



# 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

25–28 October 2004 - Washington, DC, USA

## ANTIRETROVIRAL THERAPY AND MARKERS OF INSULIN RESISTANCE IN THE MULTICENTER AIDS COHORT STUDY

*Antiviral Therapy* 2004; 9(6):L8 (abstract no. 10)

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**BACKGROUND:** Surrogate markers have not been used to estimate insulin resistance in a large cohort of HIV-infected individuals with direct comparison with HIV-seronegative controls.

**METHODS:** 533 HIV-infected and 755 HIV-seronegative men in the Multicenter AIDS Cohort Study were examined at 6-month intervals between 1999 and 2003. Fasting serum measurements, antiretroviral therapy (ART) history, demographics and clinical variables were collected at each visit. ART exposure was quantified in two ways. Firstly, recent exposure was assessed by stratifying men by ART in the preceding 6 months, that is, no ART, mono-combo ART, highly active antiretroviral therapy (HAART) without a protease inhibitor (PI) and HAART with a PI. Secondly, cumulative exposure was determined for the three major ART classes: nucleoside analogues (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs. Individual medications within each class were also investigated. Two markers of insulin resistance were used as the primary outcome variables and assessed with reference to the HIV-seronegative men: QUICKI [ $1/(\log\text{Glucose} + \log\text{Insulin})$ ] and fasting hyperinsulinaemia (insulin  $>15$   $\mu\text{U/ml}$ ). Analyses were adjusted for age, body mass index, race, nadir CD4 cell count, hepatitis C serostatus and family history of diabetes mellitus.

**RESULTS:** Each of the HIV-infected groups had higher odds of fasting hyperinsulinaemia and lower mean QUICKI compared with the HIV-seronegative men. Cumulative exposure to NRTIs had the most consistent effect, with each additional year of exposure associated with an increased odds of hyperinsulinaemia (OR=1.1, 95% CI:

1.1, 1.2) and a lower QUICKI ( $-0.06$ , 95% CI:  $-0.09$ ,  $-0.04$ ). Cumulative exposure to PIs was associated with an increased odds of hyperinsulinaemia (OR per additional year of PI exposure= $1.1$ , 95% CI:  $1.0$ ,  $1.1$ ), but a less apparent difference in mean QUICKI ( $-0.01$  per additional year of PI exposure, 95% CI:  $-0.05$ ,  $0.02$ ). Of the individual medications examined, stavudine was associated with the highest risk of hyperinsulinaemia (OR= $1.2$ , 95% CI:  $1.2$ ,  $1.3$ ).

**CONCLUSIONS:** Fasting surrogate markers suggest increased insulin resistance in HIV-infected men which is independently related to both NRTI and PI exposure.

2004-10-25  
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