Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study

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Background: The risk of diabetes mellitus (DM) in human immunodeficiency virus (HIV)–infected patients receiving highly active antiretroviral therapy (HAART) has not been well defined.

Methods: We conducted an analysis in the Multicenter AIDS Cohort Study to determine the prevalence and incidence of DM in this cohort of HIV-infected and HIV-seronegative men. Prevalence analysis included 1278 men (710 HIV seronegative and 568 HIV infected, 411 receiving HAART) with fasting glucose concentration determinations at baseline. Incidence analysis included 680 of these 1278 men who at the baseline visit had a fasting glucose concentration of 98 mg/dL (5.4 mmol/L) or less, no self-reported history of DM, and no self-reported use of antidiabetic medication. Diabetes mellitus was defined as a fasting glucose concentration of 126 mg/dL (7 mmol/L) or higher, self-reported diagnosis of DM, or self-reported use of antidiabetic medication.

Results: Fifty-seven (14%) of the 411 HIV-infected men using HAART at the baseline visit had prevalent DM compared with 33 (5%) of the 711 HIV-seronegative men (prevalence ratio=4.6; 95% confidence interval, 3.0-7.1, adjusted for age and body mass index [calculated as weight in kilograms divided by the square of height in meters]). The rate of incident DM was 4.7 cases per 100 person-years among HIV-infected men using HAART compared with 1.4 cases per 100 person-years among HIV-seronegative men (rate ratio=4.11; 95% confidence interval, 1.85-9.16, adjusted for age and body mass index), during the 4-year observation period, based on a median follow-up of 2.3 years.

Conclusion: The incidence of DM in HIV-infected men with HAART exposure was greater than 4 times that of HIV-seronegative men, representing a risk that is higher than previous estimates.

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Since the advent of highly active antiretroviral therapy (HAART) in the mid-1990s, abnormalities in glucose homeostasis have been reported with increasing frequency in persons infected with human immunodeficiency virus (HIV).1,4 Insulin resistance has been described in 41 (61%) of 67 protease inhibitor (PI)–treated, HIV-infected patients,7 and impaired glucose tolerance was observed in 25 (35%) of 71 HIV-infected patients using HAART.6 Prevalence estimates of diabetes mellitus (DM) are lower. In a cross-sectional study, 28 (6%) of 493 HIV-infected patients had DM.7

Prospective data estimating the incidence of DM are beginning to emerge.2,3 In the Women’s Interagency HIV Study, 20 (3% or 2.8 cases per 100 person-years) of the 609 HIV-infected women receiving a PI-containing HAART regimen were diagnosed as having DM during 2.9-year median follow-up period.8 In that study, case ascertainment was determined by self-reports at semiannual visits. Without the use of fasting glucose (FG) concentration determinations, however, the true incidence of DM is likely to be underestimated.

Estimates of the incidence of DM and fasting hyperglycemia based on active surveillance using recommended diagnostic techniques are needed. In this prospective study, we sought to determine the prevalence and incidence of DM in a well-characterized cohort of HIV-seronegative and HIV-infected men with heterogeneous exposure to antiretroviral therapies.

STUDY PARTICIPANTS

The Multicenter AIDS Cohort Study (MACS) enrolled 3622 homosexual and bisexual men between 1984 and 1991. These men have been seen at semianual study visits at sites located in Pittsburgh, Pa; Baltimore, Md; Chicago, Ill; and Los...
Institutional review boards at each site approved the MACS protocol and forms, and each participant gave written informed consent. The semiannual study visits consist of a detailed interview, physical examination, and collection of biological specimens, including serologic HIV antibody tests on HIV-seronegative men. Beginning in April 1, 1999, the biological specimens obtained included a fasting serum sample.

Of the 5622 men enrolled in MACS, 1837 HIV-seronegative men were administratively censored in 1996, and 1750 had died by April 1, 1999, leaving 2015 men. Of these 1773 (88%) were observed between April 1, 1999, and March 31, 2003, and 1627 had at least 1 blood specimen drawn including 1278 fasting (≥8 hours) serum samples on which the glucose concentration was determined. The visit at which a participant had an initial FG concentration determination was defined as the index visit. At the index visit, the prevalence of DM was determined, defined as an FG concentration of 126 mg/dL (7 mmol/L) or higher, self-reported DM, or self-reported use of an antidiabetic medication (ie, insulin, sulfonylureas, thiazolidinediones, biguanides, meglitinides, or α-glucosidase inhibitors). Age, body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), waist-hip ratio, educational attainment, and total cholesterol level, all measured at the index visit, and race (ie, white vs nonwhite) were ascertained for all participants.

The study population for incident analysis was composed of 680 of 1278 men. Of the 1278 men, 970 had an FG concentration of 98 mg/dL (5.4 mmol/L) or less at the index visit. Of these 970, seven hundred five had follow-up data. The exclusion of those with self-reported DM (n=22) or self-reported use of an antidiabetic medication at the index visit (n=3) yielded the 680 men used in the analysis. The FG concentration cutoff point of 98 mg/dL (which is the lower boundary of the definition of fasting hyperglycemia [ie, 100 mg/dL]10 minus about 1 SD for the glucose assay [ie, 1.8 mg/dL [0.09 mmol/L]]) was chosen to ensure that the incident study population excluded men with prevalent hyperglycemia.

END POINT ASCERTAINMENT

Two end points were examined in the incident study population. First, the date of incident DM was defined as the midpoint between the date of the last visit seen free of DM and the date of the first visit seen with DM. Incident DM was defined as an FG concentration of 126 mg/dL (7 mmol/L) or higher, self-reported DM, or current self-reported use of antidiabetic medication, each of which was ascertained at each semiannual study visit beyond the index visit. All FG concentrations were measured by the combined hexokinase/glucose-6-phosphate dehydrogenase method14 using serum samples that had been stored at −80°C and shipped to a central laboratory (Heinz Laboratory, Pittsburgh). Self-reported DM was ascertained using the following questions: “Have you ever been told by a doctor or other medical practitioner for any condition since your last visit? If yes, was there a diagnosis for your condition?” Current antidiabetic medication use was determined from a report of all medications used since the previous visit. The definition of DM as an FG concentration of 126 mg/dL or higher is consistent with the guidelines of the American Diabetes Association.12

The second end point was a combination of incident DM and incident hyperglycemia and was used in the exploratory analyses of the effects of specific antiretroviral medications and disease stage. The date of incident hyperglycemia was defined as the midpoint of the date of the last visit seen with an FG concentration of 100 and 125 mg/dL (5.6 and 6.9 mmol/L). The date of the combined end point was the first of incident DM or incident hyperglycemia. This combined end point, which included both clinically significant hyperglycemia and DM,16 was constructed to improve the precision of these analyses by increasing the number of events.

ASSESSMENT OF EXPOSURE TO ANTIRETROVIRAL THERAPY

The detailed interview given at each semiannual study visit includes extensive questions about the use of specific antiretroviral therapies. The definition of HAART followed the Department of Health and Human Services/Kaiser Panel guidelines13 and has been previously described.14 Adherence to antiretroviral therapy was assessed by response to interviewer query, “On average, how often did you take your medication as prescribed?” recorded in categories of 100%, 95% to 99%, 75% to 94%, or less than 75%, and stratified herein as 95% or higher or less than 95%.

The primary exposures of interest were HIV infection and antiretroviral therapy use. We classified men into the following 3 groups: (1) HIV seronegative, (2) HIV infected not using HAART, and (3) HIV infected using HAART. We combined HIV-infected men not using HAART (ie, 103 who were antiretroviral free, 5 using monotherapy, and 49 using combination therapy at the index visit) because of the small number of men and similar event rates. To create time-varying exposure categories, men were classified at each semiannual visit according to HIV serostatus and self-reported use of antiretroviral therapy in the prior 6 months.

Based on the results of prior studies,5,8 we explored the effect of the individual PIs most frequently used at the index visit on the rate of the combined end point by stratifying the HIV-infected HAART group by exposure to ritonavir, nelfinavir mesylate, saquinavir mesylate, and indinavir sulfate. Self-reported exposure to PIs was classified as time varying (ie, updated at each semiannual visit). To explore the effect of disease severity on the rate of the combined end point among men exposed to HAART at the index visit, we compared men with a nadir CD4 cell count greater than 300 cells/mm3 to men with nadir CD4 cell counts of 300 cells/mm3 or less. Nadir CD4 cell counts greater than 300 cells/mm3 represented approximately the upper quartile of values. This cutoff point was chosen after noting similar rates of the combined end point in the lowest 3 nadir CD4 cell quartiles.

STATISTICAL ANALYSIS

The Fisher exact and Wilcoxon nonparametric tests, as appropriate, were used to test differences in proportions and distributions between groups. The prevalence ratio (PR) and 2-sided 95% confidence intervals (CIs) for DM was calculated using a modified Poisson regression15 that allowed adjustment for age and BMI measured at the index visit. Age and BMI were modeled as restricted cubic splines with knots at the 5th, 50th, and 95th percentiles, thereby creating a smoothly joined piecewise polynomial that allowed for a flexible association between each covariate and the end point.16 Further adjustment for educational attainment did not alter the results (data not shown).

For the analysis of incident DM (or the combined end point), person-time for each participant was calculated from the date of the index visit to the date of incident DM (or the date of the combined end point) or censoring at the last observed visit free of the end point, whichever came first. Incidence rates were obtained by dividing the number of end points by the number of person-years contributed to a specific category. Two-sided 95% CIs were obtained for rates using the Poisson distribution. Rate
Table 1. Characteristics of 1278 Men at the Index Visit Between April and October 1999*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MACS (n = 5622)</th>
<th>Current Study Population (N = 1278)</th>
<th>HIV-Seronegative (n = 718)</th>
<th>HIV-Infected Not Using HAART (n = 157)</th>
<th>HIV-Infected Using HAART (n = 411)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>White subjects, No. (%)</td>
<td>4681 (83)</td>
<td>1089 (85)</td>
<td>618 (87)</td>
<td>119 (76)</td>
<td>352 (86)</td>
<td>.53</td>
</tr>
<tr>
<td>College degree, No. (%)</td>
<td>3121 (56)</td>
<td>787 (62)</td>
<td>477 (67)</td>
<td>74 (47)</td>
<td>236 (57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (IQR range), y</td>
<td>33 (28, 38)</td>
<td>48 (43, 53)</td>
<td>50 (45, 56)</td>
<td>46 (41, 50)</td>
<td>46 (42, 51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index‡ (IQR range)</td>
<td>23 (22, 25)</td>
<td>26 (24, 28)</td>
<td>26 (24, 29)</td>
<td>25 (23, 28)</td>
<td>25 (23, 27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist-hip ratio‡</td>
<td>NA</td>
<td>0.95 (0.91, 0.99)</td>
<td>0.90 (0.90, 0.99)</td>
<td>0.94 (0.91, 0.97)</td>
<td>0.95 (0.91, 0.99)</td>
<td>.17</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>NA</td>
<td>202 (176, 229)</td>
<td>201 (178, 227)</td>
<td>188 (158, 218)</td>
<td>210 (182, 239)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glucose level, mg/dL</td>
<td>NA</td>
<td>90 (83, 98)</td>
<td>90 (83, 97)</td>
<td>88 (82, 98)</td>
<td>91 (84, 101)</td>
<td>.03</td>
</tr>
<tr>
<td>Nadir CD4 count, cells/mm³</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>318 (187, 432)</td>
<td>211 (108, 318)</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of receiving HAART§</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.26 (2.63, 3.81)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study. $SI conversion factors: To convert total cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

*Data are given as medians (interquartile range), unless otherwise indicated.
†Prevalence ratio and 95% CI by modified Poisson regression, adjusted for age and BMI as restricted cubic splines.
‡Data are given as medians (interquartile range), unless otherwise indicated.
§Years from initiation of HAART to the date of index visit.

RESULTS

PREVALENCE OF DM

The 1278 men who were alive and under follow-up and had at least 1 FG concentration determination between April 1, 1999, and March 31, 2003, had similar race and educational level but were 15 years older (as expected) and had a slightly higher BMI than the entire 5622 men enrolled in MACS in 1984 (Table 1). Compared with the 411 HIV-infected men receiving HAART, the 710 HIV-seronegative men were older, had a slightly higher BMI, and a lower total cholesterol level and were more likely to have a college degree but were otherwise similar. Of the 411 HIV-infected men receiving HAART at the index visit, 110 were receiving more than 1 PI (including 13 who were receiving lopinavir therapy), 207 were receiving 1 PI (105 were receiving indinavir; 68, nelfina-

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The 680 men in the incidence analysis had characteristics similar to the overall study group of 1278 men shown in Table 1 (data not shown). Of these 680, thirty-eight developed DM, 458 completed follow-up without DM, and 184 (27%) were lost to follow-up. The median follow-up was 2.3 years (quartiles: 1.1, 3.0). Nineteen incident cases were due to an elevated FG concentration, 11 were due to a self-reported diagnosis of DM, and 8 low were due to self-reported use of antidiabetic medication.

These findings support and extend previously observed increases in both prevalent and incident fasting hyperglycemia and DM among HIV-infected subjects receiving HAART.

We report that during a 4-year follow-up period in the MACS, 24 (10%) of 229 HIV-infected subjects receiving HAART developed DM compared with 10 (3%) of 361 HIV-seronegative men. After adjustment for BMI and age, this difference represents a greater than 4-fold increase in the risk of incident DM among HIV-infected subjects receiving HAART.

These findings support and extend previously observed increases in both prevalent and incident fasting hyperglycemia and DM among HIV-infected patients receiving HAART. Initial reports estimated a 5% to 7% cumulative incidence of DM in HIV-infected patients receiving HAART,2,3,18 but these studies were relatively small, were based on retrospective record review, and used less rigorous ascertainment techniques, such as random blood glucose values.3,18 In addition, the lack of an internal comparison group in many of the initial studies precluded accurate estimates of relative risk. Justman et al1 recently reported a relative risk of incident self-reported DM of 2.0 (95% CI, 1.0-4.1) when HIV-infected women receiving a PI were compared with an HIV-seronegative subgroup prospectively followed in the Women’s Intergroup HIV Study. The higher crude rate of incident DM in the HIV-infected, HAART-exposed group in the MACS compared with the Women’s Intergroup HIV Study (4.7 vs 2.8 [95% CI, 1.6-4.1] cases per 100 person-years) may
Table 4. Incidence of Combined End Point of Diabetes Mellitus or Fasting Hyperglycemia Among 680 Men Between April 1999 and March 2003

<table>
<thead>
<tr>
<th>Patient Group (n = 680)</th>
<th>No. of End Points</th>
<th>Person-years</th>
<th>Rate per 100 Person-Years (95% CI)</th>
<th>Crude Rate Ratio* (95% CI)</th>
<th>Adjusted Rate Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>209</td>
<td>1251.7</td>
<td>16.7 (14.6-19.1)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HIV seronegative</td>
<td>93</td>
<td>609.2</td>
<td>15.3 (12.5-18.7)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HIV infected not using HAART</td>
<td>23</td>
<td>207.3</td>
<td>11.1 (7.4-16.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HIV infected using HAART</td>
<td>93</td>
<td>435.2</td>
<td>21.4 (17.4-26.2)</td>
<td>1.38 (1.03-1.84)</td>
<td>1.64 (1.21-2.33)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not applicable.

*Rate ratio and 95% confidence interval estimated by Cox regression; adjusted for age and body mass index (calculated as weight in kilograms divided by the square of height in meters) at the index visit.

We found greater than a 4-fold increase in the rate of incident DM in HIV-infected participants receiving HAART compared with HIV-seronegative participants. The 4-year risk of 10% is higher than previous estimates and supports the importance of regular screening for hyperglycemia among HIV-infected persons.
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REFERENCES


