

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

Introduction

In 1997, the US Food and Drug Administration reported the association of hyperglycaemia and new-onset diabetes mellitus type 2 (DM) with protease inhibitors (PI; saquinavir, ritonavir, indinavir and nelfinavir) [1]. Subsequent studies have confirmed the association of hyperglycemia or DM with PI [2-7]. More recently, nucleoside and nucleotide reverse-transcriptase inhibitors (NRTI) but not non-nucleoside reverse-transcriptase inhibitors (NNRTI) were found to contribute to the disturbance of glucose metabolism [8-11]. Further, associations of hyperglycemia and DM with hepatitis C (HCV) infection have been reported both in HIV-1 negative [12-14] and 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 changed over the years in response to perceived toxicity and to the availability of new drugs. Due to improved life expectancy increased cumulative exposure to antiretroviral drugs of HIV infected persons may have resulted in cumulative toxicity in some patients.

Aim of the study

To assess the impact of hepatitis co-infections 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 during follow-up.

Methods

Study population

- Participants of the Swiss HIV Cohort Study
- At least two study visits with at least one year of follow-up after 1 March 2000
- Exclusion of prevalent cases of DM

Diagnosis of DM

- Confirmed plasma glucose level >7.0 mmol/L (fasting) and >11.1 mmol/L (non-fasting)
- Verification of patients with elevated plasma glucose or receiving antidiabetic medication without an explicit diagnosis of DM by treating physicians

Definitions

- Body mass index (BMI) stratification <18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight) and >30 (obese)
- Central obesity according to the world-wide definition with sex and ethnicity-specific waist circumference cut-offs:
 - Europoids and sub-saharan Africans $m > 94$ cm, $f > 80$ cm
 - South Asians, Chinese, south and central American $m > 90$ cm, $f > 80$ cm
 - Japanese $m > 85$ cm, $f > 90$ cm
- Elevated blood pressure either one of: Diastolic >85 mmHg or systolic >130 mmHg or anti-hypertensive treatment
- HCV infection: HCV-seropositive plus HCV-RNA - positive
- Active HBV infection: HBV-seropositive and HBs- or HBe antigen, or HBV-DNA-positive
- Combination antiretroviral therapy (cART) when at least three antiretroviral drugs were given simultaneously

Statistics

Follow-up was counted from the first visit after 1 March 2000 (baseline) to the date of the first diagnosis of DM, to death or the patients last cohort visit, whichever occurred first. Associations between incident DM were analysed in univariable and multivariable Poisson regression models.

- Fixed covariables: Sex, ethnicity, injecting drug use and HBV/HCV status
- Separate models with fixed (baseline) and time-updated values of age, smoking status, central obesity, elevated blood pressure and CD4 categories
- Time-updated antiretroviral treatment information was considered in two separate models as
 - years of exposure to ART, cART, the different drug classes (NRTI, PI, NNRTI) or individual drugs
 - currently being on a specific drug class or individual drugs (yes/no)

Results

Of 8253 SHCS participants seen after 1 March 2000, 6681 (81%) had at least two follow-up visits spanning at least 1 year. Of these, we excluded 130 participants (1.9%) with a pre-existing 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. Characteristics are shown in [table 1](#). 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](#)). We then built a time-updated model by replacing the baseline variables for age, CD4 and CD4 nadir cell counts, CDC stage, smoking status, hypertension and central obesity by their time-updated counterparts (i.e. the latest available at each moment in time). Results of this time-updated model were virtually identical (details not shown), except that time-update hypertension also became significant with an incidence rate ratio (IRR) of 1.65 (96% C.I. 1.10 to 2.48). Both, the baseline and the time-updated models will be used for adjustment in subsequent analyses.

Association of hepatitis and diabetes mellitus type 2

As shown in [table 3](#), none of the HBV and HCV categories were significantly associated with the incidence of DM (all p-values >0.2). These findings remained unchanged in sensitivity analyses looking at persons without cART, on first cART regimen and on subsequent cART regimens.

Association with cumulative exposure to antiretroviral treatment

There was no clear effect of cumulative exposure to the different drug classes on the incidence of DM. Univariable IRR per year of exposure for NRTI, PI and NNRTI were 1.04 (0.99 to 1.10), 1.05 (0.98 to 1.12) and 1.02 (0.90 to 1.14). Also in the baseline and the time-updated multivariable models there was no association (all p-values >0.5).

Figure 1: Incidence rate ratios for the development of new onset diabetes mellitus based upon 123 events during 27,798 person years of follow-up of 6513 participants. Shown are associations with currently being on specific drug classes (left) and on individual PI and NRTI combinations (right). Multivariable Poisson models were adjusted for all variables listed in [table 2](#), right column.

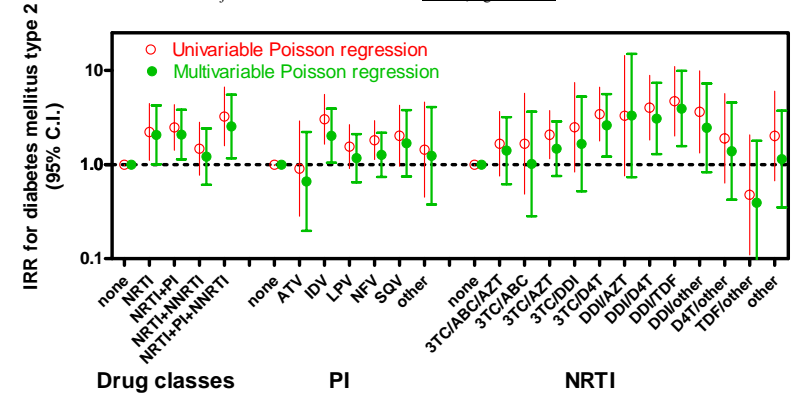


Table 1: Baseline characteristics of 6513 persons with and without new onset diabetes mellitus type 2 during follow-up.

		Total n = 6513	With new DM during follow-up, n = 123	Without DM during follow-up, n = 6390	P
Sex	female	2032 (31.2%)	25 (20.3%)	2007 (31.4%)	0.009
	male	4481 (68.8%)	98 (79.7%)	4383 (68.6%)	
Age [years]	median (IQR)	38 (34 to 44)	45 (38 to 53)	38 (34 to 44)	<0.001
	16-39	3633 (55.8%)	35 (28.5%)	3598 (56.3%)	
	40-49	1923 (29.5%)	45 (36.6%)	1878 (29.4%)	
	50-59	688 (10.6%)	24 (19.5%)	664 (10.4%)	
	60+	269 (4.1%)	19 (15.5%)	250 (3.9%)	
Mode of HIV infection	heterosexual	2434 (37.4%)	54 (43.9%)	2380 (37.3%)	0.17
	homosexual	2314 (35.5%)	40 (35.5%)	2274 (35.6%)	
	injecting 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%)	0.43
	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 [cells/ μ L]	median (IQR)	403 (241 to 593)	386 (196 to 600)	403 (242 to 592)	0.24
CD4 nadir [cells/ μ L]	median (IQR)	230 (102 to 393)	167 (50 to 333)	230 (102 to 394)	<0.001
CDC stage C	median (IQR)	1462 (22.5%)	43 (35.0%)	1419 (22.2)	0.001
HIV-1 RNA [\log_{10} copies/mL]	median (IQR)	2.37 (1.0 to 4.20)	1.83 (1.0 to 3.53)	2.39 (1.04 to 4.20)	0.12
Smoking status	never	2147 (33.0%)	51 (41.5%)	2096 (32.8%)	0.11
	previous	736 (11.3%)	14 (11.4%)	722 (11.3%)	
	current	3630 (55.7%)	58 (47.1%)	3572 (55.9%)	
Hypertension		2933 (45%)	82 (66.7%)	2851 (44.6%)	<0.001
Weight [kg]	median (IQR)	68 (60-76)	76 (66-85)	68 (60-76)	<0.001
BMI [kg/m ²]	median (IQR)	22.5 (20.6-24.7)	25.2 (23.0-27.3)	22.5 (20.6-24.7)	<0.001
	<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 [cm]	median (IQR)	82 (76 to 90)	95 (84 to 101)	82 (76 to 89)	<0.001
Central obesity ^a		1627 (25%)	78 (63.4%)	1549 (24.2%)	<0.001
HBV status ^b	negative	2414 (37.1%)	38 (30.9%)	2376 (37.2%)	0.28 ^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%)	
	n.a.	182 (2.8%)	4 (3.3%)	178 (2.8%)	
HCV infection ^c	absent	4662 (71.6%)	88 (71.5%)	4574 (71.6%)	0.68 ^b
	present	1788 (27.4%)	31 (25.2%)	1757 (27.5%)	
	n.a.	63 (1%)	4 (3.3%)	59 (0.9%)	
ART	naive	1771 (27.2%)	22 (17.9%)	1749 (27.4%)	0.019
Duration [years]	median(IQR)	1.92 (0 to 3.83)	2.60 (0.40 to 4.62)	1.90 (0 to 3.83)	0.005

Abbreviations: ART: Antiretroviral therapy; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus

^a For definitions of central obesity, HBV and HCV status refer to the methods section

^b p-value from Chi-square 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 DM based upon 6513 individuals with 123 events.

	IR (95% C.I.) [per 1000 PYFU]	IRR (95% C.I.) univariable models	IRR (95% C.I.) baseline multivariable model
Sex			
female	2.89 (1.95 to 4.28)	1	1
male	5.12 (4.20 to 6.24)	1.77 (1.14 to 2.75)	2.54 (1.53 to 4.21)
Age [years]			
16-39	2.31 (1.67 to 3.21)	1	1
40-49	5.40 (4.01 to 7.25)	2.33 (1.50 to 3.62)	1.93 (1.22 to 3.05)
50-59	8.10 (5.43 to 12.1)	3.50 (2.09 to 5.87)	2.29 (1.30 to 4.09)
60+	17.1 (10.9 to 26.8)	7.40 (4.25 to 12.9)	4.32 (2.28 to 8.16)
Mode of HIV infection			
heterosexual	5.36 (4.10 to 7.00)	1	1
homosexual	3.92 (2.88 to 5.35)	0.73 (0.49 to 1.10)	1.12 (0.63 to 1.98)
injecting drug use	3.37 (2.22 to 5.11)	0.63 (0.38 to 1.03)	0.74 (0.47 to 1.18)
other	6.99 (3.33 to 14.7)	1.30 (0.59 to 2.86)	1.09 (0.49 to 2.40)
Ethnicity			
white	4.13 (3.39 to 5.04)	1	1
black	5.74 (3.46 to 9.52)	1.39 (0.81 to 2.39)	2.10 (1.11 to 4.00)
hispanic	4.07 (1.02 to 16.3)	0.98 (0.24 to 3.99)	1.64 (0.39 to 6.78)
asian	8.91 (4.25 to 18.7)	2.15 (1.00 to 4.64)	4.88 (2.17 to 10.9)
unknown	5.10 (0.72 to 36.2)	1.23 (0.17 to 8.84)	2.80 (0.38 to 20.5)
CD4 [cells/ μ L]			
<200	6.83 (4.86 to 9.61)	1.72 (1.09 to 2.71)	1.48 (0.82 to 2.66)
200-499	3.87 (2.92 to 5.13)	0.97 (0.64 to 1.47)	0.90 (0.56 to 1.44)
500+	3.98 (2.94 to 5.38)	1	1
CD4 nadir [cells/ μ L]			
<200	5.39 (4.26 to 6.82)	1.56 (0.86 to 2.82)	0.96 (0.46 to 2.02)
200-499	3.65 (2.69 to 4.96)	1.06 (0.57 to 1.97)	0.98 (0.49 to 1.93)
500+	3.45 (2.00 to 5.95)	1	1
CDC stage			
A or B	3.74 (3.00 to 4.66)	1	1
C	6.71 (4.98 to 9.05)	1.80 (1.24 to 2.60)	1.56 (1.04 to 2.35)
Smoking status			
never	5.64 (4.29 to 7.42)	1	1
previous	4.55 (2.70 to 7.69)	0.81 (0.45 to 1.46)	0.95 (0.62 to 1.45)
current	3.70 (2.66 to 4.78)	0.66 (0.45 to 0.96)	0.66 (0.36 to 1.21)
Hypertension			
no	2.70 (1.99 to 3.67)	1	1
yes	6.49 (5.23 to 8.06)	2.40 (1.65 to 3.50)	1.47 (0.98 to 2.19)
BMI [kg/m ²]			
<18.5	1.07 (0.27 to 4.29)	0.38 (0.09 to 1.54)	dropped due to collinearity with central obesity ^a
18.5-24.9	2.85 (2.18 to 3.72)	1	1
25-29.9	8.34 (6.30 to 11.0)	2.93 (1.99 to 4.31)	1
30+	16.4 (10.3 to 26.1)	5.76 (3.38 to 9.83)	1
Central obesity			
no	2.15 (1.60 to 2.88)	1	1
yes	11.4 (9.10 to 14.2)	5.29 (3.66 to 7.63)	4.69 (3.14 to 7.00)

Abbreviations: BMI: Body mass index; IR: Incidence rate; IRR: Incidence rate ratio

^a Likelihood-ratio tests for BMI and central obesity resulted in p values of 0.18 and <0.001, respectively, indicating that BMI can be neglected.

Table 3: Univariable and multivariable Poisson regression of hepatitis-associated risk of developing DM based upon 6513 individuals with 123 events.

	IRR (95% C.I.) from univariable models	IRR (95% C.I.) from basic baseline model ^a	IRR (95% C.I.) from basic time-updated model ^b
HBV status			
negative	1	1	1
vaccinated	0.84 (0.41 to 1.75)	1.04 (0.50 to 2.18)	1.03 (0.49 to 2.16)
inactive	1.25 (0.84 to 1.88)	1.20 (0.77 to 1.85)	1.20 (0.77 to 1.86)
active	1.42 (0.66 to 3.06)	1.35 (0.62 to 2.96)	1.28 (0.59 to 2.81)
n.a.	1.23 (0.44 to 3.44)	1.36 (0.43 to 4.33)	1.40 (0.43 to 4.50)
HCV infection			
absent	1	1	1
present	0.78 (0.50 to 1.21)	1.16 (0.61 to 2.21)	1.20 (0.63 to 2.29)
n.a.	1.30 (0.48 to 3.53)	1.30 (0.42 to 4.01)	1.38 (0.44 to 4.31)

Abbreviations: IR: Incidence rate; IRR: Incidence rate ratio; HBV: Hepatitis B virus; HCV: Hepatitis C virus;

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

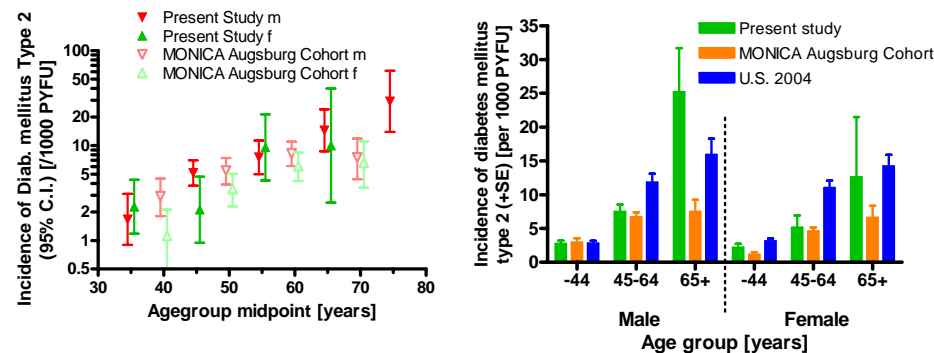
^b Model also adjusted for the variables from the basic time-updated model.

Association with current exposure to antiretroviral treatment

Current exposure to NRTI, NRTI + PI or NRTI + PI + NNRTI increased the risk of developing DM in the univariable model with IRR of 2.22 (1.11 to 4.45), 2.48 (1.42 to 4.31) and 3.25 (1.59 to 6.67), respectively, whereas there was no such association with NRTI + NNRTI (1.47 (0.77-2.82)). Adjusting with the variables from the baseline model (table 2) and the time-updated model confirmed the findings from the univariable models (figure 1, left). Since being on a PI and being on a NRTI are highly collinear we analysed individual drugs from the PI class (figure 1, middle) and the most frequent combinations of NRTI (figure 1, right) in two separate models. In the multivariable analysis, DM was independently associated with current exposure to indinavir (2.03 (1.05-3.93)), lamivudine/stavudine (2.62 (1.22-5.61)), didanosine/stavudine (3.09 (1.29-7.39)) and didanosine/tenofovir (3.94 (1.57-9.87)) but also other PI and NRTI combinations showed trends.

There were no apparent interactions between PI and NRTI combinations and results from sensitivity analyses with ART variables lagged by 1, 2 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, 2004+), nor did we find a trend over time (p=0.28). Further sensitivity analyses included separate models for: male and female, individuals aged < 50 vs. > 50 years, participants with African ethnicity, patients with ritonavir-boosted PI and patients without ART vs. on first regimen vs. on later regimens. We also included models with lagged starting and stopping dates of drugs by 1, 2 and 3 months. 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, or including lipohypertrophy and lipotrophy. Finally, estimates for the association of HCV and HBV co-infection with DM remained virtually unchanged when adjusting for antiretroviral treatment: IRR for HCV infection 1.10 (0.57 to 2.12) and for active HBV infection 1.42 (0.65 to 3.13).

Figure 2: Comparison of sex- and age-specific incidence rates of DM between the present study of HIV+ persons and HIV- individuals in the MONICA Augsburg Cohort (1998) [20] and the U.S. population in 2004 [21].



Conclusions

- The association of the incidence of diabetes mellitus type 2 with HCV or HBV coinfection was not significant
- Similar to the HIV seronegative population known factors such as male sex, older age, African or Asian ethnicities and obesity were strong predictors of diabetes mellitus type 2
- Current but not cumulative intake of several drugs and combinations was related to the development of diabetes mellitus type 2, in particular indinavir, lamivudine/stavudine, didanosine/stavudine or didanosine/tenofovir
- Compared to HIV-negative persons from the MONICA Augsburg Cohort in Germany [20] sex- and age-specific incidence rates in the Swiss HIV Cohort are similar, except for the highest age groups (figure 2 left)
- The incidence of diabetes mellitus type 2 in the US population [21] is approximately twice as high as in Germany and also higher than the findings from our study in most strata (figure 2 right)

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