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Inflammatory profile associated with insulin resistance in non-overweight versus overweight people living with HIV in Pune, Western India

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Abstract

Background: People living with HIV have greater diabetes (T2DM) than the general population despite lower prevalence of overweight/obesity. Both insulin resistance (IR), a T2DM precursor, and HIV are independently associated with chronic inflammation. Inflammation may be a pathophysiological link explaining IR in people living with HIV who are not overweight but is not well understood.

Aims: To study the association between inflammation and IR in non-overweight and overweight people living with HIV.

Methods: In a cohort of adult people living with HIV with undetectable viral load in Pune, India, we measured fasting insulin, glucose, and 9 inflammatory markers. IR was defined as HOMA-IR ≥2, and non-overweight as BMI ≤23 kg/m^2. We used modified Poisson regression to evaluate the association between inflammatory markers and IR in overweight and non-overweight.

Results: Of 288 participants, 66% (n = 189) were non-overweight. Among non-overweight, prevalence of IR was 34% (n = 65). Each doubling of MCP-1 and leptin was associated with IR

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Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2022.102551.

on univariate analysis (prevalence ratio (PR) 1.29, 95%CI 1.07–1.53, p < 0.01; PR 1.13 95%CI 1.01–1.26, p = 0.03). Leptin remained associated with IR after adjustment for age, MCP-1, gender, cholesterol, and waist circumference (adjusted PR 1.20 95%CI 1.06–1.36, p < 0.01). Among overweight, prevalence of IR was 69% and no markers were associated with IR.

Conclusions: One in 3 non-overweight people living with HIV in India with controlled viremia have IR. Leptin was associated with IR among non-overweight people living with HIV and may provide insight into the pathophysiology of metabolic disease in this population.

Keywords

Inflammation; Insulin resistance; Non-overweight; HIV

1. Introduction

Diabetes (T2DM) affects 463 million people worldwide and is estimated to increase to 700 million by 2045 [1]. This growth rate is higher among people living with HIV (PLWH), who have 2.4 times the risk of T2DM when compared to the general population [2]. In PLWH on antiretroviral therapy, the risk of T2DM is 4 fold higher than the general population, and in those who develop signs of the metabolic syndrome the risk is increased 5–9 fold more [3,4].

Overweight and obesity traditionally increase the risk of insulin resistance (IR) and subsequent T2DM. However, PLWH develop IR at lower BMI than in the general population, indicating the role of other factors in pathogenesis [5–7]. In a large study in Finland, for example, PLWH had a 10% higher prevalence of impaired fasting glucose and insulin resistance compared to the general population, despite prevalence of obesity being 6% lower [5]. Although multiple mechanisms to explain this pathophysiology, such as inflammation, antiretroviral medications, altered fat deposition, autoimmunity, and oxidative stress have been proposed, the pathogenesis is not yet fully understood [8].

Insulin resistance (IR) and HIV are both independently associated with inflammation. Increased TNFα, an inflammatory marker, is known to increase expression of proteins that suppress insulin signaling pathways in the cell. Other cytokines, including MCP-1, leptin, and IL6, have similarly been found to play a role in some mechanisms of IR. MCP-1, for example, is associated with decreased expression of genes involved in glucose transport and metabolism such as GLUT-4, hexokinase II, and IRS-2 [9]. Leptin plays a more complex role, being associated with increased IR and T2DM, but is also therapeutic in reducing glucose intolerance when used as a treatment [10,11]. PLWH have increased levels of inflammatory cytokines compared to the general population, and many of the proposed mechanisms of their increased T2DM risk may be connected to inflammation. Elevation of TNFα, for example, is connected to visceral fat accumulation, which is a risk factor for T2DM [12].

We previously reported a 38% prevalence of IR, defined as Homeostatic model assessment for insulin resistance (HOMA-IR) score >2, among PLWH. However, we observed that the majority of PLWH in our South Asian cohort (84%) were not overweight [13].

Inflammation may be a pathophysiological link explaining increased IR in PLWH despite the fact that PLWH have a similar or lower prevalence of overweight/obesity than the general population in many countries. Although studies have noted a unique pattern of association of inflammatory markers in non-obese populations in the United States, little is known about inflammatory patterns associated with IR in South Asian PLWH who are not overweight [14,15]. Therefore, we aimed to study the prevalence of IR and its association with inflammation in a cohort of non-overweight compared to overweight PLWH in India.

2. Subjects

2.1. Study design and eligibility

Participants were enrolled into a cross-sectional study from the antiretroviral therapy (ART) center of Byramjee Jeejeebhoy Government Medical College & Sassoon General Hospitals (BJGMC/SGH) in Pune, India. BJGMC/SGH is a large publicly funded tertiary healthcare center which provides free ART to approximately 5000 low and middle income PLWH. Participants were enrolled between September 01, 2015 and July 31, 2016.

Adult participants (≥18 years of age) who provided a written informed consent were eligible for enrollment. Only participants with an undetectable (<40 copies/mL) viral load (VL) were included in this analysis.

3. Materials and methods

3.1. Study procedures

Eligible participants were enrolled after informed consent in the locally spoken languages of Marathi or Hindi. Questionnaires were administered using electronic handheld devices. Anthropometric measurements for weight, height and waist circumference were taken. Weight was measured using a standardized weighing scale, height by a stadiometer, and waist circumference by using the World Health Organization (WHO) STEPwise Approach to Surveillance recommended guidelines [16].

ART information and CD4 counts were abstracted from participant records, and blood was collected following 10–12 h of overnight fasting for glucose, total cholesterol, insulin, and inflammatory markers. All study procedures were approved by the BJGMC and Johns Hopkins University institutional review boards.

3.2. Laboratory procedures

Lipid profile and glucose were measured using standard techniques by an automated analyzer (Roche Cobas c 111). Fasting levels of insulin and inflammatory markers were measured using the Bio-Plex Pro test kits for hs-CRP (mg/dL), MCP-1 (pg/mL), TNFα (pg/mL), leptin (pg/mL), resistin (pg/mL), visfatin (pg/mL), PAI-1 (pg/mL), sCD14 (ng/mL), and sCD163 (pg/mL) using antibody-based detection. Thirty percent of measurements for TNFα were out of range and therefore excluded.

3.3. Study definitions

The HOMA-IR formula was used to determine insulin sensitivity. The formula is: fasting glucose (mg/dL) multiplied by fasting insulin (mIU/L)/405. IR was defined as ≥2 based on estimates from previous population-based studies among Asians and Asian Indians (cutoff value:1.93) [17,18]. The International Diabetes Federation recommended definition for Asians was used for high waist circumference - a waist circumference ≥90 cm for men and 80 cm for women [19]. BMI cutoffs were similarly based on those recommended for Asian populations (underweight = <18.5 kg/m^2, normal weight = 18.5–23 kg/m^2, overweight = >23 kg/m^2) [20]. We categorized participants into non-overweight and overweight groups. Non-overweight included participants that were underweight or normal weight [21].

3.4. Statistical analysis

Analysis was stratified by weight categories (non-overweight and overweight). Baseline characteristics and inflammatory markers were compared between those with IR and those that were insulin-sensitive using the chi-squared test for categorical variables and Mann-Whitney *U* test for continuous variables. As significant associations between MCP-1 and IR and leptin and IR were noted in the non-overweight group, further stratification was done to determine whether it was the underweight or normal weight group that was driving the association. Inflammatory markers were $\log_2$ transformed prior to analysis.

Univariable analyses were then conducted using modified Poisson regression with robust estimation of standard errors to determine association with IR in non-overweight and overweight groups. Multivariable model included the pre-determined risk factors age, gender, waist circumference, CD4 count, tuberculosis history, and variables that were significantly associated with IR on univariable analysis. Sensitivity analyses were performed using an alternate cutoff of 3.5 for IR, which is commonly used in other populations [22]. Statistical significance was set to a two-sided p-value of 0.05. All analyses were performed using Stata version 14.0.

4. Results

4.1. Study population

We enrolled a total of 485 PLWH from September 01, 2015 to July 31, 2016. Eleven participants were excluded due to missing BMI. A further 186 were excluded for detectable VL leaving 288 participants included in the final analysis. Median age was 40.6 years (IQR 35.3–45.6), 52.3% (n = 98) were female, 47.2% (n = 135) had CD4 count >500 cells/mm 3, and 46.2% (n = 133) had IR(Table 1).

4.2. Baseline characteristics in the total cohort

Most participants were non-overweight (65.6%, n = 189). Median age, gender, and median total cholesterol were similar between non-overweight and overweight participants. High waist circumference was less prevalent in the non-overweight group (18.5 vs 82.8%, $p < 0.01$), as was CD4 count >500 (39.6 vs 61.6%, $p < 0.01$). IR was present in 34.4% (n = 65) of non-overweight and 68.7% (n = 68) of overweight participants ($p < 0.01$)(Table 1).

4.3. Baseline characteristics and inflammatory markers associated with IR in the non-overweight

Among the non-overweight, several baseline characteristics differed between participants with IR vs insulin sensitivity. IR was more commonly observed among older PLWH (median age 43.6 vs 39.4 years, p = 0.01), those with higher cholesterol (179.5 vs 167.6 mg/dL, p = 0.05), and proportionately higher among those with higher waist circumference (26.2 vs 14.5%, p = 0.05). IR was present in 31.2% (n = 48) of PLWH with low waist circumference. The proportion of participants who were on ART >1 year was similar in IR and insulin sensitive groups (95.8% vs 96.5%, p = 0.18)(Table 2).

No inflammatory markers were significantly different between participants with IR compared to those that were insulin sensitive at the $p < 0.05$ threshold. hsCRP, MCP-1, and leptin were higher in participants with IR at the $p < 0.10$ threshold ($\log_2$ of hsCRP −2.10 vs −2.18, p = 0.051; $\log_2$ of MCP-1 5.63 vs 5.43, p = 0.09; $\log_2$ of leptin 2.12 vs 1.19, p = 0.06)(Fig. 1).

4.4. Baseline characteristics and inflammatory markers associated with IR in the overweight

Among the overweight, the proportion of participants with high waist circumference was significantly greater among those with IR than those insulin sensitive (88.2% vs 71.0%, p = 0.04). Other baseline characteristics did not differ according to insulin sensitivity(Table 2). PAI-1 was higher among participants with IR ($\log_2$ of PAI-1: 6.71 vs 6.40, p = 0.06)(Fig. 2).

4.5. Association of inflammatory markers with IR on univariate and multivariable analyses

In the non-overweight, female gender (PR (Prevalence ratio) 0.66, 95% CI 0.44–0.98, p = 0.04), high waist circumference (PR 1.56, 95% CI 1.03–2.36, p = 0.04), total cholesterol (PR 1.01, 95% CI 1.00–1.01, p = 0.04), $\log_2$ of MCP-1 (PR 1.29, 95% CI 1.07–1.53, $p < 0.01$), and $\log_2$ of leptin (PR 1.13, 95% CI 1.01, 1.26), p = 0.03) were significantly associated with IR on univariable modified Poisson regression analysis. On multivariable analyses adjusting for age, gender, high waist circumference, total cholesterol, and $\log_2$ of MCP-1, the association of leptin with IR remained significant (PR 1.20, 95% CI 1.06–1.36, $p < 0.01$). On sensitivity analysis with HOMA-IR >3.5 as the cutoff, $\log_2$ of MCP-1 was associated with PR for IR of 1.37 (95% CI 0.94, 1.99, p = 0.10), $\log_2$ of leptin with PR of 1.18 (95% CI 0.97, 1.44, p = 0.10), and $\log_2$ of hsCRP with PR 1.17 (95% CI 1.01, 1.35, p = 0.03) on univariate analysis. In the overweight, only BMI was associated with IR on univariate analysis (OR 1.09, 95% CI 1.04–1.14, $p < 0.01$). Multivariable analysis was not performed(Table 3).

When the analysis was further stratified into underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–23 kg/m^2), and overweight (>23 kg/m^2), MCP-1 was significantly higher among those with IR than those insulin sensitive in the underweight group (5.99 vs 5.29, $p < 0.01$), but not in the normal weight (5.56 vs 5.47, p = 0.93) or overweight (5.71 vs 5.32, p = 0.38) groups (see Fig. 2). Leptin had a similar pattern (underweight: 1.35 vs 0.36, p = 0.05; normal weight: 1.52 vs 1.76, p 0.75; overweight: 2.86 vs 3.06, p = 0.69) (Fig. 2).

5. Discussion

In this study of IR in PLWH, nearly 1 in 3 (30.7%) non-overweight participants on ART were insulin resistant. Even among underweight participants, the prevalence was more than 1 in 10. Given that 66% of our population of PLWH was non-overweight, this study highlights the need for further understanding of the pathogenesis of insulin resistance in people who are not overweight.

Leptin was associated with IR in the non-overweight and even in the underweight after adjustment for traditional risk factors such as age, gender, cholesterol, and waist circumference. Leptin is a hormone released from adipose tissue that helps the body maintain body weight. Higher plasma leptin is associated with higher body fat [23,24]. However, in a study of adults in Mexico, a subgroup of adults with low BMI also had increased leptin levels [25]. We hypothesize that this finding and our findings could be attributable to increased visceral or intramuscular fat mass that is not measured by BMI or waist circumference. IR in underweight PLWH may also indicate greater systemic inflammation due to HIV itself or coexistent infections [26].

Among the non-overweight group, MCP-1 was similarly higher in those with IR compared to those who were insulin sensitive; there was no difference in MCP-1 in the overweight group by insulin resistance vs sensitivity. MCP-1 is a chemokine that is secreted by adipose tissue and regulates monocytes and macrophages. In the overweight, both people with IR and people who are insulin sensitive have increased adipose tissue and increased MCP-1. In the non-overweight, however, MCP-1 may indicate elevated adiposity or vascular inflammation and may be an important link between inflammation and IR [27,28]. This is particularly relevant for South Asians who are prone to types of adiposity that cannot be detected by BMI. Inflammatory markers such as MCP-1 and leptin may also lead to oxidative stress which damages insulin signaling pathways [29].

Fat distribution may also be altered in PLWH, meaning that BMI alone may not reflect the risk of IR [5]. This may be particularly prominent in our South Asian cohort because South Asians, despite having an overall lower BMI than other populations, have higher adiposity and lower lean muscle mass [30]. Detecting adiposity early in a clinical setting can enable interventions that treat IR and prevent long-term complications of metabolic disease. Waist circumference is a measure of central adiposity that can feasibly be measured in a clinic along with BMI. However, in our cohort, 41% (67/163) with IR would not have been detected by measuring waist circumference either. Future studies will incorporate body composition testing, which can assess the visceral and intramuscular adiposity that may be a driver of inflammation in these populations.

Studies in the United States have compared obese and non-obese PLWH more generally and found that hsCRP, TNFα, and sCD14 but not leptin and MCP-1 were significantly associated with BMI in the non-obese but not the obese PLWH [15]. However, they have not specifically examined the role of IR. In a study of metabolic syndrome (a clinical syndrome which includes IR as a component) in non-obese men with HIV, researchers found higher hsCRP, TNFα receptors I and II, and lower adiponectin levels associated with the metabolic

syndrome [14]. Leptin was higher in those with metabolic syndrome but not significantly so. There was no sub analysis of people specifically with IR, which is known to be more subject to inflammation. The non-overweight and non-obese phenotype is more common in India, which allowed us sufficient power to identify the significant differences detected in our study.

Our study had multiple strengths. We conducted a large, systematic study of PLWH in India. We chose a HOMA-IR cutoff of 2 as suggested by prior studies in Asians. In sensitivity analyses using a cutoff of 3.5 (the cutoff used for Western countries), we found similar directionality of associations that did not reach statistical significance, except for a significant association with hsCRP. We used a diverse panel of inflammatory markers that were most likely to be associated with metabolic syndrome. We accounted for the majority of variability in inflammation by only including PLWH with an undetectable viral load.

We also had several limitations. Given the cross-sectional design, causation could not be determined, but will be the scope of future studies. TNFα is well-studied in association with metabolic disease in previous literature, but analysis of this marker was limited in the current study due to missing values. Though we accounted for the majority of variability in inflammation by only including PLWH with an undetectable viral load, other factors such as infection and stress can also cause inflammatory markers to vary from their baseline, though this variation is likely to be random.

Our findings suggest that inflammation plays a role in IR among non-overweight PLWH in Asia and should be further studied along with patterns of fat distribution. Future clinical studies may determine how these markers can be used in predicting and preventing future metabolic disease. They may also be used for monitoring the effect of pharmacologic interventions to prevent or treat metabolic disease in PLWH.

7. Conclusions

We found that insulin resistance is present in nearly 1 in 3 non-overweight PLWH on ART, a group that is not traditionally considered to be a population at high risk for diabetes. Leptin is associated with insulin resistance among even underweight PLWH and may be indicative of a unique pattern of adipose distribution. Further study of inflammation in underweight PLWH may help understand the pathophysiology of IR in this population where BMI may not accurately indicate risk of long-term metabolic disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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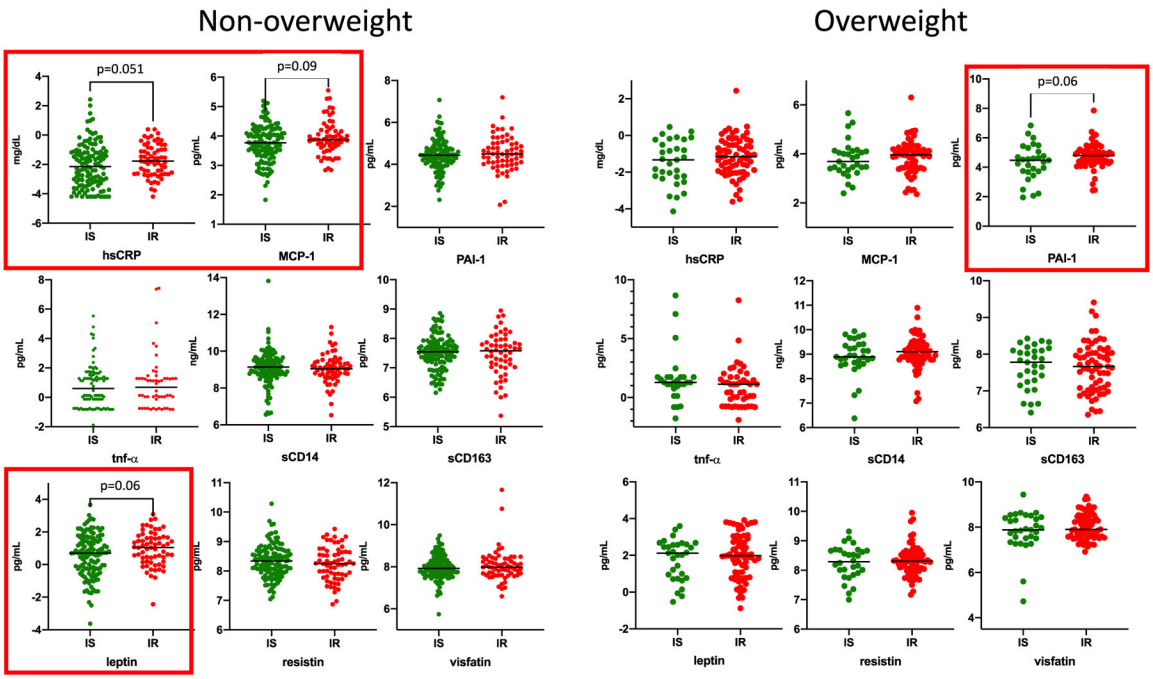

Fig. 1.

Baseline inflammatory markers by insulin sensitivity status in PLWH with undetectable viral load by weight group.

Green markers indicate levels of inflammatory markers in insulin sensitive (IS) participants. Red markers indicate levels of inflammatory markers in insulin resistant (IR) participants. Horizontal black lines indicate median values. Among non-overweight participants, median hsCRP level, median MCP-1 level, and median leptin level were higher among participants with IR than IS ($p = 0.051$, $p = 0.01$, and $p = 0.06$, respectively). Among overweight participants, PAI-1 was higher in participants with IR than with IS ($p = 0.06$).

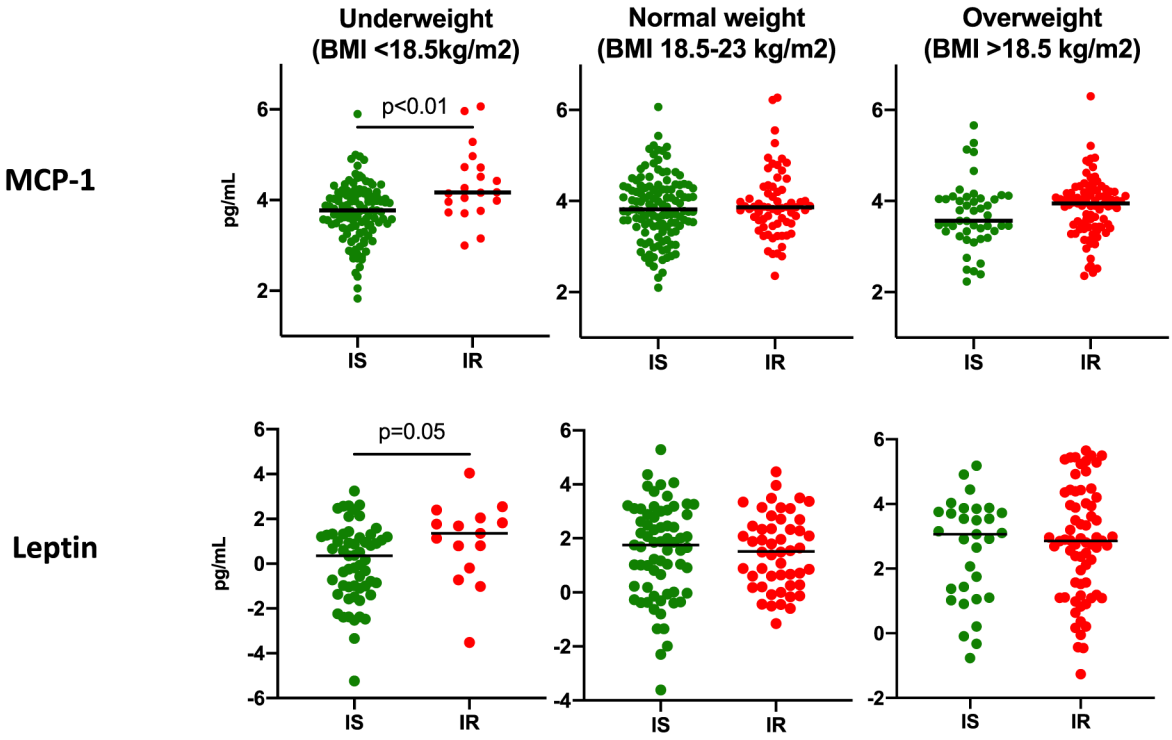

Fig. 2.

MCP-1 and leptin stratified by underweight, normal weight, and overweight groups. Green markers indicate levels of inflammatory markers in insulin sensitive (IS) participants. Red markers indicate levels of inflammatory markers in insulin resistant (IR) participants. Horizontal black lines indicate median values. Among underweight participants only, MCP-1 and leptin were higher in IR compared to IS participants ($p < 0.01$ and $p = 0.05$, respectively).

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Table 1

Baseline characteristics in overweight and non-overweight people living with HIV with undetectable viral load.

	Total N = 288	**Non-overweight N = 189**	**Overweight N = 99**	**P value**
Age (yrs)	40.6 (35.3–45.6)	40 (35–45)	41.6 (36.1–46.3)	0.26
Female (%)	158 (54.9%)	101 (53.4%)	57 (57.6%)	0.50
Total cholesterol, mg/dL	174.8 (152.6–202.9)	173.7 (153.3–199.1)	177.0 (150.4–206.8)	0.54
High waist circumference [1]	117 (40.6%)	35 (18.5%)	82 (82.8%)	<0.01*
BMI				
Underweight (<18.5 kg/m2)	72 (25.0%)			
Normal weight (18.5–23 kg/m2)	117 (40.6%)			
Overweight (>23 kg/m2)	99 (34.4%)			
CD4 count (cells/mm3)				
<350	87 (30.4%)	68 (36.4%)	19 (19.2%)	<0.01*
350–500	64 (22.4%)	45 (24.1%)	19 (19.2%)	
>500	135 (47.2%)	74 (39.6%)	61 (61.6%)	
ART >1 year	278 (96.5%)	181 (95.8%)	97 (98.0%)	0.50
1st line ART	217 (81.3%)	147 (84.0%)	70 (76.1%)	0.12
2nd line ART	50 (18.7%)	28 (16.0%)	22 (23.9%)	
Other medications				
Metformin	6 (2.1%)	6 (3.2%)	0	0.07
Sulfonylureas	8 (2.8%)	5 (2.7%)	3 (3.0%)	0.85
Insulin	3 (1.0%)	3 (1.6%)	0	0.21
Statins	4 (1.4%)	2 (1.1%)	2 (2.0%)	0.51
IR (HOMA-IR > 2)	133 (46.2%)	65 (34.4%)	68 (68.7%)	<0.01*
Severe IR (HOMA-IR > 3.5)	43 (14.9%)	22 (11.6%)	21 (21.2%)	0.04*

PLWH = people living with HIV; ART = antiretroviral therapy; IR = insulin resistant; Underweight = BMI<18.5 kg/m2, Normal weight = BMI 18.5–23 kg/m2, Overweight = BMI>23 kg/m2. High waist circumference =≥90 cm for men and ≥80 cm for women.

Table 2

Characteristics associated with IR in people living with HIV with undetectable viral load by weight group.

	Non-overweight			Overweight		
	IS N = 124	**IR N = 65**	**P value**	**IS N = 31**	**IR N = 68**	**P value**
Age (yrs)	39.4 (34.6, 43.8)	43.6 (36.4, 48.6)	0.01*	40.7 (35.6, 44.6)	41.6 (36.2, 47.4)	0.33
Female (%)	73 (58.9%)	28 (43.1%)	0.04*	22 (71.0%)	35 (51.5%)	0.07
Total cholesterol, mg/dL	167.6 (150.2, 194.4)	179.5 (158.6, 213.6)	0.055	177.9 (150.4, 206.2)	176.7 (151, 208.6)	0.99
Waist circumference						
High [1]	18 (14.5%)	17 (26.2%)	0.05*	22 (71.0%)	60 (88.2%)	0.04*
Low	106 (85.5%)	48 (73.9%)		9 (29.0%)	8 (11.8%)	
BMI						
Underweight	57 (46.0%)	15 (23.1%)	<0.01*	N/A	N/A	
Normal weight	67 (54.0%)	50 (76.9%)		N/A	N/A	
CD4 count (cells/mm3)						
<350	41 (33.6%)	27 (41.5%)	0.20	9 (29.0%)	10 (14.7%)	0.27
350–500	27 (22.1%)	18 (27.7%)		5 (16.1%)	14 (20.6%)	
>500	54 (44.3%)	20 (30.8%)		17 (54.8%)	44 (64.7%)	
ART-experienced	117 (94.4%)	64 (98.5%)	0.18	30 (96.8%)	67 (98.5%)	0.57
1st line ART	93 (83.0%)	54 (85.7%)	0.64	18 (66.7%)	52 (80.0%)	0.17
2nd line ART	19 (17.0%)	9 (14.3%)		9 (33.3%)	13 (20.0%)	

IR = insulin resistant; IS = insulin sensitive [1];>90 cm for males, >80 cm for females; ART = antiretroviral therapy.

Table 3

Association of risk factors and inflammatory markers with IR among people living with HIV with undetectable viral load by weight group.

	Non-overweight				Overweight	
	PR	**P value**	**aPR[a]**	**P-value**	**PR**	**P value**
Age	1.02 (1.00, 1.04)	0.06	1.02 (0.53, 1.98)	0.95	1.01 (1.00, 1.03)	0.13
Female	0.66 (0.44, 0.98)	0.04*	0.48 (0.30, 0.78)	0.03*	0.78 (0.60, 1.01)	0.06
High waist circumference	1.56 (1.03, 2.36)	0.04*	1.56 (1.01, 2.41)	0.05	1.55 (0.92, 2.62)	0.10
BMI	1.15 (1.04, 1.27)	<0.01*			1.09 (1.04, 1.14)	<0.01*
Total cholesterol	1.01 (1.00, 1.01)	0.04*	1.00 (1.00, 1.01)	0.08	1.00 (1.00, 1.00)	0.80
Tuberculosis history	1.19 (0.80, 1.76)	0.39	1.11 (0.75, 1.63)	0.61		
CD4 count						
<350	ref				ref	
350–500	1.01 (0.63, 1.60)	0.98			1.40 (0.84, 2.32)	0.19
>500	0.68 (0.42, 1.10)	0.11			1.37 (0.87, 2.16)	0.18
ART >1 year	2.83 (0.45, 17.97)	0.27			1.38 (0.34, 5.60)	0.65
hsCRP	1.08 (0.99, 1.18	0.08			1.06 (0.97, 1.15)	0.22
MCP-1	1.29 (1.07, 1.53)	<0.01*	1.18 (0.97, 1.44)	0.10	1.04 (0.90, 1.19)	0.63
PAI-1	1.07 (0.89, 1.29)	0.48			1.10 (0.99, 1.23)	0.06
TNFα	1.03 (0.94, 1.12)	0.55			0.95 (0.88, 1.03)	0.20
Leptin	1.13 (1.01, 1.26)	0.03*	1.21 (1.06, 1.37)	<0.01*	1.03 (0.95, 1.11)	0.50
sCD14	1.00 (0.84, 1.18)	0.98			1.10 (0.95, 1.27)	0.19
sCD163	0.95 (0.73, 1.22)	0.68			1.00 (0.86, 1.15)	0.97
Resistin	0.87 (0.68, 1.12)	0.27			1.05 (0.88, 1.25)	0.58
Visfatin	1.10 (0.92, 1.32)	0.30			1.10 (0.95, 1.27)	0.19

High waist circumference = >90 cm for males, >80 cm for females; IR = insulin resistant; IS = insulin sensitive. All inflammatory markers are reported as $\log_2$.

[a]Adjusting for BMI rather than high waist circumference yielded similar results: age (aPR 1.07, 95% CI 0.53–2.15, p = 0.86), female gender (aPR 0.55, 95% CI 0.32–0.94, p = 0.03), cholesterol (aPR 1.00, 95% CI 1.00–1.01, p = 0.16), MCP-1 (aPR 1.16, 95% CI 0.95–1.42, p = 0.14), leptin (aPR1.18, 95% CI 1.01–1.37, p = 0.04).