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Update on Bone Health

Peter R Ebeling AO MD

Head, Department of Medicine,
School of Clinical Sciences
Monash University, Australia

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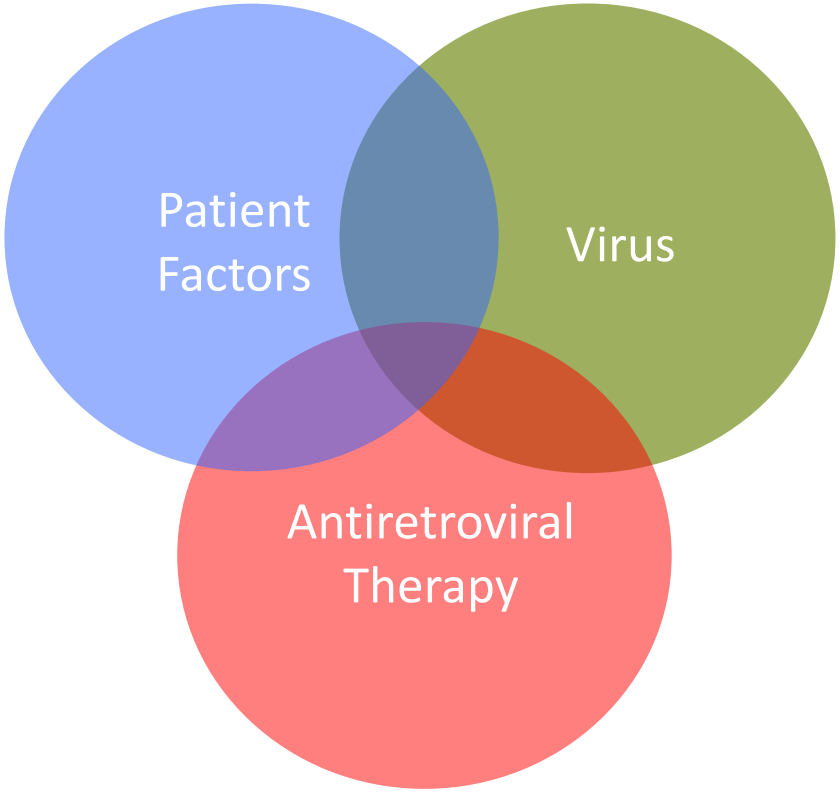
Disclosures

- Research funding from Amgen, Eli-Lilly and Alexion
- Honoraria from Amgen and Gilead

Contributors to the Risk of Osteoporosis in HIV



- Relative contributions of each of these factors to the pathogenesis of osteoporosis: key to developing strategies for prevention and treatment
- Same applies to other comorbid conditions

Adapted from J. Currier (2013)

Bone Loss – Risk Factors for the General Population – 1

- Age > 65 years
- Female
- Family history of osteoporosis and fractures
- Body mass index < 20 kg/m^2
- Alcohol consumption > 2 standard drinks per day*
- Smoking*
- Substance abuse*
- Previous low-trauma fracture
- Corticosteroid use (eg. prednisolone > 7.5 mg/day for ≥ 3 months)

*Common in populations at risk for HIV

Bone Loss – Risk Factors for the General Population – 2

- Systemic inflammation (e.g. rheumatoid arthritis)
- Chronic kidney or liver disease
- Post-menopausal
- Hypogonadism in men
- Vitamin D deficiency - inadequate exposure to sunlight (taking into account factors such as geographical location, season and skin pigmentation)
- Sedentary lifestyle

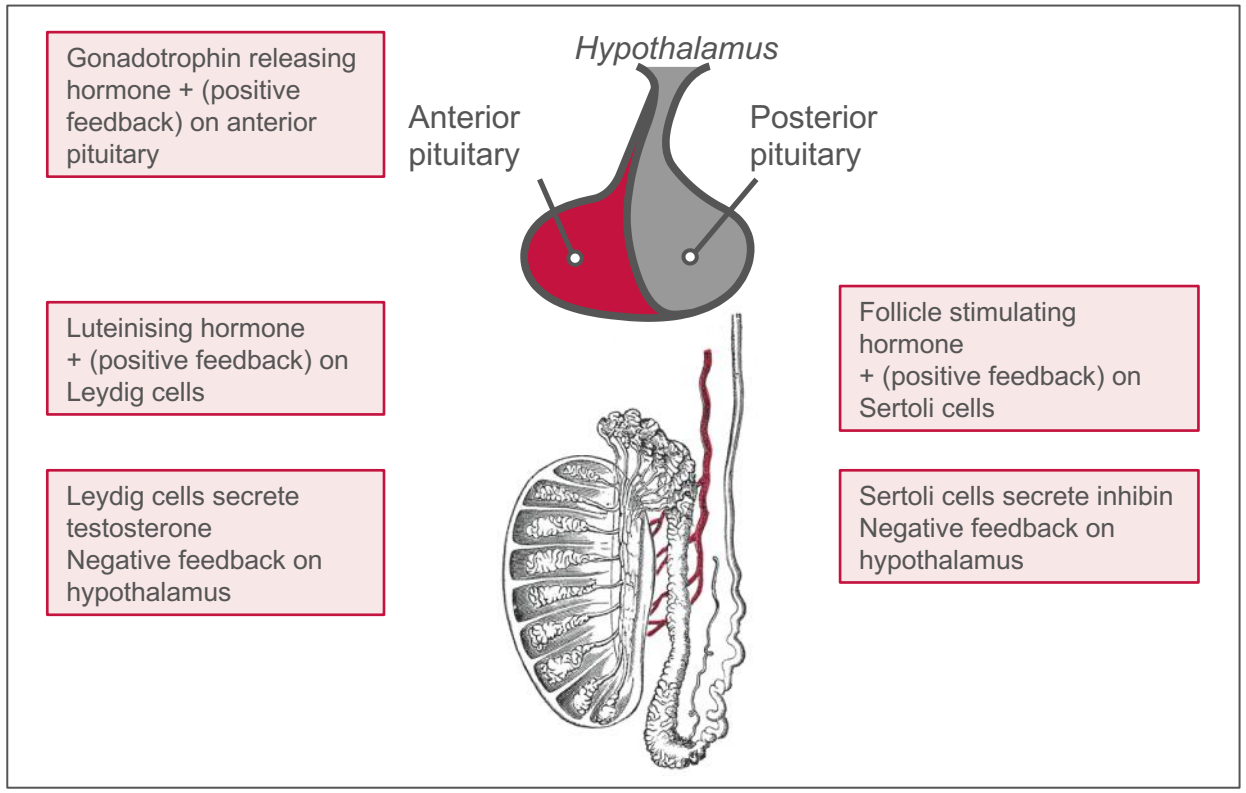
Risk Factors for Osteoporosis in PLWHIV

- Duration of HIV
- Low CD4 cell count
- Lipoatrophy
- Increased lactic acid levels
- Vitamin D deficiency, co-infection with hepatitis C, substance abuse, tobacco, alcohol use
- ART* – tenofovir disoproxil fumarate (TDF), stavudine, efavirenz, protease inhibitors, ritonavir (increases corticosteroid exposure in those taking oral or inhaled corticosteroids)

*The association of specific antiretroviral agents and bone loss has varies depending on the specific study, the risk factors evaluated and the skeletal site

*Initiation of ART may lead to bone loss, particularly over first 1-2 years' therapy

Male hypothalamic-pituitary-gonadal axis



- 57% of cases (N=245) of testosterone deficiency in men with HIV on combination ART are secondary hypogonadism[2]

1. Wong N et al. Curr Treat Options Infect Dis 2017;9(1):104–16; 2. Gomes AR et al. BMC Infect Dis 2016;16(1):628.

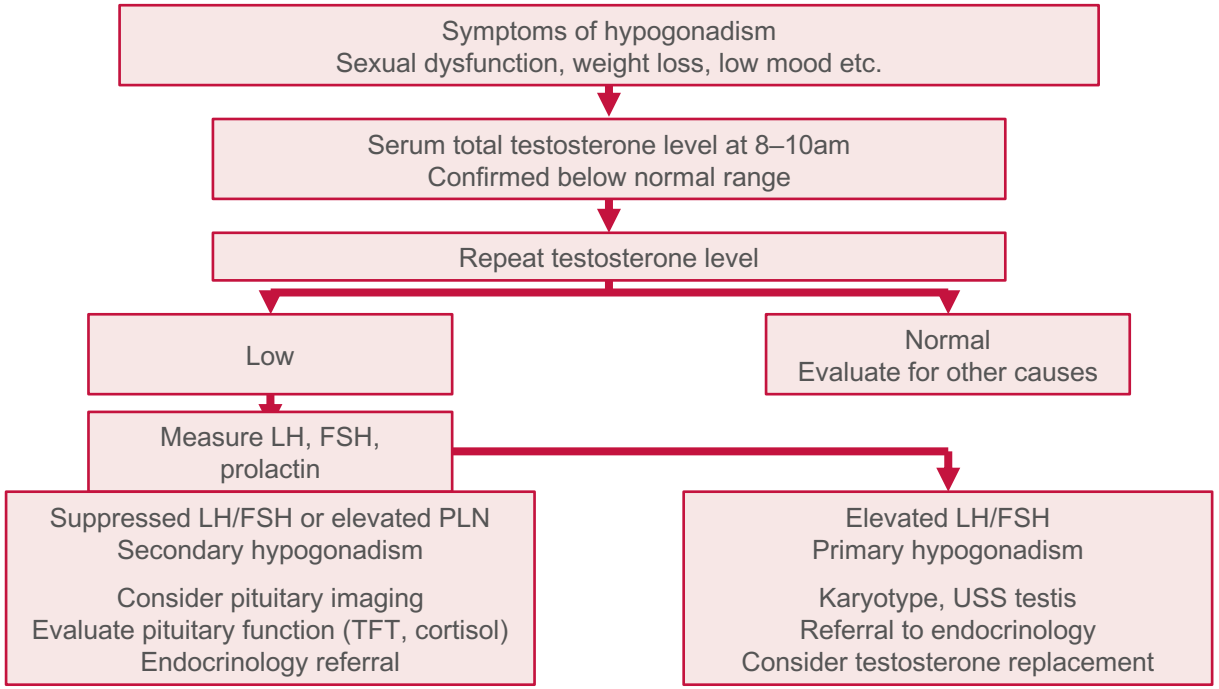
Causes of secondary hypogonadism in men with HIV

- HIV duration
- Low BMI and muscle wasting
- Hypothalamic or pituitary disease, including high prolactin levels
- Cancer (Kaposi sarcoma) or lymphoma
- Pituitary apoplexy (lymphoma, syphilis)
- Infection (M tuberculosis, toxoplasmosis, pneumocystis jiroveci, CMV, candidiasis, hepatitis B and C)
- Infiltration (sarcoidosis, histiocytosis, haemochromatosis) ± DI
- Obesity, T2DM, hypertension, increased CVD risk, age
- Anabolic steroids
- Glucocorticoids
- Opioids, methadone, psychotropic drugs
- ART and its duration

ART, antiretroviral therapy; BMI, body mass index; CMV, cytomegalovirus; CVD, cardiovascular disease; DI, diabetes insipidus; M, mycobacterium; T2DM, type 2 diabetes mellitus.

Mirza FS et al. J Endocrinol Invest 2018. doi: 10.1007/s40618-017-0812-x. [Epub ahead of print].

Evaluation of male hypogonadism



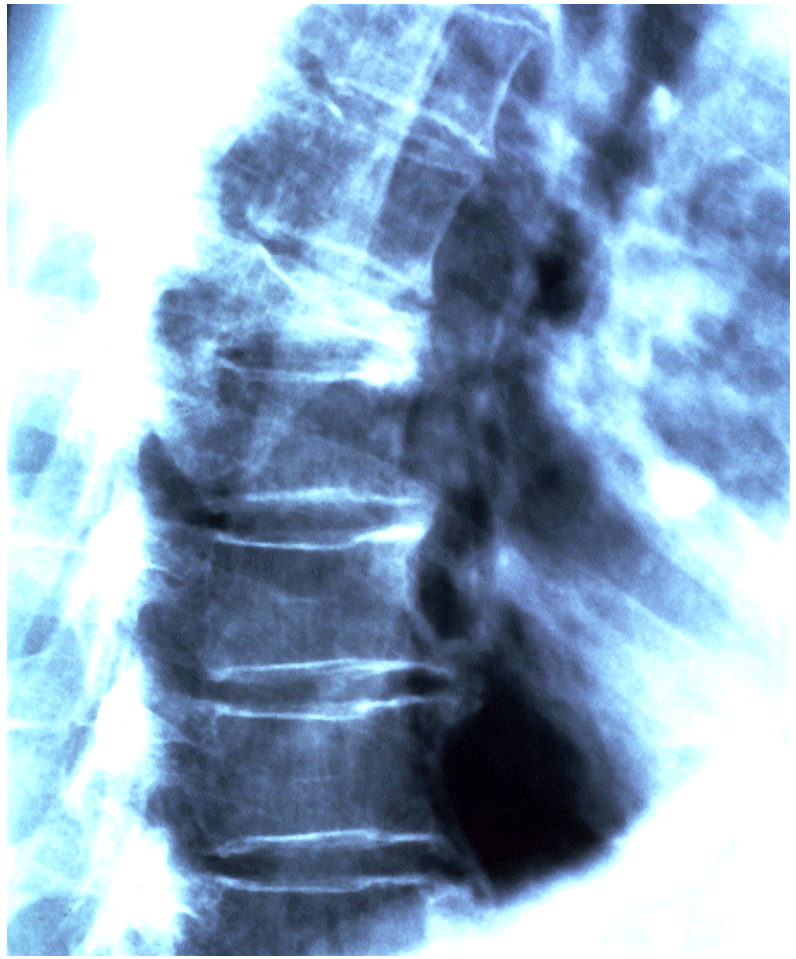
- Testosterone treatment will increase lean and muscle mass, and improve QoL and BMD

BMD, bone mineral density; FSH, follicle stimulating hormone; LH, luteinising hormone; PLN, prolactin; QoL, quality of life; TFT, thyroid function test; USS, ultrasound scan.

Wong N et al. Curr Treat Options Infect Dis 2017;9(1):104–16.

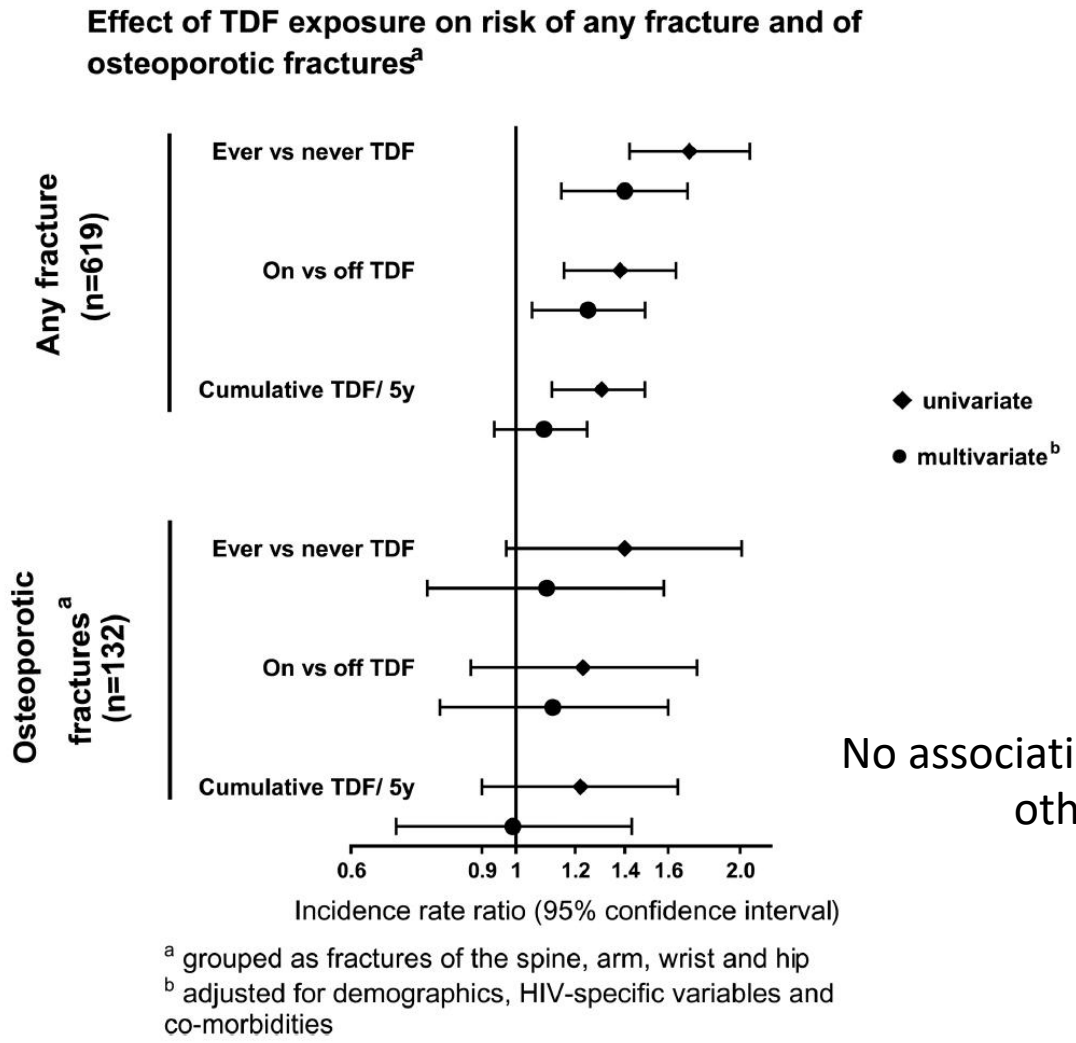
Vertebral Fractures

- Majority are asymptomatic
- Associated with increased risk of subsequent fractures
- Diagnosis requires lateral thoracic and lumbar spine X-rays (or DXA imaging)
- Associated with chronic pain, height loss, kyphosis, disability
- Common in patients with HIV with a prevalence of 11.1% and a RR of 2.30



Ebeling PR, New Engl J Med 2008
Premaor MO et al., JBMR Plus 2018

Effect of Tenofovir Disoproxil Fumarate Expossure on Fractures



No association seen for fractures and other individual ARV

Borges AH et al. CID 2017; 64: 1431-21

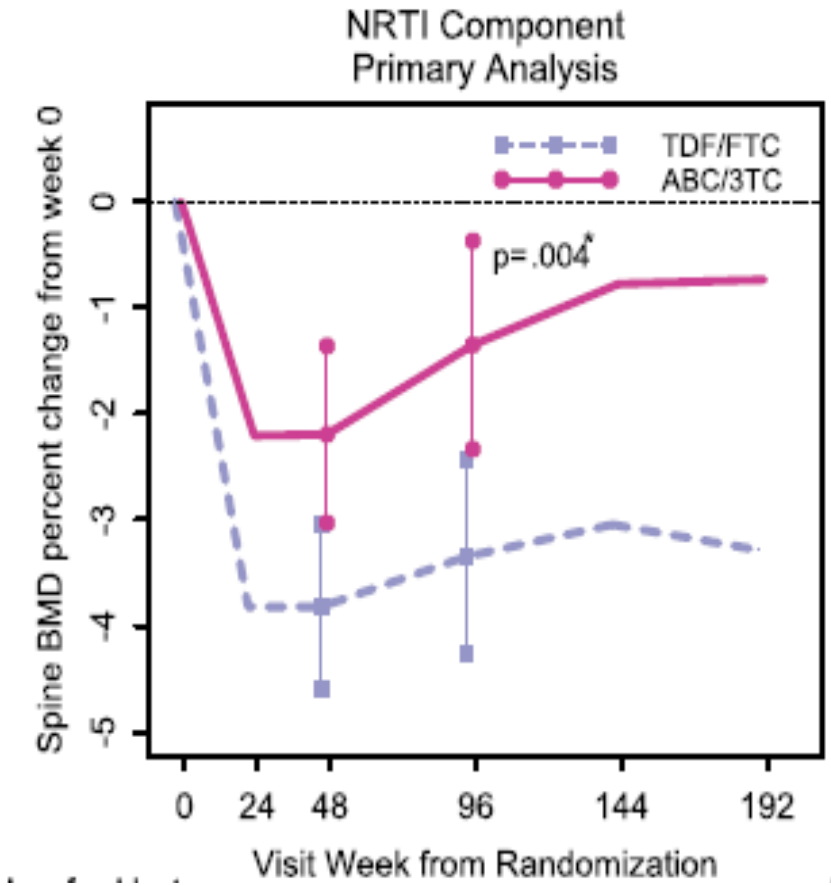
Antiretroviral Therapy and Bone Loss

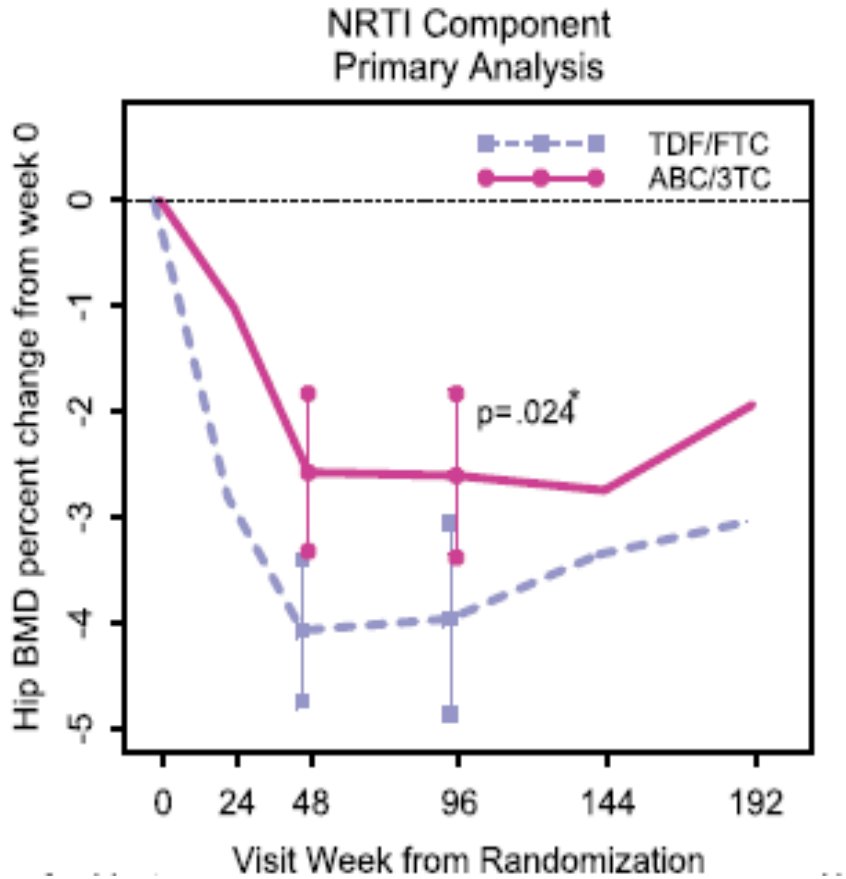
- Data indicate bone loss in HAART-naïve patients starting therapy[1]
- Bone loss appears to be transient and occurs mainly during the first year[2,3]
- Bone loss is associated with increased levels of bone turnover markers[4]
- Tenofovir disoproxil fumarate (TDF) and protease inhibitors are associated with greater loss[1,3]
- Specific association between NRTIs, especially TDF, and Fanconi syndrome causing hypophosphataemic osteomalacia (rare)[5]

HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor, TDF, tenofovir

1. Brown TT and Qaqish RB. AIDS 2006:20;2165–74, 2. McComsey G et al. J Inf Dis 2011;203:1791–801,
3. Haskelberg H et al. PLoS One 2012;7(6):e38377, 4. Bedimo RJ et al. PLoS One 2014;9(8):e106221,
5. Wohl D et al. J Acquir Immune Defic Syndr 2016

TDF-containing Regimens Cause Greater Initial Bone Loss at the Spine and Hip

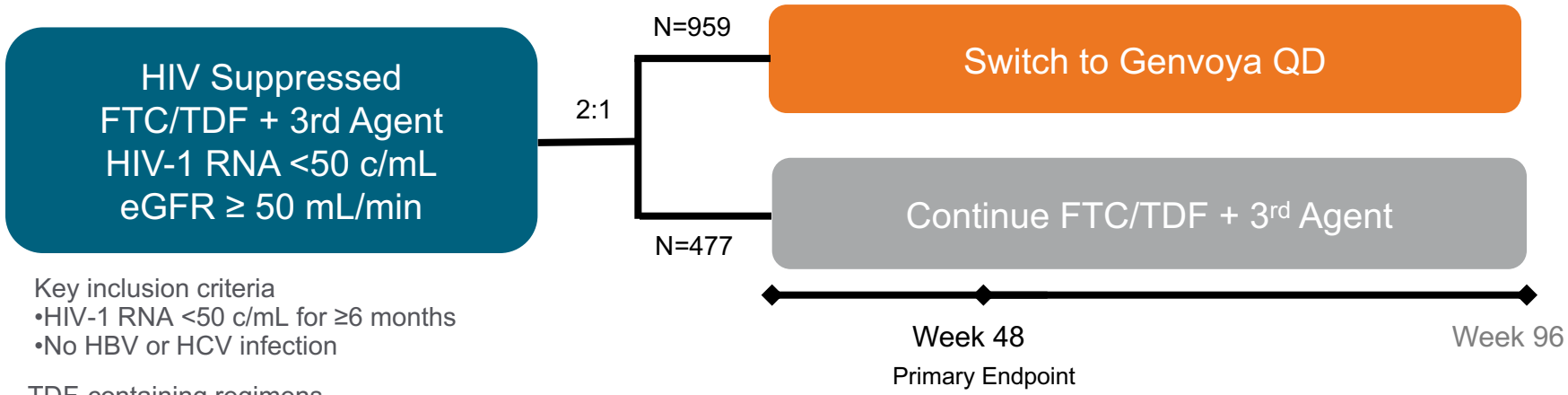




McComsey et al. J Infectious Dis 2011; 203:1791-1801.

Suppressed Adults Switched from a TDF-containing regimen to Genvoya[1-4]

- Phase 3, 96-week, multi-centered, randomized, open label, active-controlled



Key inclusion criteria
- HIV-1 RNA <50 c/mL for ≥6 months
- No HBV or HCV infection

TDF-containing regimens
- Atripla (26%, N=376), Stribild (32%, n=459), RTV or COBI-boosted ATV+FTC/TDF (42%, n=601)

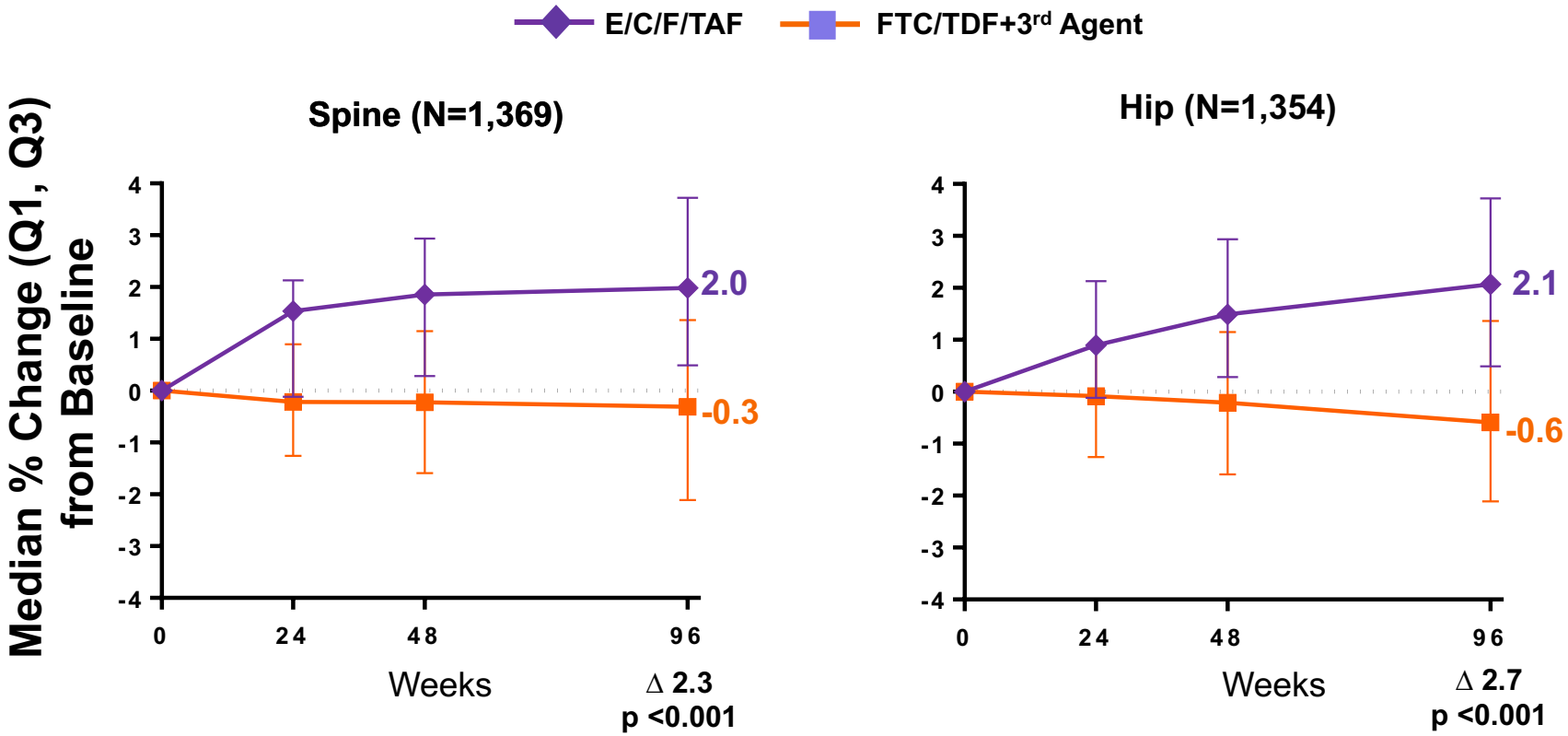
- **Primary endpoint**: proportion of patients with undetectable viral load (HIV-1 RNA < 50 copies per mL) at week 48
- **Secondary outcomes**:
  - Hip bone mineral density
  - Spine bone mineral density
  - Change in serum creatinine
  - Change in efavirenz-related symptom score

Genvoya: single-tablet regimen elvitegravir 150mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir alafenamide 10mg
STB = Stribild = single-tablet regimen elvitegravir 150mg/ cobicistat 150mg/ emtricitabine 200mg/ tenofovir DF 300mg
ATR = Atripla = single-tablet regimen efavirenz 600mg/ emtricitabine 200mg/ tenofovir DF 300mg
ATV = atazanavir, COBI = cobicistat, RTV = ritonavir

1. Mills A, et al. Lancet Infect Dis 2015;
2. Shamblaw D, et al. ICAAC 2015, San Diego, CA. Oral
3. Thompson M, et al. ID Week 2015. San Diego, CA. Oral #725
4. Rijnders B, et al. EACS 2015. Barcelona, Spain. Oral # PS10/3

Changes in Spine and Hip BMD through Week 96

- Suppressed Adults Switched from a TDF-containing regimen to E/C/F/TAF



Switching to E/C/F/TAF from a regimen containing FTC/TDF + 3rd agent resulted in progressive increase in spine and hip BMD over 96 weeks

DeJesus E, et al. ASM 2016. Boston MA. #087LB

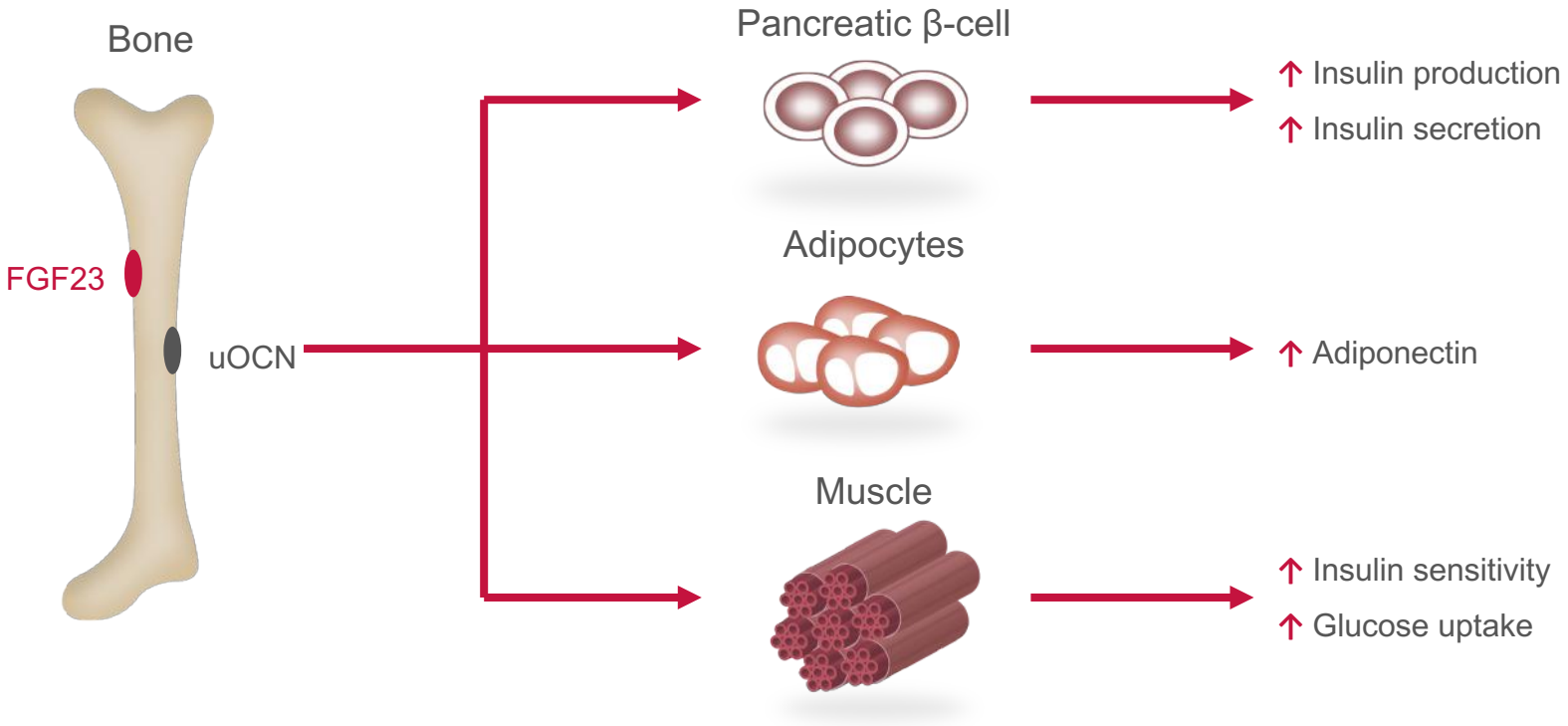
Effects on BMD over 48 Weeks in Virologically Suppressed Patients

	GENVOYA N=799	Continued FTC/TDF + Third Agent* N=397
Subjects who experienced BMD declines, %		
≥5% at the lumbar spine	1	6
≥7% at the femoral neck	1	4

*Third Agent Regimens include ATRIPLA, FTC/TDF + ATV + (COBI or RTV), and EVG/COBI/FTC/TDF.

1. GENVOYA US Prescribing Information, March 2016.

Bone as an endocrine organ



FGF23, fibroblast growth factor 23; uOCN, uncarboxylated osteocalcin.
Fukumoto S and Martin TJ. Trends Endocrinol Metab 2009;20(5):230–6.

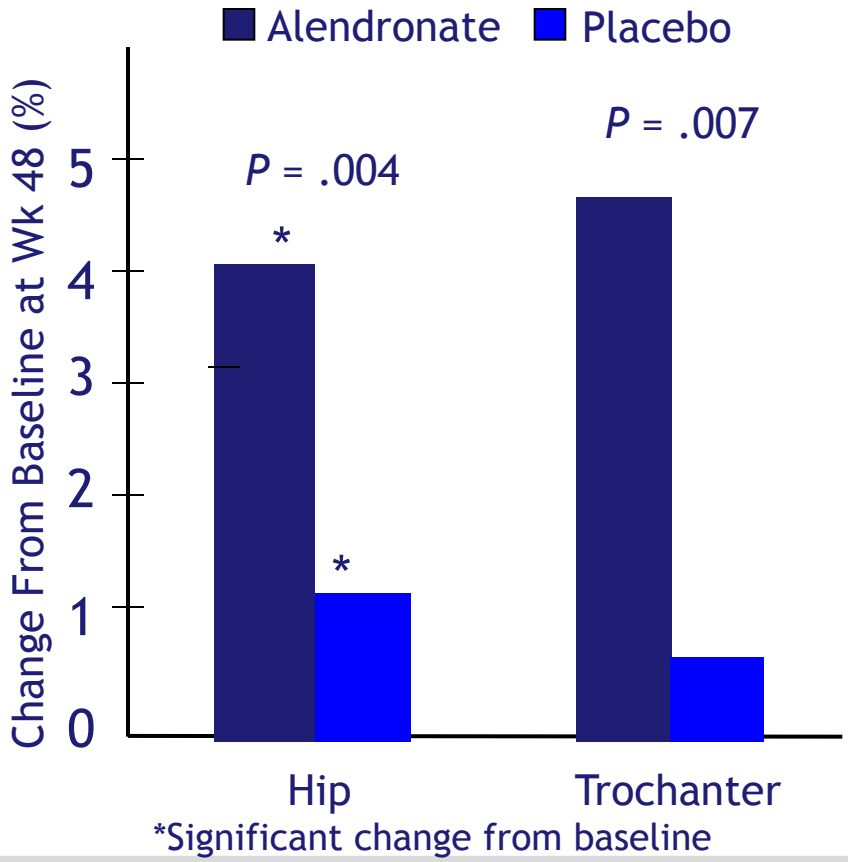
Effect of TDF on bone metabolism in adolescents and young men on PrEP

- High exposure to TDF as PrEP was associated with >3% decrease in hip BMD at 48 weeks compared to low exposure
- A decrease in FGF-23 was associated with increases in PTH and bone turnover markers
- It is likely endocrine disruption (PTH-FGF23) is a primary contributor to TDF-associated BMD decline in this age group (mean±SD age, 19.6±1.8 years)
- Bone loss and fractures are of potential concern in men starting TDF as PrEP
- Adverse effects will be greatest for those with the highest baseline absolute fracture risk, based on BMD and clinical risks

BMD, bone mineral density; F, emtricitabine; FGF-23, fibroblast growth factor 23; PrEP, pre-exposure prophylaxis; PTH, parathyroid hormone; SD, standard deviation; TDF, tenofovir disoproxil fumarate.
Havens PL et al. Clinical Infect Dis 2017;64(3):317–25.

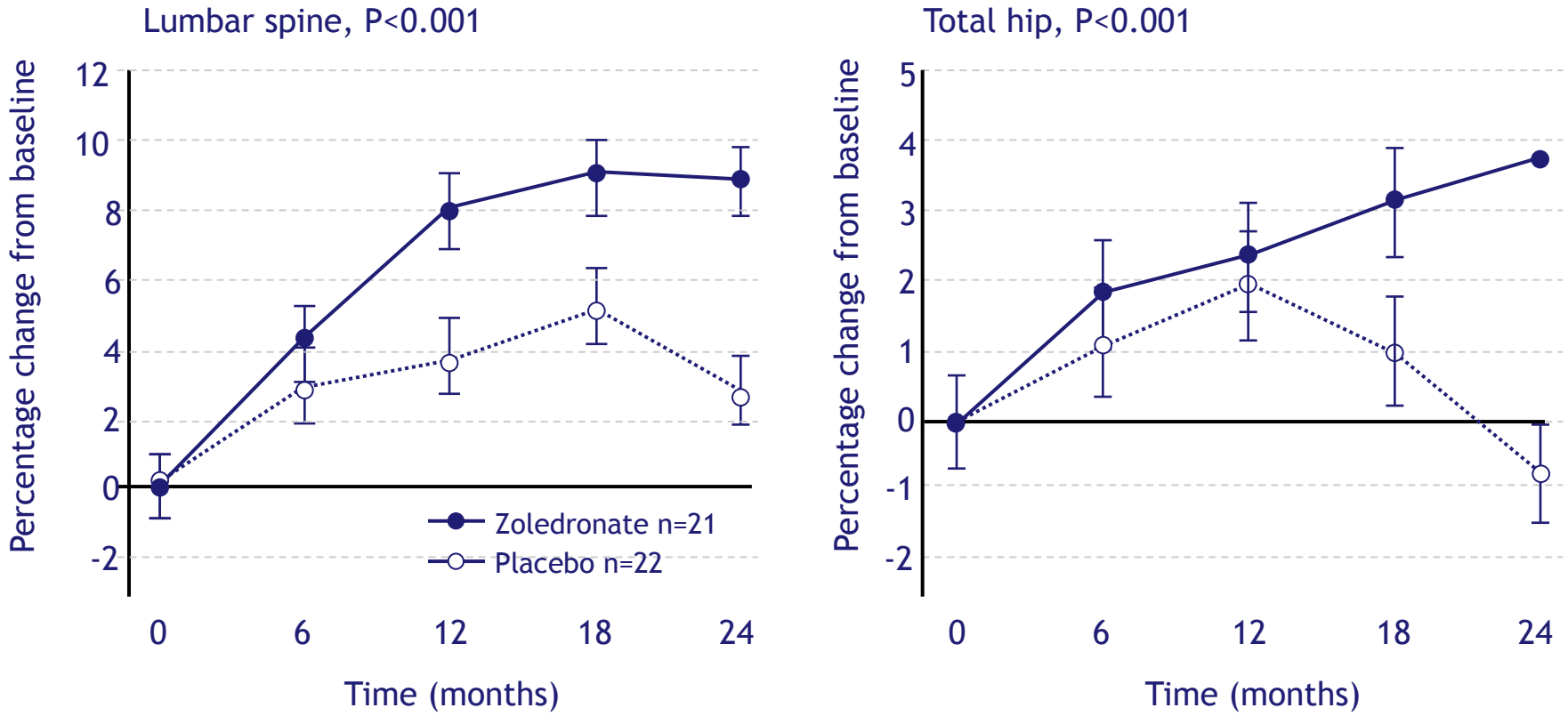
Effect of Alendronate on BMD in HIV-infected Patients

- Randomized, placebo-controlled, double-blinded phase II trial in osteopenic (lumbar T-score < -1.5) HIV-infected patients (71% men)
- Alendronate 70 mg QW + vitamin D + calcium (500 mg/200 IU BID) (n = 42)
- Placebo + vitamin D + calcium (n = 40)
- No significant AEs
- Black race associated with smaller change from baseline with alendronate (P = .003)



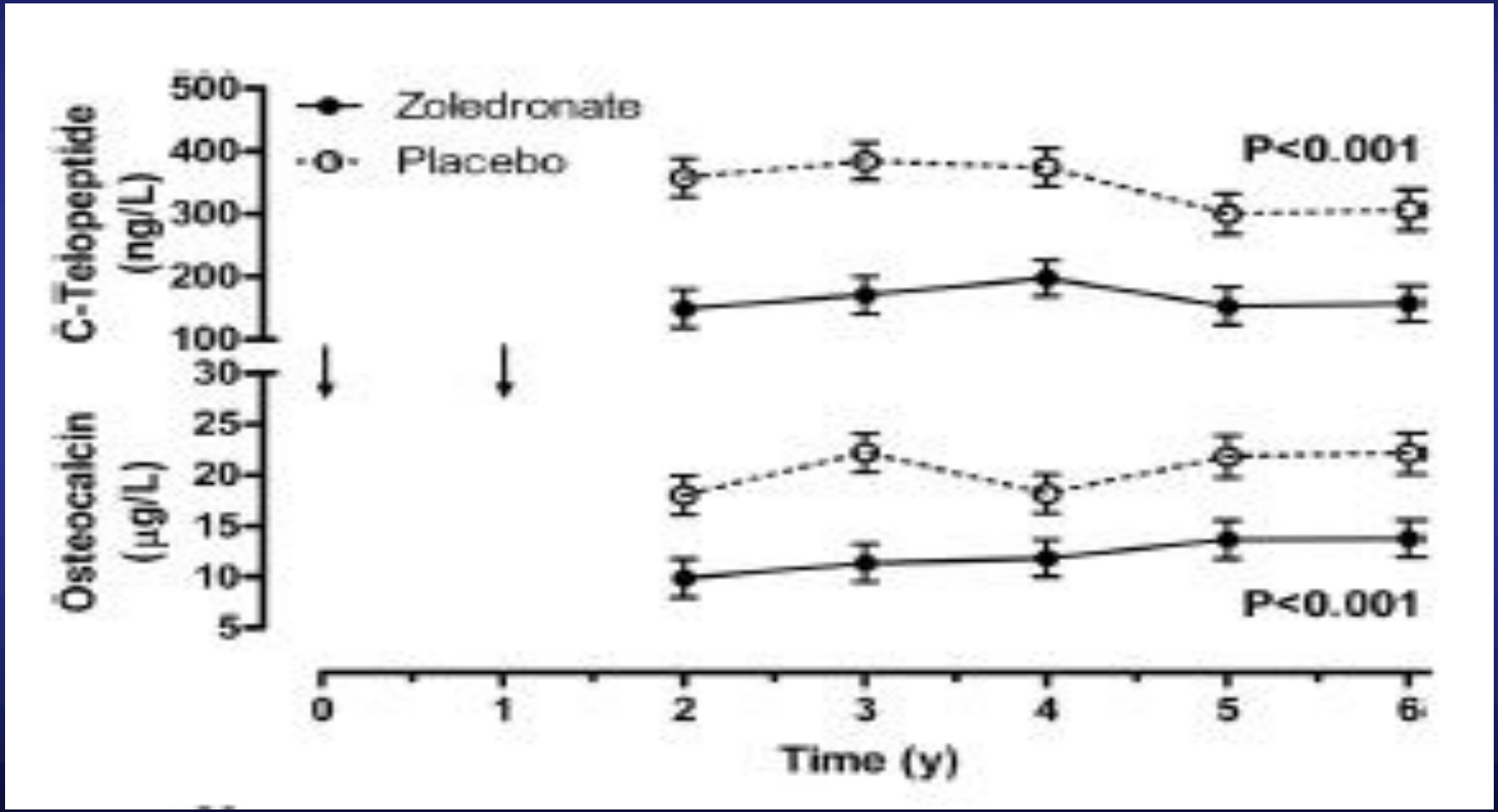
McComsey et al *AIDS* 2007;21:2473-82

Effect of iv Zoledronate on BMD in HIV Infected Men



Bolland M et al JCEM 2007;92:1283-8

Zoledronic Acid Reduces BTMs for 5 Yrs in Men with HIV

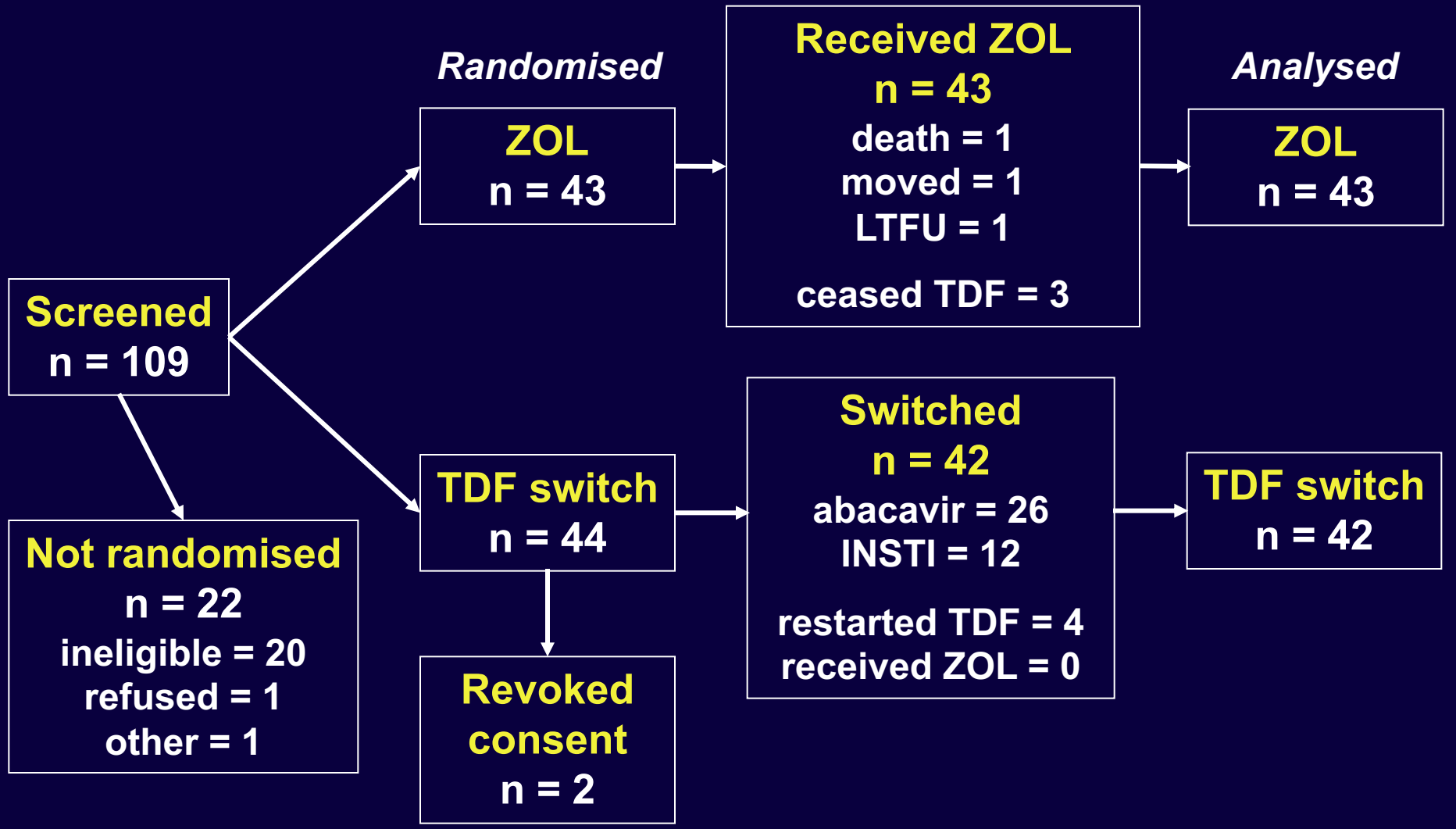


MHTP Monash Health Translation Precinct

Bolland MJ et al. *J Clin Endocrinol Metab* 2012

ZOL vs TDF switch for low BMD

CONSORT chart



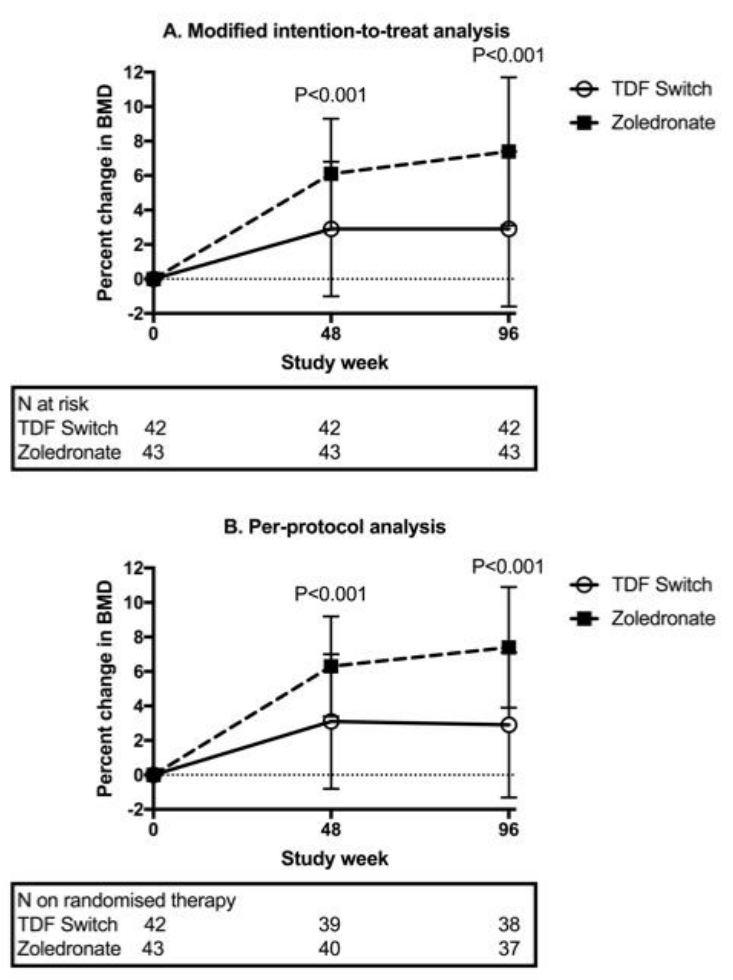
ZOL vs TDF switch for low BMD

Screening / baseline characteristics

Variable	ZOL n=43	TDF switch n=42
Age (yrs)	49	51
Sex (male %)	93	100
Ethnicity (white, %)	74	81
CD4 count (cells/mm^3)	626	609
TDF duration (yrs)	5.7	6.0
Boosted PI (%)	23	21
Weight (kg)	75	75
T-scores (median)		
spine	-1.7	-1.6
left total hip	-1.4	-1.1
eGFR (mL/min)	93	91

ZOL vs TDF switch for low BMD

BMD and fractures over 2 years



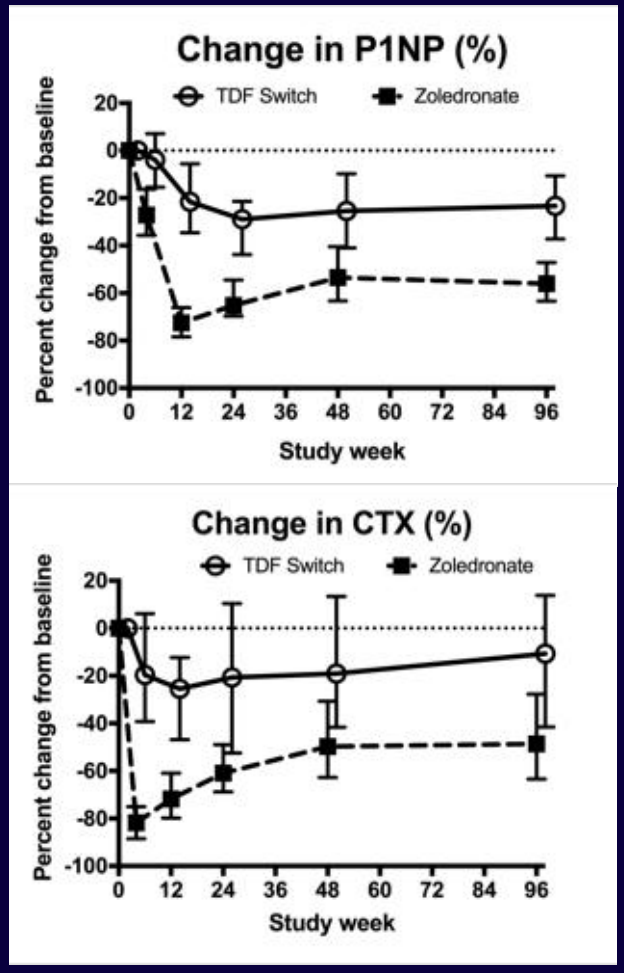
- **ZOL vs TDF-switch arms**
  - **Wk 48 3.2% (95%CI 1.7-4.7)**
  - **Wk 96 4.4% (95%CI 2.6-6.3)**
  - **both p-values <0.001**

Fractures	ZOL n=43	TDF switch n=42
Events	1	7
Patients	1 (2%)	4 (10%)

Hoy et al, AIDS 2018

ZOL vs TDF switch for low BMD

Bone turnover markers over 2 years



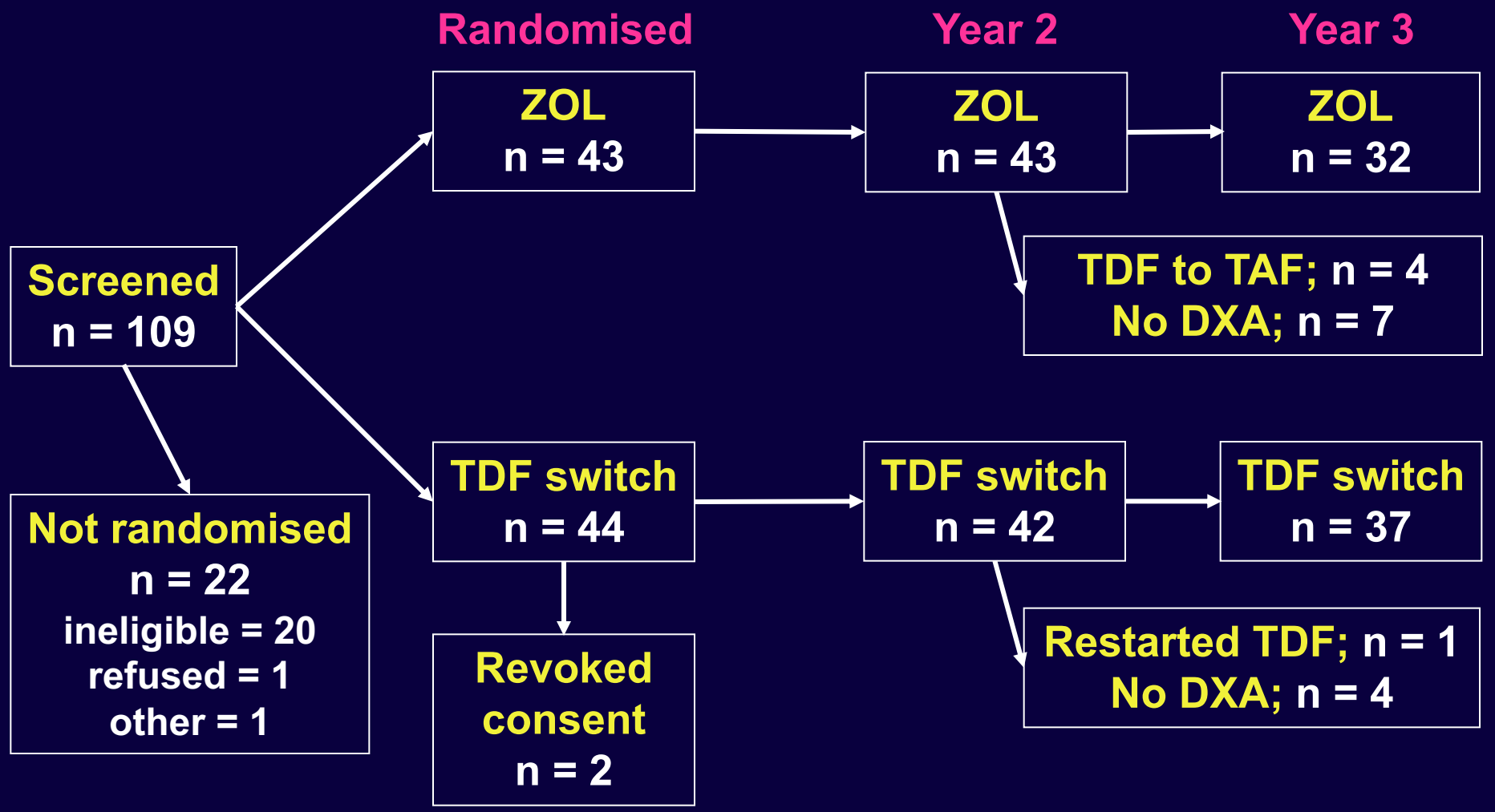
- p<0.001 at each time point and overall
- TDF switch group, decrease at Week 4 in
  - CTX: -20% vs
  - P1NP: -4%

Region	P1NP		CTX	
	r^2	P	r^2	P
Spine	-0.44	<0.001	-0.36	0.001
Hip	-0.45	<0.001	-0.23	0.051

Carr et al, CROI 2018

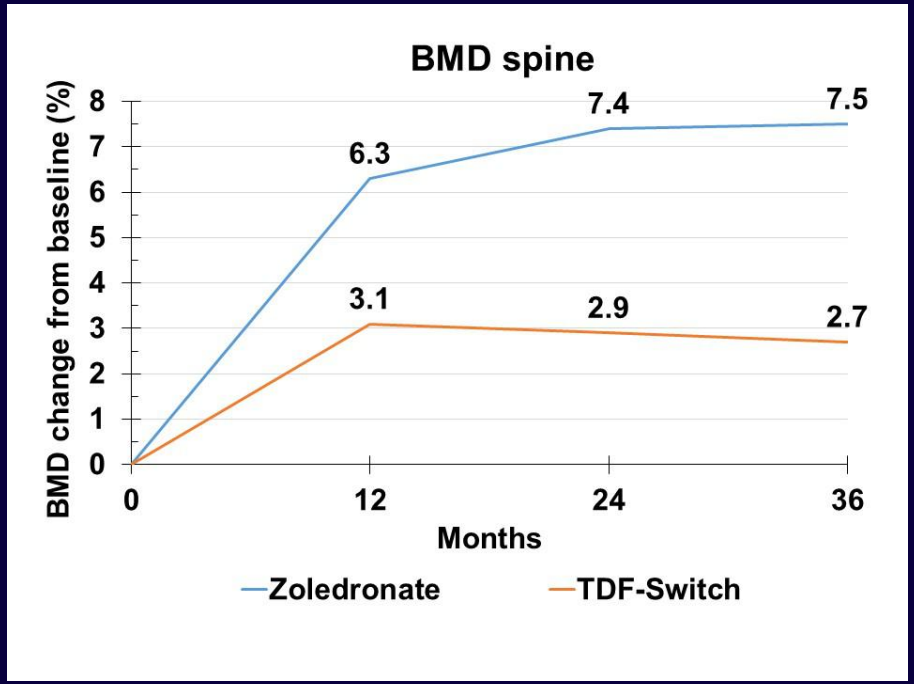
ZOL vs TDF switch for low BMD

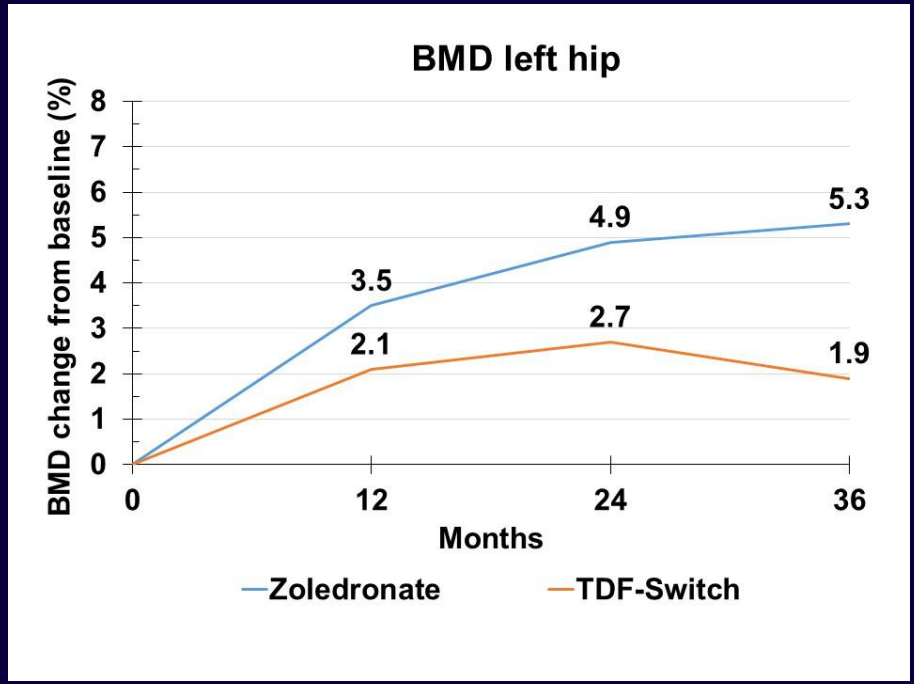
CONSORT chart (per protocol)



ZOL vs TDF switch for low BMD

Changes in BMD



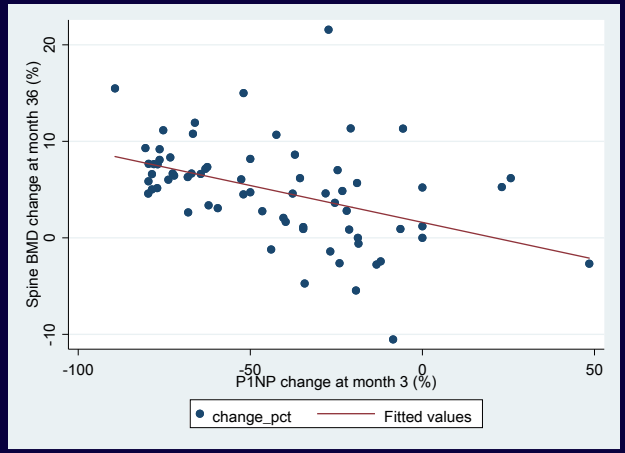
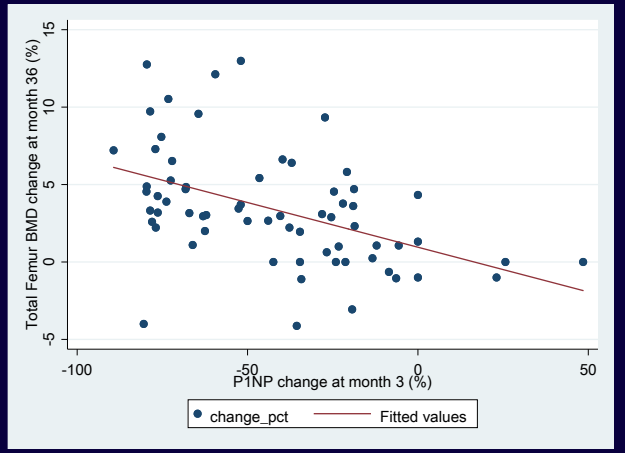
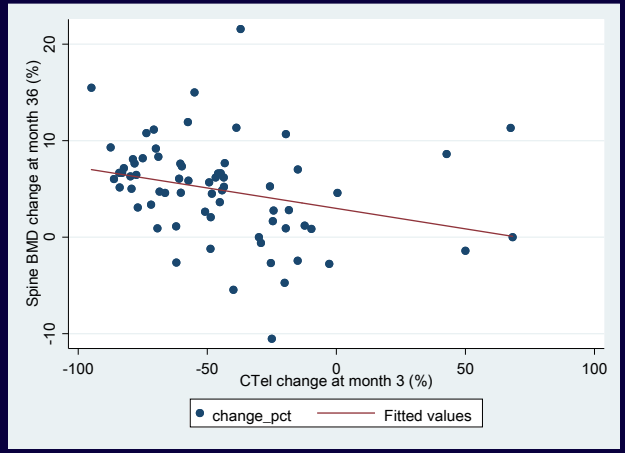
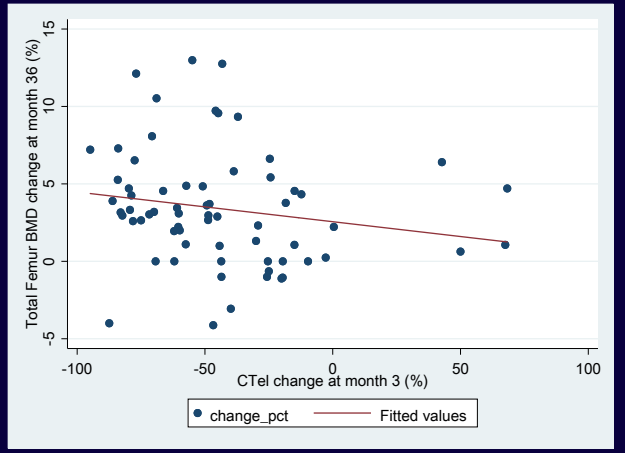


ZOL	40	40	37	32
TDF-S	40	39	38	37

ZOL	39	39	36	30
TDF-S	40	39	38	37

ZOL vs TDF switch for low BMD

Changes in BTMs M3 vs changes in BMD M36

	Spine	Left hip
P1NP (rho -0.442, P<0.001)		
CTX (rho -0.285, P<0.001)		
P1NP (rho -0.472, P<0.001)		
CTX (rho -0.181, P=0.15)		

ZOL vs TDF switch for low BMD

Fractures

Fractures		ZOL n=43	TDF switch n=42	P-value
Month 24	events	1	7	0.03
	patients	1 (2%)	4 (10%)	0.20
Month 36	events	3	10	0.04
	humerus	1	0	
	wrist	0	3	
	spine	1	1	
	ribs	1	3	
	hand / foot	0	3	
	patients	2 (5%)	6 (14%)	0.16

ZOL vs TDF switch for low BMD

Limitations

- Almost all white, adult men
- Pre-TAF, but switch to TAF unlikely to be superior to switch to ABC or INSTI
- Not powered for fracture events

ZOL vs TDF switch for low BMD

Conclusions

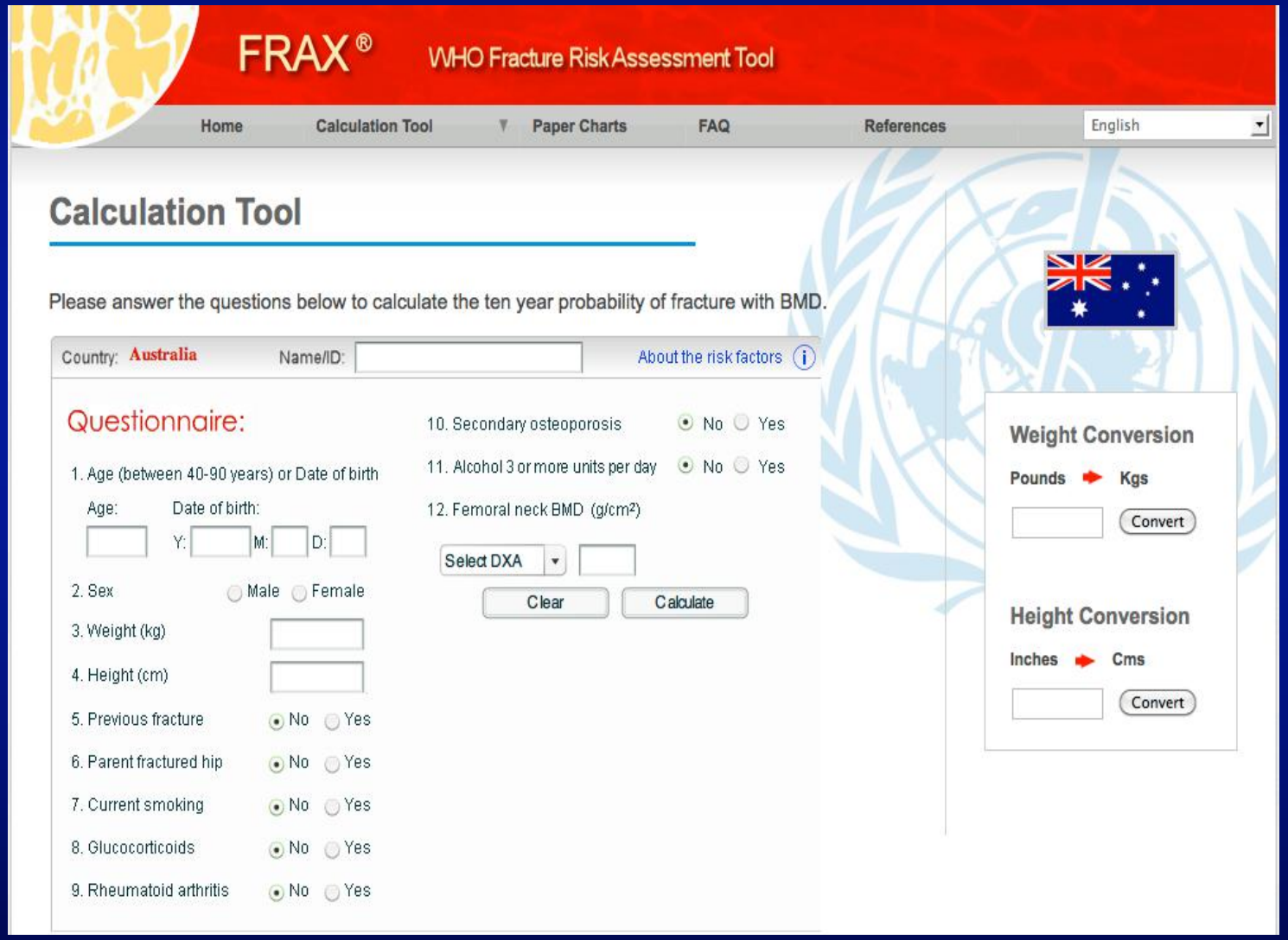
- Superiority of ZOL relative to TDF switching persisted at Month 36
- BMD increase with ZOL persisted through Month 36, even though the last dose of ZOL was at Month 12
- Early changes in P1NP better predicted BMD changes at 36 months than early changes in CTX

Bone Health – Screening

- Serum calcium, phosphate, magnesium, 25-OH vitamin D and testosterone levels
  - Frequency: annually
  - Replacement therapy as required
  - If mild or moderate vitamin D deficiency, check serum phosphate, ALP and parathyroid hormone
- Calculation of absolute fracture risk
  - FRAX® fracture risk calculator available online
  - Only useful if patient is > 40 years old
  - May underestimate risk in patients with HIV
    - Add HIV as a ‘secondary cause’ of osteoporosis

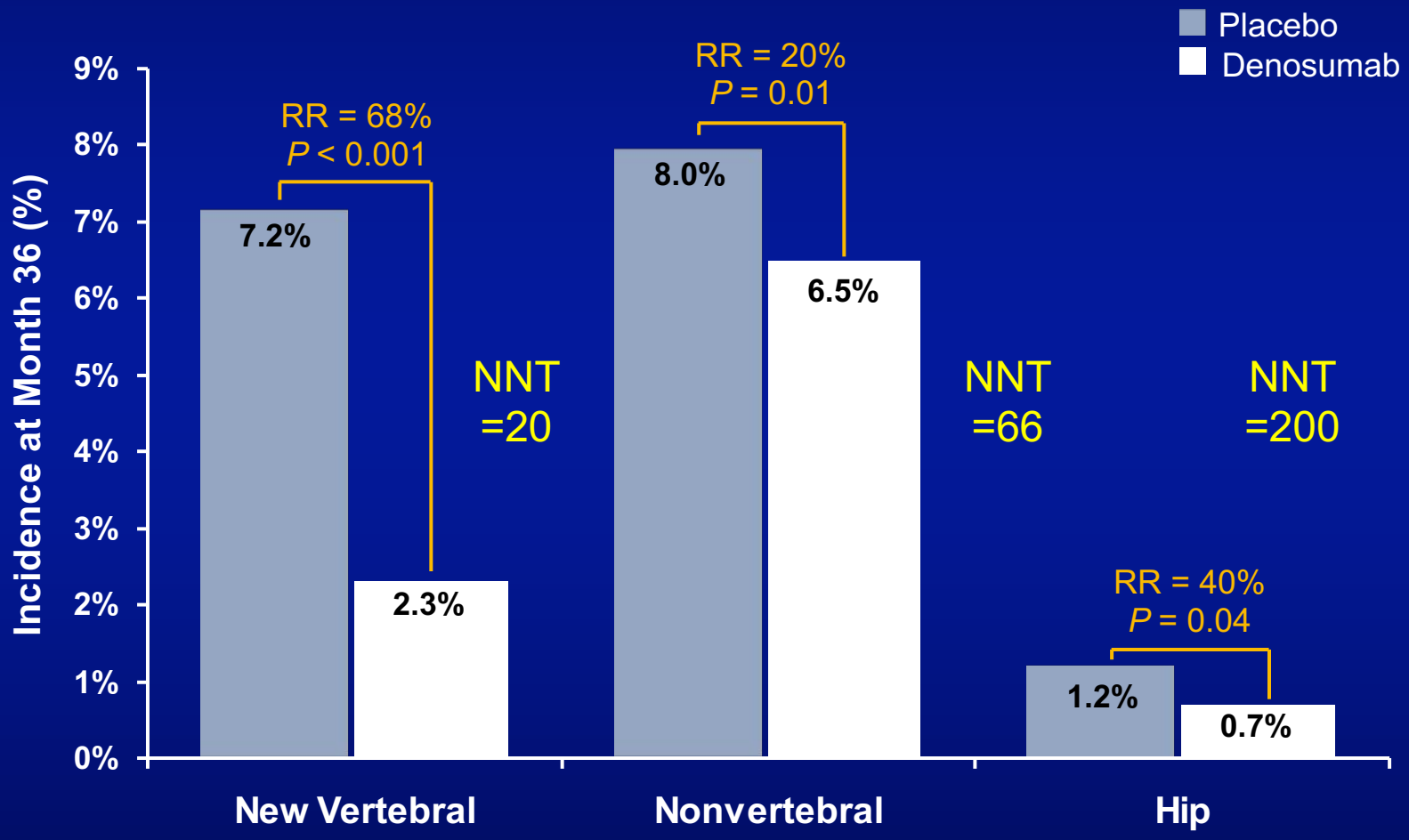
Absolute Fracture Risk Assessment Tools

FRAX ®



Effect of Denosumab on Fracture Risks at 36 Mths

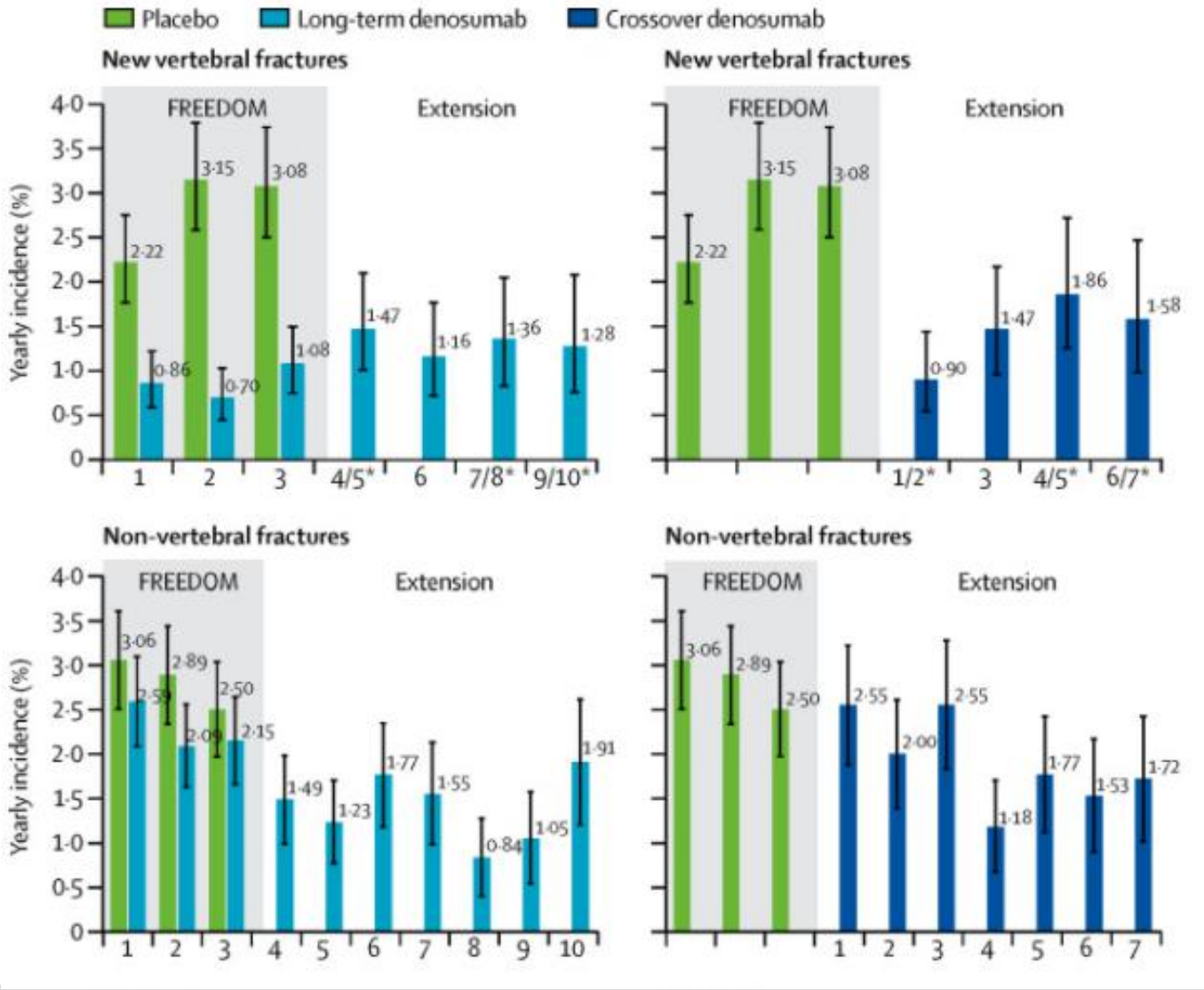
FREEDOM Trial



RR = risk reduction

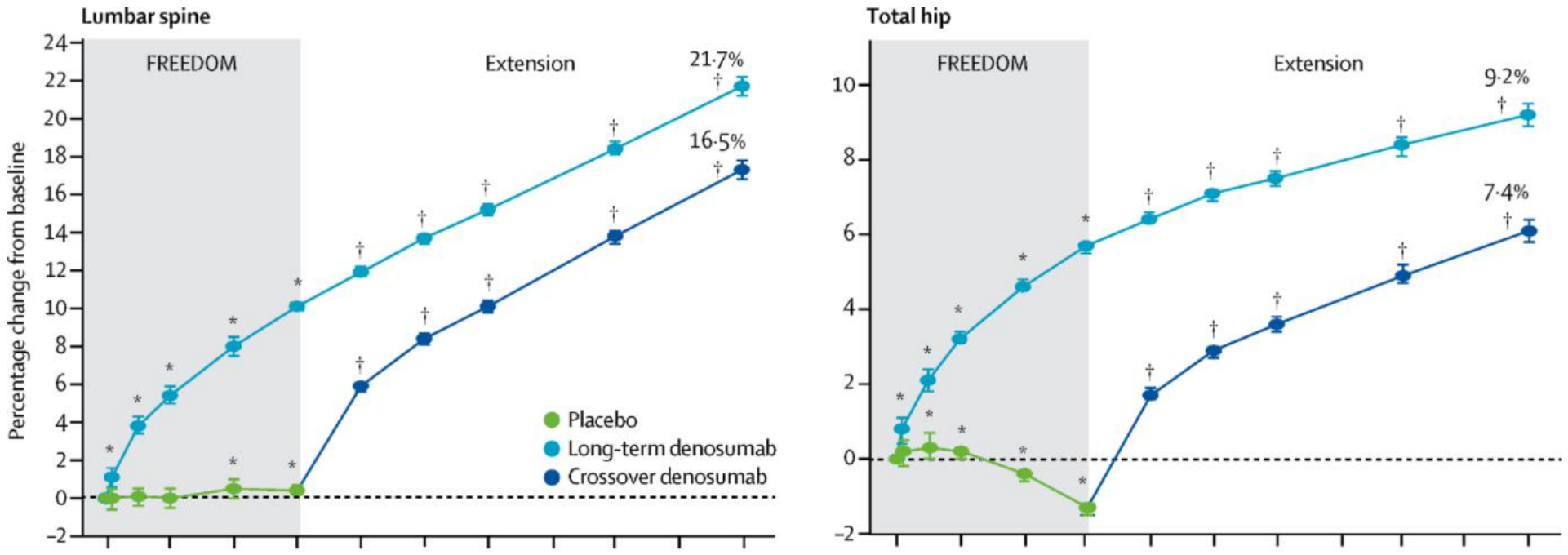
Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.

Effect of 7 or 10 Years Treatment with Denosumab on Vertebral and Non-vertebral Fractures – FREEDOM Extension Trial



Bone HG et al., Lancet Diabetes Endocrinol. 2017; 5:513-523.

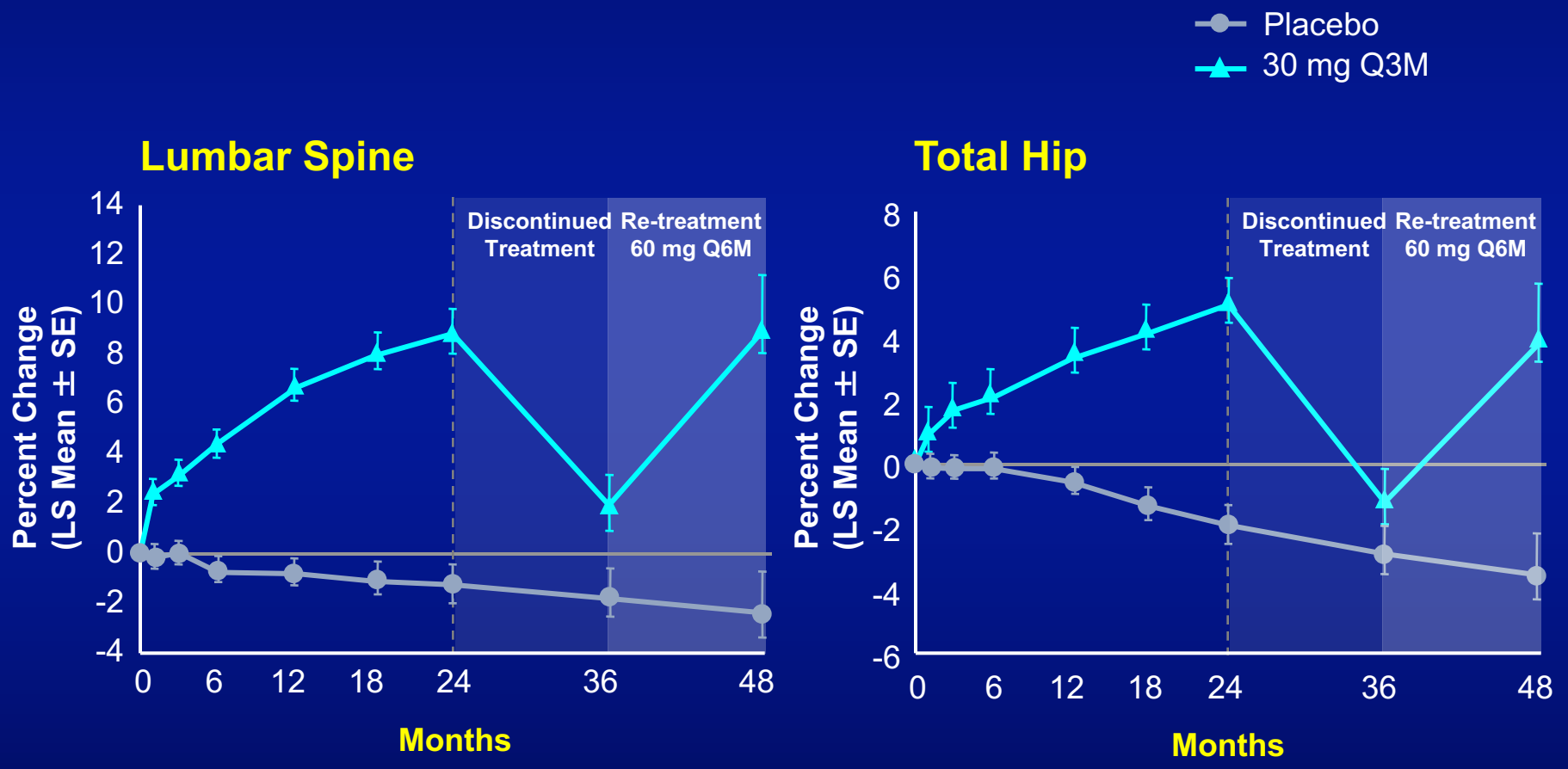
Effect of 7 or 10 Years Treatment with Denosumab on Spinal and Total Hip BMD
FREEDOM Extension Trail



Bone HG et al., Lancet Diabetes Endocrinol. 2017; 5:513-523.

Denosumab Re-treatment and Changes in Lumbar Spine and Total Hip BMD

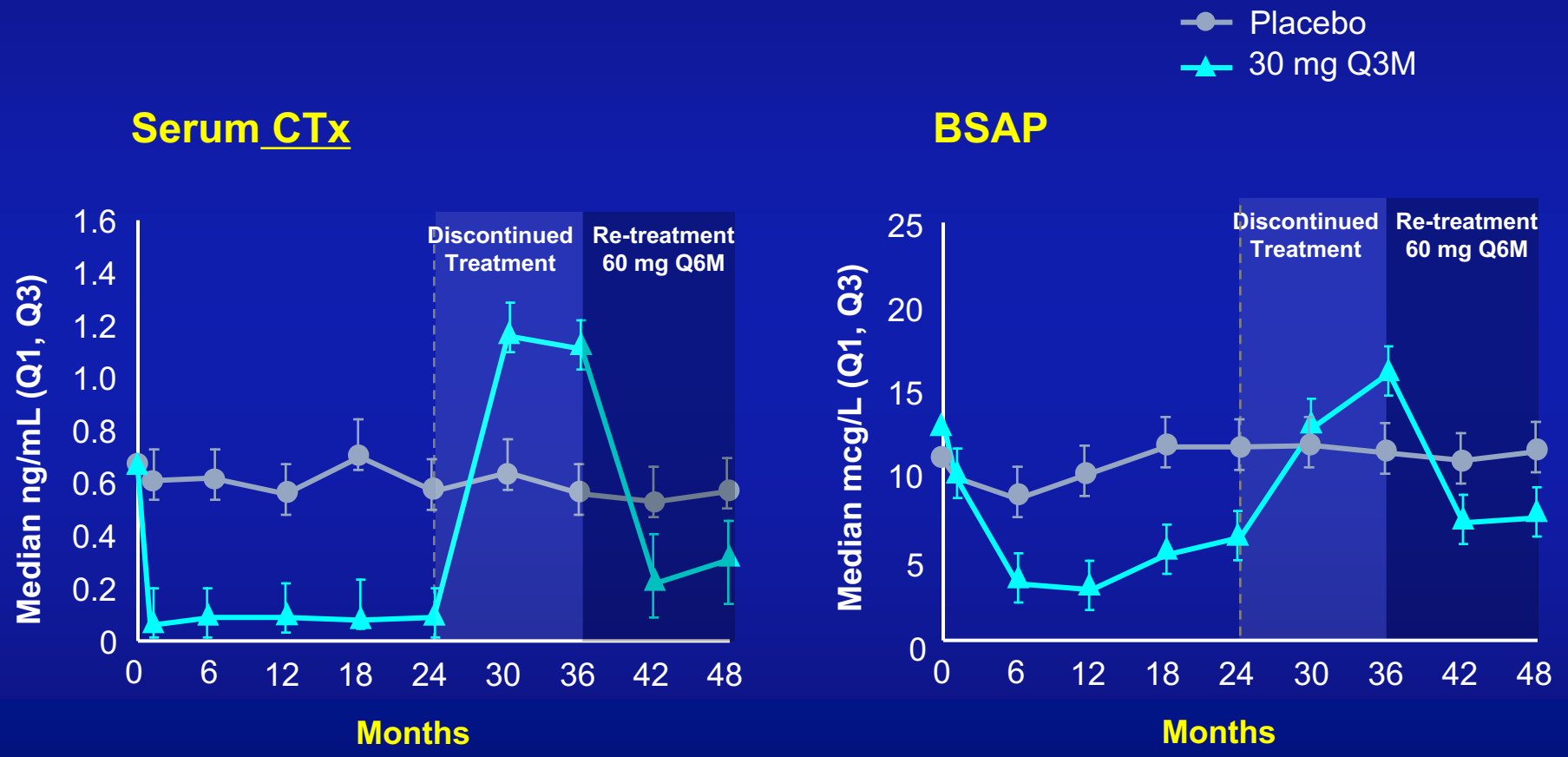
Phase 2 Study in Women With Low BMD



Miller PD, et al. *Bone*. 2008;43:222-229

Denosumab Re-treatment and Changes to Serum CTx and BSAP Levels

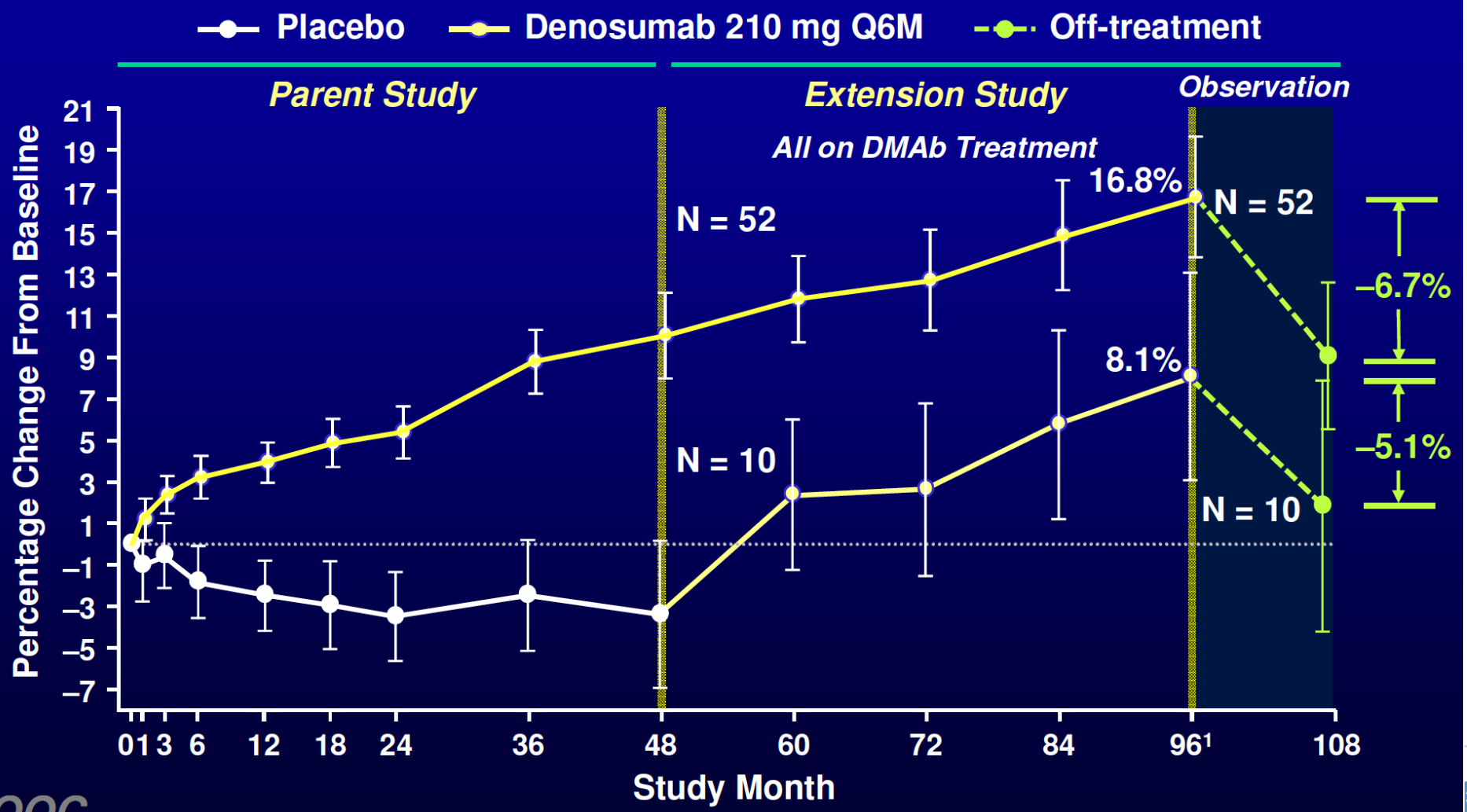
Phase 2 Study in Women With Low BMD



Miller PD, et al. *Bone*. 2008;43:222-229.

Discontinuing Denosumab After 8 Years

Lumbar Spine BMD



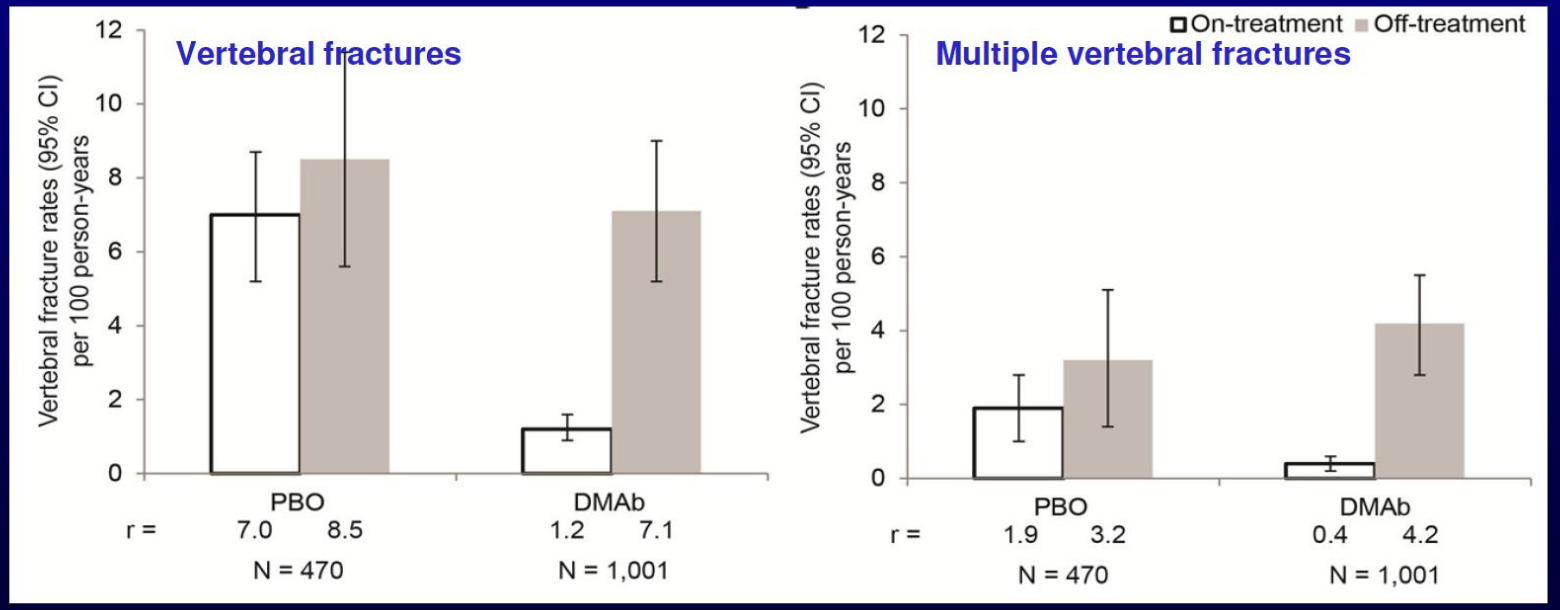
McClung M et al. *Osteoporos Int.* 2017;28:1723-32

OOC

HK registered indication is 60 mg q 6 month

Vertebral Fractures After Discontinuing Denosumab or Placebo in FREEDOM Study

- Vertebral fracture risk was assessed in patients who discontinued either placebo or denosumab in the FREEDOM study or who stopped denosumab in the FREEDOM Extension study and who had a follow-up at least 7 months after their last dose
- Fracture risk increased upon stopping denosumab but not to levels greater than seen in those who stopped placebo



Cummings SR et al., J Bone Miner Res 2018; 33:190-8

Significant Predictors of Off-treatment MVF

- Prior vertebral fracture is the strongest predictor of off-treatment vertebral fractures
- Other predictors of MVF were time off-treatment and rate of off-treatment total hip BMD loss

Significant covariates	772 patients included† OR (95% CI)	1,471 patients included* OR (95% CI)
Prior vertebral fracture‡ (yes vs no)	3.6 (1.8–7.1)	3.9 (2.1–7.2)
Off-treatment duration (per year)	1.4 (1.1–1.7)	1.6 (1.3–1.9)
Annualised off-treatment total hip BMD loss§ (per 1%)	1.2 (1.1–1.3)	NA

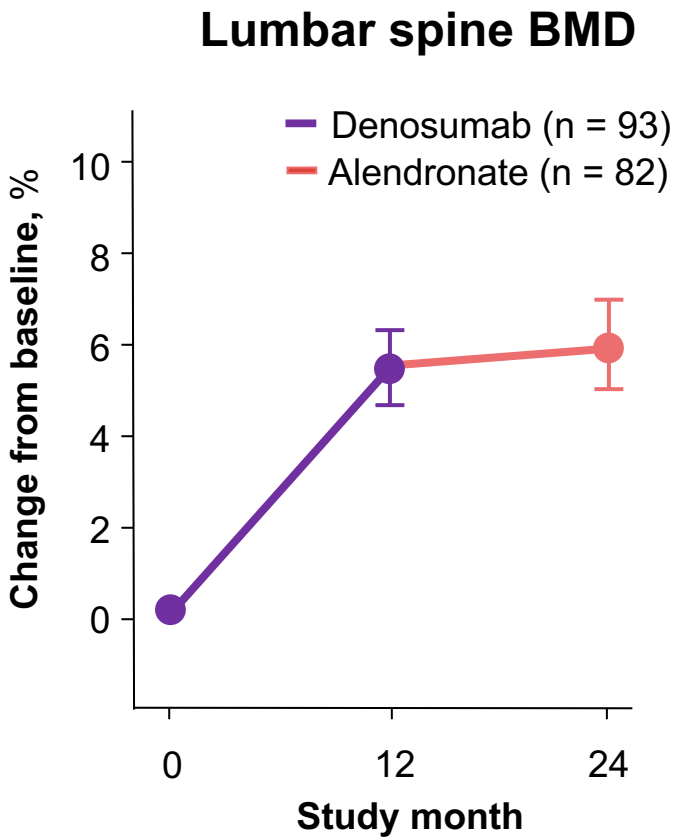
*1,471 patients included 470 patients who discontinued placebo and 1,001 patients who discontinued denosumab; †772 patients included 307 patients who discontinued placebo and 465 patients who discontinued denosumab, and had available off-treatment annualised total hip BMD change assessments; ‡"Prior VFx" includes any VFx sustained before or during treatment; §"Off-treatment annualized total hip BMD loss" was defined as annualised percent change in total hip BMD after treatment discontinuation, ie, between the last on- and off-treatment BMD assessments.
BMD = bone mineral density; CI = confidence interval; NA = not applicable; OR = odds ratio;

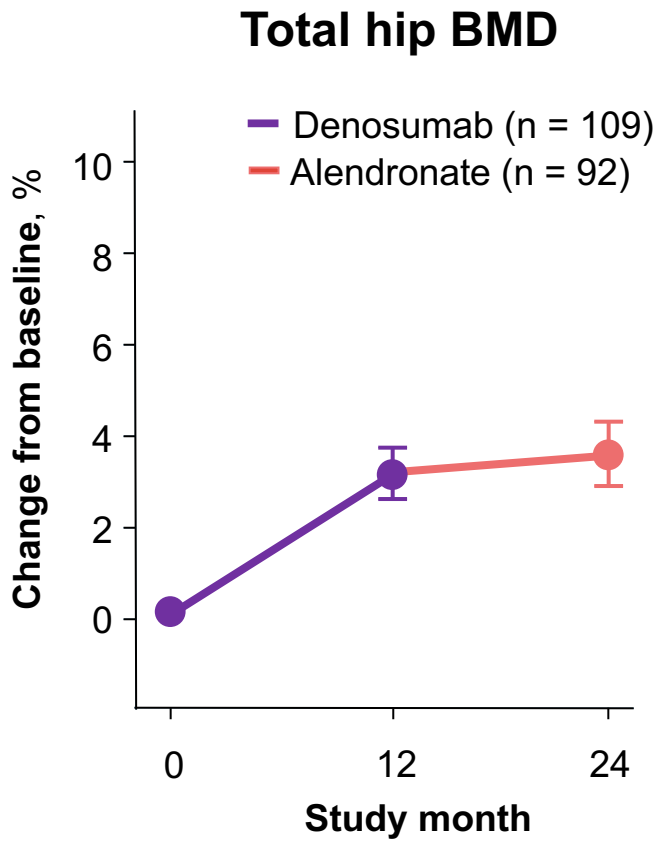
Adapted from: Cummings SR, et al. *J Bone Miner Res.* 2017; [Published only ahead of print November 4, 2017]. 10.1002/jbmr.3337.

The effects of denosumab are reversible when discontinued without follow-on therapy, and overall risk of fracture, including vertebral fracture returns to that of untreated patients. Some patients might be at high risk of developing multiple vertebral fractures[1-3]

1. Bone HG, et al. *J Clin Endocrinol Metab*. 2011;96:972–80. **2**. Brown JP, et al. *J Bone Miner Res.* 2013;28:746–52.
3. Cummings SR, et al. *J Bone Miner Res.* 2018;33:190–98.

Follow-on alendronate therapy prevented reductions in spine and hip BMD in subjects who discontinued denosumab



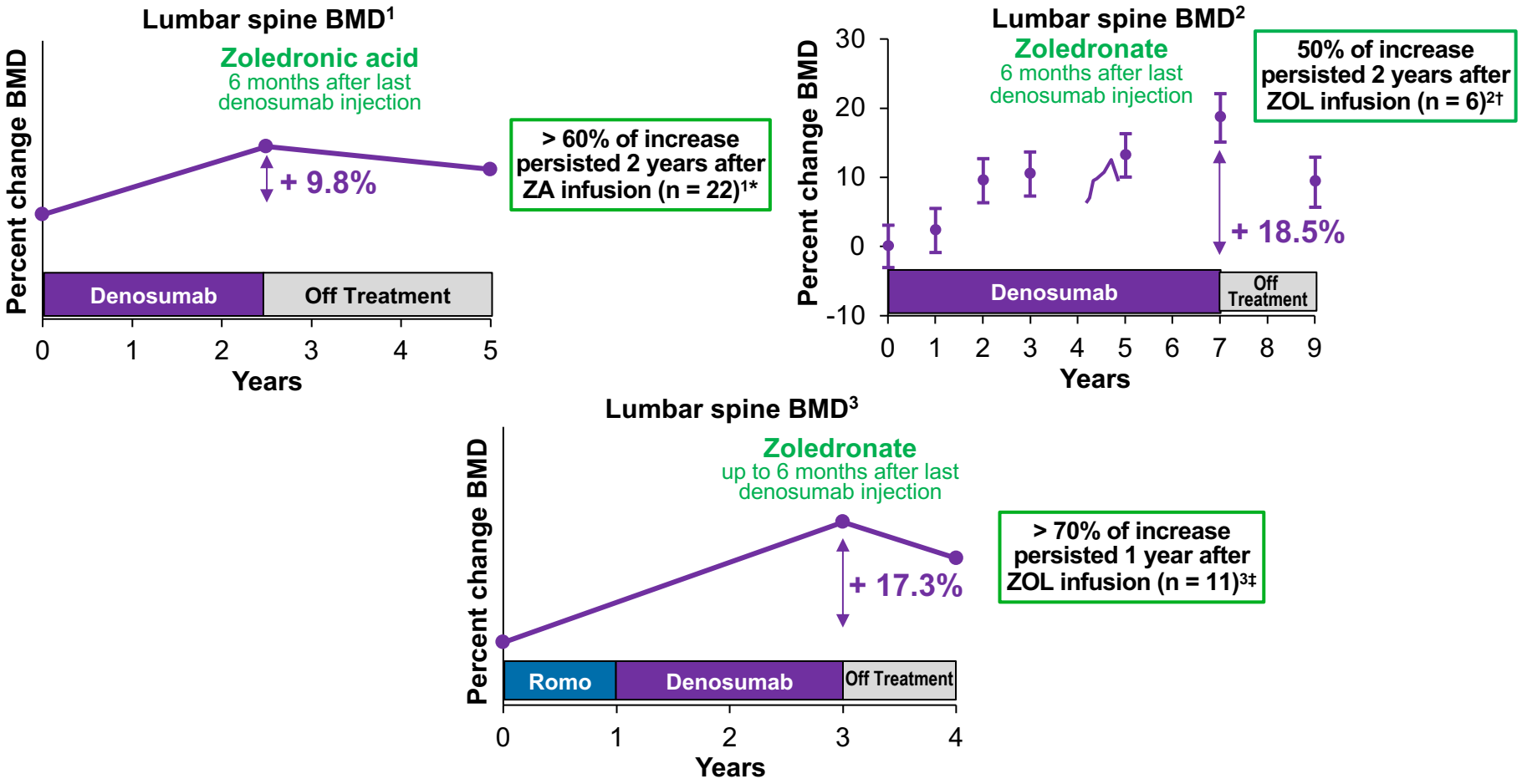


BMD=bone mineral density

1. Freemantle N, et al. *Osteoporos Int* 2012;23:317–26.

Follow-on therapy with zoledronic acid mitigates bone loss at the lumbar spine after discontinuing denosumab

Percent change lumbar spine BMD after discontinuation based on case series



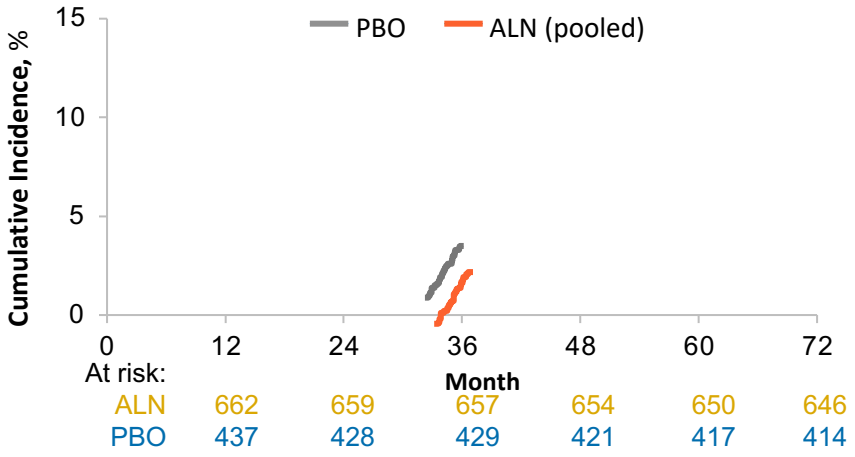
*56% of hip BMD increase was retained at 2 years. †0% of hip BMD increase was retained at 2 years. ‡87% of hip BMD increase was retained at 1 year.
BMD=bone mineral density; Romo=romosozumab; ZA=zoledronic acid; ZOL=zoledronate

1. Lehman T, et al. *Osteoporos Int.* 2017;28:3067–68. **2**. Reid IR, et al. *Calcif Tissue Int.* 2017;101:371–74.
3. Horne AM, et al. *Calcif Tissue Int.* 2018. DOI:10.1007/s00223-018-0404-6.

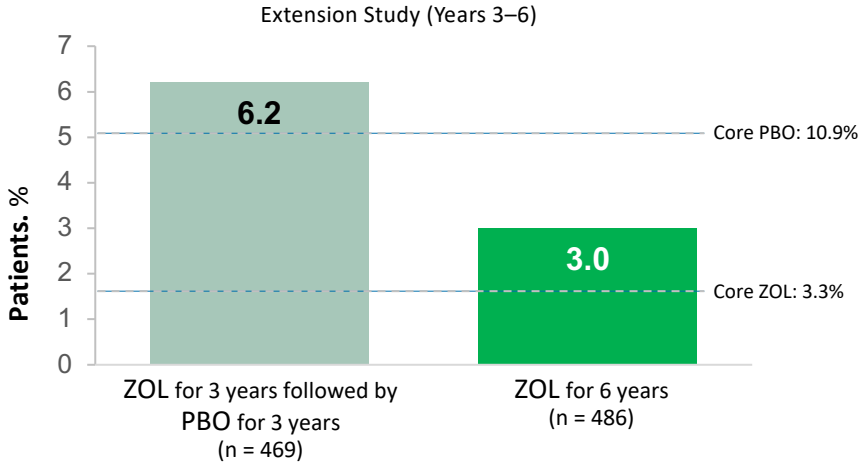
Vertebral Fractures Are the First Fractures to Manifest After Bisphosphonate Discontinuation

- After discontinuing ALN or ZOL, vertebral fractures increase over 3–5 year follow-up periods[1,2]

Clinical vertebral fractures begin to increase ~12 months after discontinuing ALN[1]*



3 years after discontinuing ZOL, morphometric vertebral fractures were 2-fold higher in PBO group vs ZOL[2]



*Morphometric vertebral fractures were not increased. †Subjects previously received ALN for an average of 5 years during (and after) FIT enrolled in FLEX and re-randomized to either PBO or ALN. ‡Other fracture types included non-vertebral, hip, forearm, and all clinical fractures.

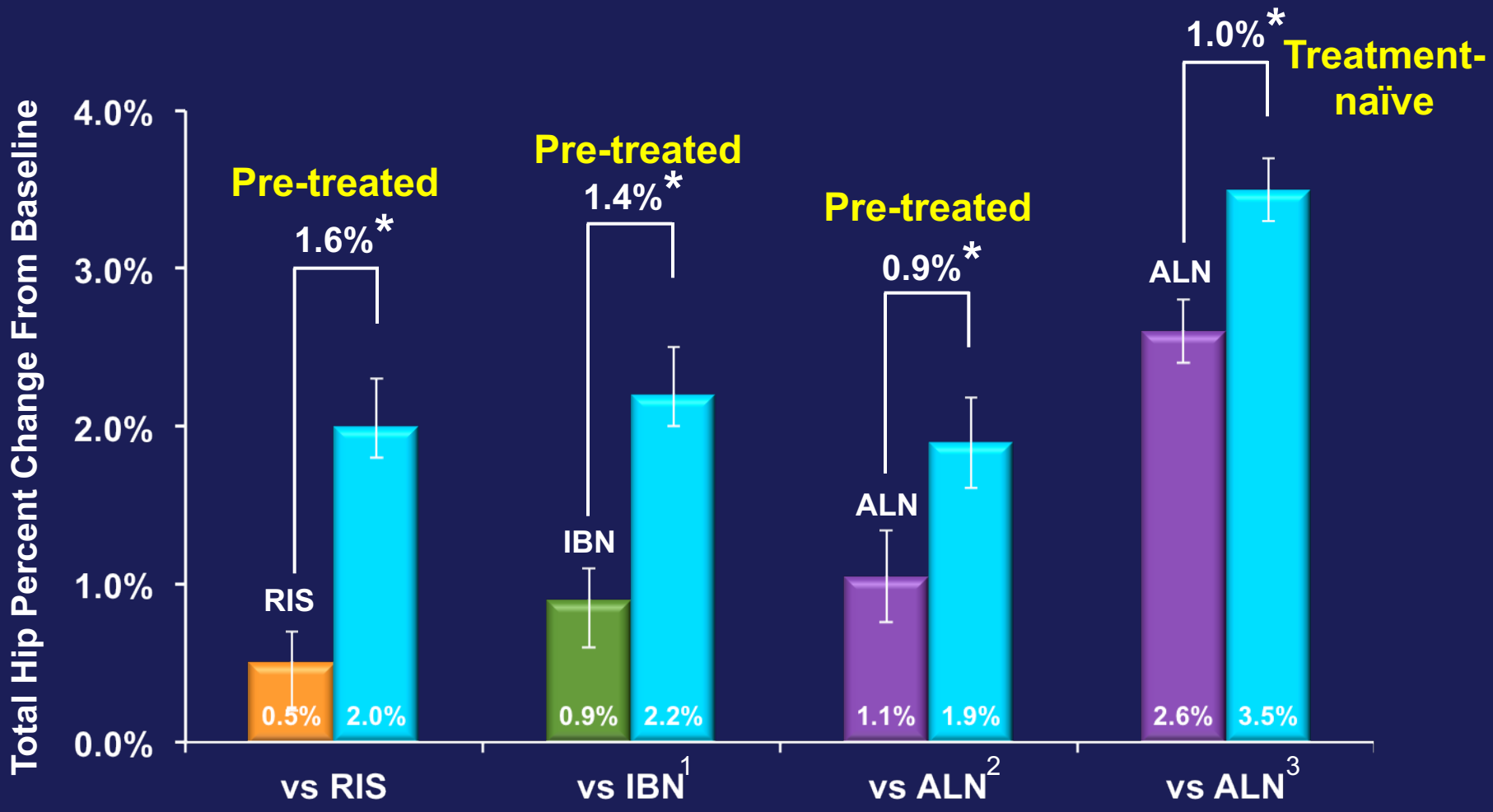
ALN=alendronate; FIT=Fracture Intervention Trial; FLEX=Fracture Intervention Trial Long-term Extension; PBO=placebo; ZOL=zoledronic acid

1. Adapted from: Black DM, et al. *JAMA.* 2006;296:2927-2938. **2.** Adapted from: Black DM, et al. *J Bone Miner Res.* 2012;27:243-254.

Why Change Therapy?

- Sequential therapy for osteoporosis may be considered
  - When there has been significant bone loss or a fracture on antiresorptive therapy for >12 months
  - In the presence of adverse events
  - Insufficient adherence, e.g. the elderly
  - Dosing inconvenience or intolerance with oral bisphosphonate therapy
  - Patients with CKD where bisphosphonates are contraindicated
  - To consolidate increases in BMD following anabolic therapy

Head-to-head Studies of Denosumab vs Bisphosphonates in Both Pre-treated or Treatment-naïve Subjects



Data are least-squares means and 95% confidence intervals. *$p < 0.0001$ denosumab vs BP.

[1]Recknor C et al. ASBMR Poster FR0388. [2]Kendler DL et al. *J Bone Miner Res*. 2010;25:72-81.

[3]Brown JP et al. *J Bone Miner Res*. 2009;24:153-161

Roux C et al, ASBMR; Minneapolis, MN; October 12-15, 2012.

Osteoporosis risk assessment, diagnosis and management

Recommendations restricted to postmenopausal women and men aged >50 years

RACGP Royal Australian College of General Practitioners | osteoporosis australia

Minimal trauma hip or vertebral fracture

DXA to establish baseline BMD – recommended but not essential

Initiate treatment with anti-osteoporosis medication
- Bisphosphonates (Grade A)
- Denosumab (Grade A women, Grade B men)
- Oestrogen replacement therapy (Grade A)
- Strontium ranelate – second line only (Grade A)

Where appropriate
- Implement falls reduction strategies (Grade A)
- Encourage exercise participation (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

Minimal trauma fracture at any other site*

DXA of spine and proximal femur (Grade A)

T-score ≤–1.5

Initiate treatment with anti-osteoporosis medication
- Bisphosphonates (Grade A)
- Denosumab (Grade A women, Grade B men)
- Oestrogen replacement therapy (Grade A)
- Strontium ranelate – second line only (Grade A)

Where appropriate
- Implement falls reduction strategies (Grade A)
- Encourage exercise participation (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

T-score >–1.5

Refer for specialist review

No history of minimal trauma fracture

Aged ≥70 years‡ (Grade D Consensus)

DXA of spine and proximal femur (Grade A)

T-score ≤–2.5?

Yes

Initiate treatment with anti-osteoporosis medication
- Bisphosphonates (Grade A)
- Denosumab (Grade A women, Grade B men)
- Oestrogen replacement therapy (Grade A)
- Strontium ranelate – second line only (Grade A)

Where appropriate
- Implement falls reduction strategies (Grade A)
- Encourage exercise participation (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

No

Assess risk factor profile (Grade B) Major risk factors that qualify for MBS reimbursement of DXA†

Non-modifiable
- Parental history of fracture

Modifiable and lifestyle
- Premature menopause†
- Hypogonadism†
- Multiple falls
- Low physical activity or immobility
- Low body weight
- Low muscle mass and strength
- Poor balance
- Protein or calcium undernutrition
- Smoking
- Alcohol >2 standard drinks/day
- Vitamin D insufficiency

Diseases or conditions§
- Rheumatoid arthritis†
- Hyperthyroidism†
- Hyperparathyroidism†
- Chronic kidney disease†
- Chronic liver disease†
- Coeliac disease or malabsorption†
- Diabetes mellitus
- Myeloma or MGUS
- Organ transplant
- Bone marrow transplant
- HIV infection
- Depression

Medications (large effect)
- Glucocorticoids†‖ (>3 months≥7.5 mg/day)
- Excess thyroid hormone replacement
- Aromatase inhibitors
- Anti-androgen therapy†

Medications (modest effect)
- SSRIs
- Anti-psychotics
- Thiazolidenediones
- Anti-epileptic medications
- PPIs

Estimate absolute fracture risk Garvan Fracture Risk Calculator or FRAX (Grade D Consensus)

High 10-year risk of fracture Hip fracture >3%, any fracture >20% OR **T-score ≤–2.5**

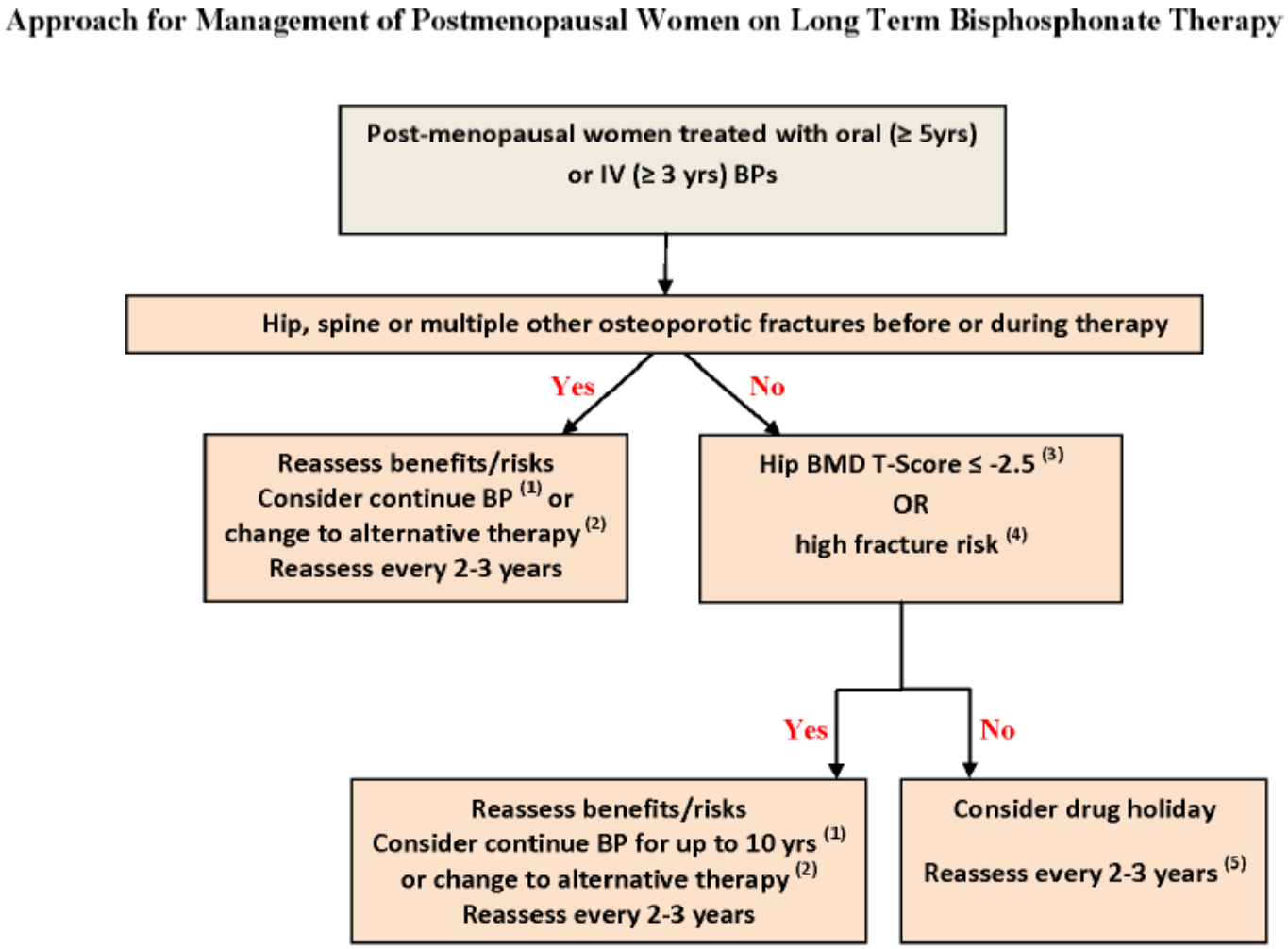
Low risk of fracture

Treatment not recommended

BMD Bone mineral density
DXA Dual energy X-ray absorptiometry
HIV Human immunodeficiency virus
MBS Medicare Benefits Schedule
MGUS Monoclonal gammopathy of undetermined significance
PPIs Proton pump inhibitors
SSRIs Selective serotonin reuptake inhibitor

* Excluding fingers and toes
† Qualifies for MBS reimbursement of BMD testing
‡ Consensus recommendation. The MBS reimburses costs for measurement of BMD testing in any person aged ≥70 years
‖ See other guidelines specific to glucocorticoid treatment for more information and recommendations regarding glucocorticoid use and risk of osteoporosis and fracture
§ Treatment of an underlying condition may improve bone strength

Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of ASBMR



Adler RA et al., J Bone Miner Res 2016

Recommendations for Management of Bone Disease in HIV

- Guidelines for ART should be followed; adjustment should avoid TDF or boosted protease inhibitors in at-risk patients

- Dietary and lifestyle management strategies for high-risk patients should be employed and anti-osteoporosis treatment initiated – the best evidence is for zoledronic acid which avoids issues with poor compliance

Brown TT et al. CID Jan 2015

EACS Bone Health Guidelines v8.2 January 2017

Reducing risk of fractures	• Aim to decrease falls by addressing fall risks[i] • Ensure sufficient dietary calcium (1-1.2 g daily) and vitamin D (800-2,000 IU daily) intake[ii] • Where appropriate, screen for osteoporosis[iii] and refer to national/regional guidelines on treatment of osteoporosis – If no guidelines available, consider bisphosphonate[iv] treatment in all osteoporotic postmenopausal women and men > 50 years old (BMD T-score ≤ -2.5) and those with a history of fragility fracture. Consider treatment based on BMD alongside consideration of other risk factors for fracture, especially age. – Use bisphosphonate and ensure adequate calcium and vitamin D intake – No significant interactions between bisphosphonates and antiretrovirals – If antiretroviral naïve, consider options for ART that preserve BMD[v] – If diagnosed with osteoporosis and requiring therapy, consider optimising ART to preserve or improve BMD • In complicated cases (e.g. young men, premenopausal women, recurrent fracture despite bone protective therapy), refer to osteoporosis specialist • If on bisphosphonate treatment, repeat DXA after 2 years and reassess need for continued treatment after 3-5 years

British HIV Association Bone Health Guidelines 2016

Tenofovir-AF may therefore be used in individuals with bone-related contraindication to tenofovir-DF

8.10.3.1 Recommendations

- We recommend against the use of tenofovir-DF in individuals aged >40 years with osteoporosis, a history of fragility fracture, or a FRAX score consistent with high risk of a major osteoporotic fracture, if acceptable alternative ARV agents are available (1B).

8.10.4 Switching treatment

8.10.4.1 Recommendations

- We recommend against continued use of tenofovir-DF in individuals >40 years who are diagnosed with osteoporosis, have sustained a fragility fracture, or have a FRAX score of >20% (major osteoporotic fracture) if acceptable alternative ARV agents are available (1C).

Tenofovir-AF as part of initial therapy is associated with significantly less decline in BMD compared with tenofovir-DF, consistent with other first-line ARV regimens [21]; in addition, switching from tenofovir-DF to tenofovir-AF containing therapy is associated with improvements in BMD [22]. Tenofovir-AF may therefore be used in individuals with bone-related contra-indication to tenofovir-DF.

Conclusions

- HIV infection is associated with an increased risk of vitamin D deficiency, osteoporosis and fracture
- The pathogenesis of osteoporosis associated with HIV infection is multifactorial and several risk factors are modifiable
- Bone health should be assessed in all HIV-infected individuals
- Treatment with bone protective therapy should be considered in patients with a fracture, after exclusion of osteomalacia, and in others with a high fracture probability

Thank You!