

2018; 1(1): 39-45

Published Online: 11/09/2018 (<http://medicine.unza.zm/research/journal>)

doi: 10.21617/jprm.2018.0102.5



## Original Paper

# Effects of Antiretroviral Therapy (Tenofovir/Lamivudine/Efavirenz) on Arterial Stiffness in Black African HIV-1 Infected Men

Phiri S.B<sup>1\*</sup>, Goma F.M<sup>1</sup>, Mulenga L<sup>2</sup>, Sitali M.C<sup>3</sup>, Mukonchi F<sup>1</sup>

<sup>1</sup>The University of Zambia, School of Medicine, Department of Physiological Sciences, Lusaka, Zambia

<sup>2</sup>The University Teaching Hospital, Department of Internal Medicine, Infectious Diseases Division, Lusaka Zambia

<sup>3</sup>The University of Zambia, Faculty of Veterinary Medicine, Department of Biomedical Sciences, Lusaka, Zambia.

Corresponding author: phirisamb@gmail.com

### To cite this article:

Phiri S.B, Goma F.M, Mulenga L, Sitali M.C, Mukonchi F. Effects of antiretroviral therapy (Tenofovir/Lamivudine/Efavirenz) on arterial stiffness in black African HIV-1 infected men. *Journal of Preventive and Rehabilitative Medicine*, Vol. 1, No. 1, 2018, pp. 39-45. doi: 10.21617/jprm.2018.0102.5

## ABSTRACT

**Background:** Cardiovascular diseases are a leading cause of morbidity and mortality worldwide, especially in people living with HIV (PLHIV) as they are said to be more prone. The introduction of combination antiretroviral therapy (cART) has greatly improved the life span of HIV-infected persons. However, its use has been implicated to be a factor in increasing arterial stiffness, a marker of cardiovascular risk. Pulse Wave Velocity (PWV), a surrogate measure of arterial stiffness, is said to be raised in PLHIV on ART.

**Aim:** This study was conducted to determine the effects of cART (Tenofovir/Lamivudine/Efavirenz) on arterial stiffness in HIV-1 infected men after the first month of treatment.

**Methods:** A prospective observational study in Lusaka, Zambia was done over a 3 month period from April to June, 2017. A systematic sampling technique with a sampling interval of 5 was used to recruit 26 HIV-1 positive newly diagnosed male cART-naïve participants, between the ages of 20 and 40 years at Adult Infectious Diseases Center (AIDC), University Teaching Hospital (UTH). Two data forms were used to collect data, a short questionnaire and Clinical entry tool for demographical and clinical information respectively. A Complior® Analyse device (Version 1.9 Beta 2013; ALAM-Medical, France) was used by noninvasively accessing superficial pulses over the carotid-femoral (cf) and carotid-radial (cr) segments.

**Results:** Major findings showed that cART was associated with a significant increase in mean crPWV and crASI from their initial measurements in stage 1 compared to the second measurements in stage 2 (crPWV 10.02±2.06 m/s Vs 11.78±1.23 m/s, p= 0.001) and (crASI 24 ± 4.62 m/s Vs 28±2.8 m/s, p= 0.002) respectively. The measurements for cfPWV and cfASI did not show a significant change statistically even though there was a numerical increase (cfPWV 8.43±1.34 m/s Vs 8.68±1.74 m/s, p= 0.490) and (cfASI 27.37 ± 3.88 m/s Vs 28.59±5.57 m/s, p= 0.295) respectively.

**Conclusion:** The cART use for a month was associated with a significant increase in PWV and ASI in arteries of HIV-1 infected participants suggesting probable interaction of cART with vascular pathophysiological factors in this population. It is advised that patients on cART be closely monitored for cardiovascular risk factors. This must start early in the treatment period.

**Key words:** Pulse wave velocity, arterial stiffness, arterial stiffness index, HIV-1 positive, combination antiretroviral therapy, black African men.

## 1. Introduction

Worldwide, cardiovascular diseases are a leading cause of morbidity and mortality [1]. Human Immunodeficiency Virus (HIV) infected individuals are relatively more prone to cardiovascular diseases (CVD) [2]. This being exacerbated by the increase in age due to the introduction of Antiretroviral Therapy (ART) that has extended the life span of these patients hence giving ample time for the CVD to develop and manifest [3, 4].

Arterial stiffness is described as hardening of the arterial walls due to endothelial wall dysfunction as well as loss of elastin [5, 6]. This affects the ability of large arteries to act as cushion for cardiac output and is an important determinant of the vascular load to the heart [7]. Arterial stiffness can be approximated by measuring the Pulse Wave Velocity (PWV), the velocity at which a pulse wave travels a given arterial segment. PWV is said to be an independent prognostic value for future CVDs and outcome [8]. However arterial stiffness can also be assessed using other markers such as high sensitivity C reactive protein, Interleukin-6, and D-dimer [9].

Studies investigating arterial stiffness in HIV-positive participants with case control design have demonstrated that HIV-positive individuals have increased arterial stiffness compared to HIV-negative individuals [10]. Duration of ART has been documented to be an indicator of further increase in arterial stiffness [8]. However, the minimum length of this duration is not known. This study was aimed at determining arterial PWV in HIV-1 infected men after a month of initiating cART.

## 2. Methodology

### Study Design and Sampling

This prospective observational study investigated arterial stiffness in HIV positive participants prior to cART and after a month of treatment. The study was conducted at AIDC of the UTH, Lusaka. A systematic sampling technique with a sampling interval of 5 was employed in this study.

### Inclusion and Exclusion Criteria

All participants recruited for the study were males, HIV positive, above 20 years of age, cART-naive and non-smokers. All the patients who were above 40 years of age, unable to consent, had history of cardiovascular diseases, with all types of diabetes mellitus, who were on blood pressure medication, with BMI above 30 and waist-hip ratio above 0.90 were excluded from the study.

### Study Procedures

The freely consenting eligible participants were interviewed to note socio-demographic data and health information such as age, smoking, marital

status, history of diabetes or use of hypoglycaemic agents or use of anti-hypertensive medication. Participant details of alcohol consumption, physical exercise, family history, other current medications and any existing pathological conditions were collected at the study visit.

Figure 1 shows the two major stages followed when carrying out the research which started with the recruitment of participants in stage one. Thereafter, participants were exposed to cART (tenofovir/lamivudine/efavirenz). After a month of cART exposure participants returned to AIDC for the second stage measurements.

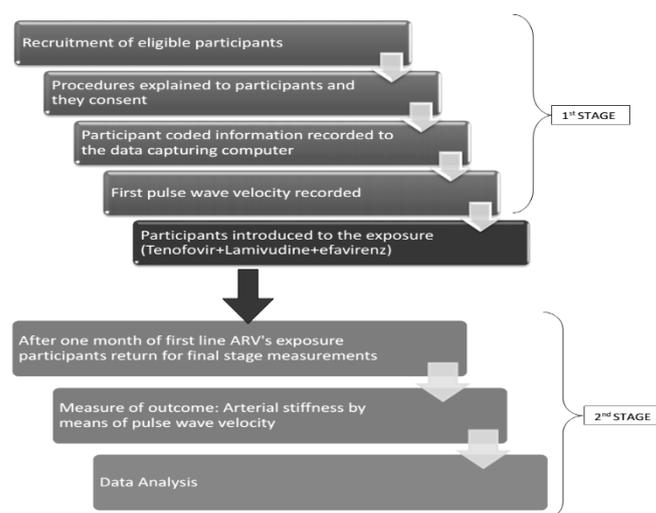


Figure 1: Showing the two major stages followed when carrying out the study

### Pulse Wave Velocity Measurements

In a calm lying participant, the length from the carotid artery (neck) to the femoral artery (groin) and to the radial artery (wrist) was measured using a standard measuring tape. The carotid sensor was slid on the neck holder. Gently, the participant's head was raised, to position the neck holder with the sensor on the carotid artery with the sensitive part of the sensor positioned above the point where the strongest carotid pressure was felt. The participant's groin was then exposed for an easy access to the femoral artery. To get the femoral and radial pressure signal, the sensor was held above the femoral and radial arteries respectively. The Complior Analyse unit was utilised for data acquisition and the values for PWV and transit time were recorded. The entire procedure took about 15 – 20 minutes per participant. Arterial Stiffness Index (ASI) Measurement.

In order to determine the ASI, pulse wave transit time (time delay between systolic peak and diastolic peak) was divided by height and computed by the Complior Analyse. The time delay between systolic peak & diastolic peak is rightly called Pulse Transit Time (PTT or  $\Delta T$ ) which is inversely proportional to

arterial stiffness [11].

### Statistical Analysis

Inferential statistics was used to analyse the data. All statistical analyses were performed using the STATISTIX statistical package for Windows Version 10, 2013. Analysis of Variance (ANOVA) was used for the comparison of participant's parameters before and after a month of cART exposure. Continuous variables were summarised using means and standard deviations.

### Ethical Consideration

The involved procedures were explained to each participant in his own language, followed by the signing of an informed consent form. Ethical approval was granted by University of Zambia Biomedical Research Ethics Committee.

## 3. Results

Demographic and anthropometric data at baseline and after one month of cART. The anthropometric and initial measurements data of HIV-1 positive cART-naïve participants is shown in the Table 1.

**Table 1: Anthropometric and baseline measurements data**

Variable (Unit)	Mean	SD	Min	Max
Age (yrs)	31.50	5.41	20.00	40.00
Height (m)	1.72	0.07	1.56	1.88
Weight (kg)	62.35	11.34	40.00	92.30
BMI (m/kg <sup>2</sup> )	21.14	3.21	16.60	29.79
WHR	0.85	0.04	0.79	0.92
HR ( bpm)	74.13	16.57	59.00	107.00
bSBP (mmHg)	122.98	10.42	104.00	146.00
bDBP (mmHg)	77.19	8.57	56.00	91.00
cSBP (mmHg)	117.46	15.07	94.00	168.00
cDBP (mmHg)	78.30	7.45	64.00	93.00
bMAP (mmHg)	92.56	8.84	78.00	110.00
cMAP (mmHg)	92.58	8.83	78.00	110.00
cfPWV (m/s)	8.43	1.34	6.10	12.00
crPWV (m/s)	10.02	2.06	5.10	13.40
cfASI (m/s)	27.37	3.88	19.92	38.65
crASI (m/s)	24.00	4.62	11.97	31.59

**BMI**=Body Mass Index; **WHR**=Waist to Hip Ratio; **b**=Brachial; **c**=central; **SBP**=Systolic Blood Pressure; **DBP**=Diastolic Blood Pressure; **MAP**=Mean Arterial Pressure; **cf**=carotid-femoral; **cr**; carotid-radial; **PWV**=Pulse Wave Velocity; **ASI**=Arterial Stiffness Index.

The anthropometric and final measurements data of HIV-1 positive participants after a month of cART exposure is shown in the Table 2.

**Table 2: Anthropometric and Final Measurements data after a month of cART.**

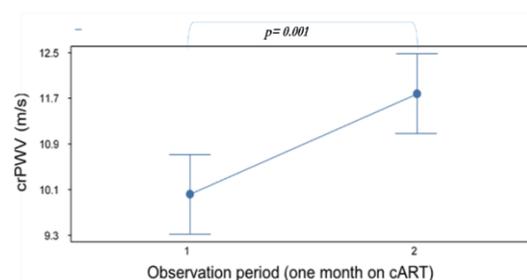
Variable	Mean	SD	Min	Max
Age (yrs)	31.50	5.41	20.00	40.00
Height (m)	1.72	0.07	1.56	1.88
Weight (kg)	63.06	11.41	41.00	92.50
BMI (m/kg <sup>2</sup> )	21.24	3.48	15.00	28.86
WHR	0.86	0.04	0.79	0.93
HR (bpm)	80.94	15.98	62.00	125.00
bSBP (mmHg)	124.38	12.78	100.00	152.00
bDBP (mmHg)	78.25	7.46	64.00	93.00
cSBP (mmHg)	121.15	14.74	99.00	182.00
cDBP (mmHg)	77.2	8.57	56.00	91.00
bMAP (mmHg)	93.38	8.54	74.00	109.00
cMAP (mmHg)	93.38	8.54	74.00	109.00
cfPWV (m/s)	8.68	1.74	6.20	13.70
crPWV (m/s)	11.78	1.23	9.30	14.20
cfASI (m/s)	28.59	5.57	20.99	44.04
crASI (m/s)	28.00	2.80	22.87	34.17

**BMI**=Body Mass Index; **WHR**=Waist to Hip Ratio; **b**=Brachial; **c**=central; **SBP**=Systolic Blood Pressure; **DBP**=Diastolic Blood Pressure; **MAP**=Mean Arterial Pressure; **cf**=carotid-femoral; **cr**; carotid-radial; **PWV**=Pulse Wave Velocity; **ASI**=Arterial Stiffness Index

### Effects of cART (Tenofovir/ Lamivudine/ Efavirenz) on the Pulse Wave Velocity.

#### Effects cART on the crPWV

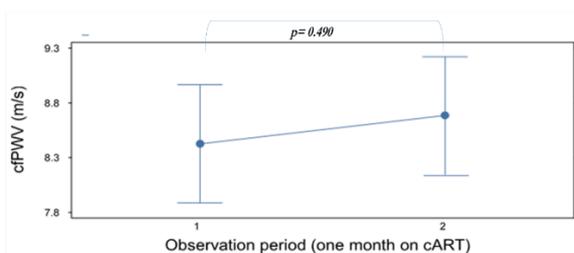
The initial mean crPWV in stage 1 was  $10.02 \pm 2.06$  m/s. This significantly increased to  $11.78 \pm 1.23$  m/s in stage 2 after one month of cART exposure ( $p=0.001$ ).



**Figure 2. Showing mean crPWV (m/s) before and after cART**

#### Effects cART on the cfPWV

The mean cfPWV in stage 1 was  $8.43 \pm 1.34$  m/s. This increased to  $8.68 \pm 1.74$  m/s in stage 2 after one month of cART exposure but was not statistically significant. There was no statistical significant difference between the observed cfPWV means in stage 1 as compared to stage 2 with  $p=0.490$  as illustrated in figure 3. Even though the two means were not significantly different there was a noticeable numerical increase.

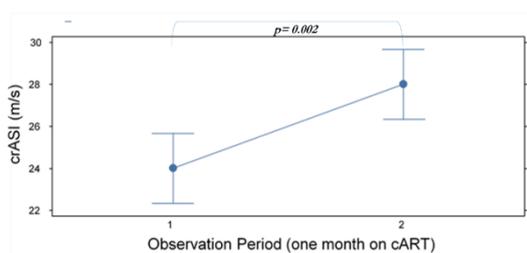


**Figure 3. Mean cfPWV (m/s) before and after cART exposure.**

#### Effects of cART on the Arterial Stiffness Index

##### Effects cART on the crASI

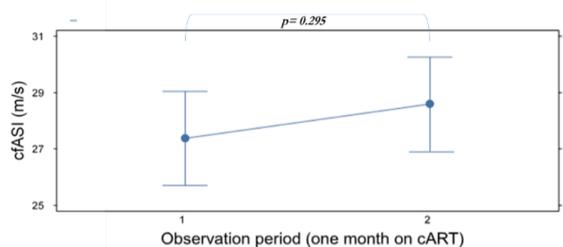
Figure 4 shows the mean crASI in stage 1 being  $24 \pm 4.62$  m/s. This increased to  $28 \pm 2.8$  m/s in stage 2 after one month of cART exposure. There was a statistically significant difference between the observed crASI means ( $p=0.002$ ).



**Figure 4. Mean crASI (m/s) before and after cART exposure.**

##### Effects of cART on the cfASI

Figure 5 shows that the mean cfASI in stage 1 was  $27.37 \pm 3.88$  m/s. Although this increased to  $28.59 \pm 5.57$  m/s in stage 2 after one month of cART exposure, the magnitude of increase was not statistically significant ( $p=0.295$ ).



**Figure 5 Showing mean cfASI (m/s) before and after cART exposure.**

## 4. Discussion

To the best of our knowledge, this study is the first to use PWV in assessing arterial stiffness in newly diagnosed HIV-infected participants in Zambia. In this study, all the participants were newly diagnosed

HIV-infected men between the ages of 20 and 40 with the mean age of  $31 \pm 5$  years and the majority of the participants were falling in the age category of 31 to 34 years. This was therefore a relatively young cohort. The arteries are said to be as old as the age of an individual, with an increase in the age there is a decrease in nitric oxide synthesis and elastin fragmentation and degradation leading to the loading of collagen fibers in the arterial tree this ultimately result in an increased arterial stiffness [12]. Although age is a known factor that has an influence on arterial stiffness [13], it is not expected to have played a major role in the alterations documented in this relatively young population. Pulse wave velocity values for HIV-1 Infected cART-Naïve Participants

The initial crPWV and cfPWV measured in stage 1 for HIV-1 infected cART-naïve participants were  $10.02 \pm 2.06$  m/s and  $8.43 \pm 1.34$  m/s respectively. These values are relatively higher in comparison with those reported by [13] of crPWV 9.09 m/s and cfPWV 8.07 m/s respectively. The difference in these mean PWV values could be due to the fact that Echeverria [13] included females in their study population. Sex is an established independent determinant of PWV, females have a lower PWV when compared to males [14]. The above variations could also be due to difference in age inclusion criterion, sample size, participant's heights, and/or race among other factors. Some studies have reported that whites have a lower PWV compared to their age/sex matched blacks [15].

The cfPWV findings in this study were comparable to the ones reported by Lekakis [10] who found cfPWV value of  $8.1 \pm 1.4$  m/s. However, the PWV values recorded in stage 1 (baseline) were relatively higher than the normal age matched reference values [16]. These higher values may be associated with the higher PWV reported in HIV-infected individuals. This is in agreement with previous studies that have shown that HIV-infected individuals have a higher PWV compared to the uninfected age matched controls [13, 17]. The HIV triggers a chronic vascular inflammatory response which ultimately leads to arteries becoming less compliant or stiff. The arterial wall structural difference in different arterial segments has a bearing on PWV. In the same line crPWV and cfPWV values are also influenced by the structural and functional properties of the radial and femoral arteries respectively [18]. Radial artery is more muscular with less elastic fibers compared to the elastic femoral artery that contains more collagen and elastic fibers which offers it an ability to accommodate more blood for a small rise in pressure [18]. Most researchers use cfPWV (synonymous to aortic PWV) to determine arterial stiffness as it is considered the gold standard in measurement of arterial stiffness [19]. Although this

is well established fact, it does not rule out the use of crPWV since arterial stiffness is also demonstrated along this arterial segment.

### **Effects of cART (Tenofovir/ Lamivudine/ Efavirenz) on Arterial Stiffness**

#### **Effects of cART on Pulse Wave Velocity (PWV)**

There was a significant increase in crPWV during the first month of cART. This was in agreement with what has been reported in other studies [20]. Duration of cART treatment is one of the factors that is associated with an increase in arterial stiffness [21]. However, these studies have evaluated changes over many months thus measuring chronic effects of cART. In this study, duration of cART exposure was for only one month, suggesting involvement of more acute pathophysiological processes that may be responsible.

A number of mechanisms have been proposed for the effects of cART on the cardiovascular system. Combination antiretroviral therapy is known to cause alteration in the lipid metabolism which result in lipodystrophy and/ or dyslipidemia. Lipodystrophy due to insulin resistance has been attributed to the impaired glucose transport and phosphorylation [22]. In another study insulin resistance was noticed after four weeks of cART exposure in HIV-infected individuals [23]. Lipodystrophy leads to stimulation of sympathetic activity, the released catecholamine (Norepinephrine) causes vascular smooth muscle contraction and reduction in the arterial distensibility hence an increase in the PWV [24, 25]. Eric [26] also reported that the use of cART in HIV-infected men was associated with a lower arterial distensibility.

There are multiple factors that have been reported which contribute to dyslipidemia observed in HIV-infected individuals on cART. These factors include altered hepatic synthesis of lipids, inflammation, oxidative stress, direct drug toxicity and also genetic factors [27-30]. Baker [31] presented randomized data that quantified the absolute effect of cART initiation on serum lipids in which they found that total cholesterol and Low density lipoprotein C (LDL-C) increases were greatest among the subgroup that was prescribed efavirenz (EFV). In the current study, EFV was one of the drugs used.

Arterial stiffness is a very complex process which results from the changes in the arterial wall at different levels. The vascular wall stability largely depends on the balance between two main scaffolding proteins collagen and elastin. Combination antiretroviral therapy used in the present study causes a reduction in the cathepsin

levels, an enzyme which breaks down collagen [32]. This may result in the dysregulation of collagen-elastin balance, with collagen production dominating over normal elastin whose quantities diminish in arterial walls and eventually result in arterially stiffness and an increase in PWV [33].

#### **Effects of cART on Arterial Stiffness Index (ASI)**

The mean crASI and cfASI observed in stage 1 of this study were higher compared to the baseline values obtained in another study [34], that observed the ASI baseline values in HIV uninfected black men smokers. The above comparison may suggest that the HIV virus has more effect on arterial stiffness than smoking.

The mean crASI in stage 1 increased significantly after one month of cART exposure. The cART was associated with a significant increase in mean crASI but not in mean cfASI. These findings may suggest that the effects of cART on arterial wall in HIV-1 infected men may occur preferentially, or earlier, on the muscular than elastic arteries [35].

### **Conclusion and Recommendation**

This study shows that cART is associated with an increase in arterial stiffness in HIV-1 infected black African men after a month of treatment. These findings suggest that the effect of cART on arterial wall may occur preferentially, or earlier, on the muscular than elastic arteries. This further proposes the invocation of more acute pathophysiological mechanisms that may be associated with processes of vasoconstriction or diminished distensibility or a combination of the two.

It is advised that PLHIV on cART be closely monitored for factors of cardiovascular pathology to mitigate against the increase in events reported in this population. Some of these pathophysiological alterations may have quite an early onset in the process of clinical management. To take these findings to the next level, further studies need to be conducted on a larger scale and longer periods of observation time.

### **Acknowledgement**

We sincerely thank the Lusaka Apex Medical University (LAMU) for the financial support rendered towards this work.

### **Conflict of Interest**

The authors declare no conflict of interest

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