Insulin resistance and type 2 diabetes are increasingly recognized as a consequence of antiretroviral therapy for HIV infection [1]. In a recent study, HIV-infected men receiving antiretroviral therapy were found to have a >4-fold increased rate of type 2 diabetes, compared with healthy control subjects [1]. Diabetes was also identified as an independent risk factor associated with the development of cardiovascular disease in a large, multinational prospective cohort of HIV-infected patients [2]. Therefore, recognition and management of diabetes and insulin resistance among HIV-infected patients is crucial for long-term health maintenance in this patient population. Although much research has been conducted to identify the etiology of insulin resistance and diabetes in HIV-infected patients [3–6], and although evidence suggests that it is likely to be multifactorial in nature, further work is needed to better understand the mechanisms of, to treat, and to prevent insulin resistance and diabetes in patients with HIV infection.

The present study conducted by Lo et al. [7] provides useful new data on the relationship between cumulative exposure to nucleoside reverse-transcriptase inhibitors (NRTIs), insulin resistance, and plasma lactate levels. In this report involving 95 HIV-infected patients (90% of whom were men, and 96% of whom were antiretroviral experienced), duration of NRTI therapy was positively correlated with lactate levels and was also associated with insulin resistance, as evaluated by the homeostatic model for assessment of insulin resistance. Other factors noted to be associated with elevated lactate levels were a decreased percentage of body fat, age, and duration of protease inhibitor therapy.

Although the present study is cross-sectional and cannot attribute causality to the observed associations, it identifies an interesting and potentially important link between lactate levels and insulin resistance. Indeed, in a multivariate analysis controlling for potential confounders, insulin resistance (as evaluated by the homeostatic model for assessment of insulin resistance) and not duration of NRTI therapy was significantly associated with lactate levels. Lo et al. [7] postulate that elevated lactate levels may directly influence insulin sensitivity, and this may be one mechanism by which NRTI exposure leads to insulin resistance. Indeed, cross-sectional studies among obese, non–HIV-infected individuals have also shown similar correlations between insulin sensitivity and baseline lactate levels [8]. Furthermore, in animal studies, direct administration of lactate led to impaired insulin-stimulated glucose uptake into muscle as a result of acute suppression of glycolysis, as well as inhibition of downstream insulin receptor substrate signaling, without any effect on glucose transporter 4 (GLUT4) [9]. On the basis of these observations and the observations made in Lo et al. [7], chronic low-grade elevations in lactate level as a consequence of NRTI exposure may contribute significantly to insulin resistance in HIV-infected patients.

The possibility remains that the effects of NRTI therapy on adipose tissue may also be important in the etiology of insulin resistance in patients with HIV infection. Furthermore, adipose-derived lactate may also be playing a role. Peripheral lipodystrophy is a recognized complication of NRTI therapy [10, 11] that may be due to mitochondrial dysfunction affecting lipid metabolism in adipocytes [12]. Several studies have demonstrated a direct association between decreased limb fat and insulin resistance in HIV-infected patients with lipodystrophy [4, 13]. Lo et al. [7] do not provide estimates of limb fat per se, but total percentage of body fat (as a surrogate marker for peripheral lipodystrophy) was inversely associated with lactate levels and duration of NRTI exposure. Increased exposure to NRTI therapy may therefore lead to fat atrophy, as well as to
increased lactate levels, which, independently or in combination, may directly contribute to impaired insulin sensitivity. Of note, oxidative stress can result in decreased adiponectin expression and increased lactate production in 3T3 L1 adipocytes [14]. Mitochondrial dysfunction associated with NRTI use may create oxidative stress and subsequent increases in lactate production from adipose tissue in patients with HIV infection and thereby contribute to insulin resistance. However, adiponectin has also been identified as a factor associated with insulin sensitivity in patients with HIV infection. In vitro exposure of adipocytes to NRTIs decreases adiponectin levels and alters lipid metabolism [15], and several studies have demonstrated a strong relationship between limb fat atrophy, decreased serum adiponectin levels, and insulin resistance in patients with HIV infection [16, 17]. Oxidative stress and/or mitochondrial insult from NRTI exposure may represent a common pathway for increased lactate levels and decreased adiponectin from adipocytes, which ultimately results in insulin resistance in patients with HIV infection who are receiving antiretroviral therapy.

Of interest, in Lo et al. [7], the cumulative duration of NRTI therapy was more predictive of lactate levels than was the presence or absence of current NRTI exposure. This observation may be limited by the relatively small number of subjects who were not currently receiving an NRTI (only 6 of 95 subjects were not currently receiving an NRTI). However, if this finding is reproducible in a larger cohort, it has important implications for the long-term consequences of NRTI exposure, and future studies assessing the possible reversibility of these effects and evaluating the differential effects of thymidine analogues and NRTI-sparing regimens on lactate levels and insulin resistance are needed.

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**References**