


Should we still care about bone? Screening, treatment, TDF vs TAF

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Outline

- HIV and ART: effects on bone
- Improvements with INSTIs and TAF
 - Management issues
 - Research areas

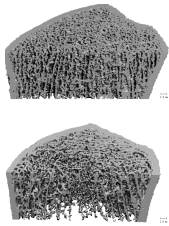
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Osteoporosis

- Systemic skeletal disease of aging
 - Low BMD
 - Microarchitectural deterioration
 - Reduced bone strength
- Fragility fractures (Vertebrae, hip, wrist)
- Diagnosis by DXA

	T scores
- Normal	> -1.0
- Osteopenia	-1.0 to -2.49
- Osteoporosis	≤ -2.5

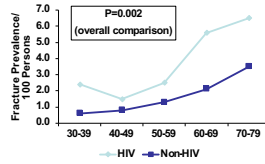
 - In older populations, risk of fracture increases 2-3 fold for each SD decrease in BMD



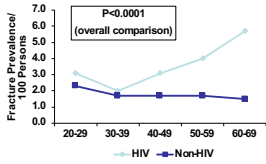
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Higher prevalence of ICD9 coded fragility fracture in HIV+

Female



Male

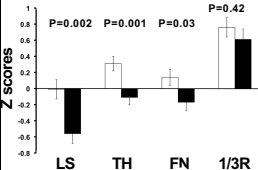


Triant et al., JCEM, 2008

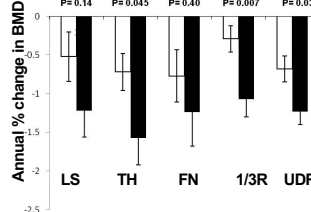
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Lower BMD and higher rate of bone loss in HIV+ than HIV- postmenopausal women

□ HIV- (N=97)
■ HIV+ (N=95)



□ HIV- (N=58)
■ HIV+ (N=82)

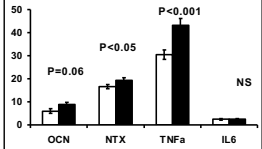


Yin et al, JCEM 2010; Yin et al, JCEM 2010

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Higher bone turnover and TNF levels, and decreased cortical thickness in HIV+ women

□ HIV- (N=58)
■ HIV+ (N=82)

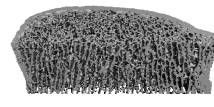


Tibia

61 year old HIV- woman

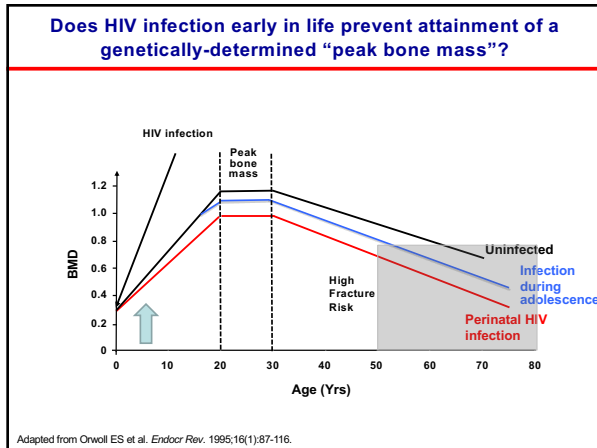


61 year old HIV+ woman

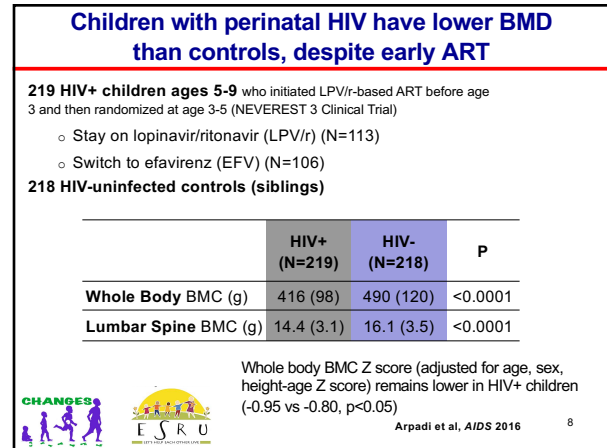


Yin et al, JCEM 2010

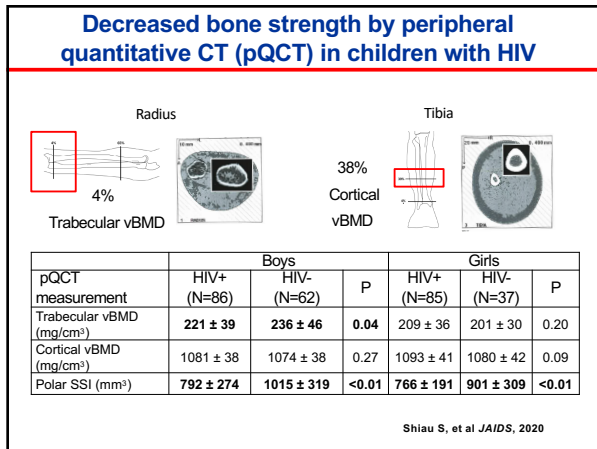
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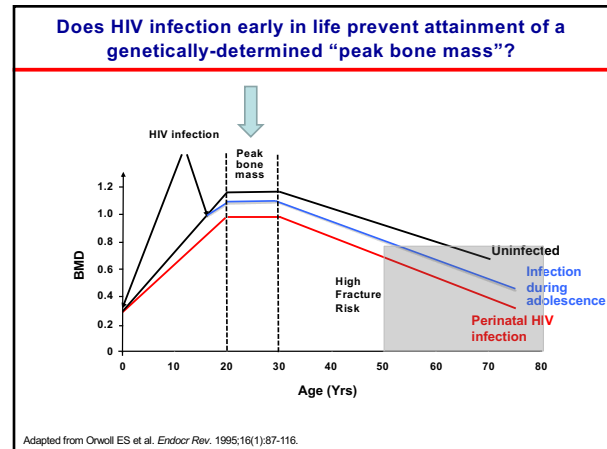
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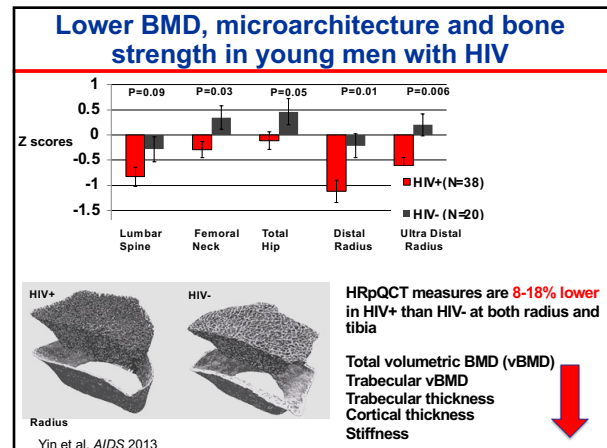
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	HIV+ perinatally-infected (N=18)	HIV+ Adolescence-infected (N=20)	HIV- (N=20)
Age	22 ± 2	23 ± 2	21 ± 2
Race/ethnicity	61% AA 39% Hispanic	50% AA 50% Hispanic	40% AA 60% Hispanic
BMI (kg/m ²)	26 ± 3	25 ± 3	25 ± 5
CD4 curr/nadir	505 / 181	531 / 292	
HIV RNA <20cp/ml	56%	65%	
ART duration *	12 years	2 years	
PI-based ART *	65%	11%	
Tenofovir	71%	94%	

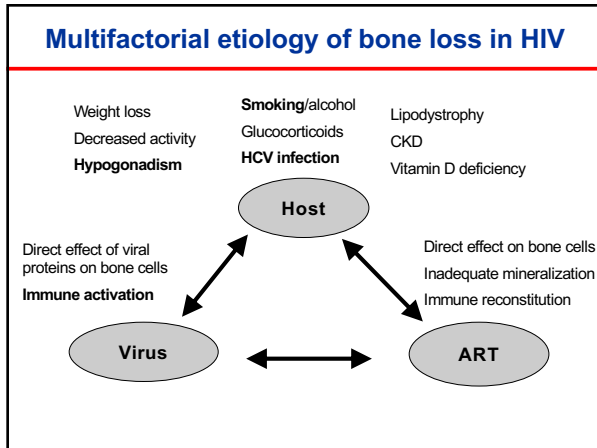
* p<0.05 comparing HIV+ vs HIV- or Perinatally- vs Adolescence-infected

Yin et al. *AIDS* 2013

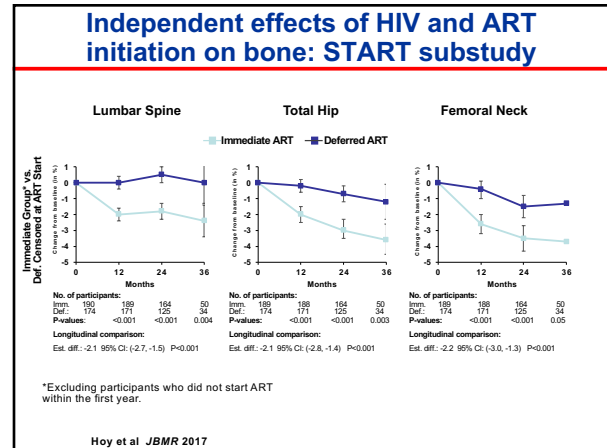
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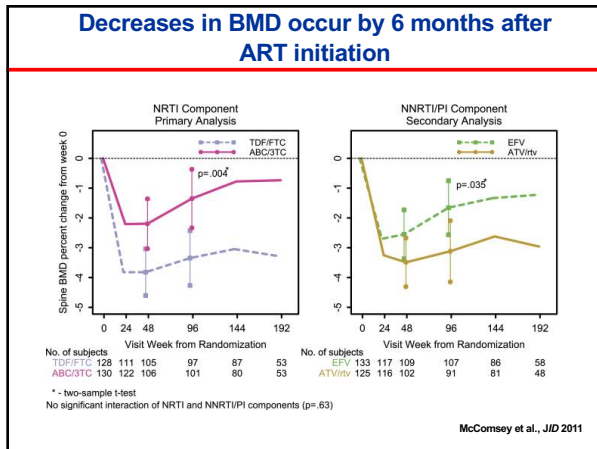
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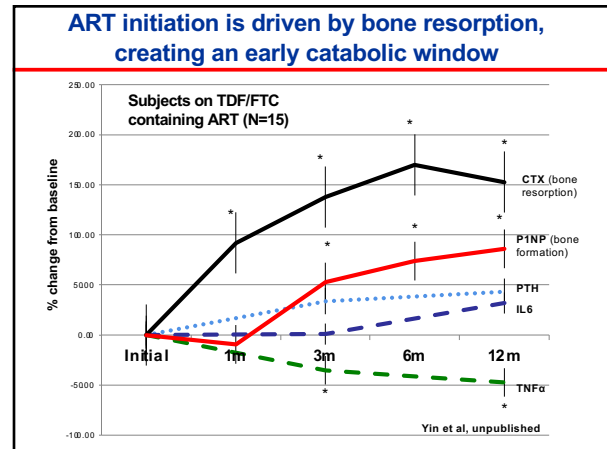
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BMD decreases 2-4% with initiation of ART regimens: TDF > ABC or RAL or TAF

Study	ART regimens	Change in LS BMD
Stellbrink, ASSERT 2010	TDF/FTC + EFV	-3.6%*
	ABC/3TC + EFV	-1.9%
McComsey, ACTG 5224s 2011	TDF/FTC	-3.3%*
	ABC/3TC	-1.3%
	ATV/r	-3.1%*
	EFV	-1.7%
Reynes, PROGRESS 2013	TDF/FTC+LPV/r	-2.5%*
	RAL+LPV/r	+0.7%
Sax, Gilead 104-111 2015	E/C/F/TDF	-2.9%*
	E/C/F/TAF	-1.3%

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Negligible BMD change with BIC/FTC/TAF or DTG/3TC/ABC

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Sax, Gilead 104-111 2015	E/C/F/TDF	-2.9%*
	E/C/F/TAF	-1.3%
Wohl, Gilead 1489 2018	BIC/FTC/TAF	-0.7%
	DTG/3TC/ABC	-0.2%

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BMD improves with ART switch

TDF → **TAF or raltegravir**

Ritonavir-boosted protease inhibitor → **raltegravir**

Study	Sample/Duration	ART regimens	Change in LS spine	Change in FN or TH BMD
Pozniak JAIDS 2017	N=242 eGFR 30-69 ml/min 48 wks	TDF/FTC/EFV/Cobi to TAF/FTC/EFV/Cobi	+2.3%*	+1.5%*
Bloch TROP 2014	N=37 48 wks	TDF+PI/r to RAL+PI/r	+3.0%	+2.5%
Curran SPIRAL-LIP 2012	N=74 48 wks	NRTIs+LPVr to NRTIs+RAL Stay on NRTIs+LPVr		+0.01 g/cm ² no change

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Tenofovir and bone loss: putative mechanisms

- Inadequate mineralization**
 - Osteomalacia in animal studies; related to proximal renal tubular dysfunction
 - In humans, hyperphosphaturia occurs in 5-30%; but hypophosphatemia and clinical osteomalacia are rare.
- Secondary hyperparathyroidism**
 - Potentially linked to 'functional' vitamin D deficiency with increased vitamin D binding protein (Havens, CID 2012)
- Direct effect on bone cells**
 - Increased osteoclast differentiation and inhibition of osteoblast differentiation (Madiero, Arthritis Rheum, 2016; Grigsby, BBRC 2010)
 - No effect on osteoblast viability from Gilead studies (Liu, PLOS 2017)

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Effect of HIV on bone histomorphometry

- 20 ART-naïve men with HIV from Sao Paulo, Brazil
- No metabolic bone disease, eGFR>60
- Paired iliac crest bone biopsies before and 12 months after initiation of TDF/FTC/EFV

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TDF/3TC/EFV increases osteoblast / osteoclast activity but does not improve mineralization defect, resulting in increased osteoid

	Pre-ART	Post-ART	Reference
Bone formation Parameters			
Osteoid volume/bone volume, %	0.77 (0.35-1.40)	2.2 (1.1-4.0)	2.99 ± 2.75
Osteoblastic surface/bone surface, %	1.33 (0.46-2.30)	4.45 (2.48-6.83)	1.2 ± 1.4
Bone resorption Parameters			
Osteoclastic surface/bone surface, %	0.14 (0.01-0.27)	0.31 (0.12-0.7)	0.03 ± 0.11
Eroded surface/bone surface, %	2.26 (1.54-3.14)	4.1 (1.90-6.20)	1.75 ± 1.21
Dynamic Parameters			
Bone formation rate, μm ³ /μm ² /d	0.02 (0.01-0.03)	0.03 (0.01-0.04)	0.13 ± 0.7
Mineralization lag time, days	50.4 (20.2-82.6)	51.7 (28.9-86.7)	21.3 ± 2.3

Ramahlo, JBM 2019

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Should we still care about bone now that we have less bone toxic regimens?

- HIV infection itself has negative effects on bone
- ART switch may not reverse cumulative effects of ART on BMD, or other insults (lifestyle, comorbidities etc)
- Vulnerable populations**
 - Children and adolescents (inadequate bone acquisition)
 - Older PWH (higher fracture risk)
- TDF will still be utilized in resource limited setting

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Suggestions for clinical management

- Screening**
 - DXA recommended in HIV+ men and women>50
 - FRAX recommended when DXA not available (European AIDS Society)
 - FRAX less accurate in PWH, but improves if you check off "secondary osteoporosis" as a risk in calculator
 - Screen for and manage secondary causes of osteoporosis
 - Vitamin D deficiency (25-OHD levels)
 - Hyperparathyroidism (PTH)
 - Subclinical hyperthyroidism (TSH, free thyroxine)
 - Hypogonadism (free testosterone in AM in men; menstrual history, FSH, estradiol in women)
 - Phosphate wasting (serum/urine phosphate to calculate fractional excretion of phosphate)
 - Less common: cushing syndrome, idiopathic hypercalciuria, celiac sprue, multiple myeloma

Brown et al CID, 2015

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Suggestions for clinical management

- **ART Management in patients with high fracture risk**
 - **For ART initiation:** avoid TDF and PI/r containing regimens; use INSTIs, abacavir or TAF.
 - **With established ART:** switch from TDF or PI/r containing regimens to INSTI, abacavir, TAF containing regimens
 - **Osteoporosis without fracture,** could first switch ART and re-evaluate DXA after 1 year, in order to delay bisphosphonate therapy
- **Bisphosphonates for patients with fracture severe osteoporosis (T score<-3.0)**

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Gaps in knowledge

- **Mechanism of ARV bone toxicity**
- **Better ways to determine who is at higher risk of bone loss with ART initiation or of fracture**
 - Biomarkers (inflammatory markers, BTMS, extracellular vesicles)
 - Advanced imaging (CT assessment of bone strength)
- **What are the relative benefits of nutritional, hormonal and lifestyle modifications?**
- **Resource limited settings**

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