CRD summary
The authors concluded that human immunodeficiency virus-positive patients who had been exposed to antiretroviral therapy or protease inhibitors had a higher rate of reduced bone mineral density and osteoporosis than non-exposed patients, but the influence of other relevant variables could not be assessed. A more cautious conclusion might have been more appropriate in view of the potentially biased included observational studies.

Authors' objectives
To compare rates of osteopenia and osteoporosis between antiretroviral therapy (ART)-treated and non ART-treated, and protease inhibitor (PI)-treated and PI-untreated human immunodeficiency virus (HIV)-positive patients. The review also compared rates of osteoporosis and osteopenia between HIV-positive and HIV-negative patients, but this abstract only refers to the effects of ART and PI interventions.

Searching
MEDLINE and EMBASE were searched from inception to November 2005 for studies published in English; the search terms were reported. In addition, a search of the Science Citation Index was undertaken based on the authors of identified studies, and reference lists of identified studies and reviews were screened.

Study selection
Study designs of evaluations included in the review
Cross-sectional studies that compared at least two groups of patients were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared ART-treatment with non ART-treatment (ART-naive) and PI-treatment with no PI-treatment were eligible for inclusion in the review. The mean duration of PI-treatment ranged from 24 to 110 months.

Participants included in the review
Studies of adults (aged over 18 years) who were HIV-positive were eligible for inclusion. The mean age of the participants in the included studies ranged from 31 to 56 years.

Outcomes assessed in the review
Studies that measured bone mineral density (BMD) using dual X-ray absorpiometry were eligible for inclusion. The review assessed the proportion of patients with reduced BMD (osteopenia and osteoporosis) and osteoporosis at any of the following sites using the World Health Organization (WHO) definitions: lumbar spine, total hip, femoral neck, distal radius or total body. The WHO defines osteopenia as a T-score between -1 and -2.5 and osteoporosis as a T-score of -2.5 or less.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and resolved any disagreements on inclusions through discussion.

Assessment of study quality
The authors stated that they assessed validity but did not explicitly report the criteria used. In the review, the role of adjusted analysis and potential confounders was discussed. The authors did not state how the validity assessment was performed.
Data extraction
Two reviewers independently extracted the data onto a standardised form. For each study, the reviewers calculated the proportion of patients with reduced BMD or osteoporosis in each treatment group. Where required, authors were contacted for additional data (details of the data sought were reported).

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using random-effects models with inverse variance weighting. For each outcome of interest, the potential for publication bias was assessed using a funnel plot and tested statistically using Begg's test.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Heterogeneity among the studies was examined using meta-regression and sensitivity analyses that included the identification of influential studies. Subgroup analysis was used to compare: PI-treated patients with patients who had never been exposed to PI; PI-untreated with PI-treated patients only in studies in which PI-untreated patients had generally received ART; and crude and adjusted analyses for 3 studies of PI-treated versus PI-untreated patients that presented adequate data.

Results of the review
A total of 17 cross-sectional studies compared ART-treated with non ART-treated patients and PI-treated with non PI-treated patients. Some studies evaluated ART and PI treatments. Ten cross-sectional studies (n=1,065) compared ART-treated and ART-untreated patients. Fourteen cross-sectional studies (n=1,201) compared PI-treated and PI-untreated patients.

ART-treated versus ART-naive patients.
In all but one study, the majority of the patients were male. In studies providing relevant data, ART groups had a higher average age and had known HIV infection for longer than ART-naive groups. In most studies the basal metabolic index was similar between groups. None of the studies adjusted for potential confounding factors. Reduced BMD was significantly more common in ART-treated patients than in ART-naive patients (OR 2.5, 95% CI: 1.8, 3.7; 10 studies). The odds of osteoporosis were significantly more common in ART-treated patients than in ART-naive patients (OR 2.4, 95% CI: 1.2, 4.8; 7 studies). No statistically significant heterogeneity was detected for either analysis (p=0.47 and p=0.73, respectively).

There was no evidence of publication bias for either outcome.

PT-treated versus PI-untreated patients.
Twelve studies provided data on the prevalence of osteoporosis, of which 11 provided information on previous exposure of the PI-untreated group to PI; of these 11 studies, 9 reported that PI-untreated patients were PI-naive and 3 reported that some of the PI-untreated patients were ART-naive. Four studies included only men, 2 included only women, and others were mixed but predominantly male. In 3 studies the gender ratio was not balanced in PI-treated and PI-untreated groups. Age and basal metabolic index were generally similar between patient groups.

Reduced BMD was significantly more common in PI-treated patients than in PI-untreated patients (OR 1.5, 95% CI: 1.1, 2.0; 14 studies).

The odds of osteoporosis were significantly greater in PI-treated patients than in PI-untreated patients (OR 1.6, 95% CI: 1.1, 2.3; 12 studies).

No statistically significant heterogeneity was detected for either analysis (p=0.25 and p=0.52, respectively).

Two studies adjusted for confounders and the authors adjusted the analysis for confounders for a third study. For these three studies, crude and adjusted analyses produced similar results.
The funnel plot of BMD showed some asymmetry but Begg’s test was not statistically significant (p=0.16). There was no evidence of publication bias for studies included in the osteoporosis analysis.

Authors’ conclusions
HIV-positive patients who had been exposed to ART or PI had a higher rate of reduced BMD and osteoporosis than non-exposed patients, but the influence of other relevant variables could not be assessed.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. It was not clear why only cross-sectional studies were included rather than potentially higher-quality controlled clinical trials. Searching only a limited number of potential sources, only including English language reports and excluding unpublished studies might have resulted in the omission of other relevant studies; the authors did examine the potential for publication bias and found no strong evidence. Methods were used to minimise reviewer error and bias in the study selection and data extraction processes. An adequate validity assessment was not performed, although the role of potential confounding factors was discussed.

The studies were combined using an appropriate meta-analysis, statistical heterogeneity was assessed and the influence of various factors on the results of PI treatment was examined. The authors’ conclusion appears to reflect the review findings, but a more cautious conclusion may have been more appropriate in view of the potentially biased included studies. The included studies were observational and differences between patient groups that account for the apparent decreases in BMD associated with treatment cannot be excluded.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that there is a need for additional controlled longitudinal studies to evaluate the effects of HIV treatment and ART and PI treatment on BMD and the risk of fractures.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.