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THE IMPACT OF NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI) TREATMENT DURATION AND INSULIN RESISTANCE ON FASTING ARTERIALIZED LACTATE LEVELS IN PATIENTS WITH HIV INFECTION

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Treatment with NRTIs is associated with hyperlactataemia, presumably mediated by NRTI inhibition of mitochondrial-DNA replication (mitochondrial toxicity). The cumulative effect of NRTI treatment could impair oxidative glucose metabolism, favouring glycolysis and lactate production. We examined the association of NRTI treatment duration and plasma lactate levels in HIV-positive patients.

METHODS: Fasting arterialized venous samples (10-min handwarming, 55°C) were obtained in HIV-infected outpatients in whom detailed antiretroviral histories were available. Plasma lactate, glucose, pO₂, serum insulin, ALT and CD4 were measured. Insulin resistance was estimated by HOMA-IR. Percent body fat was measured by DEXA. We examined the independent association of cumulative NRTI use and lactate levels using multivariable linear regression.

RESULTS: 95 participants had adequate venous arterialization (PO₂ >55 mmHg). Mean age was 44.4 ± 8.3 years; 90% were men; 95% had NRTI exposure [median 5.6 years, interquartile range (IQR) 4.3–9.6]; and 83% were currently on NRTIs. Arterialized lactate levels averaged 1.24 ± 0.46 mmol/l (range 0.53–2.72). Median HOMA-IR was 3.37 (IQR 2.24–4.63). Only two had ALT >100 mg/dl. Longer duration of NRTI use was associated with a small but significant increase in lactate in univariate analyses (0.047 mmol/l increase per year of NRTI use, *P* < 0.01), and remained so after adjusting for current NRTI use. Female sex, percent body fat, PI treatment duration and HOMA-IR were also associated with lactate level in univariate analyses, while fasting glucose, ALT and CD4 were not. After adjustment for age, sex, diabetes, percent fat and PI duration, increasing duration of NRTI therapy remained significantly associated with lactate level

(0.035 mmol/l increase/year NRTI, $P=0.04$). Alternatively, d4T duration or current use of d4T/ddI was not. Notably, when we added HOMA-IR to the above adjusted model, the relation between NRTI duration and lactate was attenuated and no longer significant (0.024 mmol/l increase/year NRTI, $P=0.14$), while HOMA-IR was significantly associated with lactate level ($P<0.01$). NRTI duration was also associated with HOMA-IR after adjusting for age, sex, percent fat and diabetes ($P=0.03$).

CONCLUSION: Increasing duration of NRTI use is associated with higher lactate levels that may be mediated, in part, through increasing insulin resistance.

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