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May 13-14, 2011
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Bone Health in Pediatric HIV Infection

George K. Siberry, MD, MPH
Pediatric Maternal AIDS (PAMA) Branch
***Eunice Kennedy Shriver* National Institute
of Child Health and Human Development**
NIH, Bethesda, MD

Disclosure of Financial Relationships

This speaker has no significant financial relationships with commercial entities to disclose.

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.



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Objectives

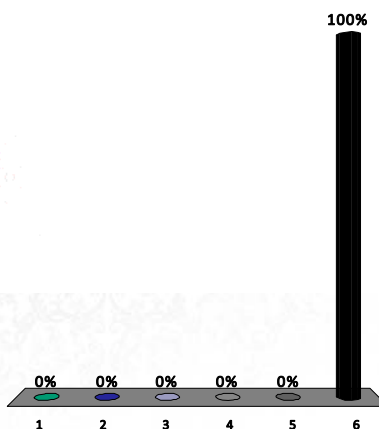
- Review the normal pattern of bone mass accrual in children and adolescents
- Review the role of vitamin D in bone mineral density
- Describe the epidemiology of and risk factors (including antiretroviral therapy) for adverse bone health outcomes in children and adolescents with HIV infection.
- Discuss management of vitamin D deficiency and low bone mineral density



Let's Get To Know Each Other!

The category that best describes me is...

1. Medical Clinician (MD, NP, PA)
2. Nurse
3. Social Worker / Counselor
4. Community Member
5. Administrator / Program Specialist
6. Other (*none of the above describes me well*)



Fetal & Infant Bone Development

Land Best Pract Res Clin Endoc Metab 2008

- **Massive placental transfer of calcium and other minerals**
 - substantial bone growth and mineralization
- **At birth, shift to dependence on infant intestinal mineral intake and renal mineral reabsorption**
- **Bone growth and laying down of bone mass predominantly in 2nd and 3rd trimester**
- **Insulin-like growth factors (especially IGF-1) control fetal somatic growth and bone metabolism (Fowden *Horm Res* 2009)**
- **Ongoing rapid bone growth and mineralization through infancy**

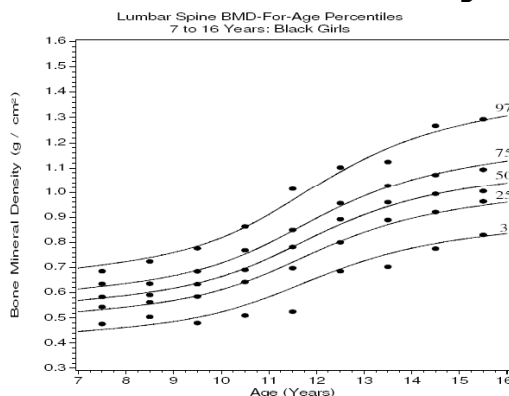


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Progression of Bone Density over Age



NICHD BMD
in Childhood
Study.
Kalkwarf *et al.*
J Clin Endo
Metab 2007

- **Normative BMD curves by SEX, RACE, AGE**
 - 7-18+ for girls; 7-17+ for boys. **No standards for <7 years old!**
- **Spine and Whole-body DXA measures best studied in children**
- ****BMD changes must be interpreted in context of expected age/maturation-related changes (Z-scores)****



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Child and Adolescent Bone Development

Loud Arch Ped Adol Med 2006; Kalkwarf J Clind Endo Metab 2007

- **≥25% of PBM in 4-yr period around pubertal max linear growth velocity**
 - >60% during puberty overall
 - Also period of normal increase in fracture risk
- **Peak bone mass (PBM) attained in 3rd decade**
 - All downhill from there.....
 - Significant predictor of postmenopausal osteoporosis



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Calcium & Vitamin D

- Adequate levels essential for development and maintenance of healthy bones
- Goal: 25-OHvitD ≥20ng/mL (50nmol/L) [lots of debate!]
- Vitamin D deficiency implicated in fractures and low BMD. ?asthma, infection, cancer, cardiovascular disease.....

TABLE 1 Selected Calcium and Vitamin D DRI Values for Children and Adolescents

Age	Calcium, mg/d		Vitamin D, IU/d	
	Recommended Intake ^a	Tolerable UL	Recommended Intake ^a	Tolerable UL
0–6 mo	200	1000	400	1000
6–12 mo	260	1500	400	1500
1–3 y	700	2500	600	2500
4–8 y	1000	2500	600	3000
9–18 y	1300	3000	600	4000

^a Recommended intake values are the RDA values for children aged 1 year and older and AI values for infants younger than 1 year.

2011 IOM
Report Recs.
Abrams
Pediatrics 2011



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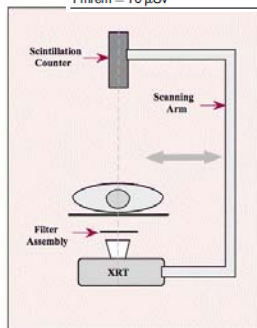
DXA: Dual-energy X-ray Absorptiometry

- Simultaneous use of 2 X-ray beams at different photon energies to differentiate bone from soft tissue
- Very low (trivial) radiation (Bachrach 2011)

Table 2 Average radiation dose from common medical and everyday sources

Source	Dose (mrem)
US annual background exposure	300
Transcontinental flight	6
Chest X-ray	5
pQCT	3
Pediatric DXA (lumbar spine only)	0.2-0.3

1 mrem = 10 μSv



Bogunavic 2009

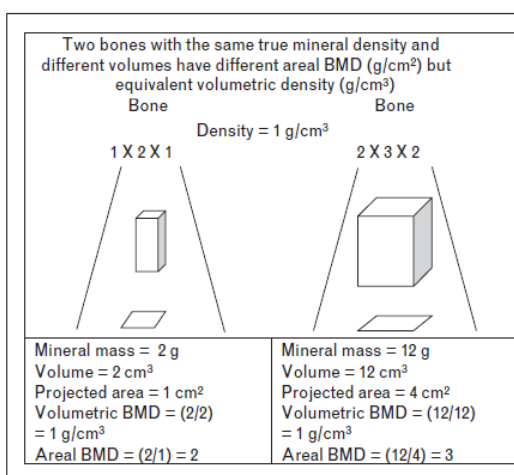
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Measuring Bone Density

Bogunavic *Curr Opin Ped* 2009

Bone mineral density often adjusted for size (eg, length/height) because smaller bones result in a smaller measured areal BMD.

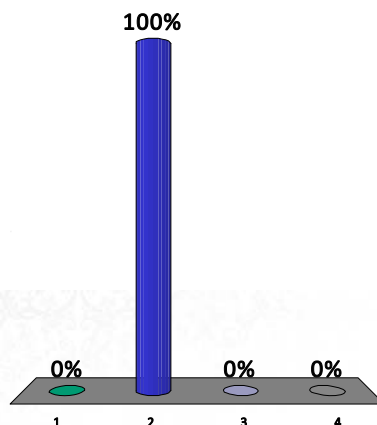
Figure 1 Impact of bone size on dual X-ray absorptiometry measurements of bone mineral density



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Choose the TRUE statement about bone density changes with age:

1. Most bone mass is laid down before puberty.
2. Peak bone mass is achieved before the end of high school.
3. Bone size does not affect measurements of BMD by DXA
4. Bone mass accrues from fetal life through early adulthood



Definitions

Land *Best Pract Res Clin Endoc Metab* 2008

- **Bone density:** mass/volume
- **Bone mineralization:** incorporation of mineral (calcium, phosphorus, and others) at sites of newly formed organic bone matrix (osteoid).
 - Increases physical density of bone
- **Osteomalacia:** failure of mineralization of newly formed osteoid (soft bones)
- **Osteopenia:** reduction in bone mass/matrix
 - decreased thickness or number of trabeculae and/or decreased thickness of the bone cortex
 - precursor of osteoporosis.

OSTEOPOROSIS -> FRACTURE RISK

- Bone mineral density measurements used as part of assessment of risk of fractures
- Most important clinical outcome (and prevention target) is FRACTURE
- Osteoporosis = increased bone fragility (density + quality) = increased risk of fracture
- Traumatic and atraumatic/fragility fractures both increased in osteoporosis
- Atraumatic or fragility fractures
 - Wrist/Prox humeral, hip, vertebral compression* fractures
 - Fall from standing height or less



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Definitions: Adults

- For postmenopausal women and men ≥ 50 yrs, WHO Definitions, by DXA scores:
 - Osteoporosis: T-score ≤ -2.5
 - Osteopenia: T-score -1.0 and -2.5
 - Normal: T-score ≥ -1.0
 - \uparrow Risk of fracture by 1.5-3.0 x for each SD (10-15%) decrease
 - BMD explains only ~50% of fracture risk
 - HIP and SPINE

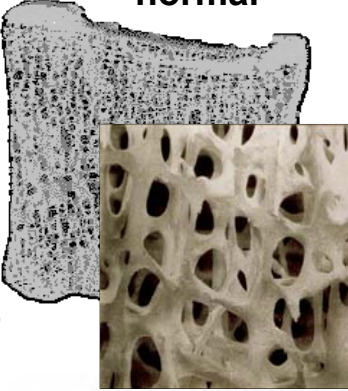


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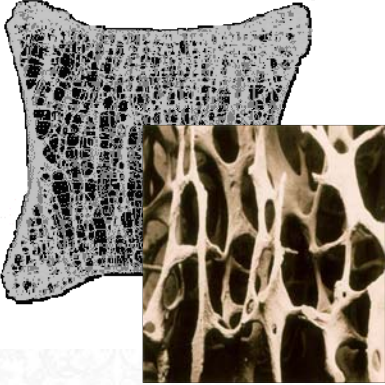
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Normal vs Osteoporosis

normal




osteoporotic



Courtesy: Todd Brown

- Poor quality architecture
- Reduced mass & density
- Prone to fracture
- Fragile




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Definitions: Children

- **DXA measurements in children**
 - SPINE + Whole Body
 - Z-score ≤ -2.0 = “Very low bone mineral density”
 - Absolute or %age BMD changes in children must be understood in context of *expected* change (Z-score, reference ranges, adjustment)
 - Osteoporosis diagnosis requires clinical evidence of bone fragility
 - Healthy children at significantly increased risk (53%) of upper limb fractures if adjusted LS BMD one SD below avg [Flynn JBMR 2007]
 - Controversy over predictive value of childhood BMD and short- and long-term fracture risk



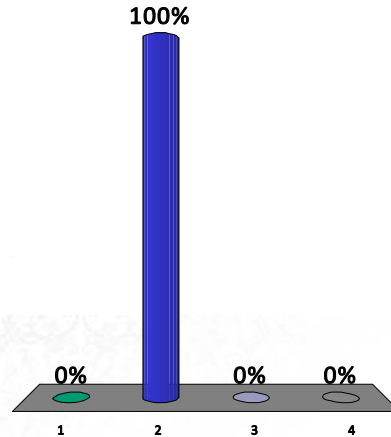
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Which of the following patients most likely has osteoporosis*?

1. 10 year old boy with Spine BMD Z-score < -3
2. 25 year old woman with Spine BMD T-score < -1.5
3. 35 year old man with Spine BMD T-score < -2.0
4. 55 year old women with Spine BMD T-score < -2.5



*Based on the information provided



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Bone and HIV Infection in Adults

- HIV infection (generally) acquired after attainment of peak bone mass (PBM)
- Increased rates of osteoporosis and low BMD
 - >3-fold ↑rate of osteoporosis and low BMD than HIV- peers
 - Higher risk on antiretroviral therapy
- Increased risk of fractures
 - 30-70% higher rates than matched HIV- controls

McComsey CID 2010; Brown AIDS 2006; Collin AIDS 2009; Triant JCEM 2008



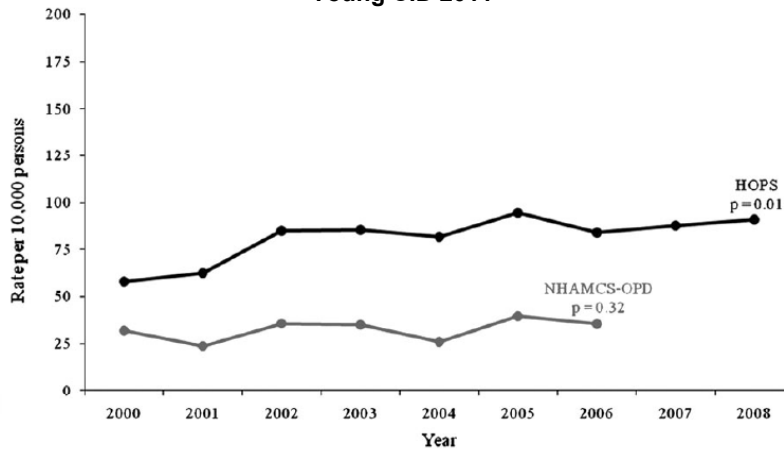
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Higher Fracture Risk in HIV-Infected Adults

Young CID 2011



Rates of bone fracture among patients in the HIV Outpatient Study (HOPS), compared with rates among patients in NHAMCS-OPD for adults aged 25–54 years. HOPS rates were indirectly standardized by age and sex using rates from NHAMCS-OPD.



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Risk Factors for Low BMD in Adult HIV

- High prevalence of traditional risk factors
 - Low BMI, alcohol/tobacco use, low vitD
- HIV-related: hypogonadism, steroid use, low vitD*
- Inflammatory state
 - Pre ART, ART initiation, Chronic ART
- Antiretroviral therapy (ART) *initiation*
 - 2-6% BMD loss in 1st 2 years (~ menopausal rate)
- Specific HIV drugs
 - Tenofovir, Stavudine, Efavirenz, Protease Inhibitors

McComsey CID 2010; Brown JAIDS 2009



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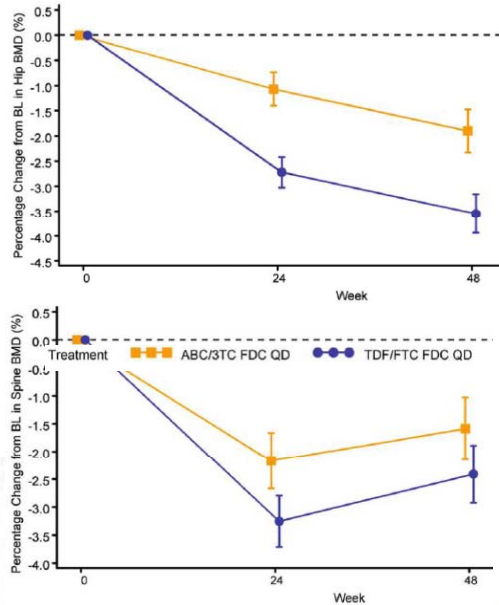
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ART Initiation

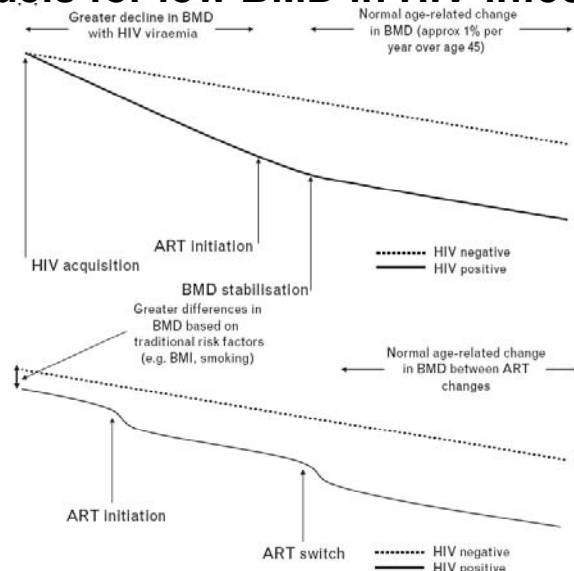
Stellbrink CID2010 ASSERT

- ART naïve adults
 - Median 37 (18-70) yrs old
- BMD↓ in all groups
- Esp. 1st 24 wks
- Different pattern in Hip (upper), Spine (lower)
- Greater loss for Tenofovir than for Abacavir



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Models for low BMD in HIV-infected Adults



Mallon
 Curr Opin
 Infect Dis
 23:1-8

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Special Case: Bone Health in Pediatric HIV Infection

BIRTH

Lumbar Spine BMD-For-Age Percentiles
7 to 16 Years: Black Girls

BMD gm/cm² Spine: L1-L4

T = -2.0 Z = -0.5

Perinatal HIV Infection

New Adolescent HIV Infection

HIV Infection in Adulthood

- Long Duration of exposure to HIV infection & treatment
- Unique developmental periods: Fetal, Infancy and Puberty
- Implications of reaching suboptimal Peak Bone Mass (PBM)

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Pediatric HIV and Bone

- **Prevalence of low BMD**
 - Studies often use small “normal” control group
 - Among over 400 perinatally HIV-infected 7-16 year-olds [Pediatric HIV AIDS Cohort Study (PHACS)], DXA Lumbar Spine Z-score:
 - <-1 in 20%
 - <-1.5 in 10%
 - <-2.0 in 5%
- **No clear evidence of increase in fractures**
 - Oldest perinatally infected only in 20s
 - **What about in 40s?**

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Factors Potentially Driving Low BMD in HIV-Infected Children & Youth

- **Traditional risk factors for poor bone health**
 - Delayed growth, puberty
 - Nutrition: vitamin D, malnutrition/low BMI
 - NonHIV drugs: steroids, medroxyprogesterone
 - Behaviors (youth): alcohol, smoking
 - Impaired mobility (cerebral palsy)
 - Disrupted renal function
- **ART in general and specific agents**
 - Cross-sectional studies: PIs, d4T, TDF
 - Particular concern about Tenofovir
 - PIs not borne out in longitudinal studies
 - Probably initiation of HAART
- **Vulnerable periods**
 - Puberty
 - Young ages
- **Bone turnover markers increased**
 - Resorption >> Formation



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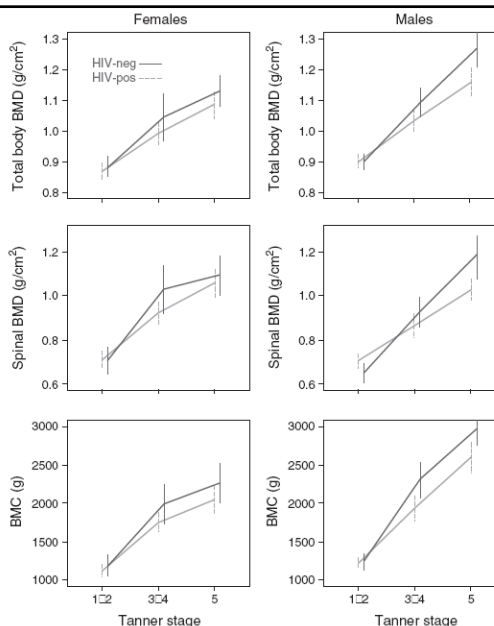
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Sex & Puberty

(Jacobson AIDS 2010 P1045)

- 7-24 yr old HIV+ and controls
- Stratified by age, Tanner (ART)
- Widening gap in BMD for HIV+ vs HIV- with progression through puberty
 - Significant for Boys; Trend for girls
- <10% on Tenofovir

Observed (unadjusted) mean BMC and BMD (95% confidence interval) by HIV status and Tanner stage. Jacobson AIDS 2010



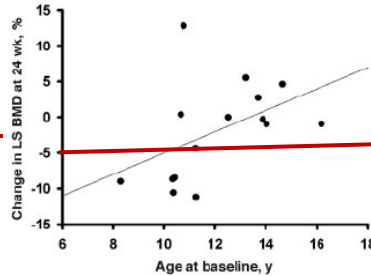
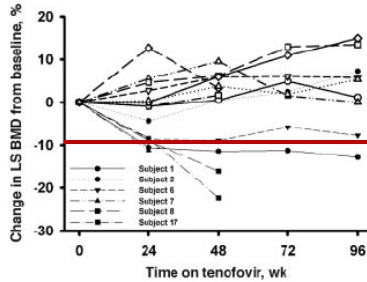
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TDF in Young, Highly-Experienced HIV-Infected Children and Decreases in Bone Mineral Density

Gafni RI et al. *Pediatrics* 2006;118:e711-8

15 treatment-experienced children (8-16 yo) starting TDF-containing salvage ART



Courtesy: Lynne Mofenson

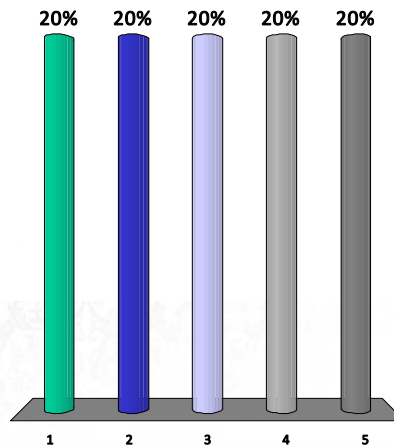
6/15 (40%) with **>1%** ↓ in spinal BMD;
5/6 had **>6%** ↓ in spine BMD (2 stopped TDF)

6 children with greatest BMD loss were significantly **younger** than the BMD stable group (10.2 vs 13.2 years, p=0.003)

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Which of the following is LEAST likely to influence BMD in HIV infection?

1. Initiation of HAART in a treatment-naïve patient
2. Starting Tenofovir
3. Switching from Lopinavir/r to Atazanavir/r
4. Pubertal stage
5. Chronic steroid use for control of pulmonary disease



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Mechanisms

- **Vitamin D metabolism**
 - 70% with 25(OH)D <30 ng/dL (~ HIV- controls)
 - Efavirenz induces CYP450 24-OHylase, leading to ↑ hydrolysis (inactivation) of 25(OH)D and 1,25(OH)₂D
 - Ritonavir inhibits vitD → 25(OH)D → 1,25(OH)₂D
- **Direct effect of HIV proteins on bone turnover**
 - ↑ Bone resorption: ↑ RANKL → ↑ osteoclastic activity
 - ↓ Bone formation: Osteoblast apoptosis
 - ARV may directly enhance ↑ RANKL
- **Dysregulated inflammatory state**
 - Pre-ART > Early ART > Chronic ART
 - ↑ TNF-alpha → ↑ osteoclast-mediated bone resorption
 - ↑ RANKL within 24wks of HAART initiation

Cozzolino AIDS 2003; Dao CID 2011; McComsey CID 2010; Ofotokun CROI2011; Pisco JAIDS 2011



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TENOFOVIR

- Acyclic nucleotide analogue with activity against HIV-1, HIV-2, and hepatitis B virus
- Tenofovir (TFV): large, negatively charged (anionic) phosphonate that is not well absorbed
- Tenofovir disoproxil fumarate (TDF): chemically altered for oral administration
- TDF converted to TFV in the body (blood, breastmilk, urine)
- TFV converted intracellularly to active form: TFV-diphosphate
- First-line agent as part of combination ART for treatment of HIV infection in adults



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Indirect Effect of Tenofovir on BMD

- **TFV-associated Proximal tubulopathy (PT)**
 - TFV eliminated by active tubular secretion + glomerular filtration
 - TFV accumulates in prox tubule via direct transport by human organic anion transporter 1 (hOAT1) on basolateral side of prox renal tubular cells
 - Secreted via the multidrug-resistance protein (MRP2) on apical side of proximal tubular cell. (**Ritonavir** inhibits MRP2.)
 - Mechanism of tubular toxicity unclear (direct effect? Mitochondrial depletion?)
- **Effects of PT on bone & mineral homeostasis**
 - Impairment of selective reabsorption (calcium, phos) of filtrate
 - ↑ urinary calcium and phos losses
 - ↑ (compensatory) bone resorption & impaired mineralization of forming bone
- **PT may also impair of 1' hydroxylation of vitD**

Fux Antivir Ther 2008; Zimmermann CID 2006; Grigsby Ther Clin Risk Mgmt 2010




Potential direct adverse bone effects of TFV

- TFV as a nucleotide analog that inhibits DNA synthesis (chain terminator) may affect mitochondrial function
- TFV, as a **phosphonate**, may have ↑ affinity for osteoclasts and/or osteoblasts
- Bone metabolism may be target of mitochondrial dysfunction effects
- ↑ relevance for metabolically most active bones (fetus, infant, adolescent)

Fux Antivir Ther 2008; Zimmermann CID 2006; Grigsby Ther Clin Risk Mgmt 2010





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Approach to Screening & Treatment

Screening for Vitamin D Deficiency

Misra Pediatrics 2008

- **Who?**
 - Poor growth, motor delay, chronic irritability
 - Chronic steroids or anticonvulsants
 - Malabsorption
 - Fractures + Low BMD
- **How?**
 - AlkPhos first; if elevated (for age), then....
 - 25OHvitD, Ca, Phos, PTH and wrist Xrays
- **Alternative (unofficial) (not in Misra 2008)**
 - 25OHvitD for HIV-infected children/youth with at least 2-3 risk factors: older age, female, non-white, obese, low milk/vitD intake, sedentary, steroids, drug use. Fracture or low BMD. TDF or EFV use.



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TABLE 7 Treatment of Vitamin D–Deficiency Rickets: Vitamin D and Calcium Supplementation and Monitoring of Therapy

Vitamin D (ergocalciferol)

Double-dose vitamin D: 20 μg (800 IU)/d \times 3–4 mo; or

Pharmacological doses of vitamin D: 25–125 μg (1000–10 000 IU) per day \times 8–12 wk depending on the age of the child, then maintain at 10–25 μg (400–1000 IU) per day; or

Stoss therapy: ~2.5–15.0 mg or 100 000–600 000 IU of vitamin D orally (over 1–5 d), then maintain at 10–25 μg (400–1000 IU) of vitamin D per day, or 1.25 mg or 50 000 IU of vitamin D₂ weekly for 8 wk orally (teenagers and adults)

Calcium

30–75 mg/kg per d of elemental calcium in 3 divided doses (start at a higher dose, and wean down to the lower end of the range over 2–4 wk)

Monitoring of therapy

At 1 mo: calcium, phosphorus, ALP

At 3 mo: calcium, phosphorus, magnesium, ALP, PTH, 25(OH)-D, urine calcium/creatinine ratio (frequency depends on severity of rickets and hypocalcemia); recheck radiologic findings in 3 mo

At 1 y and annually: 25(OH)-D

Misra
2008

- **Vitamin D (fat-soluble, stored) + calcium (can't absorb > ~1200mg/dose)**



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Screening for Low BMD

Bogunavic *Curr Opin Ped* 2009

- **Preferred technique: DXA**
 - TB (less head) + Lumbar Spine; BMC + aBMD
 - Z-score (not T-scores), at least through early 20s
- **Indications (general- not specific to HIV)**
 - Primary bone disease
 - Chronic disease with possible secondary effects on skeletal maturation (HIV?)
 - Chronic use of: steroids, anticonvulsants, medroxyprogesteron [?tobacco, ?EtOH]
 - Prolonged immobilization
 - Low-trauma fracture
 - Significant fracture history (≥ 1 LE long bone, ≥ 2 UE long bones, or vertebral compression fracture)
 - Evidence of osteopenia on X-ray



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DXA Screening: Additional Considerations

- US Pediatric HIV Guidelines (2010): “Until more data are available about the long-term effects of tenofovir on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for children in early puberty who are initiating treatment with tenofovir.”
- Pubertal delay, Growth delay, Low BMI
- Don’t miss repeated “traumatic” fractures

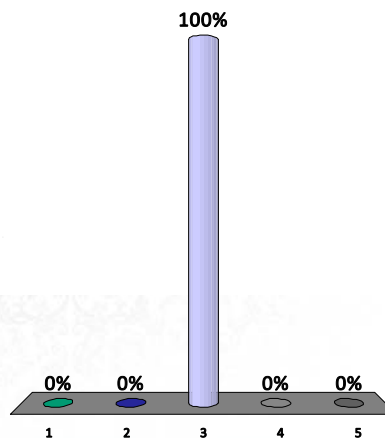


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DXA is LEAST justified for low BMD screening for which of the following scenarios?

1. 5 year-old HIV-infected child on HAART
2. 8 year-old HIV-infected child with recent femur fracture (without major trauma)
3. 11 year-old HIV-infected boy, Tanner 1, starting TDF-containing salvage HAART
4. 14 year-old HIV-infected girl presenting with her second forearm fracture
5. 17 year-old HIV-infected girl with BMI <5%ile and using medroxyprogesterone



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Management of low BMD

- **Ensure adequate calcium, vitamin D and general nutrition**
 - Diet. Selective 25-OH-vitD screening. Supplementation.
- **Modifiable behaviors**
 - Avoid Smoking, EtOH
 - Increased weight-bearing exercise (Cardiovascular and skeletal benefit!)
- **Medication modification (*if feasible*)**
 - NonHIV: steroids, medroxyprogesterone
 - HIV: TDF? Other?
- **Pediatric Bone Specialist Consultation**
 - If fractures have already occurred
 - If bisphosphonates (eg, alendronate) considered
- **Bisphosphonates clinically indicated (but not FDA-approved for children) if osteoporosis, but investigational for low BMD in absence of fractures**



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Alendronate (Bisphosphonates)

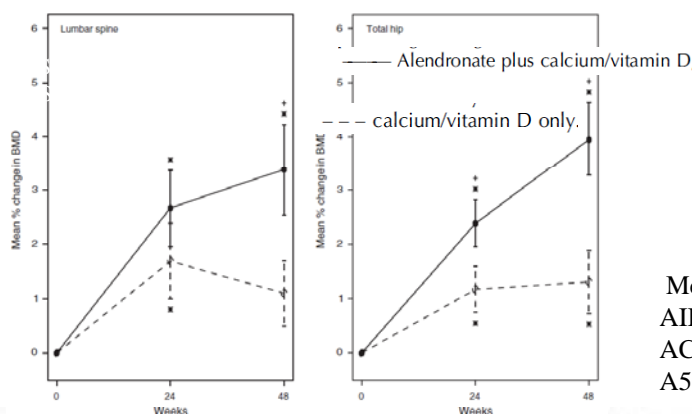
- **Resorption Inhibitor**
 - Synthetic analog of pyrophosphate
 - Binds to hydroxyapatite in bone
 - Inhibits osteoclast activity
- **Labeled indications: prevention and treatment of postmenopausal osteoporosis*; steroid-related osteoporosis; Paget's disease**
 - *demonstrated reduction in fractures
 - Children: Limited use (OI, cancer, rheum, steroid), No labeled indication
- **Striking reduction in bone resorption markers**
- **AEs: Esophageal ulcers, jaw osteonecrosis; atypical fractures**
- **Pregnancy cat C. Not a teratogen. Variable effects in animals.**
- **Long half life (?10 years) in bone, with release (at lower levels) into systemic circulation for months/years after stopped**
- **Need to ensure vitD and calcium sufficiency**



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Alendronate Efficacious for Low BMD in HIV+ Adults



McComsey
AIDS 2007
ACTG
A5163

- N=82, Med age: 48; 71% men, 77% white
- Eligibility: ≥ 25 yo, stable ART, LS T-score ≤ -1.5
- Ca500/vitD200 BID for all
- Weekly 70mg alendronate vs placebo



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IMPAACT P1076: Trial of Alendronate in Youth with Low BMD

- **Status: Open to Enrollment**
- **Eligibility: LS DXA Z-score < -1.5 or Fragility Fx**
 - 11-24 yo, Prepubertal HIV infection, Stable ART (or ART not indicated)
 - N = 51
- **Study treatment**
 - Random (1:1:1) assignment to alendronate vs placebo
 - 2 yrs ALEN vs 1 yr ALEN/1yr PLAC vs 1yr PLAC/1yr ALEN
 - 600 Calcium/400vitD to all
- **WB and LS DXA at 0, 6, 12, 18, 24, 36 months**
- **Primary Efficacy Outcome: Change in LS DXA from baseline between arms at 12 months**



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