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Antiretroviral Treatment and Osteonecrosis in Patients of the Swiss HIV Cohort Study: A Nested Case-Control Study

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ABSTRACT

We examined risk factors for avascular bone necrosis (AVN) particularly focusing on the question of whether antiretroviral treatment (ART) is associated with the emergence of osteonecrosis. After 11 years of following the entire cohort, 26 patients were found to have AVN. Compared to 260 concurrent HIV-infected controls, at risk when cases were diagnosed, patients with AVN had lower CD4 cell count nadirs (median 86.5 versus 137.5 cells/μl, $p = 0.010$) and suffered significantly more often from *Pneumocystis* pneumonia, cerebral toxoplasmosis, CMV retinitis, and atypical mycobacteriosis and had a significantly higher body mass index than controls. Duration of ART before AVN was not significantly different between cases and controls (2.92 versus 2.17 years, $p = 0.30$). In conclusion, AVN could not be attributed to time on antiretroviral treatment, but patients with AVN had histories of more severe immunosuppression and a higher body mass index than controls.

INTRODUCTION

MORBIDITY AND MORTALITY of HIV infection have improved substantially with the wide use of highly active antiretroviral therapy (HAART). The focus of health care providers in the developed world has shifted to management of increasingly complex drug regimens and of their associated toxicities such as hyperlactatemia, hyperlipidemia, fat redistribution, and bone mineral abnormalities.[1–3]

Osteonecrosis has repeatedly been described in patients infected with HIV.[4–9] Remarkably, avascular necrosis (AVN) in immunodeficient patients often occurs at multiple sites,[5,10] suggesting that an underlying systemic process may be present. Classical osteonecrosis, also termed avascular necrosis, denotes ischemic death of bone tissue. Risk factors include hyperlipidemia, smoking, alcohol consumption, corticosteroid treatment, hemodialysis, sickle cell disease, pancreatitis, Gaucher's disease, collagen vascular disease, irradiation, and hypercoagulability.[11,12] Some patients with AVN and HIV had an underlying condition that put them at risk for avascular necrosis. In others, no such risk factors could be identified, suggesting that HIV infection itself, associated comorbidities, or antiretroviral treatment were predisposing factors. Some have speculated that immune reconstitution[13,14] and hyperlipidemia, in particular hypertriglyceridemia secondary to protease inhibitor therapy, were possible etiological factors.[5,14] A link between AVN of the hip and the use of megestrol acetate has also been suggested.[15]

The incidence of avascular bone necrosis and bone mineral density abnormalities among HIV-infected patients seems to be increasing.[7–9,16] However, it is not clear whether more frequent recognition, prolonged survival of HIV-infected patients, or the use of potent antiretroviral therapy is responsible for the apparent increase in AVN. Previous studies consisted mainly of case reports and small case series. The present investigation evaluates potential risk factors for AVN using the large longitudinal database of the Swiss HIV Cohort Study before and dur-

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ing the HAART era, in particular testing the hypothesis of whether antiretroviral treatment and its duration are associated with osteonecrosis.

MATERIALS AND METHODS

The Swiss HIV Cohort study is a prospective cohort study with continuing enrollment of HIV-1-infected patients aged 16 years or older.[17] Patients are followed in one of seven outpatient clinics. Enrollment is independent of disease stage or degree of immunosuppression. Information is collected according to defined criteria at registration and follow-up visits every 6 months. Signs of lipodystrophy are also assessed every 6 months by determining the waist-to-hip ratio and clinical signs such as fat loss of extremities, abdomen, and face or fat accumulation of neck, belly, or cheeks. Comparisons with the national HIV registry have shown that the cohort includes 70% of patients with AIDS in Switzerland. CD4 lymphocyte count is measured by flow cytometry, and HIV-1 RNA by the Amplicor test (Roche Diagnostics, Rotkreuz, Switzerland; level of detection 400 copies/ml until January 1, 1998, thereafter 50 copies/ml or lower). Additional viral loads and CD4 values from routine consultations are also recorded. Antiretroviral therapy (ART) contains drug regimens (single or dual therapy) before the implementation of HAART. HAART, defined as combinations including at least three drugs with at least one protease inhibitor, a nonnucleoside reverse transcriptase inhibitor (NNRTI), or abacavir, has gradually been introduced in Switzerland since 1995. Clinical stage is defined according to the 1993 Centers for Disease Control and Prevention classification system for HIV-1 infection.

Cases of AVN were retrospectively identified from the records of HIV clinics by physicians caring for HIV-infected patients. For each case we randomly selected 10 control patients from the SHCS without known osteonecrosis who were registered in the same year and were actively followed up to at least the date when the corresponding case was diagnosed with osteonecrosis.

A chart review of all cases was performed and data were extracted using a standarized data collection sheet. A patient was defined as having AVN when there was both a clinical (bone pain) and a radiographic diagnosis (magnetic resonance imaging). Patients with AVN were then compared to the control cohort with regard to demographic characteristics as well as laboratory and treatment-related parameters. In case patients we also evaluated further risk factors previously associated with AVN such as a local trauma, use of steroids, hypercoagulable state, and life style habits such as bodybuilding and alcohol consumption. These data were not available for controls. For cases and corresponding controls, follow-up and exposure times were censored at the date the case was diagnosed with AVN. Associations between AVN and the following factors were assessed by uni- and multivariable conditional logistic regression analysis: demographics, life-style factors (BMI and smoking status), CD4 nadir and maximum viral load, and exposure times to different drugs and drug classes. For the multivariable models we considered demographic and life-style parameters as well as other factors with $p < 0.2$ in the univariable analysis. However, due to colinearity between several factors and limited number of cases we had to restrict the number of variables in the multivariable models. For statistical analysis we used Stata software (version 7/SE). All p values are two-sided.

RESULTS

The search for AVN patients in a cohort of more than 4500 patients identified 28 AVN diagnoses in 26 patients over a period of almost 11 years (annual incidence = 0.06%). We therefore compared 26 cases to 260 concurrent controls. All AVN patients had documented lesions in magnetic resonance imaging. Fourteen patients had osteonecrosis of one hip; eight patients had both hips involved. Two patients had AVN of both knees, one patient of one knee, and another one had osteonecrosis of the os naviculare of his left foot. There was a constant increase of cases throughout the study period. Only four cases were found before 1995, eight additional cases from 1996 to 1998, and 17 cases from 1999 to 2002.

Characteristics available for both cases and controls as well as p values from conditional logistic regression are summarized in Table 1. The median age at registration was 33 years in patients with AVN and 32 years in the control group. Five patients were female and 21 male. Transmission modes for acquiring HIV infection were intravenous drug use ($n = 8$), heterosexual ($n = 8$), or homosexual intercourse ($n = 8$). In one patient the source of infection was unknown and in another patient a blood-borne transmission was likely. The median years of follow-up from registration until the diagnosis of AVN or censoring, respectively, was 5.51 in cases versus 5.46 years in controls ($p = 0.92$) reflecting proper selection of controls. Serologies for hepatitis C and B virus (HCV, HBV), cytomegalovirus (CMV), and toxoplasmosis did not differ between the two groups.

Compared to 260 concurrent controls from the SHCS, individuals with AVN had a significantly lower CD4 nadir (median 86.5 versus 137.5 cells/μl, $p = 0.010$), and a trend toward higher maximum HIV-1 RNA values (median log 5.29_{10} versus log 4.98_{10}, $p = 0.12$). AVN and control patients started ART and HAART at similar times. At the timepoint of initiation of ART the median HIV RNA level was higher in cases than in controls (5.46 versus 4.49 $\log_{10}$ copies/ml, $p = 0.014$). Median duration of exposure to ART was longer in cases than in controls but did not reach statistical significance (2.92 versus 2.17 years, $p = 0.30$). There was a trend that AVN patients had a higher cumulative antiretroviral class exposure compared to the control patients (PI: 1.42 years versus 0.25 years, $p = 0.057$; NNRTI: 0 years versus 0 years, $p = 0.037$; NRTI: 4.34 years versus 3.01 years, $p = 0.062$), while exposure to individual antiretroviral drugs was not increased in AVN patients with the exception of efavirenz ($p = 0.017$), yet exposure time was very short. This greater use of efavirenz, however, is primarily explained by the trend toward earlier start with ART in cases and subsequent use of efavirenz in salvage therapy. The median increase in CD4 count after the initiation of HAART until diagnosis of AVN did not differ between cases and controls (1 year: 66 versus 96.5 cells/μl, $p = 0.44$; 2 years: 160 versus 157.5 cells/μl, $p = 0.99$). Pyrimethamine was prescribed significantly more often in patients with AVN ($p = 0.044$). There was a higher frequency of opportunistic infections (cere-

Table 1. Characteristics from Patients with AVN and Controls[a]

Patient characteristics	*Patients with AVN (n = 26)*	*Control group (n = 260)*	p *value*
Demographic data			
Median age at registration (IQR) (years)	33 (28–43)	32 (28–39)	0.35
Median height (IQR) (cm)	172 (170–178)	174 (168–179)	0.34
Gender			
Female (%)	5 (19.23)	75 (28.85)	0.30
Male (%)	21 (80.77)	185 (71.15)	
Risk factors for HIV infection			0.24
Homosexual (%)	8 (30.77)	85 (32.69)	
Heterosexual (%)	8 (30.77)	80 (30.77)	
IV drugs (%)	8 (30.77)	91 (35.0)	
Other (%)	1 (3.85)	0 (0)	
Unknown (%)	1 (3.85)	4 (1.54)	
Median date of HIV diagnosis (IQR)	5/1991 (11/1988–5/1994)	6/1991 (5/1987–10/1994)	0.78[b]
Median registration date in cohort (IQR)	3/1994 (5/1986–5/2000)	4/1994 (1/1986–3/2000)	0.99[b]
Median years of follow-up (IQR)	5.51 (1.75–8.30)	5.46 (1.42–8.26)	0.92
Life-style factors[c]			
Ever smoked (%)	22 (88.0)	165 (75.34)	0.18
Median BMI (kg/m^2) (IQR)	22.85 (20.37–25.71)	22.04 (20.4–23.83)	0.020
Fat loss (%)[d]	13 (52.0)	71 (32.42)	0.054
Fat accumulation (%)[d]	13 (52.0)	71 (34.42)	0.055
Medical history[c]			
Diabetes mellitus (%)	2 (8.0)	4 (1.83)	0.081
Hypertension (%)	8 (32.0)	46 (21.30)	0.21
C/B-defining events until diagnosis of AVN[e]			
Pneumocystis pneumonia (%)	6 (23.08)	15 (5.77)	0.003
Cerebral toxoplasmosis (%)	3 (11.54)	1 (0.38)	0.003
CMV retinitis (%)	3 (11.54)	2 (0.77)	0.006
Atypical mycobacteriosis (%)	3 (11.5)	5 (1.92)	0.014
Medication[f]			
ART and HAART			
Median year of starting ART (IQR)	1995 (1994–1997)	1996 (1994–1997)	0.88
Median year of starting HAART (IQR)	1997 (1996–1998)	1997 (1996–1998)	0.079
Median duration of ART until diagnosis of AVN (IQR) (years)	2.92 (0.41–6.00)	2.17 (0–5.30)	0.30
Median duration of HAART until diagnosis of AVN (IQR) (years)	2.27 (0–4.51)	0.66 (0–3.29)	0.18
Median cumulative ARV class exposure until diganosis of AVN (IQR) (years)			
Protease Inhibitors	1.42 (0–4.51)	0.25 (0–2.98)	0.057
NNRTI	0 (0–0.068)	0 (0–0)	0.037
NRTI	4.34 (0.82–10.64)	3.01 (0–7.98)	0.062
Median cumulative HAART/ART exposure until diagnosis of AVN			
Lamivudine			
% of patients who had medication	69	57	
IQR (years)	1.17 (0–3.12)	0.63 (0–2.42)	0.19
Zidovudine			
% of patients who had medication	65	59	
IQR (years)	1.38 (0–2.42)	0.50 (0–2.09)	0.12
Stavudine			
% of patients who had medication	50	43	
IQR (years)	0.042 (0–2.67)	0 (0–1.79)	0.47
Didanosine			
% of patients who had medication	46	36	
IQR (years)	0 (0–0.75)	0 (0–0.42)	0.94
Efavirenz			
% of patients who had medication	23	15	
IQR (years)	0 (0–0)	0 (0–0)	0.017
Indinavir			
% of patients who had medication	54	31	
IQR (years)	0.12 (0–1.42)	0 (0–0.42)	0.093

(*continued*)

TABLE 1. CHARACTERISTICS FROM PATIENTS WITH AVN AND CONTROLS[a] (CONT'D)

Patient characteristics	*Patients with AVN (n = 26)*	*Control group (n = 260)*	p *value*
Nelfinavir			
% of patients who had medication	42	28	
IQR (years)	0 (0–0.42)	0 (0–0.38)	0.72
Rifonavir			
% of patients who had medication	38	25	
IQR (years)	0 (0–0.50)	0 (0–0.08)	0.24
Saquinavir			
% of patients who had medication	31	20	
IQR (years)	0 (0–0.25)	0 (0–0)	0.98
Median exposure to opportunistic infection prophylaxis/treatment			
Cotrimoxazole			
% of patients who had medication	53.87	40.38	
IQR (years)	0.29 (0–1.67)	0 (0–1.58)	0.60
Pyrimethamine			
% of patients who had medication	23	3.85	
IQR (years)	0 (0–0)	0 (0–0)	0.044
Fluconazole			
% of patients who had medication	19	10	
IQR (years)	0 (0–0)	0 (0–0)	0.40
Laboratory values			
Median nadir CD4 count (IQR) (cells/μl)	86.5 (15–141)	137.5 (50–266)	0.010
Median CD4 count at start of ART (IQR) (cells/μl)[g]	226.5 (57–300)	227 (110–340)	0.37
Median CD4 response to HAART until diagnosis of AVN	1 year: 66 (12–158)	1 year: 96.5 (26.5–204)	0.44
or last follow-up (IQR) (cells/μl)[h]	2 years: 160 (97–273)	2 years: 157.5 (78–272)	0.99
Median area under CD4 curve (IQR) (cells/μl)[i]	296 (193–364)	370 (228–501)	0.035
Median CD8 count (IQR) (cells/μl)	639.5 (443–1110)	781.5 (554.5–1095)	0.29
Median of highest HIV RNA (IQR) ($\log_{10}$ copies/ml)	5.29 (4.71–5.67)	4.98 (4.28–5.48)	0.12
Median HIV RNA at start of ART (IQR) ($\log_{10}$ copies/ml)[j]	5.46 (4.30–5.62)	4.49 (3.98–5.03)	0.014
Median area under RNA curve (IQR) ($\log_{10}$ copies/ml)[i]	3.15 (2.78–3.76)	3.36 (2.84–4.12)	0.15
Median hemoglobin (IQR) (g/dl)[k]	13.85 (12.6–14.2)	14.0 (12.65–15.1)	0.24
Median lymphocytes (IQR) ($\times 10^9$/liter)[k]	1.23 (0.84–1.94)	1.69 (1.2–2.21)	0.062
Median leucocytes (IQR) ($\times 10^9$/liter)[k]	4.7 (3.5–6.82)	5.26 (4.16–6.78)	0.49
Median platelets (IQR) ($\times 10^9$/liter)[k]	204 (156–262)	210.5 (167.5–255)	0.80
Median fasting cholesterol level (IQR) (mmol/liter)[c]	5.3 (4.5–6.3)	5.05 (4.15–6.35)	0.90
Median fasting triglycerides (IQR) (mmol/liter)[c]	3.9 (1.9–4.78)	1.77 (1.2–3.37)	0.30

[a]IQR, interquartile range; HAART, highly active antiretroviral therapy; ART, antiretroviral therapy; AVN, avascular bone necrosis; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[b]Wilcoxon rank sum test.

[c]Data not available for all patients since data collection started only in 2000. Life-style factors: information available on smoking status in 25 patients with AVN and 219 patients of the control cohort. Medical history: available information for diabetes 25/219, hypertension 25/216, fat loss 25/219, fat accumulation 25/219. Laboratory values: available data for cholesterol level: 15/172; triglycerides 15/173.

[d]Fat loss/accumulation: in the SHCS the waist and hip circumferences are routinely measured every 6 months. Furthermore physicians evaluate if there is fat loss or fat accumullation present.

[e]Only C- or B-defining events with a $p < 0.1$ are shown. We further evaluated the following events: *Candida* esophagitis/stomatitis, tuberculosis, herpes simplex ulcerations, multidermatomal herpes zoster, oral hairy leukoplakia, lymphadenopathy, invasive cervical cancer, immunothrombocytopenia, Kaposi sarkoma, non-Hodgkin lymphoma, progressive multifocal leukoencephalopathy, cryptosporidiosis, wasting syndrome, diarrhea, fever, histoplasmosis.

[f]If less than 50% of patients had the medication the median is zero, if less than 25% of patients had the medication the IQR is zero. *p* values listed are for the duration of use and not for the proportion using the drug.

[g]Pre-ART CD4 values were available for 200 controls and 22 cases within 3 months prior to starting ART.

[h]Analysis limited to patients who started HAART; if an AVN was diagnosed, it must have been after starting HAART. Also not all of these patients had CD4 cells available at start of HAART ($n = 19$ in AVN patients, $n = 136$ in control patients).

[i]Analysis limited to patients with at least two measurements of RNA/CD4 until last follow-up or diagnosis of AVN.

[j]Pre-ART RNA values were available for 116 controls and 10 cases within 3 months prior to starting ART.

[k]Measured at entry into the cohort.

bral toxoplasmosis: 11.54 versus 0.38%, $p = 0.003$; atypical mycobacteriosis: 11.5 versus 1.92%, $p = 0.014$; CMV retinitis: 11.54 versus 0.77%, $p = 0.006$; *Pneumocystis* pneumonia: 23.08 versus 5.77%, $p = 0.003$).

Results of uni- and multivariable conditional logistic regression analyses are shown in Table 2. A higher body mass index, lower nadir CD4, exposure to NNRTIs (mainly efavirenz), and exposure to pyrimethamine were significantly ($p < 0.05$) associated with AVN in the univariable model. Nadir CD4 count and body mass index were independent significant cofactors with odds ratios of 0.56 (0.37–0.84) per 100 cells/μl higher and 4.47 (1.51–13.2) per 10 kg/m^2 in the bivariable model, respectively. We then analyzed each of the remaining variables adjusted for nadir CD4 count and body mass index in individual multivariable models (Table 2, right column). None of the variables analyzed was significant after adjustment (all $p > 0.05$) with odds ratios for nadir CD4 count and body mass index remaining virtually unchanged and significant ranging from 0.54 to 0.59 and from 3.28 to 4.68, respectively.

There was a trend toward an association of lipodystrophy with AVN (fat loss: 52% in cases versus 32.42% in controls, $p = 0.054$; fat accumulation: 52% versus 32.42%, $p = 0.055$). Groups were similar in smoking status, and regarding classic risk factors for vascular occlusive diseases such as hypertension, diabetes, and hyperlipidemia.

In contrast to a study describing a strong correlation of corticosteroid use and AVN in HIV-infected patients,[6] we found prolonged use of steroids in only one AVN patient, who was treated for his colitis ulcerosa. Four more patients received short courses of steroids: three patients had a 3-week course of steroids due to *Pneumocystis* pneumonia and one patient received an intraarticular injection because of hip pain. AVN patients neither had anticardiolipin antibodies nor a history of dialysis therapy, former trauma, or former radiation therapy. Of patients with osteonecrosis 76.9% lifted more than 10 kg daily.

Table 2. Conditional Logistic Regression of Osteonecrosis in 26 Cases and 260 Concurrent Controls

Factor	*Univariable model Odds ratio (95% CI)*	p *value*	*Multivariable models*[a] *Odds ratio (95% CI)*	p *value*
Female gender	0.58 (0.21–1.61)	0.30	0.81 (0.27–2.39)	0.70
Age at registration (per 10 years older)	1.22 (0.80–1.86)	0.35	1.11 (0.69–1.78)	0.67
Risk factors for HIV infection		0.35		0.36
Injection drug use	1		1	
Homosexual	1.10 (0.39–3.09)		1.18 (0.38–3.66)	
Heterosexual	1.16 (0.40–3.35)		1.16 (0.38–3.51)	
Other	7.92 (0.94–66.5)		7.65 (0.89–66.0)	
Body mass index (per 10 kg/m^2 higher)	3.39 (1.20–9.52)	0.020	n.a.[b]	
Ever smoked[c]	2.32 (0.67–8.04)	0.18	2.13 (0.59–7.64)	0.25
Nadir CD4 count (per 100 cells/μl higher)	0.59 (0.40–0.80)	0.010	n.a.[b]	
Maximum HIV RNA[d] (per $\log_{10}$ copies/ml higher)	1.49 (0.90–2.46)	0.12	1.03 (0.61–1.76)	0.90
Duration of ART (per year longer)	1.10 (0.92–1.33)	0.30	0.99 (0.80–1.23)	0.94
Duration of HAART (per year longer)	1.24 (0.91–1.69)	0.18	1.12 (0.81–1.56)	0.49
Class specific exposure (per year longer)				
NRTIs	1.15 (0.99–1.34)	0.062	1.09 (0.93–1.29)	0.29
PIs	1.27 (0.99–1.63)	0.057	1.17 (0.89–1.54)	0.25
NNRTIs	1.68 (1.03–2.75)	0.037	1.40 (0.73–2.68)	0.31
Exposure to individual antiretroviral drugs (per year longer)[e]				
Abacavir	1.63 (0.86–3.09)	0.14	1.40 (0.73–2.68)	0.31
Efavirenz	2.33 (1.16–4.68)	0.017	1.82 (0.88–3.80)	0.11
Indinavir	1.33 (0.95–1.86)	0.093	1.34 (0.93–1.94)	0.12
Lamivudine	1.27 (0.89–1.80)	0.19	1.17 (0.79–1.72)	0.44
Zidovudine	1.23 (0.95–1.59)	0.12	1.13 (0.85–1.50)	0.40
Exposure to prophylactic drugs[f] (per year longer)				
Pyrimethamine	1.71 (1.01–2.87)	0.044	1.57 (0.93–2.64)	0.090

[a]From individual models for each factor, adjusted for body mass index and nadir CD4 count.

[b]Body mass index and nadir CD4 count were used to adjust individual models.

[c]Information available for 241 patients (25 cases and 216 controls).

[d]Information available for 273 patients (26 cases and 247 controls).

[e]Other individual antiretroviral drugs that had been taken by at least 5% of patients (stavudine, didanosine, zalcitabine, saquinavir, ritonavir, nelfinavir, amprenavir) showed no significant differences (all $p > 0.2$) in the univariable model.

[f]Other prophylactic drugs that had been taken by at least 5% of patients (cotrimoxazole, dapsone, fluconazole, isoniazide, pentamidine) were not significant (all $p > 0.2$) in the univariable model.

DISCUSSION

In the present report, we addressed the question of whether antiretroviral treatment, in particular protease inhibitors, was involved in the pathogenesis of osteonecrosis in chronically HIV-infected patients. Our nested case control study did not reveal a significant association between the duration of ART and the occurrence of osteonecrosis. Four of our case patients were ART naive when the diagnosis of AVN was first made. This is in line with previous reports indicating that osteonecrosis had occurred before protease inhibitors became available.[5,10] A marginal trend toward longer ART duration in AVN patients and a trend toward exposure to more classes of antiretroviral drugs in osteonecrosis cases reflects our finding that AVN patients clearly presented with more advanced disease: CF4 nadirs in AVN patients were significantly lower than in controls and thus they experienced more opportunistic infections before AVN and were more often treated with pyrimethamine. The significantly higher use of efavirenz (EFV) in AVN patients underlines the trend toward an earlier start of HAART in osteonecrosis patients ($p = 0.079$) with subsequent earlier treatment failures and consecutive EFV-containing salvage therapy.

The fact that four of our cases experienced AVN when they were drug naive and the absence of a stronger CD4 cell response after initiation of HAART in our cases do not support the hypothesis that immune reconstitution is a main risk factor in the etiology of AVN as has been postulated.[14,18]

In our study, neither an association between the classic vascular risk factors diabetes, hypertension, and hyperlipidemia nor a high frequency of treatment with corticosteroids was found. Only one AVN patient was treated with steroids for more than 1 month due to recurrent inflammatory bowel disease. However, interestingly, AVN patients had a significantly higher BMI and 13 of our case patients had a history of fat redistribution (fat loss or fat accumulation). The latter findings implicate that metabolic disorders nevertheless may play an important role in the emergence of AVN.

This study has limitations. We could evaluate only information collected within the protocol of the Swiss HIV Cohort study. Thus known further potential risk factors such as the presence of anticardiolipin antibodies, alcohol consumption, and daily habits could be evaluated only in case patients. The fact that anticardiolipin antibodies were absent in all five cases, in whom they have been determined, implies that this factor does not play a major role in the emergence of AVN in HIV-infected patients. However, a potential role of alcohol use cannot be ruled out (20% of our case patients consumed more than 0.5 liters of wine or beer/day). Since symptomatic AVN is a rare disease the sample size was small but still the largest reported so far when compared to the literature. We did not adjust p values for multiple comparisons and therefore cannot rule out that some of the identified associations may have resulted by chance. The estimated annual incidence of osteonecrosis in HIV-infected patients ranges from 0.080 to 1.33%.[19] In our study we found an average annual incidence of only 0.06%, which suggests that the occurrence of AVN was potentially underestimated in our cohort. A recently published study, which utilized MRI to screen for osteonecrosis in 339 HIV-infected patients, found up to 4% of patients with asymptomatic AVN.[7] Therefore we cannot rule out that even some of our control patients had asymptomatic AVN. In conclusion, the major finding of our study is the clear association of AVN with low nadir CD4 counts and with more frequent opportunistic infections but not with antiretroviral treatment per se. Our data suggest that part of the increased incidence of AVN since 1996 may be due to improved survival of patients with advanced immunosuppression. Whether the incidence of osteonecrosis will continue to rise or, on the contrary, will fall due to earlier treatment and less severe immunosuppression will have to be determined in the future. Despite the fact that osteonecrosis in HIV-infected patients is rare, it is debilitating and often requires hip and knee replacement in a relatively young patient population. Screening for asymptomatic patients at this time is not warranted,[7] but a high index of suspicion for osteonecrosis in chronically HIV-infected patients with persistent hip, knee, or other bone pain is needed for rapid evaluation of this rare but severe disease.

APPENDIX

The members of the Swiss HIV Cohort Study are S. Bachmann, M. Battegay, E. Bernasconi, H. Bucher, Ph. Bürgisser, S. Cattacin, M. Egger, P. Erb, W. Fierz, M. Fischer, M. Flepp (Chairman of the Clinical and Laboratory Committee), P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011-Lausanne), H.J. Furrer, M. Gorgievski, H. Günthard, B. Hirschel, L. Kaiser, C. Kind, Th. Klimkait, B. Ledergerber, U. Lauper, M. Opravil, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), J. Schüpbach, R. Speck, A. Telenti, A. Trkola, P. Vernazza (Chairman of the Scientific Board), R. Weber, and S. Yerly.

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