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EFFECT OF INITIATION OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON INSULIN SENSITIVITY, AUTONOMIC NERVOUS SYSTEM FUNCTION AND BETA-ADRENERGIC MEDIATED LIPOLYSIS

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DN Reeds¹, M Al-Lozi¹, WT Cade¹, BW Patterson¹, WG Powderly², KE Yarasheski¹ and S Klein¹

¹Washington University School of Medicine, St Louis, MO, USA; ²University College School of Medicine and Medical Science, Dublin, Ireland

OBJECTIVES: HIV-associated metabolic syndrome is associated with insulin resistance, increased plasma norepinephrine concentration, increased sympathetic nervous system (SNS) activity and increased basal lipolytic rates. However, it is not known whether these abnormalities are caused by highly active antiretroviral therapy (HAART) itself or are related to treatment-related changes in body fat distribution, and whether the increase in lipolysis is due to an increase in sympathetic nervous system (SNS) activity. Accordingly, we evaluated the hypothesis that short-term treatment with HAART alters autonomic nervous system activity, insulin sensitivity and β -cell function, basal lipolytic rates and the contribution of β -adrenergic activity to lipolysis in treatment-naïve people with HIV infection.

METHODS: We measured body composition using DEXA, insulin sensitivity and disposition index (a measure of pancreatic β -cell function) using 5-h oral glucose tolerance testing with minimal modelling, lipolytic rate by infusing stable isotopically labelled [²H₂]palmitate and [²H₅]glycerol before and during 60 min of propranolol infusion and autonomic nervous system activity (plasma norepinephrine concentration [index of SNS activity], sympathetic skin response [index of SNS responsiveness] and heart-rate variability [index of cardiovagal parasympathetic tone]) in 10 asymptomatic, treatment-naïve patients with HIV infection (8 men, 4 African-American, age 32 \pm 3 years). Measurements were repeated after 4 months of HAART (six atazanavir/ritonavir, two lopinavir/ritonavir and two efavirenz-based).

RESULTS: HAART increased CD4⁺ T-cell count (371 \pm 24 versus 512 \pm 62 cells/mm³, $P < 0.04$), body mass index (26.3 \pm 1.5 versus 27.2 \pm 1.7 kg/m², $P = 0.02$) and trunk fat (9.1 \pm 2.0 versus 9.8 \pm 2.2 kg, $P = 0.05$). Insulin sensitivity declined (6.6 \pm 1.9 to 4.8 \pm 0.8 $\times 10^{-5}$ dl/kg/min, $P < 0.05$), but disposition index

remained unchanged (7.85 ± 1.3 versus $9.0 \pm 0.5 \times 10^{-15}$ dl/kg/min²/pmol/l). Plasma norepinephrine concentration (184 ± 27 versus 141 ± 12 pg/ml), palmitate rate of appearance (R_a ; 1.7 ± 0.2 versus 1.6 ± 0.2 μ mol/ kgFFM/min), glycerol R_a (3.1 ± 0.3 versus 3.0 ± 0.3 μ mol/ kgFFM/min) and propranolol suppression of palmitate R_a ($18.8 \pm 4.7\%$ versus HAART $17.7 \pm 5.3\%$) or glycerol R_a (pre $17.6 \pm 4.6\%$ versus post $19.7 \pm 4.7\%$) did not change with HAART. Basal heart rate variability was not affected by HAART ($16 \pm 3\%$ versus $18 \pm 2\%$). Sympathetic skin response amplitude declined markedly ($3,127 \pm 603$ versus 495 ± 62 mA, $P < 0.02$) with HAART, but latency was unchanged ($1,182 \pm 112$ versus $1,152 \pm 98$ ms).

CONCLUSIONS: Short-term HAART causes insulin resistance, but does not affect basal lipolytic rates or the contribution of β -adrenergic activity to lipolysis. In addition, HAART does not affect sympathetic or parasympathetic nervous system activity, but impairs SNS responsiveness. These data demonstrate that HAART likely causes insulin resistance in skeletal muscle, but not adipose tissue. The mechanisms responsible for these metabolic effects are not known, but it does not involve changes in autonomic nervous system activity.

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