



Comparative Effectiveness of Diabetic Oral Medications Among HIV-Infected and HIV-Uninfected Veterans

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OBJECTIVE

Type 2 diabetes is increasingly common in HIV-infected individuals. The objective of this study was to compare the glycemic effectiveness of oral diabetic medications among patients with and without HIV infection.

RESEARCH DESIGN AND METHODS

A longitudinal cohort study was conducted among HIV-infected and uninfected veterans with type 2 diabetes initiating diabetic medications between 1999 and 2010. Generalized estimating equations were used to compare changes in hemoglobin A_{1c} (HbA_{1c}) through the year after medication initiation, adjusting for baseline HbA_{1c} level and clinical covariates. A subanalysis using propensity scores was conducted to account for confounding by indication.

RESULTS

A total of 2,454 HIV-infected patients and 8,892 HIV-uninfected patients initiated diabetic medications during the study period. The most commonly prescribed medication was metformin ($n = 5,647$, 50%), followed by a sulfonylurea ($n = 5,554$, 49%) and a thiazolidinedione ($n = 145$, 1%). After adjustment for potential confounders, there was no significant difference in the change in HbA_{1c} level among the three groups of new users. HIV infection was not significantly associated with glycemic response ($P = 0.24$). Black and Hispanic patients had a poorer response to therapy compared with white patients, with a relative increase in HbA_{1c} level of 0.16% (95% CI 0.08, 0.24) [1.7 mmol/mol (0.9, 2.6)] ($P < 0.001$) and 0.25% (0.11, 0.39) [2.7 mmol/mol (1.2, 4.3)] ($P = 0.001$), respectively.

CONCLUSIONS

We found that glycemic response was independent of the initial class of diabetic medication prescribed among HIV-uninfected and HIV-infected adults with type 2 diabetes. The mechanisms leading to poorer response among black and Hispanic patients, who make up a substantial proportion of those with HIV infection and type 2 diabetes, require further investigation.

The survival of individuals living with HIV infection has significantly improved with the widespread use of antiretroviral therapy (ART) (1). Metabolic disorders, such as type 2 diabetes, are increasingly important determinants of morbidity and mortality in this population (2,3). HIV-infected individuals may have a poorer response to

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diabetic medical therapy compared with individuals without HIV infection (4); thus, identifying effective treatment regimens for type 2 diabetes by HIV status is critical.

Current management guidelines for type 2 diabetes in HIV-infected patients are from data established in the HIV-uninfected population, as well as from expert opinion (5,6). Along with lifestyle modifications, these guidelines recommend metformin as first-line medical therapy. However, it is not known how generalizable these guidelines are to HIV-infected patients who represent a complex population with distinct pathophysiological processes (e.g., chronic inflammation and metabolic effects of ART) (7–9) that may impact comorbid diseases, as well as the response to treatment of these conditions. Certain diabetic medications, such as metformin and thiazolidinediones (TZDs), have been shown to possess anti-inflammatory properties (10–13). We therefore hypothesized that the use of these medication classes would result in larger reductions in hemoglobin A_{1c} (HbA_{1c}) compared with sulfonylureas, and specifically among those with HIV infection versus those without HIV infection.

To address these issues, we conducted this study among a large, national cohort of HIV-infected and uninfected veterans initiating diabetic medical therapy in routine clinical care with the goal of comparing the glycemic effectiveness of the three main classes of oral diabetic medications (metformin, sulfonylureas, TZDs). We also sought to determine the impact of HIV infection on glycemic response.

RESEARCH DESIGN AND METHODS

Study Setting

This study was conducted in the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) (14). The VACS-VC is a longitudinal, prospective cohort study of HIV-infected veterans, and a 2:1 sample of age, sex, race, and site-matched HIV-uninfected veterans receiving care at Veterans Health Administration Medical Centers. The VACS-VC, which currently consists of >125,000 individuals, is assembled from national Veterans Affairs (VA) databases and provides a comprehensive resource for studies focused on aging, comorbid conditions, and alcoholism in the HIV-infected population.

Study Population

The initial source population comprised adults ≥ 18 years of age with prevalent type 2 diabetes based on Kelley's Diabetes Criteria (combinations of diagnostic codes, laboratory values, and medication prescriptions), which has been previously validated (15). Patients initiating oral monotherapy for type 2 diabetes between 1 January 1999 and 1 January 2010 were included from the initial source population. The date of the first pharmacy fill for a single oral diabetic medication from one of the three main classes (sulfonylureas, metformin, and TZDs) was denoted as the index date. To further ensure "new user" status, subjects were required 1) to have been enrolled in the cohort ≥ 6 months pre-index date, 2) not to have had a prescription filled for a diabetic medication in the 6 months preceding the index date, and 3) to have at least one refill of the new therapy during the year after the index date.

Study Design

This was a longitudinal cohort study using a new user design (16) of subjects with type 2 diabetes who initiated diabetic medical therapy. The exposures of interest were new use of a sulfonylurea, metformin, or a TZD. The primary outcome of interest was absolute change in HbA_{1c} level during the first year of therapy. We chose to evaluate glycemic change during the postindex year given that the greatest achievable reduction in HbA_{1c} level in response to oral medical therapy typically occurs in the year after medication initiation (17–19). The secondary outcome of interest was the proportion of patients in each group that achieved the American Diabetes Association (ADA) goal of an HbA_{1c} level of <7% at any time in the postindex period.

The study was approved by the institutional review board of the University of Pennsylvania. The VACS-VC was approved by the institutional review boards at the Yale School of Medicine and the VA Connecticut Human Subjects Subcommittee.

Demographic and Clinical Variables

Baseline data were collected for all subjects at the time of diabetic medication initiation, including age, sex, BMI, and race, and ethnicity. The presence of comorbid conditions and laboratory values

that may have affected the initial selection of therapy were also ascertained, including HIV infection, coronary artery disease, chronic kidney disease, congestive heart failure, and hepatitis C infection, as well as serum creatinine and liver function tests. Major psychiatric comorbid conditions, alcohol abuse, and substance abuse were also documented (4). The VACS Index score (20), which predicts 5-year, all-cause mortality after ART initiation and has also been shown to be predictive in uninfected patients (21,22), was calculated for each patient at baseline. HbA_{1c} results from 6 months prior to the first pharmacy fill date up to 12 months after the first pharmacy fill date were included. Baseline HbA_{1c} levels, number of HIV RNA copies, and CD4⁺ T-cell counts were defined as those measured in the 6-month preindex date period closest to but not after the start of diabetic medical therapy. Baseline ART regimens were classified into protease inhibitor (PI)-based ART (i.e., inclusion of a PI) or non-PI-based ART (i.e., absence of a PI).

Medication switch was defined as discontinuing the index medication and initiating another medication from a different class during the postindex year. Medication intensification was considered as the addition of another medication to the initial regimen at any time during the 12-month postindex period. A medication possession ratio (MPR) was calculated for the initial diabetic medication, as follows: number of days of medication dispensed through pharmacy fills/refills as a percentage of the total number of days of follow-up from the index date (date of the first pharmacy fill) to the last follow-up HbA_{1c} level (i.e., ratio of actual/expected) (23).

Statistical Analysis

Baseline characteristics among the three groups were compared using the Student *t* test or Wilcoxon rank sum test for continuous variables, and the χ^2 or Fisher exact test for categorical variables. Linear regression models evaluating the absolute adjusted difference between HbA_{1c} at baseline and at 12 months were developed, with the calculation of the mean (95% CI) change in HbA_{1c} by the three new-user groups. For a more meaningful assessment of HbA_{1c} change, using multiple measures

of HbA_{1c} over the 1-year period, a generalized estimating equation (GEE) model for the primary outcome analyses was used. The GEE model accounts for correlation within a subject (e.g., repeated measurements) and allowed for the incorporation of all available HbA_{1c} measurements for each subject during the first year of treatment (24). Follow-up time intervals for HbA_{1c} results were categorized at 3-month intervals for analysis, as follows: 1–3 months, 4–6 months, 7–9 months, and 10–12 months. If more than one follow-up HbA_{1c} value was available for a specific time interval, the most recent value was entered into the model. Variables that could act as potential confounders of the association between index medication class and change in HbA_{1c}, including baseline demographics and comorbid conditions, were considered for inclusion and maintained in the final model if they were statistically significant on bivariable analysis or were considered to be clinically important (25). Baseline HbA_{1c} level was retained in the model a priori, given its known influence on the initial response to therapy (26).

The above analyses were repeated using propensity scores (27) generated using multiple logistic regression to address potential confounding by indication due to choice of the initial diabetic medication class (16). Variables evaluated for inclusion in propensity scores included all demographic and clinical variables, as described above, including comorbid conditions that may have affected the initial choice of medication (e.g., chronic kidney disease).

Secondary outcome analysis of achieving the goal HbA_{1c} level was performed using multiple logistic regression, with adjustment for potential confounders in the final model as noted in the primary outcome analyses (25). For all calculations, a two-tailed *P* value of <0.05 was considered significant. All statistical calculations were performed using commercially available software (SAS version 9.2; SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics of New Users
A total of 2,454 HIV-infected patients and 8,892 HIV-uninfected patients met the study criteria and were included in the study. The mean age of the study population was 53 years (SD 9 years),

and 98% were male. Of the 11,346 new users, 5,387 (47%) were black, 4,551 (40%) were white, and 1,156 (10%) were Hispanic. The majority of patients were overweight (27%) or obese (61%), as classified by BMI.

Compared with uninfected patients, HIV-infected patients were more likely to have hepatitis C infection (39% and 15%, respectively, *P* < 0.001), an alcohol abuse diagnosis (14% and 12%, respectively, *P* < 0.001), and a drug abuse diagnosis (17% and 11%, respectively, *P* < 0.001). HIV-infected patients also had a significantly higher VACS Index score (median 28, interquartile range [IQR] 17, 43) compared with HIV-uninfected

patients (median 12, IQR 10, 22). Other baseline characteristic comparisons are shown in Table 1.

Initial Diabetic Medical Therapy and Treatment Responses in the Postindex Year

The most commonly prescribed diabetic medication was metformin (*n* = 5,647, 50%), followed by a sulfonylurea (*n* = 5,554, 49%) and a TZD (*n* = 145, 1%). Compared with new users of metformin, or TZD, patients who started receiving therapy with a sulfonylurea had a higher mean baseline HbA_{1c}, a higher median VACS Index score, and an earlier year of therapy initiation. Other characteristics

Table 1—Baseline characteristics of HIV-infected and HIV-uninfected new users of diabetic medical therapy

Characteristic*	HIV-infected new users (<i>n</i> = 2,454; 22%)	HIV-uninfected new users (<i>n</i> = 8,892; 78%)	<i>P</i> value
Age, mean (SD), years	53 (9)	53 (9)	0.95
Female sex	55 (2)	148 (2)	0.06
Race/ethnicity			0.49
White	1,041 (41)	3,537 (40)	
Black	1,136 (46)	4,251 (48)	
Hispanic	253 (10)	903 (10)	
Other	51 (2)	201 (2)	
BMI, kg/m ² †			<0.001
<18.5	20 (1)	25 (0.4)	
18.5–24.9	442 (26)	396 (7)	
25–29.9	632 (37)	1,496 (25)	
≥30	634 (37)	4,155 (68)	
Hepatitis C infection	961 (39)	1,341 (15)	<0.001
Aspartate aminotransferase, median (IQR), units/L	36 (25, 59)	26 (21, 37)	<0.001
Alanine aminotransferase, median (IQR), units/L	41 (27, 65)	34 (24, 50)	<0.001
Total bilirubin, median (IQR), mg/dL	0.7 (0.5, 1.0)	0.6 (0.4, 0.8)	<0.001
Major psychiatric disorder‡	417 (17)	1,669 (19)	0.04
Alcohol abuse	344 (14)	1,087 (12)	0.02
Drug abuse	420 (17)	951 (11)	<0.001
Chronic kidney disease	131 (5)	397 (4)	0.07
Serum creatinine, median (IQR), mg/dL	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	0.001
Coronary artery disease	103 (4)	727 (8)	<0.001
Congestive heart failure	29 (1)	166 (2)	0.02
VACS Index score, median (IQR)§	28 (17, 43)	12 (10, 22)	<0.001
Baseline HbA _{1c} , median (IQR)			
%	7.4 (6.5, 8.9)	7.4 (6.6, 9.0)	0.02
mmol/mol	57 (48, 74)	57 (49, 75)	
Medication switch	107 (4)	218 (2)	0.001
Medication intensification	529 (22)	2,043 (23)	0.10
MPR, median (IQR)	1.01 (0.79, 1.15)	0.97 (0.76, 1.13)	<0.001
Clinic visits, median (IQR)	7 (4, 11)	4 (3, 6)	<0.001

*Data are presented as *n* (%), except where otherwise noted. †31% of patients were missing BMI information. ‡Major depression, bipolar disorder, post-traumatic stress disorder, and other psychiatric disorders. §Higher scores are associated with a greater risk of all-cause mortality. ||Total visits in the postindex year period.

of new users of diabetic medications are shown in Table 2.

The mean of the absolute change in HbA_{1c} at 12 months from baseline for sulfonylurea new users was -1.43% (95% CI $-1.58, -1.29$) [-15.6 mmol/mol ($-17.3, -14.1$)], for metformin new users was -0.95% ($-1.05, -0.85$) [-10.4 mmol/mol ($-11.5, -9.3$)], and for TZD new users was -0.12%

($-0.62, 0.38$) [-1.3 mmol/mol ($-6.8, 4.2$)]. Only 3% of patients underwent a medication switch during the first year after the initiation of treatment.

In unadjusted GEE analysis, patients receiving metformin had a greater decrease in HbA_{1c} level in the year after medication initiation compared with those receiving a sulfonylurea, with

an average decrease of -0.30% ($-0.36, -0.23$) [-3.3 mmol/mol ($-3.9, -2.5$)] ($P < 0.001$). However, in the final adjusted model (Table 2), there was no significant difference in change in HbA_{1c} level between new users of metformin and new users of sulfonylureas ($P = 0.51$) or between new users of TZDs and new users of sulfonylureas ($P = 0.43$).

Table 2—Baseline characteristics of new users of diabetic medical therapy

Characteristic*	Sulfonylurea (n = 5,554; 49%)	Metformin (n = 5,647; 50%)	TZD (n = 145; 1%)	P value
Age, mean (SD), years	53 (9)	53 (8)	54 (8)	0.04
HIV status				<0.001
Uninfected	4,108 (74)	4,682 (83)	102 (70)	
HIV-infected	1,446 (26)	965 (17)	43 (30)	
Female sex	64 (1)	138 (2)	1 (1)	<0.001
Race/ethnicity				<0.001
White	2,135 (38)	2,362 (42)	54 (37)	
Black	2,732 (49)	2,597 (46)	58 (40)	
Hispanic	596 (11)	533 (9)	27 (19)	
Other	91 (2)	155 (3)	6 (4)	
Medication start year, median (IQR)	2003 (2001, 2006)	2007 (2004, 2009)	2004 (2003, 2006)	<0.001
BMI, kg/m ² †				<0.001
<18.5	28 (1)	17 (0.4)	0 (0)	
18.5–24.9	491 (16)	329 (7)	18 (16)	
25–29.9	948 (30)	1,140 (25)	40 (35)	
≥30	1,665 (53)	3,068 (67)	56 (49)	
CD4 ⁺ T-cell count, median (IQR), cells/μL‡	392 (233, 610)	487 (317, 695)	401 (315, 624)	<0.001
HIV RNA level, median (IQR), copies/mL‡	400 (50, 4,560)	75 (50, 450)	308 (50, 417)	<0.001
HIV RNA <400 copies/mL‡	459 (42)	461 (61)	19 (50)	<0.001
ART regimen‡				<0.001
No ART	197 (14)	145 (15)	1 (2)	
PI-based	808 (56)	445 (46)	20 (47)	
Non-PI-based	441 (31)	375 (39)	22 (51)	
Hepatitis C infection	1,335 (24)	945 (17)	22 (15)	<0.001
Aspartate aminotransferase, median (IQR), units/L	30 (22, 51)	27 (21, 38)	28 (22, 37)	<0.001
Alanine aminotransferase, median (IQR), units/L	38 (25, 60)	34 (25, 50)	34 (23, 50)	<0.001
Total bilirubin, median (IQR), mg/dL	0.6 (0.4, 0.9)	0.6 (0.4, 0.8)	0.6 (0.5, 0.9)	<0.001
Major psychiatric disorder§	998 (18)	1,070 (19)	18 (12)	0.07
Alcohol abuse	718 (13)	701 (12)	12 (8)	0.20
Drug abuse	671 (12)	690 (12)	10 (7)	0.15
Chronic kidney disease	327 (6)	187 (3)	14 (10)	<0.001
Serum creatinine, median (IQR), mg/dL	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	1.1 (0.9, 1.3)	<0.001
Coronary artery disease	462 (8)	356 (6)	12 (8)	<0.001
Congestive heart failure	132 (2)	61 (1)	2 (1)	<0.001
VACS Index score, median (IQR)	21 (12, 35)	16 (11, 23)	19 (12, 33)	<0.001
Baseline HbA _{1c} , median (IQR)				<0.001
%	7.8 (6.8, 9.8)	7.2 (6.5, 8.5)	6.8 (6.1, 7.9)	
mmol/mol	62 (51, 84)	55 (48, 69)	51 (43, 63)	
Medication switch	143 (3)	171 (3)	11 (8)	0.001
Medication intensification	1,371 (25)	1,156 (21)	45 (32)	<0.001
MPR, median (IQR)	0.99 (0.77, 1.14)	0.97 (0.75, 1.12)	0.99 (0.81, 1.08)	0.002
Clinic visits, median (IQR)¶	5 (3, 8)	4 (3, 7)	4 (3, 7)	<0.001

*Data are presented as n (%), except where otherwise noted. †31% of patients were missing BMI information. ‡Among HIV-infected patients. §Major depression, bipolar disorder, post-traumatic stress disorder, and other psychiatric disorders. ||Higher scores are associated with greater risk of all-cause mortality. ¶Total visits in the postindex year period.

HIV infection was not significantly associated with a change in HbA_{1c} (average decrease -0.07% [-0.8 mmol/mol; 95% CI -0.17% , 0.04% (-1.9 , 0.4 mmol/mol)], $P = 0.24$). Black and Hispanic patients had a poorer response to therapy compared with white patients, with a relative increase in HbA_{1c} of 0.16% (95% CI 0.08 , 0.24) [1.7 mmol/mol (0.9 , 2.6)] ($P < 0.001$) and 0.25% (0.11 , 0.39) [2.7 mmol/mol (1.2 , 4.3)] ($P = 0.001$), respectively. In addition, a higher BMI and higher baseline HbA_{1c} level were associated with a worse response to diabetic medical therapy. Other factors that were associated with a change in HbA_{1c} level are shown in Table 3. Findings were similar in analyses using propensity scores (data not shown), with the addition of a significant association with VACS Index score by quintile [mean decrease -0.02% (-0.03 , -0.004) [-0.2 mmol/mol (-0.3 , -0.1)] ($P = 0.02$)].

Initial Diabetic Medical Therapy in HIV-Infected Patients

A sulfonylurea was the most commonly prescribed initial medication among HIV-infected patients ($n = 1,446$, 59%). HIV-infected new users of a sulfonylurea were more likely to be receiving treatment with a PI-based ART regimen and to have a detectable HIV viral load compared with those receiving treatment with metformin or a TZD (Table 2). In a model restricted to patients with HIV infection, in which the ART regimen was included (Table 4), there was no significant difference in the change in HbA_{1c} level between new users of metformin and new users of sulfonylureas ($P = 0.12$) or between new users of TZDs and new users of sulfonylureas ($P = 0.19$). Black race was associated with a worse response to initial diabetic medical therapy, with an average increase in HbA_{1c} level of 0.19% (95% CI 0.02 , 0.37) [2.1 mmol/mol (0.2 , 4.0)] ($P = 0.03$). Receipt of a non-PI-based ART regimen was associated with a more favorable response compared with no ART, with an average decrease of HbA_{1c} in the postindex year of -0.50% (-0.88 , -0.12) [-5.5 mmol/mol (-9.6 , -1.3)] ($P = 0.01$). In a model that included the use of older ART agents that may be associated with metabolic complications, the receipt of ddI or d4T was not significantly associated with a

Table 3—Adjusted changes in HbA_{1c} in new users of diabetic medical therapy: multivariable analysis using a GEE model

Variable	Regression coefficient (95% CI)	P value
Metformin*	-0.03 (-0.11 , 0.06)	0.51
TZD*	0.18 (-0.27 , 0.64)	0.43
HIV infection	-0.07 (-0.17 , 0.04)	0.24
Age	0.001 (-0.005 , 0.008)	0.66
Male sex	-0.08 (-0.35 , 0.20)	0.58
Race/ethnicity†		
Black	0.16 (0.08 , 0.24)	<0.001
Hispanic	0.25 (0.11 , 0.39)	0.001
Other	0.20 (-0.03 , 0.42)	0.08
BMI	0.01 (0.003 , 0.02)	0.01
Hepatitis C	-0.09 (-0.19 , 0.02)	0.10
Coronary artery disease	0.02 (-0.12 , 0.17)	0.76
Congestive heart failure	0.14 (-0.48 , 0.75)	0.67
Chronic kidney disease	-0.08 (-0.26 , 0.11)	0.42
Total bilirubin	-0.18 (-0.24 , -0.11)	<0.001
MPR	-0.03 (-0.06 , 0.01)	0.19
Baseline HbA _{1c}	0.15 (0.13 , 0.17)	<0.001
Medication intensification	0.72 (0.60 , 0.83)	<0.001
VACS Index score‡	-0.02 (-0.04 , 0.001)	0.06
Total number of clinic visits in postindex year	-0.01 (-0.02 , 0.002)	0.11

*Reference category, sulfonylureas. †Reference category, white. ‡Score divided by 5.

change in HbA_{1c} level ($P = 0.55$, data not shown).

Achievement of the ADA Goal for HbA_{1c}
A total of 7,597 (67%) of patients achieved an HbA_{1c} level of $<7\%$ at any

time in the first year after starting treatment with a diabetic medication. In the final multivariable model (Table 5), there was no significant difference in the achievement of the ADA goal among the three diabetes medication groups of

Table 4—Adjusted changes in HbA_{1c} among HIV-infected new users of diabetic medical therapy: multivariable analysis using a GEE model

Variable	Regression coefficient (95% CI)	P value
Metformin*	0.14 (-0.04 , 0.31)	0.12
TZD*	0.49 (-0.24 , 1.22)	0.19
Age	-0.005 (-0.02 , 0.01)	0.41
Male sex	0.27 (-0.42 , 0.96)	0.44
Race/ethnicity†		
Black	0.19 (0.02 , 0.37)	0.03
Hispanic	0.31 (-0.004 , 0.63)	0.05
Other	0.21 (-0.12 , 0.53)	0.21
BMI	0.02 (-0.001 , 0.03)	0.07
Hepatitis C	-0.09 (-0.26 , 0.08)	0.32
Coronary artery disease	-0.15 (-0.75 , 0.46)	0.63
Congestive heart failure	-0.12 (-2.27 , 2.03)	0.91
Chronic kidney disease	-0.09 (-0.43 , 0.25)	0.61
Total bilirubin	-0.18 (-0.27 , -0.10)	<0.001
MPR	-0.005 (-0.02 , 0.01)	0.62
Baseline HbA _{1c}	0.20 (0.14 , 0.25)	<0.001
Medication intensification	0.67 (0.43 , 0.90)	<0.001
VACS Index score‡	0.004 (-0.03 , 0.03)	0.81
Total number of clinic visits in postindex year	-0.005 (-0.02 , 0.006)	0.42
PI-based ART regimen§	-0.32 (-0.71 , 0.07)	0.10
Non-PI-based ART regimen§	-0.50 (-0.88 , -0.12)	0.01

*Reference category, sulfonylureas. †Reference category, white. ‡Score divided by 5. §Reference category, no ART.

Table 5—Multivariable model of factors associated with achievement of an HbA_{1c} level of <7% in new users of diabetic medical therapy

Variable	OR (95% CI)	P value
Metformin*	0.78 (0.41, 1.46)	0.44
TZD*	0.97 (0.79, 1.19)	0.76
HIV infection	1.20 (1.03, 1.40)	0.02
Age	1.00 (0.99, 1.01)	0.87
Male sex	1.11 (0.62, 1.98)	0.74
Race/ethnicity†		
Black	0.95 (0.81, 1.11)	0.50
Hispanic	0.70 (0.54, 0.92)	0.01
Other	0.69 (0.43, 1.10)	0.12
Hepatitis C infection	1.12 (0.92, 1.36)	0.24
Coronary artery disease	0.88 (0.65, 1.20)	0.41
Congestive heart failure	1.92 (0.90, 4.11)	0.09
Chronic kidney disease	0.89 (0.61, 1.32)	0.57
BMI	0.98 (0.97, 0.99)	0.003
VACS Index score‡	1.02 (0.98, 1.05)	0.31
Total bilirubin	1.28 (1.09, 1.50)	0.003
Medication switch	0.38 (0.25, 0.56)	<0.001
Medication intensification	0.32 (0.26, 0.38)	<0.001
MPR	1.24 (1.10, 1.39)	<0.001
Baseline HbA _{1c}	0.78 (0.72, 0.81)	<0.001
Total number of clinic visits in postindex year	1.01 (0.99, 1.02)	0.50

OR, odds ratio. *Reference category, sulfonylureas. †Reference category, white. ‡Score divided by 5.

new users. HIV infection was associated with a greater likelihood of achieving an HbA_{1c} level of <7% (odds ratio 1.20 [95% CI 1.03, 1.40], *P* = 0.02).

CONCLUSIONS

In this longitudinal cohort of HIV-infected and uninfected new users of oral diabetic medical therapy, we found that glycemic response was independent of the initial class of medication after controlling for potential confounders. HIV infection similarly did not impact the initial glycemic response. Black race and Hispanic ethnicity were associated with a poorer response to diabetic medical therapy in the final multivariable model. To our knowledge, ours is the first study to date comparing the effectiveness of the three major oral diabetic medication classes specifically in an HIV-uninfected and HIV-infected patient population, and the results are further strengthened by the large, racially diverse cohort; the evaluation of several important potential confounders; and the longitudinal study design, with the capture of repeated HbA_{1c} measurements.

Comparative effectiveness studies in the uninfected population demonstrate

a similar ability of the three major oral medication classes to lower glycemia (6,28). Our ability to compare TZD use to other medication classes was limited given the small numbers of new users of TZD. However, the results of our study demonstrated that the use of metformin compared with sulfonylureas did not result in greater reductions in HbA_{1c} level, including in analyses restricted to patients with HIV infection. This finding may have been in part due to the overall well-controlled status of HIV-infected patients, including relatively high median CD4⁺ T-cell counts and rates of virologic suppression. As such, the anti-inflammatory properties of metformin may have been less important in these patients with lower degrees of chronic inflammation. Nevertheless, these results suggest that, as in the uninfected population, HIV-infected patients respond similarly to sulfonylureas and metformin. The selection of first-line treatment should take into account other factors, such as the effect on lipid levels and weight, as well as those that may be particularly important in the HIV-infected population, including interactions with ART agents and the potential for increased risk of adverse events (e.g.,

acute kidney injury) (29). Ultimately, further research is needed on the long-term safety profile of these medications in HIV-infected patients.

In contrast to the results of a prior study (4), HIV infection was not significantly associated with a response to diabetic medical therapy in the postindex year. These conflicting findings may in part be explained by differences in the characteristics of the patient populations that were assessed (e.g., earlier study years in the current study, greater numbers of clinic visits). In addition, the HIV-uninfected and HIV-infected veteran populations in the current study had similar baseline HbA_{1c} values. We found that, for HIV-infected new users, receiving treatment with a non-PI-based ART regimen compared with no ART was associated with a more favorable glycemic response to diabetic medical therapy. This improved glycemic response was not seen with a PI-based ART regimen compared with no ART. It is possible that the non-PI-based regimens demonstrated a more favorable metabolic profile compared with PI-based ART (e.g., less insulin resistance), and future studies should evaluate the impact of specific ART agents on metabolic parameters, such as HbA_{1c} level.

Traditional determinants of glycemic response to diabetic medical therapy were evident in the multivariable analysis, including higher BMI and baseline HbA_{1c} level. Notably, there was a high prevalence of overweight/obesity in our cohort. This finding likely reflects the increasing trends in overweight and obesity that have been observed in the HIV-infected population in the ART era (30), as well as risk for overweight/obesity in patients of black race. Given the association between obesity and worse glycemic control, it will be important for health care providers to aggressively address lifestyle interventions as a component of the management of diabetes in this patient population.

In addition, black race and Hispanic ethnicity were associated with a worse glycemic response to initial diabetic medical therapy, even after adjustment for baseline HbA_{1c} level. This poorer glycemic response may be due in part to genetic and biologic factors, such as drug metabolism rates. These potential determinants of glycemic response,

including their interaction with HIV infection, should be explored further. In addition, racial and ethnic disparities in diabetes care, including glycemic control, have been well described in the literature from the general population (31), with poorer glycemic control persisting even after adjustment for health care use and quality of care. Given the burden of type 2 diabetes and HIV in these populations, further studies are needed to identify optimal strategies to address these disparities in glycemic control, including in the HIV-infected population.

HIV-infected new users of diabetic medical therapy were more likely to reach the ADA HbA_{1c} goal of <7% during the postindex year. This finding may be due in part to the underestimation of glycemia by HbA_{1c} level in HIV-infected patients (32). Similar to a prior study (4), a substantial proportion of HIV-infected patients (approximately one-third) in the current study failed to achieve the ADA HbA_{1c} goal. Furthermore, only 22% of patients underwent medication intensification during the postindex year, despite the study cohort being representative of a population with high rates of medication adherence, as well as having frequent contact with the health care system (as measured via the number of clinic visits). Given the long-term cardiovascular disease risk in patients with HIV infection, intensive efforts to control hyperglycemia during the treatment of type 2 diabetes are warranted.

We found that total bilirubin levels were inversely associated with changes in HbA_{1c} values in the cohort overall, and specifically in those with HIV infection. This finding is consistent with previous studies (33,34) reporting inverse associations between total bilirubin levels and HbA_{1c} values, independent of other risk factors. Bilirubin, which results from heme catabolism, has antioxidant properties, and higher levels have been associated with a decreased risk of carotid atherosclerosis, coronary artery disease, and cerebrovascular disease (35–37). Our results extend this negative association to the HIV-infected population.

There are several potential limitations of the current study. As with any observational study, our results may be affected by residual confounding.

However, we evaluated a number of relevant variables as potential confounders in multivariable analyses, used a new user study design that minimizes prevalent-user bias, and used a longitudinal model that allowed for the inclusion of all follow-up HbA_{1c} results in analyses. We also conducted a subanalysis using propensity scores to account for confounding by indication. Furthermore, whereas ~30% of patients had missing information on BMI, it is likely that the BMI data were missing at random. In addition, pharmacy refill rates were used as a proxy for medication consumption in the calculation of medication adherence. Finally, as noted earlier, we were underpowered for the analyses that focused on TZDs.

In conclusion, there was no significant difference in the effectiveness of the three main classes of oral diabetic medications for glycemic control in HIV-uninfected and HIV-infected patients starting medical therapy in routine clinical care. Furthermore, a significant proportion of patients failed to meet the ADA-recommended HbA_{1c} goal despite frequent clinic follow-up and excellent medication adherence. Ultimately, given the increasing prevalence of type 2 diabetes in the aging HIV-infected population, further research is needed to elucidate the safety of diabetic medications in HIV-infected patients with type 2 diabetes, as well as the effects on long-term clinical complications and mortality.

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