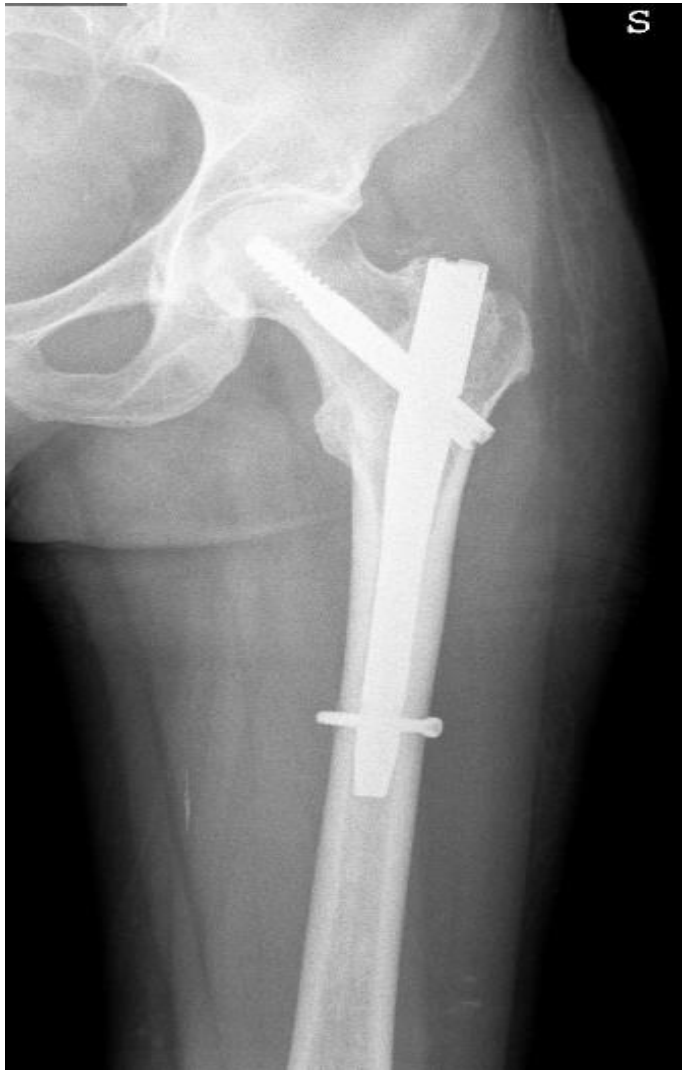
Tra falsi miti e realtà
Danno osseo e HIV: ciò che veramente conosciamo

8° WORKSHOP NAZIONALE CISAI
PERUGIA, 30 - 31 MARZO 2017
Prevenzione e gestione delle co-morbidità associate all'infezione da HIV

Cristina Gervasoni
ASST FBF Sacco

Outline

- **What do I know?**
- What do we know?
- What have we learned lately?



DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	Z - score
L2	15.23	15.63	1.026	0.0	0.6
L3	16.33	16.96	1.038	-0.4	0.3
L4	18.31	17.16	0.938	-1.1	-0.4
Total	**49.87**	**49.75**	**0.997**	**-0.7**	**-0.1**

Total BMD CV 1.0%
WHO Classification: Normal
Fracture Risk: Not Increased

DXA Results Summary:

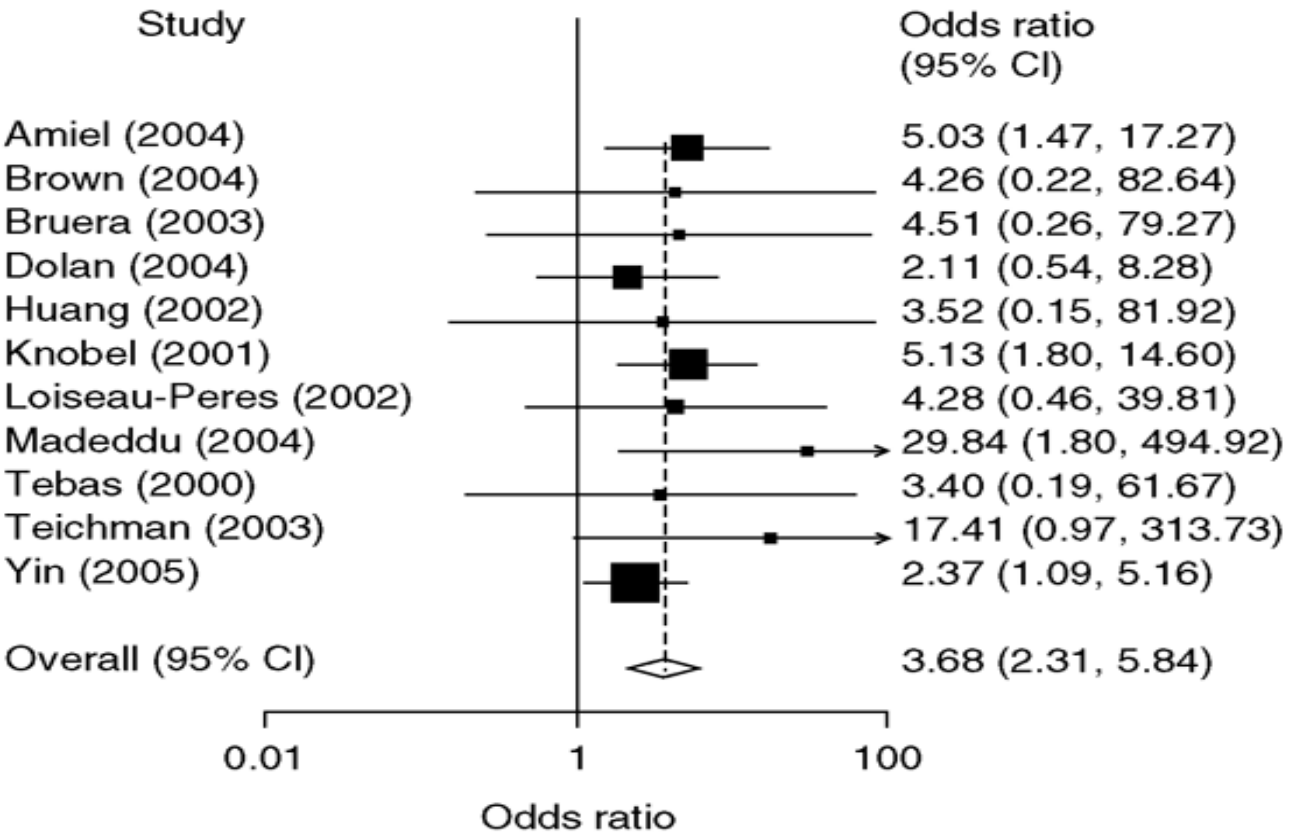
Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	Z - score
Neck	**5.20**	**4.26**	**0.818**	**-0.3**	**0.4**
Total	33.95	30.59	0.901	-0.3	0.1

Total BMD CV 1.0%
WHO Classification: Normal
Fracture Risk: Not Increased

Outline

- **What do we know?**
- What have we learned lately?

Both osteopenia and osteporosis are very common in HIV population



Brown T et al. AIDS 2006.

HIV by itself is associated with osteopenia and osteoporosis

	N=269 *
Age, median (IQR)	38 (31,44)
Male (%)	85%
White non-Hispanic Race (%)	47%
HIV RNA $\log_{10}$ c/mL, median (IQR)	4.62 (4.24,4.90)
HIV RNA ≥ 100,000 c/mL (%)	41%
CD_4 cells/mm³, median (IQR)	233 (106,334)
CD_4 < 200 cells/mm³ (%)	43%
Lumbar spine T score ≤-1 (%)	35%
BMI, Median (IQR)	24.9 (21.8, 28.2)
Limb fat kg, Median (IQR)	7.4 (4.7,10.1)

Baseline prevalence of osteopenia/osteoporosis 35%

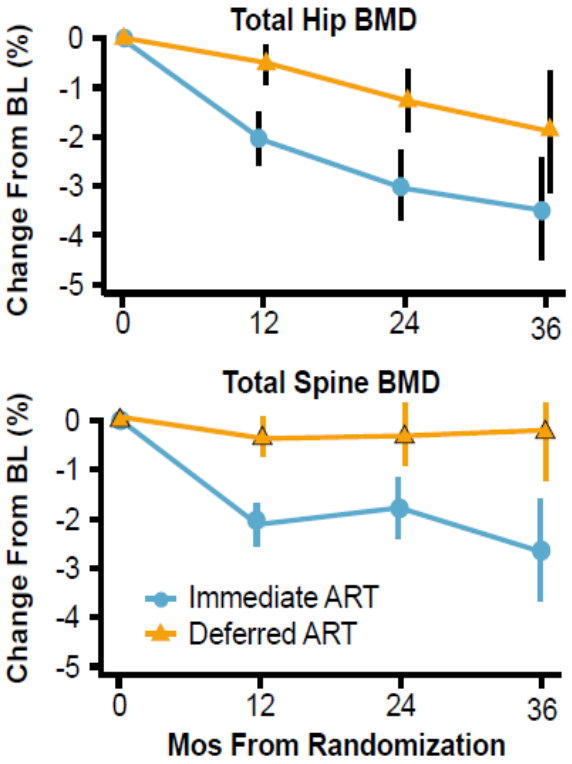
McComsey G et al. J Infect Dis 2011.

When we start ARV therapy patients lose bone

Independently of the regimen

START Substudy

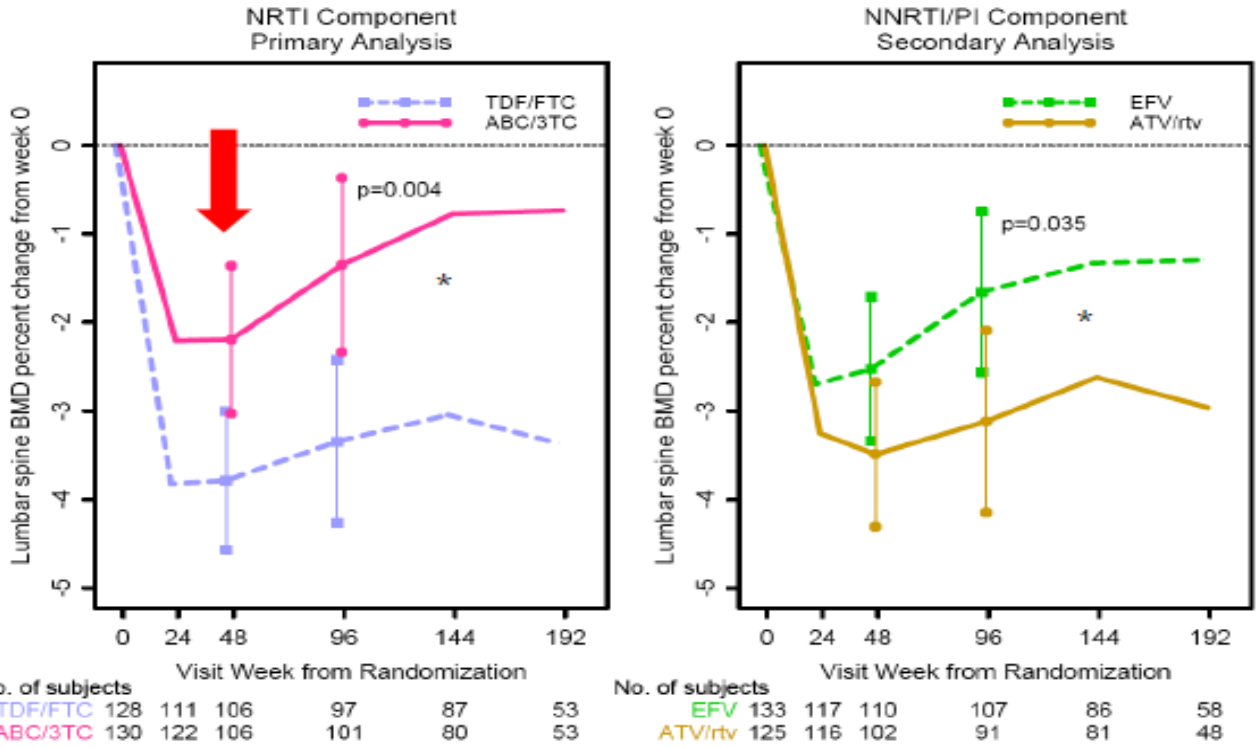
- Substudy included 193 pts in early ART arm and 204 pts in deferred ART arm with f/u
- Greater BMD loss in hip and spine with immediate vs deferred ART
  - Estimated mean difference for hip: -1.5% (95% CI: -2.3% to -0.8%; *P* < .001)
  - Estimated mean difference for spine: -1.6% (95% CI: -2.2% to -1.0%; *P* < .001)
- Osteoporosis incidence similar between arms (*P* = .27)
- PI treatment in first regimen associated with spine BMD decrease



Hoy J et al. 15th European AIDS Conference and 17th International Workshop on Co-morbidities 2015.

When we start ARV therapy patients lose bone

Some drugs more than others



* -linear regression
No significant interaction of NRTI and NNRTI/PI components (p=0.63)

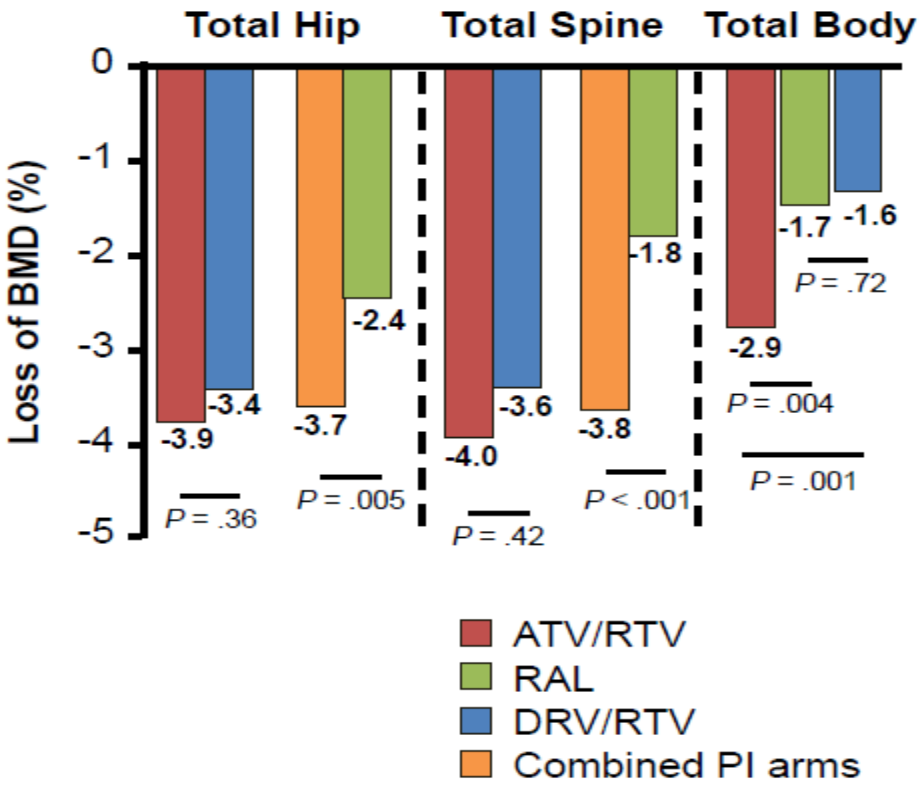
ACTG A5224s
AIDS CLINICAL TRIALS GROUP

McComsey G et al. J Infect Dis 2011.

When we start ARV therapy patients lose bone

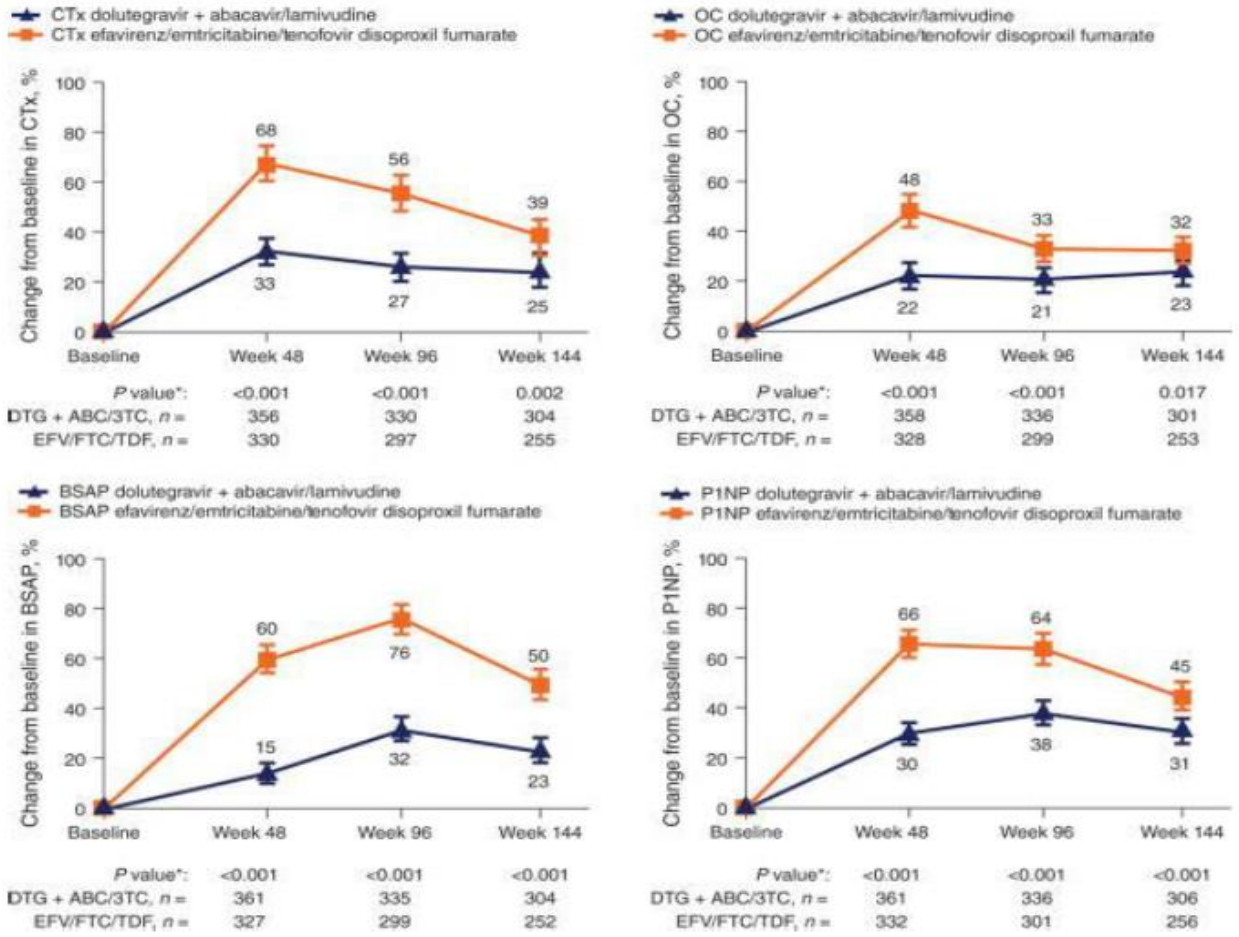
Some drugs more than others

ACTG 5257



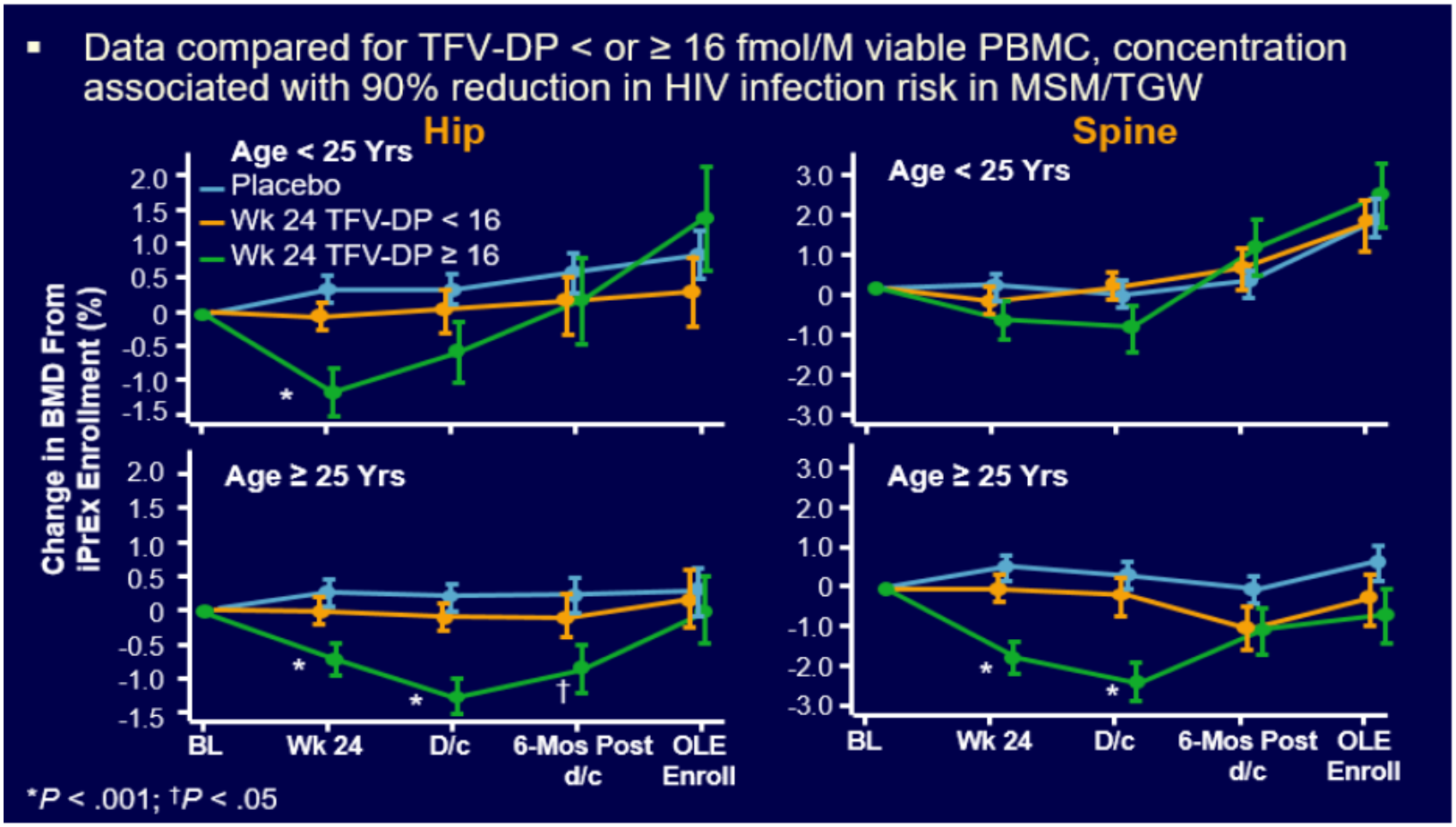
Brown T et al. J Infect Dis 2015.

Starting ARVs induces a state of rapid bone turnover



Tebas P et al. AIDS 2015.

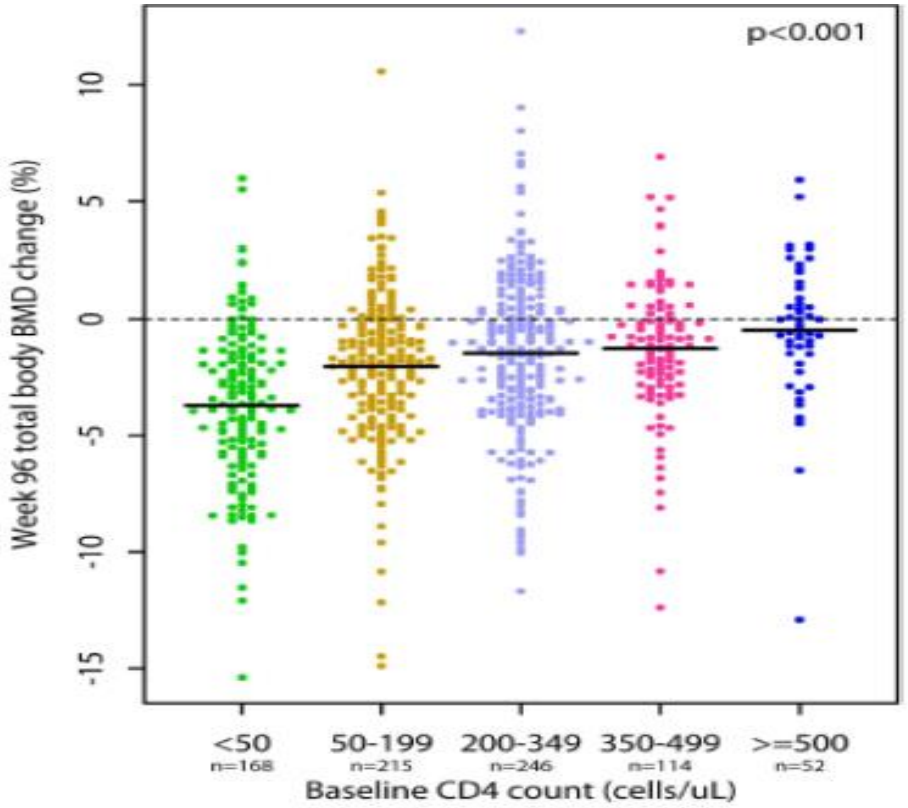
Tenofovir does something to bones independently of HIV (and looks reversible)



Grant R et al. CROI 2016

Some people lose more bone than others

Patients with lower CD4 lose more bone



Week 96 BMD change by baseline CD4 category

Grant P et al. Clin Infect Dis 2013.

Some people lose more bone than others

Patients with higher VL and with more improvement in CD4 lose more bone

Figure 3: Baseline HIV-1 RNA vs. Week 96 BMD change (—— = LOWESS curve)

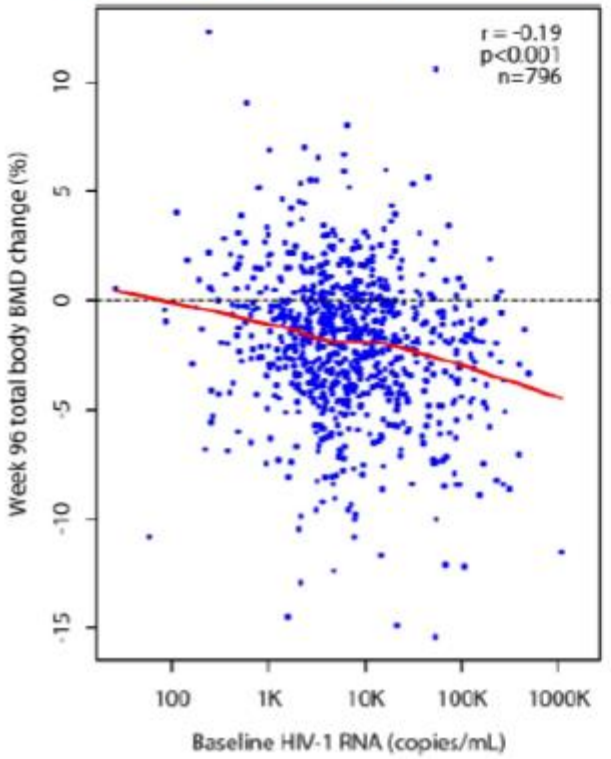
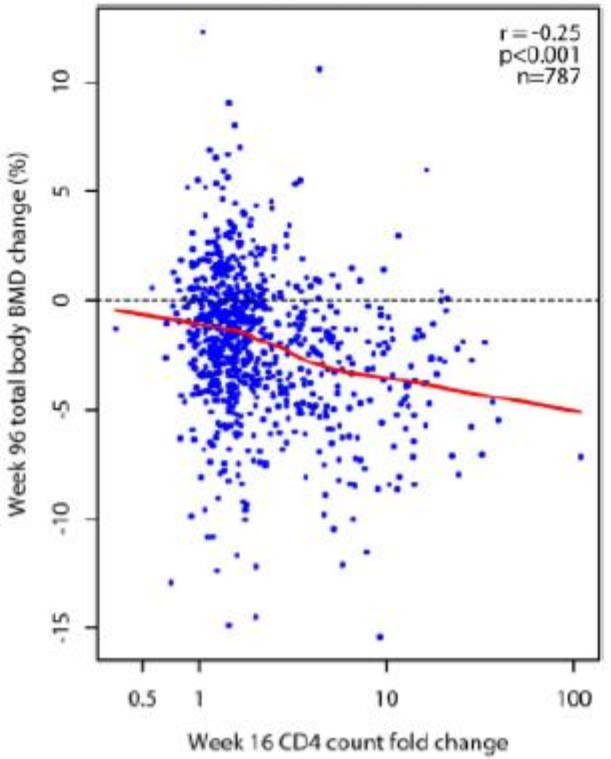


Figure 4: Week 16 CD4 fold change vs. Week 96 BMD change (—— = LOWESS curve)



Grant P et al. Clin Infect Dis 2013.

Some people lose more bone than others

Table 1. Patients characteristics clustered according to the development or not of bone diseases.

Parameters	No bone diseases ($n=48$)	Osteopenia or osteoporosis ($n=150$)	P value
TDF therapy (days)	1683 ± 1417	2209 ± 1109	<0.01
TDF concentrations (ng/ml)	142 ± 136	157 ± 139	0.51
Female sex (%)	47.9%	43.3%	0.33
Age (years)	46 ± 10	51 ± 8	<0.01
Concomitant ARV drugs (%)	50% protease inhibitor 33% NNRTI 17% other	55% protease inhibitor 35% NNRTI 10% other	0.74
BMI (kg/m^2)	23.8 ± 4.6	22.2 ± 3.9	<0.05
Serum creatinine before TDF (mg/dl)	0.80 ± 0.19	0.78 ± 0.19	0.65
Serum creatinine last f.u. (mg/dl)	1.0 ± 0.3	0.9 ± 0.3	0.16
CD4 (cells/μl)	585 ± 252	654 ± 286	0.15
HBV or HCV coinfection (%)	38%	43%	0.51

Significantly higher TDF concentrations were found in patients with altered *vs* normal osteocalcin levels (TDF concentrations: 288±173 vs. 153±115 ng/ml, P<0.01)

Involvement of TDF only in the process of bone formation

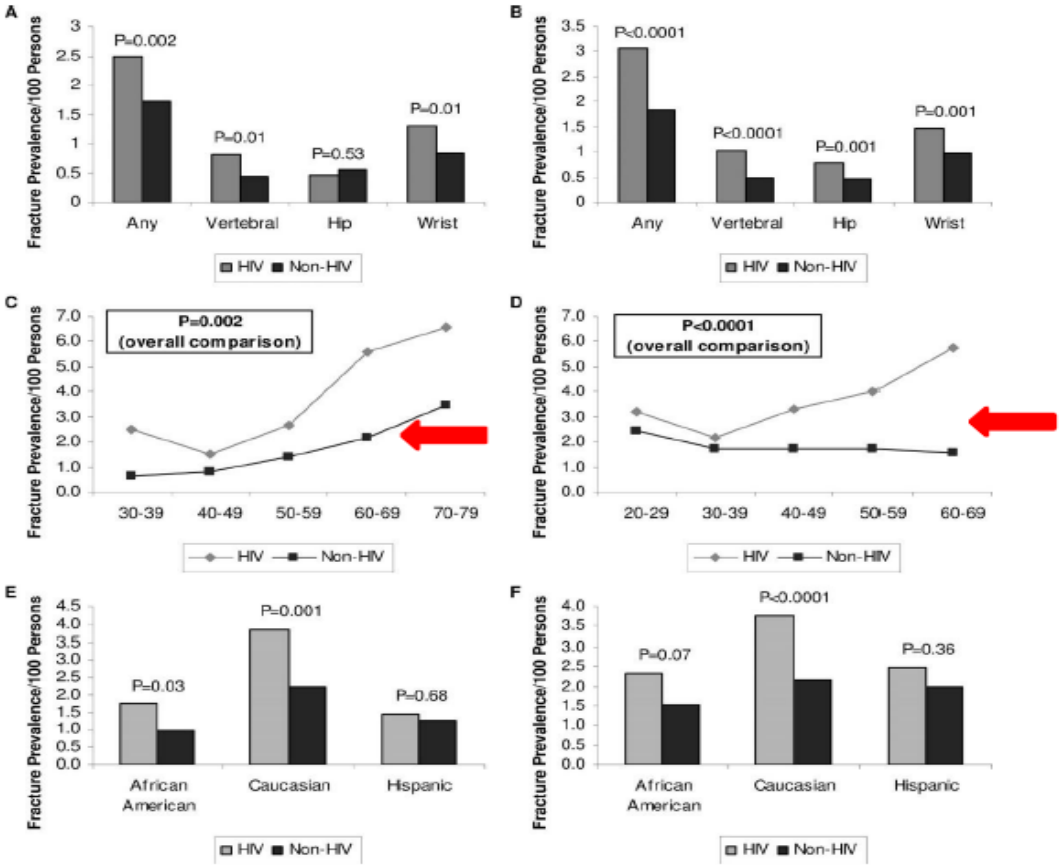
Gervasoni C et al. AIDS 2016.

Risk factors for osteoporosis or fracture

- Advanced age; female sex
- Estrogen deficiency
- Hx fracture as adult
- Hx fragility fracture in 1° relative
- Current cigarette smoking
- Alcoholism
- Low body weight (<127 lbs)
- White race or Asian race
- Low calcium intake
- Low physical activity
- Poor health/frailty; falls
- Poor eyesight (despite correction)
- Dementia; cognitive impairment
- Impaired neuromuscular fxn
- Residence in nursing home
- Hx glucocorticoids >3 mos
- Long-term heparin therapy
- Anticonvulsant therapy
- Aromatase-inhibitor therapy
- Androgen-deprivation therapy

This problem is clinically relevant

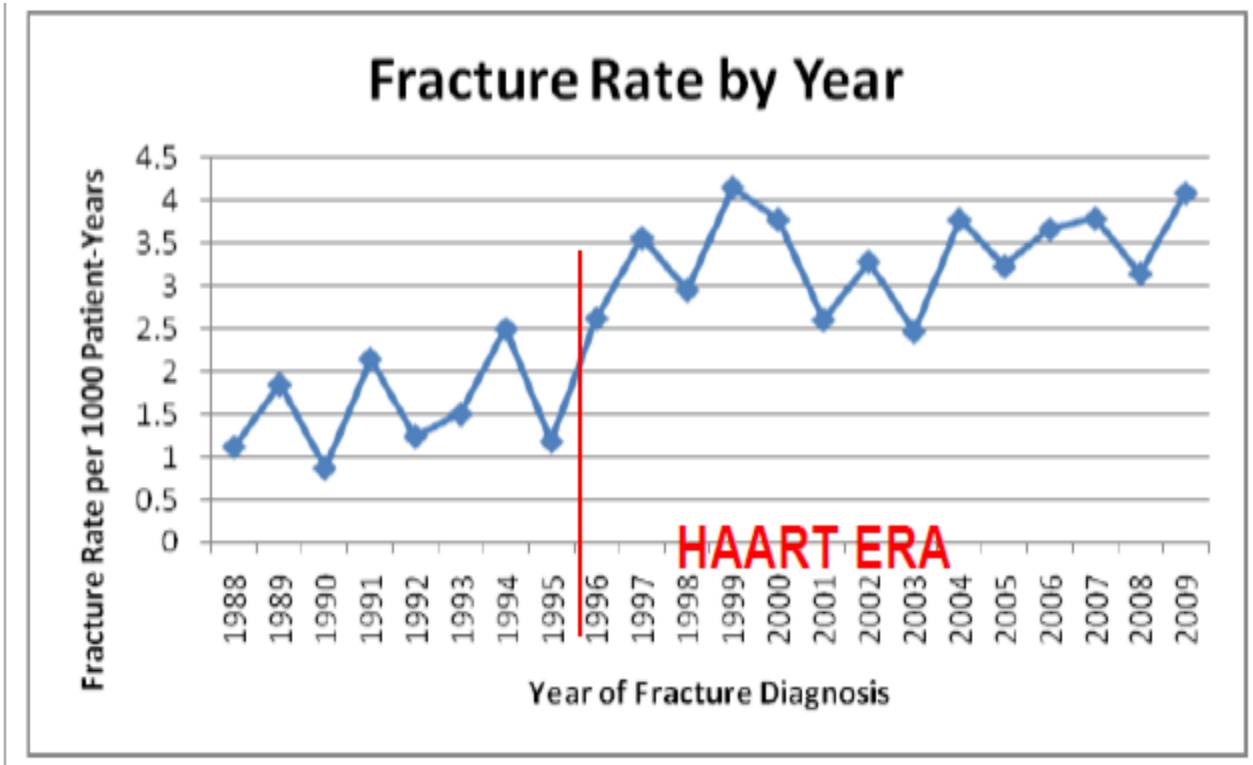
Patients with HIV have more fractures than non HIV



Traint VA et al. J Clin Endocrinol Metab 2008.

The rate of fractures has increased in the HAART era

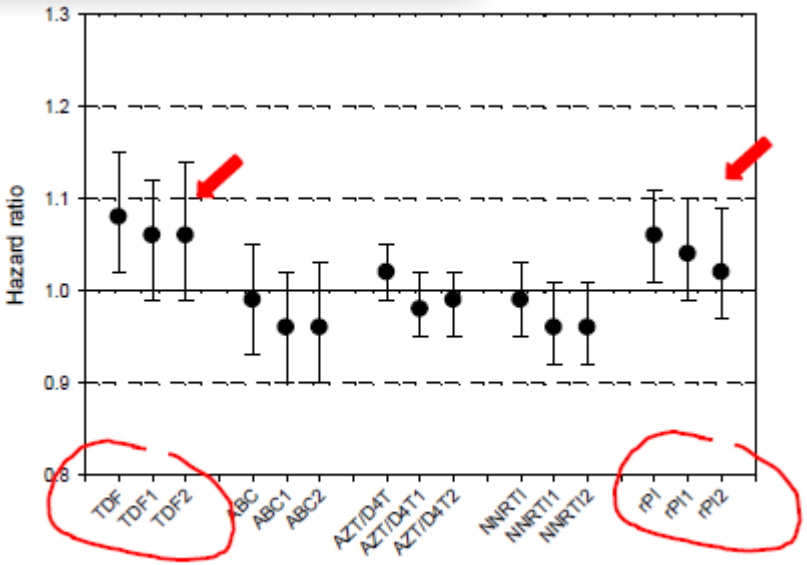
VA cohort Study



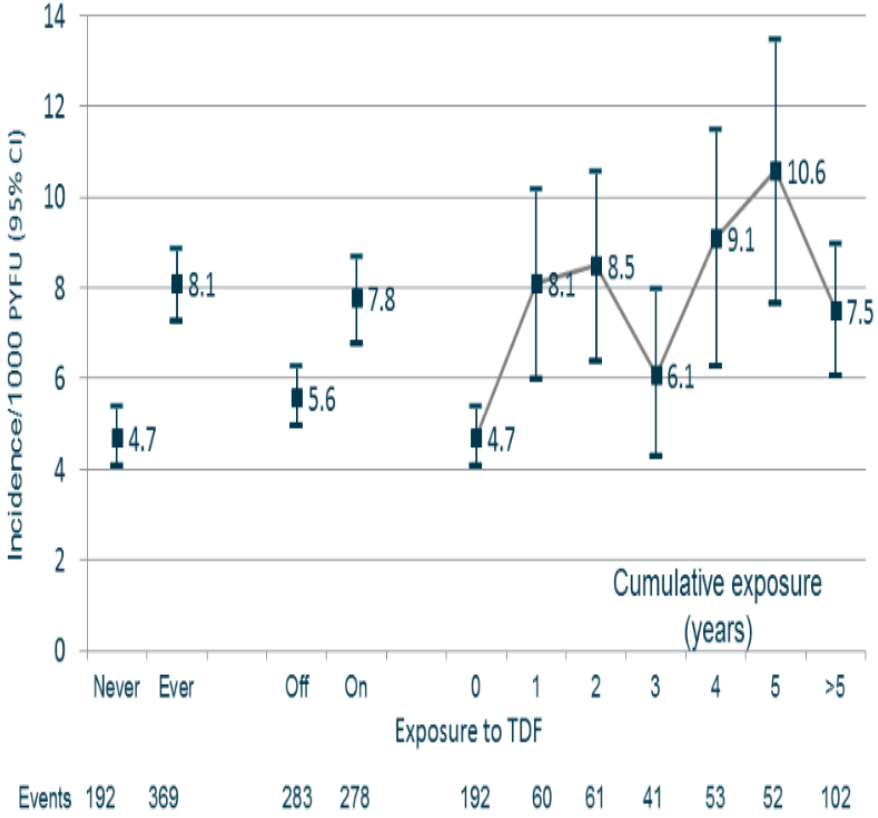
Bedimo R et al. AIDS 2012.

Tenofovir is associated with an increased the risk of fracture

VA cohort Study



EuroSIDA cohort



Bedimo R et al. AIDS 2012.

Borges AH et al. CID 2017.

Outline

- What do we know?
- **What have we learned lately?**

The pathogenic mechanism is probably immune reconstitution (plus bone toxicity of tenofovir)

ARTICLE

Received 18 Oct 2014 | Accepted 4 Aug 2015 | Published 22 Sep 2015

Role of T-cell reconstitution in HIV-1 antiretroviral therapy-induced bone loss

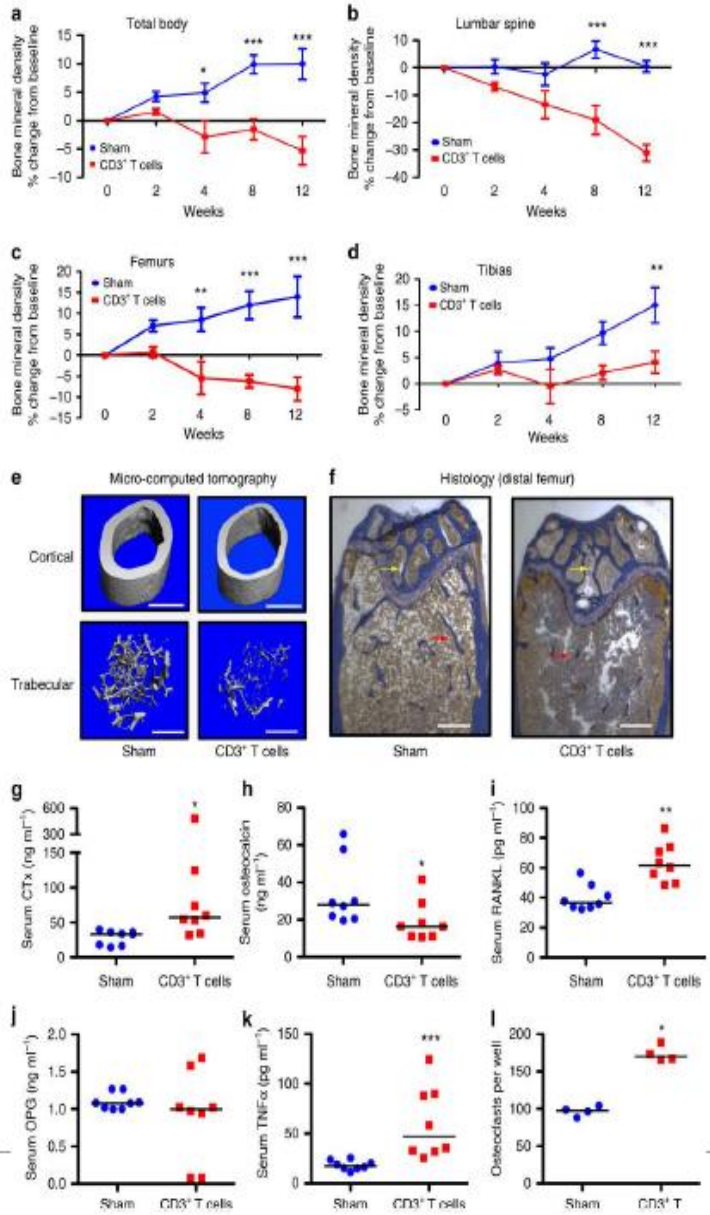
Ighovwerha Ofotokun[1,2,*], Kehmia Titanji[3,**], Tatyana Vikulina[3,**], Susanne Roser-Page[4,**], Masayoshi Yamaguchi[3], Majd Zayzafoon[5], Ifor R. Williams[6] & M. Neale Weitzmann[3,4,*]

What they did:

- transplant T cells into immunocompromised mice to mimic ART-induced T-cell expansion

What they saw:

- Bone loss associated with the reconstitution

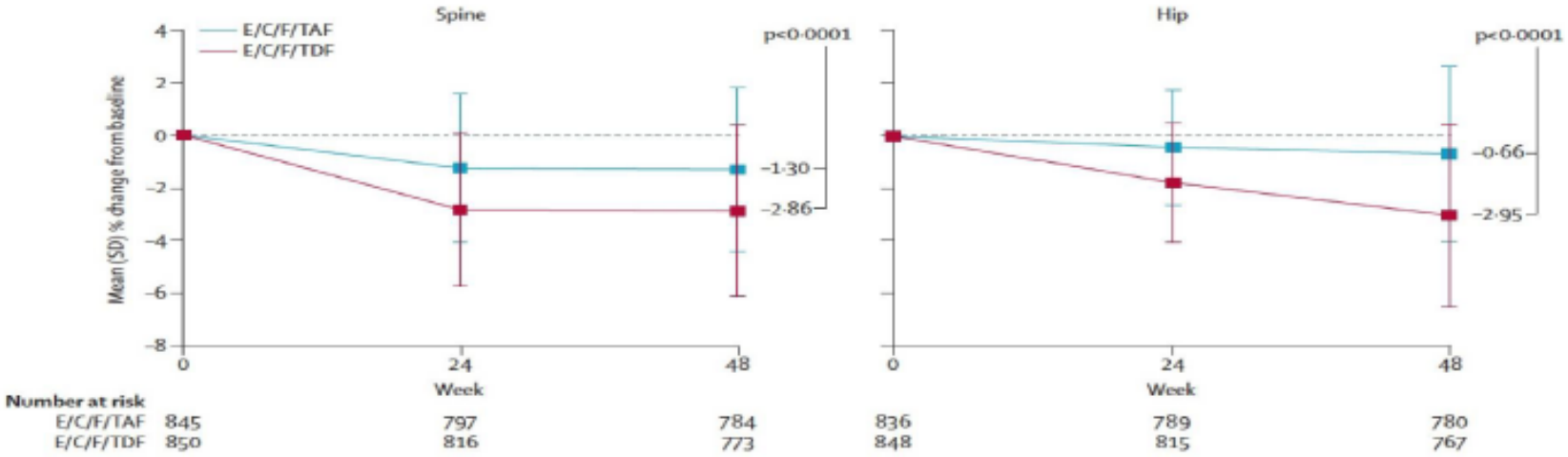


AIDS. 2016 Jan 28;30(3):405-14. doi: 10.1097/QAD.0000000000000918.

Antiretroviral therapy induces a rapid increase in bone resorption that is positively associated with the magnitude of immune reconstitution in HIV infection.

Ofotokun I[1], Titanji K, Vunnava A, Roser-Page S, Vikulina T, Villinger F, Rogers K, Sheth AN, Lahiri CD, Lennox JL, Weitzmann MN.

TAF is more bone friendly than TDF (naïve)
(GS-104-111)



BMD decline > 5 %

E/C/F/TAF: 10% spine; 7% hip

E/C/F/TDF: 22% spine; 19% hip

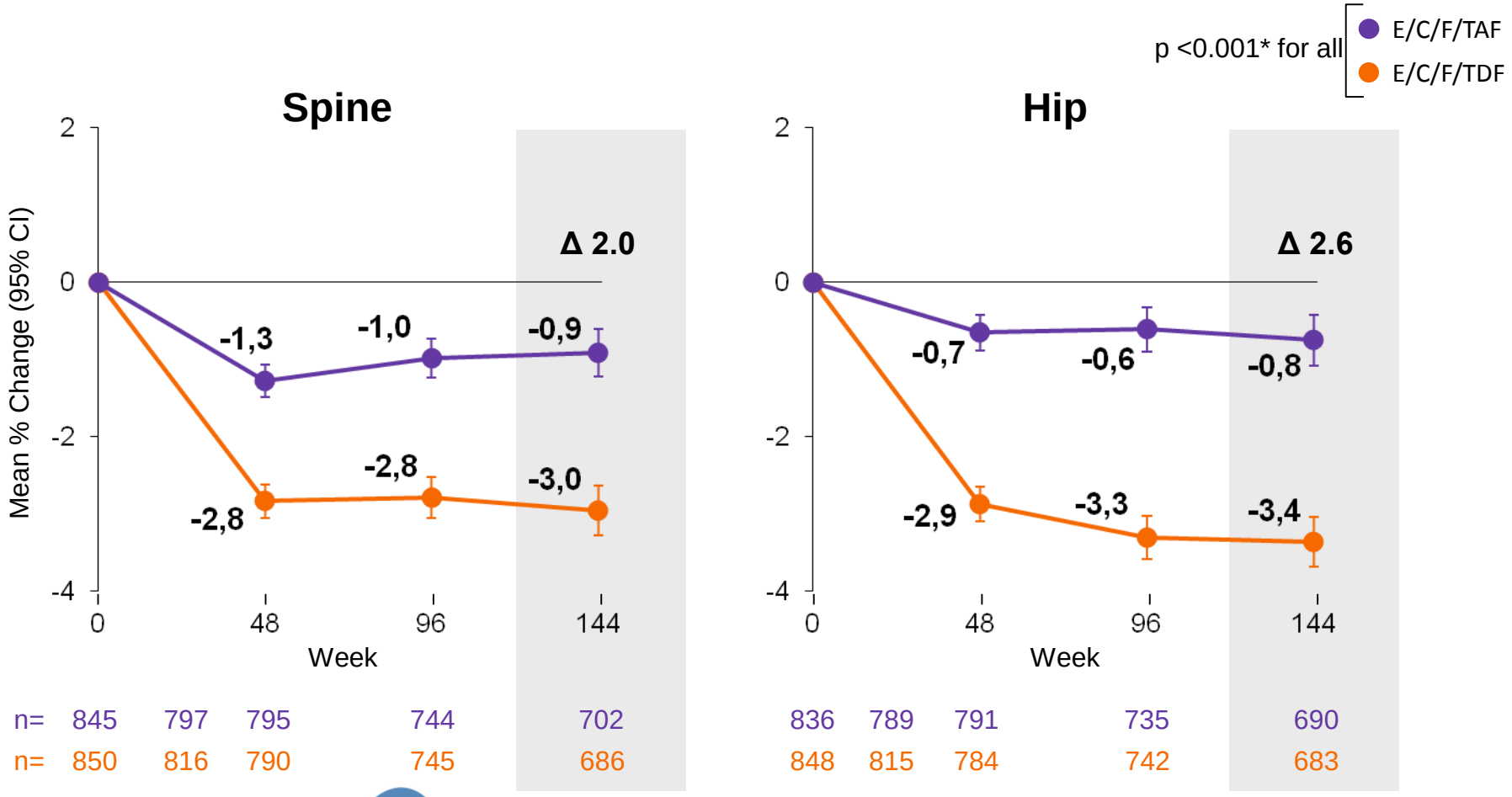
Fractures

E/C/F/TAF: 7 (0.8%)

E/C/F/TDF: 12 (1.4%)

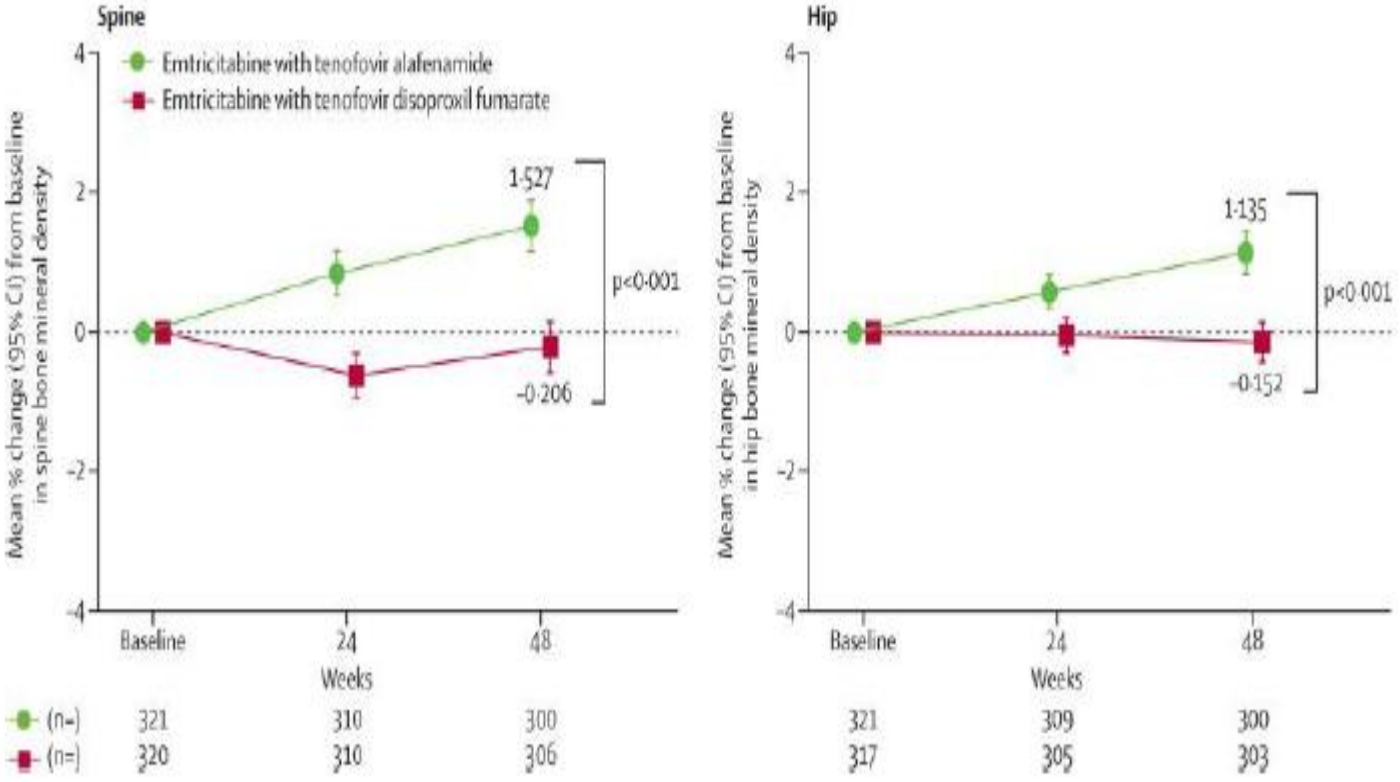
Sax P et al. Lancet 2015.

TAF is more bone friendly than TDF (naïve) (GS-104-111)



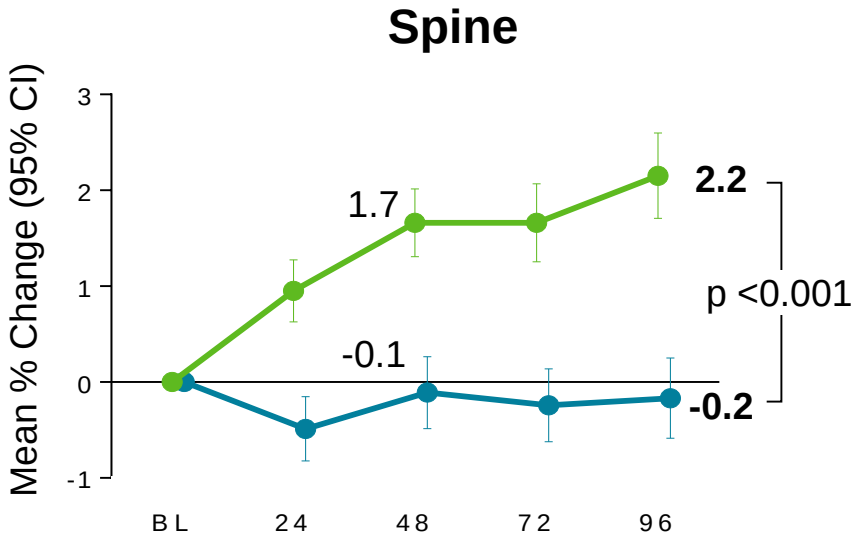
Arribas J, et al. CROI 2017. Seattle, WA. Poster #453

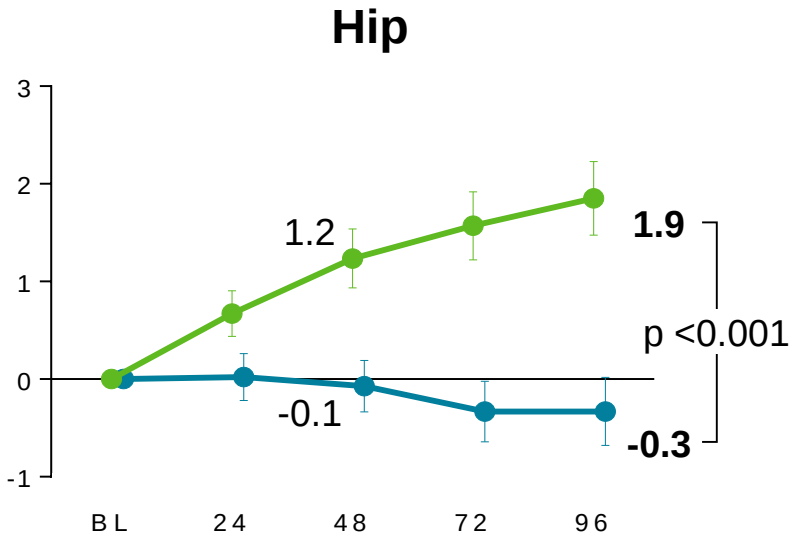
TAF is more bone friendly than TDF (switch)
(GS-1089)



Gallant et al. Lancet HIV 2016

TAF is more bone friendly than TDF (switch) (GS-1089)





n					
FTC/TAF	321	310	300	294	287
FTC/TDF	320	310	306	297	292

n					
FTC/TAF	321	309	300	293	288
FTC/TDF	317	305	303	296	289

	FTC/TAF	FTC/TDF	p value
≥ 3% increase	40%	18%	< 0.001
≥ 3% decrease	8%	19%	< 0.001

	FTC/TAF	FTC/TDF	p value
≥ 3% increase	29%	11%	< 0.001
≥ 3% decrease	6%	15%	< 0.001

Raffi, F, et al. HIV Drug Therapy 2016. Glasgow UK. O125

TAF is more bone friendly than TDF (switch in low BMD)

(GS-112-109 pooled analysis)

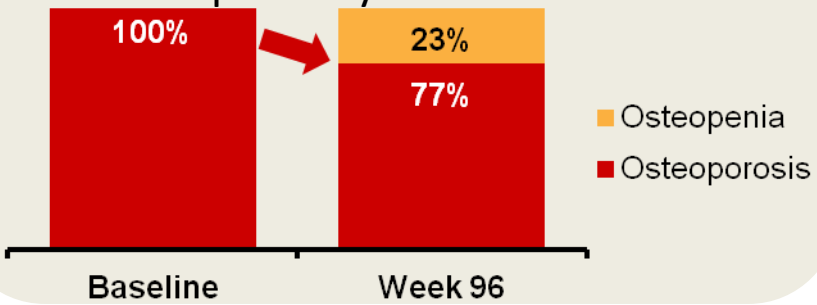
Analysis of outcomes and predictors of clinically significant BMD increases (≥5%) at W96 in the 214 subjects with low baseline BMD (T-score ≤ -2.0) in pooled TAF studies (E/C/F/TAF Studies 109 and 112)

Baseline T-score ≤ -2.0

- Significant BMD increases observed
  - Spine: +2.53% (p<0.001)
  - Hip: +2.39% (p<0.001)
- Proportion of low BMD participants experiencing ≥5% BMD increase
  - Spine: 27% (52/193)
  - Hip: 16% (32/195)

Baseline T-score ≤ -2.5

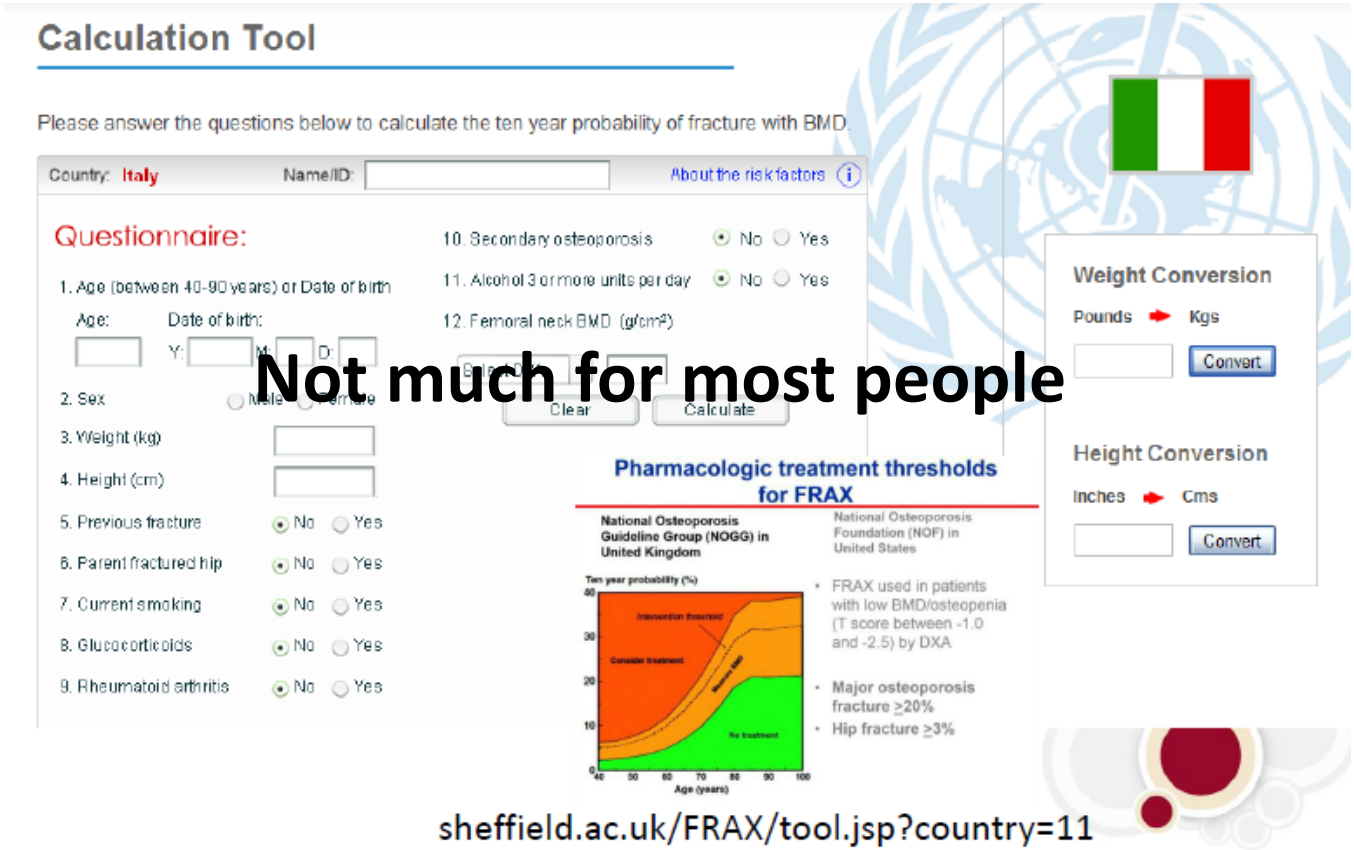
- 86 subjects with low baseline BMD also had osteoporosis*
  - 23% of these subjects improved to osteopenia by Week 96



- Factors predicting ≥5% BMD increase after a switch from TDF to TAF:
  - Urinary phosphate wasting ($FEPO_4$ ≥ 10%) or
  - High bone turnover (P1NP levels >1.72 $\log_{10}$ ng/mL)

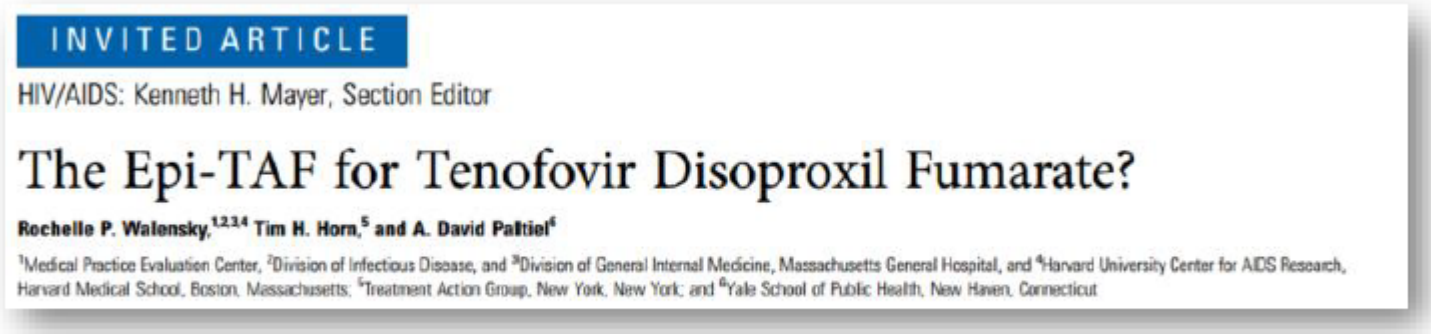
Brown T, et al. CROI 2017. Seattle, WA. Poster #683

How clinically important is this %?



sheffield.ac.uk/FRAX/tool.jsp?country=11

Cost implications



INVITED ARTICLE

HIV/AIDS: Kenneth H. Mayer, Section Editor

The Epi-TAF for Tenofovir Disoproxil Fumarate?

Rochelle P. Walensky,[1,2,3,4] Tim H. Horn,[5] and A. David Paltiel[6]

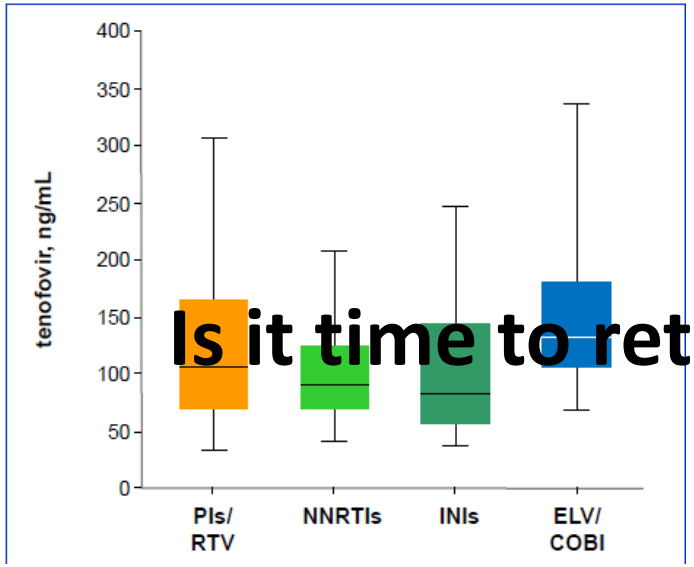
[1]Medical Practice Evaluation Center, [2]Division of Infectious Disease, and [3]Division of General Internal Medicine, Massachusetts General Hospital, and [4]Harvard University Center for AIDS Research, Harvard Medical School, Boston, Massachusetts; [5]Treatment Action Group, New York, New York; and [6]Yale School of Public Health, New Haven, Connecticut

- Using cost-effectiveness methods, we find that current conditions warrant an annual premium of up to $1000 over the average wholesale price (AWP) of TDF.
- Once generic coformulations of tenofovir/lamivudine become accessible, however, the appropriate premium for TAF will likely merit a downward adjustment

Walensky R et al. CID 2016.

Effect of cobicistat on tenofovir plasma concentrations: a cross-sectional study

Cristina Gervasoni[1], Davide Minisci[2], Sara Baldelli[2], Cristina Mazzali[2], Andrea Giacomelli[1], Laura Milazzo[1], Paola Meraviglia[1], Emilio Clementi[2], Massimo Galli[1], Dario Cattaneo[2]
[1]Department of Infectious Diseases and [2]Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy;
[3]Department of Management, Economics and Industrial Engineering (DIG), Politecnico di Milano



	Univariate analysis			Multivariate analysis		
	beta	SD	p-value	beta	SD	p-value
Concomitant ART			<.001			<.001
- COBICISTAT vs PI	0.21	0.08	0.011	0.29	0.08	0.001
- INI vs PI	-0.18	0.10	0.064	-0.20	0.10	0.046
- NNRTI vs PI	-0.17	0.06	0.007	-0.12	0.06	0.056
Gender (F vs M)	0.14	0.06	0.026	0.20	0.08	0.011
Co-infections (NO vs YES)	0.08	0.06	0.187	0.08	0.06	0.153
CD4 cell count			0.888			
- [250-500] vs [>500]	0.00	0.06	0.628			
- [250-500] vs [>500]	0.004	0.06	0.950			
Viral load (>=37 vs <37)	-0.004	0.08	0.996			
Days of TDF therapy			0.669			
- <=1yr vs >6yrs	-0.04	0.08	0.599			
- (1yr-3yrs] vs >6yrs	0.06	0.08	0.457			
- (3yr-6yrs] vs >6yrs	-0.03	0.08	0.718			
Patients' age	0.01	0.002	0.002	0.01	0.003	0.001
Body weight	-0.006	0.002	0.002	-0.01	0.002	0.014
Serum creatinine	0.53	0.10	<.001	0.57	0.11	<.001

SD: standard deviation; ART: antiretroviral therapy; PI: protease inhibitors; INI: integrase inhibitors (excluding elvitegravir [ELV]); NNRTI: non nucleoside reverse transcriptase inhibitors

Is it time to rethink at TAF trials?

Should we start/switch everybody to TAF?

- Yes
- No
- Not yet

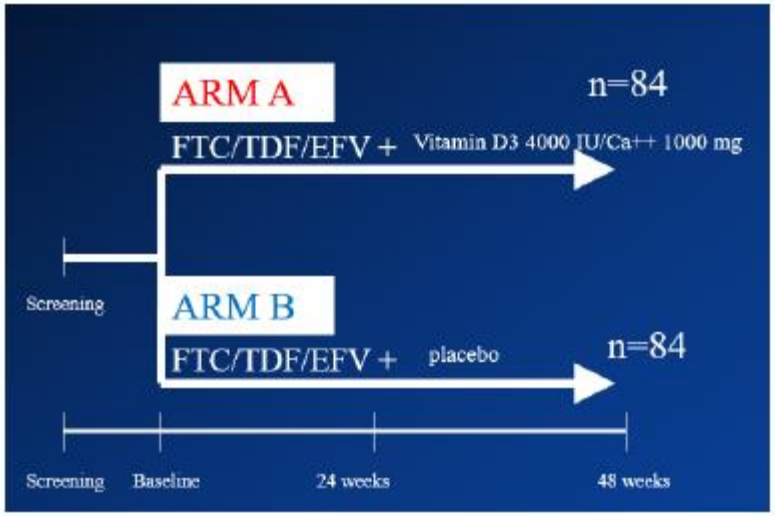
Bone loss can be partially prevented with vitamin D and Ca^{++}

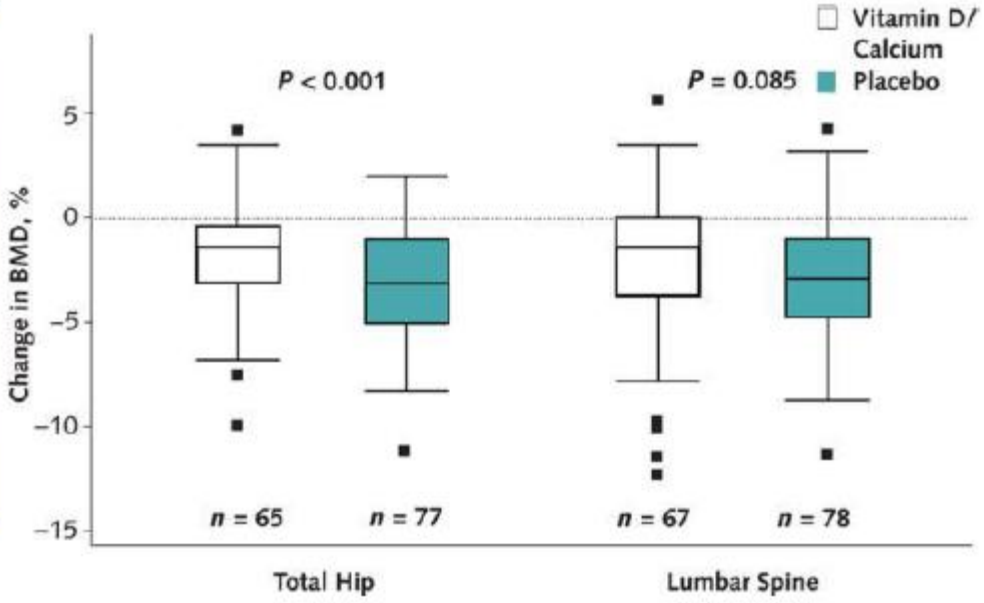
Annals of Internal Medicine ORIGINAL RESEARCH

Vitamin D and Calcium Attenuate Bone Loss With Antiretroviral Therapy Initiation

A Randomized Trial

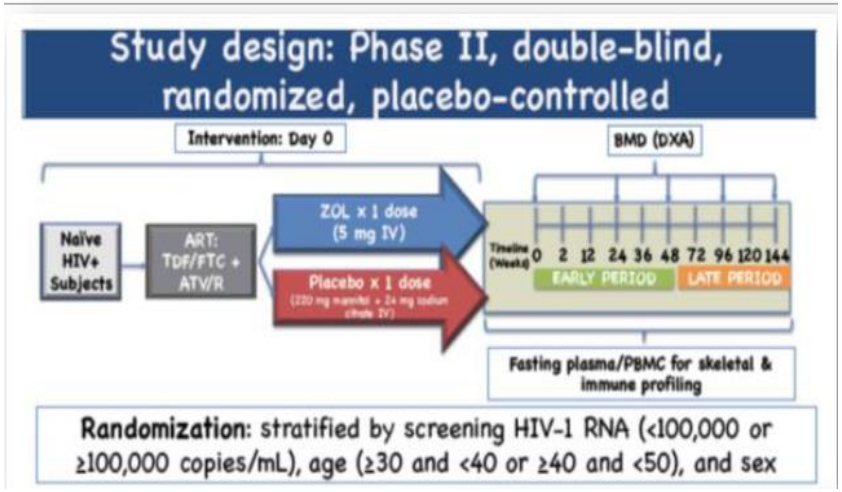
Edgar Turner Overton, MD; Ellen S. Chan, MSc; Todd T. Brown, MD, PhD; Pablo Tebas, MD; Grace A. McComsey, MD; Kathleen M. Melbourne, PharmD; Andrew Napoli, PhD; William Royce Hardin, BS; Heather J. Ribaudo, PhD; and Michael T. Yin, MD, MS

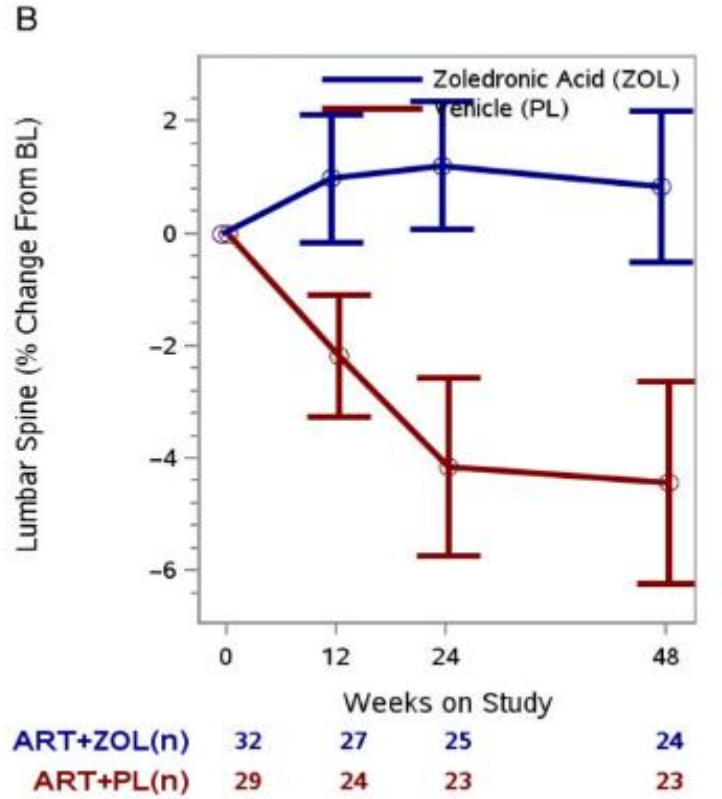




Overton E T et al. Annals of Int Med 2015.

Bone loss can be prevented with a single dose of zoledronic acid





Ofotokun I et al. CID 2016.

Should we do any of those?

- Yes
- No
- Not yet

HIV/AIDS INVITED ARTICLE

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]

[1]Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia; [3]Infectious Diseases Unit, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, and [4]Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; [5]Global Medical Affairs Virology, Global Pharmaceutical Research and Development, AbbVie, North Chicago, Illinois; [6]Endocrinology and Metabolism Unit, University Hospital "Santa Maria della Misericordia," Udine, Italy; [7]Department of Medicine, Columbia University Medical Center, New York, New York; and [8]Division of Infectious Diseases, Washington University School of Medicine, St Louis, Missouri

Thirty-four human immunodeficiency virus (HIV) specialists from 16 countries contributed to this project, whose primary aim was to provide guidance on the screening, diagnosis, and monitoring of bone disease in HIV-infected patients. Four clinically important questions in bone disease management were identified, and recommendations, based on literature review and expert opinion, were agreed upon. Risk of fragility fracture should be assessed primarily using the Fracture Risk Assessment Tool (FRAX), without dual-energy X-ray absorptiometry (DXA), in all HIV-infected men aged 40–49 years and HIV-infected premenopausal women aged ≥40 years. DXA should be performed in men aged ≥50 years, postmenopausal women, patients with a history of fragility fracture, patients receiving chronic glucocorticoid treatment, and patients at high risk of falls. In resource-limited settings, FRAX without bone mineral density can be substituted for DXA. Guidelines for antiretroviral therapy should be followed; adjustment should avoid tenofovir disoproxil fumarate or boosted protease inhibitors in at-risk patients. Dietary and lifestyle management strategies for high-risk patients should be employed and antiosteoporosis treatment initiated.

Keywords. bone disease; fragility fracture; human immunodeficiency virus; osteoporosis.

Clinical Infectious Diseases 2015.