells that line the blood vessels, relaxes the muscle cells surroundings the vessel and thereby controls blood pressure. Increased levels of free Hb may bind to NO, which causes vessels to constrict and blood pressure to increase [70] It has also been reported that increasing molecular mass of tense-state polymerized bovine Hb has a substantial effect on vasoconstriction and blood pressure by regulating NO production.[71] An obvious mechanism for blood pressure increase with increased Hb levels would be increased blood viscosity. It has been reported that elevation of hematocrit and Hb levels increases blood viscosity and that increased viscosity partly through an effect on blood

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pressure may worsen cardiovascular function[72] However, other research is inconclusive about the role of blood viscosity in high blood pressure and hypertension. Studies in hypertensive patients do support the role of increased blood viscosity in raising blood pressure [73] but not in healthy individuals. Finally, both Hb and blood pressure may be related to the renin-angiotensin-aldosterone system [74]. Post-transplant erythrocytosis in kidney transplant recipients can be managed by angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment [75] and angiotensin II may play a role in erythropoietin production [76] The role of the renin-angiotensin-aldosterone system may be incited by the sympathetic nervous system, which is known to affect erythropoietin production, because subjects with autonomic neuropathy have erythropoietin-responsive anemia[77]

Education level and hypertension. One of the factors we looked at was education level of our patients, For example, with respect to diet, do the less educated tend to have higher salt intakes than the better educated? While these and other explanations may be valid, at this time the mechanism that causes hypertension to be inversely related to education remains to be discovered[78].

The Incidence of hypertension according to the education level: in our cohort, we found that 117/170 hypertensive patients had no education (did not go to school), representing 68.8% of the total number of patients who did not go to school; we can say that being low educated was related to the presence of hypertension(statistically significant with $p<0.001$), while 34/67 among the university patients representing 50.7% had hypertension(no big difference); for intermediate education level, primary and secondary ones, we had 46% and 48.3% with $p<0.001$ as hypertension respectively, all these mean that most of the people who are educated know the way to prevent hypertension by controlling regularly their BP, by practicing exercise, by avoiding food which may increase the risk of hypertension. Only those with low education had high risk of developing hypertension and education level is associated to economic status and income.

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When comparing the education level to hypertension levels, we found that for non-educated patients, stage 1 hypertension dominated with almost half of the patients 84/170 representing 49.45%, followed by pre-hypertensive patients with 53/170 representing 31.2%, Explaining that with the stage of hypertension, the stage 1 was 71.79% of the non-educated patients, (with p<0.001, statistically significant).

Among the primary level patients, we noticed that 324/600 had prehypertension representing 54%, with p<0.001

For secondary level patients, we also noticed that over half (51.7%) 0265/513 of them had prehypertension with p<0.001 meaning that being at secondary level is not related to a risk of hypertension

For the university level, we noticed that 40.3% had hypertension stage 1(27/67)

Our result is comparable of the results found by Clemencia M. Vargas, Deborah D. Ingram, and Richard F. Gillum[79] in their cohort, the mean systolic blood pressure tended to be higher in the less than 12 years of education group than in the more than 12 years of education group. Xiaojun Chen[80] in china found similar results where education was inversely associated with mean SBP in female hypertensive. It suggests that low education may have an impact on blood pressure in females. MA Tedesco, G Di Salvo, S Caputo, Also Conversely, ISTAT[81] found that 80% of the population had little education. The Percentage of type 2 diabetic patients with little education was high (190 patients, 95%). Hypertensive patients with little education were mostly men (P < 0.001), had a high rate of hypertension in the family (P < 0.03), had a significantly Higher diastolic blood pressure (P < 0.006). A study[82] done by Dyer AR and all on 40 000 clerks from Chicago, USA, also showed a statistically significant inverse association between education and HT, that could not be accounted for by differences in age, relative weight, and heart rate.

Marital status and hypertension. In our cohort, we were also interested to see the association between marital status and hypertension According to the marital status, in total, 868/1350(64.29%) were married patients men and women followed by widow 231/1350(17.11%) , we found that being married represented 54.5% of hypertension against 45.5%

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for non-hypertension with P<0.001, while being single, the hypertension rate was 33%(37/112), the single patients had less risk of developing hypertension; for divorced or separated patients, the rate was closer for hypertension and non-hypertension(48.9% and 51.1% respectively), for those who were widow, we noticed that over half had no hypertension 58% vs 42% (with p<0.001), this can be explain by the fact that people who are married live in an emotional, stress conditions in Malawi and with the high rate of divorce in the country, most of the people who are married live in difficult situations than those who are singles, of course their social-economic situation is much better but this study did not find out for how long the patients have been married.

Hilary M. Schwandt and all [83] found similar result, in their cohort they discovered that hypertension was not common in singles, Dareek Anamaale and all[84] found similar result in Ghanaian population, After controlling for lifestyle and socio-demographic covariates, the logistic regression models showed significantly higher odds of hypertension for married (OR=2.14, 95% CI=1.30–3.53), cohabiting (OR=1.94, 95% CI=1.16–3.23) and previously married (OR=2.23, 95% CI=1.29–3.84) women, all these results can be explained by the fact that married people have more stresses in their life, though which may be one of the causes of hypertension, but once again more investigations need to be done to find the real cause of hypertension in married people.

Mortality and hypertension: The graph below shows that the survival level is lower in patients without hypertension, and most of this patients are those who were on stavudine and started HAART with very bad health conditions (p<0.001). Amonghypertensive patients, we noticed a longer period of survival in patients with hypertension and treated with BP drugs compare to patients with hypertension without BP treatment (p<0.001)

In this sample, we cannot find a clear impact of kind of ARV treatment on development of hypertension. More important seems to be life style and BMI and Education. Longer time on ARVs seems to be associated to the development of

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hypertension ($p<0.001$), but this evidence could be biased by the baseline conditions of the different subsamples. In the comparison among the different kinds of treatment age and gender did not seem to play a major role.

Our result is comparable to the result found by Larus S. Gudmundsson[85] in Comparing treated and uncontrolled (systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥95 mmHg) versus treated and controlled hypertensive subjects, followed for up to 30 years, the uncontrolled men and women were at significantly higher risk of CVD mortality, hazard ratio (HR) = 1.47 (95% confidence interval (CI): 1.06-2.02) and HR 1.70 (CI: 1.23–2.36), respectively, showing the benefit of hypertension control.

In the USA, similar result was also found by Randy K. Wexler [86], in their study they discovered that the lack of adequate control of hypertension in the United States has significant ramifications.1 Ninety-one percent of cases of heart failure are preceded by hypertension, and half of all patients who suffer a heart attack (and two thirds of those who have a first-time stroke) have a blood pressure greater than 140/90.2 During the 10-year period from 1991 to 2001, the actual number of deaths due to hypertension rose 53%.2 Considering the poor control of documented hypertension in the United States, the need for lifestyle counseling in pre-hypertensive patients poses a very serious challenge.

The control of the hypertension starts by the awareness, the counseling, the regular control and the treatment which includes diet, physical activities and the drugs).

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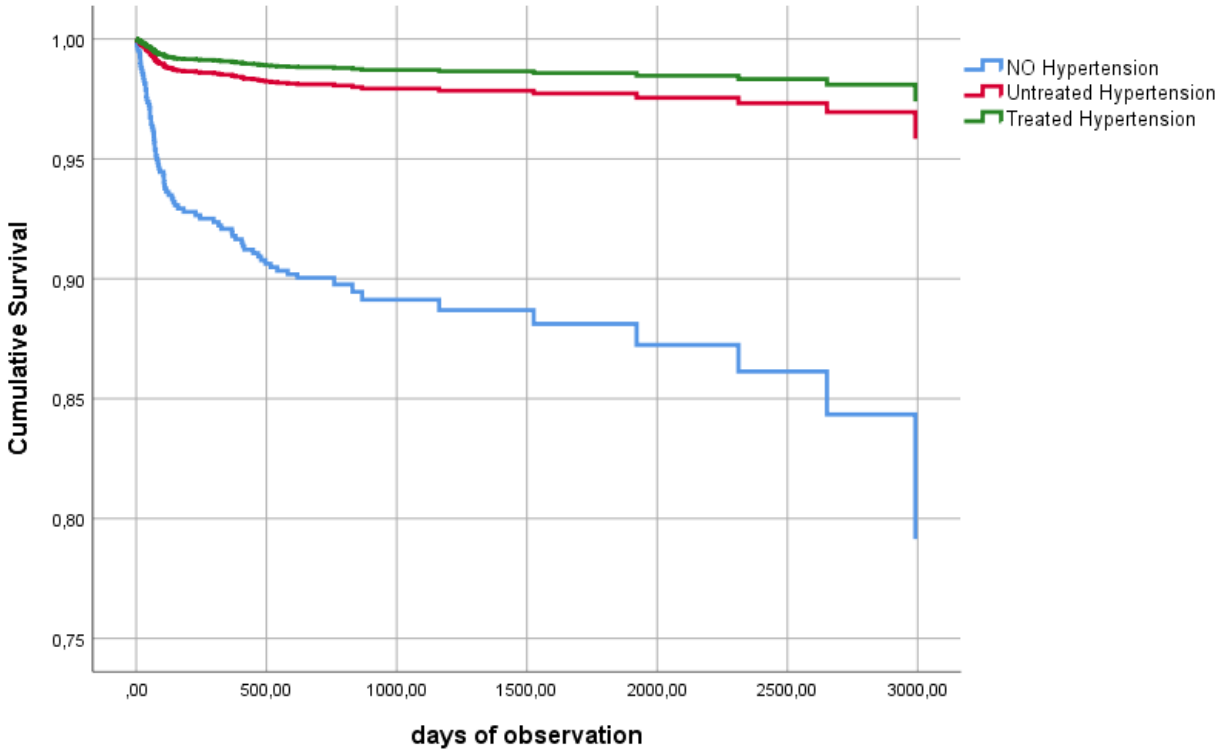

Conclusion: In conclusion, this study shows a protective action of Protease inhibitors and TDF-based regimens compared with AZT based regimen. Education level was inversely related to hypertension, being married was significantly associated to a risk of hypertension, high hemoglobin baseline, high base line BMI, high baseline line CD4 count and low baseline viral load were all related to an increased risk of hypertension.

Recommendation.

We recommend awareness of community about the risk of hypertension and especially those who are on HAART, regular BP checkup at least at every visit, treatment and good control of those with hypertension and this treatment will include diet, regular physical exercise and the BP medications.

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More investigations need to be done to find real cause of hypertension related to marital status and education level and well as the drugs

Study limitations:

Our cohort presented patient who were on HAART, therefore we were not able to compare the prevalence of hypertension with those who are HIV negative, we were unable to give more details concerning the real causes of hypertension related to low education level, marital status mainly those who were married, we need more socio economic details to clarify the relation between education level, marital status and hypertension

Abbreviation:

ABC: Abacavir

ACS: Acute coronary syndrome

AMID: Acutre myocardite infarction

ART: Anti-retroviral therapy

ARV: Antiretroviral

AZT: Zudovudine

AZV: Atazanavir

BMI: Body mass index

BP: Blood pressure

CVD: Cardiovascular disease

DAD: Data collection for adverse events for anti-HIV drugs

DBP: Diastolic blood pressure

D4T: stavudine

HAART: Highly active antiretroviral therapy

HB: Hemoglobine

HIV: Human immunodepressor virus

F: female

LPV/r: Lopinavir/ritonavir

M: Male

NCD: Non communicable disease

NRTI: Nucleoside reverse transcriptase

NNRTI: Non Nucleoside reverse transcriptase

PLWH: People living with HIV

RAAS: Rein-Angiotensin-Aldosterone System

SBP: Systolic bloop pressure

SSA: Sub saharan africa

3TC: Lamivudine

TDF: Tenofovir

VL: Viral Load

WHO: World health organization

REFERENCES

1. World Health Organization (WHO). HIV/AIDS Fact Sheet. http://www. who.int/en/news-room/fact-sheets/detail/hiv-aids. Accessed October 30, 2017.

2. World Health Organization (WHO). Global Health Sector Response to HIV, 2000-2015: Focus on Innovations in Africa. http://www.who.int/ hiv/pub/progressreports/2015-progress-report/en/. Accessed November 6, 2017.

3. Feinstein MJ, Bahiru E, Achenbach C, et al. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. Am J Cardiol. 2016;117:214–220.

4. Gazzaruso C, Bruno R, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, Filice G. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. J Hypertens. 2003;21:1377–1382. doi: 10.1097/01.hjh.0000059071.43904.dc.

5. Peck RN, Shedafa R, Kalluvya S, Downs JA, Todd J, Suthanthiran M, Fitzgerald DW, Kataraihya JB. Hypertension, kidney disease, HIV and antiretroviral therapy among Tanzanian adults: a cross-sectional study. BMC Med. 2014;12:125. doi: 10.1186/s12916-014-0125-2.

6. Xu Y, Chen X, Wang K. Global prevalence of hypertension among people living with HIV: a systematic review and meta-analysis. J Am Soc Hypertens. 2017;11:530–540. doi: 10.1016/j.jash.2017.06.004.)

7. World Health Organisation. Global Health Observatory Data, http://www. ho.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/. Accessed 25 Apr 2016

8. Liu C, Ostrow D, Detels R, Hu Z, Johnson L, Kingsley L et al. Impacts of HIV infection and HAART use on quality of life. Quality of Life Research. 2006;15(6):941-9. PubMed| Google Scholar

9-Goosby E, Dybul M, Fauci A A, Fu J, Walsh T, Needle R et al. The United States President's Emergency Plan for AIDS Relief: a story of partnerships and smart investments to turn the tide of the global AIDS pandemic. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2012;60 Suppl 3:S51-S6. PubMed | Google Scholar

10. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of Clinical Endocrinology & Metabolism. 2007;92(7):2506-12. PubMed | Google Scholar
11. Mutimura E, Crowther N J, Stewart A, Todd Cade W. The human immunodeficiency virus and the cardiometabolic syndrome in the developing world: an African perspective. Journal of the cardiometabolic syndrome. 2008;3(2):106-10. PubMed | Google Scholar
12. WHO GENEVA. Global Health estimates summary tables: Projection of deaths by cause, age and sex, by World Bank Income Group and WHO region 2013. http://wwwwhoint/healthinfo/global_burden_disease/en/. Accessed on October 12 2013. Google Scholar
13. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. World Health Organization. 2009. Google Scholar
14. Dolan SE, Hadigan C, Killilea KM, Sullivan MP, Hemphill L, Lees R S et al. Increased cardiovascular disease risk indices in HIV-infected women. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2005;39(1):44-54. PubMed | Google Scholar
15. Lundgren JD, Battegay M, Behrens G, De Wit S, Guaraldi G, Katlama C et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. HIV medicine. 2008;9(2):72-81. PubMed | Google Scholar

16. Mutede BR, Magure T, Bangure D, Gombe NT, Tshimanga M, Mungati M. Prevalence and factors associated with hypertension among anti-retroviral therapy patients aged 15 Years and above in Makonde District, Zimbabwe, 2012: an analytic cross sectional study. World J Cardiovasc Dis. 2015;5:266–77.
17. Cachay ER. MSD Manual Professional Version, Professional/Infectious Diseases/Human Immunodeficiency Virus (HIV), https://www.merckmanuals. com/professional/infectious-diseases/human-immunodeficiency-virus-(hiv)/ human-immunodeficiency-virus-(hiv)-infection. Accessed 5 Apr 2015.
18. Bloomfield GS, Hogan JW, Keter A, Sang E, Carter EJ, Velazquez EJ, Kimaiyo S. Hypertension and obesity as cardiovascular risk factors among HIV seropositive patients in Western Kenya. PLoS One. 2011;6:22288.
19. Mateen FJ, Kanters S, Kalyesubula R, Mukasa B, Kawuma E, Kengne AP, Mills EJ. Hypertension prevalence and Framingham risk score stratification in a large HIV-positive cohort in Uganda. J Hypertens. 2013;31:1372–8.
20. Grinspoon SK. Metabolic syndrome and cardiovascular disease in patients with human immunodeficiency virus. Am J Med. 2005;118 Suppl 2:23S–8S.
21. Gazzaruso C, Bruno R, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, Filice G. Hypertension among HIV patients: prevalence and relationships to insulin, resistance and metabolic syndrome. J Hypertens. 2003;21:1377–82.
22. Andrew M, Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated Kidney Toxicity in HIV-infected Patients. Am J Kidney Dis. 2011;57(5):773–80.
23. Mpondo BC, Kalluvya SE, Peck RN, Kabangila R, Kidenya BR, Ephraim L, Fitzgerald DW, Downs JA. Impact of antiretroviral therapy on renal function among HIV-infected Tanzanian adults: a retrospective cohort study. PLoS One. 2014;9:89573. Magande et al. Clinical Hypertension (2017) 23:14 Page 6 of 7
24. Msango L, Downs JA, Kalluvya SE, Kidenya BR, Kabangila R, Johnson WD, Fitzgerald DW, Peck RN. Renal dysfunction among HIV-infected patients starting antiretroviral therapy. AIDS. 2011;25:1421–5.
25. R.B. Himelman,W.S. Chung, D.N. Chernoff, N.B. Schiller, H. Hollander, Cardiac manifestations of human immunodeficiency virus infection: a two-dimensional echocardiographic study, J. Am. Coll. Cardiol. 13 (1989) 1030–1036.

26. S. Hecht, M. Berger, A. Van Tosh, S. Croxson, Unsuspected cardiac abnormalities in the acquired immune deficiency syndrome: an echocardiographic study, Chest 96 (1989) 805–808.
27. S. Kaul, M. Fishbein, R. Siegel, Cardiac manifestations of acquired immune deficiency syndrome: a 1991 update, Am. Heart J. 122 (1991) 535–544.
28. P. Rerkpattanapipat, N. Wongpraparut, L.E. Jacobs, M.N. Kotler, Cardiac manifestations of acquired immunodeficiency syndrome, Arch. Int. Med. 160 (2000) 602–608.
29. A. Becker, K. Sliwa, S. Stewart, E. Libhaber, A. Essop, C. Zambakides,M. Essop, Acute coronary syndromes in treatment—naive black South Africans with human immunodeficiency virus infection, J. Interv. Cardiol. 23 (2010) 70–77.
30. A. Knudsen, A.B. Mathiasen, R.H. Worck, J. Kastrup, J. Gerstoft, T.L. Katzenstein, A. Kjær, A.-M. Lebech, Angiographic features and cardiovascular risk factors in
human immunodeficiency virus-infected patients with first-time acute coronary syndrome, Am. J. Cardiol. 111 (2013) 63–67.
31. J. Lo, S. Abbara, L. Shturman, A. Soni, J.Wei, J. Rocha-Filho, K. Nasir, S.K. Grinspoon, Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography agiography in HIV-infected men, AIDS 24 (2010) 243–253.
32. C. Debouck, The HIV-1 protease as a therapeutic target for AIDS, AIDS Res. Hum. Retroviruses 8 (1992) 153–164.
33. A. Chandwani, J. Shuter, Lopinavir/ritonavir in the treatment of HIV-1 infection: a review, Ther. Clin. Risk Manag. 4 (2008) 1023–1033.
34. G.N. Kumar, V.K. Jayanti, M.K. Johnson, J. Uchic, S. Thomas, R.D. Lee, B.A. Grabowski, H.L. Sham, D.J. Kempf, J.F.Denissen, K.C.Marsh, E. Sun, S.A. Roberts, Metabolismand disposition of the HIV-1 protease inhibitor lopinavir (ABT-378) given in combination with ritonavir in rats, dogs, and humans, Pharm. Res. 21 (2004) 1622–1630.
35. G.N. Kumar, J. Dykstra, E.M. Roberts, V.K. Jayanti, D. Hickman, J. Uchic, Y.E. Yao, B. Surber, S. Thomas, G.R. Granneman, P.P. Division, A. Laboratories, A. Park, Potent inhibition of the cytochrome P-450 3A-mediated human liver microsomal metabolism
of a novel HIV protease inhibitor by ritonavir: a positive drug–drug interaction, Pharmacology 27 (1999) 902–908.
36. H.L. Sham, D. Betebenner, T. Herrin, G. Kumar,A. Saldivar, S. Vasavanonda,A.Molla, D. Kempf, J. Plattner, D. Norbeck, Synthesis and antiviral activities of the major metabolites
of the HIV protease inhibitor ABT-378, Biorgan. Med. Chem. Lett. 11 (2001) 1351–1353.
37. S.S. Kaplan, C.B. Hicks, Safety and antiviral activity of lopinavir/ritonavir-based therapy in human immunodeficiency virus type 1 (HIV-1) infection, J. Antimicrob. Chemother. 56 (2005) 273–276.
38. A. Hsu, G.R. Granneman, R. Bertz, Ritonavir clinical pharmakinetics and interactions with other anti-HIV agents, Clin. Pharmacokinet. 35 (1998) 275–291.
39. N. Friis-Møller, R. Weber, P. Reiss, R. Thiébaut, O. Kirk, A. d'Arminio Monforte, C. Pradier, L.Morfeldt, S. Mateu, M. Law, W. El-Sadr, S. DeWit, C.A. Sabin, A.N. Phillips, J.D. Lundgren, Cardiovascular disease risk factors in HIV patients—association with
antiretroviral therapy: results from the DAD study, AIDS 17 (2003) 1179–1193.
40. N. Friis-Møller, P. Reiss, C.A. Sabin, R.Weber, A.D.Monforte,W. El-Sadr, R. Thiébaut, S. DeWit, O. Kirk, E. Fontas, M.G. Law, A. Phillips, J.D. Lundgren, Class of antiretroviral drugs and the risk of myocardial infarction, N. Engl. J. Med. 356 (2007)
1723–1735.

41. C. Smith, C.A. Sabin, J.D. Lundgren, R. Thiebaut, R. Weber, M. Law, A. d'Arminio Monforte, O. Kirk, N. Friis-Moller, A. Phillips, P. Reiss, W. El Sadr, C. Pradier, S.W.
42. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global Burden of Hypertension: Analysis of Worldwide Data. The Lancet. 2005 Jan 15;365(9455):217-23.
43. Matchaya GC. Trends in life expectancy and the macroeconomy in Malawi MPRA. Paper No. 11949, posted 27 December 2008. Re¬trieved from: http://mpra.ub.uni-muenchen.de/11949/.
44. Msyamboza KP, Ngwira B, Dzowela T, Mvula C, Kathyola D, Har¬ries AD, Bowie C. The burden of selected chronic noncommunicable diseases and their risk factors in Malawi: nationwide STEPS survey. PLoS One. 2011 May 23;6(5):e20316.
45. Muronya W, Sanga E, Talama G, Kumwenda JJ, van Oosterhout JJ. Cardiovascular risk factors in adult Malawians on long-term antiretro¬viral therapy. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2011 Nov 1;105(11):644-9.
46. Lloyd-Sherlock P, Beard J, Minicuci N, Ebrahim S, Chatterji S. Hypertension among older adults in low-and middle-income countries: prevalence, awareness and control. International journal of epidemiol¬ogy. 2014 Feb 1;43(1):116-28.
47. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in Sub-Saharan Africa A systematic review and meta-analysis. Hypertension. 2015 Feb 1;65(2):291-8.
48. World Health Organization (WHO). Countries - Malawi (2012). Retrieved from http://www.who.int/countries/mwi/en/. 2012.)
49. (Collins Mitambo1,2, Shiraz Khan3, and all: (Improving the screening and treatment of hypertension in people living with HIV: An evidence-based policy brief by Malawi's Knowledge Translation Platform
Malawi Medical Journal 29 (2): June 2017
Non-communicable Diseases Special Issue
50. R.B. Himelman,W.S. Chung, D.N. Chernoff, N.B. Schiller, H. Hollander, Cardiac manifestations
of human immunodeficiency virus infection: a two-dimensional echocardiographic
study, J. Am. Coll. Cardiol. 13 (1989) 1030–1036.
51. S. Hecht, M. Berger, A. Van Tosh, S. Croxson, Unsuspected cardiac abnormalities in the acquired immune deficiency syndrome: an echocardiographic study, Chest 96 (1989) 805–808.
52. S. Kaul, M. Fishbein, R. Siegel, Cardiac manifestations of acquired immune deficiency syndrome: a 1991 update, Am. Heart J. 122 (1991) 535–544.
53. P. Rerkpattanapipat, N. Wongpraparut, L.E. Jacobs, M.N. Kotler, Cardiac manifestations of acquired immunodeficiency syndrome, Arch. Int. Med. 160 (2000) 602–608.
54. W.W. Grody, L. Cheng, W. Lewis, Infection of the heart by the human immunodeficiency virus, Am. J. Cardiol. 66 (1990) 203–206.

55- Celermajer, D S 1997, endothelia dysfunction. Does it matter, is it reversible? Card 30:525-333
56- metha, N and M Reilly 2005, atherosclerotic cardiovascular disease risk in HAART treated HIV-1 population, 6:5-24
57- Martin U, C, Davies, is normal pregnancy atherogenic? clinic Sc 96: 421-425

58- Crane HM, Van Rompaey SE, Kitahata MM. Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy.**AIDS**. 2006; 20:1019–1026. doi: 10.1097/01.aids.0000222074.45372.00.CrossrefMedlineGoogle Scholar

59-Peck RN, Shedafa R, Kalluvya S, Downs JA, Todd J, Suthanthiran M, Fitzgerald DW, Kataraihya JB. Hypertension, kidney disease, HIV and antiretroviral therapy among Tanzanian adults: a cross-sectional study.**BMC Med**. 2014; 12:125. doi: 10.1186/s12916-014-0125-2.CrossrefMedlineGoogle Scholar

60-Rokx C, Verbon A, Rijnders BJ. Short communication: lipids and cardiovascular risk after switching HIV-1 patients on nevirapine and emtricitabine/tenofovir-DF to rilpivirine/emtricitabine/tenofovir-DF.**AIDS Res Hum Retroviruses**. 2015; 31:363–367. doi: 10.1089/AID.2014.0278.CrossrefMedlineGoogle Schola

61-Michael Carter 2016 Hypertension in patients with HIV associated with obesity, fat loss and previous treatment with Stavudine, cardiovascular disease

62-Robert A. Ngala and Klutse Fianko, 2014. Effects of HIV Infection and Anti-retroviral Therapy on Cardiovascular Risk Factors. Trends in Molecular Sciences, 6: 1-12.

63-Crane HM, Van Rompaey SE, Kitahata MM. Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. *AIDS*. 2006; 20:1019–1026. doi: .1097/01.aids.0000222074.45372.00Crane and all

64- Peck RN, Shedafa R, Kalluvya S, Downs JA, Todd J, Suthanthiran M, Fitzgerald DW, Kataraihya JB. Hypertension, kidney disease, HIV and antiretroviral therapy among Tanzanian adults: a cross-sectional study.
BMC Med. 2014;12:125. doi: 10.1186/s12916-014-0125-2.

65- Boccara F, Auclair M, Cohen A, Lefèvre C, Prot M, Bastard JP, Capeau J, Caron-Debarle M. HIV protease inhibitors activate the adipocyte renin angiotensin system.**Antivir Ther**. 2010; *15*:363–375. doi: 10.3851/IMP1533.CrossrefMedlineGoogle Scholar

66-Leite LHM, Sampaio ABMM. Risco cardiovascular: marcadores antropométricos, clínicos e dietéticos em indivíduos infectados pelo vírus HIV. Rev Nutr [Internet]. 2011[cited 2016 May 13];24(1):79-88. Available from: http://www.scielo.br/pdf/rn/v24n1/ v24n1a08.pdf

67- Peck RN, Shedafa R, Kalluvya S, Downs JA, Todd J, Suthanthiran M, Fitzgerald DW, Kataraihya JB. Hypertension, kidney disease, HIV and antiretroviral therapy among Tanzanian adults: a cross-sectional study.
BMC Med. 2014;12:125. doi: 10.1186/s12916-014-0125

68-Christian Akem Dimala, Association between CD4 Cell Count and Blood Pressure and Its Variation with Body Mass Index Categories in HIV-Infected Patients . 2018; 2018: 1691474. Published online 2018 Jan 22. doi: 10.1155/2018/1691474

69- Femke Atsma , Ingrid Veldhuizen: Hemoglobin Level Is Positively Associated With Blood Pressure in a Large Cohort of Healthy Individuals
Originally published1 Oct 2012https://doi.org/10.1161/HYPERTENSIONAHA.112.193565Hypertension. 2012;60:936–941

70-Cabrales P,, Han G,, Nacharaju P,, Friedman AJ,, Friedman JM. Reversal of hemoglobin-induced vasoconstriction with sustained release of nitric oxide.Am J Physiol Heart Circ Physiol. 2011 ;300:H49–H56.CrossrefMedlineGoogle Scholar

71. Cabrales P,, Sun G,, Zhou Y,, Harris DR,, Tsai AG,, Intaglietta M,, Palmer AF. Effects of the molecular mass of tense-state polymerized bovine hemoglobin on blood pressure and vasoconstriction.J Appl Physiol. 2009 ;107:1548–1558.CrossrefMedlineGoogle Scholar

72-. Lowe GD,, Lee AJ,, Rumley A,, Price JF,, Fowkes FG. Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study.Br J Haematol. 1997 ;96:168–173.CrossrefMedlineGoogle Scholar

73. Devereux RB,, Case DB,, Alderman MH,, Pickering TG,, Chien S,, Laragh JH. Possible role of increased blood viscosity in the hemodynamics of systemic hypertension.Am J Cardiol. 2000 ;85:1265–1268.CrossrefMedlineGoogle Scholar

74. Salazar Vazquez BY. Blood pressure and blood viscosity are not correlated in normal healthy subjects.Vasc Health Risk Manag. 2012 ;8:1–6.MedlineGoogle Scholar

75 Klaassen RJ,, van GT,, Rischen-Vos J,, Deinum J,, Man in't Veld AJ,, Weimar W. Losartan, an angiotensin-II receptor antagonist, reduces hematocrits in kidney transplant recipients with posttransplanterythrocytosis.Transplantation. 1997 ;:780–782.CrossrefMedlineGoogle Scholar

76. Freudenthaler SM,, Schenck T,, Lucht I,, Gleiter CH. Fenoterol stimulates human erythropoietin production via activation of the renin angiotensin system.Br J ClinPharmacol. 1999 ;48:631–634.MedlineGoogle Scholar

77. Biaggioni I,, Robertson D,, Krantz S,, Jones M,, Haile V. The anemia of primary autonomic failure and its reversal with recombinant erythropoietin.Ann Intern Med. 1994 ;121:181–186.CrossrefMedlineGoogle Scholar

78- Fuchs R: Who Shall Live? New York, Basic Books, 1975

79- Clemencia M. Vargas, Deborah D. Ingram, and Richard F. Gillum: Incidence of Hypertension and Educational Attainment The NHANES I Epidemiologic Followup Study American Journal of Epidemiology

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80- Xiaojun Chen, Xuerui Tan* Associations of Education with Blood Pressure in Hypertensive Patients: A Chinese Community Survey Department of Cardiovascular Diseases, The First Affiliated Hospital of Shantou University Medical College, Shantou, China Email: *tanxuerui@vip.sina.com Received June 7, 2013; revised July 16, 2013; accepted August 2, 2013

81-MA Tedesco, G Di Salvo, S Caputo, Educational level and hypertension: how socioeconomic differences condition health care Journal of Human Hypertension (2001) 15, 727–731

82-Dyer AR, Stamler J, Shekelle RB, Schoenberger J. The relationship of education to blood pressure. Findings on 40,000 employed chicagoans. Circulation 1976; 54

83- Hilary M. Schwandt,1 Josef Coresh,1 and Michelle J. Hindin1 Marital Status, Hypertension, Coronary Heart Disease, Diabetes, and Death Among African American Women and Men: Incidence and Prevalence in the Atherosclerosis Risk in Communities (ARIC) Study ParticipantsJ Fam Issues. 2010 Sep; 31(9): 1211–1229. doi: 10.1177/0192513X10365487

PMCID: PMC4703426 NIHMSID: NIHMS303468 PMID: 26752799 Author information Copyright and License information Disclaimer

84- Derek Anamaale Tuoyire (a1) and Harold Ayetey (a2) (a3) GENDER DIFFERENCES IN THE ASSOCIATION BETWEEN MARITAL STATUS AND HYPERTENSION IN GHANA https://doi.org/10.1017/S0021932018000147Published online: 21 May 201

85- Larus S. GudmundssonMagnus JohannssonEmail authorGudmundur ThorgeirssonNikulas SigfussonHelgi SigvaldasonJacqueline C. M. Witteman Hypertension Control as Predictor of Mortality in Treated Men and Women, Followed for up to 30 Years Authors May 2005, Volume 19, Issue 3, pp 227–235 |

86- Randy K. Wexler: Treatment of Hypertension Critical in Reducing Morbidity and Mortality

The Journal of the American Board of Family Medicine May 2007, 20 (3) 322; DOI: https://doi.org/10.3122/jabfm.2007.03.070002
87-(Michael Carter)Published: 13 May 2016 .Sheila Medina-Torne, (MPH, Anuradha Ganesan, MD, Irma Barahona, First Published August 9, https://doi.org/10.1177/1545109711418361)