New-onset diabetes mellitus, clinically similar to type 2 diabetes, will affect a small proportion (1%–6%) of patients infected with human immunodeficiency virus (HIV) who are treated with HIV-1 protease inhibitors (PIs). However, insulin resistance and impaired glucose tolerance will develop during PI treatment in a considerable proportion of patients. Dyslipidemia, abdominal obesity, and loss of peripheral fat frequently coexist with insulin resistance, but it is not clear whether all of these result from a common pathogenic mechanism. Recent data suggest that insulin resistance may also be associated with HIV infection in patients not receiving PI therapy. The long-term consequences of insulin resistance in this population are not known. The effect of switching to other antiretroviral therapies has not been fully determined. Treatment of established diabetes mellitus should generally follow existing guidelines. There is no clinically useful screening test that will determine the existence and degree of insulin resistance in individual patients. It is therefore reasonable to recommend general measures to increase insulin sensitivity in all patients infected with HIV, such as weight reduction for obese persons and regular aerobic exercise.

Shortly after the introduction of HIV-1 protease inhibitors (PIs) into routine clinical use, reports linking PI use with the development of hyperglycemia began to appear [1–5]. Even in the absence of overt hyperglycemia, insulin resistance appears to be associated with the use of PIs [6–11]. Although the bulk of the evidence is consistent with a direct drug effect of PIs, some newer evidence suggests that there may also be an HIV disease–associated component [12–14]. But regardless of causality, the high prevalence of insulin resistance in patients infected with HIV, which frequently coexists with dyslipidemia [15] and abdominal obesity [12, 13, 16], raises concern about the eventual development of increased cardiovascular morbidity in this population [17].

Incidence of Overt Diabetes Mellitus

The incidence of new-onset diabetes mellitus has ranged from 1% [2] to as high as 6% [3] and 7% [18]. In the latter study [18], most of the cases of diabetes mellitus were diagnosed on the basis of 2-h blood glucose values of >200 mg/dL after oral glucose tolerance testing rather than a finding of fasting hyperglycemia. A random blood glucose level of ≥180 mg/dL was found in 26 (3.3%) of 783 patients during 1997 in 1 clinic [19]. During a 1-year period, 4 (1.4%) of 290 PI-treated subjects in a well-characterized clinical cohort developed blood glucose levels ≥200 mg/dL, which corresponded to a calculated incidence of 0.35 per 100 person-months [20]. Some cross-sectional chart review studies have failed to demonstrate an increased incidence of hyperglycemia among PI recipients, but careful longitudinal studies have shown small but significant increases of fasting glucose levels after the initiation of PI therapy [7, 15] in the absence of overt diabetes mellitus. Finally, the reversal of hyperglycemia after PI therapy was withdrawn [2, 9, 21] further suggests that PIs have a direct role in the pathogenesis of diabetes mellitus in these patients.

Prevalence of Insulin Resistance/Impaired Glucose Tolerance

As is the case in the general population, the prevalence of impaired glucose tolerance (IGT) and insulin resistance significantly exceeds the prevalence of overt fasting hyperglycemia or diabetes mellitus. In other words, frank diabetes can be considered only the “tip of the iceberg” in comparison with the more widespread asymptomatic derangements of glucose metabolism in both patients infected with HIV and the general population. IGT refers to inappropriate postprandial hyper-
glycemia in the presence of normal fasting glycemia. The term "insulin resistance" is used to describe a state in which increased concentrations of insulin are required to exert its normal biological response [22], such as the efficient entry of glucose into muscle and fat cells and the suppression of hepatic gluconeogenesis. A reduction in "insulin sensitivity" is synonymous with an increase in insulin resistance.

Cross-sectional studies have documented a high prevalence of insulin resistance and IGT among PI recipients [6, 18]. Carr et al. [18] reported that, in addition to the 7% prevalence of diabetes among PI recipients, an additional 16% had IGT, defined as a 2-h post–oral glucose value of 140–200 mg/dL, at a mean of 21 months after initiation of PI therapy. However, those authors did not systematically assess glucose tolerance among PI-naive subjects. Walli et al. [6] performed iv insulin tolerance tests in 67 recipients of nucleoside reverse transcriptase inhibitors (NRTIs) plus PIs (mean duration of treatment, 14 months), 13 therapy-naive subjects, and 18 HIV-negative control subjects. The iv insulin tolerance test provides a measure of insulin sensitivity by determining the magnitude of decreases in blood glucose in response to a standardized insulin injection [23].

The median level of insulin sensitivity (figure 1) was markedly lower among PI-treated subjects (75 μmol/L/min) than among either control subjects (177 μmol/L/min) or therapy-naive subjects (156 μmol/L/min; P = .001 for the difference between PI-treated and therapy-naive persons). Using a cut-off of 2 SD below the mean for insulin sensitivity among the HIV-negative control subjects, 41 (61%) of 67 PI-treated subjects were considered to have pathological insulin sensitivity, whereas none of 13 therapy-naive subjects did [6]. Similarly, Behrens et al. [9] reported that among PI recipients, 18 (46%) of 38 had IGT detected and 5 (13%) of 38 had diabetes detected by oral glucose tolerance testing, whereas among PI-naive subjects (of whom 10 were receiving NRTIs), 4 (24%) of 17 had IGT and none had diabetes detected. Thus, it appears that the prevalence of IGT and insulin resistance is high among subjects infected with HIV who are receiving PIs. The evidence that PI therapy itself is the primary cause of abnormal glucose metabolism is summarized in table 1.

**Pathogenesis of PI-Associated Insulin Resistance and Diabetes Mellitus**

The course of development of type 2 diabetes is generally thought of as a progression from a state of euglycemia and normal glucose tolerance, where some degree of insulin resistance and decreased pancreatic reserve of B cells is detectable, to a state of IGT and then, ultimately, sustained fasting hyperglycemia [24]. Initially the B cells are capable of compensating for insulin resistance, but as the disease progresses, compensation becomes insufficient and the postprandial hyperglycemia of IGT appears. Elevated fasting insulin levels are a marker for insulin resistance in this state. Only when the B cells are no longer capable of sustaining sufficient fasting levels of insulin will the fasting hyperglycemia occur that is characteristic of type 2 diabetes mellitus (figure 2). Although

**Table 1.** Evidence for and against the notion that human immunodeficiency virus (HIV) protease inhibitors (PIs) are primarily responsible for glucose metabolism abnormalities in antiretroviral-treated HIV-infected patients.

<table>
<thead>
<tr>
<th>Evidence for</th>
<th>Evidence against</th>
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<tbody>
<tr>
<td>Cases of diabetes mellitus that developed during PI administration resolved upon withdrawal [2,6,9]</td>
<td>C-peptide levels higher both in subjects treated with PIs and subjects not treated with PIs than in control subjects [8]</td>
</tr>
<tr>
<td>Homeostasis model assessment values and insulin levels elevated in subjects treated with PIs, but not in subjects not treated with PIs, in comparison with levels in healthy control subjects [8]</td>
<td>Failure of fasting insulin levels to fall after substitution of nevirapine for PI [61]</td>
</tr>
<tr>
<td>Hyperinsulinemia develops before body composition changes with PI therapy but not with lamivudine-based therapy [7]</td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity improves after substitution of nevirapine [21] or abacavir [33] for PI</td>
<td></td>
</tr>
<tr>
<td>Greater insulin sensitivity in subjects with stable, symptomatic HIV infection than in healthy control subjects before PIs were available [47]</td>
<td></td>
</tr>
<tr>
<td>Rapid development of insulin resistance after initiation of indinavir therapy [10]</td>
<td></td>
</tr>
<tr>
<td>PIs reduce insulin-stimulated glucose uptake by adipocytes in vitro [31]</td>
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</table>
the serial development of insulin resistance, inadequate B-cell compensation, IGT, and frank diabetes mellitus in PI-treated patients has not been well described, several lines of evidence suggest that it occurs.

PI-associated diabetes mellitus has clinical characteristics similar to those of type 2 diabetes mellitus. Case series have documented that hyperglycemia is generally not accompanied by ketosis and often responds to oral hypoglycemic agents [2]. Yarasheski et al. [11] have demonstrated insulin resistance among patients who have developed diabetes during PI therapy. The absence of anti–glutamic acid decarboxylase antibodies, typical of the autoimmune islet cell destruction in type 1 diabetes, and the presence of high fasting insulin and C-peptide levels in these diabetic subjects further suggests a pathogenesis similar to that of type 2 diabetes [11].

Prospective studies have shown the relatively rapid development of insulin resistance after the initiation of PI therapy [7, 10]. Mulligan et al. [7] reported that in 20 PI-treated subjects who were studied for a mean of 3.4 months after initiation of treatment and were evaluated by use of the homeostasis model assessment (HOMA-IR [25]), fasting insulin and glucose levels and insulin resistance increased significantly (increases of 96%, 11%, and 149%, respectively). By contrast, there were no significant changes in those parameters in a control group treated with dual nucleoside–based regimens that included lamivudine but did not contain a PI; this group had similar increases in CD4 cell counts but less virological suppression.

Regional body composition determined by dual-energy x-ray absorptiometry (DEXA) did not differ among the groups, a finding suggesting that changes in total-body or regional fat were not responsible for the observed differences. However, a sensitive method for measuring visceral fat, such as CT or MRI, was not used [7], thus raising the possibility that a change in visceral fat that was inapparent by DEXA may have contributed to the differences. In addition, an effect related to the greater degree of suppression of viral RNA among those receiving PIs may have been partially responsible for the observations among PI recipients. It is worth noting that this and other studies have failed to demonstrate systemic cortisol excess in insulin-resistant subjects [11] or those with fat redistribution [26–28].

A prospective study of 11 nondiabetic subjects infected with HIV for whom indinavir therapy was initiated, in which relatively intensive measurements of insulin resistance and insulin secretion were used, has documented the serial development of similar abnormalities [10]. After 8 weeks of indinavir-based treatment, insulin sensitivity decreased by 30%, as measured by minimal model analysis of a frequently sampled iv glucose tolerance test [29] (P = .01). HOMA-IR values and fasting glucose levels also rose. A trend toward these abnormalities was noted after just the first 2 weeks of therapy, during which indinavir was administered as monotherapy [10].

One recent study suggests that inhibition of glucose transport mediated by glut-4, the predominant isoform of glucose transporter that mediates insulin-stimulated cellular uptake of glucose in humans [30], may be one mechanism responsible for PI-associated insulin resistance [31]. Exposing 3T3-L1 adipocytes to 10 μM of indinavir, which is comparable to the peak plasma concentrations of indinavir achieved with a typical human dosing regimen [32], caused a 26% decrease in insulin-stimulated glucose uptake in these cells (P < .001). The physiological relevance of this degree of glucose uptake decrease (at this indinavir level in this particular cell line) to whole-body insulin sensitivity is not clear. Nonetheless, these observations [31] are the first direct evidence of a plausible biological mechanism for PI-related insulin resistance.

High concentrations (50 μM) of the PI agents amprenavir and ritonavir also reduced 3T3-L1 adipocyte glucose uptake by a similar degree. Early insulin signaling events and translocation of glut-4 to the cell surface were not affected. At 100 μM, all 3 PIs selectively decreased glut-4 transport activity by 42%–50% in Xenopus laevis oocytes expressing both glut-1 and glut-4, whereas the activity of glut-1 (a non–insulin responsive transporter) was not decreased [31]. Further study of this mechanism and its in vivo relevance is needed.

Are PIs Primarily Responsible for Abnormal Glucose Metabolism?

A direct effect of PIs in inducing insulin resistance in patients infected with HIV is suggested by the following: reversal of hyperglycemia after PI withdrawal [2, 6, 9]; onset of hyperinsulinemia before measurable body composition changes in PI recipients [7]; improvement in insulin sensitivity after substitution of the NNRTI nevirapine [21] or the NRTI abacavir [33] for PI; a trend toward reduced insulin sensitivity after only 2 weeks of indinavir monotherapy [10]; and an in vitro effect of PIs on insulin-stimulated glucose uptake by adipocytes [31]. These all suggest that PIs have a direct effect on inducing insulin resistance in patients infected with HIV (table 1). However, studies of PI treatment in subjects infected with HIV can be
confounded by the effects of immune reconstitution, immune activation, concurrent nucleoside reverse transcriptase therapy, and refeeding phenomena.

In the era before PIs were available, reported abnormalities in glucose metabolism were limited primarily to the pancreatic effects of drugs such as pentamidine [34–40] and didanosine [41–46]. One study of clinically stable subjects infected with HIV actually showed an increase in insulin sensitivity in comparison with that in healthy control subjects [47], as measured by the highly sensitive and reproducible euglycemic, hyperinsulinemic clamp technique. However, more recent cross-sectional data suggest that HIV infection itself and perhaps NRTI therapy may be associated with truncal obesity and insulin resistance [12, 13]. In women infected with HIV there was increased truncal adiposity and fasting hyperinsulinemia that was independent of PI use [12]. These same authors also reported increased fasting insulin levels and insulin resistance, as measured by HOMA-IR, in wasting NRTI-treated male subjects but not in wasting PI-treated men, in comparison with control subjects [13].

These data suggest that factors other than PIs can be involved but should be viewed as provocative rather than conclusive; they are not as compelling as longitudinal data documenting the development of insulin resistance in PI-treated subjects after initiation of PI therapy. It is also possible that PI therapy may exaggerate an underlying tendency to develop insulin resistance. Other drugs commonly used in the treatment of patients infected with HIV that can affect glucose metabolism are listed in table 2.

B-Cell Function and HIV

Pancreatic B-cell function, or insulin secretion, might also be affected by HIV infection or its treatment. As mentioned earlier, a decrease in B-cell responsiveness to glucose is a necessary component of the cascade of events that culminate in the development of overt diabetes mellitus [24]. It is important to note that an elevated fasting insulin level alone is not synonymous with intact B-cell function and does not serve as an estimate of B-cell responsiveness. In individuals at high risk for developing type 2 diabetes mellitus, defects in insulin secretion can be demonstrated before insulin resistance is demonstrated [48] and can predict the ultimate progression to IGT and diabetes mellitus [49, 50]. Therefore, in order for patients infected with HIV to develop PI-associated glucose intolerance and diabetes, there presumably must also be some component of either heritable or acquired B-cell dysfunction.

There are few published data on B-cell function in patients infected with HIV. Abnormalities have been reported in the proinsulin/insulin ratio, a marker of B-cell dysfunction [51], in subjects with PI-associated diabetes mellitus [11] and PI-treated subjects [9]. The first-phase insulin response to iv glucose and the 30-minute insulin:glucose response to oral glucose failed to increase among prospectively evaluated nondiabetic subjects who developed insulin resistance while receiving indinavir [10]. The finding that fasting plasma glucose rose significantly and insulin secretion failed to increase commensurate to increases in insulin resistance suggests that PI use may also be associated with defects in B-cell function. The relative contributions of genetically determined and drug-related defects in insulin secretion have not been defined in this population and deserve further study.

### Table 2. Drugs other than protease inhibitors that are commonly used in the treatment of patients infected with human immunodeficiency virus and may alter glucose metabolism.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Glucocorticoid</td>
<td>Insulin resistance</td>
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<tr>
<td>Megesterol acetate</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Androgenic steroid*</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td>B-cell dysfunction</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>B-cell dysfunction</td>
<td></td>
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</tbody>
</table>

* May increase or ameliorate insulin resistance, depending on the setting.

### Relationship between Insulin Resistance and Fat Redistribution

Comparisons between studies of lipodystrophy or fat redistribution are hampered by the different definitions of lipodystrophy used. Different studies may define “lipodystrophy” as peripheral-fat wasting or central obesity or both, and the case definition in some studies has required the existence of a concurrent metabolic abnormality. These differences appear to account for widely differing conclusions from these cohort studies [52] and may make it difficult to definitively establish relationships between body-shape abnormalities and metabolic dysregulation.

Some studies—but not all—have shown a correlation between lipodystrophy, dyslipidemia, and insulin resistance [8, 18, 53]. In the cohort described by Carr et al. [8], subjects receiving PIs had greater insulin resistance, as measured by HOMA-IR values, than did healthy control subjects, and those with clinical lipodystrophy (peripheral-fat wasting or abdominal obesity) while receiving PIs had greater HOMA-IR values than those receiving PIs but who did not have lipodystrophy. Increasing lipodystrophy severity was associated with a trend toward increasing HOMA-IR values ($P = .06$) and was predicted by higher antecedent fasting C-peptide levels ($P = .0001$) and tri-glyceride levels ($P = .026$); these findings suggest that these abnormalities may be related [8]. Similarly, among PI-treated subjects with marked facial-fat wasting, 11 (79%) of 14 had either diabetes (5 subjects) or insulin resistance (6 subjects) detected during oral glucose tolerance testing [54]. In contrast, 4 (20%) of 20 PI-treated subjects without facial-fat wasting had glucose metabolism abnormalities detected. The incidence of hypertriglyceridemia was also greater among those with facial-fat wasting (79%) than among those without (35%).

Although an association certainly exists, these abnormalities...
may not necessarily be causally related. Recent cohort studies have shown that nucleoside reverse transcriptase therapy may be associated with syndromes of peripheral-fat loss [55–58], possibly because of nucleoside-related mitochondrial toxicity [59]. Subjects who experienced lipodystrophy while receiving PIs plus NRTIs had elevated HOMA-IR values, whereas those with lipodystrophy while receiving only NRTIs did not [57], which suggests that lipodystrophy may not directly contribute to insulin resistance. Similarly, the substitution of abacavir for a PI in NNRTI-naive patients. Lipid values also improved, but fasting insulin and C-peptide levels did not improve [60]. In that study, only those subjects receiving NRTIs plus a PI had higher C-peptide levels than control subjects without fat-wasting; those with fat-wasting while receiving only NRTIs did not. Both groups had elevated triglyceride levels.

Taken together, the data suggest a strong correlation between dyslipidemia, insulin resistance, and PI use, whereas lipodystrophy per se commonly accompanies these abnormalities but may be associated more directly with nucleoside analog use. Ultimately, studies of animal models and healthy volunteers, free of the confounding influences of HIV disease-related factors and concurrent medications, should help clarify the specific role of PIs in abnormalities of glucose metabolism, as well as the interrelationships between dyslipidemia and insulin resistance.

Effects of Switching Antiviral Therapies

Use of an antiviral agent with a lesser tendency to induce insulin resistance would be expected to be beneficial, as long as virological control is maintained and troublesome new toxicities are not introduced. However, few studies have reported detailed evaluations of insulin sensitivity after such a switch. Martinez et al. [21] reported a significant improvement in a fasting insulin resistance index (FIRI, which reflects the product of fasting glucose and insulin) after substituting nevirapine for a PI in NNRTI-naive patients. Lipid values also improved, but dietary intake and physical activity information was not reported, so some of the observed improvements may have been due to other factors. A similar single-arm study that also used only fasting collections failed to confirm their results [61].

The substitution of efavirenz for a PI resulted in improvement in FIRI and serum triglyceride values for 20 subjects in a preliminary report [62]. Improvement in insulin sensitivity measured by iv insulin tolerance testing occurred after the substitution of abacavir for a PI [33]. High rates of virological relapse after substitution of an NNRTI or abacavir for a PI have not been reported, but in general the numbers of subjects reported and the duration of follow-up in many of these trials have been limited. Substitution of nelfinavir for indinavir for subjects who developed diabetes while receiving indinavir appeared promising initially [63], but longer-term follow-up has revealed virological relapses and recurrences of hyperglycemia (author’s unpublished observations).

Clinicians will need to weigh the risks of new treatment-related toxicities and the possibility of virological relapse when switching antiviral drugs in diabetic and insulin-resistant patients. At the present time, no general guidelines are available for this decision-making process.

Differences among the PIs in Their Effects on Glucose Metabolism

Few systematic comparisons of the relative tendencies of different antiretroviral agents to induce insulin resistance have yet been made. Greater insulin resistance was measured in indinavir recipients than in those treated with nelfinavir or saquinavir in a nonrandomized cross-sectional study [6], but tests of statistical significance were not reported. Carr and colleagues initially reported a greater prevalence of lipodystrophy and higher fasting insulin levels among ritonavir-saquinavir recipients than indinavir recipients [8], but follow-up of this cohort failed to show persistent differences [18]. Although data for mice suggest that different PIs have different effects on glucose and lipid metabolism [64], results have not consistently reflected the established data concerning humans, and the relevance of these data to clinical situations is not clear. Establishment of a reproducible and relevant animal model of insulin resistance and secretion, as well as comparative studies of the different PIs, is needed to help identify the agents with the least detrimental effects on glucose metabolism.

Evaluation of Patients

The clinical estimation of insulin sensitivity in individual patients is hampered by the lack of a single, clinically useful measure of insulin sensitivity. The euglycemic hyperinsulminemic clamp technique, iv insulin tolerance testing, and minimal model analysis of iv glucose tolerance testing should be considered research tools. HOMA-IR values, which are calculated from fasting insulin and glucose levels, correlate well with the findings of more invasive techniques [25], but HOMA-IR values are subject to considerable intra-individual variability and lack a clear threshold distinguishing normal from abnormal values. It has been suggested that all patients receiving PI therapy should undergo oral glucose tolerance testing on a regular basis [18], but the utility of this approach has not been evaluated, and it is not clear that the discovery of IGT in a patient with normal fasting glucose values should necessarily prompt additional diagnostic and therapeutic intervention. Certainly it is reasonable to recommend the regular measurement of fasting glucose, particularly in those patients with traditional risk factors for type 2 diabetes [65] (table 3) in all HAART recipients. The utility of other measurements should be evaluated in prospective studies.

Given the high prevalence of insulin resistance, it is a rea-
Major risk factors for type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Having a first-degree relative who has type 2 diabetes</td>
<td></td>
</tr>
<tr>
<td>Obesity (&gt;20% over ideal body weight)</td>
<td></td>
</tr>
<tr>
<td>Being Hispanic, black, native American, Asian-American, or a Pacific Islander</td>
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<tr>
<td>Age &gt;45 years</td>
<td></td>
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<tr>
<td>Prior impaired fasting glucose level or impaired glucose tolerance</td>
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<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>History of gestational diabetes mellitus or of being a large-for-gestational-age baby (&gt;4.05 kg)</td>
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</tbody>
</table>

NOTE: Table is adapted from [65].

The diabetes and insulin resistance that occur during antiretroviral therapy appear to have a clinical appearance similar to the common form of type 2 diabetes in the general population. Thus, treatments that are appropriate for established type 2 diabetes and persons at risk for type 2 diabetes are also reasonable for patients infected with HIV with these disorders. No controlled studies of diabetes mellitus treatment among patients with HIV have been performed. However, reported cases have been typically nonketotic and often treatable with oral hypoglycemic agents [2, 6, 9]. Sulfonylurea agents, which stimulate insulin secretion, and exogenous insulin are probably safe for diabetic patients infected with HIV. However, these therapies will not directly address insulin resistance and may exacerbate hyperinsulinemia. Metformin acts primarily by increasing insulin sensitivity and reducing hepatic glucose output, but because NRTI therapy may be associated with lactic acidosis [57, 66] and metformin is rarely associated with serious lactic acidosis [67–69], theoretical concern exists about the concurrent use of NRTIs and metformin.

Thiazolidinediones (or glitazones), such as rosiglitazone and pioglitazone, which increase peripheral insulin sensitivity and lower triglyceride levels, are attractive agents. They also have the potential to increase subcutaneous fat and reduce visceral adiposity [70, 71]. Study of these agents in the HIV-infected diabetic population is urgently needed, but until additional safety data become available, they cannot be recommended for routine use. An older agent in this class, troglitazone, was recently removed from the market by the Food and Drug Administration in the United States because of concerns about hepatotoxicity [72]. Although there are similar concerns about troglitazone [73, 74], the bulk of evidence suggests that this agent has minimal hepatic effects [75, 76]. Rosiglitazone lacks the extensive CYP3A4 metabolism of troglitazone and thus would be expected to have fewer potential drug interactions with PIs [75].

Metformin and the thiazolidinediones and may be useful in treatment for insulin resistance, even in the absence of diabetes mellitus. Administration of metformin was effective as therapy in a controlled, randomized study of nondiabetic subjects infected with HIV who were receiving PI therapy and had abdominal obesity with insulin resistance, as defined by a fasting insulin concentration of >20 mIU/mL plus elevated insulin levels after administration of oral glucose [77]. At the relatively high dose of 850 mg t.i.d. for 2 months, metformin treatment was associated with significant decreases in weight (2.8-kg decrease), fasting levels of glucose (12% decrease), insulin (41% decrease), C-peptide (19% decrease), and triglycerides (33% decrease). The quantity of visceral fat measured by abdominal CT scanning also decreased, whereas all these parameters remained the same or tended to increase slightly in the control group. However, because metformin use is frequently associated with anorexia and diarrhea, it was not clear whether the changes noted with use of metformin were primarily due to a direct drug effect or due to a secondary decrease in nutrient intake. A recent placebo-controlled trial using a lower dose of metformin (500 mg b.i.d.) in subjects with fasting hyperinsulinemia and abdominal obesity also showed reduced insulin resistance [78]. There was a proportional reduction in subcutaneous and visceral fat, raising the possibility that metformin could potentially worsen lipoatrophy. Controlled trials are needed of metformin and glitazones using detailed assessments of insulin sensitivity, body composition, and nutrient intake. There are insufficient data to recommend the routine use of insulin-sensitizing drugs by insulin-resistant patients infected with HIV.

It is reasonable to routinely recommend diet and exercise for those individuals at high risk for HIV-related insulin resistance or diabetes mellitus. These interventions are known to improve the insulin resistance of type 2 diabetes mellitus and are accepted general health measures [79–81]. Unfortunately, few data exist that specifically address the utility of reducing obesity in patients infected with HIV or having them exercise more. Preliminary results from a 16-week weight-training program showed that it increased muscle strength and lean mass and reduced triglyceride concentrations, but it failed to lower fasting insulin and C-peptide levels [82].

Studies of aerobic exercise, which is generally recommended for patients with type 2 diabetes [81], have not been performed with insulin-resistant patients infected with HIV. Nonetheless, it is reasonable to recommend the routine use of regular aerobic exercise as a general health measure, with the expectation that insulin sensitivity and levels of blood lipids will improve. Because aerobic training may reduce subcutaneous fat, it may exacerbate fat wasting, so modest amounts of exercise (e.g., 30 minutes of aerobic activity daily) may be preferable to more intensive training routines.
It is likewise reasonable to recommend weight reduction for obese persons, although this approach also has not been evaluated in controlled trials with patients infected with HIV. The recommendations of the American Diabetic Association for diet are conservative and represent one reasonable approach for persons infected with HIV who are diabetic or are at risk for insulin resistance [80]. Patients receiving PI therapy, plus those with the traditional risk factors for type 2 diabetes (table 3) [65], represent those at greatest risk. These individuals’ diets should be composed of 50%–60% carbohydrates, mostly complex carbohydrates, and protein intake should be 10%–20% of all calories; total fat intake should be restricted to ≤30% of total calories, with saturated fat limited to ≤10% of total calories, and total cholesterol intake should be <300 mg/d [80].

These general recommendations would also be expected to help ameliorate dyslipidemia. Again, because weight loss may exacerbate fat wasting, clinicians will need to monitor patients for this effect. Dietary and exercise prescription will be particularly problematic for those individuals who have both peripheral-fat wasting and central obesity, who may have competing dietary needs. Finally, dietary treatment of wasting should generally take precedence over treatment of dyslipidemia and insulin resistance until there is improvement in overall health and functional status.

Conclusions

Regardless of its causes, abnormal glucose metabolism that occurs during the course of HIV infection and its treatment is a prevalent condition that is typically difficult to diagnose by using routine screening tests. The sustained fasting hyperglycemia of overt diabetes mellitus represents only the “tip of the iceberg” of the entire spectrum of glucose dysregulation. The frequent coexistence of dyslipidemia and abdominal obesity raises concerns about increased cardiovascular morbidity. PI therapy is a primary cause of insulin resistance, but the effect of switching to other antiviral therapies has not been fully determined.

Metformin and the thiazolidinediones are promising drugs that may also help ameliorate body-shape abnormalities, but more clinical safety and efficacy data are needed before their routine use can be recommended. As with type 2 diabetes among the HIV-uninfected population, diet and exercise interventions are reasonable but of unproven efficacy in the HIV-infected population. Further study of the prevalence, incidence, risk factors, pathophysiology, and treatment of HIV-associated disorders of glucose metabolism is clearly needed.

Note added in proof. Since this paper was submitted, Noor and colleagues have shown that normal subjects without HIV infection develop insulin resistance when given indinavir monotherapy for 4 weeks [83]; this finding further strengthens the role of PIs in insulin resistance.

Acknowledgment

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References

63. Tebas P, Yarasheski K, Powderly WG, et al. A prospective, open-label pilot trial of a maintenance nevirapine-containing regimen in patients with undetectable viral loads on protease inhibitor regimens for at least 6 months [abstract 45]. In: Program and abstracts of the 7th Conference on Retro...


