

14TH ANNUAL CONFERENCE
OF THE BRITISH HIV ASSOCIATION (BHIVA)



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Harvard Medical School, Boston, USA

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Diagnosis, Mechanisms and Management of HIV- Associated Bone Loss

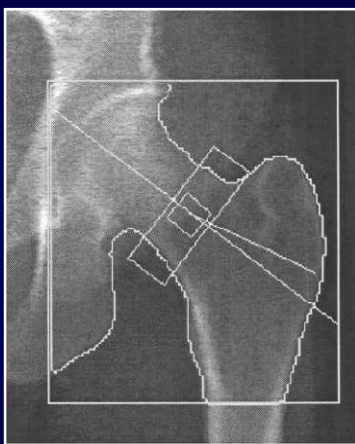
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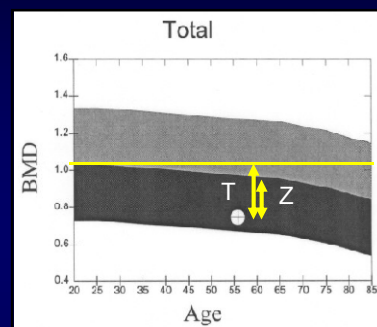
Outline

- **Assessment of Bone Density in HIV**
 - Reduced Bone Density
 - Fracture Risk
- **Pathogenesis**
 - Nutritional/Body Composition
 - Endocrine Factors
 - Antiretroviral Therapy
- **Treatment Strategies**
 - Ca/D
 - Testosterone and Exercise
 - Estrogen
 - GH/GHRH
 - Bisphosphonates

Use of DXA for BMD Analysis



Fracture risk doubles for each 1SD decrease in T score of hip



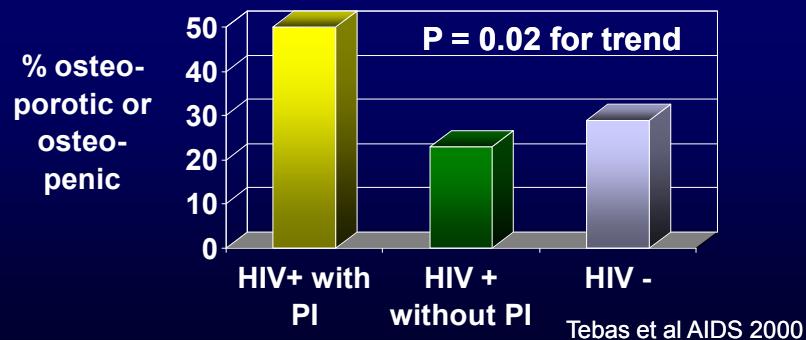
DXA Results Summary:

Region	Area (cm ²)	BMC (g)	BMD (g/cm ²)	T - Score	PR (%)	Z - Score	AM (%)
Neck	5.27	3.26	0.617	-2.3	66	-1.4	76
Troch	10.62	5.83	0.550	-1.8	71	-1.5	74
Infer	19.47	17.30	0.889	-1.7	74	-1.4	78
Total	35.37	26.39	0.746	-1.9	72	-1.5	77
Ward's	1.28	0.75	0.590	-1.4	75	0.1	102

Total BMD CV 1.0%, ACF = 1.011, BCF = 0.999, TH = 6.560
 WHO Classification: Osteopenia
 Fracture Risk: Increased

Reduced Bone Density in in the Era of HAART

- Osteoporosis or osteopenia was observed in 73% of HIV+ men compared to 30% HIV-
- The risk of osteoporosis was increased with protease inhibitor (PI) exposure

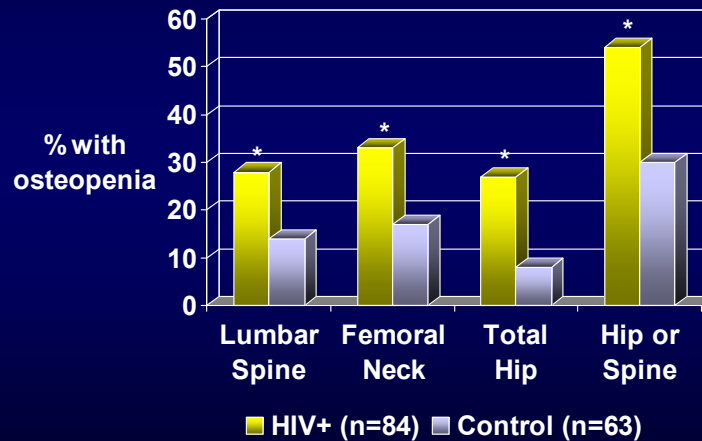


Evidence of Low Bone Density in HIV-Infected Women

- Cross-sectional study of bone density and markers in 84 HIV+ and 63 HIV- women
- Subjects were matched at baseline for age, BMI, and race

Dolan et al AIDS 2004

Prevalence of Osteopenia in HIV infected Women



* P<0.05

Dolan et al AIDS 2004

Reduced Bone Density in HIV-Infected Women

- In a multivariate regression analysis controlling for age, BMI, menstrual function and race, HIV-infected subjects were **2.6 (95% CI 1.2-5.8, p=0.02)** times more likely to demonstrate osteopenia compared to the healthy control subjects
- No relationship with PI use

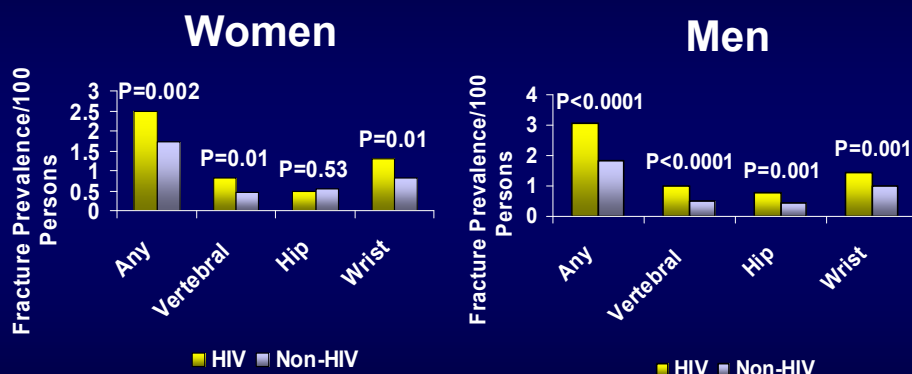
Dolan et al AIDS 2004

Fracture Risk Cohort

- 8,525 HIV and 2,208,792 non-HIV patients from a large healthcare system database (MGH and Brigham and Women's hospitals in Boston) over 11 years from 1996-2007
- ICD-9 codes used to assess fractures

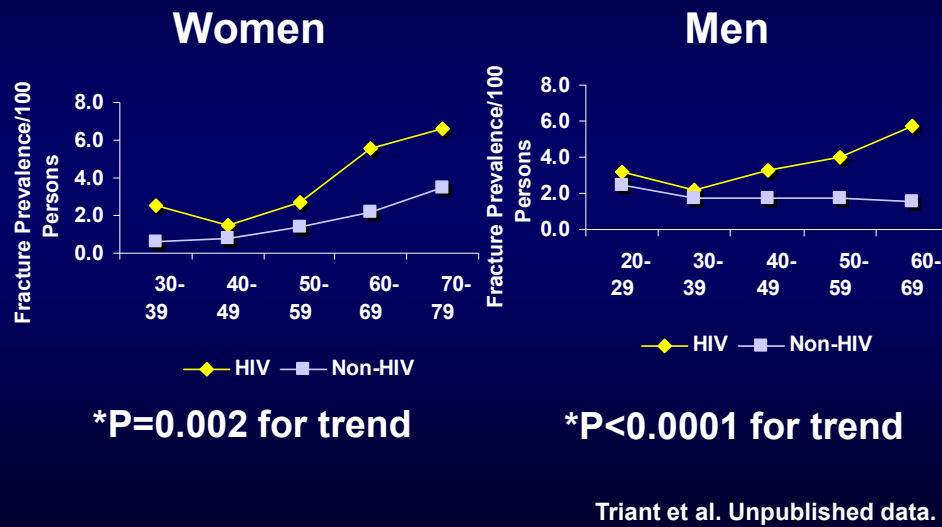
Triant et al. Unpublished data.

Fracture Prevalence by Site in HIV Infection



Triant et al. Unpublished data.

Fracture Prevalence Stratified by Age and Gender

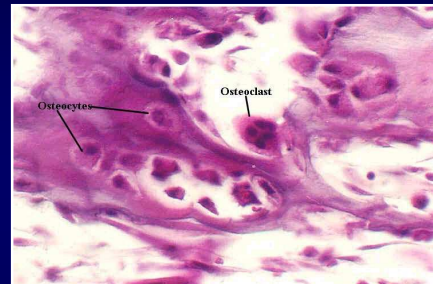
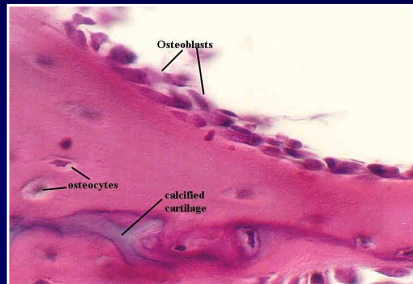


Reported Fracture Risk

- In 138 HIV+ women compared to 402 age and region-matched controls, lifetime fragility fractures were increased in HIV+ women vs. HIV- women with odds ratio 1.7 (95% CI 1.1-2.6)
- In 328 HIV+ men compared to 231 age matched controls, fracture rate was increased by 38% (P=NS)

Prior et al Osteoporos Int. 2007
Arnsten et al. AIDS 2007

Bone Turnover



Bone loss in HIV is characterized by an imbalance between bone formation and resorption

Bone Markers in HIV-Infected Women

	HIV + (N=84)	Control (n=63)
Osteocalcin (ng/mL)	22.9 (1.6)	20.4 (1.0)
Urine NTx (nM/mMCr)	39.6 (3.5)*	29.9 (2.0)
OPG (pmol/L)	4.76 (0.23) [†]	3.39 (0.17)

* P<0.05 † P<0.01

Dolan et al AIDS 2004

BMD in Older Patients with HIV Infection

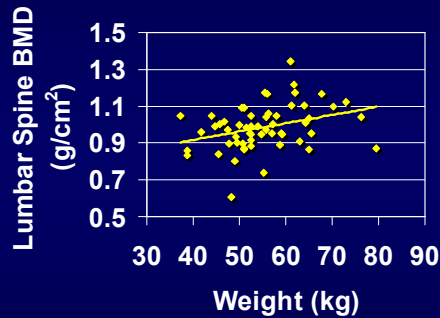
- 57 HIV-infected patients vs. 47 healthy controls over age 55
- When controlling for age, sex, race, BMI, BMD was lower in HIV group
- Low BMI was the most important risk factor
- Tenofovir use was associated with decreased BMD at spine and PI use was associated with decreased BMD at hip

Jones et al. Osteoporos Int 2007

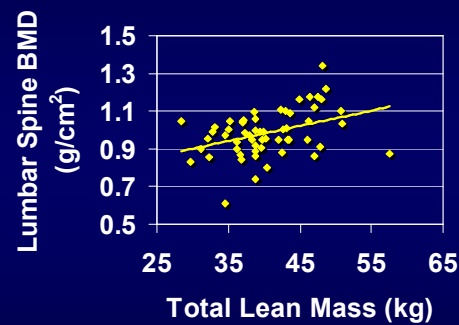
Potential Mechanisms for Reduced Bone Density

- Nutritional factors, e.g. weight loss and loss of lean body mass
- Endocrine factors, e.g. hypogonadism, estrogen deficiency and androgen deficiency in women, Vitamin D deficiency
- Changes in body composition, increased visceral adiposity, low GH
- Effects of ARV therapy and viral factors

Bone Density, Weight and Lean Mass in HIV+ Women



$r=0.33$, $P=0.01$



$r=0.38$, $P=0.003$

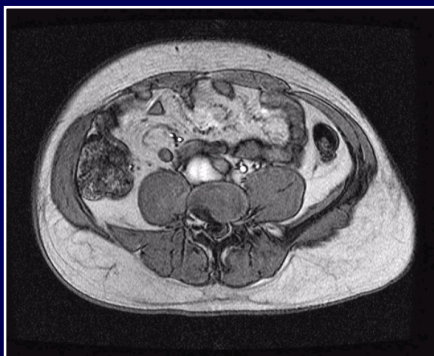
Endocrine Parameters

- Hypogonadism is observed in 20-50% of HIV+ men, contributing in part to reduced bone density
- Androgen deficiency common in HIV-infected women and is associated with reduced bone density, in both premenopausal and perimenopausal women
- HIV-infected women in menopausal transition may have greater estrogen deficiency and greater reductions in bone density, but further studies are needed in this regard
- Vitamin D deficiency- some data to suggest decreased conversion of 25D to 1,25D in HIV

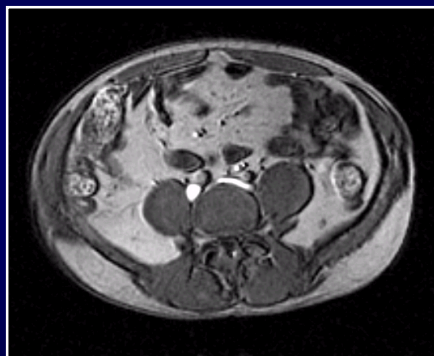
HIV Lipodystrophy

- Characterized by
 - ↑ Visceral adiposity
 - Impaired glucose tolerance
 - ↑ Lipid levels
 - ↓ Growth hormone
- Metabolic abnormalities have been associated with reduced bone density and abnormal bone turnover in this population

Visceral Fat by Cross-Sectional MRI at L4



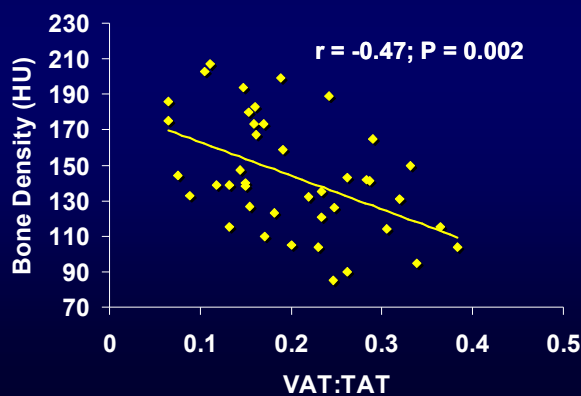
Control Subject



Subject with Lipodystrophy

Bone and Body Composition

- Lumbar spine BMD was reduced in men with HIV lipodystrophy compared with both control groups independent of PI use



P = 0.007 after multivariate regression controlling for age, BMI, lowest body weight, PI use, and extremity fat

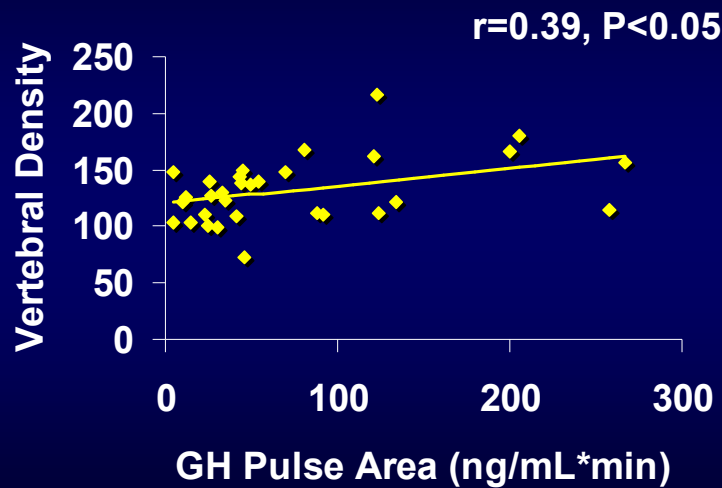
Huang et al AIDS 2001

Reduced Growth Hormone Levels and Bone Density

- GH levels are reduced in HIV lipodystrophic patients in association with increased visceral adiposity
- GH has direct effects on osteoclast and osteoblast differentiation and proliferation as well as via IGF-I
- In a cross-sectional analysis of 31 HIV+ men with lipodystrophy, bone density, GH secretion and markers of bone formation and resorption were analyzed

Koutkia et al JCEM 2005

GH Secretion and Bone Density



Koutkia et al JCEM 2005

Antiretroviral Medications

- Tebas et al demonstrated a trend of reduced bone density in association with PI use
- PIs may affect Vitamin D synthesis through suppression of 1α -hydroxylase
- Other studies have shown no association between HAART or PI use and reduced bone density

Tebas et al. AIDS 2002, Cozzolino et al. AIDS 2003, Brown et al. JCEM 2004, Fairfield et al. JCEM 2001, Huang et al. AIDS 2001

Role of PI's in Low BMD

- Study population of 128, predominantly male (86%), 68% on PI
- Presence of osteopenia or osteoporosis in 46%
- Low BMD associated with weight loss, steroid use, smoking and longer duration of HIV infection
- Low BMD not associated with PI use

Mondy et al. CID 2003

Antiretroviral Medications and Bone Density in Women

- 274 HIV+ women compared to 152 controls
- BMD was lower in ART-naïve patients than controls ($P=0.003$) and PI-HAART compared with non-PI HAART users ($P=0.01$)
- Lopinavir use was associated with low hip BMD ($r= - 0.46$, $P=0.006$) and efavirenz use with higher hip BMD ($r=0.32$, $P=0.004$)

Anastos et al. Antivir Ther 2007

Viral Effects on Bone

- Serrano et al reported reduced serum osteocalcin in patients with greater HIV disease severity
- Among HIV infected men with fat accumulation, studies have shown a significant correlation between viral load and PINP ($r=0.36$, $P=0.05$) and CTx ($r=0.35$, $P=0.05$)

Serrano et al Bone 1995
Koutkia et al JCEM 2005

Potential Treatment Strategies

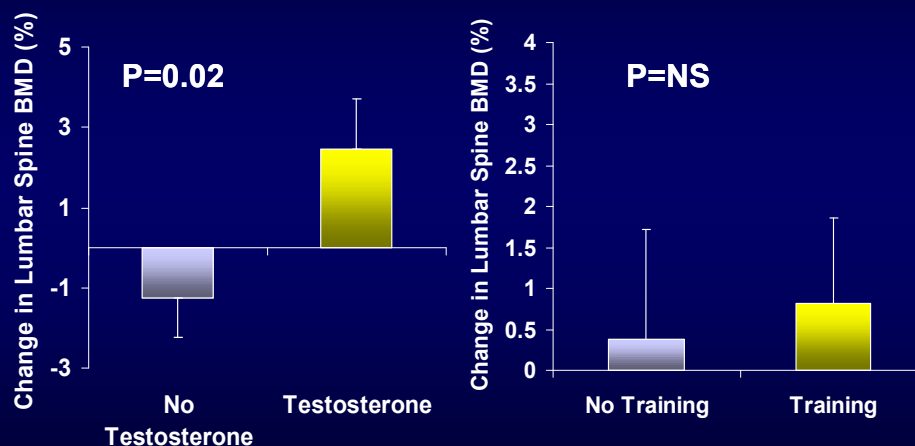
- Ca/D-incomplete data, probably reasonable as a minimum strategy, but not very effective compared to other strategies
- Testosterone (men, ? women)
- Estrogen- presumably reasonable in postmenopausal women, but no good data
- Exercise
- GH/Growth Hormone Releasing Hormone
- Bisphosphonates (Alendronate)

Testosterone and Exercise

- 50 hypogonadal HIV + men with HIV and low weight were randomized to treatment
- Testosterone 200 mg/week IM vs identical placebo x 12 weeks
- 50% received progressive resistance training x 12 weeks

Fairfield et al JCEM 2001

Testosterone & Exercise Effects on Bone



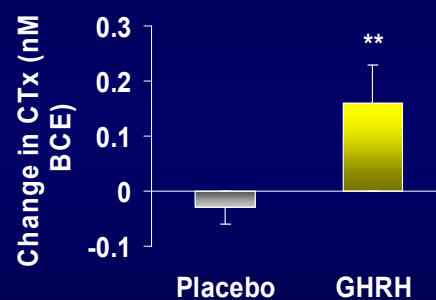
Fairfield et al JCEM 2001

Growth Hormone Releasing Hormone

- Our group conducted randomized, placebo-controlled trial of 1mg SQ BD GHRH in HIV-infected men
- At baseline, thirty-five percent of our subjects demonstrated a bone density SD score < -1.0 and 3% demonstrated a SD score of < -2.5 SD

Koutkia et al JCEM 2005

Effects of GHRH on Markers of Bone Turnover



Koutkia et al JCEM 2005

Alendronate Treatment

- 31 HIV-infected subjects were enrolled in a 48-week prospective, randomized, open-label study
- Randomized to receive 70 mg of alendronate (n=15) or no drug (n=16) weekly for 48 weeks
- All subjects received calcium and vitamin D supplementation
- Entry criteria included lumbar spine BMD T-score < -1.0

Mondy et al JAIDS 2005

Alendronate Treatment

	Alendronate + Vitamin D + Calcium	Vitamin D + Calcium Alone
Age at Baseline	46 ± 2	43 ± 2
% Male	93%	81%
BMI at Baseline	25.3 ± 0.9	24.6 ± 0.7
% Change in Lumbar Spine BMD (95% CI)	5.2% (1.3-6.4)	1.3% (-2.4-4.0)

Mondy et al JAIDS 2005

Alendronate Safety Profile

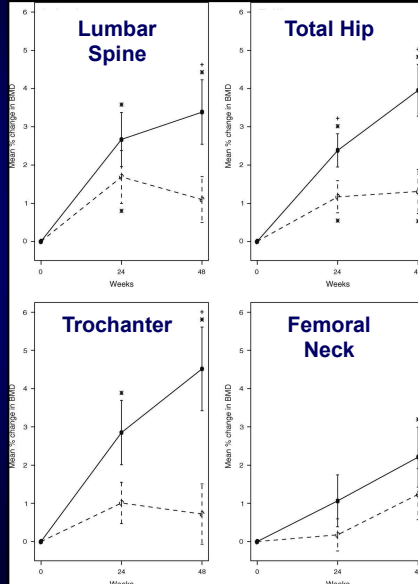
- One subject discontinued treatment in each arm
- There were no serious adverse events
- Important to know that osteonecrosis of the jaw can occur in a very small percentage of women receiving potent bisphosphonates, undergoing dental work. This was not seen but studies too small to make definitive conclusions.

Alendronate Treatment in HIV

- 82 subjects (71% male) with HIV and BMD t-score < -1.5
- Randomized, placebo-controlled trial of alendronate for 48 weeks
- All subjects received calcium and vitamin D

McComsey et al AIDS 2007

Alendronate Treatment in HIV



- No gender differences were observed
- Alendronate was well-tolerated and adverse events were not significantly increased in the treatment group

McComsey et al AIDS 2007

Conclusions

- Men and women with HIV disease are characterized by reduced bone density and disturbances in bone turnover.
- Bone loss is associated with low weight, ? HAART use (probably specific to individual agents), increased visceral adiposity, low GH, reduced testosterone and estrogen levels.
- The data are sufficient to recommend screening in high risk HIV patients, eg low weight, hypogonadal, perimenopausal, prior fracture.
- Screening for vitamin D deficiency is also probably useful, especially at northern latitudes and in patients with poor dairy intake.
- Bisphosphonate (alendronate) therapy is a safe and effective strategy to increase BMD, probably best reserved for patients with osteoporosis or osteopenia that is progressing.

Important Remaining Questions

- What is the specific etiology of bone loss in HIV?
- What role is played by specific antiretroviral therapies?
- What is the role for androgens in HIV-infected women?
- What is the role of estrogens in menopausal HIV-infected women?
- Do other bisphosphonates work in this population? Are they safe in HIV patients?
- Formal recommendations for screening and treatment? For the moment, use guidelines in non HIV, but understand unique risks and considerations related to bone loss in HIV.



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