

HIV Therapy and Diabetes Risk

The use of combination antiretroviral therapy (cART) has yielded dramatic clinical benefits for individuals with HIV infection. Benefits include suppression of viral load, improvement in CD4 lymphocyte counts, decrease in the number of opportunistic infections and length of hospital stay, and reduction in AIDS-related mortality (1,2). These advantages have come at the price of increased incidence of unanticipated adverse metabolic effects, including insulin resistance, diabetes, dyslipidemia, and lipodystrophy (2). The clinical presentation of antiretroviral-associated diabetes is consistent with that of type 2 diabetes, and evidence of islet autoimmunity is distinctly uncommon in patients with antiretroviral-associated diabetes (3). Early studies fostered the understanding that inclusion of HIV-1 protease inhibitors most likely accounts for the adverse metabolic effects. The association between protease inhibitors and diabetes was further strengthened by studies showing that switching patients to other regimens improved the hyperglycemia and hyperlipidemia observed during use of protease inhibitor-containing regimens. Focusing almost exclusively on the role of protease inhibitors, elegant studies demonstrated the rapid development of insulin resistance and concurrent impairment of insulin secretion following exposure to these agents (4). The mechanism of insulin resistance appears to involve interference with glucose transport: photo-affinity labeling has demonstrated binding of sequences within the common peptidomimetic core of HIV protease inhibitors to the major glucose transporter (GLUT4) (5). The risk factors for insulin resistance and diabetes in patients with HIV infection treated with protease inhibitors include positive family history of diabetes, weight gain, lipodystrophy, older age, and coinfection with hepatitis C (2).

Shifting the focus away from protease inhibitors, De Wit et al. (6), in this issue of *Diabetes Care*, report that the nucleoside analogs (reverse transcriptase inhibitors) stavudine, zidovudine, and didanosine were associated with significantly higher risk of incident diabetes during long-term follow-up than were other agents, includ-

ing protease inhibitors. The increased risk persisted after adjustment for several diabetes risk factors, suggesting a possible direct effect of the nucleoside analogs on glucoregulation. Exposure to stavudine conferred the greatest risk for incident diabetes (adjusted relative risk per year of exposure 1.19 [95% CI 1.15–1.24]). The data analyzed by De Wit et al. (6) derive from a large international prospective study comprised of 33,389 HIV-infected patients who were being followed up for incident diabetes. The database included more than 130,151 person-years of follow-up, and the diabetes end point was rigorously defined and ascertained. Emerging data link nucleoside analogs to insulin resistance, lipodystrophy, and mitochondrial dysfunction (7), thus providing putative mechanisms for the development of diabetes.

Curiously, De Wit et al. report that their data exonerate cumulative exposure to HIV protease inhibitors as a risk factor for incident diabetes. Historically, the nucleoside analogs were among the first agents to be deployed in antiretroviral pharmacotherapy, whereas the protease inhibitors have had the most florid associations with diabetes risk. Given their long presence in the field, any major diabetes risk from nucleoside analogs should have become evident long before now. The fact that such has not been the case is indeed puzzling. The authors make the distinction that protease inhibitors confer acute metabolic risks, whereas the nucleoside analogs confer cumulative risks. Although that may well be so, there are currently no long-term follow-up data on treatment-emergent diabetes for the different antiretroviral drug classes. Rather than positing an all-or-none phenomenon, it is more likely that different components of cART regimens might confer individual or additive risks that could trigger acute or cumulative diabetes events in the genetically predisposed. Indeed, the authors admitted that current exposure to the HIV protease inhibitor indinavir was an additional risk factor for diabetes among their study population (6).

As with all association studies, the present by De Wit et al. does not prove causality in relation to stavudine or any of

the other thymidine analogs. Moreover, treatment substitutions or interruptions for gastrointestinal, hematological, or other adverse effects are not accounted for in their analysis. Finally, the risk of type 2 diabetes (even in the HIV-infected population) remains driven predominantly by genetic predisposition (3). Unfortunately, information on family history of diabetes does not seem to have been systematically collected and included in the cohort analyses. Nonetheless, it is reassuring that the estimate for incident diabetes observed by De Wit et al. (5.72 cases per 1,000 person-years) is much lower than previous estimates from smaller studies (17–47 per 1,000 person-years) (8). Clearly, physicians who treat patients with HIV-AIDS need to be alert to the adverse metabolic effects of the expanding antiretroviral armamentarium. Furthermore, as a result of the efficacy of cART and improved nutritional status, many HIV-infected patients in remission experience significant weight gain, which is an additional risk factor for insulin resistance, diabetes, and dyslipidemia.

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Abbreviations: cART, combination antiretroviral therapy.

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References

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Achman DJ, Holmberg SD, HIV Outpatient Study Investigators: Declining morbidity and mortality among patients with advanced immunodeficiency virus infection. *N Engl J Med* 338:853–860, 1998
2. Dagogo-Jack S: New drugs and diabetes risk: antipsychotic and antiretroviral agents. In *Clinical Diabetes*. Fonseca VA, Ed. Philadelphia, Saunders, 2006, p. 569–581
3. Yarasheski KE, Tebas P, Sigmund C, Dagogo-Jack S, Bohrer A, Turk J, Halban P, Cryer PE, Powderly WG: Insulin resistance in HIV protease inhibitor-associated

- diabetes. *J Acquir Immune Defic Syndr* 21: 209–216, 1999
4. Schütt M, Zhou J, Meier M, Klein HH: Long-term effects of HIV-1 protease inhibitors on insulin secretion and insulin signaling in INS-1 beta cells. *J Endocrinol* 183:445–454, 2004
 5. Hertel J, Struthers H, Horj CB, Hruz PW: A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem* 279:55147–55152, 2004
 6. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, El-Sadr W, d'Arminio Monforte A, Fontas E, Law MG, Friis-Møller N, Lundgren JD: Incidence and risk factors for new-onset diabetes in HIV-infected patients: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *Diabetes Care* 31: XXX–XXX, 2008
 7. Fleischman A, Johnsen S, Systrom DM, Hrovat M, Farrar CT, Frontera W, Fitch K, Thomas BJ, Torriani M, Cote HC, Grinspoon SK: Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults. *Am J Physiol Endocrinol Metab* 292:E1666–E1673, 2007
 8. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, Visscher BR, Margolick JB, Dobs AS: Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med* 165:1179–1184, 2005