Association Between Systemic Inflammation and Incident Diabetes in HIV-Infected Patients After Initiation of Antiretroviral Therapy

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OBJECTIVE — To determine whether systemic inflammation after initiation of HIV-antiretroviral therapy (ART) is associated with the development of diabetes.

RESEARCH DESIGN AND METHODS — We conducted a nested case-control study, comparing 55 previously ART-naive individuals who developed diabetes 48 weeks after ART initiation (case subjects) with 55 individuals who did not develop diabetes during a comparable follow-up (control subjects), matched on baseline BMI and race/ethnicity. Stored plasma samples at treatment initiation (week 0) and 1 year later (week 48) were assayed for levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and the soluble receptors of tumor necrosis factor-α (sTNFR1 and sTNFR2).

RESULTS — Case subjects were older than control subjects (median age 41 vs. 37 years, $P = 0.001$), but the groups were otherwise comparable. Median levels for all markers, except hs-CRP, decreased from week 0 to week 48. Subjects with higher levels of hs-CRP, sTNFR1, and sTNFR2 at 48 weeks had an increased odds of subsequent diabetes, after adjustment for baseline marker level, age, BMI at week 48, CD4 count at week 48 (< vs. >200 cells/mm^3), and indinavir use (all $P_{trend} \leq 0.05$). After further adjustment for week 48 glucose, effects were attenuated and only sTNFR1 remained significant (odds ratio, highest quartile vs. lowest 23.2 [95% CI 1.28–423], $P = 0.03$).

CONCLUSIONS — Inflammatory markers 48 weeks after ART initiation were associated with increased risk of diabetes. These findings suggest that systemic inflammation may contribute to diabetes pathogenesis among HIV-infected patients.

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With the advent of effective antiretroviral therapy (ART), morbidity and mortality have decreased dramatically among HIV-infected patients and the proportion of older HIV-infected patients is rising. As a result, aging-related comorbidities, such as diabetes, have become increasingly important in the management of HIV-infected patients.

Abnormalities in glucose metabolism occur commonly in HIV-infected patients, and some cohorts have shown a higher than expected risk of insulin resistance and diabetes compared with that for HIV-negative control populations (1,2). The etiology is multifactorial. Certain protease inhibitors, such as indinavir (IDV), lopinavir, and ritonavir, have been shown to reversibly induce insulin resistance, probably by inhibition of glucose translocation through GLUT4 (3). The nucleoside reverse transcriptase inhibitors, zidovudine and stavudine, also have direct and indirect effects on glucose metabolism (4,5). Chronic infection with HIV may also contribute to glucose abnormalities among HIV-infected patients. In the Multicenter AIDS Cohort Study, insulin resistance markers were higher in all groups of HIV-infected men compared with HIV-uninfected control subjects, even among those who were not receiving ART (6), suggesting an effect of HIV infection itself.

Systemic inflammation has been associated with incident diabetes in multiple cohorts in the general population (7–9). Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, may induce insulin resistance by binding to insulin-responsive elements in skeletal muscle (10). Among HIV-infected patients, markers of systemic inflammation decrease quickly with ART initiation (11) but do not normalize (12). It is speculated that this residual inflammation with effective ART may contribute to the pathogenesis of comorbidities in HIV-infected patients, including diabetes (13). We undertook a case-control study, nested within an observational study of the AIDS Clinical Trial Group (ACTG) to determine whether markers of systemic inflammation measured 48 weeks after ART initiation were associated with the development of diabetes.

RESEARCH DESIGN AND METHODS

— The ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort was designed to enroll HIV-infected individuals previously randomized into approved parent ACTG clinical trials (parent studies) for the purpose of evaluating clinical, virological, immunological, metabolic, and pharmacological outcomes associated with long-term treatment with potent ARTs. Individuals could be treatment-naive or treatment-experienced at entry into their parent study. Enrollment into ALLRT began in January 2000. As of October 2008, 3,405 previously treatment-naive individuals

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and 1,225 treatment-experienced individuals were enrolled into ALLRT. All subjects provided written informed consent, and each ACTG study site received approval from the designated institutional review board before protocol initiation. Details of the ALLRT protocol have been described previously (14).

The eligible population for this prospective, nested case-control study included all HIV-infected individuals from treatment-naive parent studies coenrolled in ALLRT, with the exception of parent studies for which ART data were still blinded. Eligible individuals were required to have had fasting or nonfasting blood glucose measurements before and after ART initiation and during the follow-up period, as well as plasma samples taken at the time of treatment initiation and at week 48, for measurement of inflammatory markers. We used data submitted to our data management center as of October 2008.

All potential case or control subjects were required to have fasting or nonfasting blood glucose levels <100 mg/dl at the time of treatment initiation (baseline) or within 16 weeks after initiation and could not have a history of hypoglycemic medication use or diabetes. All individuals who developed diabetes ≥1 years after ART initiation were eligible to be included as case subjects. Control subjects (non–case subjects) were randomly selected from those individuals who did not develop diabetes and who maintained fasting blood glucose levels <100 mg/dl through the study period. Control subjects were matched to case subjects 1:1 by BMI at treatment initiation and by race/ethnicity. Control subjects were followed for at least as long as their matched case subject. The glucose and medication histories of each of these case subjects and control subjects were reviewed by hand by an endocrinologist (T.T.B.) to confirm their case and control status.

Laboratory methods

After identification of case subjects and control subjects, frozen plasma samples at weeks 0 and 48 were pulled from the repository at the same time and forwarded to the Johns Hopkins Bayview Advanced Chemistry Laboratory (Baltimore, MD). Markers were measured in duplicate using commercially available enzyme-labeled immunosorbent sandwich assays, and values were averaged for analysis. The intra-assay precision of these assays range from 4.4 to 7.6% coefficient of variation (average 5.6% coefficient of variation). The sensitivity of this assay system for these cytokines ranged from 0.5 to 16 pg/ml. C-reactive protein was measured using a highly sensitive ELISA (ALPCO Diagnostics, Windham, NH). The linear range of the assay standards is 0.0019–0.15 mg/l, and samples with values greater than the highest standard were diluted and reanalyzed.

Measures

Outcome. An incident case of diabetes was defined as having either two fasting blood glucose levels ≥126 mg/dl (or two consecutive nonfasting blood glucose levels ≥200 mg/dl) or a diagnosis of diabetes recorded in the medical record. The first high glucose level and the diagnosis date had to occur at least 1 year after ART initiation.

Inflammatory markers. Week 48 levels of high-sensitivity (hs-CRP), interleukin (IL)-6, and the soluble receptors of tumor necrosis factor-α (sTNFR1 and sTNFR2) were each grouped into quartiles. Baseline levels of each marker were natural log-transformed.

In addition to the matching factors BMI at baseline and race/ethnicity (white non-Hispanic, black non-Hispanic, and Hispanic), we considered several other potential confounding variables: glucose levels at week 48 (continuous), age (continuous), sex, calendar year of treatment initiation, smoking status (ever yes or no), personal and family history of any cardiovascular disease, specific antiretroviral regimens taken through week 48 (in particular use of protease inhibitors or thymidine-analog nucleoside reverse transcriptase inhibitors), $CD4^+$ cell count <200 cells/mm^3 at weeks 0 and 48, HIV-1 RNA ≥100,000 copies/ml at baseline, HIV-1 RNA <400 copies/ml at week 48, BMI at week 48 (continuous), and history of hepatitis C infection.

Statistical analysis

Demographic, health, and treatment characteristics were summarized and compared between case subjects and control subjects. *P* values from univariate conditional logistic regression models were used for statistical comparisons of all covariates by case status with the exception of race/ethnicity, which was a matching factor. Differences in marker levels at baseline and at week 48 were also summarized and compared using the Wilcoxon signed-rank test.

Conditional logistic regression was used to model the association between week 48 levels of each inflammatory marker and diabetes incidence, taking into account matching and adjusting for the other potential confounders. The lowest marker quartile was the reference category in each model. Each model included categories of week 48 marker quartile, natural log-transformed baseline marker level and age. Model building proceeded by adding, one at a time, univariate predictors of diabetes ($P \leq 0.10$). $P \leq 0.05$ was considered statistically significant. Variables that changed odds ratios by ≥15% were kept in the model as potential confounders. To assess trend in diabetes incidence over marker quartiles, quartiles for each marker were included in the model as ordinal variables. Because of concern that hyperglycemia in the nondiabetic range may lead to inflammation, we reevaluated each model after adjustment for glucose values at 48 weeks. In these models, a variable indicating whether the glucose determination was made in the fasting state (yes or no) was also included.

RESULTS

— Of the 3,405 individuals from the treatment-naive studies enrolled as of October 2008, 1,217 were from parent studies with ART data still blinded and therefore were not eligible for this analysis. Of the 2,188 remaining individuals, 2,161 (99%) had fasting or nonfasting glucose values within 16 weeks of ART initiation, and 231 (10.7%) had glucose values between 100 and 125 mg/dl pretreatment and were excluded. Another 63 individuals had either a prevalent diagnosis of diabetes, hypoglycemic medication use, fasting blood glucose ≥126 mg/dl, or nonfasting blood glucose ≥200 mg/dl at baseline and were also excluded. From this at-risk group of 1,867, 55 cases of incident diabetes (defined as occurring at least 1 year after ART initiation) were identified. An additional 22 individuals developed diabetes within the 1st year of ART initiation and were not included in analyses. Twenty-seven case subjects (49%) were identified through ≥2 fasting glucose values ≥126 mg/dl, with no clinical diagnosis or medication use recorded. Twenty-four (44%) had elevated fasting glucose and either a clinical diagnosis or medication use, and the remainder (7%) had a clinical diagnosis with or without medication use reported, but no elevated glucose. All case subjects with high glucose had high fasting glucose levels. Fifty-

Table 1—*Baseline and on-treatment characteristics of case and control subjects*

Covariate	Case subjects	Control subjects	*P* value*
n	55	55	
Sex			
Male	42 (76)	42 (76)	1.00
Female	13 (24)	13 (24)	
Age in years at week 0	41 (37–46)	37 (31–42)	0.001
Race/ethnicity			
White	26 (47)	26 (47)	
African American	13 (24)	13 (24)	—†
Hispanic	16 (29)	16 (29)	
BMI at week 0 (kg/m^2)	25.1 (22.7–30.0)	25.1 (22.7–29.8)	0.14
BMI at week 48 (kg/m^2)	28.1 (24.7–33.1)	27.6 (24.1–30.4)	0.01
hs-CRP at week 0 (mg/l)	2.41 (1.36–4.37)	1.57 (0.85–4.33)	0.07
IL-6 at week 0 (pg/ml)	1.74 (1.16–2.95)	1.32 (0.80–2.52)	0.08
TNFR1 at week 0 (pg/ml)	1,386 (1,132–1,725)	1,213 (1,081–1,470)	0.03
TNFR2 at week 0 (pg/ml)	4,741 (3,292–6,950)	4,298 (3,646–5,185)	0.14
Glucose at/before week 48 (mg/dl)			
Fasting (n = 40 case subjects; n = 35 control subjects)	102 (91–111)	83 (80–89)	<0.001
Nonfasting (n = 15 case subjects; n = 20 control subjects)	89 (81–97)	81 (76–87)	0.08 <0.001‡
Family history of CVD			
Yes	11 (20)	6 (11)	0.18
Smoking status			
Ever	28 (51)	29 (53)	0.84
Calendar year of treatment initiation			
1998–1999	20 (36)	24 (44)	
2001–2002 (none in 2000)	22 (40)	19 (34)	
2003–2004	13 (24)	12 (22)	0.69
Hepatitis C			
Ever	5 (9)	4 (8)	0.74
HIV RNA >100,000 copies/ml at week 0			
Yes	32 (58)	30 (55)	0.67
HIV RNA <400 copies/ml at week 48			
Yes	5 (9)	1 (2)	0.14
CD4 <200 cells/mm^3 at week 0			
Yes	36 (66)	23 (42)	0.02
CD4 <200 cells/mm^3 at week 48			
Yes	8 (15)	4 (7)	0.14
ART in first 48 weeks			
Any stavudine	19 (35)	14 (26)	0.32
Any zidovudine	43 (78)	37 (67)	0.19
Any nelfinavir	12 (22)	17 (31)	0.26
Any IDV	9 (16)	3 (6)	0.08
Any lopinavir/ritonavir	7 (13)	8 (15)	0.76

Data are median (interquartile range) or *n* (%). N = 110. *From univariate conditional logistic model, unless otherwise indicated. †Matching factor. ‡From a univariate conditional logistic model (continuous glucose term in model along with fasting status indicator).

five control subjects matched on race/ethnicity and BMI were identified from those individuals who did not develop diabetes and who maintained blood glucose levels <100 mg/dl throughout follow-up. For 90% of case-control pairs the difference in BMI was <1 kg/m^2; five pairs differed by a greater amount (range 1.7–6.5 kg/m^2).

The median time to diabetes incidence after week 48 was 1.9 years (interquartile range 1.3–3.8 years). In Table 1, we summarize demographic, treatment, and health characteristics for case and control subjects. Case subjects were significantly older than control subjects (median 41 vs. 37 years, $P < 0.01$). There was no difference by case status in calendar year of treatment initiation. Approximately 50% of each group had HIV RNA levels ≥100,000 copies/ml at baseline, and a greater proportion of case subjects than control subjects had CD4 counts <200 cells/mm^3 at baseline. A higher proportion of case subjects versus control subjects had some use of IDV through week 48 (16 vs. 6%, $P = 0.08$).

Case subjects had significantly higher glucose levels at week 48 than did control subjects. Seventy-five individuals (40 case subjects and 35 control subjects) had fasting glucose levels at or before week 48, and 35 individuals (15 case subjects and 20 control subjects) had only nonfasting glucose levels. Median fasting levels for case subjects and control subjects were 102 and 83 mg/dl, respectively (P value <0.001); median nonfasting values were 89 and 81 mg/dl, respectively (P value = 0.08).

Case subjects tended to have higher baseline levels of inflammatory markers than control subjects (Table 1), adding further justification for including baseline marker levels in each multivariate model. These baseline levels were not significantly associated with diabetes after adjustment for age (data not shown). In Table 2, we present the median values of each marker at baseline and week 48. hs-CRP significantly increased from week 0 to 48; all other markers decreased significantly from week 0 to 48.

Figure 1 summarizes the odds ratios for the association of each inflammatory marker at week 48 with subsequent diabetes incidence, adjusted for age, log of baseline marker value, CD4 at week 48, BMI at week 48, and IDV use through week 48. Higher hs-CRP, sTNFR1, and sTNFR2 levels, but not IL-6 levels, 1 year after ART initiation were all significantly associated with diabetes incidence before adjustment for glucose level at week 48. After additional adjustment for week 48 glucose, only sTNFR1 remained significantly associated with diabetes incidence (Table 3).

Six individuals (five case subjects and one control subject) had not reached viral suppression by week 48. In a sensitivity analysis that excluded these six individuals and their matched case/control subject, the results were relatively unchanged. For sTNFR1 the association between the highest quartile

Table 2—*Marker levels at week 0 and week 48 after initiation of antiretroviral therapy*

	Week 0	Week 48	Change (week 48–week 0)	*P* value (H_0: $\Delta = 0$)
hs-CRP (mg/l)	2.0 (1.0–4.3)	3.0 (1.5–6.1)	0.6 (−0.7 to 3.6)	0.01
IL-6 (pg/ml)	1.6 (0.9–2.7)	1.3 (0.7–2.1)	−0.2 (−0.9 to 0.4)	0.01
TNFR1 (pg/ml)	1,279 (1,109–1,573)	1,173 (992–1,388)	−109 (−387 to 40)	<0.0001
TNFR2 (pg/ml)	4,414 (3,550–6,300)	2,983 (2,310–3,795)	−1,390 (−2,932 to −479)	<0.0001

Data are median (interquartile range).

and the lowest) was somewhat attenuated and for sTNFR2 the association between the highest quartile and the lowest) was stronger (data not shown).

CONCLUSIONS — In this case-control study nested within a multicenter, observational cohort of HIV-infected individuals receiving ART, we found that, despite a decrease in most inflammatory markers with ART initiation, markers of TNF-α activation 48 weeks after treatment were associated with incident diabetes. After further adjustment for glucose levels at 48 weeks, the associations were attenuated, but higher levels of sTNFR1 remained a significant predictor of incident diabetes in adjusted analyses.

TNF-α is an proinflammatory cytokine produced by multiple cell types including macrophages, lymphocytes, and endothelial cells that contributes to the inflammatory cascade (15) and is highly expressed in both treated and untreated HIV-infected patients (12,13). TNF-α is also produced by adipose tissue and has been shown to interact with the insulin receptor substrate to attenuate the effect of insulin binding to its receptor (10). As a result, TNF-α has been proposed as a mediating factor between adiposity and insulin resistance. Blockers of TNF-α, however, such as infliximab and etanercept, have shown conflicting effects on insulin resistance in human populations (16,17).

In epidemiological studies, the association between incident diabetes and TNF activity, either measured by concentrations of the soluble receptors to TNF-α or by TNF-α itself, has also been inconsistent. In several studies, sTNFR2 was as-

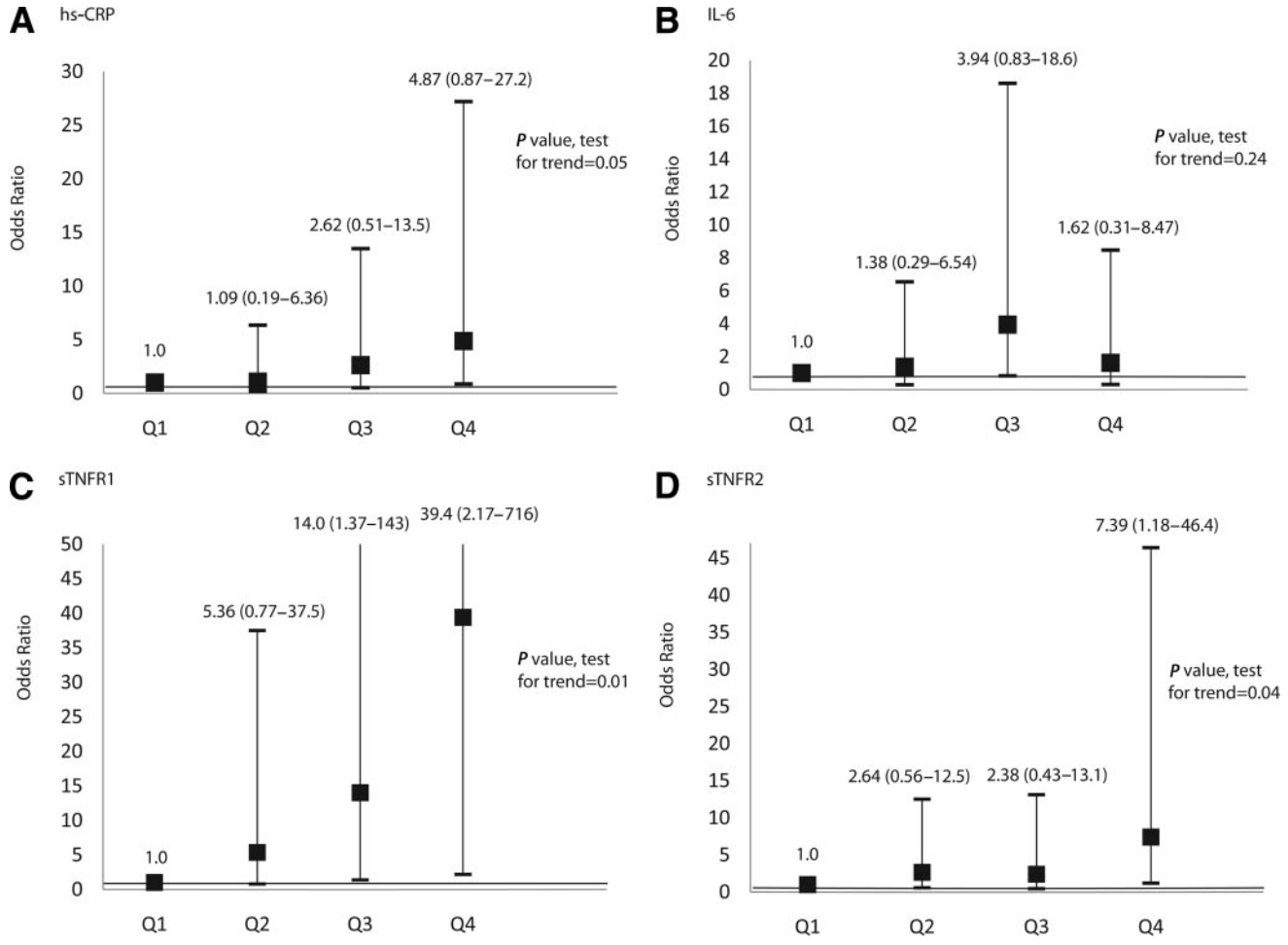

Figure 1—*Odds ratios (95% CI) for incident diabetes in HIV-infected individuals by quartile (Q) of hs-CRP (A), IL-6 (B), sTNFR1 (C), and sTNFR2 (D) measured 48 weeks after initiation of antiretroviral therapy, adjusted for baseline marker level, age, CD4 <200 cells/mm^3 at week 48, 48-week BMI, and use of IDV.*

Table 3—*Relationship between inflammatory marker level 48 weeks after initiation of ART and incident diabetes in HIV-infected persons, with and without additional adjustment for week 48 glucose levels*

Marker	Model excluding week 48 glucose	Model including week 48 glucose
hs-CRP		
Quartile 1	Referent	Referent
Quartile 2	1.09 (0.19–6.36)	0.65 (0.09–4.69)
Quartile 3	2.62 (0.51–13.5)	1.88 (0.28–12.8)
Quartile 4	4.87 (0.87–27.2)	2.52 (0.36–17.6)
P value, test for trend	0.05	0.18
IL-6		
Quartile 1	Referent	Referent
Quartile 2	1.38 (0.29–6.54)	1.52 (0.21–10.9)
Quartile 3	3.94 (0.83–18.6)	3.34 (0.53–21.1)
Quartile 4	1.62 (0.31–8.47)	1.39 (0.23–8.28)
P value, test for trend	0.24	0.94
TNFR1		
Quartile 1	Referent	Referent
Quartile 2	5.36 (0.77–37.5)	2.88 (0.34–24.5)
Quartile 3	14.0 (1.37–143)	6.09 (0.61–60.8)
Quartile 4	39.4 (2.17–716)	23.2 (1.28–423)
P value, test for trend	0.01	0.03
TNFR2		
Quartile 1	Referent	Referent
Quartile 2	2.64 (0.56–12.5)	1.49 (0.25–8.95)
Quartile 3	2.38 (0.43–13.1)	1.01 (0.12–8.31)
Quartile 4	7.39 (1.18–46.4)	4.63 (0.60–35.8)
P value, test for trend	0.04	0.27

Data are odds ratio (95% CI) vs. quartile 1. All models also include age, natural log of baseline marker level, BMI at week 48, CD4 <200 at week 48, and IDV use through week 48.

sociated with incident diabetes, but this association was lost after mutual adjustment for other inflammatory cytokines or measures of adiposity (8,9,18). We found that higher concentrations of sTNFR1 and sTNFR2 measured 48 weeks after ART initiation were associated with incident diabetes, independent of BMI, suggesting that TNF-α activity in HIV-infected individuals may contribute to the pathogenesis of diabetes. It is not known whether the origin of TNF-α is the adipose tissue, infected lymphocytes, or other cell types, but this is an important area for further inquiry.

Although all subjects were normoglycemic before ART initiation, subjects who were to develop diabetes already had significantly higher glucose concentrations at 48 weeks after ART initiation, although within the nondiabetic range. After we adjusted for glucose levels at 48 weeks, the associations between markers of TNF-α activity were attenuated, but higher levels of sTNFR1 remained associated with incident diabetes. These findings may suggest that the effect of TNF-α activity on diabetes risk is present early on in the pathogenesis of diabetes among HIV-infected individuals treated with ART and adjustment for glucose concentrations at 48 weeks obscured the early effect. Whether this effect is mediated by increased insulin resistance or a decline in β-cell function is unclear. A prospective study examining inflammatory and insulin resistance markers at earlier time points after ART initiation would be necessary to further investigate the mechanisms.

Without adjustment for week 48 glucose levels, we found that higher concentrations of hs-CRP at 48 weeks after ART initiation were associated with incident diabetes. hs-CRP has been associated with incident diabetes in the general population (7), but this association is partially explained by excess adiposity (19). Evidence against a causal effect of hs-CRP on diabetes risk is derived from a Mendelian randomization study, which found no association between haplotypes associated with higher hs-CRP concentrations and diabetes risk (20). In our study, after adjustment for 48-week glucose values, the association between 48-week hs-CRP and incident diabetes was no longer present, suggesting that hs-CRP may be an early marker of diabetes risk in HIV-infected patients starting ART. Importantly, hs-CRP is associated with other adverse outcomes in HIV-infected patients, including myocardial infarction (21) and all-cause mortality (22). Whether therapies aimed to decrease hs-CRP will improve outcomes in HIV-infected individuals is unknown.

Modern ART is very effective in suppressing HIV replication. However, in all studies of patients initiating ART, there is a subset in whom HIV is not suppressed to undetectable levels. Six subjects in the study had viral RNA >400 copies/ml at 48 weeks. In a sensitivity analysis, we excluded those who had uncontrolled HIV infection and found similar association between inflammatory markers and incident diabetes. Although not nominally statistically significant, this analysis suggests that our findings were not influenced by a small number of subjects with uncontrolled HIV.

Our study had several limitations that should be noted. Our sample size was small, and, as a result, the effect estimates were imprecise. Larger, confirmatory studies should be performed to better estimate the association between inflammation and diabetes in HIV-infected individuals initiating ART. A larger study would also have sufficient power to determine whether the association between inflammation and diabetes in HIV-infected individuals differs by sex. Second, we examined only four different inflammatory markers. Studies in the general population have shown that other markers may be associated with diabetes, such as IL-18 (23). Third, without an otherwise similar HIV-uninfected control group, it is difficult to interpret the absolute levels of inflammatory markers in our study. Finally, family history of diabetes was not available in our dataset, and therefore we were unable to adjust for this factor. However, in the Multi-Ethnic Study of Atherosclerosis (MESA) study, the inclusion of family history did not alter the relationship between inflammation and diabetes (19).

In summary, we found that inflammatory markers, particularly those associated with TNF-α activity, 48 weeks after ART initiation were associated incident diabetes. Chronic inflammation among HIV-infected individuals, even those receiving effective antiretroviral therapy has

been hypothesized to be an important contributor to the development of comorbid conditions. Our findings suggest that inflammation contributes to the pathogenesis of diabetes among treated HIV-infected individuals. The discovery of antiretroviral medication that suppresses inflammation in addition to HIV replication or adjunctive therapy targeting uncontrolled inflammation may be important in the prevention of comorbid conditions associated with chronic HIV infection, such as diabetes.

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T.T.B. designed the study, researched data, and wrote the manuscript. K.T. designed the study, performed statistical analysis, and wrote the manuscript. R.J.B. provided guidance regarding statistical analysis, contributed to the discussion, and reviewed/edited the manuscript. C.S. contributed to the discussion and reviewed/edited the manuscript. G.A.M. designed the study, obtained funding, contributed to the discussion, and reviewed/edited the manuscript.

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