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Original Article

High prevalence of insulin resistance and occurrence prior to hyperinsulinemia threshold among people living with HIV in Pune, India

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ABSTRACT

Background: Diabetes prevalence in HIV is not well characterized for India, despite the high burden of both individual diseases. Epidemiology of insulin resistance (IR): a precursor to diabetes, and its associated risk factors are also poorly understood in Asian Indian people living with HIV (PLHIV). We assessed the prevalence of diabetes and IR in Pune, India and the associated risk factors for IR.

Methods: Cross-sectional analysis of adult (≥18 years) PLHIV receiving care at Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Pune, India (BJGMC- SGH). Proportions and medians of PLHIV characteristics by diabetes status and IR were described. Homeostatic Model Assessment (HOMA) index value ≥2 was used to define IR. Line of least squares assessed the relationship between IR and hyperinsulinemia. Association between sociodemographic, clinical factors with IR was determined using logistic regression.

Results: Of 485 enrollees, 47% were men, median age was 40 years (IQR: 35–46), median CD4 counts were 389 cells/mm^3 (246–609). Thirty-five percent were centrally obese, 75% were adherent to WHO recommended physical activity guidelines. Prevalence of diabetes, prediabetes, IR were 9%, 16% and 38%, respectively. Twenty-nine percent non-diabetics had IR and it occurred much prior to the threshold for hyperinsulinemia. IR was associated with the use of ART drugs (OR: 6.6, 95% CI: 2.9–15.2 and 5.4, 95% CI: 2.2–13.6 for first- and second line ART respectively) and central obesity (OR:1.9, 95% CI: 1.1–3.4).

Conclusions: One fourth of the study population was diabetic or prediabetic and more than a third had IR. Better understanding of diabetes disease progression in relation to IR and the effect of physical activity on central obesity among Asian Indian PLHIV is mandated.

1. Introduction

Despite India having the second highest number of people living with diabetes and the third highest number of people living with HIV (PLHIV) globally, little is known about the concomitance of these two diseases among Asian Indians [1,2]. Estimates on concurrence of HIV with diabetes vary between 2% and 14% [3]: the caveat being that these figures have been largely drawn from developed countries with predominantly non-Asian study populations.

The propensity of Asian Indians for diabetes has been well described in multiple studies [4,5]. Similarly, HIV-infection has also been associated with an increased diabetes risk primarily through its viral properties and chronic inflammation, and secondarily through the effect of antiretroviral drugs [6,7]. Drugs such as Efavirenz (EFV), Zidovudine (AZT), and Atazanavir (ATV) that are part of the current antiretroviral formulary in Indian programmatic settings [8], could increase the risk of diabetes through their facilitation of hyperglycemia, mitochondrial toxicity, and visceral obesity, respectively [6,9,10]. Therefore, HIV-infection and its

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subsequent treatment superimposed on a genetic predisposition, could plausibly put Asian Indian PLHIV at a higher risk for diabetes than PLHIV of other ethnicities. Understanding the epidemiology of diabetes in HIV in India at this juncture is crucial, as the National AIDS Control Organization (NACO) continues to scale-up the dispensation of antiretroviral therapy (ART) through the recently implemented Test and Treat strategy [11].

Insulin resistance (IR) has been cited as a common mechanism for the development of diabetes among Asian Indians and PLHIV especially among those receiving antiretroviral therapy (ART) [5,7,9]. While the prevalence of IR in the general Asian Indian population is estimated to be approximately 25% and among Asian Indian HIV-infected children to be 17%, data for IR among adult Asian Indian PLHIV are conspicuously lacking [12,13]. The absence of such data not only undermines the potential incipient risk of diabetes among adult Asian Indian PLHIV but also makes the planning of mitigating interventions challenging.

Accordingly, in the current study, we sought to describe the prevalence of diabetes, prediabetes and IR among Asian Indian PLHIV. Additionally, we also assess the risk factors associated with insulin resistance.

2. Methods

2.1. Study design and eligibility

Participants were enrolled into a cross-sectional study from the ART center of Byramjee Jeejeebhoy Government Medical College & Sassoon General Hospitals (BJGMC & SGH) - a large publicly funded tertiary healthcare center in Pune, India. The center serves as one of the key nodal centers for free ART provision in western India under the aegis of NACO, catering to low and middle income PLHIV from the surrounding urban, semi-urban and rural areas. Approximately 4500 PLHIV are in active follow-up with the center presently. All enrollments into the study were done between September 01, 2015 and July 31, 2016.

Adult participants ($\geq$18 years of age) who had received ART $\leq$7 days (ART naïve) or ART $\geq$1 year (ART experienced) and provided a written informed consent were eligible for enrollment.

2.2. Study procedures

Two dedicated study counsellors approached all participants coming for care to the ART center and enrolled them into the study if the eligibility criteria were met. Informed consent was taken in the locally spoken languages of Marathi or Hindi. Questionnaires were administered using electronic handheld devices, and the data generated were securely stored on a cloud-based server maintained by Persistent Systems Inc. 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 (STEPS) recommended guidelines [14]. Blood pressure was calculated as the mean of three separate blood pressure recordings taken 5 min apart, with the participant seated. CD4 counts were abstracted from participant records, and blood was collected following 10–12 h of overnight fasting for glucose, lipid profile (Total cholesterol, serum triglycerides, serum LDL & HDL), glycated hemoglobin (HbA1c) and insulin.

All study procedures were approved by the BJGMC & SGH and Johns Hopkins University institutional review boards.

2.3. Laboratory procedures

Lipid profile and glucose were measured using standard techniques by an automated analyzer (Roche cobas c 111). Fasting levels of insulin, were measured using the Bio-Plex Pro™ human diabetes 10-plex immunoassay.

2.4. Study definitions

Diabetes was defined as HbA1c $\geq$ 6·5%, or fasting blood glucose (FBG) level of $\geq$126 mg/dL using the American Diabetes Association criteria [15]. Participants told by a physician to be diabetic or on diabetic medication, were included in the definition of diabetes. Prediabetes was defined as HbA1c of $\geq$5.7% and <6.5% or FBG of >110 and < 126. ART regimen was classified according to current NACO guidelines: first line drugs included two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) and second line drugs included two NRTIs and one boosted Protease Inhibitor (PI) [8]. Exercise was categorized as adherent or non-adherent to the Global Recommendations of Physical Activity for Health (WHO 2010), of at least 75 min vigorous aerobic activity or 150 min moderate aerobic activity per week [16]. Hyperinsulinemia was defined as fasting insulin >17 mIU/L based on India -specific ranges [17]. WHO recommended definition for Asians was used for central obesity - a waist circumference $\geq$90 cm for men and $\geq$80 cm for women [18]. The 2016 cutoffs of the American College of Cardiology/American Heart Association (ACC/AHA) ($\geq$140 mm systolic blood pressure, $\geq$90 mm diastolic blood pressure) and antihypertensive usage were used to define hypertension. Dyslipidemia was defined as participants with any of the following: total cholesterol$\geq$ 200 mg/dL, LDL$\geq$ 130 mg/dL, triglycerides$\geq$150 mg/dL, HDL<40 mg/dL. IR was calculated using the Homeostatic Model Assessment (HOMA) index derived as [(fasting glucose [mg/dL] multiplied by fasting insulin [mIU/L])/405]. We utilized the conservative cutoff of $\geq$2 to define an insulin resistant state, after considering estimates from a previous population-based study among Asian Indians (cutoff value:1.93) and another Asian study that used the described cutoff for diabetes discrimination [19]. (For the sake of brevity, an insulin resistant state as defined by the cut-off will be abbreviated as IR for the remainder of the manuscript).

2.5. Statistical analysis

Participants were classified based on their characteristics into three groups for diabetes status (diabetes, prediabetes, no diabetes) and into two for IR (insulin resistant, insulin sensitive) using proportions and medians. Fisher's exact and Kruskal-Wallis tests were used to assess significant associations between groups for categorical variables and equivalency of medians for continuous variables, when classified by diabetes status, respectively. We also determined the cutoff point for insulin that corresponded to our predetermined threshold for IR, by drawing a line of least squares through a scatterplot between HOMA-IR and insulin values, after excluding outlier insulin values using Tukey's fences. Outlier values were excluded to prevent influential values from affecting the slope of the line. Logistic regression was used to evaluate the association between sociodemographic and clinical variables with IR. Two separate multivariable models were created to examine the association of ART regimen and duration on ART with IR, to prevent collinearity between categories that contained similar information. Other covariates in the multivariable models included those identified a *priori* to have an association with IR or that had statistical significance in univariate models. Statistical significance was set to a two-sided p-value of 5%. Sensitivity analyses for the robustness of the logistic regression point estimates were performed by excluding outlier values as described earlier. All analyses were performed using Stata version 15.0 and GraphPad Prism 7.

3. Results

3.1. Study population characteristics

A total of 485 participants were enrolled during the study period. Median age was 40 years (IQR: 35–46) and 53% (n = 259) were women. Family history of diabetes was available for 59% (n = 285) of the enrollees, among which 25% (n = 70) gave a positive history. Seventy-five percent (n = 364) were compliant with WHO-recommended physical activity guidelines. Median time updated CD4 counts were 389 cells/mm^3 (IQR: 246–609) and 36% (n = 174) had CD4 counts>500 cells/mm^3. Most (67%, n = 325) enrollees had been on ART between 1 and 10 years, 20% (n = 95) were receiving second line protease inhibitor (PI) regimens, 93% (n = 88) of which was atazanavir (ATV) based. Central obesity was present among 35% (n = 164) of all those enrolled, 52% (n = 85) of whom had BMI in the normal range ($p < 0.001$). Hypertension, dyslipidemia and hyperinsulinemia were present among 23% (n = 112), 61% (n = 297) and 12% (n = 58) of the study population, respectively (Table 1).

3.2. Diabetes, prediabetes prevalence and their distribution by sociodemographic and clinical factors

The prevalence of diabetes was 9% (n = 42, 95% Confidence Interval [CI]: 6%–12%) and prediabetes was 16% (n = 78, 95% CI: 13%–20%). Diabetic and prediabetic enrollees were more likely to be older ($p < 0.001$) and male ($p < 0.05$). Family history of diabetes was common among diabetic enrollees ($p < 0.01$). Diabetic enrollees appeared to have been on ART for longer durations ($p < 0.05$) and were more likely to have received second line PI-based drugs ($p < 0.05$) when compared to prediabetic and non-diabetic enrollees. Central obesity ($p < 0.001$), hypertension ($p < 0.01$), dyslipidemia ($p < 0.001$) and hyperinsulinemia ($p < 0.001$) were more commonly observed among diabetic and prediabetic enrollees as compared to non-diabetic enrollees (Table 1).

3.3. Relationship between HOMA-IR and hyperinsulinemia

A total of 38 outlier insulin values were excluded. The line of least squares drawn for values of HOMA-IR against insulin, showed 8.5 mIU/L to be the value of insulin that corresponds to the cutoff defined for being insulin resistant (HOMA-IR value 2). This was much lower than the Asian Indian threshold for hyperinsulinemia (17mIU/L), which yielded a corresponding HOMA-IR value of 4 (Fig. 1).

3.4. Prevalence of IR and its association with sociodemographic and clinical factors

The prevalence of IR was 38% (95% CI: 33%–42%). In univariate models, the odds of IR were higher among pre-diabetics and diabetics (Odds ratio [OR]: 2.9, 95% CI:1.8–4.9 and 8.9, 95% CI: 4.1–19.3, respectively) when compared to non-diabetics. Enrollees on either first- or second line ART regimens had higher odds of being insulin resistant compared to ART-naïve enrollees (OR: 3.9, 95% CI:1.9–7.5 and OR: 3.6, 95% CI: 2.0–6.4, respectively). Similarly, central obesity (OR: 4.9, 95% CI: 3.3–7.4), hypertension (OR: 2.2, 95% CI: 1.4–3.3) and dyslipidemia (OR: 2.3, 95% CI: 1.5–3.4) were also associated with IR (Table 2).

In a multivariable model adjusted for age, sex, diabetes status, CD4 counts, ART regimen, body mass index (BMI), central obesity, hypertension and dyslipidemia, independent associations with being insulin resistant remained for those on first- and second line ART respectively (OR: 6.6, 95% CI: 2.9–15.2 and OR: 5.4, 95% CI: 2.2–13.6). Likewise, independent associations remained for PLHIV with BMI>18.5 kg/m^2 (OR for enrollees with normal BMI: 2.2, 95% CI: 1.1–3.9, OR for overweight or obese enrollees: 13.6, 95% CI: 5.1–36.3); for those with central obesity (OR: 1.9, 95% CI: 1.1–3.4) and dyslipidemia (OR: 2.4, 95% CI: 1.4–4.0) (Table 2). In a separate multivariable model with the same covariates as the first model, except for replacing ART regimen with ART duration, increasing duration on ART was associated with higher odds of being insulin resistant (OR for 1 to <5 years: 3.5, 95% CI: 1.4–8.7, OR for ≥5 to <10 years: 8.3, 95% CI: 3.5–19.7, OR for ≥10 years 11.9, 95% CI: 4.2–33.1) (Table 3).

The interpretation or the direction of the point estimates when outlier insulin values were excluded were not different from those presented in Table 2. (Sensitivity analyses estimates available as Supplementary Table 1).

4. Discussion

Diabetes or prediabetes was prevalent in one-fourth and IR in more than a third of our study population. When compared to regional age-standardized estimates for HIV-uninfected individuals, the combined prevalence of diabetes and prediabetes for our cohort is 19% higher (25% vs 21%) [20]. Likewise, the prevalence of diabetes is 102% greater than pooled estimates from South Africa, for PLHIV of a similar age distribution [21]. Our estimates for IR are also higher than what have been previously reported for Asian Indian HIV-uninfected individuals [12]. Additionally, they are comparable to those reported for Peruvian PLHIV and lower than those reported for Cameroonian PLHIV; based on a similar HOMA-IR cut-off to the one we employed [22,23]. However, the mean BMI of our study participants was 3.5 and 5 units lower than that reported for PLHIV from these respective studies, suggesting that IR occurs at a lower BMI for Asian Indian PLHIV. We also observed that IR occurred much prior to the hyperinsulinemia threshold, even when using Indian standard ranges. Further, 47% of those who qualified as insulin resistant were neither diabetic nor prediabetic (Supplementary Fig. 1).

Collectively, our findings highlight the urgency of recognizing the burden that diabetes poses for Asian Indian PLHIV, especially as PLHIV continue to age and live longer with improved ART access. They also draw attention to the inadequacy of the current guidelines for diabetes management in South Asian PLHIV [24], which do not address either prediabetes or IR. Since IR and prediabetes have been implicated with vascular dysfunction [25,26]; it is plausible that prior to the onset of clinical diabetes, an array of microvascular or sub-clinical changes have already taken place. Thus, in the presence of HIV – which is independently associated with vascular dysfunction [27], it is conceivable that these changes would have a greater impact on diabetes disease progression than observed in HIV-uninfected individuals. Pharmacological therapy only at the onset of clinical disease, may therefore not be completely effective in preventing diabetes related complications among Asian Indian PLHIV.

Not unlike a previous study from India, we found positive associations between first- and second line ART use with IR [28]. The largely overlapping confidence intervals between the two ART regimens indicate associational strengths of similar magnitudes. Increased duration on ART was also seen to be positively associated with IR, which has also been reported by a few previous studies [29,30]. However, our results also suggest that PLHIV on second line ART may have been on ART for longer durations. Dissociating the influence of the individual from the cumulative contribution of the drug regimen and ART duration, on the association with IR, is however difficult for us to do within the framework of our study design.

Table 1
Characteristics of PLHIV recruited from the ART center of BJ Government Medical College and Sassoon General Hospitals, Pune India, stratified by diabetes status.

	Total N (%)	Diabetes N (%)	Pre-diabetes N (%)	Non-diabetic N (%)	p-value
N (%)	485	42 (8.7)	78 (16.1)	365 (75.2)	–
Age (years) [(median) (IQR)]	40 (35–46)	45 (42–49)	43 (37–50)	39 (34–44)	<0.001
Age categories (years)					
18–24.9	27 (5.6)	0 (0)	0 (0)	27 (7.4)	<0.001
25–34.9	101 (20.8)	3 (7.1)	17 (21.8)	81 (22.2)	
35–44.9	225 (46.3)	17 (40.5)	29 (37.2)	179 (49.0)	
≥45	132 (27.2)	22 (52.4)	32 (41.0)	78 (21.4)	
Sex					
Male	226 (46.6)	27 (64.3)	43 (55.1)	156 (42.7)	0.01
Female	259 (53.4)	15 (35.7)	35 (44.9)	209 (57.3)	
Family history of diabetes[a]					
Yes	70 (24.6)	13 (50.0)	10 (22.2)	47 (22.1)	<0.01
No	214 (75.1)	13 (50.0)	35 (77.8)	166 (77.9)	
Exercise per week					
Adherent to WHO recommendation	364 (75.2)	28 (66.7)	55 (71.4)	281 (77.0)	0.22
Non-adherent to WHO recommendation	120 (24.8)	14 (33.3)	22 (28.6)	84 (23.0)	
Smoking					
Never smoked	409 (84.3)	33 (78.6)	64 (82.1)	312 (85.5)	0.56
Former smoker	57 (11.8)	6 (14.3)	11 (14.1)	40 (11.0)	
Current smoker	19 (3.9)	3 (7.1)	3 (3.8)	13 (3.6)	
Time-updated CD4 count (cells/mm3) [(median) (IQR)]	389 (246–609)	450 (330–703)	344 (212–536)	393 (246–607)	0.08
CD4 count (cells/mm^3)					
>500	174 (36.4)	19 (45.2)	22 (28.6)	133 (37.0)	0.23
350–500	94 (19.7)	10 (23.8)	15 (19.5)	69 (19.2)	
<350	210 (43.9)	13 (30.9)	40 (52.0)	157 (43.7)	
Duration on ART					
≤7 days	100 (20.6)	5 (11.9)	26 (33.3)	69 (18.9)	0.01
1 – <5 years	154 (31.8)	8 (19.0)	21 (26.9)	125 (34.2)	
≥5 - <10 years	171 (35.2)	21 (50)	24 (30.8)	126 (34.5)	
≥10 years	60 (12.4)	8 (19.0)	7 (8.9)	45 (12.3)	
ART regimen[b]					
Naïve	100 (20.6)	5 (11.9)	26 (33.3)	69 (18.9)	0.03
First line drugs	290 (60.0)	25 (59.5)	40 (51.3)	225 (61.6)	
Second line drugs	95 (19.6)	12 (28.6)	12 (15.4)	71 (19.5)	
BMI (kg/m^2)					
Underweight (<18.5)	141 (29.8)	1 (2.4)	19 (25.3)	121 (33.8)	<0.001
Normal (18.5–24.9)	255 (53.8)	21 (51.2)	44 (58.7)	190 (53.1)	
Overweight and Obese (≥25)	78 (16.5)	19 (46.3)	12 (16.0)	47 (13.1)	
Central Obesity					
Yes	164 (34.8)	26 (61.9)	27 (36.0)	111 (31.3)	<0.001
No	308 (65.2)	16 (38)	48 (64.0)	244 (68.7)	
Hypertension					
Yes	112 (23.4)	19 (45.2)	21 (27.3)	72 (20.0)	<0.01
No	367 (76.6)	23 (54.8)	56 (72.7)	288 (80.0)	
Dyslipidemia					
Yes	297 (61.2)	37 (84.8)	48 (61.5)	212 (58.1)	<0.001
No	188 (38.8)	5 (11.9)	30 (38.5)	153 (41.9)	
Fasting Insulin (mIU/L) [(median) (IQR)]	7.0 (4.5–11.5)	13.0 (8.5–26.6)	8.9 (5.6–12.6)	6.2 (4.3–10.1)	<0.001
Hyperinsulinemia					
Yes	58 (12.0)	18 (42.9)	12 (15.4)	28 (7.7)	<0.001
No	426 (88.0)	24 (57.1)	66 (84.6)	336 (92.3)	

Abbreviations used: ART – Antiretroviral therapy, BMI – Body mass index.
Please refer to the study definitions under the methods section of the manuscript for the other definitions.
[a] Family history of diabetes was available only for 285 participants, of which 1 participant did not know their family history for diabetes.
[b] First line and second line drugs defined as per NACO's criteria, First line drugs: 2 NRTIs + 1 NNRTI. Of 290 participants receiving first line drugs, 168 had AZT and 220 EFV as part of their regimen. Second line drugs: 2NRTIs +1 boosted PI. Of 95 participants receiving second line drugs, 88 were on ritonavir boosted ATV; naïve - ART duration ≤7 days.

Our findings corroborate findings from earlier studies that have shown central obesity, to be a risk factor for insulin resistance [5]. Interestingly, we found 78% of our study participants who were compliant with WHO-recommended exercise guidelines, to have central obesity. It is unclear whether high physical activity in this cohort has been protective against the worsening of central obesity or if central obesity has worsened despite high physical activity. This relationship will require better objectification by well powered longitudinal studies. Nevertheless, as newer recommendations for physical activity in PLHIV emerge from developed countries [31], gathering locoregional evidence on the implications of adopting such guidelines on the clinical outcomes of Asian Indian PLHIV is warranted.

To our knowledge, our study is the largest study to have reported on diabetes and insulin resistance among adult Asian Indian PLHIV, providing descriptive epidemiological evidence for comorbid conditions that are largely ignored yet predominant among Asian Indian PLHIV. We also highlight the relationship between IR and hyperinsulinemia, bringing to the forefront the possibility of an extended nascency between IR, hyperinsulinemia, and diabetes in Asian Indian PLHIV. Further, we attempt to provide an initiatory approach to describing the relationship between physical activity and central obesity among Asian Indian PLHIV, which isn't well characterized in existing literature.

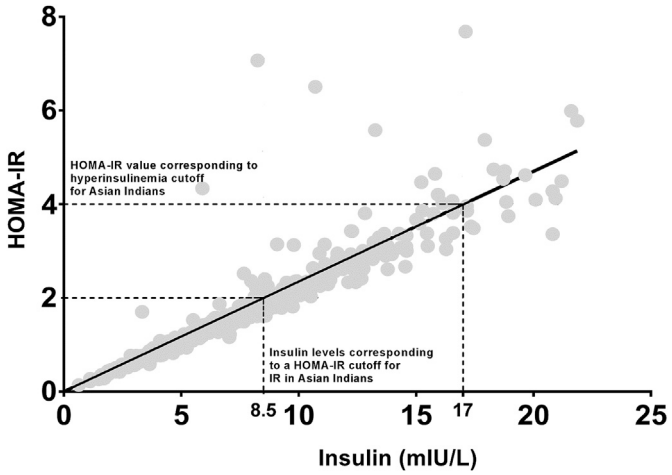

Fig. 1. Relationship between HOMA- IR and insulin showing the corresponding thresholds for being insulin resistant and hyperinsulinemic for PLHIV recruited from the ART center of BJ Government Medical College and Sassoon General Hospitals, Pune, India.

One of the main limitations of our analyses is that we were unable to derive age-standardized prevalence for diabetes. The paucity of data available for the age distribution of Pune, when enrollments into the study happened prevented us from deriving these estimates. Our enrollment method may have produced a selective cohort of individuals that had higher health seeking behavior, though this would imply a probable higher prevalence of diabetes, prediabetes and IR. It may also be difficult to extrapolate our findings to other regions of India due to its geographic, economic and ethnic heterogeneity. Moreover, given the cross-sectional design of our study, we are unable to make causal claims for any of our study findings.

In a physically active, young cohort of Asian Indian PLHIV, we found the combined prevalence of diabetes and prediabetes as well as IR to be higher than what has been reported previously. While the government of India has taken considerable strides in addressing the burgeoning diabetes epidemic in the general population with the institution of the integrated National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) [32], such initiatives for PLHIV are less forthcoming, even almost a decade after NPCDCS implementation.

Table 2
Association between sociodemographic and clinical factors with insulin resistance in PLHIV recruited from the ART center of BJ Government Medical College and Sassoon General Hospitals, Pune, India.

	Total[a] N (%)	Insulin resistant N (%)	Insulin sensitive N (%)	OR (95% CI)	aOR[b] (95% CI)
N (%)	484	182 (37.6)	302 (62.4)	–	–
Diabetes status					
Non-diabetic	364 (75.2)	106 (58.2)	258 (85.4)	Ref	Ref
Pre-diabetic	78 (16.1)	43 (23.6)	35 (11.6)	2.9 (1.8–4.9)	3.7 (1.9–7.3)
Diabetic	42 (8.7)	33 (18.1)	9 (3.0)	8.9 (4.1–19.3)	3.7 (1.4–9.6)
Median Age (years) (IQR)	40 (35–46)	42 (36–47)	40 (35–45)	–	–
Age categories (years)					
18–24.9	27 (5.6)	11 (6.0)	16 (5.3)	Ref	Ref
25–34.9	100 (20.7)	30 (16.5)	70 (23.2)	0.6 (0.3–1.5)	0.2 (0.1–0.7)
35–44.9	225 (46.5)	78 (42.9)	147 (48.7)	0.8 (0.3–1.7)	0.3 (0.1–0.7)
≥45	132 (27.3)	63 (34.6)	69 (22.8)	1.3 (0.6–3.1)	0.4 (0.1–1.2)
Sex					
Male	226 (46.7)	91 (50.0)	135 (44.7)	Ref	Ref
Female	258 (53.3)	91 (50.0)	167 (55.3)	0.8 (0.6–1.2)	0.9 (0.5–1.5)
Exercise per week					
Non-adherent to WHO recommendation	119 (24.6)	45 (24.9)	74 (24.5)	Ref	–
Adherent to WHO recommendation	364 (75.4)	136 (75.1)	228 (75.5)	0.9 (0.6–1.5)	
CD4 count categories (cells/mm^3)					
>500	173 (36.3)	76 (41.8)	97 (32.9)	Ref	Ref
350–500	94 (19.7)	43 (23.6)	51 (17.3)	1.1 (0.6–1.8)	1.9 (1.0–3.7)
<350	210 (44.0)	63 (34.6)	147 (49.8)	0.5 (0.4–0.8)	1.2 (0.7–2.2)
ART regimen[c]					
Naïve	100 (20.7)	17 (9.3)	83 (27.5)	Ref	
First line drugs	289 (59.7)	123 (67.6)	166 (55.0)	3.9 (1.9–7.5)	6.6 (2.9–15.2)
Second line drugs	95 (19.6)	42 (23.1)	53 (17.6)	3.6 (2.0–6.4)	5.4 (2.2–13.6)
BMI (kg/m^2)					
Underweight (<18.5)	141 (29.8)	21 (11.7)	120 (40.8)	Ref	Ref
Normal (18.5–24.9)	254 (53.7)	94 (52.5)	160 (54.4)	3.4 (1.9–5.7)	2.2 (1.1–3.9)
Overweight and Obese (≥25)	78 (16.5)	64 (35.7)	14 (4.8)	26.1 (12.4–54.8)	13.6 (5.1–36.3)
Central Obesity					
No	307 (65.2)	77 (43.0)	230 (78.8)	Ref	Ref
Yes	164 (34.8)	102 (57.0)	62 (21.2)	4.9 (3.3–7.4)	1.9 (1.1–3.4)
Hypertension					
No	367 (76.8)	123 (68.0)	244 (82.1)	Ref	Ref
Yes	111 (23.2)	58 (32.0)	53 (17.9)	2.2 (1.4–3.3)	1.0 (0.5–1.7)
Dyslipidemia					
No	187 (38.6)	49 (29.9)	138 (45.7)	Ref	Ref
Yes	297 (61.4)	133 (73.1)	164 (54.3)	2.3 (1.5–3.4)	2.4 (1.4–4.0)

Abbreviations used: ART: Antiretroviral therapy, BMI: Body mass index.
Family status not included as an predictor variable in regression models as missingness was>10%.
[a] Total participants: 484, as one participant had an insulin value below the level of instrument calibration.
[b] Adjusted for age, sex, diabetes status, CD4 count, ART regimen, BMI, central obesity, hypertension and dyslipidemia.
[c] ART duration has been shown in a separate table as collinearity exists between the categories of ART regimen (naïve) and ART duration (≤7 days).

Table 3
Relationship between ART duration and ART regimen and the association between ART duration and insulin resistance in PLHIV recruited from the ART center of BJ Government Medical College and Sassoon General Hospitals, Pune, India.

	Total N (%)	Naïve N (%)	First line ART N (%)	Second line ART N (%)	p-value
Duration on ART					
≤7 days	100 (20.6)	100 (100.0)	–	–	<0.001
1 – <5 years	154 (31.8)	–	128 (44.1)	26 (27.4)	
≥5 - <10 years	171 (35.2)	–	126 (43.4)	45 (47.4)	
≥10 years	60 (12.4)	–	36 (12.4)	24 (25.3)	
		Insulin resistant N (%)	**Insulin sensitive N (%)**	**OR (95% CI)**	**aOR[a] (95% CI)**
Duration on ART					
≤7 days		17 (9.3)	83 (27.5)	Ref	Ref
1 – <5 years		50 (27.5)	103 (34.1)	2.4 (1.3–4.4)	3.5 (1.4–8.7)
≥5 - <10 years		83 (45.6)	88 (29.1)	4.6 (2.5–8.4)	8.3 (3.5–19.7)
≥10 years		32 (17.6)	28 (9.3)	5.6 (2.7–11.6)	11.9 (4.2–33.1)

Abbreviations used: ART: Antiretroviral therapy.
The interpretation of the other estimates when duration is used as a covariate do not change from those presented in Table 2. These estimates are included in the supplementary file.
[a] Adjusted for age, sex, diabetes status, CD4 count, ART regimen, BMI, central obesity, hypertension and dyslipidemia.

The occurrence of IR in non-diabetic PLHIV suggest that the current NACO guidelines of screening for diabetes using random blood glucose at ART initiation with variable follow-up [8], may misrepresent the extent and spectrum of dysglycemia among Asian Indian PLHIV. Future studies should seek to understand better the role of IR in diabetes disease progression among Asian Indian PLHIV, to allow for the framing of interventional guidelines that are germane to the target population.

Conflicts of interests

None.

Ethical standards disclosure

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the BJ Government Medical College and Johns Hopkins University Ethics Committees. Written informed consent was obtained from all subjects/patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.04.009.

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