

# Achieving American Diabetes Association goals in HIV-seropositive patients with diabetes mellitus

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This retrospective study examined whether the goals set forth by the American Diabetes Association were being attained in an HIV specialty clinic run by internal medicine physicians. The charts of 40 HIV patients with diabetes were reviewed. Patients were divided into two groups: those who had seen a clinical pharmacist for medication adherence counseling ( $n = 20$ ) and those who had not ( $n = 20$ ). Overall, less than 50% of patients were achieving goals of therapy for hemoglobin A<sub>1c</sub>, cholesterol, triglycerides, and blood pressure. Only 5% were documented as receiving aspirin therapy. The medication adherence counseling was not a significant factor in the results. Clinicians need to be aware of the concomitant disease states that HIV patients have and to treat those disease states to the standard of care set forward.

Cardiovascular disease remains one of the most prevalent contributors to morbidity and mortality in the USA, accounting for 1 in every 2.7 deaths (1). The link between cardiovascular disease and diabetes is well defined, with cardiovascular disease accounting for 65% of deaths among diabetes patients (2). Due to this risk, diabetes is now recognized by the National Cholesterol Education Panel as a cardiovascular disease risk equivalent (3, 4). The elevated risk observed with diabetes is due not only to elevated blood glucose levels but also to elevated systolic and diastolic blood pressures, triglyceride levels, low-density lipoprotein (LDL) cholesterol levels, and total cholesterol levels and decreased levels of high-density lipoprotein (HDL) cholesterol (5). Therefore, the American Diabetes Association (ADA) recommends a multifactorial targeted approach in patients with diabetes to decrease this cardiovascular risk (6).

Recently, several studies have identified a link between cardiovascular risk and HIV (7, 8). It also appears that highly active antiretroviral therapy (HAART) may play a direct role in the incidence of cardiovascular disease observed in the HIV population (8–10). In addition, HIV-infected men receiving HAART are at a fourfold increased risk of developing diabetes compared with HIV-seronegative men (11). The same cardiovascular risk factors that are identified in patients with diabetes are also found in HIV patients with diabetes, and these risk factors need to be addressed along with the infectious disease issues (12).

The pharmacotherapy of HIV with HAART requires a complex clinical approach. Therefore, HIV treatment clinics

throughout the country employ several different health care professionals, including clinical pharmacists, to assess multifactorial issues in HIV treatment, including adherence.

To our knowledge, no study has examined ADA goal attainment in patients with diabetes in an HIV treatment clinic. A major concern is that the goals of management set forth by the ADA are not being attained in the HIV population with diabetes, because clinicians are concentrating primarily on HIV disease management and not on the patients' other major disease states. This study was conducted to determine if HIV-seropositive patients with diabetes were meeting the ADA goals of therapy in our internal medicine-run specialty clinic. A secondary objective was to identify the differences in attainment of ADA goals between HIV patients who were counseled by a clinical pharmacist in the HIV adherence clinic and those who were not.

## METHODS

In this retrospective study, 50 patients were identified through a computer-generated list by ICD-9 codes for HIV (V08 and 042) and diabetes mellitus type 1 and 2 (250). Ten patients were excluded from the analysis because they had not been seen in the clinic for at least 6 months. The remaining 40 patients were divided into two groups: those who had seen a clinical pharmacist in the past 2 years (intervention group;  $n = 20$ ) and those who had not (control group;  $n = 20$ ). This study was approved by the institutional review board.

The intervention consisted of patient visits or telephone calls for adherence counseling for all patients beginning new HIV medications. The same clinical pharmacist performed all adherence counseling. The intervention had three phases. The first phase, or initial visit, consisted of 1 hour with the clinical pharmacist. The goal of this visit was to assess the patient's

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ability or readiness to begin therapy, to enter into a partnership with the patient, to answer questions related to the disease state and medications, to set up a mutually agreeable medication regimen, to provide counseling on possible adverse events, and to provide adherence strategies and reminders (e.g., pill boxes, timed pagers, charts with drug stickers). The second phase consisted of a follow-up telephone call 48 hours after the start of medications. This call focused on adverse events and how the medications were being taken. The third phase of the intervention consisted of a follow-up visit at week 1, if deemed necessary by risk factors and phone follow-up results. This visit focused on reinforcement of compliance issues and dealt with ongoing or potential adverse effects. A scheduled follow-up visit occurred as needed thereafter.

The charts of both groups of patients were reviewed, and the measurements related to the ADA goals of therapy (*Table 1*)

**Table 1. American Diabetes Association goals of therapy for patients with diabetes**

Measurement	Goal value
Hemoglobin A <sub>1c</sub>	<7%
LDL cholesterol	<100 mg/dL
Triglycerides	<150 mg/dL
HDL cholesterol	>40 mg/dL in men >50 mg/dL in women
Total cholesterol	<200 mg/dL
Non-HDL cholesterol	<130 mg/dL
Systolic blood pressure	<130 mm Hg
Diastolic blood pressure	<80 mm Hg

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

**Table 2. Population characteristics**

	Control (n = 20)	Intervention (n = 20)	Total (n = 40)	P value
<b>Demographic</b>				
Males (%)	15 (75%)	16 (80%)	31 (77.5%)	0.71
Age (years)*	46.95 (7.82)	47.75 (9.5)	47.35 (8.6)	0.80
Race				0.22
White	12 (60%)	8 (40%)	20 (50%)	
Black	3 (15%)	9 (45%)	12 (30%)	
Hispanic	2 (10%)	2 (10%)	4 (10%)	
Native American	3 (15%)	1 (5%)	4 (10%)	
<b>Clinical</b>				
Body mass index (kg/m <sup>2</sup> )*	32.9 (10.06)	29.03 (4.73)	30.96 (8.01)	0.25
Normal (18.5–24.9)	3 (15%)	4 (20%)	7 (17.5%)	
Overweight (25.0–29.9)	7 (35%)	9 (45%)	16 (40%)	
Obese (30.0–34.9)	5 (25%)	6 (30%)	11 (27.5%)	
Severely obese (35.0–39.9)	1 (5%)	1 (5%)	2 (5%)	
Morbidly obese (>40.0)	4 (20%)	0 (0%)	4 (10%)	
Systolic blood pressure (mm Hg)*	135.4 (19.21)	135.2 (21.55)	135.3 (20.15)	0.90
Diastolic blood pressure (mm Hg)*	82.75 (8.28)	79.85 (8.06)	81.3 (8.2)	0.34
Smoking: never/ex/current	4/7/9	2/8/10	6/15/19	0.83
Alcohol use: never/ex/current	8/4/8	4/7/8	12/11/16	0.40
Known duration of diabetes (years)*	5.15 (3.15)	5.71 (4.61)	5.41 (3.84)	0.77
Known duration of HIV (years)*	10.1 (5.01)	9.74 (6.17)	9.92 (5.54)	0.69
<b>Biochemical</b>				
Hemoglobin A <sub>1c</sub> (%)*	7.71 (2.1)	7.79 (2.43)	7.75 (2.24)	0.96
Total cholesterol (mg/dL)*	197.35 (54.14)	183.65 (59.81)	190.5 (56.74)	0.25
LDL cholesterol (mg/dL)*	108.5 (41.76)	104.39 (46.99)	106.19 (44.12)	0.50
HDL cholesterol (mg/dL)*	39.25 (11.35)	39.15 (12.23)	39.2 (11.64)	0.90
Triglycerides (mg/dL)*	358.35 (360.89)	247.9 (240.34)	303.13 (307.77)	0.15
Non-HDL cholesterol (mg/dL)*	158.1 (51.25)	144.5 (58.13)	151.3 (54.53)	0.23
Viral load*	8510.6 (20,422.44)	45,895.75 (167,585.3)	27,203.18 (119,347.9)	0.43
CD4 count*	464.65 (271.22)	481 (257.26)	472.83 (261.05)	1.00
CD4 percentage*	24.47 (12.69)	25.06 (9.12)	24.76 (10.91)	0.94

\*Mean (SD).

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

were documented. The most recently recorded laboratory value was used to determine if goals of therapy were being met. Data collection ended on September 30, 2006. Statistical analysis was performed using the Fisher exact test for comparison of the rates of attainment of goals between the two groups.

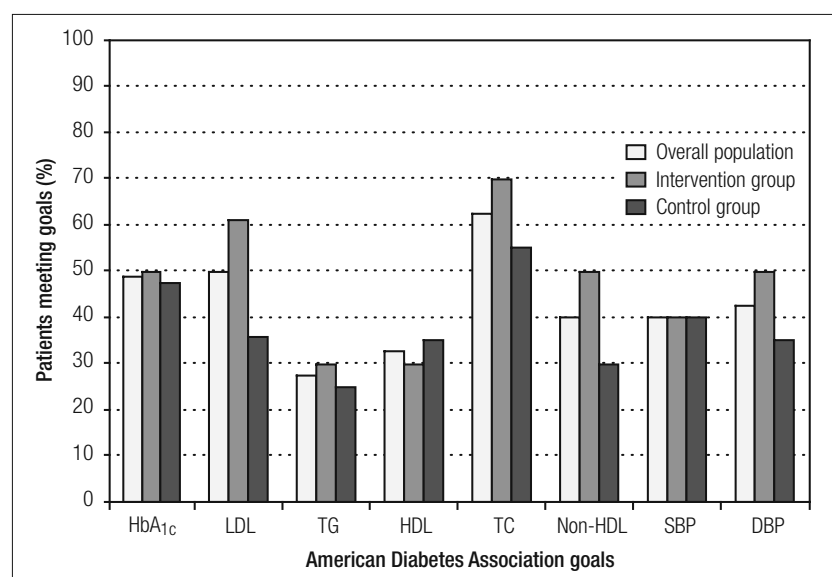
## RESULTS

The baseline demographics, clinical characteristics, and biochemical characteristics of the study population are presented in *Table 2*. The population was middle aged (47.35 years) and predominantly male (77.5%), with a duration of diabetes of 5.4 years and duration of HIV of 9.9 years. There were no statistically significant differences between the intervention and control groups related to baseline demographics.

**Table 3. Medications prescribed**

Medications	Control (n = 20)	Intervention (n = 20)	Total (n = 40)	P value
<b>HIV</b>				
Protease inhibitor				0.08
Boosted	6 (30%)	6 (30%)	12 (30%)	
Unboosted	3 (15%)	9 (45%)	12 (30%)	
None	11 (55%)	5 (25%)	16 (40%)	
NNRTI	6 (30%)	6 (30%)	12 (30%)	1.00
NRTI	16 (80%)	18 (90%)	34 (85%)	0.66
<b>Cardiovascular</b>				
Aspirin	2 (10%)	0 (0%)	2 (5%)	0.49
Statin	9 (45%)	11 (55%)	20 (50%)	0.75
ACE inhibitor/ARB	10 (50%)	10 (50%)	20 (50%)	1.00
<b>Diabetes</b>				
Insulin	6 (30%)	7 (35%)	13 (32.5%)	1.00

NNRTI indicates nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist.



**Figure.** Percentage of patients meeting American Diabetes Association goals in an HIV specialty clinic. HbA<sub>1c</sub> indicates hemoglobin A<sub>1c</sub>; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

In terms of HIV status, most patients (25/40) had undetectable viral loads and CD4 cell counts of 460 to 480 cells/ $\mu$ L. Sixty percent of patients were receiving some form of protease inhibitor (PI) therapy, with no difference between the groups (*Table 3*).

There was no statistically significant difference between the groups in regard to the attainment of ADA goals (*Figure*). For the 40 patients as a whole, <50% reached goals for hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), LDL, HDL, triglycerides, and blood pressure. Total cholesterol was the only variable in which >50% of patients attained the goal.

Only 50% of patients received an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist. Statin therapy was also only documented in about half of the patients. Of those who were on a statin, only one in five received maximum therapeutic doses. Only two patients were on documented aspirin therapy.

## DISCUSSION

We found that in our HIV specialty clinic, diabetic patients' HIV was well controlled, but their cardiovascular goals as defined by the ADA were not being met. Since the advent of HAART, the lifespan of an HIV patient has steadily increased (13). These patients can now have a normal lifespan, but with that comes an increased risk of death from noninfectious causes like cardiovascular disease and diabetes (14, 15).

It is crucial for patients with diabetes to properly manage their blood glucose levels in order to reduce the incidence of both microvascular (16, 17) and macrovascular (18) diseases. An important marker for glucose management is HbA<sub>1c</sub>. The ADA guidelines suggest that HbA<sub>1c</sub> be <7% and if possible be normal (<6%) (6). Epidemiologic data have shown that any elevation in glycemia, even in the subdiabetic range, can increase the risk of cardiovascular disease (19). In our patients, less than half met the current HbA<sub>1c</sub> goal of <7%. Up to 40% of patients on a PI-containing regimen have impaired glucose tolerance (20). This occurs through insulin resistance induced by this drug class (21, 22). Those patients who already have diabetes or who have traditional risk factors for type 2 diabetes mellitus should consider avoiding the use of a PI-based regimen as initial HIV therapy (23). In our study, 60% of patients were on a PI therapy, although most were not on their initial course of HIV therapy.

LDL cholesterol is important to control in diabetics and HIV patients. The Infectious Disease Society of America and Adult AIDS Clinical Trials Group have updated their guidelines for the evaluation and management of dyslipidemia in patients on HAART (24). These guidelines

are derived primarily from the National Cholesterol Education Program Adult Treatment Panel III guidelines (4). Controlling LDL cholesterol has been shown to reduce cardiovascular events (25). Patients with diabetes are considered to be a coronary heart disease risk equivalent and therefore have an LDL goal of <100 mg/dL (4, 24).

In HIV patients, treatment of LDL is complicated by the interactions of statins with HAART. Studies have shown that atorvastatin and pravastatin may be used with ritonavir and saquinavir, but simvastatin should be avoided (26). The preferred statins are pravastatin, atorvastatin, and fluvastatin because less toxicity has been reported with these agents (24). Ezetimibe has also been shown in smaller studies to be effective in reducing cholesterol in HIV patients (27) and may be a good second-line agent (28). Possible treatment options for HAART-related dyslipidemia include altering HAART, making lifestyle changes, and adding lipid-lowering therapy (28). Since control of viremia is an overriding concern, changes in HAART are often not a practical alternative, and therefore lifestyle changes and lipid-lowering therapy are needed. High LDL values and dyslipidemic profiles in many patients often necessitate use of a statin concomitantly with another agent (29). When fibrates and statins are combined, fenofibrate is preferred, as it has been studied in patients with PI-associated dyslipidemia and interferes less with statin metabolism (30). Careful monitoring for rhabdomyolysis is needed in patients taking a statin or fibrate—especially if a patient is taking both medications, as the combination increases the risk of these side effects.

Prior to HAART, decreased levels of HDL cholesterol (31–34) and increased levels of triglycerides (31, 32) were reported in HIV-seropositive individuals. HAART regimens that include the PI ritonavir can also induce hypertriglyceridemia (35). In contrast, some PIs like atazanavir may have minimal effects on lipid levels (36). Hypertriglyceridemia in some patients receiving PIs can be rapidly reversed by switching to the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (37–40). These effects are not observed with the NNRTI efavirenz. A change in diet can also reduce triglyceride levels but not typically to normal (41). Treatment for hypertriglyceridemia usually requires pharmacologic treatment, with fibrates being the preferred initial therapy for patients on PIs (41).

The use of aspirin therapy in our patient population was low. In patients with diabetes, aspirin therapy has been well documented to have major effects on morbidity and mortality (42–44). In patients with diabetes, platelets are hypersensitive to platelet-aggregating agents (45). Substantial evidence supports the use of low-dose aspirin as a primary (43, 44) and secondary (46) prevention strategy in diabetic patients if no contraindications exist. Only 5% of our patients were on aspirin therapy. Our low percentage could be due to a lack of documentation or a lack of encouragement by physicians to get patients on low-dose aspirin therapy. Based on current knowledge, there are no HIV-related contraindications for patients to take low-dose aspirin. As such, it is important for patients who are at high cardiovascular risk (such as patients with diabetes) to be on aspirin therapy.

The attainment of ADA goals of therapy is an important marker for outcomes in patients with diabetes. In the STENO-2 study, an intensive program to attain goals of therapy for the multiple risk factors in patients with type 2 diabetes was compared with conventional therapy and resulted in >50% reduction in cardiovascular and microvascular events (47). It has been estimated that every 1% reduction in HbA<sub>1c</sub> reduces the risk of microvascular diabetic complications by 40% (48) and every 10 mm Hg decrease in systolic blood pressure reduces the risk of diabetic complications by 12% (49).

Although our goal achievement was not 100%, the rates that we observed in our population were adequate compared with other published studies. In STENO-2, only approximately 15% of patients met the HbA<sub>1c</sub> goal of <6.5%, and 45% met the systolic blood pressure goal of <130 mm Hg (47). The goals of total cholesterol levels <175 mg/dL, diastolic blood pressure <80 mm Hg, and triglyceride levels <150 mg/dL were achieved in 70%, 70%, and 60% of patients, respectively, in their intervention group (47). Even in aggressive and well-controlled studies like the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, the average HbA<sub>1c</sub> did not remain at goal for the entire study period (16, 17). This lack of total goal attainment may be related to patients' noncompliance, intolerance to medications, or comorbidities. Nonetheless, practitioners should identify the goals of therapy for diabetes and work to achieve those goals. With the increased pressure of a pay-for-performance model, this identification and achievement will be necessary.

A possible solution to improving goal achievement could be to have a pharmacy-run clinic whose staff would meet with HIV patients with diabetes to discuss glucose monitoring, discuss medication regimens, and work to attain the ADA goals of therapy. Pharmacist-run diabetes clinics have proven effective in a variety of settings (50–52).

This study has a number of limitations: the sample size was small, a single clinic was evaluated, laboratory values were evaluated at various times after medications were started, and vascular outcomes (both macro and micro) were not measured. This clinic is also unique in that it is run by internal medicine physicians who act as the primary care physicians for these patients, whereas other HIV clinics may be subspecialty clinics addressing only HIV issues while the primary care physicians address the other disease states.

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