

In Brief

For patients with diabetes, the additional diagnosis of HIV increases the challenge of self-care management. However, in patients with HIV who develop hyperglycemia, the added responsibilities can be overwhelming. This article describes the research studies that link treatment of HIV with the development of diabetes and offers suggestions for screening patients with HIV for diabetes.

Hyperglycemia in HIV/AIDS

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For the past 20 years or more, researchers and clinicians have reported changes in glucose homeostasis in patients with HIV/AIDS. First noted in the population of patients who received pentamidine isothionate for the prevention and treatment of *Pneumocystis carinii* pneumonia, the possible etiologies for the disruption of glucose metabolism in those with HIV/AIDS continues to be a topic of discussion among infectious disease and endocrine physicians.

Effects of HIV on Glucose Homeostasis

Early articles reported that clinically stable, symptomatic HIV-infected men who were subjects in euglycemic clamp studies had higher rates of insulin clearance and increased insulin sensitivity in peripheral tissues compared with the noninfected control group.¹ The increase in non-insulin-mediated glucose uptake seen in those infected with HIV has been accounted for by an increase in nonoxidative glucose disposal.²⁻⁴ Glucose production from the liver tends to increase, but glucose cycling does not change.^{1,2} Although there are many studies linking the use of protease inhibitors (PIs) to the development of insulin resistance, there is also evidence suggesting that insulin resistance may have an HIV disease-associated component as well.⁵

Changes in Glucose Homeostasis Associated With Medication Therapy Used to prevent and treat *P. carinii*-associated pneumonia, pentamidine given by inhalation or intravenously was found to cause β -cell toxicity in a subset of patients. Initially, these patients had symptoms of acute hypoglycemia, followed by a later onset of diabetes.⁶ Factors associated with increased incidence of hypoglycemia included longer duration of pentamidine treatment, higher cumulative doses, and renal insufficiency.^{7,8} Of the patients with hypoglycemia, a small group progressed to hyperglycemia. This group also had low C-peptide levels, suggestive of significant β -cell destruction.

Megesterol acetate, used as an appetite stimulant in cachectic AIDS patients, has an intrinsic glucocorticoid-like activity that predisposed a small number of patients to hyperglycemia. Increased caloric intake and weight gain associated with the use of the drug also may have played a role in the development of diabetes.⁹

More recently, the medical records of 1,392 HIV-infected adult patients were reviewed for cases of severe hyperglycemia, defined as two or more serum values of > 250 mg/dl or diabetes treatment during clinical care. Seven patients from this group developed hyperglycemia when megesterol was started or increased.

Hyperglycemia resolved with discontinuation of the drug and recurred after megestrol was reinstated.¹⁰

Development of Hyperglycemia With the Use of PIs

HIV infection is characterized by an immunodeficient state caused by active replication of the virus. To achieve the treatment goal of maximum suppression of viral replication, clinicians use a combination therapy consisting of nucleoside reverse transcriptase inhibitors (NRTIs) and HIV-1 PIs. Commonly known as highly active antiretroviral therapy (HAART), this therapy has had success in substantially reducing viral load, slowing HIV replication, increasing CD4 lymphocyte numbers, and reducing the incidence of opportunistic infections.¹¹

Reports of insulin resistance and the development of overt diabetes increased with the routine clinical use of HIV-1 PIs. This led to the supposition that the use of this class of drugs induced hyperglycemia. Carr et al.¹² found a 7% incidence of new-onset diabetes as diagnosed by a 2-hour blood glucose value > 200 mg/dl after administration of an oral glucose tolerance test (OGTT). The incidence of diabetes was reduced to 3.3% in a study that used a random blood glucose level of ≥ 180 mg/dl as the cut point for diabetes diagnosis.⁵ A more recent analysis conducted in the Multicenter AIDS Cohort Study¹³ places the incidence of diabetes in HIV-infected men with HAART exposure at four times greater than that of HIV-seronegative men.

When PIs are discontinued or replaced with another class of medication, glucose values normalize and hyperglycemia reverses, further indicating that PIs have a role in the pathogenesis of diabetes.¹⁴ Although peripheral insulin resistance contributes to this complication, the mechanism is not completely understood.¹⁵

The Washington University Medical School conducted a study¹⁶ to determine the mechanism underlying the hyperglycemia associated with PI use. The question: Was absolute insulin deficiency or insulin resistance with relative insulin deficiency and elevated BMI contributing to HIV PI-associated diabetes? The researchers concluded that the pathogenesis of the HIV PI-associated diabetes involved peripheral insulin resistance with insulin deficiency relative to hyperglucagonemia and a high BMI, appearing more like

that of non-insulin-dependent type 2 diabetes.

The results of the study showed higher concentrations of C-peptide; circulating concentrations of insulin, proinsulin, and glucagon; and an increased proinsulin-to-insulin ratio in the hyperglycemic HIV-positive subjects. GAD antibody titers were not consistent with the autoimmune β -cell destruction usually seen in newly diagnosed type 1 diabetes. All patients had received the PI drug indinavir. In vitro, indinavir did not inhibit proinsulin-to-insulin conversion or impair glucose-induced secretion of insulin and C-peptide from the β -cells of rats.¹⁶

Indinavir has been associated with insulin resistance, glucose intolerance, and overt diabetes. However, further research indicates that certain PIs impose a greater risk of hyperglycemia than others and that hyperglycemia may not be a class effect of these drugs. Lee et al.¹⁷ studied the metabolic effects of various PIs in HIV-negative men to eliminate the pathogenic effect of HIV/AIDS on the development of various metabolic disorders. Euglycemic-hyperinsulinemic clamp procedures were performed to evaluate the effect of the drugs on metabolism. The results demonstrated that individual PIs have different metabolic effects. Indinavir induced insulin resistance with no effect on lipid metabolism, whereas lopinavir/ritonavir increased fasting triglycerides and free fatty acids but had little or no effect on insulin sensitivity. The conclusion is that PIs have varying effects on glucose metabolism and should be studied individually.¹⁸

Some PIs, such as indinavir and ritonavir, block insulin-mediated glucose disposal by a direct blockade of GLUT-4, causing insulin resistance. Other PIs, such as amprenavir and atazanavir, have no effect on this mechanism. Indinavir increases hepatic glucose production and release. With indinavir, insulin loses some of its ability to suppress hepatic glucose production; therefore, glycogenolysis and gluconeogenesis increase.¹⁸ HIV-infected patients treated for 12 weeks with nelfinavir, indinavir, lopinavir, or saquinavir had alterations in first-phase insulin release with a 25% reduction in β -cell function.¹⁹

Screening and Treatment of Diabetes in HIV-Infected Patients

Three distinctive groups emerge from the data focusing on diabetes and HIV

management: patients with HIV but undiagnosed diabetes, patients who develop diabetes during HIV treatment, and patients with diabetes before becoming HIV infected.

Although the optimal method and frequency of screening for diabetes and insulin resistance among those infected with HIV has not yet been determined, research and clinical practice in both HIV and diabetes has provided some insight for designing a basic template for screening. In 2002, recommendations of the International AIDS Society-USA Panel for the management of metabolic complications associated with antiretroviral therapy for HIV-1 infection were published.²⁰ This 12-member panel developed guidelines that were meant to assist physicians in the management of glucose, lipid, and body fat distribution abnormalities and bone disease.

Many of the HIV-infected population have the classic risk factors for the development of diabetes: positive family history, increased waist circumference, physical inactivity, and African-American or Hispanic ethnicity. Howard et al.²¹ performed OGTTs on 221 women with or at risk for HIV infection. In this group with previously undiagnosed diabetes, the OGTT results showed that 6% had diabetes and 12% had impaired glucose tolerance. Factors independently associated with the abnormal OGTT results were: age ≥ 50 years, family history of diabetes, physical inactivity, and a high number of pack-years of smoking.

This study supports screening for diabetes in the HIV care setting for women who have the classic risk factors for diabetes. However, unlike the current recommendations for diabetes screening, which use fasting glucose levels results, there is some controversy as to which test best identifies diabetes in the HIV population. The AIDS Society-USA Panel recommends the fasting plasma glucose (FPG) test as the first-line screening measurement.²⁰ FPG is to be tested before initiation of therapy and periodically thereafter. In research studies, diabetes was better detected in HIV patients by OGTT. In examining measures to detect insulin resistance, Beatty et al.²² concluded that assessing insulin response to glucose load was the most accurate predictor of insulin sensitivity in patients with HIV. In testing HIV patients for diabetes, the guidelines for administering the

OGTT and the laboratory determinants for assessing abnormalities remain the same as for the general population.

Although universal screening of all HIV patients for diabetes remains controversial, most clinicians support diabetes screening for HIV patients with risk factors, particularly positive family history and central adiposity. There is enough research evidence to suggest that patients who need HAART or NRTIs be screened for diabetes before the onset of therapy. Patients with positive diabetes risk factors are more predisposed to developing diabetes when exposed to antiretroviral therapy.²³ In those who test negative for diabetes at baseline, re-screening should be conducted during the first 3–6 months of HAART.

The avoidance of PI-based regimens should be considered in patients with preexisting glucose abnormalities or those who have first-degree relatives with diabetes. In patients who develop diabetes secondary to the use of HAART, the first option is to switch the PI to another drug within the same class.

Before switching medications, clinicians must consider any potential reduction in virological and immunological benefit. If the risk of HIV treatment failure is high, then remaining on the current agent and treating the glucose abnormality may be the best clinical decision. Indinavir appears to be the most problematic of the PIs and should not be considered as a first-line choice. Other PIs, such as nevirapine, efavirenz, or atazanavir, either improve insulin resistance or have negligible alterations in glucose metabolism and are better choices.²³

Patients with diabetes and HIV need to follow the clinical recommendations used for treating diabetes in the general population. Physical activity, a healthy, well-balanced diet, and weight loss when appropriate are the basics of diabetes management. Because diabetes related to PI use has been associated with impairment of glucose uptake by the muscle and hepatic glucose disturbances, drug selection for treating hyperglycemia should address these deficits.^{19,20}

Thiazolidinediones (TZDs), a class of medications known to increase insulin sensitivity in the peripheral tissues, reduces insulin resistance. Before administration of rosiglitazone or pioglitazone, liver function tests should be ordered. TZDs should not

be prescribed for patients with preexisting liver disease as indicated by liver enzyme levels > 2.5 times the upper limit of normal. If the baseline liver function tests are within normal limits, TZDs may be dispensed, but liver enzymes must continue to be monitored every 2 months for the first year of therapy.

Metformin, a biguanide that reduces hepatic glucose toxicity, improves insulin resistance or glucose intolerance. Studies in HIV-infected patients demonstrated that metformin use reduced insulin and triglyceride levels and decreased weight.^{24,25} Before prescribing metformin, patients must undergo laboratory screening for lactic acidemia or abnormal serum creatinine levels. Patients with venous lactate levels > 2.0 times the upper limit of normal or serum creatinine levels > 1.4 mg/dl for women and 1.5 mg/dl for men may not use metformin.

Patients who take metformin need to be educated about the clinical symptoms of lactic acidemia. Although patients with low-level lactic acidemia may have mild symptoms or no symptoms other than a disturbance in lab results, those with severe lactic acidemia may present with fatigue, weight loss, nausea, abdominal pain, dyspnea, and cardiac dysrhythmias. Furthermore, liver-related symptoms, such as tender hepatomegaly, peripheral edema, ascites, and encephalopathy can also occur. Only in rare instances is jaundice present.²⁰

Those receiving NRTI therapy, particularly for longer than 6 months, may be at higher risk for lactic acidemia. Stavudine, zidovudine, and didanosine are the drugs most associated with an increase in lactate levels. Abacavir, lamivudine, and tenofovir are the least likely to elevate lactate levels.²⁶ Although use of metformin is not contraindicated in this group of patients, clinicians should be more aware of the possibility of lactic acidemia and periodically screen for it by history and laboratory testing.

Because certain PIs diminish first-phase insulin release, medications that address this mechanism, such as the meglitinides, may improve glucose control. Clinicians need to educate patients taking meglitinide medications about the signs, symptoms, and appropriate treatment of hypoglycemia.

Although few, if any, drug interaction studies have been done, a drug-to-drug interaction can poten-

tially occur between some of the medications used to treat diabetes and the various NRTIs and PIs because of the similarity in metabolic pathways used in the action of the drug. For example, ritonavir and nelfinavir may reduce rosiglitazone exposure by inhibiting the metabolic pathway. Similarly, PIs that use the CYP 3A4 pathway may potentially have an adverse affect on repaglinide concentrations.²⁰

Patients who had diabetes before the diagnosis of HIV may be taking a combination of medications and/or insulin to control glucose levels. Insulin resistance associated with PI therapy may affect glucose control and necessitate adjustments in therapy. Self-monitoring of blood glucose can help determine when medication changes are needed. Subsequent glucose readings will assist in evaluating the therapeutic adjustments.

For the health and the safety of others, all patients who self-test their blood glucose should be taught to handle and dispose of blood-contaminated supplies appropriately. This becomes all the more important in HIV-infected patients. Testing materials contaminated by blood can be a route of HIV transmission. The safe disposal of lancets, gauze, and used glucose strips as well as the proper cleaning of meters and lancet devices needs to be reviewed with each patient. It is also important to stress that no other person should share any of the glucose monitoring supplies with the patient.

Conclusions

HIV and diabetes are both chronic diseases that significantly affect lifestyle. When they intersect, the treatment regimens required for both diseases can be overwhelming for patients. Understanding the glucose disturbances that are possible with PI therapy, performing appropriate screening for glucose intolerance and diabetes and making prudent changes in HIV therapy when necessary, and treating patients for alterations in glucose metabolism are the key components of care for at-risk patients.

Although beyond the scope of this article, other metabolic disturbances associated with HIV medications, such as lipoprotein and fat distribution abnormalities, place patients with HIV at risk for cardiac disease. Glucose metabolism alterations in HIV patients present much like those

of type 2 diabetes. Therefore, the best clinical care regimen will address all of the cardiac risk factors: insulin resistance/diabetes, lipid abnormalities, and body fat abnormalities.

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