**Title**

Concentrations of efavirenz, tenofovir, and emtricitabine in obesity: a cross-sectional study

**Running head**

ARV concentrations in obesity

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# Abstract

**Background**

Obesity is increasing worldwide including in people living with HIV (PLWH). Antiretroviral pharmacokinetic data in obesity are limited.

**Objectives**

To measure antiretroviral drug concentrations in obese and non-obese PLWH treated with the fixed- dose combination of efavirenz-tenofovir-emtricitabine. To determine pharmacokinetic differences across indicators of obesity and their associated immunovirological outcomes.

**Methods**

We conducted a cross-sectional sample analysis of two cohort studies. We measured mid-dose efavirenz, 8-hydroxy-efavirenz, tenofovir, and emtricitabine concentrations. Antiretroviral drug concentrations were analysed by body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR).

**Results**

We studied 213 participants: general obesity was detected in 20.4% using BMI, and abdominal obesity in 53.6% using WC and 62.4% using WHR respectively. The median concentrations of all antiretroviral drugs were lower amongst obese participants determined by BMI and WC, with efavirenz showing greater differences than tenofovir or emtricitabine. For BMI, results were most striking for efavirenz (1752.3 ng/ml vs 2342.9 ng/ml, *P*=0.002) with lower concentrations in obese participants. Using WC, efavirenz (1845.8 ng/ml vs 2571.2 ng/ml, *P*<0.001), tenofovir (65.8 ng/ml vs 73.2 ng/ml, *P*=0.036), and emtricitabine (159.5 ng/ml vs 221.0 ng/ml, *P*=0.005) concentrations were lower in obese participants. Eight-hydroxy-efavirenz concentrations were similar in non-obese and obese participants for WC. Using WHR, the concentrations of all antiretroviral drugs were lower in the obese population, most strikingly for emtricitabine (173.5 ng/ml vs 229.0 ng/ml, *P*=0.015). There were no immunovirological associations.

**Conclusion**

We found lower antiretroviral concentrations in all obese groups; most strikingly in participants with abdominal obesity determined by WC. Lower drug concentrations had no immunovirological associations.

**Key words**

Antiretrovirals, pharmacokinetics, efavirenz, tenofovir, emtricitabine, obesity

# Introduction

Most people living with HIV (PLWH) initiated on antiretroviral therapy (ART) gain weight 1. A Swiss HIV cohort study conducted over 22 years found a biphasic increase in body mass index (BMI) in the first 4 years after initiating antiretroviral therapy (ART) 2. Studies from sub-Saharan Africa, specifically South Africa, echo these findings 3. BMI growth curve modelling done over 11 years on a cohort of HIV-positive South Africans reported progressive increases with ART 4. An average weight gain of 4.8 kg was seen after 144 weeks of treatment with efavirenz, tenofovir and emtricitabine (EFV, TFV and FTC) 5. In a cohort of South African female patients, obesity (BMI > 30 kg/m2) increased by 13.5% (p=0.004) after 3 years on ART 6. In addition to the increase in weight and BMI, there are also significant increases in mid-arm circumference, waist circumference (WC), hip circumference and mid-thigh circumference 5.

WC and waist-to-hip ratio (WHR) are of particular interest as they are markers of central obesity that are independent risk factors for cardiovascular morbidity. WC and WHR are also more sensitive predictors of cardio-metabolic risk than BMI 7,8,9. The presence of obesity in PLWH has a compounding deleterious effect on cardiovascular disease risk but may also effect antiretroviral drug concentrations 7,10. Drug distribution may be altered in obesity by various factors. These include lipophilicity of the drug, ionization properties, blood:plasma ratio and protein binding 11,12,13. However, data on the effect of obesity on antiretroviral pharmacokinetics and treatment outcomes are limited.

A Brazilian study measured plasma concentrations of 41 PLWH on EFV-based regimens and found that lower body weight correlated with higher concentrations of EFV. All participants in the study were virologically suppressed, despite 17% of EFV plasma concentrations being lower than the therapeutic range of 1000 – 4000 ng/ml 14. A French study investigated the effect of obesity on antiretroviral drug concentrations as well as on the immunovirological response 10. This study included a total of 129 participants on an EFV-based regimen. TFV and FTC concentrations were also analysed in this study. Statistically significant results were found for EFV and TFV, with lower concentrations in obesity by 26 and 23 percent respectively. No difference was found for FTC 10. The lower EFV and TFV concentrations were not associated with viral suppression. Data on the pharmacokinetic profile in obese PLWH from African and other low to middle income countries are limited. Furthermore, antiretroviral pharmacokinetic associations with WC and waist-hip ratio (WHR), estimates of abdominal fat, have not been described. The pharmacokinetics of 8-hydroxy-efavirenz (8-OH-EFV), the primary metabolite of EFV, in obese PLWH has not been described. EFV is predominantly metabolised by CYP2B6 to 8-OH-EFV 15,16. Weight gain is associated with EFV cytochrome P450 (CYP) 2B6 (*CYP2B6*) metaboliser genotypes, with extensive metabolisers gaining the most weight and slow metabolisers gaining the least weight; the mechanism is hypothesised to be due to off-target concentration-dependent EFV mediated toxicity and impaired adipocyte differentiation in slow and intermediate metabolisers. Chronic central nervous system (CNS) efavirenz toxicity could also impair appetite 15. The formation of 8-OH-EFV has been hypothesized but not clinically proven to be associated with neurotoxicity in PWLH; its association with weight gain is unknown 17,18,19.

In the present study we investigated the pharmacokinetics of EFV, 8-OH-EFV, TFV, and FTC in obese and non-obese PLWH from South Africa using mid-dose sampling. We assessed differences in pharmacokinetics using BMI, WC and WHR as measures of obesity and abdominal obesity. Finally, we explored differences in the immunovirological parameters (HIV viral load and CD4+ T cell count) in the obese and non-obese groups.

# Methods

***Participants:*** We conducted a retrospective cross-sectional secondary data analysis from two separate cohort studies: a Cape Town cohort and a cohort study which included participants from the surrounding areas of Cape Town (EndoAfrica cohort) 19,20. Participants were included in this study if they were PLWH, over the age of 18 and on the antiretroviral regimen of EFV-TFV-FTC. We collected the following participant variables at the time of pharmacokinetic sampling: demographics, CD4+ T cell count, HIV viral load, time on ART, BMI, WC and WHR. We defined obesity as a BMI value ≥30 kg/m² for all participants 21. Abdominal obesity in men was defined as measurements of WC ≥94 cm and WHR ≥0.9 respectively, and for women measurements of ≥80 cm and ≥0.85 respectively 22,23. We included 213 participants. Not all participants had complete data capturing and were only included in the part of the analysis where their anthropometric measurements were available. For example, participants with missing height were not included in the BMI analysis. We indicated the number of participants included in each analysis. Informed consent was obtained from all the participants before performing study procedures. The study was approved by the Stellenbosch University Undergraduate Research Ethics Committee (UREC Reference #: U19/07/029).

***Pharmacokinetic sampling:*** Fasting samples were taken in the morning, 10-20 hours after the evening dose (mid-dosing). The Cape Town cohort recorded the self-reported ART dosing time. The EndoAfrica cohort investigators reminded participants both one week before and on the day of their last dose (prior to sampling) of the time they should take their ART. The time of dosing was not recorded and investigators assumed the dosing instructions were followed. A single sample was taken, with the time of sampling being recorded. The blood samples were centrifuged within an hour of collection and stored at -80°C until analysis. Pharmacokinetic sampling was done in the Cape Town cohort as part of the study procedures, while pharmacokinetic analyses were done retrospectively on stored samples from the EndoAfrica cohort.

***EFV, TFV, FTC and 8-OH-EFV measurements:*** Drug assays were performed at 3 laboratories. The Cape Town cohort samples were analysed in the Division of Clinical Pharmacology at the University of Cape Town (UCT) and in the Bioanalytical Facility, Department of Molecular and Clinical Pharmacology, at the University of Liverpool (UL); while the EndoAfrica cohort samples were analysed in the analytical laboratory in the Division of Clinical Pharmacology at Stellenbosch University (SU). The analytical laboratory in the Division of Clinical Pharmacology at UCT measured total EFV, TFV and FTC concentrations in plasma using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assays. The laboratory subscribes to the National Institute of Allergies and Infectious Diseases Division of AIDS Clinical Pharmacology Quality Assurance Antiretroviral Proficiency Testing Program. Lower limits of quantification (LLQ) for plasma EFV, TFV and FTC were 19.5 ng/ml, 10.0 ng/ml and 37.5 ng/ml, respectively. The Bioanalytical Facility, Department of Molecular and Clinical Pharmacology at the UL measured total plasma 8-OH-EFV concentrations in plasma using validated LC-MS/MS assays 24. The LLQ for plasma 8-OH-EFV was 5.0 ng/ml. The analytical laboratory in the Division of Clinical Pharmacology at SU quantified total EFV, TFV, FTC and 8-OH-EFV in plasma samples from the EndoAfrica cohort using validated LC-MS/MS assays. LLQ for plasma EFV, TFV, FTC and 8-OH EFV were 35 ng/ml, 10 ng/ml, 10 ng/ml and 10ng/ml, respectively. Concentrations below LLQ were excluded from the analysis.

***Immunovirological measurements:*** HIV-1 RNA from the EndoAfrica cohort were analysed by the National Health Laboratory Service (NHLS) using the Roche COBAS AmpliPrep/TaqMan HIV-1 Test, v2. HIV-1 RNA concentrations from the Cape Town cohort were measured using the Abbott RealTi*m*e HIV-1 assay (Abbott Park, Illinois, U.S.A.). Participants were considered virologically suppressed with a with a viral load of ≤ 50 copies per ml. CD4 counts from both cohorts were analysed by the NHLS using flow cytometry with the Beckman Coulter FC500 MPL.

***Statistical analysis***: Analyses were performed by Pearson’s r correlation and dichotomising of BMI, WC and WHR. Pharmacokinetic data distribution was assessed, and non-normal distributed data expressed as medians and interquartile range (IQR). Quantile regression was employed to control for differences in dose-sampling time. The regression holds time after dose (TAD) constant, nullifying the effect of TAD on antiretroviral drug concentrations. Antiretroviral drug concentrations were then modelled for the 25th, 50th, and 75th quantiles for the obese and non-obese groups observed in this study (BMI, WC, WHR). P-values were calculated for both TAD and measures of obesity (BMI, WC, WHR) to express the impact they had on drug concentrations in each quantile. We performed statistical analysis using IBM Corp. (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Graphs were generated using GraphPad Prism 8.4.3 (471) (Macintosh Version by Software MacKiev© 1994-2021 GraphPad Software, LLC).

**Results**

***Study participant characteristics:*** We included 213 participants in our study (**Figure 1**), 43 and 170 participants from the Cape Town and EndoAfrica cohorts respectively. The baseline characteristics are described in **Table 1**. Female participants had higher BMIs, WCs and CD4 counts.

***EFV and 8-OH-EFV pharmacokinetics:*** The pharmacokinetic results are summarised in **Table 2**. We found a sex difference in concentrations with males having higher concentrations of EFV, TFV and FTC with a significant difference of FTC (P<0.001), these results were however confounded by BMI. By contrast, males had lower 8-OH-EFV concentrations (P= 0.018). EFV concentrations were lower in all obese groups when compared to the non-obese groups. Differences were most striking for WC with a median (IQR) of 2571.2 (1675.4 – 3866.6) ng/ml vs 1845.8 (1388.3 – 2499.6) ng/ml (P = <0.001). Eight-OH-EFV concentrations were not different between the obese and non-obese participants, but were lower in male than female participants (P = 0.018).

***TFV pharmacokinetics:*** TFV concentrations were lower in all obese groups when compared to the non-obese groups. Differences were most striking for WC with the median and interquartile range being 73.2 (55.6 – 101.5) ng/ml vs 65.8 (50.7 – 87.3) ng/ml (P = 0.036).

***FTC pharmacokinetics:*** FTC concentrations were lower in all obese groups when compared to the non-obese groups. Differences were most striking for WC with the median and interquartile range being 221.0 (132.0 – 300.0) ng/ml vs 159.5 (108.5 – 225.5) ng/ml (P = 0.005).

***Quantile regression:*** Our regression findings are summarised in **Table 3**. We found that EFV and TFV concentrations were not influenced by TAD for any measure of obesity. Eight-OH EFV concentrations were strikingly influenced by TAD in the BMI and WC categories across quantiles where an increase in TAD led to a marked increase in 8-OH EFV concentration. FTC concentrations were influenced by TAD and FTC concentrations were notably affected by TAD in both the 50th and 75th quantiles. Even after adjusting for TAD, WC still had a striking impact on FTC concentrations both the 50th and 75th quantiles. For BMI, FTC concentrations were markedly influenced by TAD in the 50th and 75th quantiles. Whereas for WHR, FTC concentrations were markedly influenced by TAD in the 75th quantile. However, even when adjusting for TAD, FTC concentrations were lower in the obese population across all measures of obesity investigated.

***Immunovirological assessment:*** 164/208 participants were virally suppressed, results are shown in **Table 2** 25. We found no sex difference in the rate of viral suppression.Women had higher CD4 counts than men, but this was confounded by BMI (**Table 1**).

***BMI immunovirology:*** Prevalence of viral suppression were similar in the obese group when compared to the non-obese group for BMI, even though the obese groups had lower ART drug concentrations. Alternatively, CD4 counts of the obese group was strikingly higher, despite them having lower ART drug concentrations. The median and interquartile range being 480 (351.8 – 660.3) cells/mm³ vs 565 (339.0 – 792.3) cells/mm³ (P = 0.045).

***WC immunovirology:*** Prevalence of viral suppression were similar in the obese group when compared to the non-obese groups for WC, even though the obese groups had lower ART drug concentrations. There was no striking difference in the CD4 counts of the obese and non-obese groups for WC.

***WHR immunovirology:*** Prevalence of viral suppression were similar in the obese group when compared to the non-obese group for WHR, even though the obese groups had lower ART drug concentrations. There was no striking difference in the CD4 counts of the obese and non-obese groups for WHR.

# Discussion

We investigated the pharmacokinetics of mid-dose EFV, 8-OH-EFV, TFV, and FTC and associated immunovirological parameters between obese and non-obese individuals sampled from two cohorts in Cape Town and surrounds. To our knowledge, our study uniquely describes the pharmacokinetics of 8-OH-EFV in obesity and described the pharmacokinetics of EFV-TFV-FTC in obesity using WC and WHR as markers of abdominal obesity, in addition to BMI. Concentrations of EFV, TFV and FTC were consistently lower in the obese groups, with the most striking findings seen in the abdominally obese compared to non-obese groups defined by WC (**Figure 2**). Concentrations of 8-OH-EFV were similar in obese and non-obese participants, but higher in male participants. No associated immunovirological differences were noted between the obese and non-obese groups.

We anticipated lower concentrations of EFV, TFV and FTC in the obese groups due to associated changes in the volume of distribution of these antiretroviral drugs 13,26 . Our findings echo those of others 10. Data are emerging associating EFV extensive *CYP2B6* metaboliser status with obesity with extensive CYP2B6 metabolisers gaining the most weight when started on an EFV based regimen 15. EFV is primarily metabolised by CYP2B6 into 8-OH-EFV and we hypothesised that 8-OH-EFV concentrations would be higher in the obese group based on this association. We found that 8-OH-EFV concentrations were similar in non-obese and obese participants and it may be explained by differences in fat partitioning. We previously did not find an association between EFV metaboliser status and 8-OH-EFV in plasma in the Cape Town cohort 19. Lower EFV and 8-OH-EFV concentrations in our obese participants argue in support that lower EFV concentrations are protective against the off-target effects of higher EFV impairing weight gain.

Our study has a number of limitations. First, the assays done in this study were done in three different laboratories. Second, our sample size may have been limited to detect a significant effect size for all the measures of obesity. Third, we did not have a robust measure of adherence. An unexpected finding was the large number of participants considered to be non-adherent from the community based EndoAfrica cohort with undetectable antiretroviral concentrations. Fourth, we did not determine *CYP2B6* metaboliser status, although we measured 8-OH-EFV concentrations. Lastly, mid-dosing interval measurement of TFV and FTC is prone to significant pharmacokinetic variability. Measuring the minimum drug concentration before subsequent dosing (Cmin) is a more appropriate measure 27.

In future research, we suggest that WC and WHR be included as measures of obesity. WC and WHR have been found to be a better measure of abdominal obesity than BMI, with WC being preferred over BMI as a predictor of future cardiovascular events 28. Furthermore, EFV *CYP2B6* metaboliser status should be assessed when assessing EFV pharmacokinetics in obesity.

In summary, we found that concentrations of EFV, TFV and FTC were lower in obese participants. The differences were most striking in participants with abdominal obesity determined by increased waist circumference. Eight-OH-EFV concentrations were not strikingly different between obese and non-obese participants. The clinical relevance of lower concentrations is not clear as there were no associated differences observed in immunovirological parameters.

**Transparency declarations**

The authors report no conflicts of interest.

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| --- | --- |
| **Table 1.** Baseline characteristics of study participants (n=213) |  |
| **Characteristic** |  | **P-value\*** |
| Sex |  |  |
| Male, n (%) | 67 (31) |  |
| Female, n (%) | 146 (69) |  |
| Age in years‡  | 39.78 ± 8.82 |  |
| BMI‡ (kg/m²), n | 25 ± 6.72, n=211 |  |
| Male | 22.74 ± 4.93, n=67 | **0.001** |
|  Female | 26.06 ± 7.188, n=144 |
| CD4+ T cell count† (cells/mm³), n | 497 (370.8 – 681.8), n=210 |  |
|  Male | 455 (346 – 611), n=67 | **0.022** |
|  Female | 519 (387 – 712), n=143 |
| Time on ART† (weeks), n | 140 (89 – 216), n=213 |  |
| Waist circumference† (cm), n |  |  |
| Male | 85 (73 – 92), n=67 | 0.106 |
| Female | 87 (76 – 100), n=142 |
| Waist-hip ratio†, n |  |  |
| Male | 0.92 (0.87 – 0.98), n=62 | **<0.001** |
| Female | 0.86 (0.82 – 0.92), n=108 |

\* Male compared with female; †Median and interquartile range; ‡Mean and standard deviation

**Table 2.** ART concentrations across BMI, waist circumference, and waist-hip ratio

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Categories of tested variables** | **BMI1 (kg/m²)** | **P-value**‡ | **WC2 (cm)** | **P-value**  | **WHR3** | **P-value** | **Difference in sex** | **P-value**  |
|  | Non-obesen=168  | Obesen=43  |  | Non-obesen=97  | Obesen=112  |  | Non-obesen=64  | Obesen=106  |  | Menn=67 | Womenn=146  |  |
| **EFV†** **(ng/ml)** | 2342.9(1597.6 – 3343.8)n=168 | 1752.3(1309.8 – 2310.0)n=43 | **0.002** | 2571.2(1675.4 – 3866.6)n=97 | 1845.8(1388.3 – 2499.6)n=112 | **<0.001** | 2196.1(1639.3 – 3070.9)n=64 | 2117.6(1409.8 – 3014.4)n=106 | 0.373 | 2571.2(1623.9 – 3551.1)n=67 | 2020.5(1436.9 – 2913.0)n=146 | 0.126 |
| **8-OH-EFV†** **(ng/ml)** | 53.9(37.0 – 103.0)n=168 | 57.8(31.2 – 1280.4)n=43 | 0.808 | 52.8(27.5 – 97.1)n=97 | 54.2(36.0 – 129.1)n=112 | 0.269 | 47.8(28.6 – 71.0)n=64 | 44.5(31.0 – 63.2)n=106 | 0.263 | 45.9(32.2 – 75.9)n=67 | 60.2(35.8 – 542.6)n=146 | **0.018** |
| **TFV†** **(ng/ml)** | 71.6(53.6 – 94.9)n=164 | 61.6(52.9 – 82.8)n=43 | 0.141 | 73.2(55.6 – 101.5)n=96 | 65.8(50.7 – 87.3)n=109 | **0.036** | 75.4(56.9 – 91.7)n=63 | 72.8(51.8 – 95.8)n=105 | 0.905 | 73.2(56.9 – 96.5)n=66 | 67.3(52.9 – 88.7)n=143 | 0.188 |
| **FTC†** **(ng/ml)** | 192.5(123.0 – 279.0)n=164 | 156.0(108.0 – 236.0)n=43 | 0.080 | 221.0(132.0 – 300.0)n=97 | 159.5(108.5 – 225.5)n=108 | **0.005** | 229.0(151.0 – 323.0)n=63 | 173.5(110.0 – 257.0)n=106 | **0.015** | 246.0(150.0 – 348.0)n=67 | 156.0(116.0 – 220.0)n=141 | **<0.001** |
| **VL§** | 128/164(78.05%) | 34/42(80.95%) | 0.682 | 72/96(75.00%) | 88/108(81.48%) | 0.261 | 44/62(70.97%) | 80/105(76.19%) | 0.456 | 50/66(75.76%) | 114/142(80.28%) | 0.457 |
| **CD4**† | 480(351.8 – 660.3)n=166 | 565(339.0 – 792.3)n=42 | **0.045** | 497(369.5 – 676.5)n=97 | 505(382.0 – 691.0)n=109 | 0.638 | 503(332.0 – 726.0)n=63 | 522(372.3 – 705.8)n=104 | 0.523 | 455(346.0 – 611.0)n=67 | 519(387.0 – 712.0)n=143 | **0.022** |

†Median and interquartile range, EFV = efavirenz, 8-OH-EFV = 8-hydroxy-efavirenz, TFV = tenofovir, FTC = emtricitabine, BMI = body mass index, WC = waist circumference, WHR = waist-hip ratio, CD4 = CD4+ T cell count (cells/mm³), §Percent of participants virologically suppressed, VL = viral load (copies/ml), 1 Obesity defined as BMI ≥30 kg/m², 2 Obesity defined as WC ≥94 (men) and 80 (women), 3 Obesity defined as WHR ≥, 0.9 (men) and 0.85 (women)

**Table 3.** Quantile regression predicting ART concentrations across three different quantiles, holding time after dose constant. With associated significance of time after dose and obesity measures

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **BMI1 (kg/m²)** | **WC2 (cm)** | **WHR3** |
| **Quantiles** |  | q=0.25 | q=0.5 | q=0.75 | q=0.25 | q=0.5 | q=0.75 | q=0.25 | q=0.5 | q=0.75 |
| **EFV****(ng/ml)** | Obese (ng/ml) | 1283.3 | 1658.8 | 2401.4 | 1389.7 | 1858.5 | 2507.0 | 1399.7 | 2129.8 | 3080.9 |
| Non-obese (ng/ml) | 1547.6 | 2274.3 | 3370.2 | 1663.6 | 2561.1 | 3855.5 | 1649.2 | 2235.9 | 3210.9 |
| P-value (T) | 0.638 | 0.300 | 0.632 | 0.676 | 0.722 | 0.977 | 0.759 | 0.484 | 0.587 |
| P-value (O) | 0.116 | **0.012** | 0.206 | 0.080 | **0.001** | **0.012** | 0.121 | 0.673 | 0.856 |
| **8-OH-EFV****(ng/ml)** | Obese (ng/ml) | 34.0 | 65.6 | 623.0 | 35.9 | 80.7 | 652.3 | 30.1 | 44.2 | 63.6 |
| Non-obese (ng/ml) | 37.5 | 76.7 | 658.8 | 32.3 | 73.9 | 630.6 | 30.0 | 47.8 | 81.7 |
| P-value (Time) | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | **<0.001** | 0.261 | 0.508 | 0.118 |
| P-value (O) | 0.625 | 0.432 | 0.846 | 0.531 | 0.537 | 0.857 | 0.988 | 0.515 | 0.079 |
| **TFV****(ng/ml)** | Obese (ng/ml) | 54.6 | 62.6 | 81.7 | 50.3 | 68.3 | 87.0 | 52.1 | 74.1 | 93.1 |
| Non-obese (ng/ml) | 53.9 | 71.4 | 95.2 | 54.5 | 74.4 | 102.3 | 55.5 | 73.6 | 90.5 |
| P-value (Time) | 0.483 | 0.291 | 0.620 | 0.354 | 0.250 | 0.579 | 0.611 | 0.508 | 0.050 |
| P-value (O) | 0.924 | 0.182 | 0.206 | 0.480 | 0.264 | 0.096 | 0.642 | 0.940 | 0.779 |
| **FTC****(ng/ml)** | Obese (ng/ml) | 106.6 | 167.2 | 232.4 | 110.8 | 174.7 | 242.0 | 120.2 | 181.1 | 264.3 |
| Non-obese (ng/ml) | 134.4 | 192.5 | 271.5 | 137.5 | 214.1 | 296.2 | 169.8 | 211.9 | 315.2 |
| P-value (Time) | 0.102 | **0.002** | **0.001** | 0.098 | **<0.001** | **<0.001** | 0.061 | 0.063 | **0.043** |
| P-value (O) | 0.273 | 0.267 | 0.254 | 0.223 | **0.025** | **0.026** | 0.061 | 0.187 | 0.117 |

EFV = efavirenz, 8-OH-EFV = 8-hydroxy-efavirenz, TFV = tenofovir, FTC = emtricitabine, BMI = body mass index, WC = waist circumference, WHR = waist-hip ratio, 1 Obesity defined as BMI ≥30 kg/m², 2 Obesity defined as WC ≥94 (men) and 80 (women), 3 Obesity defined as WHR ≥, 0.9 (men) and 0.85 (women), P-value (T) = P-value for time after dose, P-value (O) = P-value for measure of obesity

**Figure 1.** Flow diagram of participant selection.

**Cape Town cohort**

 n=47

**EFV, TFV, FTC**

 n=43

**EndoAfrica cohort**

n=279

**Other ART**

n=4

 **EFV, TFV, FTC**

 n=225

 **Other ART**

n=54

**Adherenta**

n=43

**Excluded**

**Excluded**

**Included**

n=43

 **Total participants included**

n=213

**Adherenta**

n=170

**Non-adherentb**

n=55

**Included**

n=170

**Excluded**

aDeemed adherent based on self-reported dosing history, which was confirmed with detectable plasma concentrations of efavirenz, 8-hydroxy-efavirenz, tenofovir, and emtricitabine

bUndetectable plasma concentrations for any of efavirenz, 8-hydroxy-efavirenz, tenofovir, or emtricitabine (interpreted as absolute non-adherence)

EFV = efavirenz, TFV = tenofovir, FTC = emtricitabine, ART = antiretroviral therapy

**Figure 2.** Antiretroviral drug concentrations in obese and non-obese participants as defined by waist circumference.