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Body Fat Changes in People Living with HIV on Antiretroviral Therapy

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Abstract

Although more than one in two HIV-infected persons may develop central fat accumulation soon after commencing antiretroviral therapy, the association between antiretroviral therapy and body fat changes has not been consistent across primary epidemiological studies. We conducted a systematic review with meta-analyses to estimate the pooled effects of antiretroviral therapy on different measures of body fat, and to examine factors that potentially modify these effects. We searched for studies that compared body mass index, waist circumference, combined overweight/obesity, and central obesity between HIV-infected adults naive and exposed to antiretroviral therapy. Random-effects subgroup and meta-regression analyses were performed to identify potential effect-modifiers of the pooled associations. Sixty studies, comprising data on 53,199 HIV-infected participants, were eligible for the meta-analyses. Antiretroviral therapy was associated with increased body mass index (SMD: 0.17 kg/m^2; 95% CI: 0.07-0.26), waist circumference (SMD: 0.20 cm; 95% CI: 0.07-0.33), overweight/obesity (borderline significance: OR: 1.36; 95% CI: 0.99-1.86), and abdominal obesity (OR: 1.49; 95% CI: 1.16-1.90). In addition, antiretroviral therapy was associated with significant increases in body mass index, overweight/obesity, and central obesity among patients with CD4 counts < 350 cells/mm^3, but not among patients with higher CD4 counts ($P_{interaction}$ < 0.05 for all). Overall, exposure to antiretroviral therapy was associated with increased risks of generalized and central obesity, and risks may be exacerbated by lower CD4 counts. These findings suggest that weight management and obesity prevention programs may be worth considering as part of routine HIV care. **(AIDS Rev. 2016;18:198-211)**

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Key words

Antiretroviral therapy. Obesity. Central obesity. Relative weight. Body fat.

Introduction

Life expectancy of persons living with HIV has increased since the advent of highly active antiretroviral therapy (HAART)[1]; however, morbidity and mortality rates within this high-risk group remain higher than those observed in the general population[2]. The rising incidence of non-AIDS-defining illnesses, such as cardio-metabolic disorders, has been identified as one of the underlying factors that may account for this observation[2-4]. Of note, the increased life expectancy of people living with HIV may be associated with body fat changes, which are attributable to the adverse effects of antiretroviral drugs[3]. Evidence suggests that more than one in two HIV-infected patients may develop central fat accumulation soon after commencing antiretroviral therapy (ART)[5]. While ART-naive HIV-infected

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patients are already more likely to develop body fat changes compared with the general population, exposure to ART may worsen these changes[6]. Although the underlying mechanisms are unclear, studies suggest a plausible link between certain antiretroviral drugs and raised serum cortisol levels, suggestive of Cushing's disease[3], which invariably presents with central adiposity and relative weight gain.

With an estimated 35 million people living with HIV worldwide[1], and exponential increases in ART coverage rates[7], ART-associated changes in body fat may portend a considerable global health burden. However, without comprehensive assessment of the effects of ART on body fat, it would be impossible to accurately estimate or predict this burden. Therefore, we aimed to estimate the pooled effects of ART on different measures of body fat, including measures of relative weight and body fat distribution, as well as on the risk of developing overweight or obesity in persons living with HIV worldwide. We also sought to examine factors that may potentially influence these effect estimates.

Search strategy, risk of bias assessment, and statistical methods

We included studies that compared body fat measures between HIV-infected adults naïve and exposed to ART (Table 1 for full inclusion and exclusion criteria).

We searched for eligible studies from PubMed (1997 to 19 September 2015) and EMBASE (1997 to 20 September 2015) databases using the following medical subject heading (MeSH) terms and keywords: exp *highly active antiretroviral therapy/, antiretroviral therapy.mp./, antiretroviral-naive.mp./, exp *abdominal obesity/, exp *obesity/, overweight.mp./, body mass index.mp./, exp *waist circumference/ (Supplementary Appendices 1 and 2). We also scanned bibliographies of relevant articles identified by the database search. All articles yielded by the search strategy were screened by their abstracts and, where necessary, by the full texts.

Two reviewers independently extracted data from each eligible study using a piloted data extraction form and any disparities were resolved by consensus with the other investigators. Extracted data included: article citation, study design, sample size, country, country income group, mean age, sex distribution, proportion of current smokers and drinkers, mean CD4 cell count, and mean duration of HIV infection. The study outcomes included: mean body mass index (BMI) and waist circumference (WC), and prevalence estimates of combined overweight/obesity and abdominal obesity in ART-naive and ART-exposed patients. Combined overweight/obesity was defined as BMI ≥ 25 kg/m^2, whereas abdominal obesity was assessed as WC ≥ 80 cm for women and ≥ 94 cm for men[8].

The methodological quality of each study was assessed using a domain-based checklist adapted from the Cochrane risk of bias tool for non-randomized studies[9]. Essentially, we investigated for potential sources of bias including: selection of participants (selection bias), assessment of ART status (information bias), assessment of the outcomes (information bias), and loss to follow-up of participants recruited as part of cohort studies (attrition bias) (Supplementary Appendix 3).

All data were analyzed using Stata version 14 for Windows (Stata Corp, College Station, Texas). We conducted random-effects meta-analyses to estimate the overall effects of ART on body fat changes: pooled standardized mean differences (SMD) in BMI and WC, and pooled odds ratios (OR) for combined overweight/obesity and abdominal obesity. In unifying the effect measures of the pooled associations of ART with body fat changes, we re-expressed the individual odds ratios of overweight/obesity and central obesity as the standardized mean differences using the following formula[10]:

$$SMD = \frac{\sqrt{3}}{\pi} \log OR$$

The random-effects model, as opposed to the fixed-effect approach, was more appropriate to account for differences in characteristics across the included studies that may affect the pooled results[11]. Heterogeneity across studies included in the meta-analyses was measured using the *I*-squared (I^2) statistic, for which a value greater than 75% indicated considerable heterogeneity[11]. Leave-one-out sensitivity analyses were performed by omitting the included studies one at a time in order to determine whether any of the included studies had an undue influence on the pooled estimates as to alter the interpretation of the results. Publication bias was assessed using Funnel plots and Egger's regression test for funnel plot asymmetry. Where publication bias was present, we ascertained its effect on the pooled estimates using the "trim and fill" analysis of Duval and Tweedie[12]. We also examined for factors that may modify the effects of ART on body fat changes by performing random-effects subgroup and meta-regression analyses on each baseline study-level characteristic. In accordance with standard practice,

Table 1. Eligibility criteria

	Inclusion	Exclusion
Population	HIV-infected Adults	HIV-negative Adolescents and children
Exposure	ART status	ART status not reported
Outcome	Body mass index Overweight Obesity Waist circumference Abdominal/central obesity	Body fat changes not reported
Study types	Any study design including: Cross-sectional Case-control Cohort Randomized trials Full-texts Conference abstracts	Expert reviews Policy reports

ART: antiretroviral therapy.

meta-regression analyses were only performed when there were 10 or more studies in order to effectively examine for potential effect-modifiers[11]. All effect estimates were reported with 95% confidence intervals (CI) and $p < 0.05$ was considered statistically significant for meta-regression analysis.

Study selection

The details of the study selection process are illustrated in figure 1. From 801 records yielded by the literature search, 722 articles were excluded by abstracts and 12 duplicate records were withdrawn, leaving 67 articles assessed to determine eligibility for inclusion. We excluded an additional seven articles after reviewing the full texts, leaving 60 studies[13-72] eligible for inclusion in the systematic review and meta-analyses.

Characteristics of participants in the included studies

Table 2 summarizes the characteristics of the study participants in all 60 studies, including cohort (n = 22) and cross-sectional (n = 38) studies. In total, our study population comprised 53,199 HIV-infected adults across 26 countries, with females accounting for 43%. There were 39 studies (65%) conducted in low- and middle-income countries; however, studies conducted in high-income countries comprised approximately 82% of the study population. Mean age of our study population was 39.0 ± 8.4 years (age range: 30.9-48.7), and participants from high-income countries (mean age 40.9 ± 8.5 years) were, on average, older than those from low- and middle-income countries (mean age 38.1 ± 8.3 years). More than one in four (28.7%) were current smokers and 18.1% were current drinkers.

The results of the methodological assessment of the included studies are shown in Supplementary Table 1. Sampling bias was low in only 22 studies[14,19-22,31,32,36,42,45,46,48,58,59,63,65-67,68-71]; exposure criterion with regard to ART status was clearly described in all included studies; body fat assessment was validated and similar between antiretroviral-naive and exposed patients in all but 11 studies[27,28,35,39,49,50,61,63,66,69,71]; adjustment for confounding was performed in 40 studies[13-21,24-26,28,29,31-39-48,54,58,60,63,65,67,68,70,71]; and loss to follow-up was less than 20% in 16 of the 19 included cohort studies[21,23-25,30-32,40,42,45-47,62,65,68,71].

Overall impact of antiretroviral therapy on body fat changes

Changes in body fat measures

Mean BMI was significantly higher among ART-exposed patients, compared with ART-naive patients (pooled SMD: 0.17 kg/m^2; 95% CI: 0.07-0.26; 50 studies; 17,041 participants) (Fig. 2). Heterogeneity across the 50 studies was considerable and statistically significant (I^2 statistic = 90%; $p < 0.001$). Funnel plot

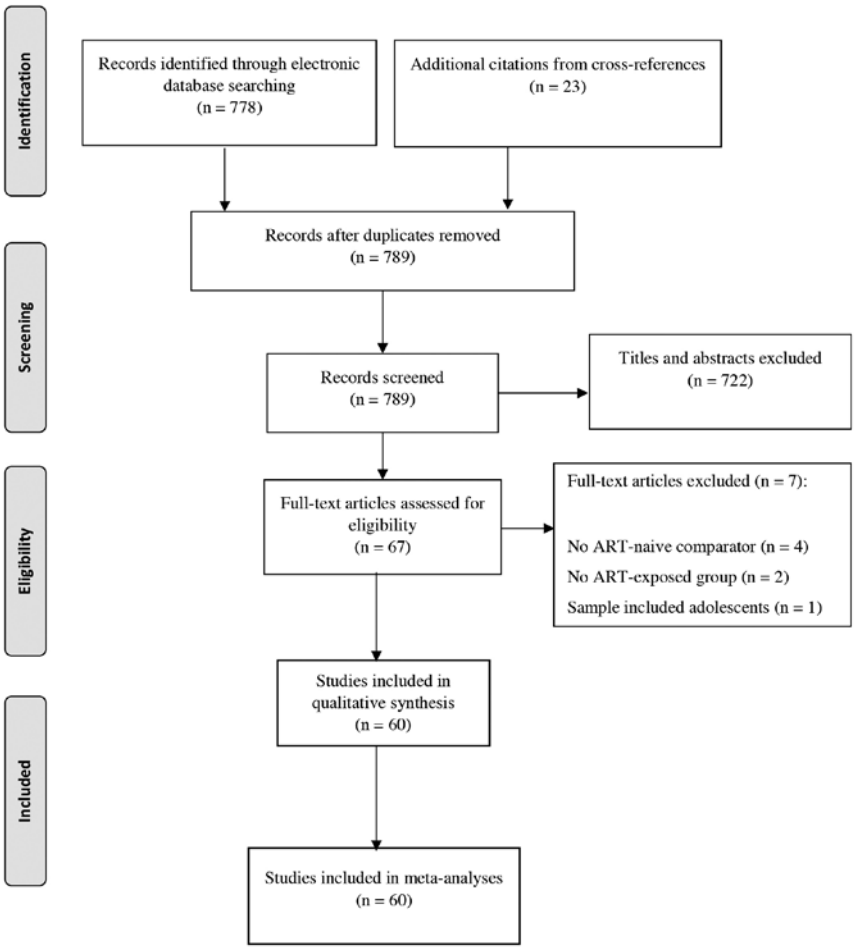

Figure 1. *Flow diagram showing study selection. ART: antiretroviral therapy.*

asymmetry was absent, suggesting no evidence of publication bias (Supplementary Fig. 1). Leave-one-out sensitivity analysis showed that no study included in the meta-analysis had any undue influence on the pooled association (Supplementary Fig. 2).

Similarly, mean WC was significantly higher among HIV-infected patients on ART, compared with treatment-naive patients (pooled SMD: 0.20 cm; 95% CI: 0.07-0.33; I^2 = 72.8%; 17 studies; 3,641 participants) (Fig. 3). Funnel plot asymmetry was absent, suggesting no evidence of publication bias (p = 0.65 for Egger's regression test for funnel plot asymmetry) (Supplementary Fig. 3). The pooled effect of ART on WC did not change significantly following serial omission of the included studies (Supplementary Fig. 4).

Combined overweight/obesity

Exposure to ART was borderline significantly associated with increased risk of overweight/obesity: 4,441 (13%) of 34,166 HIV-infected patients on ART were overweight or had become obese, compared with 1,797 (9.9%) of 18,220 ART-naive patients (pooled OR: 1.36; 95% CI: 0.99-1.86; I^2 = 90.5%; 21 studies) (Fig. 4).

Table 2. Characteristics of the included studies

Authors	Year	Study design	Country	Income group	N	F (%)	Age (years)	HIV duration (months)	CD4 count (cells/μl)	Smokers (%)	Alcohol (%)
Abebe, et al.	2014	Cross-sectional	Ethiopia	Low/middle	232	72.3	35.3 ± 10	20.7 ± 14.7	364 ± 199		
Adewole, et al.	2010	Cohort	Nigeria	Low/middle	130	69.0				23.0	31.0
Akinboro, et al.	2013	Cohort	Nigeria	Low/middle	140	68.0	35.0 ± 8.8		288 ± 232		
Awotedu, et al.	2010	Cross-sectional	South Africa	Low/middle	196	81.0	36.9 ± 10.4				
Ayodele, et al.	2013	Cross-sectional	Nigeria	Low/middle	265	67.5	38.7 ± 8.7		313 ± 230	1.9	7.2
Baekken, et al.	2008	Cohort	Norway	High	542	27.1	42.9 ± 9.9				
Bergersen, et al.	2003	Cross-sectional	Norway	High	283	20.0	43.1 ± 10.2	77.0 ± 56.0	384 ± 206	54.5	
Blass, et al.	2008	Cross-sectional	Germany	High	44	18.2	40.0 ± 7.1		441 ± 265		
Blumer, et al.	2008	Cohort	Netherlands	High	39		42.3 ± 7.0		260 ± 148		
Bonfati, et al.	2012	Cohort	Italy	High	188	24.5	39.5 ± 11.1				
Carey, et al.	2013	Cross-sectional	India	Low/middle	108	53.8	36.3 ± 7.6	46.0			
Denue, et al.	2012	Cohort	Nigeria	Low/middle	227	49.0	40.3 ± 9.3	56.0 ± 53.0	246 ± 168	5.3	
Denue, et al.(a)	2013	Cohort	Nigeria	Low/middle	229	51.1	43.5 ± 9.3		246 ± 167	5.7	4.9
Denue, et al.(b)	2013	Cohort	Nigeria	Low/middle	107	68.2	39.4 ± 9.3		229 ± 174		
Dimodi, et al.	2014	Cross-sectional	Cameroon	Low/middle	463	74.7				5.1	35.2
Domingos, et al.	2009	Cross-sectional	Brazil	Low/middle	292	40.0	41.0 ± 13.0	46.6		15.4	
Eira, et al.	2012	Cross-sectional	Brazil	Low/middle	56		42.8 ± 7.1	101.4 ± 51.0	328 ± 183	57.1	
Ekali, et al.	2013	Cross-sectional	Cameroon	Low/middle	143	72.0	39.5 ± 9.8		253 ± 167		
Esposito, et al.	2008	Cohort	South Africa	Low/middle	30	100.0	30.9 ± 5.6		164 ± 69		
Fontas, et al.	2004	Cohort	Multiple	High	7483	24.0	38.0 ± 2.5		470 ± 90		
Friis-moller, et al.	2003	Cohort	Multiple	High	17,852	24.0	39.0 ± 2.8		430 ± 88		
Goedecke, et al.	2013	Cross-sectional	South Africa	Low/middle	744	100.0	33.0 ± 5.3		371 ± 147		
Grandominico, et al.	2008	Cohort	USA	High	52	9.6	35.9 ± 10.1		298 ± 163	57.1	
Hansen, et al.	2009	Cross-sectional	Denmark	High	466	18.6	45.5 ± 10.2	115.2 ± 81.6	519 ± 233		
Howard, et al.	2014	Cross-sectional	UK	High	100						
Jaff, et al.	2015	Cross-sectional	South Africa	Low/middle	86	100.0	47.0 ± 5.1				
Jantarapakde, et al.	2014	Cross-sectional	Thailand	Low/middle	580	53.8	37.0 ± 8.2	60.0 ± 62.2	406 ± 208	16.3	
Kiage, et al.	2013	Cohort	Zambia	Low/middle	118	55.9	35.0 ± 7.9		136 ± 50	4.4	9.6
Kingsley, et al.	2008	Cross-sectional	USA	High	615	0					
Koethe, et al.	2015	Cohort	Multiple	High	14,084	13.0					
Koppel, et al.	2000	Cross-sectional	Sweden	High	340	4.1	40.5 ± 8.5	88.5 ± 54.5	484 ± 236		

(Continued)

Table 2. Characteristics of the included studies *(Continue)*

Authors	Year	Study design	Country	Income group	N	F (%)	Age (years)	HIV duration (months)	CD4 count (cells/μl)	Smokers (%)	Alcohol (%)
Lekakis, et al.	2009	Case-control	Greece	High	56	4.0	40.0 ± 13.0	42.0 ± 27.5	452 ± 260	73.0	
Magenta, et al.	2011	Cohort	Switzerland	High	74	12.0	40.0 ±1 0.0		258 ± 112	65.0	
Malapati, et al.	2014	Cohort	India	Low/middle	229		46.3 ± 9.3		246 ± 167		
Mariz, et al.	2011	Cross-sectional	Brazil	Low/middle	2,018	37.86				27.0	33.9
Mital, et al.	2013	Cross-sectional	India	Low/middle	200			35.4 ± 7.9		17.5	11.5
Mittal, et al.	2013	Cross-sectional	India	Low/middle	40	32.5	36.1 ± 7.2				
Muhammad, et al. (a)	2013	Cross-sectional	Nigeria	Low/middle	200	53.0	32.5 ± 7.6	72.5 ± 35.8	319 ± 206	9.0	
Muhammad, et al. (b)	2013	Cross-sectional	Nigeria	Low/middle	200	53.0	32.5 ± 7.6	72.5 ± 35.8	319 ± 206	9.0	
Mustapha, et al.	2011	Cross-sectional	Nigeria	Low/middle	100		32.9 ± 7.5				
Ngala, et al.	2013	Cross-sectional	Ghana	Low/middle	305	61.0	38.5 ± 8.7				
Ngondi, et al.	2007	Cohort	Cameroon	Low/middle	138	57.97	36.1 ± 7.1		209 ± 222		
Ogundahunsi, et al.	2008	Cross-sectional	Nigeria	Low/middle	110		38.7 ± 10.1		355 ± 185		
Ogunmola, et al.	2014	Cross-sectional	Nigeria	Low/middle	250	62.4	37.6 ± 8.6		374 ± 223		
Palacios, et al.	2006	Cohort	Spain	High	95	18.0	40.0 ± 10.1	56.1 ± 57.1	165 ± 125	68.0	
Peck, et al.	2014	Cross-sectional	Tanzania	Low/middle	301	67.8	40.3 ± 7.8		314 ± 159	2.7	13.9
Pefura Yone, et al.	2011	Cross-sectional	Cameroon	Low/middle	276	60.5	39.7 ± 8.7		308 ± 186		
Shahmanesh, et al.	2004	Cross-sectional	UK	High	55	18.2	40.0 ± 10.4		424 ± 225	41.8	
Silva, et al.	2010	Cross-sectional	Brazil	Low/middle	314	44.6	37.7 ± 7.9	51.0 ± 46.2	531 ± 313	26.7	
Singh, et al.	2014	Cohort	India	Low/middle	100	35.0	36.4 ± 9.6		151 ± 67		
Smith, et al.	2004	Cross-sectional	UK	High	394	15.0		84.0 ± 15.0	426 ± 87	45.0	7.0
Soares, et al.	2015	Cross-sectional	Brazil	Low/middle	152	33.0	42.5 ± 8.5	72.0 ± 48.0	444 ± 88		
Sogaard, et al.	2010	Cohort	Denmark	High	95	15.8	48.7 ± 4.1		571 ± 99	35.8	
Sreekantamurthy, et al.	2014	Cross-sectional	India	Low/middle	101	0	43.5 ± 6.3	64.9 ± 30.2			
Tadewos, et al.	2012	Cross-sectional	Ethiopia	Low/middle	226	65.1	35.5 ± 8.5		408 ± 219	11.5	
Wanke, et al.	2005	Cohort	USA	High	49	14.29	40.6 ± 8.0		242 ± 205	35.0	
Weerakkody, et al.	2013	Cross-sectional	Sri Lanka	Low/middle	268	42.2	39.5 ± 9.6	42.5 ± 36.2	390 ± 243	20.1	
Wilson, et al.	2009	Cross-sectional	UK	High	458	16.81	39.5 ± 8.9	66.0 ± 48.8	545 ± 83	41.5	21.8
Zannou, et al.	2009	Cohort	Benin	Low/middle	79	59.5	38.0 ± 9.7		105 ± 69	8.9	22.8
Zeng, et al.	2010	Cross-sectional	China	Low/middle	82	39.0	38.4 ± 6.4		405 ± 191	50.0	

ART: antiretroviral therapy; F: female; N: number of participants.

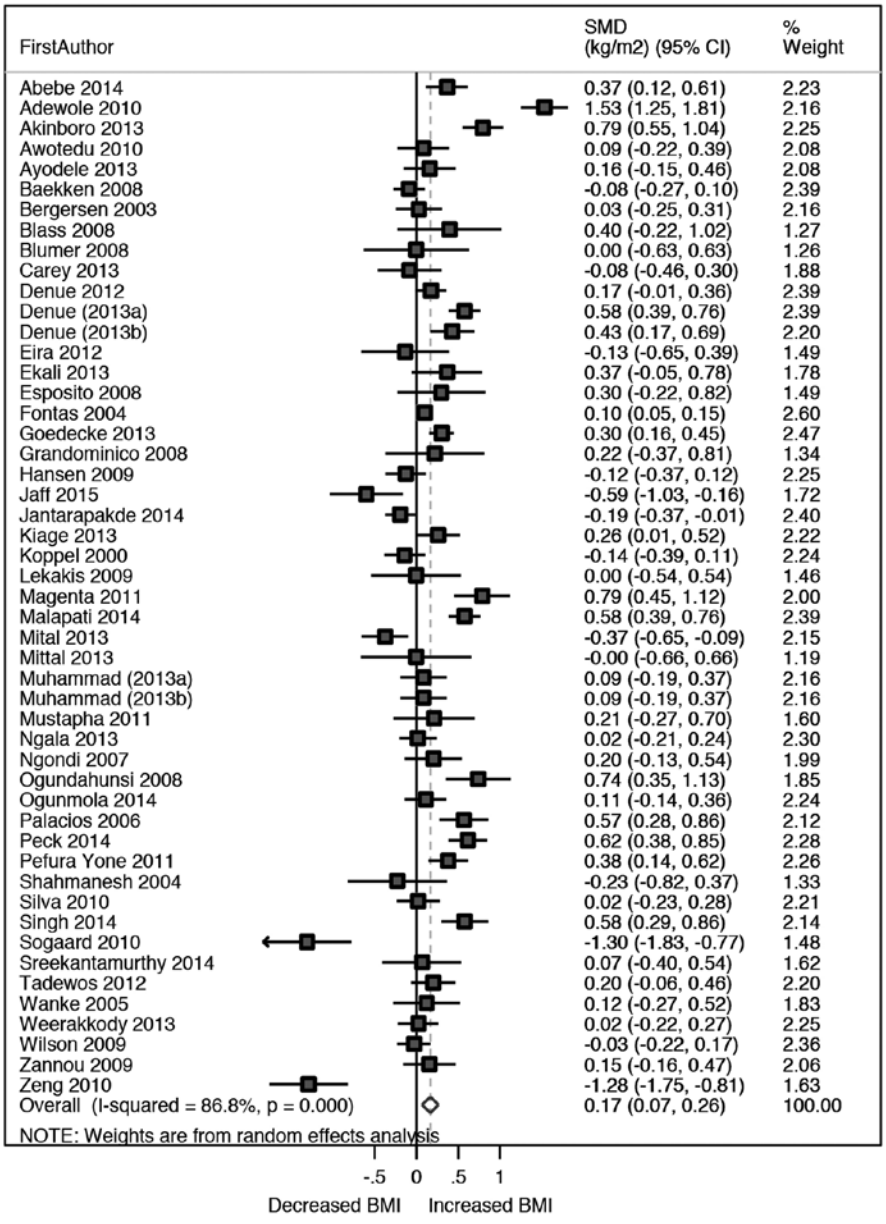

Figure 2. *Meta-analysis of the association between antiretroviral therapy and body mass index. BMI: body mass index; CI: confidence interval; SMD: standardized mean difference. I-squared quantifies the amount of heterogeneity across the included studies. The p value (p = 0.000) at base of the forest plot corresponds to the statistical significance of the heterogeneity across the included studies.*

Re-expressing the individual odds ratios as standardized mean differences also revealed a borderline significant association between ART and overweight/obesity (pooled SMD: 0.01; 95% CI: 0.00-0.02). Analysis of publication bias revealed no evidence of small-study effects (Supplementary Fig. 5). Sensitivity analysis showed no significant change in the pooled effect estimate following serial omission of the included studies, which confirms stability of the results (Supplementary Fig. 6).

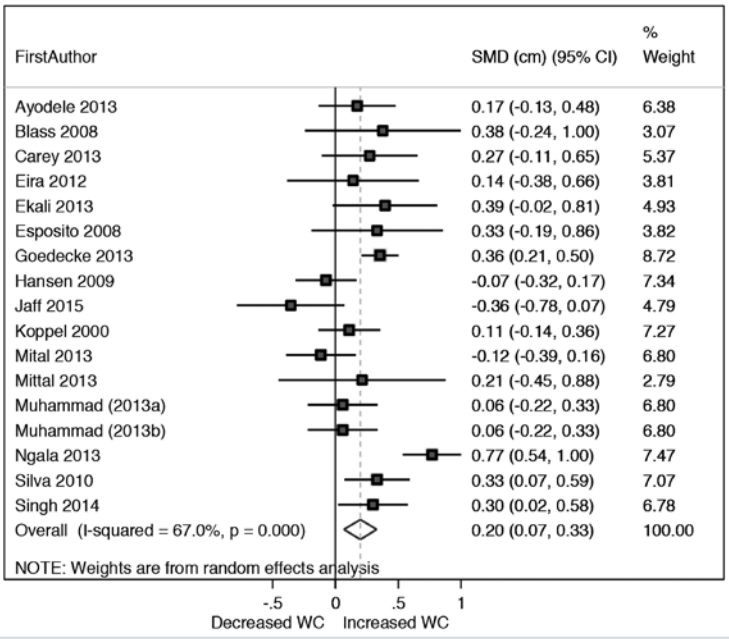

Figure 3. *Meta-analysis of the association between antiretroviral therapy and waist circumference. WC: waist circumference; CI: confidence interval; SMD: standardized mean difference. I-squared quantifies the amount of heterogeneity across the included studies. The p value (p = 0.000) at base of the forest plot corresponds to the statistical significance of the heterogeneity across the included studies.*

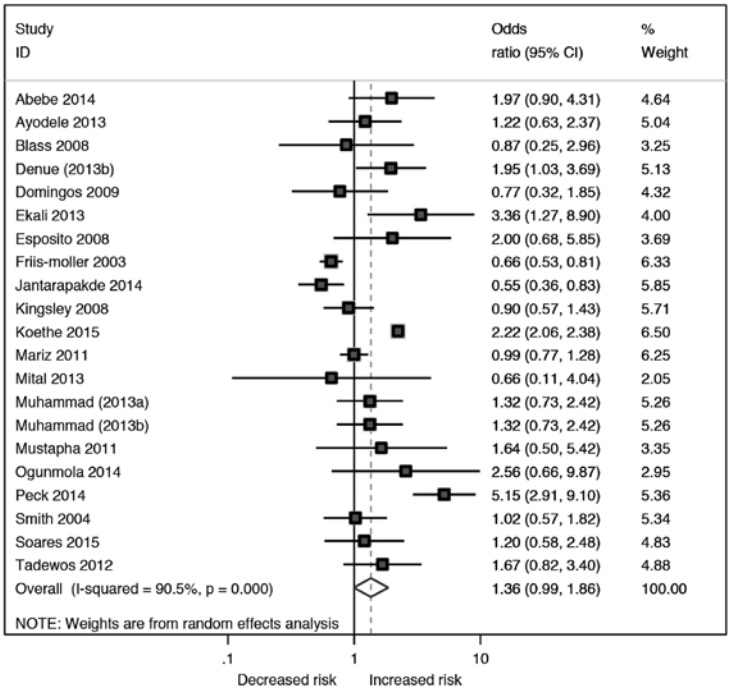

Figure 4. *Meta-analysis of the association between antiretroviral therapy and the risk of combined overweight/obesity. CI: confidence interval. I-squared quantifies the amount of heterogeneity across the included studies. The p value (p = 0.000) at base of the forest plot corresponds to the statistical significance of the heterogeneity across the included studies.*

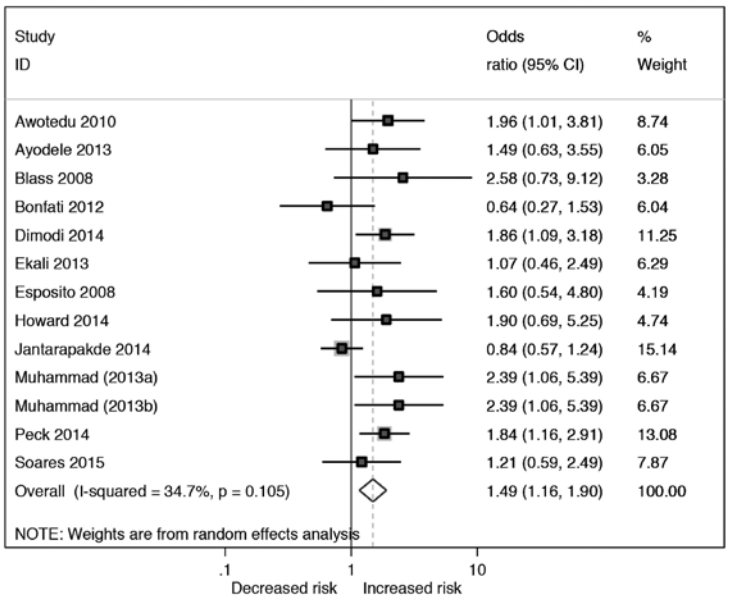

Figure 5. *Meta-analysis of the association between antiretroviral therapy and the risk of central obesity. CI: confidence interval. I-squared quantifies the amount of heterogeneity across the included studies. The p value (p = 0.105) at base of the forest plot corresponds to the statistical significance of the heterogeneity across the included studies.*

Central obesity

Antiretroviral therapy was significantly associated with increased risk of abdominal obesity: 609 (32.3%) of 1,888 HIV-infected patients on ART developed abdominal obesity, compared with 244 (25.3%) of 963 ART-naive patients (pooled OR: 1.49; 95% CI: 1.16-1.90; I^2 = 34.7%; 13 studies) (Fig. 5). Re-expressing the individual odds ratios as standardized mean differences also revealed a significant association between ART and central obesity (pooled SMD: 0.01; 95% CI: 0.005-0.02). No evidence of publication bias was found (p = 0.35 for Egger's test for small-study effects) (Supplementary Fig. 7), and sensitivity analysis revealed no significant change in the pooled effect following the omission of the included studies one at a time (Supplementary Fig. 8).

Figure 6 summarizes the associations of ART with changes in body fat measures and the risks of combined overweight/obesity and central obesity.

Factors that may influence the associations of antiretroviral therapy with body fat changes as identified by subgroup and meta-regression analyses

Table 3 summarizes the findings of the subgroup and meta-regression analyses. Exposure to ART was significantly associated with increased BMI in HIV-infected patients with CD4 counts < 350 cells/mm^3 (pooled SMD: 0.37 kg/m^2; 95% CI: 0.26-0.47), but not among HIV-infected patients with CD4 counts ≥ 350 cells/mm^3 (pooled SMD: –0.01 kg/m^2; 95% CI: –0.14-0.12) (p = 0.002 for interaction). The impact of ART on the risk of overweight/obesity was twice as high among HIV-infected patients with CD4 cell counts < 350 cells/mm^3 (pooled OR: 2.00; 95% CI: 1.28-3.14), compared to those with CD4 cell counts ≥ 350 cells/mm^3 (pooled OR: 1.01; 95% CI: 0.70-1.45) (p = 0.048 for interaction). The association of ART with increased risk of central obesity was also

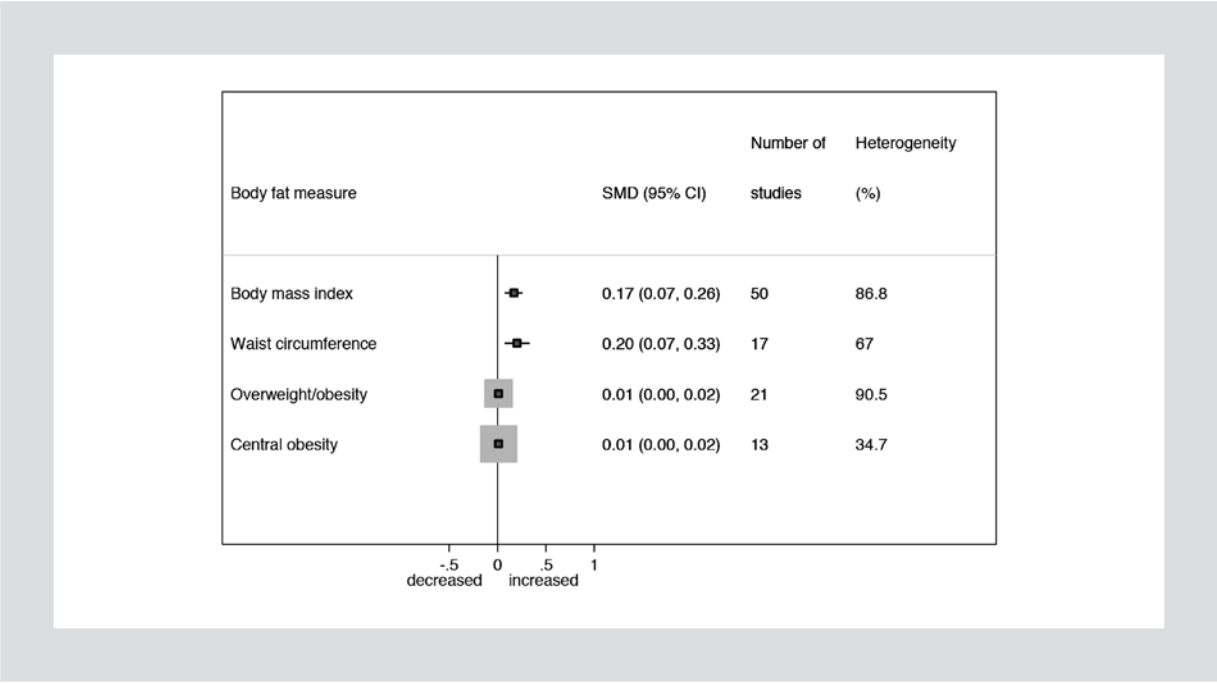

Figure 6. *Forest plot showing a summary of the pooled associations between antiretroviral therapy and body fat changes. SMD: standardized mean difference (pooled). The odds ratios of the categorical outcomes (overweight/obesity and central obesity) have been re-expressed as standardized mean differences in order to unify the pooled effect measures. The exact effect sizes for overweight/obesity and central obesity are: (SMD = 0.010; 95% CI: 0.000-0.021) and (SMD = 0.013; 95% CI: 0.005-0.021), respectively.*

significantly higher in patients with CD4 cell counts < 350 cells/mm^3 (pooled OR: 1.78; 95% CI: 1.32-2.40), compared to patients with CD4 counts ≥ 350 cells/mm^3 (pooled OR: 1.09; 95% CI: 0.66-1.80) (p = 0.044 for interaction). These findings are consistent with previous evidence linking obesity to lower CD4 cell counts[73]. These findings may also be coherent with the attenuation of immune competence associated with overweight/obese states[74]. Unlike cross-sectional studies (SMD: 0.05; 95% CI: –0.06-0.16), cohort studies were more likely to report a significant association between ART and increased BMI (SMD: 0.35 cm; 95% CI: 0.16-0.53) (p = 0.018 for interaction). However, variations by study design in the pooled association between ART and BMI may be explained by the substantially higher proportions of participants in cohort studies compared to cross-sectional studies. We found no evidence of statistically significant differentials in the associations of ART with increasing WC, combined overweight/obesity, and abdominal obesity.

Clinical and public health implications

The findings of this review have important clinical and public health implications for people living with HIV worldwide. For instance, even small shifts in body fat measures may portend a considerable global public health impact on the incidence of obesity and its untoward effects among these people[12].

Secondly, as ART coverage rates continue to increase globally to meet the high prevalence and incidence of HIV infection, the burden of obesity and obesity related deaths among HIV-infected persons may also increase, especially in sub-Saharan African settings where HIV infection is most rampant and increases in ART coverage rates are the steepest compared to the other geographical regions[75]. The mere awareness of the public health implications of expanding ART coverage rates would be an important first step towards tackling the potential burden associated with ART-related obesity and other cardio-metabolic disorders.

From a clinical perspective, patients with low CD4 cell counts may constitute a higher-risk subgroup within HIV-infected populations, emphasizing the potential value of baseline CD4 count in predicting future body fat changes in clinical settings following the initiation of ART. In addition, the inclusion of weight management and obesity prevention programs as part of routine HIV care should be considered by health professionals and researchers working in the field.

Table 3. Subgroup estimates of antiretroviral-associated changes in body fat measures

Study-level subgroups	Body mass index (kg/m2)			Overweight/obesity			Waist circumference (cm)			Central obesity		
	N	Pooled SMD (95% CI)	p value	N	Pooled OR (95% CI)	p value	N	Pooled SMD (95% CI)	p value	N	Pooled OR (95% CI)	p value
Overall	50	0.17 (0.07-0.26)		21	1.36 (0.99-1.86)		17	0.20 (0.07-0.33)		13	1.49 (1.16-2.31)	
Study design												
Cohort	19	0.35 (0.16-0.53)		4	1.50 (0.65-3.44)		2	0.31 (0.06-0.55)		2	0.95 (0.39-2.31)	
Cross-sectional	31	0.05 (-0.06-0.16)	0.018	17	1.31 (0.98-1.75)	0.583	15	0.18 (0.04-0.33)	0.573	11	1.56 (1.21-2.01)	0.903
Income group												
Low/middle income	35	0.21 (0.08-0.34)		16	1.48 (1.07-2.03)		14	0.22 (0.08-0.37)		10	1.52 (1.17-1.97)	
High income	15	0.04 (–0.11-0.19)	0.208	5	1.05 (0.99-1.86)	0.592	3	0.05 (–0.14-0.23)	0.415	3	1.36 (0.57-3.21)	0.999
Females												
< 20%	13	0.04 (–0.18-0.27)		4	1.24 (0.66-2.33)		3	0.05 (–0.14-0.23)		1	2.58 (0.73-9.12)	
20-50%	8	-0.001 (–0.20-0.19)	0.141	4	0.84 (0.62-1.14)	0.822	3	0.31 (0.13-0.49)	0.364	2	0.93 (0.50-1.71)	0.990
> 50%	23	0.28 (0.12-0.43)	0.722	11	1.73 (1.11-2.71)	0.609	9	0.24 (0.05-0.44)	0.375	9	1.57 (1.17-2.09)	0.998
Mean age (years)												
< 40	30	0.17 (0.07-0.26)		12	1.35 (0.95-1.94)		11	0.31 (0.17-0.44)		8	1.36 (0.94-1.96)	
≥ 40	18	0.12 (–0.08-0.31)	0.744	5	1.77 (1.00-3.11)	0.569	5	0.03 (–0.18-0.19)	0.097	3	1.69 (1.17-2.45)	0.960
Smokers (%)												
< 20	11	0.16 (–0.02-0.35)		8	1.28 (0.72-2.28)		–	–		–	–	
20-50	8	-0.12 (–0.67-0.42)	0.324	2	1.00 (0.79-1.23)	0.819	–	–	–	–	–	–
> 50	6	0.28 (–0.03-0.59)	0.731	–	–		–	–	–	–	–	–
HIV duration (years)												
< 3	2	(–0.72-0.72)		–	–		–	–		–	–	
3-5	7	0.08 (–0.11-0.27)	0.738	–	–		–	–	–	–	–	–
> 5	8	-0.02 (–0.12-0.07)	0.870	–	–		–	–	–	–	–	–
Mean CD4 count (cells/mm^3)												
< 350	22	0.37 (0.26-0.47)		7	2.00 (1.28-3.14)		7	0.18 (0.05-0.31)		6	1.78 (1.32-2.40)	
≥ 350	18	-0.01 (–0.14-0.12)	0.002	8	1.01 (0.70-1.45)	0.048	5	0.21 (0.02-0.39)	0.837	4	1.09 (0.66-1.80)	0.045
Sample size												
≤ 200	30	0.15 (–0.05-0.35)		9	1.51 (1.15-1.98)		11	0.12 (–0.01-0.25)		9	1.58 (1.18-2.12)	
201-500	16	0.19 (0.06-0.32)	0.843	7	1.70 (0.99-2.90)	0.840	5	0.27 (–0.04-0.56)	0.354	3	1.79 (1.30-2.48)	0.975
> 500	4	0.04 (–0.13-0.21)	0.567	5	0.94 (0.49-1.84)	0.697	1	0.36 (0.21-0.50)	0.370	1	0.84 (0.57-1.24)	0.941
Selection bias												
High/unclear	34	0.13 (0.01-0.24)		14	1.27 (0.95-1.69)		15	0.19 (0.05-0.33)		9	1.48 (1.10-1.98)	
Low	16	0.24 (0.03-0.45)	0.384	7	1.42 (0.81-2.49)	0.543	2	0.30 (–0.02-0.63)	0.620	4	1.51 (0.87-2.62)	0.971

CI: confidence interval; N: number of studies; OR: odds ratio; SMD: standardized mean difference.

Strengths and limitations

Our findings must be interpreted with caution, given the observational nature of the data which precludes causality; however, this gap in the literature highlights the need for additional evidence, especially from observation longitudinal studies and randomized clinical trials, to investigate the plausibility of a causal link between ART exposure and body fat changes. Secondly, less than 20% of our study population was resident in low- and middle-income countries (where the burden of HIV infection is most severe, and increases in ART coverage rates are the steepest), potentially reducing generalizability of our findings across different geographic and socioeconomic settings. Thirdly, with more than 60% of the included studies assessed as having a high risk of selection bias, the methodological quality across the included studies may be moderate at best. In justifying the inclusion of these studies in our review, we reiterate that the risk of bias in each included study was not considered as a criterion for study selection, as "it is important to assess risk of bias in all studies in a review irrespective of the anticipated variability in either the results or the validity of the included studies"[76]. Nonetheless, we can affirm with confidence that selection bias had no significant impact on the overall results, as determined by meta-regression analysis. Furthermore, the dearth of studies reporting on lifestyle factors meant that we could not assess the overall impact of diet, alcohol consumption, and physical activity on the overall associations. We could also not rule out the potential confounding effects of immune reconstitution syndrome (IRIS), especially as 34% of the study participants presented with one or more AIDS-defining illnesses. For instance, body fat changes may occur in patients with IRIS, which is a constellation of clinical signs and symptoms caused by an exaggerated immune response and often following the initiation of ART in severely immunocompromised patients[77]. Lastly, we could not assess the impact of ART on more sensitive measures of body fat, such as fat mass, given the dearth of studies reporting these outcomes.

Nonetheless, the strengths of our study should also be highlighted. In addition to presenting the most comprehensive evidence and first pooled analyses examining the effects of ART on body fat changes, we also identified potential modifiers of these effects, which represents novel evidence to advance the field. Meta-analyses were performed using the random-effects model to account for the observed heterogeneity across the included studies. Furthermore, our findings are not likely to be invalidated by publication bias or by undue influence from any included studies.

Conclusion

This meta-analysis of over 50,000 HIV-infected subjects is the first of its kind to provide comprehensive estimates of the impact of ART on body fat changes. Our findings reveal that exposure to ART is associated with significant increases in measures of relative weight (BMI) and body fat distribution (WC), which may be exacerbated in patients with lower CD4 cell counts. It is unlikely that the main findings reflect a return to health, given that ART may also increase the risks of generalized and central obesity. Whether or not the associations of ART with body fat changes are causal in nature should be investigated by future prospective studies and randomized clinical trials. Care and treatment guidelines for people living with HIV may entail routine weight management and obesity prevention programs.

Supplementary Data

Supplementary data is available at AIDS Reviews journal online (http://www.aidsreviews.com).

This data is provided by the author and published online to benefit the reader. The contents of all supplementary data are the sole responsibility of the authors.

Acknowledgements

CUN, OAU, and SS designed the study. CUN, OAU, and PKK searched the literature, screened the references, extracted and analyzed the data. All authors interpreted the data. CUN drafted the manuscript. All authors critically revised the report and approved submission of the final version of the manuscript.

Declaration of interest

We declare no competing interests. CUN acknowledges support from the University of Warwick Chancellor's Scholarship (ID 1160088). OAU acknowledges support from the FAS Marie Curie International Post Doc grant (2012–0064).

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