

HIV and Osteoporosis

Dr Karen Walker-Bone

Associate Professor (Hon Consultant) Rheumatology

MRC Lifecourse Epidemiology Unit

Southampton

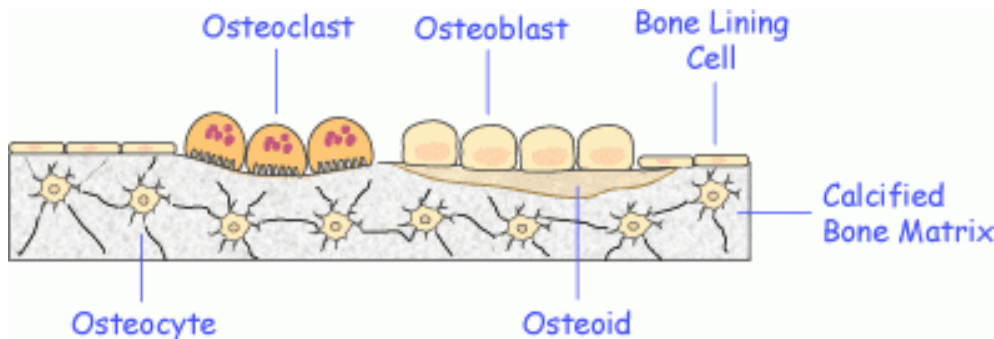
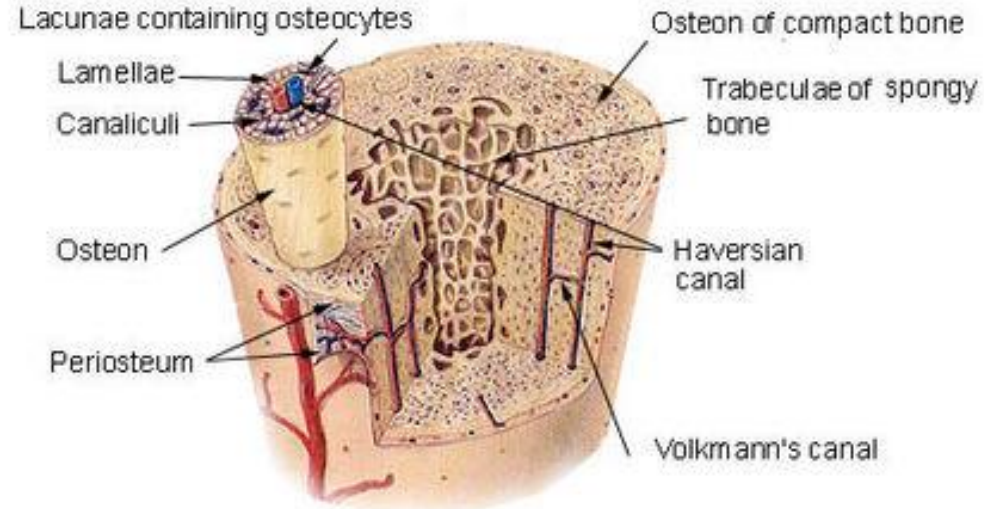
Aims

- Healthy bone
- Definition of osteoporosis
- Diagnosis of osteoporosis
- Risk factors
- Vitamin D and osteomalacia
- Guidelines for screening
- Management of osteoporosis

Healthy bone

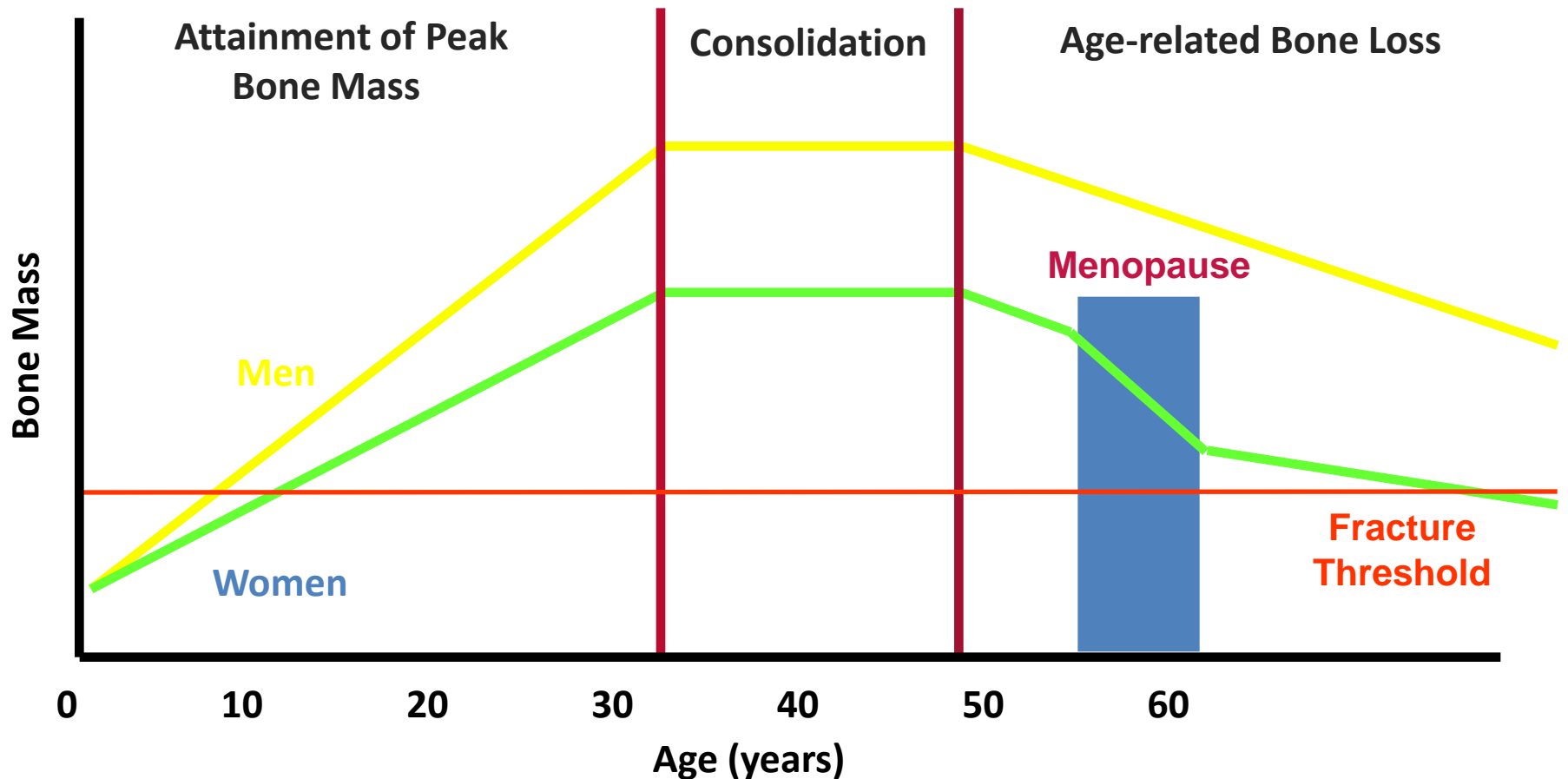
- Most bones have a basic structure composed of:
 - an outer cortical zone (resists deformation)
 - an inner trabecular or spongy zone (complex system of internal supports)
- Bone marrow fills the spaces within the trabeculae

Compact Bone & Spongy (Cancellous Bone)



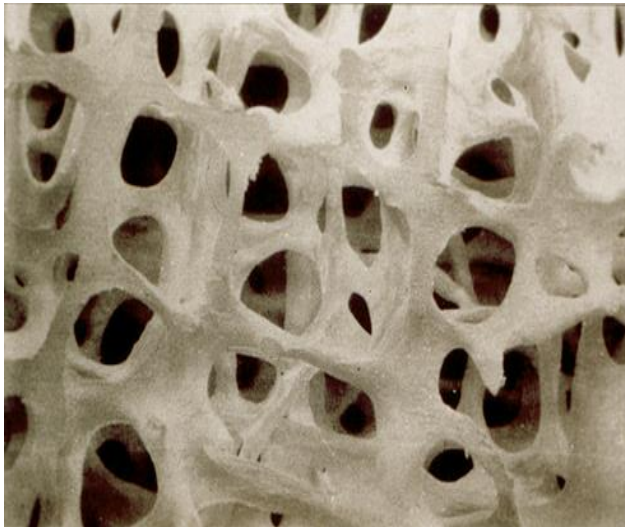
- Bone undergoes constant remodelling with bone formation by osteoblasts and resorption by osteoclasts

Age related changes in bone mass

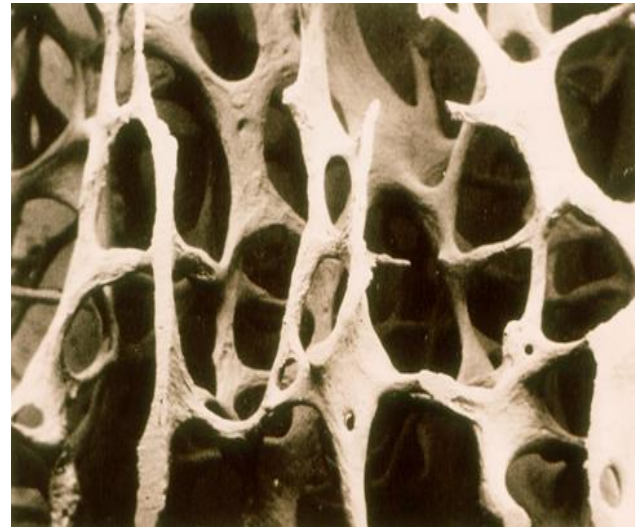


Definition of Osteoporosis

‘A disease characterised by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk’



Normal bone

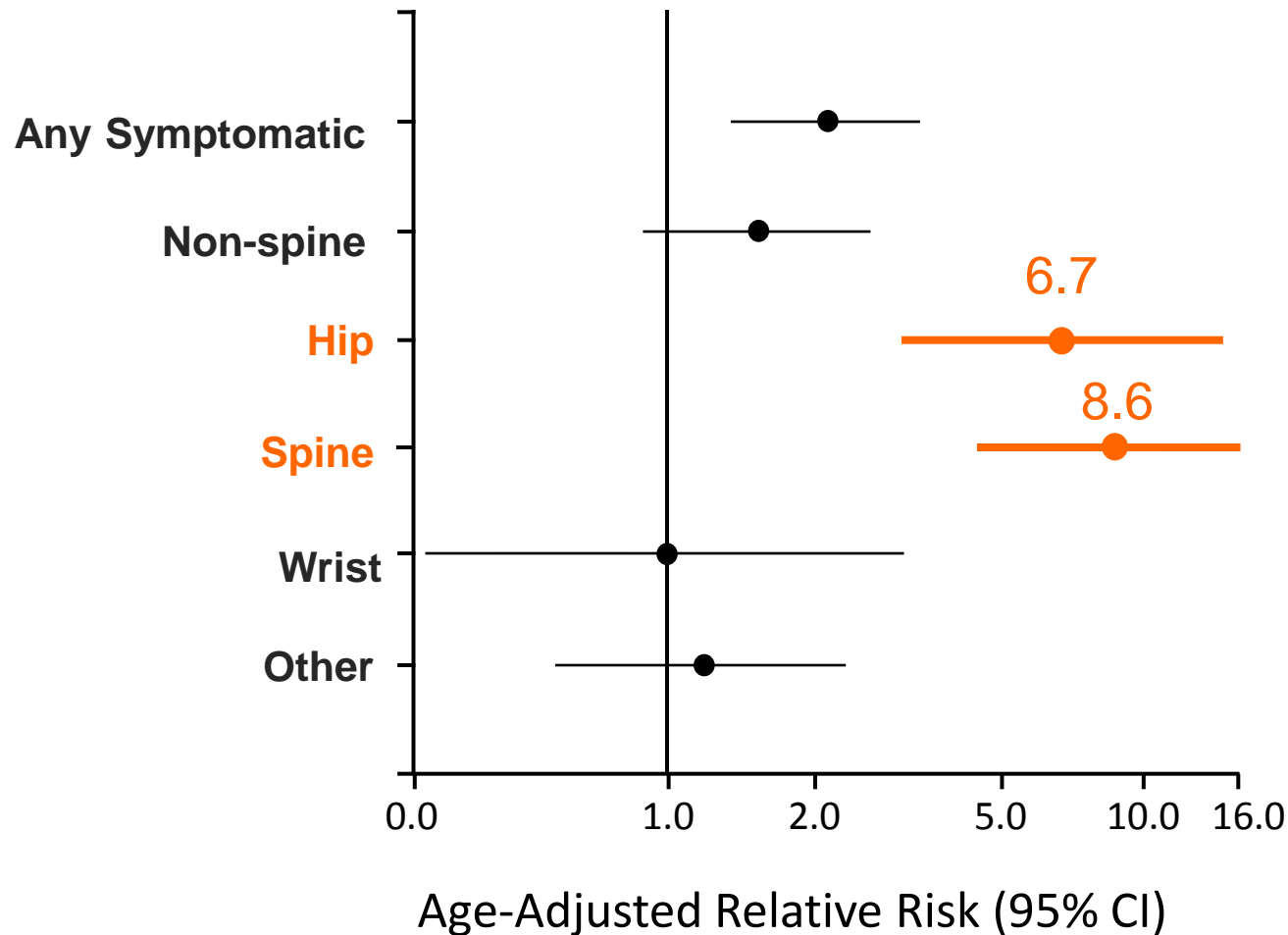


Osteoporosis

Clinical Manifestations

- Fracture
- Hip / vertebrae / Colles'
- Humerus / pelvis / ankle
- Vertebral fracture is sub-clinical in 60-70% of cases
 - Height loss
 - Kyphosis
 - Back pain

Relative Risk of Death Following Clinical Fractures Fracture Intervention Trial (FIT)*



Cauley JA, et al. *Osteoporos Int.* 2000;11:556-561.

*6459 postmenopausal women ages 55-81 years followed for an average of 3.8 years.

Prior fracture and subsequent fracture risk

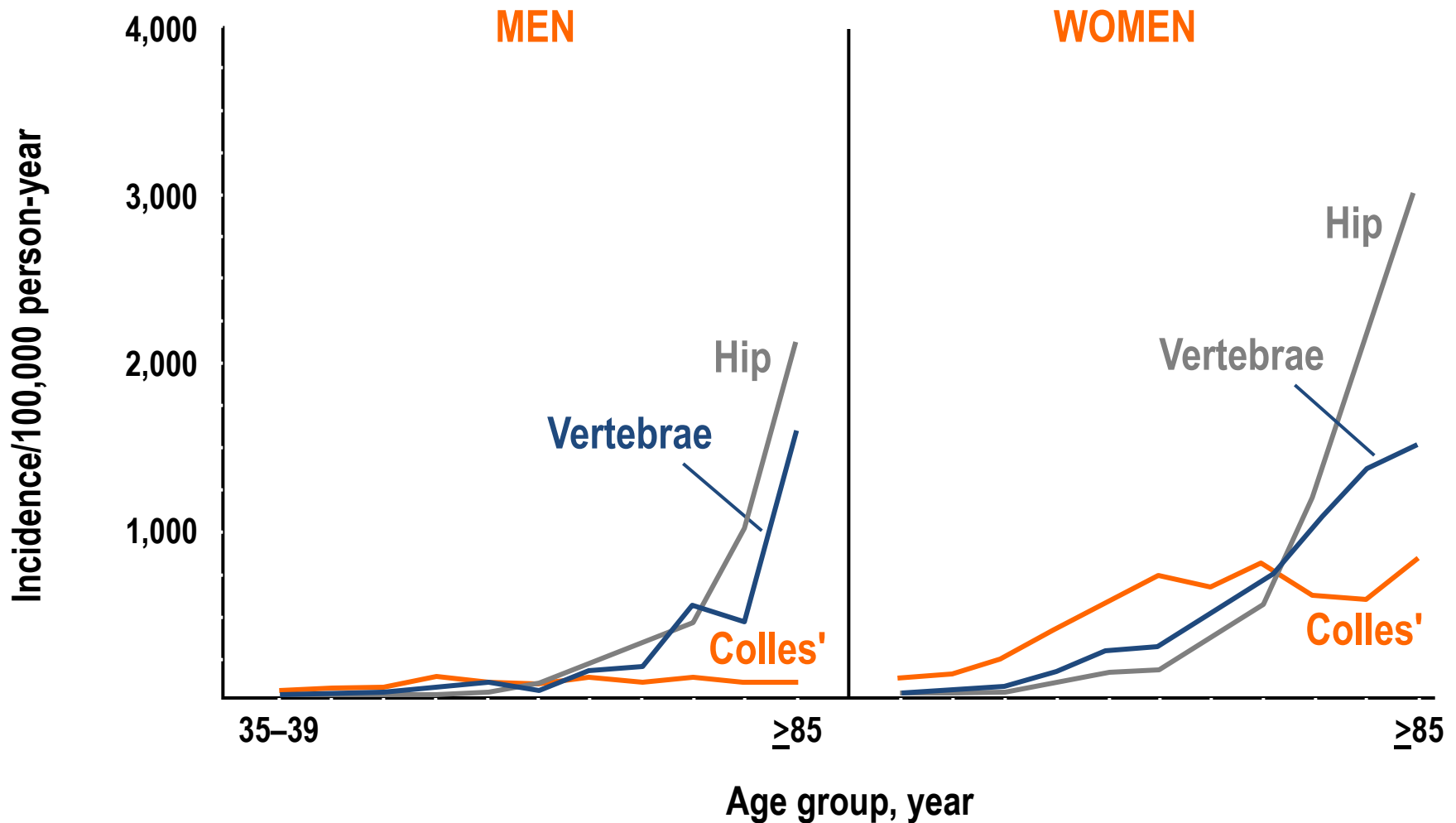
Pooled risks: 34 studies

Prior fracture	Subsequent fracture (RR)			
	Wrist	Spine	Hip	Any
Wrist	3.6	7.2	1.5	2.0
Spine	1.4	19.0	2.1	2.7
Hip	-	2.5	1.6	1.7
Pooled	2.3	7.2	1.8	1.8

Epidemiology of osteoporosis in the UK

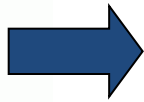
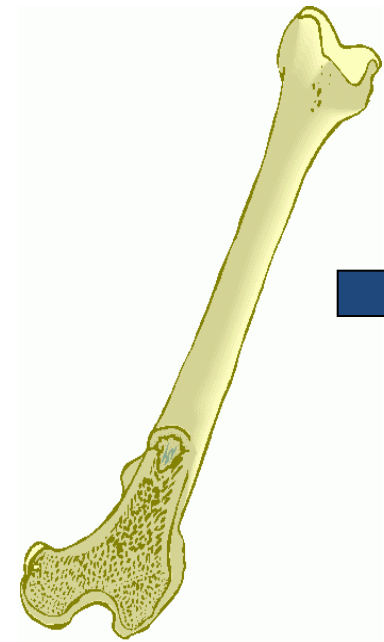
- Approximately 250,000 fragility fractures annually in the UK
- Lifetime risk for 50 year old woman: 1:2 and 50 year old man 1:5
- Cost fractures: £1.7 billion in UK
- 70,000 hip fractures occur each year
 - Occupy 20% of orthopaedic beds
 - Totals up to 800,000 bed-days
 - 50% of hip fracture patients lose the ability to live independently
 - Up to 20% hip fracture patients die during the subsequent year as a result of fracture

Incidence rates of common osteoporotic fractures

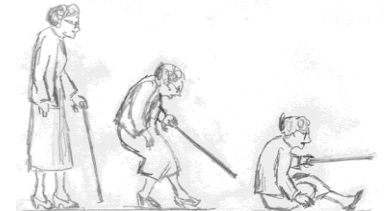
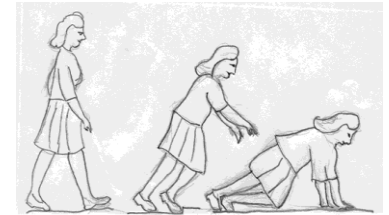


Aetiology of fracture

High- or low-
impact trauma

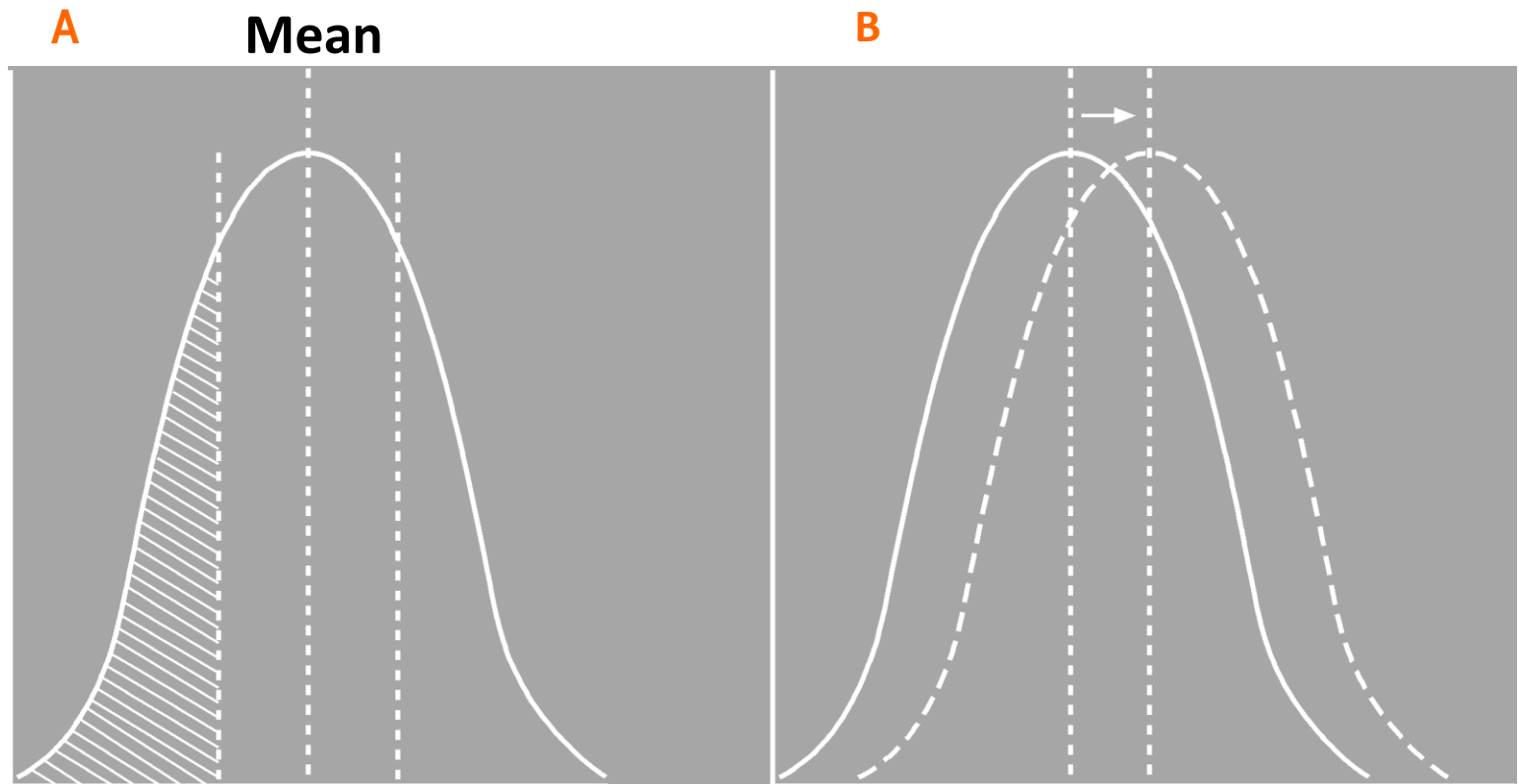


Bone quantity
and quality



Osteoporosis is a condition for which prevention, rather than cure, is clearly desirable..

Preventive strategies for osteoporosis



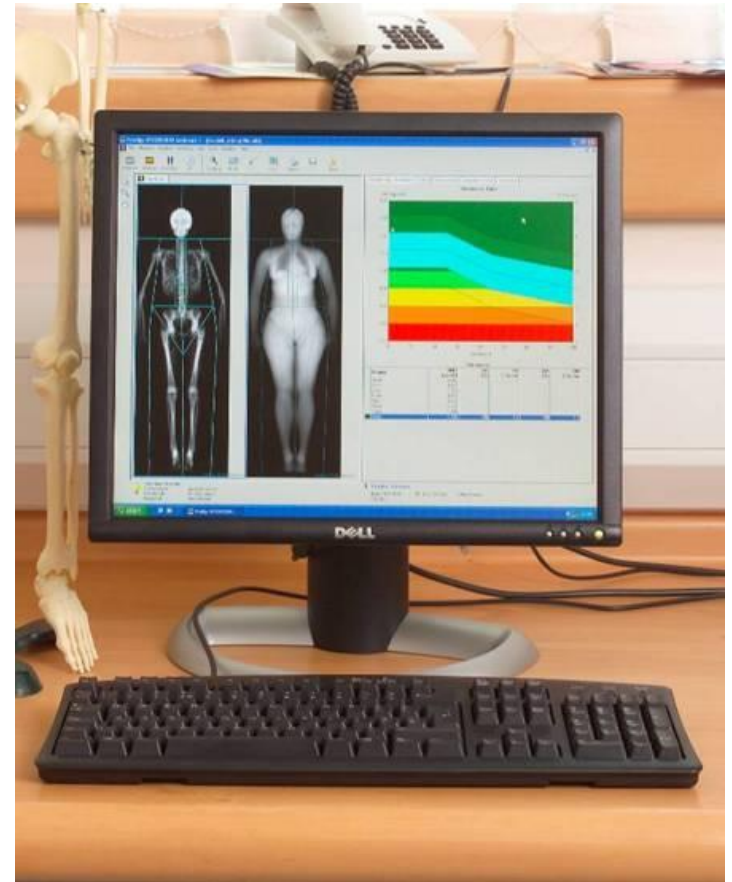
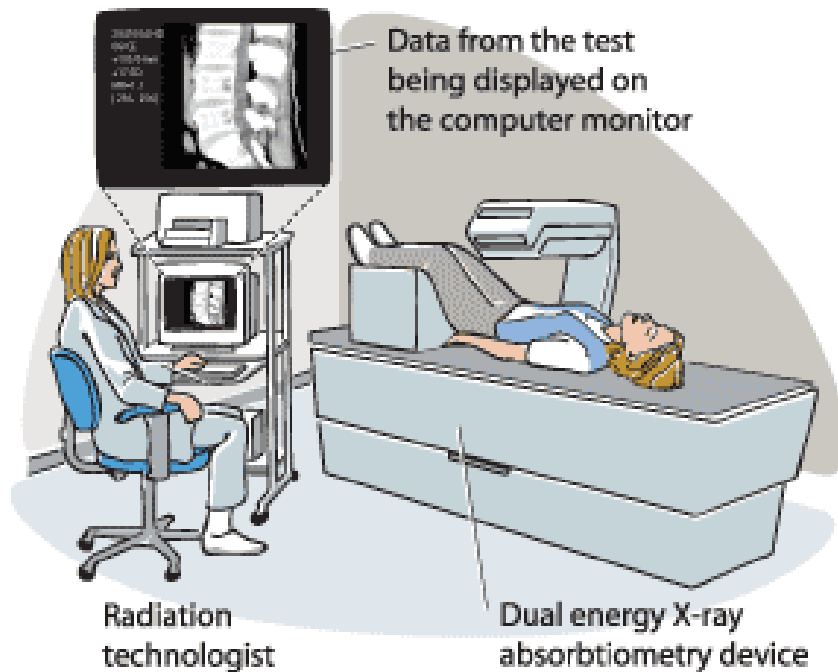
Bone density

**Target those with a low
bone density**

Bone density

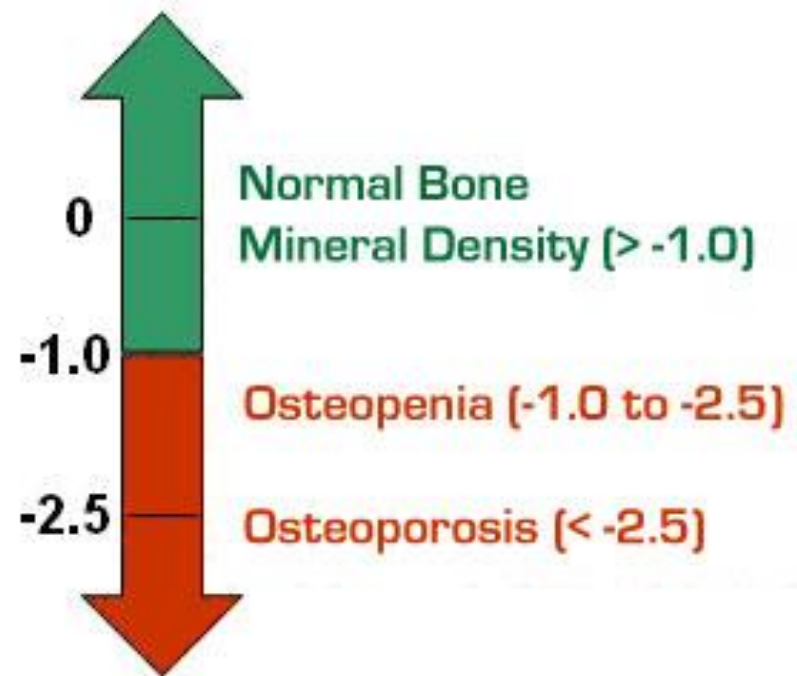
**Move entire distribution by
intervening in everyone**

The Diagnosis of Osteoporosis



DEXA: Definitions of osteoporosis

- T scores = standard deviation comparisons with the mean of a female population at peak bone mass
- MINUS T score indicates less than young adult mean
- Osteoporosis is defined as T score < -2.5 (WHO)
- Osteopenia is defined as T score < -1.0 (WHO)
- Z scores are age- and sex-matched reference scores



About DEXA

- Usually measured at spine (L1-L4) and proximal femur (axial and appendicular)
- Can be estimated throughout the skeleton
- Lumbar spine readings may be inaccurate in the presence of: scoliosis; osteophytes; extra-skeletal calcification; vertebral deformity
- Estimates areal bone mineral mass only – cannot take into account FALLS or structural or geometric factors
- Has been validated for estimating subsequent risk of fracture among men and women aged > 50 years (but not in those aged < 50 years)

Risk Factors for Low BMD in HIV-Infected Patients

Traditional

Female gender	Decreased physical activity
Smoking	
Caucasian	Decreased bone acquisition
Family history	Amenorrhoea/ premature menopause
Increasing age	
Alcohol	Opiates

Secondary

Chronic diseases

(e.g. hyperthyroidism, hyperparathyroidism, liver disease, rheumatological conditions, eating disorders, etc.)

Hypogonadism

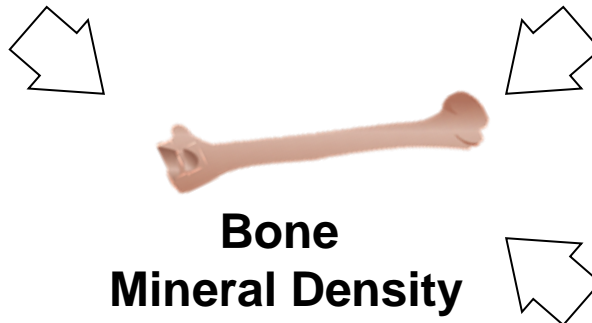
Renal dysfunction

Malnutrition/low BMI

Medications

(e.g. glucocorticoids, anticonvulsants, anticoagulants)

Vitamin D deficiency



**Bone
Mineral Density**

HIV-related

Antiretroviral therapy
(e.g. PIs, NRTIs)

Viral factors
(e.g. p55 gag, gp120)

Immunologic effects
(e.g. cytokines - $\text{TNF}\alpha$, IL-6)

Ageing

Prevalence of Low BMD is Higher in HIV-Infected Patients

Publication	Number of patients		Overall prevalence of low BMD, %	
	HIV+	HIV–	HIV+	HIV–
Tebas <i>et al</i> 2000	95	17	40	29
Knobel <i>et al</i> 2001	80	100	87.5	30
Huang <i>et al</i> 2002	15	9	66.6	11
Loiseau-Peres <i>et al</i> 2002	47	47	68	34
Bruera <i>et al</i> 2003	111	31	64.8	13
Teichman <i>et al</i> 2003	50	50	76	4
Amiel <i>et al</i> 2004	148	81	82.5	35.8
Brown <i>et al</i> 2004	51	22	63	32
Dolan <i>et al</i> 2004	84	63	63	35
Madeddu <i>et al</i> 2004	172	64	59.3	7.8
Yin <i>et al</i> 2005	31	186	77.4	56
Total	884	670	40-87.5%	4-35.8%

Derived from Brown TT & Qaqish RB. AIDS 2006; 20:2165-2174

Bone mineral and HIV infection

- Generally small studies (<1000 patients in total)
- Grouped osteoporosis and osteopenia together ('low bone mass')
- Heterogeneous populations: infected males and females, different acquisition HIV
- Variable attention to confounding risk factors e.g. use of glucocorticoids, cigarette smoking

Osteopenia: 33-65% (OR 6.4, 95% CI 3.7-11.3)

Osteoporosis: 6-16% (OR 3.7, 95% CI 2.3-5.9)

HIV and fracture

- Growing evidence that the increased prevalence of osteopenia and osteoporosis is associated with the expected effect on fracture rates in HIV patients

Triant VA et al. JCEM 2008;93:3499-3504

Grund et al, AIDS, 2009

FRAX[®] WHO Fracture Risk Assessment Tool

- Determines 10 year absolute risk of fracture
- Risk factors used in FRAX[®] calculation
 - Femoral neck T-score (BMD)
 - Age
 - Sex
 - Low body mass index
 - Previous low trauma fracture
 - Family history of hip fracture
 - Current cigarette smoking
 - Steroid exposure
 - Rheumatoid arthritis
 - Secondary causes of osteoporosis
 - High alcohol intake (≥ 3 units/day)

The screenshot shows the FRAX WHO Fracture Risk Assessment Tool web interface. The header is red with the FRAX logo and title. Below the header is a navigation bar with links: HOME, CALCULATION TOOL, PAPER CHARTS, FAQ, and REFERENCES. A language selection dropdown is on the right. The main section is titled 'Calculation Tool' and contains a message: 'Please answer the questions below to calculate the ten year probability of fracture with BMD.' On the left, there are flags for the UK and US, and conversion tools for weight (pound to kg) and height (inch to cm). The main form is titled 'Questionnaire' and contains 12 numbered questions. Questions 1-4 are for age, sex, weight, and height. Questions 5-9 are for previous fracture, parent fracture, current smoking, glucocorticoids, and rheumatoid arthritis. Questions 10-12 are for secondary osteoporosis, alcohol intake, and femoral neck BMD. Each question has radio buttons for 'No' and 'Yes'. There are 'Clear' and 'Calculate' buttons at the bottom right of the questionnaire.

FRAX[®] WHO Fracture Risk Assessment Tool

HOME CALCULATION TOOL PAPER CHARTS FAQ REFERENCES Select a Language

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: UK Name / ID: About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth: Age: Y: M: D: 11. Alcohol 3 or more units per day: No Yes

2. Sex: Male Female 12. Femoral neck BMD (g/cm²): Select DXA: Clear Calculate

3. Weight (kg): 4. Height (cm): 10. Secondary osteoporosis: No Yes

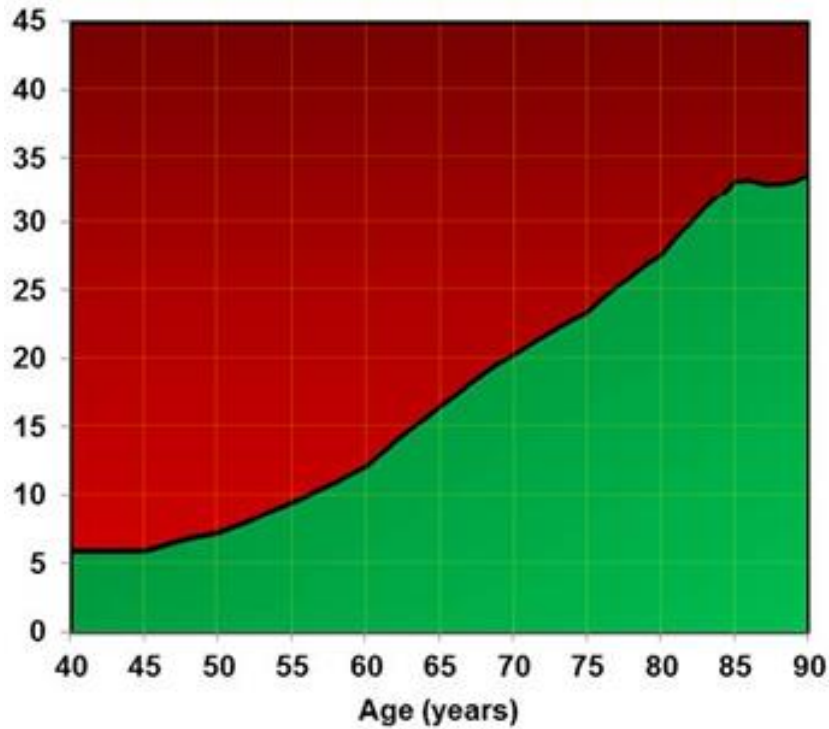
5. Previous fracture: No Yes 6. Parent fractured hip: No Yes

7. Current smoking: No Yes 8. Glucocorticoids: No Yes

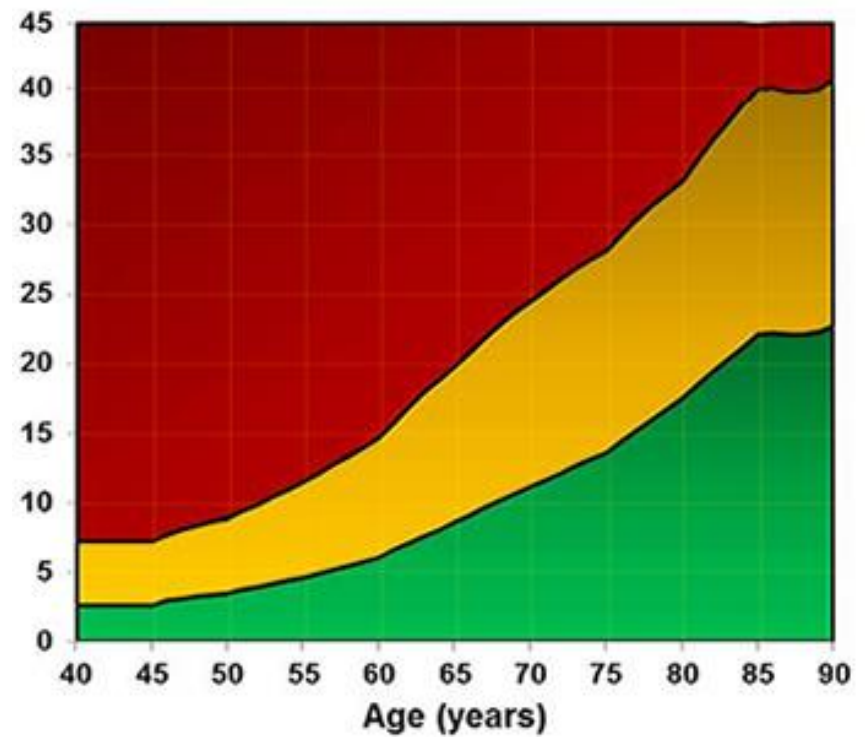
9. Rheumatoid arthritis: No Yes

NOGG guidance algorithms

WITH A BMD MEASUREMENT



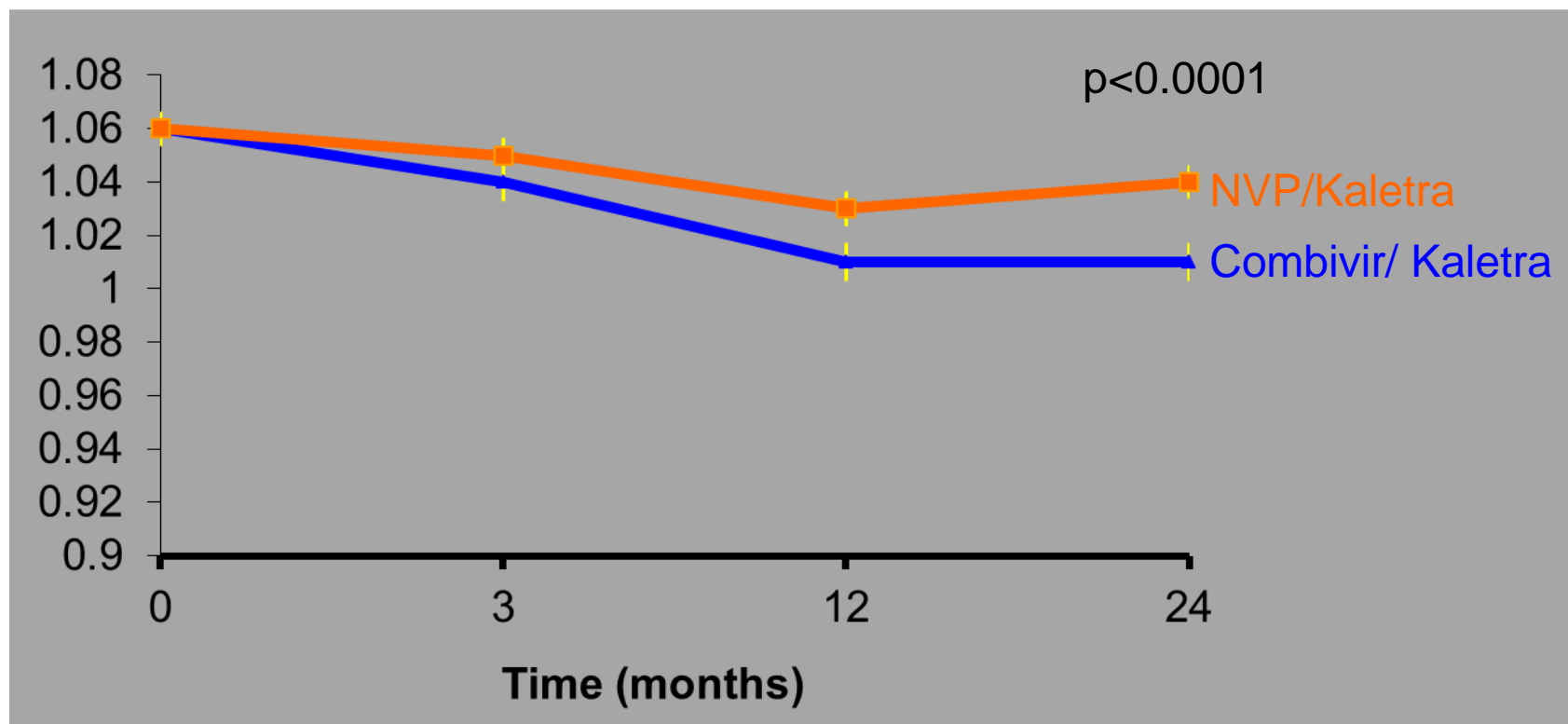
WITHOUT A BMD MEASUREMENT



Antiretroviral therapy and bone

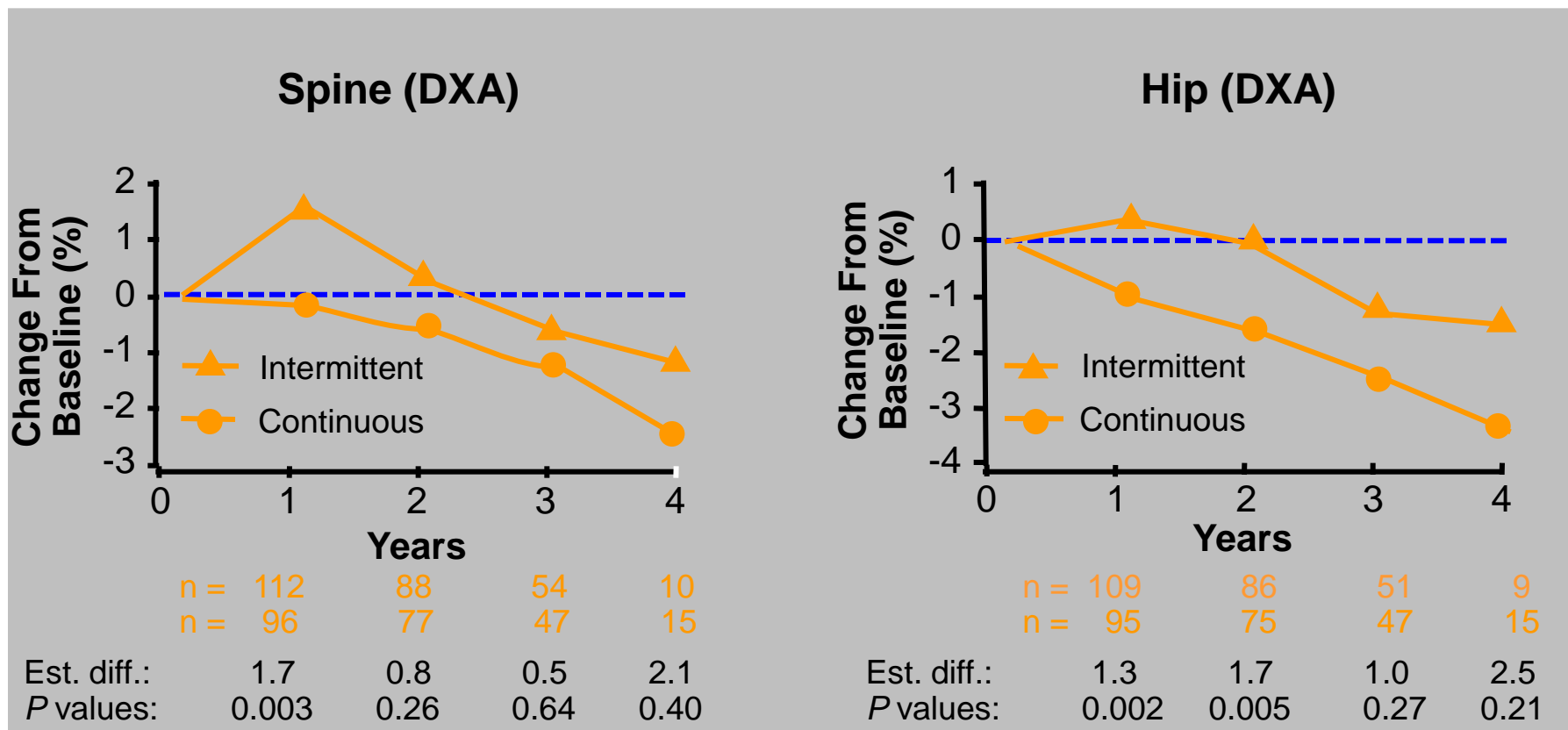
Longitudinal studies of naïve patients commencing HAART

Lumbar spine BMD
measured by DEXA
g/cm²



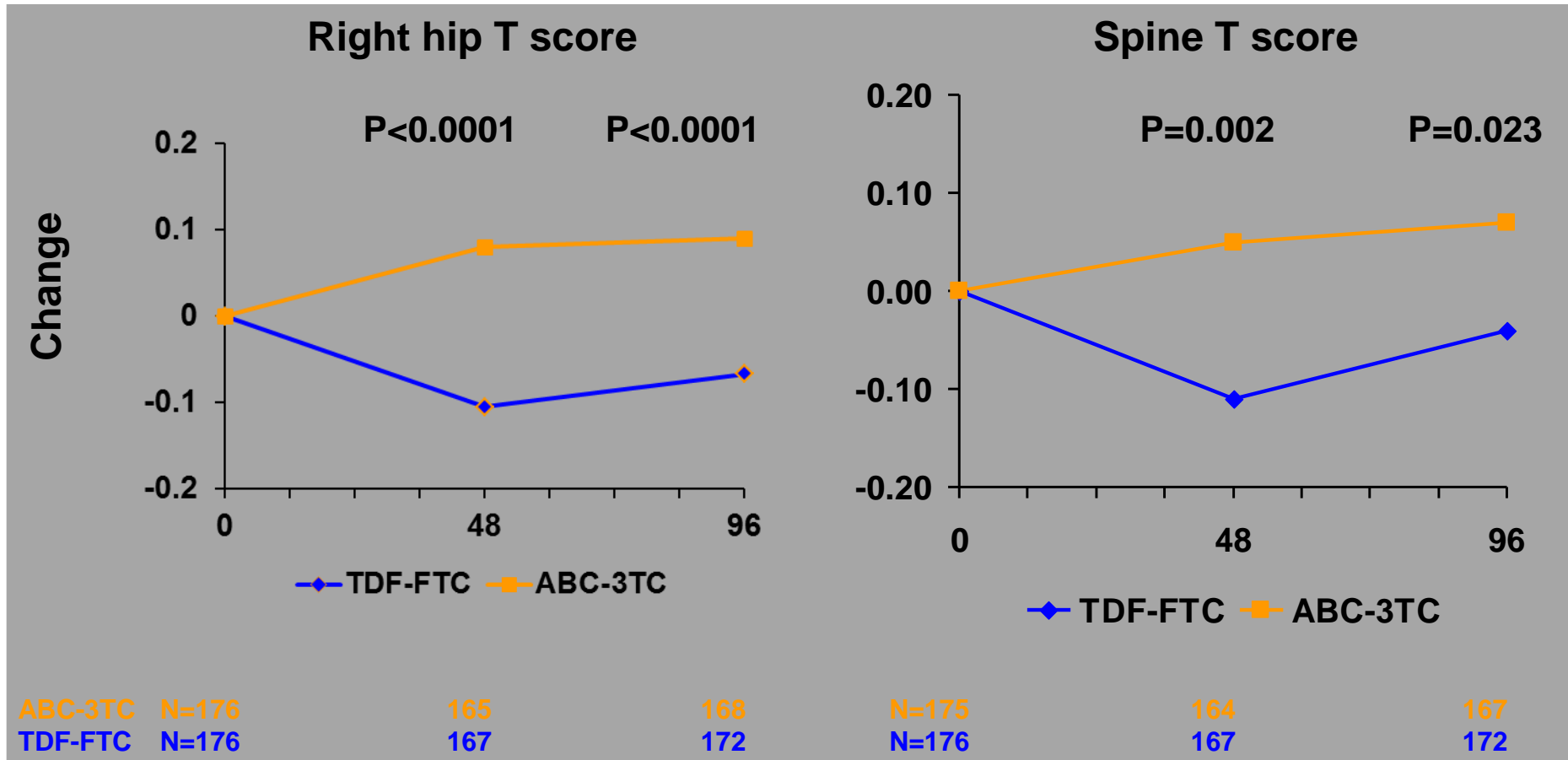
Van Vonderen et al, AIDS 2009

Longitudinal comparison of BMD among those using ART continuously vs. intermittently (SMART sub-study)



BMD: Effect of ART

Truvada reduces BMD more than Abacavir:
Results of a 96 week trial in ART-experienced patients



Long term cART

- Bone loss appears to slow beyond 2 years after commencement of cART
- Rate of bone loss after 96 months cART still greater than that seen in non-HIV controls (unmatched participants in long term follow-up studies)
- BMD fell by mean -1.01% at lumbar spine and -1.56% at hip in HIV cases as compared with changes of +0.04% spine and -0.31% hip in HIV-negative patients (significantly greater at spine but not hip)
- People with higher baseline CD4+ counts lost less BMD on cART commencement

Management of low bone mass in HIV

- Cochrane review
- 3 RCTs Alendronate
- Heterogeneity!!
- Alendronate, calcium and vitamin D well-tolerated and improved BMD after 1 year vs. calcium/D alone¹
- Two studies showing that Zoledronate infusions increase bone mass^{2,3}

Lin & Rieder, 2007

Huang et al, AIDS 2009 and Bolland et al, JCEM, 2007

Side effects of bisphosphonates

- Osteonecrosis of the jaw
- Oesophageal cancer
- Atypical femoral shaft fractures
- All RARE in people taking 'osteoporosis' treatment levels of bisphosphonates (exaggerated by use in cancer for bone metastases)
- Drug holiday?
- 5 years therapy then re-assess DEXA/risk factors

Other drugs for osteoporosis

- HRT
- Raloxifene
- Strontium ranelate
- Denosumab
- Parathyroid hormone (teriparatide)
- Do work with your local osteoporosis specialist..

Treatment of low bone mass in HIV

- Always check vitamin D status (DXA does not separate osteomalacia) and supplement if deficient
- Calcium and vitamin D should be prescribed in anybody treated with bisphosphonates
- No evidence as yet that bisphosphonates or any other treatment modality prevent fractures in HIV patients

Conclusion

- Osteoporosis is yet another comorbidity
- Fragility fractures occur age > 60 years in women and >70 years in men in general population
- Falls
- People with one fragility fracture are at the GREATEST risk of others
- Vertebral osteoporosis usually sub-clinical
- Effects of cART recognised but probably should not unduly influence decision-making except in unusual cases
- Bisphosphonates are cheap but NOT risk-free!
- There are expanding options for the treatment of osteoporosis

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National
Osteoporosis
Society