Insulin Resistance and Diabetes

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Metabolic complications associated with HIV disease and its treatment—including insulin resistance and diabetes, abnormal cholesterol and triglyceride levels (dyslipidemia), and body fat gain or loss—remain a medical mystery and a topic of intense interest for AIDS researchers and people with HIV alike. While these complications sometimes have been collectively referred to as "lipodystrophy syndrome," it remains unclear whether or how they are related and what causes them (see "HAART Attack: Metabolic Disorders during Long-Term Antiretroviral Therapy," *BETA*, April 1999).

Scientists are urgently trying to better understand these conditions, which may have a negative impact on quality of life, interfere with adherence to antiretroviral therapy, and lead to long-term health problems. High blood glucose levels (hyperglycemia) and dyslipidemia are a particular concern because in the population at large they have been linked with increased risk of heart disease (see "Cardiovascular Disease in People with HIV," *BETA*, Summer/Autumn 2002). Much research is underway and new clues are steadily emerging, but Daniel Kuritzkes, MD, of Boston's Brigham and Women's Hospital predicts, "We'll need several more years of follow-up to get a better perspective."

Blood Glucose Abnormalities: the Basics

The body requires sugar, or glucose, to provide energy for all its functions. A hormone called insulin allows glucose to enter individual cells. Normally, after eating, beta cells in the pancreas (an abdominal organ) produce more insulin to process the incoming sugar. Glucose and insulin levels in the blood also regulate the breakdown of glycogen (a stored form of energy) and the production of new glucose (gluconeogenesis) by the liver, as well as the release of fatty acids from fat cells (adipocytes). When normal glucose metabolism goes awry, several disorders may develop.

Insulin resistance is a condition in which the body's cells do not respond properly to the hormone and cannot take up glucose, which then builds up in the bloodstream. This causes the beta cells to release extra insulin, leading to high blood insulin levels (hyperinsulinemia). Over time, the beta cells can fail to secrete enough insulin. When the body cannot produce sufficient insulin, or the cells do not respond to it efficiently, the result is hyperglycemia—impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Eventually, this process can lead to diabetes mellitus (sugar diabetes), a condition characterized by persistent hyperglycemia (see sidebar on this page).

There are two primary forms of diabetes mellitus: type 1 and type 2. (Diabetes insipidus is an uncommon condition characterized by excess urine production unrelated to blood sugar abnormalities. Pregnant women may also develop a transient condition known as gestational diabetes. This article is limited to diabetes mellitus).

Type 1 diabetes (also called juvenile onset or insulin-dependent diabetes mellitus [IDDM]) typically occurs at a young age and is believed to result from the destruction of insulin-producing beta cells by the immune system. People with type 1 diabetes produce little or no insulin and usually must receive daily insulin injections.

Type 2 diabetes (also called adult onset, insulin-resistant, or non–insulin-dependent diabetes mellitus [NIDDM]) typically develops later in life—though it is now being seen in children—and commonly occurs in people who are overweight. (See sidebar on page 36 for more diabetes risk factors.) Type 2 diabetes is a progressive illness that involves a gradual decline in insulin sensitivity and production. It can take years or decades for mild insulin resistance to progress to full-blown diabetes, and many people with impaired insulin sensitivity never develop frank (clinically apparent) diabetes. Those with type 2 diabetes can often be treated with diet modification, increased exercise, weight loss, and/or oral medications, and usually do not require insulin injections. The blood glucose abnormalities that develop in people with HIV resemble type 2, not type 1, diabetes.

Insulin resistance and diabetes are a concern because untreated high blood sugar can lead to a wide range of long-term health problems, including kidney dysfunction, retina damage leading to blindness, nerve damage, erectile dysfunction in men, and pregnancy complications in women. In fact, diabetes is the sixth leading cause of death in the U.S. Yet these complications can occur even in people

Progression of Insulin Resistance to Type 2 Diabetes

Normal:

- Normal insulin production and cell sensitivity to insulin
- Characterized by normal blood glucose and insulin levels (fasting glucose below 100 mg/dL or glucose below 140 mg/dL after an oral glucose tolerance test)

Insulin resistance:

- Loss of insulin sensitivity and compensation by increased insulin production
- Characterized by high blood insulin levels (fasting insulin over 15 units/mL)

Impaired fasting glucose (IFG):

- Progressive reduction in insulin sensitivity
- Characterized by moderately elevated fasting blood glucose (fasting glucose 100–125 mg/dL)

Impaired glucose tolerance (IGT):

- Continued lack of insulin sensitivity and reduced ability to produce insulin to compensate for food intake
- Characterized by hyperglycemia after eating (glucose 140–199 mg/dL after an oral glucose tolerance test)

Diabetes mellitus:

- Insufficient insulin production for proper cellular functioning
- Characterized by persistent hyperglycemia both when fasting and after eating (fasting glucose over 125 mg/dL, or glucose over 200 mg/dL after an oral glucose tolerance test, or random nonfasting glucose over 200 mg/dL if accompanied by diabetes symptoms)

Risk Factors for Blood Glucose Abnormalities

- Genetic predisposition
- Family history (sibling or parent with insulin resistance or type 2 diabetes)
- Overweight or obesity (high body mass index)
- Abdominal fat accumulation, or "pot belly" (increased waist-to-hip ratio: over 1.0 for men or 0.8 for women)
- Sedentary lifestyle (minimal physical activity)
- Age over 40
- African American, Latino, Asian American, Pacific Islander, or Native American ethnicity
- History of gestational diabetes during pregnancy
- Other signs of insulin resistance syndrome (e.g., high blood pressure, dyslipidemia)
- Other signs of lipodystrophy syndrome (e.g., body fat gain or loss)
- Past tests showing insulin resistance, impaired glucose tolerance, or hyperglycemia
- History of polycystic ovary syndrome
- Use of certain medications (e.g., niacin, glucocorticoids, megestrol acetate [Megace], human growth hormone, phenytoin [Dilantin])

who never progress from impaired glucose tolerance to frank diabetes.

Hyperglycemia can also contribute to blood vessel abnormalities and cardiovascular disease, including heart attacks and strokes. This process is not well understood—especially in people with HIV—but it is thought that excess sugar in the blood may promote blood clotting and make cholesterol more likely to adhere to blood vessel walls. Both the Caerphilly Heart Study, which followed more than 2,500 men in a Welsh town between 1979 and 1983, and the Prospective Cardiovascular Munster (PROCAM) study, which followed 2,754 men, found that diabetes was associated with about a 2.5-fold increased risk of heart disease.

Insulin Resistance and HIV

Before the availability of highly active antiretroviral therapy (HAART), blood glucose abnormalities were infrequently seen in people with HIV. But in June 1997, soon after protease inhibitors (PIs) came into widespread clinical use, the U.S. Food and Drug Administration (FDA) issued a health advisory warning of an association between PIs and hyperglycemia and diabetes mellitus. Since then, there have been continued reports of insulin resistance in people using anti-HIV therapy.

Different studies have yielded widely varying estimates of the prevalence of impaired glucose metabolism in people on HAART, in part because they have used different tests and inconsistent definitions of the condition. The prevalence of frank diabetes mellitus in people with HIV is relatively low, with studies reporting rates from 0.5% to 15%. But, says Michael Dubé, MD, of Indiana University School of Medicine, diabetes is "only the tip of the iceberg." Impaired glucose tolerance is considerably more common, affecting an estimated 15–25%, and research suggests that some degree of insulin resistance may occur in one-half of people taking PIs.

Research also indicates that coinfection with the hepatitis C virus (HCV)—which affects as many as 40% of people with HIV in the U.S.—increases the risk of blood glucose abnormalities. Studies have shown that people with chronic hepatitis C are more likely to develop insulin resistance and type 2 diabetes. For example, Shruti Mehta, MPH, and colleagues from Johns Hopkins University in Baltimore found that people with HCV were four times more likely to develop type 2 diabetes than HCV negative people; however, they found no association between hepatitis B and diabetes. Mehta's team also found that HIV/HCV-coinfected people were five times more likely to develop hyperglycemia than those with HIV alone. Similarly, Michel Duong, MD, and colleagues from Dijon studied 29 HIV/HCV-coinfected individuals receiving HAART, 76 people with HIV alone, and 121 with HCV alone. Both the coinfected subjects and those with HCV alone had a significantly higher rate of insulin resistance than those with only HIV.

Although it is not clear how chronic hepatitis promotes blood sugar abnormalities, it is believed that liver damage affects the metabolism of glycogen and the production of glucose. In a letter published in the December 15, 2003 issue of the *Journal of Acquired Immune Deficiency Syndromes* (*JAIDS*), Raymond Chung, MD, and colleagues from Harvard Medical School and Massachusetts General Hospital in Boston reported that elevated alanine transaminase (ALT) liver enzyme levels—an indication of liver inflammation—predicted insulin resistance in HIV positive individuals with lipodystrophy whether or not they were coinfected with hepatitis B or C.

It is not yet known whether blood glucose abnormalities in people with HIV will have the same negative health consequences as they do in the population at large, though there is little reason to expect otherwise.

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According to Dr. Dubé, the high prevalence of insulin resistance in people with HIV taking HAART "raises concern about the eventual development of increased cardiovascular morbidity in this population." And, say Oluwatoyin Falusi, MD, and Judith Aberg, MD, of the Adult AIDS Clinical Trials Group (AACTG) Cardiovascular Disease Focus Group, "Even if [HIV positive] patients are not at increased risk for cardiovascular disease, they are at least at the same risk as HIV negative, age-matched persons with similar risk factors."

Indeed, the prevalence of blood glucose abnormalities is substantial in the general population. An estimated 6–9% of Americans have diabetes, although rates are considerably higher among older people (20% of those over age 65) and among African Americans (13%), Latinos (10%), Native Americans (15%), and Asian Americans and Pacific Islanders. As many as one-third of Americans have some degree of insulin resistance. A recent report by the National Center for Health Statistics stated that the rate of diabetes had increased 27% between 1997 and 2002, which many attribute to the rising incidence of obesity.

Some experts have suggested that the increasing incidence of blood glucose abnormalities in people with HIV is due to the fact that, thanks to effective treatment, such individuals are now living long enough to experience the normal problems associated with aging. (Interestingly, HIV positive children on HAART rarely develop insulin resistance, although they do develop elevated blood fat levels.) But many others believe that HAART—especially PIs—or HIV itself share much of the blame.

Causes of Blood Glucose Disorders

Blood sugar abnormalities are due to too much glucose (e.g., reduced uptake of glucose by cells, increased production of glucose by the liver), too little insulin (decreased insulin release by beta cells), or some combination of both. A number of different theories have been put forth to explain the increased occurrence of insulin resistance and diabetes in people with HIV. While the bulk of research implicates PIs, other explanations cannot be discounted, and it is likely that multiple factors are at play simultaneously.

Protease Inhibitors

As noted previously, insulin resistance and diabetes were not common in people with HIV before the advent of HAART, and many studies have found an association between blood glucose abnormalities and PI therapy. In fact, PI use appears to be more directly related to disorders of glucose metabolism than to other metabolic complications such as body fat gain or loss.

Kathleen Mulligan, MD, of the University of California at San Francisco (UCSF) and colleagues analyzed data from 20 HIV positive individuals who started treatment with a PI, nine who received only nucleoside reverse transcriptase inhibitors (NRTIs), and 12 who received no antiretroviral therapy. Those who started a PI-based regimen had elevated fasting insulin and blood glucose levels, which suggest increased insulin resistance, as well as increased triglyceride and LDL ("bad") cholesterol levels. Signs of insulin resistance were apparent after an average of 3.4 months. However, no body shape changes were seen during this period. The group treated with only NRTIs did not experience similar glucose and lipid abnormalities.

Georg Behrens, MD, of Hannover Medical School in Germany and colleagues reported that 46% of 38 PI recipients in their study had impaired glucose tolerance and 13% had diabetes, compared with 24% and none, respectively, among PI-naive subjects. Ravi Walli, MD, and colleagues from Ludwig-Maximilians-Universität in Munich reported that 61% of 67 PI-treated subjects had reduced insulin sensitivity, which was seen in none of the 13 HIV positive, treatment-naive controls. Frank Goebel, MD, and colleagues, also from Munich, detected some degree of insulin resistance in 55% of people receiving PIs, compared with 27% of those receiving NRTIs, but Thierry Saint-Marc, MD, and associates from Hôpital Edouard Herriot in Lyon found that only PIs—not NRTIs—were associated with glucose abnormalities.

However, some physicians believe these insulin resistance rates are too high. "We simply do not see insulin resistance in 50% of patients taking PIs," says George Beatty, MD, MPH, of UCSF.

In the large Women's Interagency HIV Study (WIHS), women receiving PIs were significantly more likely to report that they had diabetes than HIV negative women (2.8 cases per 100 person-years vs 1.4 cases per 100 person-years, respectively). Interestingly, in this study HIV positive women who received no antiretroviral therapy or received only NRTIs were even less likely to report diabetes than HIV negative women (1.2 cases per 100 person-years).

Among the PIs, indinavir (Crixivan) has been most strongly associated with impaired glucose metabolism. Dr. Dubé and colleagues detected signs of insulin resistance in people with HIV within eight weeks of starting indinavir. Another study showed reduced insulin sensitivity as soon as two weeks after starting the drug. Mustafa Noor, MD, from the Veterans Affairs Medical Center in San Francisco and colleagues found that insulin resistance (but not elevated lipid levels or visceral fat accumulation) developed within four weeks of the 48-week study period, after increases in triglyceride and LDL cholesterol levels and abdominal fat accumulation had already occurred. Most trial data suggest that the newer PI atazanavir (Reyataz) has a minimal effect on glucose and lipid metabolism, but the drug requires further long-term study.

It is unclear exactly how PIs affect glucose metabolism, but research points to a variety of possible mechanisms, including reduced glucose uptake by peripheral cells, decreased insulin production by beta cells in the pancreas, and increased glucose production by the liver.

Several laboratory, animal, and clinical studies suggest that PIs may directly interfere with the transport of glucose into cells. An insulin-sensitive protein called Glut-4 plays a key role in transporting glucose into fat and muscle cells after eating. In laboratory studies using 3T3-L1 adipocytes (a type of fat cell), Haruhiko Murata, PhD, and colleagues from Washington University in St. Louis found that indinavir and other PIs reduced glucose uptake by inhibiting Glut-4 activity. At 100 micrometers (µm), indinavir reduced glucose uptake by 63%, while a 10 µm dose (closer to the concentrations used in humans) caused a 26% decrease. This inhibition occurred within minutes, and was reversed when indinavir was removed. In another study in frog egg cells, indinavir, amprenavir, and ritonavir (Norvir) reduced glucose uptake by 45%, 42%, and 54%, respectively. Noting that mutant mice lacking Glut-4 have almost no subcutaneous (under the skin) fat, the authors suggested that peripheral lipoatrophy (fat loss in the limbs and face) in people with HIV may be mediated by PIs' effect on the transport protein.

A related protein, Glut-2, allows beta cells in the pancreas to take up glucose to monitor blood sugar levels and regulate insulin release. Joseph Koster, PhD, and colleagues, also from Washington University, found that indinavir in doses similar to those used in humans—and other PIs at higher concentrations—inhibit the activity of Glut-2, thus reducing glucose uptake by beta cells. If the beta cells cannot detect elevated glucose levels, the authors suggest, they will not produce extra insulin to compensate, leading to hyperglycemia. These laboratory findings may help explain data from Dr. Dubé's team showing that reduced insulin sensitivity and increased fasting glucose did not trigger beta cells to release more insulin in people taking indinavir.

Proposing yet another mechanism, Dr. Capeau and colleagues found that in laboratory tests, PIs (indinavir, nelfinavir, and amprenavir) inhibit the production and activity of sterol regulatory element binding protein (SREBP), a key fat cell messenger that triggers stem cells to differentiate into adipocytes. SREBP also stimulates increased production of peroxisome proliferating activation factor gamma (PPAR-gamma), which promotes cellular glucose uptake in the presence of insulin.

Marc van der Valk, MD, from the University of Amsterdam and colleagues reported that in addition to decreased cell sensitivity to insulin, glucose production by the liver is increased in people taking PIs. Using the hyperinsulinemic euglycemic clamp technique (discussed below in the "Diagnosis and Monitoring"

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after starting indinavir in HIV negative volunteers. In one of their studies, glucose disposal (uptake of glucose by cells) was reduced after a single dose of the drug. Because Dr. Noor's study subjects were neither HIV positive nor taking other classes of antiretroviral drugs, these results offer evidence that indinavir itself directly triggers insulin resistance.

Some other PIs appear less likely than indinavir to cause blood glucose abnormalities. For example, Dr. Walli and colleagues found that indinavir led to greater insulin resistance than either saquinavir (Fortovase, Invirase) or amprenavir (Agenerase). At the 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV in October 2001, Jacqueline Capeau, MD, and associates from INSERM in Paris reported that in laboratory studies, indinavir had the greatest inhibitory effect on a regulatory protein that helps control insulin resistance (discussed below), followed by nelfinavir (Viracept) and to a lesser extent amprenavir. Dr. Dubé's team saw a trend toward decreased insulin sensitivity in people treated with amprenavir, but only at the end

section), the researchers found that hepatic glucose production was 47% higher in the PI recipients than in HIV negative control subjects. In addition, insulin suppressed glucose production less in the PI group than in controls. Similarly, Dr. Noor's team found that hepatic glucose production (both gluconeogenesis and glycogenolysis, or breakdown of stored sugar) increased within four weeks of starting indinavir.

In an article in the December 2000 issue of *Clinical Infectious Diseases,* Dr. Dubé summarized the evidence for a direct effect of PIs in inducing blood glucose abnormalities. This includes the rapid development of glucose abnormalities soon after starting PI therapy, the reversal of glucose abnormalities when PIs are halted, the onset of insulin resistance before changes in body fat distribution occur, and plausible biological mechanisms. People with other risk factors for diabetes (for example, family history or obesity) may be especially susceptible to the effect of PIs on blood glucose.

Blood Glucose and Lipodystrophy

Much remains to be learned about the relationship between blood glucose abnormalities and other metabolic manifestations in people with HIV. As Dr. Dubé notes, while blood fat abnormalities, abdominal obesity, and loss of peripheral fat frequently coexist with insulin resistance, "It is not clear whether all of these result from a common pathogenic mechanism."

In the HIV negative population, glucose abnormalities, elevated triglyceride levels, decreased HDL ("good") cholesterol, high blood pressure, and visceral abdominal obesity often occur together—a syndrome variously known as insulin resistance syndrome, metabolic syndrome, or syndrome X. Here, too, it is unclear how these conditions are linked, but they occur together often enough to suggest they are interrelated.

Research indicates that altered glucose metabolism, dyslipidemia, and fat gain or loss are linked in people with HIV as well, and some researchers suggest that glucose abnormalities may in fact be attributable to body fat changes. Studies have shown, for example, that the accumulation of visceral abdominal fat can promote insulin resistance. Reduced insulin sensitivity may also result when fat cells are broken down—a process called lipolysis—as occurs during peripheral lipoatrophy. Further, research in mice suggests that loss of subcutaneous fat is associated with fat accumulation in insulin-sensitive tissues such as the liver and skeletal muscle, again contributing to insulin resistance.

Andrew Carr, MD, and colleagues from St. Vincent's Hospital in Sydney found that among people taking PIs, insulin resistance was more common in those with body shape changes—either abdominal obesity or peripheral fat loss. Dr. Carr's group also reported that people with "buffalo hump" (accumulation of fat at the back of the neck) were at higher risk for insulin resistance and diabetes, although other studies have yielded conflicting results.

Similarly, Colleen Hadigan, MD, from Massachusetts General Hospital and colleagues found that among 101 HIV positive people in the Framingham Offspring Study (a large study of cardiovascular risk), those with body fat changes were more likely to have impaired glucose tolerance (evidenced by elevated insulin levels and increased glucose levels after a glucose tolerance test) and frank diabetes. In another study, Dr. Hadigan's team found that insulin levels were most elevated in HIV positive women with abdominal fat accumulation, independent of PI use. The same research group also reported insulin resistance in men with AIDS-related wasting syndrome who were treated with NRTIs but not PIs, and noted that reduced lean body mass and increased abdominal fat were the primary predictors of hyperinsulinemia. In addition, they found that when 52 HIV positive hypogonadal (low testosterone level) men with AIDS-related wasting were given supplemental testosterone therapy, their insulin sensitivity improved as their lean body mass increased. (It should be noted, however, that supplemental testosterone may provide no additional benefit in men who already have normal levels.)

Dr. Corinne Vigouroux of INSERM and colleagues found that among study participants receiving PIs, 11 out of 14 (79%) with severe facial wasting had either insulin resistance or diabetes, compared with just four out of 20 (20%) without facial fat loss. In this study, elevated triglycerides were also more common in the group with facial wasting (79% vs 35%). Dennis Mynarcik, MD, from the State University of New York at Stony Brook and colleagues reported that among 12 HIV negative study subjects, 15 HIV positive participants with lipodystrophy, and 14 HIV positive individuals without lipodystrophy, insulin resistance was greatest in those with fat loss. Likewise, Ove Andersen, MD, and colleagues from Hvidovre University in Copenhagen reported that loss of limb fat was the strongest predictor of insulin resistance and decreased insulin production, independent of the type of antiretroviral therapy used.

Some researchers suggest that glucose abnormalities may in fact be attributable to body fat changes.

Symptoms of Hyperglycemia and Diabetes

- Increased thirst
- Increased hunger
- Copious urination
- Fatigue
- Poor concentration
- Blurred vision
- Unexplained weight loss or gain
- Slow healing of cuts and sores

Free Fatty Acids

Some research suggests that the relationship between body fat changes and glucose abnormalities may be mediated by free fatty acids. Normally, fatty acids are released when blood sugar levels are low to provide the liver with "raw material" for gluconeogenesis. High blood levels of free fatty acids—related to both visceral fat accumulation and peripheral fat loss—may interfere with normal glucose regulation and are associated with greater insulin resistance.

Dr. Hadigan's group found that HIV positive individuals receiving antiretroviral therapy (58% on PIs, 74% on NRTIs) experienced heightened fasting lipolysis that increased further after consuming glucose, an indication of reduced insulin sensitivity (normally, lipolysis decreases after glucose consumption). Those with the greatest rates of lipolysis had the most severe insulin resistance. When an agent called acipimox was used to lower free fatty acid levels, insulin sensitivity improved, but it did not return to normal, suggesting that other factors were also involved.

If the hypothesis that body fat changes promote blood glucose abnormalities holds true, PIs may play an indirect role in glucose disorders by altering lipid metabolism and causing body fat abnormalities, perhaps in addition to their more direct effect. NRTIs (especially d4T [stavudine, Zerit]) also may indirectly contribute to glucose abnormalities by causing peripheral fat loss. As noted above, Dr. Goebel and colleagues detected evidence of insulin resistance in 27% of HIV positive people treated with NRTIs (although the rate in those receiving PIs was twice as high). Dr. Mulligan, too, found that insulin sensitivity was reduced by 10% in people taking antiretroviral regimens that excluded PIs. Further, Dr. Andersen's team reported that glucose disposal was reduced in people with elevated lactic acid levels, a possible indication of NRTI-induced damage to the mitochondria, energy-producing organelles in cells that are involved in glucose metabolism.

Interestingly, research has not implicated non-nucleoside reverse transcriptase inhibitors (NNRTIs) in blood glucose abnormalities, although they have been linked with other metabolic manifestations in some studies.

Yet other data indicate that blood glucose abnormalities are not directly caused by body fat changes or dyslipidemia. Dr. Mulligan and colleagues, for example, found that blood glucose abnormalities developed just a few months after people began taking PIs, well before body shape changes occurred. Dr. Saint-Marc's team reported that when individuals with peripheral fat loss switched from d4T (which is strongly associated with lipoatrophy) to either abacavir (Ziagen) or AZT (zidovudine, Retrovir), they experienced increased subcutaneous fat but no improvement in insulin resistance.

Dr. van der Valk and colleagues demonstrated that when PIs were stopped for 96 weeks in eight HIV positive men with lipodystrophy, glucose production decreased and lipolysis was reduced, although no body fat changes were seen. In a study of diet and exercise in obese HIV positive women, Ellen Engelson, EdD, of Columbia University in New York City and associates found that after completing a 12-week weight loss program, the women experienced reductions in both visceral and subcutaneous fat, but no corresponding improvements in insulin sensitivity. And, as noted previously, HIV positive children treated with PIs develop blood lipid abnormalities, but not insulin resistance or body fat changes.

There are not yet enough data to definitively say whether body fat or blood lipid changes cause glucose abnormalities, blood sugar disorders contribute to lipodystrophy, some common mechanism underlies both manifestations, or the conditions occur together but are otherwise independent.

Other Possible Causes

Although plentiful evidence links blood glucose abnormalities in people with HIV to antiretroviral therapy with PIs (and possibly NRTIs) and body fat changes, other factors—including immune activation and HIV infection itself—may also play a role.

Some researchers have suggested that HIV may damage the beta cells in the pancreas, thus decreasing insulin production and causing impaired glucose metabolism, although little research directly supports this hypothesis. In the pre-HAART era, glucose abnormalities were sometimes seen in people taking medications such as pentamidine and ddI (didanosine, Videx), which can cause inflammation of the pancreas (pancreatitis). An early theory held that high levels of cortisol (a hormone associated with stress and chronic illness) might contribute to glucose abnormalities and other metabolic manifestations, since excess cortisol production causes Cushing's syndrome, characterized by many of the same symptoms. However, more recent research has shown that cortisol levels generally are not elevated in HIV positive people with metabolic complications.

Glucose abnormalities may also be associated with altered levels of cytokines (chemical messengers produced by cells), including tumor necrosis factor (TNF). An increased

number of TNF receptors (cell proteins that bind to TNF) is an indication of inflammation, or immune activation, which can potentially occur as HAART enables immune system recovery. Research by Dr. Mynarcik and others has shown that elevated TNF receptor levels are associated with both insulin resistance and lipoatrophy. Donald Kotler, MD, of St. Luke's-Roosevelt Hospital Center in New York City has said he believes that "TNF drives body fat changes and insulin resistance." It is possible that imbalances in other cytokines—such as interleukin-1, interleukin-6, or interleukin-10 (low levels of which are associated with autoimmune diabetes)—may also contribute to altered glucose metabolism in people with HIV.

Finally, three hormones produced by fat cells—leptin, adiponectin, and resistin—may contribute by as yet unknown mechanisms to glucose abnormalities and other metabolic complications in HIV positive and HIV negative people alike. Leptin, which helps regulate appetite, has made the news in recent years because administration of the hormone leads to weight loss in obese mice; in addition, it has been successfully used to treat people with congenital lipodystrophy. Leptin also promotes normal insulin activity. Adiponectin improves insulin sensitivity as well, while resistin inhibits the action of insulin. For example, Claire Steppan, MD, and colleagues from the University of Pennsylvania found that administration of antibodies that target resistin normalized blood glucose levels in mice. Studies have found decreased leptin and adiponectin levels in HIV positive people with body fat abnormalities. Ongoing research should shed further light on how these hormones affect metabolism and whether they can be manipulated to treat metabolic complications in humans. (See "Open Clinical Trials" on page 49 for a study of leptin in people with HIV-associated lipodystrophy.)

In summary, there is a growing consensus that multiple factors contribute to blood glucose abnormalities in people with HIV. In the words of Carl Grunfeld, MD, PhD, of UCSF, "Understanding each of these contributors and how they interact is essential to understanding the effects of therapy for HIV infection."

Diagnosis and Monitoring

Various tests may be used to diagnose blood glucose abnormalities. (See sidebar on page 35 for types of glucose abnormalities and associated laboratory values.) One common measure is fasting glucose. In this test, blood sugar is measured after a person has fasted for eight hours, with no food or beverages except water. Another test that may be used is the oral glucose tolerance test. In this assay, blood glucose is measured, the individual drinks a sugar solution (usually 75 grams) after fasting overnight, and glucose is measured again every 30–60 minutes for two hours to see if blood glucose levels rise and fall normally.

Additional tests may be done to assess hyperglycemia. The hemoglobin A1c (glucosylated hemoglobin) test measures how much glucose adheres to red blood cells, and is used to determine average blood sugar levels over the course of 2–3 months.

Assessing insulin resistance is more challenging than detecting hyperglycemia. The "gold standard" for diagnosing insulin resistance is the hyperinsulinemic euglycemic clamp technique (also known as an insulin tolerance test). In this test, a standard amount of insulin is infused intravenously, then glucose is administered until a normal blood glucose level is attained. The test is complex and expensive, and therefore tends to be used in research settings but not in routine clinical care.

Physicians may also measure fasting insulin levels. A fasting blood insulin of 15 units/mL or higher is suggestive of insulin resistance. Once the fasting insulin level is known, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score can be calculated. An insulin-to-glucose ratio may also be determined. However, standardized tests of blood insulin are not widely available. Because it is difficult to directly measure insulin levels, the fasting glucose and two-hour glucose tolerance tests are often used to indirectly assess insulin resistance.

In the November 1, 2002 issue of *JAIDS,* the International AIDS Society-USA (IAS-USA) published guidelines for the management of metabolic complications associated with antiretroviral therapy in people with HIV. The IAS recommends that fasting glucose should be measured before initiating HAART, 3–6 months after starting or switching drugs, and at least annually during PI therapy. People who have risk factors for blood glucose abnormalities (see sidebar on page 36), signs and symptoms of hyperglycemia (see sidebar on page 40), known impaired glucose tolerance, or severe body fat changes may benefit from oral glucose tolerance testing. Some physicians prefer regular glucose tolerance tests for all people receiving PIs. The IAS guidelines do not recommend direct monitoring of insulin levels.

Management of Blood Glucose Abnormalities

In many cases, blood glucose abnormalities can be managed by lifestyle changes, including weight loss, increased exercise, and diet modifications. These steps are usually undertaken first. Sometimes antiretroviral drugs from other classes can be substituted for PIs that promote insulin resistance. In some cases, however, antidiabetic drugs may be needed to control hyperglycemia. As noted previously, people with type 2 diabetes—the type associated with HIV and its treatment—usually do not require insulin injections.

Due to the lack of studies looking at treatment of blood glucose abnormalities in people with HIV, the IAS guidelines (compiled by a panel of 12 researchers and clinicians with expertise in metabolic complications) are similar to recommendations

Oral Antidiabetic Drug Classes

Class name	Action	How used	Side effects	Specific drugs
Biguanides	decrease glucose production by the liver, increase cell sensitivity to insulin	taken 2–3 times daily with meals	abdominal pain, nausea, diarrhea; may cause lactic acidosis; may cause kidney toxicity	metformin (Glucophage)
Thiazolidinediones (glitazones)	increase cell sensitivity to insulin, increase glucose uptake by cells	typically taken once or twice daily with food	may cause liver toxicity; may increase cholesterol levels	pioglitazone (Actos), rosiglitazone (Avandia)
Sulfonylureas	stimulate the production of insulin by beta cells, help cells use insulin more efficiently	typically taken once or twice daily immediately before meals	weight gain, gastrointestinal upset, skin rash; may cause blood sugar levels to drop too low (hypoglycemia); may cause kidney toxicity	glimepiride (Amaryl), glipizide (Glucotrol), glyburide (Micronase, Glynase), acetohexamide (Dymelor), chlorpropamide (Diabinese), tolazamide (Tolinase), tolbutamide (Orinase)
Metglitinides	stimulate the release of insulin by beta cells	taken before each meal	weight gain; may cause blood sugar levels to drop too low	repaglinide (Prandin)
Alpha-glucosidase inhibitors	inhibit the digestion of starches and certain sugars, resulting in a slower increase in blood glucose after eating	taken at the beginning of a meal	intestinal gas, bloating, diarrhea	acarbose (Precose), miglitol (Glyset)

established by the American Diabetes Association and other groups for the HIV negative population.

Only a small proportion of people with insulin resistance will go on to develop type 2 diabetes, which remains uncommon in people with HIV. It is not clear why insulin resistance progresses in some people but not others, and most physicians (and the IAS guidelines) do not recommend aggressive medical treatment for people with early-stage insulin resistance. However, because mild insulin resistance can sometimes progress rapidly to frank diabetes, regular blood glucose monitoring is important.

Lifestyle Changes

The IAS guidelines recommend a balanced diet and regular exercise regardless of the type of antiretroviral therapy a person is using. Because obesity can contribute to insulin resistance and diabetes, the guidelines also recommend maintaining a healthy body weight and losing weight if necessary—although this can be a challenge for individuals with abdominal fat gain, peripheral fat loss, or both simultaneously.

Even for people with no signs of impaired glucose metabolism and no risk factors for diabetes, maintaining a healthy weight, engaging in regular exercise, and eating a healthy diet are good practice. The Diabetic Primary Prevention Trial found that weight loss, exercise, and a healthy diet slowed the progression of hyperglycemia and delayed the onset of type 2 diabetes in an HIV negative cohort. Although these measures have not been extensively studied in people with HIV, they are potentially even more important for people taking PIs and experiencing metabolic complications. The National Institutes of Health (NIH) recommends that people exercise for at least 30 minutes each day; something as simple as regular walking can contribute to improved health.

A healthy diet is low in fat, sodium, and refined sugar, and high in fruits, vegetables, and whole grains. The American Diabetes Association recommends that carbohydrates should comprise about 50–60% of total daily calorie intake and fats should be limited to 30% or less (favoring unsaturated fats over saturated fats, hydrogenated fats, and trans fatty acids). But the type of carbohydrates consumed may be more

important than the total amount. Complex carbohydrates—starchy foods (such as potatoes, rice, corn, pasta, seeds, beans) and dietary fiber—are digested more slowly and stimulate less insulin production than simple carbohydrates (sugars, refined flour). Studies, including one by Dr. Hadigan's team in HIV positive people with lipodystrophy, have shown that dietary fiber promotes insulin sensitivity and helps maintain normal glucose levels. Moreover, research suggests that reducing calories can improve insulin sensitivity even before weight loss occurs. In HIV positive people who have problems with wasting, however, a low-calorie diet may not be appropriate.

When it comes to nutrition and HIV, more is not necessarily better. Sounding a note of caution, Grace McComsey, MD, and colleagues from Case Western Reserve University in Cleveland reported recently that in ten HIV positive, NRTI-treated individuals with lipoatrophy or lactic acidosis, administration of antioxidants (vitamin C, vitamin E, and N-acetyl cysteine) led to worsened insulin resistance and significantly elevated fasting glucose levels. These results are interesting because some past research has suggested that antioxidants may improve insulin sensitivity. Given the current climate of uncertainty, people with HIV should consult a physician—and ideally an HIV-knowledgeable dietitian—before making any major dietary changes.

Antiretroviral Selection and Substitution

Concern about blood glucose abnormalities and other metabolic complications has contributed to changes in how clinicians approach antiretroviral therapy. For example, it is now recommended that treatment be delayed in asymptomatic individuals until the CD4 cell count falls below 350 cells/mm^3 or viral load rises above 55,000 copies/mL. In addition, according to the IAS guidelines, it is reasonable to consider avoiding lipid-elevating PIs (especially as first-line therapy) in people with pre-existing glucose metabolism abnormalities or risk factors for diabetes.

For those who have already started therapy, several studies have shown that switching from PIs to antiretroviral drugs from other classes can help normalize blood glucose levels and prevent progression from insulin resistance to frank diabetes. For example, Esteban Martinez, MD, of University Hospital Clinic in Barcelona and colleagues demonstrated in two separate studies that switching from PIs to nevirapine (Viramune) or efavirenz (Sustiva) significantly improved insulin sensitivity. Similarly, Dr. Walli's team reported reduced insulin resistance when abacavir was substituted for a PI.

However, it is important that any HAART regimen maintain adequate viral suppression. For this reason, there is an emerging consensus that treatment interruptions generally should not be used to ameliorate antiretroviral side effects. Likewise, it is becoming apparent that regimens containing only NRTIs may not have enough antiviral potency. While substitution of an NNRTI for a PI to reduce insulin resistance is a reasonable approach, in some cases only a PI will provide sufficient strength. According to Jessica Justman, MD, and colleagues from the WIHS study team, "In view of the clinical benefits of PI therapy, concern about diabetes per se should not dissuade patients or practitioners from using this potent class of antiretrovirals." Fortunately, the newer PIs—particularly atazanavir—appear to be less likely than older members of this drug class to cause glucose abnormalities. As always, people with HIV should consult a physician before stopping or changing therapy.

Medical Treatment

If lifestyle changes are not adequate and eliminating PIs is not an option, several types of oral antidiabetic medication may be used to control insulin resistance and hyperglycemia (see chart on page 42). Few controlled studies of antidiabetic drugs have been completed in people with HIV, so clinical practice is based on research in the HIV negative population, taking into account what is known about side effects and interactions with other medications, including antiretrovirals. According to the IAS guidelines, metformin (Glucophage) or the thiazolidinedione (or glitazone) drugs—in particular, rosiglitazone (Avandia)—are preferred for HIV positive people with blood glucose abnormalities.

Metformin and other drugs in its class (the biguanides) work by decreasing glucose production by the liver and improving cell sensitivity to insulin. Some, though not all, studies show that these drugs may also improve body fat distribution and reduce blood lipid levels. Long-term use of metformin has been associated with a decreased risk of heart attacks in the general population. Dr. Hadigan and colleagues compared metformin with a placebo in a randomized, three-month study of 26 HIV positive people with signs of insulin resistance and body fat abnormalities. Those treated with metformin had decreased

Resources

American Diabetes Association
www.diabetes.org

National Institute of Diabetes and Digestive and Kidney Diseases
www.niddk.nih.gov/health/diabetes/diabetes.htm

Centers for Disease Control and Prevention
www.cdc.gov/diabetes

insulin levels after an oral glucose tolerance test, and also experienced significant weight loss and decreased visceral fat. There was no change in blood lipid levels. The authors concluded, "This study suggests that a relatively low dosage of metformin reduces insulin resistance and related cardiovascular risk parameters in HIV-infected patients with lipodystrophy." In another randomized study, Dr. Saint-Marc's team found that metformin improved fasting insulin levels, decreased triglyceride levels, and reduced visceral fat. However, Dr. Martinez and colleagues reported that in their study, metformin had only a minimal effect on insulin resistance, abdominal fat, and blood lipid levels.

Thiazolidinedione drugs improve insulin sensitivity. They work by activating PPAR-gamma, a cytokine that promotes the production of adipocytes and stimulates cells to take up more glucose. As with the biguanides, some studies show that the thiazolidinediones may help improve body fat distribution and normalize blood lipid levels.

In a study by Jussi Sutinen, MD, and colleagues from Helsinki University Central Hospital, 30 HIV positive subjects with lipodystrophy received either rosiglitazone or a placebo. After 24 weeks, insulin levels decreased in the rosiglitazone group but not in the placebo arm. However, triglyceride and cholesterol levels rose among those taking rosiglitazone, and there was no effect on visceral or subcutaneous fat distribution. "Rosiglitazone seemed to ameliorate insulin resistance judged by the decreased serum insulin concentrations and percentage of liver fat," the authors concluded.

Marie Gelato, MD, and colleagues from the State University of New York at Stony Brook found that in eight HIV positive individuals treated with rosiglitazone for 6–12 weeks, insulin resistance improved, as it did in Dr. Sutinen's study, but in addition visceral fat decreased and subcutaneous fat increased. Dr. Hadigan's team also found that rosiglitazone was associated with improved insulin sensitivity and increased subcutaneous fat in a study of 28 HIV positive participants, but in that study total and LDL cholesterol levels rose in the treatment arm.

Most physicians do not routinely recommend the older sulfonylurea drugs (which work by increasing insulin secretion by beta cells) for people with impaired glucose metabolism associated with antiretroviral therapy. These drugs do not directly improve insulin sensitivity and may worsen hyperinsulinemia.

Because the various antidiabetic drugs work by different mechanisms, a combination approach may be beneficial. The AIDS Clinical Trials Group is currently recruiting participants for ACTG 5082, a randomized study comparing metformin plus rosiglitazone with metformin alone or rosiglitazone alone in HIV positive people with insulin resistance and lipodystrophy (see "Open Clinical Trails" on page 50 for details).

Drug Interactions and Contraindications

Due to their potential side effects and drug interactions, antidiabetic drugs should be used with caution or avoided under certain circumstances. For example, metformin can cause lactic acidosis, a rare, life-threatening condition linked to mitochondrial toxicity associated with NRTIs (especially d4T and ddI). Therefore, people who are taking certain NRTIs or have a history or symptoms of elevated lactic acid should choose another medication or undergo careful monitoring while taking metformin. This drug should also be avoided or used with care in people with kidney problems.

The most common side effects of metformin are nausea and diarrhea (especially when the drug is first started), which could be a problem if the drug is used with antiretroviral drugs that cause similar symptoms. And, because metformin has been shown to cause weight loss, it may be a poor choice for HIV positive people with severe wasting. Conversely, for others it might be advantageous that the drug does not cause weight gain.

The thiazolidinediones can cause liver toxicity, and should be used with extreme caution and careful monitoring in people with signs of liver damage or pre-existing liver disease, including chronic hepatitis B or C. They may also present a problem for people taking antiretroviral drugs that are metabolized by the liver and are themselves associated with liver toxicity. One drug in this class, troglitazone (Rezulin), was taken off the market in 2000 after being linked to fatal liver failure. But rosiglitazone, a newer agent, appears to have less impact on the liver and fewer interactions with PIs. In a further note of caution, researchers reported in the September 9, 2003 issue of the *Mayo Clinic Proceedings* that rosiglitazone and pioglitazone (Actos) were associated with fluid buildup in the lungs and heart failure in six HIV negative men with pre-existing heart and kidney dysfunction.

Because blood glucose abnormalities and other metabolic complications often occur together in people with HIV, it is important to be aware of potential interactions between antidiabetic medications and drugs used to treat other, possibly related, conditions. For example, some research has shown that niacin (Niaspan), which is used to lower blood lipid levels, may worsen insulin resistance. People with HIV should inform their physicians and other health-care providers about all therapies they are taking, including prescription and over-the-counter medications, herbal remedies, nutritional supplements, and recreational drugs.

Conclusion

The understanding of insulin resistance, diabetes, and other metabolic complications in people with HIV has evolved rapidly in recent years, but much remains to be learned. While the exact causes of blood glucose abnormalities are not yet known, several contributing factors—including

protease inhibitors and body fat changes—have been implicated.

Fortunately, research has yielded some useful information about managing blood glucose abnormalities in HIV positive people taking antiretroviral therapy. Regular blood glucose monitoring can detect abnormalities at an early stage, before they progress to more serious conditions. Regardless of HIV status or type of therapy, lifestyle changes including weight loss (if indicated), increased exercise, and a balanced diet can make a major contribution to good health. In some cases PIs, which have been most strongly associated with blood sugar problems, can be replaced with drugs from a different class—but it is important to construct a regimen that is potent enough to maintain viral suppression. And if needed, antidiabetic medications—which are increasingly being studied in HIV positive people—are available to help control glucose and insulin abnormalities.

By working with their health-care providers to maintain a healthy blood sugar level, people with HIV can potentially prevent the development of serious long-term complications such as diabetes and cardiovascular disease.

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IN THEIR OWN WORDS

continued from page 3

only mistake is to live in the wrong part of the world. Their leaders are visionary enough to demand that the wealthy nations—we and our leaders—give everybody the same right to benefit from the progress of science. Their efforts to give the world a wake-up call deserve all our support and respect."

Mauro Guarinieri is chair of the European AIDS Treatment Group. He lives in Bologna.

Lei Chou

"What a depressing question! No, last year's crop of new anti-HIV drugs clearly demonstrated the shortcomings of a profit-based approach to clinical research and development. The three 'me-too' drugs responded to the demand of the HIV market with lower pill burden and easier dosing, but provided no significant clinical improvements such as addressing the issues of cross resistance and side effects. While T-20 [enfuvirtide, Fuzeon] does employ a new site of inhibition, it is beset by the difficulty in administration and its high cost of production, limiting its usefulness. Meaningful basic science research that is likely to find a cure is primarily done by academic and small biotech firms due to the high investment risks. Big drug companies that are profiting handsomely under the current approach of lifelong maintenance therapy have no profit incentive to change that."

Lei Chou manages the Access Project of the AIDS Treatment Data Network in New York City.

Gabe Lamazares

"I do feel that real progress is being made in the realm of combination therapy, especially in reducing pill burden, minimizing side effects, and simplifying regimens. Looking at the state of treatment even five years ago when I began therapy, I appreciate the quantum leap in treatment efficacy and tolerability. But, sorry to say, none of the advances of the past year seem to have put us any closer to a cure—a treatment that can either eradicate the virus from the system or put it into remission for a long time without daily dosing. Though we can, in many cases, keep HIV in check, we still cannot get free of it; it remains a constant companion, a time bomb that has stopped ticking for the moment. There are a few experimental 'eradication protocols' in clinical trials, but these are still shots in the dark. Where is the cure?"

Gabe Lamazares is a treatment educator and counselor at the Alliance of AIDS Services—Carolina in Raleigh.