BoneCast

CSA Edition

Evaluation and Management of Bone Fragility in HIV

Dr Polyzois Makras

IOF International Osteoporosis Foundation

Evaluation and Management of Bone Fragility in HIV

Polyzois Makras
Endocrinologist
251 Hellenic Air Force & VA Gen. Hospital
Athens, Greece

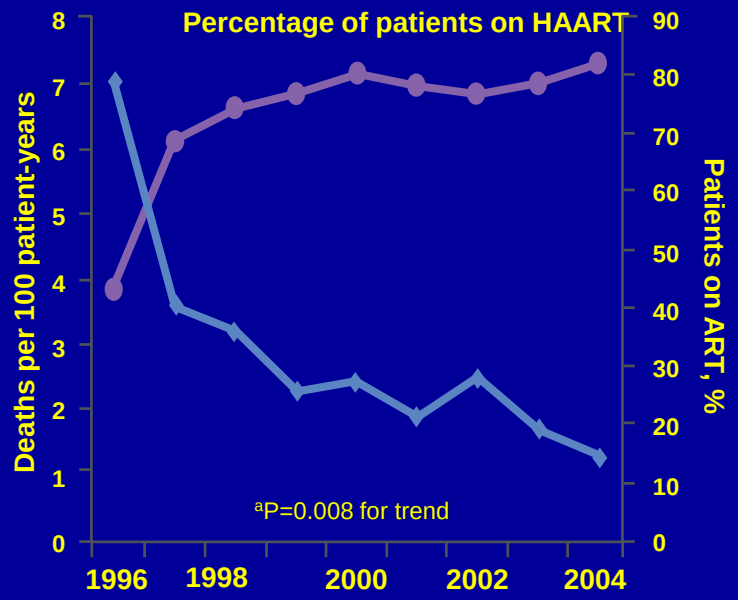
Conflicts of interest

- Lecture fees, advisory boards: Amgen, Gilead, Galenica, Genesis, Pfizer, ELPEN, Vianex, UniPharma, Leo, Rafarm, UCB, Takeda, ITF, Innovis Pharma, BENNETT

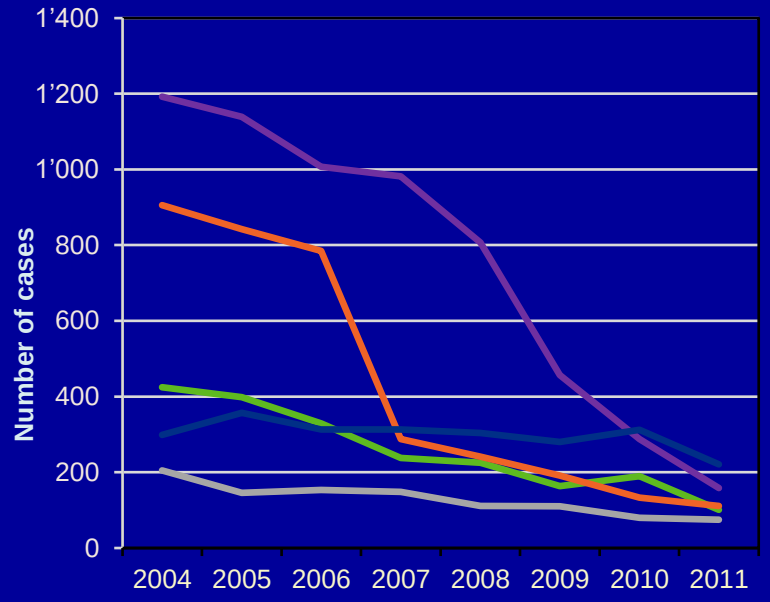
- Research grant : Amgen, Gilead, Galenica, ITF

HIV-positive patients are living longer

Effect of HAART on mortality over time[1]



Decrease in AIDS death rates (2004–2011)[2]

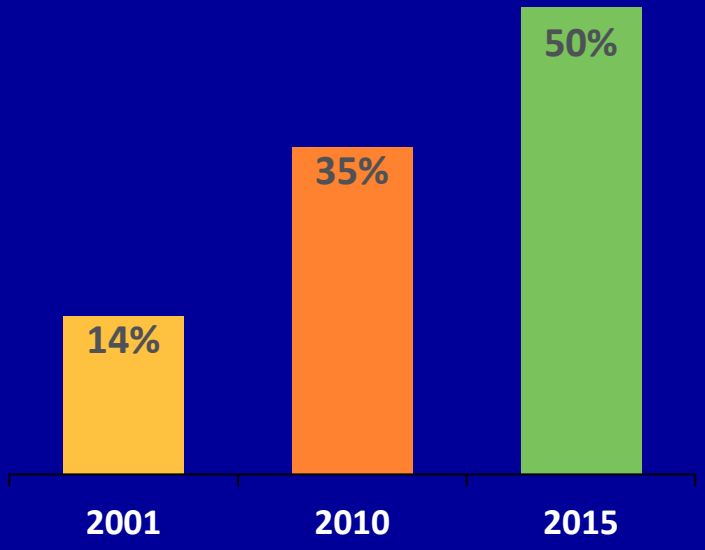


In the United States, a 20-year-old HIV-positive patient can now expect to live into his/her early 70s[3]

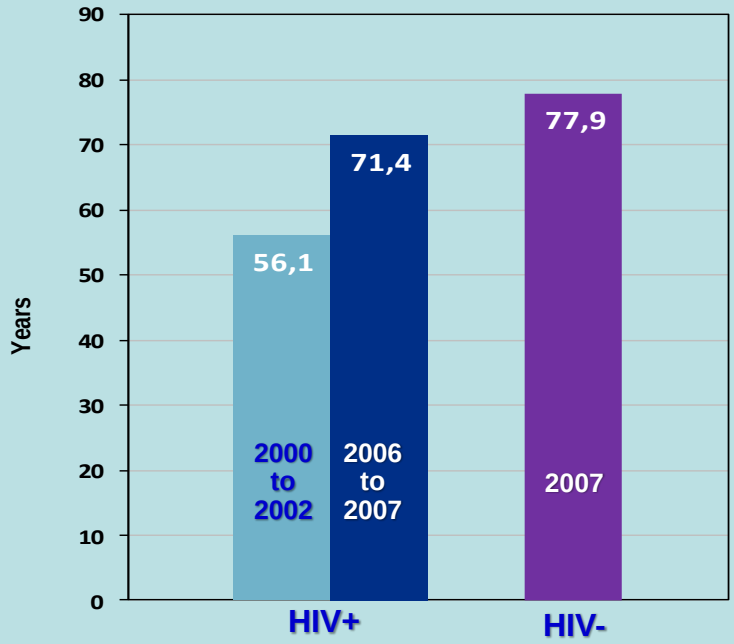
1. Palella FJ et al. JAIDS 2006;43:27–34;
2. Adapted from World Health Organization. 2011 HIV/AIDS Surveillance Report;
3. Samji H et al. PLoS One 2013;8(12):e81355

Average life expectancy of an HIV-positive patient is increasing and is now close to that of the uninfected population

Estimated percentage of persons living with HIV/AIDS who are aged ≥50 years[1–3,6]



US life expectancy[4,5]

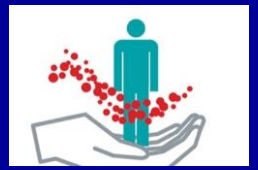


1. Centers for Disease Control and Prevention (CDC). HIV/AIDS Surveillance Report: Cases of HIV Infection and AIDS in the United States and Dependent Areas, 2005; 2. CDC. Diagnoses of HIV Infection in the United States and Dependent Areas, 2011; 3. Effros RB et al. Clin Infect Dis 2008;47:542–553; 4 . Samji H et al. 2013. PLoS One;8(12):e81355; 5. Arias E. Natl Vital Stat Rep 2011;59:1-60. 6. Scherrer AU et al. Int J Epidemiol 2021

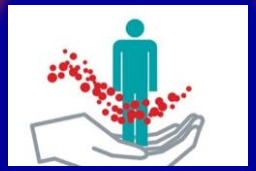
Current situation

Viral suppression

Inflammation



Patient



Chronic disease

HAART

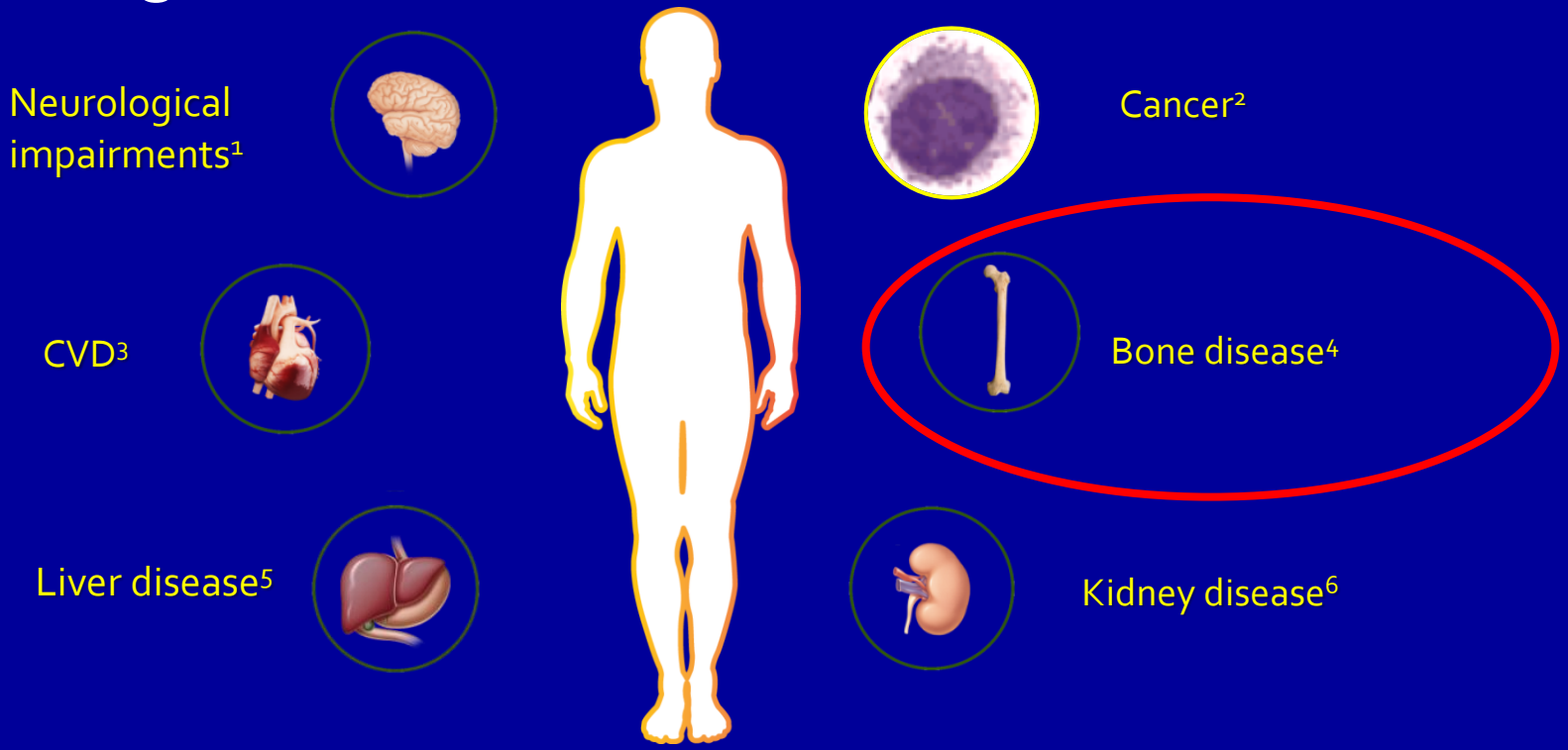
Comorbidities

Accumulating risks

Long-term impact of HIV and ARVs

Beyond undetectable

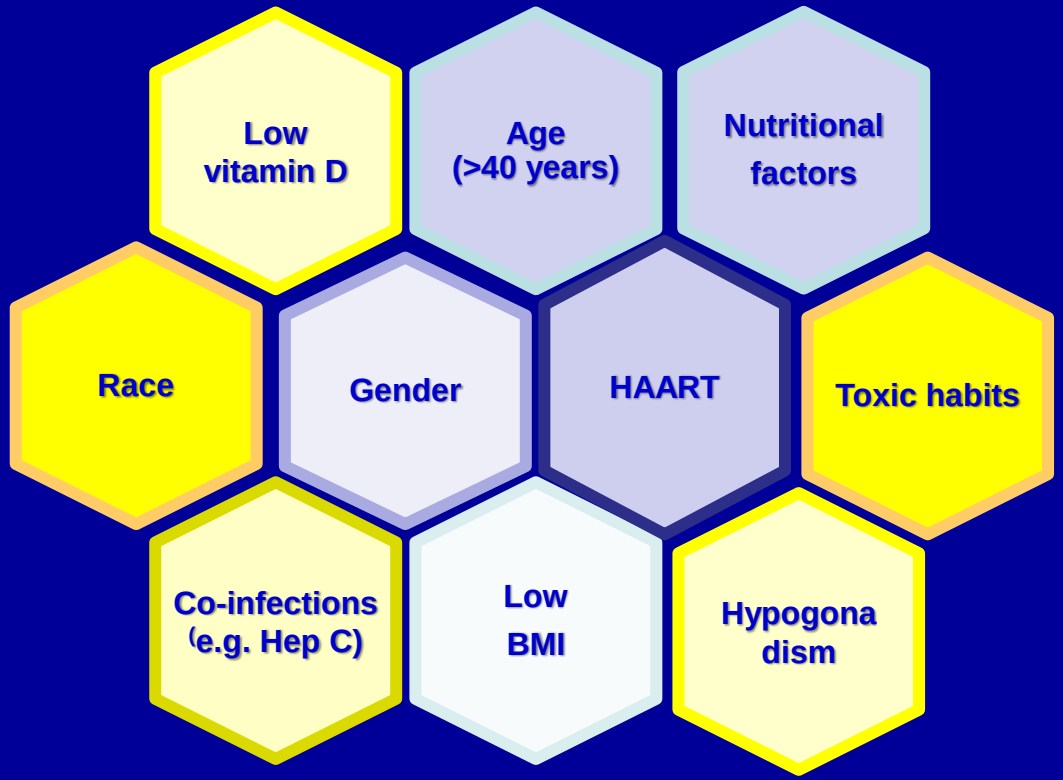
HIV infection and HAART: long-term effects on human health



1. McArthur JC et al. Ann Neurol 2010;67:699–714; 2. Nguyen ML et al. 18th IAC. Vienna, Austria 2010. Abstract WEAB0105;
3. Freiberg MS et al. JAMA Intern Med 2013;173:614–622; 4. Brown TT et al. AIDS 2006;20:2165–2174;
5. Towner WJ et al. JAIDS 2012;60:321–327; 6. Lucas GM et al. Clin Infect Dis 2014;59:e96–e138

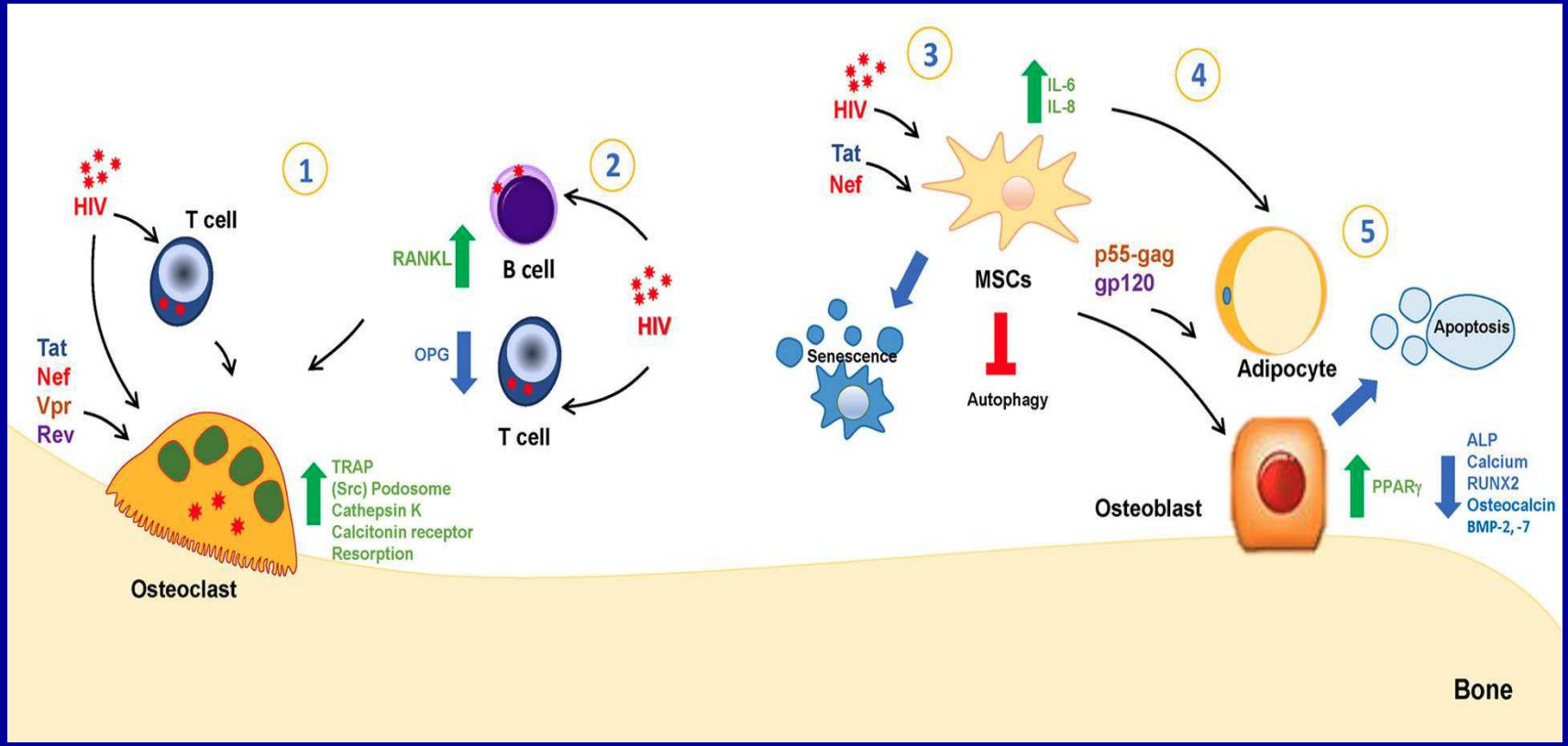
Bone disease

Multi-factorial effect on bone strength



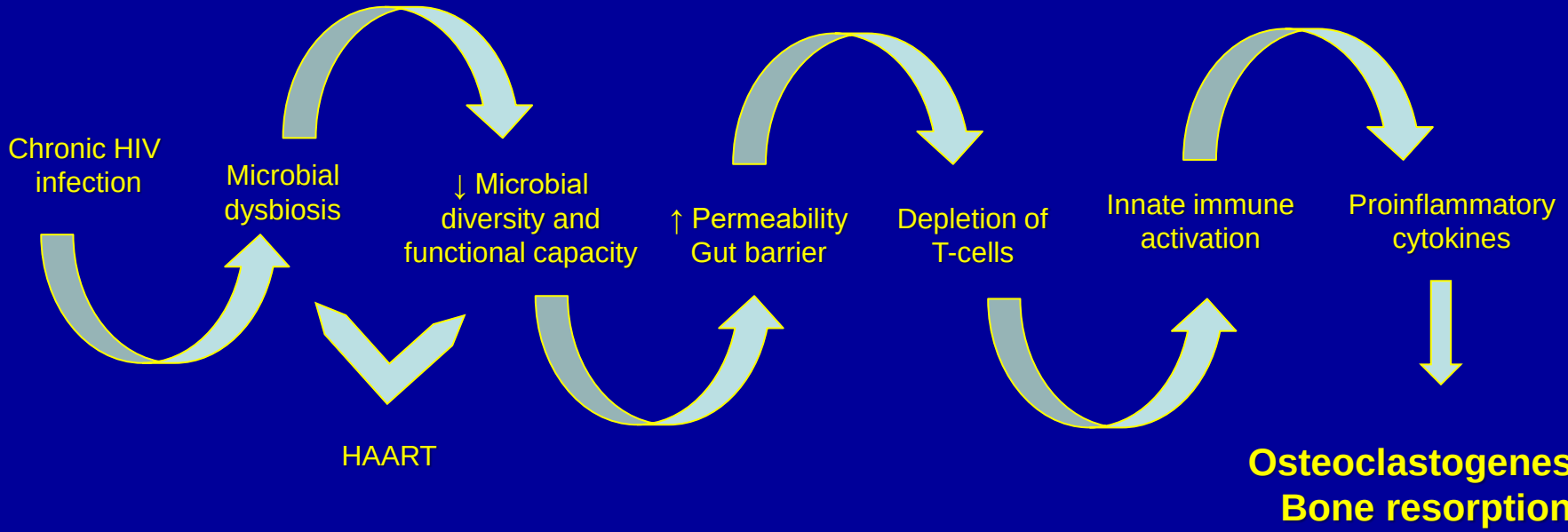
Das S et al. Recent Pat Antiinfect Drug Discov 2014; Biver E. CTI 2022

Virus Activity



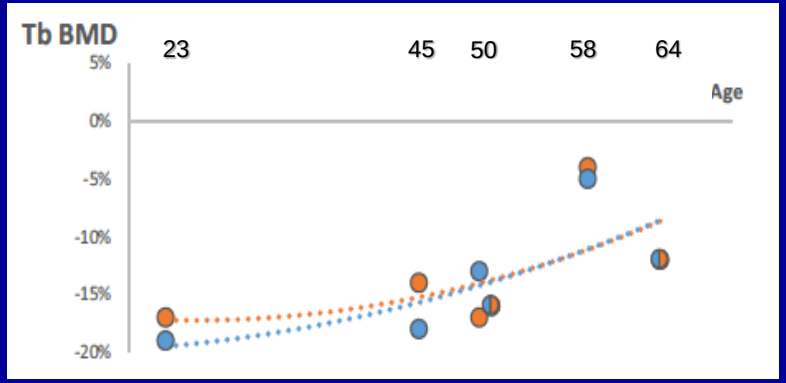
Adapted by Delpino M, Quarleri J, Front Endocrinol ,2020

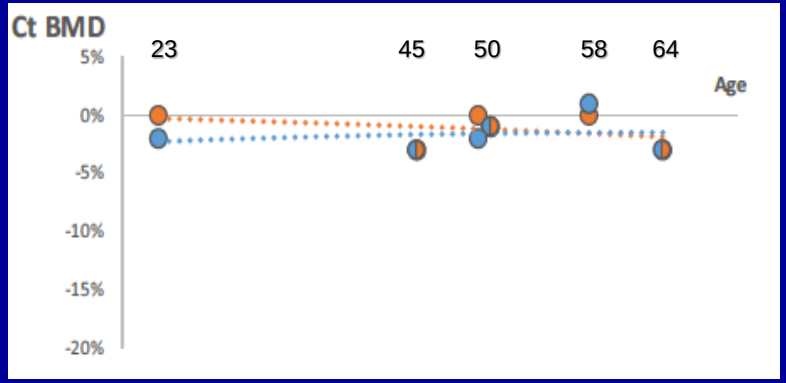
Gut microbiome



Bone microstructure - histomorphometry

- Alterations in volumetric BMD predominate in trabecular than cortical bone

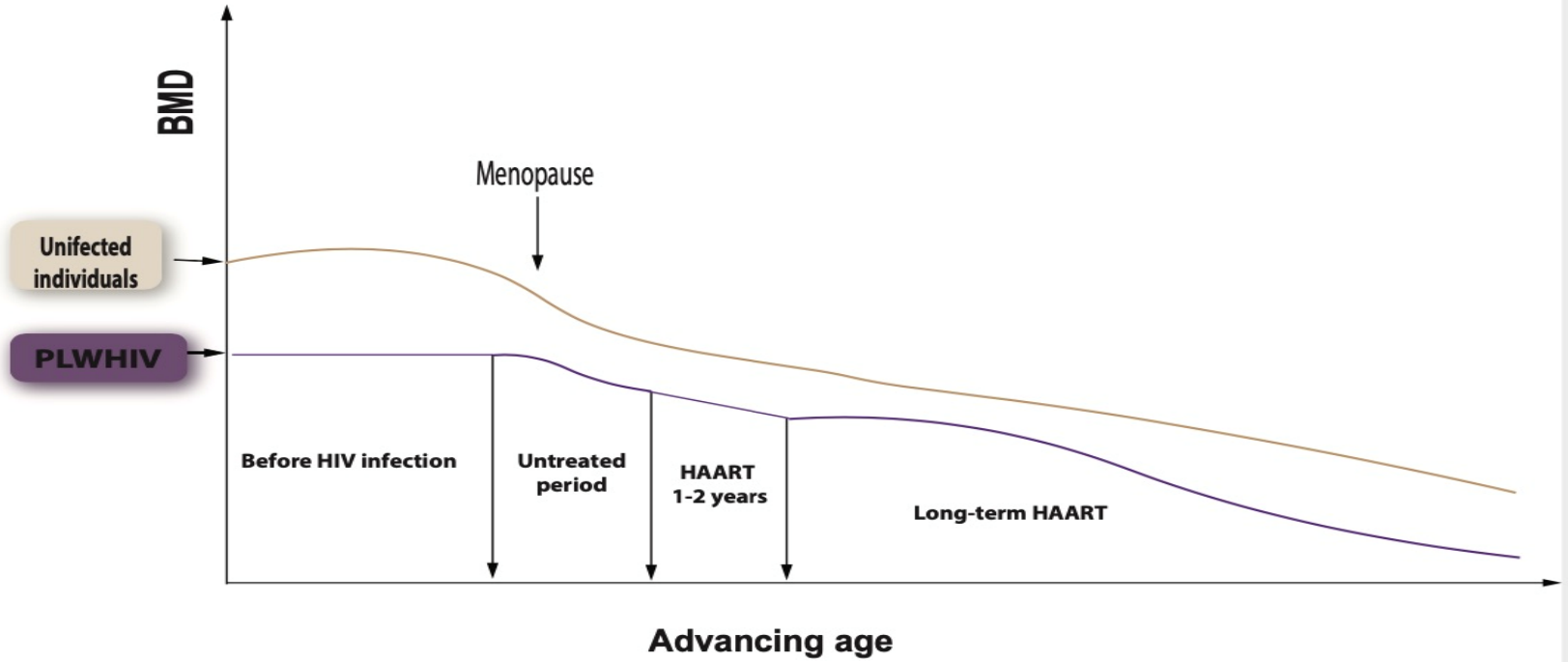


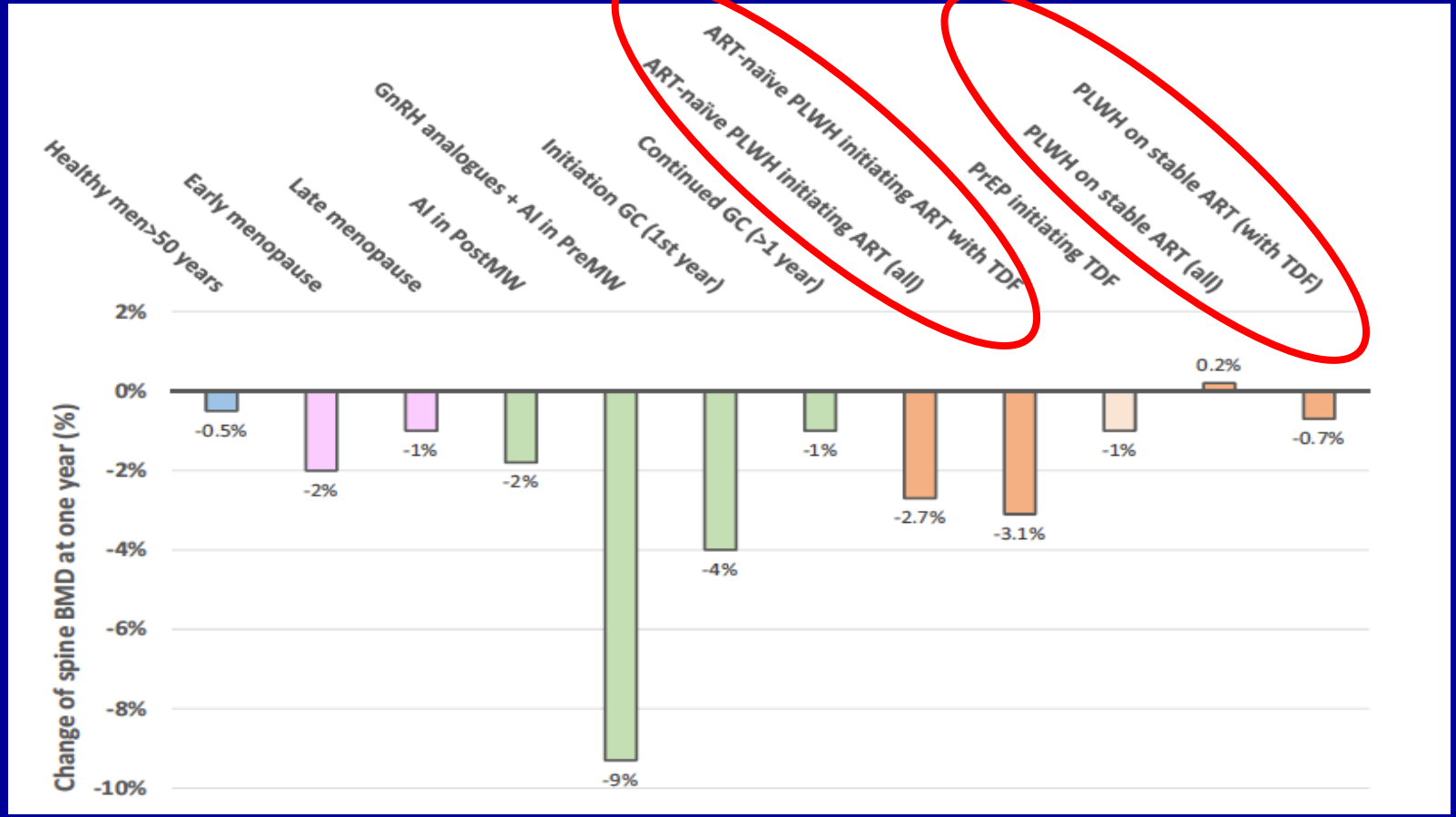


- Untreated: low bone turnover (defective formation and mineralization)
- HAART: increased bone remodelling (still mineralization defect, increased osteoid)

Biver E. CTI 2022

BMD Changes during aging in general population and PLWHIV

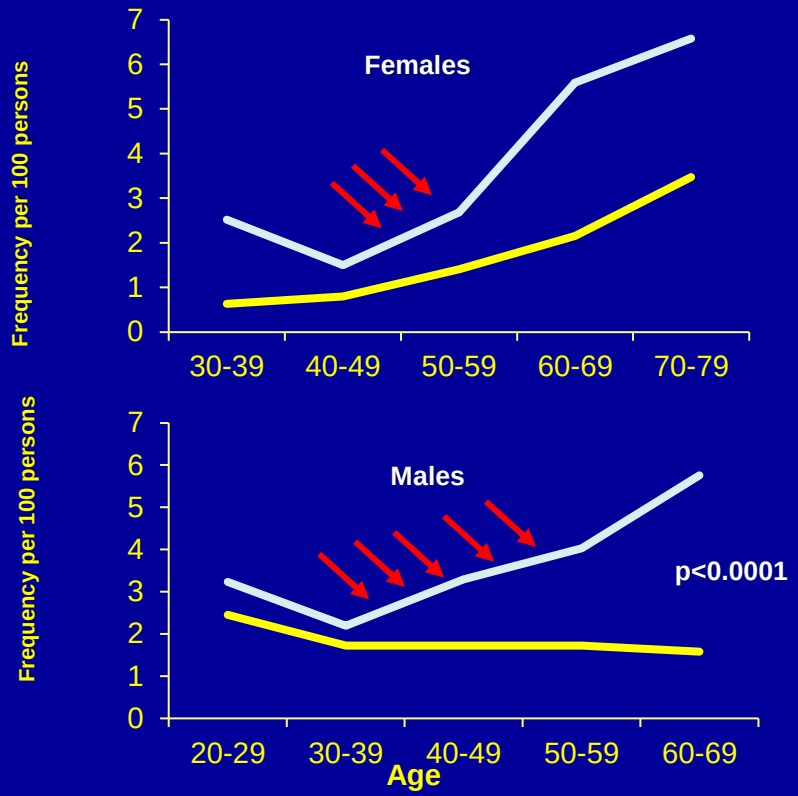




Biver E. CTI 2022

Increased risk of bone loss and fractures

- 6.4-fold increased risk of low BMD and a 3.7-fold increased risk of osteoporosis[1]
- Prevalence of osteoporotic fracture up to 60% higher [2]
- Nearly x5 increased risk in hip fracture incidence independent of sex, age, smoking[3]
- 58% believe that they are at low risk of fracture[4]
- Younger patients still developing will be adversely impacted with BMD-lowering HIV treatments[5]



Incidence of fractures in 8.525 HIV(+) and 2.208.792 controls

1996–2008[2]

Controls

HIV (+)

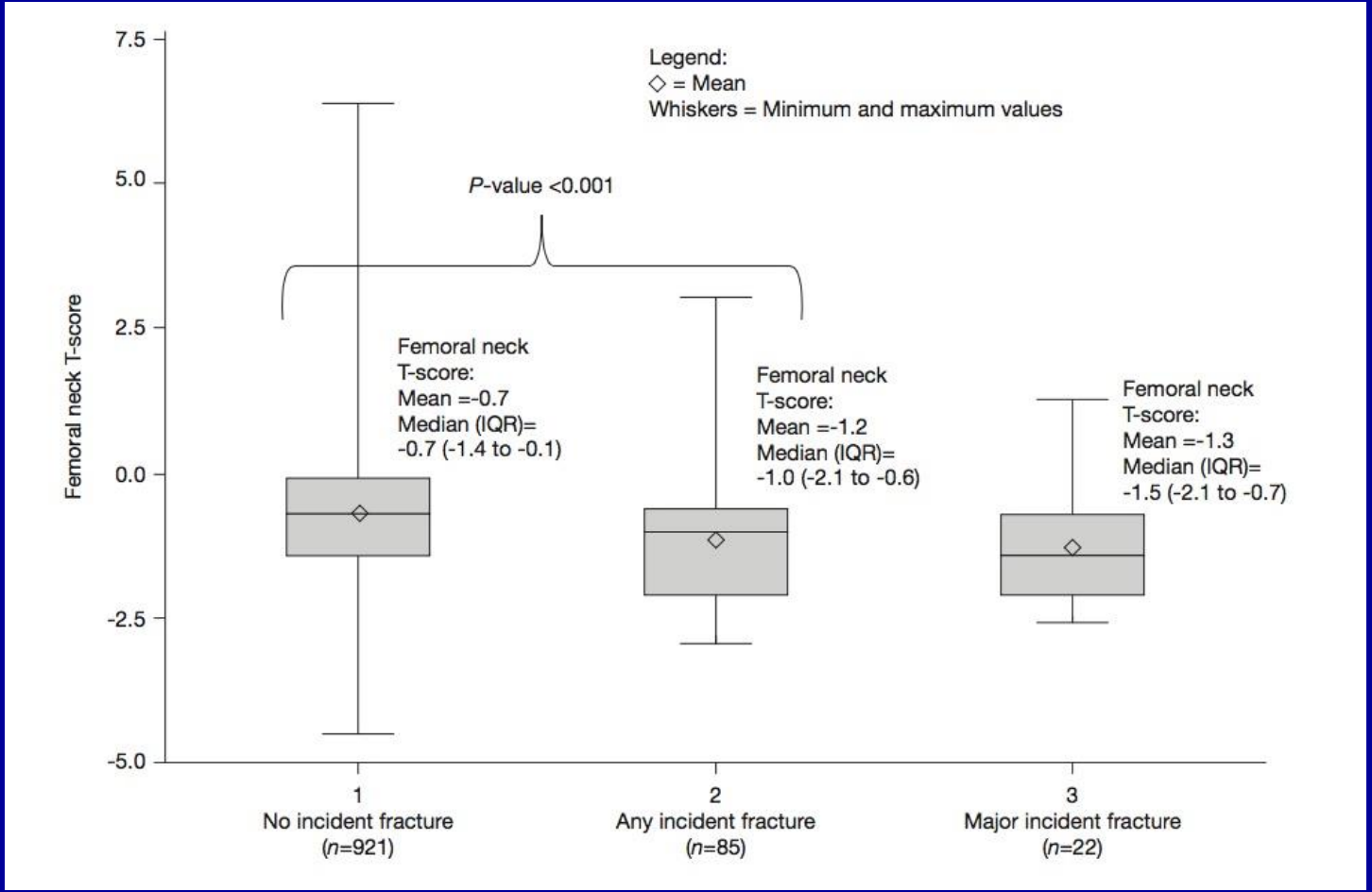
1. Brown TT et al. AIDS 2006 2. Triant VA et al. JCEM 2008 3. Guerri-Fernandez R et al. JBMR 2013 4. Taras J et al. Patient Prefer Adherence 2014 5. Mora S et al. AIDS 2001

n=1006, 83%♂

Mean age: 43 years

36% osteopenia,
4% osteoporosis

85 fractures



Battalora L. et al, Antiviral Therapy, 2016

Effect of HAART

HAART classes

- **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)**

  Examples : tenofovir, abacavir, emtricitabine, lamivudine, stavudine, zidovudine, etc

- **Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

  Examples: delavirdine, efavirenz, nevirapine, and rilpivirine

- **Protease inhibitors (PIs)**

  Examples: atazanavir, darunavir, indinavir, ritonavir, lopinavir

- **Integrase Strand Transfer Inhibitors (INSTIs)**

  Examples: raltegravir, dolutegravir, elvitegravir

- **Fusion inhibitors (FIs)**

  Example: enfuvirtide

- **Chemokine Receptor Antagonists (CCR5 Antagonists)**

  Example: maraviroc

The standard of care is a combination of: two NRTIs (typically tenofovir-emtricitabine) plus one NNRTI or INSTI

Eggleton JS, Nagalli S. Treasure Island (FL): StatPearls Publishing; 2022

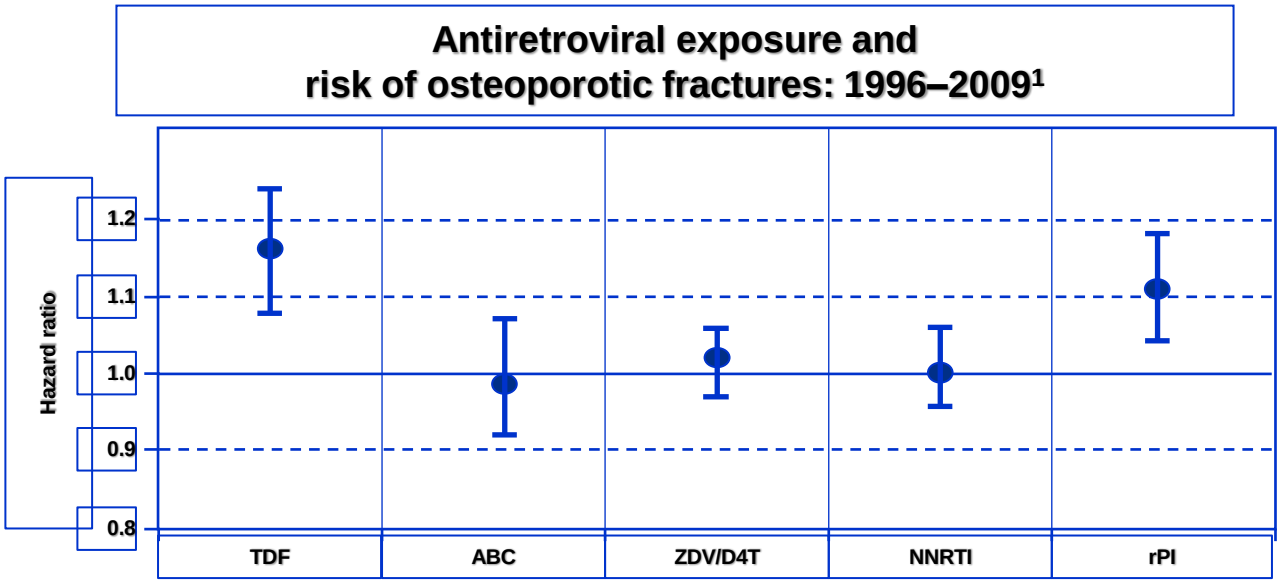
HAART is correlated with BMD loss of 2% - 6% during the first 1-2 years from onset

Study	Pts, N	Duration, Wks	ART	Change in BMD, %		
				Spine	Hip	Total
Gallant 2004[1]	602	144	EFV + TDF/3TC EFV + D4T/3TC	-2.2 -1.0	-2.8 -2.4	- -
Brown 2009[2]	106	96	LPV/RTV + ZDV/3TC EFV + ZDV/3TC	- -	- -	-2.5 -2.3
Duvivier 2009[3]	71	48	PI Non-PI	-4.4 to -5.8 -1.5	-2.4 to -3.7 -2.7	- -
van Vonderen 2009[4]	50	104	LPV/RTV + ZDV/3TC LPV/RTV + NPV	-5.1 -2.6	-6.3 -2.3	- -
Stellbrink 2010[5]	385	48	EFV + TDF/FTC EFV + ABC/3TC	-3.6 -1.9	-2.4 -1.6	- -
McComsey 2011[6]	269	96	TDF/FTC ABC/3TC ATV/RTV EFV	-3.3 -1.3 -3.1 -1.7	-4.0 -2.6 -3.4 -3.1	- - - -

1. Gallant JE, et al. JAMA. 2004;292:191-201. 2. Brown TT, et al. JAIDS. 2009;51:554-561. 3. Duvivier C, et al. AIDS. 2009;23:817-824. 4. van Vonderen MG, et al. AIDS. 2009;23:1367-1376. 5. Stellbrink HJ, et al. CID. 2010;51:963-972. 6. McComsey GA, et al. JID. 2011;203:1791-1801.

Osteoporotic fracture risk in HIV-positive patients on HAART

Veterans Health Administration (VHA)'s Clinical Case Registry (CCR), from 1988–2009



- ARVs can exacerbate low BMD issues

  Initiation of therapy is associated with a 2–6% decrease in BMD over the first two years of treatment[2]

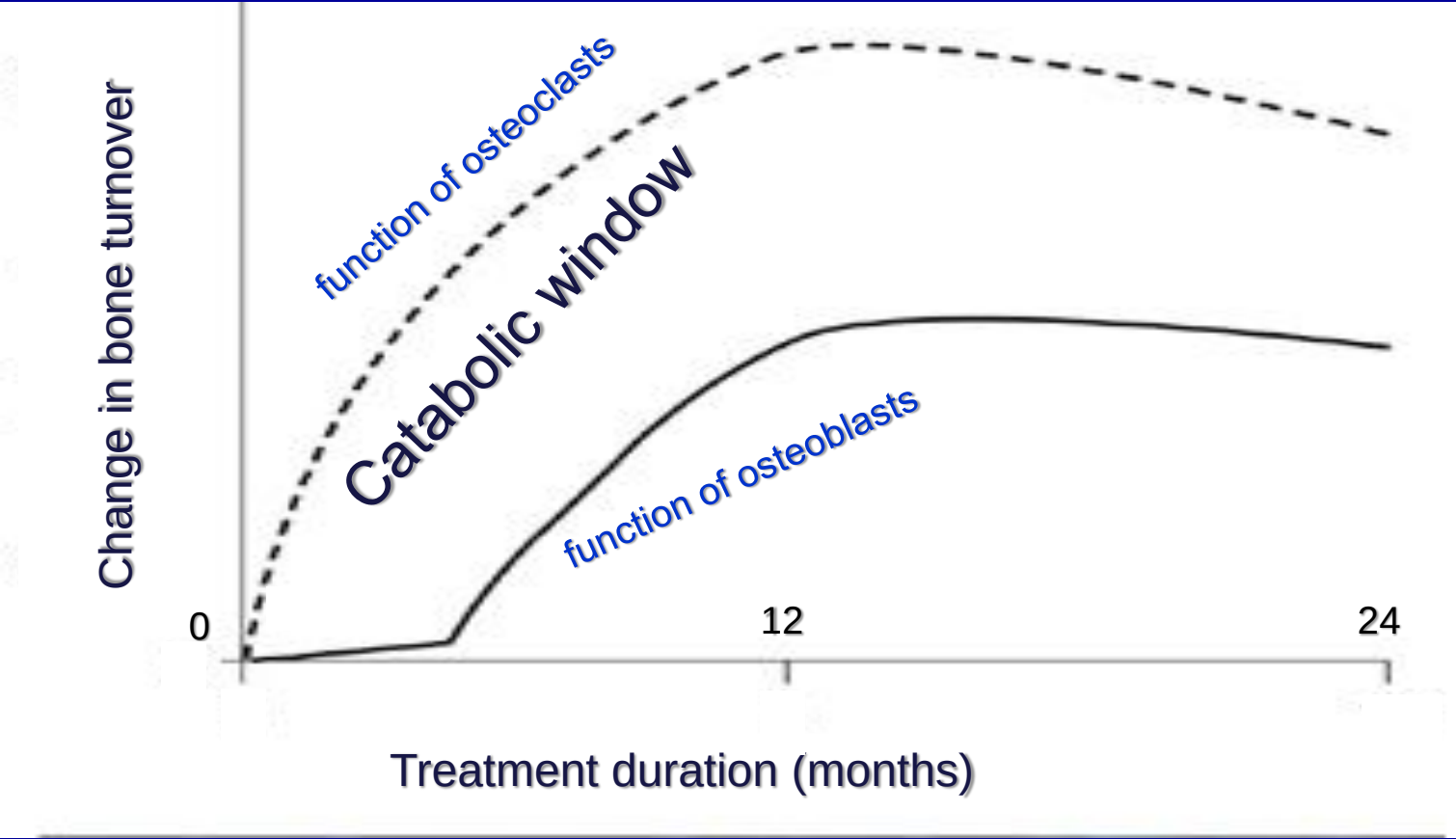
Bedimo R. et al. AIDS, 2012; McComsey GA et al. Clin Infect Dis, 2010

Effect of HAART on BMD and bone metabolism

- Although muscle mass and cytokine (IL-6, TNF-α) levels improve, BMD continues to decrease after onset of 1st and 2nd line HAART
- Bone remodelling increases following treatment's onset (especially with TDF)
- There is an initial increase in osteoclastic function followed much later by an increase in the function of osteoblasts ("catabolic" window) for the first 48 weeks – stabilization thereafter

Cotter AG, Mallon PWG, Curr Opin HIV Aids, 2014

Schematic presentation of bone remodelling following HAART initiation

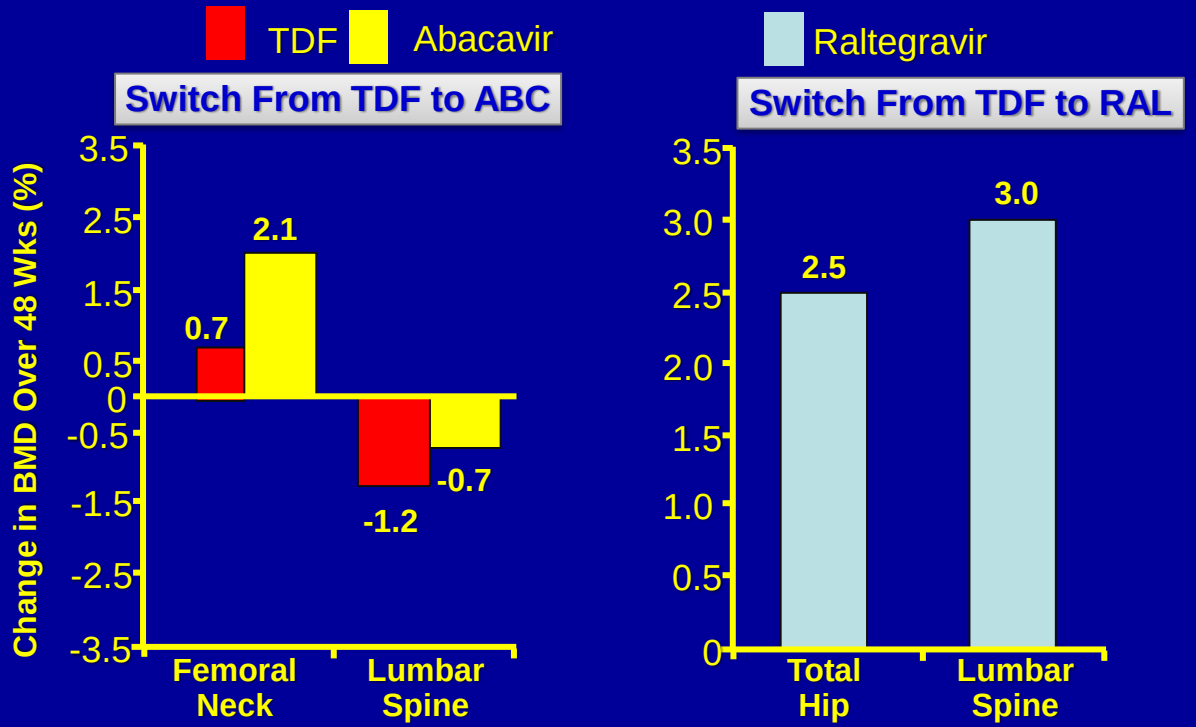


Tenofovir disoproxil fumarate (TDF)

- Hypophosphataemia due to dysfunction of the renal proximal tubule ➔ bone absorption to maintain phosphate levels
- High levels of Vit. D binding protein ➔ functional vit. D deficiency [with normal levels of 25(OH)D]➔ secondary hyperparathyroidism
- Decrease of BMD during the first 24 weeks (1-3% more than other ART) and further aggravation until 96 weeks
- Switch from TDF-containing treatment to TDF-free one improves bone markers (decrease of bone remodeling) and decrease sclerostin, leading to increase of BMD

Grant PM, Cotter AG, Current Opinion in HIV and AIDS, 2016; Hileman CO et al. Current Opinion in Endocrinology, 2015

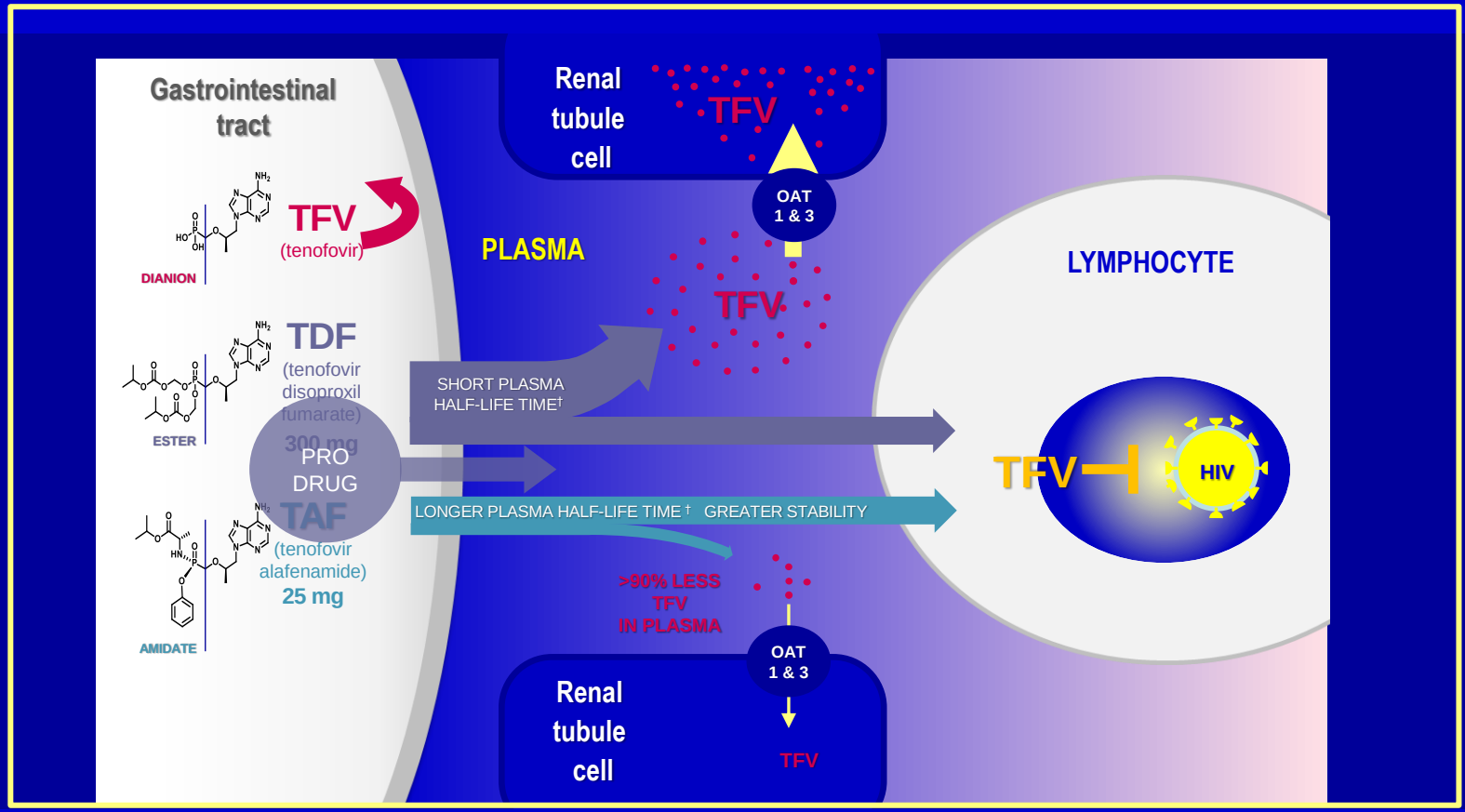
Switch From TDF to ABC or From TDF to RAL in Pts With Low BMD



Negredo E, et al. J Antimicrob Chemother. 2014; Bloch M, et al. HIV Med. 2014

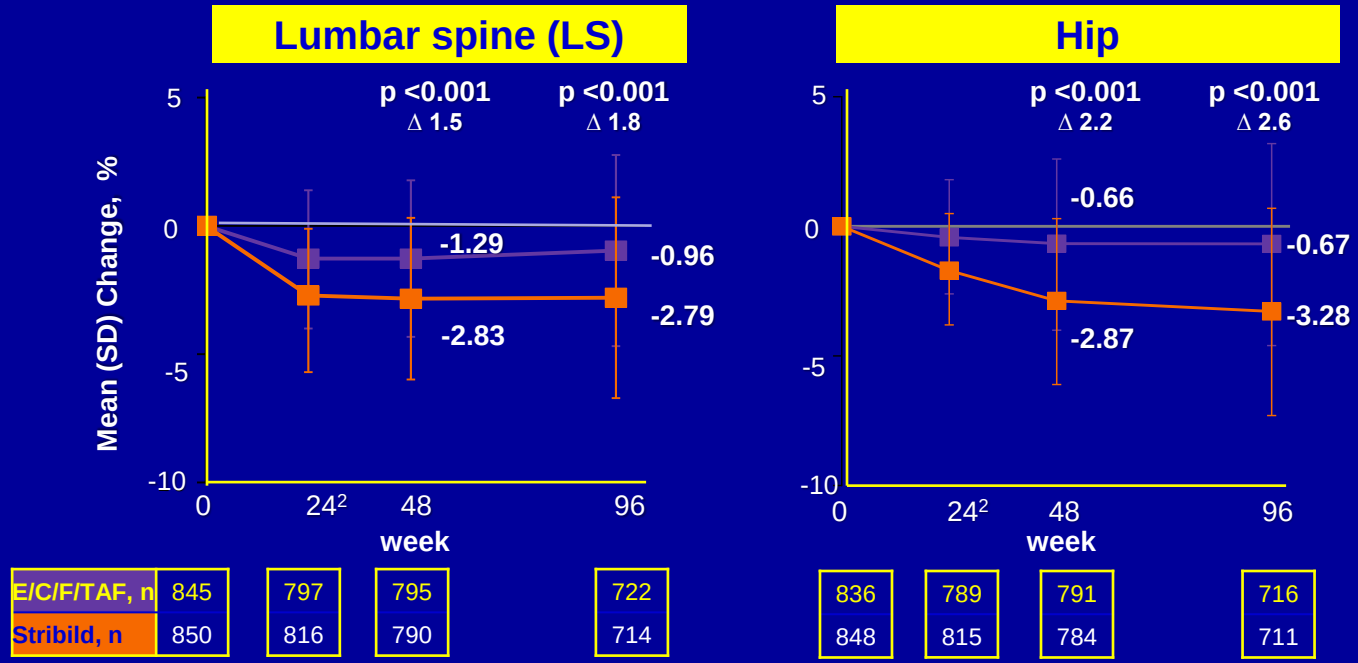
TDF (tenofovir disoproxil fumarate) and TAF (pro-drug of tenofovir; tenofovir alafenamide)

Mechanism of action



Lee W et. *Antimicr Agents Chemo* 2005; Birkus G et al. *Antimicr Agents Chemo* 2007; Babusis D, et al. *Mol Pharm* 2013; Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; Sax P, et al. *JAIDS* 2014. 2014; Sax P, et al. *Lancet* 2015.

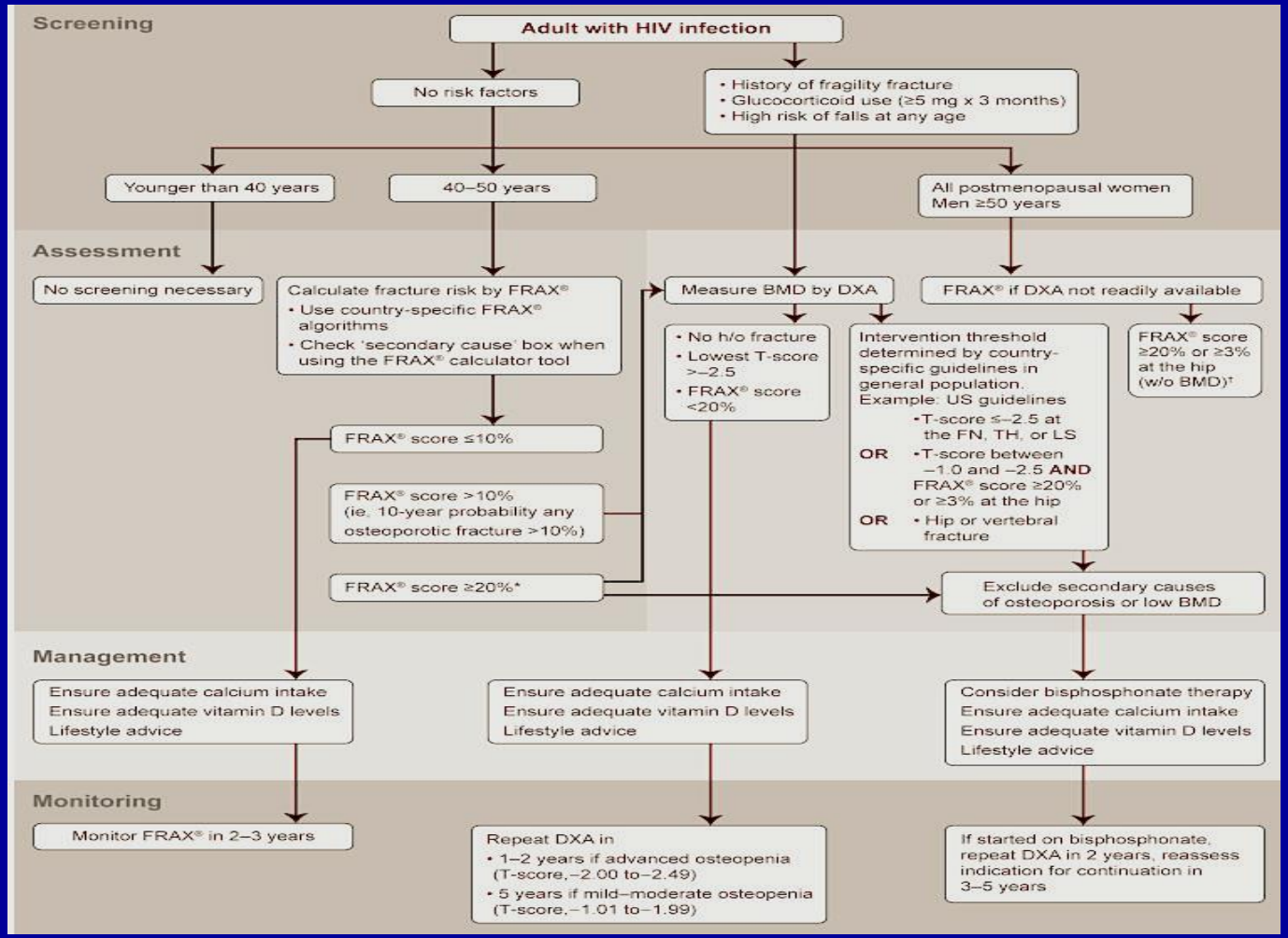
Changes (%) in BMD LS and Hip at week 96



Less BMD loss with E/C/F/TAF which was maintained at 96 weeks, no further decrease after week 48

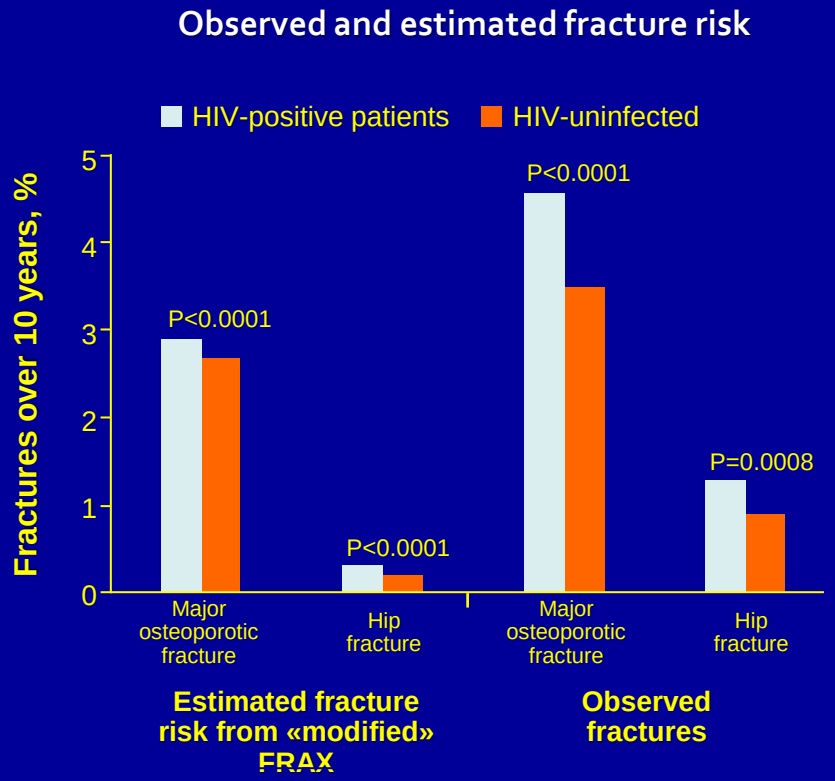
-E/C/F/TAF=single tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
-Stribild= single tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

Wohl D. et al., JAIDS, 2016



Brown TT et al., Clin Infect Dis, 2015

FRAX probably underestimates the fracture risk among HIV (+)



VACS Virtual Cohort Study

2003–2009

- Based on their FRAX score 97% of HIV-positive men with an actual fracture would not have been flagged for treatment
- Considering HIV infection as reason for 'secondary' osteoporosis improved the accuracy of FRAX prediction

Yin M et al. J Acquir Immune Defic Syndr, 2016

No difference were found between the cost effective 10-year major osteoporotic fracture probabilities of PLWH and uninfected population both within females [14.32 ± 2.28 (HIV +) Vs. 12.52 ± 1.61 (HIV -), p=0.32] and males [10.03 ± 1.40 (HIV +) Vs. 13.12 ± 3.02 (HIV -), p=0.17].

No differences were found between the cost effective 10-year hip fracture probabilities of HIV infected and uninfected male population [3.56 ± 1.01 (HIV +) Vs. 3.21 ± 0.76 (HIV -), p=0.23].

Higher cost-effective thresholds of females ≥ 70-years old [9.4 ± 1.94 (HIV +) Vs. 5.55 ± 1.18 (HIV -), p=0.01], while for the younger population no significant differences were found [1.7 ± 0.3 (HIV +) Vs. 1.5 ± 0.18 (HIV -), p=0.28].

Makras et al. JMNI 2017

No difference in FRAX based cost effective intervention thresholds among PLWH and uninfected population in Greece

- Up to 75 years

  major osteoporotic Fx: 10%

  Hip Fx: 2,5%

- >75 years

  major osteoporotic Fx: 15%

  Hip Fx: 5%

Makras et al Osteoporos Intern 2015; Makras et al. JMNI 2017

Alendronate

Alendronate in people living with HIV: main published studies

References	Study design	Population	Vitamin D and calcium	Results
Guaraldi	Randomized to alendronate or not 52 weeks	N=41, receiving ARVT T-score <−1	Calcium/vitamin D supplements	No differences of BMD between groups. Decrease in serum type I collagen N-telopeptides in the alendronate group
Mondy	Randomized to alendronate or not 48 weeks	N=31, receiving ARVT T-score <−1	Calcium/vitamin D supplements	Alendronate increased lumbar spine BMD
Negredo	Randomized to alendronate or not 96 weeks	N=25, receiving ARVT T-score <−2.5	Dietary calcium and vitamin D counseling	Alendronate improved lumbar spine BMD at week 48 Improvements in trochanter BMD were obtained at week 96
McComsey	Randomized placebo-controlled 48 weeks	N=82, receiving ARVT lumbar spine T-score <−2.1	Calcium/vitamin D supplements	Alendronate improved BMD at the lumbar spine, total hip and trochanter, but not at the femoral neck
Rozenberg	Randomized placebo-controlled 96 weeks	N=44, receiving ARVT T-score ≤−2.5 (75% in alendronate group and 71% in placebo group)	Calcium/vitamin D supplements	Alendronate improved BMD

ARVT, antiretroviral therapy.

Negredo E, Warriner AH, Curr Opin HIV Aids, 2016

Zoledronate

Zoledronate in HIV-infected patients: main published studies

References	Study design	Population	Vitamin D and calcium	Results
Bolland	Randomized placebo-controlled study Zoledronate 4 mg 96 weeks	$N=43$, receiving ARVT T-score <-0.5	Calcium/vitamin D supplements	Zoledronate improved lumbar and spine BMD
Bolland	Extension study (1 year) of those who completed the previous study No intervention	$N=33$, receiving ARVT T-score <-0.5	Calcium/vitamin D supplements	Results suggest antiresorptive effects of zoledronate during last 2 years
Bolland	Extension study (4 years) No intervention	$N=35$, receiving ARVT T-score <-0.5	Calcium/vitamin D supplements	The effect in BMD and turnover markers of two annual 4-mg doses of zoledronate persist for at least 5 years after the second dose
Huang	Randomize placebo-controlled study Zoledronate 5 mg 48 weeks	$N=30$, receiving ARVT T-score <-1	Calcium/vitamin D supplements	T-scores significantly improved in zoledronate recipients as compared with minimal changes in those receiving placebo
Negredo	Randomized (two zoledronate: one control) study Zoledronate 5 mg 96 weeks	$N=31$, receiving ARVT T-score ≤ -1	Dietary calcium and vitamin D counseling	Similar benefits for BMD of a single dose of zoledronate in 2 years and of two doses after 96 weeks

ARVT, antiretroviral therapy.

Negredo E, Warriner AH, Curr Opin HIV Aids, 2016

Bone Reports 15 (2021) 101128

Contents lists available at ScienceDirect

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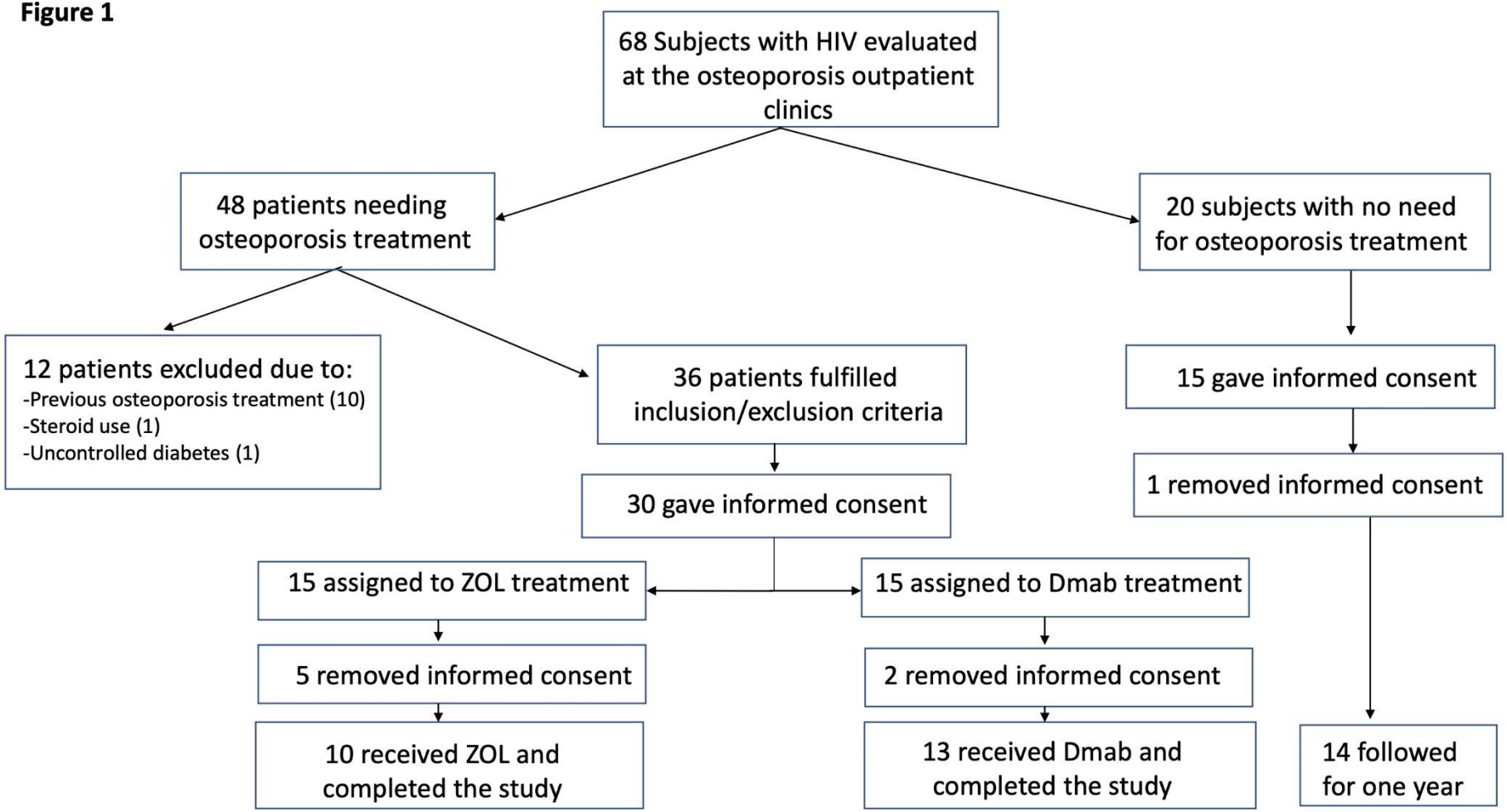
journal homepage: www.elsevier.com/locate/bonr

Denosumab versus zoledronate for the treatment of low bone mineral density in male HIV-infected patients

Polyzois Makras [a,*], Panagiotis Petrikkos [b], Athanasios D. Anastasilakis [c], Artemis Kolynou [d], Angeliki Katsarou [b], Olga Tsachouridou [d], Symeon Metallidis [e], Maria P. Yavropoulou [f]

Figure 1



Makras P. et al. Bone Reports, 2021

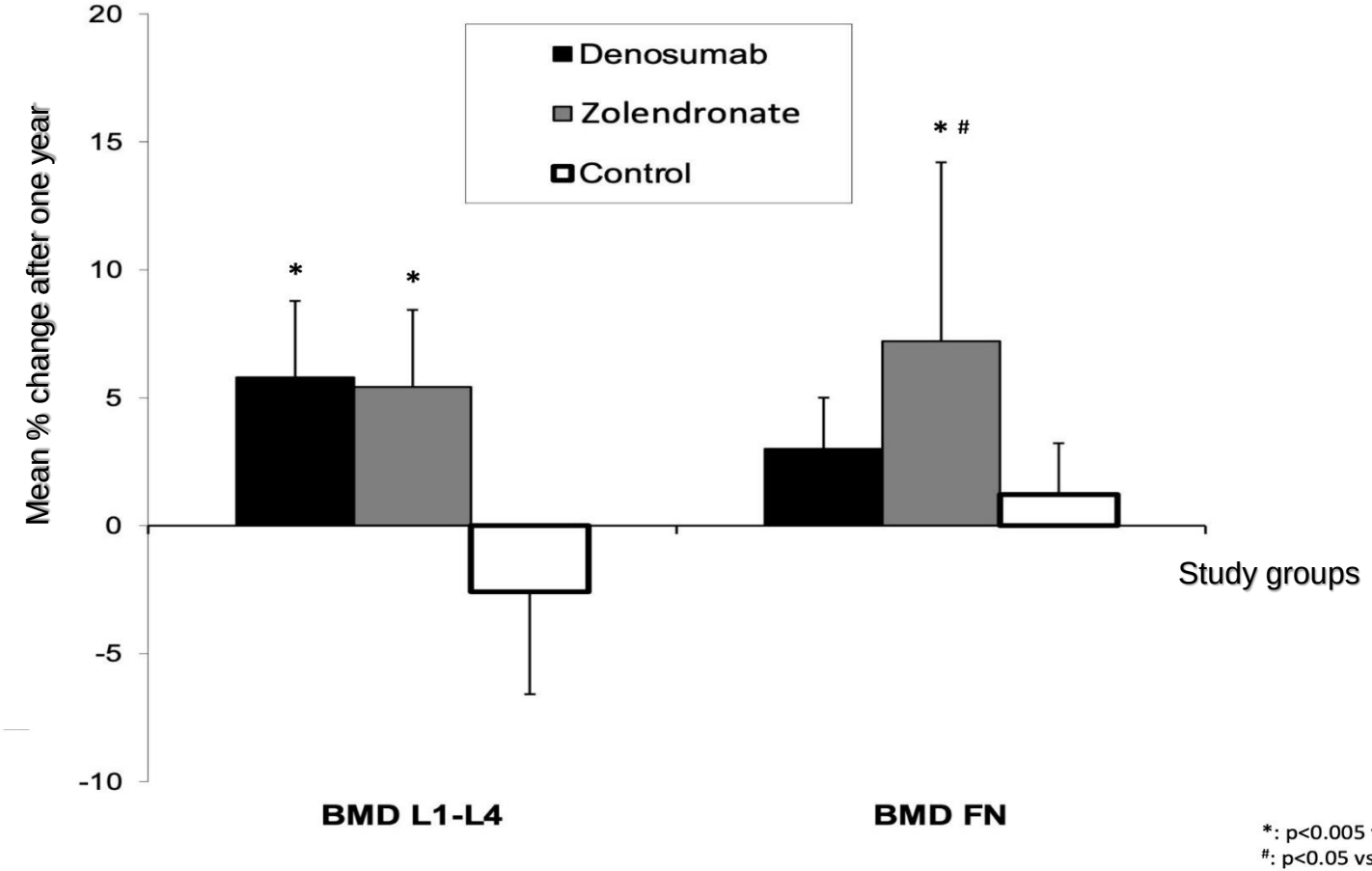
BMD and FRAX score at baseline

	Dmab group (n=13)	ZOL group (n=10)	Control (n=14)	p-value #
FRAX Hip (%)	1.85±0.80 [a]	1.99±1.24 [a]	0.38±0.53	**<0.001**
FRAX MOF (%)	6.94±1.64 [a]	4.74±2.20 [a]	2.20±0.92	**<0.001**
BMD L1-L4	1.002±0.156 [b]	1.000±0.140 [b]	1.200±0.166	**0.003**
BMD FN	0.748±0.04 [a]	0.763±0.04 [a]	0.963±0.08	**<0.001**
T-score L1-L4	-1.79±1.28 [b]	-1.86±1.17 [b]	-0.29±1.45	**0.006**
T-score FN	-2.44±0.30 [c]	-2.13±0.71 [c]	-0.83±0.66	**<0.005**

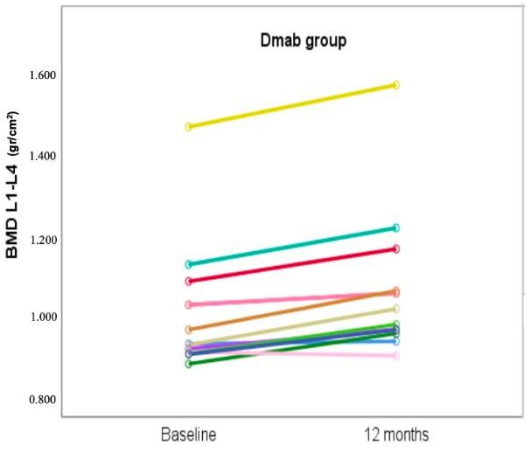
#: Comparison between 3 groups.

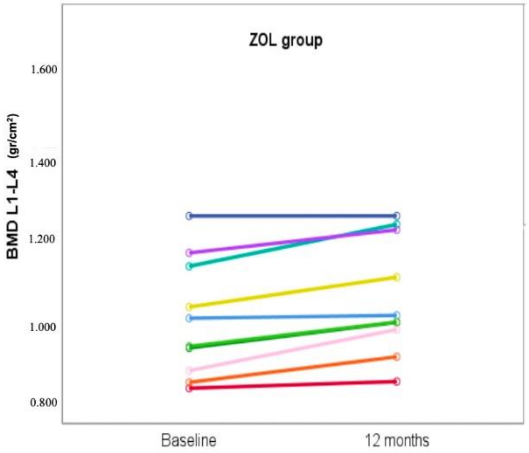
[a]: $p<0.001$ vs. Control; [b]: $p<0.05$ vs. Control; [c]: $p<0.005$ vs. Control

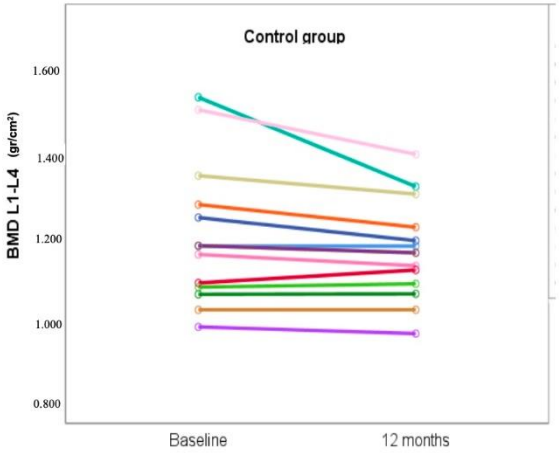
Makras P. et al. Bone Reports, 2021

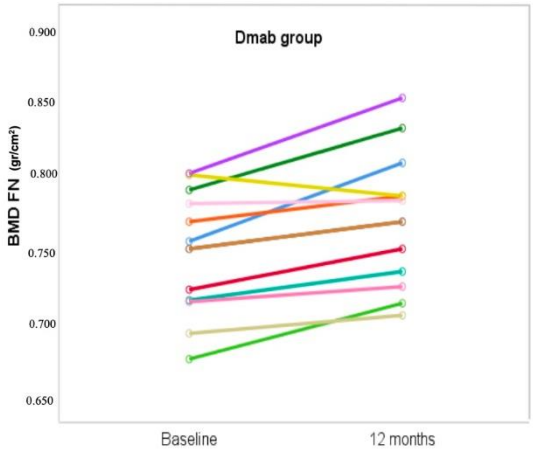


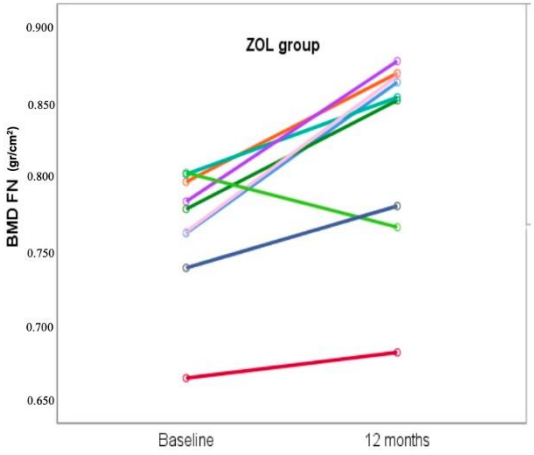
Makras P. et al. Bone Reports, 2021

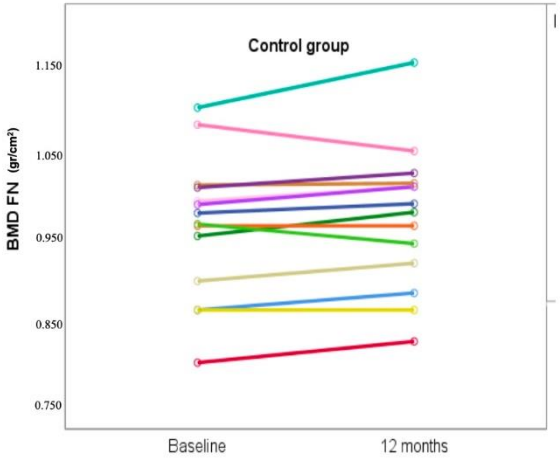












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Conclusions

- HIV patients are living longer now, having an average life expectancy quite close to that of the general population, and presenting long term effects from all aspects of the disease.
- There is an increased risk of bone loss and fractures (10 years earlier than the general population).
- Untreated HIV bone disease is low turnover become a high turnover one after HAART initiation
- HAART is possible to further induce bone loss during the first 1-2 years (especially tenofovir disoproxil fumarate, TDF) which stabilizes afterwards.
- Therapeutic options: bisphosphonates (alendronate, zolendronate), denosumab (?).
- When calculating FRAX score, HIV disease should be considered as a reason for secondary osteoporosis.

Thank you for your attention!

THANK YOU

On behalf of IOF, we thank you for your participation
in this webinar

BoneCast

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Our vision is a world without fragility fractures,
in which healthy mobility is a reality for all.

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