

# Osteoporosis and HIV: Optimal Evaluation and Management to Prevent Fractures

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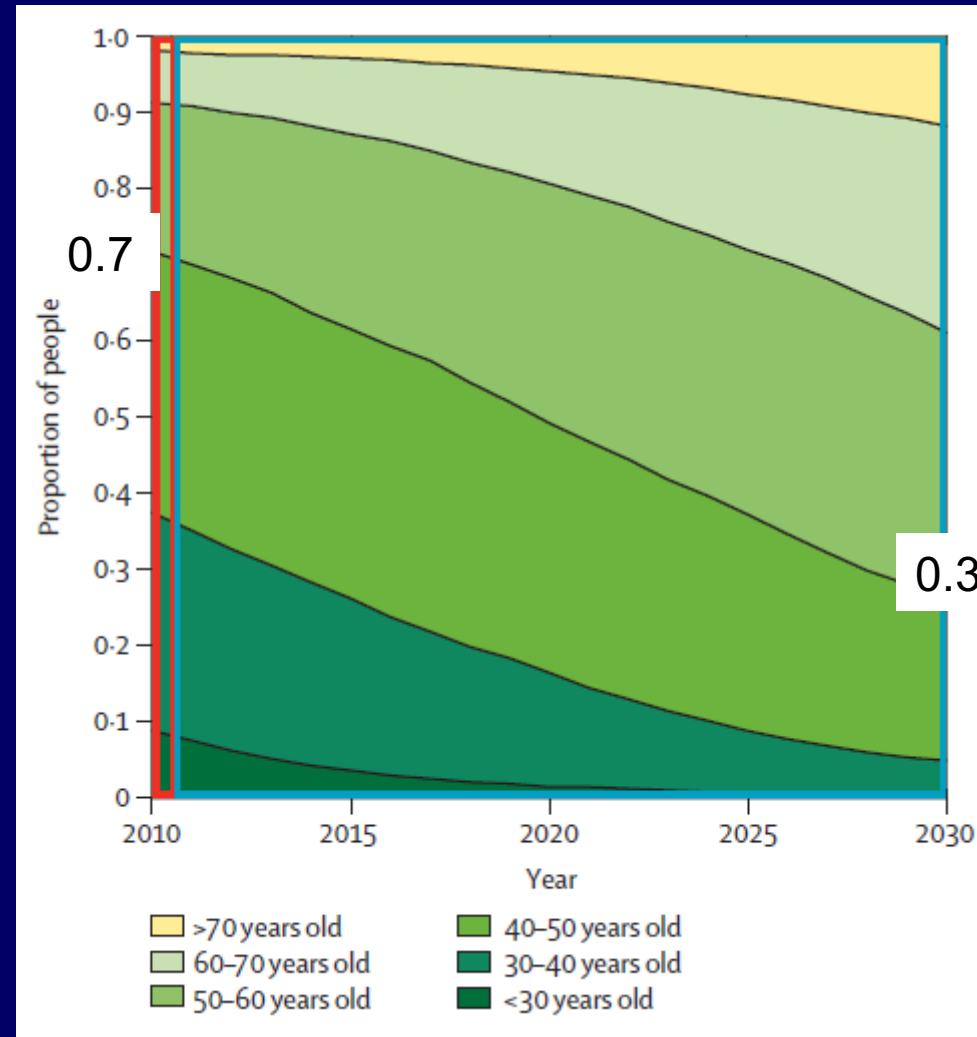
Division of Endocrinology, Diabetes, & Metabolism

Johns Hopkins University

# Disclosures

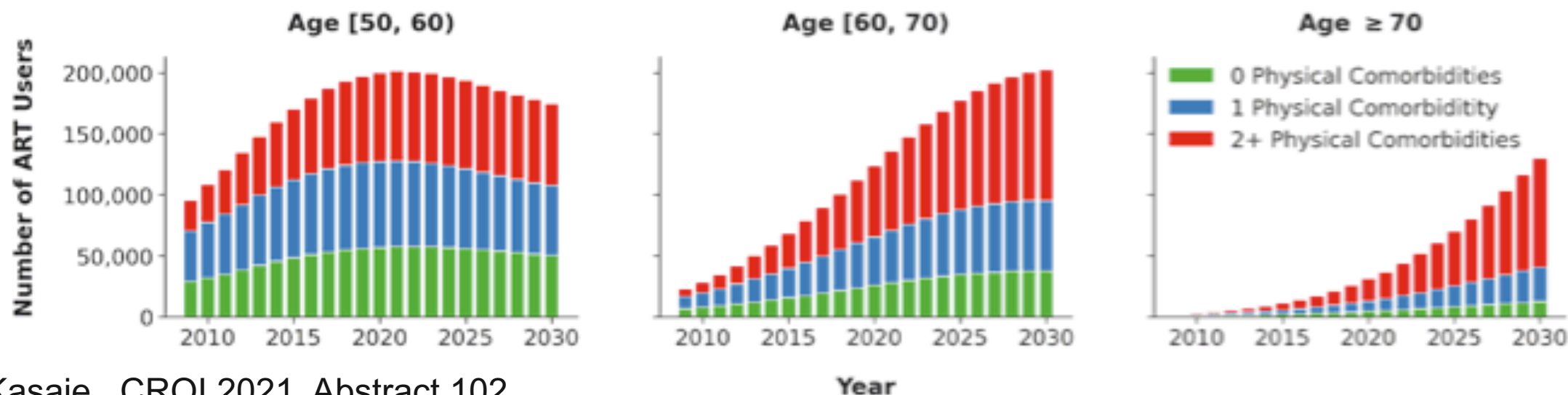
- Dr Brown has served as a consultant to Gilead Sciences, Inc, GlaxoSmithKline, Janssen, Merck & Co, Inc, Theratechnologies, EMD Serono, and ViiV Healthcare.

# The Aging of the HIV Population: Netherlands

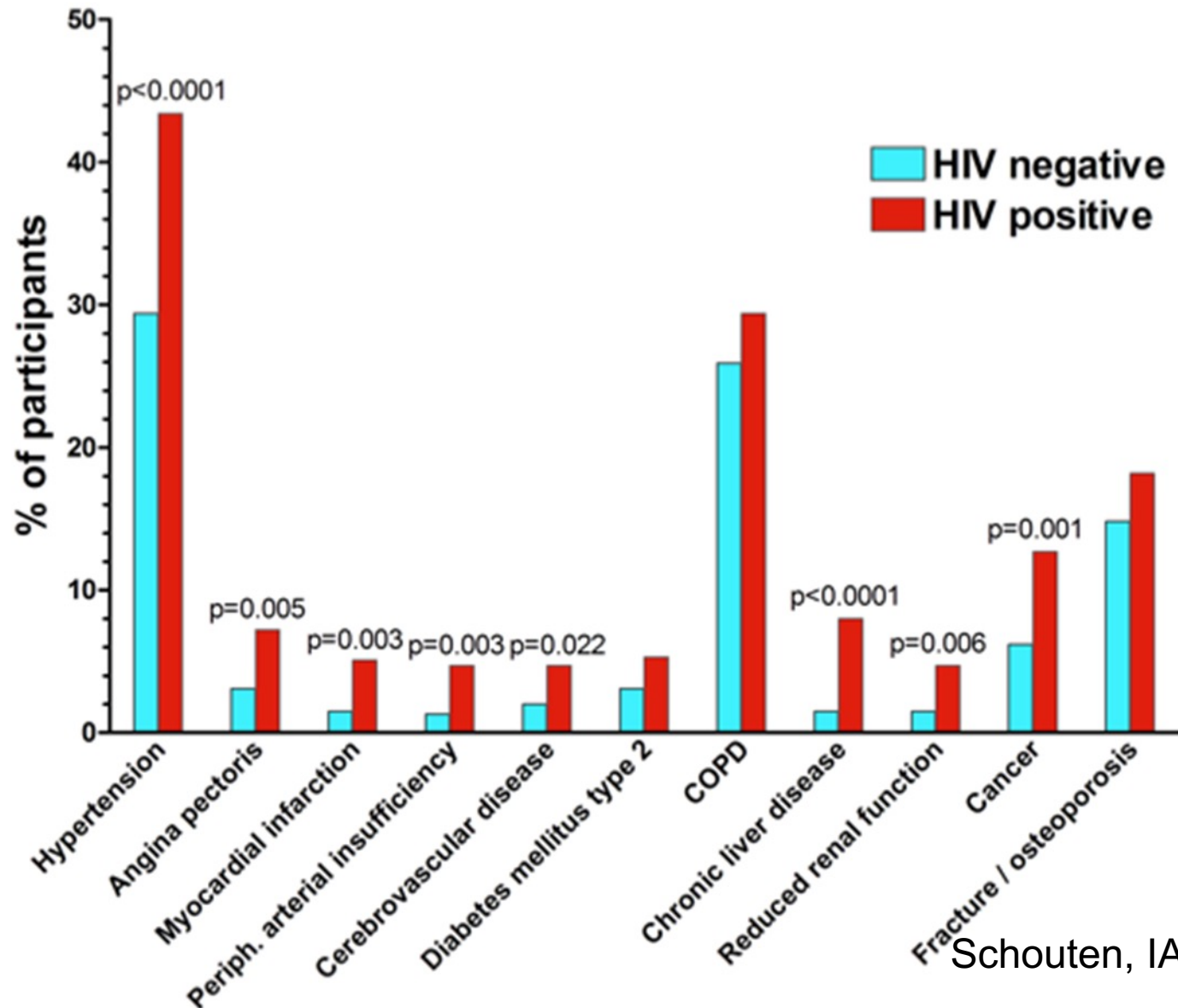


# Multimorbidity will increase markedly in PWH over the next 10 years

- Older age-groups experience an **increase in population size and prevalence of multimorbidity**
- Among those  $\geq 70$  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



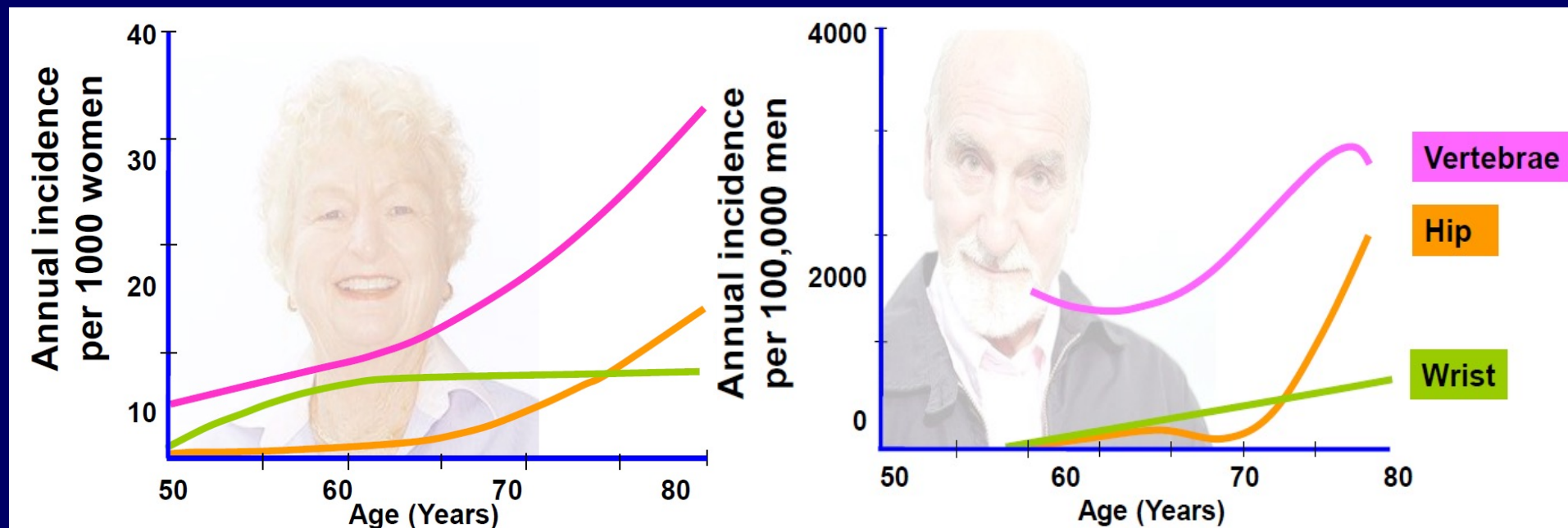
# Comorbidity distribution



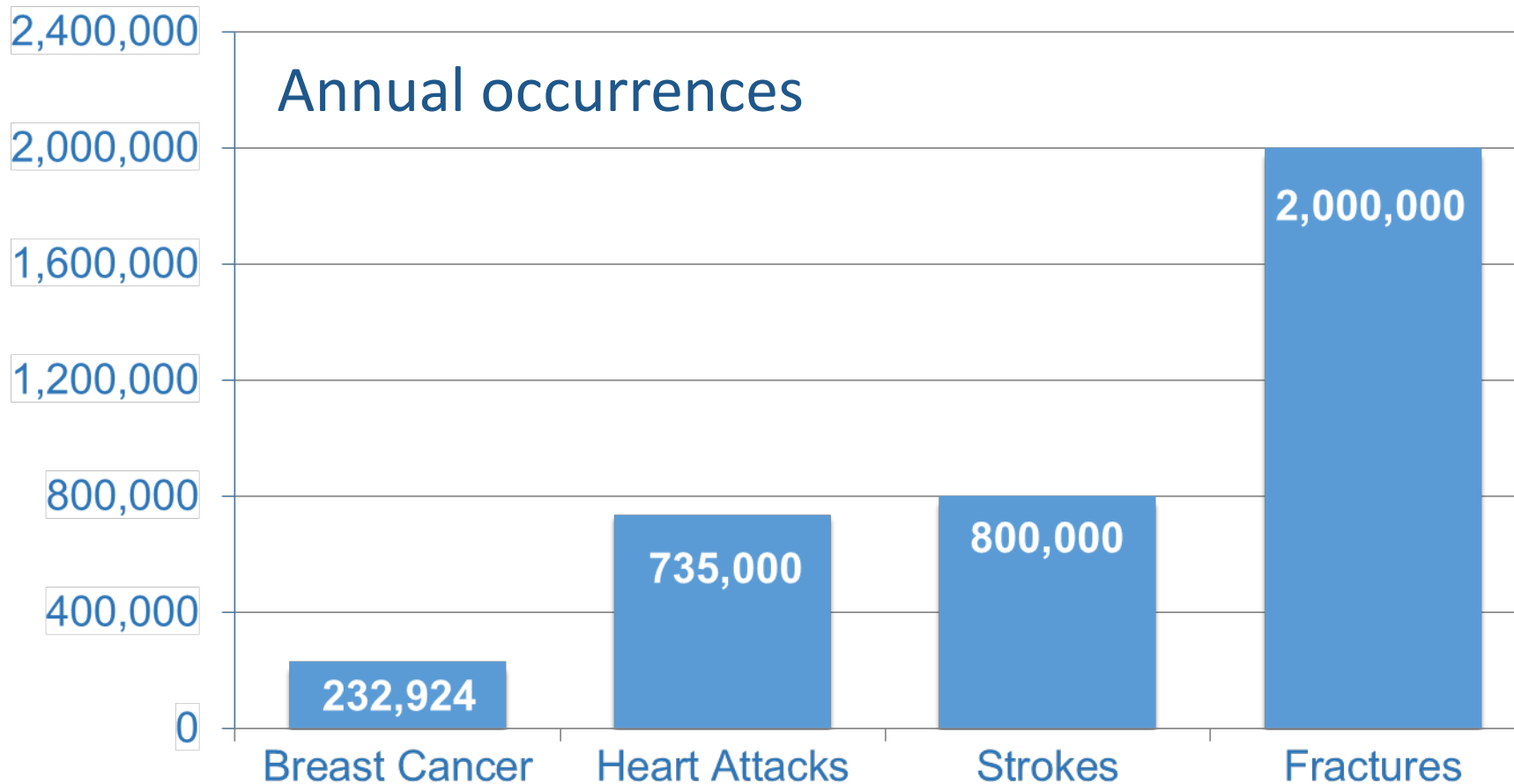
# Why worry about osteoporosis?

- 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



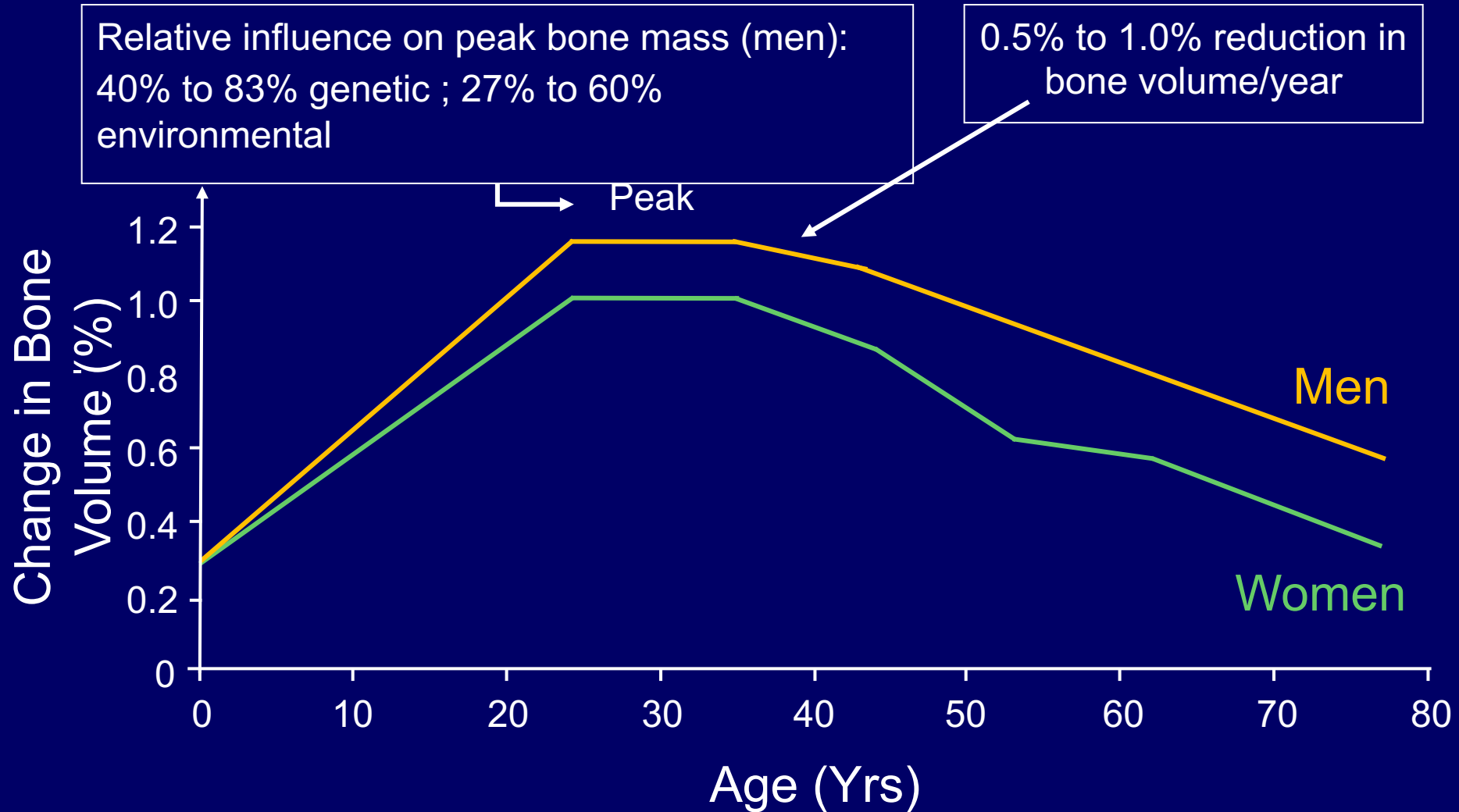
## Compared to Other Health Issues



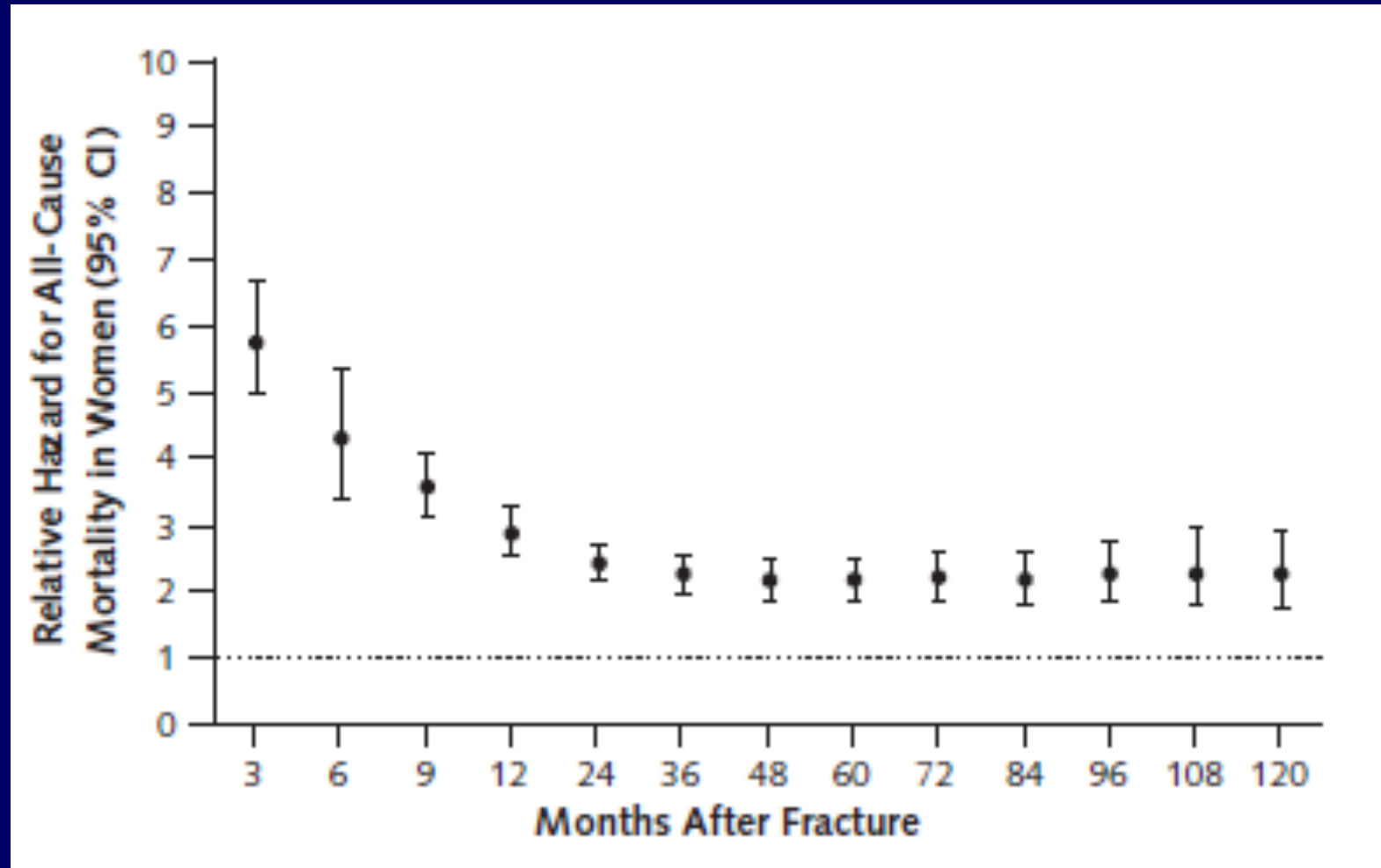
Centers for Disease Control & Prevention 2016  
Centers for Disease Control & Prevention, 2015  
Centers for Disease Control & Prevention, 2015  
National Osteoporosis Foundation, 2015



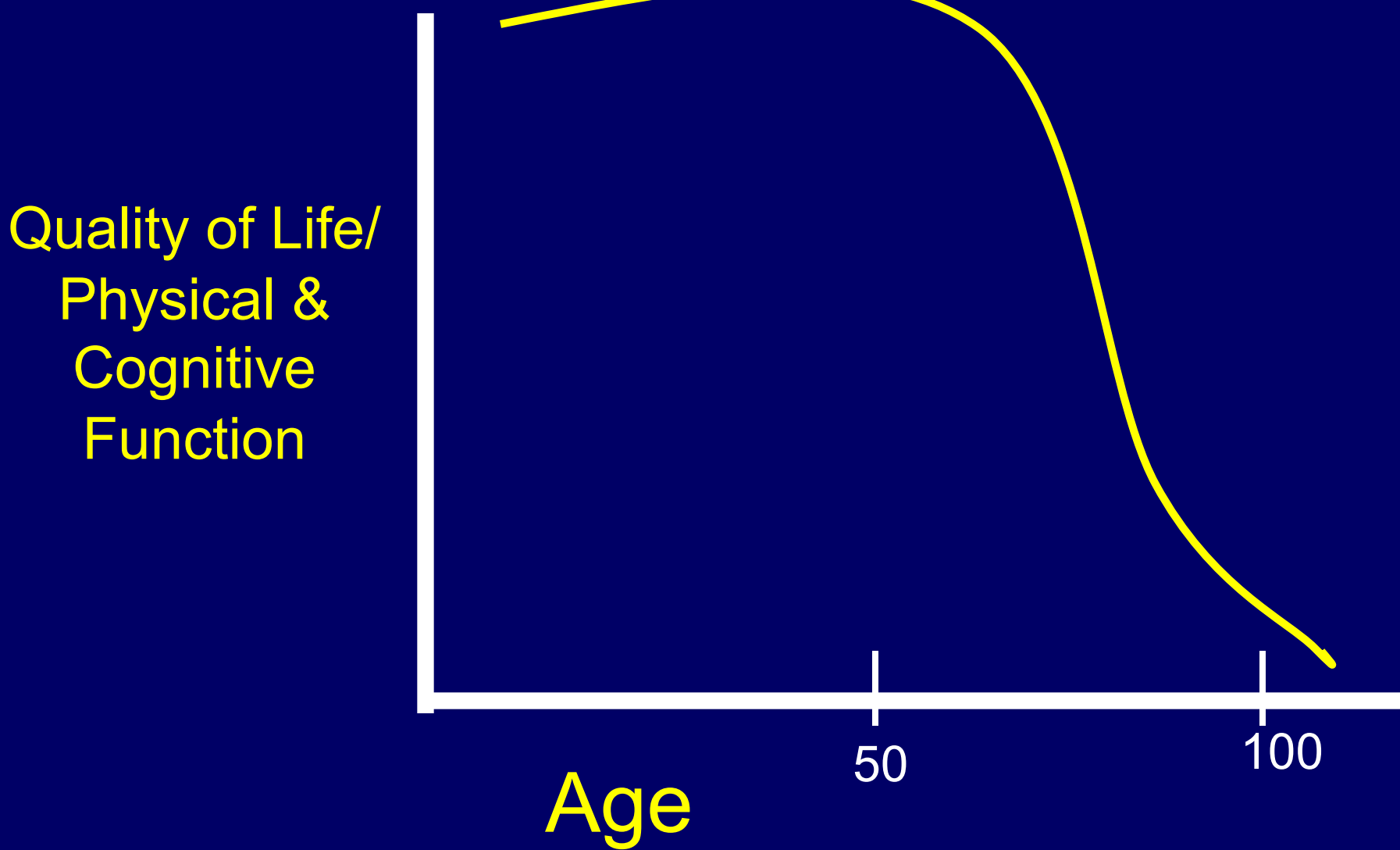
# BMD Decreases With Age



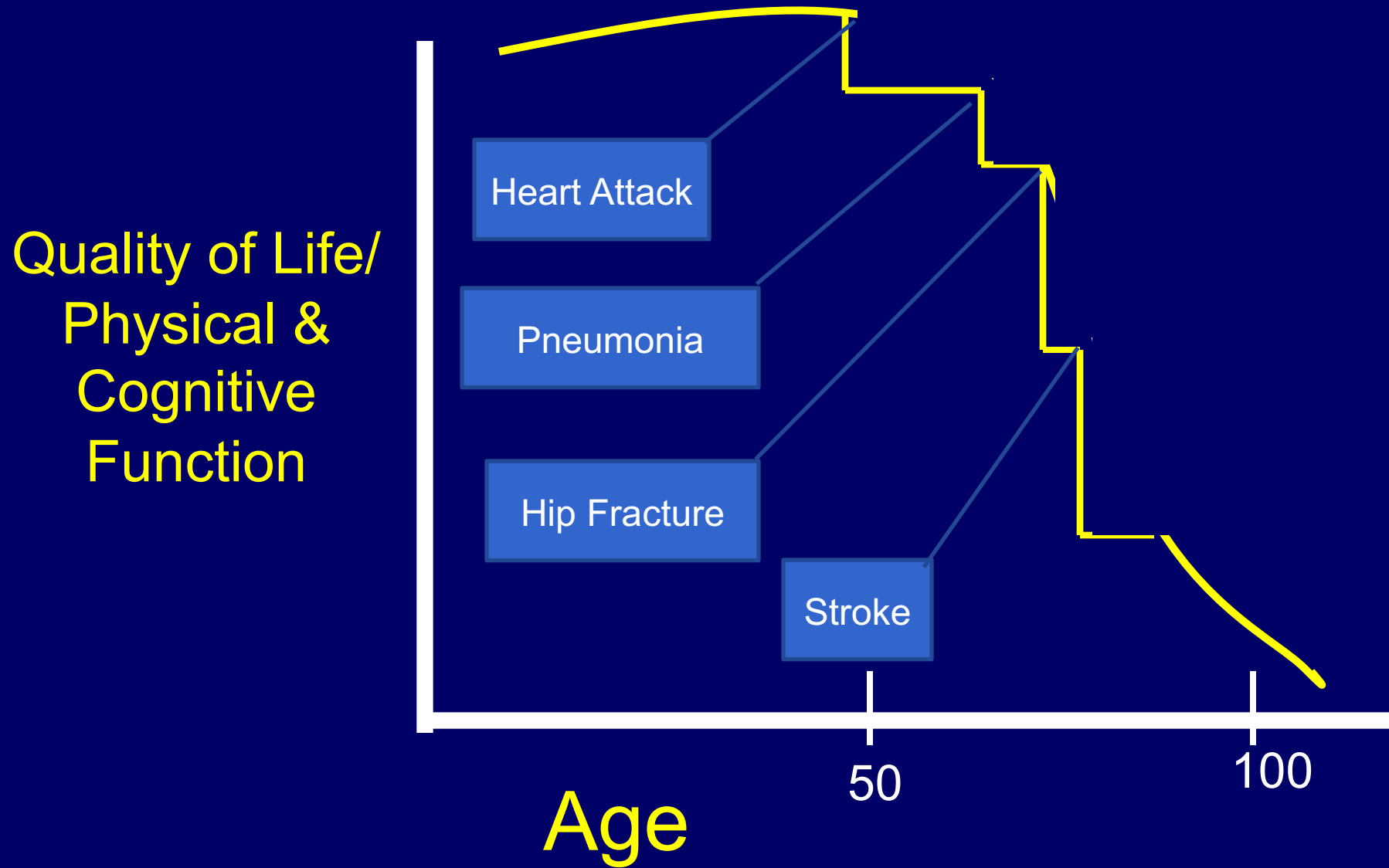
# Increase Mortality After Fragility Fractures



# Physical & cognitive function generally declines over time

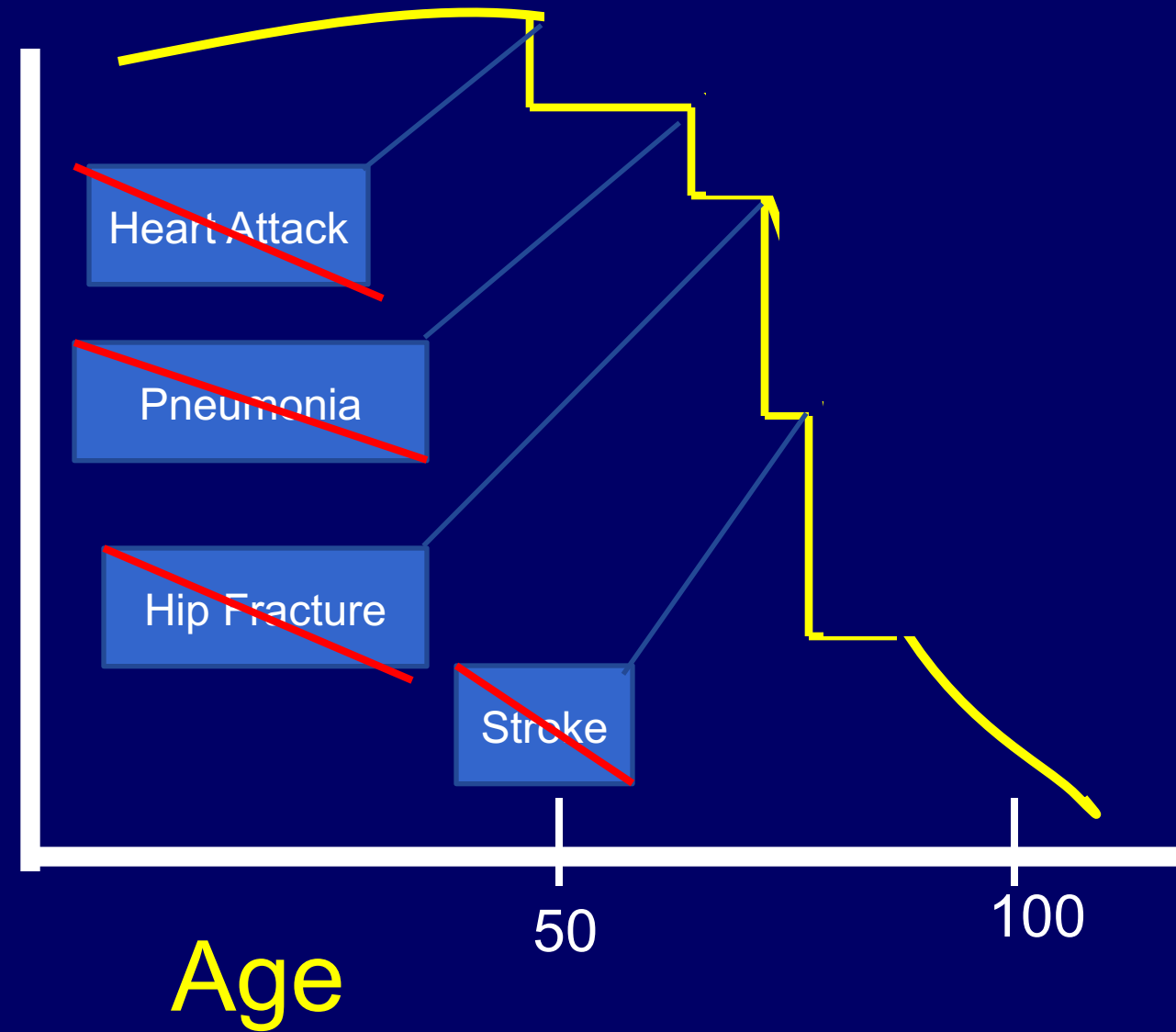


# Decline in Function May Not Be Gradual

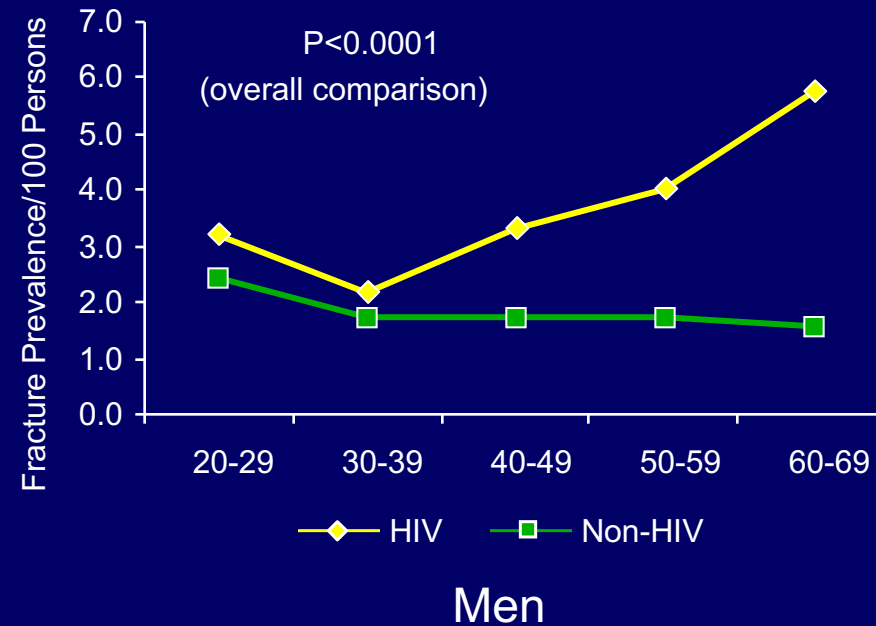
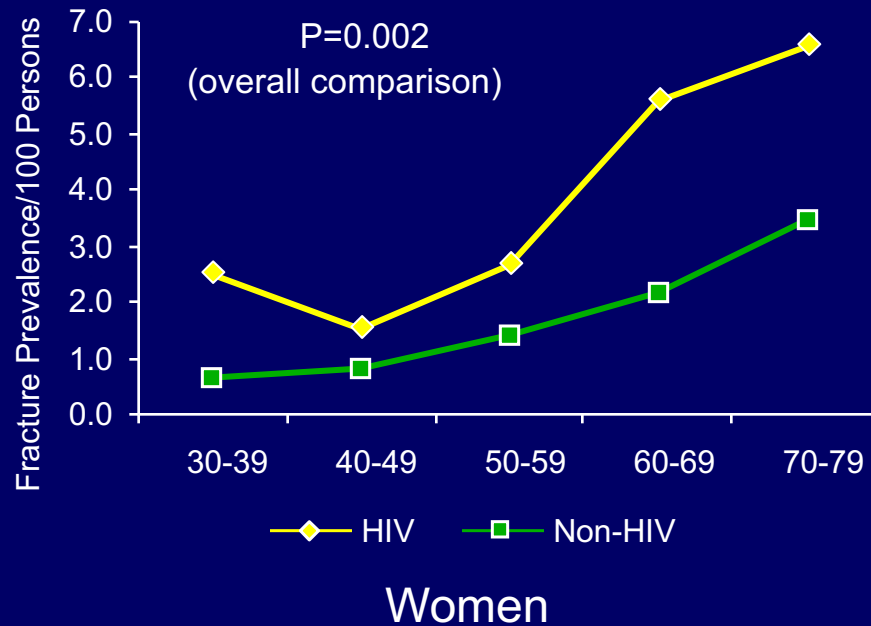


# Preventing comorbid events, including fracture, is critical to maintain function

Quality of Life/  
Physical &  
Cognitive  
Function



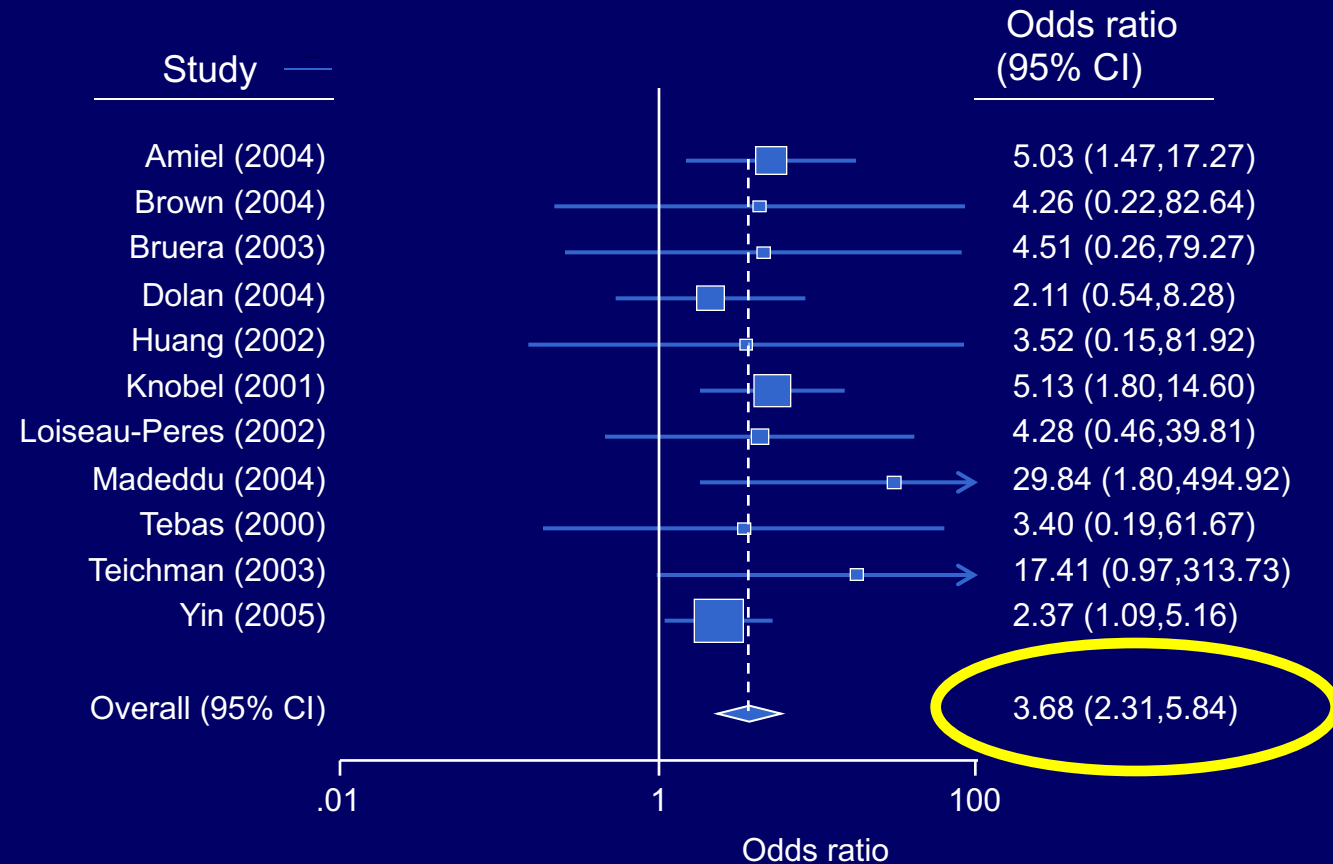
# Fracture Prevalence in HIV-infected and non-HIV-infected Persons in MGH/Partners Healthcare System: 1996-2008



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

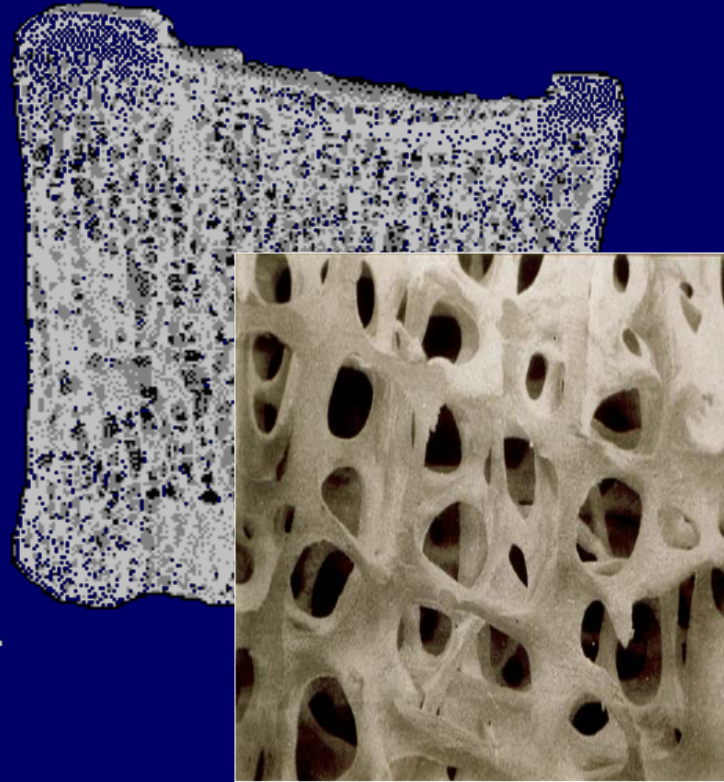
Osteoporosis:

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

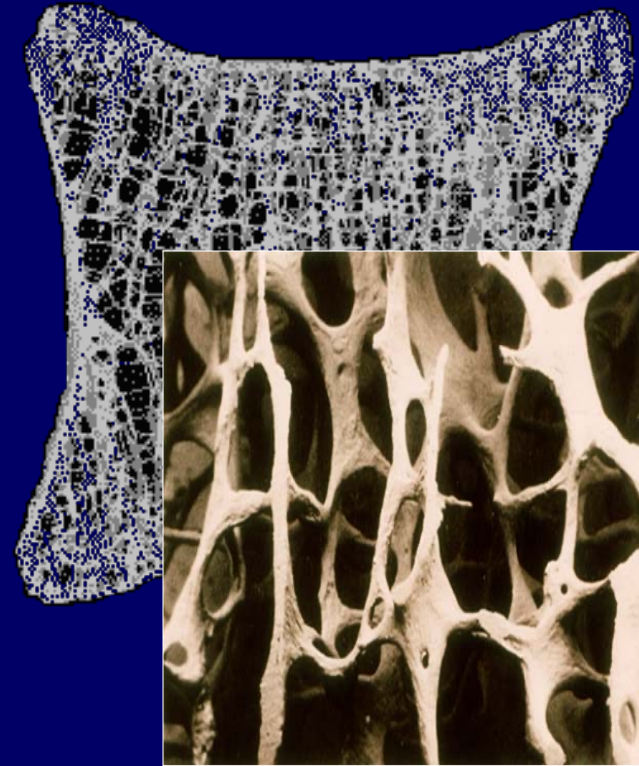


# Vertebral body: Normal vs Osteoporosis

normal



osteoporotic



# Definitions

## Operational Definition (DXA)- WHO Definition

- Osteoporosis: T-score  $\leq -2.5$
- 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:

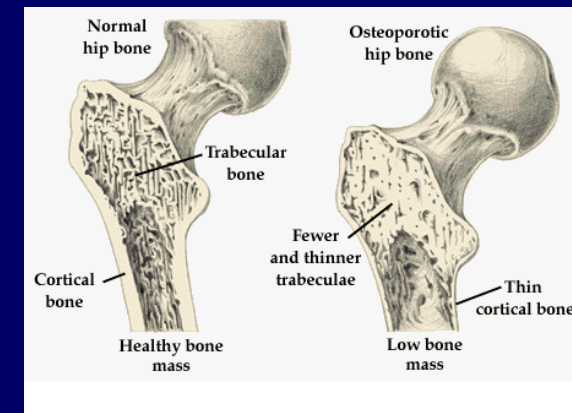
- Z-score ( $\leq -2.0$ ) used in men  $< 50$  years and premenopausal women
- BMD explains only about 50% of fracture risk

# DXA Scanning



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

Sites differ in proportions of cortical and trabecular bone

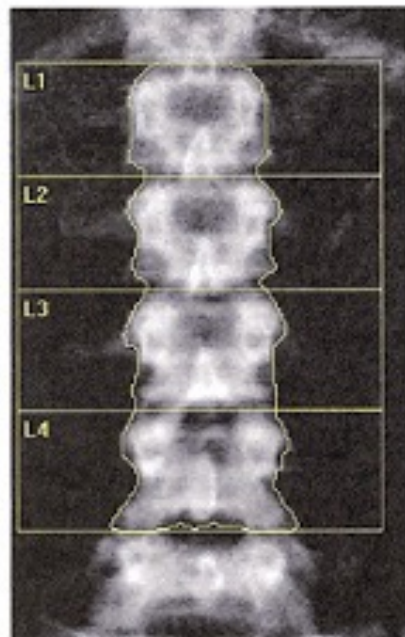


Name: Express Scans, 2  
 Patient ID:  
 DOB: August 24, 1944

Sex: Female  
 Ethnicity: White

Height: 65.0 in  
 Weight: 150.0 lb  
 Age: 61

Referring Physician:



**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:

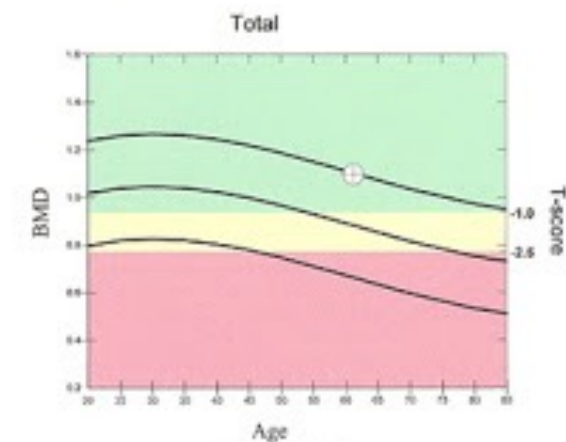
**DXA Results Summary:**

Region	Area (cm <sup>2</sup> )	BMC (g)	BMD (g/cm <sup>3</sup> )	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
<b>Total</b>	<b>65.41</b>	<b>71.72</b>	<b>1.096</b>	<b>0.4</b>	<b>105</b>	<b>1.9</b>	<b>124</b>

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

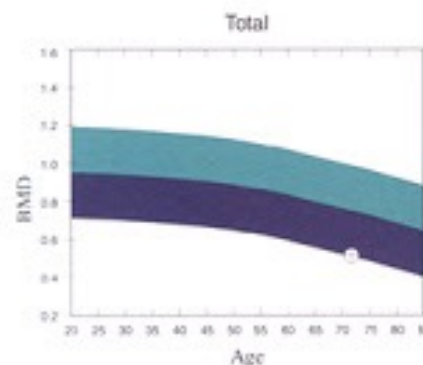
Operator: AR  
 Model: QDR  
 Comment: BASELINE

**DXA Results Summary:**

Region	Area (cm <sup>2</sup> )	BMC (g)	BMD (g/cm <sup>3</sup> )	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
<b>Total</b>	<b>34.20</b>	<b>17.39</b>	<b>0.508</b>	<b>-3.6</b>	<b>-2.0</b>
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

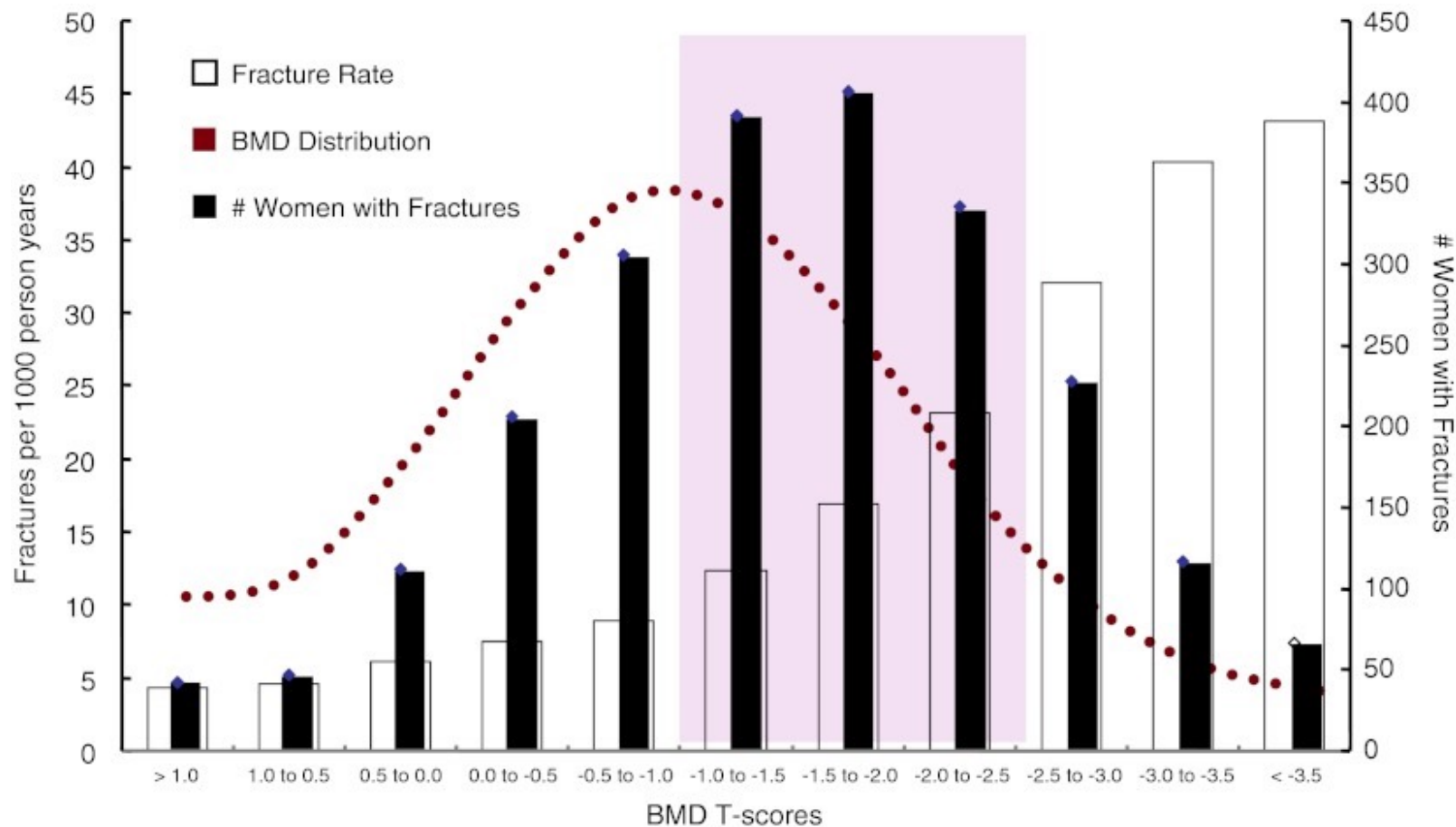
Physician's Comment:



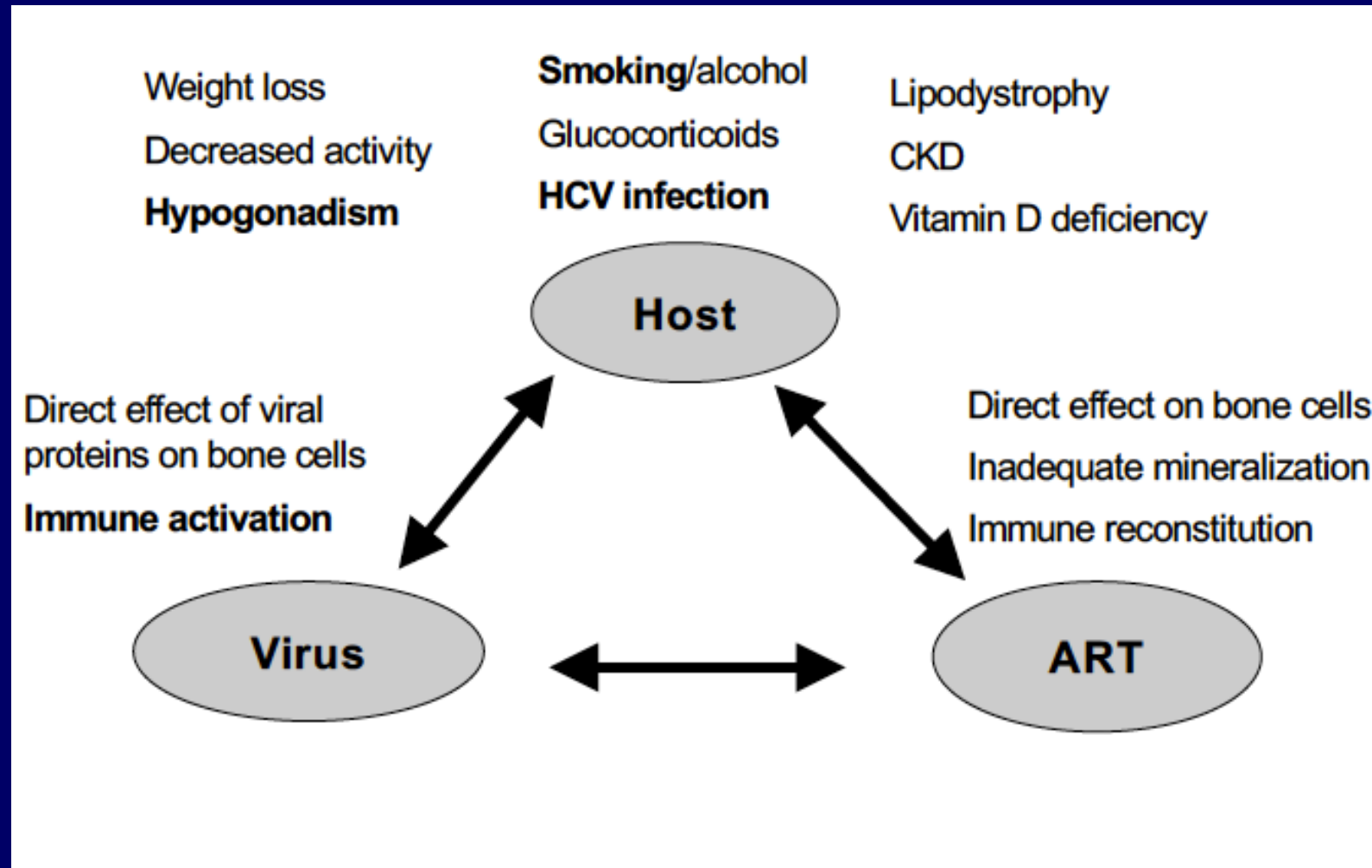
M-021 US/International



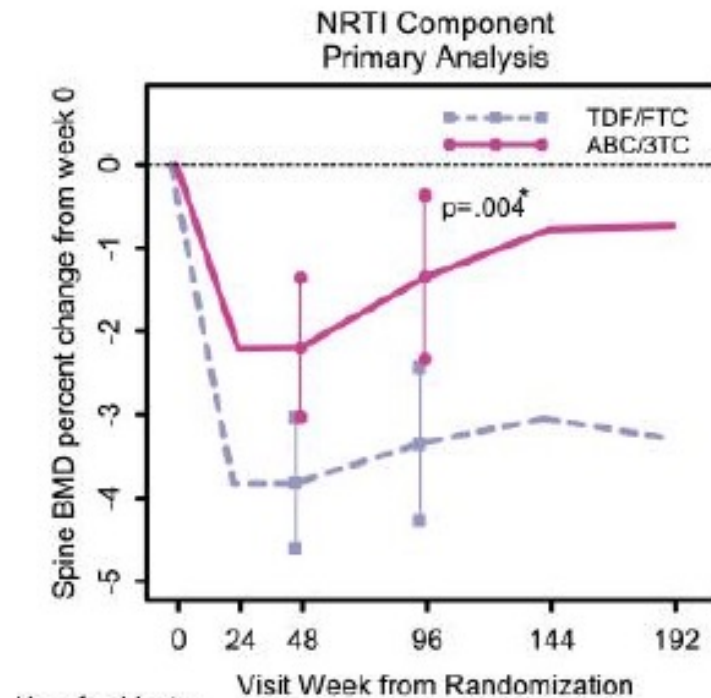
# Fractures Happen at all BMDs



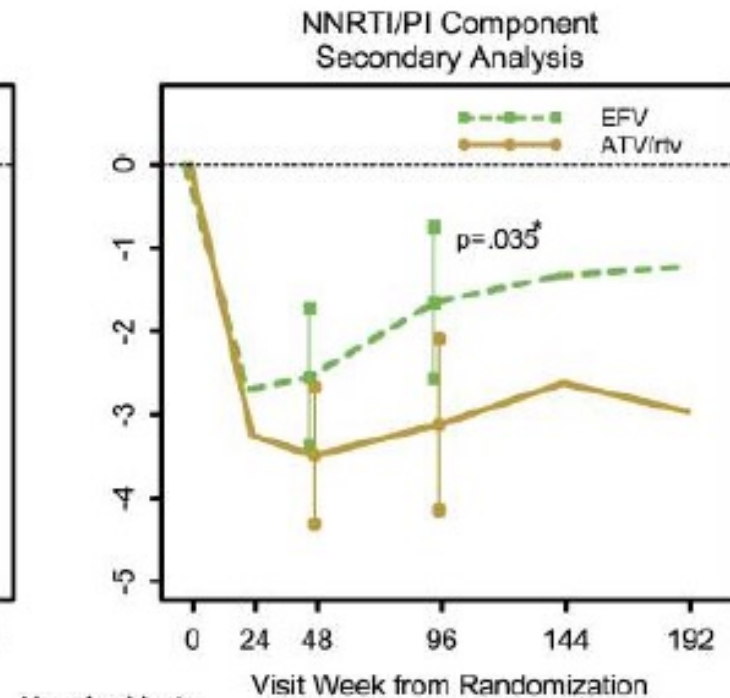
# Multifactorial Etiology of Bone Loss in HIV



# 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

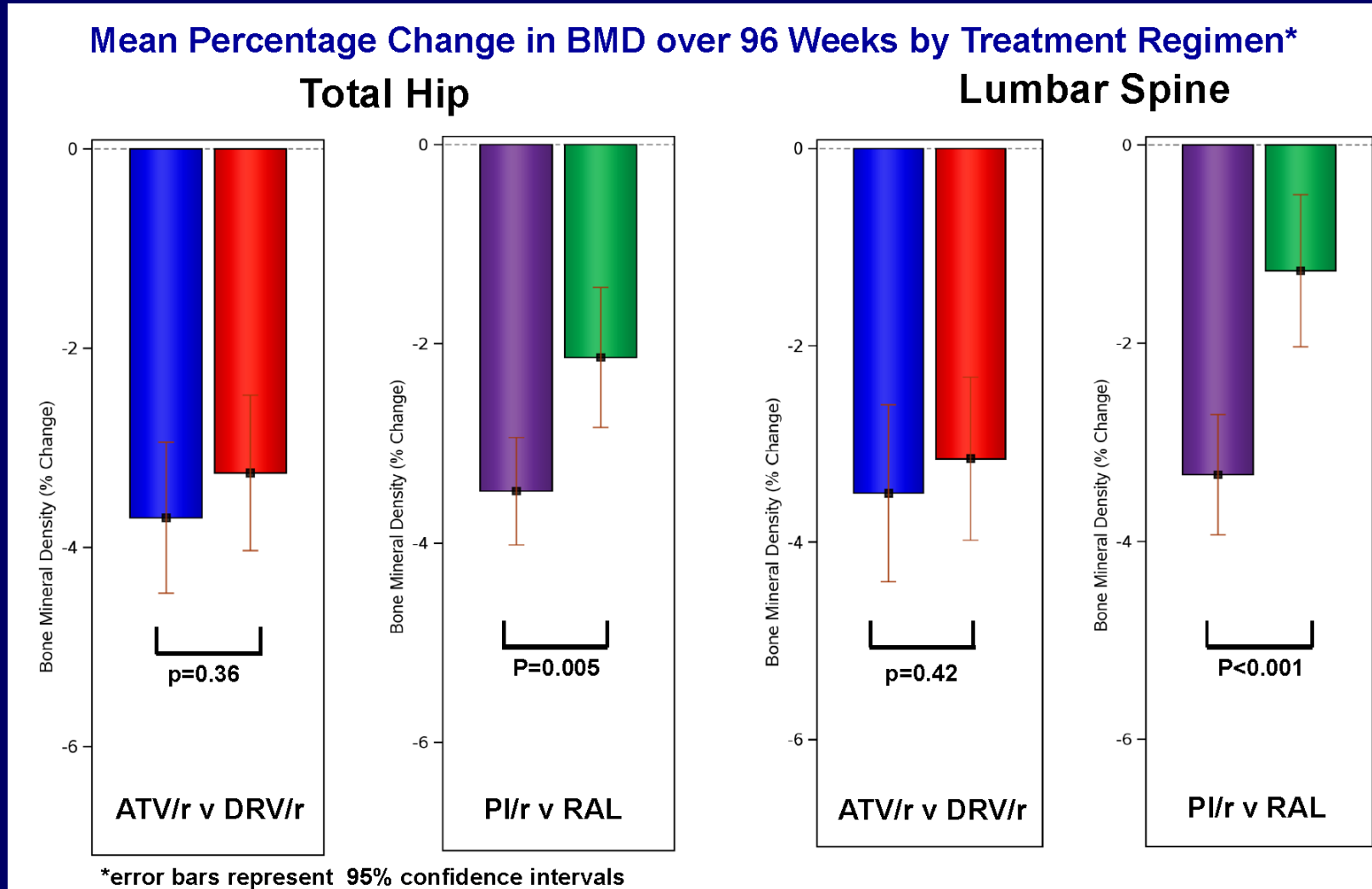
No significant interaction of NRTI and NNRTI/PI components ( $p = .63$ )

# Bone Loss with ART Initiation: TDF

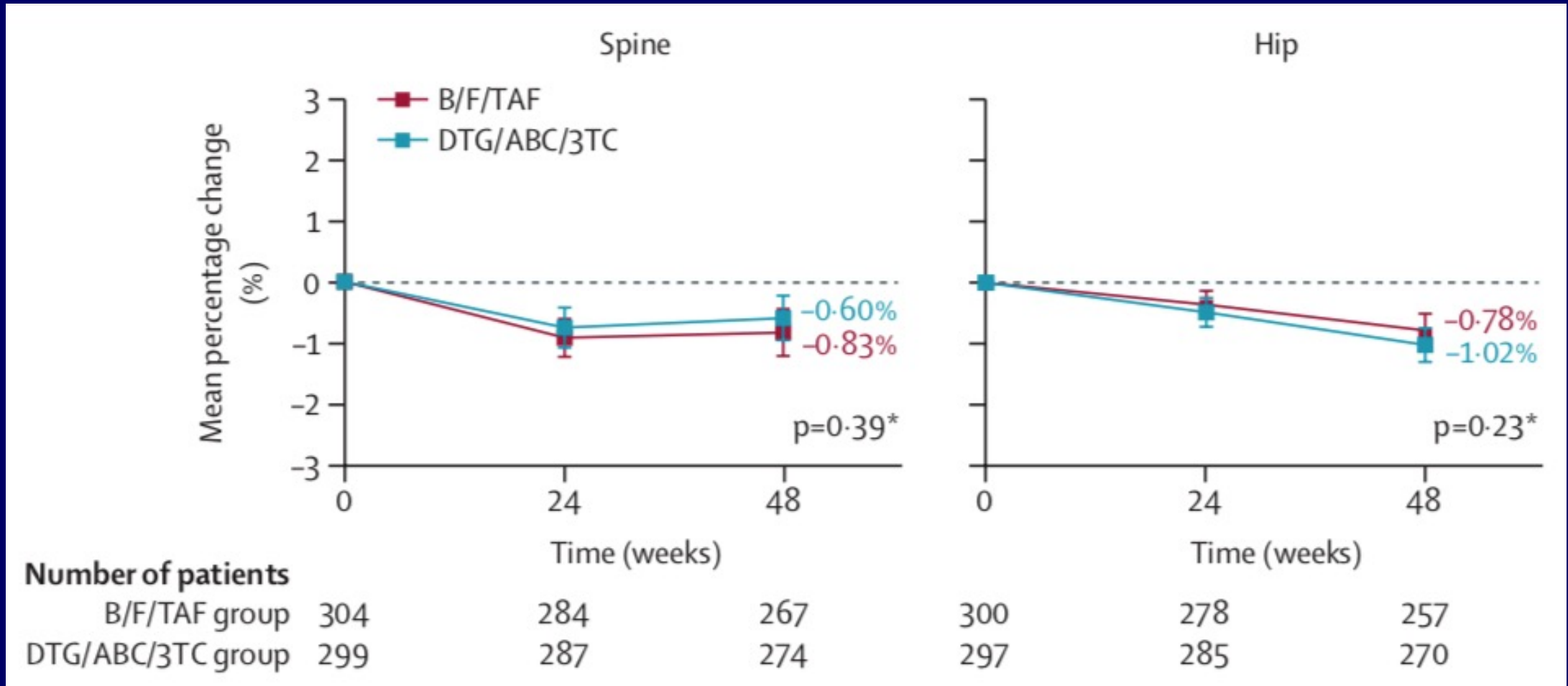
Study	ART regimens	Change in LS BMD
Stellbrink, <b>ASSERT</b> 2010	<b>TDF/FTC + EFV</b>	<b>-3.6%*</b>
	ABC/3TC + EFV	-1.9%
McComsey, <b>ACTG 5224s</b> 2011	<b>TDF/FTC</b>	<b>-3.3%*</b>
	ABC/3TC	-1.3%
	<b>ATV/r</b> EFV	<b>-3.1%*</b> -1.7%
Reynes, <b>PROGRESS</b> 2013	<b>TDF/FTC+LPV/r</b>	<b>-2.5%*</b>
	RAL+LPV/r	+0.7%
Sax, <b>Gilead 104-111</b> 2015	<b>E/C/F/TDF</b>	<b>-2.9%*</b>
	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
<b>Pozniak JAIDS 2017</b>	N=242 eGFR 30-69 ml/min 48 wks	<b>TDF/FTC/EVG/Cobi to TAF/FTC/EVG/Cobi</b>	<b>+2.3%*</b>	<b>+1.5%*</b>
<b>Bloch TROP 2014</b>	N=37 48 wks	<b>TDF+PI/r to RAL+PI/r</b>	<b>+3.0%</b>	<b>+2.5%</b>
<b>Curran SPIRAL-LIP 2012</b>	N=74 48 wks	<b>NRTIs+LPVr to NRTIs+RAL Stay on NRTIs+LPVr</b>		<b>+0.01 g/cm<sup>2</sup>*</b> no change

# How can we prevent fractures in PWH?

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

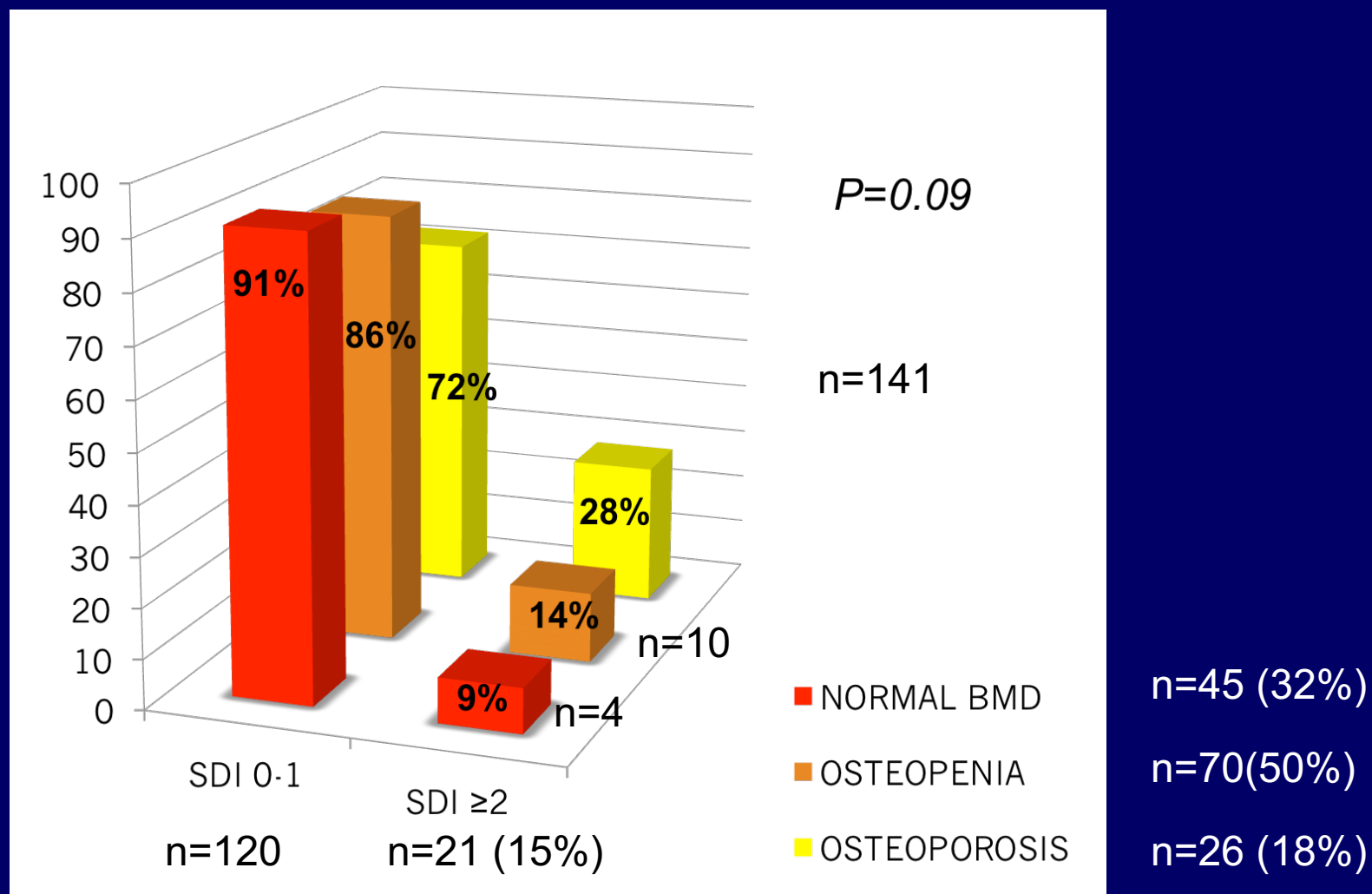
# US Bone Health and Osteoporosis Foundation (BHOF) Guidelines for DXA Screening

- Those with a fragility fracture after age 50
- Women  $\geq 65$  yrs, Men  $\geq 70$  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  $\geq 5$  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

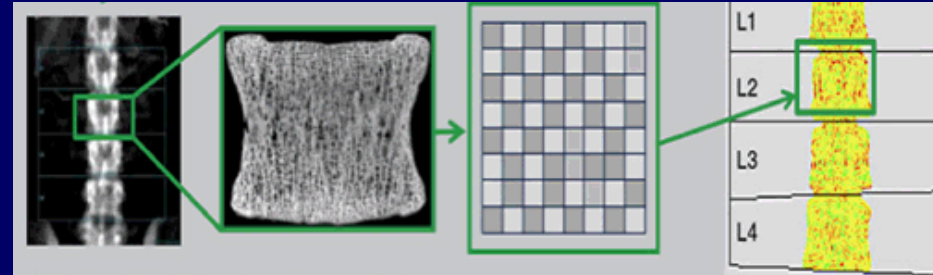
- Skeletal
  - Spine X-rays
  - Trabecular Bone Score



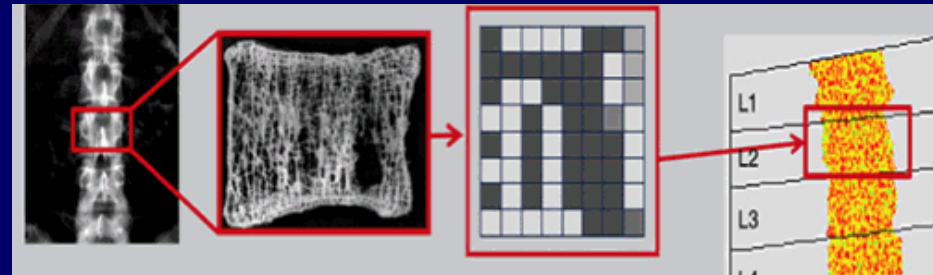
# Trabecular Bone Score as Noninvasive Measure of Bone Microstructure

- 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
$\geq 1.35$	Normal
$> 1.20$ to $< 1.35$	Intermediate
$\leq 1.20$	Degraded

# How can we prevent fractures in PWH?

- ART switching
  - avoid TDF & PIs in individuals with higher fracture risk
- Appropriate screening
  - DXA: Men  $\geq 50$  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  $\leq -2.5$  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  $\geq 50$  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.



### Weight Conversion:


pound:

[convert](#)

### Height Conversion:

inch:

[convert](#)

Country : **US(Black)**   Name / ID :    [About the risk factors](#) 

**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 hip    No    Yes

7. Current smoking    No    Yes

8. Glucocorticoids    No    Yes

9. Rheumatoid arthritis    No    Yes

10. Secondary osteoporosis    No    Yes

11. Alcohol 3 more units per day    No    Yes

12. Femoral neck BMD  

**FRAX underestimates fracture risk in PWH**  
 Yang, AIDS, 2018

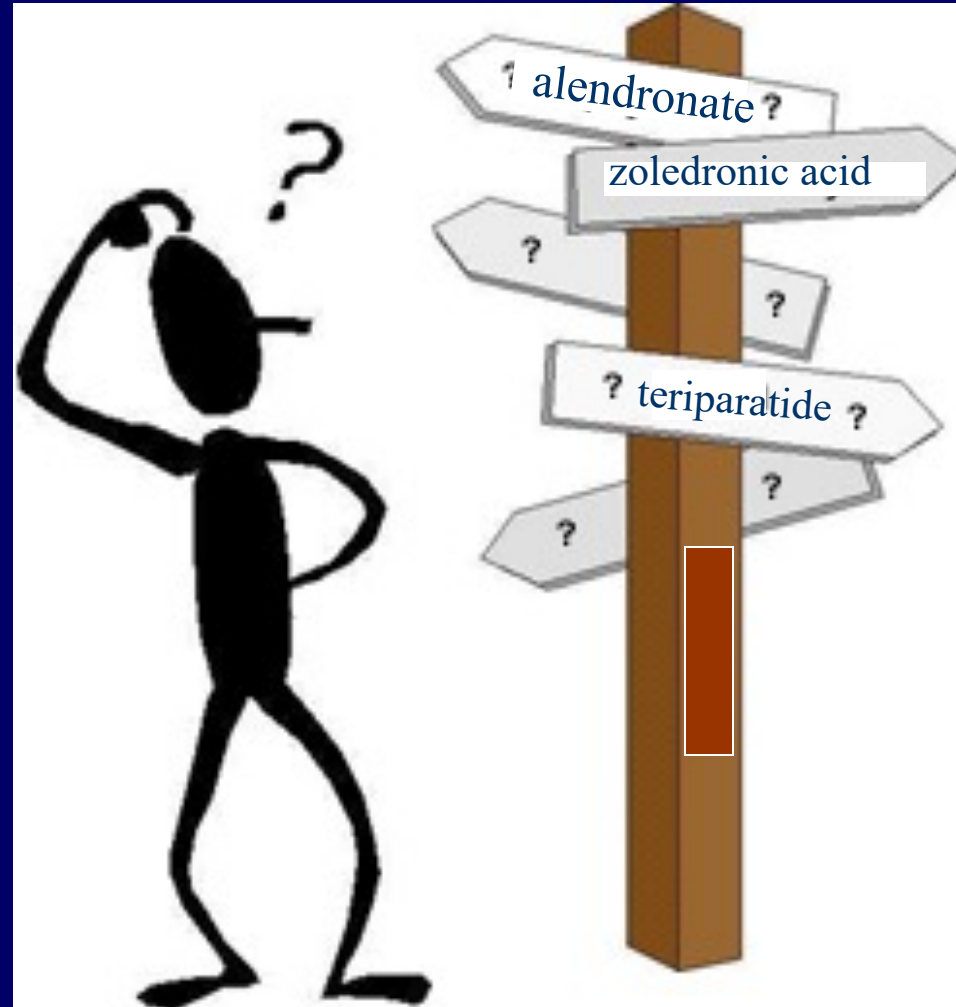
**Should treatment thresholds be any different in PWH?**

### 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% <sup>†</sup>
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% <sup>†</sup>	+3.8% vs -0.8% <sup>†</sup>
Huang, 2009 (N=30)	< -1.5	Zoledronic acid 5 mg/year (1 yr)	+3.7% vs +0.7%*	+3.2% vs -1.8%*

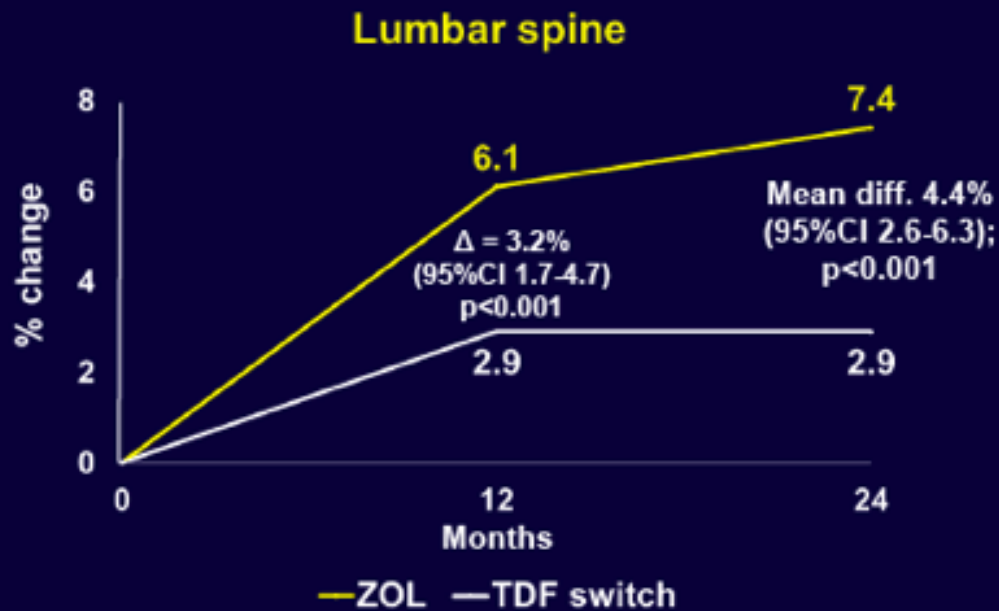
\*P < 0.05; <sup>†</sup>P < 0.001; NS = not significant

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.

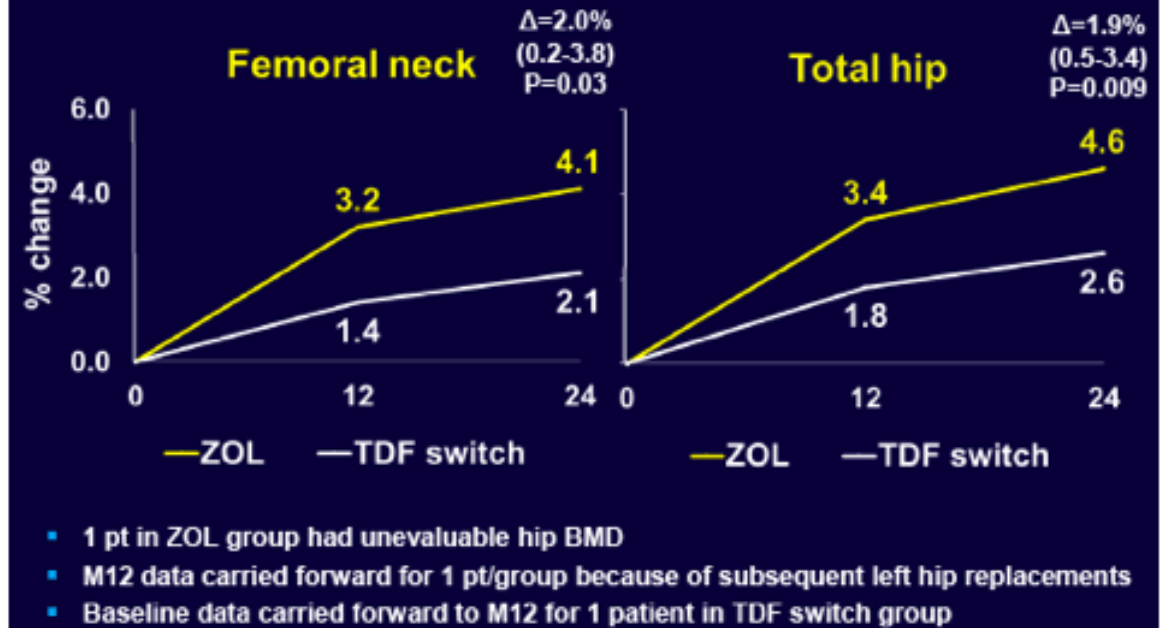


# Switch off TDF vs Bisphosphonate: ZEST Study

## 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

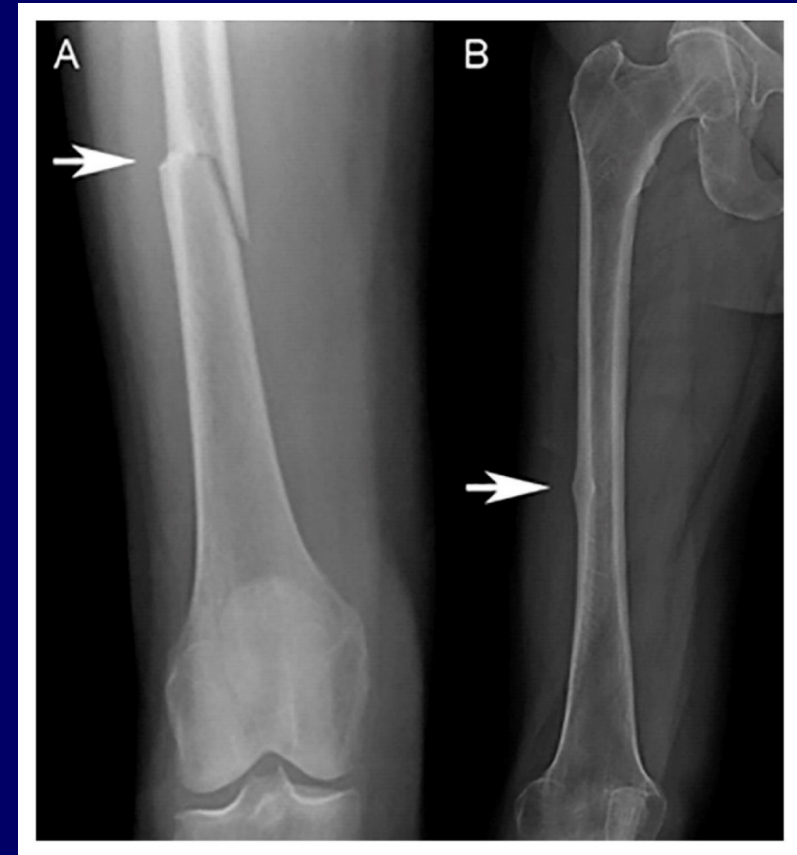
## IV (zoledronic acid)

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

# Antiresorptives: Long Term Adverse Events

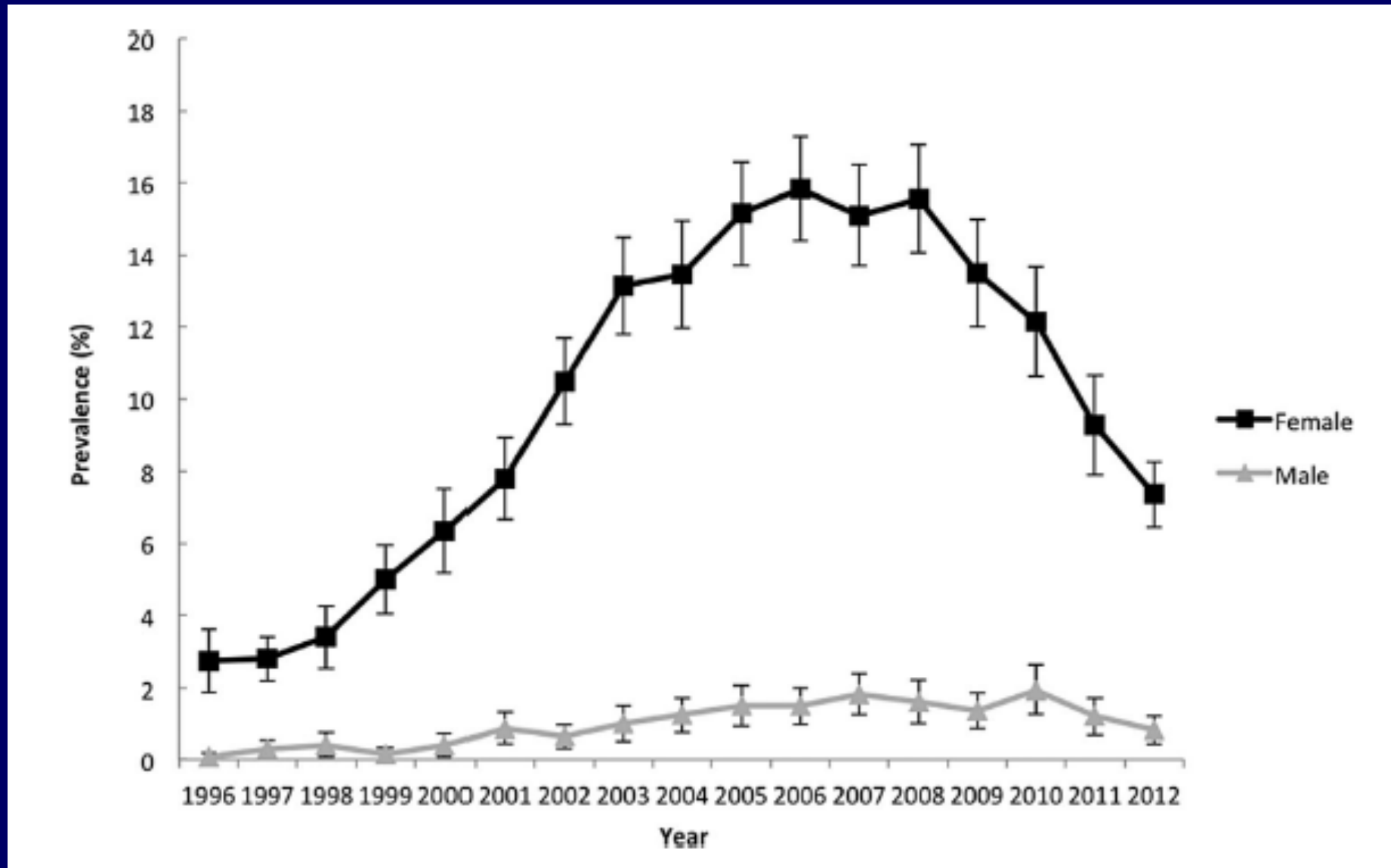


**Osteonecrosis of the Jaw**  
1 to 10 cases per 100,000 person-years



**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

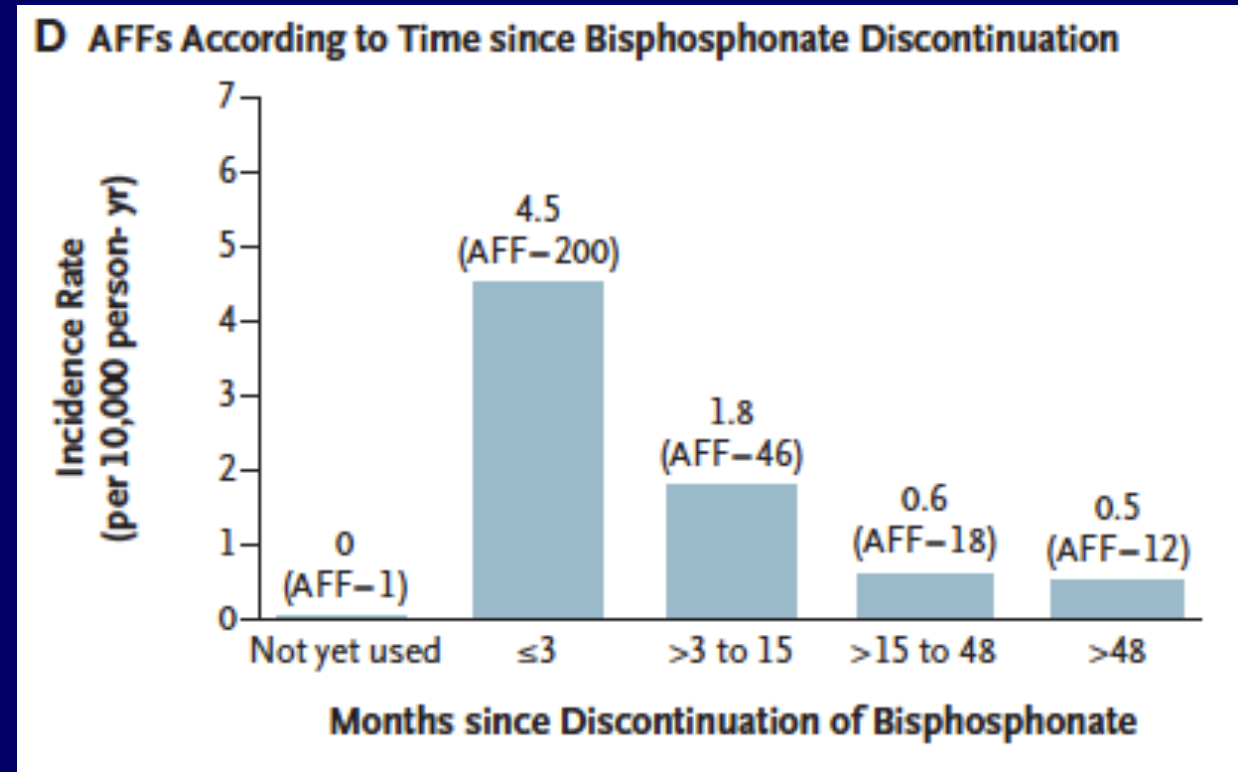
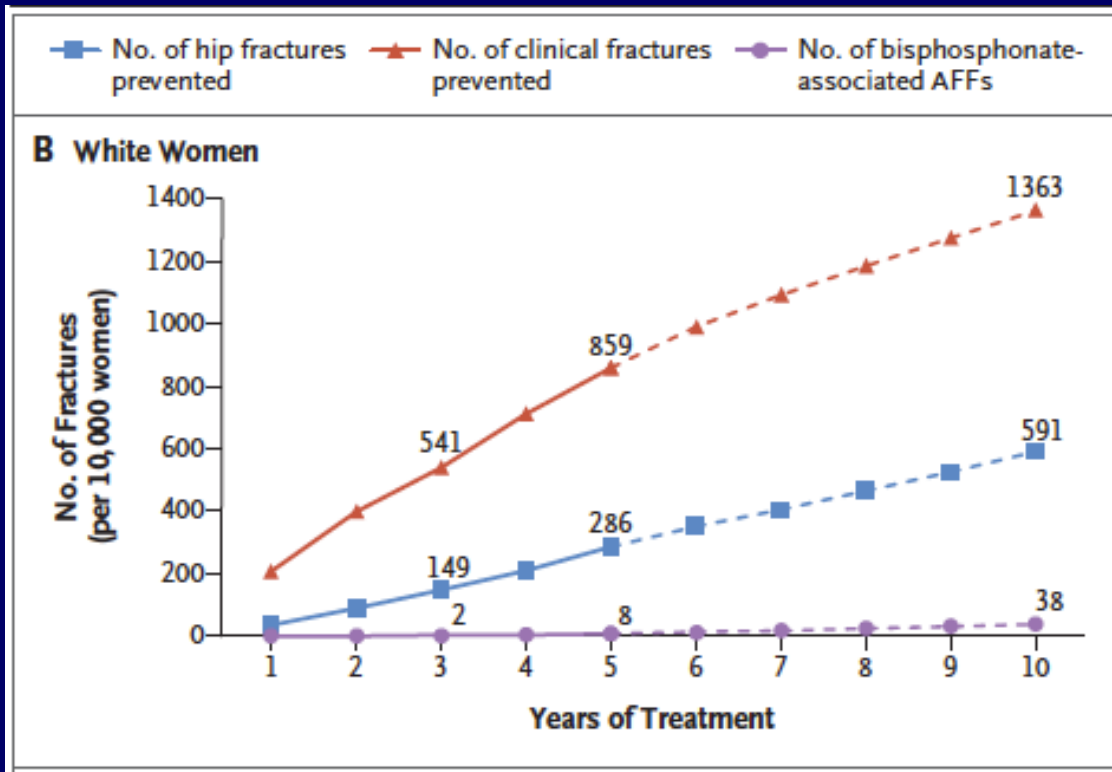
Patient Category	Recommendation
<p>High-risk:            T-score still <math>\leq -2.5</math> at the hip,            previous fracture of the hip or spine            or ongoing high-dose glucocorticoid            therapy.</p>	Drug holiday not justified.
<p>Moderate risk:            Hip bone mineral density value is            now <math>&gt; -2.5</math> (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?

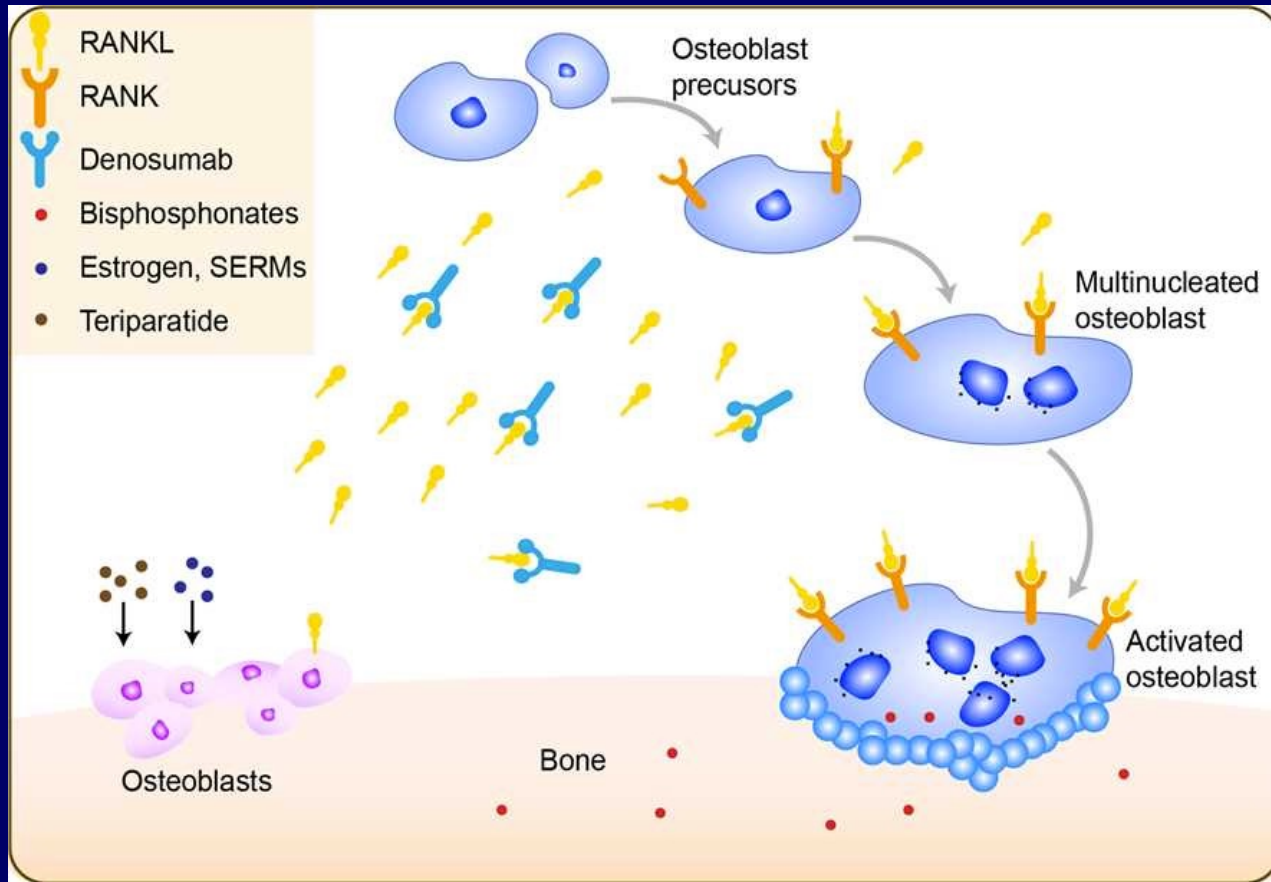
How to monitor?

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

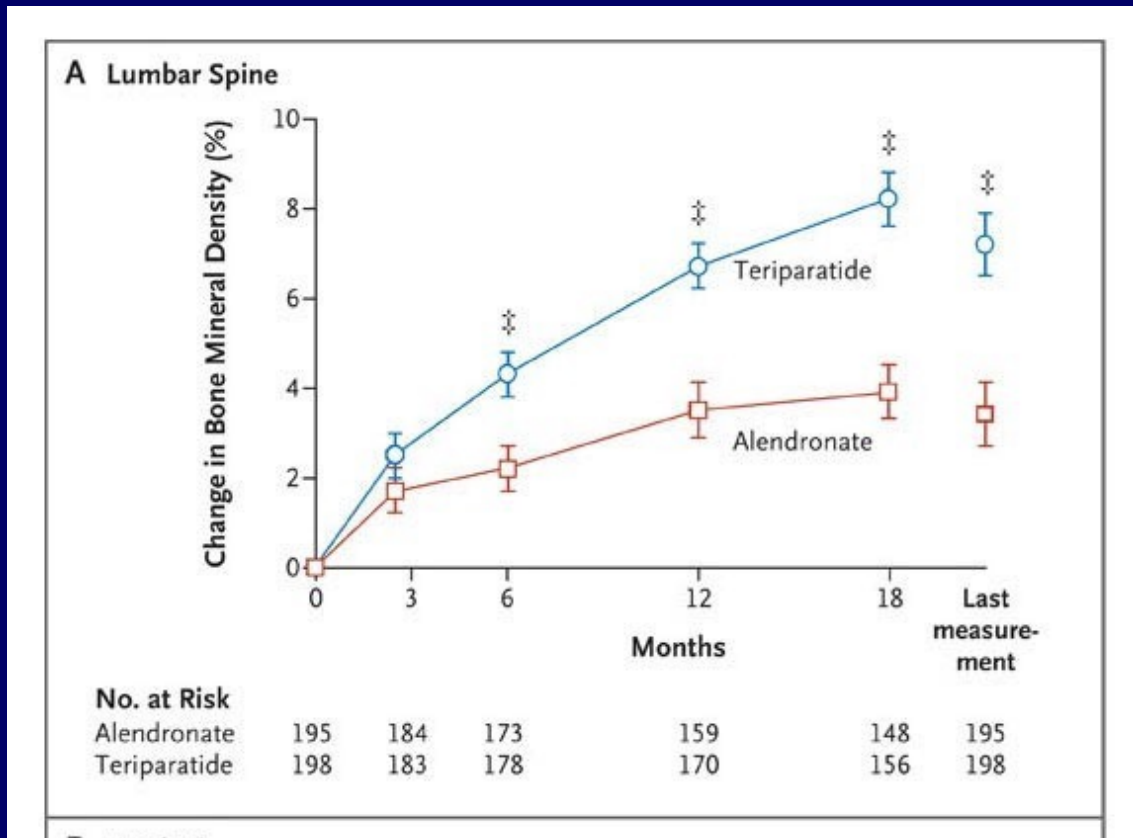
## Anabolic

### (Osteoblast Directed)

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



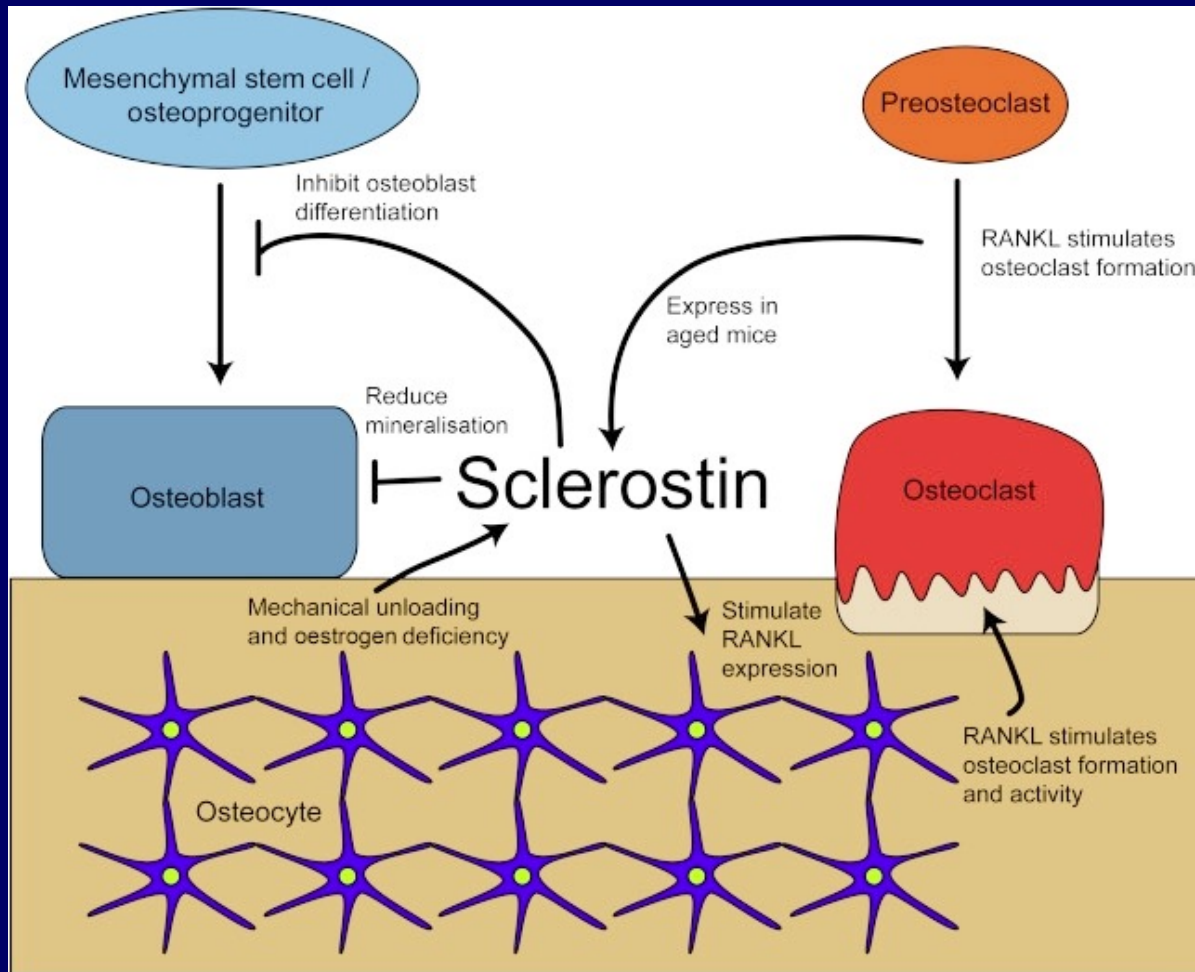
# PTH/PTHrP Analogs



- 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

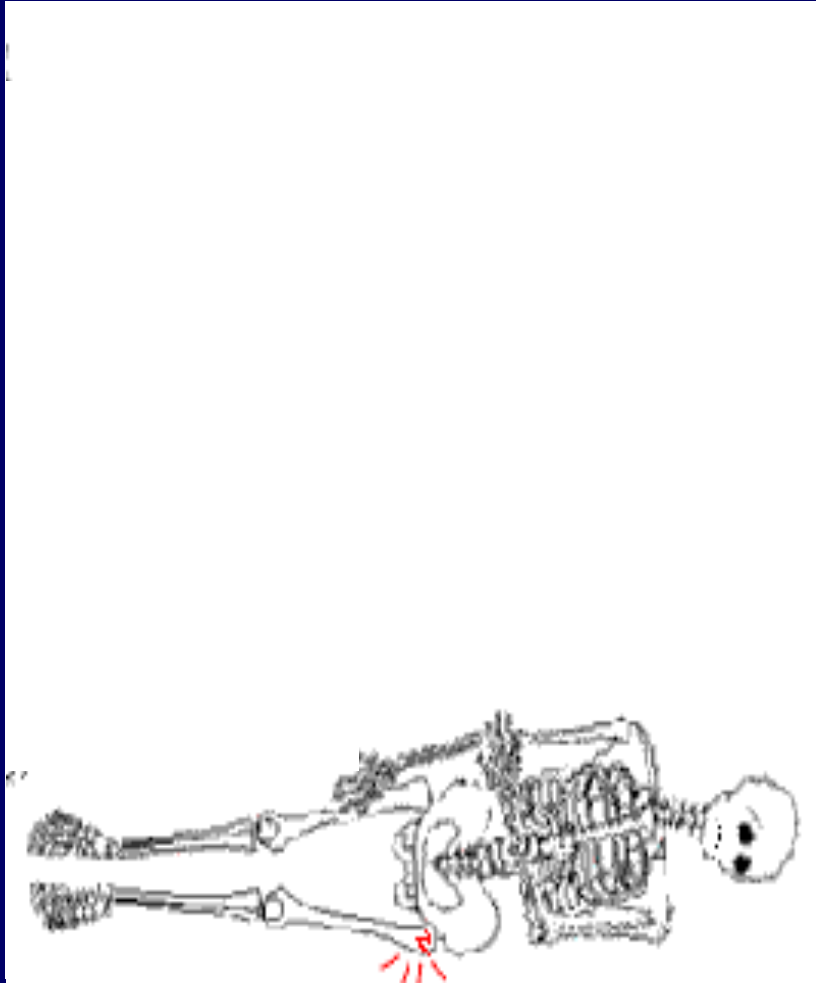
Teriparatide increases BMD more than alendronate  
In glucocorticoid-induced osteoporosis

# 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

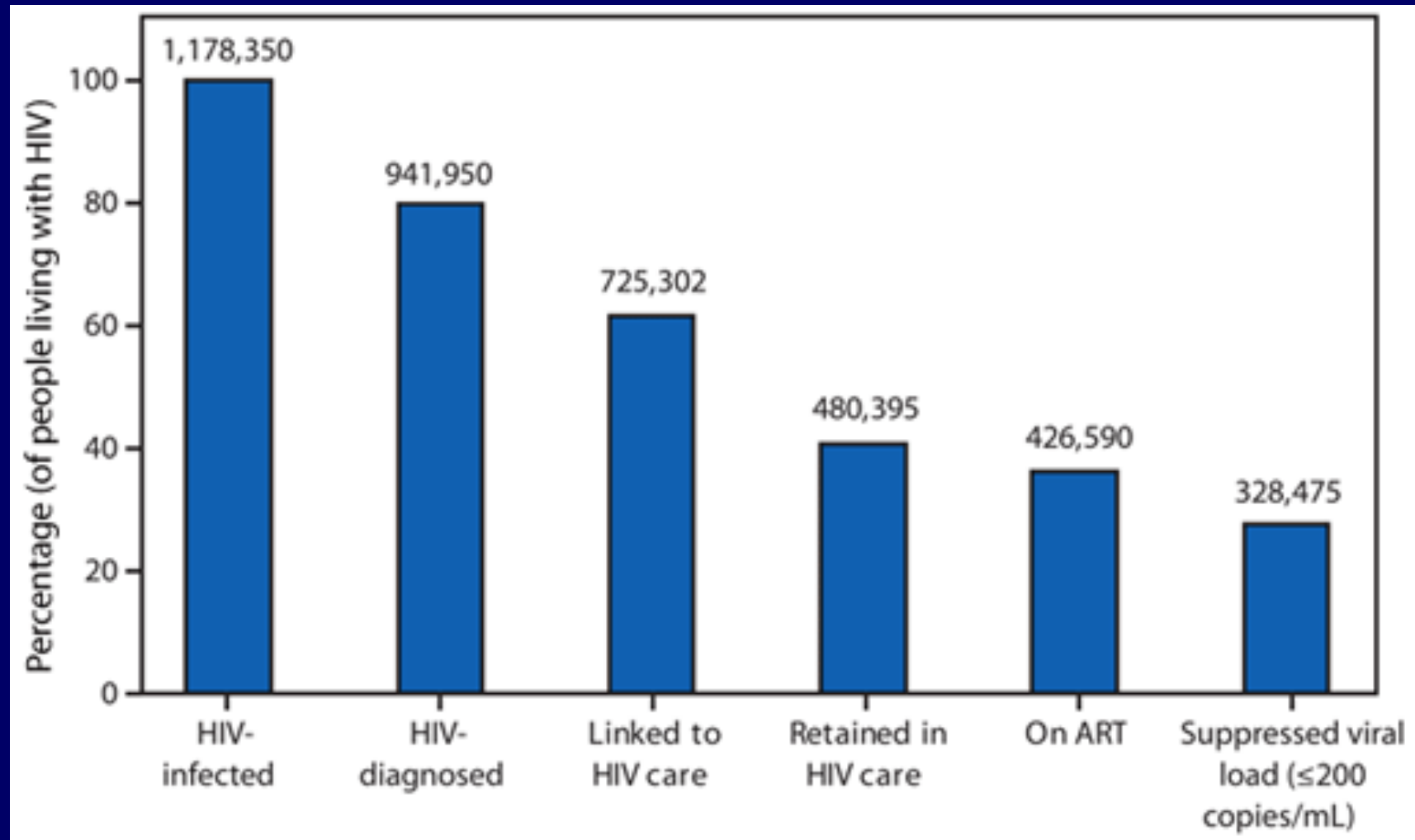
# Strategies to Prevent Falls

- 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

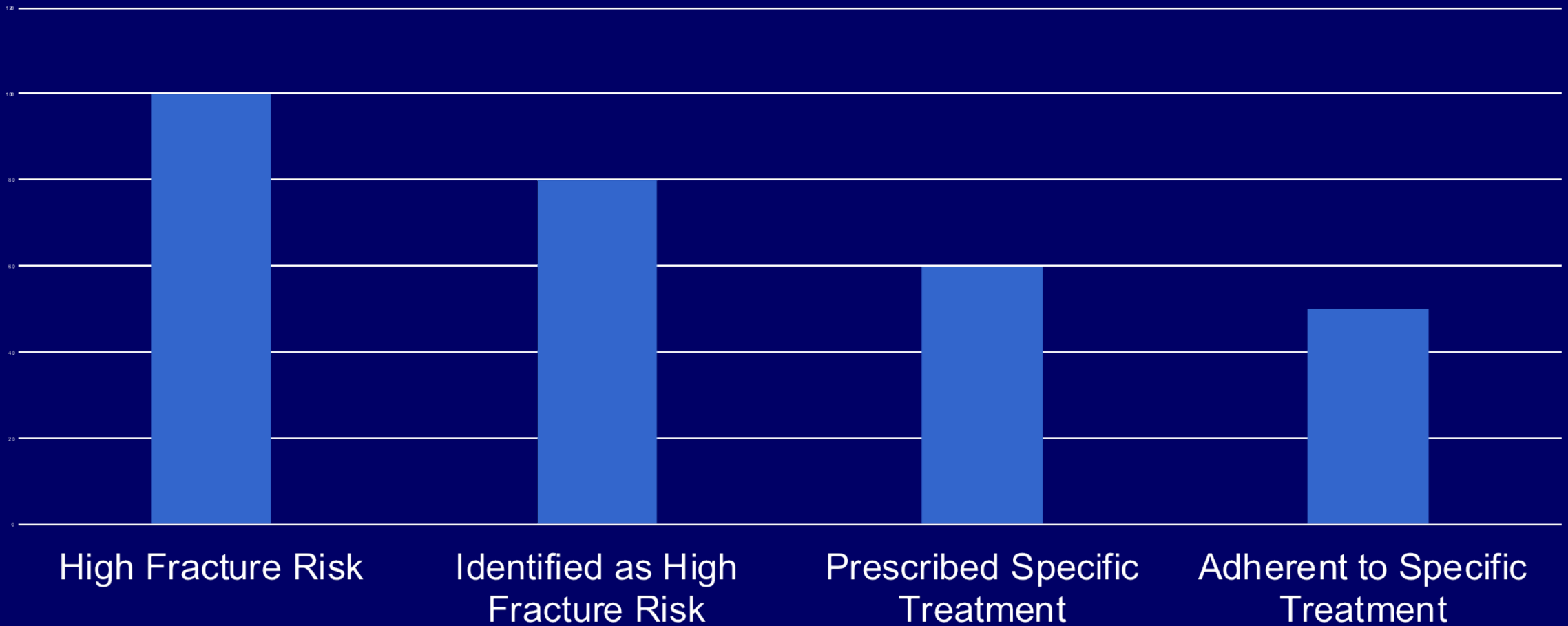
# Conclusions

- 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



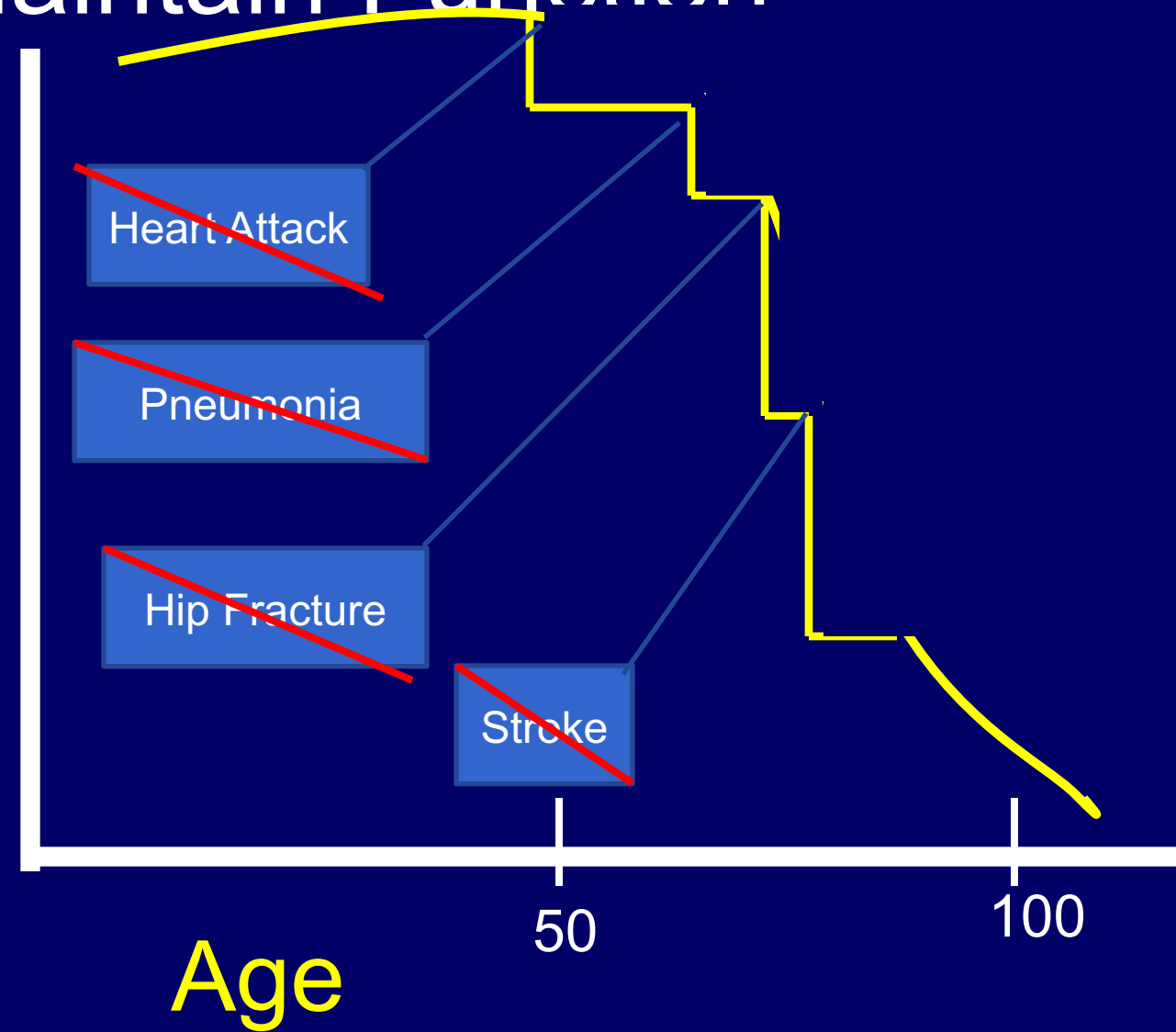
# Closing the Gaps for Fracture Prevention in PWH



For Illustration Only; numbers are fictional

# Preventing Comorbid Events is Critical to Maintain Function

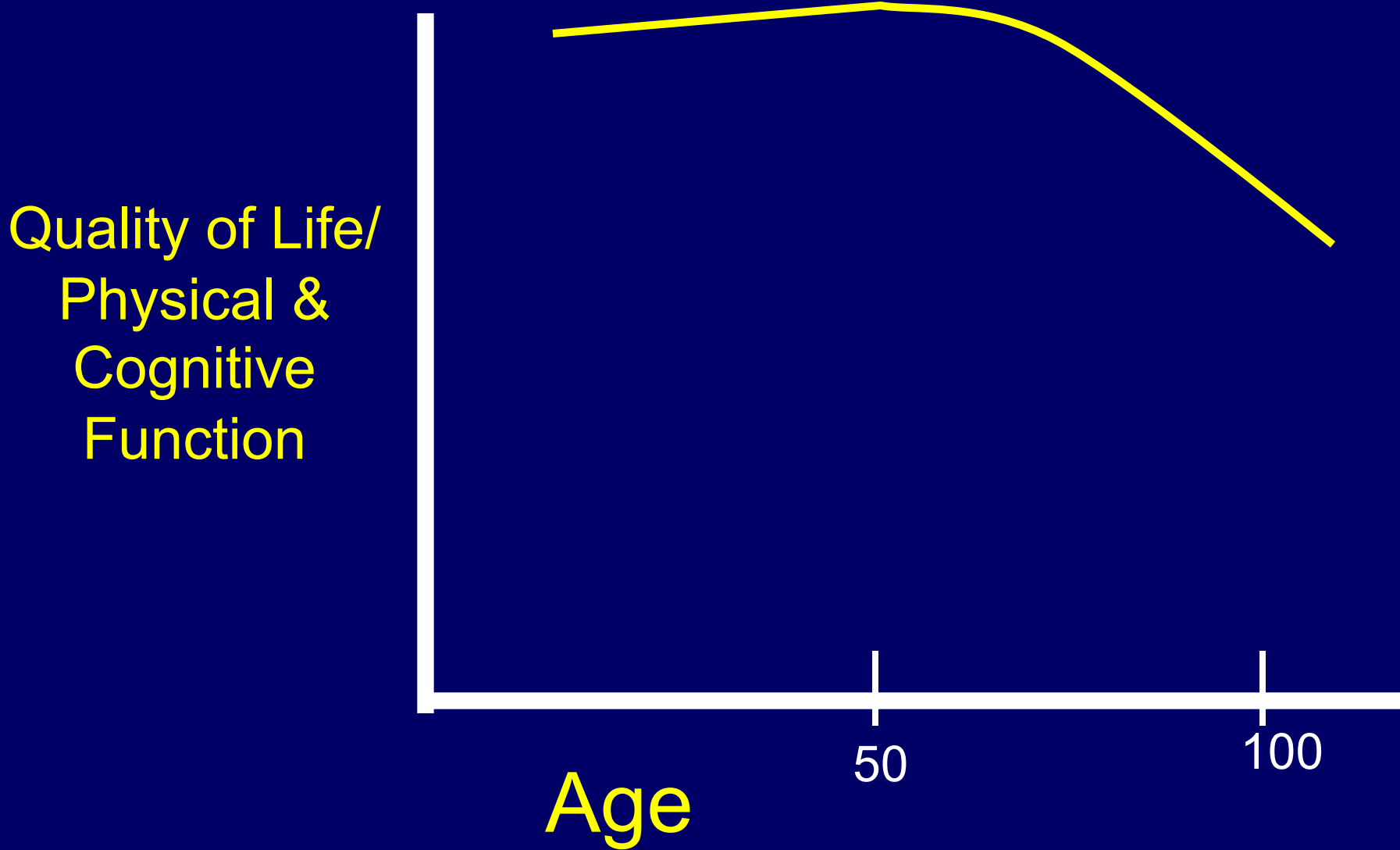
Quality of Life/  
Physical &  
Cognitive  
Function



Age



# Preventing Comorbid Events is Critical to Maintain Function



# Acknowledgment

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