Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study

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(See the Editorial Commentary by Saag, on pages 1140–2.)

Background. Patterns of morbidity and mortality among human immunodeficiency virus (HIV)–infected individuals taking antiretroviral therapy are changing as a result of immune reconstitution and improved survival. We studied the influence of aging on the epidemiology of non-AIDS diseases in the Swiss HIV Cohort Study.

Methods. The Swiss HIV Cohort Study is a prospective observational cohort established in 1988 with continuous enrollment. We determined the incidence of clinical events (per 1000 person-years) from January 2008 (when a new questionnaire on non–AIDS-related morbidity was introduced) through December 2010. Differences across age groups were analyzed using Cox regression, adjusted for CD4 cell count, viral load, sex, injection drug use, smoking, and years of HIV infection.

Results. Overall, 8444 (96%) of 8848 participants contributed data from 40 720 semiannual visits; 2233 individuals (26.4%) were aged 50–64 years, and 450 (5.3%) were aged ≥65 years. The median duration of HIV infection was 15.4 years (95% confidence interval [CI], 9.59–22.0 years); 23.2% had prior clinical AIDS. We observed 994 incident non-AIDS events in the reference period: 201 cases of bacterial pneumonia, 55 myocardial infarctions, 39 strokes, 70 cases of diabetes mellitus, 123 trauma-associated fractures, 37 fractures without adequate trauma, and 115 non-AIDS malignancies. Multivariable hazard ratios for stroke (17.7; CI, 7.06–44.5), myocardial infarction (5.89; 95% CI, 2.17–16.0), diabetes mellitus (3.75; 95% CI, 1.80–7.85), bone fractures without adequate trauma (10.5; 95% CI, 3.58–30.5), osteoporosis (9.13; 95% CI, 4.10–20.3), and non–AIDS-defining malignancies (6.88; 95% CI, 3.89–12.2) were elevated for persons aged ≥65 years.

Conclusions. Comorbidity and multimorbidity because of non-AIDS diseases, particularly diabetes mellitus, cardiovascular disease, non–AIDS-defining malignancies, and osteoporosis, become more important in care of HIV-infected persons and increase with older age.

Antiretroviral therapy (ART) has improved quality of life and increased life expectancy among human immunodeficiency virus (HIV)–infected individuals. Consequently, patterns of mortality [1] and morbidity [2] are changing among the human immunodeficiency virus (HIV)–infected population. The focus of care has shifted away from immunodeficiency-related opportunistic infections or AIDS-defining malignancies to ART-related problems (including toxicities, drug-drug interactions, or antiretroviral drug resistance) and, more recently, to various non-AIDS diseases [3–5]. Such comorbidites, often occurring sequentially or concurrently, may be the consequence of long-term ART toxicities, a state of chronic inflammation because of HIV infection [6], lifestyle-related risks for disease, and aging [7]. Many studies assessing the occurrence of comorbid conditions in

Received 23 February 2011; accepted 10 June 2011; electronically published 13 October 2011.

[a]Members of the study are listed in the Acknowledgments.

Presented in part: 18th Conference on Retroviruses and Opportunistic Infections, 27 February–2 March 2011, Boston, MA. Poster O–161.

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Clinical Infectious Diseases 2011;53(11):1130–9

1058-4838/2011/5311-0015$14.00
DOI: 10.1093/cid/cir626

HIV-infected persons have had a disease-specific focus, comparing the prevalence or incidence of a single clinical event among HIV-infected patients with that among demographically similar HIV-uninfected individuals [8–12], but only a few studies have aimed to investigate the extent and consequences of multimorbidity in the HIV-infected population.

In the Swiss HIV Cohort Study (SHCS), the proportion of older participants has increased in recent years (Figure 1). We aimed to study the influence of aging on the epidemiology of non-AIDS diseases in our cohort. We calculated incidences and hazard ratios for different clinical events and compared participants in different age groups (<50, 50–64, and ≥65 years of age). Because of the prospective and in-depth design of the cohort, we were able to adjust for many factors known to be associated with HIV disease progression or risk factors associated with non-AIDS comorbidity.

METHODS

Study Design and Data Collection

The SHCS is a prospective observational cohort study with continued enrollment of HIV-infected persons aged ≥16 years who attend outpatient clinics at 7 cohort centers, affiliated regional hospitals, or private practitioners collaborating with the centers. Standardized data collection forms containing demographic, psychosocial, clinical, laboratory, and treatment information are completed every 6 months by physicians and study nurses [13, 14].

HIV-associated opportunistic infections and malignancies have been documented since 1988, and immune reconstitution inflammatory syndrome has been reported since 2005. The SHCS is participating in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort, which has collected detailed information on cardiovascular end points and diabetes mellitus since 1999; end points are centrally reviewed and validated [15]. In 2008, the D:A:D cohort introduced additional end point forms and adjudication procedures for renal disease, liver disease, and non-AIDS malignancies. In addition, in 2008, the SHCS started to collect information on bone-related events, bacterial pneumonia, and pancreatitis. Detailed information on alcohol consumption has been collected in the SHCS since August 2005; detailed data on injection and noninjection drug consumption have been reported since April 2007.

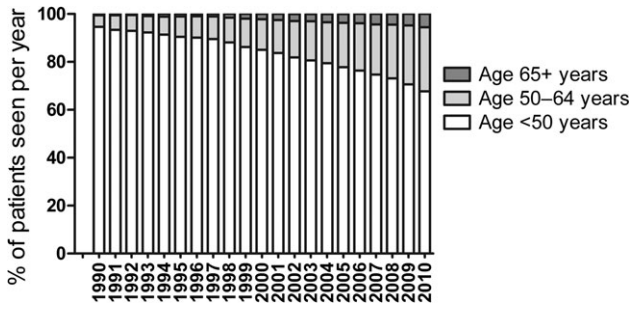

Figure 1. Age distribution among active participants of the Swiss HIV Cohort Study over time.

Study Participants

SHCS participants with at least 1 cohort visit from 1 January 2008 through 31 December 2010 were included in the analyses. Participants were categorized into 3 age groups: <50, 50–64, and ≥65 years of age. We limited the analysis to the 3 main HIV transmission categories: men who have sex with men, heterosexual individuals, and injection drug users. The protocol of the SHCS was approved by local ethical committees, and written informed consent was obtained from all participants.

Definitions

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Hypertension was diagnosed in participants with a diastolic or a systolic blood pressure ≥90/≥160 mm Hg or in those who took antihypertensive medications. If participants reported physical changes in face, arms, legs, abdomen, buttocks, breasts, or neck and if this physical change was confirmed during examination, the patient was assigned to have lipoatrophy or lipoaccumulation, depending on the situation. As a correlate of kidney function, estimates of the glomerular filtration rate were calculated using the Modification of Diet in Renal Disease equation [16]. Active hepatitis B virus (HBV) infection was defined as positive HBV surface antigen or HBV e antigen or HBV DNA. Hepatitis C virus (HCV) infection was defined as positive HCV antibody and positive HCV RNA. Alcohol use was stratified according to the World Health Organization definition into severe (for female patients, >40 g/d; for male patients, >60 g/d), moderate (for female patients, 20–40 g/d; for male patients, 40–60 g/d), and light use (for female patients, <20 g/d; for male patients, <40 g/d). The term "clinical AIDS" was used if an individual had a previous AIDS-defining infection or malignancy.

To assess the effects of viral load on clinical events, we captured the ART status at the last cohort visit before a new event or at the patient's last cohort visit, whichever was applicable. Information on ART included age at start of therapy, era of starting ART (mono/dual versus combination ART), ART status (ART-naive, currently not receiving ART, receiving ART with HIV RNA level <50 copies/mL, receiving ART with HIV RNA ≥50 copies/mL), adherence to ART during the 4 weeks before the last cohort visit, years of cumulative exposure to ART, current drug regimens (ART combinations based on protease inhibitor [PI], nonnucleoside reverse-transcriptase inhibitor [NNRTI], NNRTI and PI, or nucleoside reverse-transcriptase inhibitor [NRTI]), and individual drugs. The term "mono/dual" was used in case of ART initiation with 1 or 2 antiretroviral drugs, and the term "combination ART" was used for ≥3 drug combinations.

Statistical Analysis

Trends across age groups for different characteristics and conditions were analyzed using nonparametric tests for trend. Incidences of clinical events were calculated as the number of new events divided by the number of person-years of follow-up. Follow-up was counted from the first visit after 1 January 2008 to the date of the first diagnosis of new clinical events or the patient's last cohort visit, whichever occurred first.

Associations with age were analyzed in uni- and multivariable Cox proportional hazards regression models. Multivariable models were adjusted for latest square-root–transformed CD4 cell counts, latest $\log_{10}$-transformed HIV RNA level, female sex, former and current injection drug use, former and current smoking, and duration of HIV infection. Duration of HIV infection was calculated as years since seroconversion with use of imputed dates of seroconversion [17]. Eight percent of clinical observations (in particular, liver-associated events and bacterial pneumonias) had to be deleted because of missing covariables. Competing risk-of-death analyses, according to the method of Fine and Gray [18], were performed for the different clinical outcomes.

We used Stata, version 11.1 (StataCorp), for analyses.

RESULTS

From 1 January 2008 through 31 December 2010, 8844 participants contributed to 40,720 cohort visits and 22 591 person-years of follow-up. Four hundred four participants were excluded because they either had HIV-2 infection (n = 11) or did not belong to the main HIV transmission groups (perinatal, 46; blood, 77; other, 60; and unknown transmission, 210 participants).

Baseline Characteristics of Participants

Demographic and clinical characteristics of participants, stratified by age groups, are shown in Table 1. The median age of our cohort was 45 years (interquartile range [IQR], 39–51 years). Of 8444 individuals, 5761 (68%) were <50 years of age, 2233 (26%) were 50–64 years of age, and 450 (5%) were ≥65 years of age. Overall, 2464 (29%) were female, and 1963 (23%) had prior clinical AIDS. The nadir CD4 cell count was 190 cells/μL (IQR, 84–288 cells/μL), and the latest CD4 cell count was 528 cells/μL (IQR, 377–711 cells/μL).

In persons aged >65 years and those aged 50–64 years, the median duration of HIV infection was 15.7 years (IQR, 11.8–21.5 years) and 18.2 years (IQR, 12.8–23.5 years), respectively. Older persons aged >65 years were less likely to belong to the injection drug use HIV transmission group (0.7% in the >65 years age group vs 17.4% in the 50–64 years age group), were less likely to be HCV infected (6.2% vs 24.9%) and were less likely to be current smokers (16.9% vs 41.2%). Test-for-trend analyses across age groups showed associations with virtually all baseline conditions. The probability of prior clinical AIDS, cardiovascular risk factors, diabetes mellitus, or lipodystrophy was increasing with age, and renal function was decreasing with age.

Antiretroviral Therapy Status and Non-HIV Comedication

A total of 7184 (85%) of 8444 participants were taking ART, and 5834 (81%) of the 7184 participants had an undetectable viral load at the last cohort visit in the reference period or just before the clinical event (Table 2). The median age at start of ART was 36 years (IQR, 31–43 years), and the median duration of treatment was 6.4 years (IQR, 0.929–11.7 years). One-third of participants were receiving a PI-based regimen, and one-third were receiving an NNRTI-based regimen. Older patients were more frequently taking ART, had more frequently suppressed viral replication, and were more frequently taking non-HIV comedications. Of 8444 participants, 2591 (31%) received at least 1 non-HIV comedication. Figure 2*A* shows the percentage of participants with their respective numbers of non-HIV medication, stratified by age. One hundred fifteen (5.2%) of 2233 participants aged 50–64 years and 64 (14.2%) of 450 participants aged >65 years received ≥4 comedications.

Incidence of Clinical Events

Numbers of non-AIDS comorbidities, HIV-related complications, hospitalizations, and deaths, stratified by age, are shown in Table 3. One hundred seventy-seven (2.10%) of 8444 persons died. The leading causes of death were malignancies (40 [23%] of 177), infectious diseases (14.6%), and cardiovascular events (12.4%).

Of the 8444 participants, 1812 (21.5%) were hospitalized during the reference period. Somatic reasons (79.9%), psychiatric reasons (13.5%), and injuries (6.6%) accounted for most hospitalizations. Of 8444 cohort participants, 95 developed a new AIDS-defining illness and 100 developed a Centers for Disease Control and Prevention (CDC) stage B disease. We observed 994 incident non-AIDS clinical events during the reference period. Among the 115 non-AIDS malignancies, malignant neoplasm of the liver was the most frequent (16 [12.7%] of 115), followed by neoplasms of the lung (10.3%), prostate (7.14%), breast (5.56%), and skin (5.56%). Numbers of different non-AIDS comorbidities, stratified by age, are provided in Figure 2*B*. One hundred one (4.5%) of 2233 participants aged 50–64 years and 23 (5.3%) of 450 participants aged >65 years had ≥4 comorbidities.

The incidence rate (IR) of death was 7.81 deaths per 1000 person-years (95% confidence interval [CI], 6.74–9.05 deaths per 1000 person-years), of any hospitalization was 87.5 hospitalizations per 1000 person-years (95% CI, 83.5–91.7 hospitalizations per 1000 person-years), of clinical AIDS was 4.32 cases per 1000 person-years (95% CI, 3.53–5.28 cases per 1000 person-years), and of any clinical event was 53.3 cases per 1000 person-years (95% CI,

Table 1. Clinical Baseline Characteristics of 8444 HIV-Seropositive Cohort Participants, Stratified by Age

Variable	Total	Age group			*P* value[a]
		<50 years	50–64 years	≥65 years	
Patients, no. (%)	8444 (100)	5761 (68.2)	2233 (26.4)	450 (5.3)	
Female, no. (%)	2464 (29.2)	1932 (33.5)	453 (20.3)	79 (17.6)	<.001
HIV transmission groups, no. (%)					.322
MSM	3627 (42.9)	2401 (41.6)	1017 (45.5)	209 (46.4)	
Heterosexual	3393 (40.2)	2328 (40.4)	827 (37.0)	238 (52.9)	
IDU	1424 (16.8)	1032 (17.9)	389 (17.4)	3 (0.70)	
Prior clinical AIDS, no. (%)	1963 (23.2)	1160 (20.1)	660 (29.5)	143 (31.8)	<.001
Age at HIV diagnosis, median years (IQR)	29 (23–36)	26 (21–31)	37 (30–43)	54 (48–60)	<.001
Years HIV-infected, median (IQR)	15.4 (9.59–22.0)	14.0 (8.58–21.1)	18.2 (12.8–23.5)	15.7 (11.8–21.5)	<.001
First CD4 cells/μL, median (IQR)	350 (180–542)	367 (200–554)	310 (147–527)	285 (127–480)	<.001
Nadir CD4 cells/μL, median (IQR)	190 (84–288)	206 (102–306)	149 (62–245)	161 (67–254)	<.001
Years CD4 <200 cells/μL, median (IQR)	0.916 (0–12.5)	0 (0–10.1)	3.19 (0–18.3)	1.98 (0–14.5)	<.001
CD4 cells/μL at last visit, median (IQR)	528 (377–711)	532 (383–717)	523 (370–710)	471 (329–627)	<.001
BMI, kg/m[b], median (IQR)	23.5 (21.2–26.1)	23.3 (21.1–25.9)	23.8 (21.3–26.5)	24.2 (22.1–26.7)	<.001
Smoking, no. (%)					<.001
Never	2688 (31.8)	1828 (31.7)	657 (29.4)	203 (45.1)	
Ever	2009 (23.8)	1185 (20.6)	654 (29.3)	170 (37.8)	
Current	3735 (44.2)	2740 (47.5)	919 (41.2)	76 (16.9)	
Hypertension, no. (%)[b]	4753 (56.3)	2839 (49.3)	1559 (69.8)	355 (78.9)	<.001
Diabetes mellitus, no. (%)	350 (4.1)	121 (2.1)	156 (7.0)	73 (16.2)	<.001
Fat loss, no. (%)[c]	1425 (16.9)	682 (11.8)	611 (27.4)	132 (29.3)	<.001
Fat accumulation, no. (%)[d]	1514 (17.9)	822 (14.3)	568 (25.4)	124 (27.6)	<.001
Hepatitis B virus coinfection, no. (%)	339 (4.0)	255 (4.4)	67 (3.0)	17 (3.8)	<.001
Hepatitis C virus coinfection, no. (%)	1915 (22.7)	1332 (23.1)	555 (24.9)	28 (6.2)	<.001
Depression, no. (%)	1282 (15.2)	852 (14.8)	382 (17.1)	48 (10.7)	.911
MDRD, mL/min, median (IQR)	101 (86.5–111)	106 (92.4–115)	93.8 (79.5–102)	75.2 (62.1–87.0)	<.001
Drug use, no. (%)					
Illicit injectables in the past 6 months	217 (2.6)	176 (3.1)	41 (1.8)	0 (0)	<.001
Illicit noninjectables in the past 6 months	1522 (18.0)	1202 (20.8)	315 (14.1)	5 (1.1)	<.001
Opiate substitution treatment program	771 (9.1)	576 (10.0)	195 (8.7)	0 (0)	<.001
Alcohol use, no. (%)[e]					.001
Moderate	411 (4.9)	261 (4.5)	120 (5.4)	30 (6.7)	
Severe	217 (2.6)	151 (2.6)	56 (2.5)	10 (2.2)	

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; IDU, injecting drug users; BMI, body mass index; IQR, interquartile range; MDRD, modification of diet in renal disease; CHD, coronary heart disease.

[a] Test for trend across age-groups.

[b] Definition of hypertension: ≥160/≥90 mm Hg.

[c] Fat loss in any of the following regions: face, arms, legs, buttocks, breasts, neck. Presence of a least one patient-reported physical change confirmed on physical examination, irrespective of antiretroviral therapy or it's composition.

[d] Fat accumulation in any of the following regions: Face, arms, legs, buttocks, abdomen, breasts, and neck. Presence of a least one patient-reported physical change confirmed on physical examination, irrespective of antiretroviral therapy or it's composition.

[e] Alcohol consumption categorized according to the WHO criteria: moderate (20-40 g for women and 40-60 g for men) or severe health risk (>40 g per day for women and >60 g for men).

50.3–56.6 cases per 1000 person-years). IRs for selected non-AIDS events, IRs per age stratum, and results of test-for-trend analyses are summarized in Table 3. Incidences for death and hospitalization were elevated in older participants, compared with those aged <50 years. Also, IRs for bacterial pneumonia, stroke, coronary angioplasty, myocardial infarction, procedures on other arteries, bone fracture with assumed adequate or inadequate trauma, osteoporosis, new diabetes event, pancreatitis, and non-AIDS malignancy were higher for older participants (all $P < .05$).

Age-Associated Risks for Non-AIDS Events

Uni- and multivariable hazard ratios (HRs) for death, hospitalizations, HIV-associated, and non-AIDS events are shown

Table 2. Treatment Characteristics of 8444 HIV-Seropositive Cohort Participants, Stratified by Age

Variables	Total	Age group			*P* value[a]
		<50 years	50–64 years	≥65 years	
ART					
Age at ART start, years, median (IQR)	36 (31–43)	33 (29–37)	44 (39–49)	60 (55–64)	<.001
Era of starting ART, no. (%)					<.001
Mono/Dual	2212 (26.2)	1210 (21.0)	850 (38.1)	152 (33.8)	
Combination ART	5681 (67.3)	4084 (70.9)	1309 (58.6)	288 (64.0)	
Status at last visit, no. (%)					<.001
ART-naive	551 (6.5)	467 (8.1)	74 (3.4)	10 (2.2)	
ART interrupted	709 (8.4)	544 (9.4)	137 (6.1)	28 (6.2)	
On ART, VL <50 copies/mL	5834 (69.1)	3808 (66.1)	1685 (75.5)	341 (75.8)	
On ART, VL >50 copies/mL	1350 (16.0)	942 (16.4)	337 (15.1)	71 (15.8)	
Regimens at last visit, no. (%)					<.001
PI-based	2888 (34.2)	2042 (35.4)	710 (31.7)	136 (30.12)	
NNRTI-based	2765 (32.8)	1813 (31.5)	782 (35.0)	170 (37.8)	
PI + NNRTI–based	472 (5.6)	244 (4.2)	194 (8.7)	34 (7.6)	
NRTI only	356 (4.2)	225 (3.9)	100 (4.5)	31 (6.9)	
Other ART	703 (8.3)	426 (7.4)	236 (10.6)	41 (9.1)	
Use of new drugs at last visit, no. (%)					
Etravirine	417 (4.9)	257 (4.5)	140 (6.3)	20 (4.4)	.029
Enfurvitide	9 (0.1)	4 (0.07)	4 (0.2)	1 (0.2)	.128
Raltegravir	572 (6.8)	308 (5.3)	230 (10.3)	34 (7.6)	<.001
Maraviroc	54 (0.6)	29 (0.5)	20 (0.9)	5 (1.1)	.020
Darunavir/Ritonavir	688 (8.1)	456 (7.9)	198 (8.9)	34 (7.6)	.464
Adherence to ART during last 4 weeks, no. (%)					.021
Never missed a dose	5753 (83.8)	3762 (83.3)	1634 (84.2)	357 (88.2)	
1 missed dose/month	755 (11.0)	514 (11.4)	209 (10.8)	32 (7.9)	
>1 missed dose/month	354 (5.2)	241 (5.3)	97 (5.0)	16 (4.0)	
Time on ART, median (IQR)					
Overall years	6.40 (0.929–11.7)	4.70 (0–10.1)	9.84 (4.25–13.6)	9.84 (5.08–13.6)	<.001
Years on mono/dual	1.50 (0.498–3.74)	1.17 (0.288–3.25)	2.00 (0.748–4.15)	1.87 (0.711–4.20)	<.001
Non-ART medication, no. (%)					
Antihypertensives (not ACE inhibitors)	831 (9.8)	323 (5.6)	367 (16.4)	141 (31.3)	<.001
Antihypertensives (ACE inhibitors)	935 (11.1)	355 (6.2)	432 (19.4)	148 (32.9)	<.001
Lipid-lowering agents	1071 (12.7)	356 (6.2)	527 (23.6)	188 (41.8)	<.001
Oral antidiabetics	179 (2.1)	51 (0.9)	87 (3.9)	41 (9.1)	<.001
Insulin	116 (1.4)	40 (0.7)	50 (2.2)	26 (5.8)	<.001
Antiplatelet drugs	488 (5.8)	121 (2.1)	237 (10.6)	130 (28.9)	<.001
Antidepressants	846 (10.0)	560 (9.7)	251 (11.2)	35 (7.8)	.659

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; VL, viral load; PI, Protease inhibitor, NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; ACE, Angiotensin-converting enzyme.

[a] Test for trend across age groups.

in Table 4. In participants aged 50–64 years and ≥65 years, univariable HR for death and the following comorbidities were elevated, compared with younger persons: bacterial pneumonia, stroke, coronary angioplasty, myocardial infarction, procedure on other arteries, bone fractures with assumed adequate or inadequate trauma, osteoporosis, diabetes mellitus, pancreatitis, and non–AIDS-defining malignancies (all $P < .05$). After multivariable adjustment, associations with age remained unchanged for these end points. The global *P* value for age, obtained through a comparison of the likelihoods between models that did not include age, was $P < .001$ for most clinical events, suggesting that the overall effect of age on clinical events was strong.

Strong associations ($P < .001$) of covariables with the different end points were found in the respective multivariable models. Square-root CD4 cell counts were inversely associated with the development of bacterial pneumonias (HR, 0.939; 95% CI, 0.916–0.961), bone fractures without adequate trauma

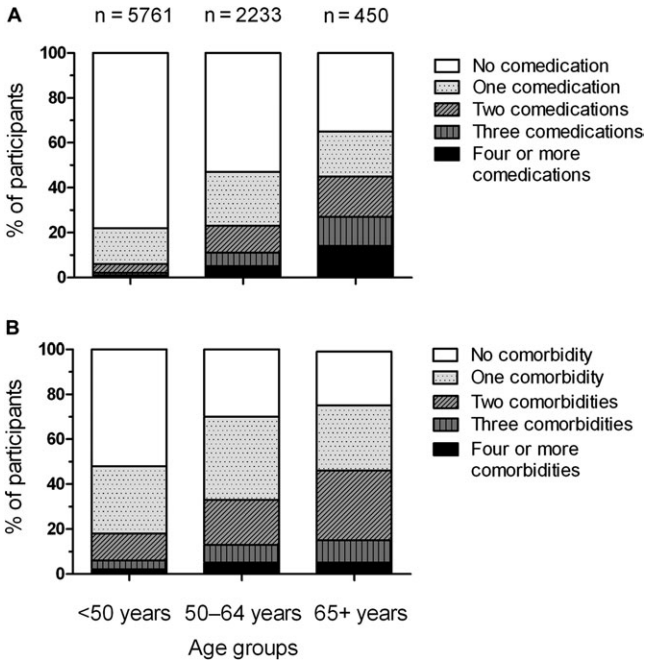

Figure 2. *A*, Numbers of different classes of non–human immunodeficiency virus (HIV) medication, stratified by age. Classes of non-HIV medications were antihypertensives, lipid-lowering agents, oral antidiabetics, insulin, antiplatelet drugs, and antidepressants. *B*, Numbers of different non-AIDS comorbidities, stratified by age. Classes of non-AIDS comorbidities were bacterial pneumonia, cerebral infarction, coronary angioplasty, myocardial infarction, procedure on other arteries, pulmonary embolism, deep vein thrombosis, fracture with adequate or inadequate trauma, osteoporosis, avascular necrosis of bone, diabetes mellitus, pancreatitis, liver-associated event, kidney-associated event, non-AIDS malignancy, arterial hypertension, hyperlipdemiemia, depression, active injection drug use, and active hepatitis B or C.

(HR, 0.897; 95% CI, 0.847–0.950), osteoporosis (HR, 0.906; 95% CI, 0.866–0.947), new AIDS-defining events (HR, 0.908; 95% CI, /INS> 0.877–0.941), and death (HR, 0.880; 95% CI, 0.858–0.903). Log_{10}–transformed viral load was associated with HIV-associated events (CDC B defining event: HR, 1.64 [95% CI, 1.48–1.82]; CDC C event: HR, 1.51 [95% CI, 1.37–1.68]). Female sex was positively associated with osteoporosis (HR, 2.98; 95% CI, 1.77–5.03). Former injection drug use was associated with bacterial pneumonia (HR, 2.68; 95% CI, 1.90–3.78), liver-associated events (HR, 5.71; 95% CI, 2.99–10.87), and death (HR, 2.78; 95% CI, 1.93–4.02); current injection drug use was associated with bacterial pneumonia (HR, 3.15; 95% CI, 1.81–5.49) and liver-associated events (HR, 5.81; 95% CI, 2.02–16.7). Former smoking was associated with death (HR, 2.78; 95% CI, 1.93–4.02); current smoking was associated with bacterial pneumonia (HR, 2.17; 95% CI, 1.42–3.33) and death (HR, 2.40; 95% CI, 1.53–3.76). Duration of HIV infection was inversely associated with the development of CDC B events (HR, 0.957; 95% CI, 0.936–0.978).

Sensitivity Analyses

We performed competing risk-of-death analyses with the assumption that different end points might be underestimated in older HIV-infected individuals, because they were more likely to die before experiencing a comorbid disease. We found that uni- and multivariable associations with age remained unchanged.

DISCUSSION

We prospectively assessed incident non-AIDS comorbidity and studied the association between age and clinical end points. Over a 36-month period, 8444 participants were followed up for 22 591 person-years. The rates for death, AIDS-defining diseases, and any clinical end point were 7.81 deaths per 1000 person-years (95% CI, 6.74–9.05 deaths per 1000 person-years), 4.32 cases per 1000 person-years (95% CI, 3.53–5.28 cases per 1000 person-years), and 53.3 cases per 1000 person-years (95% CI, 50.3–56.6 cases per 1000 person-years), respectively. We observed 994 incident non-AIDS events in the reference period, and non-AIDS events outnumbered HIV-related events. HRs for stroke, myocardial infarction, bone fractures with assumed adequate or inadequate trauma, osteoporosis, diabetes mellitus, and non-AIDS malignancies were higher for age groups 50–64 years and ≥65 years, compared with participants <50 years of age. After multivariable adjustment for CD4 cell counts, viral load, sex, former and current injection drug use, former and current smoking, and duration of HIV infection, associations with age remained robust.

A comparison of our results with an age-matched HIV-uninfected population with similar comorbidity or behavior is difficult, because we had no suitable HIV-uninfected control group in our country. Also, comparisons with the European Cancer Observatory [19] or the MONICA Augsburg Cohort (MAC) , a large cohort of HIV-uninfected persons in Germany [20, 21], are problematical, because the age distribution is different. Nevertheless, comparison of such data suggest a higher overall IR of cancer (IR, 3.764 cases per 1000 person-years) in our cohort of HIV-infected persons and higher IRs of myocardial infarction (IR derived from MAC, 3.51 cases per 1000 person-years; 95% CI, 3.17–3.87 cases per 1000 person-years), and diabetes mellitus (IR derived from MAC, 5.32 cases per 1000 person-years; 95% CI, 4.84–5.83 cases per 1000 person-years) in our SHCS participants aged 50–64 years.

Previous studies compared cross-sectional prevalence [9, 12, 22–26] or IRs [8, 10, 11, 27, 28] of comorbid disease between HIV-infected and HIV-uninfected individuals. In HIV-infected individuals, higher rates of bone fractures [9], osteoporosis [25], pulmonary disease [26], non–AIDS-defining malignancies [8, 27, 28], and cardiovascular disease [10, 11], were reported. However, such data deserve careful interpretation, because most of these studies were population-based, lacked prospective

Table 3. Overall and Age-Related Incidence Rates of Clinical Events, Hospitalizations, and Deaths, From 1 January 2008 Through 31 December 2010

End points	Total[a] no. (%)	Rate (95% CI) per 1000 person-years	Rate (95% CI) per 1000 person-years, by age group			*P* value[b]
			<50	50–64	≥65	
Non-AIDS Comorbidities	994 (100)					
Bacterial pneumonia	201 (20.1)	9.03 (7.87–10.4)	7.54 (6.27–9.05)	12.8 (10.2–16.0)	9.41 (5.21–17.0)	.005
Cerebral infarction	39 (3.9)	1.73 (1.26–2.37)	0.784 (0.445–1.38)	2.81 (1.75–4.52)	8.53 (4.59–15.9)	<.001
Coronary angioplasty	76 (7.6)	3.38 (2.70–4.23)	1.31 (0.843–2.02)	7.32 (5.35–9.84)	10.3 (5.84–18.1)	<.001
Myocardial infarction	55 (5.5)	2.44 (1.88–3.18)	0.849 (0.493–1.46)	5.98 (4.31–8.29)	5.08 (2.28–11.3)	<.001
Procedure on other arteries	31 (3.1)	1.37 (0.967–1.95)	0.718 (0.398–1.30)	2.81 (1.75–4.52)	2.54 (0.819–7.87)	.001
Pulmonary embolism	16 (1.6)	0.709 (0.434–1.16)	0.522 (0.261–1.04)	0.989 (0.444–2.20)	1.69 (0.423–6.77)	.089
Deep vein thrombosis	32 (3.2)	1.42 (1.00–2.00)	1.31 (0.843–2.03)	1.65 (0.888–3.07)	1.69 (0.422–6.74)	.539
Fracture, adequate trauma	123 (12.4)	5.48 (4.60–6.54)	3.67 (2.82–4.77)	8.67 (6.61–11.4)	12.8 (7.73–21.3)	<.001
Fracture, inadequate trauma	37 (3.7)	1.64 (1.19–2.26)	0.783 (0.445–1.38)	3.14 (2.00–4.93)	5.08 (2.28–11.3)	<.001
Osteoporosis	61 (6.1)	2.71 (2.11–3.48)	1.50 (0.998–2.26)	4.64 (3.21–6.72)	8.49 (4.57–15.8)	<.001
Avascular necrosis of bone	22 (2.2)	0.974 (0.642–1.48)	0.979 (0.590–1.62)	0.824 (0.342–1.98)	1.69 (0.442–6.75)	.783
Diabetes mellitus	70 (7.0)	3.12 (2.46–3.94)	2.09 (1.48–2.96)	4.65 (3.21–6.74)	8.56 (4.61–15.9)	<.001
Pancreatitis	28 (2.8)	1.24 (0.857–1.80)	0.783 (0.445–1.38)	2.31 (1.37–3.90)	1.69 (0.422–6.75)	.017
Liver-associated event[c]	57 (5.7)	2.53 (1.95–3.28)	2.22 (1.59–3.11)	3.64 (2.40–5.53)	0.843 (0.119–5.9)	.538
Kidney-associated event[d]	31 (3.1)	1.37 (0.967–1.95)	1.18 (0.741–1.87)	1.65 (0.888–3.07)	2.53 (0.818–7.86)	.176
Non–AIDS-defining malignancy	115 (11.6)	5.12 (4.27–6.15)	2.42 (1.75–3.34)	9.66 (7.47–12.5)	17.2 (11.1–26.7)	<.001
HIV-related events	195 (100)					
CDC stage B event	100 (51.3)	4.52 (3.72–5.51)	4.95 (3.94–6.22)	3.52 (2.29–5.39)	4.25 (1.77–10.2)	.257
CDC stage C event	95 (48.7)	4.32 (3.53–5.28)	3.88 (3.00–5.02)	5.08 (3.55–7.27)	6.05 (2.89–12.7)	.134
Hospitalizations	1812 (100)					
Somatic disease	1484 (79.9)	74.4 (70.7–78.3)	63.1 (59.0–67.4)	91.5 (83.7–100)	142 (121–168)	<.001
Injury	119 (6.6)	5.30 (4.43–6.35)	4.39 (3.46–5.58)	5.65 (4.04–7.91)	15.4 (9.71–24.4)	<.001
Psychiatric disease	245 (13.5)	11.0 (9.73–12.5)	11.8 (10.3–13.8)	10.0 (7.77–12.9)	5.07 (2.28–11.3)	.028
Deaths	177 (100)	7.81 (6.74–9.05)	5.92 (4.82–7.28)	9.68 (7.50–12.5)	22.5 (15.4–33.8)	<.001

Abbreviation: CDC, Centers for Disease Control and Prevention; CI, confidence interval.

[a] Some observations had to be deleted due to missing covariables.

[b] Test for trend across age groups.

[c] Events like nonalcoholic steatosis hepatis (n = 10), diagnosis of liver cirrhosis by histology (n = 15), spontaneous bacterial peritonitis (n = 2), bleeding form gastric or esophageal varices (n = 14), diagnosis of portal hypertension (n = 10), hepatic encephalopathy stage III–IV (n = 3), and liver transplantation (n = 3) were summarized as ''liver-associated events.''

[d] Events like kidney biopsy (n = 21), kidney transplantation (n = 1) and permanent dialysis (n = 9) were summarized as ''kidney-associated events.''

capture of end points, often relied on retrospective analysis of *International Classification of Disease* diagnosis codes, and did not control for long-term ART use and other important risks, such as smoking, alcohol, or substance use. Furthermore, it is especially important to consider that HIV-infected persons differ from HIV-uninfected control subjects with respect to metabolic changes because of long-term toxicity of ART [29–31], with respect to alcohol consumption, smoking, body mass index, and rates of HBV or HCV coinfections. This co-occurrence of multiple diseases or risk factors leads to novel patterns of multimorbidity that substantially differ by HIV status and age [23].

Effects of age and HIV infection on single non-AIDS diseases were previously reported [8–12, 23]. Comparisons between HIV-infected and HIV-uninfected persons showed higher rates of bone fractures [9], acute myocardial infarction [10, 11], diabetes mellitus [12], and non–AIDS-defining cancers [8, 28] among older HIV-infected individuals. The Veterans Aging Cohort Study (VACS) reported that HIV-infected participants aged ≥50 years more likely suffered from hypertension, diabetes mellitus, vascular disease, pulmonary disease, and renal disease, whereas substance use and psychiatric disorders were less likely in this age group [23]. The small cross-sectional National Health and Nutrition Examination Survey found a higher prevalence of hypertension, hypertriglyceridemia, low bone mineral density, and lipodystrophy in HIV-infected persons aged ≥50 years, compared with matched HIV-uninfected control subjects, and suggested that HIV accelerates biological aging [24]. However, the concept of premature aging of HIV-infected persons appears to be controversial, particularly when considering the investigation on effects of age on non–AIDS-defining malignancies by Shiels et al [32]. They compared age at diagnosis for different types of cancer in HIV-infected and HIV-uninfected populations

Table 4. Uni- and Multivariable Hazard Ratios for Clinical Events From 1 January 2008 Until 31 December 2010, Stratified by Age

	Univariable analyses			Multivariable analyses		
Events	50–64 HR (95% CI)[a]	≥65 HR (95% CI)[a]	*P* value	50–64 HR (95% CI)[a]	≥65 HR (95% CI)[a]	*P* value[d]
Non-AIDS comorbidities						
Bacterial pneumonia	1.69 (1.27–2.26)	1.25 (0.673–2.32)	.002	1.89 (1.40–2.55)	2.04 (1.08–3.88)	<.001
Cerebral infarction	3.59 (1.72–7.52)	10.9 (4.70–25.2)	<.001	3.96 (1.86–8.42)	17.7 (7.06–44.5)	<.001
Coronary angioplasty	5.60 (3.30–9.50)	7.86 (3.84–16.1)	<.001	4.72 (2.76–8.10)	7.43 (3.51–15.7)	<.001
Myocardial infarction	7.05 (3.74–13.3)	5.99 (2.27–15.7)	<.001	5.95 (3.12–11.3)	5.89 (2.17–16.0)	<.001
Procedure on other arteries	3.92 (1.83–8.36)	3.53 (0.987–12.7)	.001	4.29 (1.97–9.36)	5.04 (1.34–19.1)	<.001
Pulmonary embolism	1.90 (0.660–5.48)	3.25 (0.691–15.3)	.272	1.87 (0.632–5.52)	3.93 (0.760–20.4)	.251
Deep vein thrombosis	1.26 (0.590–2.68)	1.29 (0.302–5.52)	.815	1.29 (0.594–2.80)	2.06 (0.453–9.40)	.608
Fracture, adequate trauma	2.37 (1.63–3.46)	3.52 (1.99–6.23)	<.001	2.28 (1.55–3.36)	4.71 (2.57–8.63)	<.001
Fracture, inadequate trauma	4.01 (1.95–8.25)	6.46 (2.42–17.2)	<.001	3.93 (1.88–8.24)	10.5 (3.58–30.5)	<.001
Osteoporosis	3.09 (1.78–5.36)	5.65 (2.69–11.9)	<.001	3.60 (2.04–6.34)	9.13 (4.10–20.3)	<.001
Avascular necrosis of bone	0.838 (0.305–2.30)	1.72 (0.393–7.51)	.720	0.767 (0.274–2.15)	2.32 (0.489–11.0)	.493
Diabetes mellitus	2.23 (1.34–3.70)	4.09 (2.01–8.31)	<.001	2.23 (1.33–3.76)	3.75 (1.80–7.85)	<.001
Pancreatitis	2.94 (1.36–6.36)	2.15 (0.481–9.61)	.023	3.27 (1.48–7.24)	3.85 (0.799–18.5)	.01
Liver-associated event[b]	1.64 (0.959–2.80)	0.379 (0.519–2.77)	.082	1.29 (0.748–2.23)	0.494 (0.066–3.72)	.440
Kidney-associated event[c]	1.40 (0.647–3.04)	2.16 (0.637–7.34)	.426	1.41 (0.638–3.14)	2.84 (0.781–10.3)	.303
Non-AIDS malignancy	3.98 (2.64–6.02)	7.11 (4.13–12.3)	<.001	3.73 (2.45–5.69)	6.88 (3.89–12.2)	<.001
HIV-related events						
CDC stage B event	0.771 (0.438–1.15)	0.860 (0.348–2.13)	.361	1.00 (0.616–1.66)	1.18 (0.468–2.95)	.945
CDC stage C event	1.31 (0.842–2.03)	1.56 (0.714–3.42)	.341	1.56 (0.990–2.44)	1.84 (0.826–4.12)	.100
Hospitalizations						
Somatic disease	1.45 (1.30–1.62)	2.27 (1.89–2.71)	<.001	1.59 (1.42–1.78)	2.88 (2.39–3.48)	<.001
Injury	1.28 (0.851–1.94)	3.50 (2.08–5.88)	<.001	1.35 (0.882–2.06)	4.82 (2.75–8.44)	<.001
Psychiatric disease	0.841 (0.628–1.13)	0.423 (0.189–0.963)	.042	0.976 (0.724–1.32)	0.867 (0.379–1.99)	.936
Death	1.63 (1.17–2.26)	3.80 (2.47–5.84)	<.001	1.67 (1.19–2.33)	6.25 (3.90–10.0)	<.001

Multivariable models were adjusted for latest square-root–transformed CD4, female sex, former injecting drug use, never injecting drug use, former smoking, never smoking, latest $\log_{10}$-transformed HIV-RNA copies/mL and years of HIV infection.

Abbreviations: HR, hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus.

[a] Participants <50 years old formed the reference group.

[b] Events like nonalcoholic steatosis hepatis, diagnosis of liver cirrhosis by histology, spontaneous bacterial peritonitis, bleeding form gastric or esophageal varices, diagnosis of portal hypertension, hepatic encephalopathy stage III–IV, and liver transplantation were summarized as ''liver-associated events.''

[c] Events like kidney biopsy, kidney transplantation and permanent dialysis were summarized as ''kidney-associated events.''

[d] Likelihood ratio test for global *P* value of age.

after adjustment for age differences between groups and concluded that their analyses do not support premature aging as a cause of cancer in HIV-infected persons.

Residual immunodeficiency and a state of chronic inflammation may add to risk of age-associated non-AIDS diseases also among persons taking ART [6]. We observed that individuals with higher CD4 cell counts were less likely to develop HIV-associated and non-AIDS events, and they were less likely to die. A detectable HIV RNA level was associated with the development of bacterial pneumonia, new CDC B– and C–defining events, and certain non-AIDS end points. Patients with lower CD4 cell counts are known to have a higher mortality [2], but they also seemed to develop age-related events more frequently in our analyses. This is in line with results from the VACS, which showed that low CD4 cell counts and detectable viral loads were associated with vascular and pulmonary diseases [23].

Strengths of our study include its statistical power, because of the large number of patient-years, and the prospective collection of incident events with use of structured event reporting forms. Because of the design of the cohort, we were able to control for many cofactors known to be associated with HIV progression or occurrence of comorbid events. Several limitations should also be noted. First, we could not compare incidences of disease in HIV-infected patients with those in a demographically similar HIV-uninfected reference group. This complicates the interpretation of IRs in persons aged >65 years, leaving questions open, such as whether increased comorbidity simply reflects being older or whether risk of comorbidity is increased because of reduced immune recovery, despite HIV control, in persons who are infected at an older age. Second, although SHCS institutions provide primary care and, thus, continuously document patients' history and clinical end

points, it cannot completely be excluded that participants attended other institutions for care and that such information was not reported by participants or care providers. There is no formal record linkage with other hospitals. Third, outcome is particularly different in injection drug users, because they more often suffer from liver-related comorbidities or smoking-related complications, are less likely to participate in a cohort study, and are underrepresented in older age groups. However, we considered such differences of participants' characteristics and behavior by adjusting the multivariable models also for former versus current injection drug use and former versus current smoking.

In conclusion, non-AIDS comorbidities, particularly cardiovascular disease, osteoporosis, diabetes mellitus, and non–AIDS-defining malignancies, become increasingly important in HIV-infected persons and increase with older age. In addition to disease-specific research, studies on comprehensive HIV care need to focus on patterns of consecutive comorbidity and concurrent multimorbidity. Because age is a nonmodifiable factor, it is particularly important to carefully screen for and prevent age-related modifiable risks of non-AIDS comorbidity.

Notes

Acknowledgments. We thank all involved physicians, study nurses, and, most importantly, participants of the SHCS.

Barbara Hasse had full access to all the data of the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Barbara Hasse, Bruno Ledergerber and Rainer Weber designed the study; Barbara Hasse wrote the first draft; and Barbara Hasse, Bruno Ledergerber and Rainer Weber wrote the final version of the manuscript. Bruno Ledergerber analysed the data. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript, and approved the final manuscript.

Financial support. This work was supported by the Swiss National Science Foundation (through the SHCS). The funding source had no influence on design or conduct of the study.

The members of the Swiss HIV Cohort Study are as follows: Barth J, Battegay M, Bernasconi E, Böni J, Bucher HC, Bürgisser P, Burton-Jeangros C, Calmy A, Cavassini M, Dubs R, Egger M, Elzi L, Fehr J, Fischer M, Flepp M, Francioli P (President of the SHCS), Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (Chairman of the Scientific Board), Hasse B, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G,Martinez de Tejada B, Müller N, Nadal D, Pantaleo G, Rauch A, Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Telenti A, Trkola A, Vernazza P, von Wyl V, Weber R, Yerly S.

Potential conflicts of interest. B. Hasse has received travel grants from Astra Zeneca, Essex Chemicals, Gilead Sciences and Wyeth. B. L. has received travel grants, grants or honoraria from Abbott, Aventis, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Roche and Tibotec. H. F. has participated in advisory boards of ViiVHealthcare, Bristol-Myers Squibb, Gilead, Merck Sharp & Dome, Boehringer-Ingelheim, Janssen. H. F's institution has received unrestricted educational grants from Abbott, ViiV Healthcare, BMS, Roche, Gilead, Merck Sharp & Dome, Boehringer-Ingelheim, Janssen-Cilag. M. B. has received travel grants, speaker's honoraria and/or research grants from Abbott, Boehringer Ingelheim, Gilead Sciences, Hoffmann La Roche, Merck Sharp&Dome, Tibotec and ViiV. BHi reported no conflict of interest. M. C. received travel grants from Abbott, Boehringer-Ingelheim, Gilead and Merck Sharp & Dome. B. B. has received travel grants from Gilead Sciences, Abbott, BMS, Janssen-Tibotec, Roche and MSD. E. B. has participated in advisory boards of Abbott, Boehringer-Ingelheim, Gilead, Merck Sharp & Dome, Janssen, and ViiV Healthcare. E. B's institution has received unrestricted education grants from Abbott, Gilead and ViiV Healthcare. R. W. has received travel grants or speakers honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dome, Pfizer, LaRoche, TRB Chemedica and Tibotec; and was a member of an endpoint adjudication panel of phase II and III antiretroviral treatment studies of Tibotec.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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