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# Insulin resistance by homeostasis model assessment in HIV-infected patients on highly active antiretroviral therapy: cross-sectional study

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## Abstract

**Background:** The highly active antiretroviral therapy (HAART) has altered the course of HIV infection, transforming it from a fatal illness to a chronic condition, reducing morbidity and mortality. However, this therapy has led to an increased incidence of metabolic problems such as insulin resistance, dyslipidemia, lipodystrophy and impaired glucose metabolism.

The objectives of this study are to determine the prevalence of insulin resistance (IR) in a cohort of human immunodeficiency virus (HIV)-infected patients on highly active antiretroviral therapy (HAART) and to investigate the potentially associated factors.

**Methods:** We conducted a cross-sectional study including 219 adult patients with HIV on HAART. IR was determined through the homeostasis model assessment (HOMA-IR) mathematical model, using fasting plasma glucose (FPG) and insulin. Bivariate and multivariate analyses were performed to assess the association between demographic information, clinical characteristics and laboratory results, and IR.

**Results:** 75 (34.2 %) [95 % confidence interval (CI) 28.9–40.9] HIV-patients on HAART showed IR. 61 (81 %) of these patients were on HAART for more than one year, which was mainly composed by non-protease inhibitors drugs (88 %). Metabolic syndrome (MS) was found in 59 (26.9 %) subjects. In the multivariate analysis, the factors associated with IR were age  $\geq$  46 years (Prevalence ratio = 2.767, 95 % CI 1.325 to 5.780) and greater body mass index (BMI) (Prevalence ratio = 1.148, 95 % CI 1.054 to 1.250).

**Conclusions:** The prevalence of IR was 34.2 %. Factors associated with IR were age and BMI. We did not find any significant association between IR and protease inhibitors (PI), which may be explained by the small number of patients using PI as part of their HAART regimen included in our study.

**Keywords:** Insulin resistance, HIV, HAART, HOMA, Metabolic syndrome

## Background

World Health Organization and UNAIDS report about 39.5 million HIV-infected people worldwide and about 2 million people in Latin America. In 2009, around 70,000 people were estimated to be infected in Peru. The advent of HAART has altered the course of HIV infection, transforming it from a fatal illness to a chronic condition and thereby reducing morbidity and mortality [1]. However, antiretroviral therapy has also led to an increased

incidence of metabolic problems such as IR, dyslipidemia, lipodystrophy and impaired glucose metabolism [2].

HAART comprises a combination of at least three active antiretroviral drugs against the virus which belong to different classes of drugs with different sites of action. The preferred initial regimen is the combination of two nucleoside reverse transcriptase inhibitors with a non-nucleoside reverse transcriptase inhibitor or with a PI. The adverse effects of these medications include metabolic disorders. The antiretroviral drugs most frequently associated with the development of lipodystrophy and IR are the PIs such as lopinavir, ritonavir and nelfinavir [3].

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IR, impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) are part of a plurimetabolic syndrome associated with HAART, thus, the detection of this syndrome should be systematic. Guidelines recommend testing FPG at the time of HIV diagnosis, before initiating HAART, and every 6–12 months during treatment [4]. Also, performing an oral glucose tolerance test when a patient presents with abnormal fasting glucose is recommended [5]. This strategy allows the detection of most cases of T2DM; however, it misses some cases of IR. An early diagnosis of IR could allow for lifestyle modification in order to prevent progression to T2DM.

The HOMA mathematical model is a clinical and epidemiological tool used to estimate IR based on plasma levels of fasting glucose and insulin [6]. In order to investigate the prevalence of IR and the potentially implicated factors, we conducted a cross-sectional study in a cohort of Peruvian HIV-patients on HAART using the HOMA-IR. Moreover, we described the prevalence of MS according to the criteria proposed by The National Cholesterol Education Program's Adult Treatment Panel III report [7].

## Methods

### Ethics statement

The study was approved by the Institutional Review Board of the Universidad Peruana Cayetano Heredia and of the Hospital Nacional Cayetano Heredia. All the patients gave written informed consent to participate. Authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

### Study description

A cross-sectional study of adult patients with HIV infection on HAART was carried out between June and October 2012 at the Institute of Tropical Medicine "Alexander von Humboldt", in the Hospital Nacional Cayetano Heredia in Lima, Peru.

Patients recruited were adults over 18 years of age diagnosed with HIV infection on HAART. We excluded patients with a known history of carbohydrate metabolism disorders (IGT, T2DM), diseases that alter insulin sensitivity (Cushing syndrome, Acromegaly, Polycystic ovary syndrome), use of corticosteroids, and pregnancy.

We obtained clinical records that included the following variables: age, gender, family history of diabetes in a first degree relative, smoking, blood pressure, weight, height, BMI, waist circumference, regimen and duration of HAART.

We obtained a fasting serum sample to measure levels of glucose, insulin, and lipids. Insulin level determination was performed using the immunoradiometric assay based on the separation of antibody-coated tube (INS-Irma DIASource-Belgium). This method has a detection

limit, defined as the concentration resulting in two standard deviations above the average link of the zero calibrator, 1 uIU/mL. The coefficient of variation intra-assay and inter-assay were 1.5 % and 6.5 % respectively.

Blood glucose was measured by the glucose oxidase method. Hyperglycemia was considered as a fasting glucose value  $\geq 100$  mg/dL. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were determined by enzymatic method. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula.

The presence of IR was determined by the HOMA mathematical model using the following formula:  $[\text{Insulin } (\mu\text{U/ml}) \times \text{glucose (mmol/L)}] / 22.5$ . We defined IR as a HOMA-IR value  $\geq 2.1$ . This cutoff point was determined in a previous study conducted at the Hospital Nacional Cayetano Heredia in subjects with normal glucose tolerance tests [8].

### Statistical analyses

Continuous variables were summarized using means and standard deviations, and comparisons between groups with and without IR were made using the Student's *t*-test. Categorical variables were summarized by frequencies and percentages, and their association with the outcome variable (IR) was determined using Fisher's exact test. Exposure variables with a "p" value below 0.10 in the bivariate evaluation were tested in multivariate models using "Generalized Linear Models" with the backward stepwise method, removing variable with p values over 0.05. Prevalence ratios, with their corresponding confidence intervals, were calculated as measures of excess risk.

The analysis was performed with the statistical program Stata SE version 11 (College Station, TX).

## Results

### Participant's characteristics

In this study, the response rate was 100 %. The demographic information, family and social history of 219 subjects are presented in Table 1. The mean age of the study population was  $38.4 \pm 10.1$  years. Most of the participants were male (67.1 %), 23.3 % had a first-degree family history of T2DM and 24.7 % patients were smokers. Regarding the treatment, (76.3 %) subjects were on HAART over a year and the most commonly used regimen did not include a PI (90.9 %).

### Clinical characteristics and laboratory results

The mean BMI was  $24.5 \pm 3.6$ . Most patients had a normal weight (55.3 %), 32.0 % overweight, 8.2 % obese and 4.6 % underweight. The mean abdominal circumference in men and women was  $88.8 \pm 9.0$  cm and  $87.1 \pm 10.3$  cm, respectively (Table 2). Laboratory results are shown in Table 3.

**Table 1** Comparison of general characteristics of HIV-infected patients on HAART with and without insulin resistance (IR)

General characteristics (n = 219)	Total (n = 219)	No IR (n = 144)	IR (n = 75)	PR	P
Male, n (%)	147 (67.1)	96 (66.7)	51 (68.0)	1.041	0.844
Age					0.007
≤ 35 years, n (%)	95 (43.4)	70 (48.6)	25 (33.3)	1.000	Reference
36-45 years, n (%)	74 (33.8)	50 (34.7)	24 (32.0)	1.232	0.398
≥ 46 years, n (%)	50 (22.8)	24 (16.7)	26 (34.7)	1.976	0.002
Hispanics, n (%)	190 (86.7)	124 (86.1)	66 (88.0)	1.119	0.709
Family history of T2DM, n (%)	51 (23.3)	34 (23.6)	17 (22.7)	0.965	0.877
Cigarette smoker, n (%)	54 (24.7)	40 (27.8)	14 (18.7)	0.701	0.186
>1 year on HAART, n (%)	167 (76.3)	106 (73.6)	61 (81.3)	1.357	0.249
HAART regimen with PI, n (%)	20 (9.1)	11 (7.6)	9 (12.0)	1.357	0.235

Abbreviations: HAART highly active antiretroviral therapy; IR insulin resistance; PR prevalence ratio; PI protease inhibitor; T2DM type 2 diabetes mellitus

### Prevalence of insulin resistance and metabolic syndrome

The prevalence of IR was 34.2 % (95 % CI 28.9 – 40.9). MS was found in 26.9 % subjects and was more prevalent in the IR group (44.0 % vs 18.1 %) ( $p < 0.001$ ). The most frequently components of MS were low HDL-C, hypertriglyceridemia, and hyperglycemia (Table 4).

Hyperglycemia was found in 103 (47 %) subjects, 9 (4.1 %) of them had serum glucose >125 mg/dl. 8 (3.7 %) patients had hypertension. The prevalence of hypertriglyceridemia and low HDL-C was 48.4 % and 57.5 % respectively (Table 4).

### Comparison between the groups with and without insulin resistance

Subjects with IR were older, had higher BMI, and were more likely to have hyperglycemia, central obesity and diastolic hypertension. With regard to the lipid profile, although the patients with IR had higher triglycerides levels, no significant differences were found when the variable was categorized as hypertriglyceridemia. There

were no differences in gender, family history of T2DM, cigarette smoking, duration of HAART, using PI and systolic blood pressure (SBP).

In multivariate analysis, the factors associated with IR were age ≥46 years (PR = 2.767, 95 % CI 1.325 to 5.780) and greater BMI (PR = 1.148, 95 % CI 1.054 to 1.250) (Table 5).

### Discussion

In our study, the prevalence of IR was 34 %, two times higher than that of the non-HIV-infected population<sup>9</sup>. The reported prevalence rates of IR among HIV-patients on HAART are highly variable, ranging from 13 % to 45.7 % [9]. Because our study did not have a control group of patients without HIV infection, the HOMA-IR's cutoff was 2.1, which was based on a previous study conducted at the Hospital Nacional Cayetano Heredia in subjects without HIV infection and with similar geographical and ethnic characteristics. This value corresponds to the 75<sup>th</sup> percentile value determined by that

**Table 2** Clinical characteristics of HIV-infected patients on HAART with and without insulin resistance (IR)

Clinical characteristics	Total (n = 219)	No IR (n = 144)	IR (n = 75)	P
SBP, mmHg	104.7 ± 11.9	103.6 ± 11.4	106.8 ± 12.6	0.060
DBP, mmHg	68.5 ± 8.2	67.5 ± 7.8	70.4 ± 8.6	0.013
Weight, Kg	64.7 ± 11.5	63.0 ± 11.6	67.9 ± 10.7	0.003
BMI, Kg/m <sup>2</sup>	24.5 ± 3.6	23.8 ± 3.6	25.6 ± 3.5	0.001
BMI categories				0.001
Underweight, n (%)	10 (4.6)	9 (6.3)	1 (1.3)	0.535
Normal weight, n (%)	121 (55.3)	91 (63.2)	30 (40.0)	Reference
Overweight, n (%)	70 (32.0)	35 (24.3)	35 (46.7)	0.011
Obesity, n (%)	18 (8.2)	9 (6.3)	9 (12.0)	<0.001
Abdominal circumf. (cm)	88.3 ± 9.5	86.8 ± 9.8	91.1 ± 8.2	0.001
Male, cm	88.8 ± 9.0	88.2 ± 9.2	90.1 ± 8.5	0.219
Female, cm	87.1 ± 10.3	83.9 ± 10.3	93.3 ± 7.2	<0.001

Abbreviations: BMI body mass index, DBP diastolic blood pressure, SBP systolic blood pressure, SD standard deviation

**Table 3** Laboratory results of HIV-infected patients on HAART with and without insulin resistance (IR)

Laboratory results	Total (n = 219)	No IR (n = 144)	IR (n = 75)	P
Triglycerides, mg/dL	189.4 ± 147.8	172.5 ± 120.6	221.9 ± 186.1	0.019
LDL-C, mg/dL	114.5 ± 50.4	110.5 ± 51.9	122.3 ± 46.8	0.101
HDL-C, mg/dL	41.5 ± 14.1	42.1 ± 14.4	40.2 ± 13.5	0.336
FPG, mg/dL	100.9 ± 19.8	97.4 ± 11.8	107.6 ± 28.6	<0.001
HOMA index	2.6 ± 3.0	1.2 ± 0.5	5.3 ± 3.7	<0.001
Female	2.6 ± 2.9	1.2 ± 0.5	5.5 ± 3.6	<0.001
Male	2.5 ± 3.0	1.1 ± 0.5	5.2 ± 3.8	<0.001

Abbreviations: FPG fasting plasma glucose, HDL-C high-density lipoprotein cholesterol, HOMA homeostasis model assessment, LDL-C low-density lipoprotein cholesterol

study for subjects without HIV infection, normal OGTT and normal weight. It is higher than the cutoff point of a study made with Peruvian Andean adults living at 4100 m above sea level (HOMA = 1.4) and lower than the value found for Peruvian metropolitan population living at sea level (HOMA = 3.56) [10].

Through bivariate analysis, we found the following variables to be associated with IR: age, diastolic blood pressure, weight, BMI, abdominal circumference and FGP. All of these variables are components traditionally associated with the development of IR in the general population [11]. Our study did not find a significant association between IR and the use of PIs, in contrast to other reports which showed a clear association [12, 13], this may be explained by the small number of patients [20 (9 %)] using PI as part of their HAART regimen included in our study. In addition, we found that 9 of the 20 patients on PI used atazanavir, which has not been associated with IR in published studies [14]. On the other hand, the prevalence of IR was not significantly higher among patients who were more than one year on HAART compared to those who were less time on treatment, suggesting that IR occurs early. However, our study does not allow us to assess if the IR worsens with the course of the HIV infection. To evaluate this correlation, it would be necessary to conduct a longitudinal study. The long-term effects of antiretroviral drugs are poorly understood. Jemsek JG et al. found that the

alteration of insulin sensitivity in the early stages of anti-retroviral therapy tends to normalize over time [15].

In the multivariate analysis, through a logistic regression model using the variables that were significant in the bivariate analysis, we found that patients older than 46 years have almost three times more risk of IR compared with younger subjects. Similarly, we found an increased risk of IR with higher BMI; for each unit increase in BMI, the risk of IR increased by 15 %. The prevalence of MS in our series was 27 %, similar to the prevalence reported in American and Latin American series in patients with HIV infection [16, 17], and higher than the prevalence found in the Peruvian adult population without HIV infection (22 %) [18]. With regard to the components of MS, in our study, similar to other studies of MS in HIV patients, dyslipidemia and hyperglycemia predominant followed by obesity and hypertension. Also, a high percentage of patients with MS had normal weight, which differs from previous reports about MS in the general population, where abdominal obesity and hypertension are the principal components [19].

We found an alarmingly high prevalence of hyperglycemia (47 %), higher than that reported in other studies of HIV patients on HAART (38 %) [20], these results suggest that HIV treatment is an important factor in the development of IR and other metabolic disorders such as IGT and T2DM. Unfortunately, our study did not

**Table 4** Comparison of metabolic syndrome and its components in HIV-infected patients on HAART with and without IR

Metabolic syndrome's components	Total (n = 219)	No IR (n = 144)	IR (n = 75)	PR	P
Metabolic Syndrome, n (%)	59 (26.9)	26 (18.1)	33 (44.0)	2.131	<0.001
Central Obesity, n (%)	49 (22.4)	25 (17.4)	24 (32.0)	1.633	0.007
Hypertriglyceridemia, n (%)	106 (48.4)	66 (45.8)	40 (53.3)	1.218	0.297
Low HDL-C, n (%)	126 (57.5)	81 (56.3)	45 (60.0)	1.107	0.600
Hyperglycemia, n (%)	103 (47.0)	58 (40.3)	45 (60.6)	1.689	0.008
100–125 g/dL	94 (42.9)	57 (39.6)	37 (49.3)	1.86	0.038
> 125 g/dL	9 (4.1)	1 (0.7)	8 (10.7)	2.75	0.004
High Blood Pressure, n (%)	8 (3.7)	4 (2.8)	4 (5.3)	1.486	0.258

Abbreviations: HDL-C high-density lipoprotein cholesterol, IR insulin resistance

**Table 5** Multivariate logistic regression analysis for IR in HIV-infected patients on HAART

Factor	PR	P	95 % CI	
Age (years)		0.014		
≤ 35	1.000	Reference		
36-45	1.070	0.848	0.533	2.150
≥ 46	2.767	0.007	1.325	5.780
BMI	1.148	0.002	1.054	1.250

Abbreviations: *BMI* body mass index, *CI* confidence interval, *PR* prevalence ratio

perform oral glucose tolerance test so that there may be cases of T2DM undiagnosed.

The prevalence of hypertension was 3.7 %, lower than that found in a previous study (16 %) [21]. This low prevalence may be due to the lower age of the enrolled patients.

The study's limitations were the lack of a control group of HIV-uninfected subjects to define a more precise HOMA-IR's cutoff point and the clinical evaluation of lipodystrophy. In addition, variables such as CD4 count and viral load were omitted. These variables have been considered factors associated with IR in this specific population. Squillace N et al. found a significant association between a high CD4 count and IR [22]. However, El-Sadr WM et al. has shown an inverse relationship between CD4 count and IR [23]. These inconsistent associations, on regard the CD4 count, might reflect underlying immunological mechanisms that could affect the insulin sensitivity. Therefore, those two variables must be included in future studies as possible underlying factors. Finally an oral glucose tolerance test was not performed to diagnose T2DM.

## Conclusion

In conclusion, this study shows a significant percentage of HIV-infected patients on HAART present IR. Factors associated with IR were age and BMI. Since these patients have a high frequency of dyslipidemia and tobacco consumption, the detection of IR and its risk factors will allow for the assessment of each patient's metabolic risk and will also promote addressing modifiable risk factors to prevent the development of T2DM and cardiovascular disease.

We did not find any significant association between IR and protease inhibitors, which may be explained by the small number of patients using PI as part of their HAART regimen included in our study.

Based on our results, we suggest following current guidelines for the use of antiretroviral therapy in HIV patients, which recommend performing laboratory tests, such as fasting glucose or OGTT, during follow-up. The use of HOMA-IR in these patients will require further

longitudinal studies in order to demonstrate its usefulness in early predicting diabetes or IGT in this population.

## Abbreviations

BMI: Body mass index; CI: Confidence interval; FPG: Fasting plasma glucose; HAART: Highly active antiretroviral therapy; HDL-C: High-density lipoprotein cholesterol; HIV: Human immunodeficiency virus; HOMA: Homeostasis model assessment; IGT: Impaired glucose tolerance; IR: Insulin resistance; LDL-C: Low-density lipoprotein cholesterol; MS: Metabolic syndrome; PI: Protease inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

MAG, FAM, JV, CGT, CPC and RT have made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data. Also, all of them have been involved in the manuscript draft and all of them have approved the final version of the article.

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Received: 18 March 2015 Accepted: 22 May 2015

Published online: 30 May 2015

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