Factors Associated with Prognostic or Treatment Outcomes in HIV/AIDS Patients with and without Hypertension in Eswatini

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Research Article

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Abstract

Background: Non-communicable diseases are increasing faster in HIV/AIDS patients than in the general population. We studied the association between hypertension and other possibly confounding factors on retroviral load and CD4-cell count in hypertensive and non-hypertensive HIV/AIDS patients receiving antiretroviral therapy (ART) at a large hospital in Eswatini over a 4-year period.

Method: We performed a retrospective longitudinal review of the medical records of 560 ART patients divided into non-hypertension and hypertension groups (n=325 and n=235) from July 27 to September 8, 2018. Generalized Estimated Equation was used to analyze the longitudinal data.

Results: Hypertensive patients were more likely to have improved CD4-cell counts than non-hypertensive patients (OR=1.83, [1.37–2.44]). ART patients with hypertension were more likely to have detectable retroviral loads, though not significant (OR=1.37 [0.77-2.43]). In non-hypertensive patients, second line ART was significantly associated with retroviral load (OR=8.61 [2.93-25.34]) and adverse side effects (OR=3.50 [1.06-11.54]), while isoniazid preventive therapy was significantly associated with CD4-cell counts (OR=1.68 [1.16 – 2.45]). In hypertensive patients, factors associated with retroviral load were HIV stage (OR=2.84 [1.03–7.85]) and adherence (OR = 8.08 [1.33–49.04]). In both groups, CD4-cell counts significantly and steadily increased over time (p-value <0.001).

Conclusions: Results show a significant association between hypertension and CD4 cell counts but not retroviral load. In ART patients with and without hypertension, the factors associated with prognostic markers were different. More attention may need to be paid to ART patients with well controlled HIV statuses to monitoring and controlling of hypertension status.

Introduction

Non-communicable diseases (NCDs) caused 39.6 million deaths worldwide and 1.1 million deaths in sub-Sahara Africa in 2015, cardiovascular diseases were accounting for a large proportion, about half globally [1]. Hypertension, is a major risk factor for cardiovascular, cerebrovascular, and renal disorders, and directly contribute to about 58% deaths attributed to cardiovascular diseases [2]. It is often observed among people living with HIV/AIDS (PLHIV), especially in low- and middle-income countries [3] and has been associated with such risk factors as increased body weight, increasing age, ethnicity, hypersodic diet, alcohol abuse, sedentary lifestyle, unfavorable socioeconomic factors, genetic predisposition, and other cardiovascular risk factors [4].

Sub-Sahara Africa represents the most HIV/AIDS-affected part of the world, followed by Asia and the Pacific. Almost 40 million (37.9) people were living with HIV in 2018, a year seeing 1.7 million new cases and 770,000 HIV/AIDS deaths worldwide [5]. Eswatini, located in the southern part of Africa, has the world's highest prevalence of HIV/AIDS. In Eswatini 27% of the population being 15 years and older have HIV/AIDS [6]. Still, that country has made great progress in the control of the disease. Based on the 2011 and 2017 household Swaziland HIV Incidence Measurement Surveys (SHIMS 1 and 2), which included blood sampling, Eswatini had reduced its incidence by half between 2011 and 2016 (2.4% vs. 1.70%) [6].

Therefore, antiretroviral therapy (ART) has transformed HIV/AIDS from a catastrophic disease to a manageable chronic disease [7–9]. However, this increased survival puts PLHIV at greater risk to NCDs like among others hypertension and cardiovascular conditions [10]. While cardiovascular diseases have been associated with duration of infections as well as with retroviral load and CD4-cell counts, both prognostic markers for HIV [11] and how the management of cardiovascular disease affects these prognostic markers for HIV are not known [12].

Retroviral load and CD4-cell counts are regularly used as biomarkers of health status in people infected with HIV and as indicators of their response to ART [13]. Retroviral load, an important ongoing indicator of the disease state, is monitored upon entry of care, initiation of treatment, and then regularly throughout the treatment of all PLHIV [14]. In patients who have no resistant mutations and who adhere to treatment strategies, ART-retroviral load reduction is expected to be achieved within 8 to 24 weeks [14]. WHO recommends that retroviral load be tested around six months after the initiation of ART, and yearly thereafter if retroviral load has been successfully reduced [15]. CD4-cell counts provide an overall picture of the immune status of PLHIV and are often used to determine health status and decided when to initiate and discontinue the use of medications to treat opportunistic infections [13].

In 2014, the UNAIDS launched its Fast-Track Strategy, also known as 90 (tested)-90 (treated)-90 (successfully treated) treatment target, hoping to improve the response to the HIV epidemic by various low- and middle-income countries [16]. This strategy was a part of UNAIDS' effort to meet their Sustainable Goal 3, ending the epidemic of AIDS and other communicable disease by 2030 [16]. About 85 percent (84.7) of those responding to SHIMS2 reported knowing their HIV status, 87.4% of those who were HIV positive reported receiving ART, and 91.9% of those on ART reported successful viral suppression. HIV blood tests were administered to all participants. Around 73 percent (76.0% female; 67.6% male) of adults aged 15 years and older who had tested positive for HIV had successfully reduced retrovirus loads (< 1000 copies/mL), regardless of whether they knew their HIV status or were receiving ART (some did not want to know test results). Younger HIV-positive adults (55% female; 15–24 years old) were also found to have successfully reduced viral loads (< 1000 copies/mL) [6].

No study has investigated the impact of NCDs on HIV ART outcomes as yet, especially with reference to hypertension. Therefore, we retrospectively reviewed 560 medical charts of one hospital treating PLHIV to identify those with and without hypertension and followed the results of their annual

retroviral loading and CD4 cell count tests for four years and analyzed the data controlling for age, gender, treatment, adverse effects, adherence, and year.

Material And Methods

Study Design and Sample

In this longitudinal study, we reviewed the medical charts of PLHIV at Raleigh Fitkin Memorial (RFM) Hospital in the central part of Eswatini to follow changes in retroviral load and CD4 cell count in ART patients with and without hypertension over a four-year study period. As seen in Fig. 1, we first identified more than 4,500 patients receiving ART at the healthcare facility. To be included, patients had to provide the following characteristics: thirty years old or older, tested seropositive for HIV, being on ART for at least two years, have normal kidney and liver functions prior to ART, not taking any hormonal contraceptives, and be free of any other diseases other than HIV and physician diagnosed hypertension prior to ART. After exclusion, we were left with 560 ART patients (mean age 44 year SD of ± 8.61; 44.8% 30–40 years old; 62.9% female). They were divided into 325 non-hypertensive patients (41.3 years SD ± 7.12; 60.6% female) and 235 hypertensive patients (47.3 years SD ± 9.44; 60.6% female). There was a significant difference in the prevalence of hypertension in the three age groups (30–40 years, 41–50 years, and > 50 years) (*P*-value < 0.001).

Dependent and Independent Variables

In this study, prognosis was not defined as survival but as improvement or worsening of the HIV disease status as defined by two dependent (outcome) variables: retroviral loads and CD4-cell counts, an indicator of opportunistic infection. Better prognosis was defined by lower viral load of NAM/aidsmap threshold of ≤ 50 copies/mL and a higher CD4-cell count which, according to WHO, would be a threshold of ≥ 500 cells/μL) [17]. A worse prognosis was defined as having a retroviral load above and CD4-cells count below these thresholds.

The main independent variable for this study was the presence of hypertension. Other independent variables were also included because they could possibly affect outcomes and confounding results. Based on our literature review, they were adherence, age, sex, isoniazid preventive therapy (IPT), residence or administrative region, WHO HIV staging, year of study, and adverse effects. Adherence was categorized in this study into underuse, close adherence and overuse of prescribed ART medications based on pill counts collected from the patients' medical records. Pill count scores below 90% (underuse) were defined as poor adherence, those between 95% – 105% (close adherence) were defined as good adherence, and > 105% (overuse) were defined as excessive. The patients were divided into three age ranges, 30–40 years, 41–50 years, and > 50 years.

Data Collection and Management

The data from medical records were extracted using a 28-item standardized case-report form with three sections, one collecting socio-demographic data, another collecting medical history, and the other collecting laboratory results. The data were collected from July 27, 2018 to September 8, 2018 by the principal investigator. To ensure anonymity and confidentiality, no identifying information (such as names) was recorded. Instead, each patient was assigned an identification code to be matched anonymously with his or her data.

Data Analysis

Group continuous variables were analyzed descriptively and expressed as median with interquartile range (IQR) and mean ± standard deviation (SD) and categorical variables were expressed as frequency and percentages. Means (± SD) were used for normally distributed continuous data and median and IQR for skewed data. Chi-square (χ^2) test was used to compare proportional differences between different levels of categorical independent variables. For multivariate analysis, the Generalized Estimated Equations (GEE) model was employed to study the relationship between independent variables and dependent variables in a unified analysis and subgroup analysis. Odds ratios were reported with 95% confidence intervals (CI). *P*-values < 0.05 were considered significant. All statistical operations were performed using IBM SPSS version 22.

Ethical Considerations

The protocol for this study was approved by the National Health Research Review Board (NHRRB) at the Eswatini Ministry of Health on July 24, 2018. The need for written consent was waived by the NHRRB because anonymity of the participants was ensured during the patients' files review, and there was no direct contact or interaction with participants. All methods were carried out in accordance with the relevant guidelines and regulations which pertain to use of humans as participants of a study.

Results

Participant characteristics

As can be seen in Table 1, male participants had a mean age of 44 years (SD ± 8.61) (female 62.9%). Non-hypertensive male participants were 41.7 years old (SD ± 7.12) (female 60.6%), and hypertensive male participants 47.3 years (SD ± 9.44) (female 66%). Most subjects were 30–40 years old, 33.4% were 41–50, and 29.4% >50. Fifty-six percent (56%) of the non-hypertensive patients were 30–40 years old. Of those who had hypertension,

36.2% were 41–50 years old and 34.5% were > 50. The difference in prevalence of hypertension among the three age groups was significant (Chi-square, *P*-value < 0.001).

Table 1
Socio-demographic Characteristics of Study Subjects

		Total (N = 560)	*Presence of Hypertension*		P-value
			No (n = 325)	Yes (n = 235)	
Age	30–40	251 (44.8%)	182 (56.0%)	69 (29.4%)	< 0.001*
	41–50	187 (33.4%)	102 (31.4%)	85 (36.2%)	
	> 50	122 (21.8%)	41 (12.6%)	81 (34.5%)	
Mean age ± SD		44.04 ± 8.61	41.71 ± 7.12	47.26 ± 9.44	
Sex	Female	352 (62.9%)	197 (60.6%)	155 (66.0%)	0.2
	Male	208 (37.1%)	128 (39.4%)	80 (34.0%)	
Settlement	Rural	348 (62.1%)	210 (64.6%)	138 (58.7%)	0.09
	Urban and Peri-Urban	212 (37.9%)	115 (35.4%)	97 (41.3%)	
Region	Within Manzini	396 (70.7%)	220 (67.7%)	176 (74.9%)	0.04*
	Outside Manzini	164 (29.3%)	105 (32.3%)	59 (25.1%)	

*SD: standard deviation N: total study population n: subset of study population *: statistically significant P-value >: greater than <: less than*

As can be seen in Table 2, **94**.8% of participants were diagnosed as having WHO HIV stage one disease with the remaining approximately 5% stages two, three, or four. Of those with hypertension, 91.5% had stage one disease. Those diagnosed having stages 2, 3, and 4 were amalgamated into a "stage 2 and higher" group. The stage one group had a significantly higher prevalence of hypertension than the amalgamated stage group (91.5% vs. 8.5%; Chi-square *P*-value = 0.003). Ninety-eight percent of all participants were receiving first line treatment. Those receiving first line treatment had a significantly higher prevalence of hypertension than those receiving second line treatment (99.6% vs. 0.4%; P-value = 0.03). Almost 3.8 percent of the participants (non-hypertensive 2.5%, hypertensive 5.5%) had adverse side effects to ART, with no significant difference between the two groups.

Table 2
Clinical Characteristics of Study Participants

		Total (N = 560)	Presence of Hypertension		P-value
			No (n = 325)	Yes (n = 235)	
W.H.O. HIV Staging	Stage 1	531 (94.8%)	316 (97.2%)	215 (91.5%)	0.003*
	Stage 2–4	29 (5.2%)	9 (2.8%)	20 (8.5%)	
INH Preventive Therapy	No	256 (45.7%)	154 (47.4%)	102 (43.4%)	0.35
	Yes	304 (54.3%)	171 (52.6%)	133 (56.6%)	
ART Line of Treatment	1st Line	549 (98.0%)	315 (96.9%)	234 (99.6%)	0.03*
	2nd Line	11 (2.0%)	10 (3.1%)	4 (0.4%)	
Has Adverse Effects for ART	No	539 (96.3%)	317 (97.5%)	222 (94.5%)	0.07
	Yes	21 (3.8%)	8 (2.5%)	13 (5.5%)	
Had Drug Substitution	No	504 (90.0%)	299 (92.0%)	205 (87.2%)	0.04*
	Yes	56 (10.0%)	26 (8.0%)	30 (12.8%)	
Adherence	Poor	119 (21.3%)	72 (22.2%)	47 (20.0%)	0.76
	Good	391 (69.8%)	223 (68.6%)	168 (71.5%)	
	Excessive	50 (8.9%)	30 (9.2%)	20 (8.5%)	

*N: total study population n: subset of study population *: statistically significant P-value INH: isoniazid W.H.O.: World Health Organization HIV: Human Immunodeficiency Virus ART: Antiretroviral Therapy*

Viral Loads and CD4-cell Counts

Table 3 provides a summary of our two HIV related outcomes, which were successfully controlled retroviral load (< 50 copies/mL, controlled status) and healthy CD4-cell count (≥ 500 cells/μL), in non-hypertensive and hypertensive participants. A large majority in both groups had retroviral loads < 50 copies/mL over a four-year period, ranging from 93.2–97.4% in non-hypertensive participants and 95.1–97.2% in those with hypertension. Poorly controlled retroviral load (≥ 50 copies/mL) was found in 2.9%, 4.5%, 4.6% and 4.5% of all participants in 2015, 2016, 2017, and 2018, respectively. With regard to immune status among all participants, 65.3%, 59.9%, 53.9% were found to have CD4-cell counts of < 500 cells/μL in 2015, 2016, and 2017, while more than half had CD4-cell counts of ≥ 500 cells/μL in 2018. Median CD4-cell counts expressed along with interquartile (IQR) ranges were 398 (257–568) in 2015, 441 (302–613) in 2016, 476.5 (349–613) in 2017, and 521.5 (368–689) in 2018.

Table 3
HIV Related Outcomes

		WITHOUT HYPERTENSION				WITH HYPERTENSION				TOTAL			
		Time (year)				Time (year)				Time (year)			
		2015 (n = 325)	2016 (n = 325)	2017 (n = 325)	2018 (n = 325)	2015 (n = 235)	2016 (n = 235)	2017 (n = 235)	2018 (n = 235)	2015 (N = 560)	2016 (N = 560)	2017 (N = 560)	2018 (N = 560)
Viral Load	< 50	315 (96.9%)	316 (97.2%)	309 (95.1%)	311 (95.7%)	229 (97.4%)	219 (93.2%)	225 (95.7%)	224 (95.3%)	544 (97.1%)	535 (95.5%)	534 (95.4%)	535 (95.5%)
	≥ 50	10 (3.1%)	9 (2.8%)	16 (4.9%)	14 (4.3%)	6 (2.6%)	16 (6.8%)	10 (4.3%)	11 (4.7%)	16 (2.9%)	25 (4.5%)	26 (4.6%)	25 (4.5%)
Median (IQR)		*10 (5–16)*	*11 (6–16)*	*11 (6–17)*	*11 (6–16)*	*10 (6–15)*	*11 (6–16)*	*12 (6–17)*	*12 (6–16)*	*10 (6–15)*	*11 (5–16)*	*11 (6–17)*	*11 (6–16)*
CD4-Cell Count	< 500	224 (73.9%)	217 (67.2%)	182 (56.3%)	162 (50.5%)	117 (53.4%)	117 (49.8%)	119 (50.6%)	92 (39.5%)	341 (65.3%)	334 (59.9%)	301 (53.9%)	254 (45.8%)
	≥ 500	79 (26.1%)	106 (32.8%)	141 (43.7%)	159 (49.5%)	102 (46.6%)	118 (50.2%)	116 (49.4%)	141 (60.5%)	181 (34.7%)	224 (40.1%)	257 (46.1%)	300 (54.2%)
Median (IQR)		*338 (234–514)*	*402 (284–569)*	*456 (330–617)*	*496 (352–665)*	*466 (318–624)*	*501.5 (347–672)*	*497 (371–706)*	*463.5 (406–718)*	*398 (257–568)*	*441 (302–613)*	*476.5 (349–652)*	*521.5 (368–689)*

N: total study population n: subset of study population IQR: interquartile range <: less than ≥: greater than or equals to

Overall viral load and CD4-cell count trends in those with and without hypertension

According to Fig. 2, the probability that retroviral loads would be ≥ 50 copies/mL was 3.1% in non-hypertensive participants and 2.8% in those with hypertension in 2015 and 2016, respectively, though not significant (95% CIs 2.7%-3.5% for 2015; 2.4%-3.1% for 2016). Overall trend was not significant (*P*-value = 0.17). Hypertensive participants had a 2.6% (95% CI: 2.4%-2.8%) and 6.8% (95% CI: 6.3%-7.3%) probability of having retroviral loads of ≥ 50 copies/mL in 2015 and 2016, respectively. This increase was marginal and overall trend was insignificant (*P*-value = 0.80). The difference between the two groups was also insignificant (*P*-value = 0.70). As can be seen in Fig. 3, there was significant change in probability of having CD4-cell counts ≥ 500 cells/μL in both groups over the study period (*P*-value < 0.001). There was also a significant difference in the increased probability between the two groups (*P*-value = 0.01) overall, except in 2017 when hypertensive participants saw only a slight decrease.

Association between confounding factors and outcomes in all participants

A Generalized Estimated Equations (GEE) model was used to study the association between possible confounding factors (hypertension, age, sex, residency, IPT, WHO HIV stage, ART line of treatment, adverse/side effects, drug substitution, adherence, and time) and our outcome variables. As can be seen in Table 4, hypertensive participants were more likely to have detectable retroviral loads (OR = 1.37), after adjustment for other variables, though insignificant (*P*-value = 0.29). Participants receiving second line ART treatment were more likely to have a detectable retroviral load (OR = 7.91; P-value < 0.001). Table 5 shows that hypertensive participants were also more likely to have CD4-cell counts ≥ 500 cells/μL (OR = 1.83; P-value < 0.001). There were other variables, including age, gender, IPT, retroviral load, and adherence, significantly associated with CD4-cell counts. Patients 41–50 years old, males, and those with detectable retroviral loads were less likely to have CD4-cell counts of ≥ 500 cells/μL compared to their counterparts (OR = 0.73, *P*-value = 0.048; OR = 0.48, *P*-value < 0.001; and OR = 0.62, *P*-value = 0.04, respectively). Participants with good adherence were more likely to have CD4-cell counts of ≥ 500 cells/μL (OR = 1.64, *P*-value = 0.01). The year of study was also significantly related to this outcome variable, 2015 vs. 2016 (OR = 1.32, *P*-value = 0.004), 2017 (OR = 1.71, *P*-value < 0.001), and 2018 (OR = 2.44, *P*-value < 0.001).

Table 4
Factors Associated with Viral Load

Parameter	Odds Ratio	95%CI of Odds Ratio		*P*-value
		Lower	Upper	
Hypertension vs. Non-hypertension	1.37	0.77	2.43	0.29
Age > 50 years vs. Age 30–40 years	0.76	0.36	1.60	0.48
Age 41–50 years vs. Age 30–40 years	0.87	0.49	1.55	0.64
Male vs. Female	1.06	0.61	1.83	0.84
On IPT vs. Not on IPT	1.50	0.85	2.64	0.16
HIV Stage 2–4 vs. HIV Stage 1	1.31	0.49	3.50	0.59
2nd Line Treatment vs. 1st Line Treatment	7.91	2.53	24.68	< 0.001*
Had Adverse Effects vs. Had no Adverse Effects	1.89	0.73	4.86	0.19
Had Drug Substitution vs. Had no Drug Substitution	1.73	0.85	3.52	0.13
Excessive Adherence vs. Poor Adherence	1.89	0.78	4.61	0.16
Good Adherence vs. Poor Adherence	0.80	0.39	1.66	0.55
2018 vs. 2015	1.60	0.84	3.07	0.15
2017 vs. 2015	1.68	0.91	3.09	0.10
2016 vs. 2015	1.61	0.91	2.86	0.10
**: statistically significant P-value IPT: Isoniazid Preventive Therapy HIV: Human Immunodeficiency Virus*				
>: greater than CI: confidence interval <: less than vs.: versus				

Table 5
Factors Associated with CD-4 Cell Counts

Parameter	Odds Ratio	95%CI of Odds Ratio		*P*-value
		Lower	Upper	
Hypertension vs. Non-hypertension	1.83	1.37	2.44	< 0.001*
Age > 50 years vs. Age 30–40 years	0.95	0.66	1.38	0.81
Age 41–50 years vs. Age 30–40 years	0.73	0.532	0.997	0.048*
Male vs. Female	0.48	0.36	0.64	< 0.001*
On IPT vs. Not on IPT	1.53	1.16	2.01	0.002*
HIV Stage 2–4 vs. HIV Stage 1	0.83	0.44	1.53	0.54
2nd Line Treatment vs. 1st Line Treatment	0.73	0.29	1.89	0.52
Had Adverse Effects vs. Had no Adverse Effects	0.54	0.26	1.11	0.10
Had Drug Substitution vs. Had no Drug Substitution	1.01	0.64	1.59	0.96
Excessive Adherence vs. Poor Adherence	1.47	0.88	2.47	0.14
Good Adherence vs. Poor Adherence	1.64	1.15	2.33	0.01*
2018 vs. 2015	2.44	2.00	2.98	< 0.001*
2017 vs. 2015	1.71	1.40	2.09	< 0.001*
2016 vs. 2015	1.32	1.09	1.60	0.004*
Viral load ≥ 50 c/mL vs. Viral load < 50 c/mL	0.62	0.40	0.98	0.04*
**: statistically significant P-value IPT: Isoniazid Preventive Therapy HIV: Human Immunodeficiency Virus*				
>: greater than ≥: greater than or equals to CI: confidence interval <: less than vs.: versus				

Association between confounding factors and outcomes in non-hypertensive and hypertensive participants

As can be seen in Table 6, in non-hypertensive participants, there was a significant association between retroviral load and adverse/side effects as well as line of ART (OR = 3.50, *P*-value = 0.04 and OR = 8.61, *P*-value < 0.001, respectively). In hypertensive participants, retroviral load was significantly associated with 2015 vs. 2016 time-point, HIV stage, and adherence (OR = 2.85, *P*-value = 0.02; OR = 2.84, *P*-value = 0.04; OR = 8.08, *P*-value = 0.02). Table 7 shows a significant association between sex, IPT, time of study, as well as retroviral load and CD4-cell counts in non-hypertensive participants (*P*-value < 0.05). In hypertensive participants, CD4-cell counts were significantly associated with age, gender, line of treatment, adherence, and time to some extent (*P*-value < 0.05). In both subgroups, males were less likely to have CD4-cell counts ≥ 500 cells/μL (non-hypertensive, OR = 0.53, *P*-value = 0.001; hypertensive, OR = 0.36, *P*-value < 0.001).

Table 6
Factors associated with viral load, stratified by the presence of hypertension

	Without Hypertension		**With Hypertension**	
Parameter	**Odds Ratio (95% CI)**	P-**value**	**Odds Ratio (95% CI)**	P-**value**
Age > 50 vs. Age 30–40 years	0.48 (0.13–1.79)	0.28	0.66 (0.22–1.97)	0.45
Age 41–50 vs. Age 30–40 years	0.95 (0.43–2.10)	0.90	0.70 (0.27–1.85)	0.47
Male vs. Female	0.78 (0.37–1.67)	0.53	1.44 (0.62–3.33)	0.39
On IPT vs. Not on IPT	1.80 (0.84–3.86)	0.13	1.05 (0.44–2.51)	0.91
HIV Stage 2–4 vs. HIV Stage 1	0.34 (0.07–1.70)	0.19	2.84 (1.03–7.85)	0.04*
2nd Line Treatment vs. 1st Line Treatment	8.61 (2.93–25.34)	< 0.001*	—	—
Had Adverse Effects vs. No Adverse Effects	3.50 (1.06–11.54)	0.04*	1.35 (0.38–4.73)	0.66
Had Drug Substitution vs. No Drug Substitution	2.22 (0.83–5.94)	0.11	1.33 (0.46–3.79)	0.60
Excessive Adherence vs. Poor Adherence	0.72 (0.21–2.46)	0.60	8.08 (1.33–49.04)	0.02*
Good Adherence vs. Poor Adherence	0.45 (0.18–1.10)	0.08	2.75 (0.45–16.83)	0.27
2018 vs. 2015	1.45 (0.62–3.42)	0.39	1.90 (0.66–5.43)	0.23
2017 vs. 2015	1.69 (0.79–3.63)	0.18	1.71 (0.59–4.97)	0.32
2016 vs. 2015	0.89 (0.37–2.14)	0.80	2.85 (1.22–6.69)	0.02*
**: statistically significant P-value IPT: Isoniazid Preventive Therapy HIV: Human Immunodeficiency Virus*				
>: greater than CI: confidence interval <: less than vs.: versus —: independent variable has colinearity with independent variable				

Table 7
CD4-cell count association with independent variables, stratified by hypertension

	Without Hypertension		With Hypertension	
Parameter	**Odds Ratio (95% CI)**	P-**value**	**Odds Ratio (95% CI)**	P-**value**
Age > 50 vs. Age 30–40 years	0.98 (0.54–1.77)	0.94	0.89 (0.54–1.45)	0.63
Age 41–50 vs. Age 30–40 years	0.88 (0.58–1.32)	0.53	0.61 (0.37–0.98)	0.05*
Male vs. Female	0.53 (0.36–0.78)	0.001*	0.36 (0.22–0.57)	< 0.001*
On IPT vs. Not on IPT	1.68 (1.16–2.45)	0.01*	1.44 (0.95–2.17)	0.09
HIV Stage 2–4 vs. HIV Stage 1	1.24 (0.40–3.81)	0.71	0.54 (0.24–1.20)	0.13
2nd Line Treatment vs. 1st Line Treatment	0.54 (0.18–1.63)	0.28	4.67 (2.01–10.86)	< 0.001*
Had Adverse Effects vs. No Adverse Effects	0.60 (0.16–2.27)	0.45	0.54 (0.22–1.37)	0.19
Had Drug Substitution vs. No Drug Substitution	1.69 (0.87–3.29)	0.12	0.62 (0.35–1.09)	0.10
Excessive Adherence vs. Poor Adherence	0.77 (0.38–1.56)	0.47	4.03 (1.78–9.12)	0.001*
Good Adherence vs. Poor Adherence	1.37 (0.87–2.14)	0.17	2.15 (1.15–4.05)	0.02*
2018 vs. 2015	3.09 (2.37–4.04)	< 0.001*	1.92 (1.39–2.67)	< 0.001*
2017 vs. 2015	2.37 (1.80–3.12)	< 0.001*	1.17 (0.85–1.60)	0.34
2016 vs. 2015	1.43 (1.10–1.86)	0.01*	1.22 (0.90–1.67)	0.20
Viral Load ≥ 50 c/mL vs. Viral Load < 50 c/mL	0.46 (0.25–0.84)	0.01*	0.77 (0.38–1.57)	0.48
**: statistically significant P-value IPT: Isoniazid Preventive Therapy HIV: Human Immunodeficiency Virus*				
>: greater than CI: confidence interval <: less than vs.: versus				

Discussion

In our analysis of all ART patients, the present study found a significant association between hypertension and CD4 cell counts but not retroviral load. This means that hypertensive patients were more likely to have improved CD4-cell counts compared to non-hypertensive patients. In non-hypertensive patients there was a significant association between improved CD4-cell counts and being female, IPT, undetectable retroviral load, and time of study. In hypertensive patients, the variables significantly associated with improved CD4-cell count were younger age, 2nd line of ART, better adherence, and time of study.

This study found an increase in CD4-cell counts over time in both groups of patients, as has been previously reported [18–20]. The hypertensive patients were found to have higher CD4-cell counts. Other studies found no significant difference in CD4-cell counts in ART patients with and without hypertension [21, 22]. Our results could be explained by the possibility that patients being treated and counseled for hypertension may have better lifestyle habits as they attempt to bring it under control and this may lead to better immune system functioning. However, it is interesting to note that people with hypertension usually have higher BMIs [23]. Koethe *et al.* have reported an association between pre-ART BMI and 12-month change in CD4-cell counts (*P*-value < 0.001) and concluded that a BMI indicative of threshold obesity predicted greater CD4-cell count gains at the beginning of ART [24].

We also found male ART patients to be less likely to have CD4-cell count improvement than females in both groups. One study of 7,354 patients initiating ART between April 2004 and April 2010 in South Africa also found men on ART have less CD4-cell improvement than women [25]. However, a review of eight cohort studies of European populations reported that more women than men seroconverted to HIV, developed AIDS and died with higher CD4-cell counts [26].

We also found that patients receiving IPT were more likely to have higher CD4-cell counts. IPT contributes significantly to prevent incidences of active TB among PLHIV [27, 28]. Therefore, the combination of IPT and ART probably lead to a boost in immunity. We found this to be significant among those without hypertension but insignificant among those with hypertension, possibly suggesting an adverse interaction between hypertension or hypertension medications and IPT.

We found patients with close adherence to prescriptions to be more likely to have higher CD4-cell counts than those under medication, similar to a longitudinal study in Hunan and Hubei provinces in China [29]. One prospective twelve-month cohort study associated adherence levels of 100%, 80%-90%, and 0%-79% with CD4-cell count increases of 179, 159, and 53 cells/μL, respectively, (*P*-value < 0.001) [30]. In our subgroup analysis,

overmedication was associated significantly with better CD4-cell counts, more particularly with hypertensive patients. Close adherence was also associated significantly with better CD4-cell counts, more particularly with hypertensive patients. However, based on the literature, close adherence is important for everyone, regardless of whether they have hypertension or not. Despite its seemingly lack of effect on immunity, overuse could possibly lead to increased drug toxicity in some patients.

We found patients receiving second line ART to have higher CD4-cell counts than those receiving first line treatment, especially among those with hypertension. Antihypertensive drugs could possibly affect effectiveness of ART. For example, two kinds of ART drugs, NNRTIs (like NVP and EFV) and PIs, are metabolized primarily by CYP34A in the CYP450 system, the same pathway is involved in the metabolism of the hypertension drugs indapamide, calcium channel blockers, and losartan [31].

Patients with detectable viral loads were found to be less likely to have higher CD4-cell counts (OR = 0.62, *P*-value = 0.04). This association was found to be more significant in those without hypertension (OR = 0.46, *P*-value = 0.01), suggesting that the additional healthcare those patients with hypertension were receiving improved their immune system functioning.

While age was not found to be associated with CD4-cell counts, we did find an association between age and increased and decreased CD4-cell counts in patients with hypertension. Among these patients, those 41–50 years old were less likely to have higher CD4-cell counts than those 30–40 years old. Healthy individuals also gradually became immunodeficient over the long term [32, 33]. However, one observational study of HIV patients in Australia found no long-term decline in CD4-cell counts in ART patients [34], suggesting that the level of immune recovery achieved during the first five years of treatment were sustained through long-term ART. In conclusion, it is possible that the presence of hypertension might contribute to decreasing CD4-cell counts in those who are older, though this would require further studies.

This study is based on a retrospective analysis of already collected data from chronic patient files and factors like, alcohol use and smoking status were not available in the files.

Conclusions

ART patients with hypertension were more likely to have higher CD4-cell counts compared to ART patients without hypertension in the whole group analysis. Underuse and overuse of medications, advanced HIV stages, adverse effects, line of treatment, age and sex predicted higher retroviral loads (ART failure) and lower CD4-cell counts in patients with hypertension. More attention may need to be paid to ART patients with well controlled HIV statuses to monitor and control their hypertension status. Medical professionals, who may be overly concerned to control HIV/AIDs, may want to return their focus to the possible development of other chronic diseases, particularly hypertension, because these non-communicable diseases could later result in ART failure.

Abbreviations

ALT: Alanine Aminotransferase Test

ART: Antiretroviral Therapy

ARVs: Antiretrovirals

AST: Aspartate Aminotransferase Test

CI: Confidence Interval

CKD: Chronic Kidney Disease

CYPs: Cytochromes P450

DBP: Diastolic Blood Pressure

EsMoH: Eswatini Ministry of Health

GEE: Generalized Estimated Equations

HAART: Highly Active Antiretroviral Therapy

INH: Isonicotinylhydrazide (Isoniazid)

IPT: Isoniazid Preventive Therapy

NCDs: Non-communicable Diseases

NICE: National Institute for Health and Care Excellence

NNRTIs: Non-nucleoside Reverse Transcriptase Inhibitors

NRTIs: Nucleoside Reverse Transcriptase Inhibitors

OR: Odds Ratio

PAGAA: Panel on Antiretroviral Guidelines for Adults and Adolescents

PAHO: Pan American Health Organization

PEPFAR: President's Emergency Plan for AIDS Relief

PIs: Protease Inhibitors

PLHIV: People Living with HIV

RFMH: Raleigh Fitkin Memorial Hospital

SBP: Systolic Blood Pressure

SCr: Serum Creatinine

SHIMS: Swaziland HIV Incidence Measurement Survey

SNAP: Eswatini National Program

Declarations

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Figures

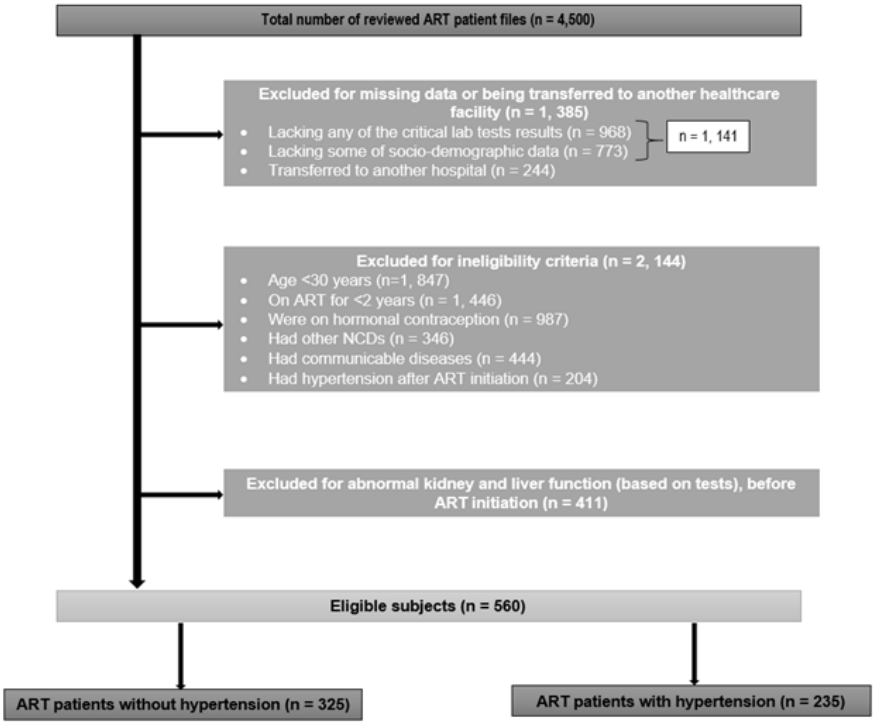
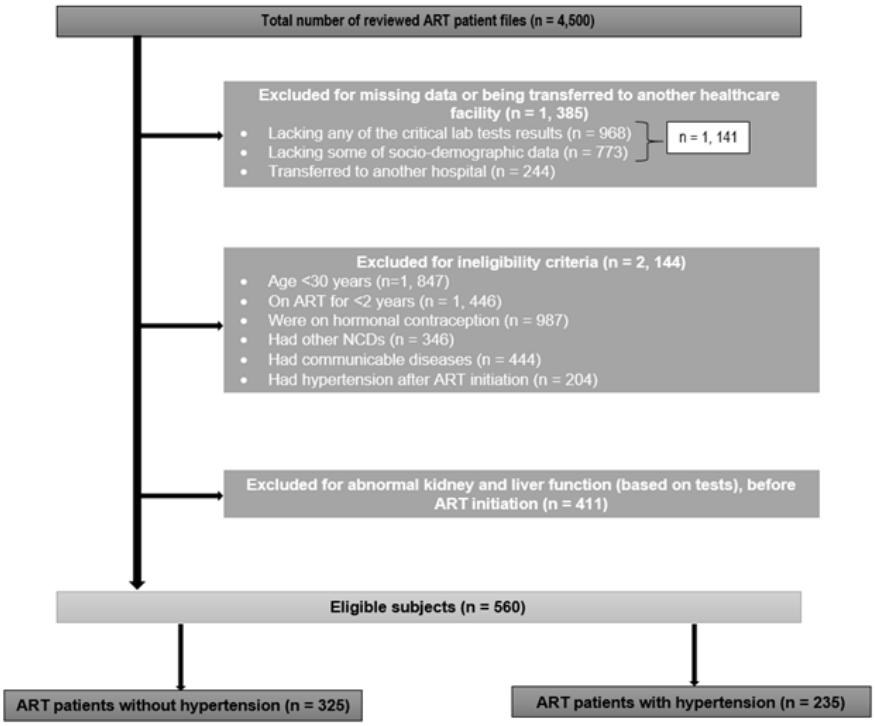


Figure 1

Flow Chart for Exclusion Criteria and Subject Selection Process



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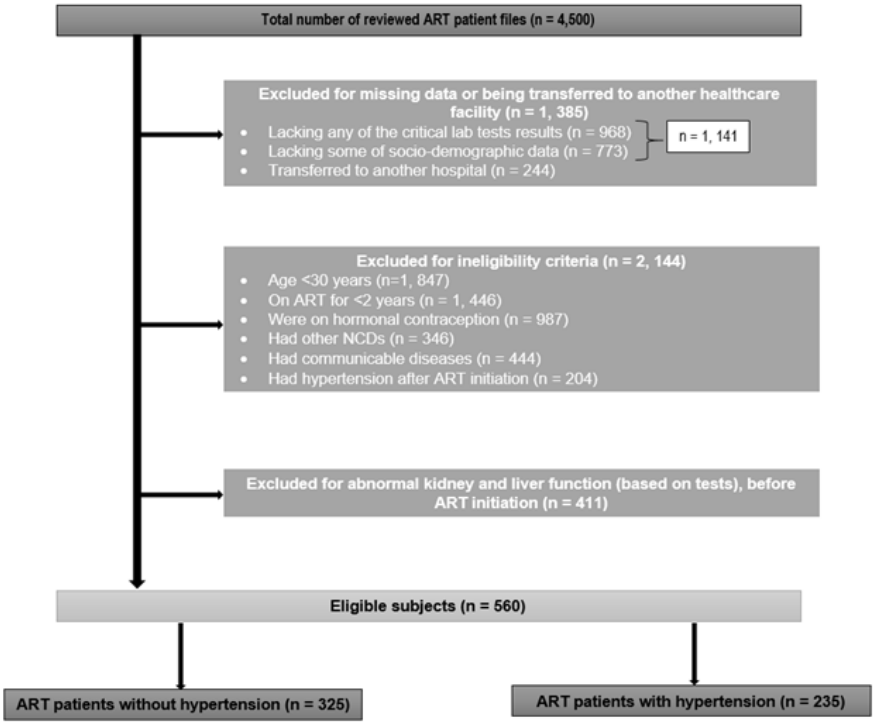

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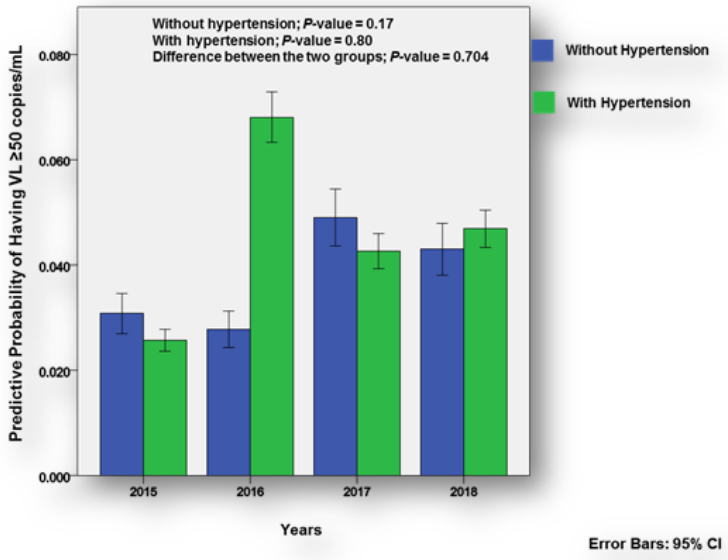
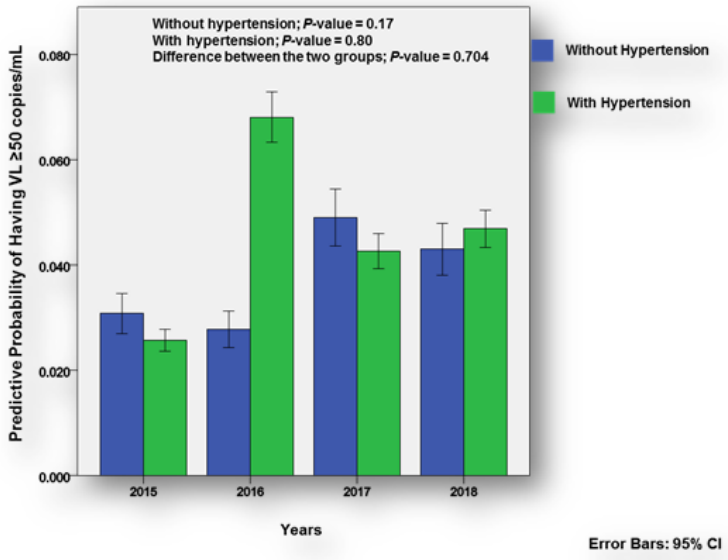


Figure 2

Predictive Probability in Relation to Viral Loads



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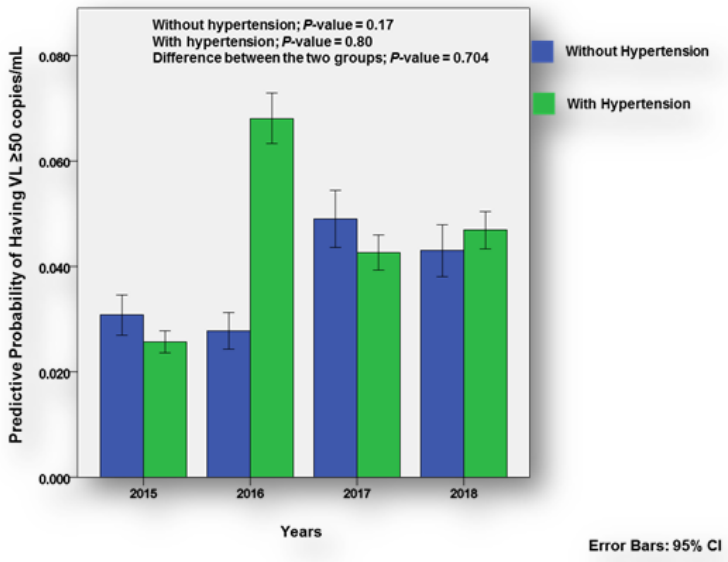

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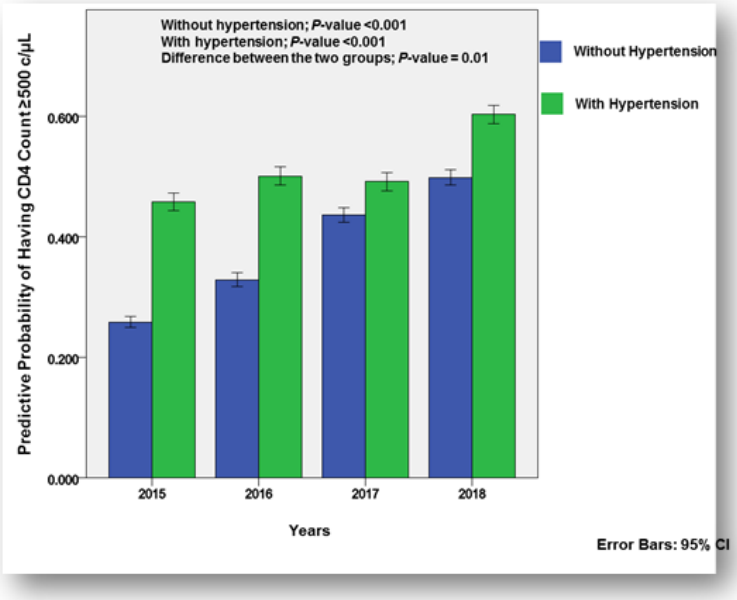
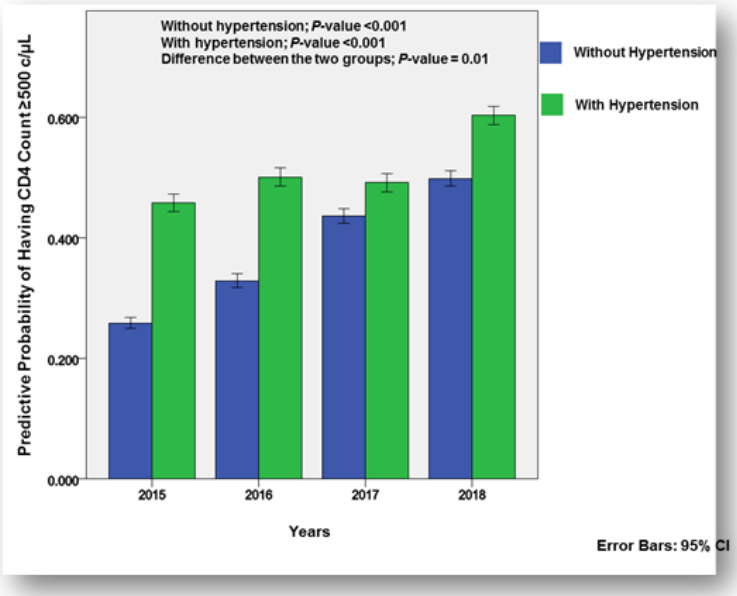


Figure 3

Predictive Probability in Relation to CD4-Cell Counts



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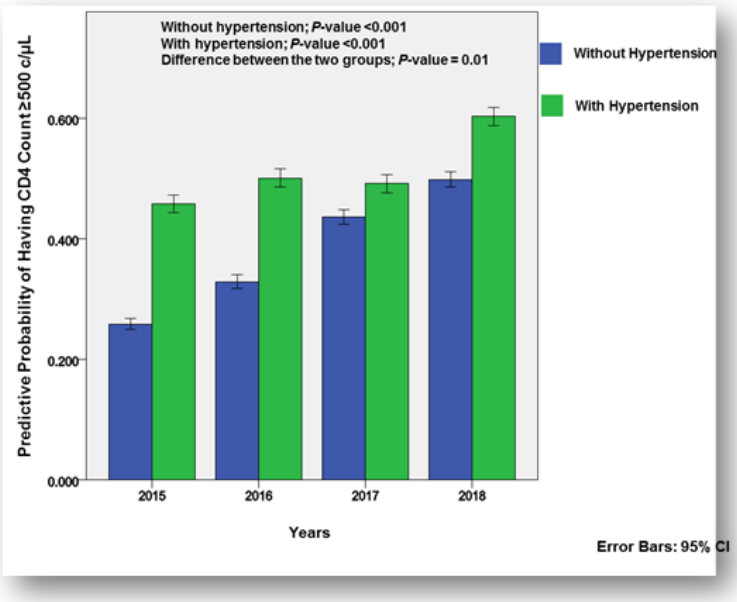

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