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Title: Blood pressure and body composition during first year of antiretroviral therapy in people with HIV compared to HIV-uninfected community controls

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Abstract

Background: Body composition changes may explain rapid increase in blood pressure (BP) in People with HIV (PWH) during the first year of antiretroviral therapy. Longitudinal studies are lacking.

Methods: We analyzed data from a cohort study of PWH and HIV-uninfected adults from the same communities in Mwanza, Tanzania. BP and body composition data were collected at baseline and 12 months follow-up. We used multivariable linear regression to compare BP changes in PWH and HIV-uninfected adults, and the relationship between changes in body composition and changes in BP.

Results: BP data was available for 640 PWH and 299 HIV-uninfected adults. Sixty four percent were women and the mean age was 38 years. In PWH, systolic BP (mmHg) increased from 114–118, but decreased from 125–123 in HIV-uninfected. Diastolic BP (mmHg) increased from 76–78 in PWH but remained unchanged (82) in HIV-uninfected. Fat mass increased by 1.6 kg on average in PWH and was strongly correlated with change in BP in PWH but not in HIV-uninfected adults. Even after adjusting for changes in body composition the BP in PWH increased more rapidly than in HIV-uninfected adults. In the fully adjusted model, PWH experienced a 4.9 (95% CI: 3.6–7.7) greater increase in systolic BP and a 1.24 (95% CI: 0.02–2.45) greater increase in diastolic BP.

Conclusions: Change in fat mass explains only part of BP increase in PWH starting antiretroviral therapy. BP monitoring and interventions to prevent excessive increase in fat mass are warranted in this population.

BACKGROUND

Since the rollout of highly active antiretroviral therapy (ART) in many sub-Saharan Africa (SSA) countries, there has been a considerable reduction in HIV-related morbidity and mortality.[1] Despite the benefits of ART, cardiovascular disease continues to rise in people with HIV (PWH).[2,3]

High blood pressure (BP), the most common modifiable risk condition for cardiovascular disease,[4] is highly prevalent among PWH.[5] In particular, HIV-infected adults appear to experience a rapid increase in BP during the first few years after ART initiation.[6]

The rapid increase in BP in PWH starting ART may be associated with healthy weight gain – the so-called “return to health” phenomenon - during the first few years of ART.[7] Prior to ART initiation PWH in SSA are often malnourished[8] and have lower BP than HIV-uninfected individuals.[4,6,9] Longitudinal studies are needed to understand the associations between weight gain and change in BP in PWH starting ART.

We conducted a one-year prospective cohort study involving a large sample of PWH starting ART and HIV-uninfected adults selected from the same communities. We investigated the relationship between changes in body composition with BP over time. Our hypotheses for the study were: (1) changes in BP are strongly correlated with change in body composition in PWH during the first year of ART; and (2) changes in body composition explain some, but not all of the greater increase in BP in PWH.

METHODS

Study design

This one-year prospective cohort study was nested in a larger study on diabetes and associated complications in HIV patients in Mwanza, the Chronic Infections, Co-morbidities and Diabetes in Africa (CICADA) study, registered at https://clinicaltrials.gov as NCT03106480.

Recruitment of study participants

Participant recruitment strategies have been described in detail elsewhere;[10] the current study included only ART-naïve PWH and HIV-uninfected controls newly recruited from January to November 2017. In summary, PWH were recruited from five HIV care and treatment clinics (CTC) in Mwanza before starting ART. Health care workers from selected CTC were trained about the aims of the study and participants' eligibility criteria. PWH were considered eligible for the study if ≥18 years old, resident in the study area and not planning to relocate during the study period, had documented HIV–positive test results at CTC, and were willing to start ART immediately after study enrollment.

A computer-generated random list of 50% of enrolled ART-naïve PWH was used for random selection of HIV-uninfected adults for enrollment into the study. A field worker visited the street where the index PWH lived. With the help of the street leader, a complete list of households in the area was prepared. Thereafter, we randomly selected three households which were visited one by one until an eligible adult was found. In a situation where we did not find an eligible adult in the first list of randomly selected households, the process was repeated until a potentially eligible participant was identified. HIV-uninfected individuals were tested to ensure their HIV negative status and considered eligible if they resided in the study area and were not planning to relocate during the study period. HIV-uninfected adults were group matched to have the

same frequency as PWH for sex, neighborhood residence, and age (within five year age groups). Pregnant women and terminally ill individuals were excluded from the study.

Data collection

During enrolment visit at the National Institute for Medical Research (NIMR) clinic in Mwanza, study staff confirmed participants' eligibility and administered informed consent. Thereafter we used the World Health Organization (WHO) STEPwise Approach to Chronic Disease Risk Factor Surveillance (STEPS) tool[11] to assess cardiovascular risk factors. We used a clinical questionnaire to collect information on history of hypertension. Body weight was measured using a digital scale (SECA, Hamburg, Germany) to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm using a stadiometer (SECA, Hamburg, Germany). Both weight and height were measured three times and the median values were used to calculate body mass index (BMI). We used a bio-impedance analyzer (Tanita BC418, Tokyo, Japan) to measure fat mass (kg) and fat-free mass (kg). We measured BP using a standard protocol.[12] We used a digital BP monitor (Omron Health Care Manufacturing Vietnam Co., Ltd, Binh Duong Province, Vietnam) with small, medium, or large cuff depending on mid-upper arm circumference to measure BP three times. BP was measured while participants were seated quietly for at least 5 minutes with feet on the floor and the arm at heart level. We measured BP once on each arm and took a third measurement on the arm with the highest BP reading. Participants were asked to keep silent during BP measurements. The average of the three BP readings was used in the analysis.

At 12 months follow-up, we re-administered the clinical questionnaire to collect data on ART, history of hypertension and drug use for hypertension. Anthropometry, body composition and BP data were also collected at 12 months.

Laboratory samples and tests

Using blood samples collected at the enrollment visit, full blood counts were measured using Beckman Coulter AcT5diffAL1779 hematology analyzer (Beckman Coulter Inc., Miami, USA). We measured $CD4^+$ T-cell counts (cells/μL) using CyflowPartec machine (*Partec*GmbH, Munster, Germany).

Definitions

Hypertension was defined as systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg or on treatment for hypertension.[12] Anemia was defined according to the WHO criteria as hemoglobin level (g/dL) <12 for women or <13 for men.[13] Unhealthy alcohol drinking was defined as habitual alcohol drinking of more than two standard drinks/day for women or more than three standard drinks/day for men. BMI (Kg/m^2) was categorized as underweight (<18.5), normal weight, and overweight/obesity (≥25). Abdominal obesity was defined following WHO guidelines as waist circumference >94 cm for men or >80 cm for women.[14]

Data analysis

Data were analysed using Stata 16 data analysis software (College Station, Texas, USA). Participants were included in the analysis if they had BP measurements at enrollment and 12 months follow-up visits. Continuous variables were summarised as appropriate using mean and standard deviation (SD). Categorical variables were summarised using frequency, counts and percentages. We compared baseline characteristics between PWH and HIV-uninfected groups using Pearson's chi-square for proportions or Student's t-test for continuous variables. Mean BP, BMI, fat mass, and fat-free mass were compared between baseline and 12 months follow-up using Student's t-test. The changes in these measures were calculated as the difference between the 12 months follow-up and baseline measurement.

We used linear regression to investigate the effect of HIV on change in BP and mediation of change in body composition on change in SBP. Firstly we individually assessed the effect of HIV, change in weight and change in fat mass on change in SBP. We then determined the effect of these variables on change in SBP adjusted for age and sex. To determine the confounding effect of baseline SBP we further adjusted for baseline SBP in the model with HIV adjusted for age and sex. Secondly, we modelled the effect of HIV on change in SBP adjusted for weight or fat mass. Finally, to determine mediation effect of change in body composition, we fitted a linear regression models with change in weight or change in fat mass as covariates adjusted for age, sex and HIV status. We repeated similar analyses with change in DBP as an outcome variable. Participants on medication for hypertension, which may differ between the two time points, were included in the analysis. To assess whether BP taken when participants were on medication for hypertension influenced the results, we conducted sensitivity analysis excluding patients on treatment for hypertension.

We investigated associations between changes in weight, waist circumference, fat mass and fat-free mass with change in SBP or DBP using regression coefficients and scatter plots. In cases where we noted very large changes in these estimates from baseline to 12 months follow-up visit, we checked the source documents to verify actual values recorded at both study visits.

Ethical considerations

The study was approved by the NIMR Medical Research Coordinating Committee (Ref: NIMR/HQ/R.8a/Vol.IX/2264) and Catholic University of Health and Allied Sciences/Bugando Medical Centre ethics committee (CREC/543/2022) in Tanzania, the London School of Hygiene and Tropical Medicine ethics committee (LSHTM Ref. 11989) and the National Committee on

Health Research Ethics in Denmark (Case No.1608499). We administered written informed consent to all potential study participants and enrolled only those who consented.

RESULTS

Participant enrollment and follow-up

We enrolled a total of 1289 participants (**Figure 1**) but 348 participants did not attend 12 months follow-up for various reasons including death (n=108), refusal (n=44), terminal illness (n=2), and loss to follow-up (n=194). Two participants with missing BP data were excluded. In this analysis we therefore included 939 participants; 640 (68.2%) PWH and 299 (31.8%) HIV-uninfected who attended both baseline and 12 months follow-up visits.

Participants' baseline characteristics

The mean age of participants was 38 years and 64% were females (**Table 1**). The level of education was low with only 86 (14%) PWH and 73 (24%) HIV-uninfected reported to have attended secondary or higher level of education. The proportion of current smokers was 10% in PWH and 6% in the HIV-uninfected group. A total of 214 (34%) PWH and 84 (28%) HIV-uninfected individuals were unhealthy alcohol drinkers. The mean hemoglobin was significantly lower in PWH; 60% of PWH had anemia versus 19% in the HIV-uninfected group. Nearly half (45%) of PWH had $CD4^{+}$T-cell count <200 cells/cells/μL. Nearly 90% of PWH received non-nucleoside reverse transcriptase inhibitor (NNRTI) based ART regimens.

Baseline body composition

Being overweight was common, particularly in the HIV-uninfected group (38%). However, 144 (23%) PWH and 24 (8%) HIV-uninfected were underweight. The mean fat mass in PWH was 13

kg (SD=9) compared to 18 kg (SD=10) in HIV-uninfected adults. Mean fat-free mass were 44 kg (SD=7) and 46 kg (SD=8), respectively (**Table 2**).

BP and hypertension

The baseline mean SBP and DBP was lower in PWH compared to the HIV-uninfected group ($p<0.001$). The mean baseline SBP was 114 mmHg (SD=18) in PWH and 125 mmHg (SD=19) in the HIV-uninfected group (**Table 2**). A sensitivity analysis excluding participants on medication for hypertension yielded similar BP estimates at both time points.

At baseline, 93 (15%) PWH and 79 (26%) HIV-uninfected participants had hypertension. At 12 months, 138 (22%) PWH and 101 (34%) HIV-uninfected adults had hypertension. The cumulative incidence of hypertension at 12 months of follow-up was 8% in PWH and 10% in HIV-uninfected individuals. Only 10 participants at baseline and 17 at 12 months follow-up were on antihypertensive medications. The most commonly used antihypertensive drugs were diuretics, calcium channel blockers, and angiotensin converting enzyme inhibitors and many participants had been prescribed a combination of two or three antihypertensive drug classes.

Association of change in body composition with change in BP

The change in BP was correlated with change in body weight in PWH (**Figure 2 and 3**), but not in HIV-uninfected adults (**Supplementary Figures 1 and 2**). A one kilogram increase in body weight was associated with 1.1 mmHg (95% CI: 0.1–1.3; $p<0.001$) increase in SBP and 0.5 mmHg (95% CI: 0. 4–0.6; $p<0.001$) increase in DBP in PWH one year after ART initiation.

Similarly, during the one year of study follow-up, change in fat mass was correlated with change in BP in PWH starting ART (**Figures 2 and 3**) and in HIV-uninfected adults although the

correlation was stronger in PWH compared to the HIV-uninfected group (**Supplementary Figures 1 and 2**). A one kilogram increase in fat mass was associated with 1.4 mmHg (95% CI: 1.1–1.7; p<0.001) increase in SBP and 0.8 mmHg (95% CI: 0.6–1.0; p<0.001) increase in DBP in PWH. In HIV-uninfected participants, increase in fat mass only significantly associated with a 0.6 mmHg (95% CI: 0.3–0.9; p<0.001) increase in DBP.

Results from the multivariable linear regression model showed that change in weight and change in fat mass were both associated with change in BP and the results were consistent even after adjusting for age, sex and HIV status (**Table 3 and Supplementary Table 1**). Each kilogram increase in fat mass was associated with 1.1 mmHg (95% CI: 0.9–1.4; p<0.001) increase in SBP and 0.8 mmHg (95% CI: 0.6–0.9; P<0.001) increase in DBP. Similarly, one kilogram increase in weight was associated with 0.9 mmHg (95% CI: 0.7–1.1; p<0.001) increase in SBP and 0.4 mmHg (95% CI: 0.3–0.5) increase in DBP

Change in BP over one year after adjusting for baseline BP

In the linear regression model adjusted for age, sex and baseline BP the difference in change in BP in PWH compared to HIV-uninfected adults was 2.2 mmHg (95% CI: 0.3–4.2*;* p<0.001) for SBP (**Table 3**) and 0.3 mmHg (95% CI: -0.9–1.5; p=0.59) for DBP (**Supplementary Table 1**). Of note, this model did not adjust for changes in weight which were considerable in PWH.

Change in BP over one year after adjusting for changes in body composition

During the first year of ART initiation, we noted a significant increase in BP in PWH compared to HIV-uninfected individuals followed simultaneously (**Table 3**). On average, SBP increased by 6.3 mmHg (95% CI: 4.3–8.3; p<0.001) in PWH after adjusting for age and sex. In the final model adjusted for the effect of change in total body weight, the mean SBP increased by 4.9 mmHg

(95% CI: 3.0–6.8; p<0.001) in PWH. Neither change in BP nor change in weight differed significantly by ART regimen.

DISCUSSION

From our comparative cohort study, we report that BP increases more rapidly in PWH during the first year of ART compared to HIV-uninfected controls from the same population. This finding reinforces data from other recent comparative cohort studies[6,15] that reported significantly greater increase in BP in PWH during the first years of ART initiation compared to HIV-uninfected adults.

It has been hypothesized that healthy increases in weight observed after ART initiation – "return to health" – may explain the rapid increase of BP seen in many PWH during the first year of ART.[16] Dramatic "return to health" changes are common in SSA where most PWH present late with advanced HIV disease and severe wasting.[8] The average increase in fat mass and fat-free mass in PWH in our study were 1.6 kilograms and 0.9 kilograms, respectively. In Africa, PWH still present with wasting and both fat mass and fat-free mass increase rapidly after ART initiation.[17-20]

We report that multiple indices of body composition are strongly correlated with changes in BP in PWH during the first year of ART including fat-free mass, fat mass and waist circumference. Of these markers of body composition, increase in fat mass is the most strongly correlated with increases in both SBP and DBP with narrow confidence intervals for effect size. A one kilogram increase in fat mass was associated with 1.4 mmHg increase in SBP and 0.8 mmHg increase in DBP. The association between changes in fat mass and SBP was not statistically significant in HIV-uninfected adults, but would likely become evident over longer time periods.

In PWH, change in body weight was nearly as strong a predictor of change in BP as change in fat mass. Therefore, change in body weight is a reasonable proxy for the effect of changing body composition on BP in PWH. A one kilogram gain in weight or fat mass during the first year of ART can be associated with almost 1 mmHg increase in SBP in PWH. A similar trend was seen for separate adjustment for the effect of fat mass and weight on mean change in DBP in PWH. Since weight gain is common in PWH initiating ART,[21-24] future studies of change in BP in PWH should at least adjust for changes in body weight over time,[25] if not changes in fat mass.

Changes in body composition during the first year of ART and other confounders explain only a quarter of the increase in BP observed in PWH during this time period. In our fully adjusted models, the increase in SBP during the first year of ART was 4.9 mmHg compared to 6.2 mmHg in the unadjusted model. Similar trends were seen for DBP. These findings suggest that "return to health"[7] explains some but not all of the increase in BP observed during the first year of ART in PWH. Other studies have suggested that immune reconstitution, chronic inflammation, microbial translocation, sympathetic activation, and arterial stiffness might also contribute to these changes in BP.[25] These other factors deserve further investigation.

The strengths of our study include the repeated body composition measurements at baseline and 12 months follow-up visits and that we followed up both PWH and HIV-uninfected controls from the same population for comparison of longitudinal changes in BP. Study limitations included short follow-up period and not measuring longitudinal changes in inflammatory markers in order to account for effect of change in systemic inflammation over time on change in BP. We also lack data on diet and lifestyle (including alcohol use) at the one year time point. These may be important contributors to changes in BP, although we expect that both diet and lifestyle improve over time in PWH. In addition, our results might be biased by differential loss to follow-up between PWH and HIV-uninfected adults. Moreover, we lack documentation on which arm

the third and final BP measurement was done so we averaged of all three BP readings to get the final BP measurement at each visits.

In conclusion, “return to health” as measured by changes in weight explains some but not all of the rapid increase in BP observed in PWH during the first year of ART. Studies assessing change in BP over time in PWH should adjust for change in fat mass or weight. Rapid increase in BP and fat mass in PWH are likely to contribute to the higher burden of cardiovascular disease in this population. Cost effective interventions, such as regular BP monitoring with low-cost medication initiation as needed and lifestyle advice for diet and exercise to reduce excessive increases in fat mass, to address these risk factors in PWH are needed and should be provided in the early ART period.

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DISCLOSURE

All authors declare no competing interest

Data availability

The Medical Research Coordinating Committee (MRCC) of the National Institute for Medical Research (NIMR) in Tanzania does not allow data to be transferred or shared without their permission. Therefore, data will be available upon request and approval by the Tanzanian MRCC. Researchers who meet the criteria to access confidential data may request access to the data through the following contact details: The MRCC secretariat, National Institute for Medical Research, 2448, Baraka Obama Road, P O Box 9653, Dar es Salaam, Tanzania. Email address: ethics@nimr.or.tz

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Authors' contributions

BBK, MFO, SF, KJ, RK, HF, DF, GP and RP designed the study. BBK, BWK, and GP supervised the study. BBK and BWK coordinated study clinic operations and fieldwork. BBK performed data analysis and prepared the original manuscript. JT provided technical input in the data analysis. All co-authors contributed in the subsequent versions of the manuscript and approved the final version.

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Supplementary information is available at http://www.oup.com/ajh

Figure Legends

Figure 1: Participant enrollment and follow-up flow chart for 939 study participants included in this analysis

Figure 2: Association of changes in body composition with change in systolic blood pressure in people with HIV during the first year of ART

Figure 3: Association of changes in body composition with change in diastolic blood pressure in people with HIV during the first year of ART

Table 1: Baseline characteristics for 939 participants: 640 people with HIV (PWH) and 299 HIV-uninfected adults

Variable[1]	PWH n = 640	HIV-uninfected n = 299	p-value
Age (yrs); mean (standard deviation)	38.2 (11.0)	38.7 (11.1)	0.57
Sex, female	405 (63.3)	194 (64.9)	0.63
Education level[2]			<0.001
No formal education	91 (14.3)	20 (6.7)	
Primary	461 (72.2)	206 (68.9)	
Secondary/tertiary	86 (13.5)	73 (24.4)	
Socioeconomic status[2, 3]			<0.001
Lower tertile	235 (36.8)	65 (21.7)	
Middle tertile	208 (32.6)	98 (32.8)	
Upper tertile	195 (30.6)	136 (45.5)	
Smoking history[2]			0.006
Never smoked	496 (77.7)	259 (86.6)	
Ex-smoker	77 (12.1)	23 (7.7)	
Current smoker	65 (10.2)	17 (5.7)	
Alcohol consumption[2]			0.248
Non-drinker	412 (64.6)	209 (69.9)	
Moderate current drinker	12 (1.9)	6 (2.0)	
Unhealthy current drinker[4]	214 (33.5)	84 (28.1)	
Weight (Kg), mean (standard deviation)[3]	57.2 (11.5)	64.4 (13.6)	<0.001
Body Mass Index (kg/m^2), mean (standard deviation)	21.4 (4.2)	24.2 (5.0)	<0.001
Underweight (<18.5)	144 (22.5)	24 (8.0)	
Normal (18.5 - <25)	395 (61.7)	162 (54.2)	
Overweight/obese (>25)	101 (15.8)	113 (37.8)	
Abdominal obesity[5]	151 (23.6)	119 (39.8)	<0.001
Fat mass (kg), mean (standard deviation)[2]	12.7 (9.0)	17.6 (10.4)	<0.001
Fat-free mass (kg), mean (standard deviation)[2]	43.9 (7.3)	46.1 (8.0)	<0.001
Hemoglobin (g/dL), mean (standard deviation)[2]	11.6 (2.3)	13.5 (1.9)	<0.001
Anemia[6]	376 (58.8)	55 (18.5)	<0.001
CD4 count (cells/μL)			
<200	288 (45.0)	-	
200 – 500	257 (40.2)	-	
>500	95 (14.8)	-	
Antiretroviral therapy regimen			
NNRTI [7] - based regimen	546 (88.9)		
Protease inhibitors - based regimen	68 (11.1)		

[1]Summary estimates are number (%) unless specified as mean (standard deviation); [2]Missing values: PWH - 2 missing education level, socioeconomic status, smoking and alcohol consumption, and 15 missing fat mass and fat-free mass, 26 missing antiretroviral drug regimen; HIV-uninfected - 1 missing fat mass and fat-free mass and 2 missing hemoglobin; [3]Socioeconomic status calculated using principal component analysis; [4]Habitual alcohol drinking of more than two standard drinks for women or more than three standard drinks for men; [5]Waist circumference >94 cm for men or >80cm for women; [6]Hemoglobin level <12 mg/dL for women or <13 mg/dL for men; [7]Non-nucleoside reverse transcriptase inhibitors

Table 2: Baseline and 12 months follow-up BP[1] and body composition indices in PWH[2] and HIV-uninfected adults

Variable means (standard deviations)	PWH (n=640)			HIV-uninfected (n=299)		
	Baseline	12 months	p-value[3]	Baseline	12 months	p-value[3]
Systolic blood pressure (mmHg)	114 (18)	118 (19)	<0.001	125 (19)	123 (21)	0.30
Diastolic blood pressure (mmHg)	76 (12)	78 (12)	0.001	82 (12)	82 (13)	0.81
Body mass index (kg/m^2)	21.4 (4.2)	22.4 (4.2)	<0.001	24.2 (5.0)	24.5 (4.9)	0.38
Fat mass (kg)[4]	12.7 (9.0)	14.3 (9.0)	0.001	17.6 (10.4)	18.2 (10.4)	0.51
Fat-free mass (kg)[4]	43.9 (7.3)	44.8 (7.3)	0.02	46.1 (8.0)	46.6 (8.0)	0.45
On antihypertensive medications	4 (1.3)	6 (0.9)		8 (2.7)	9 (1.4)	

[1]Blood pressure; [2]People with HIV, [3]p-value for change in variable from baseline to first year by Student's t-test;
[4]Missing baseline fat mass and fat-free mass data for 15 PWH and 1 HIV-uninfected participants at enrolment and for 5 PWH and 1 HIV-uninfected at first year follow-up

Table 3: Effect of HIV on ΔSBP[1] 12 months after ART[2] initiation: mediation by body composition changes

	Effect of HIV on ΔSBP[1]		Effect of change in weight on ΔSBP[1]		Effect of change in fat mass[3] on ΔSBP[1]	
	β (95% CI)[4]	p	β (95% CI)[4]	p	β (95% CI)[4]	p
Crude	6.2 (4.1, 8.2)	<0.001	1.0 (0.8, 1.2)	<0.001	1.3 (1.0, 1.5)	<0.001
Adjusted for:						
Age and sex	6.3 (4.3, 8.3)	<0.001	1.0 (0.8, 1.1)	<0.001	1.2 (1.0, 1.5)	<0.001
Baseline systolic blood pressure	2.2 (0.3, 4.2)	<0.001	-	-	-	-
Age sex and change in weight	4.9 (3.0, 6.8)	<0.001	-	-	0.6 (0.1, 1.1)	0.02
Age, sex and change in fat mass	5.1 (3.1, 7.0)	<0.001	0.6 (0.2, 0.9)	0.002	-	-
Age, sex and HIV status	-	-	0.9 (0.7, 1.1)	<0.001	1.1 (0.9, 1.4)	<0.001

[1]Change in systolic blood pressure, [2]Antiretroviral therapy, [3]Fat mass missing for one participant, [4]95% confidence Interval