

Osteopenia in HIV-infected men: association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy

Andrew Carr^a, John Miller^b, John A. Eisman^c and David A. Cooper^{a,b}

Background: Osteopenia has been associated with antiretroviral therapy, particularly with protease inhibitors. Osteopenia in HIV-uninfected men is associated with mitochondrial defects.

Methods: Bone density was assessed by dual-energy X-ray absorptiometry (DEXA) in 221 HIV-infected men (mean age 43 years) recruited to a lipodystrophy prevalence survey. Additional parameters assessed were demographics, exercise, smoking, type(s) and duration of all antiretroviral therapy, lipodystrophy (overall and by region), CD4 counts, HIV RNA, fasting metabolic parameters (lipid, glycaemic, lactate, liver enzymes, testosterone) and regional body fat and lean mass (DEXA and L4 abdominal computed tomographic scan).

Results: Thirty-two patients were drug-naive; 42 were receiving nucleoside analogue reverse transcriptase inhibitors (NRTI) and 147 were receiving these plus protease inhibitors. Osteoporosis (t -score < -2.5 SD below normal) was found in seven (3%) and osteopenia (t -score -1.0 to -2.5 SD) in 44 (22%). No patient had had a fracture since being infected with HIV. The only factors independently associated on logistic regression with osteopenia or osteoporosis were higher lactate levels, even if asymptomatic [odds ratio (OR) 2.39 per 1 mmol/l increase; 95% confidence interval (CI) 1.39–4.11; $P = 0.002$], and lower weight prior to commencing antiretroviral therapy (OR 1.06 per 1 kg decrease; 95% CI 1.02–1.11; $P = 0.006$). There was no independent association with any other parameter, including type or duration of antiretroviral therapy and lipodystrophy at any site. Lower total bone mineral density was associated with lower weight prior to commencing antiretroviral therapy whereas lower spinal bone mineral density was associated mostly with higher lactate.

Conclusion: Osteopenia in HIV-infected men is common, asymptomatic and is associated with asymptomatic NRTI-related lactic acidemia and lower weight pre-antiretroviral therapy.

© 2001 Lippincott Williams & Wilkins

AIDS 2001, **15**:703–709

Keywords: osteoporosis, lactic acidemia, mitochondrial toxicity, antiretroviral therapy

Introduction

Osteoporosis is a recently described adverse event in patients with HIV infection. Prior to the introduction of long-term highly active antiretroviral therapy, healthy HIV-infected adults generally had normal bone

mineral density that was stable over time [1]. This suggests that known risk factors for osteopenia that have always been common in HIV-infected patients, such as smoking, reduced exercise, hypogonadism and cytokine activation, may not play a major role in HIV-related osteopenia.

From the ^aHIV, Immunology and Infectious Diseases Clinical Services Unit, St Vincent's Hospital, the ^bNational Centre in HIV Epidemiology and Clinical Research and the ^cGarvan Institute for Medical Research, University of New South Wales, Sydney, Australia.

Requests for reprints to Associate Professor A. Carr, HIV, Immunology and Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney 2010, Australia; e-mail: acarr@stvincents.com.au

Received: 18 October 2000; revised: 19 January 2001; accepted: 30 January 2001.

Two more recent studies found an increased (42% and 38%) prevalence of osteopenia in HIV-infected adult outpatients receiving combination antiretroviral therapy. In one study, osteopenia was linked to protease inhibitor therapy, although potential confounding factors such as nucleoside analogue drug type and duration, smoking, exercise, testosterone, lean body mass and weight prior to therapy were not studied [2]. The second study found a high prevalence in lipodystrophic adults recruited to a randomized study of protease inhibitor cessation [3]. However, no difference in bone density was seen between the two randomized groups after 48 weeks. Although no potential risk factor for osteoporosis was identified, this study population all had lipodystrophy and extensive pretreatment with nucleoside analogues and protease inhibitors. Although both these studies reported no fractures, osteoporotic fractures have been reported in two HIV-infected African women [4].

Osteoporosis has been linked to mitochondrial deletions in young HIV-uninfected males with no other clinical features of mitochondrial disease, although some had asymptomatic lactic acidemia [5,6]. Lactic acidemia is a well-described mitochondrial toxicity of HIV nucleoside analogue therapy [7–13]. To address the possibility that HIV-associated osteopenia might have a mitochondrial pathogenesis, the prevalence of osteopenia or osteoporosis, and of factors associated with their presence, was assessed in a cohort of adult men in whom numerous parameters including lactate and body composition had been studied.

Methods

Subjects

The study population of 221 men comprised 32 antiretroviral-naïve patients without lipodystrophy, 14 nucleoside analogue recipients with lipodystrophy, 28 nucleoside analogue recipients without lipodystrophy, 103 nucleoside analogue plus protease inhibitor recipients with lipodystrophy and 44 nucleoside analogue plus protease inhibitor recipients without lipodystrophy [7]. The 14 nucleoside analogue recipients with lipodystrophy were taking part in a study evaluating lipodystrophy and lactic acidemia in patients naïve to protease inhibitor therapy and they represented all such outpatients seen between June 1998 and January 1999. The remaining patients were all healthy HIV-infected male outpatients seen for routine care between October, 1998 and February, 1999, who were consecutively recruited to the Australian lipodystrophy prevalence survey (11 of the 14 cases were seen during the latter period and were also recruited to the prevalence survey). No patient had an AIDS-defining condition in the 3 months prior to study.

Age, known duration of HIV infection, presence of AIDS, smoking, current exercise level (graded as sedentary, mild, moderate, high; [14]), types and durations of all antiretroviral therapy, weight (including weight prior to commencing antiretroviral therapy), symptoms and signs associated with lactic acidemia (fatigue, nausea, weight loss of at least 3 kg during the preceding 3 months [ref. 7]), CD4 count, HIV RNA load, electrolytes, liver enzymes, plasma lactate, testosterone and lipid and glycaemic parameters were assessed. For collection of all metabolic parameters, patients undertook no vigorous exercise for 24 h, fasted overnight for 10 h but with free water intake. Lactate measures were not repeated. No assessment of nutritional status, calcium intake, steroid use or exercise type was made. Patient files were reviewed for evidence of prior fracture since diagnosis of HIV infection; prior CD4 lymphocyte counts and plasma HIV RNA results were not recorded.

Body composition was measured within 4 weeks of clinical and metabolic assessments by dual-energy X-ray absorptiometry (DXA; Lunar DPXL, Madison, Wisconsin, USA) in a single scanner. Bone parameters recorded included total body bone mineral density, total body bone mineral density *t*-score (density compared with healthy male Australians aged 20–45 years) and total body bone mineral density *z*-score (density compared with Australian age, weight, race and sex-matched adults). Spinal bone mineral density was estimated from the total body scans; for that reason spine *t*-scores and *z*-scores could not be determined. Intra-abdominal and extra-abdominal fat at the L4 vertebral level was estimated by single-cut computed tomography.

Osteopenia was defined according to World Health Organization (WHO) criteria by a total body bone mineral density *t*-score 1.0–2.5 SD below mean normal (an average *t*-score in young men is zero; an average *z*-score in a given age, sex and racial group is also zero), and osteoporosis by a total body bone mineral density *t*-score of > 2.5 SD below mean normal [15]. Lactic acidemia was defined by serum lactate > 2.0 mmol/l and lipodystrophy by patient report (standardized questionnaire) of peripheral lipodystrophy (fat loss from face, arms, buttocks or legs) and/or central fat accumulation (abdomen, dorsocervical fat pad) that was confirmed by physical examination [7].

Because of the small number of patients with osteoporosis, these patients were combined with the osteopenic patients for all analyses. Comparisons between patients with osteopenia or osteoporosis and those with normal bone density used the Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables. Parameters associated with osteopenia or osteoporosis were assessed using logistic regression. All

parameters were examined individually, and those parameters significantly (2-sided $P \leq 0.05$) associated with osteopenia or osteoporosis were entered into a stepwise regression model. Stepwise logistic regression was also used to evaluate any association of each parameter with lactic acidemia. Parameters associated with total bone mineral density and spinal bone mineral density were assessed using linear regression. All parameters were examined individually, and parameters significantly associated with reduced total bone mineral density or spinal bone mineral density were entered into respective stepwise regression models. As three of the 14 nucleoside analogue recipients with lipodystrophy were studied prior to the lipodystrophy survey, analyses were repeated with exclusion of these three patients; these analyses gave similar results and are not presented.

Results

Subjects

The mean age of the 221 patients was 43 (SD 9) years; the mean duration of HIV infection was 7.6 (4.5) years; 44 (20%) patients had AIDS, 116 (52%) patients had lipodystrophy, 44 (20%) had lactic acidemia and 32 (14%) had symptomatic lactic acidemia (Table 1). The mean CD4 count was 485×10^6 cells/l (SD 284) and plasma viral load was $3.17 \log_{10}$ copies/ml (SD 0.96). No patient had a documented fracture since being diagnosed with HIV infection.

The mean (SD) total body bone mineral density in the 221 patients was 1.22 g/cm^2 (0.15), equivalent to a t -score of -0.05 (1.17) and a z -score of 0.16 (1.08). Of 51 (23%) patients who had reduced total body bone mineral density, 44 (20%) had osteopenia, and seven (3%) had osteoporosis. Reduced total bone mineral density was found in two (6%) drug-naïve patients, 11 (26%) nucleoside analogue recipients and 36 (25%) nucleoside analogue plus protease inhibitor recipients. Australian population data, from which our t -scores are derived, suggest that 16% of age- and race-matched healthy men would be expected to have osteopenia, suggesting the prevalence in the nucleoside analogue plus protease inhibitor recipients was about 50% greater than expected ($P = 0.019$).

The mean total bone mineral density t -score was 0.58 (1.00) in drug-naïve patients, -0.01 (1.22) in nucleoside analogue recipients, and -0.16 (1.16) in nucleoside analogue plus protease inhibitor recipients ($P = 0.023$). Mean spinal bone mineral density was 1.13 g/cm^2 (0.13) in drug-naïve patients, 1.06 g/cm^2 (0.12) in nucleoside analogue recipients and 1.04 g/cm^2 (0.11) in nucleoside analogue plus protease inhibitor recipients ($P = 0.008$).

Patients with osteopenia or osteoporosis had longer durations of HIV infection and of stavudine therapy, higher HIV viral load and lactate (and the known associated parameters of low bicarbonate and raised alkaline phosphatase), more symptomatic lactic acidemia, more lipodystrophy (but not more central fat accumulation), lower body weight pre-antiretroviral therapy and lower current weight, lean body mass, total fat mass and peripheral fat mass (Table 1).

The only parameters independently associated with osteopenia or osteoporosis were higher lactate [odds ratio (OR) 2.39 per 1 mmol/l increase; 95% confidence interval (CI) 1.39–4.11; $P = 0.002$] and lower weight prior to commencing antiretroviral therapy (OR 1.06 per 1 kg decrease; 95% CI 1.02–1.11]; $P = 0.006$; Table 2). Osteopenia was associated with both symptomatic and asymptomatic lactic acidemia and was significantly associated with lactate at any level > 2.0 mmol/l. In turn, factors independently associated with lactic acidemia were current didanosine therapy (OR 6.10; 95% CI 2.67–13.89; $P < 0.0001$) and current stavudine therapy (OR 2.90; 95% CI 1.25–6.71; $P = 0.013$). There was no association with current smoking; current exercise level; the use, duration or type of protease inhibitor or non-nucleoside analogue therapy; central fat accumulation (abdomen or dorso-cervical spine); total or high density lipoprotein cholesterol; triglycerides; glucose; insulin; C-peptide; or estimated insulin resistance (data not shown).

The only parameters independently associated with lower total bone mineral density were greater age, lower lean body mass and greater duration of stavudine therapy (Table 3). In contrast, for lower spinal bone mineral density, the only independently associated parameters on linear regression were greater age, higher lactate levels and greater total duration of all nucleoside analogue therapy.

Discussion

The present study has confirmed previous studies that found osteopenia to be common in HIV-infected adult males receiving antiretroviral therapy even after adjustment for age. This osteopenia may result from mitochondrial toxicity of nucleoside analogues because osteopenia was associated with lactic acidemia (and lactic acidemia in turn with nucleoside analogue therapy), and the significant association on univariate logistic regression with nucleoside analogue therapy (a major cause of lactic acidemia) was lost after adjustment for lactate level (Table 2).

Overall, the data suggest that the cumulative duration and magnitude of lactic acidemia induced by nucleoside

Table 1. Characteristics of patients with normal or reduced bone density.

Parameter	Bone density		P value
	Normal	Reduced ^a	
Number (%)	170 (77)	51 (23)	
Demographic data			
Age [years; mean (SD)]	42.1 (0.7)	45.4 (1.3)	0.066
HIV duration [years; mean (SD)]	7.7 (0.4)	9.2 (0.6)	0.040
AIDS [No. (%)]	31 (18)	13 (26)	0.368
Smoker [No. (%)]	53 (31)	16 (31)	1.00
CD4 count [$\times 10^6$ cells/l; mean (SD)]	513 (24)	457 (45)	0.259
HIV RNA [\log_{10} copies/ml; mean (SD)]	3.13 (0.08)	2.86 (0.11)	0.045
Current antiretroviral therapy [No. (%)]			
Zidovudine	51 (30)	3 (6)	0.017
Didanosine	29 (17)	15 (29)	0.119
Stavudine	83 (49)	36 (71)	0.013
Lamivudine	61 (36)	16 (36)	1.00
Zalcitabine	9 (5)	4 (8)	0.697
Non-nucleoside analogue	26 (15)	11 (21)	0.342
Protease inhibitor	117 (69)	40 (79)	0.344
Duration of therapy (months)			
Zidovudine	25.8 (2.3)	27.8 (3.9)	0.389
Didanosine	7.5 (1.0)	10.3 (2.5)	0.152
Stavudine	12.9 (1.1)	18.0 (1.7)	0.015
Lamivudine	17.7 (1.1)	22.0 (2.1)	0.084
Zalcitabine	6.3 (1.1)	9.4 (2.5)	0.086
All nucleoside analogues	44.3 (3.0)	51.5 (4.3)	0.117
All protease inhibitors	16.4 (1.1)	20.3 (2.2)	0.105
Symptoms and signs [No. (%)]			
Peripheral lipoatrophy	73 (43)	35 (69)	0.005
Abdominal obesity	65 (38)	26 (51)	0.211
Buffalo hump	14 (8)	6 (12)	0.533
Symptomatic lactic acidemia	18 (11)	14 (27)	0.033
Peripheral neuropathy	24 (14)	5 (10)	1.00
Body composition (mean, SD)			
Weight pre-antiretroviral therapy (kg)	76.0 (0.8)	71.1 (2.1)	0.012
Weight (kg)	74.7 (0.7)	70.2 (1.9)	0.003
Weight change on therapy (kg)	-1.1 (0.5)	-1.1 (1.2)	0.138
Total lean mass (kg)	57.2 (0.5)	53.5 (1.2)	0.002
Total fat mass (kg)	14.9 (0.5)	13.2 (1.2)	0.043
Limb fat mass (kg)	5.4 (0.3)	4.6 (0.5)	0.031
Visceral abdominal fat (cm ²)	117 (7)	140 (16)	0.244
Subcutaneous abdominal fat (cm ²)	105 (6)	89 (11)	0.117
Total body t-score	0.42 (0.07)	-1.62 (0.09)	-
Total body z-score	0.55 (0.07)	-1.15 (0.11)	-
Total bone mineral density (g/cm ²)	1.26 (0.01)	1.22 (0.01)	-
Spinal bone mineral density (g/cm ²)	1.07 (0.13)	1.01 (0.11)	-
Metabolic parameters (mean, SD)			
Lactate (mmol/l)	2.1 (0.3)	3.9 (0.2)	0.002
Anion gap (mmol/l)	13.5 (0.2)	14.4 (0.4)	0.066
Bicarbonate (mmol/l)	26.4 (0.2)	25.5 (0.4)	0.050
Albumin (g/dl)	44 (0.3)	43 (0.8)	0.211
Alanine aminotransferase (IU/l)	38 (3)	57 (9)	0.097
Alkaline phosphatase (IU/l)	98 (4)	122 (12)	0.042
Cholesterol (mmol/l)	5.5 (0.1)	5.8 (0.2)	0.223
HDL cholesterol (mmol/l)	1.02 (0.05)	1.09 (0.05)	0.432
Triglyceride (mmol/l)	2.9 (0.2)	3.1 (0.4)	0.523
Glucose (mmol/l)	4.9 (0.1)	4.9 (0.1)	0.740
Insulin (IU/l)	10.9 (0.9)	12.6 (1.8)	0.171
C-peptide (μ g/l)	2.6 (0.1)	2.9 (0.3)	0.612
Insulin resistance (mIUmmol/l ²) ^b	2.55 (0.26)	2.87 (0.45)	0.199
Testosterone (mmol/l)	19.7 (0.8)	19.4 (0.9)	0.633

^aIncludes 44 patients with osteopenia and seven patients with osteoporosis.

^bEstimated by homeostasis model assessment [7]

reverse transcriptase inhibitors may be most responsible for the increase in loss of bone mineral mass in our patients. Osteopenia was not directly associated, however, with any particular nucleoside analogue (although

only 13 patients were receiving abacavir and so no conclusion about its impact can be made). This suggests that osteopenia can develop with any nucleoside analogue but mostly if lactic acidemia is present.

Table 2. Factors associated with osteopenia or osteoporosis on logistic regression.

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Demographic						
Duration HIV infection (per year)	1.09	1.00–1.18	0.051	1.09	0.99–1.20	0.077
Age (per additional year)	1.05	1.01–1.09	0.026	1.04	0.99–1.09	0.137
Body composition						
Weight pre-therapy (per additional 1 kg)	0.95	0.91–0.99	0.013	0.94	0.90–0.98	0.006
Total lean tissue mass (kg)	0.90	0.83–0.96	0.003	0.93	0.84–1.02	0.113
Peripheral lipoatrophy (any site)	3.07	1.40–6.71	0.004	1.73	0.72–4.07	0.215
Current weight (per additional 1 kg)	0.95	0.91–0.99	0.015	1.00	0.93–1.07	0.919
Current BMI (per additional 1 kg/m ²)	0.87	0.75–0.98	0.045	1.05	0.85–1.30	0.628
Metabolic						
Lactate (per 1.0 mmol/l increase)	1.98	1.24–3.14	0.004	2.39	1.39–4.11	0.002
Bicarbonate (per 1.0 mmol/l increase)	0.84	0.72–0.98	0.024	0.82	0.72–1.08	0.107
ALT (per 10 IU/l increase)	1.10	1.02–1.18	0.010	1.01	0.96–1.14	0.391
Albumin (per 1 mg/dl increase)	0.91	0.83–1.00	0.041	0.96	0.85–1.08	0.464
ALP (per 10 IU/l increase)	1.06	1.00–1.11	0.043	1.02	0.96–1.10	0.514
Antiretroviral therapy						
Total duration stavudine (per year)	1.36	1.12–1.71	0.020	1.24	0.87–1.72	0.198
Current zidovudine	0.31	0.12–0.85	0.023	0.55	0.19–1.61	0.275
Current stavudine	2.61	1.24–5.50	0.012	1.48	0.60–3.65	0.389

OR, odds ratio; CI, confidence interval; BMI, body mass index; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Parameters listed are all those for which $P < 0.05$ on univariate logistic regression [there was no association with symptomatic lactic acidemia, smoking, exercise level, duration of any other nucleoside analogue, overall duration of nucleoside analogue therapy, use, duration or type of protease inhibitor or non-nucleoside analogue therapy, central fat accumulation (abdomen or dorsocervical spine) or with hyperlipidaemia or insulin resistance]. On multivariate analysis, lactate and body weight pre-therapy are presented adjusted for each other, and other parameters are adjusted for both these parameters.

Didanosine was most linked to lactic acidemia but was not significantly associated with osteopenia. Given the observed nucleoside analogue duration effect, it may be the relatively shorter period of didanosine therapy was sufficient to raise lactate but not to lower bone mineral density.

There are at least two possible explanations as to why lactic acidemia could be associated with osteopenia. As noted, mitochondrial deletions have been associated with osteoporosis and lactic acidemia in young adult males with no other overt signs of mitochondrial disease [5,6]. It remains to be determined, however, whether the observed increase in lactate derives from bone or is merely a parallel phenomenon. A second possibility to explain the link between lactic acidemia and osteopenia is that increased lactate production elsewhere (such as the liver) is being buffered by calcium hydroxyapatite from bone for subsequent urinary excretion, as has been observed in studies of increased protein intake, which also incurs a significant acid load. The predominant association of lactic acidemia with reduced spinal bone density might be explained by the fact that cancellous/trabecular bone, which forms the greater proportion of vertebral bone, is a more labile store of calcium than is cortical long bone, and so the spine might be more susceptible to the effects of lactic acidemia and/or nucleoside analogues.

There was no independent association between osteo-

penia and protease inhibitor duration, use or type. Similarly, neither hyperlipidemia nor insulin resistance, both common complications of protease inhibitor therapy, was linked with osteopenia or reduced spinal bone density [16,17]. This may explain why protease inhibitor withdrawal in a randomized study found no beneficial impact on bone density over 48 weeks [3]. Nevertheless, the association of reduced spinal bone mineral density with protease inhibitor duration deserves further investigation. Assessment of osteopenia in studies of nucleoside analogue withdrawal will also be important.

As osteoporosis to date is relatively rare and almost exclusively asymptomatic, there appears little need to screen routinely for osteoporosis or to alter nucleoside analogue therapy based on bone density data until it is established prospectively whether nucleoside analogues cause osteopenia and whether their cessation can lead to improved bone density. However, it may be prudent to address modifiable risk factors in patients found to have osteopenia, such as smoking, alcohol abuse, physical inactivity and hypogonadism. It will also be important to determine the prevalence of and risk factors for osteoporotic fractures in larger studies.

There are inherent weaknesses of the present study. First, the study was not prospective nor randomized, and so the possibility remains that unmeasured biases might underlie the associations observed. This seems unlikely, however, as not only was lactic acidemia

Table 3. Factors associated with reduced total body bone mineral density and spinal bone mineral density on linear regression.

Variable	Total body bone mineral density				Spinal bone mineral density			
	Univariate		Multivariate		Univariate		Multivariate	
	Δ BMD	<i>P</i> value	Δ BMD	<i>P</i> value	Δ BMD	<i>P</i> value	Δ BMD	<i>P</i> value
Demographic								
Age (per additional year)	-0.003	0.020	-0.003	0.042	-0.004	0.0006	-0.003	0.015
HIV RNA (\log_{10} copies/ml)	-0.022	0.092	0.022	0.137	0.023	0.026	0.015	0.165
Body composition (per 1 kg increase)								
Weight pre-therapy	-0.003	0.020	0.002	0.376	0.001	0.190	0.002	0.070
Current weight	0.002	0.045	3.8×10^{-4}	0.823	0.001	0.273	0.001	0.306
Total lean tissue mass	0.006	0.004	0.006	0.003	0.003	0.050	0.003	0.059
Metabolic								
Lactate (per 1.0 mmol/l increase)	-0.018	0.134	-0.001	0.958	-0.033	0.0004	-0.034	0.007
ALT (per 1 IU/l increase)	-2.9×10^{-4}	0.301	-2.5×10^{-5}	0.947	-4.8×10^{-4}	0.033	-8.4×10^{-5}	0.740
ALP (per 1 IU/l increase)	-3.0×10^{-4}	0.118	-2.7×10^{-5}	0.910	-3.0×10^{-4}	0.049	-5.0×10^{-5}	0.762
Cholesterol (per 1 mmol/l increase)	-0.16	0.056	-0.006	0.535	-0.016	0.013	-0.009	0.182
Antiretroviral therapy								
Duration NRTI therapy (per month)	-2.9×10^{-5}	0.95	1.5×10^{-4}	0.697	-0.001	0.004	-0.001	0.039
Duration stavudine (per month)	-0.002	0.034	-0.002	0.054	-0.002	0.011	-0.001	0.070
Duration lamivudine therapy (per month)	-0.0001	0.628	-1.7×10^{-5}	0.986	-0.002	0.003	-0.002	0.060
Duration PI therapy (per month)	-0.002	0.021	-0.003	0.062	-0.002	0.005	-0.001	0.049
Current stavudine	-0.048	0.034	-0.002	0.054	-0.049	0.007	-0.023	0.238

Δ BMD, change in bone mineral density per unit of each parameter; ALT, alanine aminotransferase; ALP, alkaline phosphatase; NRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor.

Parameters listed are all those for which $P < 0.05$ on univariate linear regression for either spinal or total bone mineral density. On multiple linear regression analysis of total bone mineral density, age and total lean mass are presented adjusted for each other, and other parameters adjusted for both these parameters. On multiple linear regression analysis of spinal bone mineral density, lactate, age and total duration of nucleoside analogue therapy are presented adjusted for each other, and other parameters adjusted for these parameters.

significantly associated with osteopenia, but so also were low bicarbonate and raised alkaline phosphatase, both features of lactic acidemia [7,10–15]. Second, the study has not evaluated women (in whom osteopenia is likely to be more common), children or various racial groups. Third, HIV-negative adult men were not studied. Australian population data (from which the *t*-scores and *z*-scores are derived) suggest, however, that about 16% of age- and race-matched healthy men would be expected to have osteopenia. This would indicate a prevalence in HIV-infected men of approximately 50% higher than expected. Lastly, whole body DEXA, rather than specific bone DEXA, was used for estimation of bone parameters, although a high correlation between both methods for estimation of bone mass and density has been observed [2]. Prospective studies will be required to define the relative contributions of antiretroviral therapy and HIV infection to osteopenia.

Lactate is not routinely measured in nucleoside analogue recipients, and nucleoside analogue therapy is generally ceased only in patients with symptomatic lactic acidemia greater than 5 mmol/l. As asymptomatic (low-level) lactic acidemia occurs in 12–20% of nucleoside analogue recipients [7,13] and is now linked to osteopenia, measurement of lactate in nucleoside analogues recipients without symptoms of lactic acidemia who have a fracture, osteoporosis or other risk factors for osteoporosis should be considered.

Acknowledgements

We would like to thank Matthew Law and Katherine Samaras for advice regarding the statistical analyses, Christine Morton for assistance with data collection, Lesley Campbell for review of the manuscript, and the patients for their participation.

Sponsorship: The National Centre in HIV Epidemiology and Clinical Research is supported by the Commonwealth Department of Health and Aged Care through the Australian National Council on AIDS, Hepatitis C and Related Diseases and its Research Advisory Committee.

References

1. Paton NJ, Macallan DC, Griffin GE, Pazianas M. **Bone mineral density in patients with human immunodeficiency virus infection.** *Calcif Tissue Int* 1997, **61**:30–32.
2. Tebas P, Powderly WG, Claxton S *et al.* **Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy.** *AIDS* 2000, **14**:F63–F67.
3. Hoy J, Hudson J, Law M, Cooper DA. **Osteopenia in a randomised, multicentre study of protease inhibitor substitution in patients with lipodystrophy syndrome and well-controlled HIV viraemia: extended follow-up to 48 weeks.** Second International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. Toronto, September 2000 [abstract P32].
4. Stephens EA, Das R, Madge S, Barter J, Johnson MA. **Symptomatic osteoporosis in two young HIV-positive African women.** *AIDS* 1999, **13**:2605–2606.
5. Varanasi SS, Francis RM, Berger CE, Papiha SS, Datta HK. **Mitochondrial DNA deletion associated oxidative stress and severe male osteoporosis.** *Osteoporos Int* 1999, **10**:143–149.
6. Papiha SS, Rathod H, Briceno I, Pooley J, Datta HK. **Age-related somatic mitochondrial DNA deletions in bone.** *J Clin Pathol* 1998, **51**:117–120.
7. Carr A, Miller J, Law M, Cooper DA. **A syndrome of lipodystrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome.** *AIDS* 2000, **14**:F25–F32.
8. Freiman JP, Helfert KE, Hamrell MR, Stein DS. **Hepatomegaly with severe steatosis in HIV-seropositive patients.** *AIDS* 1993, **7**:379–385.
9. Chatta G, Arief AI, Cummings C, Tierney IM. **Lactic acidosis complicating the acquired immunodeficiency syndrome.** *Ann Intern Med* 1993, **118**:37–39.
10. Bissuel F, Brunell F, Habersetzer F *et al.* **Fulminant hepatitis with severe lactate acidosis in HIV-1-infected patients on didanosine therapy.** *J Intern Med* 1994, **235**:367–372.
11. Fontage IS, Belitos PC, Chaisson RE, Moore RD. **Hepatomegaly and steatosis in HIV-infected patients receiving nucleoside analogue antiretroviral therapy.** *Am J Gastroenterol* 1995, **90**:1433–1436.
12. Lenzo NP, Garas BA, French MA. **Hepatic steatosis and lactic acidosis associated with stavudine treatment in an HIV patient: a case report.** *AIDS* 1997, **11**:1294–1296.
13. Boubaker K, Sudre P, Flepp M *et al.* **Hyperlactatemia and antiretroviral therapy in the Swiss HIV Cohort Study.** *Seventh Conference on Retroviruses and Opportunistic Infections.* San Francisco, January 2000 [abstract 57].
14. Jeppeson J, Hein HO, Suadicani P, Gyntelberg F. **Triglyceride concentration and ischemic heart disease: an eight year follow-up in the Copenhagen male study.** *Circulation* 1998, **97**:1029–1036.
15. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. **Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease.** *Osteoporos Int* 1994, **4**:325–331.
16. Carr A, Samaras K, Thorisdottir A, Kaufmann G, Chisholm DJ, Cooper DA. **Diagnosis, prediction and natural course of HIV protease inhibitor-associated lipodystrophy, hyperlipidaemia and diabetes mellitus.** *Lancet* 1999, **353**:2893–2899.
17. Danner SA, Carr A, Leonard J *et al.* **Safety, pharmacokinetics and preliminary efficacy of ritonavir, an inhibitor of HIV-1 protease.** *N Engl J Med* 1995, **333**:1528–1533.