

# Prevalence and associated factors of insulin resistance among HIV-infected patients receiving antiretroviral therapy: a cross-sectional study from Tunisia

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## Abstract

**Introduction:** Antiretroviral therapy (ART) has significantly improved prognosis of human immunodeficiency virus (HIV) infection by reducing both morbidity and mortality rates. However, this therapy leads to an increased incidence of metabolic disorders, such as insulin resistance (IR). The aim of this study was to determine the prevalence of IR in non-diabetic HIV-infected patients receiving ART, and to investigate the potentially associated factors.

**Material and methods:** We conducted a cross-sectional study among 67 non-diabetic HIV-infected patients receiving ART. IR was determined through homeostasis model assessment (HOMA-IR). Bivariate and multivariate analyses were performed to investigate the association between demographic, clinical, and biological variables, and IR.

**Results:** A total of 67 HIV-infected patients were enrolled, among whom 43 (64.2%) were males, and the median age was 38.7 years. The prevalence of metabolic syndrome was 28.3%, and IR was found in 30 patients (44.7%). Seventeen of these patients had not a metabolic syndrome. HOMA-IR values were ranging between 2 and 3.99 in 11 patients (64.7%), between 4 and 6 in 5 patients (29.4%), and was greater than 6 in one patient. In the multivariate analysis, there was no significant association between body mass index, CD4+ count, ART regimen, and IR.

**Conclusions:** Asymptomatic IR, responsible in the long-term for the occurrence of other serious metabolic disorders, is common among HIV-infected patients, and cannot be predictable. Screening of insulin resistance by measuring HOMA-IR is the main parameter for early detection of metabolic risk and personalized management.

HIV AIDS Rev 2025; 24, 3: 195-200  
DOI: <https://doi.org/10.5114/hivar/150818>

**Key words:** insulin resistance, HIV infection, risk factors, prevalence.

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**Article history:**  
Received: 25.01.2022  
Revised: 08.06.2022  
Accepted: 08.06.2022  
Available online: 20.08.2025



## Introduction

According to the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) reports, across the globe, there were approximately 38 million people living with human immunodeficiency virus (HIV) in 2019, of these, 25.4 million (67%) were accessing antiretroviral therapy (ART) [1]. Since the introduction of highly active ART, the course of HIV infection has been changed, and life expectancy has increased [2]. However, it also led to an increased incidence of metabolic diseases, such as insulin resistance (IR), dyslipidemia, lipodystrophy, and impaired glucose metabolism [3, 4].

IR is a metabolic disorder characterized by a decrease in sensitivity of insulin receptors within target cells, resulting in failure of insulin to stimulate glucose uptake in this target tissue [5, 6]. This disorder in HIV patients has been associated with an increased risk of cardiovascular diseases and mortality, and particularly with development of diabetes mellitus [7, 8].

The aim of this study was to investigate the prevalence of IR and the potentially implicated factors among HIV-infected non-diabetic population undergoing a combination of ART.

## Material and methods

### Study description

A cross-sectional study in adult HIV-infected patients undergoing ART was carried out between September 2018 and February 2019 at the Department of Infectious Diseases, Fattouma Bourguiba University Hospital, Monastir, Tunisia. Inclusion criteria were age above 18 years and ART treatment for at least 3 months. Pregnant women, patients with a prior diagnosis of diabetes mellitus and/or receiving a hypoglycemic treatment or other therapies, which could alter blood glucose or insulin levels, such as corticosteroids or chemotherapy, were excluded. The study was approved by our hospital institutional ethical committee, and all patients provided informed consent.

### Data collection

Data were collected from patients' charts and during interviews, which included questions on socio-demographic aspects (age, gender, smoking, and alcohol use), clinical and biological factors (time of HIV infection, centers disease control [CDC] stage, lymphocytes CD4 count, HIV RNA level, and HCV co-infection), and therapeutic variables (regimen and duration of ART). Anthropometric measurements (weight, height, body mass index [BMI], and circumference waist) were also determined, as previously published.

After 12-hour fasting, blood samples were taken for biochemical tests of blood glucose, total cholesterol, high density lipoprotein cholesterol (HDL-c), triglycerides, and plas-

ma insulin. Low density lipoprotein cholesterol (LDL-c) was calculated using the Friedwald formula.

## Definitions

Metabolic syndrome was defined according to the International Diabetes Federation (IDF). The IDF definition required a waist circumference (> 94 cm in men, and > 80 cm in women) associated with at least two of the followings:

1. High triglyceride  $\geq 149$  mg/dl (1.7 mmol/l).
2. Low high density lipoprotein cholesterol (HDL-c) < 40 mg/dl (1.03 mmol/l) in men, and < 50 mg/dl (1.29 mmol/l) in women.
3. Blood pressure  $\geq 130/85$  mmHg.
4. Fasting plasma glucose  $\geq 100$  mg/dl ( $\geq 5.6$  mmol/l).

The presence of IR was determined by the homeostasis model assessment (HOMA) mathematical model using the following formula: [insulin (uIU/ml) glucose (mmol/l)]/22.5.

We defined IR as a HOMA-IR value  $\geq 2.4$ .

## Statistical analysis

Data were analyzed using IBM SPSS version 20.0. Results were presented as count (percentage) for categorical variables, and mean or median for quantitative variables. Continuous variables were compared using the Student's *t*-test for normal distribution, and the Mann Whitney *U* test for non-normal one. Categorical variables were analyzed with the  $\chi^2$  test or Fisher's test when applicable. Bivariate analysis was performed to identify factors associated with IR. Exposure variables with *p*-value below 0.05 in bivariate evaluation were tested in multivariate models using logistic regression analysis with HOMA-IR  $\geq 2.4$  as dependent variable. *P*-value < 0.05 was considered statistically significant.

## Results

A total of 67 HIV-infected patients were included in the study among whom, 43 (64.2%) were males, and the median age was 38.7 years. The mean duration of HIV infection from diagnosis to inclusion in the study was 8 years (range, 6 months – 30 years). The median CD4+ count was 443/mm<sup>3</sup> (range, 20-2326/mm<sup>3</sup>) at the moment of recruitment, and 331/mm<sup>3</sup> (8-1450/mm<sup>3</sup>) at the moment of diagnosis. CD4 nadir in the study population was 165.65/mm<sup>3</sup> (range, 8-676/mm<sup>3</sup>). The average level of viral load before treatment was 254,260.3 copies/ml (range, 3,000-2,700,000 copies/ml). Forty-four patients (65.6%) had an undetectable viral load at the moment of enrollment. No patient had a history of high blood pressure or dyslipidemia. The co-infection with HCV was noted in 8 cases (11.9%), but no patient presented a co-infection with HBV or other comorbidities. The mean body mass index (BMI) was 24.3 kg/m<sup>2</sup>, and 12 (37.3%) patients were obese (BMI > 30 kg/m<sup>2</sup>). The waist circumference was 90.1  $\pm$  12.8 cm (range, 64-125 cm). It was

87.4 cm in males and 95.3 cm in females ( $p = 0.031$ ). Only 3 patients of the study cohort had lipodystrophy. A total of 36 patients (53.7%) received ART based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) and 29 (43.3%) used protease inhibitors (PIs), for an average of 50.8 months. The most commonly used nucleoside reverse transcriptase inhibitors (NRTIs) were tenofovir (52.2%) and zidovudine (44.7%). Efavirenz was the only NNRTI prescribed, while lopinavir/ritonavir and atazanavir were prescribed in 26 and 3 cases, respectively. Biologically, the mean total cholesterol and triglycerides levels were 4.1 mmol/l and 1.46 mmol/l, respectively. The average level of plasma insulin was  $13.21 \pm 6.9$  mIU/l (range, 3–36.2 mIU/l) (Table 1).

Metabolic syndrome was observed in 19 patients of the study population (28.3%), while IR in 30 patients (44.7%), 17 of whom did not have a metabolic syndrome. Among patients with IR and without metabolic syndrome, 11 (64.7%) had an HOMA-IR level between 2.5 and 3.99, 5 (29.4%) had an HOMA-IR between 4 and 6, and one patient had an HOMA-IR  $> 6$  (Figure 1).

The 48 patients having no metabolic syndrome were divided into 2 groups: group A, 17 PLHIV with IR; and group B, 31 PLHIV without IR.

The distribution of age and gender were uniform in the two groups ( $p > 0.05$ ). HIV infection has been evolving for 4 years in the group A, and for 6.3 years in the group B ( $p = 0.12$ ). Body mass index (BMI) was 23.8 and 23.5 kg/m<sup>2</sup> in the group A and B, respectively ( $p = 0.84$ ). Five patients in the group A (29.4%) and 8 patients in the group B (25.8%) had a low CD4<sup>+</sup> count ( $< 200/\text{mm}^3$ ). PI regimens were prescribed in 10 cases (58.8%) in the group A and 15 cases (48.4%) in the group B, without statistical difference. However, zidovudine use was significantly frequent in the group A (64.7% vs. 35.5%,  $p = 0.049$ ) (Table 2).

In the multivariate analysis, no significant association between age, BMI, CD4<sup>+</sup> count, ART regimen, and IR was seen (Table 3).

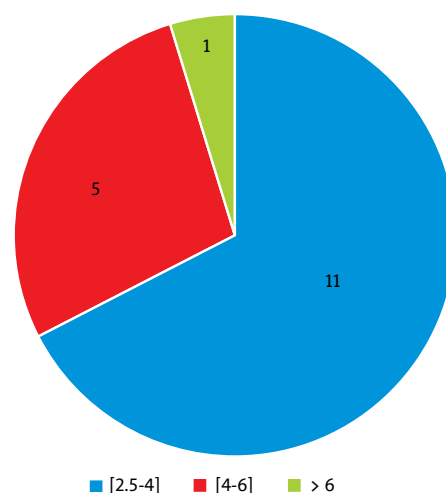
## Discussion

IR is a major health concern. It usually occurs due to reduced insulin sensitivity in peripheral tissues, specifically skeletal muscle and adipose tissue, and is associated with obesity and future development of diabetes. Also, IR is associated with an increased risk of cardiovascular events and death [7, 8]. The hyperinsulinemic-euglycemic clamps procedure, originally described in 1979, is considered the gold standard for determining whole-body insulin sensitivity [9, 10]. However, it remains an expensive and invasive procedure. Indirect methods estimating the IR level have been used much more widely in clinical studies, including oral glucose tolerance testing and mathematical modeling, i.e., the homeostasis model assessment (HOMA) [11] and quantitative insulin sensitivity check index (QUICKI) [12]. Threshold values of HOMA-IR in a high metabolic risk population, have not been defined in the literature; they varied from 2 to 3.8, depending on race, gender, and even

**Table 1.** Characteristics of the study population

Characteristic	Result
<b>Epidemiological</b>	
Median age (years)	38.7
Male gender, <i>n</i> (%)	43 (64.2)
Alcohol use, <i>n</i> (%)	32 (47.8)
HCV co-infection, <i>n</i> (%)	8 (11.9)
<b>Clinical</b>	
Median duration of HIV diagnosis (years)	7
BMI (kg/m <sup>2</sup> )	24.3
<b>Biological</b>	
Blood glucose (mmol/l)	$4.77 \pm 0.94$
Total cholesterol (mmol/l)	$4.2 \pm 1.12$
HDL cholesterol (mmol/l)	1.15
Triglycerides (mmol/l)	$1.5 \pm 0.96$
Plasma insulin (mIU/l)	$13.21 \pm 6.9$
<b>Immuno-virological</b>	
CD4 <sup>+</sup> count (mm <sup>3</sup> )	443
Undetectable HIV viral load, <i>n</i> (%)	42 (62.9)
<b>Therapeutic</b>	
2 NRTIs + 1 NNRTIs, <i>n</i> (%)	36 (53.7)
2 NRTIs + 1 PI, <i>n</i> (%)	29 (43.3)
3 NRTIs, <i>n</i> (%)	2 (3.0)

HCV – hepatitis C virus, BMI – body mass index, HDL – high-density lipoprotein, NRTIs – nucleoside reverse transcriptase inhibitors, NNRTIs – non-nucleoside reverse transcriptase inhibitors, PI – protease inhibitor



**Figure 1.** Distribution of patients according to HOMA-IR

some pathologies [13–15]. In a Portuguese study with 1,784 non-diabetic patients with a BMI  $< 25$  kg/m<sup>2</sup> and a fasting blood glucose level  $< 1$  g/l, IR defined by HOMA-IR was  $\geq 2.33$  [16]. On the basis of these data, we opted for HOMA-IR threshold value of 2.4.

**Table 2.** Comparison of demographic, clinical, and therapeutic characteristics of PLHIV in 2 groups

Characteristics	Group A IR+ (n = 17)	Group B IR- (n = 31)	p-value
Demographic			
Mean age (years)	37.6	36.4	0.62
Sex (M/F)	10/7	22/9	0.39
Clinical			
Median duration of HIV diagnosis (years)	4	6.3	0.12
Co-infection, n (%)	2 (11.7)	2 (6.4)	0.52
BMI (kg/m <sup>2</sup> )	23.8	23.5	0.84
Immuno-virological			
CD4+ count < 200/mm <sup>3</sup> , n (%)	5 (29.4)	8 (25.8)	0.80
Detectable HIV viral load, n (%)	5 (29.4)	15 (48.4)	0.20
Therapeutic			
NNRTIs, n (%)	7 (41.2)	16 (51.6)	0.49
PI, n (%)	10 (58.8)	15 (48.4)	0.36
Zidovudine, n (%)	11 (64.7)	11 (35.5)	<b>0.049</b>
Tenofovir, n (%)	6 (35.3)	19 (61.3)	0.08

BMI – body mass index, NNRTIs – non-nucleoside reverse transcriptase inhibitors, PI – protease inhibitor

**Table 3.** Factors associated with insulin resistance

Factors	OR	IC	p-value
Age > 40 years	1.2	0.32-4.47	0.80
Evolution of HIV infection > 5 years	0.75	0.22-2.57	0.65
BMI ≥ 25 kg/m <sup>2</sup>	1.0	0.27-3.73	0.97
CD4+ count < 200/mm <sup>3</sup>	1.2	0.32-4.47	0.80
Detectable HIV viral load	0.44	0.12-1.56	0.20
PI regimen	0.52	0.52-5.74	0.36
Zidovudine	1.1	0.78-5.19	0.07

BMI – body mass index, PI – protease inhibitor

Abnormalities of insulin sensitivity are increasingly reported in HIV-infected populations. It may be related to effects of HIV as well as antiretroviral therapy. The prevalence of IR in our study was 44.7%. Recent estimates of IR prevalence among HIV-infected patients ranged from approximately 20% (defined as HOMA-IR ≥ 3.8) [17] to as high as 50% in Schulte-Hermann *et al.* study [18], where IR was defined as HOMA-IR > 2.

Several research revealed that IR was associated with advanced age and male gender [18, 19]. In the current study, BMI did not show any association with IR, while in Samaras *et al.* [20] and Noumegni *et al.* [21] studies, obesity was an independent risk factor for IR. Hepatitis C co-infection, which is seen frequently among HIV-infected persons, has also been shown to be a IR predictor in some studies [22, 23]. It could be explained by a facilitating effect of this infection on ART toxicity. In our current analysis, HCV co-infection

was not associated with a higher level of insulinemia. Boufassa *et al.* [24] and El Sader *et al.* [25] reported that lymphocyte CD4+ count < 200/mm<sup>3</sup> was associated with IR. This could be due to the chronic nature of inflammation, which seems to be an important underlying mechanism in the development of disturbed glucose metabolism [26]. In our study, there was no association found between these two variables. Also, no significant difference in HIV viral load in patients having IR compared with the control group was observed. Similar results were found in literature [24]. On the other hand in our study, the use of zidovudine was significantly higher in patients with IR, but there was no association between IR and PIs use. These results differ from previously reported [5, 22, 27]. Furthermore, the development of IR was considered primarily in PLHIV using PIs. Walli *et al.* [28] reported pathologic insulin sensitivity in a high percentage (61%) of PI users. Previously, it has been

shown that in HIV, PIs selectively and potentially decrease the intrinsic transport activity of the insulin regulated glucose transporter isoform GLUT4 [29], especially in older drugs of this class. However, such treatment was not taken by our participants, apart from ritonavir, which was used as a low-dose booster. Older ARVs from the class of NRTIs have also been associated with mitochondrial dysfunction, altered adipogenesis, impaired glucose transport, decreased uptake of fatty acids in adipose tissue, and impaired lipolysis [30]. In a D:A:D study [19], the exposure to stavudine, didanosine, and zidovudine was associated with an increased risk of IR and new-onset diabetes.

This study shows a high prevalence of IR in non-diabetic HIV-infected patients receiving ART, but this was not associated with epidemiological or clinical factors. The asymptomatic IR, responsible in the long-term for the occurrence of other serious metabolic disorders, is common among HIV-infected patients and cannot be predicted. Non-invasive estimates of IR appear to perform well in HIV-infected patients, but clinically relevant cutoffs are uncertain. In HIV-infected patients, IR is common; therefore, unified definitions and validated cutoffs to guide risk stratification and target prevention of IR will be critical. Since none of the parameters examined were associated with an increased risk of IR, we believe that screening for IR with HOMA-IR should be performed in all HIV-infected adults.

## Conclusions

As IR is an independent risk factor for cardiovascular disease, its presence should lead to full assessment and management of other cardiovascular risk factors potentially present, including formal exclusion of a diagnosis of diabetes mellitus. Given the increased risk of cardiovascular events observed in HIV-infected individuals, hypertension, obesity, dyslipidemia, and smoking status should be assessed and aggressively managed combined with IR control.

## Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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