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Growth curve modelling to determine distinct body mass index trajectory groups in HIV-positive adults on ART in South Africa

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Abstract

Objective: Obesity is a major long-term concern in HIV-positive patients due to the pathogenic link between obesity and non-communicable chronic diseases (NCD). We aim to characterize changes in body mass index (BMI) over time on antiretroviral therapy (ART) and investigate the association between weight gain and survival in South Africa.

Design & Methods: Prospective cohort study among HIV-positive adults on first-line ART between April 2004–2015 in Johannesburg, South Africa. We used latent-class growth modelling (adjusted for age, gender, and CD4 count) to identify groups of individuals with similar patterns of change in BMI over time.

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Author Contributions

Conceived and designed the experiments: ATB, KB, MPF, AS. Analyzed the data: ATB, KB. Wrote the first draft of the manuscript: ATB, KB, MPF. Contributed to the writing of the manuscript: ATB, KB, SR, AS, NJC, JG,FR,NC,IS, LL, MPF. Agree with the manuscript's results and conclusions: ATB, KB, SR, AS, NJC, JG,FR,NC,IS, LL, MPF. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

Conflicts of Interest and Source of Funding

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LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1.pdf

Results: 11,263 patients were included. The best fit model involved two linear and two quadratic trajectories. 35% of patients categorized into group one (mean BMI at ART initiation, 20.4 kg/m²; mean BMI after 8 years of follow-up, 20.9 kg/m²), 38% into group two (24.5 to 26.2 kg/m²), 21% into group three (29.5 to 32.6 kg/m²) and 6% into group four (36.5 to 40.0 kg/m²). Over the 8 years of follow-up, 6% of our cohort went down in BMI standard category, while 45% went up. The largest increase occurred in the first 12 months on ART. In years two through eight, we saw a more gradual increase in BMI.

Conclusion: The largest gain in BMI in HIV patients occurred in the first year on ART. During follow-up, over 50% of our population changed BMI categories putting them at increased risk for NCDs. Consistent counselling on nutritional and lifestyle changes could help improve ART patients' long term health outcomes.

Keywords

antiretroviral therapy; body mass index; trajectory; HIV; middle-income country; South Africa; public sector

INTRODUCTION

Rates of obesity globally have nearly tripled since 1975. In 2016, an estimated 1.9 billion (39%) adults worldwide were overweight or obese[1]. The largest increase has been in low- and middle-income countries (LMICs) where demographic, social, and economic changes such as urbanization, expanded education, increased industrialization, and rising incomes have occurred rapidly[2]. These changes have resulted in substantial lifestyle modifications including a more highly processed diet and decreased physical activity[3–7]. All have contributed to the rise in obesity, resulting in an increased risk of metabolic disorders and cardiovascular diseases.

South Africa has been at the forefront of the obesity epidemic in sub-Saharan Africa. Between 1998 and 2008, the estimated proportion of the South African adult population who were overweight or obese increased from 29.1 to 31.1% among males (a relative increase of 6.9%), and from 56.2 to 59.5% among women (5.9%)[8]. Despite goals to reduce obesity by 10%, as proposed by the South African government's 2013 strategic plan[9, 10], recent data suggest the overall proportion of adult South Africans who are overweight or obese is likely to increase further by 2020[11], resulting in higher mortality from non-communicable diseases (NCD).

Obesity has also become a major concern among HIV-positive individuals, given their increased cardiovascular risk due to both the HIV virus itself[12, 13] and to antiretroviral therapy (ART)[14–18]. After the introduction of ART, regional body fat distribution abnormalities due to the nucleoside reverse transcriptase inhibitor (NRTI) stavudine became important metabolic concerns for patients[14]. With the phasing out of stavudine use in first-line ART since 2010, when stavudine was replaced with tenofovir in most LMICs, lipotrophy[16] has received less attention. Since then, concern regarding HIV patients has shifted towards obesity, attributable to improved health due to effective ART, normal aging, and obesity trends similar to those seen in the general population[17–20].

There is a lack of research on the effects of obesity on patient outcomes in LMICs and even less so within the HIV-infected population. In South Africa, statistics from HIV clinics show a high prevalence (33%) of obesity in HIV positive patients[21, 22], and a substantial proportion (58%) of those on ART become overweight or obese within one year of treatment initiation[22]. Since obesity contributes to the incidence of NCDs and those on ART are already more susceptible to a range of these conditions, the synergistic effect is potentially devastating[23–26]. Few studies have elucidated weight change patterns that are indicative of the future severity of the obesity epidemic in HIV positive patients on ART in South Africa. Previous studies of weight change in HIV-positive cohorts have focused only on the first 12 to 24 months on ART when weight gain may be considered beneficial[21, 22]. To address this research gap, we used latent-class growth modelling techniques to identify groups of individuals following similar progressions of BMI over time on ART in addition to assess BMI progression and associated attrition between 2004–2015 in a large, public-sector, HIV-positive, South African population.

METHODS

Cohort description

We conducted a prospective cohort study over eight years of follow-up among HIV-positive adults on standard first-line ART between April 2004–2015 at Themba Lethu Clinic (TLC) in Johannesburg, using the Themba Lethu Clinical Cohort[27]. TLC began initiating patients onto ART in 2004 under South Africa’s public-sector treatment program. Care and treatment at TLC is provided according to national treatment guidelines[28–31]. The standard first-line regimen until April 2010 was stavudine or zidovudine plus lamivudine and efavirenz; after April 2010, tenofovir or zidovudine replaced stavudine[28–31]. As of April 2017, the cohort included over 40,000 patients, of whom over 35,000 had initiated ART. Patient data, including demographic characteristics, clinical conditions, laboratory test results, and medications, are entered on site by a clinician or a data entry clerk into a live data capturing system called TherapyEdge-HIV™. Weight and height are routinely measured at medical visits. Mortality is recorded in the patient clinical record and confirmed via linkage with the National Vital Registration system[32, 33].

Eligible patients

All ART-naïve, non-pregnant, HIV-positive adult patients (ages 18–75 years) newly initiating standard first-line ART were eligible for the analysis. We excluded patients with missing date of ART initiation or baseline CD4 count and those without enough weight and height measurements to calculate at least 10 measures of BMI (kg/m^2) at least one month apart.

Use of data was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M140201). Approval for analysis of de-identified data was granted by the Institutional Review Board of Boston University (H-29768).

Body Mass Index (BMI)

Baseline BMI was calculated from weight and height measured at ART initiation or from an average of measurements taken between 30 days prior to or 7 days after initiation. Weight and height at visits occurring between 1 month and 8 years after ART initiation were used to calculate subsequent BMI observations. When multiple measurements were available for a single month, all available weight and height measurements were averaged before calculating the monthly BMI. Observations with implausible measurements (<25 or >200 kg for weight, <120 or >200 cm for height) were excluded as were measurements suggesting implausible changes between visits (>4 standard deviations from that patient's average height and weight). Less than 1% of available measurements were considered implausible, suggesting that the measured height and weight observations appear accurate. For visits where height was unavailable, height from previous/subsequent visits was used. BMI was categorized as underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), obese class I (30.0–34.9 kg/m²), obese class II (35.0–39.9 kg/m²), and obese class III (>40 kg/m²)[34]. Patients could change BMI categories over time, but once assigned to a trajectory group, as explained below, patients remained there throughout follow-up.

Outcome

Patients were categorized as alive, deceased, lost to follow-up, transferred out, or down-referred (transfer of stable patients to a primary health care facility) based on their last available information. Our primary outcome, attrition was defined as a combination of all-cause mortality and loss to follow-up (defined as being at least three months late for the patient's last scheduled visit to the clinic).

Statistical analysis

Group-based trajectory modeling, a semi-parametric statistical technique[35–37], was used to identify patients following similar patterns of change in BMI over time since ART initiation. Grouping individuals based on all available BMI measurements allows us to identify latent BMI trajectory groups rather than relying on *a priori* decisions to group patients based simply on their BMI at ART initiation or their absolute change in BMI over time. The group-based trajectory modeling approach classifies individuals into latent group-based trajectories and estimates model parameters using maximum likelihood[38]. A maximum of four trajectories were chosen a priori in order to maintain simplicity. Consistent with prior established norms for fitting group-based trajectory models[35, 36] [1,2], we started with a single quadratic trajectory model and compared model fit statistics (Bayesian Information Criteria (BIC)) to two-group, three-group, and four-group models in a stepwise fashion, leaning towards parsimony in number of groups. Change in BIC was used to choose between more complex and simpler models[38]. We then fit the shape of the patterns of BMI over time comparing BIC values for 81 models consisting of linear, quadratic, and cubic trajectories. Time-fixed covariates, including gender, age (continuous), and CD4 count ART initiation (continuous) and the outcome of attrition were then incorporated into the chosen model.

Individual patients were assigned to a single trajectory group based on maximum posterior probability of measurement[35]. High average posterior probabilities indicate that the model discriminates between individuals with differential patterns of change and can serve as an approximation for the internal reliability of each trajectory[35]. After selecting the appropriate model, we calculated the average posterior probability of group membership for each BMI trajectory identified. We considered values of greater than 0.8 as an indication of adequate internal reliability[35]. We also assessed proportions of membership for each trajectory group to ensure membership of at least 5% of the sample[35].

Survival analysis

We used a Cox proportional hazard model to investigate the association between trajectory group membership and attrition. The model was adjusted for gender, age (18–24, 25–29, 30–39, 40–49 and 50), NRTI, non-nucleoside reverse transcriptase inhibitor (NNRTI), CD4 count (0–49, 50–99, 100–199, 200–349 and 350), WHO stage, and hemoglobin stage at ART initiation. A Kaplan-Meier survival curve was used to compare survival times for each trajectory group. As patients were not eligible unless they had at least 10 BMI measurements, person-time was calculated from the individual's 10th BMI observation to either: 1) attrition, 2) transfer, or 3) close of the dataset (December 2015), whichever occurred first, in order to prevent immortal person-time bias.

Analyses were performed using STATA version 15 (StataCorp, College Station, Texas, USA). The “traj” plugin was used in the group-based trajectory modelling[37].

RESULTS

Cohort description

A total of 11,263 patients were eligible for the analysis (Supplemental Online Content 1, Figure 1). The cohort was predominately female (60.2%), with a median age of 37.6 years (interquartile range (IQR) 32.3–44.2), median CD4 count of 109 cells/mm³ (IQR: 42–184), and median BMI of 22.0 kg/m² (19.5–25.4)(Table 1). At ART initiation, 13.1% of female patients and 2.8% of male patients were considered obese (BMI ≥ 30 kg/m²). Patients were predominately initiated on a standard first-line regimen containing either stavudine (63.0%) or tenofovir (34.6%) plus lamivudine and efavirenz (94.0%). Patients had a median follow-up time from ART initiation to last available visit of 96 months (IQR: 51–96). 61% of the sample was followed for 8 years after ART initiation.

Growth curve model

Four-group trajectory models were selected based on model fit statistics. The best fit of the four-group models involved two linear and two quadratic trajectories (Table 1 and Figure 1), with 34.5% patients categorized into group one (lowest baseline BMI, increasing), 37.8% into group two (second lowest baseline BMI, increasing), 21.3% into group three (second highest baseline BMI, increasing), and 6.4% into group four (highest baseline BMI, increasing). The average posterior probability of group membership was over 0.95 for all groups, suggesting the chosen model able to accurately categorize individuals with similar patterns of change. When stratified by the four BMI trajectory groups, there was a higher

proportion of females in group two (61.3%), three (77.8%), and four (89.3%) than in group one (42.6%). Median baseline CD4 count increased as trajectory group increased, with a median CD4 count of 101.5 cells/mm³ (IQR: 40–177) in group one and 127 cells/mm³ (IQR: 52–201) for those in group four. Patients in group one (29.6%), two (27.5%), and three (27.5%) had a higher proportion of patients with CD4 counts <50 cells/mm³ than did group four (23.8%). Patients in group one had a higher proportion of patients with tuberculosis (16.0%).

Predictors of body mass index group membership

Males had slightly lower, odds than females of being a member of group two when compared to group one, but male gender was not a predictor of membership for group three or four. Increasing age decreased the odds of being in trajectory groups two, three, or four compared to group one, while increasing CD4 increased the odds of being in group two, three or four (i.e. the three highest BMI groups) compared to group one (Supplemental Online Content 1, Table 1).

Body mass index change over time on ART

Over the 8 years of follow-up, over 50% (n=5,736) of our population changed BMI categories: 6.2% (n=698) went down, while 44.7% (n=5,038) went up in BMI category. The scatterplot of BMI and time shows an even spread of the data and a positive relationship between months since ART initiation and BMI measured at that corresponding time point for all four BMI trajectory groups (see Supplemental Online Content 1, Figure 2).

Patients in group one started at a mean BMI of 19.1 kg/m² (WHO normal weight) at ART initiation and remained in the WHO normal weight category with an increase to a mean BMI of 20.9 kg/m²; the mean BMI in group two shifted from 22.5 kg/m² (WHO normal weight) to 26.2 kg/m² (WHO overweight); the mean BMI in group three transitioned from 26.8 kg/m² (WHO overweight) to 32.6 kg/m² (WHO obesity class I); group four had the largest increase from an average BMI of 33.3 kg/m² (WHO obesity class I) at the start of ART to 40.0 kg/m² (WHO obesity class II) (Table 2).

We also used transition matrices to assess patients shifting from BMI WHO category at ART initiation to last available BMI overall for the cohort (Table 3) and stratified by all four BMI trajectory groups (Supplemental Online Content 1, Tables 2–5) The majority of patients in group one were categorized as WHO normal weight at their last BMI measurement, while for the other three groups the majority of patients were overweight, obese I, obese II and obese III (Supplemental Online Content 1, Tables 3–5).

Survival analysis results

Overall, there were 1,802 attrition events (615 died, 1352 were lost to follow-up) in the cohort over 773,352 person-years. The incidence of attrition was 2.8 events per 100 person-years (95% CI, 2.7–2.9) (Table 4).

The probability of survival was 0.77 (95% CI: 0.76–0.79) in group one, 0.82 (95% CI: 0.81–0.83) in group two, 0.86 (95% CI: 0.84–0.87) in group three, and 0.87 (95% CI: 0.84–0.89)

in group four (Figure 2). Patients in group one had a 22% increased hazards of attrition (hazard ratio (HR): 1.22; 95% CI: 1.09–1.36) over the follow-up period compared to those in group two, while group three and group four had approximately a 15% decreased hazards when compared to group two (Table 4).

Looking at change in BMI (between ART initiation and last available measurement) instead of BMI trajectory group, we observe that every 1 kg/m² increase in BMI is associated with 9% reduction in hazards of attrition (0.89–0.92). Additionally, males vs. females, patients <30 years of age vs. 30–39 years, those on stavudine or zidovudine vs. tenofovir, and patients with poorer health status at ART initiation (i.e. CD4 counts <200 cells/mm³ and WHO stage) had an increase in the hazards of attrition over the follow-up period.

DISCUSSION

We identified four BMI trajectory groups in a large cohort of HIV-positive adults on ART over an eight year observational period. The majority (38%) of patients in our cohort were categorized into BMI group two (second lowest baseline BMI), while 35% fell into group one (lowest BMI), 21% fell into group three (second highest BMI), and 6% fell into group four (highest BMI).

Although wasting was common early in the HIV epidemic, it has become less common with the introduction of ART in both high-income and LMICs[39–42]. With the exception of HIV-associated lipodystrophy linked to certain types of antiretroviral medications[43], there has been a large improvement in the health of HIV positive patients initiating ART, leading to a decline in wasting and an increase in obesity as HIV patients are living longer and gaining weight at rates similar to the general population[42, 44]. In our study, close to 30% of patients were categorized as overweight or obese at ART initiation, consistent with previous research on black African populations[45].

We found that increasing CD4 count increased the odds of being in BMI trajectory group two, three, or four compared to group one. Our results are comparable with previous research reporting that overweight and obese individuals have higher CD4 counts than their normal or underweight counterparts[46–48]. However, previous longitudinal studies assessing this association revealed contradicting results, with some studies reporting comparable immunological status between patients categorized as normal, overweight, and obese[49] and one study suggesting that obese individuals had significantly smaller increases in CD4 after initiation of ART compared to normal weight individuals[50]. One plausible explanation for our findings is that leptin, an adipocyte-derived hormone that influences body weight[51], may be involved in the pathway of overweight and obesity to immune functioning in HIV patients. Additionally, increased levels of leptin have been found to be related to improved immunological health[52]. An alternatively explanation could be related to a patients nadir CD4 and a patients time on ART, neither of which were assessed in our study. If normal weight patients were more immunosuppressed when they initiated ART, their ability to control viral replication and to restore immune function could have been compromised, limiting their ability to achieve higher CD4 counts compared to patients who started treatment at higher CD4 counts[46].

We found that patients in trajectory group one, which has the lowest mean BMI at both baseline and after 8 years of follow-up, had increased hazards of attrition when compared to those in group two, while those in group three and group four had decreased the hazards of attrition. This could be due to the fact that 8 years of follow-up may not be long enough for obesity-related illness to lead to mortality/attrition. We could see the association between being overweight and obese and attrition decline as time on ART increases and patients in our population in the higher BMI categories begin to develop other NCDs, ultimately increasing their risk of death and loss from care. A recent meta-analysis containing data from nearly four million subjects showed a U-shaped relationship between BMI and mortality, with mortality increasing as soon as BMI exceeded 25 kg/m², supporting this notion[53].

This observed association could also be explained by what is known as the “obesity paradox”, which suggests that being overweight or obese can be protective and associated with greater survival in patients with certain chronic diseases, like HIV[54]. Improved outcomes have been observed in overweight and obese patients with type 2 diabetes, chronic kidney disease, chronic heart failure, chronic obstructive pulmonary disease, and coronary artery disease compared with normal-weight and underweight counterparts[55–59]. As such, patients with chronic disease who are able to maintain weight may be healthier, while those losing weight may suffer from more advanced disease markers (e.g., underlying inflammation, increased cytokines)[60].

Alternative explanations could be misclassification bias[61,62], reverse causation[63], or a form of selection bias known as collider stratification bias[64]. First, the use of BMI may not be as accurate a marker of body fat as waist circumference measurement, resulting in misclassification bias in our study[61,62]. Adjusting for waist circumference, if available, could have nullified or reversed the observed association between higher BMI trajectories and attrition in our study. Second, reverse causation could have underestimated the risk of mortality amongst patients that are classified as overweight or obesity in our cohort. The majority of HIV patients lose weight prior to death due to end stage consequences of dying. Thus, being overweight or obese would appear protective because impending death process is leading to a reduction in weight not that heavy weight in and of itself is protective[63]. Third, collider bias can result in the distortion of an association between BMI and death by conditioning on a common cause of weight change and death, such as HIV disease progression[64]. In our study advanced HIV disease could be a much stronger risk factor for death than being overweight or obese, resulting in higher BMI appearing protective because its presence indicates the absence of a more harmful risk factor[64].

Our findings should be considered alongside other potential study limitations. First, because our study reports data from large public sector government HIV clinics, our results may not be generalizable to the overall population. Second, lack of documentation of weight and height measurements could be causing us to incorrectly estimate the proportion of patients falling into the four separate BMI trajectory groups; however, we would anticipate the missingness to be random and not have a large impact on our estimates. Third, as our BMI trajectories are among HIV-positive patients that survive to initiate ART and have at least ten BMI measurements after treatment initiation, survivor bias could be an issue in our study.

This could have resulted in a bias downwards in our estimate of the proportion of patients in BMI trajectory group one in addition to biasing our estimates of attrition in BMI trajectory groups three and four towards the null. Fifth, because the trajectory model uses logistic regression to investigate the association between risk factors and group membership, we may overestimate the strength of these associations. Finally, as we do not have access to an HIV-negative population for comparison we are unable to assess any association between HIV status and BMI trajectory.

Conclusion

The largest gain in BMI in HIV patients on ART in our cohort occurred in the first 12 months on ART. Over the 8 years of follow-up, over 50% of our population changed BMI categories: 6.2% went down in BMI category, while 44.7% went up in BMI category, putting them at increased risk for life threatening non-communicable chronic diseases. We also found that patients in group 3 and 4, which generally consist of those with higher BMIs, had a decrease in the hazards of attrition compared to patients with normal BMI. Further research in cohorts with potentially longer periods of follow-up is need to determine if this association between BMI and attrition is valid. Additionally, consistent counselling on nutritional and lifestyle changes could help improve ART patients long term health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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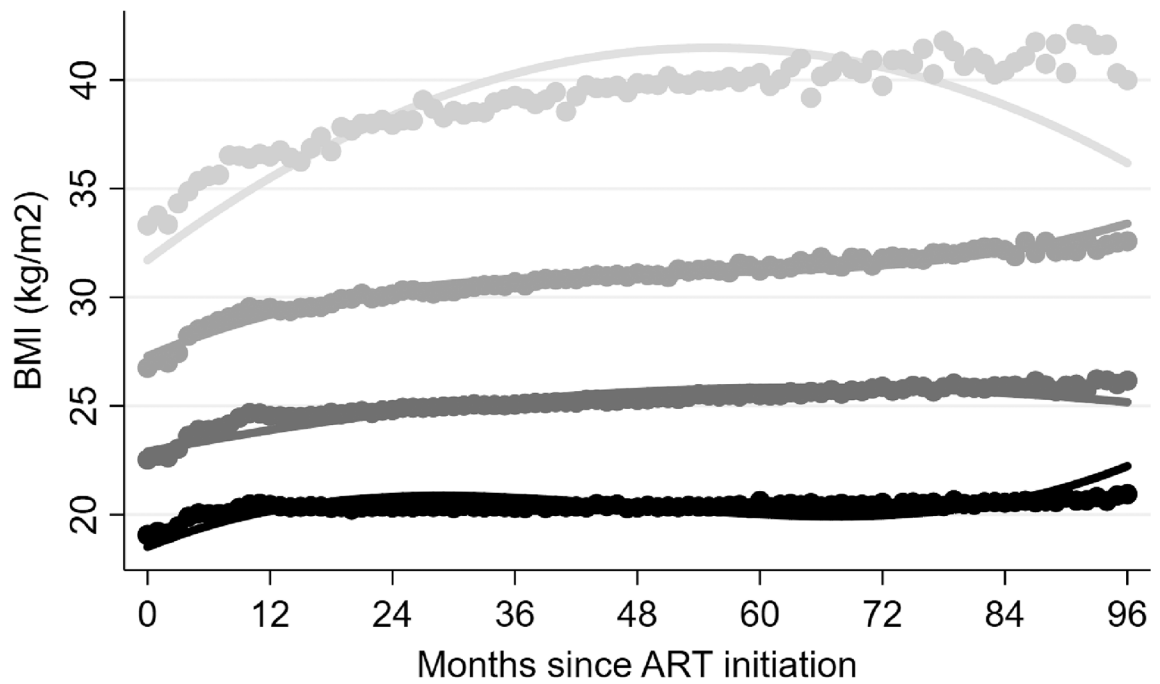
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Trajectory group color	BMI latent trajectory group	Group membership probabilities	Intercept-BMI at ART initiation (SE*)	Linear term (SE*)	Quadratic term (SE*)	Cubic term (SE*)
—	Group 1	34.5%	18.51 (0.03)	0.19 (0.00)	-0.00 (0.00)	0.00 (0.00)
—	Group 2	37.8%	22.90 (0.03)	0.09 (0.00)	-0.00 (0.00)	-
—	Group 3	21.3%	27.28 (0.04)	0.20 (0.00)	-0.00 (0.00)	0.00 (0.00)
—	Group 4	6.4%	31.71 (0.05)	0.35 (0.00)	-0.00 (0.00)	-

Figure 1. Adult body mass trajectories after ART initiation at TLC 2004–2017. Based on 256,609 total BMI observations. (N=11,263)

*standard error

**dots on the graph are observed group means at each month.

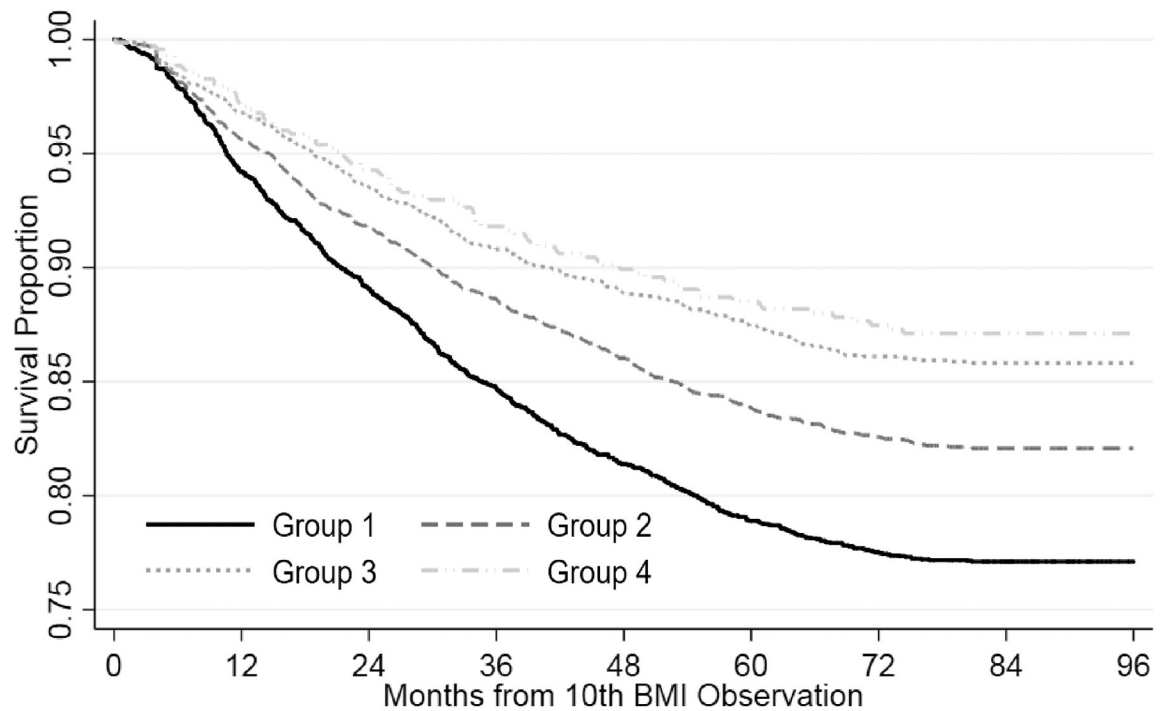


Figure 2. Kaplan Meier curve displaying attrition stratified by BMI trajectory group, Themba Lethu Clinic, Johannesburg, South Africa (N=11,263)

As patients were not eligible unless they had at least 10 BMI measurements, person-time was calculated from the individual's 10th BMI observation to either: 1) attrition (death and loss to follow-up), 2) transfer, or 3) close of the dataset (December 2015), whichever occurred first.

Table 1. Demographic and clinical characteristics at ART initiation stratified by BMI trajectory groups (N=11,263)

Characteristics	Group 1 (n=3,882)	Group 2 (n=4,258)	Group 3 (n=2,401)	Group 4 (n=722)	Total (n=11,263)
Gender					
Female	1652 (42.56%)	2609 (61.27%)	1869 (77.84%)	645 (89.34%)	6775 (60.15%)
Male	2230 (57.44%)	1649 (38.73%)	532 (22.16%)	77 (10.66%)	4488 (39.85%)
Age					
median (range)	37 (18.1–72.5)	37.4 (32.1–71.5)	38.7 (18.2–72.2)	39.5 (18.5–66.8)	37.6 (18.1–72.5)
<50	1148 (29.57%)	1172 (27.52%)	659 (27.45%)	172 (23.82%)	3151 (27.98%)
50–100	763 (19.65%)	776 (18.22%)	436 (18.16%)	129 (17.87%)	2104 (18.68%)
100–200	1276 (32.87%)	1525 (35.81%)	761 (31.70%)	237 (32.83%)	3799 (33.73%)
200–350	627 (16.15%)	703 (16.51%)	493 (20.53%)	157 (21.75%)	1980 (17.58%)
>350	68 (1.75%)	82 (1.93%)	52 (2.17%)	27 (3.74%)	229 (2.03%)
median (IQR)	101.5 (40–177)	112 (43–181)	113 (43–192)	127 (52–201)	109 (42–184)
HIV viral load					
100,000	376 (9.69%)	425 (9.98%)	248 (10.33%)	73 (10.11%)	1122 (9.96%)
>100,000	339 (8.73%)	368 (8.64%)	185 (7.71%)	54 (7.48%)	946 (8.40%)
missing	3167 (81.58%)	3465 (81.38%)	1968 (81.97%)	595 (82.41%)	9195 (81.64%)
Hemoglobin					
median (IQR)	11.8 (10.2–13.4)	11.8 (10.3–13.3)	11.9 (10.5–13.1)	12 (10.7–13.2)	11.9 (10.4–13.3)
missing	82 (2.11%)	101 (2.37%)	57 (2.37%)	21 (2.91%)	261 (2.32%)
Tuberculosis					
no	3260 (83.98%)	3755 (88.19%)	2127 (88.59%)	667 (92.38%)	9809 (87.09%)
yes	622 (16.02%)	503 (11.81%)	274 (11.41%)	55 (7.62%)	1454 (12.91%)
NRTI					
tenofovir	1184 (30.50%)	1424 (33.44%)	941 (39.19%)	353 (48.89%)	3902 (34.64%)
zidovudine	83 (2.14%)	95 (2.23%)	62 (2.58%)	28 (3.88%)	268 (2.38%)
stavudine	2615 (67.36%)	2739 (64.33%)	1398 (58.23%)	341 (47.23%)	7093 (62.98%)
NNRTI					
efavirenz	3686 (94.95%)	3985 (93.59%)	2232 (92.96%)	685 (94.88%)	10588 (94.01%)
nevirapine	196 (5.05%)	273 (6.41%)	169 (7.04%)	37 (5.12%)	675 (5.99%)
ART start date					
< April 2010	2524 (65.02%)	2690 (63.18%)	1387 (57.77%)	349 (48.34%)	6950 (61.71%)
April 2010	1358 (34.98%)	1568 (36.82%)	1014 (42.23%)	373 (51.66%)	4313 (38.29%)
Baseline BMI					
median (IQR)	19.1 (17.7–20.5)	22.6 (20.7–24.2)	26.7 (24.3–29.1)	33.2 (30.0–36.3)	22.0 (19.5–25.4)
underweight	1523 (39.23%)	297 (6.98%)	29 (1.21%)	3 (0.42%)	1852 (16.4%)
normal weight	2342 (60.33%)	3225 (75.74%)	717 (29.86%)	45 (6.23%)	6329 (56.19%)
overweight	16 (0.41%)	704 (16.53%)	1214 (50.56%)	133 (18.42%)	2067 (18.35%)
obese I	0 (0.00%)	30 (0.70%)	409 (17.03%)	286 (39.61%)	725 (6.44%)

Characteristics	Group 1 (n=3,882)	Group 2 (n=4,258)	Group 3 (n=2,401)	Group 4 (n=722)	Total (n=11,263)
obese II	1 (0.03%)	1 (0.02%)	29 (1.21%)	180 (24.93%)	211 (1.87%)
obese III	0 (0.00%)	1 (0.02%)	3 (0.12%)	75 (10.39%)	79 (0.70%)
Number of BMI Measurements	22 (15-30)	22 (15-30)	21 (15-30)	20 (14-27)	22 (15-30)
Total follow-up time*	96 (49.5-96.0)	96 (49.0-96.0)	96 (56.2-96.0)	96 (59.6-96.0)	96 (51.1-96.0)
Follow-up time for survival analysis**	96.0 (28.4-96.0)	96.0 (30.5-96.0)	96.0 (36.5-96.0)	96.0 (38.2-96.0)	96.0 (30.8-96.0)
alive	2254 (58.06%)	2584 (60.69%)	1558 (64.89%)	485 (67.17%)	6881 (61.09%)
deceased	267 (6.88%)	183 (4.30%)	74 (3.08%)	26 (3.60%)	550 (4.88%)
lost to follow-up	508 (13.09%)	470 (11.04%)	220 (9.16%)	54 (7.48%)	1252 (11.12%)
transferred out	519 (13.37%)	565 (13.27%)	350 (14.58%)	102 (14.13%)	1536 (13.64%)
down referred	334 (8.60%)	456 (10.71%)	199 (8.29%)	55 (7.62%)	1044 (9.27%)

IQR=Interquartile Range; BMI=body mass index; ART= Antiretroviral Therapy; NNRTI=Non-Nucleoside Reverse Transcriptase Inhibitor

* Total follow-up time= months between ART initiation and last available BMI measurement

** Follow-up time for survival analysis= months between 10th BMI observation and last available BMI measurement. 10th observation cutoff used to avoid immortal person-time bias because only patients with 10+ BMI measurements were included in our study.

Table 2.Mean (SD^{**}) body mass index (kg/m²) by group (N=11,263)

	ART Initiation	1 year (12 months)*	8 years (96 months)*	Last available	Change in BMI from ART to 1 year*	Change in BMI from 1 year to 8 years*	Change in BMI overall
Group 1	19.06 (2.19)	20.44 (1.92)	20.92 (2.29)	20.32 (2.23)	1.41 (2.24)	0.10 (2.11)	1.26 (2.61)
Group 2	22.52 (2.77)	24.54 (1.99)	26.16 (2.41)	25.48 (2.58)	1.90 (2.98)	1.09 (2.88)	2.95 (3.77)
Group 3	26.76 (3.67)	29.49 (2.69)	32.63 (3.21)	31.28 (3.05)	2.59 (3.74)	2.36 (4.63)	4.52 (4.70)
Group 4	33.32 (5.77)	36.48 (4.49)	40.02 (4.88)	39.46 (5.12)	3.23 (4.63)	3.86 (4.60)	6.14 (6.27)
Total	22.93 (4.98)	25.01 (5.10)	26.26 (5.93)	25.83 (6.05)	1.97 (3.13)	1.15 (3.34)	2.91 (4.13)

* Estimates are for those with available measurements at specified time points

** Standard deviation

Table 3.

(A) Transition matrix for BMI at ART initiation and last available BMI for full sample (n=11,263).

		Last Available BMI						Total
		Underweight	Normal	Overweight	Obese I	Obese II	Obese III	
BMI at ART Initiation	Underweight	527 (4.7%)	1104 (9.8%)	182 (1.6%)	32 (0.3%)	5 (0.0%)	2 (0.0%)	1852 (16.4%)
	Normal	233 (2.1%)	3603 (32.0%)	1876 (16.7%)	482 (4.3%)	112 (1.0%)	23 (0.2%)	6329 (56.2%)
	Overweight	8 (0.1%)	255 (2.3%)	935 (8.3%)	632 (5.6%)	189 (1.7%)	48 (0.4%)	2067 (18.4%)
	Obese I	1 (0.0%)	22 (0.2%)	109 (1.0%)	321 (2.9%)	195 (1.7%)	77 (0.7%)	725 (6.4%)
	Obese II	-	2 (0.0%)	5 (0.0%)	42 (0.4%)	83 (0.7%)	79 (0.7%)	211 (1.9%)
	Obese III	-	1 (0.0%)	1 (0.0%)	4 (0.0%)	15 (0.1%)	58 (0.5%)	79 (0.7%)
Total		769 (6.8%)	4987 (44.3%)	3108 (27.6%)	1513 (13.4%)	599 (5.3%)	287 (2.6%)	N=11263

Table 4.

Crude and adjusted Cox proportional hazard models assessing the association between BMI trajectory groups and attrition (N=11,263)

Variable	Number of events/ person years	Incidence rate/100 person years (95% CI)	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95% CI)
Overall	1802/64446	2.8 (2.7–2.9)	-	-
BMI trajectory groups				
Group 1	775/21534	3.60 (3.35–3.86)	1.32 (1.19–1.47)	1.22 (1.09–1.36)
Group 2	653/24255	2.69 (2.49–2.91)	Reference	Reference
Group 3	294/14293	2.06 (1.83–2.31)	0.77 (0.67–0.89)	0.85 (0.74–0.98)
Group 4	80/4364	1.83 (1.47–2.29)	0.70 (0.55–0.88)	0.85 (0.67–1.09)
Gender				
Female	992/38653	2.57 (2.41–2.73)	Reference	Reference
Male	810/25793	3.14 (2.93–3.36)	1.23 (1.12–1.35)	1.19 (1.07–1.31)
Age at ART initiation				
18–24	95/2130	4.46 (3.65–5.45)	1.62 (1.31–2.01)	1.70 (1.37–2.11)
25–29	272/7734	3.52 (3.12–3.96)	1.30 (1.13–1.49)	1.30 (1.13–1.50)
30–39	766/28353	2.69 (2.51–2.89)	Reference	Reference
40–49	460/18551	2.48 (2.26–2.72)	0.93 (0.83–1.04)	0.97 (0.86–1.09)
50	209/7577	2.76 (2.41–3.16)	1.04 (0.89–1.21)	1.11 (0.95–1.29)
NRTI				
tenofovir	328/26244	1.25 (1.12–1.39)	Reference	Reference
zidovudine	41/1497	2.74 (2.02–3.72)	2.08 (1.50–2.87)	2.14 (1.54–2.97)
stavudine	1433/36705	3.90 (3.71–4.11)	2.85 (2.53–3.21)	2.63 (2.32–2.98)
NNRTI				
efavirenz	1690/60907	2.77 (2.65–2.91)	Reference	Reference
nevirapine	112/3539	3.16 (2.63–3.81)	1.12 (0.93–1.36)	1.01 (0.84–1.23)
CD4 count at ART initiation (per 100 cells/μl)				
0–49	556/17767	3.13 (2.88–3.40)	1.97 (1.29–3.02)	1.31 (0.83–2.05)
50–99	362/11903	3.04 (2.74–3.37)	1.92 (1.25–2.95)	1.33 (0.84–2.09)
100–199	663/20851	3.18 (2.95–3.43)	2.00 (1.31–3.05)	1.49 (0.95–2.33)
200–349	199/12457	1.60 (1.39–1.84)	1.05 (0.68–1.64)	1.01 (0.64–1.61)
350+	22/1467	1.50 (0.99–2.28)	Reference	Reference
WHO stage at ART initiation				
I/II	1303/50631	2.57 (2.44–2.72)	Reference	Reference
III/IV	499/13815	3.61 (3.31–3.94)	1.37 (1.24–1.52)	1.17 (1.04–1.30)
Hemoglobin at ART initiation (g/dL)				
<10	392/11941	3.28 (2.98–3.62)	1.20 (1.07–1.34)	1.06 (0.94–1.20)
10	1375/50952	2.70 (2.56–2.85)	Reference	Reference
Change in BMI**	-	-	0.92 (0.91–0.93)	0.91 (0.89–0.92)

CI=confidence interval; BMI=body mass index; NNRTI=Non-Nucleoside Reverse Transcriptase Inhibitor; WHO=World Health Organization

* All predictors are measured at ART initiation. Model adjusted for gender, BMI, age, NRTI, NNRTI, WHO stage, CD4 count at ART initiation, hemoglobin levels at ART initiation.

** HR shows the change in hazard for every one kg/m^2 increase in BMI from ART initiation and last available measurement. Adjusted model includes gender, BMI, age, NRTI, NNRTI, WHO stage, CD4 count at ART initiation, hemoglobin levels at ART initiation. Adjusted model does not include BMI trajectory group due to collinearity with change in BMI variable.

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