Glycemic Control in HIV-Infected Patients with Diabetes Mellitus and Rates of Meeting American Diabetes Association Management Guidelines

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Abstract

Limited data exist on the prevalence of inadequate glycemic control and rates of meeting American Diabetic Association (ADA) management guidelines in HIV-infected adults with diabetes mellitus. We conducted a retrospective cross-sectional study of 142 HIV-infected adults with type 2 diabetes at an urban academic HIV clinic during 2008. We estimated the prevalence of and assessed associations with inadequate glycemic control, defined as hemoglobin A_{1c} $\geq 7.5\%$ for $\geq 50\%$ of quarters over the year, and determined rates of meeting ADA clinical goals. Ninety-two percent of patients received antiretroviral therapy. The prevalence of inadequate glycemic control was 33% (95% confidence interval [CI] 25%–42%). Compared to patients with adequate control, those with inadequate control had fewer years since HIV diagnosis (12.7 versus 15.1, $p = 0.01$), increased use of insulin (60% versus 20%, $p < 0.001$) or any diabetic medication (98% versus 85%, $p = 0.02$), and higher triglyceride levels (238 versus 168 mg/dL, $p = 0.008$). Rates of achieving ADA goals were 42% for blood pressure, 66% for low-density lipoprotein cholesterol (LDL-C), 33% for high-density lipoprotein cholesterol, and 31% for triglycerides. Thirty-six percent of patients who did not meet the LDL-C goal received statin therapy. Forty-seven percent of patients were screened for retinopathy and 19% of patients without preexisting renal disease were screened for nephropathy. In conclusion, the prevalence of inadequate glycemic control in HIV-infected patients with diabetes is similar to published data from the general population. Suboptimal rates of meeting ADA blood pressure and lipid goals and adherence to screening guidelines demonstrate need for further clinician and patient education.

Introduction

WITH THE ADVENT OF effective and well-tolerated antiretroviral therapy, the life expectancy of HIV-infected patients continues to increase.¹ While AIDS-related deaths are decreasing, the proportion of deaths in HIV-infected patients related to causes other than AIDS is increasing.^{2,3} Diabetes mellitus is a particular comorbid illness that warrants attention as a threat to HIV-infected patients; 10.7% of the overall United States population above the age of 20 have diabetes, and the prevalence is even greater among African Americans and Hispanics.⁴ Diabetes prevalence is estimated to more than double by 2050.⁵ Both HIV infection and use of antiretroviral medications to treat HIV may be risk factors for diabetes.^{6–8} In the Multicenter AIDS Cohort Study, incidence of diabetes in HIV-infected men on antiretroviral therapy was more than four times greater than that of HIV-uninfected men, and both nu-

cleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) have been associated with incident diabetes among HIV-infected patients.^{6–8} Overrepresentation of minorities in patients with HIV infection and diabetes may further contribute to the convergence of these two chronic diseases.

The importance of glycemic control to prevent both microvascular and macrovascular complications in patients with diabetes is well established. In the UK Prospective Diabetes Study (UKPDS), subjects with diabetes from the general population who were randomized to intensive glycemic control achieved a median hemoglobin A_{1c} (HbA_{1c}) of 7.0%, versus 7.9% in the control group, and had significant risk reductions in microvascular endpoints, myocardial infarctions, and death from any cause during 10 years of posttrial follow-up.^{9,10}

Although the prevalence of inadequate glycemic control in the general population has been estimated in numerous large

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studies, only two studies have estimated this prevalence in HIV-infected patients.^{11–15} Furthermore, while age, number of years since diabetes diagnosis, insurance status, hyperlipidemia, body mass index (BMI), and poor self-care have been associated with inadequate glycemic control in the general diabetic population, no study has explored these associations in HIV-infected patients with diabetes.^{16–18} HIV-infected patients with diabetes have unique potential cofactors for inadequate glycemic control, including the use of specific antiretroviral medications. Both NRTIs and PIs have been associated with insulin resistance and incident diabetes.^{6–8,19} In addition to estimating the prevalence of inadequate glycemic control, the primary objective of this study was to assess possible risk factors for inadequate glycemic control in HIV-infected patients with diabetes receiving primary care in a large, urban, academic HIV clinic.

As with HIV care, care of patients with diabetes is multifaceted, involving more than just glycemic control. Randomized controlled trials have demonstrated benefit to intensive control of blood pressure and lipids in patients with diabetes, leading to the formation of American Diabetic Association (ADA) goals for blood pressure and lipids.^{20–23} Furthermore, the ADA recommends yearly screening for microvascular complications such as retinopathy and nephropathy. Secondary objectives of this study include estimating rates of achieving ADA goals in HIV-infected patients with diabetes, adherence to ADA screening guidelines, and assessing associations with not meeting ADA goals.

Methods

This was a retrospective cross-sectional study of patients receiving care at a multidisciplinary, urban, academic HIV clinic with two locations in Manhattan, New York. The clinic had approximately 2000 active patients in 2008. With each physician visit, patients also had an opportunity to meet with a psychiatrist, social worker, nurse, and nutritionist. The clinic's electronic medical record was used to identify all patients over the age of 18 who had a HbA_{1c} checked in two different quarters of 2008. Only patients with a physician note that documented the presence of type 2 diabetes mellitus during any visit in 2007 were included in the study. Patients diagnosed with diabetes in 2008 were excluded. Patients with multiple HbA_{1c} values during any 3-month quarter of the year had these values averaged to yield a single quarterly HbA_{1c}. Inadequate glycemic control was defined as having a quarterly HbA_{1c} $\geq 7.5\%$ during at least half of the quarters where HbA_{1c} was checked during 2008. The prevalence of inadequate glycemic control was calculated by dividing the number of patients who met inclusion criteria and had inadequate glycemic control over the total number of patients who met inclusion criteria.

The following data were recorded for each patient: demographics, including age, gender, HIV transmission risk group, race/ethnicity, insurance status on January 1, 2008, and language used during visits; height and weight closest to January 1, 2008; use of antiretrovirals, diabetic medications, atypical antipsychotics, β -blockers, lipid-altering medications, and antidepressants from October 2007 to December 2008; all HbA_{1c}, urine albumin-to-creatinine, and urinalysis measurements during 2008; the first blood pressure measurement, lipid panel, creatinine, HIV viral load, and CD4 cell count of each quarter of 2008; year of diagnosis of diabetes and HIV;

CD4 cell count nadir; number of years on antiretroviral medications; presence of active hepatitis C; documentation of an ophthalmologic examination during 2008 and presence or absence of diabetic retinopathy; number of clinic visits between October 2007 and December 2008 with a primary care physician, psychiatrist, social worker, nutritionist, and endocrinologist; hospitalizations between October 2007 and December 2008; percentage of medical appointments broken by the patient, documentation of depression or psychiatric illness by a psychiatrist, and use of illegal substances, daily tobacco, or alcohol between October 2007 and December 2008; and training level of the primary care physician. The rationale for assessing certain parameters beginning in October 2007, as indicated above, was that HbA_{1c} measured in January 2008 reflected glucose control during the last quarter of 2007. All values for blood pressure, lipids, HIV viral load, and CD4 cell count were averaged to yield a single yearly value for each patient. Each of these variables was assessed for associations with inadequate glycemic control.

Rates of meeting the following 2008 ADA goals were determined by comparing the single yearly value for each patient, as calculated above, to the following targets: blood pressure $<130/80$ mm Hg, HDL cholesterol >40 mg/dL in men and >50 mg/dL in women, LDL cholesterol <100 mg/dL, and triglycerides <150 mg/dL. Associations between the above variables and meeting ADA goals were assessed. We also determined rates of adherence to ADA yearly screening guidelines for microalbuminuria by whether a urine albumin-to-creatinine ratio was checked in 2008 and diabetic retinopathy by whether an ophthalmologic examination was documented in 2008. All patients who did not meet the ADA LDL cholesterol goal and were not on a statin had further review of the medical record to determine reasons why statins were not initiated.

For each patient group, the values for CD4 cell count, lipids, and blood pressure were reported as a median of all of the single yearly values for each patient, as calculated above. Categorical variables were compared for associations with inadequate glycemic control and meeting ADA goals using either Pearson's χ^2 or Fisher's exact tests. Continuous variables were compared using Wilcoxon rank-sum or Student's *t* tests. For all analyses, $p < 0.05$ was considered to be statistically significant for 2-tailed tests. All calculations were performed using STATA, version 10.0 (StataCorp, College Station, TX). The protocol was approved by the Weill Cornell Medical College Institutional Review Board.

Results

Three hundred twenty-seven patients had an HbA_{1c} checked during one of the first three quarters of 2008. One hundred forty-three patients were excluded because they did not have a physician diagnosis of diabetes during any visit in 2007, 31 because they did not have HbA_{1c} values from two different quarters of 2008, 9 because they were younger than age 18, and 2 because they had type 1 diabetes. A total of 142 patients met inclusion criteria, of whom 47 met our definition of inadequate glycemic control, yielding a prevalence of inadequate glycemic control of 33% (95% confidence interval [CI] 25%, 42%). The mean of quarterly HbA_{1c} values was $<7\%$ in 81 (57%) patients and $<8\%$ in 111 (78%) patients.

Table 1 summarizes demographics and clinical characteristics in patients with and without inadequate glycemic

TABLE 1. CHARACTERISTICS OF HIV-INFECTED PATIENTS WITH DIABETES MELLITUS AND ADEQUATE OR INADEQUATE GLYCEMIC CONTROL

Characteristic	Inadequate glycemic control (N = 47)	Adequate glycemic control (N = 95)	p Value
Demographics			
Age, mean (years)	52.3 ± 8.4	51.7 ± 9.2	0.70 ¹
Male sex	32 (68%)	62 (65%)	0.74 ²
Men who have sex with men	18 (38%)	32 (34%)	0.59 ²
Race/ethnicity			
African-American	16 (34%)	39 (41%)	0.42 ²
Hispanic	20 (43%)	33 (35%)	0.37 ²
White	7 (15%)	19 (20%)	0.46 ²
Medicaid recipient	37 (78%)	70 (74%)	0.51 ²
Body mass index (BMI), median (kg/m ²)	29.0 (24.9–33.7)	28.0 (24.8–32.1)	0.34 ³
Obese (BMI ≥ 30)	20 (44%)	32 (34%)	0.30 ²
HIV-related			
Years since HIV diagnosis, mean	12.7 ± 5.9	15.1 ± 4.9	0.01 ¹
CD4 cell count, median (cells/μL)	451 (312–608)	492 (351–601)	0.53 ³
CD4 cell count nadir, median (cells/μL)	137 (33–213)	135 (46–205)	0.77 ³
HIV RNA <48 copies/mL throughout 2008	23 (49%)	57 (60%)	0.21 ²
Mean HIV RNA <1,000 copies/mL in 2008	36 (77%)	79 (83%)	0.35 ²
Use of antiretroviral medications	42 (89%)	89 (94%)	0.51 ⁴
NRTI	42 (89%)	87 (92%)	0.76 ⁴
NNRTI	16 (34%)	41 (43%)	0.30 ²
PI	25 (54%)	57 (60%)	0.44 ²
Metabolic			
HbA1c, median (%)	8.4 (7.8–9.8)	6.2 (5.8–6.6)	<0.001 ³
Years since diabetes diagnosis, median	7 (4–10)	6 (3–9)	0.14
Use of diabetes medications	46 (98%)	81 (85%)	0.02 ⁴
Metformin	28 (60%)	47 (49%)	0.26 ²
Thiazolidinediones	15 (32%)	28 (29%)	0.77 ²
Sulfonylurea	21 (45%)	34 (36%)	0.31 ²
Insulin	28 (60%)	19 (20%)	<0.001 ²
Yearly mean lipid values (2008), median (mg/dL)			
Total cholesterol	170 (156–201)	170 (149–196)	0.54 ³
LDL cholesterol	87 (60–108)	92 (68–103)	0.76 ³
HDL cholesterol	38 (31–42)	40 (35–50)	0.07 ³
Triglyceride level	238 (158–385)	168 (123–260)	0.008 ³
Cardiovascular			
Yearly mean blood pressure, median (mm Hg)			
Systolic blood pressure	131 (121–135)	129 (118–133)	0.15 ³
Diastolic blood pressure	79 (75–83)	78 (73–80)	0.15 ³
Yearly mean GFR < 60 mL/min (via Cockcroft-Gault)	9 (19%)	26 (27%)	0.29 ²
Social/medical care			
Tobacco use (>7 cigarettes/wk)	10 (21%)	26 (27%)	0.43 ²
Substance abuse	11 (23%)	32 (34%)	0.21 ²
Psychiatric disease	24 (51%)	46 (48%)	0.77 ²
% MD appointments broken, median	18% (0–30%)	12% (0–25%)	0.28 ³
# of visits between Oct 2007 and Dec 2008, median			
Primary care physician	6 (5–7)	6 (5–7)	0.72 ³
Psychiatrist	1 (0–4)	0 (0–4)	0.76 ³
Social worker	5 (4–7)	5 (4–6)	0.94 ³
Nutritionist visit	21 (45%)	35 (37%)	0.37 ²
Endocrinologist visit	24 (51%)	35 (37%)	0.11 ²
Hospitalization	6 (13%)	26 (27%)	0.05 ²
Active hepatitis C	13 (28%)	23 (24%)	0.66 ²

Note: Data are number (and %) of patients, mean ± standard deviation, or median (interquartile range). For CD4 cell count, lipids and blood pressure, the median of the mean of all individual values during 2008 is reported. *p* Values < 0.05 are in bold.

¹Student's *t* test. ²Pearson's chi-square. ³Wilcoxon rank-sum test. ⁴Fisher's exact test.

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; GFR, glomerular filtration rate.

FIG. 1. Percentage of patients who met American Diabetic Association (ADA) goals for diabetes care. The ADA goals were as follows: blood pressure (BP) < 130/80, low-density lipoprotein cholesterol (LDL) < 100 mg/dL, high-density lipoprotein cholesterol (HDL) > 40 mg/dL in men and > 50 mg/dL in women, triglyceride level (TG) < 150 mg/dL, non-HDL cholesterol < 130 mg/dL.

control. For the entire study population, the mean age was 52.1 ± 8.7 years and the majority of patients were African-American or Hispanic and Medicaid recipients. The mean duration of HIV diagnosis was 14.2 ± 5.3 years, and 92% were on antiretroviral therapy. The majority had HIV viral loads below the minimal level of quantification and relatively high CD4 cell counts (median 477). The average patient saw a physician and social worker at least every 2–3 months. There was a high prevalence of obesity (37%), psychiatric illness (49%), and daily tobacco use (25%). Protease inhibitor (PI)-based antiretroviral regimen use (58% of patients) was more common than non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen use (40%). Twenty (14%) patients were on atypical antipsychotics, 5 on corticosteroids, 5 on megestrol acetate, and none were on growth hormone.

The median of HbA_{1c} values for the 47 patients with inadequate glycemic control was 8.4%, compared to 6.2% for the 95 patients with adequate glycemic control. Compared to patients with adequate control, those with inadequate glycemic control had a more recent diagnosis of HIV (mean: 12.7 versus 15.1 years, $p = 0.01$), were more likely to be on insulin (60% versus 20%, $p < 0.001$) or any diabetes medication (98% versus 85%, $p = 0.02$), and had higher triglyceride levels (median: 238 versus 168 mg/dL, $p = 0.008$). There were no significant differences between groups for age, gender, ethnicity, insurance status, BMI, duration of diabetes diagnosis, CD4 cell count, HIV viral load, antiretroviral use, LDL cholesterol, substance abuse, psychiatric disease, adherence to medical appointments, number of visits to health care providers, or active hepatitis C virus infection. Patients with inadequate glycemic control tended to have lower HDL cholesterol levels (median: 38 versus 40 mg/dL, $p = 0.07$) and lower rates of hospitalization (13% versus 27%, $p = 0.05$), although these differences did not meet statistical significance.

Blood pressure and full lipid profiles were checked in 2008 in 139 (98%) and 128 (90%) of patients respectively. Given inaccuracies in calculating LDL cholesterol with triglyceride levels ≥ 400 mg/dL, LDL cholesterol was only calculated in 116 (82%) patients. Rates of achieving ADA goals are shown in Figure 1. Fewer than half of the patients met ADA goals for blood pressure, HDL cholesterol, and triglyceride levels. Patients on PI-based antiviral therapy were less likely to meet the ADA goal for HDL cholesterol than patients on NNRTI-based therapy (25% versus 49%, $p = 0.005$). This finding did

not differ by whether newer-generation PIs (atazanavir, tipranavir, or darunavir: 24%) or older-generation PIs (indinavir, saquinavir, fosamprenavir, nelfinavir, or lopinavir: 26%) were used. Although patients on PI-based regimens were not significantly less likely to meet the ADA triglyceride goal (26% versus 40%, $p = 0.11$), they had higher triglyceride levels than patients on an NNRTI-based regimen (median: 235 versus 162 mg/dL, $p = 0.002$). Patients less likely to meet the ADA goal for triglycerides were those taking a triglyceride-lowering medication (niacin, fibrates, or omega-3 fatty acids: 4% versus 38%, $p = 0.001$) and those using older-generation NRTIs (zidovudine, stavudine, or didanosine: 14% versus 40%, $p = 0.004$), whereas African-Americans (43% versus 24%, $p = 0.03$) and women (44% versus 24%, $p = 0.03$) were more likely to meet the this goal despite taking triglyceride-lowering medication less frequently (women: 6% versus 26%, $p = 0.006$; African Americans: 11% versus 24%, $p = 0.05$). No significant associations were identified for meeting ADA blood pressure or LDL cholesterol goals, and there were no differences in achieving any blood pressure or lipid goal based on age, viral load, presence of psychiatric disease, obesity, or substance abuse, consultation with a nutritionist or endocrinologist, or use of atypical antipsychotics or statins.

Of the 39 patients who did not meet the ADA goal for LDL cholesterol, 25 (64%) were never on statin therapy during 2008. Twenty-three (92%) of these 25 patients had a yearly mean LDL cholesterol of between 100–130 mg/dL. In 16 (64%) of these 25 patients, either the elevated LDL level was not addressed in the medical chart or the primary care provider considered the level to have met the appropriate target, whereas only 4 (16%) of these patients declined therapy or attempted lifestyle modification to lower LDL cholesterol. In the remaining 5 (20%) of these patients, the last LDL cholesterol level of the year was <100 mg/dL.

Twenty-seven (19%) patients had a urine albumin-to-creatinine ratio checked during 2008 to screen for microalbuminuria, of whom 13 (48%) had evidence of microalbuminuria. Of the 91 patients without evidence of kidney disease (estimated creatinine clearance >60 mL/min AND no proteinuria on urinalysis), 17 (19%) were screened for microalbuminuria. Four of these 17 patients (24%) had evidence of microalbuminuria, and all 4 either initiated or were already taking angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Sixty-six (47%) patients

had an eye examination by an ophthalmologist documented during 2008 to screen for diabetic retinopathy. Of the 59 patients where results of this examination were available, 13 (22%) had evidence of diabetic retinopathy.

Discussion

This cross-sectional study of HIV-infected patients with diabetes mellitus found a prevalence of inadequate glycemic control of 33%. Associations with inadequate glycemic control included a more recent diagnosis of HIV, use of insulin or any diabetes medication, and higher triglyceride levels. Although 66% of patients met the ADA goal for LDL cholesterol, fewer than half met the ADA goal for blood pressure and other lipid components. PI use was associated with lower rates of meeting the ADA goal for HDL cholesterol, whereas being male or not of African American ethnicity and use of an older NRTI were associated with lower rates of meeting the ADA goal for triglycerides. Only 47% of patients had a documented ophthalmologic examination, and only 19% were screened for microalbuminuria.

Our definition of inadequate glycemic control used a HbA_{1c} cutoff of 7.5%, instead of the ADA goal of 7%, based on a review of randomized controlled trial data. While UKPDS showed a reduction in both microvascular and macrovascular disease in the intensive therapy group (median HbA_{1c} 7.0%) compared to the control group (median HbA_{1c} 7.9%), data from ACCORD showed increased mortality in its intensive therapy arm that achieved a median HbA_{1c} of 6.4%.^{9,24} Quarterly HbA_{1c} values, which averaged all HbA_{1c} values during each quarter, were used in our definition instead of using all values during the year to ensure than one time period was not overrepresented in the assessment of glycemic control over the entire year. We used the proportion of quarterly HbA_{1c} values $\geq 7.5\%$ rather than a mean of these values to measure glycemic control because a mean may have been overly influenced by quarters of very low HbA_{1c} values, such as during an episode of acute illness. Although our assessment of inadequate glycemic control is unique and difficult to compare across other studies, our rates of having a mean HbA_{1c} $>7\%$ (43%) and $>8\%$ (22%) were similar to Adeyemi et al.,¹⁴ a previous cohort of HIV-infected diabetic patients (46% and 28%). These rates are also similar to rates from HIV-uninfected patients with diabetes who participated in the 2003–2004 National Health and Nutrition Examination Survey (NHANES, 44% and 24%).¹¹ When assessed together, results from our study and Adeyemi et al suggest that HIV-infected patients with diabetes have similar rates of inadequate glycemic control as HIV-uninfected patients with diabetes.

Our study did not find an association between use of NRTIs or PIs and inadequate glycemic control, despite their known effects on insulin sensitivity. The ability to detect these potential associations may have been limited by the cross-sectional study design. Physicians of patients with inadequate glycemic control may have previously discontinued antiretroviral medications known to alter insulin sensitivity and initiated medications thought to have less impact on insulin sensitivity. Furthermore, our study did not demonstrate associations between inadequate glycemic control and risk factors previously identified in HIV-uninfected patients with diabetes, such as longer duration of diabetes and younger age.^{16–18,25} We also did not demonstrate associations with

inadequate glycemic control for a number of other factors that intuitively would impact glycemic control such as insurance status, obesity, substance abuse, psychiatric disease, and adherence to medical appointments. This study suggests that prediction of glycemic control in HIV-infected patients with diabetes from individual characteristics is difficult. Furthermore, the fact that the majority of patients with inadequate glycemic control were on insulin suggests that in certain patients with diabetes glycemic control is difficult to achieve despite aggressive intervention. The study did find that a shorter duration of HIV diagnosis was associated with inadequate glycemic control, although reasons for this association are unclear. The association between high triglyceride levels and inadequate glycemic control highlights the connection between insulin resistance and dyslipidemia frequently found in HIV-infected patients.

The rate of achieving the ADA blood pressure goal of $<130/80$ mm Hg (42%) in this group was lower than that reported in Adeyemi et al.¹⁴ However, 81% of our patients had a mean blood pressure of $<140/90$ mm Hg, and evidence of improved patient outcomes from decreasing blood pressure to $<130/80$ mm Hg compared to $<140/90$ mm Hg in patients with diabetes is conflicting.^{21,26} Our rate of achieving the ADA goal for LDL cholesterol (66%) was greater than rates from two previous studies of HIV-infected diabetics (56% and 50%) and studies of HIV-uninfected patients with diabetes in which fewer than 50% achieved this goal.^{14,15,27,28} However, of patients who did not meet this goal, only approximately one third were on statin therapy. Given that randomized trials have demonstrated that statins significantly reduce major cardiovascular events in patients with diabetes with LDL cholesterol only modestly above target range, education of HIV primary care providers on the importance of aggressive statin use in patients with diabetes is essential.^{22,23} The observed rates of meeting ADA goals for HDL cholesterol and triglycerides in this study were much lower (33% and 31%) than the rate for LDL cholesterol, and were lower than those reported in Adeyemi et al.¹⁴ Given the retrospective designs of our study and Adeyemi and colleagues, the proportions of lipid profiles obtained in a fasting state are unknown. It is possible that our study may have included a greater proportion of nonfasting lipid profiles than in Adeyemi and colleagues, leading to an artificial elevation of triglyceride levels and subsequent lowering of the calculated LDL cholesterol. Due to this concern, we also measured non-HDL-cholesterol, a value that encompasses the major atherogenic lipoproteins and does not vary significantly in the postprandial state.²⁹ Our rate of meeting the ADA non-HDL-cholesterol goal (<130 mg/dL) was 50%. The fact that HIV-infected patients tend to have higher triglyceride levels and lower HDL and LDL cholesterol levels than HIV-uninfected patients may partially explain why the LDL cholesterol goal was more likely to be achieved than the HDL or triglyceride goals.^{30,31}

Here, unlike in previous studies in both HIV-infected and HIV-uninfected patients, women were not less likely to achieve ADA blood pressure and lipid goals, even for HDL cholesterol where women have higher targets.^{14,28,32} In fact, women were more likely to meet the triglyceride goal despite taking triglyceride-lowering medications less frequently. Patients on PI-based antiretroviral regimens of all types, including newer-generation agents shown to be more

lipid-neutral in studies of patients without diabetes, had lower HDL and higher triglyceride levels compared to patients on NNRTI-based regimens.³³ Again, the lack of differences found between older and newer-generation PIs may have been related to the cross-sectional study design, as patients with dyslipidemia may have been previously switched from older to later-generation PIs. Few patients were on PI-based regimens that did not include ritonavir, so the contribution of ritonavir to these associations could not be investigated. This study also found a lower rate of meeting the triglyceride goal with older-generation NRTIs. These results are consistent with randomized clinical trial data that have shown higher HDL cholesterol and lower triglycerides levels with NNRTI-based regimens when compared to PI-based regimens and higher triglyceride levels with older-generation NRTIs compared to later-generation NRTIs.^{34,35}

We found very low rates of screening for microalbuminuria (19%) in patients without evidence of proteinuria or chronic kidney disease. Given the insensitivity of a traditional urinalysis to detect microalbuminuria and the availability of an effective intervention, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, to prevent diabetic nephropathy in patients with microalbuminuria, education of HIV primary care providers on the importance of this screening test is essential.^{36,37} We also found low rates of screening for diabetic retinopathy, as fewer than half of patients had a documented ophthalmologic examination.

To our knowledge, this study is the first to examine potential associations with inadequate glycemic control in HIV-infected patients with diabetes mellitus and the first to assess rates of screening for retinopathy and nephropathy in this population. Strengths of the study include use of an entire year of laboratory data to estimate the prevalence of inadequate glycemic control and rates of meeting ADA goals and screening guidelines. We did not rely on ICD-9 codes to identify patients with diabetes, a method that could have biased our sample by including only diabetic patients under the care of physicians with better documentation practices. Instead we reviewed all physician notes during the prior year to identify patients with a physician diagnosis of diabetes. In fact, none of the 143 patients excluded because they did not have a physician diagnosis of diabetes ever had a hemoglobin A_{1c} $\geq 7.5\%$. Patients who were diagnosed with diabetes during 2008 were excluded because we did not want high HbA_{1c} levels that may accompany a new diagnosis to influence the results.

In addition to the limitations inherent to the cross-sectional study design, this study has several other limitations. True associations may not have been identified due to a lack of power. Since only patients with HbA_{1c} values from two different quarters of the year were included, our sample likely included patients that were more adherent to medical appointments than the overall population of HIV-infected patients with diabetes. Similarly, all patients received care at an academic clinic with extensive resources. Thus, we may have underestimated the rate of inadequate glycemic control and overestimated the rates of achieving ADA goals and adherence to guidelines. We also did not assess rates of neuropathy screening and annual comprehensive foot examinations as these assessments were not routinely documented in the charts. Use of antiplatelet agents was not analyzed given recent changes in ADA guidelines regarding their use for primary prevention of cardiovascular disease in patients with

diabetes.³⁸ The primary care physician for all but one of the patients was an attending physician, so the impact of provider type could not be assessed. Similarly, very few patients were not on antiretroviral therapy, so the impact of antiretroviral medication use in general on glycemic control and meeting ADA goals could not be assessed. An additional limitation is a concern of the accuracy of glycated hemoglobin as a measure of glycemic control in HIV-infected patients with diabetes. In a cross-sectional study comparing HIV-infected versus HIV-uninfected adults with diabetes, HbA_{1c} was found to underestimate glucose levels by 29 mg/dL in HIV-infected patients.³⁹ However, a recent study of women with diabetes found that HbA_{1c} values in HIV-infected women were only slightly lower than values in HIV-uninfected women after adjusting for concurrently measured fasting glucose concentrations.⁴⁰

In summary, we found that the prevalence of inadequate glycemic control in this cross-sectional study of HIV-infected patients with diabetes was similar to a previous study in this population and similar to the prevalence in HIV-uninfected patients.^{11,14} However, with the exception of the LDL cholesterol goal, rates of achieving ADA goals and adherence to screening guidelines were low. Our clinic offers HIV-infected patients very comprehensive care, including onsite psychiatrists, social workers, nutritionists, and nursing educators to assist with diabetes management. If fewer than half of patients with diabetes in our clinic are meeting ADA goals for blood pressure and lipids, and guidelines for retinopathy and nephropathy screening, then it is likely that other clinics with fewer resources that care for HIV-infected patients with diabetes also have low rates. A multifaceted approach is required to improve these rates. Potential interventions include increased education of HIV primary care providers on the most up-to-date recommendations in the care of the diabetic patient, the use of checklists to remind physicians of the need for yearly screening procedures, and the implementation of a targeted multidisciplinary program to improve diet, adherence to blood glucose monitoring, and regular exercise. Further studies are warranted to assess the efficacy of these and other potential interventions to improve both glycemic control and rates of meeting ADA goals and screening guidelines.

Acknowledgments

This work was supported in part by T32 AI007613 and K24 AI078884 from the National Institute of Allergy and Infectious Diseases and the Bristol-Myers Squibb Virology Fellows Research Training Program. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the funders.

Author Disclosure Statement

Marshall J. Glesby has received research support from Pfizer and has served as an ad hoc consultant to Bristol-Myers-Squibb and Pfizer; Michael J. Satlin and Donald R. Hoover have no potential conflicts of interest to disclose.

References

1. Lima VD, Hogg RS, Harrigan PR, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS* 2007;21:685–692.

2. Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: Changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2007;44:27–34.
3. Yang CH, Huang YF, Hsiao CF, et al. Trends of mortality and causes of death among HIV-infected patients in Taiwan, 1984–2005. *HIV Med* 2008;9:535–543.
4. Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2007. www.cdc.gov/diabetes (Last accessed June 28, 2010).
5. Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005–2050. *Diabetes Care* 2006;29:2114–2116.
6. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med* 2005;165:1179–1184.
7. Ledergerber B, Furrer H, Rickenbach M, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis* 2007;45:111–119.
8. Justman J, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr* 2003;32:298–302.
9. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–853.
10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589.
11. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? *Diabetes Care* 2008;31:81–86.
12. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care* 1999;22:403–408.
13. Fox KM, Gerber Pharmd RA, Bolinder B, Chen J, Kumar S. Prevalence of inadequate glycemic control among patients with type 2 diabetes in the United Kingdom general practice research database: A series of retrospective analyses of data from 1998 through 2002. *Clin Ther* 2006;28:388–395.
14. Adeyemi O, Vibhakar S, Max B. Are we meeting the American Diabetes Association goals for HIV-infected patients with diabetes mellitus? *Clin Infect Dis* 2009;49:799–802.
15. Bury JE, Stroup JS, Stephens JR, Baker DL. Achieving American Diabetes Association goals in HIV-seropositive patients with diabetes mellitus. *Proc (Bayl Univ Med Cent)* 2007;20:118–123.
16. Benoit SR, Fleming R, Philis-Tsimikas A, Ji M. Predictors of glycemic control among patients with Type 2 diabetes: A longitudinal study. *BMC Public Health* 2005;5:36.
17. Blaum CS, Velez L, Hiss RG, Halter JB. Characteristics related to poor glycemic control in NIDDM patients in community practice. *Diabetes Care* 1997;20:7–11.
18. Nichols GA, Hillier TA, Javor K, Brown JB. Predictors of glycemic control in insulin-using adults with type 2 diabetes. *Diabetes Care* 2000;23:273–277.
19. Tien PC, Schneider MF, Cole SR, et al. Antiretroviral therapy exposure and insulin resistance in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2008;49:369–376.
20. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. *Lancet* 2007;370:829–840.
21. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy, and strokes. *Kidney Int* 2002;61:1086–1097.
22. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016.
23. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696.
24. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559.
25. Goudswaard AN, Stolk RP, Zuithoff P, et al. Patient characteristics do not predict poor glycaemic control in type 2 diabetes patients treated in primary care. *Eur J Epidemiol* 2004;19:541–545.
26. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585.
27. Kirk JK, Huber KR, Clinch CR. Attainment of goals from national guidelines among persons with type 2 diabetes: A cohort study in an academic family medicine setting. *N C Med J* 2005;66:415–419.
28. Putzer G, Roetzheim R, Ramirez AM, Sneed K, Brownlee HJ Jr, Campbell RJ. Compliance with recommendations for lipid management among patients with type 2 diabetes in an academic family practice. *J Am Board Fam Pract* 2004;17:101–107.
29. Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ. Postprandial plasma lipoprotein changes in human subjects of different ages. *J Lipid Res* 1988;29:469–479.
30. Wohl D, Scherzer R, Heymsfield S, et al. The associations of regional adipose tissue with lipid and lipoprotein levels in HIV-infected men. *J Acquir Immune Defic Syndr* 2008;48:44–52.
31. Currier J, Scherzer R, Bacchetti P, et al. Regional adipose tissue and lipid and lipoprotein levels in HIV-infected women. *J Acquir Immune Defic Syndr* 2008;48:35–43.
32. Ferrara A, Mangione CM, Kim C, et al. Sex disparities in control and treatment of modifiable cardiovascular disease risk factors among patients with diabetes: Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care* 2008;31:69–74.
33. Carey D, Amin J, Boyd M, Petoumenos K, Emery S. Lipid profiles in HIV-infected adults receiving atazanavir and atazanavir/ritonavir: Systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2010;69:1878–1888.
34. van der Valk M, Kastelein JJ, Murphy RL et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS* 2001;15:2407–2414.
35. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy

- in antiretroviral-naïve patients: A 3-year randomized trial. *JAMA* 2004;292:191–201.
36. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993;118:577–5781.
37. Parving HH, Lenhert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–878.
38. Executive Summary: Standards of medical care in diabetes—2010. *Diabetes Care* 2010;33(Suppl 1):S4–S10.
39. Kim PS, Woods C, Georgoff P, et al. A1C underestimates glycemia in HIV infection. *Diabetes Care* 2009;32:1591–1593.
40. Glesby MJ, Hoover DR, Shi Q, et al. Glycated haemoglobin in diabetic women with and without HIV infection: Data from the Women's Interagency HIV Study. *Antivir Ther* 2010;15:571–577.

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