

## Research letters

## Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis

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**Discontinuation of primary prophylaxis against toxoplasma encephalitis was studied in 199 HIV-1-infected patients on antiretroviral combination treatment who had experienced a sustained increase in their CD4 count. During a follow-up of 272 person-years, no cases of toxoplasma encephalitis arose.**

The introduction of potent antiretroviral therapy has led to a substantial decline in HIV-1 associated morbidity and mortality.<sup>1</sup> Primary prophylaxis against *Pneumocystis carinii* pneumonia (PCP) can be discontinued in patients with treatment-associated restoration of the immune response.<sup>2</sup> HIV-1-infected patients who are co-infected with *Toxoplasma gondii* are at risk of developing toxoplasma encephalitis. Prophylaxis against PCP with co-trimoxazole or dapsone combined with pyrimethamine also prevents toxoplasma encephalitis.<sup>3-5</sup> Whether stopping primary prophylaxis is safe in patients seropositive for *T gondii* is currently unclear. Current guidelines state that the numbers of patients who have been assessed are insufficient to recommend routine discontinuation of prophylaxis.<sup>5</sup> We did a study that extended a previous analysis done by the Swiss HIV Cohort Study<sup>2</sup> of discontinuation of primary prophylaxis to a larger group of patients with longer follow-up, and focused on patients co-infected with *T gondii*.

The Swiss HIV Cohort Study is a continuing prospective multicentre study of adult HIV-1-infected patients.<sup>1</sup> Patients on primary prophylaxis who were seropositive for IgG antibodies to *T gondii* were eligible if they responded to antiretroviral combination treatment with an increase in their CD4 counts to at least 200 cells/ $\mu$ L and 14% of peripheral lymphocyte count, and if the CD4 count remained higher than these thresholds for at least 12 weeks. The protocol stipulated that patients had to be withdrawn from the study and primary prophylaxis restarted if the CD4 count fell to lower than 200 cells/ $\mu$ L or 14% in two consecutive measurements. A definite or presumptive diagnosis of toxoplasma encephalitis, as defined by the 1993 classification system for HIV-1 infection was the primary endpoint. We took discontinuation of primary prophylaxis to be safe if the upper 95% CI of the incidence of toxoplasma encephalitis was lower than the upper 95% CI recorded in a historical comparison group of 437 seropositive patients with CD4 counts of 200–500 cells/ $\mu$ L who were followed up in the Swiss HIV Cohort Study in 1990–94.<sup>2</sup> In patients with CD4 counts higher than 200 cells/ $\mu$ L, primary prophylaxis against PCP and toxoplasma encephalitis is not recommended.<sup>5</sup> The frequency in the historical comparison group was 1.2 episodes per 100 person-years (95% CI 0.4–2.8).

The ethics committees of all seven centres approved the study and we obtained written informed consent from all patients. Follow-up was from the date primary prophylaxis was stopped to the date of last contact, of reaching an

endpoint, or of withdrawal. Events were assumed to have a Poisson distribution, and exact 95% CI were calculated for the incidence of endpoints. We calculated one-sided upper 95% CI if no event was recorded. We used Stata software (version 6.0) for statistical analysis.

240 patients fulfilled the entry criteria, 199 (82.9%) of whom had been enrolled in the current study as of December, 1999. The patients enrolled and not enrolled did not differ significantly for age, sex, transmission mode, clinical stage, or peak CD4 cell count. In 176 (88.4%) patients, the discontinued prophylactic agent was co-trimoxazole. The median duration of prophylaxis was 26 months. Characteristics at baseline and at study end are shown in table 1. In 11 (5.5%) patients, follow-up was censored before the closing date: four resumed prophylaxis because their CD4 count fell to lower than the threshold values of 200 cells/ $\mu$ L or 14%, two because of recurrent respiratory infections, two could not be located, one withdrew consent, and two died—one of non-Hodgkin lymphoma and one of an overdose of heroin. No

Characteristics	
Median (IQR) age (years)	39 (35–47)
Sex (men)	141 (70.9%)
<b>Transmission group</b>	
Homosexual men	84 (42.2%)
Heterosexual contact	60 (30.2%)
Injecting drug users	47 (23.6%)
Other	8 (4.0%)
<b>Clinical stage at baseline</b>	
CDC stage A	56 (28.1%)
CDC stage B	90 (45.2%)
CDC stage C	53 (26.6%)
<b>Median (IQR) CD4 count (cells/<math>\mu</math>L)</b>	
Lowest count	111 (59–150)
At study entry	340 (278–408)
At study end	424 (325–571)
Time higher than levels after stopping prophylaxis (weeks)	19 (14–26)
<b>Antiretroviral regimen at time of discontinuation</b>	
2 drugs	15 (7.5%)
$\geq 3$ drugs	184 (92.5%)
$\geq 1$ protease inhibitor	171 (89.5%)
<b>Prophylactic regimen discontinued</b>	
Co-trimoxazole	176 (88.4%)
Dapsone/pyrimethamine	10 (5.0%)
Pentamidine/pyrimethamine	13 (6.5%)
<b>Median (IQR) viral load (<math>\log_{10}</math> copies/mL)</b>	
At study entry	2.0 (2.0–2.8)
At study end	1.4 (1.3–2.7)
<b>Viral load &lt;200 copies/mL</b>	
At study entry	128 (64.3%)
At study end	137 (68.8%)

CDC=Centers for Disease Control and Prevention.

**Table 1: Characteristics of 199 patients who discontinued primary prophylaxis**

Characteristics	
Median (range) follow-up (years)	1.4 (0.1–2.4)
Total follow-up (years)	272.0
Number of toxoplasma encephalitis events	0
Incidence of toxoplasma encephalitis per 100 patient-years (95% CI)	0 (0–1.1)

Table 2: Incidence of toxoplasma encephalitis after stopping primary prophylaxis in 199 patients

patient developed toxoplasma encephalitis. The upper 95% CI of the incidence was 1.1 per 100 person-years, which is lower than the predefined threshold incidence of 2.8 per 100 person-years (table 2). There was no case of PCP during follow-up.

Stopping of primary prophylaxis is safe in patients infected with *T gondii* who have responded to potent antiretroviral treatment with a sustained raise in immunological markers. This finding is reassuring and especially important in regions where the prevalence of toxoplasma infection is high, including central and western Europe. Our study was observational and selection bias could have been introduced, for example if patients at low risk were preferentially included. The Swiss cohort has national coverage and includes about 70% of patients with advanced HIV-1 disease in the country. Bias was, therefore, unlikely. Although the median follow-up was 1.5 years and some patients were followed up for longer than 2 years, we cannot exclude an increased risk of toxoplasma encephalitis several years after stopping prophylaxis. Such an occurrence seems unlikely, however, since immune function increases with time after combination treatment is started. Two-thirds of our study participants had plasma HIV-1 RNA loads lower than 200 copies/mL when they discontinued prophylaxis. It is unclear whether our data can be extrapolated to patients who have uncontrolled viraemia while on combination antiretroviral treatment.

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## Oral statins and increased bone-mineral density in postmenopausal women

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**Experimental evidence suggests that the cholesterol-lowering drugs statins increase bone formation. We report a significant increase of bone-mineral density associated with taking statins in postmenopausal women.**

The treatment of osteoporosis remains a major challenge, despite an increasing array of therapeutic agents, including bisphosphonates, hormone replacement therapy, and selective oestrogen receptor modulators. Despite widespread use, however, these agents all rely on decreasing osteoclastic absorption of bone for their effect. No widely used licensed treatment that increases bone formation exists yet. The most potent bone-inducing factors are growth factors, such as bone morphogenetic proteins, but the therapeutic use of such factors is hampered by difficulty in delivering these agents to bone and their by widespread effects on other organ systems.

Experimental evidence has shown that the statins, a class of cholesterol-lowering drugs, might increase bone formation.<sup>1</sup> The statins lovastatin and simvastatin increased new bone formation in rodents associated with increased expression of the bone morphogenetic protein-2 gene. This finding was true when statins were added to bone cultures in vitro, by subcutaneous injection to sites overlying bone, and after oral administration in normal and ovariectomised animals.

We investigated the possibility that bone formation would increase in postmenopausal women taking statins for hypercholesterolaemia. The women studied were participants of the Chingford study, a population-based cohort of 1003 women living in the UK, seen annually since 1989.<sup>2</sup>

We measured bone-mineral density at the spine and hip with a DXA QDR 2000 scanner (Hologic) during the same visit at which statin status was established. Records showed that 41 women were taking statins at the time of the scan. The most commonly used statin was simvastatin (21 women, 51%), followed by pravastatin (ten women, 24%), atorvastatin (six women, 15%), and fluvastatin (four women, 10%). The median (IQR) length of statin use was 48 (9–78) months. Each woman was matched with two or three controls, selected from the same population, who were closest in age and the date on which examination took place. We compared bone-mineral density at the hip and spine between the two groups and analysed the data by independent *t* test and ANCOVA (table).

Bone-mineral density at the spine and the hip (femoral neck) remained significantly higher in the 41 statin users than in the 100 controls (table), and remained higher at the spine and hip after adjustment for age, height, and weight.

	Controls (n=100)	Statins (n=41)	p
Age (years)	66.9 (5.4)	66.4 (5.3)	0.61
Height (cm)	161.5 (6.1)	161.2 (5.9)	0.54
Weight (kg)	66.3 (10.6)	71.3 (12.8)	0.02
Years since menopause	18.9 (6.0)	18.7 (6.1)	0.86
Number on HRT	20 (20%)	13 (32%)	0.14
Number of smokers	21 (26%)	6 (23%)	0.74
Prevalence	21 (21%)	7 (17%)	0.49
HRT duration (months)	19.3 (30.0)	27.8 (23.1)	0.40
Spine BMD (g/cm <sup>2</sup> )	0.89 (0.14)	1.00 (0.16)	0.001
Spine BMD adjusted*	0.91 (0.13)	0.99 (0.16)	0.001
Hip BMD (g/cm <sup>2</sup> )	0.70 (0.13)	0.76 (0.13)	0.002
Hip BMD adjusted†	0.68 (0.15)	0.76 (0.13)	0.05

HRT=hormone replacement therapy; BMD=bone-mineral density. Mean (SD) shown unless otherwise indicated. \*Smokers based on 106 women, excluding ex-smokers; †adjusted with ANCOVA for age, height, weight, HRT, and smoking status.

**Comparison of characteristics and bone-mineral density for controls and statin users**