

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.¹ 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 1989.²

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 ²)	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 ²)	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

Different areas of the hip, including trochanter and total hip, yielded similar crude results to the femoral neck (trochanter 0.65 *vs* 0.7, $p=0.02$; total hip 0.83 *vs* 0.89, $p=0.008$). Since hormone replacement therapy has a major effect on bone-mineral density, we also did an analysis excluding individuals taking hormone replacement therapy (71 controls, 23 statin users). The results for the spine bone-mineral density were similar and remained significant (0.89 *vs* 0.97, $p=0.01$). In 46 women whose lipid concentrations were higher than 7.5 mmol at baseline, excluding those taking statins, bone-mineral density did not differ at the spine or hip. (spine 0.89 *vs* 0.90, $p=0.43$; hip 0.69 *vs* 0.70, $p=0.51$).

A preliminary abstract suggests that statins protect against fracture,³ but our data do not support such findings. Although our study was cross-sectional, major confounders were unlikely to have caused the degree of association we saw. Some caution is needed, however, when interpreting these results. Although we showed no clear differences between controls and women not on statins who had high cholesterol concentrations, it is still possible that hypercholesterolaemia or a related trait might be associated with increased bone-mineral density.

The exact mechanism of action of statins is unclear, but they have been shown to decrease the production of mevalonate, a precursor of cholesterol production, by inhibiting the enzyme HMG-CoA reductase.⁴ This pathway is important in the action of certain antiresorptive bisphosphonates used to treat osteoporosis.⁵ Our findings may have major implications for the design of future treatments for osteoporosis aimed at increasing bone-mineral density by inducing bone formation. Randomised controlled trials of statins are needed to confirm these observations.

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Reassessing artificial bowel sphincters

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The artificial sphincter has now been used for the treatment of patients with faecal incontinence since 1996. Presently, results in the UK do not match those reported from the rest of Europe, with infection caused by meticillin-resistant *Staphylococcus aureus* being the most common cause of failure.

The artificial bowel sphincter was introduced in 1996 for the treatment of patients with severe faecal incontinence

that was not responsive to conventional therapies.¹ Before introduction of the new purpose-designed bowel sphincter¹ now known as the Acticon (American Medical Systems, Minnetonka, USA), there were three separate pilot studies, applying the artificial urinary sphincter and modifications of this device to patients with faecal incontinence.² The reported overall success rate was 76% in 37 patients, with follow-up ranging from 4–76 months. The Acticon was formally tested in a limited number of European centres from June, 1996, to March, 1998. The results were again encouraging with a 74% success rate in 86 patients at a median follow-up of 12 months (range 2–19 months). Our institution, one of the European centres, previously reported success in five of six patients at a median follow-up of 10 months (range 5–13 months).

Six centres have now implanted the American Medical Systems (AMS) artificial bowel sphincter in patients in the UK. An audit of the results at the latest follow-up in February 2000 shows that of 18 implants, 12 have required removal and one has been successfully revised (personal communication from AMS UK). The overall success rate was 33% at a median follow-up of 26 months (range 2–39 months). Reasons for device removal included implant sepsis ($n=seven$), cuff erosion through the perineum (two), poor wound healing (one), difficulties with rectal evacuation (one), and psychological inability to adapt to the device (one). All but one of the infections were caused by meticillin-resistant staphylococcus aureus (MRSA).

Results from Europe remain encouraging. The most recent report,³ a three-centre audit of 24 patients, shows a 75% success rate at a median follow-up of 20 months (range 10–35 months). Seven devices have been removed with three successfully reimplanted. One patient has had difficulty with evacuation, and one patient remains incontinent.

There are no long-term results available yet for the artificial bowel sphincter. Christiansen and colleagues³ present long-term results on the artificial urinary sphincter and a modification of this device. Eight of 17 patients who were implanted before 1993 still had a functioning device. Five of these eight patients have required revision operations. Of the remaining nine patients, two have died of unrelated causes, three had the device removed after infection, and four for mechanical problems.

The short and medium term results for the use of artificial bowel sphincter in the UK are not equal to those reported from Continental Europe. The main difference would appear to be the rate of infection, with MRSA being a predominant feature. Once established, sepsis is rarely controlled by antibiotics or drainage, and removal of the whole system is usually necessary. It is known from previous studies on implanted prosthetic devices⁴ that infection is subclinical in some cases, requiring culture of the device itself before the existence of a pathogen can be proven. It is possible, therefore, that the reported cases of poor wound healing and perhaps some cases of pain and device erosion are also secondary to occult sepsis.

A higher proportion of devices were reimplanted or revised in patients, in the European studies. There has only been one reported revision in the UK for an obvious fracture of the connecting tubing diagnosed on radiological imaging. Low revision rates will result in a higher overall percentage of reported failure rates even if the patients' continence scores have been improved from those recorded preoperatively.

Mechanical failure is now rare with the purpose-designed device. Accounting for less than 4% of initial failures, these can usually be surgically revised with a high success rate.³ There is no evidence to suggest that patient selection has