Osteoporos Int (2007) 18:1345–1353
DOI 10.1007/s00198-007-0428-7

ORIGINAL ARTICLE

Fragility fractures and bone mineral density in HIV positive women: a case-control population-based study

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Received: 16 January 2007 / Accepted: 11 April 2007 / Published online: 31 July 2007

Abstract
Summary This Canadian study of bone health showed that HIV+ women were more likely to have had fragility fractures (OR 1.7) but had BMD values that were not different than women from a national population-based cohort.
Introduction Given that 17.5 million women globally are HIV-infected and living longer on anti-retroviral therapy (ART+), it is essential to determine whether they are at risk for osteoporosis as is currently assumed.
Methods Assessment of osteoporosis risk factors and lifetime low-trauma (fragility) fracture history used a common interviewer-administered questionnaire and phantom-adjusted bone mineral density (BMD). This study compared HIV+ Canadian women with age- and region-matched control women (1:3) from a national population-based study of osteoporosis.
Results One hundred and thirty-eight HIV+ women (100 ART+, 38 ART-) were compared with 402 controls. There were no differences in age (37.7 vs. 38.0 years), BMI (25.0 vs. 26.2), family history of osteoporosis, exercise history, alcohol or calcium intakes, age at menarche, oral contraceptive use or parity. HIV+ cases included more Aboriginal and Black women (12.5% and 16.2 vs. 2% and 1%, respectively), smoked and used injection drugs (53%) more, were more often treated with glucocorticoids, had oligomenorrhea, and reported 10-kg weight cycling. Significantly more HIV+ women reported lifetime fragility fractures (26.1% vs. 17.3; OR 1.7, 95% CI 1.1, 2.6). HIV+ and control women did not differ in BMD: spine 1.0±0.12 vs.1.0±0.14 g/cm^2 (diff. 0.0, 95% CI −0.27, 0.27) or total femur 0.91±0.15 vs. 0.93±0.12 g/cm^2 (diff 0.02, 95% CI +0.005, −0.045).
Conclusion HIV+ women reported significantly more past osteoporotic fractures than population-based controls despite normal BMD. Research is needed to assess bone microarchitecture and develop a reliable fracture risk assessment tool for HIV+ women.

Keywords Bone mineral density · Case-population-control · Fragility fractures · HIV positive · Premenopausal · Women

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Introduction

Women and men infected with the human immunodeficiency virus (HIV+) are living longer with improved quality of life, but have increased risk of chronic diseases such as osteoporosis [1]. Potential causes of osteoporosis in HIV+ women include classical risk factors of low body mass index, weight loss, cigarette, alcohol, and/or narcotic or intravenous drug use and disturbed menstrual cycles, all of which are common in this population. In addition there may be other HIV+ specific risks including, the increasingly perceived link between inflammation and increased bone resorption, malabsorption of calcium, low blood cell counts (hematopoetic and bone remodelling cells are from the same lineage), lipodystrophy and related increased abdominal visceral fat, and lactic acidemia. Finally, it has also been suggested that anti-retroviral drugs (either in general, or specific agents) might have detrimental effects on bone metabolism [2], although this remains controversial and confounds the cohort studies published to date.

HIV+ women have been reported to have low bone mineral density (BMD) [2] and fractures. As shown in Table 1, a total of 25 fractures (that are presumed to be caused by moderate or low trauma) have been reported to date in HIV+ women from five studies [4–8]. Unfortunately, previous studies of BMD in HIV+ women have used dual energy X-ray absorptiometry (DXA) instrument standards [5, 9] that are subject to the healthy cohort bias [10] or data were controlled by convenience samples [3, 6, 11].

To date no sample of HIV+ women with population-based controls has been assessed for low BMD and fracture. It is now known that fragility fractures and BMD vary across regions [12], and thus any multicentre study should match controls by geographical region. The purpose of this study was to determine whether women who were HIV+ and participating in the Canadian Women's HIV+ Study (CWHS) [13] differed in osteoporosis risk factors, BMD or low-trauma fracture from age and region-matched women participating in the population-based national Canadian Multicentre Osteoporosis Study (CaMOS) [14].

Table 1 Previously reported fractures in HIV+ women*

Reference number	Year of publication	Numbers of women	Percentage menopausal	Numbers of fractures
4	1999	2	0	2
5	2004	14	...	14
8	2004	5	...	6
6	2005	31	100%	1
7	2004	60	7%	2
Totals	...	112	...	25

*Ellipses indicate information not available or not applicable.

A second part of this study compares BMD and fractures in women on antiretroviral therapy (ART) for ≥ one year with those who have never been exposed to antiretoviral therapy (to be reported separately; personal communication, DR Burdge).

Methods

Study design

This was a cross-sectional, multicentre, national case-control study. HIV+ women from regional centres of the CWHS were compared with control women from the same regions in the population-based CaMOS. The study was coordinated out of the Oak Tree Clinic at Children's and Women's Health Centre of British Columbia in Vancouver, British Columbia, Canada, with enrolment between May 2001 and September 2003. Primary outcome variables were lumbar spine BMD and lifetime fragility fractures defined as having occurred with a force no greater than a fall from a standing height.

Subjects

Cases were HIV+ non-pregnant women (age 18 and older) from CWHS sites in urban regions in central and western Canada-from Toronto (two medical centres), Hamilton, Kingston, Quebec City, Montreal, Saskatoon, and Vancouver. The majority of the HIV+ women were already enrolled in the CWHS, and were invited to participate in the current study of bone mineral density and fragility fracture. If women were not already enrolled in the CWHS they were offered participation in both studies (under separate consent) at enrollment. The CWHS, at baseline in 1993, had enrolled 413 women from 28 sites in 11 urban centres across Canada [13]. By 1998, 316 women remained in this study [13].

Because the current study was pre-planned to have as a secondary outcome the comparison of BMD and fragility fracture by ART use or not, cases had to either have never used antiretroviral therapy (ART-), or to have used ART for a minimum of a full year (ART+). This exclusion criterion resulted in no women from the Vancouver Centre being unable to participate-the number excluded at other centres is unknown. Except for those who were pregnant, no other consenting women were excluded. Eight of 28 CWHS centres (29%) participated and 138 HIV+ women of the estimated 260 (53%) of women remaining in the CWHS by 2001 [13], participated in this osteoporosis study.

HIV+ women were matched within 5-years of age and by region with controls from seven (of nine) CaMOS centres. Three controls were randomly selected from

women in the baseline CaMOS study for every HIV+ woman. Because the number of premenopausal women (aged 25–45) in each CaMOS centre approximated 70, yet the number of women in each of the CWHS centres varied widely (from five to 104/centre), it was not always possible to obtain more than one age- and region-matched case for the two of the seven centres. For example, some of the 104 cases from Vancouver's Oak Tree Clinic had to be matched more loosely by age (±2 to ±9 years) with Vancouver CaMOS controls. Also, because there were no controls from Montreal, each Montreal case was matched with one from Quebec City (the nearest regional CaMOS centre). Whenever second or third regional controls were unavailable, age-matched controls were randomly selected from across all CaMOS centres.

The CaMOS methodology has been described in detail elsewhere [14]. In brief, the objectives of CaMOS were to ascertain the number of prevalent and incident fractures, obtain clinical measures of BMD and describe the risk factors for osteoporosis in a population-based sample of 9,423 non-institutionalized adult Canadian women and men recruited in 1996–1997. This age and sex-stratified sample included two-thirds women and one-third men, and more elderly participants-at baseline the CaMOS mean age was 62 years. A stratified random sampling technique, utilizing all residential telephone subscribers in postal code areas within a 50-km radius of nine urban centres coast to coast was employed to recruit men and women aged 25 years or more. A participation rate of about 63% was achieved for women fifty years of age and younger. Given that Health Canada reports an HIV+ prevalence of 3–5/10,000 pregnant Canadian women [15], it is estimated that less than one percent of the premenopausal CaMOS controls would be HIV+. None provided this medical history or reported taking ART.

CWHS and CaMOS studies were both approved by the universities affiliated with each of the centres. Consent for this study was additionally obtained from the Clinical Research Ethics Board of the University of British Columbia, by the research review committee of Children's and Women's Health Centre of British Columbia, and by the review boards of the universities in each of the eight CWHS centres. All cases provided written informed consent. CaMOS controls' data were used without additional consent.

Methods

Demographics, medications, reproduction, lifestyle (including exercise in kilojoules energy expenditure/day and cigarettes in 20-pack use/lifetime), dietary (calcium intake) and family osteoporosis histories were included in the interviewer-administered CaMOS Baseline Questionnaire (©1995). Reproductive history included age at menarche, number of live births (parity), the occurrence and duration of absent menstrual flow, hysterectomy and ovariectomy surgeries, menopause and whether women had received hormonal therapy. Falls in the past month and past fracture history were also included, by site of fracture, and type of fracture. Low-moderate trauma (fragility) fractures were included but high trauma and pathological fractures due to malignancy were excluded. By convention, a low-trauma or fragility fracture is defined clinically as one that occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma. Examples of high trauma fracture include those due to a motor vehicle accident, fall from greater than a standing height, or from interpersonal violence, all of which were excluded from this study. Staff trained by local CaMOS personnel, were utilized to interview cases in each of the centres.

The CWHS questionnaire for HIV+ women collected information regarding date of HIV diagnosis, detailed ART history, CD4 counts (including CD4 nadir), history of opportunistic infection, as well as injection drug and other substance use histories.

Clinical and laboratory assessments of both cases and controls included measurements of height and weight without shoes, in light clothing-these were used to calculate body mass index (BMI, weight in kg divided by height in metres squared). BMD by dual energy X-ray absorptiometry (DXA) of the lumbar vertebrae (L_{1-4}), and the non-dominant femoral neck and total femur were measured in cases and controls. Five of the CaMOS centres used Hologic® and two used Lunar® instruments; all data were converted to Hologic® values for analysis. Differences in DXA instruments were removed by measurement of the CaMOS European Spine and Bonafide Phantoms [16] on each of the DXA units used for cases and controls, thus allowing all data to be standardized for accurate comparison. All DXA data were electronically captured and read centrally by a single expert who was blinded to the source of the data. DXA data from cases and controls were directly compared in g/cm^2 because the CaMOS population-based age-matched controls provided the reference standard [10]. It was, therefore, not necessary to use T- or Z-scores in reporting DXA data for the HIV+ women.

Statistical analysis

BMD was analyzed as a continuous variable and fragility fractures as a dichotomous variable with a count. The primary outcome variables were spine BMD and number of lifetime fragility fractures. Data were described using means and standard deviations (SD) or proportions with 95% confidence intervals (CI). Odds ratios were calculated to describe differences between cases and controls. Impor-

tance was attached to any confidence intervals that did not span zero.

Results

A total of 138 HIV+ women (cases) were enrolled and compared with 402 age and geographic region-matched (control) women from CaMOS. Characteristics of the 138 HIV+ cases are as follows: their mean age was 38 years and they had been diagnosed as HIV+ for a mean of 50±47 (SD) months. Fifty-three percent of all cases gave a history of intravenous drug use (IDU). One hundred of the 138 cases had been treated with anti-retroviral therapies (ART) for a mean of 45.9±28.85 months. Seventy-three percent of those on ART had been treated with protease inhibitors.

Cases and controls were well matched for demographics including age and BMI (Table 2). However, the HIV+ population included more Black and First Nations women and fewer Caucasian women. Alcohol use averaged about two drinks a week and didn't differ in cases and controls. Cases reported smoking a greater number of 20-unit packets of cigarettes in their lifetimes with a median of 3832 versus 1962 packets in controls (diff=927; 95% CI 1733, 121).

Socio-economic variables showed important differences (Table 2). Similar proportions of cases and controls lived alone (22.1 and 17.4%, respectively). However 23.8% of cases compared with only 5.4% of controls were adults living solely with one or more child (Odds ratio [OR] 5.18, 95% CI 2.7, 9.9). Fewer cases than controls also lived with another adult (76.2% versus 94.6%). As would be expected, more cases than controls were on disability income support (34.6 versus 1.5%; OR 19.7; 95% CI 7.7, 50.5) and fewer were working full time (22.8 versus 52.0%). Education beyond high school was also significantly more common in controls than in the HIV+ women (68% versus 55%; OR 0.6; 95% CI 0.37, 0.86).

The majority of both the cases (119/136; 87%) and controls (326/401; 81.4%) were pre- or perimenopausal, consistent with their relatively young ages (mean 37.7 and 38 years, respectively). Reproduction history did not differ importantly in HIV+ cases compared with controls in age at menarche, parity, oral contraceptive use and the rare use of estrogen or progestin therapy (Table 3). However, significantly more HIV+ women (29.4%) gave a history of skipping more than three menstrual cycles in their lifetimes compared with 15.4% in controls (OR 2.3, 95% CI 1.5, 3.6).

Amenorrhea for greater than one year occurred in a similar proportion of HIV+ women (17/136; 12.5%) and CaMOS controls (75/402; 18.7%). A total of 12/136 (8.8%) HIV+ women, and 46/401(11.5%) controls were truly menopausal, either naturally or through bilateral ovariectomy (surgical menopause). Natural menopause had occurred in similar numbers of HIV+ women (10/136; 7.3%) and controls (44/401; 11%). Two HIV+ women and 12 control women had surgical menopause with bilateral ovariectomy at time of hysterectomy. Six (4.4%) of the HIV+ women and 30 (7.5%) controls were menstruating regularly until the time of hysterectomy without bilateral ovariectomy.

Importantly, early menopause (≤40 years) occurred in 5 (3.7%) HIV+ women compared to 8 (2%) controls. Three (0.7%) HIV+ women and 1 (0.2%) control woman had true

Table 2 Demographic, socioeconomic and life-style variables of cases and controls*

Variable	Cases (*N*=138)	Controls (*N*=402)	Difference† (95% CI)	Odds ratio‡ (95% CI)
Age	37.7±8.5	38.0±8.2	0.3 (−1.3, 1.9)	...
Ethnicity§				
Caucasian	66/ 136 (48.5)	277/402 (68.9)	...	0.4 (0.28, 0.63)
Black	22/136 (16.5)	4/402(1.0)	−15 (−21.4, −8.9)	18.7 (6.3, 55.3)
First Nations	17/136 (12.52)	8/402 (2.0)	−10.5 (−16.2, −4.7)	6.8 (2.88, 16.2)
Education§ > high school	75/136 (55.1)	274/402 (68.2)	−13.1 (−22.5, −3.5)	0.6 (0.37, 0.86)
Body mass index	25.3±5.5	26.2±5.9	0.9 (−0.23, 2.03)	...
Exercise (Kj/wk)	4443±3424	4688±3678	245 (−456, 946)	...
Dietary calcium¦	731	702	...	...
(Median, mg/d)	Range 21–4300	Range 16–3000		
Alcohol (drinks/week)	2.1±3.7	2.1±3.6	0 (−0.7, 0.7)	...
Cigarettes (packs/life)	4521±4254 median=3832	3594±4127 median=1962	−927(−1773, −121)	...

*Cases are 138 HIV+ women from eight participating centres of the Canadian Women's HIV Study, controls are 402 population-based, age and region matched women from the Canadian Multi-Centre Osteoporosis Study. Values are expressed as mean (standard deviation) unless otherwise indicated. Ellipses indicate not applicable or not significant.

†Difference with 95% Confidence Interval (CI) calculated for variables that are importantly different.

‡Odds ratios with 95% Confidence Interval (CI) calculated for variables that are importantly different.

§Values are expressed as number (percentages).

¦Values are expressed as number and range.

Table 3 Reproductive variables in cases and controls*

Variable	Cases	Controls	Difference† (95% CI)	OR (95% CI)
Menarche age‡	13.0±1.6	12.7±1.5	−0.3 (−0.59, −0.01)	...
Parity ‡ (live births)	1.5±1.0	1.9±0.99	0.40 (0.21, 0.59)	...
OCP use§	112/136 (82.4)	327/402 (81.3)	−1.1 (−8.5, 6.4)	...
Oligomenorrhea (>3 cycles)	40/136 (29.4)	62/402 (15.4)	−14 (−22.4, −5.6)	2.3 (1.5, 3.6)
Menopausal (natural**, surgical¦)	12/136 (8.8) (N=10, S=2)	46/401 (11.5) (N=34, S=12)	...	...
Menopause <40 yr (natural**, Surgical¦)	5/136 (3.7) (N=3, S=2)	8/401 (2) (N=1, S=7)	...	...
Hysterectomy, pre-perimenopausal	6/136 (4.4)	30/401 (7.5)	...	...
Estrogen therapy	13/36 (9.6)	44/402 (10.9)	1.3 (−4.4, 7.2)	...
Progestin therapy	12/135 (8.9)	33/402 (8.2)	0.7 (−6.2, 4.8)	...

*Cases are 138 HIV+ women from eight participating centres of the Canadian Women's HIV Study, controls are 402 population-based, age and region matched women from the Canadian Multicentre Osteoporosis Study. Values are expressed as number (percentages) unless otherwise indicated.
†Difference with 95% confidence interval (CI) calculated for variables that are importantly different.
‡Values are expressed as mean ± standard deviation.
§OCP indicates oral contraceptive pill.
¦ Bilateral ovariectomy.
** Natural menopause is defined as one year without flow.

early menopause (non-surgical). The numbers of women in each group are low, making definite conclusions impossible. Data regarding menopause are summarized in Table 3.

Although a family history of osteoporosis was similar between cases and controls (13.6% vs. 14.2%), other osteoporosis risk factors were more common in HIV+ women compared with controls (Table 4). In addition to greater cigarette use and more skipped periods, cases exceeded controls in pharmacotherapy with glucocorticoids. Furthermore, 39.1% of HIV+ women reported a lifetime history of weight loss and regain of more than 10 kilograms (20 pounds) compared with 18.7% of controls (OR 2.8, 95% CI 1.8, 4.3). Falls were not different between cases and controls-11.0% of HIV+ women had fallen in the past month, which was similar to 8.2% of CaMOS controls (diff=2.8, 95% CI -3.1, 8.7).

HIV+ cases experienced significantly more lifetime fragility fractures-26.1% of cases compared with 17.7% of controls had suffered a low-trauma fracture (OR=1.7, 95% CI 1.1, 2.6). Fracture sites in women who were HIV+ were similar to controls, with the most prevalent being of the ankle, foot and forearm (data not shown). As is conventional in the osteoporosis literature, we have not counted as fragility fractures those of the ankle and foot. About one fifth of the fractures were of the forearm. The numbers of fractures in the two groups were too few and the numbers of sites too many to make a statistical site-specific comparison between the HIV+ women and controls. A multivariate logistic regression analysis of predictors of fragility fracture did not find that HIV+ status, per se, contributed significantly to fracture risk after the differences between the two groups in smoking, pharmacological steroids, oligomenorrhea and weight cycling were taken

Table 4 Osteoporosis risk factors (in addition to cigarette use, Table 1)*

Variable	Cases (*N*=138)	Controls (*N*=402)	Difference† (95% CI)	Odds ratio‡ (95% CI)
Systemic steroid therapy	11/136 (8.1)	12/402 (2.9)	5.1 (−9.9, 0.2)	2.9 (1.2, 6.6)
Oligomenorrhea (>3 cycles)	40/136 (29.4)	62/402 (15.4)	−14 (−22.4, −5.6)	2.3 (1.5, 3.6)
Weight cycling (>20 lbs)	54/138 (39.1)	75/402 (18.7)	−20.4 (−29.5,−11.5)	2.8 (1.8, 4.3)
Falls in previous month§	15/136 (11.0)	33/402 (8.2)	2.8 (−3.1, 8.7)	...
Family history of osteoporosis§	15/110 (13.6)	54/381 (14.2)	0.6 (−6.7, 7.8)	...

*Cases are 138 HIV+ women from eight participating centres of the Canadian Women's HIV Study, controls are 402 population-based, age and region matched women from the Canadian Multicentre Osteoporosis Study. Values are expressed as percentages unless otherwise indicated. Ellipses indicate not applicable or not significant.
†Difference with 95% confidence interval (CI) calculated for variables that are importantly different.
‡Odds ratios with 95% confidence interval (CI) calculated for variables that are importantly different.
§Values are expressed as number (percentages).

into account. Despite a higher prevalence of fragility fractures, bone mineral density of lumbar spine, femoral neck and total femur did not differ between cases and controls (Table 5).

Discussion

These data provide strong evidence that HIV+ women are at greater risk for fragility fractures, and thus the diagnosis of osteoporosis, than women in the general population. Over a quarter of the HIV+ women in this study reported that they had experienced a fragility fracture in their lifetimes, and the risk of having a fragility fracture was 1.7 times that of population matched controls. This was despite the HIV+ women having normal average weight and BMI, being relatively young (average age 38 years) and largely premenopausal. This information is particularly important, given that there are currently an estimated 17.5 million women living with HIV globally.

The HIV+ women in this study had more classical risk factors for osteoporosis, including more systemic steroid therapy, heavier smoking histories, more oligomenorrhea and more weight cycling, than the control women. They also had much higher rates of injection or illicit drug use. It is therefore somewhat puzzling that dual energy X-ray absorptiometry bone mineral density values in the HIV+ women did not differ from controls. Areal BMD reflects an estimate of the mineral within a bone region — it should have few confounds from osteophytes and extra-osseous calcium in women in this young age group.

There are two potential explanations for this observation of significantly greater numbers of lifetime fragility fractures but normal, average bone density in HIV+ women. One is that HIV+ status may be associated with structural bone differences that are not reflected in areal bone density. This is suggested by data from a previous study showing that only four of 11 women with fractures had osteoporosis by BMD [5]. However, these results also fit with increasing awareness that bone geometry and microarchitecture are of key importance as risks for osteoporotic fracture. Further research is required to explore the geometric properties of bone in HIV+ women, and we are planning studies of the proximal femur in both cases and controls using hip structural analysis [17].

A more obvious possibility to explain higher fracture rates in HIV+ women despite similar bone density values is that, given average higher BMD values in Black women [18], and a greater proportion of Black women in the cases compared with controls (16% versus 1.0%) the average BMD in cases is skewed upward by this greater prevalence of Black women. The BMD values at the three sites by race, as shown in Table 5 suggest that slightly higher values at the total hip and femoral neck in Black women may offset the lower values in First Nations women. Results of the spine bone density comparison, our primary BMD outcome, however, cannot explain the fact that BMD values are the same. Spine BMD values in the Black women in this

Table 5 Bone mineral density (BMD) and lifetime fragility fractures*

Variable	Cases (N=138)	Controls (N=402)	Difference† (95% CI)	Odds ratio‡ (95% CI)
$L_{1–4}$ Spine BMD (g/cm^2)	1.0±0.12	1.0±0.14	0.0 (0.27, −0.27)	...
Caucasian	1.0±0.11	1.04±0.13	...	...
Black	0.99±0.12	0.97±0.14	...	...
First Nations	0.94±0.13	1.0±0.12	...	...
Proximal femur BMD (g/cm^2)	0.91±0.15	0.93±0.12	−0.02 (0.005, −0.045)	...
Caucasian	0.91±0.15	0.95±0.12	...	...
Black	0.95±0.16	0.99±0.18	...	...
First Nations	0.86±0.10	0.97±0.19	...	...
Femoral neck BMD (g/cm^2)	0.82±0.14	0.81±0.11	−0.004 (0.19, −0.028)	...
Caucasian	0.81±0.14	0.81±0.12	...	...
Black	0.92±0.18	0.94±0.17	...	...
First Nations	0.74±0.11	0.84±0.15	...	...
Lifetime fragility fractures§	36/138 (26.1)	71/402 (17.3)	−8.4 (−16.6, −0.2)	1.7 (1.1, 2.6)

*Cases are 138 HIV+ women (Caucasian=66; Black=22; First Nation=17) from eight participating centres of the Canadian Women's HIV Study, controls are 402 population-based, age and region matched women (Caucasian=277; Black=4; First Nations=8) from the Canadian Multicentre Osteoporosis Study. Values are expressed as mean ± standard deviation unless otherwise indicated. Ellipses indicate not applicable or not significant.

†Difference with 95% confidence interval (CI) calculated for variables that are importantly different.

‡Odds ratios with 95% confidence interval (CI) calculated for variables that are importantly different.

§Values are expressed as number (percentages).

population were lower than in Caucasians. This may be because most of the Black HIV+ women in Canada are first or second generation immigrants from the Caribbean or Africa, rather than long-time North American residents. These immigrant women may have had chronic malnutrition before coming to Canada and are clearly different from African Americans who tend to have higher BMD than Caucasian Americans.

Only 25 fractures have previously been reported in five studies of bone mineral density and osteoporosis in HIV+ women [4–8] (Table 1). Most of these did not specify the type of fracture by amount of trauma. This study adds to the existing literature by reporting 36 additional fragility fractures, comparing lifetime fragility fractures with a population-based age- and region-matched control group and describing a large number of potential osteoporosis risk factors. Future studies of osteoporosis in HIV+ women need to obtain information about fractures and to determine whether or not these are related to osteoporosis or are due to trauma or malignancy.

A major strength of this study is that careful methodology allowed accurate comparison of BMD despite at least 12 different DXA machines made by two manufactures and in sites separated by over 3,000 kilometers. Also, a shared interviewer-administered osteoporosis questionnaire allowed direct comparison of self-reported data that may relate to osteoporosis and fracture.

While the majority of the HIV+ women in this study were recruited from the Vancouver centre, cases are reasonably representative of Canadian HIV+ women. Women were recruited from seven regional centres across central and western Canada, and their age, race and education appear similar to the 1998 CWHS cohort [13]. A higher percentage of the HIV+ women in this study reported intravenous drug use (53 versus 14%) than in the CWHS [2]. However Health Canada reported in May 2005 that 38.5% of all the women testing HIV+ in Canada from 1985–2003 likely acquired the infection through IDU [13] suggesting that our study population may be similar to HIV+ women in Canada in intravenous drug use. Aboriginal and Black Canadians account for 3.3% and 2.2% of Canada's population, respectively. In 2003, they accounted for 14.4% and 20.7% of reported AIDS cases, and thus the ethnicity of our study HIV+ women clearly parallels the Canadian epidemiologic data.

It was expected that HIV+ women would be of lower socio-economic status than the general population, and this might be associated with smaller body sizes and hence higher osteoporosis risks [19]. Although we did not find a body size difference, this study did confirm several lower socio-economic status indicators including less education, more women living alone with dependent children and being more likely to be on disability.

This study is limited by the lack of explicit questions about HIV status and intravenous drug use in the population-based controls. It is clearly likely that more of the HIV+ women have used intravenous drugs than have women in the general population. Half of the HIV+ women reporting intravenous drug use had a history of 10-kg weight cycling. The use of narcotics, cocaine or amphetamine and their related weight losses probably account for the higher proportion of HIV+ women who reported oligomenorrhea, despite similar parity and menarche age as control women. Addressing intravenous drug use is, therefore, an important aspect of care, and, like smoking, a risk factor for osteoporosis that is potentially amenable to intervention.

The majority of both cases and controls were pre- or perimenopausal. However, 8.8% of the HIV+ women, and 11.5% of controls were truly menopausal, either naturally or through bilateral ovariectomy (surgical menopause). Five (3.6%) HIV+ women and eight (2.0%) control women had early (<40 yrs) menopause, with three HIV+ women having early non-surgical menopause.

Hypogonadism in its most subtle forms, such as variations in menstrual cycle length and ovulation disturbances (including anovulatory and short luteal phase cycles), are important for BMD [19–21]. Little is known about menstrual cycles and ovulation in HIV+ women. A menstrual calendar study in 802 women, of whom 273 were HIV+, showed that HIV+ women had more variable cycle lengths and a tendency toward abnormally short cycles [19]. These cycle changes were associated with higher viral loads and lower CD4 T-cell counts [19]. Variable, sparse data suggest that ovulation is disturbed in HIV+ women-three small studies of HIV+ women with regular cycles showed that 22% (from a Vancouver study [22]), 29% and 48%, respectively, were anovulatory [21, 23]. Although heterogeneous, these data show a higher percentage of anovulatory cycles than in the two available population-based studies of ovulation (12 and 18 percent, respectively) [19, 24]. Early menopause before age 40, although shown in only three HIV+ women in this study, may also occur more frequently in HIV+ women [23].

It remains to be determined whether part of the reason for increased fractures in this population of HIV+ women relates to the majority of the population who were treated with modern highly active antiretroviral therapy [2]. Literature results are mixed about whether ART use is associated with bone loss because of adverse drug effects or with bone gain as HIV+ women become less ill, more mobile, gain weight, and have less inflammation. Investigation of fracture and BMD in these cases by ART use or not, is currently ongoing (Burdge, personal communication).

There are currently no guidelines for the treatment of pre- or perimenopausal osteoporosis and fracture and

certainly none for HIV+ women. Optimizing vitamin D and calcium intakes, assisting with withdrawal from intravenous drug use, and obtaining and maintaining optimal exercise and normal weight are likely important. Cyclic medroxyprogesterone (10 mg/d) or oral micronized progesterone (300 mg at bedtime) for 14 days a cycle may be helpful given the increased prevalence of menstrual cycle and ovulation disturbances shown in this and other studies [21–24], and because cyclic progestin therapy has been shown in a randomized placebo-controlled trial to increase spinal bone density in healthy, active young women with abnormal menstrual cycles [25].

Summary and conclusion

In summary, this cross-sectional case population-based control study clearly shows, for the first time, that pre- and perimenopausal women who are HIV+ are at increased risk for fragility fracture compared with women in the general population. It did not, however, show that spinal BMD is lower, suggesting that BMD is not a sensitive predictor of fracture risk in younger women who are HIV+. These data further suggest that osteoporosis-related risk factors may eventually be used to predict the fracture risk shown here-these include cigarette abuse, 10- kilogram weight cycling history, oligomenorrhea and past treatment with glucocorticoids. These risk factors should be sought to help predict risk for fragility fracture in HIV+ women.

It is clear that fracture risks should be addressed as part of the routine care of HIV+ women. Further investigation is needed to develop a reliable fracture risk assessment approach for HIV+ women.

Acknowledgements The authors thank all the women who participated. This study would not have been possible without approval from the Data Analysis and Publications Committee of the Canadian Multicentre Osteoporosis Study and the cooperation of C. Berger and the CaMOS Data Management Centre. Dr. D. Burdge and C. Morris obtained funding for this study as a grant from CANFAR. The following physician directors of individual Canadian Women's HIV Study centres, in addition to the authors (DRB, CH, MBK and SW) contributed importantly to this study: A Rachlis; F. Smaill; S Trottier, W Wobeser, and K Williams. The bone mineral density measurements were made possible with the assistance of Dr. K. Kruse and the Osteoporosis Clinic at the Women's Health Centre in Vancouver. Dr. Stuart Jackson provided quality assurance and converted all DXA data based on common phantom data. Dr. R. Sebaldt oversaw data entry for the CWHS data.

The Canadian Multicentre Osteoporosis Study was funded by the Senior's Independence Research Program, through the National Health Research and Development Program of Health Canada (Project No. 6605-4003-OS), The Medical Research Council of Canada, MRC-PMAC Health Program, Merck Frosst Canada Inc., Eli Lilly Canada Inc., Procter and Gamble Pharmaceuticals Canada Inc., Novartis Pharmaceuticals Inc., Aventis Pharma Inc., The Dairy Farmers of Canada, The Arthritis Society.

References

1. Thomas J, Doherty SM (2003) HIV infection-a risk factor for osteoporosis. J Acquir Immune Defic Syndr 33(3):281–291
2. Guaraldi G, Ventura P, Albuzza M, Orlando G, Bedini A, Amorico G et al (2001) Pathological fractures in AIDS patients with osteopenia and osteoporosis induced by antiretroviral therapy. AIDS 15(1):137–138
3. Dolan SE, Huang JS, Killilea KM, Sullivan MP, Aliabadi N, Grinspoon S (2004) Reduced bone density in HIV-infected women. AIDS 18(3):475–483
4. Stephens EA, Das R, Madge S, Barter J, Johnson MA (1999) Symptomatic osteoporosis in two young HIV-positive African women. AIDS 13(18):2605–2606
5. McComsey GA, Huang JS, Woolley IJ, Young B, Sax PE, Gerber M et al (2004) Fragility fractures in HIV-infected patients: need for better understanding of diagnosis and management. J Int Assoc Physicians AIDS Care (Chic.Ill.) 3(3):86–91
6. Yin M, Dobkin J, Brudney K, Becker C, Zadel JL, Manandhar M et al (2005) Bone mass and mineral metabolism in HIV+ postmenopausal women. Osteoporos.Int published on-line March 2005
7. Madeddu G, Spanu A, Solinas P, Calia GM, Lovigu C, Chessa F et al (2004) Bone mass loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. Q J Nucl Med Mol Imaging 48(1):39–48
8. Martin K, Lawson-Ayayi S, Miremont-Salame G, Blaizeau MJ, Balestre E, Lacoste D et al (2004) Symptomatic bone disorders in HIV-infected patients: incidence in the Aquitaine cohort (1999–2002). HIV Med 5(6):421–426
9. Bruera D, Luna N, David DO, Bergoglio LM, Zamudio J (2003) Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS 17(13):1917–1923
10. Tenenhouse A, Joseph L, Kreiger N, Poliquin S, Murray TM, Prior JC et al (2000) Estimation of prevalence of low bone density in Canadian women and men using a population-specific DEXA reference standard: the Canadian Multicentre Osteoporosis Study (CaMos). Osteoporos Int 11:897–904
11. Loiseau-Peres S, Delaunay C, Poupon S, Lespessailles E, Ballouche N, Arsac P et al (2002) Osteopenia in patients infected by the human immunodeficiency virus. A case control study. Joint Bone Spine 69(5):482–485
12. O'Neil TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ et al (1996) The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. J Bone Mineral Res 11:1010–1018
13. Hankins C, Lapointe N, Walmsley S (1998) Participation in clinical trials among women living with HIV in Canada. Canadian Women's HIV Study Group. CMAJ 159(11):1359–1365
14. Kreiger N, Tenenhouse A, Joseph L, Mackenzie MD, Poliquin S, Brown JP et al (1999) The Canadian Multicentre Osteoporosis Study (CaMos): Background, rationale, methods. Can J Aging 18:376–387
15. Archibald, C. HIV/AIDS EPI Updates. http://www.phac-aspc.gc.ca. 1-13-2006. Ref Type: Electronic Citation
16. Pearson D, Cawte SA, Green DJ (2002) A comparison of phantoms for cross-calibration of lumbar spine DXA. Osteoporos Int 13(12):948–954
17. Petit MA, Beck TJ, Lin HM, Bentley C, Legro RS, Lloyd T (2004) Femoral bone structural geometry adapts to mechanical loading and is influenced by sex steroids: The Penn State Young Women's Health Study. Bone 35(3):750–759
18. Luckey MM, Wallenstein S, Lapinski R, Meier DE (1996) A prospective study of bone loss in African-American and White women-a clinical research center study. J Clin Endocrinol Metab 81:2948–2956

19. Sowers M, Randolph JF, Crutchfield M, Jannausch ML, Shapiro B, Zhang B et al (1998) Urinary ovarian and gonadotropin hormone levels in premenopausal women with low bone mass. J Bone Min Res 13(7):1191–1202
20. Prior JC, Vigna YM, Schechter MT, Burgess AE (1990) Spinal bone loss and ovulatory disturbances. N Engl J Med 323:1221–1227
21. Sioban H, Schuman P, Cohen M, Ohmit SE, Cu-Uvin S, Lin X et al (2000) Effect of HIV infection on menstrual cycle length. J Acquir Immune Defic Syndr 24:68–75
22. Money DM, Arikan YY, Remple V, Sherlock C, Craib K, Birch P et al (2003) Genital tract and plasma human immunodeficiency virus viral load throughout the menstrual cycle in women who are infected with ovulatory human immunodeficiency virus. Am J Obstet Gynecol 188(1):122–128
23. Clark RA, Mulligan K, Stamenovic E, Chang B, Watts H, Benson C (2001) Frequency of anovulation and early menopause among women enrolled in selected adult aids clinical trials group studies. JID 184:1325–1327
24. Swain MC, Bulbrook RD, Hayward JL (1974) Ovulatory failure in a normal population and in patients with breast cancer. J Obstet Gynaecol Br Commonw 81(8):640–643
25. Prior JC, Vigna YM, Barr SI, Rexworthy C, Lentle BC (1994) Cyclic medroxyprogesterone treatment increases bone density: a controlled trial in active women with menstrual cycle disturbances. Am J Med 96:521–530