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Incidence and Risk Factors for Overweight and Obesity after Initiation of Antiretroviral Therapy in Dar es Salaam, Tanzania

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Abstract

Objective: To describe the incidence of and risk factors for overweight and obesity following antiretroviral therapy (ART) initiation. **Methods:** We used Cox proportional hazards models to investigate risk factors for incident overweight and obesity in 79 074 individuals aged 15 years or older who initiated ART in Dar es Salaam, Tanzania. **Results:** Twenty-five percent of the patients became overweight and 10% became obese. The incidence rate of obesity was 3.2 per 100 person-years (95% confidence interval [CI]: 3.1-3.3) in patients who were of normal weight before starting ART and 22.6 per 100 person-years (95% CI: 21.9-23.3) in those who were overweight. Lower CD4 count was associated with a higher risk of overweight and obesity (*P* value for trend < .0001). **Conclusion:** There is a high burden of overweight and obesity after starting ART, leading to proportions of these 2 conditions that are similar to those in the general population.

Keywords

antiretroviral therapy, overweight, obesity, incidence, risk factors

Introduction

The scale-up of HIV treatment and care services in sub-Saharan Africa (SSA) has resulted in a large increase in the number of patients on antiretroviral therapy (ART).[1] In Tanzania, over 470 000 (31%) of the 1.5 million HIV-positive adults had been started on ART by 2014.[2] Wider access to ART in similar settings has led to fewer deaths due to HIV/AIDS and has also been shown to result in increased life expectancy at birth.[3] Additionally, many patients now start ART before progressing to advanced stages of HIV due to changes in treatment guidelines.[4]

Increased survival predisposes HIV-positive individuals to conditions associated with aging. Several studies have described increasing proportions of overweight and obesity in people living with HIV/AIDS in SSA.[5-7] In a large cross-sectional study in Dar es Salaam, Tanzania, we found that 18% of HIV-positive individuals were overweight ($25 \leq$ body mass index [BMI] < 30) and 7% were obese (BMI ≥ 30).[5] Population-based studies comparing overweight and obesity prevalence in HIV-positive individuals to HIV-negative individuals are limited in SSA. Demographic surveillance data from rural South Africa showed a similar prevalence of overweight in HIV-positive and HIV-negative individuals.[7] With more HIV-positive patients becoming overweight and obese, there is a need for improvements in monitoring and managing excessive weight gain in patients on ART. This requires a better understanding of risk factors for overweight and obesity in this population. There is also limited data on progression to overweight and obesity in patients started on ART in SSA. More studies have instead evaluated short-term trends in

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weight changes, with a specific focus on monitoring clinical outcomes of ART.[7-9] A few studies have evaluated long-term trends, but none specifically looked at predictors of incident overweight and obesity.[8-11] Data outside SSA are also limited. Tate et al followed up ART-naive patients receiving care in the United States and found that 20% became overweight or obese within 2 years of being on ART.[12] Another study in a Swiss HIV cohort found that weight gain after ART initiation was biphasic, with the first and more rapid phase occurring within a year of being on treatment.[13] This is followed by a slower phase of weight gain over the next 3 years. Although these studies explain some trends in weight gain, none explicitly describes the incidence of obesity and overweight and their risk factors. The observed weight trends in these studies may also not be generalizable to SSA because of environmental and socioeconomic differences that influence weight gain.[14] The goal of this study was to describe the incidence of overweight and obesity after initiation of ART in an urban setting in SSA and to explore risk factors for the 2 conditions.

Methods

Study Population

We used data that are prospectively collected at HIV Care and Treatment Clinics in Dar es Salaam, Tanzania. These clinics are funded by the US President's Emergency Plan for AIDS Relief through one of its recipient agencies, Management and Development for Health (MDH). Treatment protocols follow national guidelines as set by the Tanzanian National AIDS Control Program.[15] All patients aged 15 years or older (N = 113 468) who had been started on ART between November 2004 and September 2014 were considered for the analysis. This number includes patients who had started ART at other clinics and later transferred to MDH-supported clinics. We excluded the following categories of patients: pregnant at baseline (n = 13 579), missing baseline BMI (n = 16 170), and those who were obese at baseline (n = 4645). The final analysis sample included 79 074 patients.

Data Collection

Patients were routinely followed up at the clinics after enrollment into care and after being started on ART. Height and weight were measured by a trained nurse at the time of enrollment according to standard techniques.[16] Weight was then updated at subsequent clinic visits. Where necessary, demographic, clinical, and laboratory data were updated on case report forms. Laboratory tests including patients' CD4 counts and hemoglobin levels were done at the time of ART initiation and updated every 6 months. All data were entered into a secure computerized database that underwent regular data quality checks.

The outcomes of interest were incident overweight and obesity after ART initiation. Body mass index was calculated as the patient's weight in kilograms divided by the square of their height in meters. We categorized BMIs <18.5 kg/m^2 as underweight, 18.5 $\leq$ BMI < 25.0 kg/m^2 as normal weight, 25 $\leq$ BMI < 30 kg/m^2 as overweight, and BMI $\geq$30 kg/m^2 as obese. For the analysis on incident overweight, we included patients who were either underweight or normal weight at ART initiation. All patients with a BMI <30 kg/m^2 were assessed for incident obesity. Patients were censored at the time of event, death, and pregnancy and at the end of follow-up. Women who became pregnant were not reentered into the analysis after the end of their pregnancies.

We assessed several demographic and clinical indicators as potential risk factors for overweight and obesity. These included sex, marital status, parity, year of ART initiation, and age. Clinical data included the patient's baseline BMI category, time-varying CD4 count, hemoglobin level, and previous opportunistic infections. We also controlled for previous ART exposure, whether a patient was on a first- or second-line regimen of ART, and their adherence to ART. We defined nonadherence as $\geq$5% noncompliance with scheduled ART pickup visits, a measure that has been shown to be predictive of virologic failure.[17] Additionally, we included the type of nucleoside reverse transcriptase inhibitor (NRTI) in the ART regimen and the type of non-nucleoside reverse transcriptase inhibitor.

Statistical Analysis

We used the Andersen-Gill formulation of Cox proportional hazards models[18] to examine associations between time-varying risk factors with incident overweight and obesity. We used restricted cubic spline models to assess the possibility of nonlinear relationships between the outcomes of interest with continuous covariates. Missing indicators were created for missing values of potential risk factors. All covariates with P values $\leq$0.20 in univariate analyses were included in the multivariate model. All analyses were performed using SAS software version 9.3 (SAS Institute, Inc).

Ethical Consideration

The study was approved by the institutional review boards of the Tanzanian National Institute of Medical Research, at Muhimbili University of Health and Allied Sciences, and of the Harvard T.H. Chan School of Public Health. No patient consent was required for this study because data that were used are routinely collected during health care delivery. Anonymized data were used in all analyses.

Results

Baseline data of 79 074 patients who were included in this analysis are shown in Table 1. The median age was 37 years (interquartile range [IQR], 31-44 years); 65% were female and 43% were married. At the time of ART initiation, 22 203 (28%) were underweight, 45 231 (57%) normal weight, and 11 640 (15%) overweight. The median CD4 count at the time of ART initiation was 149 cells/μL (IQR: 64-256 cells/mm^3) and 81% of the patients were ART naive. Twenty-three percent had a history of tuberculosis (TB) infection, and 47% were started on zidovudine (ZDV)-containing regimen and 61% on efavirenz (EFV)-containing regimen.

Table 1. Patient Characteristics at Initiation of Antiretroviral Therapy in Dar es Salaam, Tanzania.[a]

Variable	Underweight (n = 22 203)	Normal Weight (n = 45 231)	Overweight (n = 11 640)	Total Sample (N = 79 074)[b]
Age, median (IQR), years	36.4 (30.4-43.1)	36.9 (31.2-43.8)	38.0 (32.4-44.9)	36.9 (31.1-43.8)
Age category, years				
15 to <30	5065 (22)	8948 (20)	1852 (16)	15 865 (20)
30 to <40	9206 (42)	19 278 (42)	4891 (42)	33 375 (42)
40 to <50	5416 (24)	11 687 (26)	3357 (29)	20 460 (26)
50+	2493 (11)	5271 (12)	1525 (13)	9289 (12)
Sex				
Male	8662 (39)	16 409 (36)	2620 (22)	27 691 (35)
Female	13 541 (61)	28 822 (64)	9020 (78)	51 383 (65)
Married				
No	13 410 (60)	25 442 (56)	6336 (54)	45 188 (57)
Yes	8793 (40)	19 789 (44)	5304 (46)	33 886 (43)
District				
Ilala	8429 (38)	17 252 (38)	4987 (42)	30 668 (39)
Kinondoni	6759 (31)	15 058 (33)	3893 (34)	25 710 (33)
Temeke	6990 (32)	12 854 (29)	2742 (24)	22 586 (29)
Facility level				
Hospital	15 853 (73)	31 444 (72)	8071 (74)	55 368 (73)
Health center	2434 (11)	4279 (10)	973 (8)	7686 (10)
Dispensary	3417 (16)	7706 (18)	1823 (17)	12 946 (17)
Year started on ART				
2004-2005	543 (3)	1148 (3)	351 (3)	2042 (3)
2006	1567 (7)	3382 (8)	893 (8)	5842 (7)
2007	2576 (12)	4369 (10)	943 (8)	7888 (10)
2008	3103 (13)	5376 (11)	1152 (10)	9631 (12)
2009	2936 (13)	5378 (12)	1150 (10)	9464 (12)
2010	2735 (12)	5344 (12)	1483 (13)	9562 (12)
2011	2240 (10)	4353 (10)	1175 (10)	7768 (10)
2012	2573 (11)	6097 (14)	1650 (14)	10 320 (13)
2013	2229 (10)	5404 (12)	1484 (13)	9117 (12)
2014	1701 (8)	4380 (10)	1359 (12)	7440 (9)
BMI, median (IQR), kg/m^2	16.9 (15.7-17.7)	21.1 (19.8-22.7)	26.8 (25.8-28.1)	20.5 (18.2-23.3)
Hemoglobin category, g/dL				
<8.5	3570 (30)	3567 (16)	462 (10)	7599 (20)
8.5-10.9	5230 (43)	9090 (42)	1719 (36)	16 039 (42)
≥11	3277 (27)	9055 (41)	2602 (54)	14 934 (38)
CD4 count, median (IQR), cells/mm^3	110 (40-216)	158 (73-261)	186 (104-297)	149 (64-256)
CD4 count category, cells/mm^3				
<50	5266 (29)	6435 (18)	1112 (12)	12 807 (20)
50-99	3221 (18)	5341 (14)	1015 (11)	9577 (15)
100-199	4533 (25)	10 902 (30)	2795 (31)	18 230 (29)
≥200	5086 (28)	1 3363 (37)	4026 (44)	22 475 (36)
History of tuberculosis				
No	8754 (71)	19 067 (78)	5061 (85)	32 882 (77)
Yes	3648 (29)	5395 (22)	877 (15)	9920 (23)
Previous ART use				
No	19 159 (86)	36 277 (80)	9002 (77)	64 438 (81)
For HAART	3024 (13)	8873 (20)	2599 (22)	14 496 (18)
For PMTCT	20 (0)	81 (0)	39 (0)	140 (1)
ARV regimen				
First line	22 106 (99)	45 086 (99)	11 597 (99)	78 789 (99)
Second line	97 (1)	145 (1)	43 (1)	285 (1)
NRTI				
Zidovudine	9958 (45)	21 505 (48)	5557 (48)	37 020 (47)
Stavudine	7715 (35)	13 855 (31)	3262 (28)	24 832 (31)
Tenofovir	4426 (20)	9697 (22)	2778 (24)	16 901 (22)
NNRTI				
Nevirapine	8040 (36)	17 655 (39)	4894 (42)	30 589 (39)
Efavirenz	14 091 (66)	27 442 (61)	6700 (58)	48 233 (61)

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; BMI, body mass index; HAART, highly active antiretroviral therapy; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PMTCT, prevention of mother-to-child transmission of HIV.

[a]Except where indicated, figures are for n (%) of patients.

[b]Total numbers might not add up to 79 074 due to missing data.

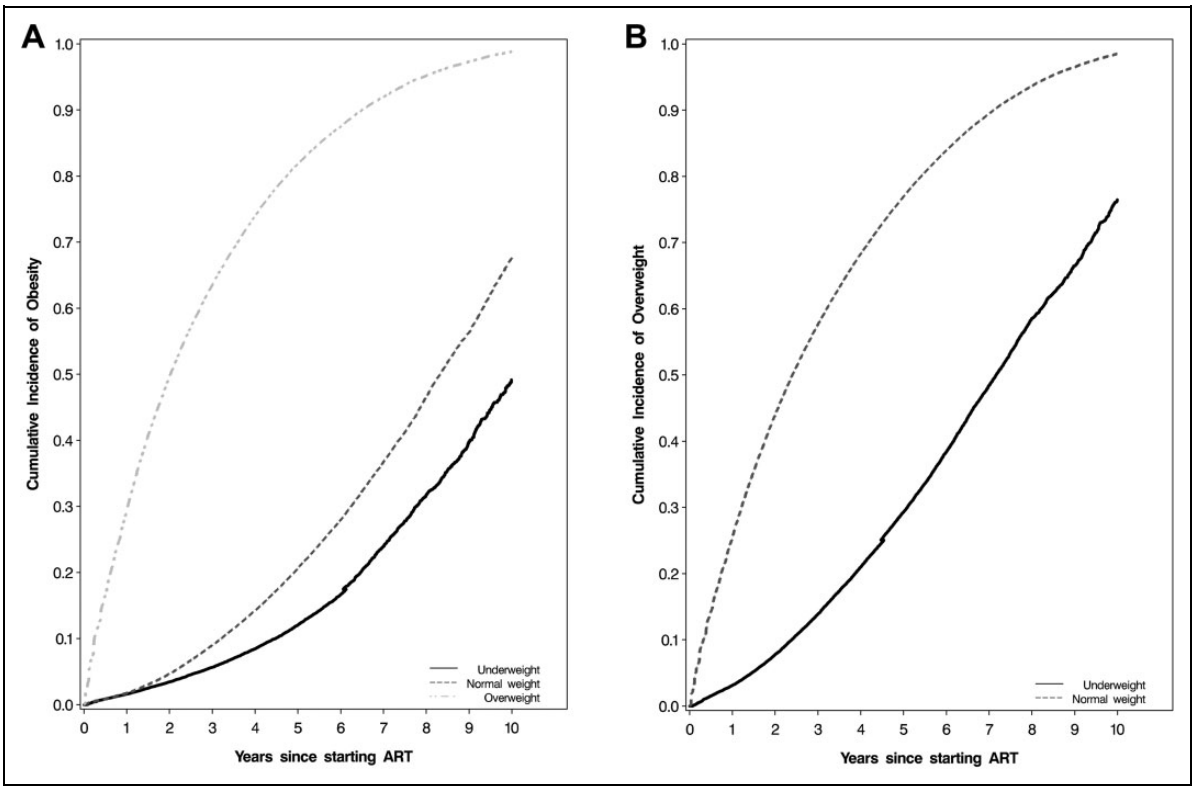

Figure 1. Cumulative incidence of overweight (A) and obesity (B) after ART initiation. ART indicates antiretroviral therapy.

Incidence of Obesity and Overweight

During 160 951 person-years of follow-up, 7848 (10%) patients became obese with incidence rate (IR) of 4.9 per 100 person-years (95% confidence interval [CI]: 4.8-5.0). The median follow-up time of patients assessed for incident obesity was 1.3 years (IQR: 0.3-3.3 years). Covariate-adjusted Kaplan-Meier plots for incident obesity by baseline BMI category are presented in Figure 1, panel A. Overweight patients had a higher incidence of obesity (IR: 22.6 per 100 person-years, 95% CI: 21.9-23.3) than those who were normal weight at baseline (IR: 3.2 per 100 person-years, 95% CI: 3.1-3.3) and those who were underweight (IR: 1.5 per 100 person-years, 95% CI: 1.4-1.7).

During 107 858 person-years of follow-up, 16 503 (25%) patients became overweight with an IR of 14.9 per 100 person-years (95% CI: 14.7-15.2). The median follow-up time for patients assessed for incident overweight was 0.8 years (IQR: 0.2-2.3 years). Normal weight patients had a higher incidence of overweight (IR: 20.9 per 100 person-years, 95% CI: 20.6-21.2) than those who were underweight at baseline (IR: 5.1 per 100 person-years, 95% CI: 4.8-5.3; Figure 1, panel B). Sixteen percent (n = 2612) of patients who became overweight after starting ART progressed to obese states at later date. The median follow-up time to obesity in this subgroup was 2.7 years (IQR: 1.3-5.0 years) and a majority (92%) had been normal weight at the time of ART initiation.

Risk Factors for Overweight and Obesity

Univariate and multivariate analyses of risk factors for obesity are presented in Table 2. After adjusting for potential confounders, women had double the risk of obesity than men (Relative Risk [RR]: 2.16, 95% CI: 2.04-2.30). Being married was not associated with an increased risk of obesity (RR: 0.97, 95% CI :0.92-1.01) and neither was age (P value for trend = .8). Patients from the most affluent district, Kinondoni, had a higher risk of obesity than those from Ilala, a less affluent area (RR: 1.05, 95% CI: 1.00-1.11). Those from Temeke, the least affluent district, however did not have a lower risk of obesity than patients from Ilala (RR: 0.98, 95% CI: 0.93-1.04).

Compared to patients who were underweight at baseline, normal weight patients had double the risk of becoming obese (RR: 2.17, 95% CI: 1.99-2.36), while those who were overweight had a 14.72-fold increase in risk (95% CI: 13.54-16.00). More recent year of ART initiation was associated with a higher risk of obesity ($P < .0001$). Patients started on ART in 2014 had almost 3 times the risk of becoming obese as compared to those who started ART between 2004 and 2005 (RR: 2.91, 95% CI: 2.38-3.56). Those with previous exposure to ART for highly active antiretroviral therapy (HAART) had an 8% lower risk of becoming obese than those who were ART naive (RR: 0.92, 95% CI: 0.87-0.97). Using the same reference category, those who had used ART for prevention of mother-to-child transmission of HIV (PMTCT) had a less than half the risk for obesity (RR: 0.36, 95% CI: 0.17-0.75).

Table 2. Risk Factors for Obesity (BMI ≥30) after ART Initiation.[a]

	Univariate		Multivariate		Multivariate Excluding Underweight at Baseline[b]	
Variable	RR (95% CI)	*P* Value[c]	RR (95% CI)	*P* Value[c]	RR (95% CI)	*P* Value[c]
Sex		<.0001		<.0001		<.0001
Male	Reference		Reference		Reference	
Female	2.77 (2.62-2.93)		2.16 (2.04-2.30)		2.20 (2.07-2.35)	
Age category		.8		.8		.8
15-30	Reference		Reference		Reference	
30 to <40	1.28 (0.84-1.95)		1.29 (0.86-1.96)		1.31 (0.85-2.04)	
40 to <50	1.13 (0.66-1.93)		1.06 (0.62-1.79)		1.10 (0.62-1.93)	
50+	1.07 (0.49-2.32)		1.09 (0.51-2.35)		1.09 (0.49-2.40)	
Married		.001		.2		.3
No	Reference		Reference		Reference	
Yes	0.93 (0.89-0.97)		0.97 (0.92-1.01)		0.98 (0.93-1.03)	
Year started ART		<.0001		<.0001		<.0001
2004-2005	Reference		Reference		Reference	
2006	1.17 (1.03-1.32)		1.10 (0.97-1.24)		1.11 (0.98-1.26)	
2007	1.60 (1.42-1.80)		1.45 (1.29-1.63)		1.45 (1.28-1.64)	
2008	1.74 (1.55-1.96)		1.36 (1.21-1.54)		1.38 (1.22-1.57)	
2009	2.24 (1.99-2.53)		1.46 (1.28-1.65)		1.45 (1.27-1.65)	
2010	2.65 (2.35-3.00)		1.26 (1.10-1.43)		1.25 (1.09-1.43)	
2011	3.55 (4.60-5.94)		1.40 (1.22-1.60)		1.43 (1.24-1.65)	
2012	5.23 (4.60-5.94)		1.67 (1.46-1.91)		1.72 (1.50-1.98)	
2013	11.72 (10.23-13.41)		2.36 (2.04-2.74)		2.53 (2.17-2.94)	
2014	30.42 (25.24-36.66)		2.91 (2.38-3.56)		3.05 (2.48-3.75)	
District		<.0001		.0007		.04
Ilala	Reference		Reference		Reference	
Kinondoni	1.08 (1.02-1.13)		1.05 (1.00-1.11)		1.03 (0.97-1.09)	
Temeke	0.89 (0.84-0.94)		0.98 (0.93-1.04)		0.97 (0.91-1.03)	
Facility level		<.0001		<.0001		<.0001
Hospital	Reference		Reference		Reference	
Health center	0.78 (0.71-0.85)		0.83 (0.75-0.91)		0.86 (0.78-0.94)	
Dispensary	0.73 (0.68-0.77)		0.81 (0.76-0.87)		0.83 (0.77-0.89)	
Baseline BMI (kg/m^2)	<.0001		<.0001		<.0001	
<18.5	Reference		Reference		Excluded	
18.5-24.9	2.15 (1.98-2.34)		2.17 (1.99-2.36)		Reference	
25.0-29.9	17.80 (16.41-19.32)		14.72 (13.54-16.00)		6.75 (6.44-7.08)	
CD4 count, cells/mm^3		<.0001		<.0001		<.0001
<50	1.42 (1.30-1.55)		1.53 (1.40-1.68)		1.56 (1.41-1.71)	
50-99	1.43 (1.31-1.57)		1.47 (1.34-1.61)		1.51 (1.37-1.66)	
100-199	1.31 (1.24-1.39)		1.25 (1.18-1.33)		1.28 (1.21-1.36)	
≥200	Reference		Reference		Reference	
Previous ART use		.4		<.0001		.0003
No	Reference		Reference		Reference	
For HAART	0.84 (0.80-0.88)		0.92 (0.87-0.97)		0.94 (0.88-0.99)	
For PMTCT	0.66 (0.31-1.38)		0.36 (0.17-0.75)		0.32 (0.14-0.72)	
Adherence		.5		.03		<.0001
High	Reference		Reference		Reference	
Low	1.01 (0.97-1.06)		0.95 (0.91-1.00)		0.94 (0.90-0.99)	
History of tuberculosis	<.0001		0.4		0.8	
No	Reference		Reference		Reference	
Yes	0.68 (0.62-0.74)		0.96 (0.87-1.05)		0.99 (0.89-1.09)	
NRTI		<.0001		<.0001		<.0001
Zidovudine	Reference		Reference		Reference	
Stavudine	0.86 (0.81-0.91)		1.26 (1.18-1.34)		1.27 (1.19-1.37)	
Tenofovir	0.70 (0.59-0.83)		0.80 (0.74-0.86)		0.80 (0.74-0.87)	
NNRTI		.4		<.0001		<.0001
Nevirapine	Reference		Reference		Reference	
Efavirenz	1.02 (0.96-1.09)		1.16 (1.01-1.24)		1.17 (1.10-1.25)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PMTCT, prevention of mother-to-child transmission of HIV; RR, relative risk.
[a]N = 79 074.
[b]n = 56 871.
[c]Wald tests for trend for median scores of categorized continuous variables; Wald test for categorical and binary variables.

Lower CD4 count was associated with a higher risk of obesity (*P* value for trend <.0001). Patients with CD4 counts of less than 50 cells/mm^3 had a 1.53-fold increased risk of becoming obese as compared to those with counts of 200 cells/mm^3 or higher (95% CI: 1.40-1.68). Using the same reference category, those with a CD4 count between 50 and <100 cells/mm^3 had a 1.47-fold increased risk (95% CI: 1.34-1.61) and those with a CD4 count between 100 and <200 cells/mm^3 had a 1.25-fold increased risk (95% CI: 1.18-1.33). We found a similar trend after excluding patients who were underweight at baseline from the analysis.

Previous opportunistic infections were not associated with lower risk of obesity. In the univariate analysis, previous TB infection was associated with a lower risk of obesity (RR: 0.68, 95% CI: 0.62-0.74), but this association was not statistically significant after controlling for other factors (RR: 0.96, 95% CI: 0.87-1.05). Patients who were nonadherent to ART had a 5% lower risk of becoming obese (RR: 0.95, 95% CI: 0.91-1.00). Being on a tenofovir (TDF)-based regimen was associated with a 20% lower risk of becoming obese as compared to being on ZDV-based regimen (RR: 0.80, 95% CI: 0.74-0.86). Additionally, being on an EFV-based ART regimen was associated with a 1.16-fold increased risk of obesity as compared to being on a nevirapine (NVP)-based regimen (95% CI: 1.01-1.24).

Risk factors for becoming overweight are shown in Table 3. Normal weight patients had a 3.96-fold higher risk of becoming overweight when compared to those who were underweight at baseline (95% CI: 3.78-4.15). Risk factors for overweight were mostly similar to those of obesity, but with the exception of age and history of infection with TB. Contrary to the observed nonsignificant association between age and risk of obesity, older patients were more likely to become overweight (*P* value for trend <.0001). Similarly, patients with previous TB infection had a 6% lower risk of becoming overweight (RR: 0.94, 95% CI: 0.89-1.00), despite a null association for risk of obesity.

Discussion

This study found that a large proportion of HIV-positive individuals progressed to overweight and obese states after being started on ART (25% and 10%, respectively). To our knowledge, this is the first study to prospectively assess these 2 outcomes in this population. Taking into account that 14% of patients were overweight and 6% obese at ART initiation, the observed proportions of overweight and obese patients during follow-up are similar to those that have been reported in Tanzania's general population.[19]

The proportion of patients that progress to overweight and obesity in this urban setting is likely to be higher than that of rural areas that have been shown to have lower a prevalence of the 2 conditions.[20,21] Our findings also show that the risk of overweight and obesity in this population is increasing with each subsequent year, an association that may be explained by secular trends of the 2 conditions in the general population.[19] This trend is more likely to be a result of return to the baseline risk of overweight and obesity in the general population, as opposed to higher risk of these conditions in patients on ART when compared to HIV-negative individuals.

The increasing rates of nonideal BMI are more concerning in HIV-positive individuals because of the challenge of managing HIV and comorbidities associated with high BMI.[22] Additionally, HIV-positive individuals are at higher risk than the general population for conditions linked to high BMI, such as cardiovascular diseases and chronic kidney disease.[23,24] Despite the increased risk, there are opportunities of being diagnosed and receiving care for these conditions during patients' HIV clinic visits. Models for delivery of this care have been described in theory but are yet to be demonstrated in most low-income settings.[25]

Several risk factors for overweight and obesity in the general population were also associated with excessive weight gain in HIV-positive individuals who are started on ART. There are several plausible explanations for the higher risk in women, an association that has been reported in several studies.[26,27] Women in this setting seek HIV care earlier than men and are started on ART before progressing to advanced stages of HIV.[28] However, given that we control for baseline BMI and time-varying CD4 counts, which are indicators of immune status, the higher risk is likely be due to nonclinical factors. Larger female body sizes are socially more ideal in some African settings and this preference has been associated with overnutrition.[26,29] It is also possible that some of these women intentionally gain more weight as has been shown in studies that found significantly higher BMI in HIV-positive women on ART than in matched HIV-negative controls.[30,31] Hurley et al also found larger increases in body weight in HIV-positive women who wished to gain weight than in those who did not wish to.[10] More research is needed on social influences on weight among HIV-positive individuals.

Several studies have reported higher weight gain in patients with low immunity at baseline, but reasons for this association have not been discussed.[10,11,13,30] One study found that this trend is sustained throughout the 2 phases of weight recovery after ART initiation.[13] One study described larger increases in lean body mass (LBM) in patients with low immunity at baseline.[33] Recovery of lost LBM could in part explain the higher risk of overweight and obesity in patients with lower immunity. A large proportion of patients in our study are likely to have lost a lot of LBM including those who were normal weight and overweight at baseline. However, those with lower CD4 counts are likely to have lost more LBM leading to larger increases in weight after starting ART.

Previous studies have found conflicting associations between age and weight gain in patients on ART with some finding no association,[11-13] and others reporting statistically significant higher weight gain in older patients.[30,32] This difference in findings is possibly be due to heterogeneity in the association between age and weight gain.[13] We found that older patients were more likely to become overweight than younger ones but did not find age association for obesity.

Table 3. Risk Factors for Overweight (25 ≤ BMI < 30) after ART Initiation.[a]

	Univariate		Multivariate[b]		Multivariate Excluding Underweight at Baseline[b]	
Variable	RR (95% CI)	*P* Value[c]	RR (95% CI)	*P* Value[c]	RR (95% CI)	*P* Value[c]
Sex		<.0001		<.0001		<.0001
Male	Reference		Reference		Reference	
Female	2.00 (1.93-2.07)		1.91 (1.84-1.98)		1.91 (1.84-1.98)	
Age category, years		<.0001		<.0001		<.0001
15-30	Reference		Reference		Reference	
30 to <40	1.18 (0.91-1.52)		1.20 (0.93-1.55)		1.16 (0.88-1.53)	
40 to <50	1.91 (1.32-2.77)		2.03 (1.40-2.93)		2.22 (1.48-3.35)	
50+	3.31 (1.85-5.93)		3.76 (2.11-6.71)		4.27 (2.30-7.95)	
Married		.1		.7		.4
No	Reference		Reference		Reference	
Yes	0.97 (0.94-1.00)		1.01 (0.97-1.04)		1.01 (0.98-1.05)	
Year started ART		<.0001		<.0001		<.0001
2004-2005	Reference		Reference		Reference	
2006	1.16 (1.06-1.27)		1.01 (0.92-1.10)		1.03 (0.94-1.14)	
2007	1.57 (1.44-1.72)		1.31 (1.20-1.43)		1.31 (1.19-1.44)	
2008	1.79 (1.65-1.95)		1.27 (1.17-1.39)		1.29 (1.17-1.41)	
2009	2.06 (1.89-2.25)		1.39 (1.27-1.53)		1.41 (1.27-1.55)	
2010	2.27 (2.08-2.48)		1.31 (1.20-1.44)		1.32 (1.19-1.46)	
2011	2.77 (2.52-3.04)		1.44 (1.31-1.59)		1.48 (1.34-1.65)	
2012	3.93 (3.59-4.30)		1.86 (1.69-2.05)		1.95 (1.75-2.16)	
2013	7.99 (7.26-8.78)		2.70 (2.43-3.00)		2.88 (2.58-3.23)	
2014	19.77 (17.47-22.38)		3.71 (3.23-4.26)		4.12 (3.56-4.76)	
District		<.0001		<.0001		.0003
Ilala	Reference		Reference		Reference	
Kinondoni	1.11 (1.07-1.15)		1.03 (0.99-1.07)		1.02 (0.98-1.06)	
Temeke	0.98 (0.95-1.02)		0.94 (0.91-0.98)		0.92 (0.88-0.96)	
Facility level		<.0001		<.0001		<.0001
Hospital	Reference		Reference		Reference	
Health center	0.82 (0.77-0.87)		0.82 (0.77-0.87)		0.84 (0.79-0.90)	
Dispensary	0.67 (0.64-0.70)		0.71 (0.68-0.74)		0.72 (0.69-0.76)	
Baseline BMI (kg/m^2)		<.0001		<.0001		–
<18.5	Reference		Reference		Excluded	
18.5-24.9	4.54 (4.34-4.75)		3.96 (3.78-4.15)			
CD4 count (cells/mm^3)		<.0001		<.0001		<.0001
<50	1.67 (1.58-1.76)		1.65 (1.56-1.74)		1.81 (1.70-1.92)	
50-99	1.60 (1.51-1.69)		1.49 (1.40-1.57)		1.60 (1.51-1.70)	
100-199	1.48 (1.42-1.53)		1.34 (1.29-1.40)		1.42 (1.36-1.48)	
≥200	Reference		Reference		Reference	
Previous ART use		<.0001		.001		.003
No	Reference		Reference		Reference	
For HAART	0.84 (0.81-0.87)		0.96 (0.93-1.00)		0.96 (0.93-1.00)	
For PMTCT	0.66 (0.41-1.08)		0.49 (0.30-0.80)		0.50 (0.30-0.83)	
Adherence		.1		<.0001		<.0001
High	Reference		Reference		Reference	
Low	0.98 (0.95-1.01)		0.91 (0.88-0.94)		0.91 (0.88-0.94)	
History of tuberculosis		<.0001		.04		<.0001
No	Reference		Reference		Reference	
Yes	0.78 (0.74-0.83)		0.94 (0.89-1.00)		0.92 (0.87-0.98)	
NRTI		<.0001		<.0001		<.0001
Zidovudine	Reference		Reference		Reference	
Stavudine	1.23 (1.19-1.27)		1.39 (1.33-1.46)		1.36 (1.30-1.44)	
Tenofovir	1.01 (0.97-1.06)		0.83 (0.79-0.87)		0.82 (0.78-0.87)	
NNRTI		<.0001		<.0001		<.0001
Nevirapine	Reference		Reference		Reference	
Efavirenz	0.93 (0.90-0.96)		1.10 (1.06-1.15)		1.09 (1.05-1.14)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PMTCT, prevention of mother-to-child transmission of HIV; RR, relative risk.
[a]N = 67 434.
[b]n = 45 231.
[c]Wald tests for trend for median scores of categorized continuous variables; Wald test for categorical and binary variables.

The null association between previous TB infection with risk of obesity is indicative of absence of long-term effects of HIV-related immunosuppression on weight gain. Our findings also suggest that adequate viral load suppression is required for weight recovery. This is supported by the lower risk of overweight and obesity in patients with poor adherence, those with previous exposure to ART for PMTCT, and those who were initiated on HAART at other sites.

Earlier recommendations for PMTCT have been linked to virologic failure resulting from use of regimen with less than 3 antiretroviral drugs, as well as from withdrawing ART at the end of the pregnancy.[34-36] The lower risk of overweight and obesity in patients initiated on HAART at other treatment sites can be explained by drug resistance that develops when patients are off ART before enrolling at other HIV treatment sites.[35] Alternatively, some of these patients have been on ART for a while and regained some weight before transferring to MDH-supported clinics.

The higher risk of overweight and obesity in patients on EFV has previously been described.[32,37] One of these studies also showed that this trend is reversed in the second year, with patients on NVP gaining more weight than those on EFV.[32] We found no studies that compared body fat changes for these 2 drugs which could explain these differences. Our findings on associations between several NRTIs with overweight and obesity are not consistent with those from previous studies. Patients on TDF and other contemporary drugs have been shown to gain more weight than those on thymidine analogues like stavudine (d4T) or ZDV.[13,38,39] The lower risk of overweight and obesity in patients on TDF in this analysis could have resulted from the shorter follow-up duration of patients who were started on TDF as compared to those on ZDV or d4T. Most of patients on TDF (88%) have been on ART for less than 2 years because the other 2 NRTIs were the available first-line choice of drugs in this setting before 2012. Also, the higher risk of overweight and obesity in patients on d4T in our study is suggestive of worse lipodystrophy in patients on d4T, an association that has been found in other studies.[40] We however did not have data on waist–hip ratios to ascertain worse central obesity in patients on d4T. A more conclusive comparison of the effects of NRTIs in this population would require a longer follow-up of patients on TDF and other anthropometric measures besides weight gain.

Our analysis has several strengths. First, we prospectively followed up a large cohort of HIV-positive patients for 2 outcomes that have not been studied in this or similar settings. Second, we controlled for several baseline and time-varying covariates in a setting with limited prospective data on HIV-positive patients and for a duration that covers most of the period that ART has been available in SSA. Third, our analysis included patients who were underweight at baseline, a subset of HIV-positive patients that constitutes a large proportion of patients started on ART in SSA (28% in this population). We also show that our findings are unchanged when we exclude patients who were underweight when initiating ART.

One limitation of this study was the lack of time-varying data on plasma HIV viral loads, a known predictor of weight gain in patients on ART.[27,31,33] We however controlled for other predictors of treatment failure including adherence ART and time-varying CD4 count. Another limitation was the short follow-up duration of patients who were started on TDF-containing regimen and the lack of data on other anthropometric measures that limited our ability to conclusively examine the effects of NRTIs. We were also unable to include lamivudine (3TC) in the NRTI comparisons because almost all patients in the study were taking it or emtricitabine, a drug with similar properties as 3TC.

Last, we had no data on socioeconomic factors that are known to influence weight gain such as household income and diet. We however control for district of residence, which in this setting is correlated with affluence and find that patients from the wealthiest district were more likely to become overweight and obese.

In conclusion, HIV-positive patients are increasingly progressing to overweight and obesity after starting ART. This trend will become of more concern in part due to the secular increases of overweight and obesity in low-income setting and also as a result of earlier initiation of ART as per World Health Organization recommendations. Routine HIV care should include screening and interventions for overweight and obesity in patients with identified risk factors. The high proportion of HIV-positive patients with overweight and obesity also presents a challenge to offering health care in settings that have not yet fully met treatment needs for HIV and other infectious diseases. More research is needed on long-term trends and clinical effects of overweight and obesity in HIV-positive patients.

Authors' Note

W.F. jointly conceived the study with A.K. A.K analyzed the data and wrote the manuscript with supervision from W.F., T.B., and D.S. All authors discussed results and contributed to the manuscript at different stages.

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