

Osteoporosis and HIV: Optimal Evaluation and Management to Prevent Fractures

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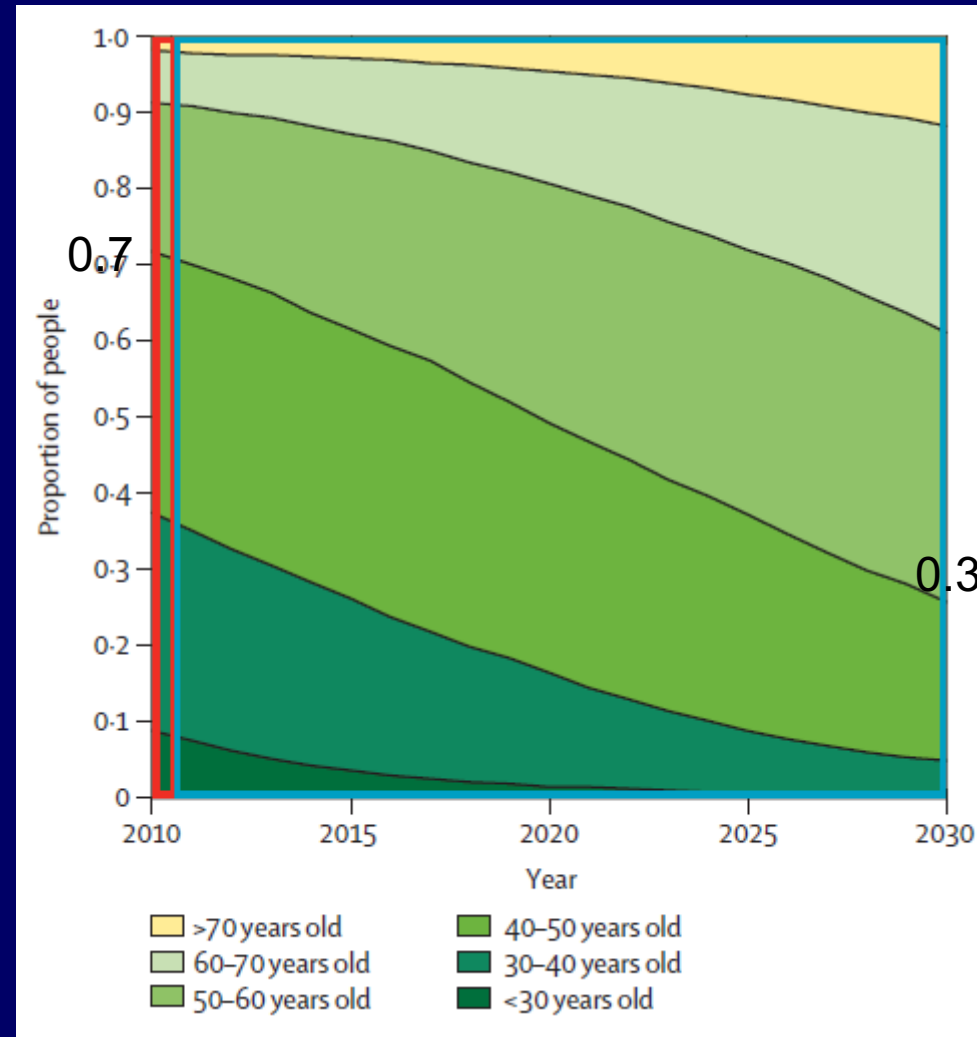
Division of Endocrinology, Diabetes, & Metabolism

Johns Hopkins University

Disclosures

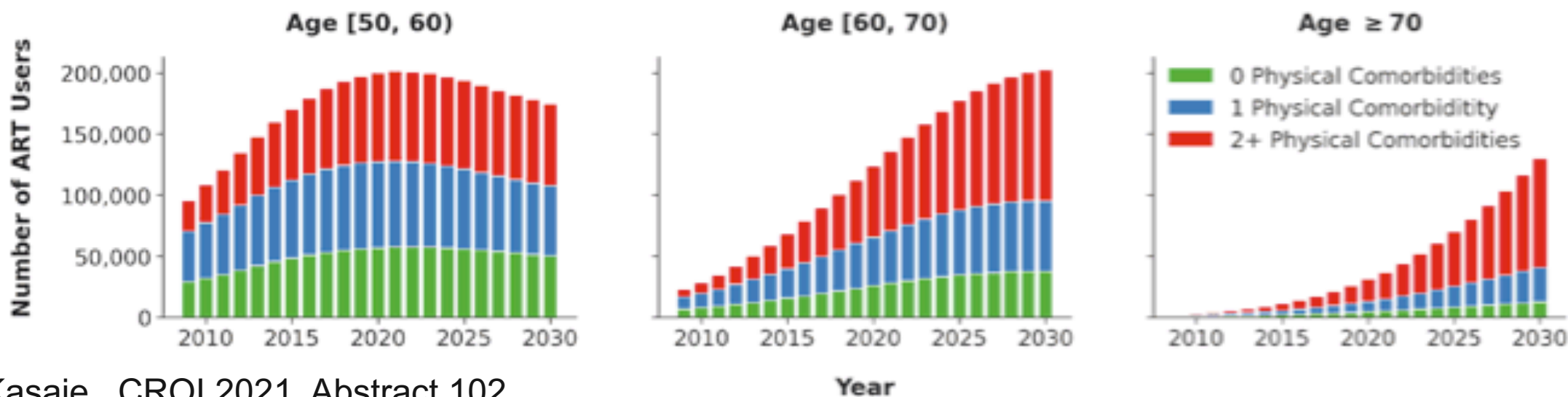
- Dr Brown has served as a consultant to Gilead Sciences, Inc, GlaxoSmithKline, Janssen, Merck & Co, Inc, Theratechnologies, EMD Serono, and ViiV Healthcare.

The Aging of the HIV Population: Netherlands

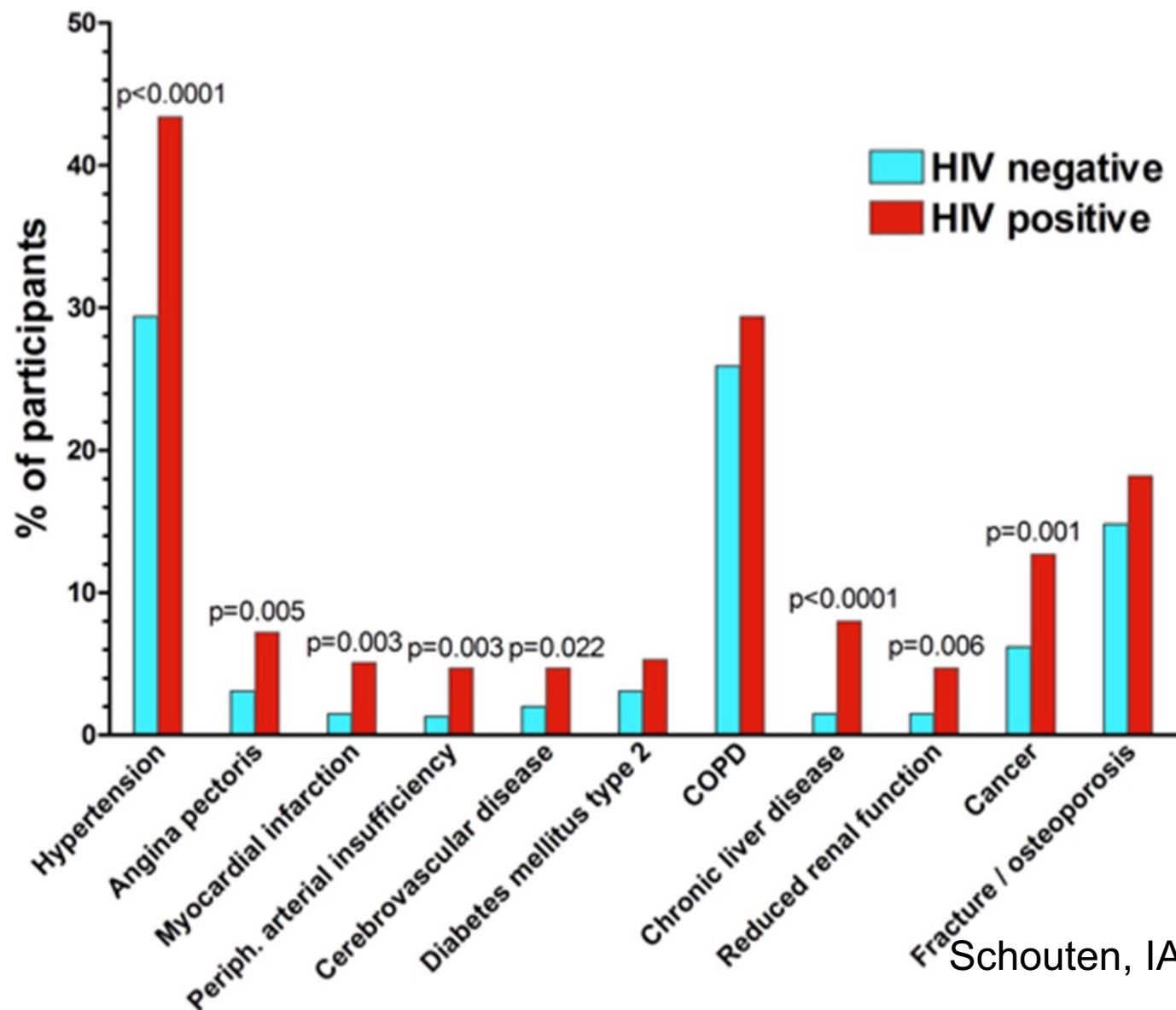


Multimorbidity will increase markedly in PWH over the next 10 years

- Older age-groups experience an **increase in population size and prevalence of multimorbidity**
- Among those ≥ 70 yrs, 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



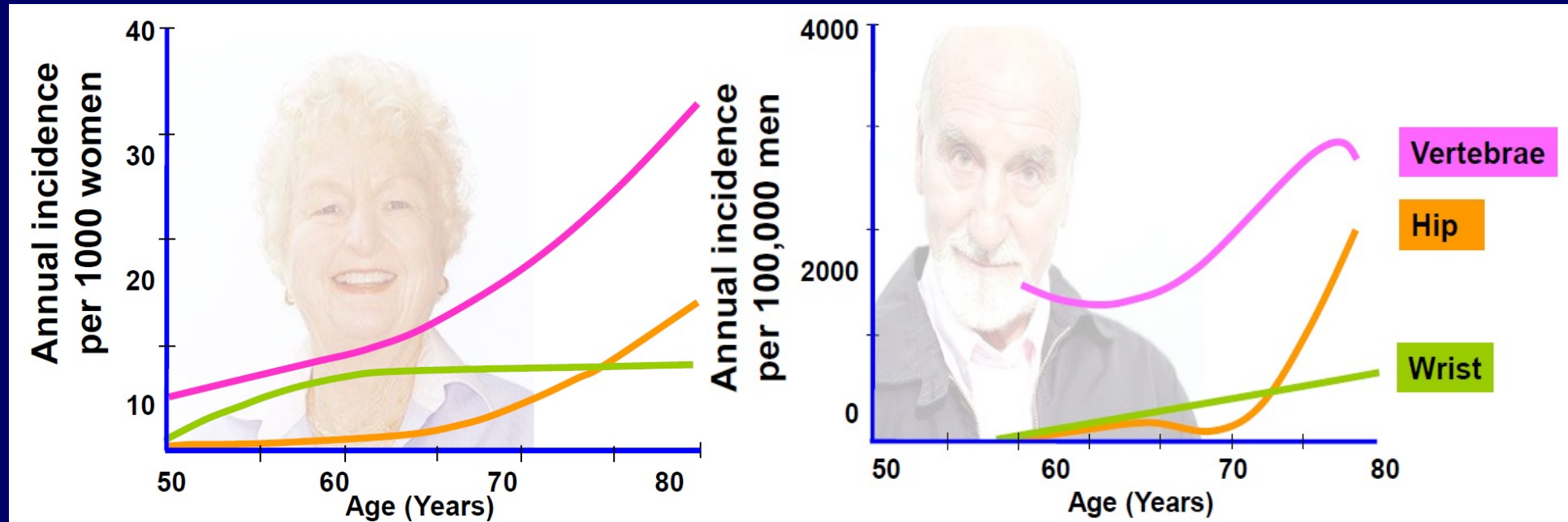
Comorbidity distribution



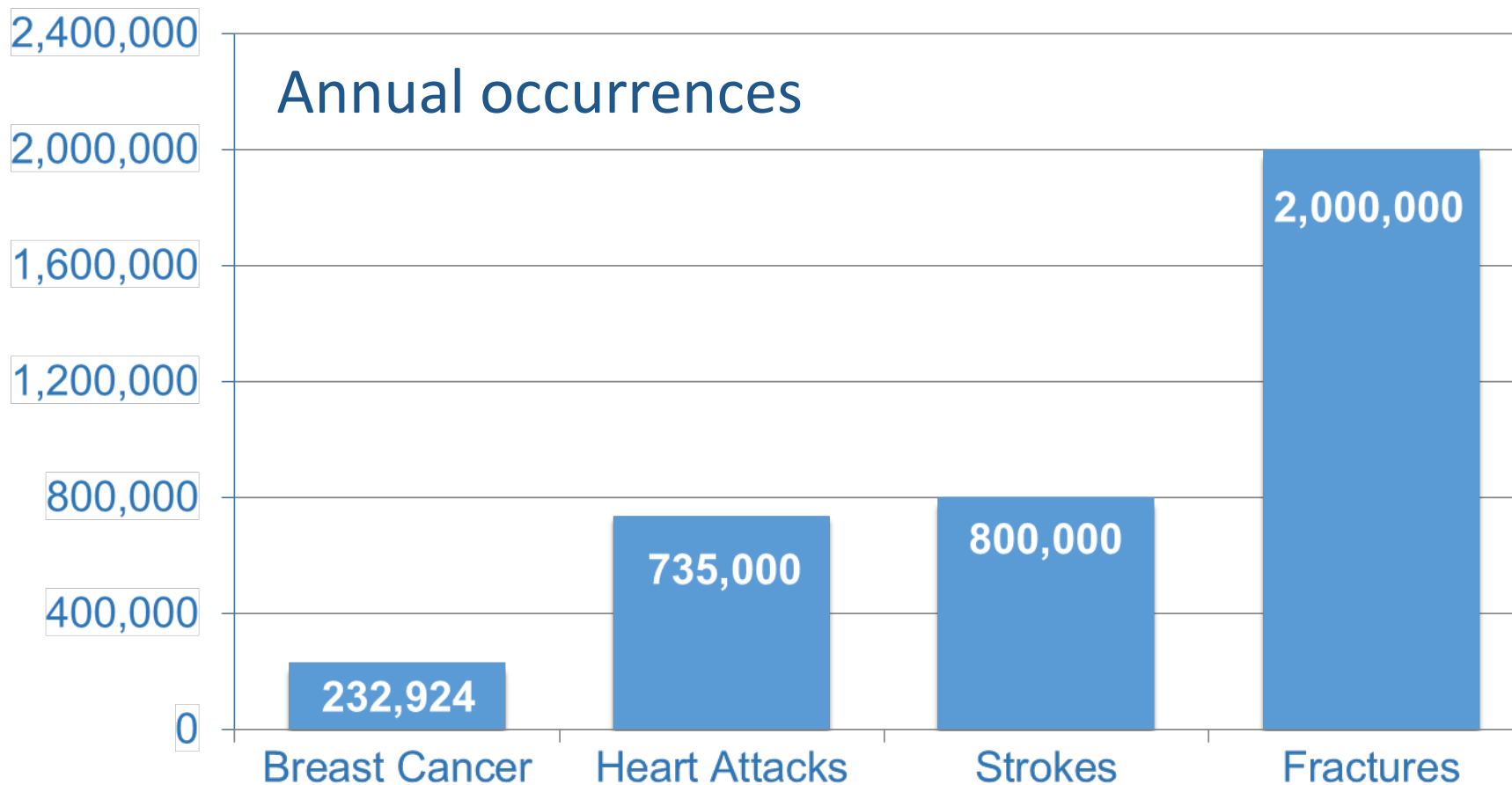
Why worry about osteoporosis?

- Osteoporosis is common among older populations and more common in PWH compared to matched HIV SN
- Osteoporotic fractures are a major source of morbidity & mortality
- 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

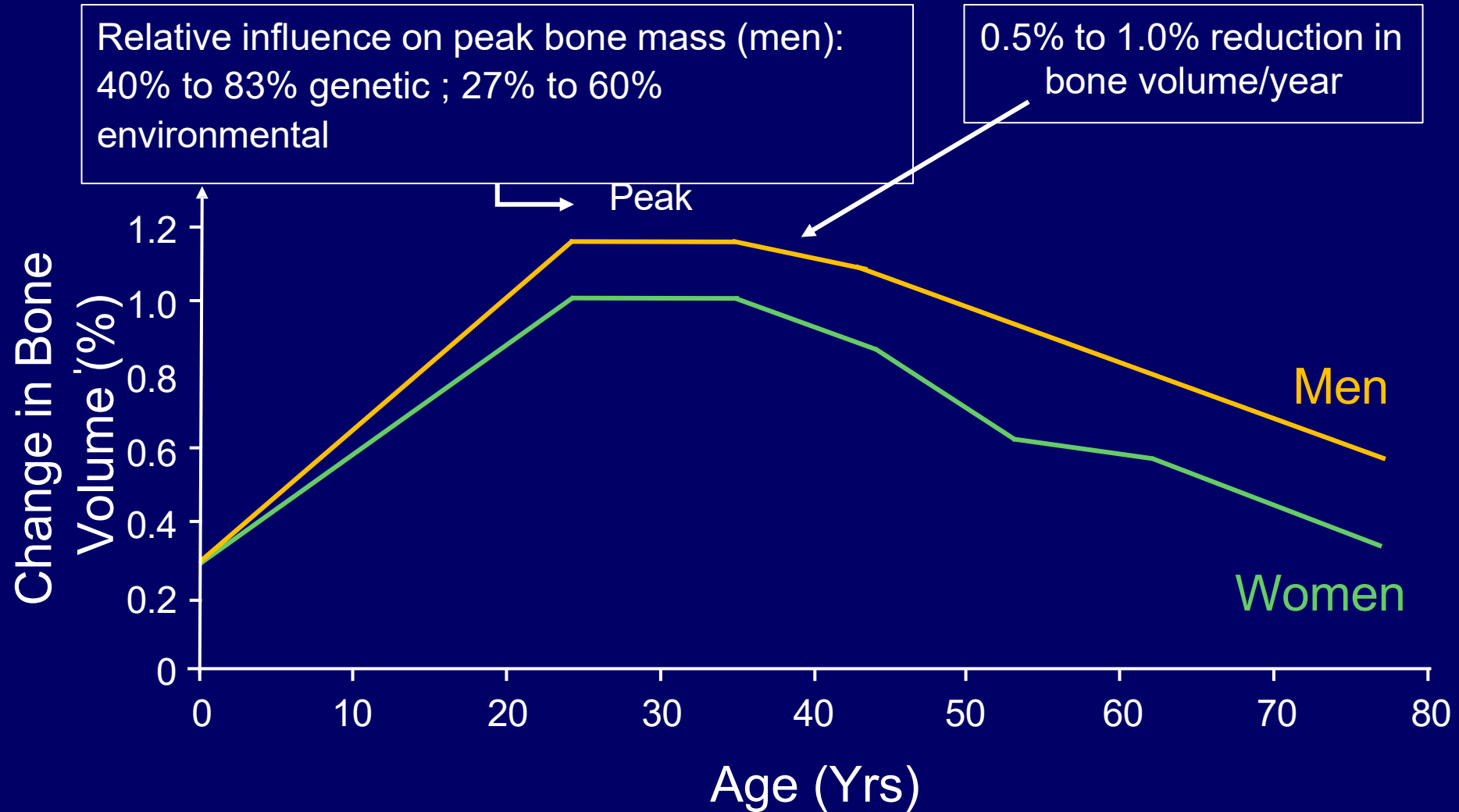


Compared to Other Health Issues

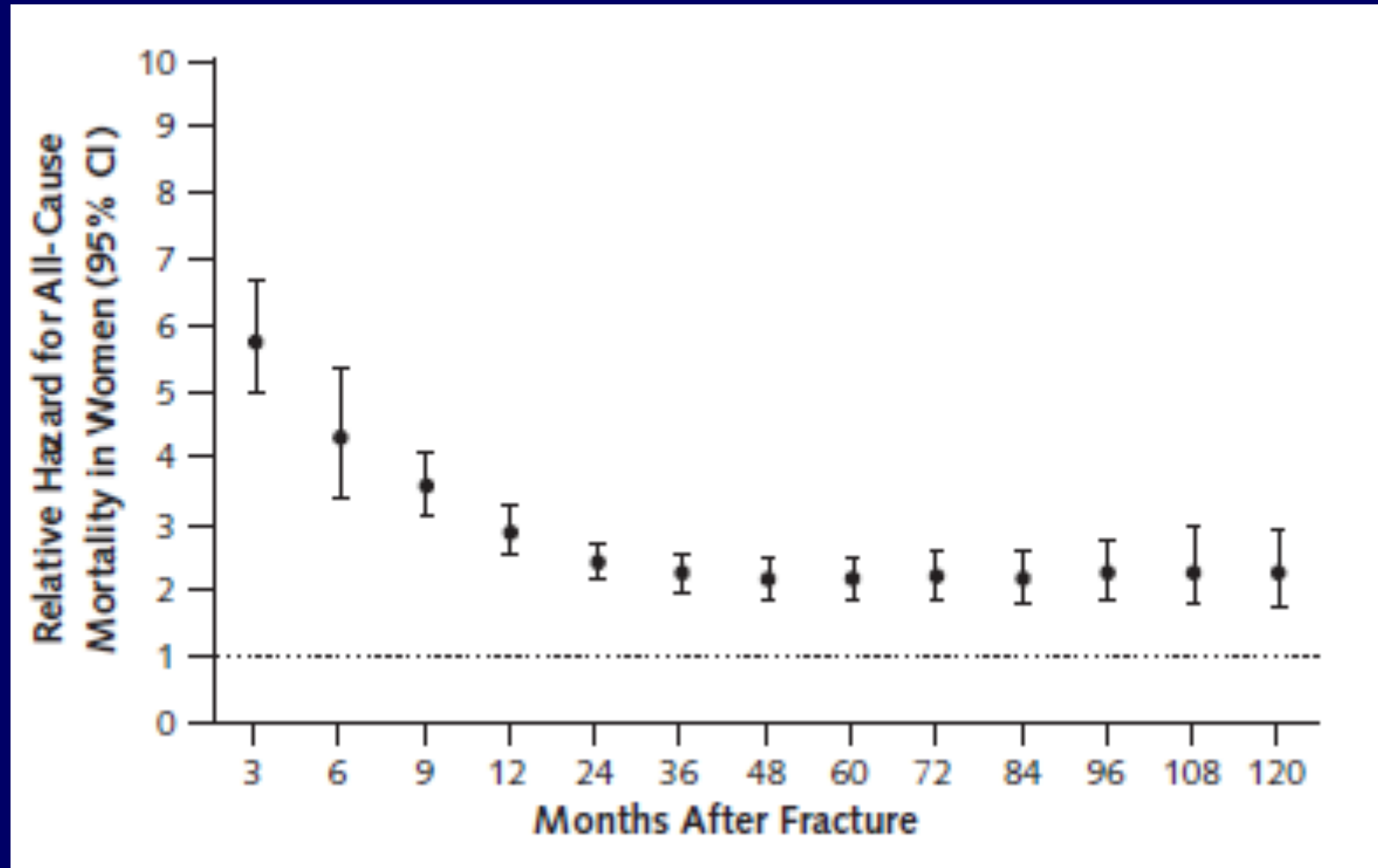


Centers for Disease Control & Prevention 2016
Centers for Disease Control & Prevention, 2015
Centers for Disease Control & Prevention, 2015
National Osteoporosis Foundation, 2015

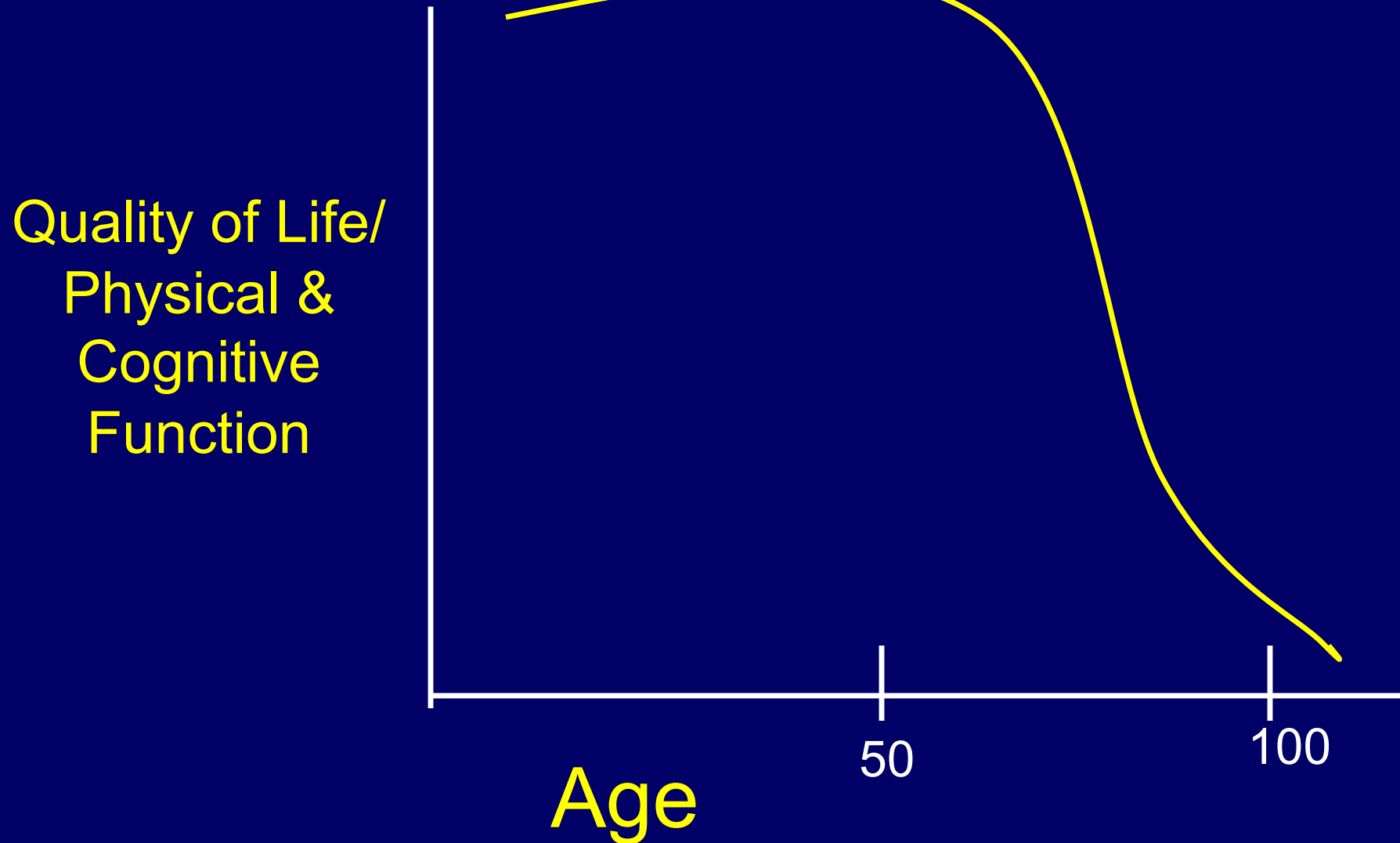
BMD Decreases With Age



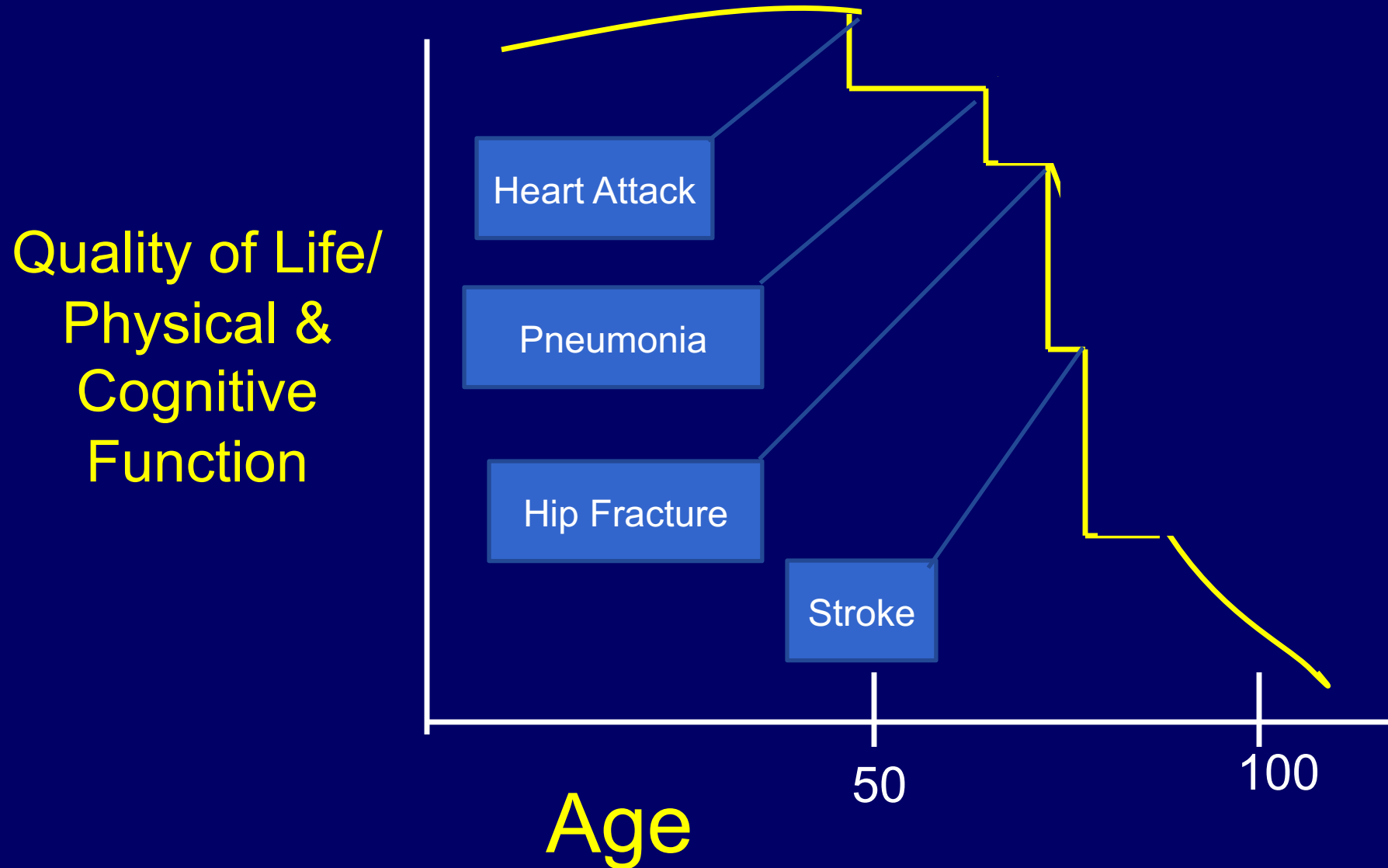
Increase Mortality After Fragility Fractures



Physical & cognitive function generally declines over time

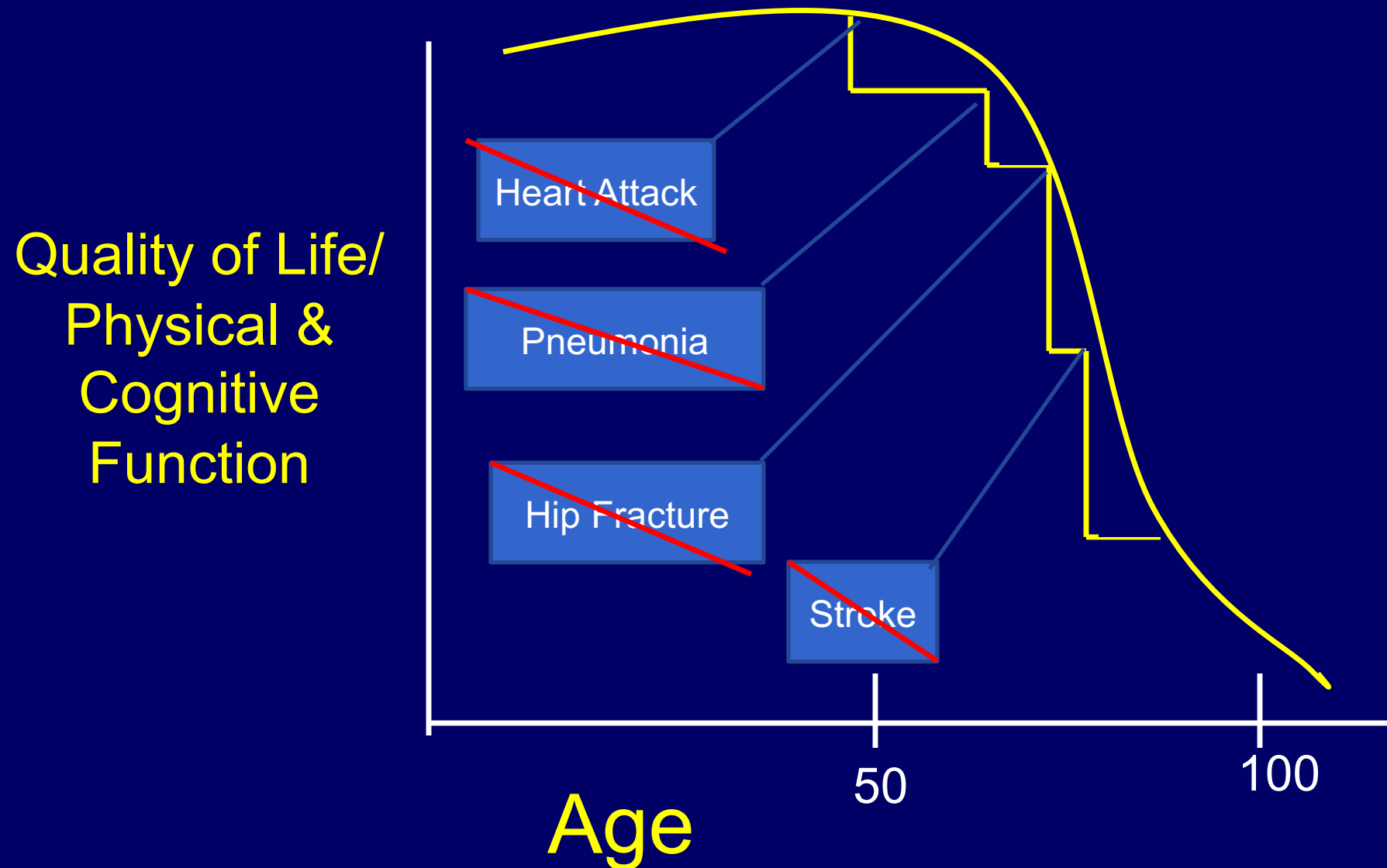


Decline in Function May Not Be Gradual

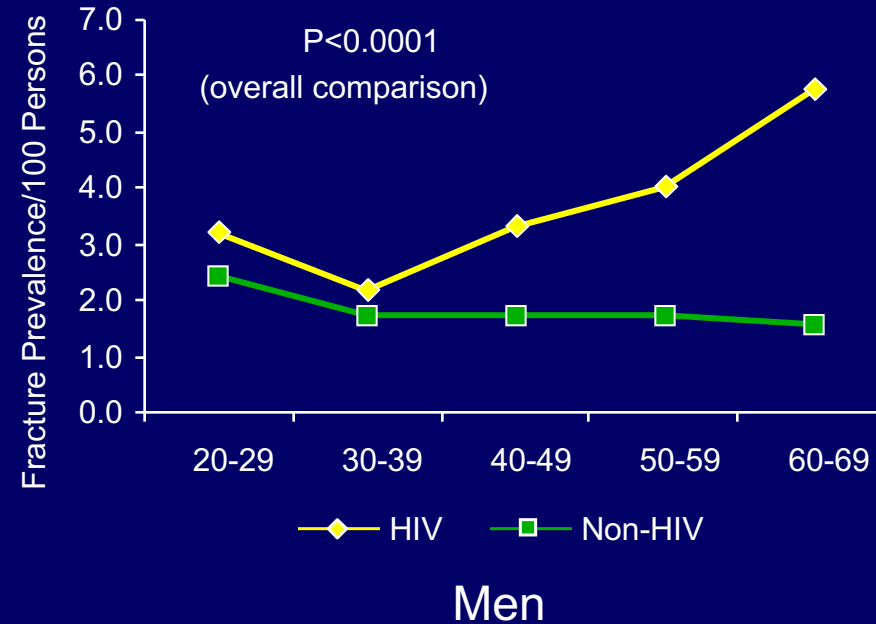
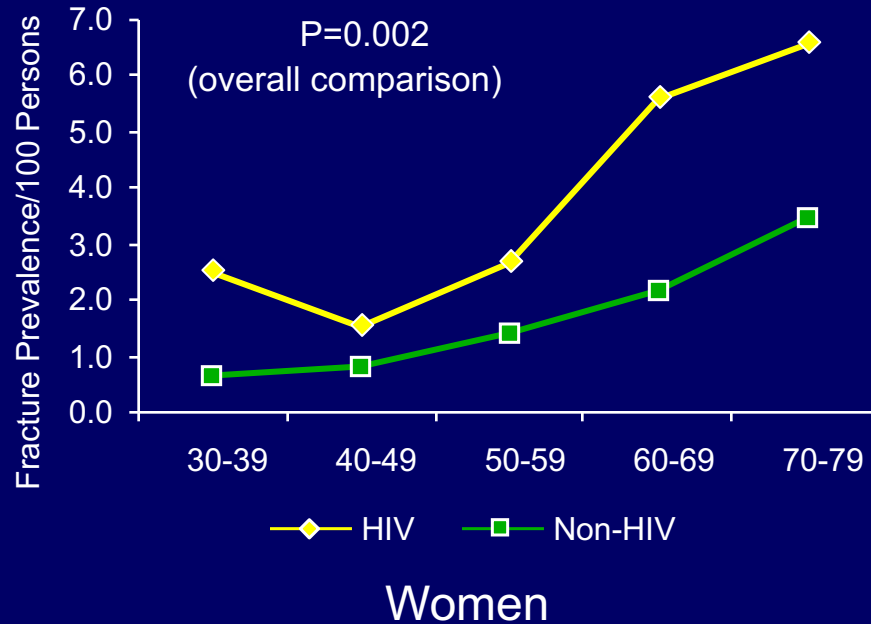


Preventing comorbid events, including fracture, is critical to maintain function

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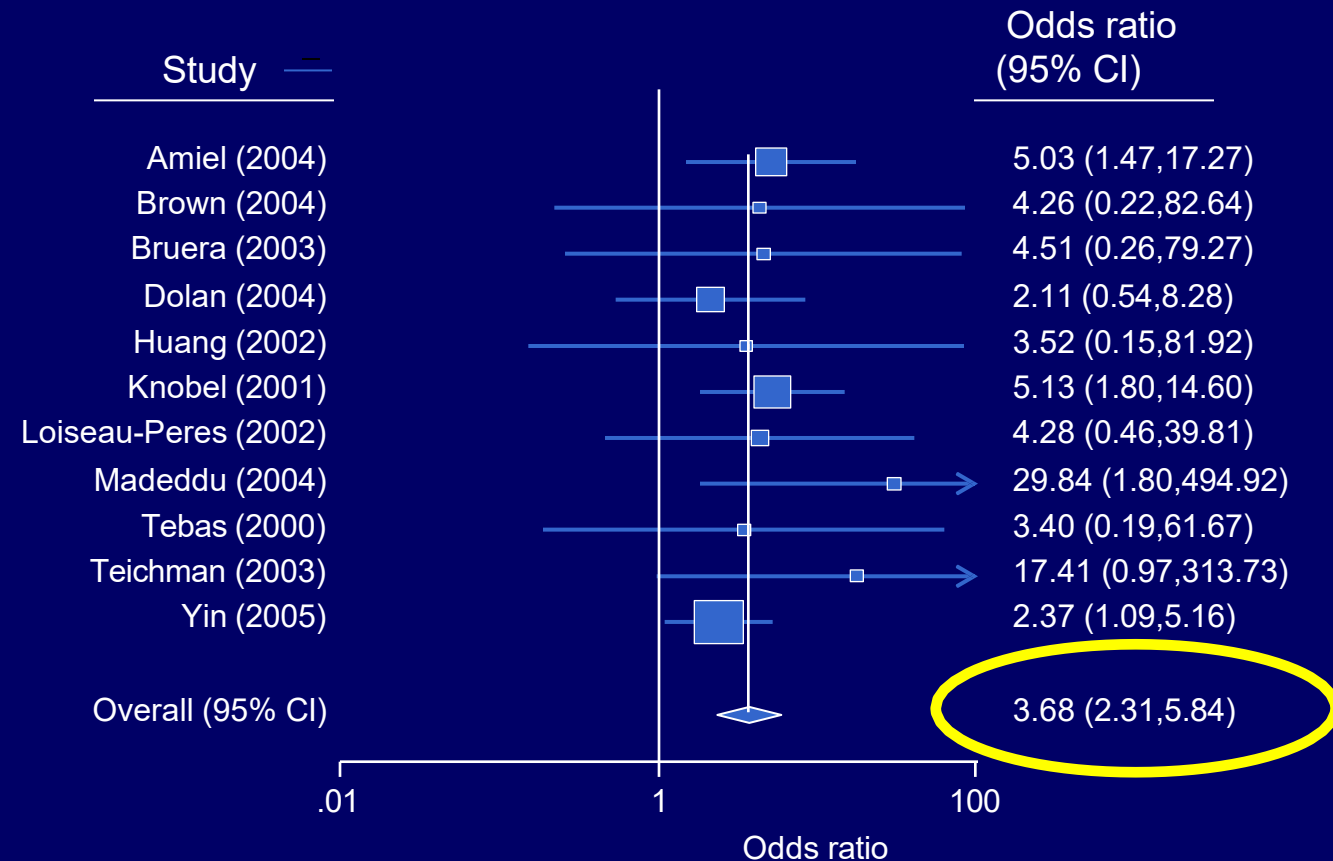
Fracture Prevalence in HIV-infected and non-HIV-infected Persons in MGH/Partners Healthcare System: 1996-2008



8,525 HIV-infected
2,208,792 non HIV-infected patients

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

Overall prevalence of osteoporosis in HIV-infected patients 15%



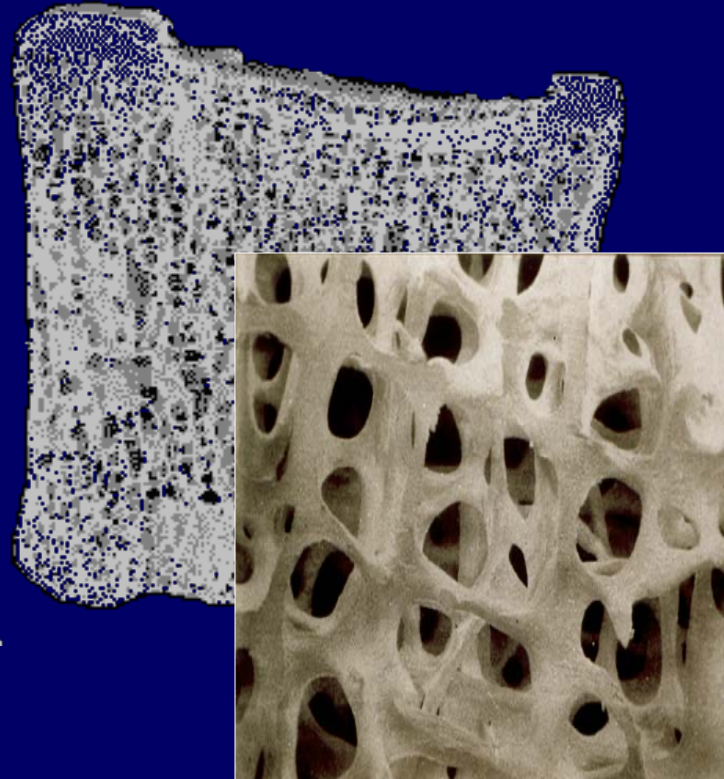
Definitions

Osteoporosis:

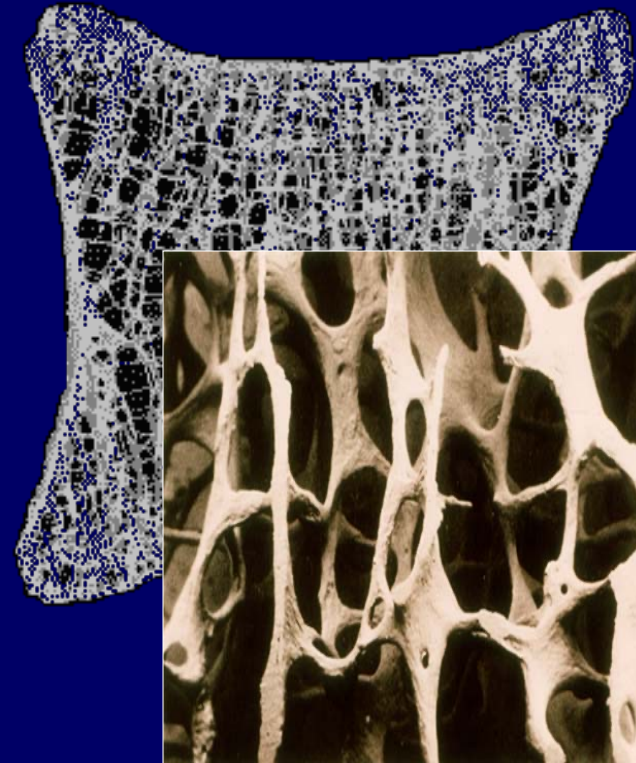
“systemic skeletal disorder characterized by **low bone mass** and **microarchitectural deterioration of bone tissue**, with a consequent increase in bone fragility and **fracture**”

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:

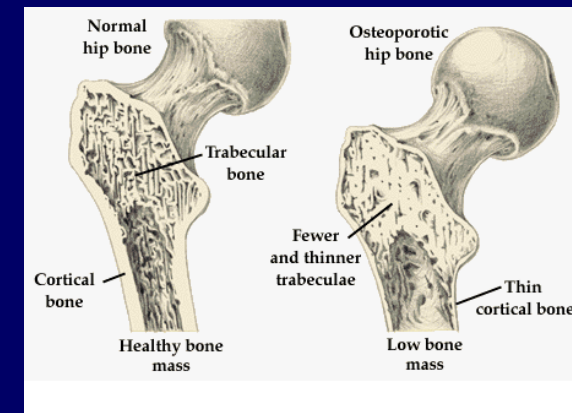
- Z-score (≤ -2.0) used in men < 50 years and premenopausal women
- BMD explains only about 50% of fracture risk

DXA Scanning



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

Sites differ in proportions of cortical and trabecular bone



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:

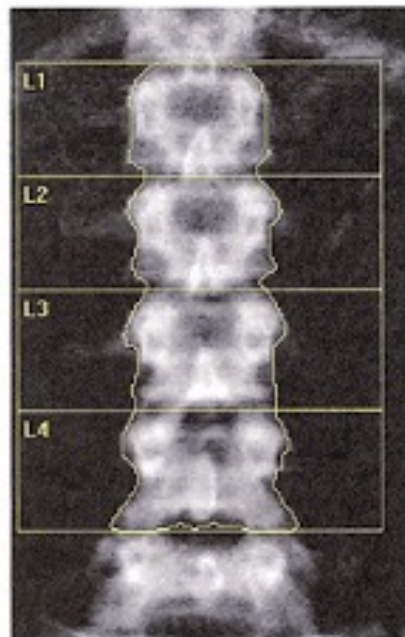


Image not for diagnostic use
 k = 1.138, d0 = 48.0
 116 x 149

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:

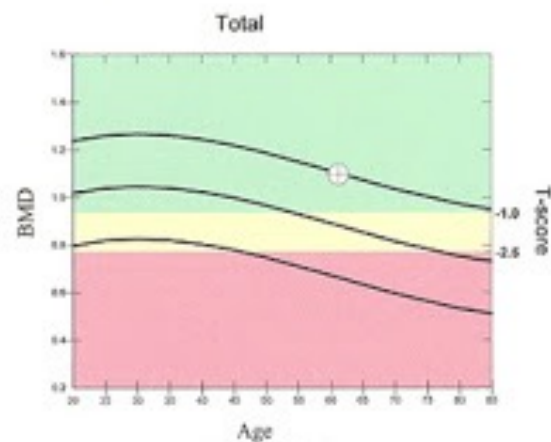
DXA Results Summary:

Region	Area (cm ²)	BMC (g)	BMD (g/cm ³)	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

Physician's Comment:



Fracture Risk
 Not Increased Increased High
 T-score vs. White Female; Z-score vs. White Female. Source: Hologic

Bedford Osteoporosis Center

35 Crosby Drive
 Bedford, MA 01730

Telephone: 781-999-7300

E-Mail: info@hologic.com

Fax: 781-290-0614

Name: Smith, Jane
 Patient ID: 00368
 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:

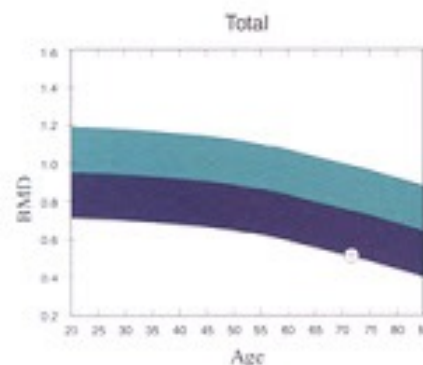
Scan Date: 11/2/98 ID: B11029500
 Scan Type: f Left Hip
 Analysis: 11/2/99 10:31 Version 8.26
 Left Hip

Operator: AR
 Model: QDR
 Comment: BASELINE

DXA Results Summary:

Region	Area (cm ²)	BMC (g)	BMD (g/cm ³)	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



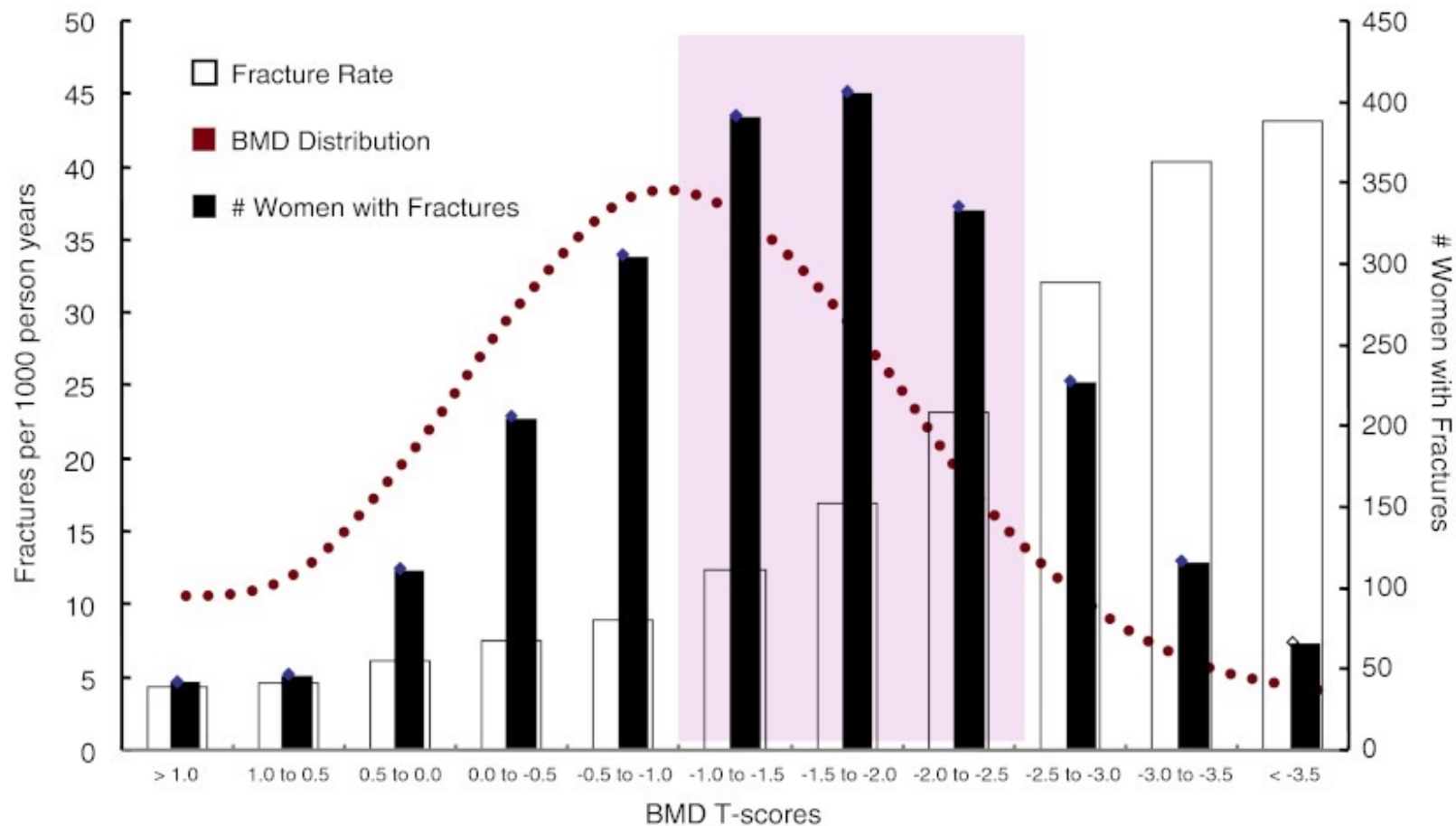
Reference curve and scores matched to White Female
 Source: NHANES

Physician's Comment:

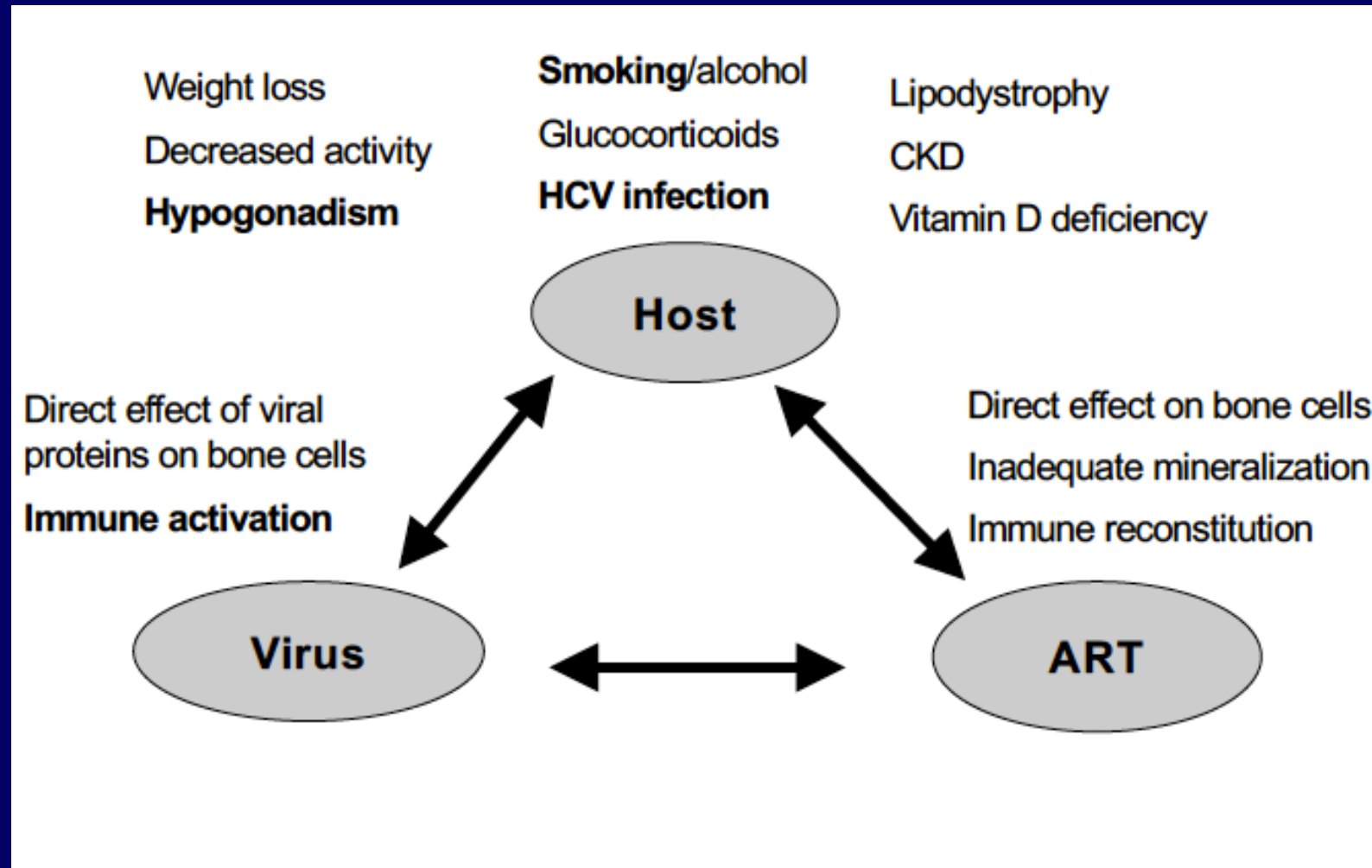


M-021 US International

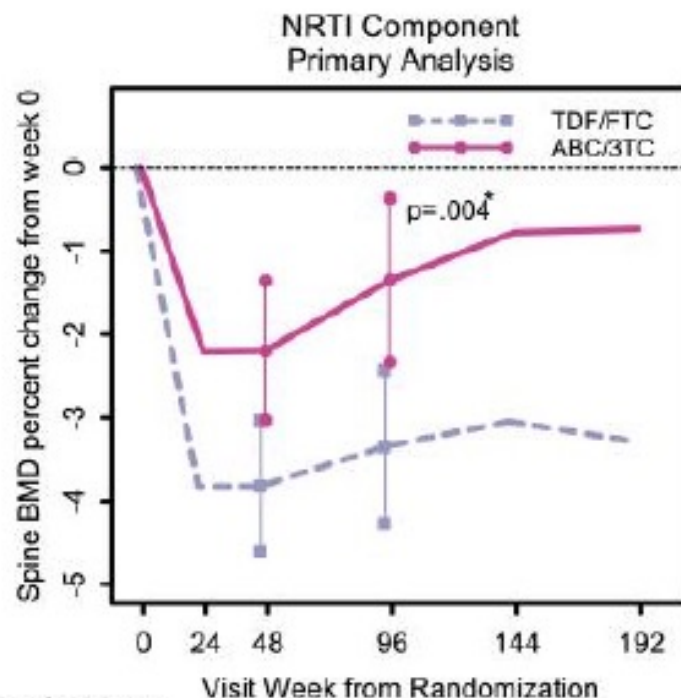
Fractures Happen at all BMDs



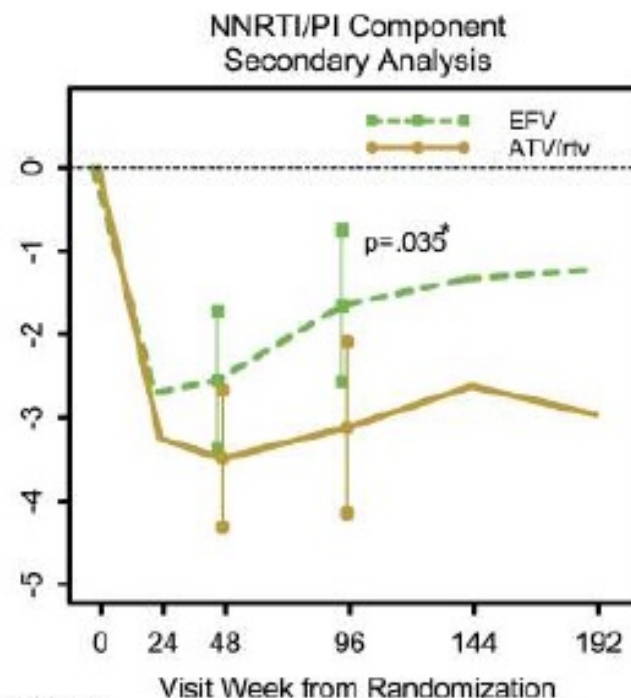
Multifactorial Etiology of Bone Loss in HIV



Bone Loss Occurs First 6 Months after ART Initiation



No. of subjects	0	24	48	96	144	192
TDF/FTC	128	111	105	97	87	53
ABC/3TC	130	122	106	101	80	53



No. of subjects	0	24	48	96	144	192
EFV	133	117	109	107	86	58
ATV/r	125	116	102	91	81	48

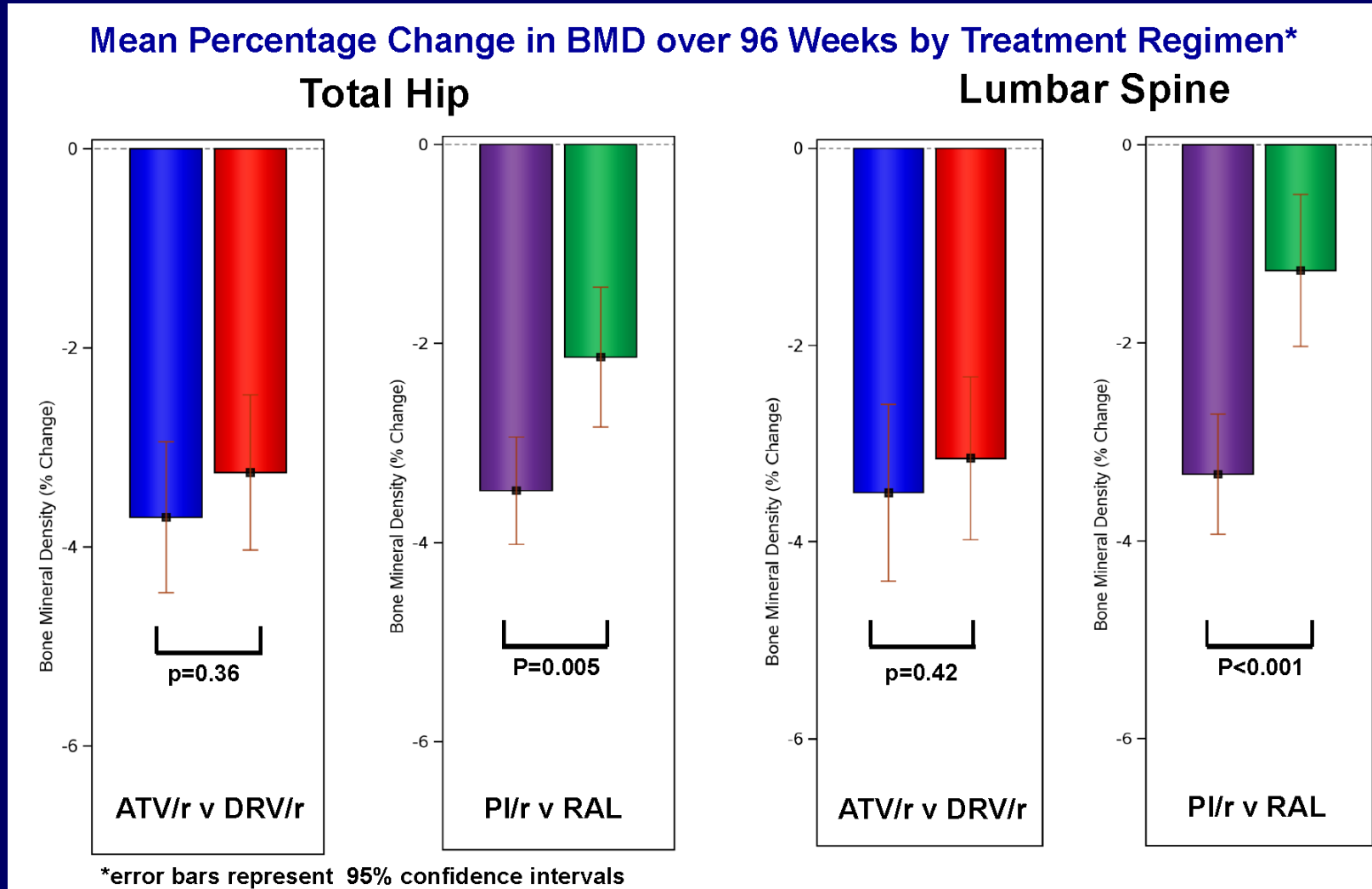
* - two-sample t-test

No significant interaction of NRTI and NNRTI/PI components ($p = .63$)

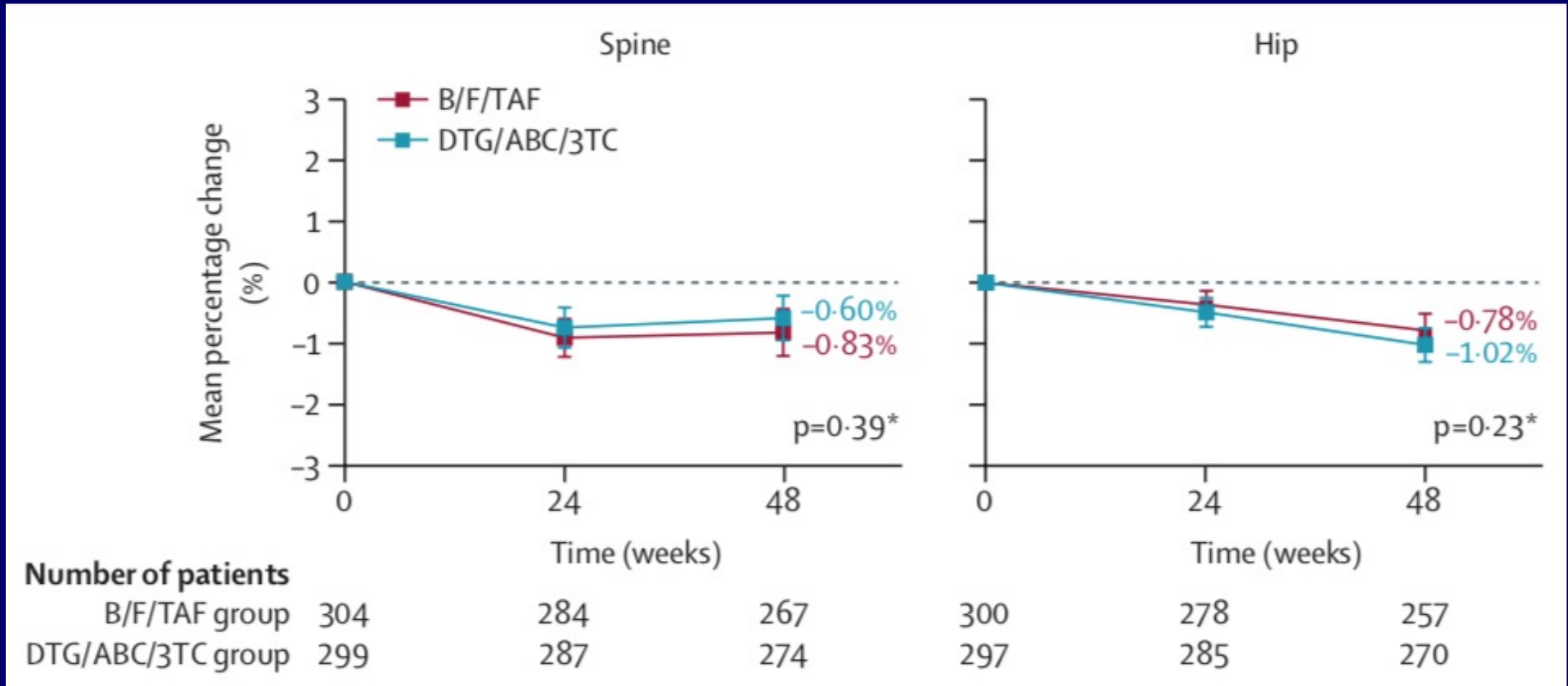
Bone Loss with ART Initiation: TDF

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

Bone Loss After ART Initiation: PIs vs RAL




Starting ART without TDF or PIs: 0.5-1.0% Bone Loss



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/cm²* 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

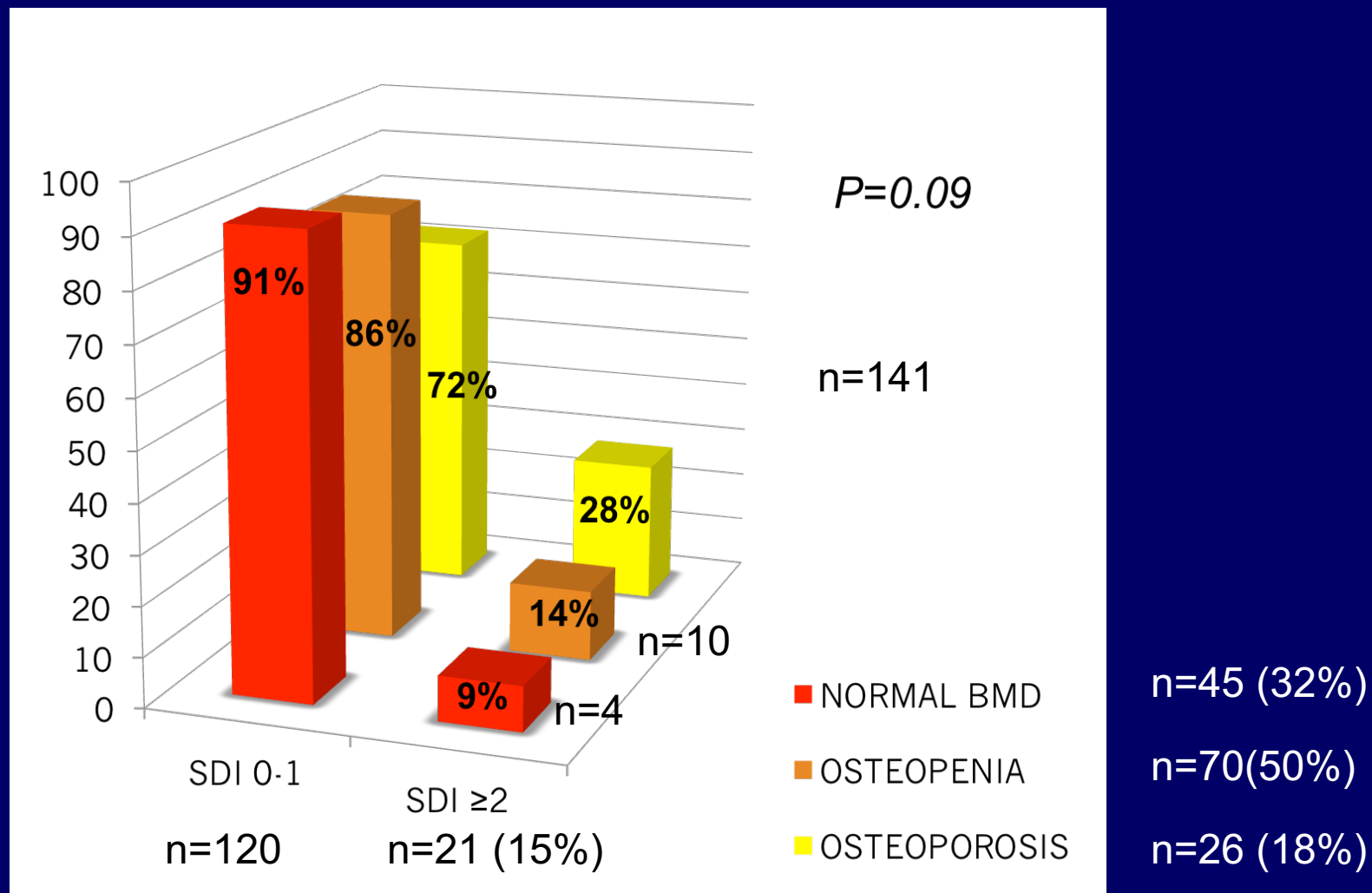
US Bone Health and Osteoporosis Foundation (BHOF) Guidelines for DXA Screening

- 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 \geq 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



2/3 of those with subclinical vertebral fractures did not have osteoporosis

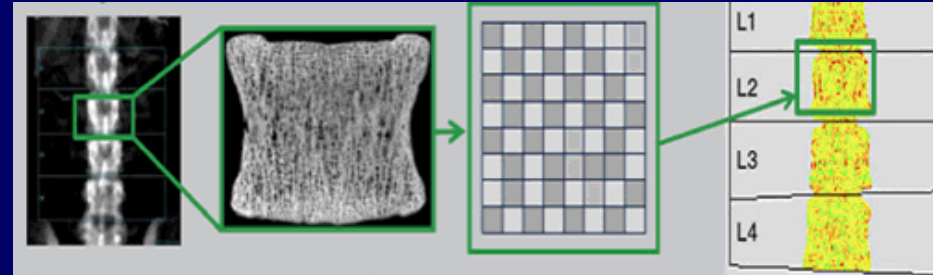
Other Modalities to Assess Fracture Risk

- Skeletal
 - Spine X-rays
 - Trabecular Bone Score

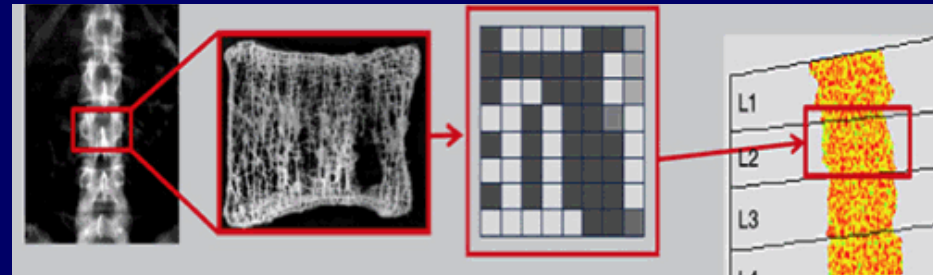
Trabecular Bone Score as Noninvasive Measure of Bone Microstructure

- 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

How can we prevent fractures in PWH?

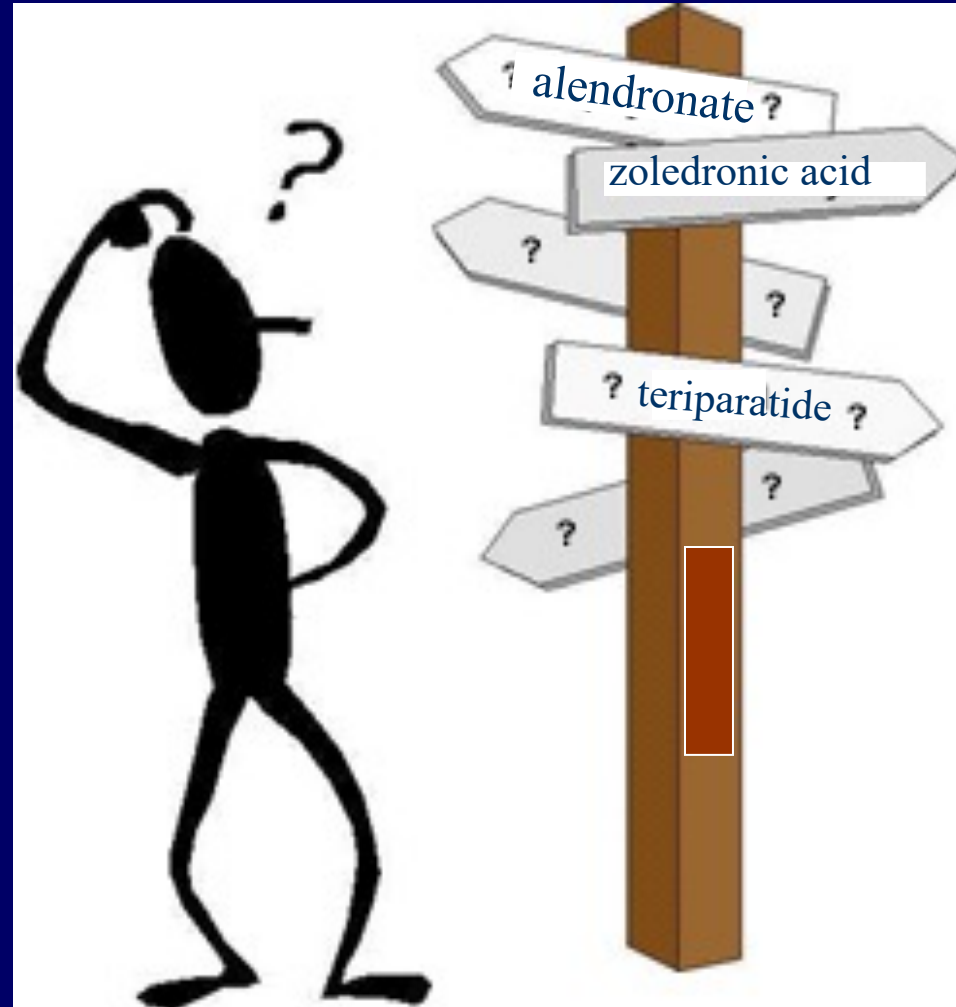
- ART switching
 - avoid TDF & PIs in individuals with higher fracture risk
- Appropriate screening
 - DXA: Men ≥ 50 y & all post-menopausal women
 - Caveat: Explains only about 50% of fracture risk
- Identifying appropriate candidates for treatment

US BHOFF 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 $\geq 3\%$ or 10-year all major osteoporosis-related fracture $\geq 20\%$ based on FRAX model

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

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

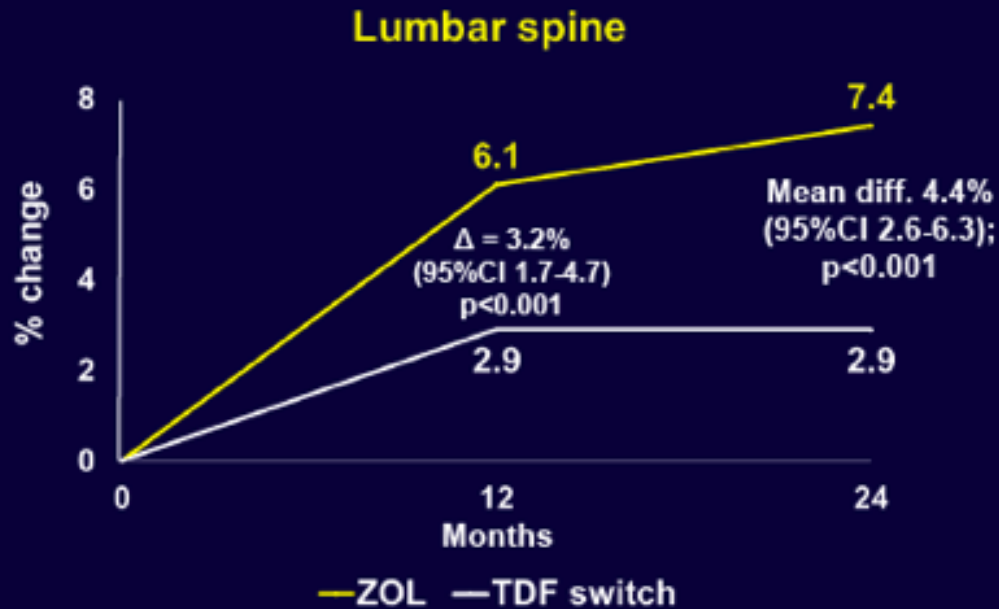
Author, year (N)	T-score	Medication (duration)	Spine	Hip
Guaraldi, 2004 (N=41)	< -1.0	Alendronate 70 mg/wk (1 yr)	NS	NS
Mondy, 2005 (N=31)	< -1.0	Alendronate 70 mg/wk (1 yr)	+5.2% vs +1.3%*	NS
McComsey, 2007 (N=82)	< -1.5	Alendronate 70 mg/wk (1 yr)	+3.1% vs +1.1%*	+4.0% vs +1.4% [†]
Rozenberg, 2012 (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

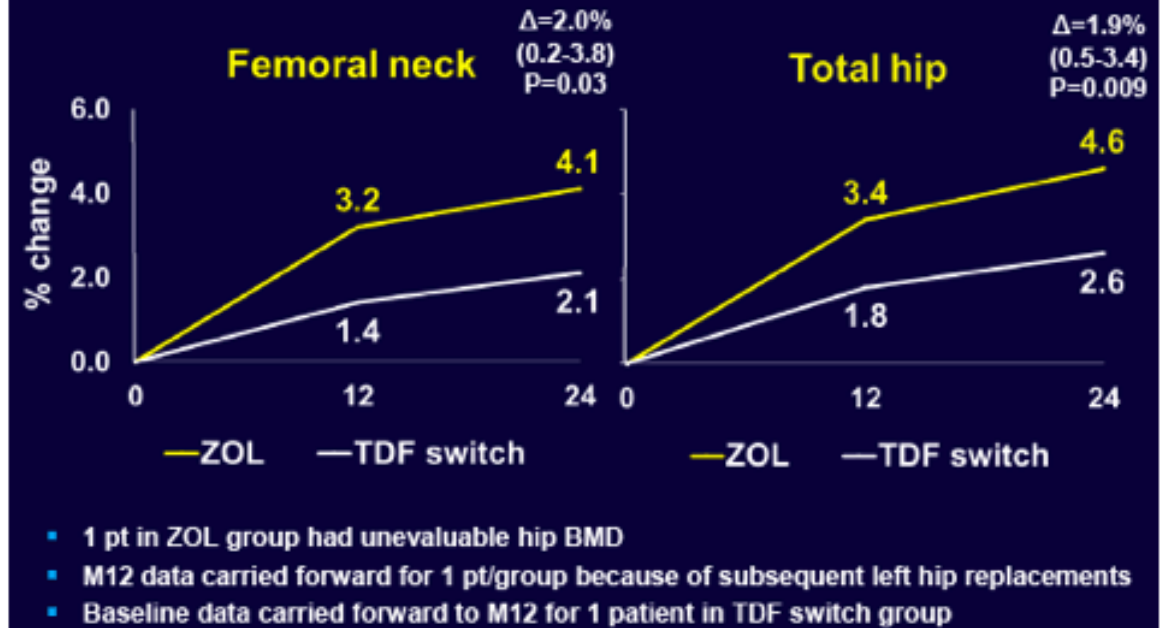
Guaraldi G, et al. *HIV Clin Trials*. 2004;5(5):269-77; Mondy K, et al. *J Acquir Immune Defic Syndr*. 2005;38(4):426-31; McComsey GA, et al. *AIDS*. 2007;21(18):2473-82; Rozenberg S, et al. *AIDS Res Hum Retroviruses*. 2012;28(9):972-80; Bolland MJ, et al. *J Clin Endocrinol Metab*. 2007;92(4):1283-8;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

Switch off TDF vs Bisphosphonate: ZEST Study

ZOL vs TDF switch for low BMD Changes in BMD



ZOL vs TDF switch for low BMD Changes in BMD - hip



Oral vs IV Bisphosphonate

Oral (alendronate)

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

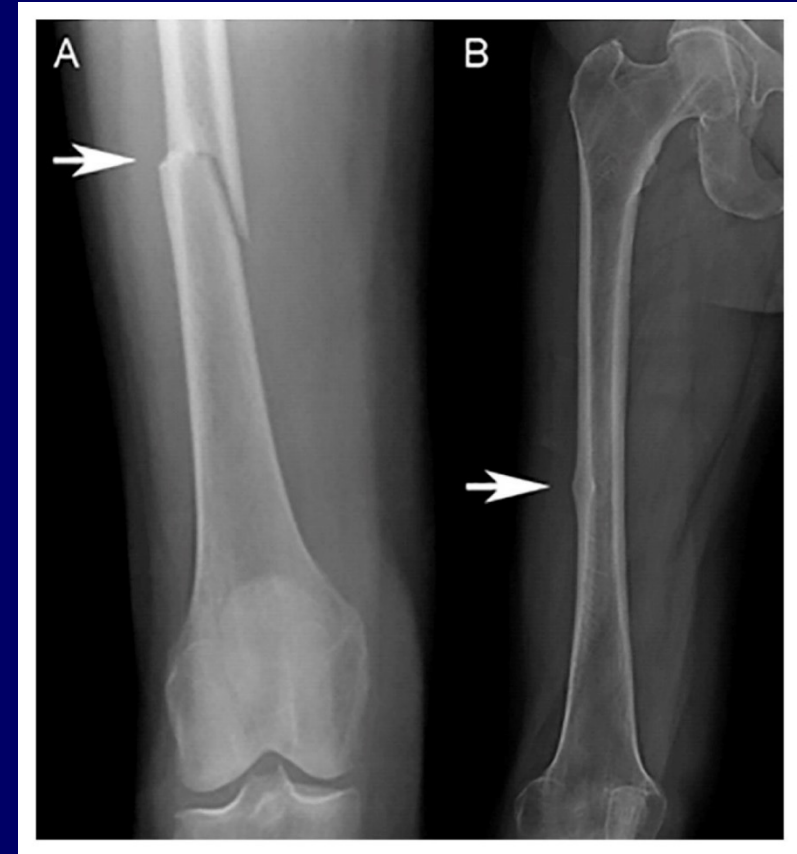
IV (zoledronic acid)

- Clinic administered
- Acute phase reaction
(20-30% with first dose)
- Hypocalcemia
- Directly observed
therapy

Antiresorptives: Long Term Adverse Events

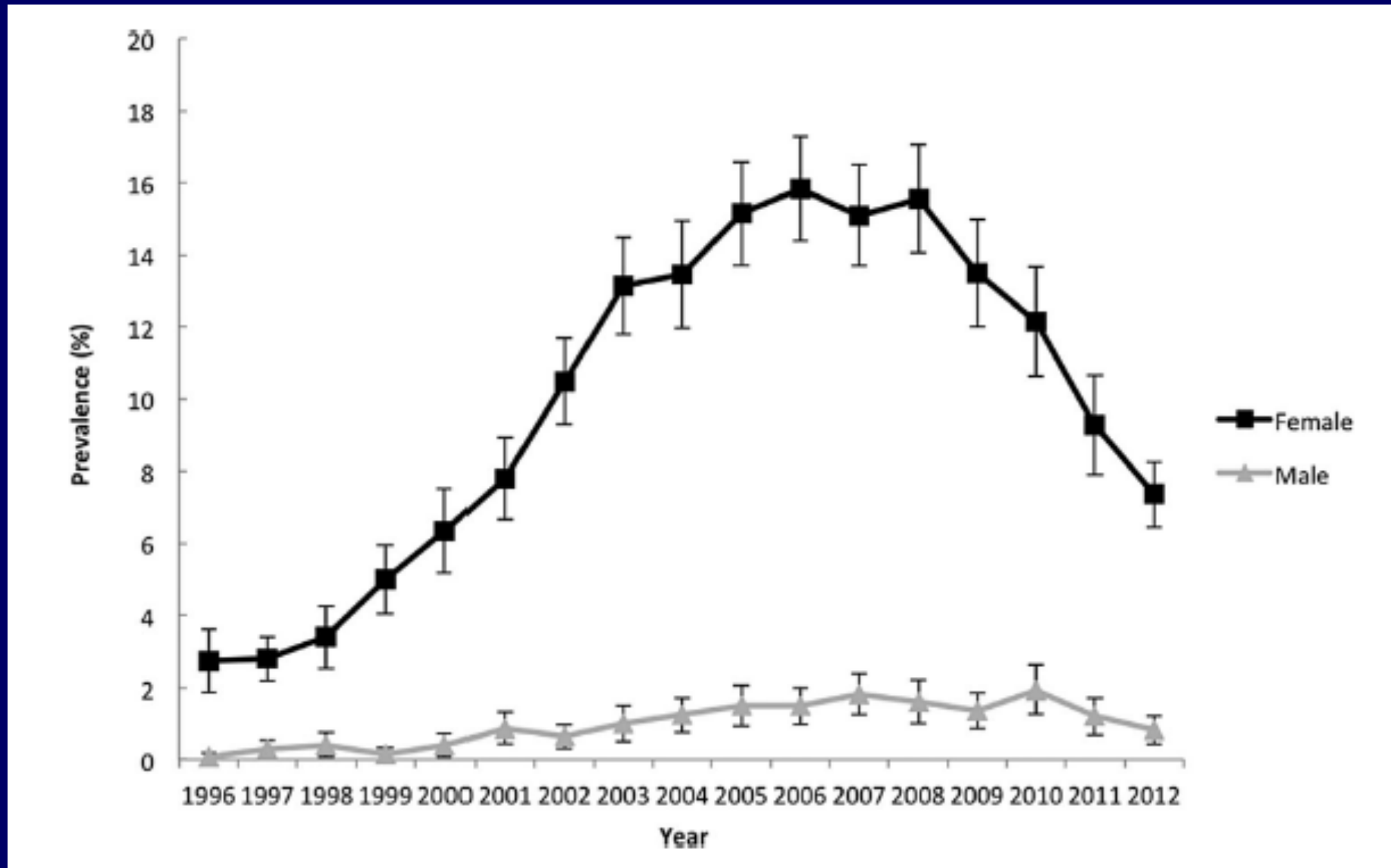


Osteonecrosis of the Jaw
1 to 10 cases per 100,000 person-years



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

Declining Use of Bisphosphonates



Bisphosphate Holiday

Table 2 Recommendations for Drug Holiday from Bisphosphonates

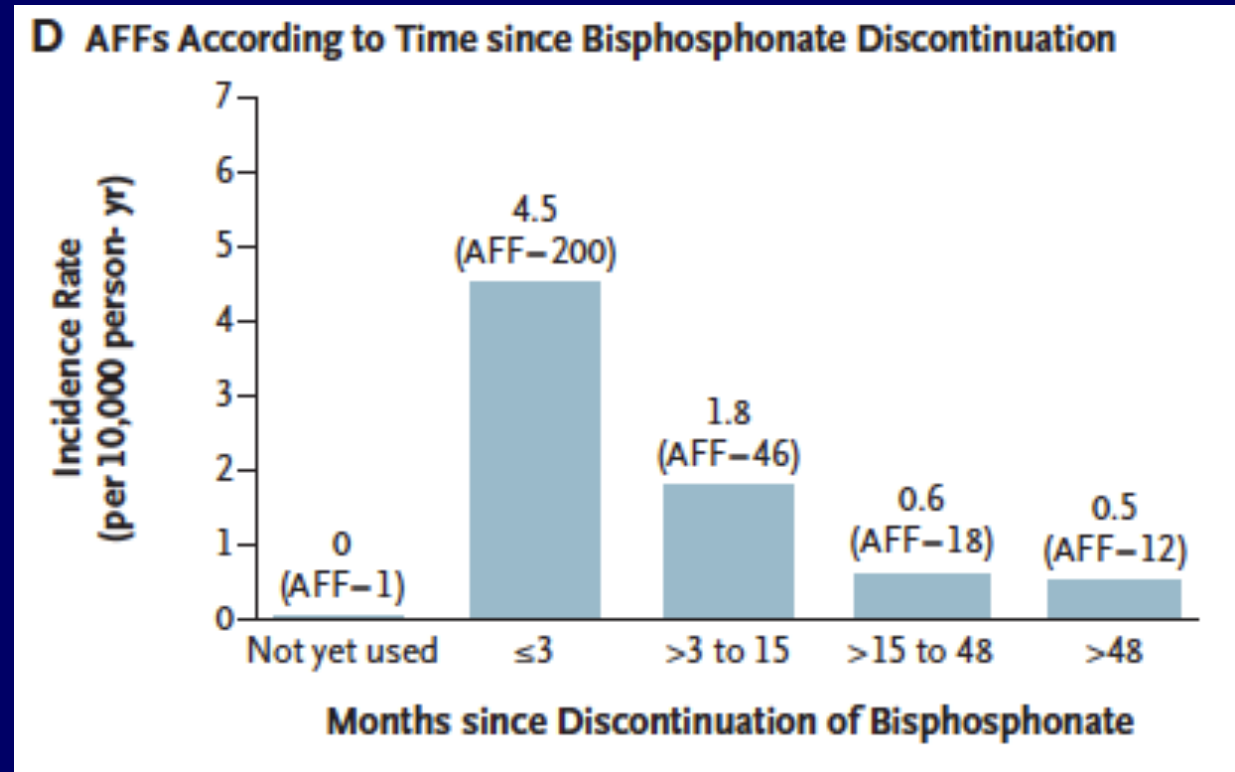
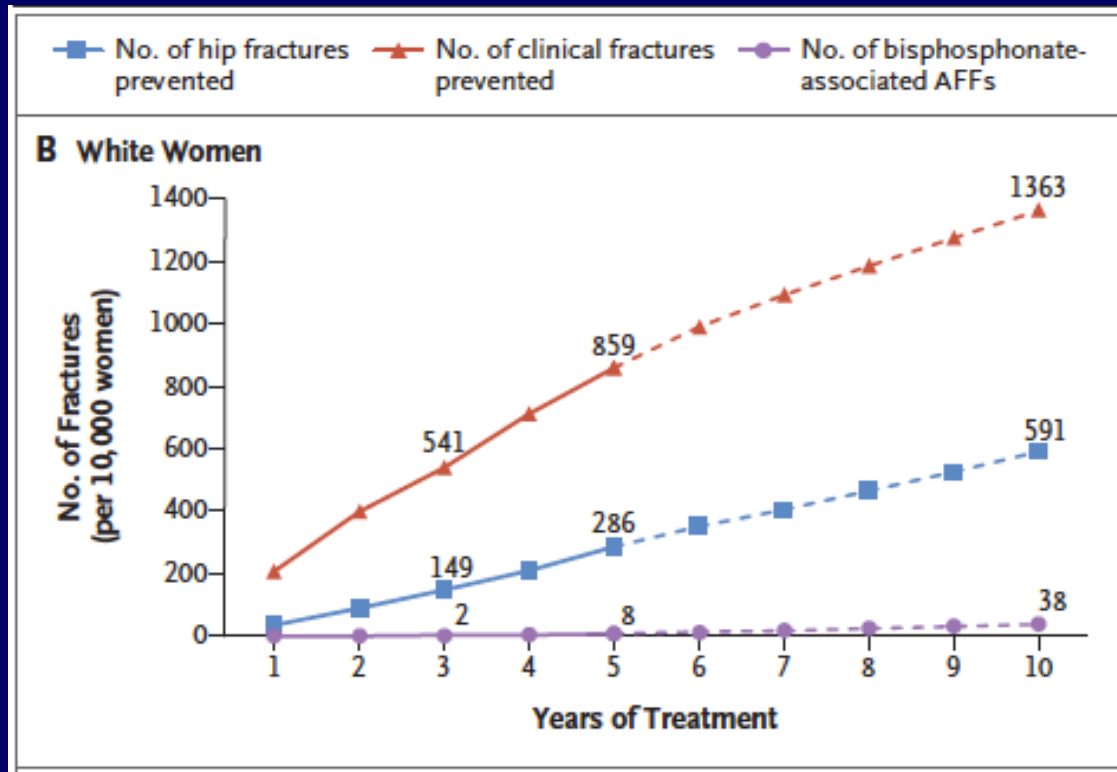
Patient Category	Recommendation
<p>High-risk: T-score still ≤ -2.5 at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.</p>	Drug holiday not justified.
<p>Moderate risk: Hip bone mineral density value is now > -2.5 (T-score), and no prior hip or spine fracture.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

How long?

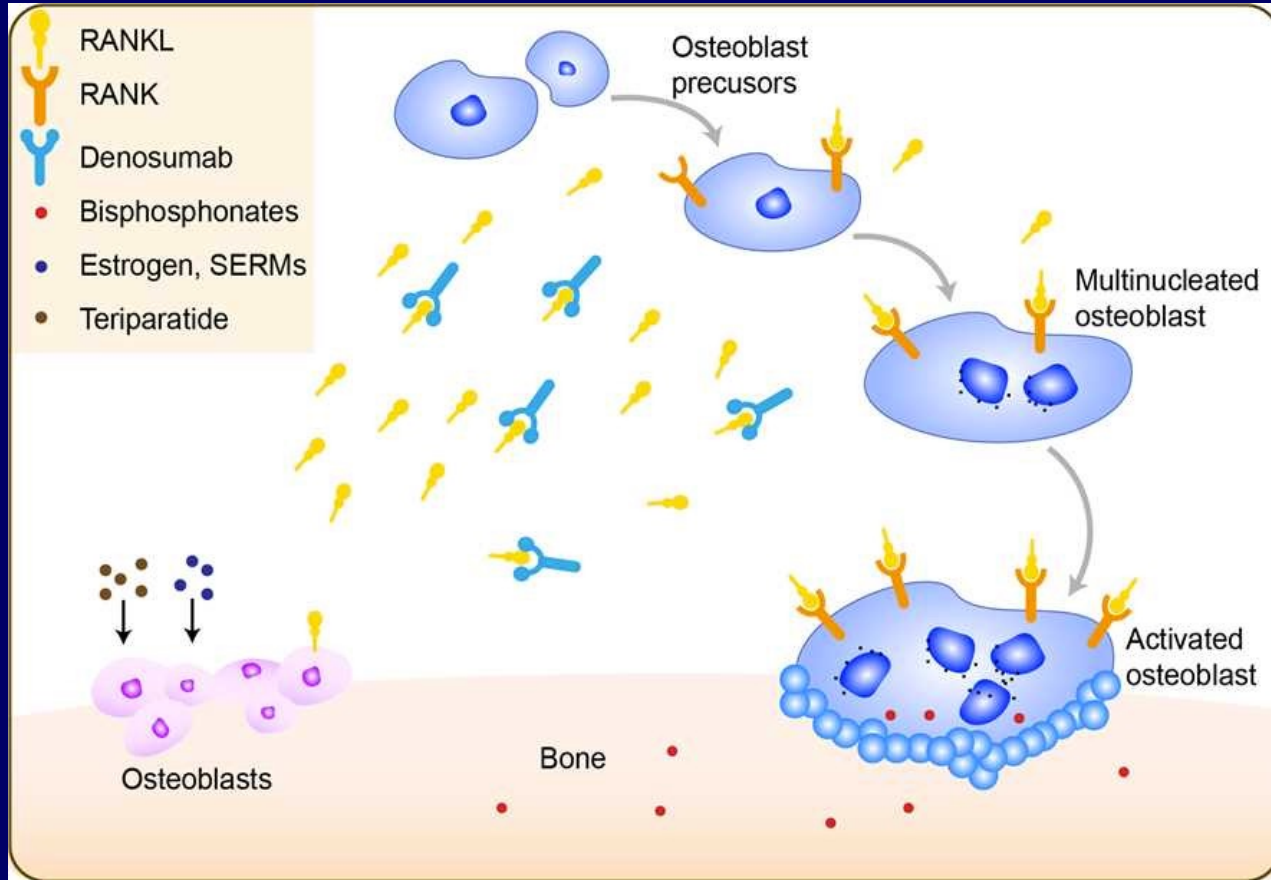
How to monitor?

What medications after the holiday?

Fragility Fracture v Atypical Femoral Fracture



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)

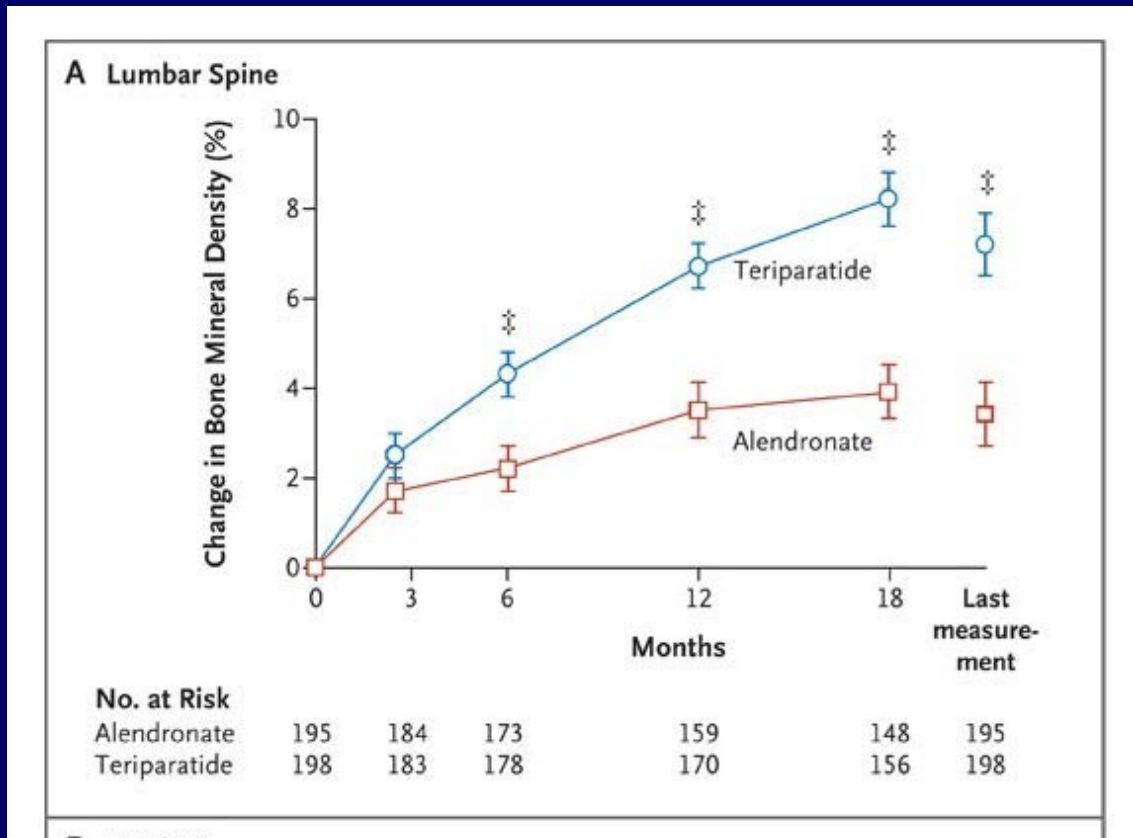
- bisphosphonates
- SERMs (raloxifene)
- denosumab
- hormone replacement therapy

Anabolic

(Osteoblast Directed)

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

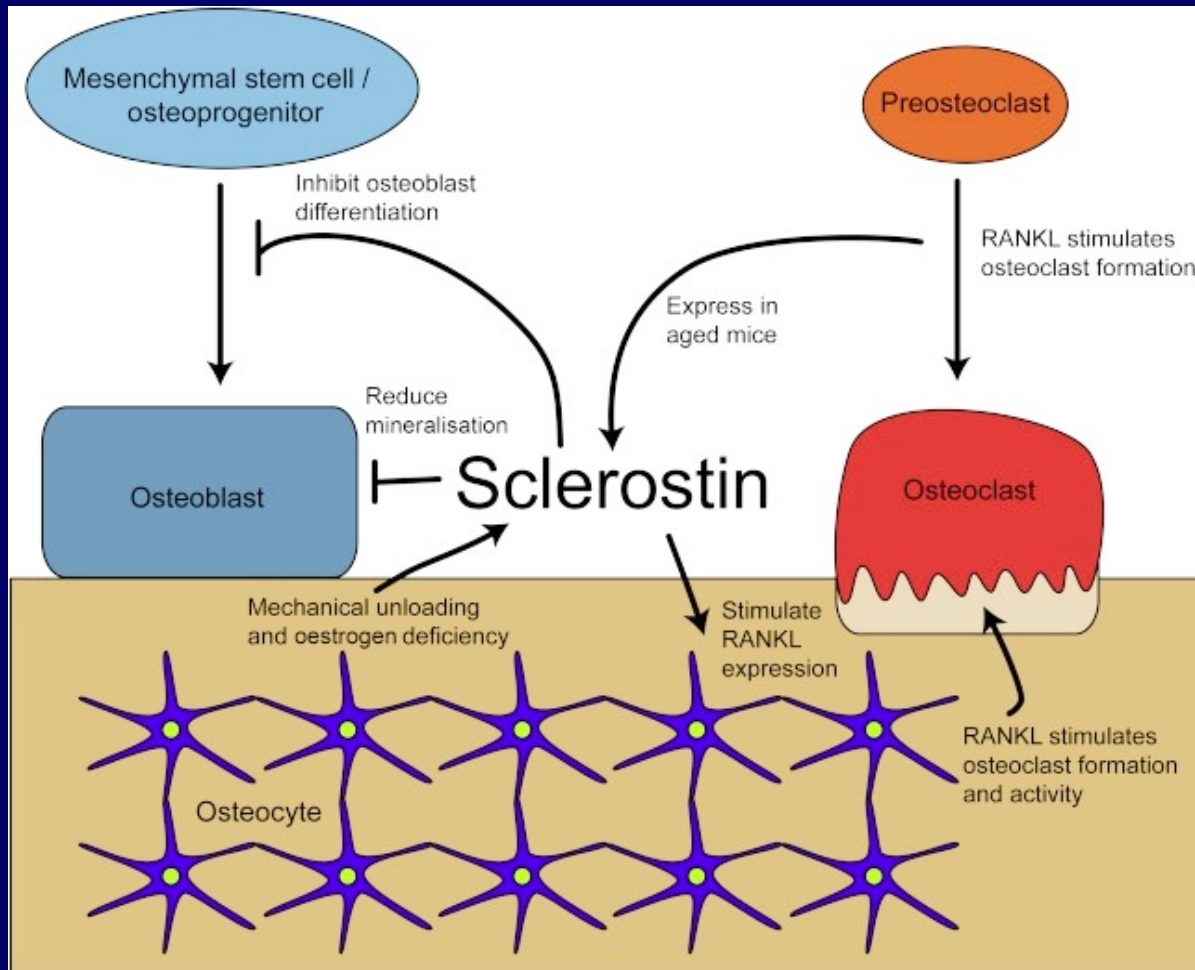
PTH/PTHrP Analogs



- 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

Teriparatide increases BMD more than alendronate
In glucocorticoid-induced osteoporosis

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

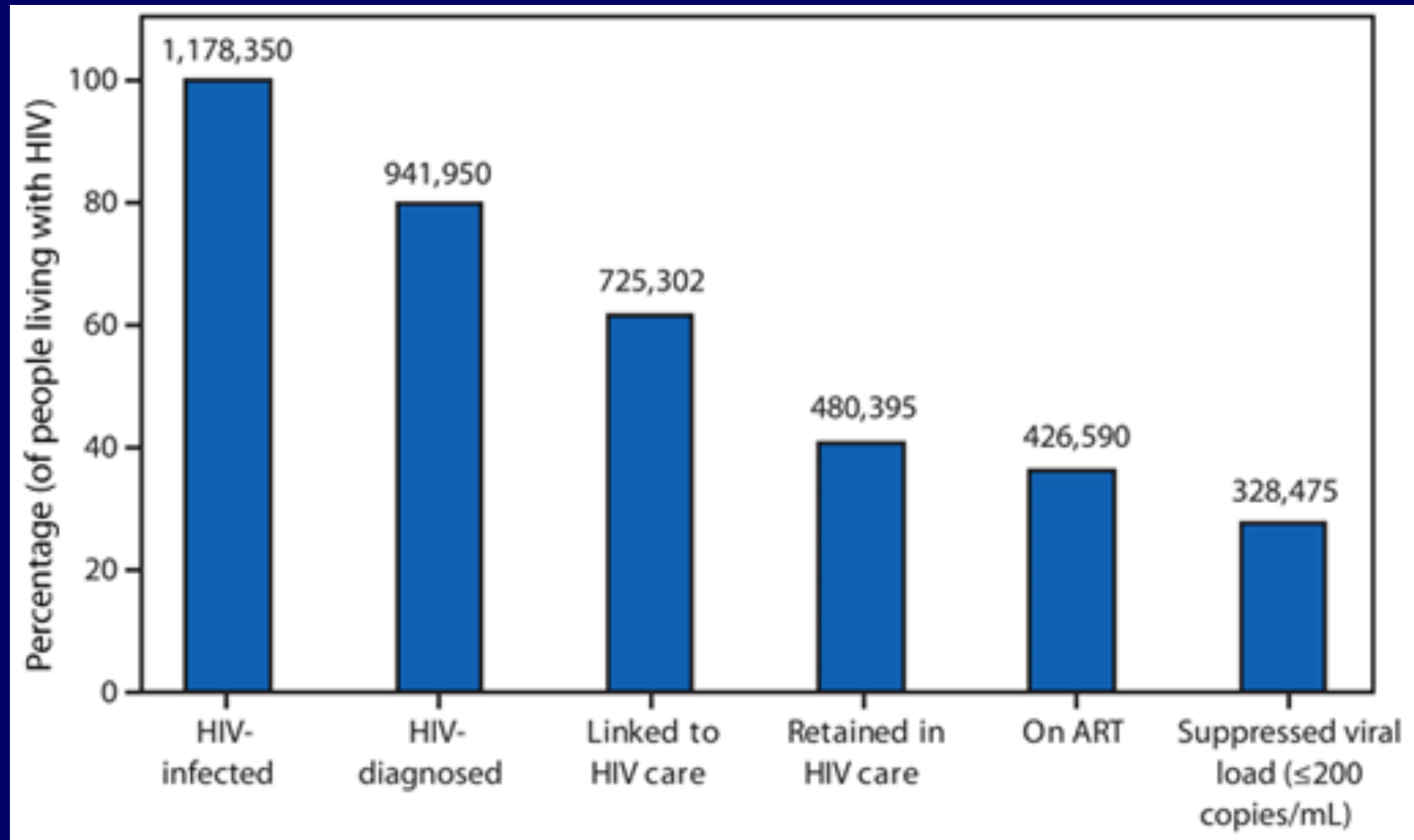
Strategies to Prevent Falls

- 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

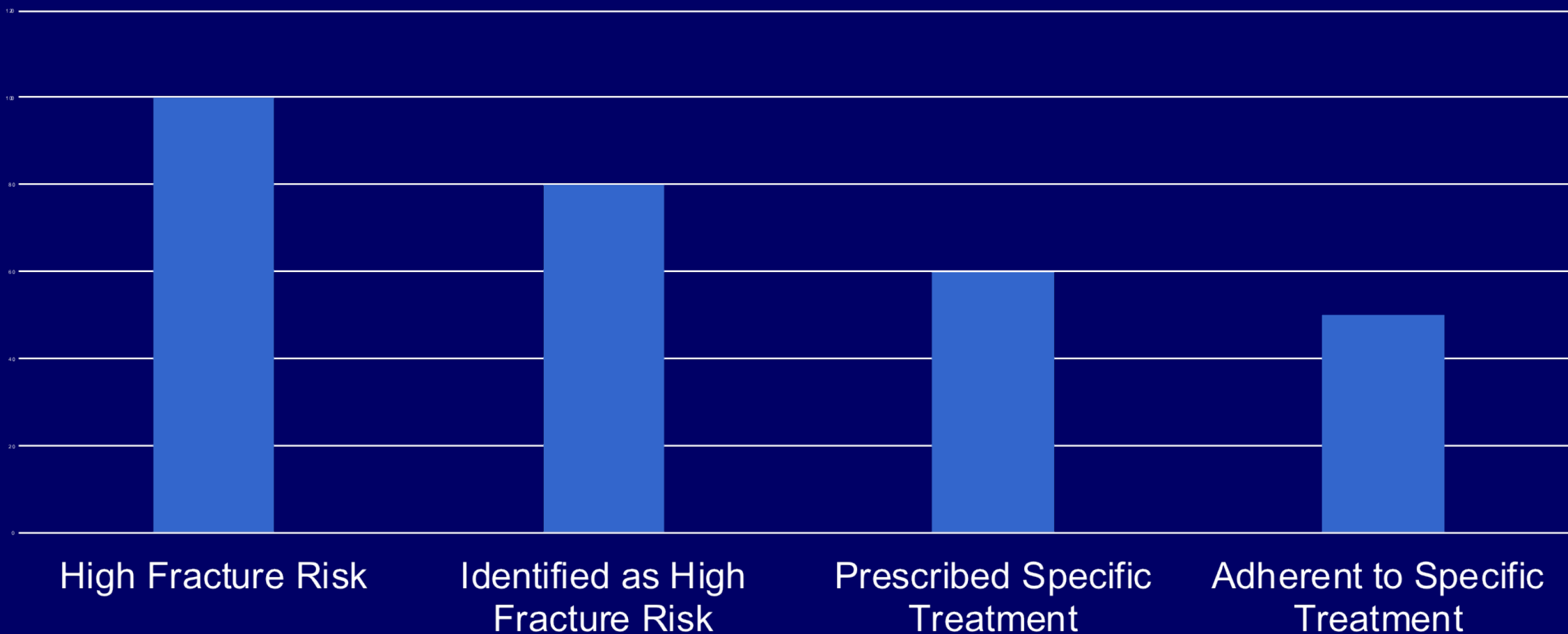
Conclusions

- 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



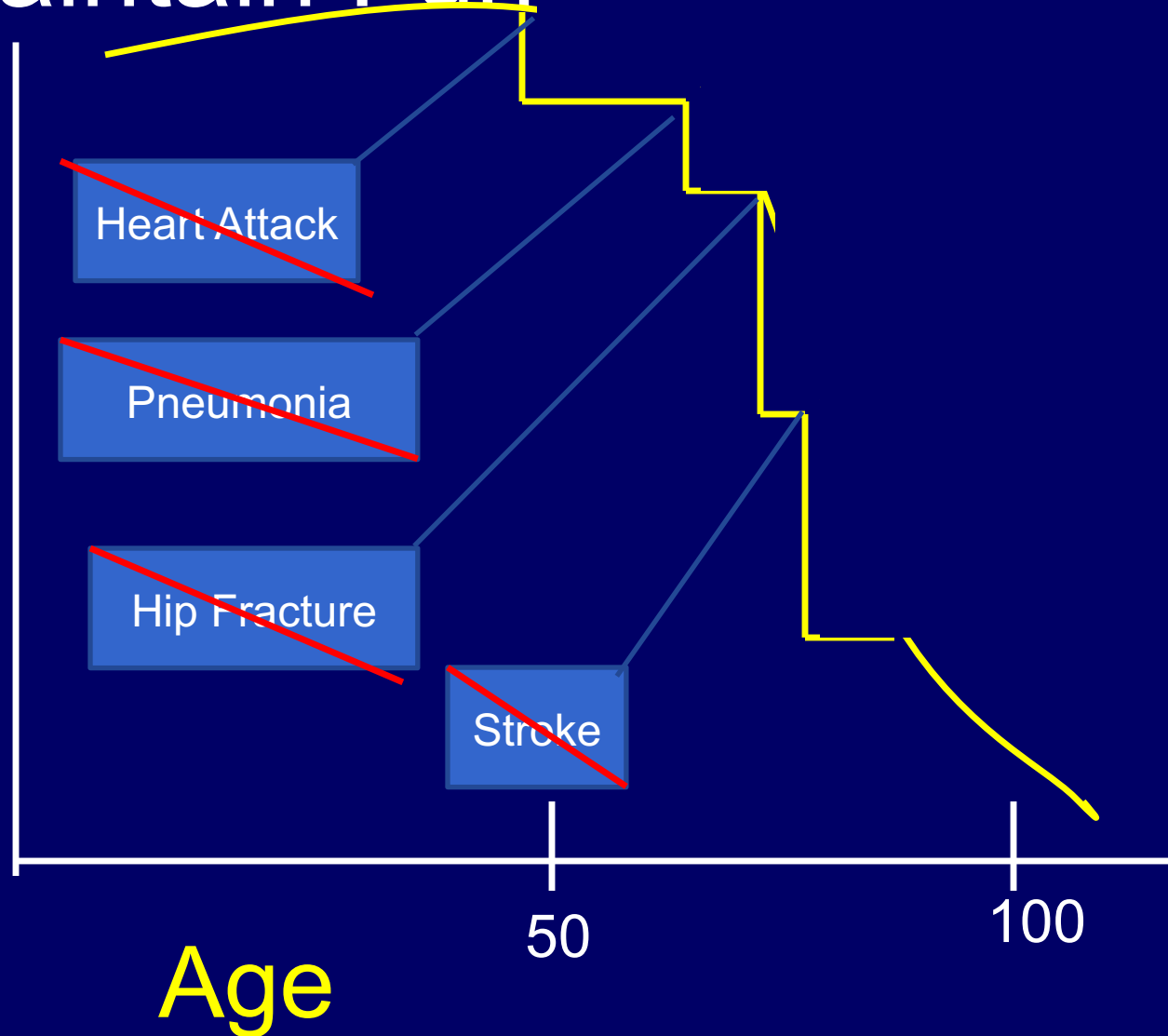
Closing the Gaps for Fracture Prevention in PWH



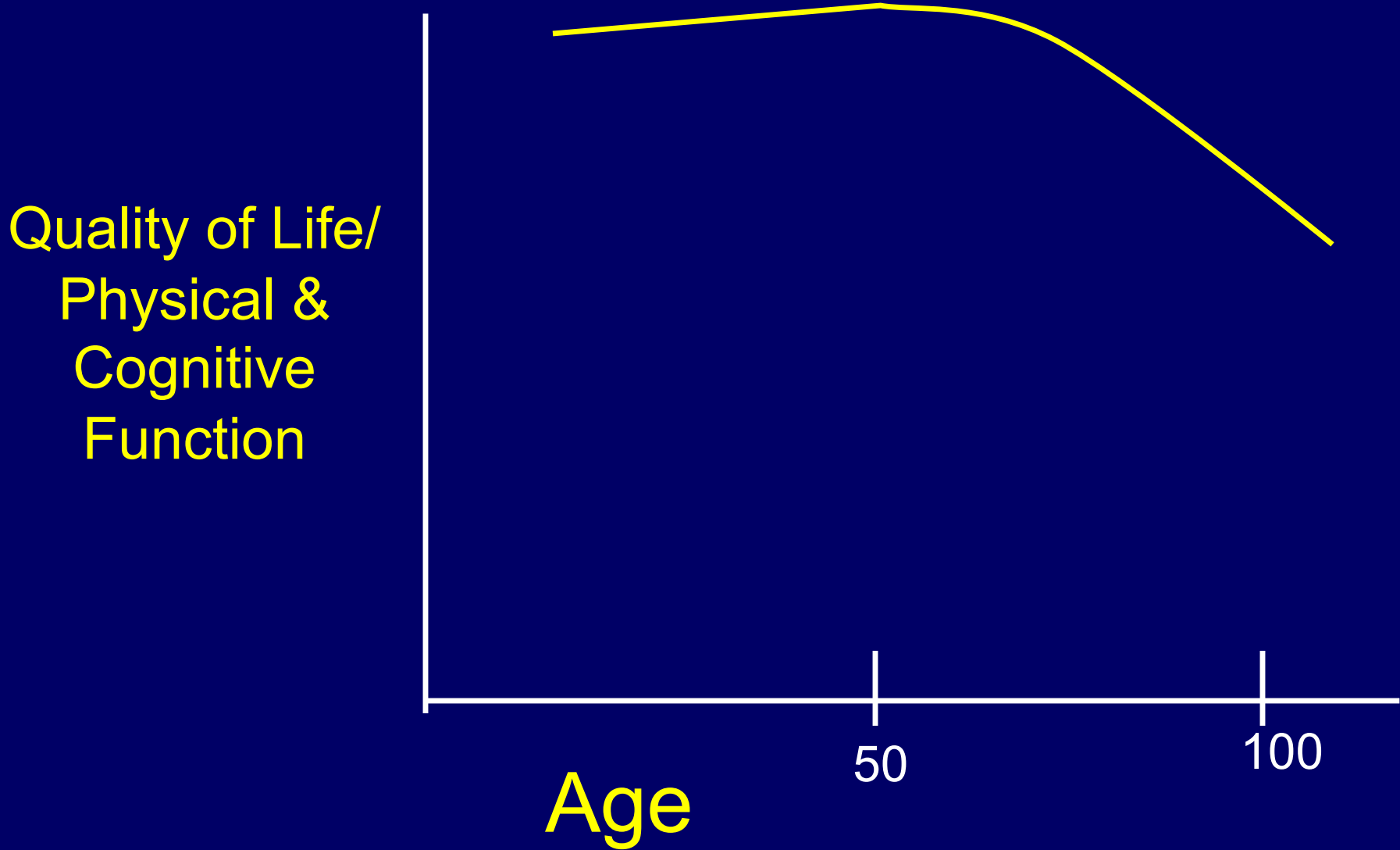
For Illustration Only; numbers are fictional

Preventing Comorbid Events is Critical to Maintain Function

Quality of Life/
Physical &
Cognitive
Function



Preventing Comorbid Events is Critical to Maintain Function



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