Moreira et al., HIV Curr Res 2016, 1:1
DOI: 10.4172/2572-0805.1000101

HIV: Current Research
ISSN: 2572-0805

Short Communication Open Access

# HIV-Positive Inflammatory Activity Monitoring Correlated to Peripheral Insulin Resistance - Hire Study

**Henrique Pires Moreira[1*], Débora Veras da Ponte[1], Ana Carolina dos Santos Araújo[1], André Pereira de Brito Neves1, Rebecca Santos Souza[1], Lean de Sousa Oliveira[1], Gabriel Dantas Sarubbi[1], Bruno Almeida Sampaio[1], Laís Gomes Neves[1], Luita Almeida da Silveira[1], Samuell Silva Soares[1], Fabrício de Maicy Bezerra[1,2], Huylmer Lucena Chaves[1] and Melissa Soares Medeiros[1,2,3]**

[1]*Centro Universitario Unichristus, Brazil*
[2]*Hospital São José de Doenças Infecciosas, Brazil*
[3]*Hospital Geral de Fortaleza - Fortaleza, Brazil*

**Abstract**

HIV-positive patients have an increased risk of hyperglycemia factors associated with inflammatory activity and antirretrovirals treatment, and this can directly impact in survival and life quality. This study proposed to evaluate impact and risk factors for insulin resistance in HIV patients. Total of 218 patients were included and we detected increase in glucose levels after HAART initiation (18.5% vs. 36.7%, p=0.0025). High fasting glucose levels were pointed as risk factor for symptomatic clinic during follow-up (RR=1.35; IC 95% 1,01-1,80; p=0.002), and higher monocyte/lymphocyte ratio was associated with hospitalization after treatment start (p=0.033).

**Keywords:** HIV; Glucose; Monocyte/lymphocyte ratio; Hospitalization

## Introduction

Peripheral Insulin resistance has been associated to abnormal body fat distribution, changes in lipid and carbohydrate metabolism, persistence of inflammatory system activation, and antiretroviral therapy [1-3]. Alterations in HIV patient's glycemic profile, as diabetes, activate inflammatory system, especially with higher viral load and prolonged symptomatic periods [4-6]. Antiretroviral therapy is associated with a significant increase in blood glucose levels by different pathways: increases peripheral insulin resistance modifying cellular insulin signaling or lipid metabolism, increases homocysteine levels, blocking glucose interfering with GLUT-4 transporter (protease inhibitors), or mitochondrial toxicity (nucleoside reverse transcriptase) [7-13]. Higher total cholesterol/HDL (Castelli Index 1) causes mitochondrial oxidative stress [14,15].

A study evidenced increases of 2.2 times in hospitalization rates in diabetic HIV patients, between 1994 and 2004 [16]. Brazil study evidenced an annual increase of 4.1% in diabetes prevalence of HIV infected patients [17]. Recently, Shikuma demonstrated a correlation between increased monocytes cells and peripheral insulin resistance in HIV patients [18,19]. It was observed decreases in T-$CD_4$ cells associated with increased monocytes [20]. Studies are evidencing a possible role of monocytes in chronic inflammatory pathophysiology [21].

Study is a multicenter retrospective cohort, including patients over 18 years, with previous diagnosis of HIV infection and followed up at Hospital Geral de Fortaleza (HGF) and Clínica Escola de Saúde (CES) at Unichristus Center University. The Epi Info software 3.5.1 was used for statistical analysis.

## Results and Discussion

Total of 218 patients were included and 161 (73.9%) male. Mean age was 37.6 ± 11.4 years. Time of follow-up median was 21 months. Arterial Hypertension prevalence before HIV diagnosis was 10.6% (N=23), diabetes mellitus 2.8% (N=6) and dyslipidemia 4.1% (N=9). Final follow-up evidenced 18 patients (8.3%) symptomatic (diarrhea 44.4% and syphilis 38.9%). During monitoring period, were detected 30 patients (13.8%) requiring hospitalization, and 1.8% admitted more than once. Causes of hospitalization were neurotoxoplasmosis (11 admissions - 36.6%), bacterial pneumonia, pulmonary tuberculosis and multifocal leukoencephalopathy, each with 3 admissions (10%). Tenofovir associated to Efavirenz and Lamivudine was started in 62.9%.

Before ARV therapy, 18.6% patients had blood glucose above 100 mg/dL. After ARV, prevalence increased to 36.7% (12 months), 44.3% (26 months) and 45.9% (33 months), ($p$=0.0025).

Higher glucose levels above 100 mg/dL before antiretroviral therapy was considered a risk factor for symptoms related to HIV at final follow-up (RR=1.35, 95% CI: 1.01 to 1.80, p=0.002). There was a positive correlation between lower monocytes/lymphocytes ratio and no admission related to HIV (p=0.01). ART Therapy is essential for infected patients survival, but it contributes as risk factors for diabetes and cardiovascular diseases [22-26]. Monocytes/lymphocyte ratio could be used as inflammatory activation biomarker for monitoring, and signalizing as risk for hospitalization (Table 1).

Monocytes/lymphocytes ratio was controlled in hyperglycemic group after start ARV, evidencing immunology control of inflammation related to blood glucose. Most patients had a suppressed viral load in final follow-up (97.3%), witch could not be implicated in hospital admission. Elevated monocytes levels in HIV patients are associated with pro-inflammatory mediators production and immune alterations [27,28]. It described an immune system deregulation evidenced by reduced $CD_{4+}$ T cells associated with increased number of monocytes. However, this was not observed in present study, since monocytes increased during follow-up as T-$CD_4$ cells. We also detected unchanged T-$CD_8$ cells account, suggesting others possible uncontrolled inflammatory components involved in our population, which must be studied in future.

***Corresponding author:** Moreira HP, Centro Universitario Unichristus, Brazil, Tel: +(21) 2493-24; E-mail: henriquepm_@hotmail.com

**Received** May 21, 2016; **Accepted** May 31, 2016; **Published** June 07, 2016

**Citation:** Moreira HP, da Ponte DV, Araújo ACDS, de Brito Neves AP, Souza RS, et al. (2016) HIV-Positive Inflammatory Activity Monitoring Correlated to Peripheral Insulin Resistance - Hire Study. HIV Curr Res 1: 101. doi:10.4172/2572-0805.1000101

| | Normoglycemic (<100 mg/dL) | Hyperglycemic (≥100 mg/dL) | *P* |
|---|---|---|---|
| Mean age (years) | 34.5 | 43.2 | 0.003 |
| Mean CD4+ b-ART | 422 | 318 | 0.286 |
| Mean CD4+ a-ART (1st test) | 518 | 489 | 0.830 |
| Mean CD4+ a-ART (2nd test) | 596 | 548 | 0.213 |
| Mean CD4+ a-ART (3rd test) | 548 | 510 | 0.532 |
| Mean CD4+ a-ART (4th test) | 571 | 583 | 0.975 |
| Castelli index b-ART | 4.48 | 4.78 | 0.377 |
| Castelli index a-ART (1st test) | 4.58 | 5.27 | **0.013** |
| Castelli index a-ART (2nd test) | 4.86 | 5.60 | 0.129 |
| Castelli index a-ART (3rd test) | 5.12 | 5.58 | 0.448 |
| Mean monocytes b-ART | 398 | 395.7 | 0.701 |
| Mean monocytes a-ART (1st test) | 453.2 | 376.5 | 0.057 |
| Mean monocytes a-ART (2nd test) | 484.8 | 418 | **0.041** |
| Mean monocytes a-ART (3rd test) | 432.6 | 506.7 | 0.217 |
| Mean monocytes a-ART (4th test) | 491.1 | 408.2 | 0.624 |
| Mean CD4/CD8 b-ART | 0.43 | 0.27 | **0.024** |
| Mean CD4/CD8 a-ART (1st test) | 0.54 | 0.45 | 0.410 |
| Mean CD4/CD8 a-ART (2nd test) | 0.66 | 0.55 | 0.253 |
| Mean CD4/CD8 a-ART (3rd test) | 0.64 | 0.59 | 0.245 |
| Mean CD4/CD8 a-ART (4th test) | 0.69 | 0.61 | 0.282 |
| **Note**: *b-ARV: before ARV, a-ARV: after ARV; There was significant correlation between CD4/CD8 ratio and blood glucose before ARV use. Normal blood glucose levels after ART are associated with lower Castelli Index (4.58 vs. 5.27, *p*=0.013). Elevated blood glucose was more prevalent in older persons before ARV (p=0.003). | | | |

**Table 1:** Correlation blood glucose, lipid profile and immunology/virology data from HIV patients during follow-up.

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