

Incidence of and risk factors for insulin resistance in treatment-naïve HIV-infected patients 48 weeks after starting highly active antiretroviral therapy

Rosario Palacios¹, Nicolás Merchante², Juan Macías², Mercedes González¹, Jesús Castillo³, Josefa Ruiz¹, Manuel Márquez¹, Jesús Gómez-Mateos⁴, Juan A Pineda² and Jesús Santos^{1*}

¹Unidad de Enfermedades Infecciosas, Hosp. Virgen de la Victoria, Málaga, Spain

²Servicio de Medicina Interna, Unidad de Enfermedades Infecciosas, Hosp. Universitario de Valme, Sevilla, Spain

³Servicio de Análisis Clínicos, Hosp. Universitario de Valme, Sevilla, Spain

⁴Unidad de Enfermedades Infecciosas, Hosp. Universitario de Valme, Sevilla, Spain

*Corresponding author: Tel: +34 95 103 2594; Fax: +34 95 103 2593; E-mail: med000854@saludalia.com

Objectives: to assess the incidence and risk factors for insulin resistance (IR) in a cohort of naïve HIV-infected patients 48 weeks after starting highly active antiretroviral therapy (HAART).

Design: prospective, two centre, observational, cohort study.

Methods: One-hundred and thirty-seven patients who started HAART and maintained the same regimen for 48 weeks were included. IR was determined by the homeostasis model assessment (HOMA-IR) method. Individuals with a HOMA-IR value >3.8 were defined as insulin resistant. Independent associations with the development of IR at 48 weeks were evaluated.

Results: Seventeen (12.4%) individuals showed a HOMA-IR value >3.8 at baseline and were excluded for incidence analyses. Fifteen patients developed IR at 48 weeks of

HAART, giving an incidence of 13%. Independent predictors of the development of IR were indinavir exposure (β -coefficient 5.45, 95% confidence interval [CI] 1.30–22.8; $P=0.02$), and hepatitis C virus (HCV) antibody positivity (β -coefficient 5.22, 95% CI 1.34–20.33; $P=0.01$). The appearance of IR was associated with a higher BMI (β -coefficient 1.72 for each 2 kg/m² increase, 95% CI 1.54–1.94; $P=0.02$) and with the presence of lipodystrophy at 48 weeks (β -coefficient 5.59, 95% CI 1.45–21.5; $P=0.01$).

Conclusions: HAART induces the development of IR in previously naïve non-insulin-resistant HIV-infected individuals, with an incidence of 13% in the first year of therapy. Indinavir exposure, and HCV coinfection are associated with an increased risk of developing IR.

Introduction

Prolonged use of highly active antiretroviral therapy (HAART) is associated with the lipodystrophy syndrome, which includes abnormal fat redistribution, dyslipidaemia and glucose metabolism disorders [1,2]. Cross-sectional studies have reported a prevalence of diabetes mellitus (DM) of 2–7% among HIV-infected patients on HAART, and an additional 35% have impaired glucose tolerance [1–11]. Insulin resistance (IR) has been reported in 61% of HIV-infected patients treated with protease inhibitors (PIs) [12]. Prospective studies have estimated an incidence of DM in these patients of 1–14% [8,11,13–15]. However, less is known about the incidence of IR in naïve HIV-infected patients after starting HAART [16,17]. The development of glucose disorders in HIV-infected patients has been related with the use of certain antiretrovirals, mainly PIs, resulting in lipodystrophy,

traditional risk factors for DM, and chronic hepatitis C virus (HCV) infection. However, these data are from population-based studies [8–10,18–20] and the pathogenesis of these disorders remains to be defined [20,21]. Awareness of the incidence and risk factors for IR in these patients would aid in the prevention and management of glucose disorders. The aim of our study was to assess the incidence and risk factors for IR in a cohort of naïve HIV-infected patients 48 weeks after starting HAART.

Patients and methods

Setting and design

We undertook a prospective, observational study in two hospitals situated in southern Spain and which have a combined catchment population of 1 million people.

Patients

All HIV-infected patients from the two institutions who started HAART between June 2002 and June 2003 were screened for the study. HAART was composed of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or at least one PI, or it was composed of abacavir plus two other NRTIs. The indication for HAART and its regimen were left to the criteria of the patient's physician. All patients had to satisfy the following inclusion criteria: maintenance of the same antiretroviral regimen for 48 weeks, availability of frozen samples, and an adherence higher than 95%. Patients were excluded if they were pregnant, breast feeding, were current alcohol or illegal drug abusers, suffered from an acute opportunistic event, were taking drugs which could modify glucose metabolism, or had a prior diagnosis of DM. Patients who stopped HAART or switched from PIs to NNRTIs or *vice versa* during the study period were withdrawn.

All patients were informed about the nature of the study and all of them gave their informed consent for study participation. The study was approved by the Ethics Committee of one of the participating hospitals (Hosp de Valme, Seville).

Data collection

Clinical, anthropometrical and laboratory data were recorded at the start of HAART and at 48 weeks. Height was determined at baseline, and weight at baseline and at 48 weeks, and the body mass index (BMI) was calculated as weight (kg) divided by height (m²). Blood was drawn after a 12 h fast for the measurement of routine laboratory values, such as plasma lipids, glucose, creatinine, transaminases, CD4⁺ T cells and HIV RNA. Fasting samples of serum obtained after centrifugation were stored at -80°C until assayed. Serum insulin levels were measured by electrochemiluminescence immunoassay using an autoanalyser (Elecsys 1010/2010; Elecsys Modular Analytics E170; Roche, Basle, Switzerland). The homeostasis model assessment of IR (HOMA-IR) was calculated on the basis of fasting values of plasma glucose and insulin, according to the HOMA equation: HOMA-IR = fasting insulin (mIU/l) × fasting glucose (mmol/l) / 22.5 [23]. IR was defined as a HOMA value >3.8. This or similar values have been selected as the cut-off point to define IR in previous studies, as it represents the 90th percentile in white populations with low-risk for diabetes [24,25].

The presence of the lipodystrophy syndrome was defined according to the modified criteria of Carr *et al.* [26]. Clinical assessment involved self-reported fat loss from the face, buttock, arms and/or legs, or fat accumulation in the abdomen, parotid glands and/or breasts, confirmed by physical examination.

Table 1. Baseline characteristics of the 120 patients

Sex	
Male	91 (75.8)
Female	29 (24.2)
Age, years	38.2 (32.3–42.6)
BMI, kg/m ²	23.1 (20.5–25.0)
Smokers	69 (65.7)
Family history of diabetes*	16 (21.0)
HIV transmission category	
Intravenous drug use	41 (34.2)
Heterosexual	39 (32.5)
Homosexual	37 (30.8)
Estimated duration of HIV infection, months	58.3 (1.3–123.6)
AIDS	47 (39.2)
CD4 ⁺ T cells, cells/ μ l	222 (64–313)
Mean VL, log ₁₀	5.39 (4.67–5.22)
Chronic HCV infection	43 (36.4)

*This information was missing in 44 patients. Quantitative variables are expressed as mean (IQR), and categorical variables are expressed as *n* (%). BMI, body mass index; HCV, hepatitis C virus; VL, viral load.

Statistical analysis

Continuous variables were compared by the Student's *t*-test or the Mann-Whitney *U* test if they did not follow a normal distribution. Either the χ^2 test and Yates correction or Fisher's exact test was used to analyse the degree of association of categorical variables. The main outcome variable was the HOMA-IR value at 48 weeks of HAART, which was categorized as equal to or less than versus higher than 3.8. Factors included in the univariate analysis were sex, age, smoking, HCV serology, family history of DM, HIV transmission group (dichotomized as homosexual versus heterosexual versus intravenous drug use), duration of HIV infection, HIV clinical stage (dichotomized as AIDS versus non AIDS), type of antiretroviral therapy classified as PI-based regimen versus NNRTI-based regimen, each antiretroviral drug as an independent variable, values at baseline and at 48 weeks of BMI, lipid profile, and CD4⁺ T-cell count, and baseline HIV viral load. At 48 weeks, HIV viral load was categorized as undetectable (<50 copies/ml) or detectable, and lipodystrophy was also included dichotomized as present or not present. To assess the effect of independent variables on the diagnosis of IR, variables demonstrating a univariate association ($P < 0.05$) with the outcome variable were included in two logistic regression models: the first included baseline variables or risk factors for IR, and the second included IR related factors at 48 weeks. Patient data were collected in a computerized database for later statistical analysis with SPSS®, version 11.0 for Windows (Chicago, IL, USA).

Results

Features of the study patients

During the study period, HAART was started in 198 patients, of whom 137 fulfilled the inclusion criteria. Seventeen (12.4%) were excluded due to the presence of IR at entry. Thus, the analysis includes 120 patients who completed the follow-up. The baseline characteristics of these 120 patients are shown in Table 1. There were 43 HCV-positive patients, two of whom had a clinical diagnosis of cirrhosis. Thirty-two of the coinfecting patients had undergone a liver biopsy, and only one was diagnosed with cirrhosis. None of the HCV-coinfecting patients received antiviral therapy for HCV during the study period.

Incidence of insulin resistance

At 48 weeks the levels of glucose, insulin and HOMA-IR rose (Table 2). Fifteen patients developed IR, giving an incidence of 13%. In addition, 5 (3.6%) patients were diagnosed with DM (fasting glucose ≥ 126 mg/dl), three of whom also developed IR, and the other two had baseline IR.

Predictors of insulin resistance

Associations between baseline parameters and IR at 48 weeks are shown in Table 3. Those patients who developed IR had a higher percentage of positive HCV serology, and a higher exposure to indinavir (IDV). The baseline triglyceride levels were also higher in patients who developed IR, but this was not statistically significant in the multivariate analysis. There were no other clinical or demographic factors associated with IR. The duration of HIV infection, the stage of the disease, and the immunological parameters were similar in both groups of patients.

Factors associated with insulin resistance

Association between IR and other parameters at 48 weeks of follow-up are outlined in Table 4. Data on lipodystrophy were available in 113 cases, and it was present in 17 (15.0%) of them. The appearance of IR was associated with a higher BMI and with the presence of lipodystrophy at 48 weeks, with no differences between the type of fat redistribution. Those patients with IR also presented higher levels of triglycerides at 48 weeks compared with those patients without IR.

Discussion

We observed an increase in the HOMA-IR during the first year of HAART, leading to an incidence of IR among these HIV-infected patients of 13%. We found that risk factors for DM in the general population, such as chronic HCV infection, and HIV-related factors, such as the use of IDV, were independent predictors of the development of IR in our cohort.

Little is known about the causes of glucose metabolism disorders in HIV-infected patients on HAART, and several pathogenic mechanisms have been suggested [27,28]. The group of antiretrovirals most frequently involved in glucose metabolism disorders is PI [8,9,11,15,18,29,30–32]. In a case-control study [9], we found that duration of PI exposure was associated with the development of DM, and in a prospective study, Justman *et al.* [15] observed that PI use was associated with a threefold increase in DM. IDV is the PI most frequently involved in the appearance of IR in experimental studies [18,30–32]. Administration of IDV to healthy HIV-negative volunteers led to a reduction in insulin sensitivity with as little as a single dose [18]. PI directly inhibit the Glut4 isoform, which mediates the transport of glucose, thus decreasing insulin

Table 2. Comparison of the study variables at baseline and at 48 weeks

Variable	Baseline	48 weeks	P-value
BMI, kg	23.1 (20.5–25.0)	24.5 (21.5–26.4)	0.0001
Total cholesterol, mg/dl	151 (123–182)	192 (157–222)	0.0001
HDL cholesterol, mg/dl	34 (24–39)	47 (35–57)	0.0001
LDL cholesterol, mg/dl	91 (68–105)	114 (83–135)	0.0001
Triglycerides, mg/dl	132 (84–166)	163 (86–192)	0.005
Glucose, mg/dl	90 (81–98)	95 (86–101)	0.0001
Insulin, μ U/ml	7.24 (4.54–9.31)	10.15 (5.35–11.776)	0.002
HOMA-IR	1.61 (0.96–2.21)	2.53 (1.21–2.81)	0.002
CD4 ⁺ T cells, cells/ μ l	222 (64–313)	404 (228–524)	0.04
ND VL	0%	81.7%	0.0001

Quantitative variables are expressed as the mean (IQR). BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; ND VL, non-detectable viral load.

Table 3. Associations between IR and baseline parameters (predictive factors)

	Univariate			Multivariate		
	IR	No IR	P-value	β -Coefficient	(95% CI)	P-value
<i>n</i> (%)	15 (12.5)	105 (87.5)	–	–	–	–
Clinical and demographic						
Age	36.8 (31.6–40.7)	38.2 (32.3–43)	0.55	–	–	–
Male sex, %	86.6	75	0.51	–	–	–
HIV risk, %	–	–	0.46	–	–	–
Intravenous drug use	46.6	34	–	–	–	–
Heterosexual	40	31	–	–	–	–
Homosexual	13.3	32	–	–	–	–
Smokers, %	81.8	64	0.32	–	–	–
Family history of DM, %	6.6	14.2	1.0	–	–	–
HCV positivity, %	66.6	32.6	0.01	5.22	(1.34–20.33)	0.01
Genotype 1	28.5%	71.4%	–	–	–	–
Genotype 3	14.2%	85.7%	–	–	–	–
HCV VL, log ₁₀	6.50 (5.86–6.80)	6.58 (5.53–6.55)	0.81	–	–	–
Baseline BMI, kg/m ²	24.8 (21.1–26.9)	22.9 (20.6–24.9)	0.10	–	–	–
Baseline metabolic variables						
Glucose, mg/dl	94 (83–98)	89 (80–99)	0.20	–	–	–
Insulin, μ UI/ml	9.2 (7.0–12.5)	6.8 (4.2–9.0)	0.01	–	–	–
TC, mg/dl	158 (109–215)	152 (125–183)	0.69	–	–	–
LDL cholesterol, mg/dl	105 (72–148)	91 (70–105)	0.26	–	–	–
HDL cholesterol, mg/dl	38 (21–66)	34 (25–38)	0.56	–	–	–
Triglycerides, mg/dl	177 (95–193)	127 (84–165)	0.03	0.99	(0.98–1.001)	0.10
HIV disease						
Duration of HIV, months	90.2 (1.6–180,1)	54.3 (1.5–88)	0.15	–	–	–
AIDS, %	46.6	38	0.57	–	–	–
CD4 ⁺ T-cell nadir, cells/ μ l	202 (49–223)	182 (63–261)	0.65	–	–	–
Baseline HIV VL, log ₁₀	5.95 (4.87–5.78)	5.40 (4.35–5.46)	0.005	–	–	–
Antiretroviral therapy, <i>n</i> (%)						
NRTI						
Zidovudine	8 (53.3)	57 (54.2)	0.61	–	–	–
Lamivudine	14 (93.3)	88 (83.8)	0.46	–	–	–
Didanosine	5 (33.3)	40 (38.0)	0.77	–	–	–
Stavudine	2 (13.3)	12 (11.4)	0.58	–	–	–
Abacavir	1 (6.6)	11 (10.4)	0.51	–	–	–
Tenofovir	0	4 (3.8)	0.56	–	–	–
Triple NRTI	1 (6.6)	9 (8.5)	0.24	–	–	–
PI, global*						
Indinavir	5 (33.3)	11 (10.4)	0.03	5.45	(1.30–22.8)	0.02
Nelfinavir	1 (6.6)	16 (15.2)	0.46	–	–	–
Saquinavir	2 (13.3)	8 (7.6)	0.61	–	–	–
Lopinavir	2 (13.3)	9 (8.5)	0.63	–	–	–
NNRTI						
Nevirapine	0	18 (17.1)	0.05	–	–	–
Efavirenz	6 (40.0)	40 (38.0)	0.60	–	–	–

*In the IR group two patients received double protease inhibitors (PIs), three received ritonavir-boosted PIs, and three received non-boosted PIs. In the non-IR group, five patients received double PI, 14 ritonavir-boosted PIs, and 19 non-boosted PIs. Three non-IR patients received a PI (nelfinavir) plus a non-nucleoside reverse transcriptase inhibitors (NNRTI; nevirapine). Quantitative variables are expressed as the mean (interquartile range). BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HCV, hepatitis C virus; HDL, high-density lipoprotein; IR, insulin resistance; LDL, low-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TC, total cholesterol; VL, viral load.

glucose disposal [21,30–32], and also reducing pancreatic insulin secretion [22]. In our study, the use of PI as a group was not associated with IR, which could be

due to limited power of the study. We also explored the association of several specific PI with the risk of IR, and only IDV was significantly associated with an

Table 4. Associations between IR and other parameters at 48 weeks of follow-up (associated factors)

	Univariate			Multivariate		
	IR	No IR	P-value	β -Coefficient	95% CI	P-value
n (%)	15 (12.5)	105 (87.5)				
BMI, kg/m ²	27.1 (22–30)	24.2 (21.5–26.2)	0.02	1.72*	1.54–1.94	0.02
BMI increase	2.27 (0.1–4.6)	1.32 (-0.2–2.5)	0.22	–	–	–
CD4, cells/ μ l	479 (186–769)	387 (235–482)	0.17	–	–	–
CD4 change, cells/ μ l	243 (48–434)	166 (73–231)	0.09	–	–	–
Metabolic variables and reported changes in body shape						
Glucose, mg/dl	113 (93–119)	93 (85–99.7)	0.0001	–	–	–
Insulin, μ U/ml	27.6 (18.6–31.1)	7.5 (5.1–9.7)	0.0001	–	–	–
Total cholesterol, mg/dl	182 (143–227)	193 (157–223)	0.52	–	–	–
Total cholesterol change, mg/dl	26.5 (-7.0–66.5)	40.3 (11.0–61.5)	0.38	–	–	–
LDL cholesterol, mg/dl	92 (66–112)	115 (85–137)	0.09	–	–	–
LDL cholesterol change, mg/dl	-9.4 (-37.3–21.0)	23.0 (1.7–41.2)	0.01	–	–	–
HDL cholesterol, mg/dl	44 (38–48)	48 (35–59)	0.38	–	–	–
HDL cholesterol change, mg/dl	4.5 (-8.9–19.5)	14.0 (4.2–22.1)	0.17	–	–	–
Triglycerides, mg/dl	233 (99–309)	150 (84–172)	0.01	–	–	–
Triglycerides change, mg/dl	22.6 (-26.5–85.0)	23.9 (-33.0–51.0)	0.96	–	–	–
Lipodystrophy, %	5/14 (35.7)	12/99 (12.1)	0.03	5.59	1.45–21.5	0.01
Lipoatrophy	1 (20)	8 (66.6)	–	–	–	–
Lipohypertrophy	1 (20)	–	–	–	–	–
Mixed lipodystrophy	3 (60)	4 (33.3)	–	–	–	–

*For each 2 kg/m² increase. Quantitative variables are expressed as the mean (interquartile range). HDL, high-density lipoprotein; HOMA-IR, insulin resistance-homeostasis model assessment; IR, insulin resistance; LDL, low-density lipoprotein.

increased risk of this metabolic disorder. As far as we are aware, most prior studies analysing the effect of IDV on glucose metabolism have been experimental. The only longitudinal analysis to determine the influence of IDV on insulin sensitivity in HIV infected patients is that of Dubé MP *et al.* [33], which prospectively evaluated 11 individuals at 2 weeks after starting IDV monotherapy, and at another 6 weeks after starting IDV-based triple therapy, but potential weaknesses in this study include lack of a control group, the low number of patients and the short duration of follow-up. This, therefore, would be the largest clinical, longitudinal study to confirm the association between the use of IDV and the development of IR. We found no association between the development of IR and other antiretrovirals. Nevertheless, conclusions on single drugs and their contribution to the development of IR should be interpreted considering the overlap of treatment components, and that the study was not designed and powered enough to address the individual contribution of drugs to the development of IR.

IR is one of the components of the lipodystrophy syndrome associated with HIV infection and its treatment [1,5,6,8,19]. Increased visceral fat and lipoatrophy may contribute to altered glucose homeostasis [8,19,26,27,34,35]. In our cohort, 15.0% of the patients developed lipodystrophy during the first year

of HAART, and it was associated with the presence of IR. Those patients with any kind of abnormal body fat redistribution had a fivefold increase in IR compared with those who did not have this HAART-related adverse effect. Although it was not significant in the multivariate analysis, triglyceride levels at baseline and at 48 weeks were higher in patients with IR compared with patients without IR. This observation has also been reported by Yoon *et al.* [10], and it is consistent with data from the general population [36].

IR is a common condition in chronic hepatitis C [37,38]. In this sense, HCV infection seems to induce IR irrespective of liver cirrhosis is present in patients without HIV infection [39]. However, the role of HCV infection in the development of IR in HIV/HCV-coinfected patients has not been evaluated. In a large prospective cohort of HIV/HCV-coinfected patients [29], HCV infection was associated with a higher incidence of type 2 diabetes but IR was not studied. Only in a cross-sectional survey [40], HIV/HCV-coinfected patients showed higher values of HOMA-IR than HIV-monoinfected patients. This is the first longitudinal study to demonstrate that among HIV-infected patients IR appears more frequently in individuals with HCV antibody positivity. The relative importance of these phenomena in the evolution of liver disease remains unclear. Several studies suggest that IR is associated

with liver fibrosis progression in patients with chronic hepatitis C without HIV infection [39,41–44]. By contrast, IR was not associated with liver fibrosis progression in HIV/HCV-coinfected patients in a recent survey [45]. Finally, as cirrhosis itself is associated with impaired glucose tolerance and diabetes, and IR is a characteristic feature of cirrhosis [46], the role played by the degree of liver damage due to HCV infection in the association between HCV and IR must be considered. Cirrhosis was not included in the analysis, as a liver biopsy was not available for all the patients in our cohort.

This study has some limitations, mainly the short follow-up, the lack of control groups for comparison (HIV uninfected, HIV infected but not on HAART), and the lack of data regarding liver histology, and the lack of objective measurements of changes in fat distribution. Nevertheless, other aspects of the study need to be emphasized. First, although there are prospective data estimating the incidence of DM in HIV-infected patients [29], as far as we know this is the only prospective study to analyse the incidence of IR, which could aid identification of patients at risk for glucose disorders prior to the development of overt DM. In addition, all the patients were naïve at the time of entry to the study, and all maintained the same regimen during the follow-up. Thus, bias due to exposure to several different regimens is avoided. And finally, all blood samples were obtained after a 12 h overnight fast to avoid an overdiagnosis of dyslipidaemia and hyperglycaemia.

In summary, our findings show a high incidence of IR in HIV-infected patients after the first 48 weeks of HAART, and suggest an interrelation of genetic factors, treatment-related lipodystrophy, and liver injury in the pathogenesis of IR. Patients with a high BMI, with lipodystrophy and HCV coinfection should probably be more closely monitored for glucose metabolism disorders.

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