Osteoporosis in HIV+ adults

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Conflicts of interest

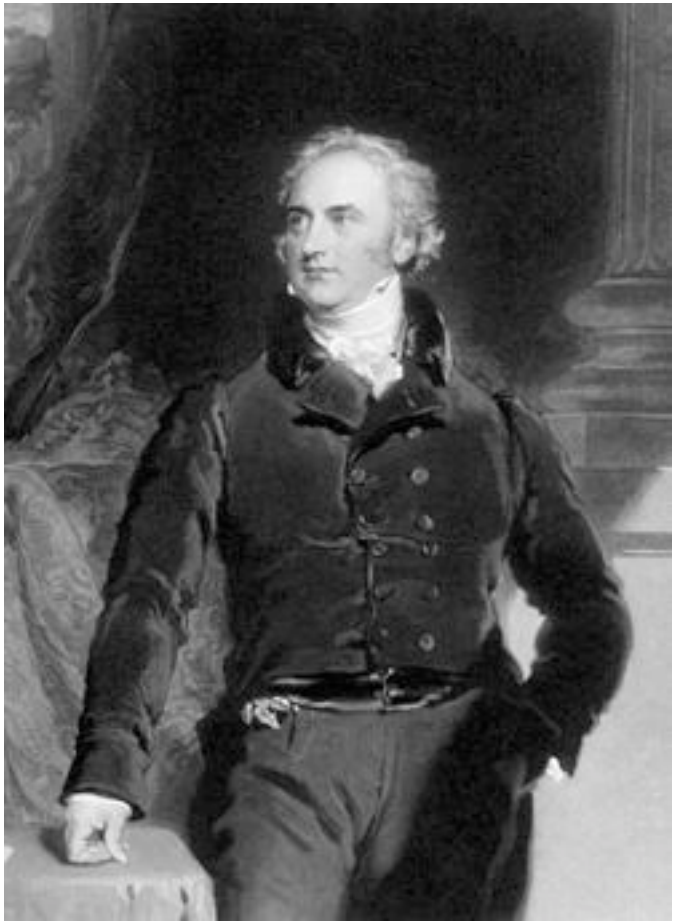
- None

Overview

- Review of bone metabolism
- Pathogenesis of osteoporosis in HIV+ adults
- Epidemiology of osteoporosis and fractures in HIV+ populations
- Clinical considerations:
  - Screening & Diagnosis
  - Treatment
  - Prevention

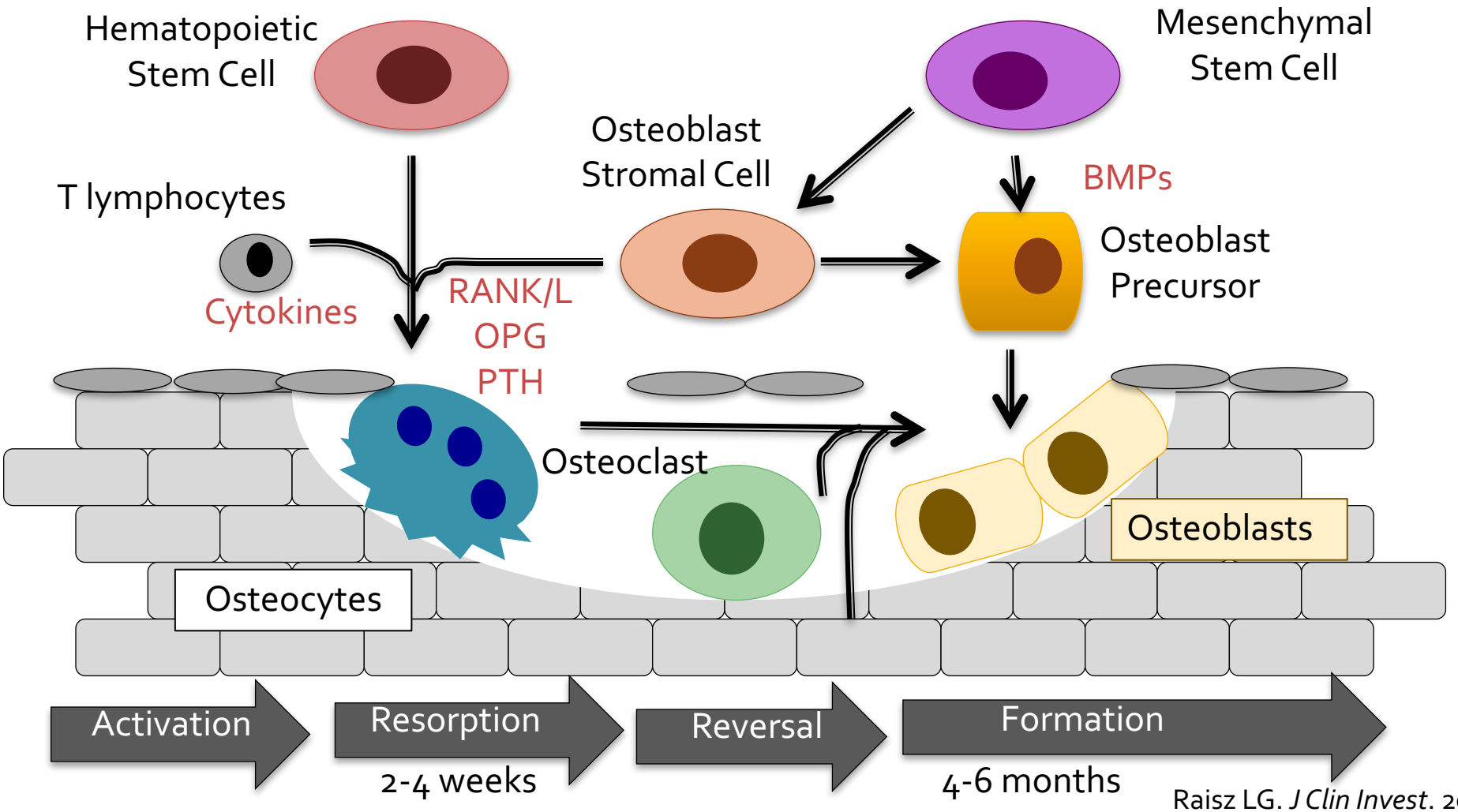
Osteoporosis in History

- 19th c. – English surgeon Sir Astley Cooper noted "the lightness and softness that (bones) acquire in the later stages of life"
- 1940 – Dr. Fuller Albright (USA) linked it to postmenopausal state
- Current definition – continuum in which "multiple pathogenic processes converge to cause a loss of bone mass and deterioration of skeletal microarchitecture"



Raisz LG. *J Clin Invest*. 2005

Bone remodeling overview

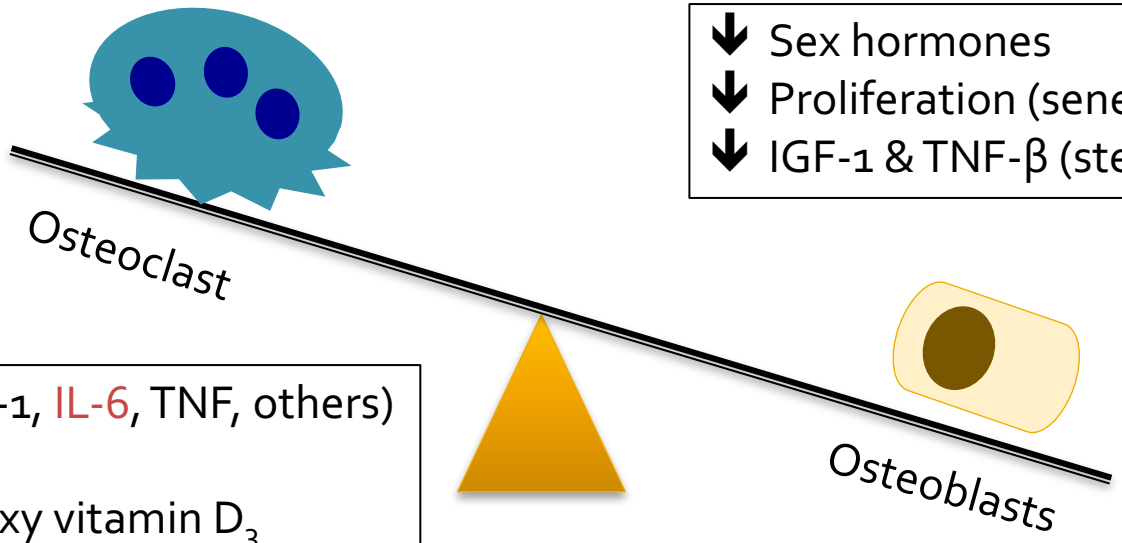


Raisz LG. *J Clin Invest*. 2005

Osteoporosis: tipping the balance

Promotion of Activation & Bone Resorption

Suppression (or delay) of Bone Formation



↓ Sex hormones
↓ Proliferation (senescence)
↓ IGF-1 & TNF-β (steroids)

↑ Cytokines (IL-1, IL-6, TNF, others)
↑ PTH
↑ 1,25-dihydroxy vitamin D_3

⊤

Estrogen, androgen, glucocorticoids, and thyroid hormone

Manolagas SC. *Endocrine Rev*. 2000

Raisz LG. *J Clin Invest*. 2005

Risk factors for Osteoporosis

TRADITIONAL

- Age
- Non-black or white race
- Latitude furthest from equator
- Family history
- Low BMI
- Prior fragility fracture
- Alcohol abuse
- Tobacco use
- Glucocorticoids
- Proton pump inhibitors
- Anticonvulsants
- Falls

CO-MORBIDITY RELATED

- Hepatitis C & B viruses
- Male hypogonadism, premature menopause
- Substance abuse
- Growth hormone deficiency
- Diabetes
- Chronic liver disease
- Chronic renal disease
- COPD
- HIV

Compston J. *J Int Medicine*. 2016
Curtis EM et al. *Clin Medicine*. 2016

Why HIV+ adults are at increased risk for osteoporosis

↑ Traditional Risk Factors

↑ Co-morbidity Risk Factors

HIV Virus

ART

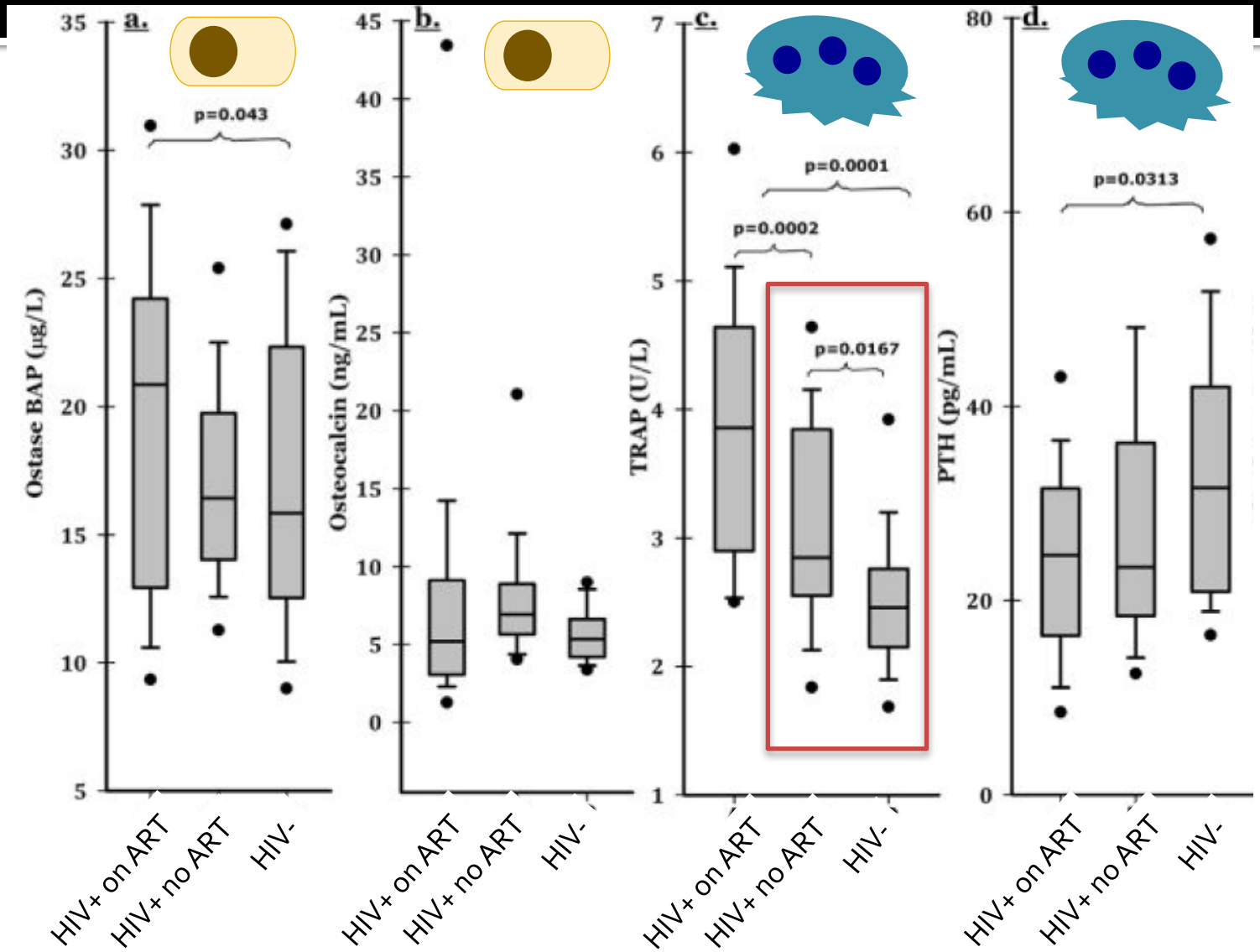
Immune System

HIV viremia & bone mineral density

- HIV viremia → stimulates bone turnover
- Increased markers of bone resorption and formation in the setting of HIV viremia

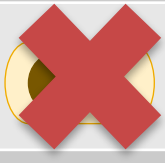
Mallon PW. *Curr Opin HIV AIDS*. 2014

Differences in blood biomarkers



Aziz N et al. *J AIDS Clin Res*. 2014

Before & After HIV Infection

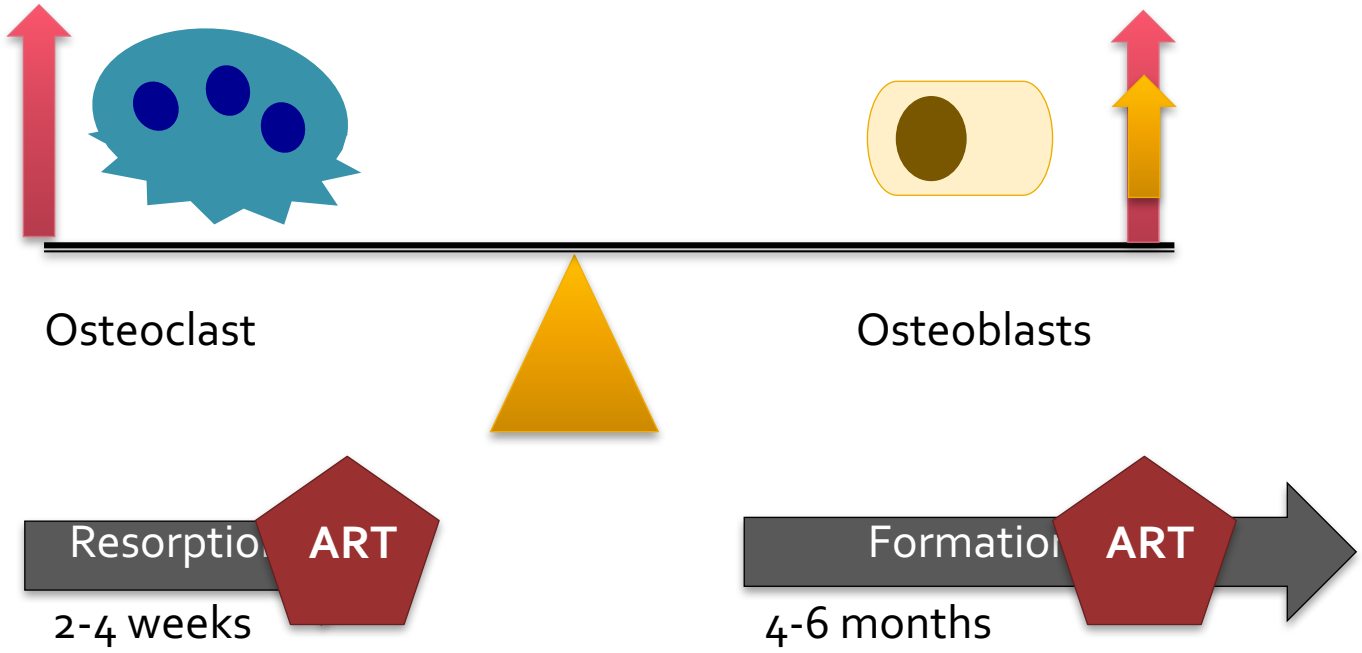
Parameter (median)	Activity	Pre-HIV infection	Pre-ART initiation	P value
C-telopeptide		0.300	0.265	0.31
P1NP[a]		47.37	43.40	0.21
Osteocalcin		7.02	4.60	0.04
Sclerostin		0.031	0.031	0.93
25-OH vitD_3	Deficiency linked with resorption	**36.58**	**33.10**	**0.06**

[a] Procollagen type-1N terminal propeptide

Slama L et al. *J Antimicrob Chemother*. 2017

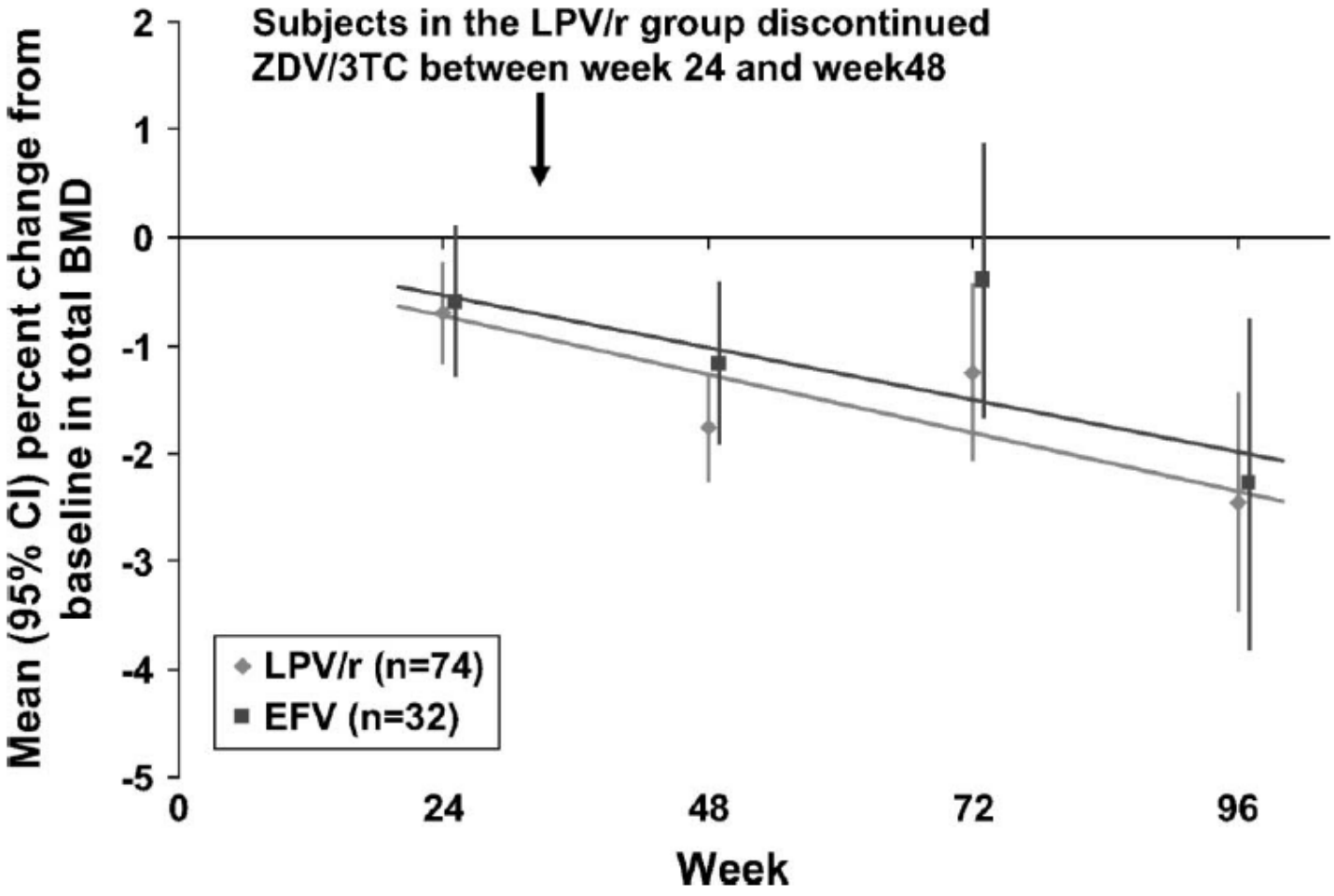
So what happens with ART?

ART initiation (in viremic patients) is associated with a 2-6% loss of bone mineral density in the first year.



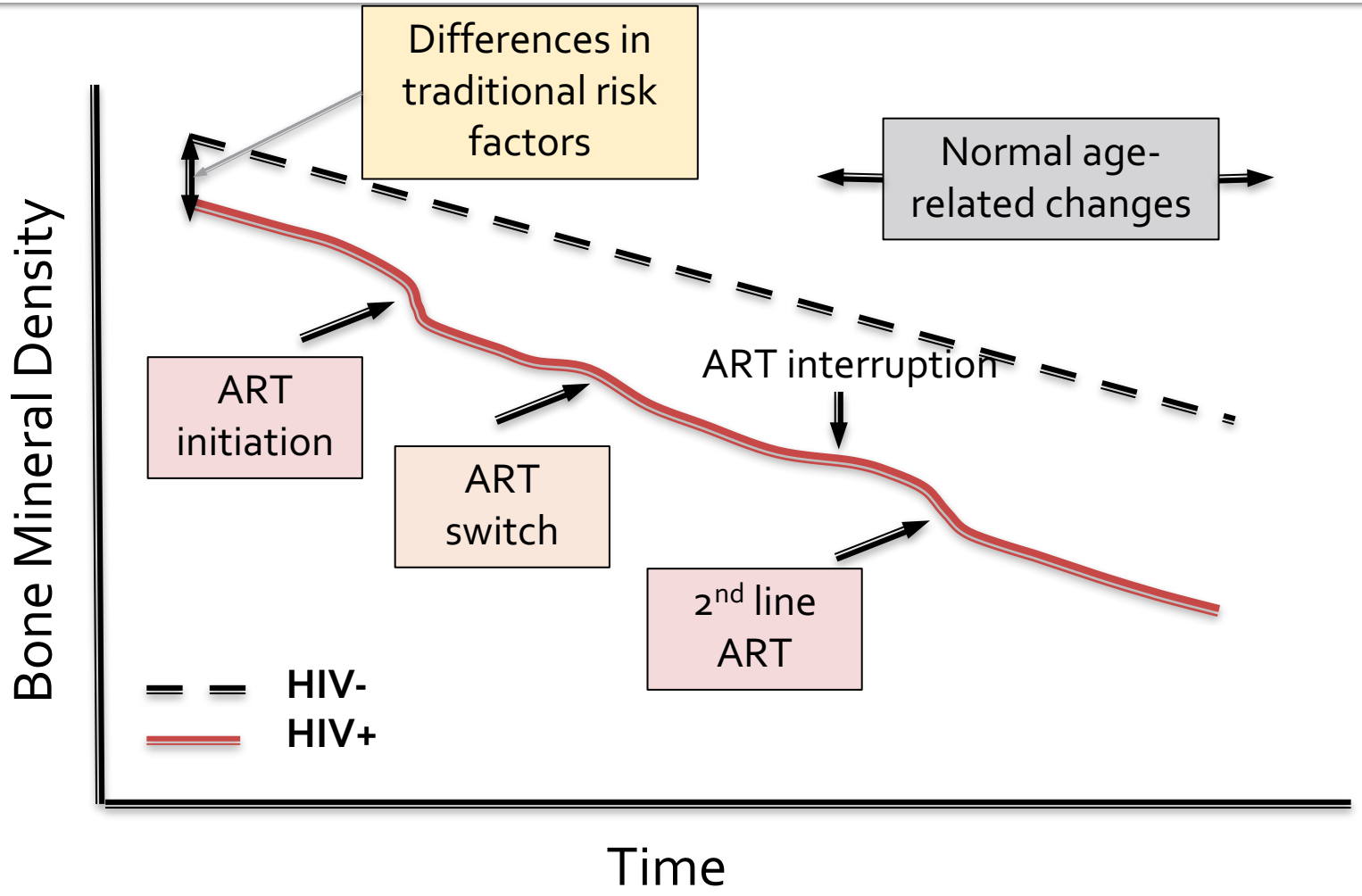
Mallon PW. *Curr Opin HIV AIDS*. 2014

LPVr/AZT/3TC vs. EFV/AZT/3TC



Brown TT et al. *JAIDS*. 2009

Working hypothesis/paradigm



Mallon PW. *Curr Opin HIV AIDS*. 2014

Not all ART is created equal…

- **Tenofovir disoproxil fumarate (TDF)** has been associated with BMD loss
  - In HIV+ initiating ART
  - In ART therapy switches
  - In HIV- adults on PrEP

Stellbrink HJ et al. *Clin Inf Dis*. 2010

McComsey GA et al. *J Infect Dis*. 2011

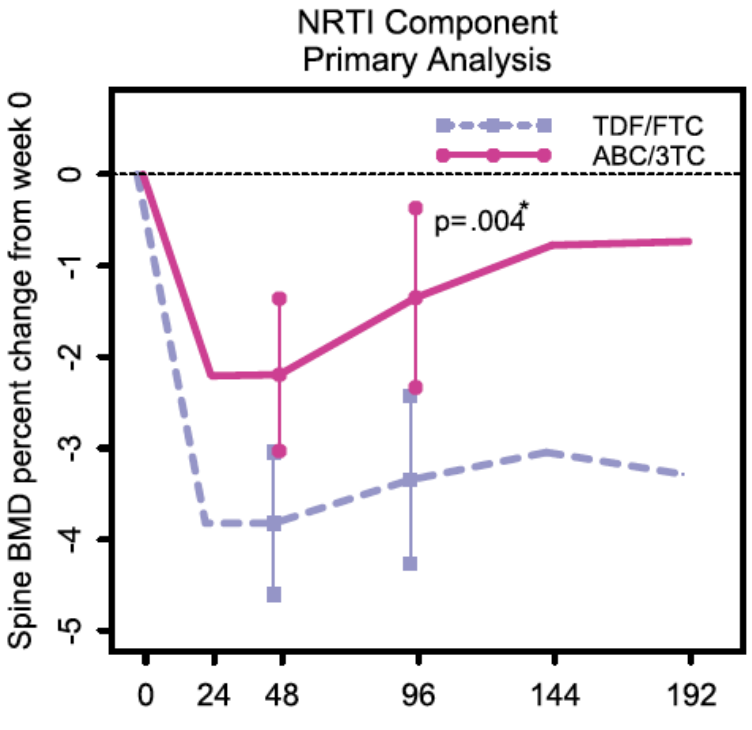
Cotter AG et al. *J Clin Endocrinol Metab*. 2013

Glidden DV et al. *JAIDS*. 2017

And many more…

ACTG 5224s (substudy of A5202): TDF/FTC+(ATVr or EFV) vs. ABC/3TC+(ATVr or EFV)

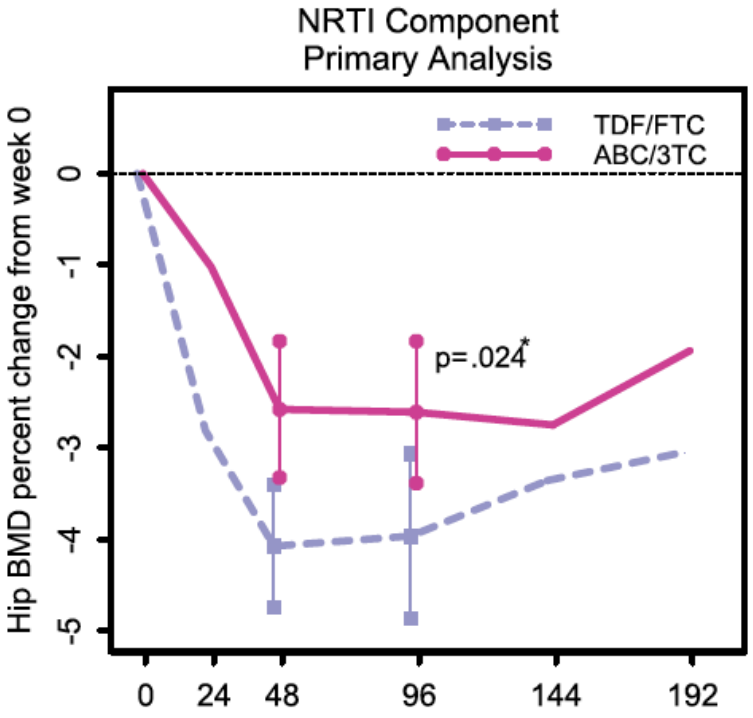
Spine BMD



No. of subjects						
TDF/FTC	128	111	105	97	87	53
ABC/3TC	130	122	106	101	80	53

* - two-sample t-test

Hip BMD



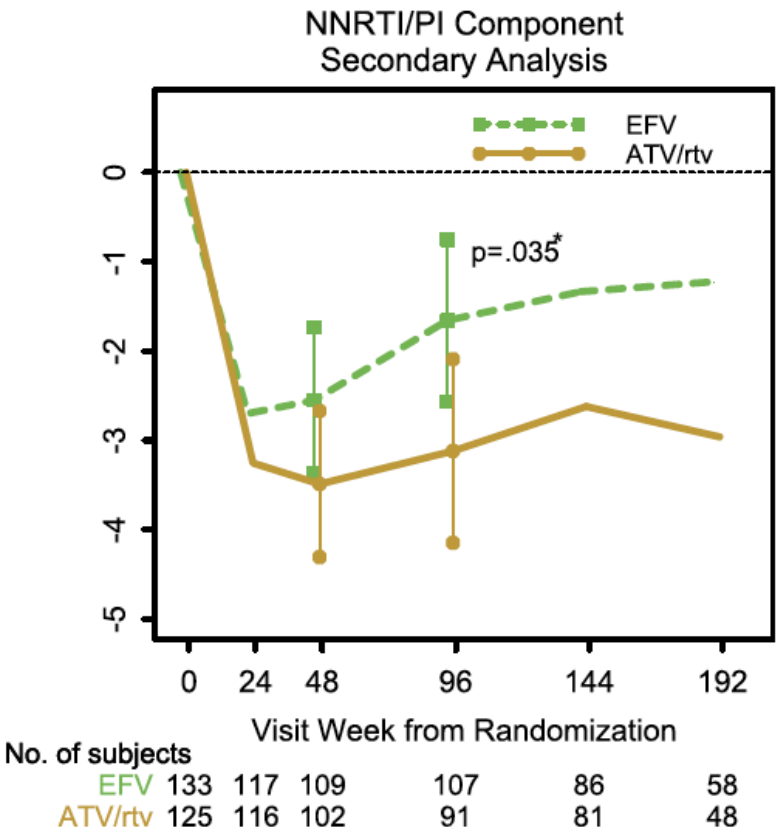
No. of subjects						
TDF/FTC	126	109	104	96	85	53
ABC/3TC	128	119	104	99	79	54

* - two-sample t-test

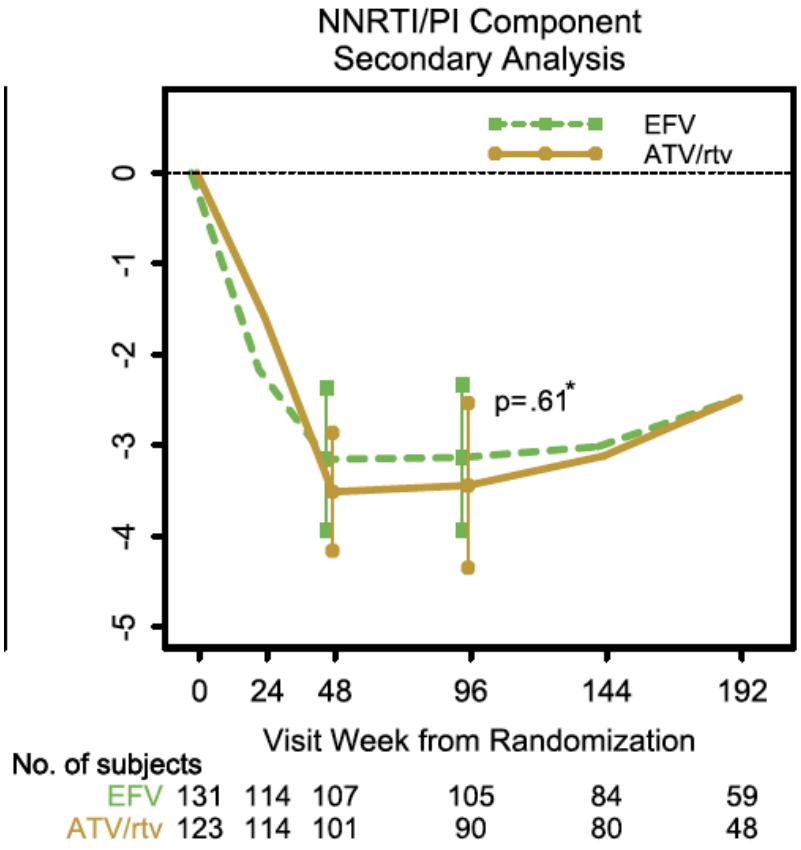
McComsey GA et al. *J Infect Dis*. 2011

Also noted…

Spine BMD



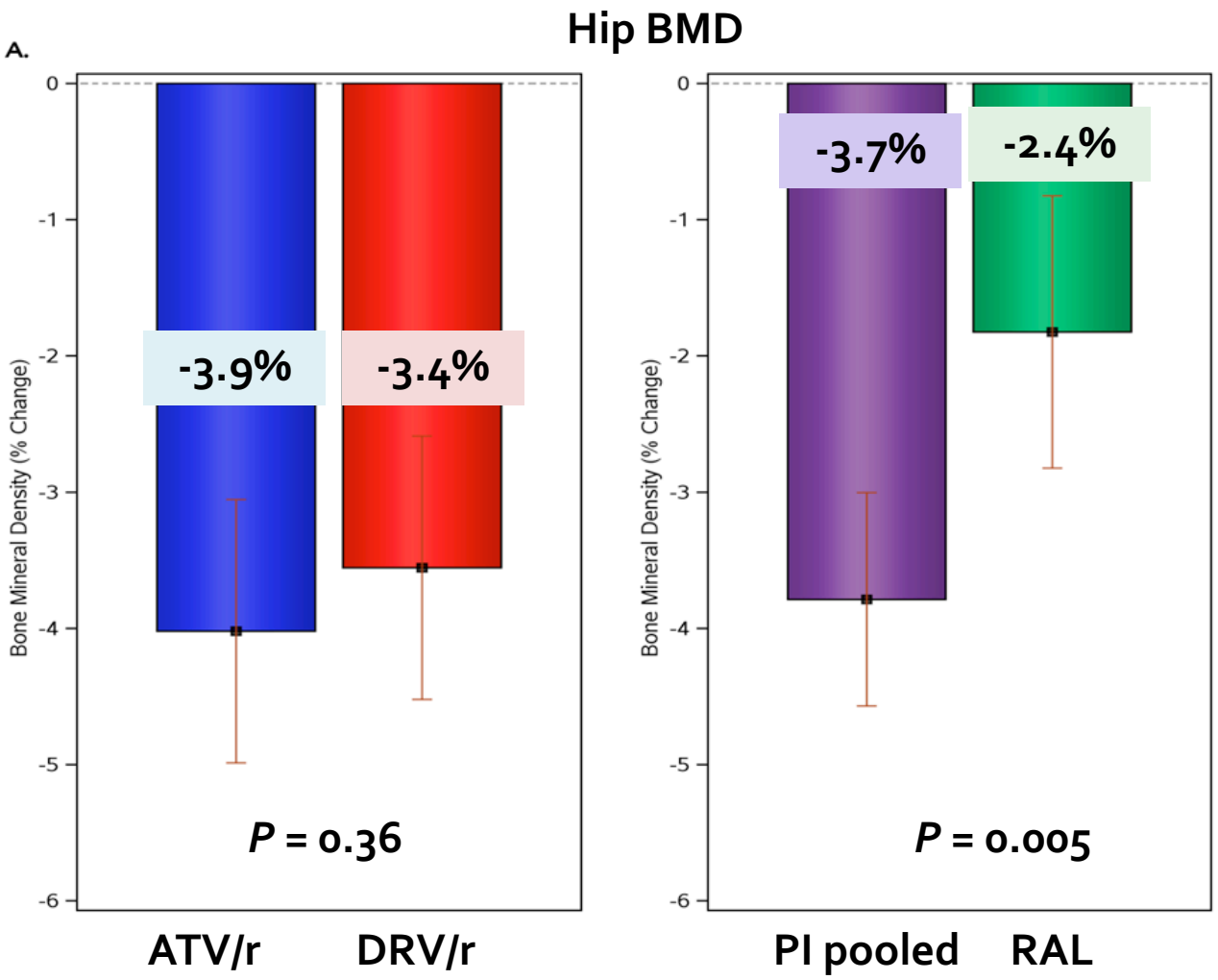
Hip BMD



McComsey GA et al. *J Infect Dis*. 2011

Protease inhibitors & BMD

- A5257
- ATV/r vs. DRVr vs. RAL, all paired with TDF/FTC
- BMD results at 96 wks
- L-spine results similar



Brown TT et al. *J Infect Dis*. 2015

Proposed mechanisms of ART & bone changes

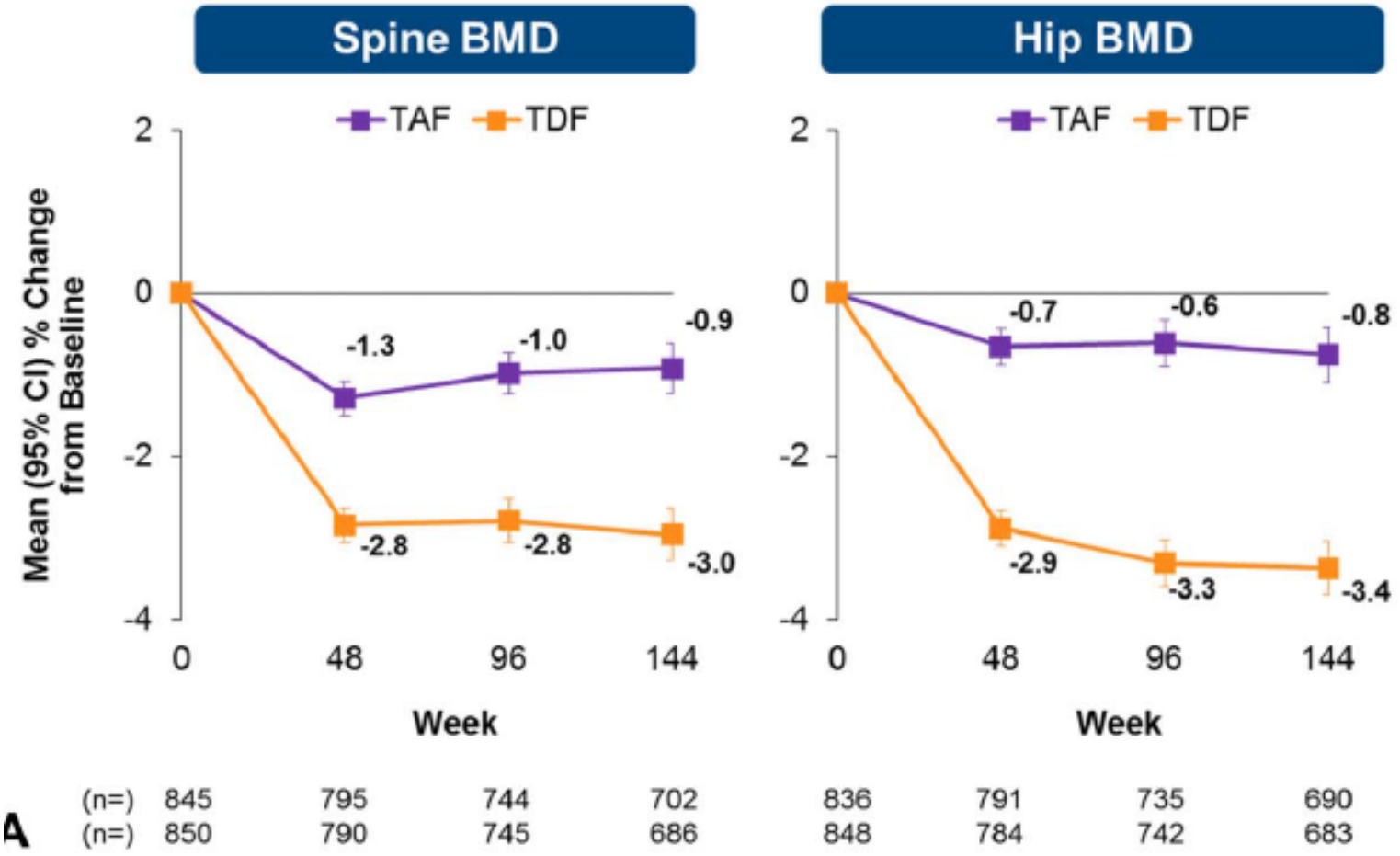
- Poorly defined mechanisms for how ARVs cause differential bone effects

ARV	Proposed mechanism
PIs	↑ osteoclastgenesis, inhibition of osteoblasts
AZT	↑ osteoclastgenesis
TDF	Renal tubular dysfunction (hypophosphatemia)
EFV	↓ Vitamin D due to CYP P450 inhibition

Compston J. *BoneKEy Rep*. 2015

Tenoforvir alafenamide (TAF)

EVG/c/TDF/FTC vs. EVG/c/TAF/FTC @ 144 weeks



Arribas JR et al. *JAIDS*. 2017

Reversible ART effects: Switch studies

Design	Original ARV	Switched to	Results of switch
Open-label, randomized trial (n=86)	PI/r	RAL vs. no switch	Statistically significant ↑ in femoral neck BMD after 48 wks
Open-label, non-randomized trial of pts with low BMD (n=37)	TDF + PI/r	RAL + PI/r	Statistically significant ↑ in femoral neck BMD after 24 and 48 wks
Pooled data from 2 clinical trials (n=214 pts with low BMD)	TDF-containing regimen	EVG/c/F/TAF	Statistically significant ↑ in L-spine and hip BMD after 96 wks

Curran A et al. *AIDS*. 2012

Bloch M et al. *HIV Med*. 2014

Brown TT et al. *CROI poster 683*. 2017

To review so far…

- Bone metabolism is driven by an interacting balance of resorption and formation
- HIV+ adults have many traditional risk factors for low BMD
- HIV infection independently alters bone metabolism
- ART initiation leads to drop in BMD
  - TDF and PIs are associated with greatest effects
  - ART switch from these can reverse BMD loss

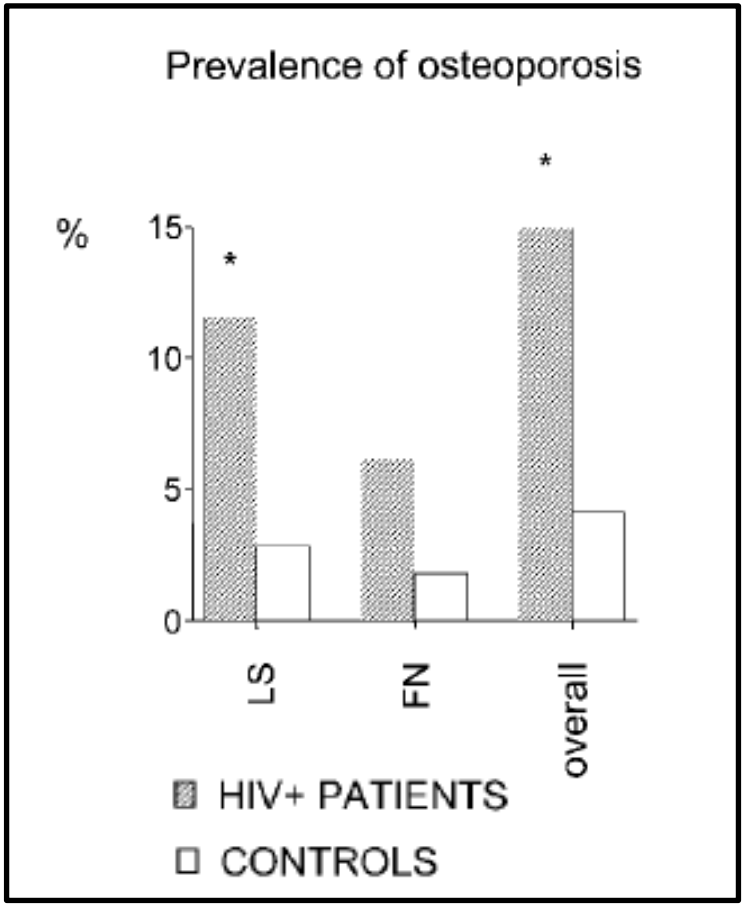
Epidemiology & Clinical Considerations

Clinical Definitions

- **Osteopenia:** mild thinning of the bone. DXA T-score (compared to young healthy adult) between -1 and -2.5 standard deviations
- **Osteoporosis:** severe thinning of bone. DXA T-score $\leq$ -2.5
- **Fragility Fracture:** any fall from a standing height or less, that results in a fracture. Most common sites: hips spine, and wrist.

Epidemiology

- HIV+ men and women have consistently been found to have high rates of low BMD
- Similarly, they also have been found to have higher rates of osteoporosis



Arnsten JH et al. *Clin Inf Dis*. 2006

Anastos K et al. *Antivir Ther*. 2007

Amiel C et al. *J Bone Miner Res*. 2004

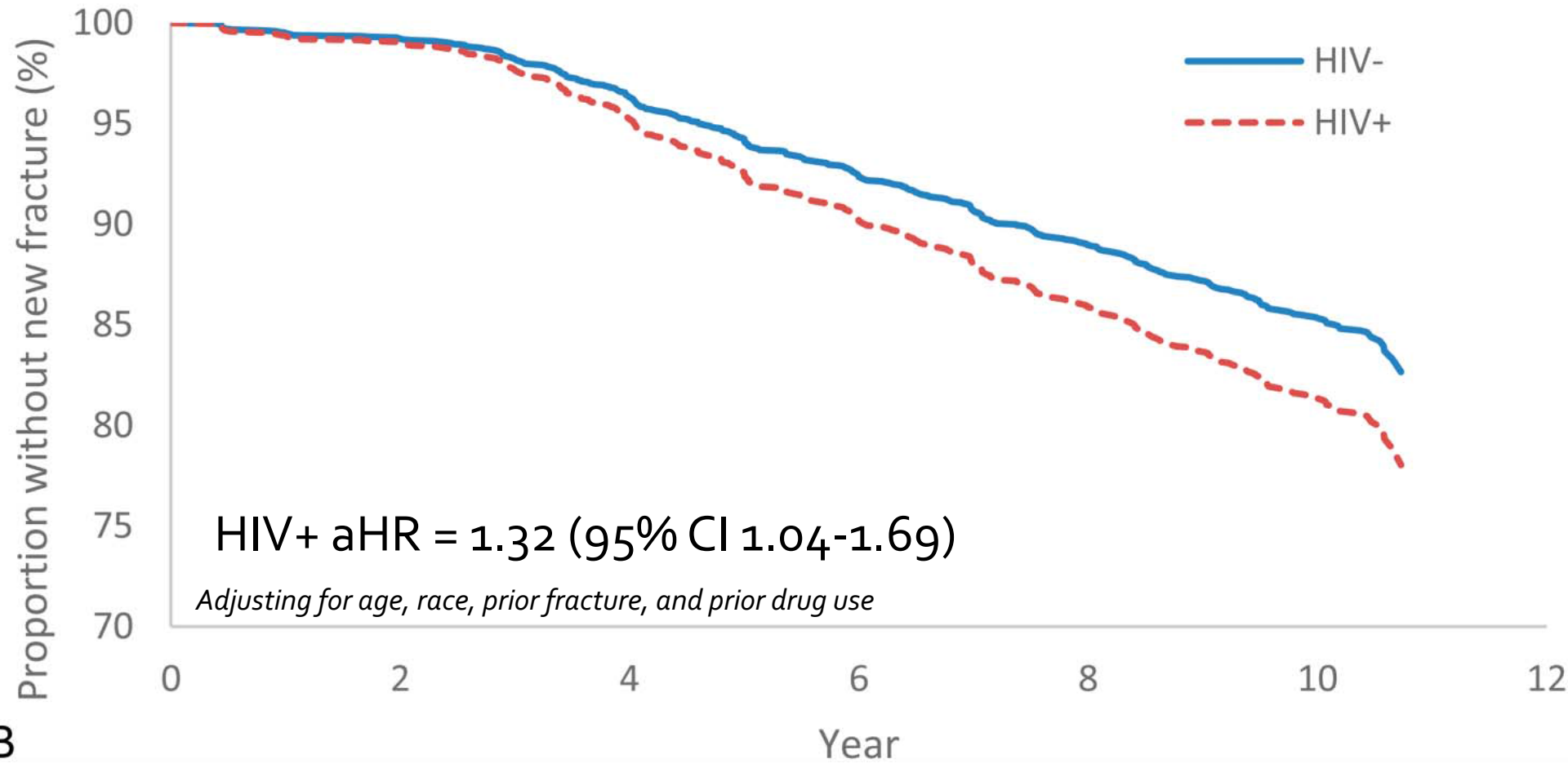
HIV+ & fragility fracture risk

- VACS cohort study – HIV+ (n=40,115) and HIV- (n=79,203) males

	Model 1 HR (95%CI)
HIV infection	**1.32 (1.20-1.47**
Age (per 10yrs)	
White race	
Alcohol abuse	
Liver disease	
Current steroid use	
Smoker	
Any PPI use	
BMI	

Womack JA et al. *PLoS One*. 2011

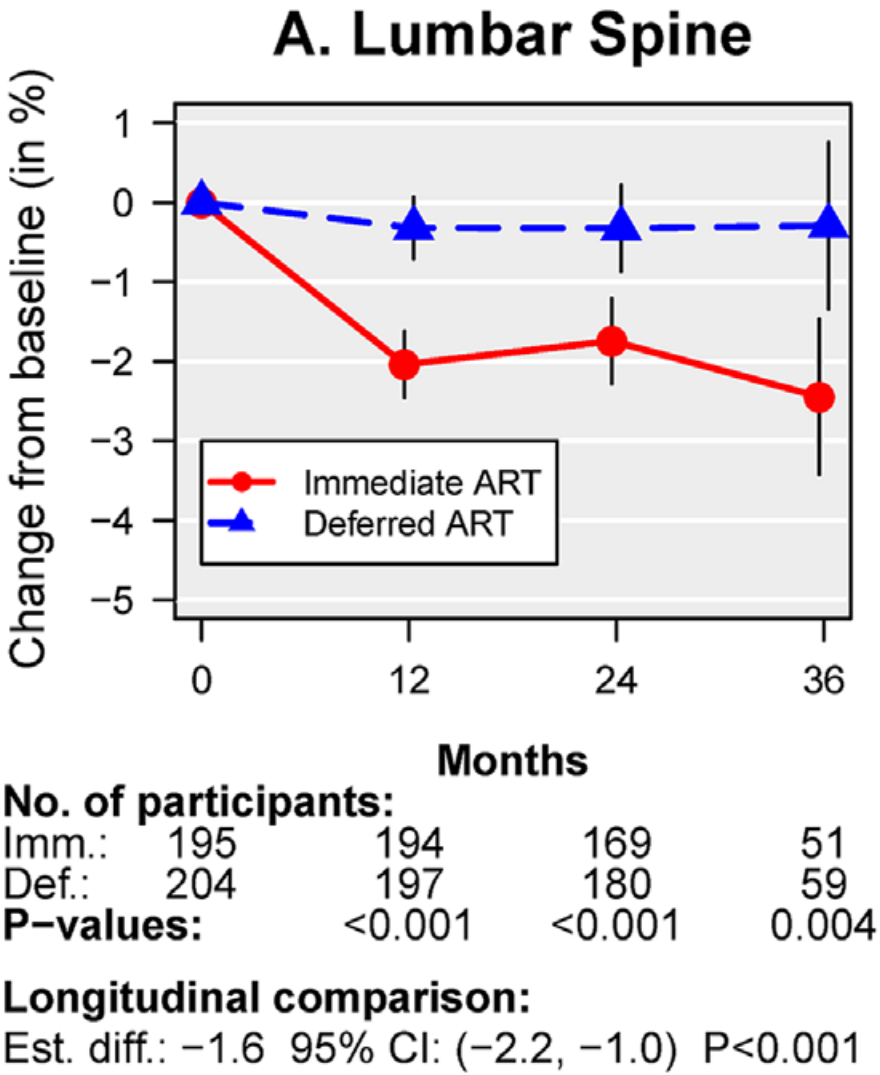
Risk of fractures in HIV+/- women



Sharma A et al. *JAIDS*. 2015

Key risk factors for bone outcomes in HIV+ adults

Osteoporosis (or low BMD)
Older age
White race
BMI
ART initiation (esp TDF and PI use)
Low CD4 & high VL at ART start
Early ART initiation



Grant PM et al. *Clin Inf Dis*. 2013

Hoy JF et al. *J Bone Miner Res*. 2017

Key risk factors for bone outcomes in HIV+ adults

Osteoporosis (or low BMD)
Older age
White race
BMI
ART initiation (esp TDF and PI use)
Low CD_4 & high VL at ART start
Early ART initiation

Fractures	HR or RR range
Age (per 10 yrs)	1.3 – 1.5
White race	1.4-1.9
BMI	0.9
Previous fracture	1.7-3.8
Drugs /cigs/ EtOH	1.3-1.6
Smoking	1.3
HCV / liver disease	1.4-1.6
CD_4 nadir <200 or ADI	1.6-3.1
Current PI	1.4
Current /cum TDF*	**1.1-1.3**
History of falls	**4.9**

Grant PM et al. *Clin Inf Dis*. 2013

Hoy JF et al. *J Bone Miner Res*. 2013

Bedimo R et al. *AIDS*. 2012

Borges AH et al. *Clin Inf Dis*. 2017

Womack JA et al. *PLoS One*. 2011

Arnsten JH et al. *Clin Inf Dis*. 2006

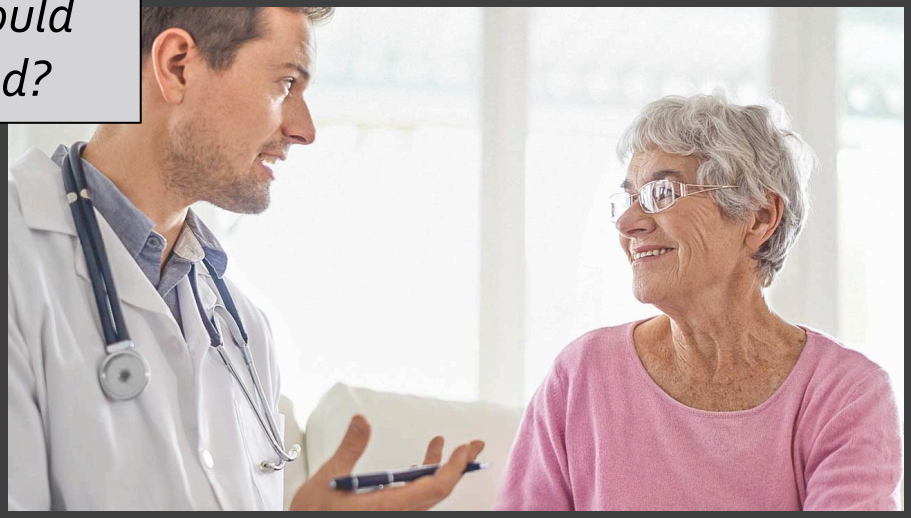
Sharma A et al. *JAIDS*. 2015

Gedmintas L et al. *Osteoporos*. 2017

HIV clinical application

Who should be screened?

When & how should they be screened?



How should they be treated based on those results?

How can BMD loss be prevented?

How can fractures be prevented?

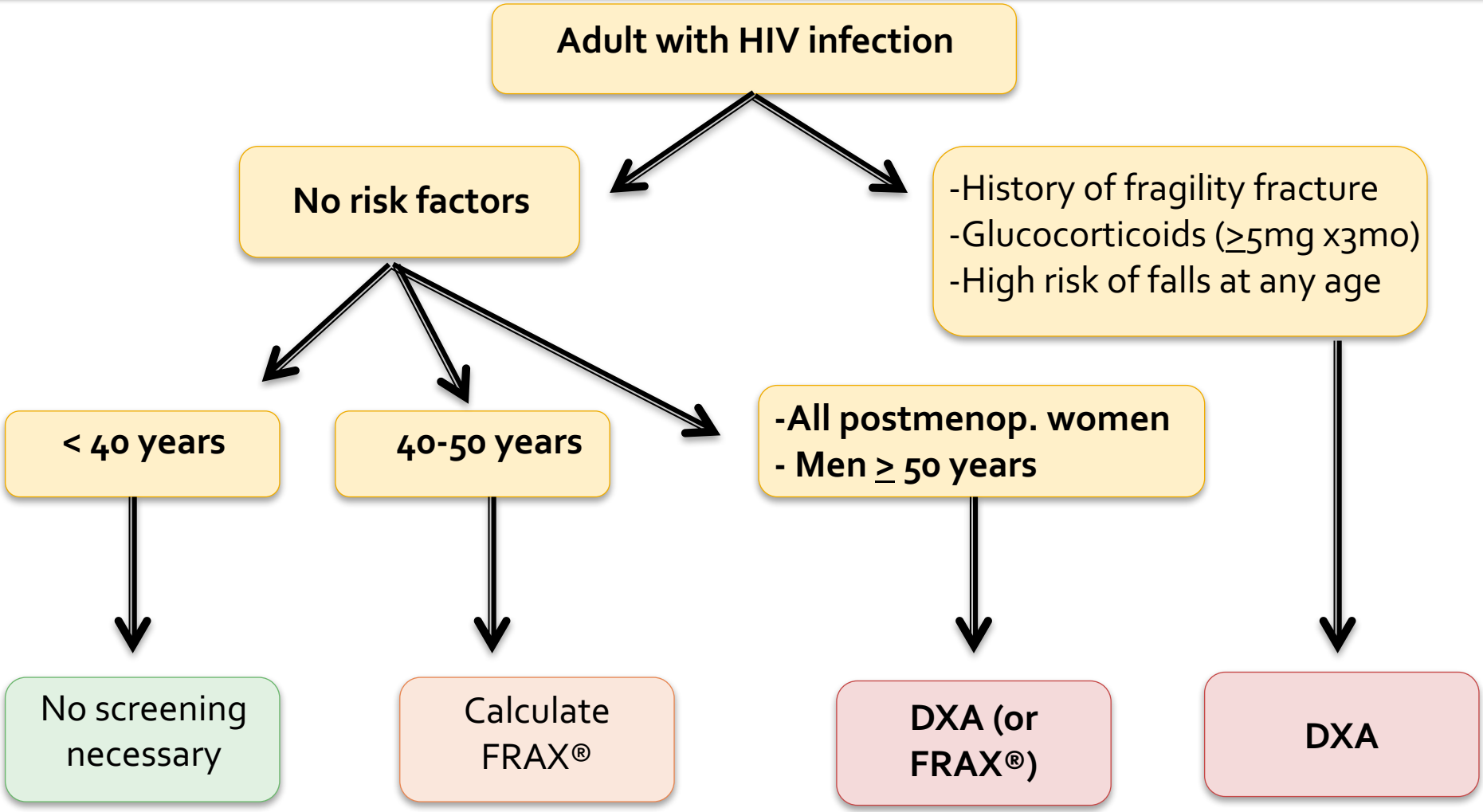
HIV/AIDS INVITED ARTICLE Clinical Infectious Diseases® 2015;60(8):1242–51

Kenneth H. Mayer, Section Editor

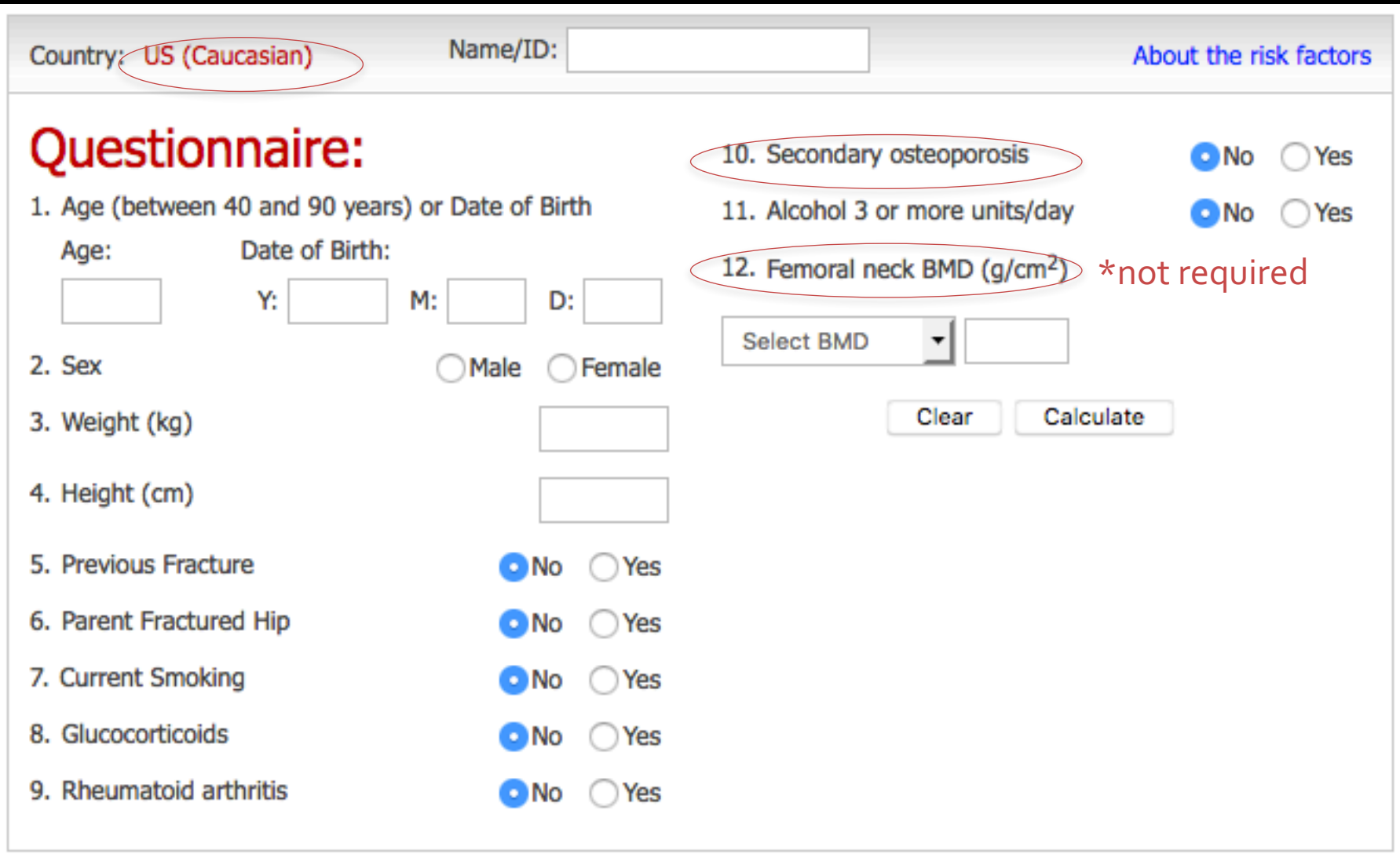
Recommendations for Evaluation and Management of Bone Disease in HIV

Todd T. Brown,[1] Jennifer Hoy,[2] Marco Borderi,[3] Giovanni Guaraldi,[4] Boris Renjifo,[5] Fabio Vescini,[6] Michael T. Yin,[7] and William G. Powderly[8]

Screening


Adult with HIV infection
No risk factors
-History of fragility fracture
-Glucocorticoids (≥5mg x3mo)
-High risk of falls at any age
< 40 years
40-50 years
-All postmenop. women
- Men ≥ 50 years
No screening necessary
Calculate FRAX®
DXA (or FRAX®)
DXA

FRAX® - 10 year fracture risk



Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

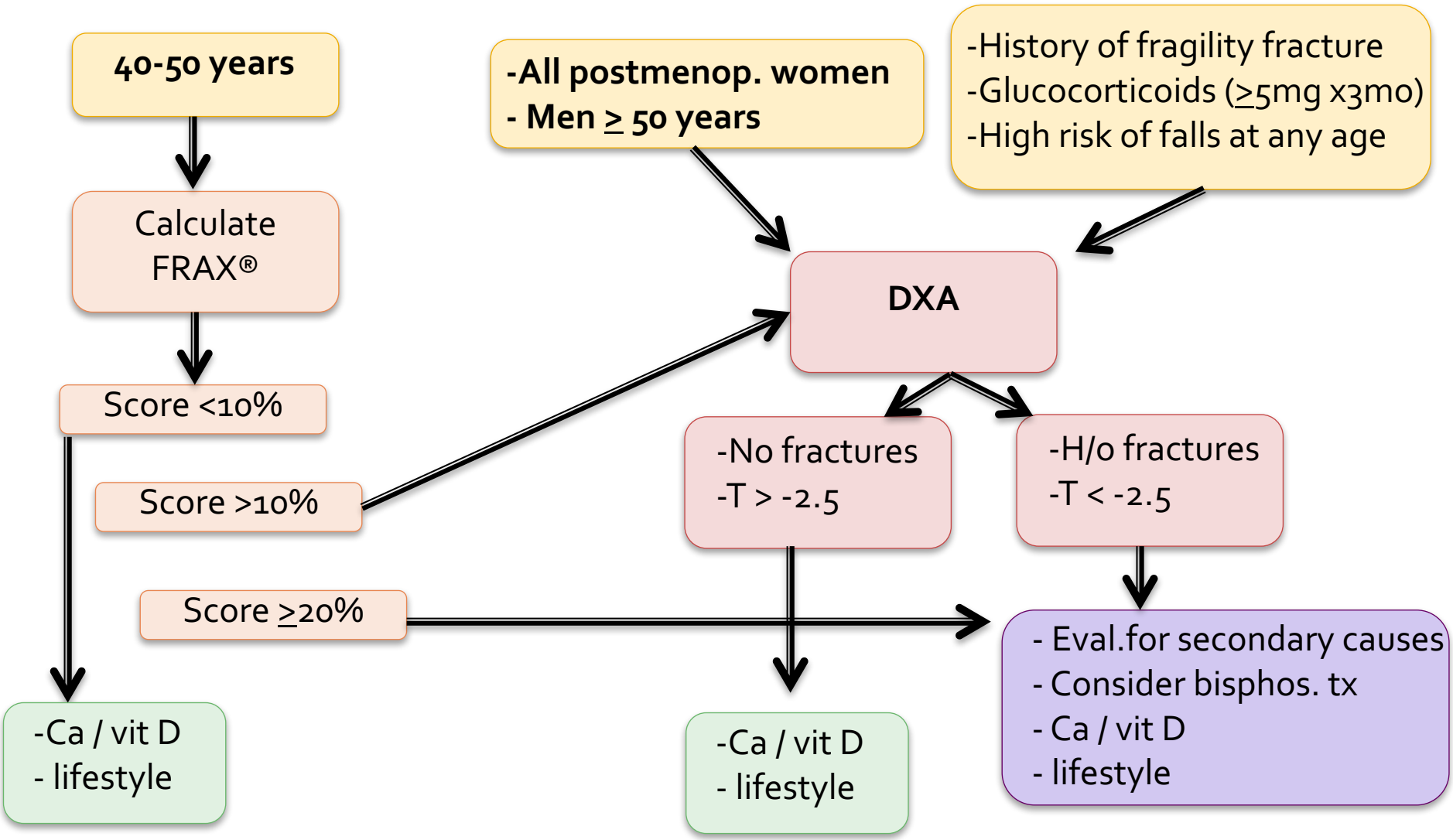
1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex ○ Male ○ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ● No ○ Yes
6. Parent Fractured Hip ● No ○ Yes
7. Current Smoking ● No ○ Yes
8. Glucocorticoids ● No ○ Yes
9. Rheumatoid arthritis ● No ○ Yes
10. Secondary osteoporosis ● No ○ Yes
11. Alcohol 3 or more units/day ● No ○ Yes
12. Femoral neck BMD (g/cm^2) *not required

Select BMD

Clear Calculate

https://www.sheffield.ac.uk/FRAX/tool.aspx?country=23

Assessment & Management



Monitoring

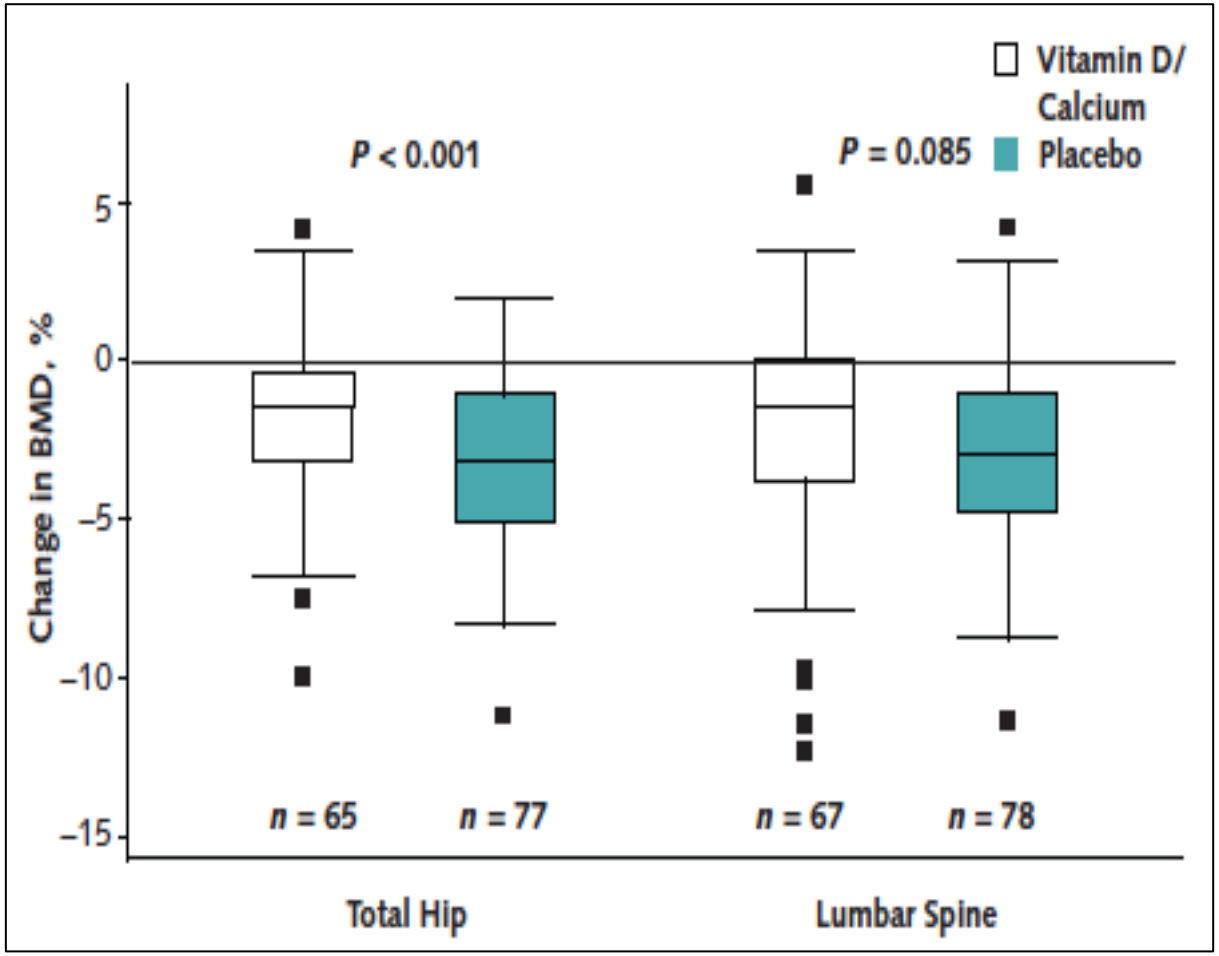
	Group	
LOW	**40-50 years of age** **FRAX® < 10%**	Repeat FRAX® every 2-3 years
MODERATE	**Postmenop. Women** **Men ≥ 50 years** **FRAX® >10%** **DXA with osteopenia**	Repeat DXA in • 1-2 years if advanced osteopenia (Tscore, -2.0 to -2.49) • 5 years if mild-moderate osteopenia (Tscore -1.01 to 1.99)
HIGH	**DXA with osteoporosis** **Started on bisphosphonate**	Repeat DXA in 2 years, reassess indication for continuation in 3-5 years

Prevention

	Group	
LOW	**40-50 years of age** **FRAX® < 10%**	- smoking, EtOH avoidance - regular exercise - check 25-OH vitamin D if at risk
MODERATE	**Postmenop. Women** **Men ≥ 50 years** **FRAX® >10%** **DXA with osteopenia**	- smoking, EtOH avoidance - regular exercise (weight-bearing) - check 25-OH vitamin D, goal = 30 ng/mL - **consider ART switch off TDF & PIs**
HIGH	**DXA with osteoporosis** **Started on bisphosphonate**	- smoking, EtOH avoidance - regular exercise (weight-bearing) - check 25-OH vitamin D, goal = 30 ng/mL - ART switch off TDF & PIs - **falls prevention** (Sedating meds? Stairs? Dementia/depression? Balance?)

Early intervention/prevention?

- 165 ART adults starting EFV/TDF/FTC
- Randomized to Ca/vitD_3 vs. placebo
- Outcome: BMD @ 48 wks



Overton ET et al. *Ann Intern Med*. 2015

Conclusions

- HIV+ adults are at increased risk for low BMD and osteoporosis
  - Traditional risk factors & HIV/ART effects
- ART initiation is associated with a 2-6% BMD loss
- New ARVs (II, TAF) have less effects on BMD
- Screening for osteoporosis and fracture risk begins at age 40-50 years
- Prevention of low BMD and fractures is relevant for all ages

Thank you!