Factors Associated with the Incidence of Type 2 Diabetes Mellitus in HIV-Infected Participants in the Swiss HIV Cohort Study

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Background. Human immunodeficiency virus (HIV)–infected persons may be at increased risk for developing type 2 diabetes mellitus because of viral coinfection and adverse effects of treatment.

Methods. We studied associations of new-onset diabetes mellitus with hepatitis B virus and hepatitis C virus coinfections and antiretroviral therapy in participants in the Swiss HIV Cohort Study, using Poisson regression.

Results. A total of 123 of 6513 persons experienced diabetes mellitus during 27,798 person-years of follow-up (PYFU), resulting in an incidence of 4.4 cases per 1000 PYFU (95% confidence interval [CI], 3.7–5.3 cases per 1000 PYFU). An increased incidence rate ratio (IRR) was found for male subjects (IRR, 2.5; 95% CI, 1.5–4.2), older age (IRR for subjects >60 years old, 4.3; 95% CI, 2.3–8.2), black (IRR, 2.1; 95% CI, 1.1–4.0) and Asian (IRR, 4.9; 95% CI, 2.2–10.9) ethnicity, Centers for Disease Control and Prevention disease stage C (IRR, 1.6; 95% CI, 1.04–2.4), and obesity (IRR, 4.7; 95% CI, 3.1–7.0), but results for hepatitis C virus infection or active hepatitis B virus infection were inconclusive. Strong associations were found for current treatment with nucleoside reverse-transcriptase inhibitors (IRR, 2.22; 95% CI, 1.11–4.45), nucleoside reverse-transcriptase inhibitors plus protease inhibitors (IRR, 2.48; 95% CI, 1.42–4.31), and nucleoside reverse-transcriptase inhibitors plus protease inhibitors and nonnucleoside reverse-transcriptase inhibitors (IRR, 3.25; 95% CI, 1.59–6.67) but were not found for treatment with nucleoside reverse-transcriptase inhibitors plus nonnucleoside reverse-transcriptase inhibitors (IRR, 1.47; 95% CI, 0.77–2.82).

Conclusions. In addition to traditional risk factors, current treatment with protease inhibitor– and nucleoside reverse-transcriptase inhibitor–containing regimens was associated with the risk of developing type 2 diabetes mellitus. Our study did not find a significant association between viral hepatitis infection and risk of incident diabetes.

In 1997, the US Food and Drug Administration reported the association of hyperglycemia and new-onset type 2 diabetes mellitus (DM) with protease inhibitors (PIs; saquinavir, ritonavir, indinavir, and nelfinavir) [1]. Subsequent studies have confirmed the association of hyperglycemia or DM with PI use [2–7]. More recently, nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs), but not nonnucleoside reverse-transcriptase inhibitors (NNRTIs), were found to contribute to the disturbance of glucose metabolism [8–11]. Furthermore, associations of hyperglycemia and DM with hepatitis C virus (HCV) infection have been reported both in HIV-negative [12–14] and HIV-positive [15–17] populations. Potential mechanisms may include HCV-induced insulin resistance mediated by proinflammatory cytokines [18], immune reactions against pancreatic β-cells, or direct infection of β-cells by HCV [19].

Patterns of use of antiretroviral regimens have

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changed over the years in response to perceived toxicity and to the availability of new drugs. Because of improved life expectancy, increased cumulative exposure to antiretroviral drugs in HIV-infected persons may have resulted in cumulative toxicity in some patients. This study was designed to assess the impact of hepatitis coinfection on the development of new-onset DM in the Swiss HIV Cohort Study (SHCS), taking into account changes in anthropometric risk factors and antiretroviral therapy (ART) during follow-up.

METHODS

Study population. The SHCS is an ongoing, prospective, clinic-based study that was established in 1988 and that continuously enrolls and observes HIV-1–infected individuals aged ⩾16 years at 5 university outpatient clinics, 2 large district hospitals, affiliated regional hospitals, and private practices [20]. The study was approved by local ethical review boards, and written informed consent was obtained from all participants.

For this analysis, we included SHCS participants if they had at least 2 study visits with at least 1 year of follow-up after 1 March 2000. Patients with prevalent cases of DM were excluded.

Ascertainment of DM. As part of the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) protocol [21], cardiovascular risk factors and events, including plasma glucose levels and diagnosis of DM, have been routinely collected and verified at biannual follow-up visits since 1 March 2000. DM is diagnosed according to the criteria of the Expert Committee on the Diagnosis and Classification of DM [22], with confirmed plasma glucose level cut-off values of >7.0 mmol/L (fasting) and >11.1 mmol/L (nonfasting). Treating physicians were contacted to ascertain the status of patients with glucose levels that exceeded the cut-off value or who were receiving antidiabetic medication without an explicit diagnosis of DM.

Definitions. Body mass index (BMI), calculated as weight in kilograms divided by the square of the height in meters, was stratified into <18.5 (underweight), 18.5–24.9 (normal), 25–29.9 (overweight), and ⩾30 (obese) [23], without modification for Asians [24]. For central obesity, we used the new worldwide definition [25], with sex- and ethnicity-specific waist circumference cut-off values as follows: Europeans and sub-Saharan Africans, ⩾94 cm for males and ⩾80 cm for females; south Asians, Chinese, and south and central Americans, ⩾90 cm for males and ⩾80 cm for females; and Japanese, ⩾85 cm for males and ⩾90 cm for females. Elevated blood pressure was defined as present in patients with diastolic blood pressure ⩾85 mmHg or systolic blood pressure ⩾130 mmHg or who were receiving antihypertensive treatment. HCV infection was defined as present in patients who were seropositive for HCV and who had test results positive for HCV RNA. Active hepatitis B virus (HBV) infection was defined as present in patients who were seropositive for HBV and hepatitis B surface antigen or hepatitis B e antigen or who had test results positive for HBV DNA.

Statistical analysis. We defined the rate of new-onset DM as the number of cases of DM divided by the total number of person-years of follow-up (PYFU). Follow-up was counted from the first visit after 1 March 2000 (baseline) to the date of the first diagnosis of DM, death, or the patient's last cohort visit, whichever occurred first.

Associations between incident DM were analyzed in univariable and multivariable Poisson regression models. Fixed covariables were sex, ethnicity, injection drug use as the presumed mode of HIV acquisition, and HBV and/or HCV infection status. The following characteristics were analyzed in 2 separate models as fixed (baseline) and time-updated covariables, respectively: Age (prespecified strata of 16–39 years old, 40–49 years old, 50–59 years old, and ⩾60 years old), smoking status (never smoked, former smoker, or current smoker), central obesity, elevated blood pressure, and $CD4^+$ cell count, stratified according to Centers for Disease Control and Prevention categories (<200 cells/μL, 200–499 cells/μL, and ⩾500 cells/μL) [26].

Dates of starting and stopping treatment with antiretroviral drugs were documented prospectively by the treating physician and checked for plausibility and completeness by trained data managers prior to entry into the SHCS database. We defined combination ART (cART), as distinct from any ART, as an ART regiment in which at least 3 antiretroviral drugs were given simultaneously. Time-updated antiretroviral treatment information included (1) years of exposure to ART, cART, the different drug classes (NRTI, PI, and NNRTI), or individual drugs and (2) current receipt of a specific drug class or individual drugs. The time-updated cumulative exposure variables are increasing with continuous intake and are kept constant after discontinuation of the specific treatment (drug class or drug), whereas current treatment variables can have alternating values of 0 and 1 over time, depending on whether the specific treatment is currently received (1) or not (0). Because of obvious collinearities, we present separate multivariable models for cumulative exposure and current exposure variables.

Characteristics of different patient groups were compared using Wilcoxon rank-sum tests for continuous variables and χ^2 tests or Fisher's exact test for categorical variables. We used Stata software, version 9.2 (StataCorp), for analysis.

Sensitivity analysis. We performed different sensitivity analyses by adjusting for calendar period (2000–2001, 2002–2003, and 2004 and after), looking for trends over time, and using separate models for male and female subjects, individuals aged <50 years and those aged ⩾50 years, participants with African ethnicity, patients receiving ritonavir-boosted PI regimens, and patients who were not receiving ART versus patients receiving their first regimen versus patients receiving later reg-

imens. We considered continuous values for years of cumulative exposure, but we also tested the linear relationship by stratifying exposure into 0 years, >0 to *x* years, and >*x* years, with *x* taking the values 1 year, 2 years, and 3 years.

Because current antiretroviral drug use could be subject to reversed causality problems (e.g., patients who switched to another drug because of increasing glucose levels and whose diagnosis of DM was then attributed to the newly initiated drug regimen), we performed several sensitivity analyses in which we lagged the starting and stopping dates of drugs by 1 month, 2 months, and 3 months, yielding estimates for regimens that the patients had received 1 month, 2 months, or 3 months prior to the diagnosis of DM. Finally, we checked whether findings were influenced by the inclusion of other time-updated anthropometric measures, such as BMI, waist-to-hip ratio, and perceived lipohypertrophy and lipoatrophy, or by the exclusion of hypertension, because this may be on the causal pathway to DM.

RESULTS

Of 8253 SHCS participants seen after 1 March 2000, 6681 (81%) had at least 2 follow-up visits over a period of at least 1 year. Of these, we excluded 130 patients (1.9%) with a preexisting diagnosis of DM and 38 individuals for whom waist circumference or BMI were unknown. The present study is thus based on 6513 individuals with follow-up visits between 1 March 2000 and 17 July 2006. Baseline characteristics are listed in table 1. Participants (31% of whom were female) had a median age of 38 years and were well distributed between the major HIV transmission categories. Almost one-quarter of the patients had illness that was classified as Centers for Disease Control and Prevention disease stage C, and 73% were receiving or had received ART for a median duration of 1.9 years. Baseline and nadir $CD4^+$ cell counts were 403 cells/μL and 230 cells/μL, respectively. HCV infection was diagnosed in 27.4% of subjects, and HBV infection was active in 5.3%. The mean duration of follow-up was 4.3 years, and the cumulative follow-up for all subjects was 27,798 PYFU. During the follow-up period, 123 patients developed new-onset DM, resulting in an incidence of 4.42 cases per 1000 PYFU (95% CI, 3.71–5.28 cases per 1000 PYFU). In the course of the study, 341 patients (5.2%) died, and 656 patients (10.1%) were lost to follow-up. Injection drug users and persons with nonwhite ethnicity were more likely to become lost to follow-up (injection drug users vs. non–injection drug users, 15.0% vs. 8.6%; nonwhite ethnicity vs. white ethnicity, 13.5% vs. 7.3%; $P < .001$, by the χ^2 test). In addition, persons lost to follow-up had less advanced HIV infection than did persons who were not lost to follow-up, with a higher median nadir $CD4^+$ cell count (270 cells/μL vs. 226 cells/μL; $P < .001$) and fewer individuals with Centers for Disease Control and Prevention disease stage C at baseline (18% vs. 23%; $P = .004$).

Multivariable models. Baseline demographic, clinical, and anthropometric covariables known to be potentially associated with an increased risk of developing DM were used to build a baseline multivariable Poisson model (table 2.). Male sex, older age, African or Asian ethnicity, clinical AIDS, and central obesity were strong predictors of DM. Simultaneous estimates for BMI and central obesity are potentially inaccurate because of collinearity. Therefore, we removed BMI from the multivariable model.

We then built a time-updated model by replacing the baseline variables for age, $CD4^+$ cell count, nadir $CD4^+$ cell count, Centers for Disease Control and Prevention disease stage, smoking status, hypertension, and central obesity with their time-updated counterparts (i.e., the latest data available at each moment in time). Results of this time-updated model were virtually identical (data not shown), except that time-update hypertension also became statistically significant, with an incidence rate ratio (IRR) of 1.65 (95% CI, 1.10–2.48). Both the baseline model and the time-updated model will be used for adjustment in the following analyses.

Association of hepatitis and DM. Next, we analyzed the contribution of HBV and HCV infection to the development of DM in univariable models and together with the baseline and time-updated models (table 3). None of the HBV and HCV infection categories were associated with the incidence of DM (all *P* values were >.2). These findings remained unchanged in sensitivity analyses involving persons not receiving cART, persons receiving their first cART regimen, and persons receiving subsequent cART regimens (all interaction terms had *P* values >.6). To unmask potential confounding by ART-induced DM, we then included treatment-associated cofactors.

Association of antiretrovial treatment and DM. There was no clear effect of cumulative exposure to the different drug classes on the incidence of DM; univariable IRR per year of exposure to NRTI, PI, and NNRTI therapy were 1.04 (95% CI, 0.99–1.10), 1.05 (95% CI, 0.98–1.12) and 1.02 (95% CI, 0.90–1.14), respectively. Also, in the baseline and the time-updated multivariable models, as well as in 3 models with cumulative exposure (stratified into none, 0–1 year, and >1 year; none, 0–2 years, and >2 years; and none, 0–3 years, and >3 years), there was no statistically significant association (all *P* values were >.5).

However, current exposure to NRTI therapy, NRTI and PI combination therapy, or NRTI, PI, and NNRTI combination therapy increased the risk of developing DM in the univariable model, with IRRs of 2.22 (1.11–4.45), 2.48 (1.42–4.31), and 3.25 (1.59–6.67), respectively; there was no such association with current exposure to NRTI and NNRTI combination therapy, which was associated with an IRR of 1.47 (0.77–2.82).

Table 1. Baseline characteristics of 6513 subjects with and without new-onset type 2 diabetes mellitus (DM) during follow-up.

Variable	All subjects (n = 6513)	Subjects with new DM during follow-up (n = 123)	Subjects without DM during follow-up (n = 6390)	P
Sex				
Female	2032 (31.2)	25 (20.3)	2007 (31.4)	.009
Male	4481 (68.8)	98 (79.7)	4383 (68.6)	
Age				
Median years (IQR)	38 (34–44)	45 (38–53)	38 (34–44)	<.001
16–39 years old	3633 (55.8)	35 (28.5)	3598 (56.3)	
40–49 years old	1923 (29.5)	45 (36.6)	1878 (29.4)	
50–59 years old	688 (10.6)	24 (19.5)	664 (10.4)	
⩾60 years old	269 (4.1)	19 (15.5)	250 (3.9)	
Mode of HIV infection				
Heterosexual sex	2434 (37.4)	54 (43.9)	2380 (37.3)	.17
MSM	2314 (35.5)	40 (35.5)	2274 (35.6)	
Injection drug use	1531 (23.5)	22 (17.9)	1509 (23.6)	
Other	234 (3.6)	7 (5.7)	227 (3.5)	
Ethnicity				
White	5441 (83.5)	98 (79.7)	5343 (83.6)	.43
Black	688 (10.6)	15 (12.2)	673 (10.5)	
Hispanic	124 (1.9)	2 (1.6)	122 (1.9)	
Asian	192 (3.0)	7 (5.7)	185 (2.9)	
Unknown	68 (1.0)	1 (0.8)	67 (1.1)	
$CD4^+$ cell count, median cells/μL (IQR)	403 (241–593)	386 (196–600)	403 (242–592)	.24
$CD4^+$ cell count nadir, median cells/μL (IQR)	230 (102–393)	167 (50–333)	230 (102–394)	<.001
CDC disease stage C	1462 (22.5)	43 (35.0)	1419 (22.2)	.001
HIV RNA load, median $\log_{10}$ copies/mL (IQR)	2.37 (1.0–4.20)	1.83 (1.0–3.53)	2.39 (1.04–4.20)	.12
Smoking status				
Never smoked	2147 (33.0)	51 (41.5)	2096 (32.8)	.11
Former smoker	736 (11.3)	14 (11.4)	722 (11.3)	
Current smoker	3630 (55.7)	58 (47.1)	3572 (55.9)	
Hypertension	2933 (45)	82 (66.7)	2851 (44.6)	<.001
Weight, median kg (IQR)	68 (60–76)	76 (66–85)	68 (60–76)	<.001
BMI				
Median value (IQR)	22.5 (20.6–24.7)	25.2 (23.0–27.3)	22.5 (20.6–24.7)	<.001
<18.5	433 (6.6)	4 (3.2)	429 (6.7)	
18.5–24.9	4597 (70.6)	53 (43.1)	4544 (71.1)	
25–29.9	1275 (19.6)	53 (43.1)	1222 (19.1)	
⩾30	208 (3.2)	13 (10.6)	195 (3.1)	
Waist circumference, median cm (IQR)	82 (76–90)	95 (84–101)	82 (76–89)	<.001
Central obesity[a]	1627 (25)	78 (63.4)	1549 (24.2)	<.001
HBV infection status[a]				
Negative	2414 (37.1)	38 (30.9)	2376 (37.2)	.28[b]
Vaccinated	440 (6.8)	7 (5.7)	433 (6.8)	
Inactive	3133 (48.1)	64 (52.0)	3069 (48.0)	
Active	344 (5.3)	10 (8.1)	334 (5.2)	
Not available	182 (2.8)	4 (3.3)	178 (2.8)	
HCV infection status[a]				
Absent	4662 (71.6)	88 (71.5)	4574 (71.6)	.68[b]
Present	1788 (27.4)	31 (25.2)	1757 (27.5)	
Not available	63 (1)	4 (3.3)	59 (0.9)	
ART naive	1771 (27.2)	22 (17.9)	1749 (27.4)	.019
Duration of ART, median years (IQR)	1.92 (0–3.83)	2.60 (0.40–4.62)	1.90 (0–3.83)	.005

NOTE. Data are no. (%) of subjects, unless otherwise indicated. ART, antiretroviral therapy; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men.

[a] For definitions of central obesity and HBV and HCV infection status, see Methods.

[b] P value from χ^2 test including only categories with available information.

Table 2. Univariable and multivariable Poisson regression of baseline demographic, clinical, and anthropometric covariables potentially affecting the risk of developing type 2 diabetes mellitus, based on 6513 individuals with 123 events.

Variable	IR per 1000 PYFU (95% CI)	IRR univariable models (95% CI)	IRR baseline multivariable model (95% CI)
Sex			
Female	2.89 (1.95–4.28)	1	1
Male	5.12 (4.20–6.24)	1.77 (1.14–2.75)	2.54 (1.53–4.21)
Age, years			
16–39	2.31 (1.67–3.21)	1	1
40–49	5.40 (4.01–7.25)	2.33 (1.50–3.62)	1.93 (1.22–3.05)
50–59	8.10 (5.43–12.1)	3.50 (2.09–5.87)	2.29 (1.30–4.09)
⩾60	17.1 (10.9–26.8)	7.40 (4.25–12.9)	4.32 (2.28–8.16)
Mode of HIV infection			
Heterosexual sex	5.36 (4.10–7.00)	1	1
MSM	3.92 (2.88–5.35)	0.73 (0.49–1.10)	1.12 (0.63–1.98)
Injection drug use	3.37 (2.22–5.11)	0.63 (0.38–1.03)	0.74 (0.47–1.18)
Other	6.99 (3.33–14.7)	1.30 (0.59–2.86)	1.09 (0.49–2.40)
Ethnicity			
White	4.13 (3.39–5.04)	1	1
Black	5.74 (3.46–9.52)	1.39 (0.81–2.39)	2.10 (1.11–4.00)
Hispanic	4.07 (1.02–16.3)	0.98 (0.24–3.99)	1.64 (0.39–6.78)
Asian	8.91 (4.25–18.7)	2.15 (1.00–4.64)	4.88 (2.17–10.9)
Unknown	5.10 (0.72–36.2)	1.23 (0.17–8.84)	2.80 (0.38–20.5)
$CD4^+$ cell count, cells/μL			
<200	6.83 (4.86–9.61)	1.72 (1.09–2.71)	1.48 (0.82–2.66)
200–499	3.87 (2.92–5.13)	0.97 (0.64–1.47)	0.90 (0.56–1.44)
⩾500	3.98 (2.94–5.38)	1	1
$CD4^+$ cell count nadir, cells/μL			
<200	5.39 (4.26–6.82)	1.56 (0.86–2.82)	0.96 (0.46–2.02)
200–499	3.65 (2.69–4.96)	1.06 (0.57–1.97)	0.98 (0.49–1.93)
⩾500	3.45 (2.00–5.95)	1	1
CDC disease stage			
A or B	3.74 (3.00–4.66)	1	1
C	6.71 (4.98–9.05)	1.80 (1.24–2.60)	1.56 (1.04–2.35)
Smoking status			
Never smoked	5.64 (4.29–7.42)	1	1
Former smoker	4.55 (2.70–7.69)	0.81 (0.45–1.46)	0.95 (0.62–1.45)
Current smoker	3.70 (2.86–4.78)	0.66 (0.45–0.96)	0.66 (0.36–1.21)
Hypertension			
No	2.70 (1.99–3.67)	1	1
Yes	6.49 (5.23–8.06)	2.40 (1.65–3.50)	1.47 (0.98–2.19)
BMI			
<18.5	1.07 (0.27–4.29)	0.38 (0.09–1.54)	NA[a]
18.5–24.9	2.85 (2.18–3.72)	1	…
25–29.9	8.34 (6.30–11.0)	2.93 (1.99–4.31)	…
⩾30	16.4 (10.3–26.1)	5.76 (3.38–9.83)	…
Central obesity			
No	2.15 (1.60–2.88)	1	1
Yes	11.4 (9.10–14.2)	5.29 (3.66–7.63)	4.69 (3.14–7.00)

NOTE. BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CDC, Centers for Disease Control and Prevention; IR, incidence rate; IRR, incidence rate ratio; MSM, men who have sex with men; NA, not applicable; PYFU, person-years of follow-up.

[a] Dropped because of collinearity with central obesity. Likelihood-ratio tests for BMI and central obesity resulted in *P* values of .18 and <.001, respectively, indicating that BMI could be neglected.

Adjusting with the variables from the baseline model (table 2) and the time-updated model confirmed the findings from the univariable models (figure 1). It should be noted that receiving a PI and receiving an NRTI are highly collinear, because, until recently, PIs were usually combined with pairs of NRTIs. Therefore, we analyzed individual drugs from the PI class and the most frequent combinations of NRTIs in 2 separate models and combined in a single model. Again, these 3 models were repeated multivariably with adjustment for the baseline and time-updated variables. Results were similar (figure 1). In this multivariable analysis, DM was independently associated with current exposure to indinavir (IRR, 2.03 [95% CI, 1.05–3.93]), lamivudine-stavudine (IRR, 2.62 [95% CI, 1.22–5.61]), didanosine-stavudine (IRR, 3.09 [95% CI, 1.29–7.39]), and didanosine-tenofovir (IRR, 3.94 [95% CI, 1.57–9.87]), but other PI and NRTI combinations also showed trends.

There were no apparent interactions between PI and NRTI combinations, and results from sensitivity analyses with ART variables lagged by 1 month, 2 months, and 3 months yielded consistent results (data not shown). Findings also did not change when the model was adjusted for calendar period (2000–2001, 2002–2003, or 2004 and after), and we did not find a statistically significant trend over time ($P = .28$). Further sensitivity analyses included separate models for male and female subjects, for individuals aged <50 years and those aged ⩾50 years, for participants with African ethnicity, for patients with ritonavir-boosted PI regimens, and for patients receiving no ART versus patients receiving their first ART regimen versus patients receiving later regimens. None of these analyses revealed appreciable alterations of the main findings. Similarly, findings were unchanged in models incorporating BMI or waist-to-hip ratio instead of central obesity, including lipohypertrophy and lipoatrophy, or excluding hypertension. Finally, estimates for the association of HCV and HBV coinfection with DM remained virtually unchanged when adjusting for antiretroviral treatment: HCV infection was associated with an IRR of 1.10 (95% CI, 0.57–2.12), and active HBV infection was associated with an IRR of 1.42 (95% CI, 0.65–3.13).

DISCUSSION

In this analysis of 6513 participants who were followed-up for 27,798 person-years in the SHCS, we found an incidence of DM of 4.42 cases per 1000 PYFU. Similar to the HIV-seronegative population, factors such as male sex, older age, African or Asian ethnicity, and obesity were strong predictors of DM in this population [27–29].

Because there are no data available for the incidence of DM in Switzerland, we compared our results with published results of a large cohort of HIV-negative persons from Germany for the period 1984–1998 [27]. As shown in figure 2, the sex- and age-specific incidence rates are very similar, except for the highest age groups. There are, however, substantial differences in prevalence and incidence of DM between Europe and the United States. The incidence in the United States [30] is approximately twice as high as the incidence in Germany, and it is also higher than the findings from our study in most strata (figure 2). This higher background incidence may, therefore, partly explain the observed higher incidences in US cohorts of HIV-infected persons, such as the Multicenter AIDS Cohort Study [7], which reported incidences of 47 cases per 1000 PYFU (95% CI, 32–71 cases per 1000 PYFU) among individuals receiving cART, 17 cases per 1000 PYFU (95% CI, 6–45 cases per 1000 PYFU) among individuals not receiving cART, and 14 cases per 1000 PYFU (95% CI, 8–26 cases per 1000 PYFU) among HIV-seronegative individuals. Other factors contributing to the high incidences in the Multicenter AIDS Cohort Study [7] may include that the definition of DM was based on a single fasting plasma glucose determination without confirmation, that the subjects had a median BMI that was 3 greater than that in our study, and that their subjects had a median age that was ∼10 years older than that of our subjects. From 1994 through 1998, the Women's Interagency HIV Study found incidences of 28 cases per 1000 PYFU (95% CI, 16–41 cases per 1000 PYFU) among individuals receiving PI-containing regimens, 12 cases per 1000 PYFU (95% CI, 7–18 cases per 1000 PYFU) among individuals receiving NRTIs or NNRTIs only or no ART, and 13 cases per 1000 PYFU (95% CI, 7–22 cases per 1000 PYFU) among HIV-seronegative participants [6]. Although age and BMI data appear to be similar to data in our study, 55% and 26% of HIV-infected Women's Interagency HIV Study participants were black and Hispanic, respectively, compared with only 22.7% and 2.6% of women with black and Hispanic ethnicity in our study. Analysis of the Veterans Affairs administrative database, which includes almost 27,000 male individuals free of DM at baseline, identified substantial increases in the risk of developing DM in the cART period, compared with the pre-cART period, among nonwhite individuals and older individuals [15]. In addition, HCV seropositivity in the cART era was associated with a rather modest, but statistically significant, hazard ratio of 1.39 (95% CI, 1.27–1.53) in the multivariable analyses. Our study may have failed to find a significant association with HCV infection because of our limited sample size.

Several antiretroviral drugs and drug combinations were related to the development of DM; in particular, these include indinavir, lamivudine-stavudine, didanosine-stavudine, and didanosine-tenofovir. Although several studies have reported associations between DM and PI use [1–7], only limited data are available on the association of DM or hyperglycemia with exposure to NRTIs. Regimens including stavudine plus indinavir were found to increase the risk for DM in an Italian study [8], and hyperglycemia was associated with regimens that included

Table 3. Univariable and multivariable Poisson regression of hepatitis-associated risk of developing type 2 diabetes mellitus, based on 6513 individuals with 123 events.

Infection status, by virus	IRR from univariable models (95% CI)	IRR from basic baseline model[a] (95% CI)	IRR from basic time-updated model[b] (95% CI)
Hepatitis B virus			
Negative	1	1	1
Vaccinated	0.84 (0.41–1.75)	1.04 (0.50–2.18)	1.03 (0.49–2.16)
Inactive infection	1.25 (0.84–1.88)	1.20 (0.77–1.85)	1.20 (0.77–1.86)
Active infection	1.42 (0.66–3.06)	1.35 (0.62–2.96)	1.28 (0.59–2.81)
NA	1.23 (0.44–3.44)	1.36 (0.43–4.33)	1.40 (0.43–4.50)
Hepatitis C virus			
Infection absent	1	1	1
Infection present	0.78 (0.50–1.21)	1.16 (0.61–2.21)	1.20 (0.63–2.29)
NA	1.30 (0.48–3.53)	1.30 (0.42–4.01)	1.38 (0.44–4.31)

NOTE. IRR, incidence rate ratio; NA, not available.

[a] Model also adjusted for all of the variables from the basic baseline model (table 2).

[b] Model also adjusted for all of the variables from the basic time-updated model.

didanosine plus tenofovir in Spain [10]. In another report from the Multicenter AIDS Cohort Study, increased insulin resistance was associated with cumulative exposure to regimens containing indinavir, stavudine, and lamivudine [9].

Several mechanisms have been postulated to explain how antiretroviral drug toxicity may lead to insulin resistance and DM. Insulin sensitivity is reduced by a single dose of indinavir [31], and there are specific effects of PIs on the glucose transporter GLUT4 [32] and of NRTIs on mitochondria. Among the currently used NRTIs, the strongest association with mitochondrial toxicity, measured as inhibition of the mitochondrial DNA polymerase-γ, is found for didanosine and stavudine (known as the d-drugs) [33]; notably, these 2 drugs were strongly associated with DM in our study. Lipodystrophy is a crucial aspect of the association of cART with insulin resistance, leading to relative preponderance of visceral fat, hepatic steatosis, and fat deposition at other "ectopic" sites. In the fatless mouse animal model, diabetes and insulin resistance develop but respond to transplantation of subcutaneous fat [34]. HIV-infected persons with lipodystrophy, compared with those without lipodystrophy, have a reduction in plasma adiponectin and adipose tissue adiponectin mRNA levels of ~50%, correlating with insulin resistance and with increased cytokine levels [35]. Finally, there may also be a direct effect of HIV on the pancreas,

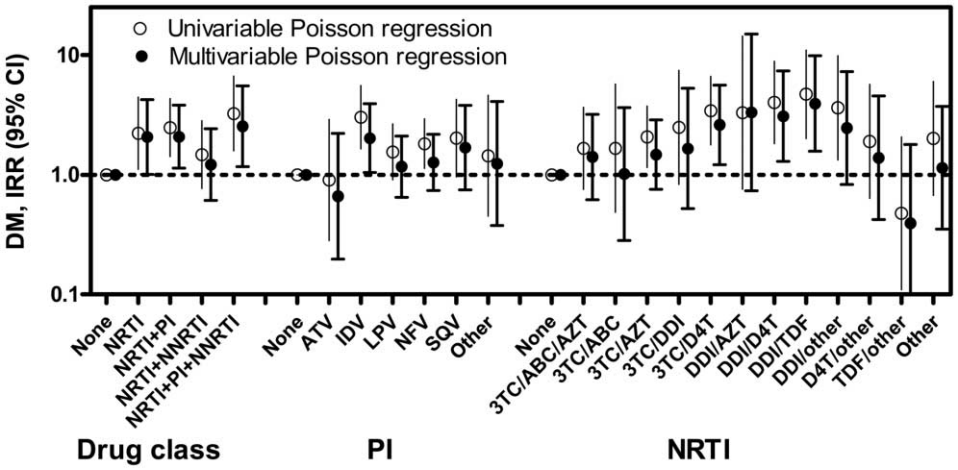

Figure 1. Incidence rate ratios (IRRs) for the development of new-onset type 2 diabetes mellitus (DM) based on 123 events among 6513 participants with 27,798 person-years of follow-up. Shown are associations with current receipt of specific drug classes and individual protease inhibitor (PI) and nucleoside or nucleotide reverse-transcriptase inhibitor (NRTI) combinations. Multivariable Poisson models were adjusted for all variables listed in table 2. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; SQV, saquinavir; TDF, tenofovir.

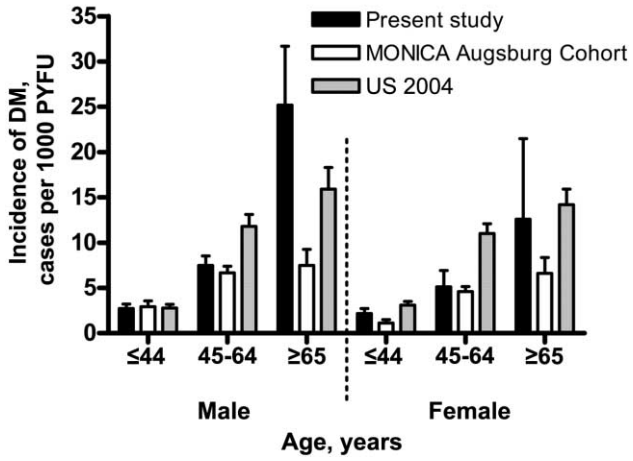

Figure 2. Comparison of sex- and age-specific incidence rates of type 2 diabetes mellitus (DM) between the present study of HIV-infected persons, the MONICA Augsburg Cohort (persons not infected with HIV) [27], and the US population in 2004 [30]. Whiskers indicate standard error. PYFU, person-years of follow-up.

because there have been reports of the spontaneous resolution of DM in patients starting cART [36, 37].

The strengths of this clinic-based study are the large number of patient-years with prospectively collected anthropometric data and plasma glucose and treatment information, as well as the verification of hyperglycemia values in relation to a DM diagnosis by the treating physicians. Unfortunately, we do not have information on family history of DM and adherence to antiretroviral drug regimens.

As the life expectancy of HIV-infected persons with access to cART has dramatically increased over the last decade, the risks for metabolic problems have also increased. Strong predictors for DM are nonmodifiable characteristics, such as age and ethnicity, but, importantly, the strong predictors also include obesity, which should become a major target for prevention. Furthermore, there are risks for DM associated with ART, especially therapy with PIs and some NRTI combinations. Because of their association with other metabolic disorders, regimens containing stavudine and didanosine are avoided as long as possible in developed countries, but they belong to first-line regimens in resource-limited areas. Together with the probably genetically determined elevated DM risk associated with Asian and African ethnicity, this may have an important impact on the long-term tolerability of anti-HIV treatment in the regions that are most affected.

In conclusion, type 2 DM is a serious but partially preventable complication in HIV-infected persons. In this study, we have identified several drugs and drug combinations that are associated with an increased risk of DM. As the number of antiretroviral drugs increases, continued monitoring in large cohort studies and collaborations remains an important prerequisite for the early identification of new toxicities and long-term side effects.

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