Increased Risk for Type 2 Diabetes Mellitus With HIV-1 Infection

John G. Ryan, DrPH
Department of Family Medicine and Community Health, University of Miami Miller School of Medicine, Miami, Florida

ABSTRACT

Background: The proportion of people with HIV-1 infection who have coexisting type 2 diabetes mellitus (DM) is increasing. The higher incidence of type 2 DM in this patient population is associated with increased survival from HIV-1 infection due to advanced HIV treatment strategies and therapies, as well as a complex interaction of diabetes risk factors, including family history, body composition, comorbidities, HIV treatment modality, and disease progression.

Objective: The purpose of this article was to describe the impact of these contributing factors on the risk for type 2 DM among people with HIV-1 infection and the available treatment options for managing type 2 DM in these patients.

Methods: The Ovid MEDLINE database was searched for English language articles published between January 2005 and June 2009. Various search strategies were applied to identify appropriate articles. The references listed in the retrieved documents were searched for additional articles. Nonhuman studies were excluded.

Results: Abnormal glucose homeostasis and metabolic disturbances associated with HIV-1 infection appear to have become widespread after the introduction and application of potent antiretroviral therapy, including protease inhibitors (PIs), ritonavir-boosted PIs, nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs). PIs and NNRTIs may have pathogenic roles in insulin resistance, whereas the stage and progression of HIV-1 infection affect lipid values and glucose homeostasis. It is estimated that as many as 80% of patients currently treated with PIs develop insulin resistance compared with ~2% before the introduction of highly active antiretroviral therapy. Evidence suggests that statins may be contraindicated as a combination therapy with PIs when comanaging dyslipidemia and HIV-1 infection. Pharmacotherapy for HIV-1 infection must be monitored closely for its impact on patients' metabolic and cardiovascular systems, and necessary modifications made while monitoring and maintaining the stability of the viral load.

Conclusions: The metabolic effects of combination therapies for HIV infection, including PIs, ritonavir-boosted PIs, NRTIs, and NNRTIs, appear to increase the risk for insulin resistance, type 2 DM, and poor cardiovascular disease outcomes. Because of differences in the pharmacokinetic properties between statins and PIs, it is critical for clinicians to properly manage combination antiretroviral therapy, as well as pharmacotherapy for DM and dyslipidemia, when managing patients with HIV-1 infection and insulin resistance. Clinicians must consider the stage of HIV disease and the demographic characteristics of patients with these comorbid diseases, both of which require careful attention to medical management, pharmacotherapy, and patient adherence to treatment recommendations. (*Insulin*. 2010;5:37–45)
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Key words: HIV-1, type 2 diabetes mellitus, dyslipidemia, insulin resistance, hepatitis C virus, protease inhibitors.

INTRODUCTION

Abnormal glucose homeostasis and metabolic disturbances associated with HIV-1 infection include lactic acidosis, reduced bone mineral density, hypertriglyceridemia, hypercholesterolemia, abnormal fat distribution (also known as lipodystrophy), and abnormal carbohydrate metabolism.[1] These conditions became increasingly common among people with HIV-1 infection after the widespread introduction and subsequent use of potent antiretroviral therapy, such as highly active antiretroviral therapy (HAART).[2] The introduction of HAART has changed the natural history of HIV-1 infection and led to marked reductions in morbidity and mortality. However, mounting evidence suggests an association between HAART and increased metabolic and cardiovascular risk, including risk for type 2 diabetes mellitus (DM).

Today, estimates of the proportion of patients treated with protease inhibitors (PIs) who develop insulin resistance may be as high as 80%[3,4] compared with ~2% before the advent of HAART.[5,6] Relatively recent prospective data from long-term studies of HIV-1–infected patients provide further evidence of an increased risk for metabolic complications.[7,8] These studies also suggest an even more complex interaction among the risk factors of family history, body composition, comorbidity with hepatitis C virus (HCV), HIV treatment modality, and disease progression.[7,8]

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The purpose of this article was to describe the impact of these contributing risk factors for type 2 DM among patients with HIV-1 infection and the treatment options available for these patients.

METHODS

The Ovid MEDLINE database was searched for English language articles published between January 2005 and June 2009. Various search strategies were applied to identify appropriate articles. The references listed in the retrieved documents were searched for additional articles. Nonhuman studies were excluded.

RESULTS

Risk Factors for Type 2 DM Among HIV-1–Infected Patients

Family History

Although linked in some small-scale studies,[7,9] the extent to which family history may be associated with new cases of type 2 DM among individuals with HIV-1 infection is equivocal. For example, in a study of 150 HIV-infected patients (50 cases and 100 controls) receiving combination antiretroviral therapy in Taiwan,[9] incident DM was associated with family history (P = 0.02), exposure to zidovudine[a] (P = 0.115), and current use of PIs (P = 0.03). Cases were defined as HIV-infected patients aged ≥15 years with new-onset DM diagnosed on the basis of ≥2 separate fasting blood glucose (FBG) levels >126 mg/dL during follow-up. Patients were excluded from the study if they had prevalent DM at the time of recruitment to the cohort, or if hyperglycemia was evident with coexisting pancreatitis, or concomitant use of steroids or total parenteral nutrition. A case-control study of 147 participants at an urban HIV clinic,[7] in which 2 controls (n = 98) were matched to each case of incident DM (n = 49), found that increased body mass index (BMI) (P = 0.012), family history (P = 0.014), and the presence of alanine aminotransferase (P = 0.012) were associated with type 2 DM.

On the other hand, a family history of type 2 DM was not associated with the incidence of DM among women participating in the Women's Interagency HIV Study (WIHS).[10] This large, prospective, observational study enrolled 3766 women from 6 US cities (Bronx, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington, DC) during the periods 1994 to 1995 and 2001 to 2002. In a substudy of 2088 participants who did not have evidence of DM at enrollment (1524 with HIV and 564 without HIV), family history was not associated with incident DM (P = 0.289). Incident DM was defined as having an FBG level ≥126 mg/dL, reported use of antidiabetes medication, or a documented diagnosis of DM with subsequent confirmation based on the patient's FBG level or documented use of antidiabetes medication.

A second large, prospective, observational study—the Multicenter AIDS Cohort Study (MACS)[11]—also did not provide evidence for an association between family history of DM and incident DM among individuals infected with HIV-1. The MACS enrolled 5622 homosexual and bisexual HIV-seronegative and HIV-infected men, with heterogeneous exposure to antiretroviral therapies between 1984 and 1991. Participants were followed through semiannual study visits at sites located in Pittsburgh, Baltimore, Chicago, and Los Angeles. Study data included basic demographic characteristics, results of a focused physical examination, detailed clinical data (from which participants could be classified as having generalized lymphadenopathy and self-identified AIDS-related clinical signs or symptoms of specific sexually transmitted diseases ≥6 months before study entry), and sexual histories. The HIV status of each participant was unknown at baseline. Of the 5622 participants enrolled in the MACS, 1278 had ≥1 blood specimen drawn between April 1, 1999, and March 31, 2003, from which fasting (≥8 hours) serum concentrations were determined. After adjusting for family history of DM in a reanalysis of the MACS data,[12] the ratio of HIV-infected men receiving HAART compared with men without HIV decreased 5%, from 4.1 (95% CI, 1.85–9.16) to 3.9 (95% CI, 1.75–8.72).

Body Composition

Intra-abdominal adiposity and peripheral fat depletion are morphologic phenomena that occur in lipodystrophy and lipoatrophy. Both lipodystrophy and lipoatrophy have been found in the majority of HIV-1–infected patients receiving antiretroviral therapy.[13] These abnormalities in body composition have been reported in 40% to 50% of HIV-1–infected patients who were followed in an ambulatory setting.[14–16] Reported prevalence rates of body fat redistribution varied widely, from 11% to 83%; the prevalence of lipoatrophy may be even higher.[17]

Cumulative exposure to nucleoside reverse transcriptase inhibitors (NRTIs), along with current use of thymidine analogues, particularly stavudine,[b] has been implicated in these metabolic abnormalities.[18–21] Fat redistribution through these syndromes is likely to contribute to altered secretion of adipokines, promotion of insulin resistance, and the cluster of cardiometabolic risk factors associated with metabolic syndrome, including obesity, impaired fasting glucose (IFG), hypertension, low levels of high-density lipoprotein cholesterol (HDL-C), and elevated triglyceride levels.[22] Both metabolic syndrome and insulin resistance are factors in the development of type 2 DM and cardiovascular disease (CVD).[23]

Insulin resistance is characterized by the body's inability to respond to and use the insulin that it produces from pancreatic β-cells. The risk of insulin resistance and diabetes in HIV-infected patients receiving antiretroviral therapy stems from the same environmental risk factors that are responsible for the increased incidence of these conditions in the general population, and from the metabolic impact associated with antiretroviral therapy.[24] Insulin is essential for

[a]Trademark: Retrovir® (GlaxoSmithKline, Research Triangle Park, North Carolina).

[b]Trademark: Zerit® (Bristol-Myers Squibb Company, Princeton, New Jersey).

delivering glucose to skeletal muscle and the liver for energy. The transition from normal glucose tolerance to impaired glucose tolerance (IGT) occurs when the imbalance from insufficient amounts of insulin are available to deliver glucose to skeletal muscle and the liver, along with decreased uptake of glucose by skeletal muscle, results in higher concentrations of glucose in the bloodstream. The determination of IGT is based on the patient's fasting (no caloric intake for ≥8 hours) plasma glucose (FPG) level. An oral glucose tolerance test (OGTT) is performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[25] The criterion for IGT is an FPG level ≥126 mg/dL, or a 2-hour postload plasma glucose level ≥200 mg/dL during an OGTT.[26]

HCV Infection

Chronic infection with HCV has been linked to a greater prevalence of type 2 DM, insulin resistance, and dyslipidemia in non–HIV-infected populations.[27,28] It is estimated that the coinfection rate of HIV and HCV is 30%.[29,30] Persons coinfected with HIV-1 and HCV may have higher incidences of insulin resistance and lipodystrophy associated with the use of antiretroviral therapy than persons infected with HIV-1 but not HCV.[31] Consequently, strong evidence suggests that HCV infection and antiretroviral drugs are contributors to insulin resistance among HIV-1–infected individuals.[32,33] Coinfection with HCV has not consistently been found to be a risk factor for incident DM. In a study previously described,[7] no statistical association between incident DM and coinfection with HCV was identified (P = 0.066), although coinfection was more common in case patients than in controls.

Coinfection may have synergistic effects on glucose and lipid metabolism in the liver of HIV-1–infected individuals.[34] Although HIV and HCV have been linked to metabolic syndrome, they demonstrate similar pathophysiologic pathways. The same risk factors for metabolic syndrome (older age, high BMI, and insulin resistance) are also associated with hepatic and metabolic dysfunction, leading to steatosis with steatohepatitis and other complications. Accumulation of visceral adipose tissue is thought to increase free fatty acid influx to the liver. In addition, visceral adipose tissue is likely to secrete cytokines and adipokines that act on the liver.[34]

HIV Treatment Modality

Evidence linking treatments for patients with HIV-1 infection and metabolic complications has been reported since the early days of HIV treatment. A subset of patients who received pentamidine[c] (by inhalation or intravenously) for the treatment and prevention of *Pneumocystis jiroveci* pneumonia (previously called *Pneumocystis carinii* pneumonia) was found to have β-cell toxicity with symptoms of acute hypoglycemia. A small group of these patients progressed to hyperglycemia with low C-peptide levels, suggesting significant β-cell destruction.[35–37]

More recently, evidence from 3 large, prospective, observational studies—the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study,[38–40] the MACS,[11,12,41,42] and the WIHS[10]— provided new insights into potential associations between HIV therapy and incident DM. The D:A:D study investigated the risk of myocardial infarction (MI) in 33,347 HIV-infected participants.[38,39,43,44] Incident DM was a secondary study end point. Patients were enrolled in 1 of 11 cohorts from December 1999 to April 2001 and followed up with visits to outpatient clinics scheduled as part of regular care until January 2005.[45] All eligible patients were under active follow-up at the time of initiation, irrespective of antiretroviral treatment status. Data were collected on HIV infection, risk factors for MI, and the incidence of MI. In these patients, representing >130,151 patient-years of follow-up (PYFU), DM was diagnosed in 744 patients, with an incidence of 5.72 per 1000 PYFU. The incidence of DM increased with cumulative exposure to combination antiretroviral therapy. Compared with patients who were not exposed to the nucleoside analogues stavudine, zidovudine, and didanosine,[d] patients who were exposed had an increased incidence of DM: stavudine (relative risk [RR] = 1.13; P = 0.001), zidovudine (RR = 1.05; P = 0.01), and didanosine (RR = 1.06; P = 0.02). Conversely, patients who were exposed to ritonavir[e] (RR = 0.94; P = 0.01) and nevirapine[f] (RR = 0.89; P = 0.001) experienced a reduced risk.[40]

In the MACS,[41] after adjusting for age and BMI, 14% of the HIV-infected men using HAART at the index visit had prevalent type 2 DM compared with 5% of the HIV-seronegative men. The rate of incident type 2 DM was 4.7 cases per 100 person-years among HIV-infected men using HAART compared with 1.4 cases per 100 person-years among HIV-seronegative men during the 4-year observation period, suggesting that the incidence of type 2 DM in HIV-infected men exposed to HAART was >4 times that in HIV-seronegative men. The WIHS[46] also revealed 2.8 cases of incident type 2 DM per 100 person-years during a 2.9-year follow-up period, or 3% of patients.

HIV Disease Progression

The stage of HIV disease and rate of viral replication were found to directly influence lipid values and glucose homeostasis in the absence of antiretroviral therapy.[47] Inflammation (elevated proinflammatory markers, including C-reactive protein, tumor necrosis factor-α, interleukin-6, and low levels of adiponectin) is known to contribute to the progression of insulin resistance and type 2 DM. A similar profile has been reported for patients treated for HIV-1 infection.[48] Increased noninsulin-mediated glucose uptake among

[c]Trademark: Nebupent® (Astellas Pharma US, Inc., Deerfield, Illinois).

[d]Trademark: Videx® (Bristol-Myers Squibb Company, Princeton, New Jersey).
[e]Trademark: Norvir® (Abbott Laboratories, North Chicago, Illinois).
[f]Trademark: Viramune® (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut).

patients with HIV-1 infection is explained by increased nonoxidative glucose disposal.[49] Advanced HIV disease is associated with lower HDL-C and low-density lipoprotein cholesterol levels and higher very-low-density lipoprotein cholesterol and triglyceride levels.[5]

Treatment

Managing HIV-1 Infection

Great strides have been made in the treatment of HIV-1 infection, due in large part to the contributions of HAART (any potent combination of agents that can reduce the plasma HIV level to less than the level that can be detected by assay).[50] HAART is known to alter the condition from one with a high mortality rate to one with long-term survival with appropriate pharmacotherapy managed by clinicians, along with patient self-management, with particular emphasis on medication adherence and stress reduction. Nevertheless, pharmacotherapy for HIV-1 infection must be monitored closely for impact on other systems and modified as needed to reduce cardiovascular, hepatic, and renal risks as significant comorbidities, while maintaining the stability of the viral load. Based on a number of publications in the peer-reviewed medical literature,[51–56] the US Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents[57] suggests that better medical outcomes are achieved when individuals infected with HIV-1 are treated in the outpatient setting by a clinician with expertise in HIV infection.

Treatment for HIV-1 infection should incorporate current recommendations by the DHHS panel[57] and the International AIDS Society–USA panel,[58] while also taking into consideration the patient's risk profile for abnormal glucose metabolism. Both the DHHS panel and the AIDS Society–USA panel recommend initiating therapy with 2 NRTIs, plus a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a PI (boosted with ritonavir or unboosted). The selection of nevirapine or abacavir[g] as an initiation regimen should take into consideration factors such as comorbid conditions, potential adverse drug effects, potential drug interactions with other medications, pregnancy or the potential for pregnancy, results of genotypic drug-resistance testing, gender, patient adherence potential, and convenience of use.[57]

The preferred NRTI combination recommended by the DHHS panel[57] is tenofovir/emtricitabine.[h] Alternative dual NRTI combinations are: abacavir/lamivudine[i]; didanosine with lamivudine or emtricitabine[j]; and zidovudine/lamivudine.[k]

The preferred NNRTI is efavirenz,[l] except during the first trimester of pregnancy or in women with a high potential for pregnancy. The alternative NNRTI is nevirapine.

The DHHS panel[57] recommends specific ritonavir-boosted (r) PIs or unboosted PIs when initiating treatment for HIV-1 infection. The preferred PIs include: atazanavir/r[m] once daily (AI); darunavir/r[n] once daily (AI); fosamprenavir/r[o] twice daily (BI); and lopinavir/ritonavir (coformulated)[p] once or twice daily (AI).

Alternative PIs include: unboosted atazanavir once daily; unboosted fosamprenavir twice daily; fosamprenavir/r once daily; and saquinavir/r twice daily.

In cases in which tenofovir[q] or efavirenz is used with atazanavir, ritonavir 100 mg/d must also be given. The reader is referred to a more thorough description of the DHHS guidelines, which are updated whenever relevant.[59]

The AIDS Society–USA panel[58] recommends use of the NRTI combinations tenofovir/emtricitabine or abacavir/lamivudine, plus either the NNRTI efavirenz or a ritonavir-boosted PI. However, efavirenz is associated with lipoatrophy when given with thymidine analogue reverse transcriptase inhibitors; the ritonavir-boosted PIs lopinavir and fosamprenavir are associated with hyperlipidemia, including hypertriglyceridemia.[58] For patients with a high-risk profile for metabolic disorders, the ritonavir-boosted PIs atazanavir, darunavir, and saquinavir have not been associated with abnormal glucose homeostasis, although these agents have disadvantages that must be considered, including occasional nephrolithiasis, reduced effectiveness when combined with proton pump inhibitors (atazanavir), rash (darunavir), high pill burden (saquinavir), and increased bioavailability of certain statins used concomitantly (eg, saquinavir).[58,60] Alternatively, substitution of the PI component of the regimen with an NNRTI (nevirapine[61] or efavirenz[62]) or the NRTI abacavir[63] has been associated with short-term improvements in insulin resistance and may be considered for patients at risk for DM.[2]

Managing Type 2 DM in Patients With HIV-1 Infection

Fat redistribution in the form of lipoatrophy and lipodystrophy, common syndromes among patients with HIV-1 infection, is associated with insulin resistance and metabolic disorders,[60,64] including IFG, DM, hypertriglyceridemia, and reduced levels of HDL-C.[46] Patients without DM but with a high-risk profile based on the presence of ≥1 of 3 factors (ie, type 2 DM in a first- or second-degree relative; belonging to

[g]Trademark: Ziagen® (GlaxoSmithKline, Research Triangle Park, North Carolina).
[h]Trademark: Truvada® (Bristol-Myers Squibb Company, Princeton, New Jersey, and Gilead Sciences, Inc., Foster City, California).
[i]Trademark: Epzicom® (GlaxoSmithKline, Research Triangle Park, North Carolina).
[j]Trademark: Emtriva® (Bristol-Myers Squibb Company, Princeton, New Jersey, and Gilead Sciences, Inc., Foster City, California).
[k]Trademark: Combivir® (GlaxoSmithKline, Research Triangle Park, North Carolina).
[l]Trademark: Sustiva® (Bristol-Myers Squibb Company, Princeton, New Jersey).
[m]Trademark: Reyataz® (Bristol-Myers Squibb Company, Princeton, New Jersey).
[n]Trademark: Prezista® (Tibotec Therapeutics, Bridgewater, New Jersey).
[o]Trademark: Lexiva® (GlaxoSmithKline, Research Triangle Park, North Carolina).
[p]Trademark: Kaletra® (Abbott Laboratories, North Chicago, Illinois).
[q]Trademark: Viread® (Gilead Sciences, Inc., Foster City, California).

a certain race/ethnic group, such as Native American, African American, Hispanic American, Asian/South Pacific Islander; or signs of insulin resistance or conditions associated with insulin resistance[65]) or manifesting fat redistribution should be tested for IFG using an OGTT and considered for treatment according to current American Diabetes Association (ADA) recommendations[26] to prevent DM and poor cardiovascular outcomes.

All patients with IGT should be counseled to reduce their risk for poor cardiovascular outcomes through lifestyle modifications such as increased physical activity and a low-fat, high-fiber diet. Although there is insufficient evidence to support targeted exercise and dietary interventions for patients with HIV-1 infection,[66,67] no evidence to the contrary has been found. Therefore, as in non–HIV-infected patients, lifestyle interventions should be recommended for this patient population.[26] Increased physical activity and nutritional counseling may be helpful for HIV-1–infected patients by supporting decreased body fat without loss of muscle tissue, thereby potentially reducing the risk of poor cardiovascular outcomes.

Optimal pharmacotherapy for insulin resistance and IGT in patients with HIV-1 infection is not adequately understood.[68] However, appropriate pharmacotherapy should be initiated for DM when clinically relevant treatment outcomes are not achieved with diet and exercise alone. Generally speaking, antidiabetes drugs should be started at the lowest dose and patients should be treated to control[69–71] by gradually titrating the dose upward until targets are reached or adverse effects develop.[26] Sulfonylureas are typically a first step in the pharmacologic treatment of DM; however, unlike insulin secretagogues and insulin, sulfonylureas may cause hypoglycemia.[26] In light of early observations linking pentamidine treatment to hypoglycemia,[37] care should be taken when considering use of sulfonylureas in combination treatment for *Pneumocystis jiroveci* pneumonia.

The ADA recommends that an insulin-sensitizing agent such as metformin be considered for patients at very high risk for developing DM (combined IFG and IGT, plus other risk factors such as a glycosylated hemoglobin level >6.0%, hypertension, low HDL-C level, elevated triglyceride levels, or DM in a first-degree relative) who are obese and <60 years of age.[26]

Insulin-sensitizing agents include the biguanide metformin and the thiazolidinediones (TZDs) rosiglitazone[r] and pioglitazone.[s] A third TZD, troglitazone,[t] approved in 1997, was withdrawn from the market in 2000 because of hepatotoxicity and liver failure. Although the molecular mode of action is not clear,[72] metformin enhances insulin sensitivity, reduces hepatic glucose production,[73] and elicits direct effects on insulin action in skeletal muscle.[72] HIV-1–infected patients with type 2 DM who were treated with metformin[13,74] had significant reductions in mean fasting insulin ($P = 0.01$) at 120 minutes after treatment compared with patients who received placebo. Patients who received metformin had significant reductions in weight ($P = 0.005$) and diastolic blood pressure ($P = 0.009$) after 3 months compared with patients who received placebo. Furthermore, patients who received metformin had decreased visceral adipose tissue 3 months after starting treatment compared with patients who received placebo.[13,74] The metformin-treated patients also experienced reductions in their diastolic blood pressure and their risk of CVD.[13]

Rosiglitazone was found to improve both glucose control (by enhancing peripheral insulin sensitivity) and fatty acid metabolism.[72,75–77] Rosiglitazone also was associated with positive effects on lipoatrophy, insulin sensitivity, and metabolic indices, including adiponectin levels in HIV-1–infected patients with lipoatrophy and insulin resistance, compared with placebo.[78] The weight-reducing properties of rosiglitazone in HIV-1–infected patients appears to contradict the modest weight gain experienced by non–HIV-infected patients exposed to TZD therapy, suggesting the need for further study.[60] On the other hand, rosiglitazone appears to be associated with increased cholesterol levels in this patient population.[78]

No contraindications to the use of insulin in this patient population were found in the published medical literature. However, insulin use requires that patients or their caregivers have good visual and motor skills and cognitive ability.[26]

Managing Dyslipidemia in Patients With HIV-1 Infection

HIV-1 infection has been associated with dyslipidemia, both as a consequence of the infection itself[42] and as an effect of pharmacologic treatment.[79] Dyslipidemia, as a metabolic disorder and risk factor for CVD, must be treated aggressively in patients with or without HIV infection to manage and prevent CVD.

Nonpharmacologic therapies such as dietary interventions should be recommended when managing dyslipidemia in HIV-1–infected patients with type 2 DM. Although no dietary studies that address dyslipidemia among HIV-1–infected patients have been published, it may be prudent to recommend diets high in omega-3 essential fatty acids, monounsaturated fats, and polyunsaturated fats because these substances have been shown to benefit some non–HIV-infected patients with hypertriglyceridemia.[60] It is important to ensure that patients with HIV-1 infection and hypercholesterolemia who are on a low-fat diet also receive nutritional counseling to avoid unnecessary weight and muscle loss. Other lifestyle interventions that should be considered in cases of elevated serum triglyceride levels include increased physical activity to build muscle and decreased alcohol consumption.

Pharmacologic therapy is required when patients do not achieve treatment goals for serum lipid levels through diet

[r]Trademark: Avandia® (GlaxoSmithKline, Research Triangle Park, North Carolina).
[s]Trademark: Actos® (Takeda Pharmaceuticals North America, Inc., Deerfield, Illinois).
[t]Trademark: Rezulin® (Parke-Davis, division of Warner-Lambert, Morris Plains, New Jersey; no longer available).

and exercise. Although various doses of atorvastatin[u] (5, 20, and 80 mg) have been associated with lower serum triglyceride levels (–26.5%, –32.4%, and –45.8%, respectively) compared with placebo (–8.9%)[80] and higher doses of simvastatin (40 and 80 mg) have been associated with a reduction of >26% in serum triglyceride levels,[81,82] this class of drugs competes for the same enzyme system in the liver in the presence of the PIs ritonavir and saquinavir.[60,83] The bioavailability of atorvastatin and simvastatin appears to be strongly increased (by 343% and 267%, respectively) in the presence of ritonavir and saquinavir. Conversely, the bioavailability of pravastatin was decreased by ~50% in the presence of ritonavir and saquinavir, suggesting that statins may not be ideal for concomitant use with PIs. However, when use of a statin is necessary, the choice of statin should take into consideration the efficacy of the agent and the predicted magnitude of interaction. Furthermore, it is important to remember that concomitant use of these 2 drug classes requires regular liver function testing and that the typical HIV-infected patient is using multiple medications, each of which may alter the pharmacokinetic properties of a statin.[60]

Fibric acid derivatives may be the best class of medications for treating hypertriglyceridemia and low HDL-C levels, the primary conditions associated with lipodystrophy,[84] because they have been shown to reduce serum triglyceride levels by up to 55%.[85] Agents in this drug class (eg, clofibrate, fenofibrate,[v] gemfibrozil) apparently do not interact with antiretroviral medications.[60] The use of fibric acid derivatives with statins has been associated with an increased risk of myotoxicity; however, the literature search revealed no reports of rhabdomyolysis among HIV-1–infected patients treated with diet and exercise, gemfibrozil, atorvastatin, or gemfibrozil plus atorvastatin.[86] Use of these agents may be the safest means by which to lower serum triglyceride levels, but care must be taken to monitor patients receiving this treatment for gastrointestinal adverse effects.[60] Diet and exercise remain the first line of treatment for lowering triglyceride levels while not introducing the adverse effects associated with pharmacotherapy.

Niacins and resins are not recommended for the treatment of hyperlipidemia in HIV-infected patients. Adverse effects of these agents include flushing, hepatotoxicity, hyperglycemia, and gastrointestinal problems that reduce their effectiveness.[60] A more thorough explanation of drug interactions and toxicity is beyond the scope of this review. The reader is referred to the references for a more thorough discussion of these important aspects of effective medical management of HIV-1–infected patients in whom metabolic complications such as dyslipidemia may also be present.

[u]Trademark: Lipitor® (Parke-Davis, division of Pfizer Inc, New York, New York).
[v]Trademark: Tricor® (Abbott Laboratories, North Chicago, Illinois).

CONCLUSIONS

The long-term prognosis for patients with HIV-1 infection has improved significantly with the use of combination antiretroviral therapy, including PIs, ritonavir-boosted PIs, NRTIs, and NNRTIs. However, the metabolic effects of these combination therapies, along with fat redistribution, which is common among patients with HIV-1 infection, increase the risk for insulin resistance, type 2 DM, and poor CVD outcomes. This new risk for people infected with HIV-1 accompanies increased survival, causing clinicians to shift their focus to the chronic care of HIV-1 infection, incorporating traditional medical risk factors such as type 2 DM and CVD into the medical management of these patients. PIs and NRTIs appear to represent 2 HIV drug classes with a pathogenic role in insulin resistance and, subsequently, DM. However, other risk factors for coexisting type 2 DM in this patient population include body composition and comorbidities (eg, HCV). Family history as a risk factor for type 2 DM remains equivocal at this time; however, clinical prudence suggests that a family history of DM should be considered when managing patients with HIV-1 infection. Furthermore, the progression and stage of HIV disease directly affect lipid values and glucose homeostasis. Medical evidence provides clinical guidance when treating HIV-1–infected patients for insulin resistance and type 2 DM using insulin-sensitizing agents (eg, metformin, TZDs) and for treating dyslipidemia with statins (eg, atorvastatin, simvastatin, pravastatin). However, no published evidence is available to provide clinical guidance when comanaging HIV-1 and type 2 DM using insulin. Because of the differences in pharmacokinetic properties between the statins and PIs, it is critical for clinicians who manage patients with HIV-1 infection and insulin resistance to properly manage both combination antiretroviral therapy and the pharmacotherapy for DM and dyslipidemia, taking into consideration the stage of HIV disease and the demographic characteristics of the patient.

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REFERENCES

1. Calza L, Manfredi R, Chiodo F. Insulin resistance and diabetes mellitus in HIV-infected patients receiving antiretroviral therapy. *Metab Syndr Relat Disord*. 2004;2:241–250.
2. Schambelan M, Benson CA, Carr A, et al, for the International AIDS Society-USA. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an International AIDS Society-

USA panel. *J Acquir Immune Defic Syndr*. 2002;31:257–275.

3. Calza L, Manfredi R, Chiodo F. Dyslypidaemia associated with antiretroviral therapy in HIV-infected patients. *J Antimicrob Chemother*. 2004;53:10–14.
4. Koster JC, Remedi MS, Qiu H, et al. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*. 2003;52:1695–1700.
5. El-Sadr WM, Mullin CM, Carr A, et al. Effects of HIV disease on lipid, glucose and insulin levels: Results from a large antiretroviral-naive cohort. *HIV Med*. 2005;6:114–121.
6. Kilby JM, Tabereaux PB. Severe hyperglycemia in an HIV clinic: Preexisting versus drug-associated diabetes mellitus. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;17:46–50.
7. Yoon C, Gulick RM, Hoover DR, et al. Case-control study of diabetes mellitus in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2004;37:1464–1469.
8. Shikuma CM, Day LJ, Gerschenson M. Insulin resistance in the HIV-infected population: The potential role of mitochondrial dysfunction. *Curr Drug Targets Infect Disord*. 2005;5:255–262.
9. Lo YC, Chen MY, Sheng WH, et al. Risk factors for incident diabetes mellitus among HIV-infected patients receiving combination antiretroviral therapy in Taiwan: A case-control study. *HIV Med*. 2009;10:302–309.
10. Tien PC, Schneider MF, Cole SR, et al. Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study. *AIDS*. 2007;21:1739–1745.
11. Kaslow RA, Ostrow DG, Detels R, et al. The Multicenter AIDS Cohort Study: Rationale, organization, and selected characteristics of the participants. *Am J Epidemiol*. 1987;126:310–318.
12. Brown TT, Cole SR, Li X. Antiretroviral therapy and the prevalence and incidence of diabetes—Reply. *Arch Intern Med*. 2005;165:2537.
13. Hadigan C, Corcoran C, Basgoz N, et al. Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. *JAMA*. 2000;284:472–477.
14. Lichtenstein KA, Ward DJ, Moorman AC, et al, for the HIV Outpatient Study Investigators. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS*. 2001;15:1389–1398.
15. Bernasconi E, Boubaker K, Junghans C, et al, for the Swiss HIV Cohort Study. Abnormalities of body fat distribution in HIV-infected persons treated with antiretroviral drugs: The Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr*. 2002;31:50–55.
16. Miller J, Carr A, Emery S, et al. HIV lipodystrophy: Prevalence, severity and correlates of risk in Australia. *HIV Med*. 2003;4:293–301.
17. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med*. 2005;352:48–62.
18. Mallon PW, Miller J, Cooper DA, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. *AIDS*. 2003;17:971–979.
19. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: Results of a substudy from a comparative trial. *AIDS*. 2002;16:2447–2454.
20. Lichtenstein KA, Delaney KM, Armon CC, et al, for the HIV Outpatient Study Investigators. Incidence of and risk factors for lipoatrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. *J Acquir Immune Defic Syndr*. 2003;32:48–56.
21. Galli M, Ridolfo AL, Adorni F, et al. Body habitus changes and metabolic alterations in protease inhibitor-naive HIV-1-infected patients treated with two nucleoside reverse transcriptase inhibitors. *J Acquir Immune Defic Syndr*. 2002;29:21–31.
22. Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med*. 1999;159:1104–1109.
23. Wilson PW, D'Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112:3066–3072.
24. Tebas P. Insulin resistance and diabetes mellitus associated with antiretroviral use in HIV-infected patients: Pathogenesis, prevention, and treatment options. *J Acquir Immune Defic Syndr*. 2008;49(Suppl 2):S86–S92.
25. Cohen P, Dix D. The oral glucose tolerance test: An objective method of interpretation. *Acta Diabetologica*. 1984;21:181–189.
26. American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care*. 2009;32(Suppl 1):S13–S61.
27. Mehta SH, Brancati FL, Strathdee SA, et al. Hepatitis C virus infection and incident type 2 diabetes. *Hepatology*. 2003;38:50–56.
28. Moucari R, Asselah T, Paradis V, et al. Insulin resistance in 424 chronic hepatitis C patients: Association with HCV replication and advanced fibrosis. *J Hepatol*. 2007;46(Suppl 1):S11. Abstract 21.
29. Staples CT Jr, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): The effect of coinfection on survival. *Clin Infect Dis*. 1999;29:150–154.
30. Bräu N, Bini EJ, Shahidi A, et al. Prevalence of hepatitis C and coinfection with HIV among United States veterans in the New York City metropolitan area. *Am J Gastroenterol*. 2002;97:2071–2078.
31. Visnegarwala F, Chen L, Raghavan S, Tedaldi E. Prevalence of diabetes mellitus and dyslipidemia among antiretroviral naive patients co-infected with hepatitis C virus (HCV) and HIV-1 compared to patients without co-infection. *J Infect*. 2005;50:331–337.
32. Castaneda-Sceppa C, Bermudez OI, Wanke C, Forrester JE. Predictors of insulin resistance among Hispanic adults infected with or at risk of infection with the human immunodeficiency virus and hepatitis C virus. *J Viral Hepat*. 2008;15:878–887.
33. Jain MK, Aragaki C, Fischbach L, et al. Hepatitis C is associated with type 2 diabetes mellitus in HIV-infected persons without traditional risk factors. *HIV Med*. 2007;8:491–497.
34. Slama L, Le Camus C, Serfaty L, et al. Metabolic disorders and chronic viral disease: The case of HIV and HCV. *Diabetes Metab*. 2009;35:1–11.
35. Osei K, Falko JM, Nelson KP, Stephens R. Diabetogenic effect of pentamidine. In vitro and in vivo studies in a patient with malignant insulinoma. *Am J Med*. 1984;77:41–46.
36. Spollett GR. Hyperglycemia in HIV/AIDS. *Diabetes Spectr*. 2006;19:163–166.

37. Bouchard P, Sai P, Reach G, et al. Diabetes mellitus following pentamidine-induced hypoglycemia in humans. *Diabetes*. 1982;31:40–45.
38. Friis-Møller N, Weber R, Reiss P, et al, for the DAD Study Group. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. *AIDS*. 2003;17:1179–1193.
39. Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction [published correction appears in *N Engl J Med*. 2004;350:955]. *N Engl J Med*. 2003;349:1993–2003.
40. De Wit S, Sabin CA, Weber R, et al, for the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. Incidence and risk factors for new-onset diabetes in HIV-infected patients: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care*. 2008;31:1224–1229.
41. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the Multicenter AIDS Cohort Study [published correction appears in *Arch Intern Med*. 2005;165:2541]. *Arch Intern Med*. 2005;165:1179–1184.
42. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289:2978–2982.
43. Worm SW, De Wit S, Weber R, et al. Diabetes mellitus, preexisting coronary heart disease, and the risk of subsequent coronary heart disease events in patients infected with human immunodeficiency virus: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study). *Circulation*. 2009;119:805–811.
44. Worm SW, Sabin CA, Reiss P, et al. Presence of the metabolic syndrome is not a better predictor of cardiovascular disease than the sum of its components in HIV-infected individuals: Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care*. 2009;32:474–480.
45. Sabin CA, Worm SW, Weber R, et al, for the D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration [published correction appears in *Lancet*. 2008;372:292]. *Lancet*. 2008;371:1417–1426.
46. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis*. 2001;32:130–139.
47. Dubé MP. Disorders of glucose metabolism in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2000;31:1467–1475.
48. Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2009;50:499–505.
49. Mulligan K, Grunfeld C, Hellerstein MK, et al. Anabolic effects of recombinant human growth hormone in patients with wasting associated with human immunodeficiency syndrome. *J Clin Endocrinol Metab*. 1993;77:956–962.
50. Tungsiripat M, Aberg JA. Dyslipidemia in HIV patients. *Cleve Clin J Med*. 2005;72:1113–1120.
51. Kitahata MM, Koepsell TD, Deyo RA, et al. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. *N Engl J Med*. 1996;334:701–706.
52. Kitahata MM, Van Rompaey SE, Shields AW. Physician experience in the care of HIV-infected persons is associated with earlier adoption of new antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2000;24:106–114.
53. Kitahata MM, Van Rompaey SE, Dillingham PW, et al. Primary care delivery is associated with greater physician experience and improved survival among persons with AIDS. *J Gen Intern Med*. 2003;18:95–103.
54. Landon BE, Wilson IB, McInnes K, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med*. 2005;165:1133–1139.
55. Laine C, Markson LE, McKee LJ, et al. The relationship of clinic experience with advanced HIV and survival of women with AIDS. *AIDS*. 1998;12:417–424.
56. Delgado J, Heath KV, Yip B, et al. Highly active antiretroviral therapy: Physician experience and enhanced adherence to prescription refill. *Antivir Ther*. 2003;8:471–478.
57. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Dept of Health and Human Services. November 3, 2008; 1–139. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 4, 2009.
58. Hammer SM, Eron JJ Jr, Reiss P, et al, for the International Aids Society-USA. Antiretroviral treatment of adult HIV infection: 2008 Recommendations of the International AIDS Society-USA Panel. *JAMA*. 2008;300:555–570.
59. US Dept of Health and Human Services. AIDS*info*. Clinical Guidelines Portal. http://www.aidsinfo.nih.gov/Guidelines/. Accessed November 10, 2009.
60. Leow MK, Addy CL, Mantzoros CS. Clinical review 159: Human immunodeficiency virus/highly active antiretroviral therapy-associated metabolic syndrome: Clinical presentation, pathophysiology, and therapeutic strategies. *J Clin Endocrinol Metab*. 2003;88:1961–1976.
61. Martinez E, Conget I, Lozano L, et al. Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. *AIDS*. 1999;13:805–810.
62. Martínez E, García-Viejo MA, Blanco JL, et al. Impact of switching from human immunodeficiency virus type 1 protease inhibitors to efavirenz in successfully treated adults with lipodystrophy. *Clin Infect Dis*. 2000;31:1266–1273.
63. Walli R, Herfort O, Michl GM, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. *AIDS*. 1998;12:F167–F173.
64. Oseid S, Beck-Nielsen H, Pedersen O, Sovik O. Decreased binding of insulin to its receptor in patients with congenital generalized lipodystrophy. *N Engl J Med*. 1977;296:245–248.
65. American Diabetes Association. Screening for type 2 diabetes. *Diabetes Care*. 2004;27(Suppl 1):S11–S14.
66. Yarasheski KE, Tebas P, Stanerson B, et al. Resistance exercise training reduces hypertriglyceridemia in HIV-infected men treated with antiviral therapy. *J Appl Physiol*. 2001;90:133–138.
67. Roubenoff R, Schmitz H, Bairos L, et al. Reduction of abdominal obesity in lipodystrophy associated with human immunodefi-

ciency virus infection by means of diet and exercise: Case report and proof of principle. *Clin Infect Dis*. 2002;34:390–393.

68. Wiwanitkit V. Primary care for diabetes in HIV-infected patients. *Online J Health Allied Scs*. 2007;6. http://www.ojhas.org/issue22/2007-2-1.htm. Accessed November 4, 2009.
69. Miller CD, Ziemer DC, Kolm P, et al. Use of a glucose algorithm to direct diabetes therapy improves A1C outcomes and defines an approach to assess provider behavior. *Diabetes Educ*. 2006;32:533–545.
70. Shah BR, Hux JE, Laupacis A, et al. Clinical inertia in response to inadequate glycemic control: Do specialists differ from primary care physicians? *Diabetes Care*. 2005;28:600–606.
71. Ryan JG. Cost and policy implications from the increasing prevalence of obesity and diabetes mellitus. *Gend Med*. 2009; 6(Suppl 1):86–108.
72. Karlsson HK, Hällsten K, Björnholm M, et al. Effects of metformin and rosiglitazone treatment on insulin signaling and glucose uptake in patients with newly diagnosed type 2 diabetes: A randomized controlled study. *Diabetes*. 2005;54:1459–1467.
73. Bailey CJ, Turner RC. Metformin. *N Engl J Med*. 1996;334:574–579.
74. Saint-Marc T, Touraine JL. Effects of metformin on insulin resistance and central adiposity in patients receiving effective protease inhibitor therapy. *AIDS*. 1999;13:1000–1002.
75. Mayerson AB, Hundal RS, Dufour S, et al. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes*. 2002;51:797–802.
76. Lebovitz HE, Dole JF, Patwardhan R, et al, for the Rosiglitazone Clinical Trials Study Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes [published correction appears in *J Clin Endocrinol Metab*. 2001;86:1659]. *J Clin Endocrinol Metab*. 2001;86:280–288.
77. Miyazaki Y, He H, Mandarino LJ, DeFronzo RA. Rosiglitazone improves downstream insulin receptor signaling in type 2 diabetic patients. *Diabetes*. 2003;52:1943–1950.
78. Hadigan C, Yawetz S, Thomas A, et al. Metabolic effects of rosiglitazone in HIV lipodystrophy: A randomized, controlled trial. *Ann Intern Med*. 2004;140:786–794.
79. Fontas E, van Leth F, Sabin CA, et al, for the D:A:D Study Group. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: Are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis*. 2004;189:1056–1074.
80. Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA*. 1996;275:128–133.
81. de Sauvage Nolting PR, Buirma RJ, Hutten BA, Kastelein JJ, for the Dutch ExPRESS Investigator Group. Two-year efficacy and safety of simvastatin 80 mg in familial hypercholesterolemia (the Examination of Probands and Relatives in Statin Studies With Familial Hypercholesterolemia [ExPRESS FH]). *Am J Cardiol*. 2002;90:181–184.
82. Stein E, Plotkin D, Bays H, et al. Effects of simvastatin (40 and 80 mg/day) in patients with mixed hyperlipidemia. *Am J Cardiol*. 2000;86:406–411.
83. Fichtenbaum C, Gerber J, Rosenkranz S, et al. Pharmacokinetic interactions between protease inhibitors and selected HMG-CoA reductase inhibitors. Presented at: 7th Conference on Retroviruses and Opportunistic Infections; January 30–February 2, 2000; San Francisco, Calif. Abstract LB6.
84. Calza L, Manfredi R, Chiodo F. Use of fibrates in the management of hyperlipidemia in HIV-infected patients receiving HAART. *Infection*. 2002;30:26–31.
85. Jellinger PS, Dickey RA, Ganda OP, et al, for the AACE Lipid Guidelines Committee. AACE medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis [published correction appears in *Endocr Pract*. 2008;14:802–803]. *Endocr Pract*. 2000;6:162–213.
86. Henry K, Melroe H, Huebesch J, et al. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet*. 1998;352:1031–1032.

Address correspondence to: John G. Ryan, DrPH, Director, Division of Primary Care/Health Services Research and Development, Department of Family Medicine and Community Health, University of Miami Miller School of Medicine, PO Box 016700 (R-700), Miami, FL 33101–6700. E-mail: JGRyan@med.miami.edu