Osteoporosis and HIV: Optimal Evaluation and Management to Prevent Fractures

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Professor of Medicine and Epidemiology
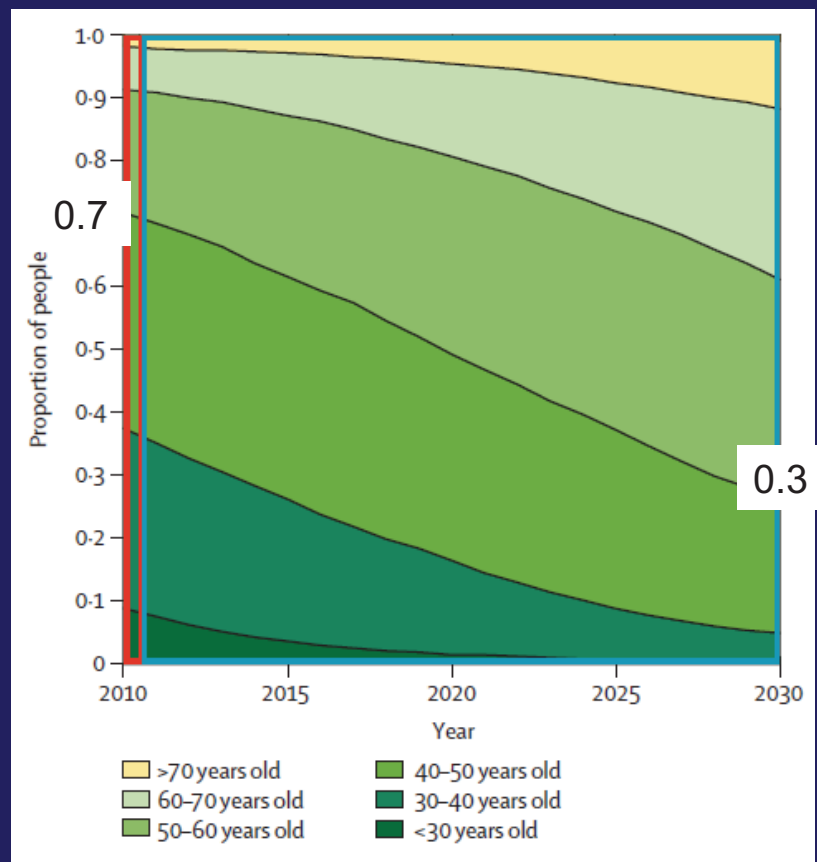
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Disclosures

- Dr Brown has served as a consultant to Gilead Sciences, Inc, GlaxoSmithKline, Janssen, Merck & Co, Inc, Theratechnologies, EMD Serono, and ViiV Healthcare.

# The Aging of the HIV Population: Netherlands

Smit, Lancet Inf Diseases, 2015

Multimorbidity will increase markedly in PWH over the next 10 years

- Older age-groups experience an **increase** in **population size** and **prevalence of multimorbidity**

- Among those ≥ 70yrs, the projected prevalence of multimorbidity increases from 58% (in 2020) to 69% (in 2030), corresponding to an additional 71,000 individuals living with 2+ physical comorbidities beside HIV by 2030
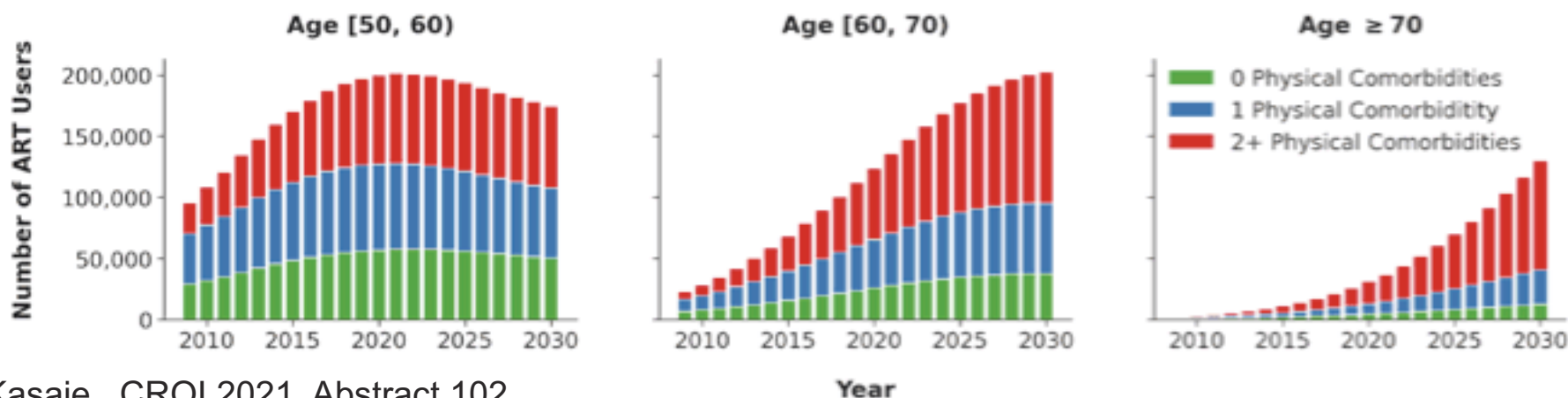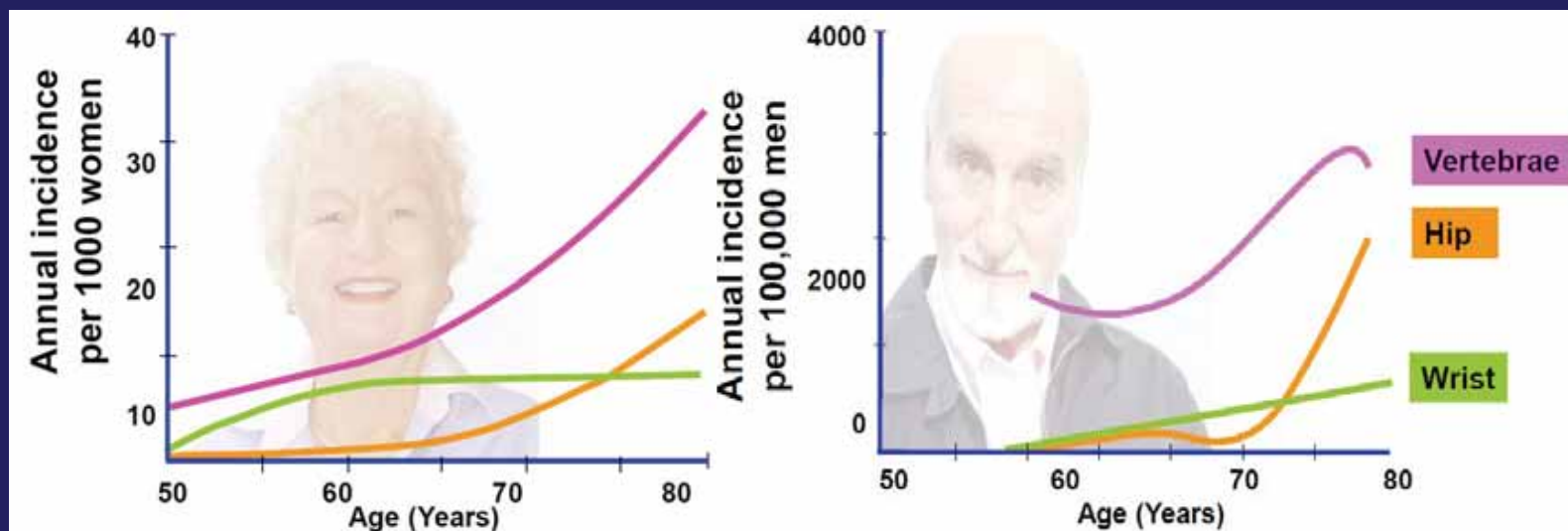

Kasaie , CROI 2021, Abstract 102
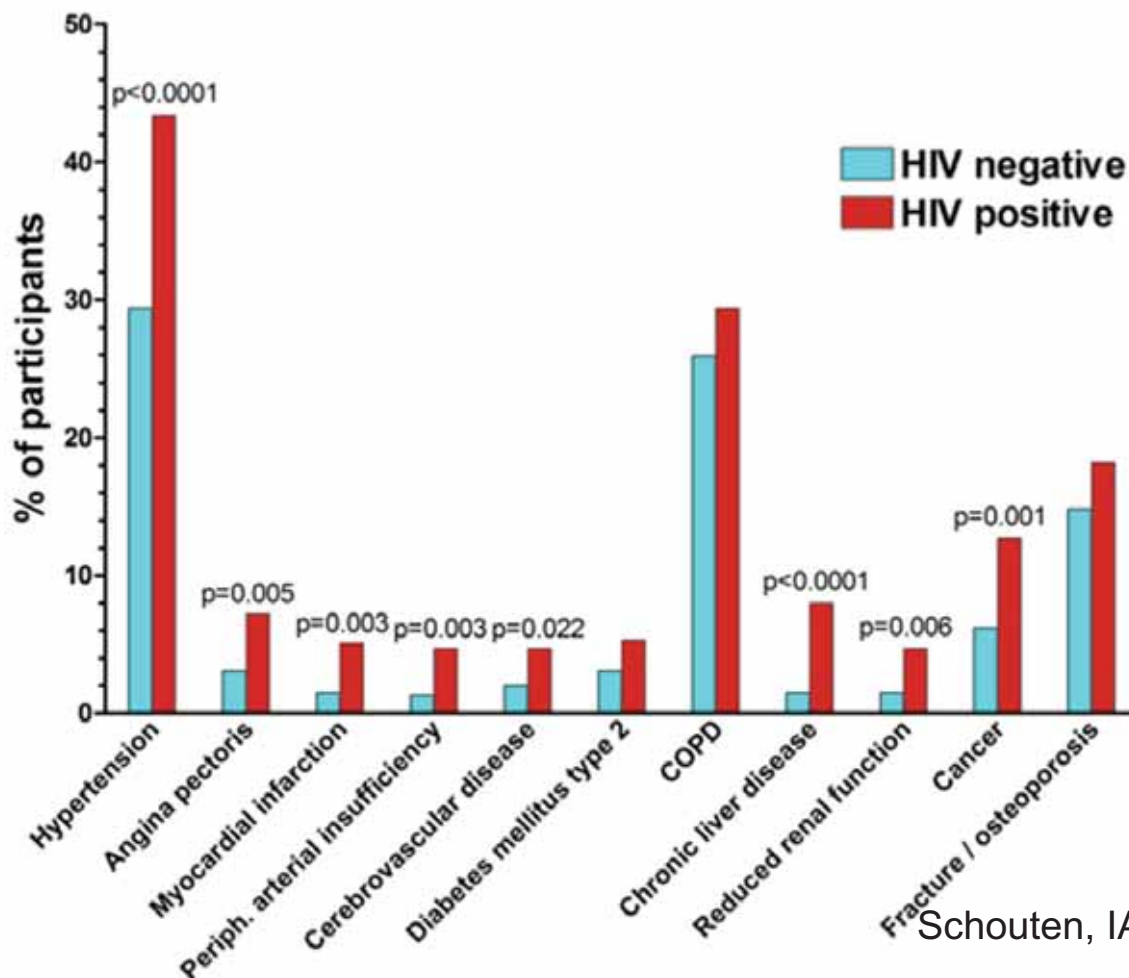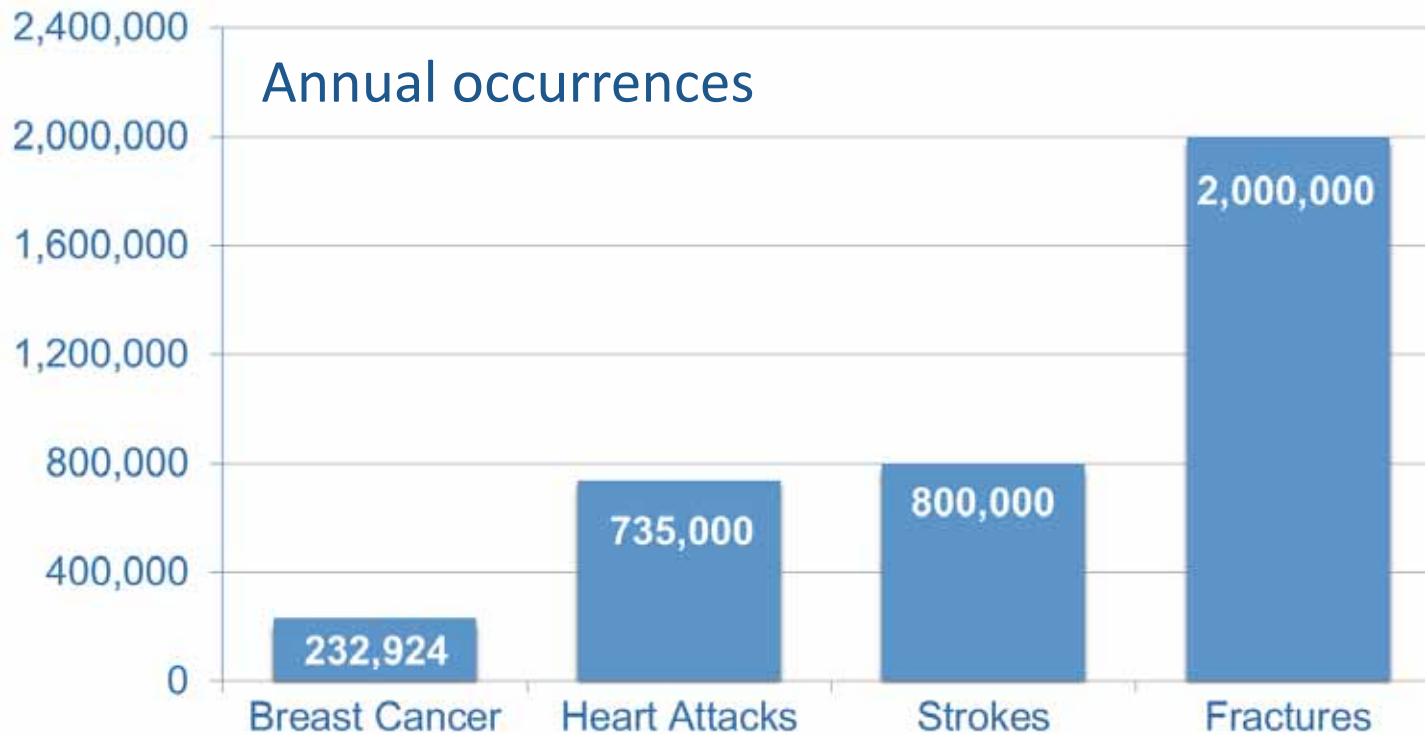
Schouten, IAS, 2012

Why worry about osteoporosis?

- Osteoporosis is common among older populations and more common in PWH compared to matched HIV SN
- Osteoprotic fractures are a major source of morbidity & <u>mortality</u>
- Osteoporosis is a silent disease until fractures occur
- Osteoporosis can be detected in a pre-clinical stage and fractures can be prevented
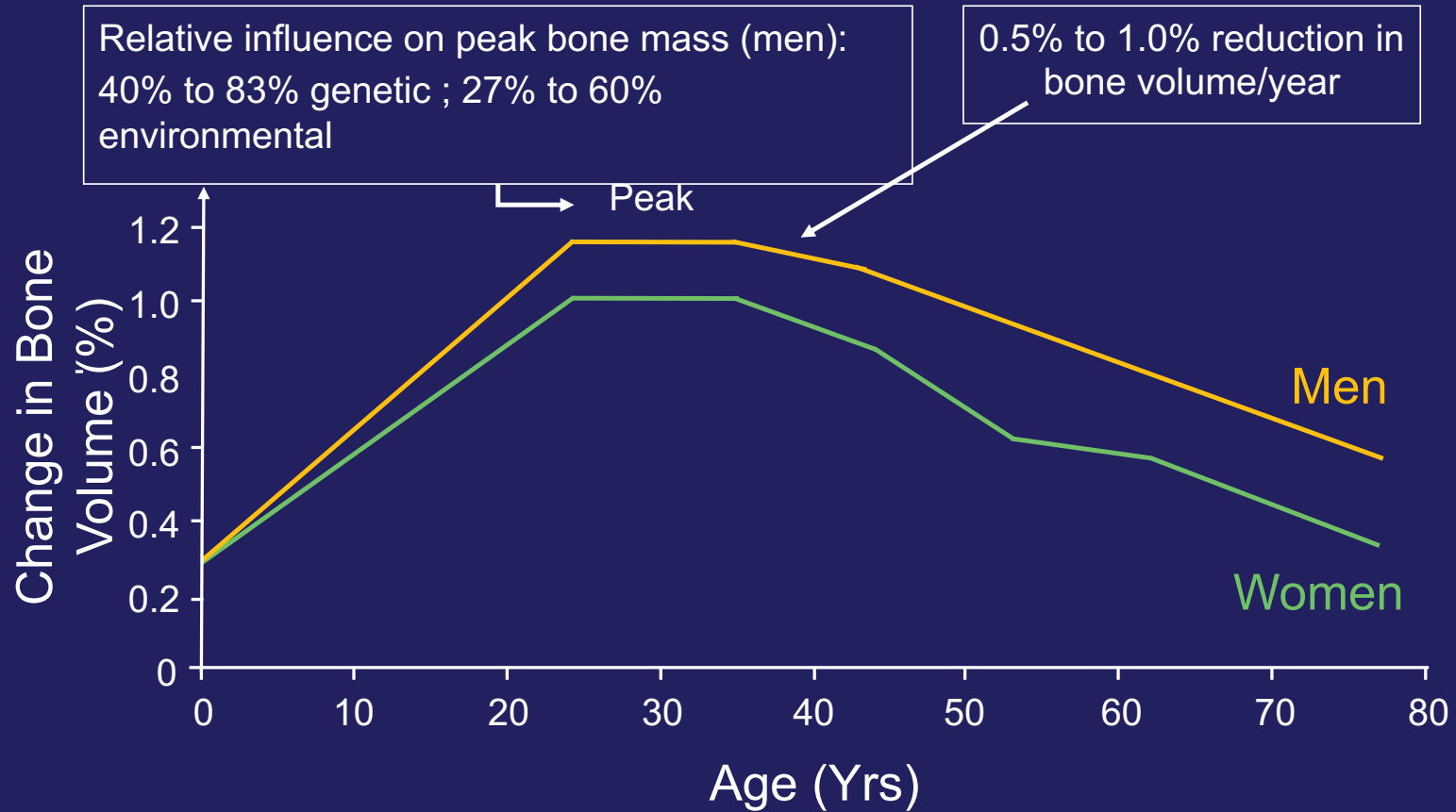
Fragility Fractures in Women and Men over 50 years

Wasnich RD, Osteoporos Int. 1997

Compared to Other Health Issues

Annual occurrences

2,400,000
2,000,000
1,600,000
1,200,000
800,000
400,000
0

232,924 — Breast Cancer
735,000 — Heart Attacks
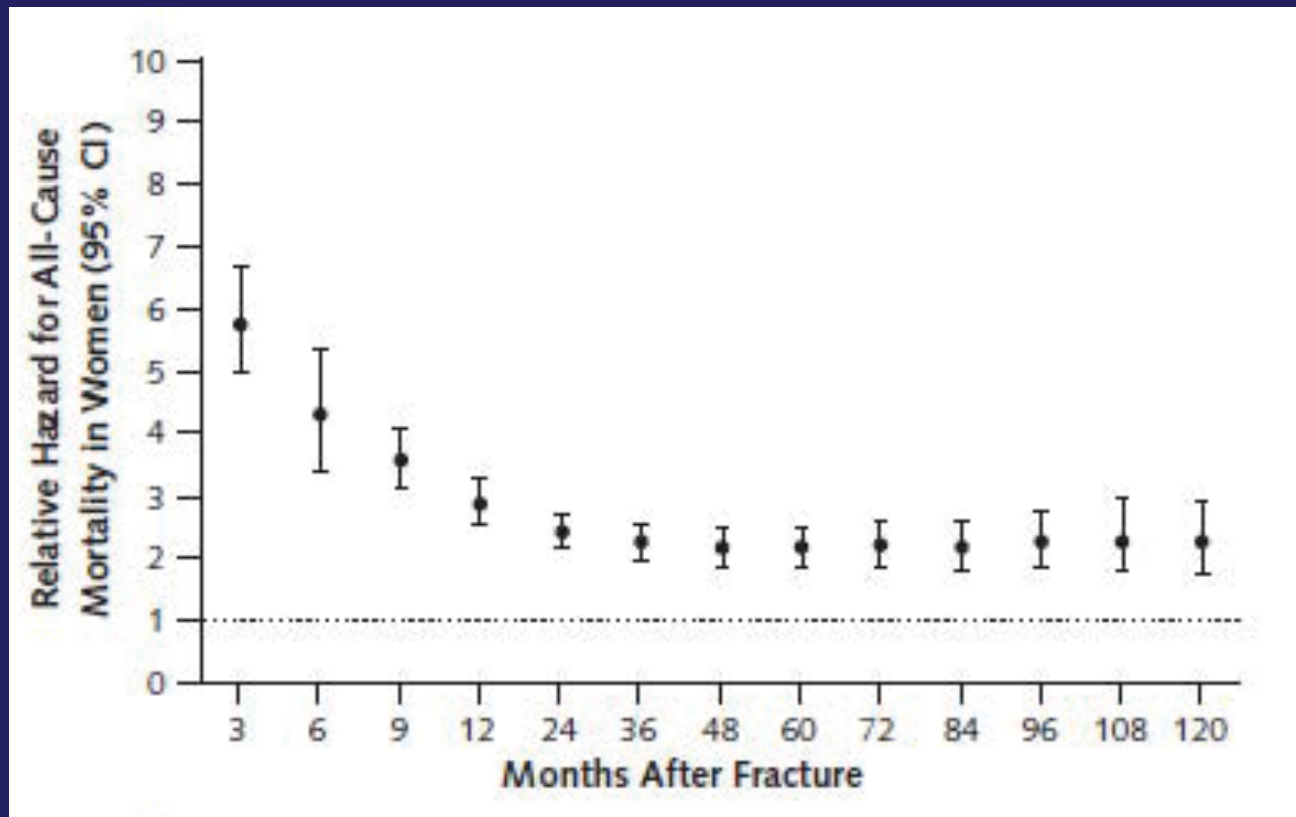800,000 — Strokes
2,000,000 — Fractures

Centers for Disease Control & Prevention 2016
Centers for Disease Control & Prevention, 2015
Centers for Disease Control & Prevention, 2015
National Osteoporosis Foundation, 2015

AMERICAN BONE HEALTH

BMD Decreases With Age

Relative influence on peak bone mass (men):
40% to 83% genetic ; 27% to 60% environmental

0.5% to 1.0% reduction in bone volume/year

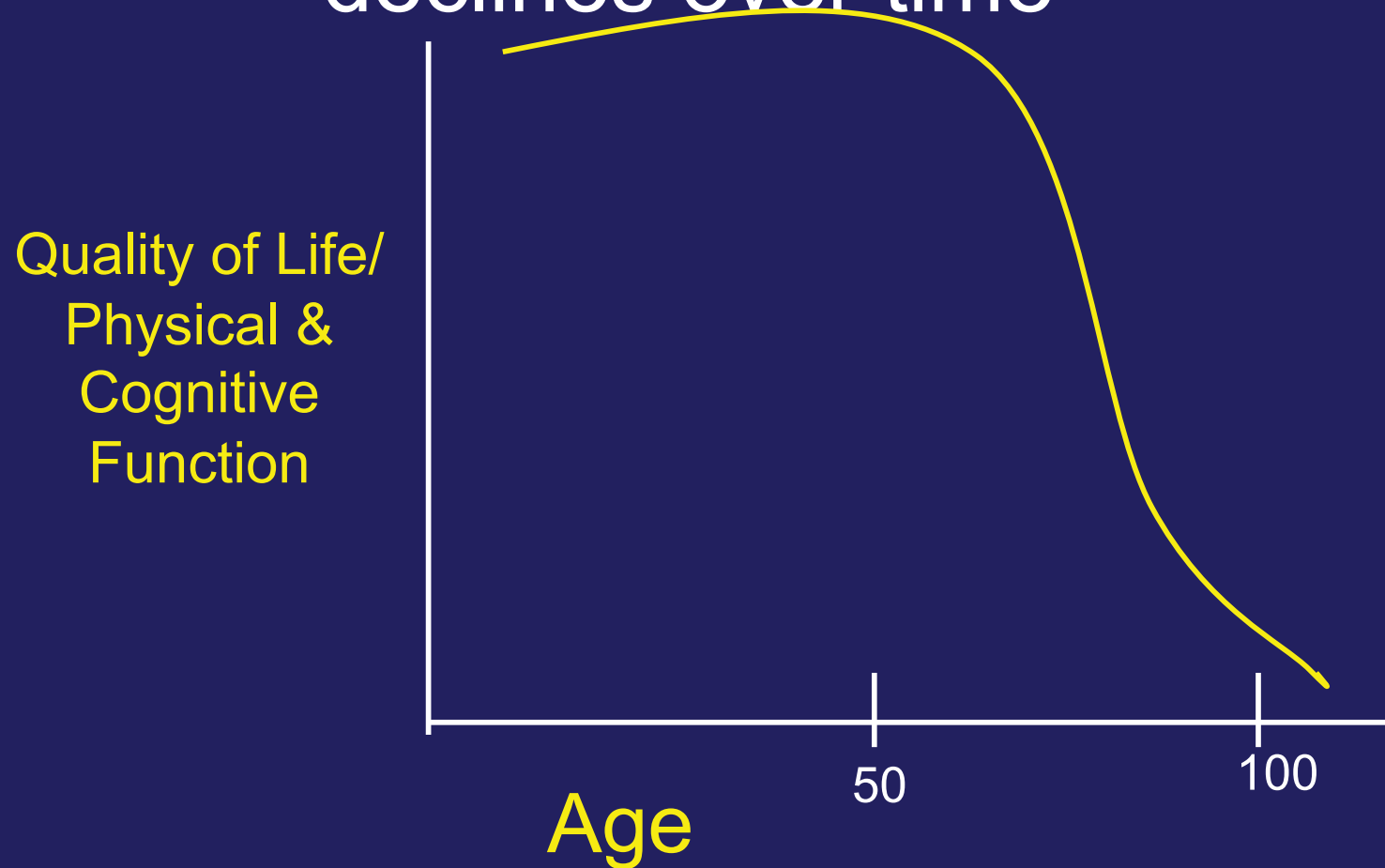Orwoll ES et al. *Endocr Rev*. 1995;16(1):87-116.

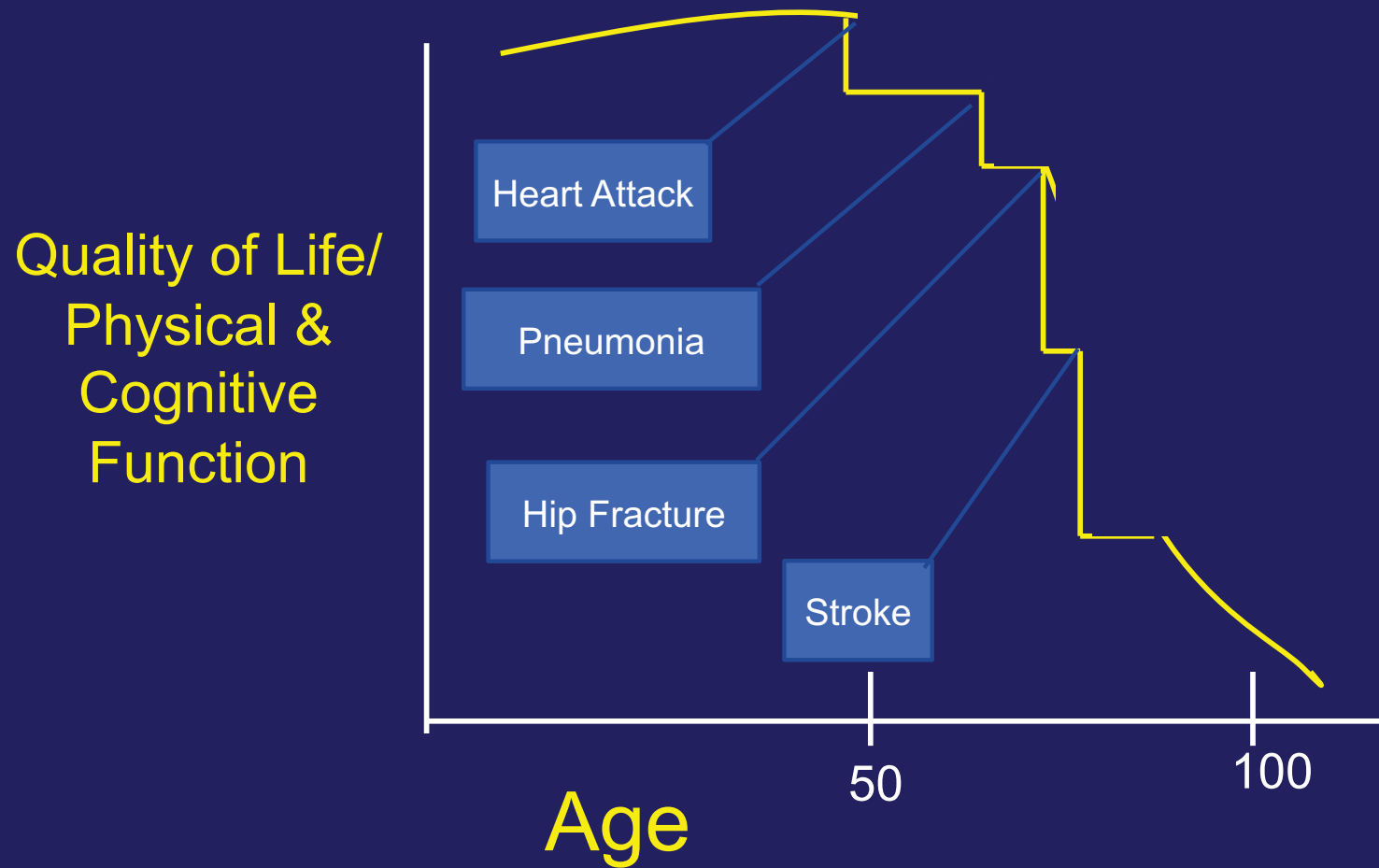# Increase Mortality After Fragility Fractures

Haentjens, Annals Int Medicine, 2010

Physical & cognitive function generally declines over time

Decline in Function May Not Be Gradual

Quality of Life/ Physical & Cognitive Function

Heart Attack

Pneumonia

Hip Fracture

Stroke

50

100

Age

Preventing comorbid events, including fracture, is critical to maintain function
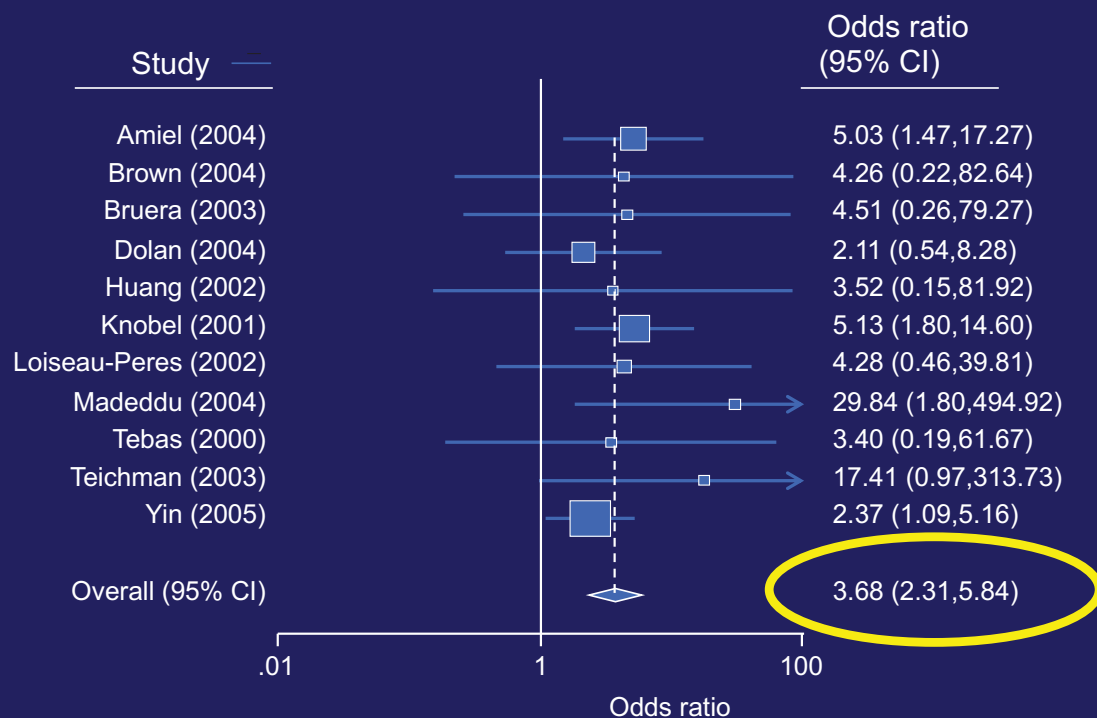
Slide 13 of 84
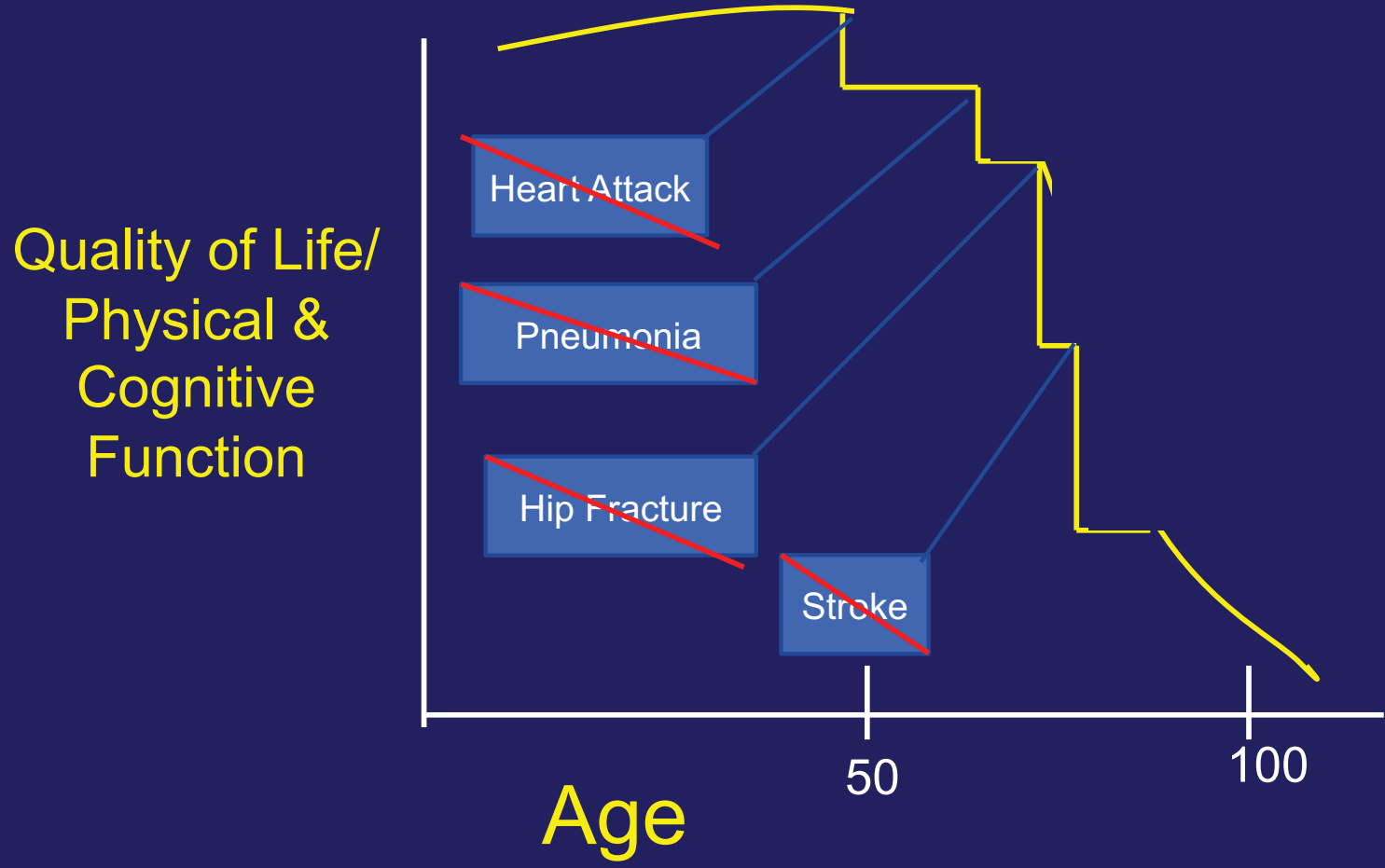
Fracture Prevalence in HIV-infected and non-HIV-infected Persons in MGH/Partners Healthcare System: 1996-2008
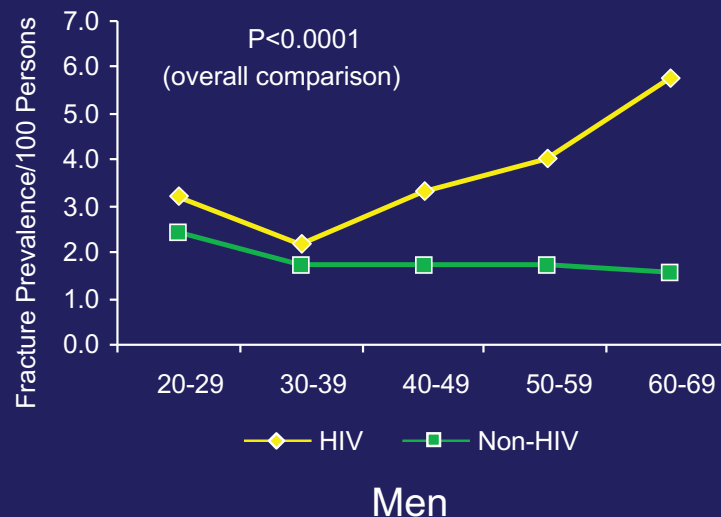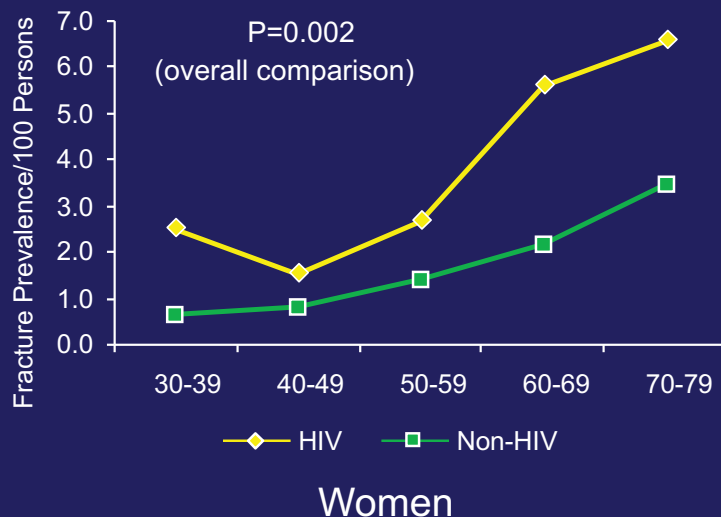
8,525 HIV-infected
2,208,792 non HIV-infected patients

14

Triant, *JCEM*, 2008

Prevalence of Osteoporosis in HIV-infected Patients vs HIV-uninfected Controls: A Meta-analysis

Overall prevalence of osteoporosis in HIV-infected patients 15%

| Study	Odds ratio (95% CI)
Amiel (2004)	5.03 (1.47,17.27)
Brown (2004)	4.26 (0.22,82.64)
Bruera (2003)	4.51 (0.26,79.27)
Dolan (2004)	2.11 (0.54,8.28)
Huang (2002)	3.52 (0.15,81.92)
Knobel (2001)	5.13 (1.80,14.60)
Loiseau-Peres (2002)	4.28 (0.46,39.81)
Madeddu (2004)	29.84 (1.80,494.92)
Tebas (2000)	3.40 (0.19,61.67)
Teichman (2003)	17.41 (0.97,313.73)
Yin (2005)	2.37 (1.09,5.16)
Overall (95% CI)	3.68 (2.31,5.84)

.01   1   100
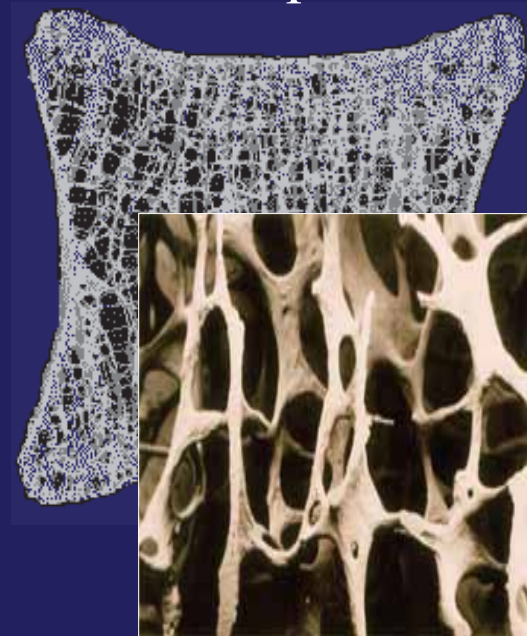
Odds ratio

Brown, AIDS, 2006

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Definitions

Osteoporosis:

"systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and fracture"

Consensus Conference Am J Med. 1993

Vertebral body: Normal vs Osteoporosis

normal
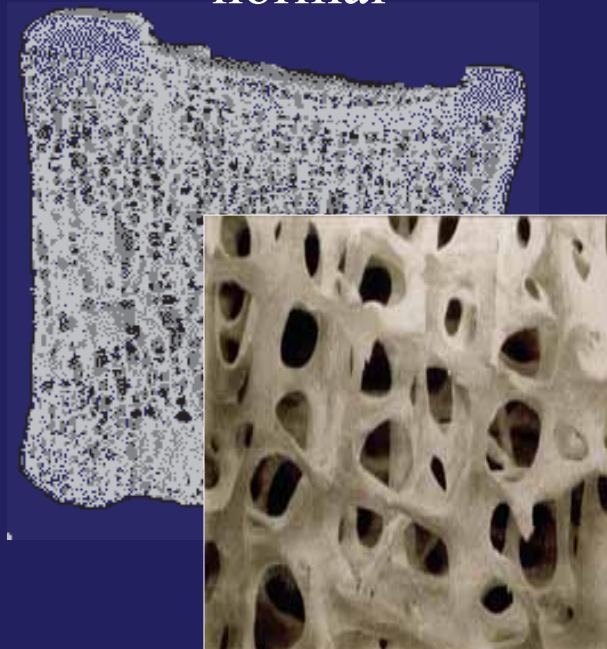
osteoporotic

Definitions

Operational Definition (DXA)- WHO Definition
- Osteoporosis: T-score ≤ -2.5
- Osteopenia: T-score= -1.0 to -2.4
- Normal: T-score > -1.0

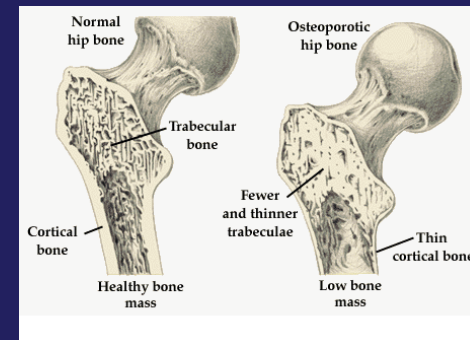↑ Risk of fracture by 1.5-3.0 x for each SD decrease

Caveats:
- Z-score (≤-2.0) used in men < 50 years and premenopausal women
- BMD explains only about 50% of fracture risk

DXA Scanning

- Lumbar Spine
- Hip
  - Femoral neck
  - Total hip
- Forearm (distal 1/3)

Sites differ in proportions of cortical and trabecular bone

Left Panel

Name: Express Scans, 2
Patient ID:
DOB: August 24, 1944

Sex: Female
Ethnicity: White

Height: 65.0 in
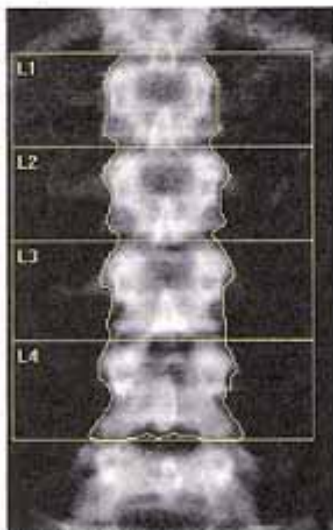Weight: 150.0 lb
Age: 61

Referring Physician:

Image not for diagnostic use
k = 1.138, d0 = 48.0
116 x 149

Scan Information:

Scan Date: November 12, 2005   ID: A11120501
Scan Type: x Lumbar Spine
Analysis: November 12, 2005 09:48 Version 12.4:3
Lumbar Spine
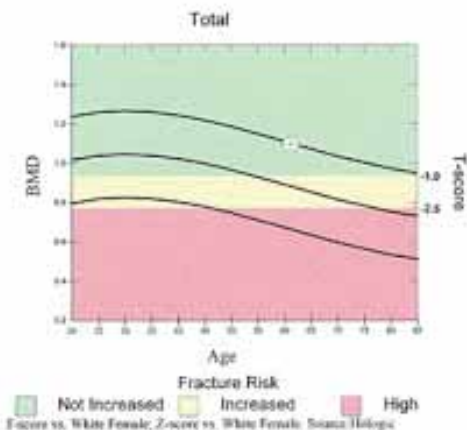Operator:
Model: Discovery C (S/N 81202)
Comment:

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
L1	14.41	14.44	1.002	0.7	108	2.0	129
L2	15.27	16.33	1.069	0.4	104	1.8	123
L3	16.99	19.69	1.159	0.7	107	2.2	127
L4	18.74	21.27	1.135	0.2	102	1.8	121
Total	65.41	71.72	1.096	0.4	105	1.9	124

Total BMD CV 1.0%, ACF = 1.000, BCF = 1.000, TH = 3.855

WHO Classification: Normal
Fracture Risk: Not Increased

Total

Fracture Risk

Not Increased   Increased   High

T-score vs. White Female; Z-score vs. White Female; Source Hologic

Physician's Comment:

HOLOGIC

Right Panel

Bedford Osteoporosis Center
35 Crosby Drive
Bedford, MA 01730

Telephone: 781-999-7300   E-Mail: info@hologic.com   Fax: 781-280-0614

Name: Smith, Jane
Patient ID: 00568
DOB: February 19, 1927

Sex: Female
Ethnicity: White
Menopause Age: 46

Height: 61.0 in
Weight: 121.0 lb
Age: 71

Referring Physician: Wilson

Image not for diagnostic use

Scan Information:

Scan Date: 11/2/98   ID: B11029500
Scan Type: f Left Hip
Analysis: 11/2/99 10:31 Version 8.26
Left Hip
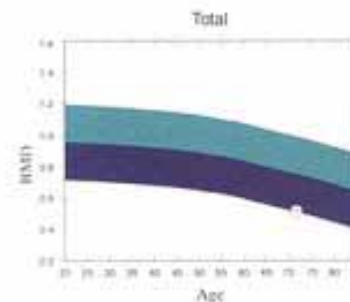Operator: AR
Model: QDR
Comment: BASELINE

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-Score	Z-Score
Neck	5.08	2.07	0.408	-4.0	-2.1
Trochanter	12.61	4.62	0.366	-3.3	-1.9
Inter	16.52	10.70	0.648	-2.9	-1.6
Total	34.20	17.39	0.508	-3.6	-2.0
Ward's	1.04	0.20	0.193	-4.6	-2.0

Total BMD CV 1.0%, ACF=1.031, BCF=1.020, TH=5.208

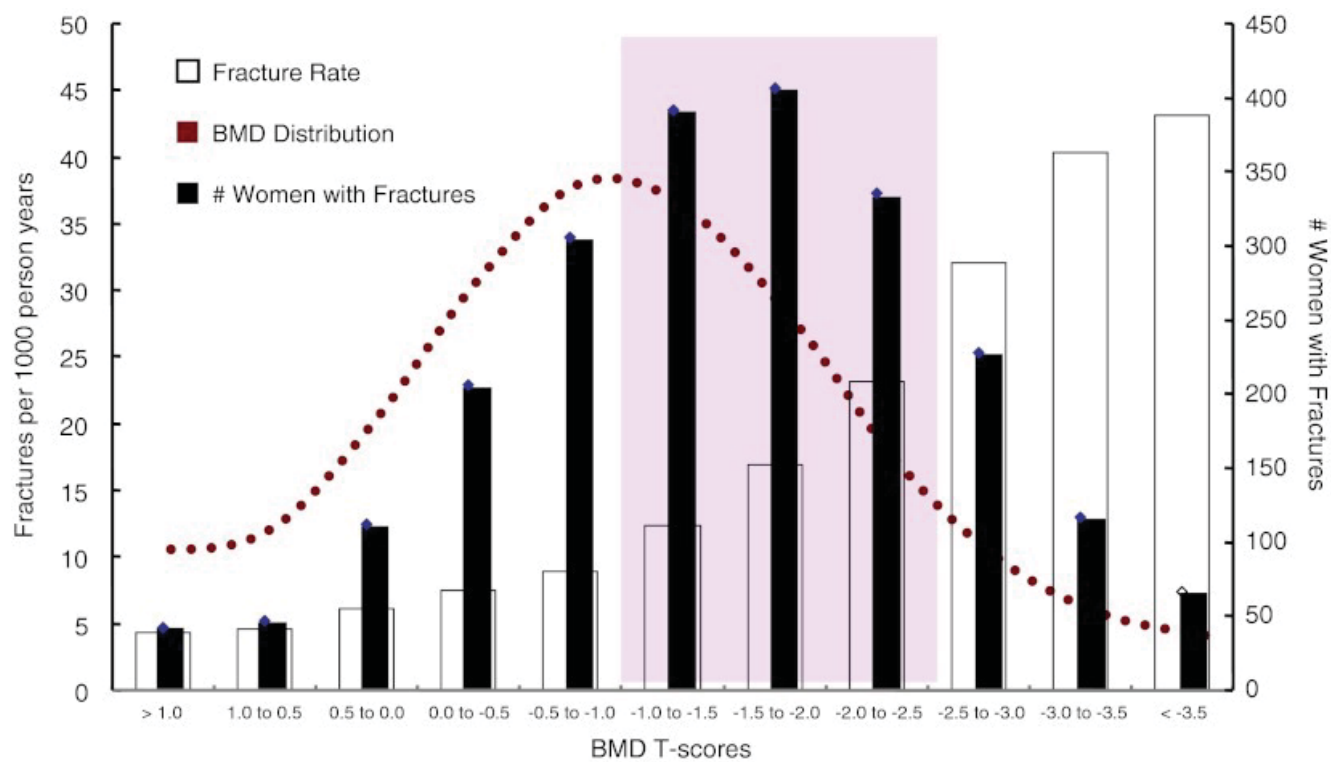WHO Classification: Osteoporosis
Fracture Risk: High

Total

Reference curve and scores matched to White Female
Source: Hologic

Physician's Comment:

HOLOGIC

M-027 US/International

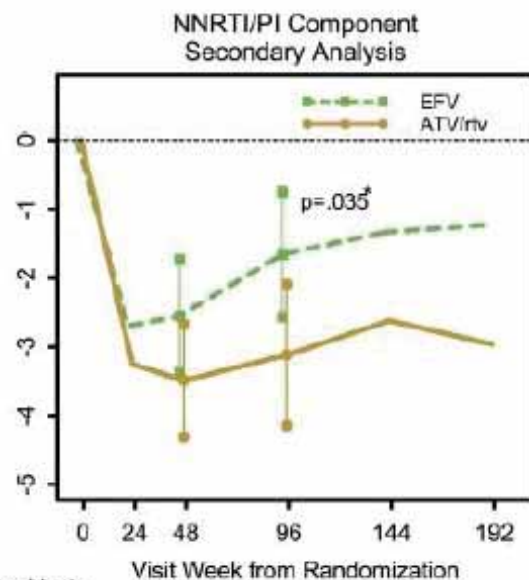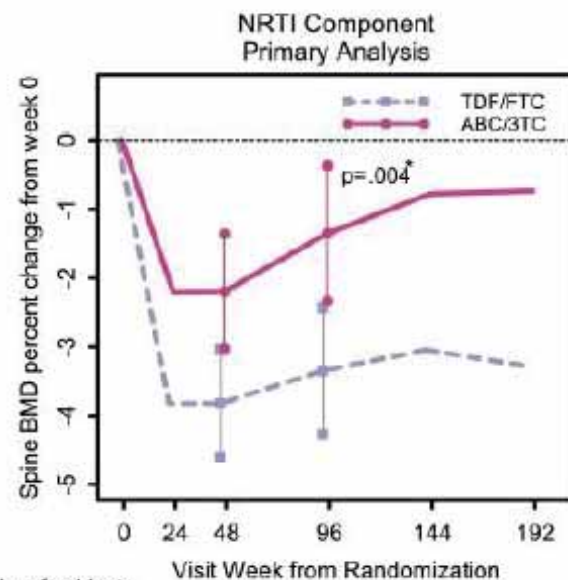# Fractures Happen at all BMDs

Multifactorial Etiology of Bone Loss in HIV
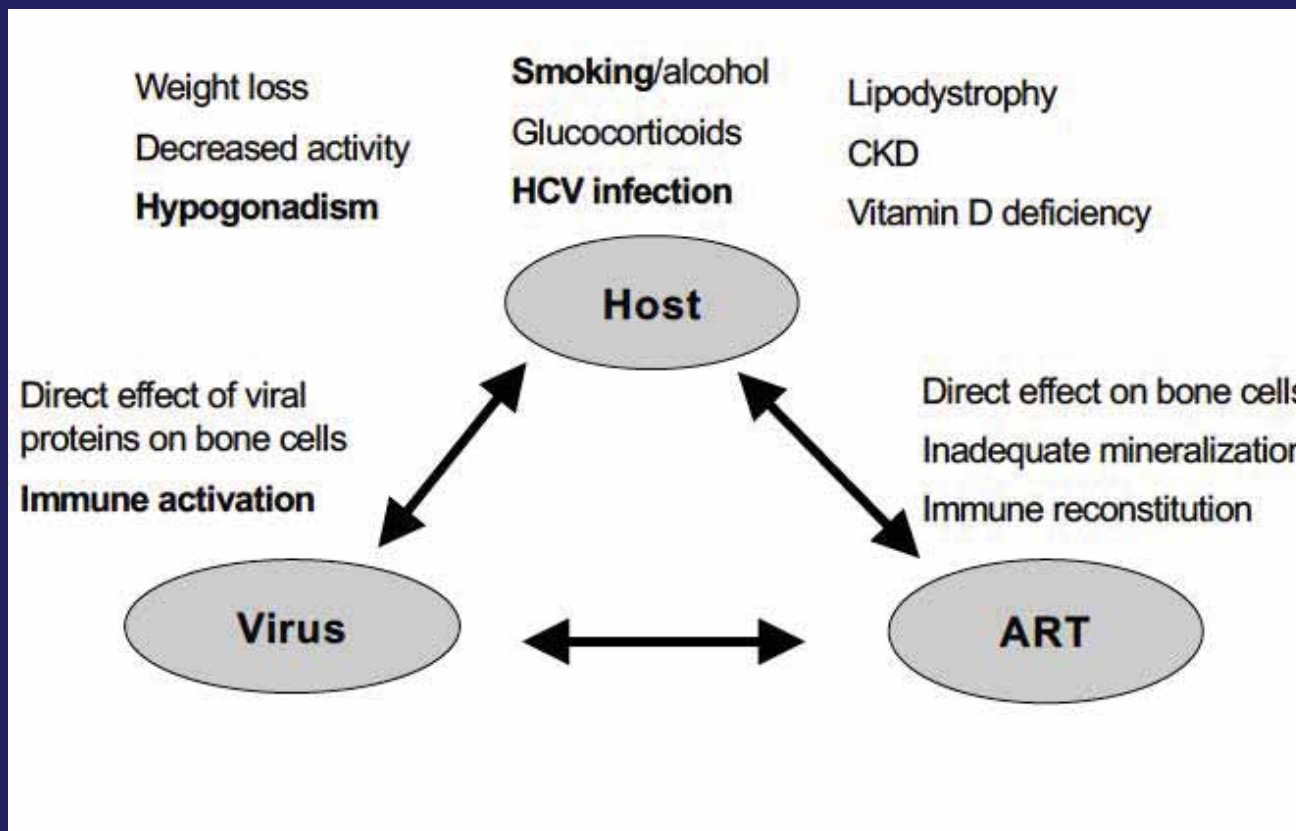
Bone Loss Occurs First 6 Months after ART Initiation

McComsey et al., *JID* 2011

Bone Loss with ART Initiation: TDF

Study	ART regimens	Change in LS BMD
Stellbrink, **ASSERT** 2010	**TDF/FTC + EFV** ABC/3TC + EFV	-3.6%* -1.9%
McComsey, **ACTG 5224s** 2011	**TDF/FTC** ABC/3TC **ATV/r** EFV	-3.3%* -1.3% -3.1%* -1.7%
Reynes, **PROGRESS** 2013	**TDF/FTC+LPV/r** RAL+LPV/r	-2.5%* +0.7%
Sax, **Gilead 104-111** 2015	**E/C/F/TDF** E/C/F/TAF	-2.9%* -1.3%

Bone Loss After ART Initiation: PIs vs RAL

Brown, JID, 2015
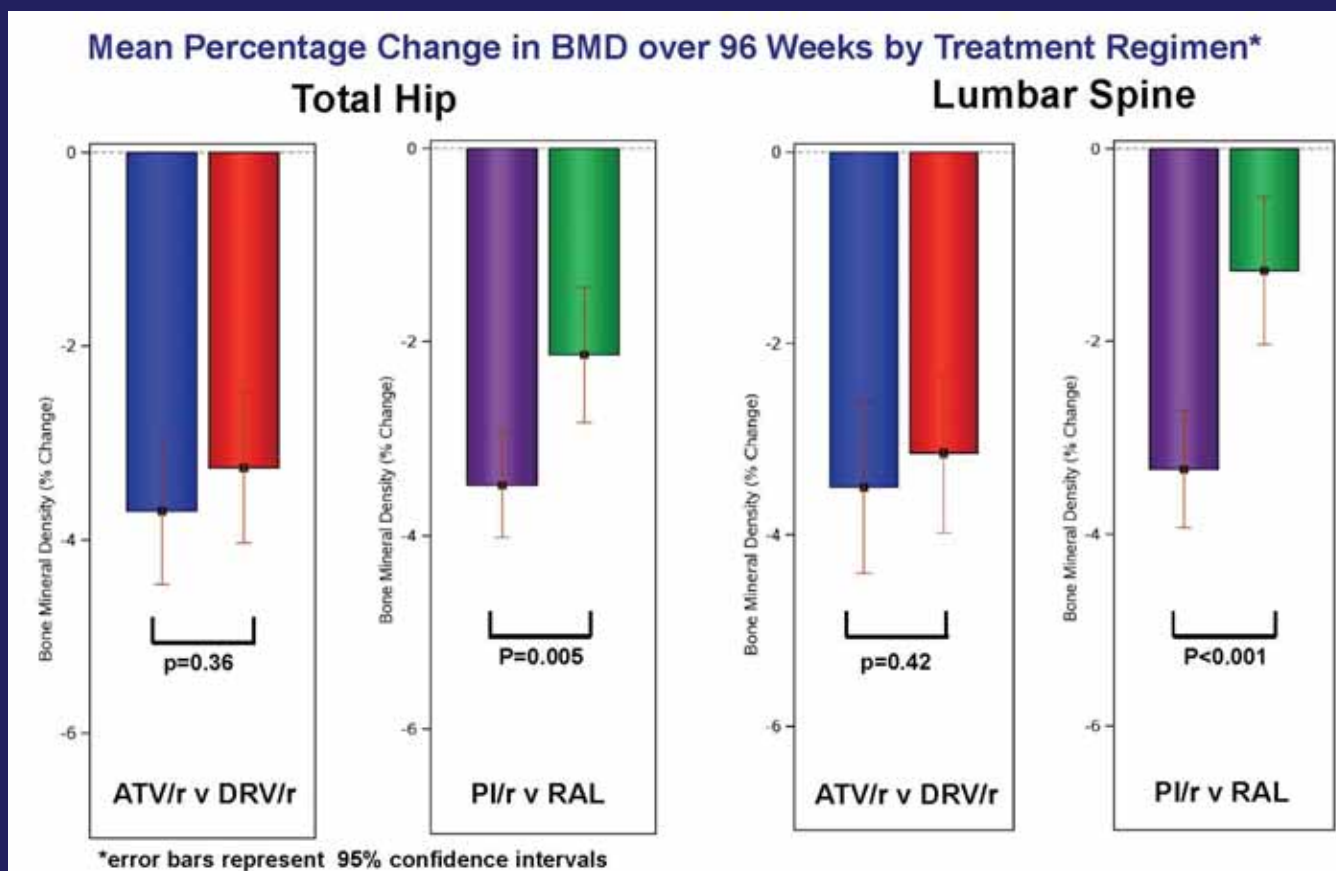
Starting ART without TDF or PIs: 0.5-1.0% Bone Loss
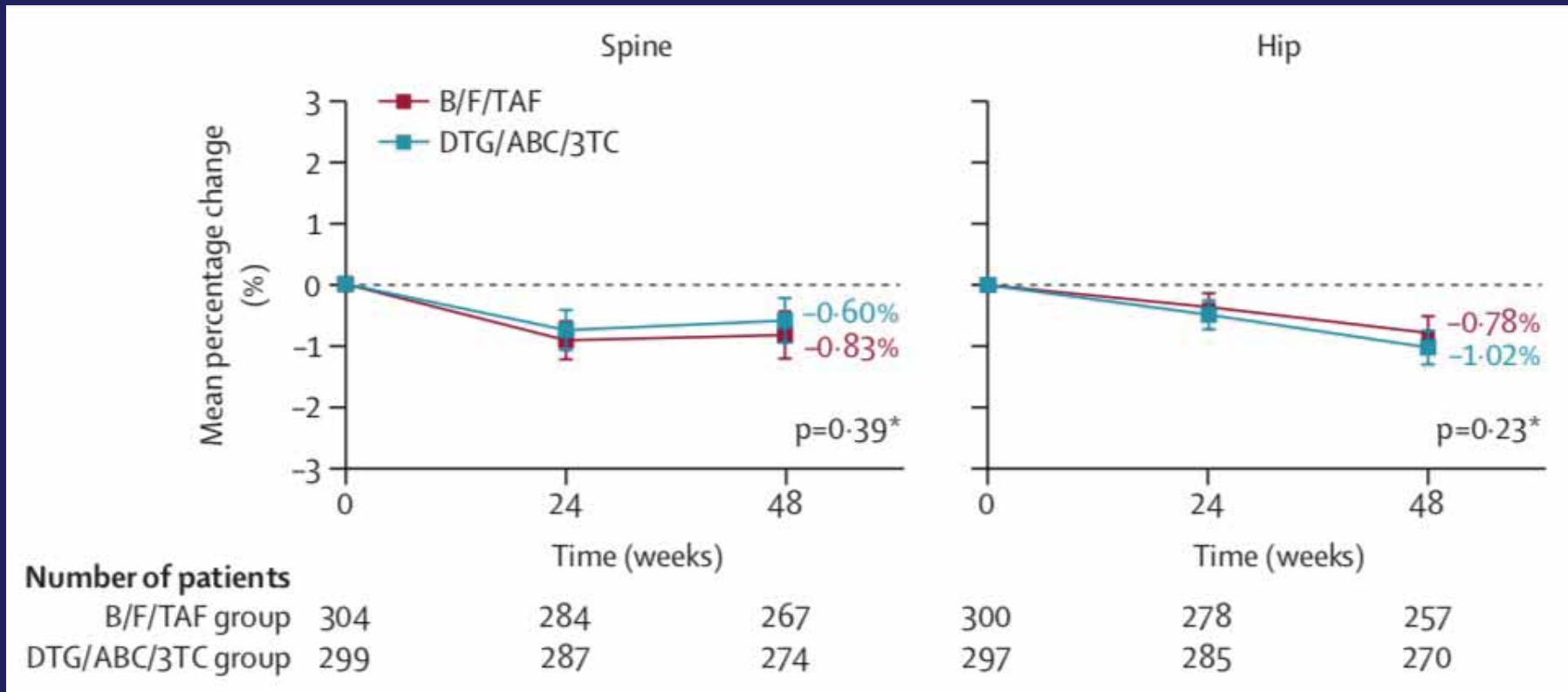
Gallant, Lancet, 2017

BMD improves with ART switch

TDF ⟹ TAF or raltegravir

Ritonavir-boosted protease inhibitor ⟹ raltegravir

Study	Sample/ Duration	ART regimens	Change in LS spine	Change in FN or TH BMD
Pozniak JAIDS 2017	N=242 eGFR 30-69 ml/min 48 wks	TDF/FTC/EVG/Cobi to TAF/FTC/EVG/Cobi	+2.3%*	+1.5%*
Bloch TROP 2014	N=37 48 wks	TDF+PI/r to RAL+PI/r	+3.0%	+2.5%
Curran SPIRAL-LIP 2012	N=74 48 wks	NRTIs+LPVr to NRTIs+RAL Stay on NRTIs+LPVr		+0.01 g/cm^{2}* no change

How can we prevent fractures in PWH?

- ART switching
  - avoid TDF & PIs in individuals with higher fracture risk
- Appropriate screening
  - DXA: Men ≥ 50 y & all post-menopausal women
    - Caveat: Explains only about 50% of fracture risk

Brown, CID, 2015

US Bone Health and Osteoporosis Foundation (BHOF) Guidelines for DXA Screening

- Those with a fragility fracture after age 50

- Women ≥ 65 yrs, Men ≥ 70 yrs

- Younger postmenopausal women and men 50-69 years with clinical risk factors for fracture

- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ three months) associated with low bone mass or bone loss

Other Modalities to Assess Fracture Risk

- Skeletal
  - Spine X-rays

Subclinical Vertebral Fracture in an Italian Cohort

$P=0.09$

91%

86%

72%

28%

14%

9%

n=141

n=10

n=4

SDI 0-1
n=120

SDI ≥2
n=21 (15%)

■ NORMAL BMD   n=45 (32%)

■ OSTEOPENIA   n=70 (50%)

■ OSTEOPOROSIS   n=26 (18%)
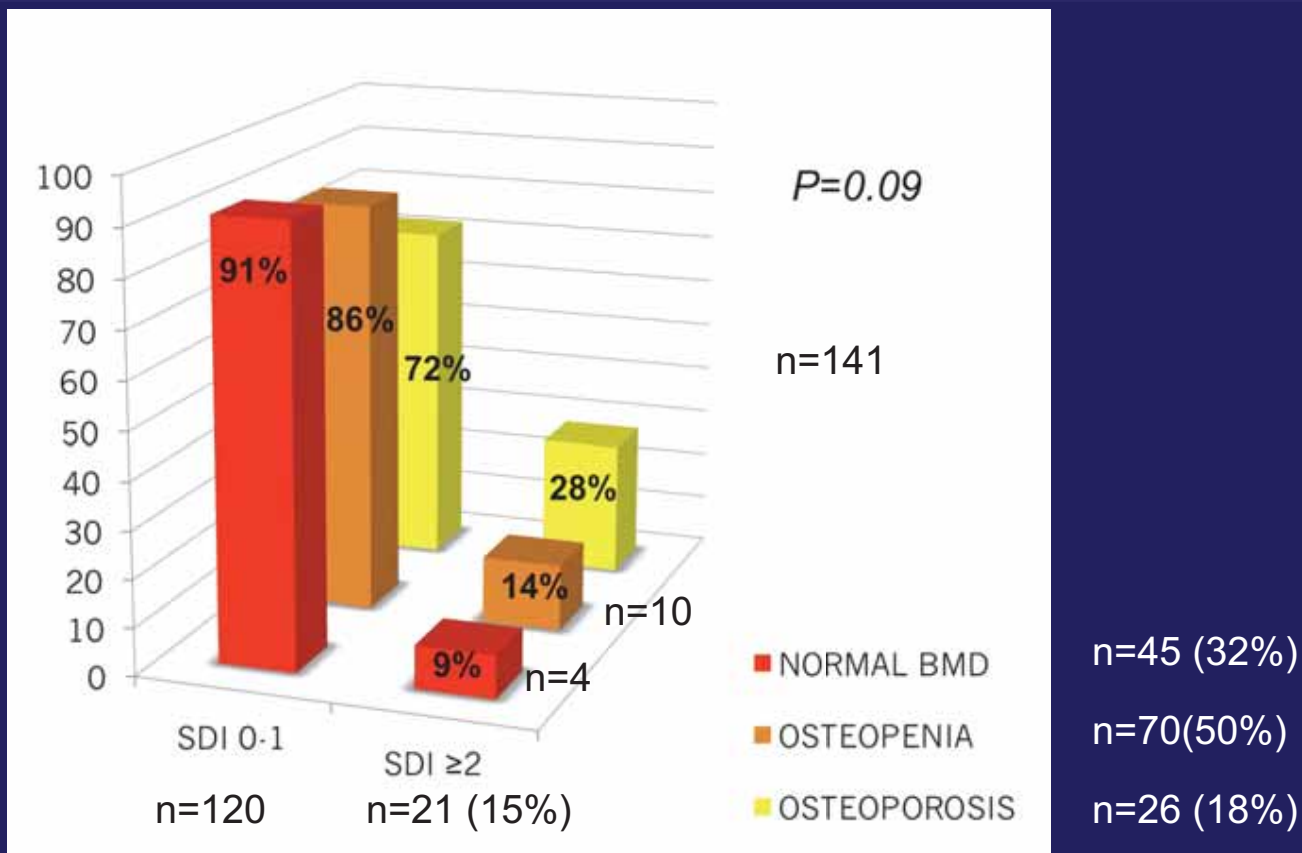
2/3 of those with subclinical vertebral fractures did not have osteoporosis

Other Modalities to Assess Fracture Risk

- Skeletal
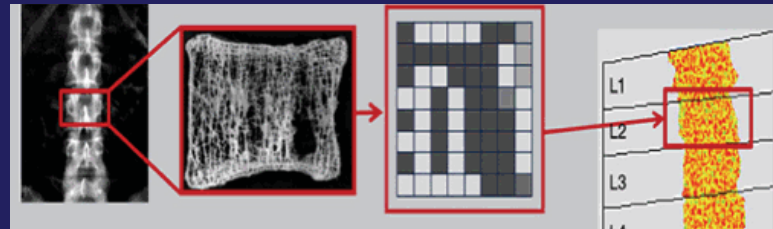 - Spine X-rays
  - Trabecular Bone Score

Trabecular Bone Score as Noninvasive Measure of Bone Microstructure

- TBS is an indirect measure of bone microstructure: higher score = better microstructure

- Derived from standard LS DXA images

  - Bone texture inhomogeneity determined by pixel variations (ie, trabecular textural index)

  - Software installed on existing DXA scanner, so no extra scan time or radiation exposure

  - Archived LS DXA images can be assessed retrospectively

- FRAX can adjust for TBS

Healthy well-structured trabecular bone (TBS = 1.360):
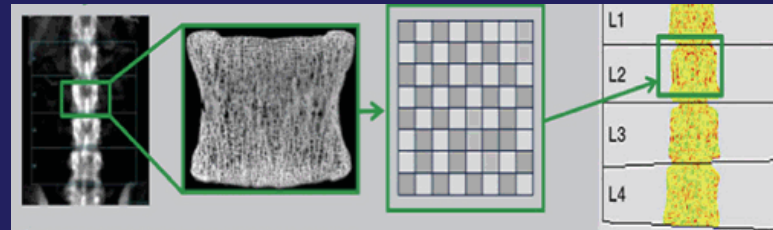
Osteoporosis altered trabecular bone (TBS = 1.102):

TBS Value	Bone Microstructure Status
≥ 1.35	Normal
> 1.20 to < 1.35	Intermediate
≤ 1.20	Degraded

Sharma A, et al. International Comorbidities WS 2016. Abstract O04.
New tools to predict fracture risk. http://www.mayoclinic.org.

Slide credit: clinicaloptions.com

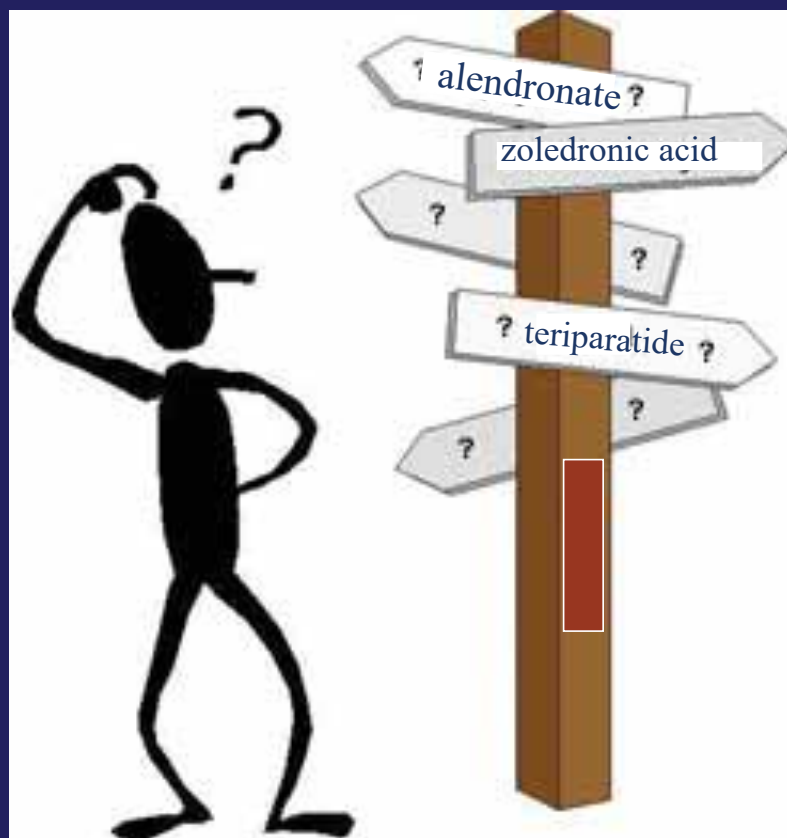# How can we prevent fractures in PWH?

- ART switching
  - avoid TDF & PIs in individuals with higher fracture risk

- Appropriate screening
  - DXA: Men ≥ 50 y & all post-menopausal women
    - Caveat: Explains only about 50% of fracture risk

- Identifying appropriate candidates for treatment

US BHOF Guidelines: Whom to Treat*

- Those with hip or vertebral fractures
- Those with BMD T-scores ≤ -2.5 at the femoral neck, total hip, or spine by DXA
- Those with T-score b/t -1 and -2.5 (osteopenia) at above sites AND 10-year hip fracture probability ≥ 3% or 10-year all major osteoporosis-related fracture ≥ 20% based on FRAX model

*applies to post-menopausal women and men ≥ 50 years

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 : US(Black)   Name / ID :   About the risk factors (i)

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: Date of birth:
          Y: M: D:

2. Sex   Male   Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture   No   Yes

6. Parent fractured

7. Current smoking

8. Glucocorticoids   No   Yes

9. Rheumatoid arth

10. Secondary osteoporosis   No   Yes

11. Alcohol 3 more units per day   No   Yes

12. Femoral neck BMD
    Select ▼

    Clear   Calculate

FRAX underestimates fracture risk in PWH
Yang, AIDS, 2018

Should treatment thresholds be any different in PWH?

Risk factors

For the clinical risk factors a yes or no response is asked for. If the field is left blank, then a "no" response is

http://www.shef.ac.uk/FRAX/

What treatment should be given?

General Recommendations

- Calcium
  - goal: 1200 mg daily, preferably from diet
- Vitamin D supplementation
  - at least 800 IU or target 25OHD > 20 ng/mL (50 nmol/L)
- Smoking cessation
- Alcohol reduction
- Weight-bearing exercise
- Discontinuation of medications associated with osteoporosis (eg, steroids, TZDs, proton pump inhibitors)

Pharmacologic Therapies for Osteoporosis

Antiresorptive

(Osteoclast Directed)

- bisphosphonates
- SERMs (raloxifene)
- denosumab
- hormone replacement therapy

Anabolic

(Osteoblast Directed)

- PTH/PTHrP Analogs (teriparatide, abaloparatide)
- romosozumab

Bisphosphonates

– Reduce vertebral & non-vertebral fractures by 25-50% in non-HIV

Author, year (N)	T-score	Medication (duration)	Spine	Hip
Guaraldi, 2004 (N=41)	< -1.0	Alendronate 70 mg/wk (1 yr)	NS	NS
Mondy, 2005 (N=31)	< -1.0	Alendronate 70 mg/wk (1 yr)	+5.2% vs +1.3%*	NS
McComsey, 2007 (N=82)	< -1.5	Alendronate 70 mg/wk (1 yr)	+3.1% vs +1.1%*	+4.0% vs +1.4%[†]
Rozenberg, 2012 (N=44)	< -2.5	Alendronate 70 mg/wk (2 yrs)	+7.4% vs +4.1%	NS
Bolland, 2007 (N=43)	< -0.5	Zoledronic acid 4 mg/year (2 yrs)	+8.9% vs +2.6%[†]	+3.8% vs -0.8%[†]
Huang, 2009 (N=30)	< -1.5	Zoledronic acid 5 mg/year (1 yr)	+3.7% vs +0.7%*	+3.2% vs -1.8%*

P < 0.05; [†]P < 0.001; NS = not significant

Guaraldi G, et al. *HIV Clin Trials*. 2004;5(5):269-77; Mondy K, et al. *J Acquir Immune Defic Syndr*. 2005;38(4):426-31; McComsey GA, et al. *AIDS*. 2007;21(18):2473-82; Rozenberg S, et al. *AIDS Res Hum Retroviruses*. 2012;28(9):972-80; Bolland MJ, et al. *J Clin Endocrinol Metab*. 2007;92(4):1283-8; Huang J, et al. *AIDS*. 2009;23(1):51-7.

Switch off TDF vs Bisphosphonate: ZEST Study

Hoy, AIDS, 2018

3% Women
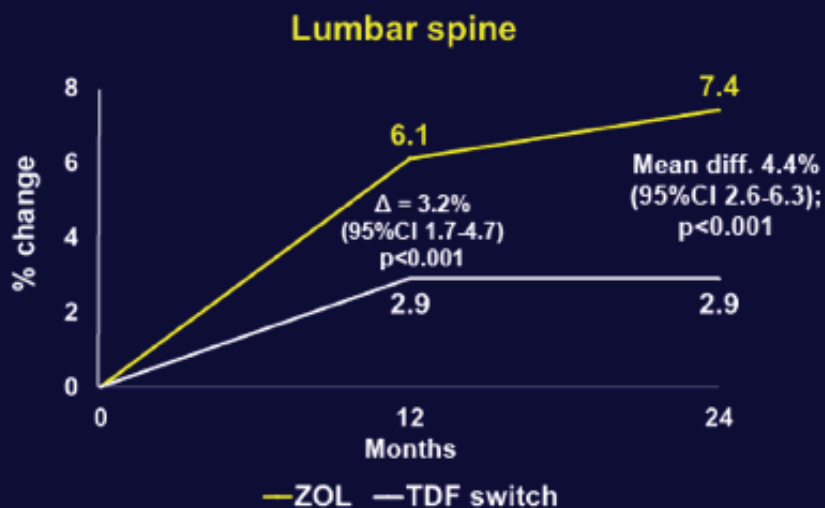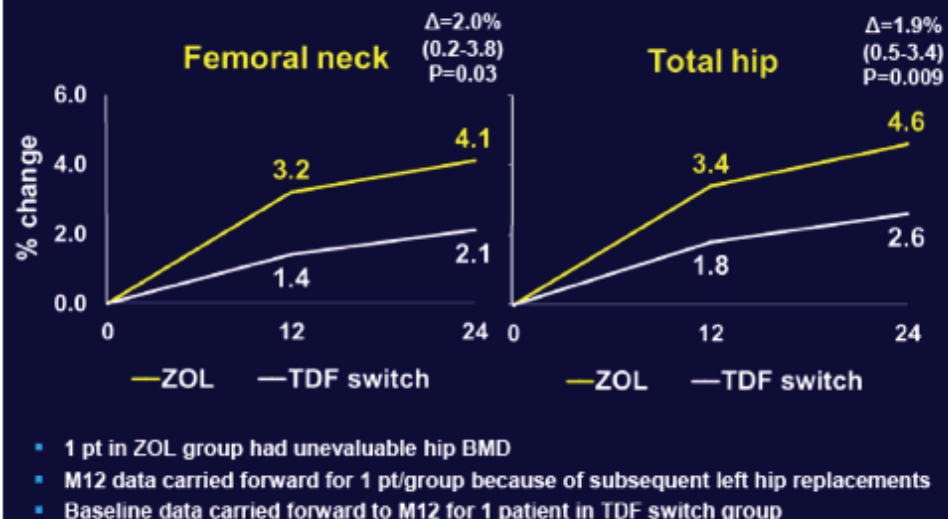
Oral vs IV Bisphosphonate

Oral (alendronate)

- Lower Cost
- GI problems
- Poor bioavailability
- Poor compliance/ persistence

IV   (zoledronic acid)

- Clinic administered
- Acute phase reaction (20-30% with first dose)
- Hypocalcemia
- Directly observed therapy
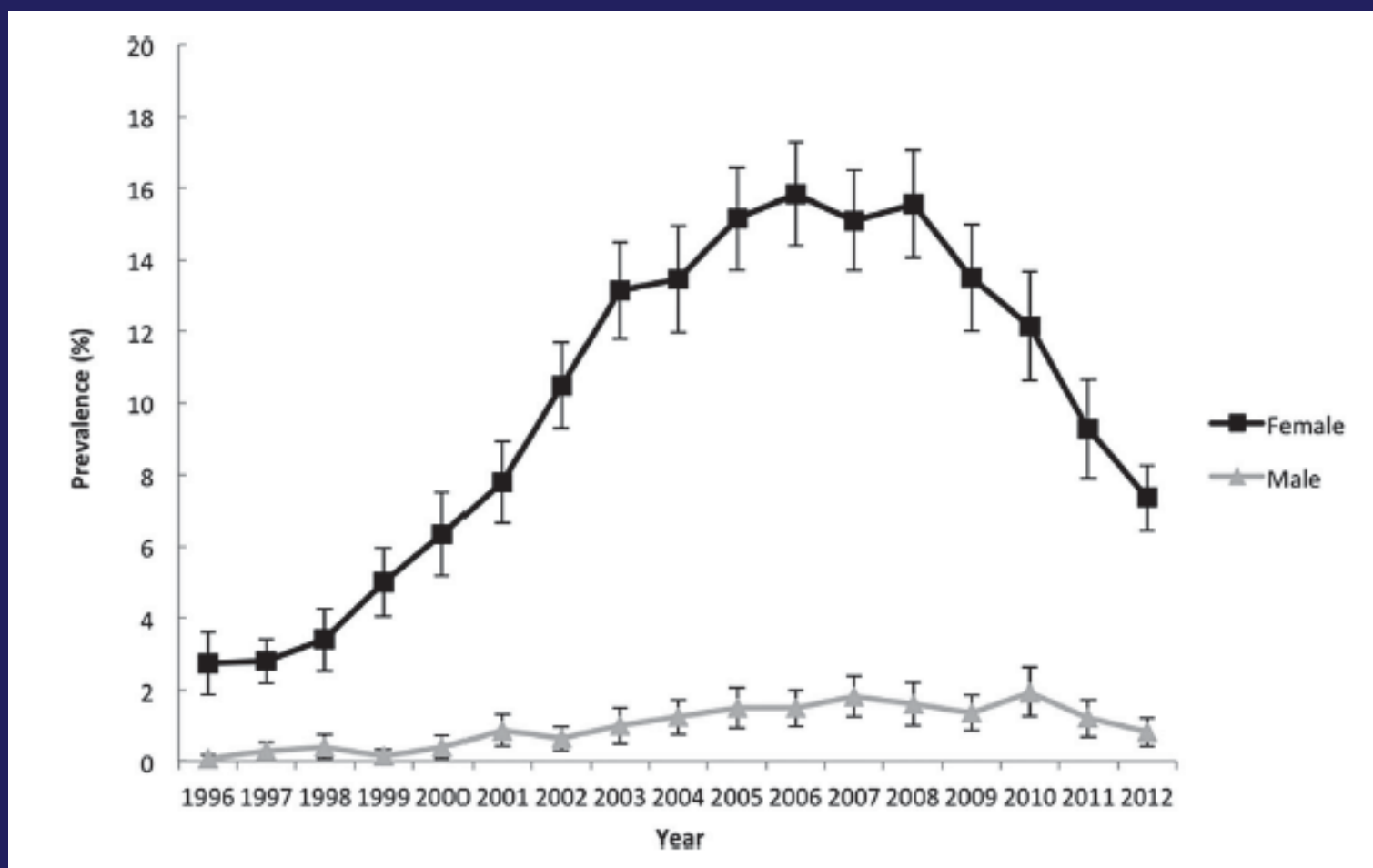
Antiresorptives: Long Term Adverse Events

Osteonecrosis of the Jaw
1 to 10 cases per 100,000 person-years

Atypical Femoral Fracture
3.2 to 50 cases per 100,000 person-years

Declining Use of Bisphosphonates

Jha, JBMR, 2015

Bisphosphate Holiday

Table 2   Recommendations for Drug Holiday from Bisphosphonates

| Patient Category	Recommendation
High-risk: T-score still ≤−2.5 at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.	Drug holiday not justified.
Moderate risk: Hip bone mineral density value is now >−2.5 (T-score), and no prior hip or spine fracture.	Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy. No information about ibandronate and drug holidays.
Low risk: Did not meet current treatment criteria at the time of treatment initiation.	Discontinue therapy

How long?
How to monitor?
What medications after the holiday?

McClung, Am J Medicine, 2013

Fragility Fracture v Atypical Femoral Fracture

Black, NEJM, 2020
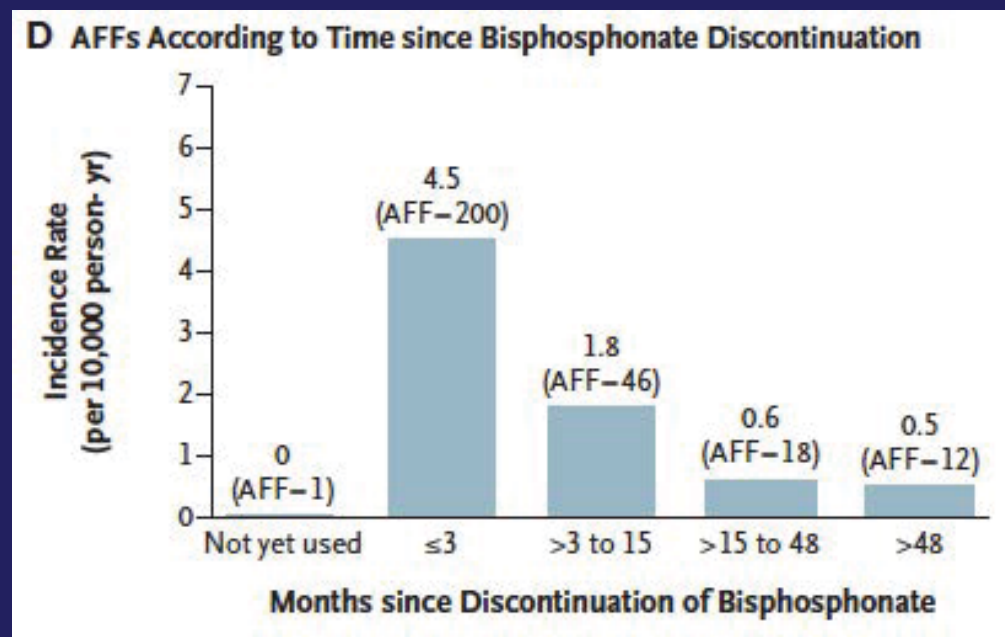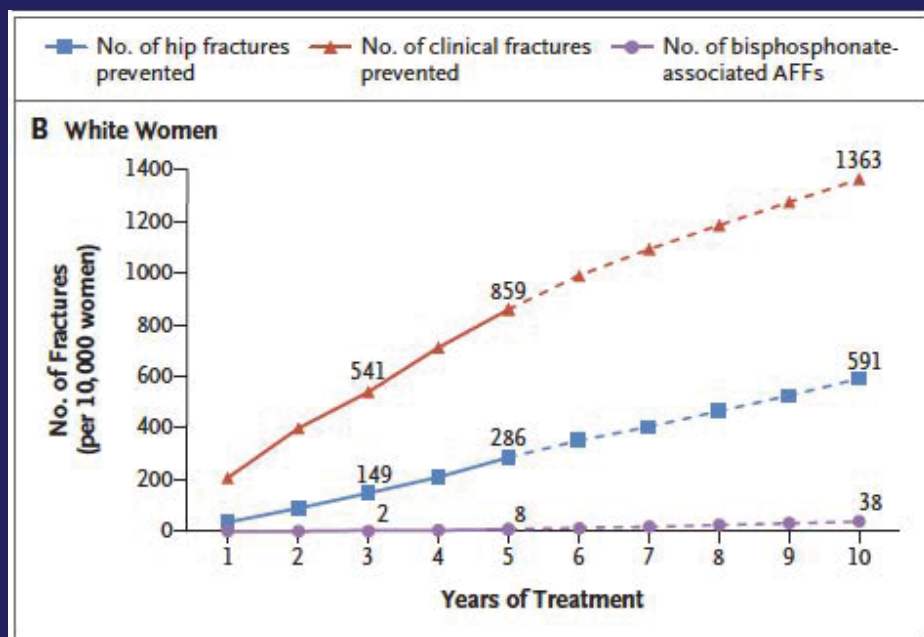
Denosumab
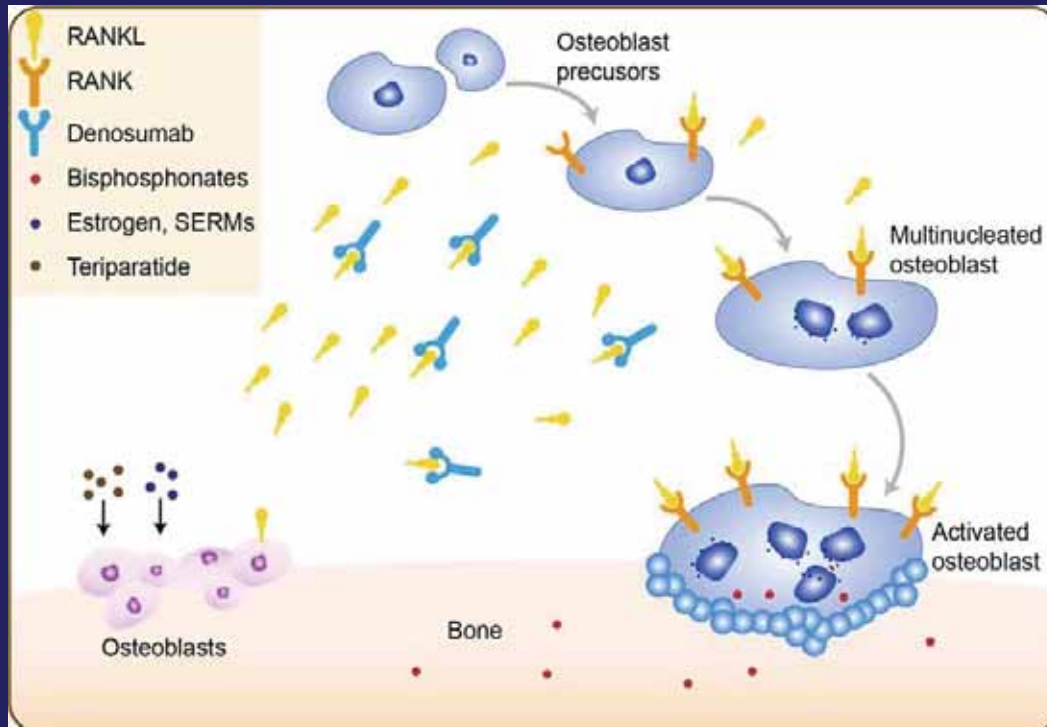
- Monoclonal to RANKL
- Decrease osteoclast activation
- Increase BMD, decrease fracture risk
- ? Risk of infection: use judiciously in HIV, particularly in those with low CD4
- Given q 6 months
- Vertebral fracture after discontinuation -> follow with BPs
- Can be given in those with low GFR; concern for hypocalcemia

# Pharmacologic Therapies for Osteoporosis

Antiresorptive (Osteoclast Directed)

- bisphosphonates
- SERMs (raloxifene)
- denosumab
- hormone replacement therapy

Anabolic (Osteoblast Directed)

- PTH/PTHrP Analogs (teriparatide, abaloparatide)
- romosozumab

PTH/PTHrP Analogs

Teriparatide increases BMD more than alendronate
In glucocorticoid-induced osteoporosis

Saag, NEJM, 2007
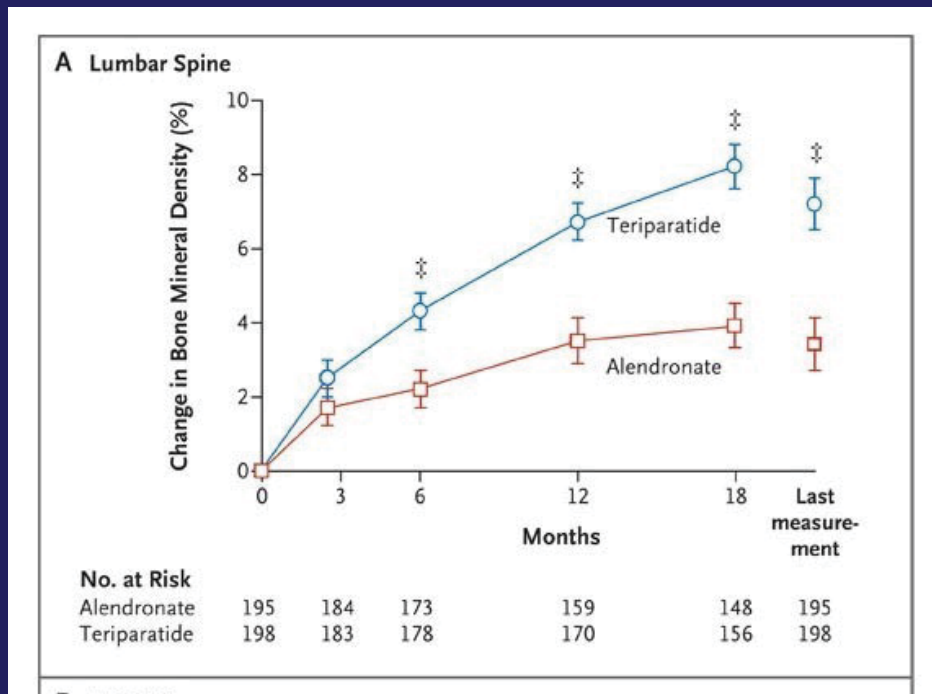
- Generally given after BP failure
- Can be first line in severe osteoporosis
- 18-24 month duration of therapy
- Need to follow with an antiresorptive
- Daily SC injection

Romosozumab
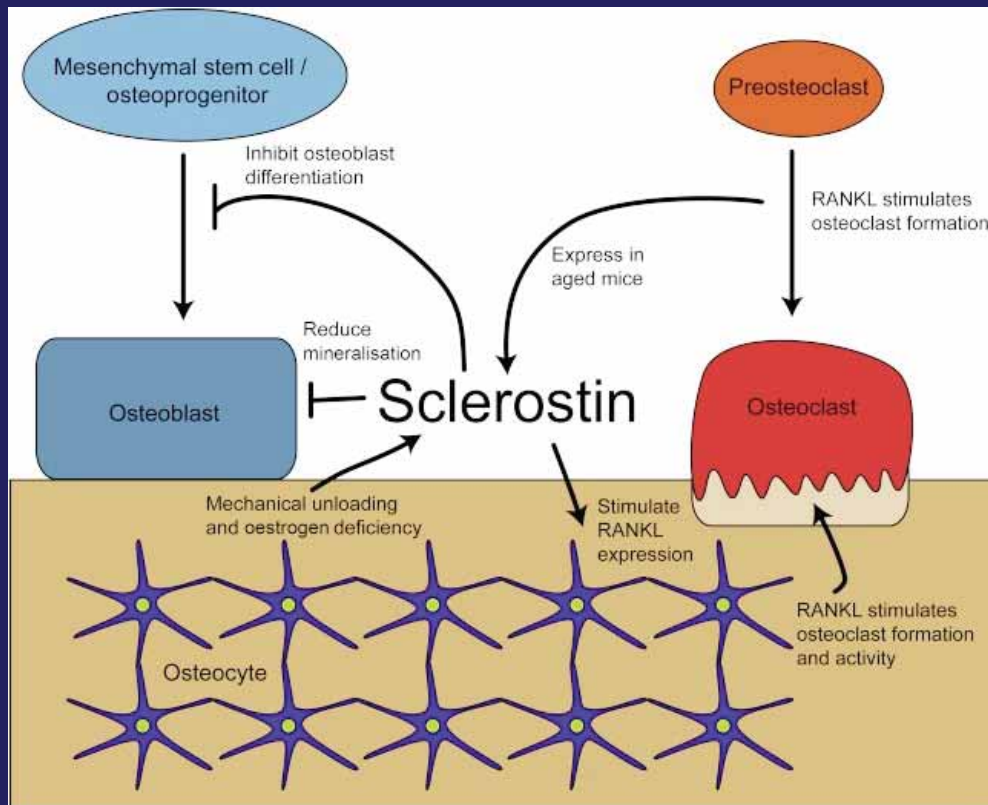
- Monoclonal antibody to sclerostin
- Increases osteoblast activity; Inhibits osteoclast activity
- Given for 1 year; monthly injections
- Greater BMD gains v ALN vs TRPT
- Greater fracture risk reduction vs ALN
- For severe osteoporosis or intolerance to other meds

Preventing falls will prevent fractures

Risk Factors for Falls

- Sedative use

- Cognitive or visual impairment

- Lower-extremity disability

  – Neuropathy

- Muscle Weakness

- Frailty

http://courses.washington.edu/bonephys

Strategies to Prevent Falls

- Assess Fall Risk (Are you worried about falling?)
- Physical Therapy Assessment for Strength and Balance
- Environmental Assessment/Modification
  - keep bathroom lights on
  - avoid loose rugs
  - remove clutter

  - keep wires behind furniture
- Behavioral Assessment/Modification
  - avoid excess alcohol, drugs
  - consider de-prescribing
 - wear sturdy shoes
  - avoid slippery/uneven surfaces

Conclusions

- Fractures likely to be a major source of morbidity for aging PWH.

- DXA screening should be more aggressive in PWH

- Bisphosphonates should be considered first line therapy

- Adherence to treatment is a major challenge

- Many questions remain re: the optimal duration of treatment & sequencing of medications

- Fall prevention is essential to prevent fractures.

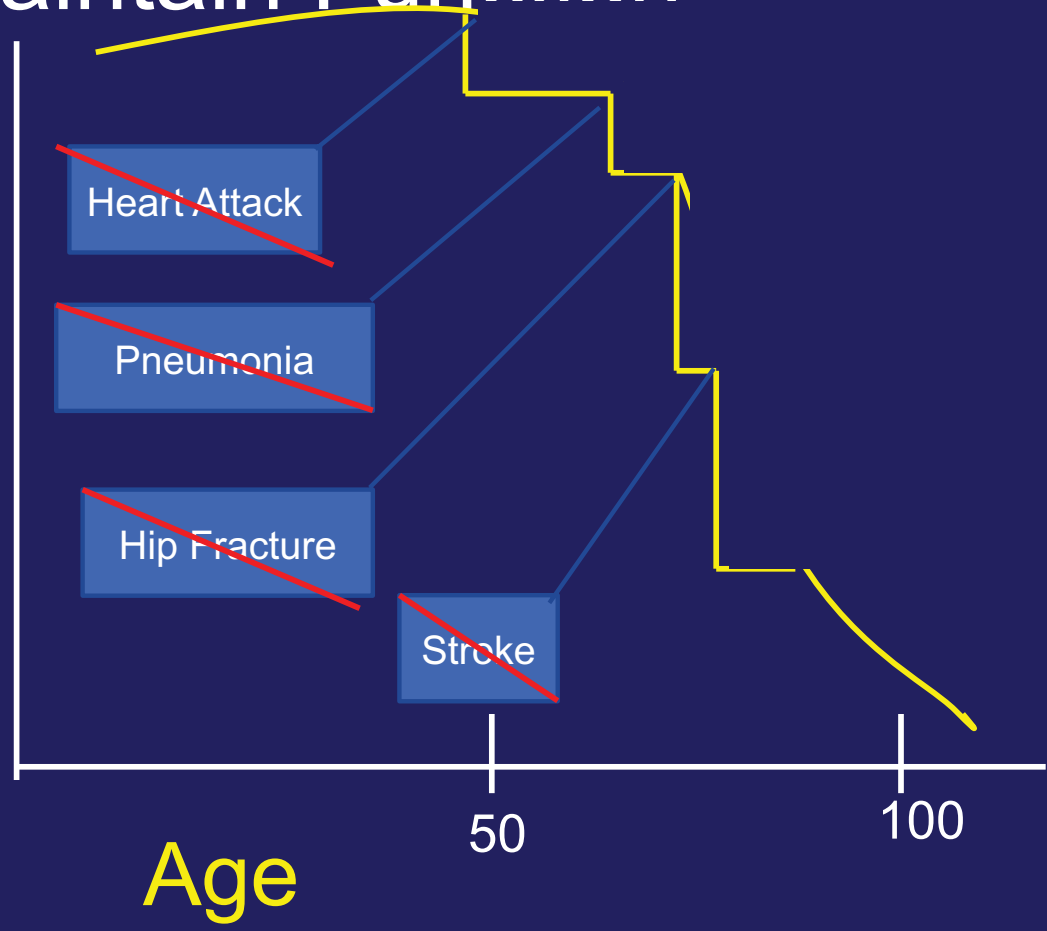# HIV Treatment Cascade: Identifying and Closing the Gaps in Care
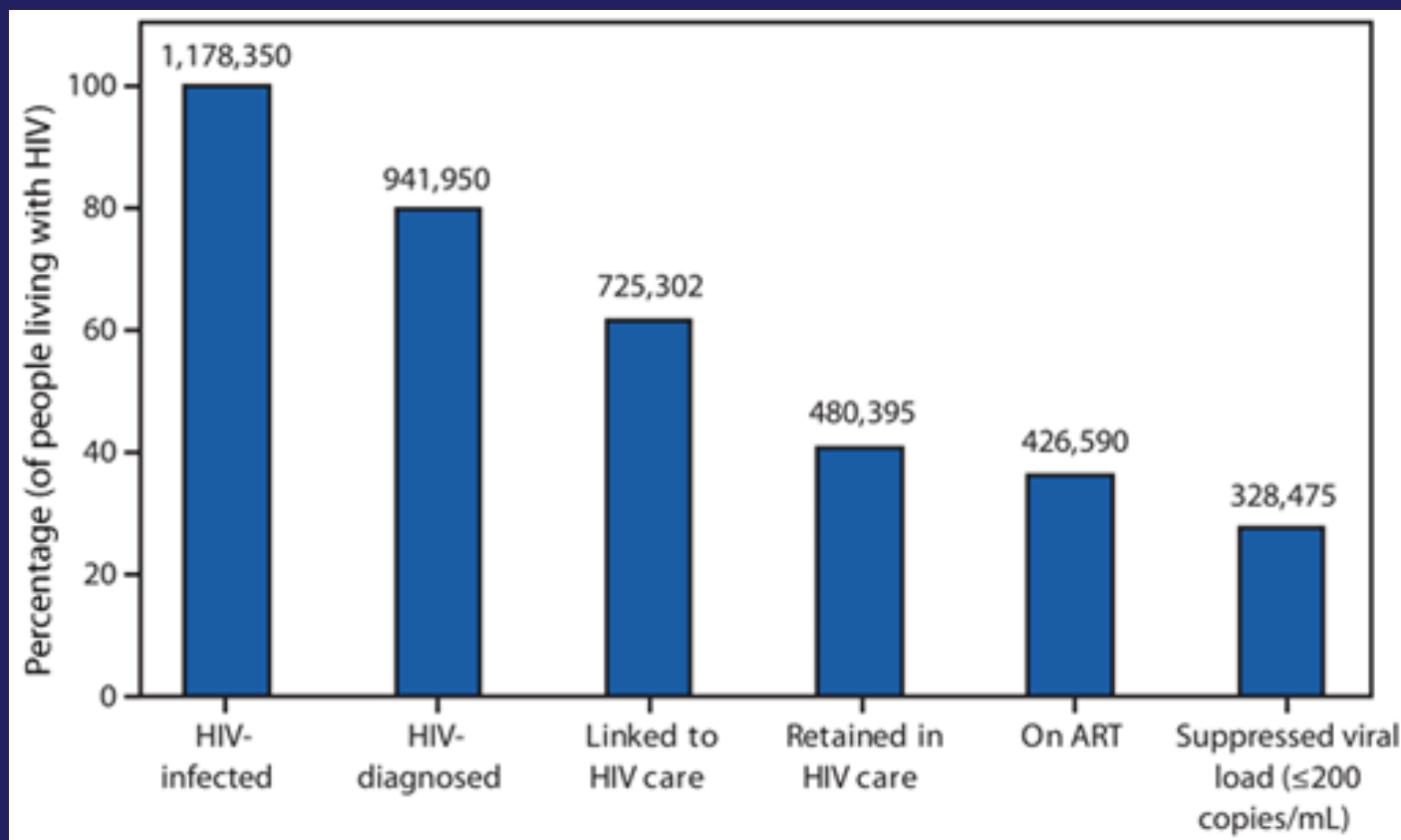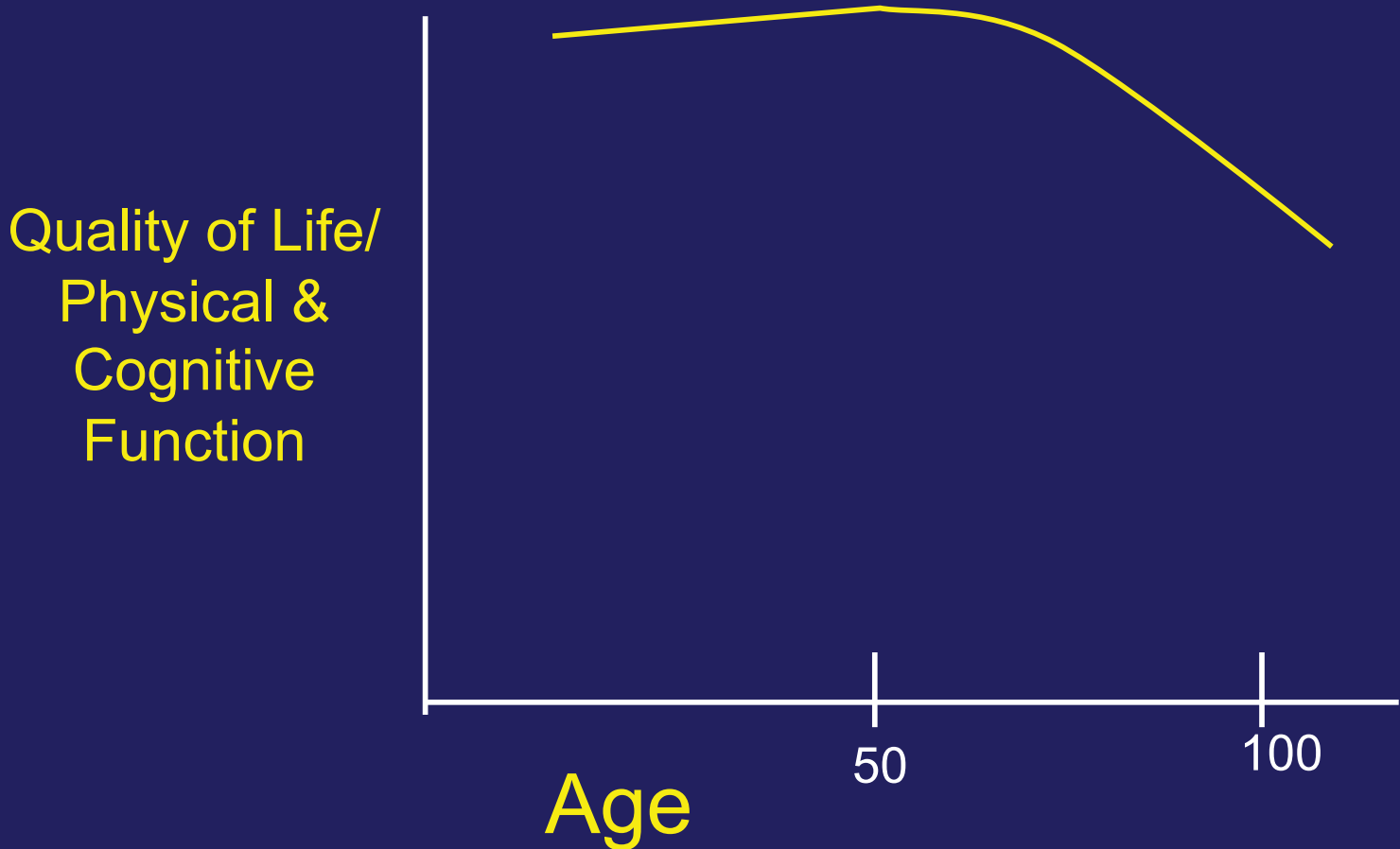
Closing the Gaps for Fracture Prevention in PWH
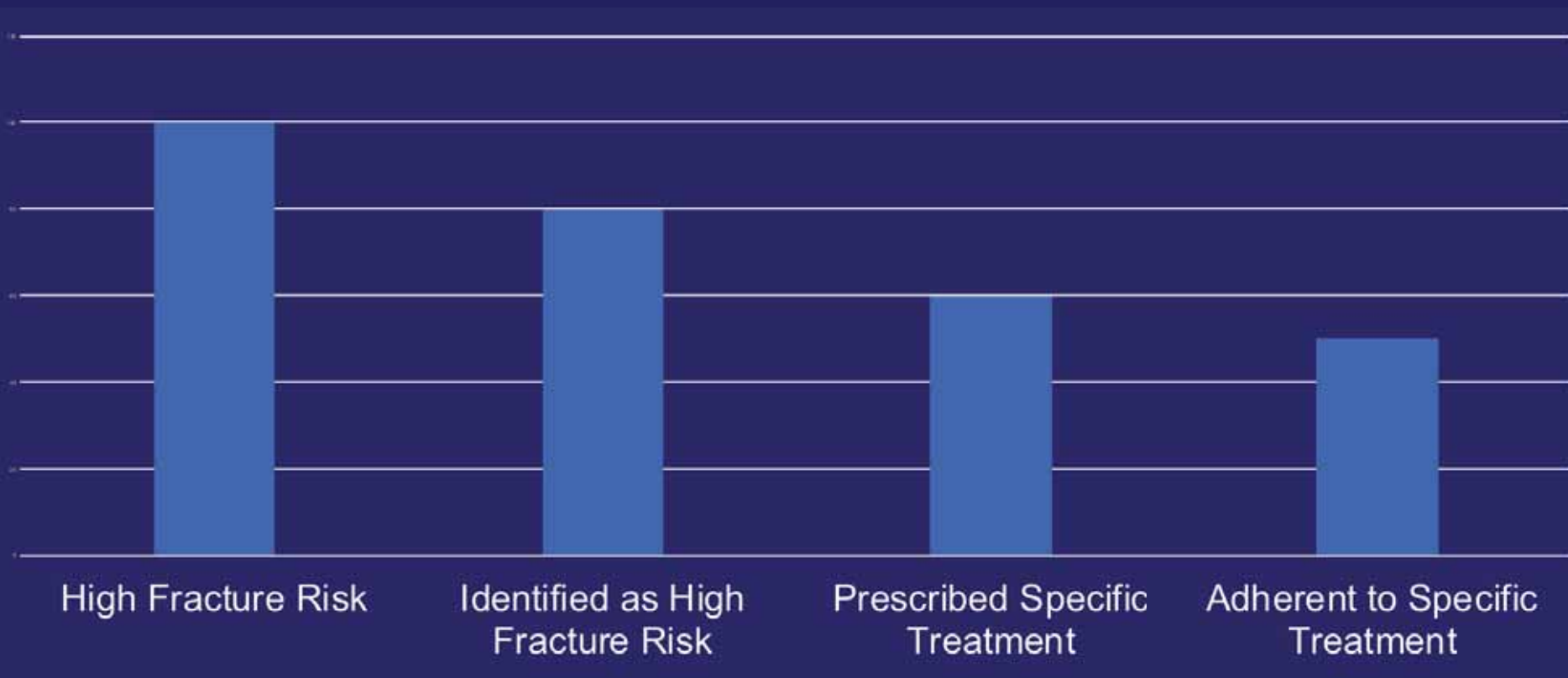
For Illustration Only; numbers are fictional

Preventing Comorbid Events is Critical to Maintain Function

Preventing Comorbid Events is Critical to Maintain Function

Quality of Life/ Physical & Cognitive Function

Age

50

100

Acknowledgment

AETC AIDS Education & Training Center Program
Mountain West