MAJOR ARTICLE

Incidence and Risk Factors for Chronic Elevation of Alanine Aminotransferase Levels in HIV-Infected Persons without Hepatitis B or C Virus Co-Infection

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Background. Chronic liver disease in human immunodeficiency virus (HIV)–infected patients is mostly caused by hepatitis virus co-infection. Other reasons for chronic alanine aminotransferase (ALT) elevation are more difficult to diagnose.

Methods. We studied the incidence of and risk factors for chronic elevation of ALT levels (greater than the upper limit of normal at ⩾2 consecutive semi-annual visits) in participants of the Swiss HIV Cohort Study without hepatitis B virus (HBV) or hepatitis C virus (HCV) infection who were seen during the period 2002–2008. Poisson regression analysis was used.

Results. A total of 2365 participants were followed up for 9972 person-years (median age, 38 years; male sex, 66%; median $CD4^+$ cell count, 426/μL; receipt of antiretroviral therapy [ART], 56%). A total of 385 participants (16%) developed chronic elevated ALT levels, with an incidence of 3.9 cases per 100 person-years (95% confidence interval [CI], 3.5–4.3 cases per 100 person-years). In multivariable analysis, chronic elevated ALT levels were associated with HIV RNA level >100,000 copies/mL (incidence rate ratio [IRR], 2.23; 95% CI, 1.45–3.43), increased body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) (BMI of 25–29.9 was associated with an IRR of 1.56 [95% CI, 1.24–1.96]; a BMI ⩾30 was associated with an IRR of 1.70 [95% CI, 1.16–2.51]), severe alcohol use (1.83 [1.19–2.80]), exposure to stavudine (IRR per year exposure, 1.12 [95% CI, 1.07–1.17]) and zidovudine (IRR per years of exposure, 1.04 [95% CI, 1.00–1.08]). Associations with cumulative exposure to combination ART, nucleoside reverse-transcriptase inhibitors, and unboosted protease inhibitors did not remain statistically significant after adjustment for exposure to stavudine. Black ethnicity was inversely correlated (IRR, 0.52 [95% CI, 0.33–0.82]). Treatment outcome and mortality did not differ between groups with and groups without elevated ALT levels.

Conclusions. Among patients without hepatitis virus co-infection, the incidence of chronic elevated ALT levels was 3.9 cases per 100 person-years, which was associated with high HIV RNA levels, increased BMI, severe alcohol use, and prolonged stavudine and zidovudine exposure. Long-term follow-up is needed to assess whether chronic elevation of ALT levels will result in increased morbidity or mortality.

Human immunodeficiency virus (HIV)–associated morbidity and mortality have decreased dramatically and continuously since the introduction of combination antiretroviral therapy (cART) [1–3]. Because of improved life expectancy, non–AIDS-defining diseases and drug-related toxicities have emerged as a key issue in the management of these patients. Liver-related conditions are the most frequent cause of non–AIDS-related death among the HIV-infected population [4]. The main causes of hepatopathy in HIV-infected persons are hepatitis C virus (HCV) and hepatitis B virus (HBV) infections.

Patients with HIV infection frequently have elevated liver function test results [5]. The cause and clinical sig-

Received 15 July 2009; accepted 28 September 2009; electronically published 19 January 2010.

Presented in part: 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, 8–11 February 2009 (abstract 750).

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Clinical Infectious Diseases 2010;50:502–11
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1058-4838/2010/5004-0008$15.00
DOI: 10.1086/649922

source: https://doi.org/10.7892/boris.2728 | downloaded: 12.10.2024

nificance of these levels, particularly in the absence of chronic viral hepatitis, often are unclear and make their assessment and management difficult. Several studies have evaluated liver disease in patients with HCV and HBV co-infections, and most examinations have focused on severe liver enzyme elevations (defined as 3–5 times the upper limit of normal or more) [6–8]. However, the majority of patients only have mild-to-moderate increased liver enzyme levels. A recently published study examined liver biopsy findings among HIV-infected patients receiving antiretroviral therapy (ART) with unexplained chronic elevated transaminase levels and found a high rate of histological abnormalities: 22 (73%) of 30 patients had either liver fibrosis and/or steatosis [9]. These results emphasize the importance of chronic elevated ALT levels.

Two cross-sectional studies investigated predictors of liver enzyme elevation in HIV-infected patients without HCV or HBV infection. However, the first study excluded patients with risk factors or evidence for nonalcoholic fatty liver disease and alcohol abuse [10]. The second study used only a single elevated alanine aminotransferase (ALT) value, which is subject to the high intraindividual variability of liver tests. Furthermore, it is not clear whether ALT values were collected concurrent with clinical events or per protocol [11].

Because of the lack of data regarding elevated ALT levels among HIV-positive patients without chronic viral hepatitis, we studied the incidence of and risk factors for chronic ALT elevation as a sign for chronic liver disease in a large prospective, longitudinal multicenter cohort.

METHODS

Study population. The Swiss HIV Cohort study (SHCS) is an ongoing, prospective cohort study that was established in 1988 and that continuously enrolls and observes HIV-infected individuals aged ⩾16 years at 5 university outpatient clinics, 2 large cantonal hospitals, affiliated regional hospitals, and private practices [12]. Information and laboratory values, including liver enzyme levels, are collected according to defined criteria at registration and follow-up visits every 6 months. The study was approved by local ethics review boards, and written informed consent was obtained from all participants.

For this analysis, we included SHCS participants without HBV and HCV infection and at least 3 consecutive semiannual visits with ALT determinations who were seen after 1 January 2002, which was the date on which ALT values were regularly collected in the SHCS. The last follow-up visit was in December 2008. Patients with prevalent elevated ALT levels at the time of the baseline visit were excluded from the study. Baseline visit was defined as the first visit after 1 January 2002.

Definitions. Chronic ALT elevation was defined as an ALT level greater than the upper limit of normal at 2 or more consecutive semiannual visits. HCV infection was defined as present in patients who were seropositive for HCV or who had test results positive for HCV RNA. HBV infection was defined as present in patients who were positive for hepatitis B surface antigen or hepatitis B e antigen or hepatitis B core antibodies or who had detectable HBV DNA during the study period. Body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) was stratified into <18.5 (underweight), 18.5–24.9 (normal), 25–29.9 (overweight), and ⩾30 (obese) [13]. Central obesity was defined according to the new worldwide definition [14], with sex- and ethnicity-specific waist circumference cut-off values. Hypercholesterolemia and hypertriglyceridemia were defined as present in patients with total cholesterol >6.5 mmol/L and triglycerides >1.7 mmol/L, respectively. Diabetes mellitus was diagnosed according to the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [15], with confirmed plasma glucose level cut-off values of >7.0 mmol/L (fasting) and >11.1 mmol/L (nonfasting). Elevated blood pressure was defined as present in patients with diastolic blood pressure ⩾85 mmHg or systolic blood pressure ⩾130 mmHg. Smoking status was stratified into never, former, and current smoking. Alcohol use was stratified into severe use (female patients, >40 g/day; male

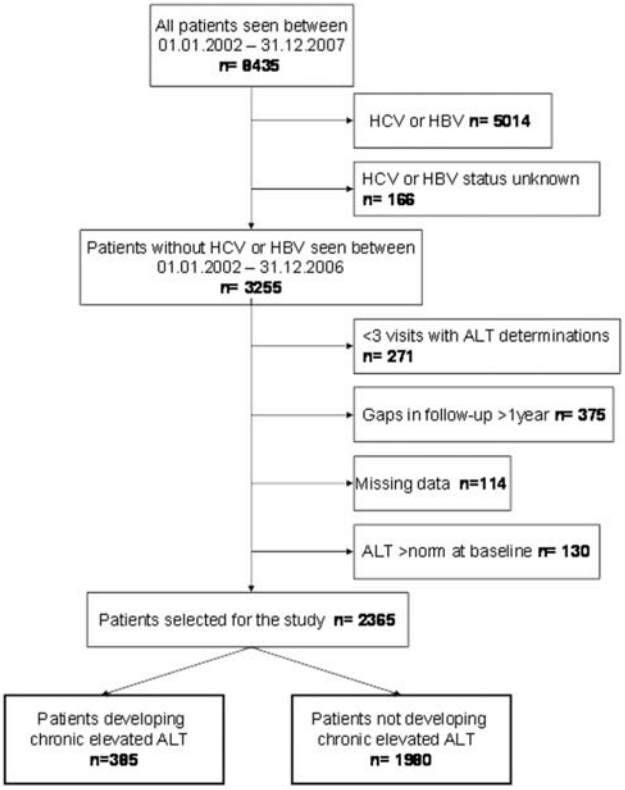

Figure 1. Patient flowchart for study of incidence and risk factors for chronic elevation of alanine aminotransferase (ALT) levels in human immunodeficiency virus (HIV)–infected persons without hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection.

Table 1. Baseline Characteristics of 2365 Patients with and Patients without Incident Chronic Elevation of Alanine Aminotransferase (ALT) Levels during Follow-Up

Variable	All subjects (n = 2365)	Chronic elevation of ALT during follow-up: Yes (n = 385)	Chronic elevation of ALT during follow-up: No (n = 1980)	P
Sex				
Female	800 (34)	138 (36)	662 (33)	.4
Male	1565 (66)	247 (64)	1318 (67)	
Age, median years (IQR)	38 (33–45)	40 (35–47)	38 (33–45)	<.001
Race				
White	1989 (84)	337 (88)	1652 (83)	.06
Black	234 (10)	23 (6)	211 (11)	
Hispanic	62 (3)	12 (3)	50 (3)	
Asian	77 (3)	12 (3)	65 (3)	
Other	3 (0.1)	1 (0.3)	2 (0.1)	
Mode of HIV infection				
Heterosexual sex	1242 (53)	217 (56)	1025 (52)	.1
MSM	982 (42)	150 (39)	832 (42)	
IDU	26 (1)	6 (2)	20 (1)	
Other	115 (5)	12 (3)	103 (5)	
Date of HIV infection diagnosis, median date (range)	May 2000 (Apr 1996–May 2004)	Sep 1997 (May 1994–Jan 2001)	Mar 2001 (Sep 1996–Oct 2004)	<.001
Baseline $CD4^+$ cell count				
Median cells/μL (IQR)	426 (269–614)	492 (313–695)	420 (264–597)	<.001
0–199 cells/μL	340 (14)	36 (9)	304 (15)	
200–499 cells/μL	1105 (47)	159 (41)	946 (48)	
⩾500 cells/μL	917 (39)	189 (49)	728 (37)	
Nadir $CD4^+$ cell count, median cells/μL (IQR)	249 (119–403)	216 (99–361)	256 (124–409)	.002
HIV RNA level in ART-naive patients, median $\log_{10}$ copies/mL (IQR)	4.5 (3.9–5.1)	4.5 (4.0–5.0)	4.5 (3.9–5.1)	.9
ART-treated patients with undetectable HIV RNA level	1649 (70)	239 (62)	1410 (71)	<.001
Peak HIV RNA level, median $\log_{10}$ copies/mL (IQR)	4.9 (4.1–5.4)	4.9 (4.3–5.3)	4.9 (4.1–5.4)	>.99
Previous clinical AIDS	402 (17)	81 (21)	321 (16)	.02
BMI, median value (IQR)	23 (21–25)	24 (22–26)	23 (21–25)	<.001
<18.5	98 (4)	13(3)	85 (4)	
18.5–24	1587 (68)	226 (59)	1361 (70)	
25–29	539 (23)	119 (31)	420 (21)	
⩾30	113 (5)	22 (6)	91 (5)	
Central obesity[a]	651 (28)	146 (38)	505 (26)	<.001
Lipodystrophy				
Atrophy	310 (13)	76 (20)	234 (12)	<.001
Fat accumulation	316 (13)	88 (23)	228 (12)	<.001
Diabetes mellitus	52 (2)	6 (2)	46 (2)	.3
Total cholesterol[b]				
Median mmol/L (IQR)	4.9 (4.2–5.8)	5.3 (4.5–6.4)	4.8 (4.1–5.7)	<.001
>6.5 mmol/L	275 (12)	78 (21)	197 (10)	
HDL cholesterol[b]				
Median mmol/L (IQR)	1.2 (1.0–5.8)	1.2 (1.0–6.4)	1.2 (1.0–5.7)	.8
<1.0 mmol/L (male patients) or <1.3 mmol/L (female patients)	885 (39)	144 (39)	741 (39)	
Triglycerides[b]				
Median mmol/L (IQR)	1.6 (1.0–2.6)	2.0 (1.3–3.6)	1.5 (1.0–2.4)	<.001
>1.7 mmol/L	1051 (46)	215 (58)	836 (44)	
Arterial hypertension[c]	1042 (44)	192 (50)	850 (43)	.01
Smoking status[d]				
Never	1274 (54)	210 (55)	1064 (54)	.03
Former	103 (4)	26 (7)	77 (4)	

Table 1. ***(Continued.)***

Variable	All subjects (n = 2365)	Chronic elevation of ALT during follow-up: Yes (n = 385)	Chronic elevation of ALT during follow-up: No (n = 1980)	P
Current	977 (42)	149 (39)	828 (42)	
Active IDU[d]	6 (0.3)	0 (0)	6 (0.3)	.3
Alcohol consumption[e]				
Mean g/day (IQR)	14.4 (6–20)	18.4 (6–20)	13.7 (6–20)	.4
None	646 (27)	108 (28)	538 (27)	.004
Light	1393 (59)	206 (54)	1187 (60)	
Moderate	220 (9)	42 (11)	178 (9)	
Severe	106 (4)	29 (8)	77(4)	
ART				
Naive	812 (34)	74 (19)	738 (37)	<.001
Currently interrupted	228 (10)	37 (10)	191 (10)	
Receiving treatment	1325 (56)	274 (71)	1051 (53)	
Duration, median years (IQR)	1.2 (0–5.0)	3.6 (0.4–5.7)	0.6 (0–4.8)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; HDL, high density lipoprotein; IDU, injection drug use; MSM, men who have sex with men.

[a] For central obesity definition, see Methods.

[b] Normal values are as follows: total cholesterol <6.5 mmol/L, HDL cholesterol >1 mmol/L for male patients and >1.3 mmol/L for female patients, and triglycerides <1.7 mmol/L.

[c] For arterial hypertension definition, see Methods.

[d] Smoking and active IDU within the 6 months prior to baseline visit.

[e] For alcohol consumption, we used the highest consumption value measured.

patients, >60 g/day), moderate (female patients, 20–40 g/day; male patients, 40–60 g/day) and light use (female patients, <20 g/day; male patients, <40 g/day) according to the World Health Organization definition.

Statistical analysis. We defined the incidence of chronic ALT elevation as the number of cases of chronic ALT elevation divided by the total number of person-years of follow-up (PYFU). Associations between incident chronic ALT elevation and demographic, clinical, anthropometric, and drug-related covariables were analyzed in univariable and multivariable Poisson regression models. Fixed covariables were sex, ethnicity, mode of HIV acquisition, and HIV Centers for Disease Control and Prevention (CDC) disease stage. For alcohol consumption, we used the highest consumption value measured, even when it was reported by patients after development of chronic elevation of ALT, assuming that drinking habits remain steady. Time-updated covariables were age, smoking status, BMI, central obesity, lipodystrophy, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, arterial hypertension, $CD4^+$ cell count, HIV RNA level, and continuous and categorical years of exposure to cART, the different drug classes (nucleoside reverse-transcriptase inhibitors [NRTIs], protease inhibitors [PIs] and nonnucleoside reverse-transcriptase inhibitors [NNRTIs]), and individual drugs. We focused on cumulative drug exposure and did not analyze current drug exposure. The end point of chronic ALT elevation is not suitable to detect acute effects of current drug exposure. In patients with an acute hepatotoxicity, the suspected drugs were changed immediately to a less toxic regimen, and persistent ALT elevation may be attributed to the new treatment, causing reverse causality problems [16]. We first built a multivariable model with demographic, clinical, and anthropometric covariables, including alcohol consumption. Next, we included cumulative exposure to the different drug classes and individual drugs. To disentangle the strong association with stavudine from associations with the other drugs, we repeated the multivariable models with inclusion of stavudine exposure. We did not formally check for interactions because of the high number of potential combinations but checked for effect modifications during the model building process. Characteristics of different patient groups were compared using χ^2 tests or Wilcoxon rank-sum tests; for mortality, Kaplan-Meier estimates and log-rank test were used. All analyses were performed using Stata software, version 10.1 (Stata).

RESULTS

Patient characteristics. Of 8435 SHCS participants seen between 1 January 2002 and 31 December 2007, 3255 (39%) were HBV and HCV negative. Of these patients, we excluded 760 with <3 follow-up visits, gaps in follow-up, or missing data. A total of 130 patients (5%) were excluded because of preexisting elevated ALT levels at time before or at time of baseline visit (these patients had a significantly longer median period of exposure to ART, compared with that for patients without prev-

Table 2. Univariable and Multivariable Poisson Regression of Demographic, Clinical, and Anthropometric Covariables Potentially Affecting the Risk of Developing Chronic Elevation of Alanine Aminotransferase (ALT) Levels Based on 2365 Individuals with 385 Events Followed Up for 9972 Person-Years

Variable	IR per 1000 PYFU (95% CI)	IRR univariable models (95% CI)	IRR multivariable model [a] (95% CI)
Sex			
Female	40 (33–47)	1	1
Male	38 (34–43)	0.96 (0.78–1.19)	0.84 (0.63–1.11)
Age, per 10 years		1.06 (0.97–1.17)	1.0 (0.90–1.11)
Race			
White	40 (36–44)	1	1
Black	24 (16–36)	0.60 (0.39–0.91)	0.52 (0.33–0.82)
Hispanic	50 (28–88)	1.25 (0.70–2.23)	1.14 (0.64–2.06)
Asian	42 (24–73)	1.05 (0.59–1.86)	1.11 (0.62–2.01)
Unknown	67 (9–473)	1.67 (0.23–11.9)	2.22 (0.31–16.0)
Mode of HIV infection			
Heterosexual sex	40 (35–46)	1	1
MSM	38 (32–44)	0.94 (0.76–1.15)	1.03 (0.79–1.36)
IDU	47 (21–104)	1.16 (0.52–2.61)	1.38 (0.61–3.14)
Other	25 (14–44)	0.62 (0.35–1.11)	0.62 (0.35–1.12)
$CD4^+$ cell count, cells/μL			
0–199	34 (22–53)	0.80 (0.49–1.27)	0.61 (0.37–1.01)
200–499	35 (30–41)	0.81 (0.66–0.99)	0.73 (0.58–0.91)
⩾500	43 (38–49)	1	1
Nadir $CD4^+$ cell count, cells/μL			
0–199	41 (36–47)	1.01 (0.70–1.45)	1.33 (0.89–1.99)
200–499	36 (30–42)	0.88 (0.61–1.26)	1.02 (0.70–1.50)
⩾500	41 (29–57)	1	1
HIV RNA level			
0–10,000 copies/mL	37 (33–42)	1	1
10,000–100,000 copies/mL	39 (29–52)	1.05 (0.77–1.43)	1.22 (0.88–1.70)
⩾100,000 copies/mL	69 (46–103)	1.85 (1.22–2.80)	2.23 (1.45–3.43)
BMI			
<18.5	22 (12–41)	0.66 (0.35–1.24)	0.64 (0.34–1.21)
18.5–24	34 (30–38)	1	1
25–29	51 (43–61)	1.52 (1.22–1.89)	1.56 (1.24–1.96)
⩾30	57 (40–81)	1.69 (1.16–2.45)	1.70 (1.16–2.51)
Smoking status			
Never	40 (34–47)	1	1
Former	47 (39–57)	1.17 (0.91–1.50)	1.04 (0.79–1.38)
Current	33 (28–39)	0.81 (0.64–1.02)	0.79 (0.62–1.00)
Alcohol consumption			
None	40 (33–48)	1	1
Light	35 (31–40)	0.89 (0.70–1.12)	0.91 (0.71–1.16)
Moderate	44 (32–59)	1.10 (0.77–1.57)	1.13 (0.78–1.62)
Severe	67 (46–96)	1.68 (1.12–2.53)	1.83 (1.19–2.80)

NOTE. BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CI, confidence interval; IDU, injection drug use; IR, incidence rate; IRR, incidence rate ration; MSM, men who have sex with men; PYFU, person-years of follow-up.

[a] Adjusted for all variables listed. Age, $CD4^+$ cell count, nadir $CD4^+$ cell count, HIV RNA level, BMI, and smoking status were analyzed as time-updated covariables. For alcohol consumption, we used the highest consumption value measured.

Table 3. Multivariable Poisson Regression of Combination Antiretroviral Therapy (cART), Different Antiretroviral Classes, and Single Drugs (Time-Updated Cumulative Exposure) Potentially Affecting the Risk of Developing Chronic Elevated Alanine Aminotransferase (ALT) Levels

Antiretroviral therapy or individual antiretroviral drugs per year exposure	IRR from univariable models (95% CI)	*P*	IRR from multivariable models[a] (95% CI)	*P*	IRR from multivariable models including stavudine exposure[b] (95% CI)	*P*
cART	1.04 (1.01–1.07)	.015	1.05 (1.01–1.08)	.015	1.00 (0.96–1.04)	.9
NRTI	1.05 (1.02–1.08)	<.001	1.06 (1.03–1.09)	<.001	1.03 (0.99–1.07)	.1
Unboosted PI	1.06 (1.02–1.11)	.002	1.07 (1.02–1.11)	.003	1.03 (0.98–1.07)	.3
Boosted PI	1.02 (0.97–1.07)	.5	1.01 (0.96–1.07)	.6	0.98 (0.93–1.04)	.5
NNRTI	1.03 (0.98–1.08)	.2	1.03 (0.98–1.08)	.2	1.01 (0.96–1.06)	.6
NRTI, by drug						
Stavudine	1.11 (1.07–1.16)	<.001	1.12 (1.07–1.17)	<.001	…	…
Zidovudine	1.02 (0.99–1.05)	.3	1.02 (0.98–1.06)	.3	1.04 (1.00–1.08)	.028
Didanosine	1.06 (1.00–1.12)	.045	1.07 (1.01–1.13)	.024	1.03 (0.97–1.09)	.4
Lamivudine	1.04 (1.01–1.07)	.019	1.04 (1.00–1.08)	.039	1.02 (0.98–1.05)	.4
Abacavir	0.10 (0.94–1.05)	.9	0.99 (0.93–1.04)	.7	0.98 (0.93–1.04)	.5
Emtricitabine	0.44 (0.25–0.77)	.004	0.45 (0.25–0.78)	.005	0.47 (0.27–0.82)	.008
Tenofovir	0.96 (0.86–1.06)	.4	0.96 (0.86–1.07)	.5	0.93 (0.84–1.04)	.2
PI, by drug						
Nelfinavir	1.07 (1.02–1.12)	.006	1.07 (1.02–1.12)	.007	1.03 (0.98–1.09)	.2
Lopinavir	1.02 (0.95–1.11)	.6	1.02 (0.94–1.11)	.7	1.01 (0.93–1.10)	.8
Saquinavir	1.05 (0.97–1.13)	.2	1.04 (0.96–1.12)	.3	0.97 (0.89–1.05)	.4
Indinavir	1.05 (0.98–1.12)	.2	1.03 (0.97–1.10)	.3	1.00 (0.93–1.07)	>.99
Atazanavir	0.91 (0.76–1.09)	.3	0.89 (0.74–1.07)	.2	0.87 (0.73–1.04)	.1
Ritonavir, full dose	0.98 (0.87–1.11)	.7	0.98 (0.87–1.12)	.8	0.95 (0.83–1.09)	.5
NNRTI, by drug						
Efavirenz	0.99 (0.94–1.05)	.8	0.99 (0.94–1.05)	.8	0.98 (0.92–1.04)	.5
Nevirapine	1.10 (1.02–1.18)	.012	1.10 (1.02–1.18)	.013	1.07 (0.99–1.15)	.07

NOTE. IRR, incidence rate ratio; NNRTI nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.
[a] The different drugs were individually adjusted for the covariables listed in Table 2.
[b] The different drugs were individually adjusted for the covariables listed in Table 2 and the cumulative exposure to stavudine per year.

alent elevated ALT levels, particularly to stavudine and zidovudine; data not shown). The present study is thus based on 2365 HIV-infected individuals with normal ALT values at baseline visit (Figure 1).

Baseline characteristics of patients with and patients without incident chronic elevation of ALT during follow-up are summarized in Table 1. The proportion of men was 66%. The median age of the patients was 38 years, and 84% were white. Baseline and nadir (ie, lowest ever) $CD4^+$ lymphocyte counts were 426 and 249 cells/μL, respectively. Median duration of antiretroviral therapy was 1.2 years; 34% of patients were treatment naive, 10% had interrupted ART, and 56% were receiving treatment. HIV RNA levels were below the level of detection in 70% of ART-treated patients. Several of the baseline variables were associated with the development of chronic ALT elevation.

During the follow-up period, 385 patients (16%) developed chronic elevated ALT levels during 9972 PYFU, resulting in an incidence of 3.9 cases per 100 PYFU (95% CI, 3.5–4.3 cases per 100 PYFU). The incidence significantly decreased over time, with an IRR of 0.84 (95% CI, 0.79–0.88) per year. The incidence was 5.6 cases per 100 PYFU (95% CI, 4.7–6.8 cases per 100 PYFU) during the period 2002–2003, 4.5 cases per 100 PYFU (95% CI, 3.8–5.3 cases per 100 PYFU) during the period 2004–2005, and 2.8 cases per 100 PYFU (95% CI, 2.3–3.3 cases per 100 PYFU) during the period 2006–2008.

Univariable and multivariable models. The results of the univariable and multivariable Poisson regression analyses are displayed in Table 2. Black ethnicity and $CD4^+$ cell count of 200–500 cells/μL, compared with >500 cells/μL, were negative predictors for chronic elevated ALT levels. An HIV RNA level >100,000 copies/mL was a strong positive predictor. There was no effect of age, sex, HIV transmission category, CDC stage C, nadir $CD4^+$ cell count, smoking, and receipt of medications other than ART, except lipid-lowering drugs, on the incidence of chronic elevated ALT levels. Results of the univariable and multivariable model were identical.

Association of metabolic parameters and chronic elevated ALT levels. In univariable and multivariable analysis, in-

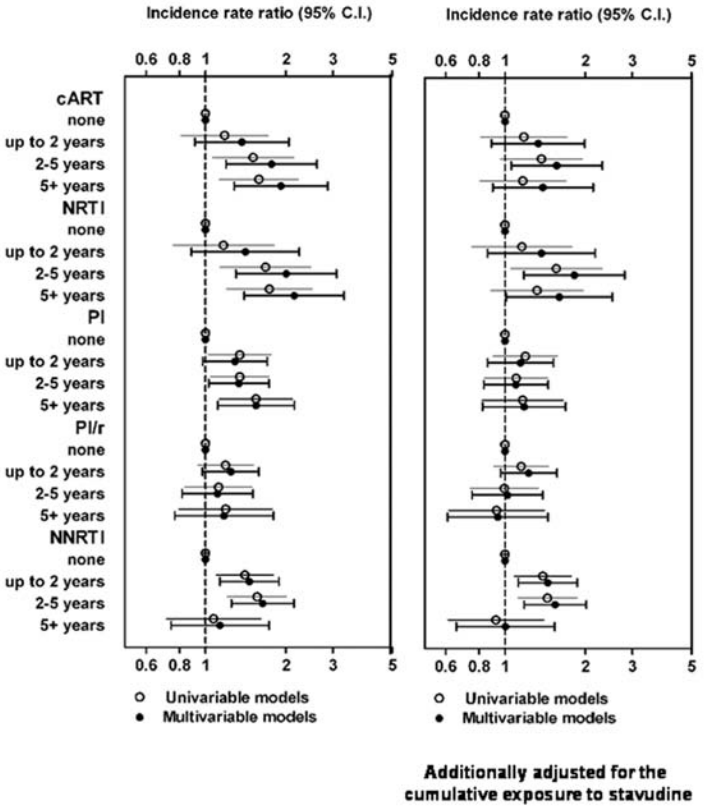

Figure 2. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the development of new chronic elevation of alanine aminotransferase (ALT) levels based on 385 events among 2365 participants with 9972 person years of follow-up. Shown are associations with receipt of combination antiretroviral therapy (cART) and specific drug classes for 0 years, 2 years, 5 years, and >5 years. *Left panel*, multivariable models were individually adjusted for the variables listed in Table 2. *Right panel,* multivariable models were individually adjusted for the variables listed in Table 2 and cumulative exposure to stavudine. cART, combination antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted protease inhibitor.

creased BMI was significantly associated with chronic elevated ALT levels (BMI of 25–29.9 was associated with an IRR of 1.56 [95% CI, 1.24–1.96]; BMI of ⩾30 was associated with an IRR of 1.70 [95% CI, 1.16–2.51]). Other risk factors for nonalcoholic fatty liver disease [17, 18], including central obesity (IRR, 1.66; 95% CI, 1.36–2.03), lipoatrophy (IRR, 1.50; 95% CI, 1.19–1.90), lipohypertrophy (IRR, 1.79; 95% CI, 1.43–2.23), hypercholesterolemia (IRR, 1.63; 95% CI, 1.25–2.12), hypertrigliceridemia (IRR, 1.75; 95% CI, 1.43–2.15), use of lipid-lowering drugs (IRR, 1.48; 95% CI, 1.11–1.98), and arterial hypertension (IRR, 1.27; 95% CI, 1.04–1.55) were also predictors for chronic elevated ALT levels in the univariable analyses, but these variables were not included in the multivariable model because of collinearity or the same causal pathway. Diabetes mellitus was not statistically significant in the univariable analysis (IRR, 1.05; 95% CI, 0.59–1.87).

Association of alcohol use and chronic elevated ALT levels. We analyzed the contribution of severe, moderate, and light alcohol use to the development of elevated ALT levels in univariable and multivariable models. Only severe alcohol use was significantly associated with the incidence of elevated ALT levels; moderate and light alcohol use showed no association.

Association of ART and chronic elevated ALT levels. Associations of ART and chronic elevated ALT are shown in Table 3 and Figure 2. Cumulative exposure (as a continuous variable) to cART, NRTIs, and unboosted PIs increased the risk of developing chronic elevated ALT in the univariable and multivariable model. Among individual antiretroviral drugs, the strongest relationship with chronic elevated ALT levels was with exposure to stavudine (IRR per year of exposure, 1.12; 95% CI, 1.07–1.17; $P < .001$). There was also a significant effect of didanosine, lamivudine, nelfinavir, and nevirapine. However, after adjustment for stavudine exposure, none of the antiretroviral classes or individual drugs remained significant. After adjusting to stavudine, exposure to zidovudine was associated with an increased risk of chronic ALT elevation, whereas exposure to emtricitabine was conversely associated (Table 3). When we stratified cumulative exposure into categorical variables (never, <2 years, 2–5 years, >5 years), cART, NRTI, and unboosted PI exposure ⩾2 years were a risk factor for chronic

elevated ALT levels but did not remain predictive after adjustment for stavudine exposure. NNRTI exposure of <5 years duration showed an association with elevated ALT level (Figure 2). Nevirapine as a categorical variable was a risk factor for chronic ALT elevation with short-term use (<2 years) with and without adjustment for stavudine exposure (data not shown).

Sensitivity analyses. In separate models, we analyzed ⩾3 consecutive elevated ALT values instead of ⩾2 at semiannual visits. The incidence for 3 consecutive elevated ALT values was 2.1 cases per 100 PYFU (95% CI, 1.9–2.4 cases per 100 PYFU) in 228 patients with 10,628 PYFU. Univariable and multivariable evaluations with this modified definition yielded consistent results.

Clinical outcome. Four (1.0%) of the patients with elevated ALT levels versus 30 (1.5%) of the patients without elevated ALT levels died. Five-year mortality did not differ significantly between patients with and patients without development of chronic elevated ALT levels: 0.3% (95% CI, 0.04%–2.2%) versus 1.6% (95% CI, 1.1%–2.5%), respectively ($P = .14$). Reasons for death in the elevated ALT group were suicide, myocardial infarction, bladder cancer, and acute peritonitis.

At last visit, 86.0% of the patients with elevated ALT levels versus 78.8% of those with normal ALT levels were receiving ART, 9.6% versus 10.8% had interrupted ART, and 4.4% versus 10.4% were ART naive ($P = .001$). For those who were receiving ART, HIV load was suppressed equally in both groups (87% vs 85%), and the median $CD4^+$ cell count was 593 cells/μL (range, 430–767 cells/μL) versus 525 cells/μL (range, 384–714 cells/μL). Number of treatment changes per year, including treatment switches and interruptions, did not differ between the 2 groups (data not shown).

DISCUSSION

In this large longitudinal cohort analysis, the incidence of chronic elevated ALT levels (ie, elevation for ⩾6 months) was 3.9 cases per 100 PYFU. In adjusted analyses, increased BMI, high alcohol use, and prolonged exposure to stavudine and zidovudine were associated with chronic ALT elevation.

In contrast to cross-sectional analyses, in which the temporal sequence of exposure and outcome is often not ascertained, the longitudinal design chosen for our study should allow for a more precise determination of predictors. To our knowledge, there are no data available for the incidence of ALT elevation in an HIV-infected population without chronic viral hepatitis. However, several studies have reported on the prevalence of elevated ALT levels in the general population and among HIV-infected persons. The large National Health and Nutrition Examination Survey (NHANES) III study, representing a civilian noninstitutionalized population in the United States, found a prevalence of 13.5% in HCV- and HBV-negative individuals [19]. A German cohort study of orthopedic surgery patients without chronic viral hepatitis noted a prevalence of 11.3% [20] and in HIV-infected persons without viral hepatitis the prevalence was in the same range with 15% [11]. These figures are in accordance with our study with a prevalence of 13.2% in a single ALT measurement at baseline (data not shown).

Our results confirm that the main causes of chronic liver disease in HIV-infected patients without hepatitis B and C co-infections are alcohol consumption, non-alcoholic fatty liver disease (NAFLD) and antiretroviral drugs.

Several mechanisms of antiretroviral drugs resulting in liver enzyme elevation have been postulated: mitochondrial toxicity related to NRTIs, hypersensitivity, primarily caused by nevirapine and metabolic injury, mainly associated to PIs through their effects on metabolic factors [21]. In our analysis the strongest relationship with the development of chronic elevated ALT was with exposure to stavudine. Furthermore, with decreasing stavudine use over time, the incidence of ALT elevation was significantly decreasing during the observation period. The association with this dideoxynucleoside analogues does not surprise, as it is a strong inhibitor of mitochondrial DNA synthesis resulting in a high mitochondrial toxicity [22]. Stavudine has been implicated in the development of hepatic steatosis [23, 24]. The other dideoxynucleoside analogues, didanosine, has recently been postulated as a cause for noncirrhotic portal hypertension [25, 26], but in our study showed only a trend with chronic elevated ALT. Nevirapine, known to cause early acute hepatitis produced by a hypersensitivity mechanism [27], was associated with elevated ALT as a categorical variable during the first 2 years of exposition (data not shown).

It was to be expected that the traditional risk factors for non-alcoholic fatty liver disease, namely increased BMI, central obesity, lipodystrophy and dyslipidemia, as well as severe alcohol consumption were associated with the development of elevated ALT, a surrogate marker for hepatic steatosis [28]. Hepatic steatosis is common in HIV-infected persons with metabolic abnormalities with [23, 29] and without HCV co-infection [9, 30, 31]. In addition to the metabolic aberrations and severe alcohol use, ART-related mitochondrial toxicity might also contribute to hepatic steatosis, but hepatic steatosis might also be a predisposing factor for antiretroviral hepatotoxicity [32]. This needs to be further evaluated.

Our finding of black ethnicity as a negative predictor for ALT elevation is in agreement with other investigations, which found an inverse association of black ethnicity and NAFLD in the general population [33] and among HIV-infected patients [24, 31, 34]. However, it is unknown whether ethnic or genetic factors may play a role in protecting from hepatopathy.

Similar to 2 other reports, our study found that a high HIV load was an independent risk factor for the development of chronic elevated ALT levels [11] and steatosis [29]. The mechanisms associated with this observation are possibly attributa-

ble to immune activating and pro-apoptotic effects of HIV on hepatocytes, which have been demonstrated in several studies (reviewed in [35]).

The NHANES III study found a strong association between liver-related mortality and elevated ALT levels in a cohort of patients from the general population without chronic viral hepatitis [19]. In addition, elevated ALT levels in HIV-infected patients reported as adverse events cause by ART was associated with a higher mortality independently from chronic viral hepatitis co-infection [36]. This is in contrast to our data, which did not show a higher mortality, presumably because of a relatively short observation period.

The strengths of this study are the large number of patient-years with prospectively collected anthropometric, laboratory, and clinical data, including the assessment of alcohol use. ALT determination was according to study protocol and was not triggered by symptoms or clinical events. Limitations include the use of a laboratory surrogate marker (ie, elevated ALT level) as a sign for hepatopathy, instead of examination of liver tissue. However, liver biopsies were not feasible in this large epidemiologic study, and elevated ALT level is considered to be a highly specific indicator for liver injury, which is the most commonly used marker for chronic liver disease. Regarding the high intraindividual variability of liver tests [37], we used 2 consecutive elevated ALT values over a period of 6 months. Because we excluded patients with preexisting elevated ALT levels at baseline (these patients had longer exposure to ART, particularly to NRTIs), the incidence of chronic ALT elevation in patients receiving ART may be underestimated. We did not consider hemochromatosis, autoimmune hepatitis, or infections other than HCV and HBV infection, such as hepatitis A virus, cytomegalovirus, or Epstein-Barr virus infections, but as they are very infrequent causes of chronic elevation of ALT levels among HIV-infected persons, no significant influence on the analysis would be expected. Finally, results from cohort analyses need to be interpreted with caution because of the potential for unmeasured confounding.

In summary, we evaluated the incidence of and factors associated with chronic elevated ALT levels among HIV-infected patients without HBV and HCV co-infection. Chronic ALT elevation is frequent in this population. Besides those factors classically recognized as predisposing to hepatic steatosis in HIV-negative individuals, such as being overweight and having elevated alcohol consumption, high HIV RNA levels and exposure to stavudine and zidovudine were associated with chronic elevated ALT levels. Our findings may have clinical implications, given that several studies suggest an association of chronic elevated ALT levels and an increased mortality [19, 36] and a high rate of severe histological abnormalities [9]. Early recognition and management of metabolic factors (eg, being overweight or having dyslipidemia), prevention or treatment of severe alcohol use, early initiation of cART if the HIV RNA level is high, and avoidance of stavudine and zidovudine are recommended in patients with chronically elevated ALT levels. Long-term follow-up is needed to assess whether chronic ALT elevation will result in increased morbidity or mortality.

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Acknowledgments

Financial support. This study has been financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation.

Potential conflicts of interest. H.K. has received travel grants from Abbott and Tibotec. B.L. has received travel grants, grants, or honoraria from Abbott, Aventis, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Roche, and Tibotec. M.B. has received travel grants, grants, or honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche, and Tibotec. A.R. has received travel grants or speakers honoraria from Essex, Abbott, Roche, and GlaxoSmithKline. E.B. received honoraria or travel grants from Abbott, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Merck Sharp & Dome, Pfizer, and Tibotec. N.J.M. has received grants from Novartis and Roche. 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. All other authors: no conflicts.

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