

Endocrine Complications of HIV/AIDS : Adrenal Insufficiency and Osteoporosis

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Case Presentation: WC

- 56 year-old white male referred to Endocrine clinic for evaluation and treatment of diabetes mellitus
- HIV dx'd 1990, nadir CD4 86, from 1996 to 2002 on AZT/3Tc/NFV, currently TDF/FTC/NVP/ATV/r
- Depression
- Alcoholism
- Bilateral Avascular Necrosis of the Hip
- Central Adiposity

Case Presentation: WC

- Developed DM on NFV, resolved after switch to NVP (2002)
- 1/07- polyuria, polydipsia, A1c 8.2%- started on pioglitazone
- 2/07- Admitted with hyperglycemia (~400 mg/dL), dizziness. Treated with hydration, insulin

Case Presentation: WC

Possible Aggravating Factors

- Seroquel (quetiapine)
- ? steroids

Case Presentation: WC

- Received intra-articular triamcinolone injections on 10/06 and 1/07
- Last injection one week before hyperglycemia admission

Cortisol 1 $\mu\text{g}/\text{dL}$

ACTH undetectable

Steps in Evaluating Adrenal Insufficiency

- ✓ Consider the diagnosis

When to think about adrenal insufficiency?

- Orthostatic Symptoms
- Unexplained fatigue/weakness
- Unexplained hypotension
- Unexplained N/V/D
- Salt Craving
- Hyperpigmentation
- Anterior pituitary dysfunction
- Hyperkalemia
- Hyponatremia
- Hypoglycemia
- Cushingoid features/hyperglycemia/osteoporosis

Steps in Evaluating Adrenal Insufficiency

- ✓ Consider the diagnosis
- ✓ Establish the diagnosis

What is the best screening test for adrenal insufficiency?

1. 1 mcg ACTH stimulation test
2. 250 mcg ACTH stimulation test
3. 8AM serum cortisol level
4. Metyrapone test

8 AM Cortisol for the Diagnosis of Adrenal Insufficiency

< 5 $\mu\text{g/dL}$ (138 nmol/L), 100% specificity, 36% sensitivity

> 15 $\mu\text{g/dL}$ (414 nmol/L), essentially rules out diagnosis

5-15 $\mu\text{g/dL}$, do ACTH stimulation test

Caveat: In patients with hypoalbuminemia, consider free serum cortisol concentrations

Caveat: Should be repeated and put in clinical context

Establishing the Diagnosis of AI when Cortisol is 5-15 $\mu\text{g/dL}$

- Classic (250 μg) ACTH stimulation test
 - Normal: 30 or 60 min cortisol $>$ 18 $\mu\text{g/dL}$ (497 nmol/L)
 - At 95% specificity, sensitivity 97% for 1 $^{\circ}$, but 56% for 2 $^{\circ}$ / 3 $^{\circ}$
- Low dose (1 μg) ACTH stimulation test
 - More sensitive for 2 $^{\circ}$ / 3 $^{\circ}$ AI
 - Be careful of the “no-dose” test

Steps in Evaluating Adrenal Insufficiency

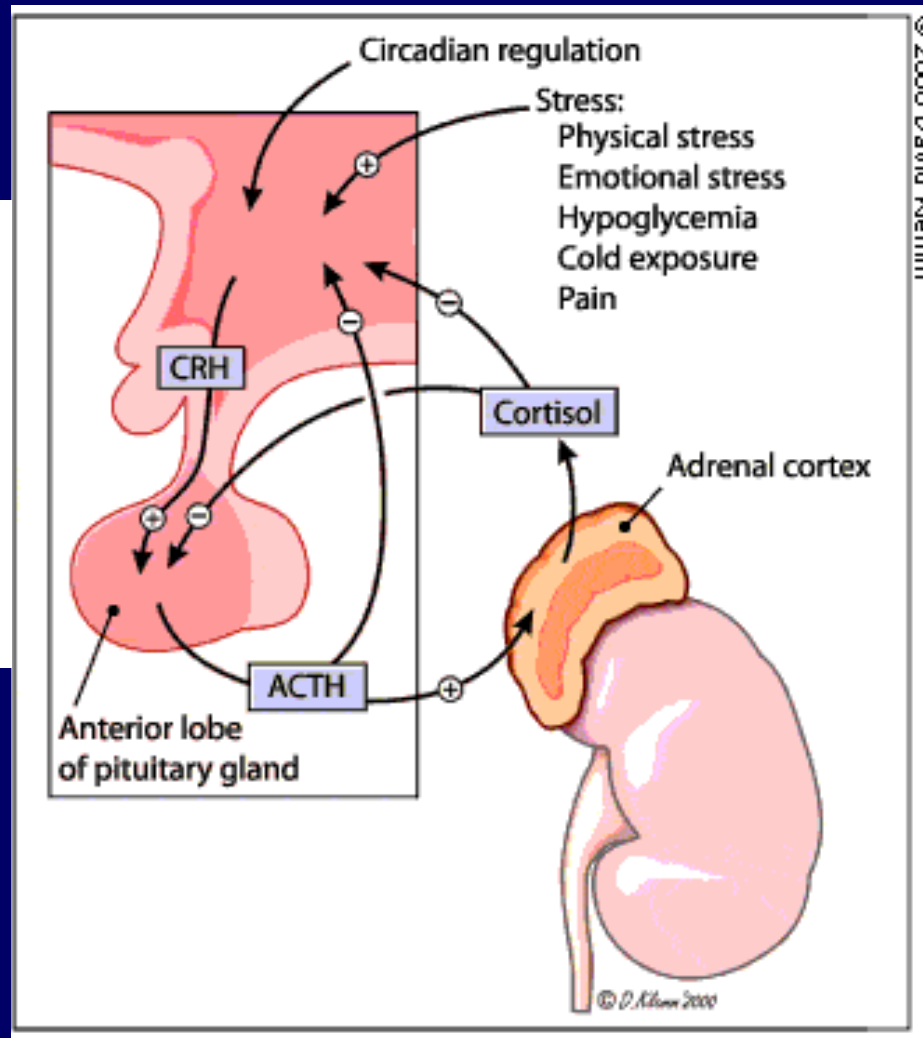
- ✓ Consider the diagnosis
- ✓ Establish the diagnosis
- ✓ Distinguish primary from secondary adrenal insufficiency

The Hypothalamic-Pituitary Adrenal Axis

SECONDARY / TERTIARY ADRENAL INSUFFICIENCY:

Hypothalamic or pituitary dysfunction

No Mineralocorticoid Defect



PRIMARY ADRENAL INSUFFICIENCY:

Adrenal dysfunction

Mineralocorticoid Defect

High K⁺

Salt Craving

Steps in Evaluating Adrenal Insufficiency

- ✓ Consider the diagnosis
- ✓ Establish the diagnosis
- ✓ Distinguish primary from secondary adrenal insufficiency

ACTH level

Steps in Evaluating Adrenal Insufficiency

- ✓ Consider the diagnosis
- ✓ Establish the diagnosis
- ✓ Distinguish primary from secondary adrenal insufficiency
- ✓ Determine underlying cause

Causes of Adrenal Insufficiency

Primary

Infection

CMV

TB

HIV

Histoplasmosis

Cryptococcus

Toxoplasmosis

Tumor

Kaposi Sarcoma

Lymphoma

Autoimmune

Hemorrhage

Medications

Ketoconazole

Rifampin

Etomidate

Secondary/Tertiary

Infection/Infiltration:

TB

Sarcoid

Hemochromatosis

Isolated ACTH Deficiency

Tumor

Trauma

Medications

Exogenous Steroids

Megesterol

Changing Face of Adrenal Insufficiency in HIV

Primary

Infection

CMV

TB

HIV

Histoplasmosis

Cryptococcus

Toxoplasmosis

Tumor

Kaposi Sarcoma

Lymphoma

Autoimmune

Hemorrhage

Medications

Ketoconazole

Rifampin

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Secondary/Tertiary

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TB

Sarcoid

Hemochromatosis

Isolated ACTH Deficiency

Tumor

Trauma

Medications

Exogenous Steroids

Megesterol

Case Reports of Steroid Induced Adrenal Insufficiency in HAART Era

Unexpected effects of inhaled fluticasone in an HIV patient with asthma.
Nocent C, Raheison C, Dupon M, Taytard A., J Asthma. 2004;41(8):793-5.

Adrenal insufficiency and diabetes mellitus secondary to the use of topical corticosteroids for cosmetic purpose. Sobngwi E, Lubin V, Ury P, Timsit FJ, Gautier JF, Vexiau P. Ann Endocrinol,(Paris). 2003 Jun;64(3):202-4

Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in HIV-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors. Semmes K, Pett S, Gowers A, McMurdock

Inhibitors of CYP3A4 (eg RTV) can dramatically increase steroid concentrations

Two Phenotypes

Cushingoid

- Lipodystrophic changes may delay or mask diagnosis
- Moon facies is the distinguishing feature



Adrenal Insufficiency

- Fatigue
- Lassitude
- Dizziness
- Intermittent steroid exposure or steroid discontinuation

Commonly Used Steroids and their Interaction with CYP3A4

Important Interaction

Oral

- Hydrocortisone

Inhaled

- budesonide (Pulmicort)
- fluticasone (Flovent)

Minimal Interaction

Oral

- Prednisone
- Dexamethasone

Inhaled

- beclomethasone
(Vanceril)
- flunisolide
(Aerobid)
- triamcinolone
(Azmacort)

Caveat: Classification based on theoretical interactions

Management of Adrenal Insufficiency

- Corticosteroids:
 - Prednisone 5-7.5 mg/d
 - Hydrocortisone 20-30 mg/d in divided doses
 - Dexamethasone 0.5-0.75 mg/d(Recommendation A)
- Mineralocorticoid (for Primary AI) :
 - Fludrocortisone 0.1-0.2 mg/d
 - Monitor by salt craving, orthostatic sx, plasma renin activity(Recommendation A)
- Androgens (especially women) (for Primary AI)
 - DHEA 50 mg/d(Recommendation C)

Should WC be treated with oral steroids?

1. Yes
2. No
3. Don't know

Management of Steroid Induced Adrenal Insufficiency

- Assess need for steroid
 - consult with prescribing provider
 - consider switch to steroid with less interaction
- If taper possible, support with oral steroids (prednisone 5 mg qd, dex 0.5 mg qd)
- Taper oral steroids very slowly (3-12 months)
- Use AM cortisol as a guide to endogenous HPA activity
- If taper is not possible, consider changing ART

Other Important Issues in Adrenal Insufficiency

- Stress Dose coverage
 - 3x3 rule (triple the dose for 3 days)
 - Major surgery/illness HC 100 mg q8
- Medic Alert Bracelet
- Patient Education

Case Presentation: WC

- H/O tibia /fibula fracture after a fall when intoxicated

Osteoporosis Risk Factors

- Alcoholism
- Prior hypogonadism
- Steroid Exposure
- Mother with osteoporosis

Case Presentation: WC

Dual X-ray Absorptiometry

	T-score	Z-score
L1-L4	-1.7	-1.2
Femoral Neck	-2.5	-1.7
Total Hip	-2.4	-2.0

Definitions

Functional Definition (DXA)- WHO Definition

- Osteoporosis: T-score < -2.5
- Osteopenia: T-score = -1.0 to -2.5
- Normal: T-score > -1.0

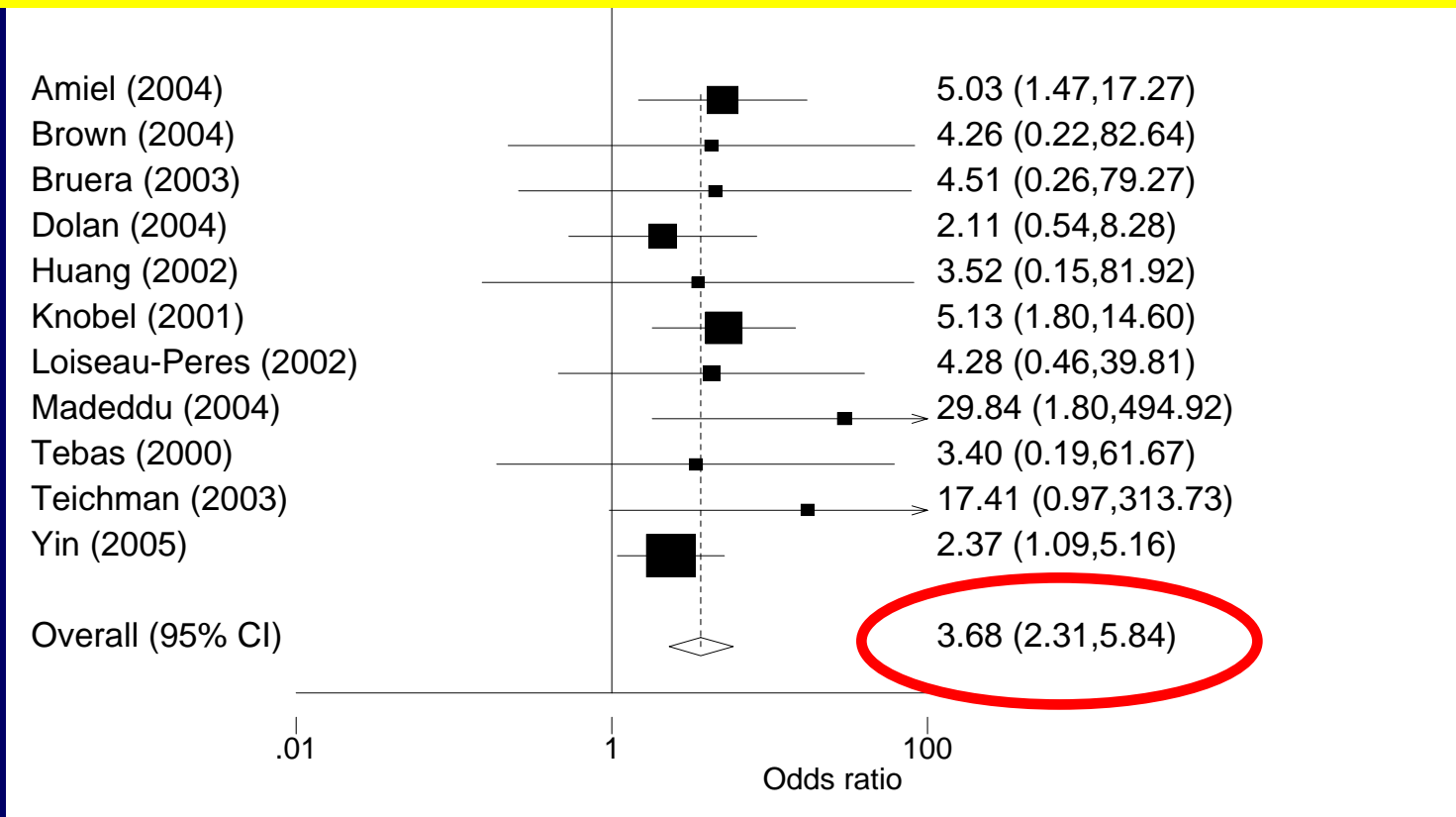
↑ Risk of fracture by 1.5-3.0 x for each SD decrease

Caveats:

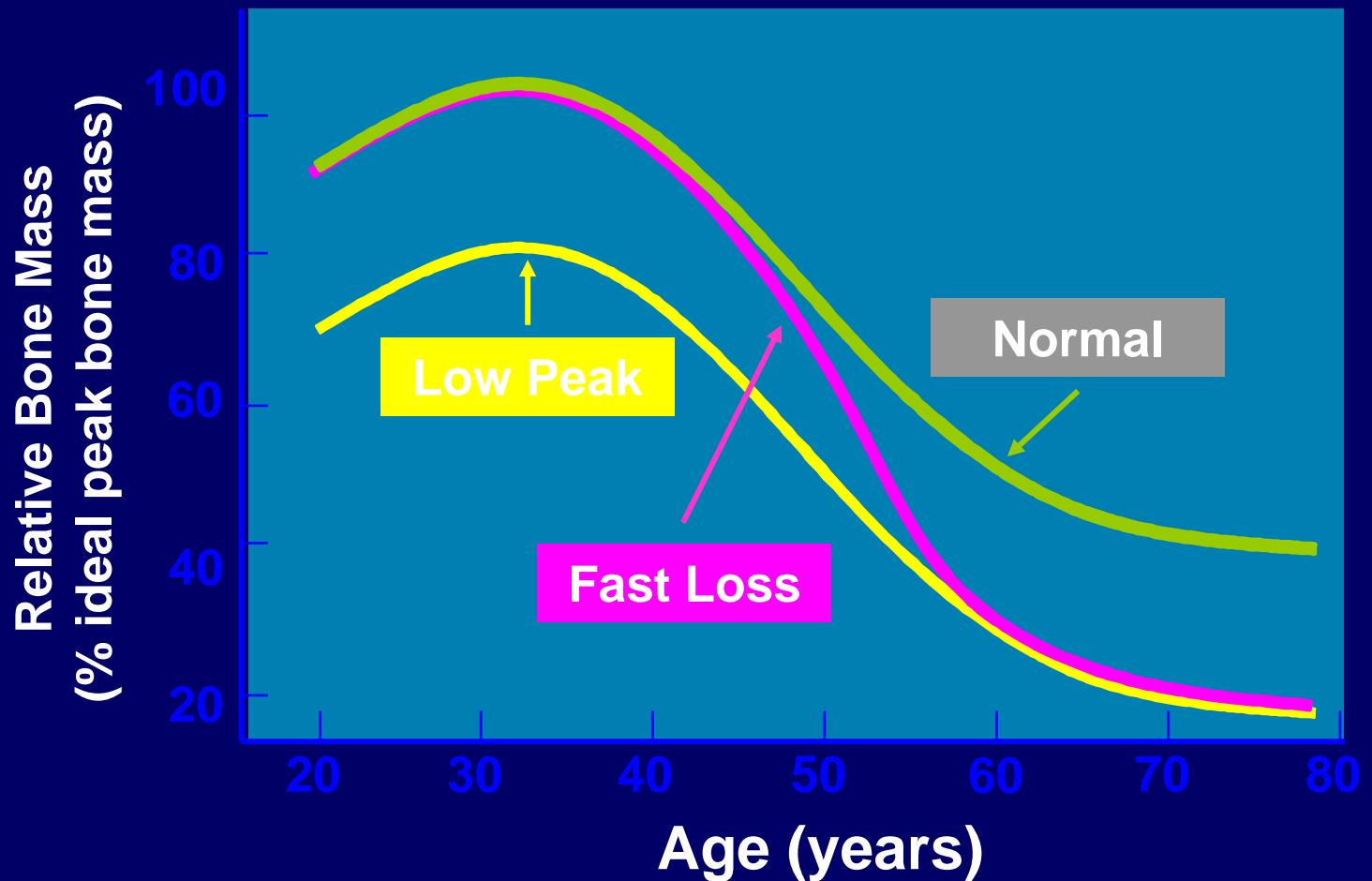
- Unclear if WHO definition should apply to men, premenopausal women
- BMD explains only about 50% of fracture risk

Prevalence of Osteoporosis in HIV-infected Patients vs HIV-uninfected Controls: A Meta-analysis

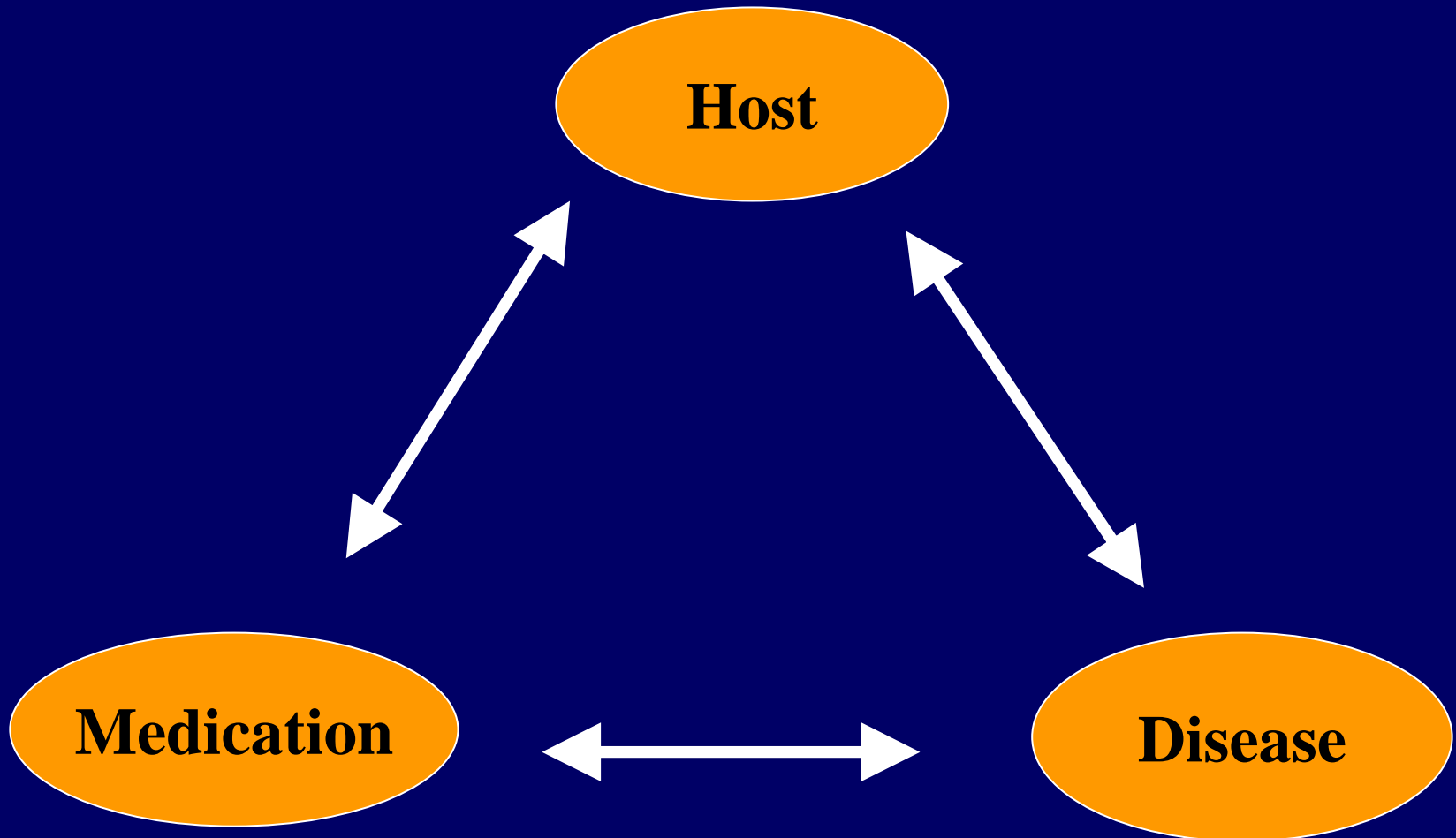
Overall prevalence of osteoporosis in HIV-infected patients 15%



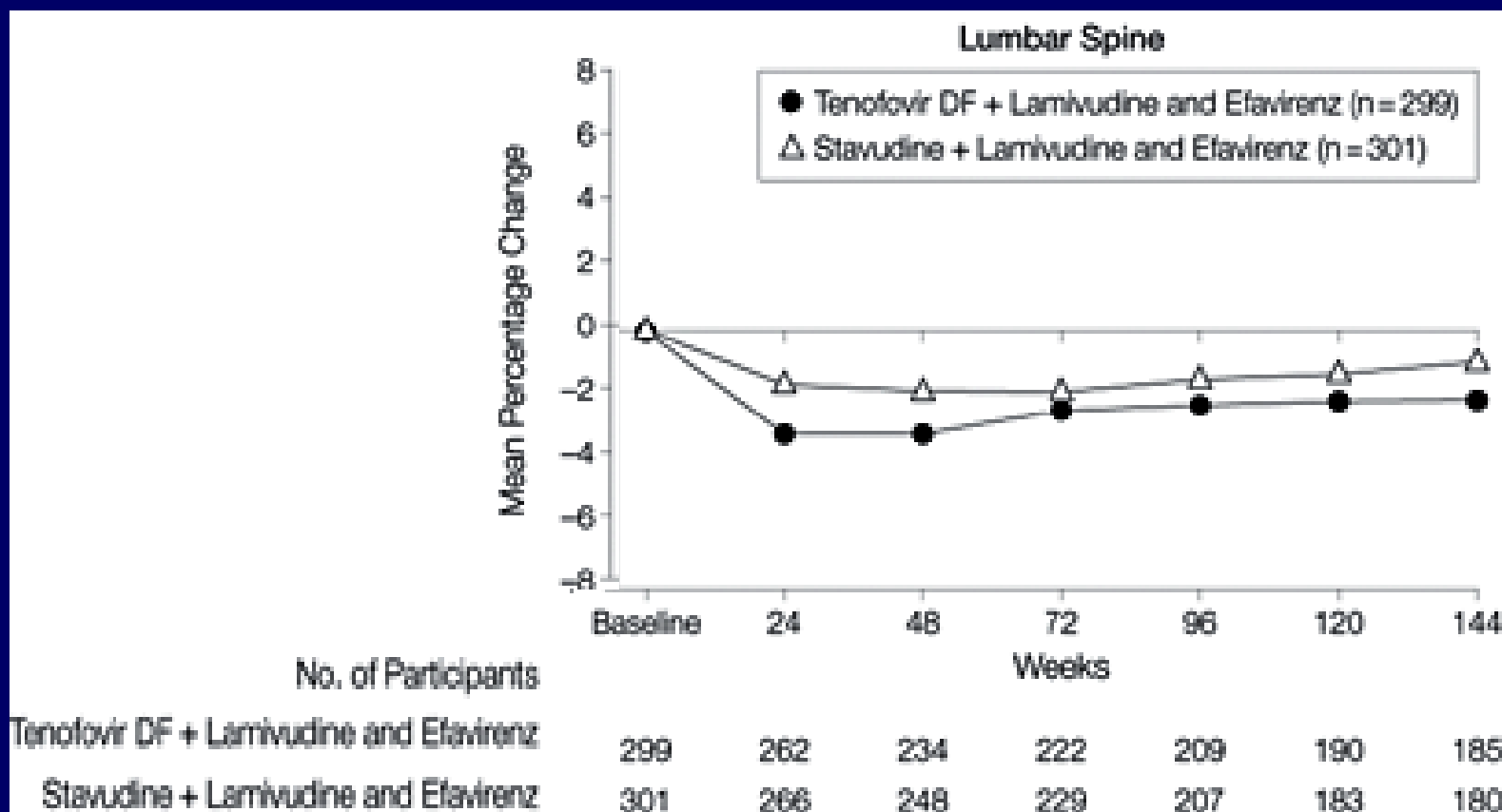
Etiology of Osteoporosis: Fast Bone Loss or Low Peak Bone Mass?



Multifactorial Etiology of Reduced Bone Mineral Density in HIV



Percentage Change in Lumbar Spine BMD with ART Initiation: Gilead 903



When to Screen?

- Current recommendations suggest not screening unless another risk factor is present or h/o fragility fracture
(Schambelan, IAS-USA Panel, JAIDS, 2002)
- Problems:
 - Risk of fragility fractures unknown
 - Treatment is effective, but long term outcomes, toxicities unknown, especially in young patients

Screening Candidates: High Risk Patients

- Hypogonadism
- Alcoholic
- h/o significant steroid exposure
- h/o wasting
- h/o fragility fractures or height loss



What if the patient has osteopenia or osteoporosis?

- Evaluate for secondary causes
 - Vitamin D deficiency → 25 OH Vit D
 - Hyperparathyroidism → PTH, Ca⁺⁺
 - Subclinical Hyperthyroidism → TSH
 - Idiopathic Hypercalciuria → 24 h urinary calcium
 - Hypogonadism → Males: Testosterone; Females: Menstrual History
 - Celiac Sprue → Tissue Transglutaminase
 - Phosphate wasting → Serum Phosphate

45 year old male, HIV+, no history of fragility fracture, h/o hypogonadism (treated), no other risk factors, Spine T-score -2.3, Total hip T-score -2.0. Secondary cause work-up negative.

Would you treat this patient with anti-resorptive medication?

- 1) Yes
- 2) No
- 3) Don't know

Treatment Options

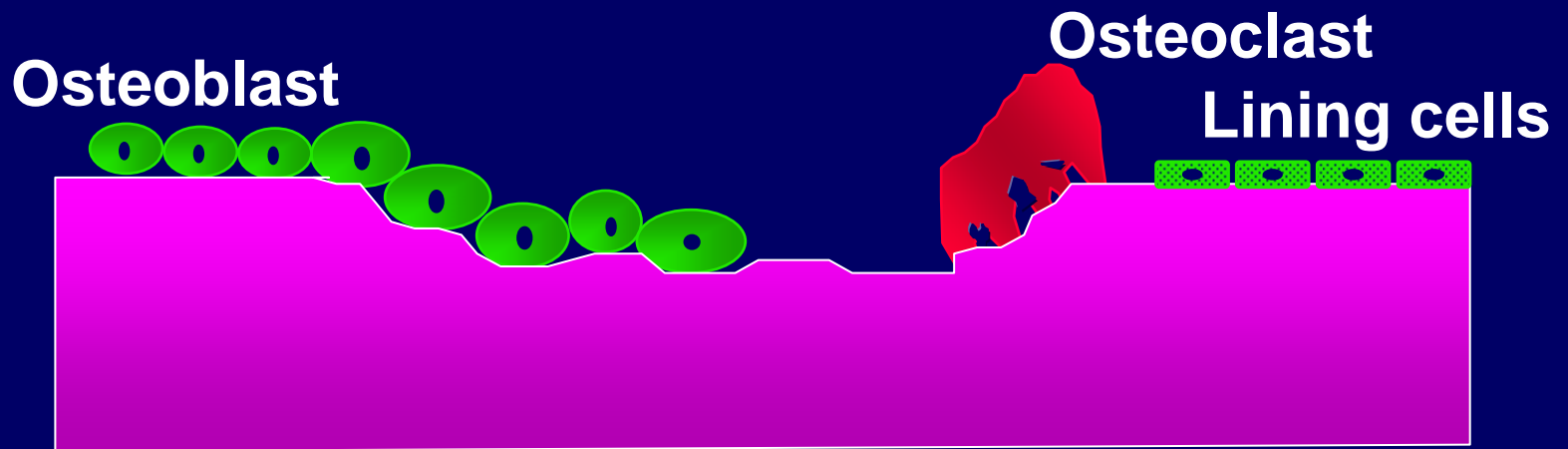
- Treat if T-score < -2.5 or a history of fragility fracture
- Calcium- 1200-1500 mg/day;
Vitamin D- 400-800 IU
- Weight bearing exercise

Treatment Options

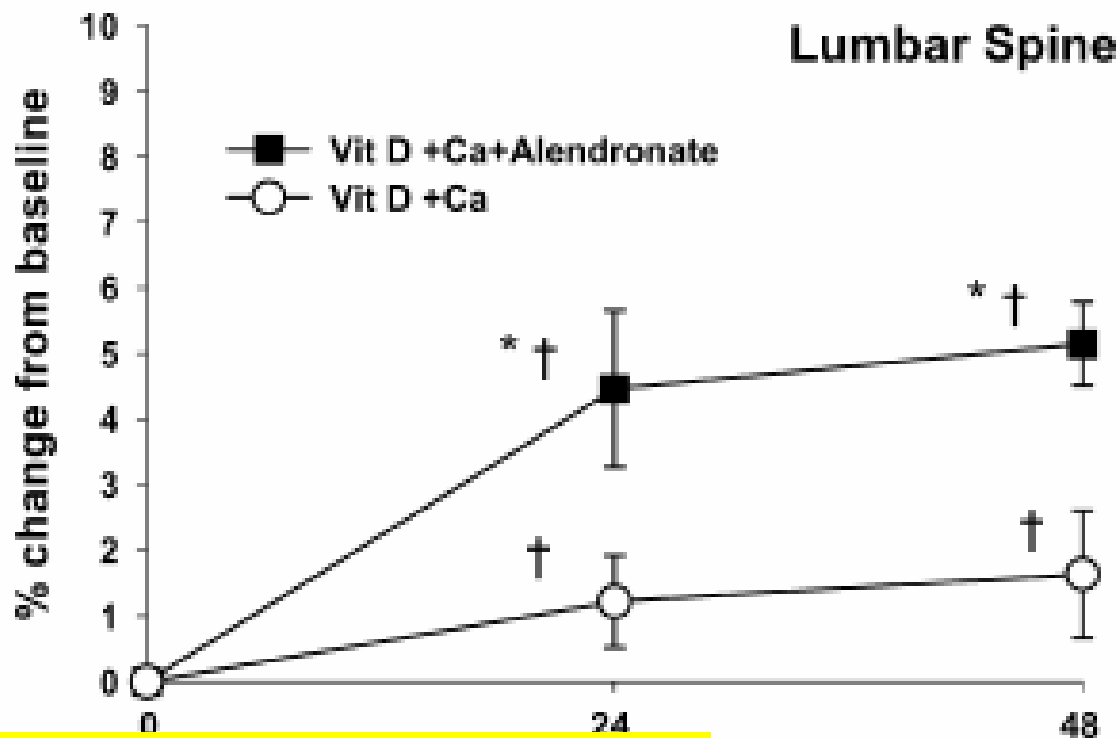
Bisphosphonates

- Actonel (risedronate) 35 mg each week
- Fosamax (alendronate) 70 mg each week
- Ibandronate (oral or IV)

- Work by inhibiting osteoclast function
(Recommendation A)



Alendronate improves BMD in HIV patients with osteopenia/osteoporosis



Concerns:

How long to treat?

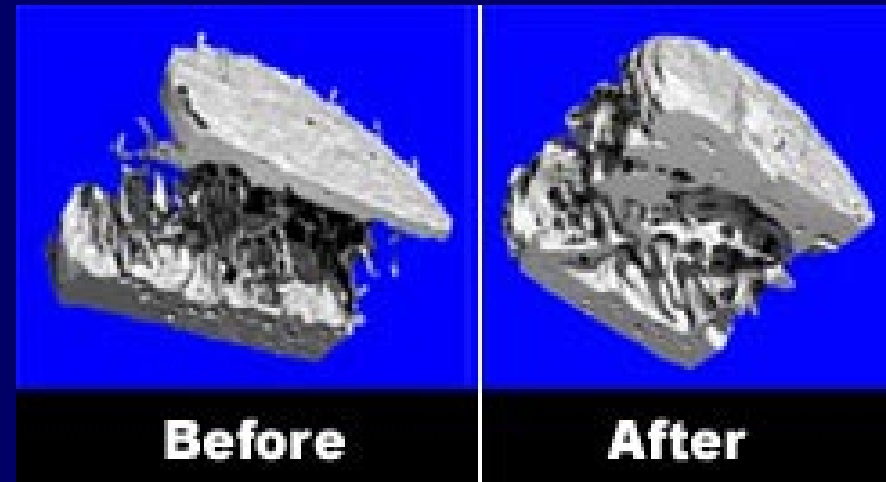
Is low bone turnover a good thing?

Mondy, JAIDS, 2005

Treatment Options

Teriparatide (Forteo)

- ↑new bone formation
- Daily injection
- Given 12-24 months
- Reserved for patients with continued bone loss or fracture on bisphosphonates
- No data in HIV-infected patients



Recommendation B

Treatment Options

For Post-Menopausal Women:

- Raloxifene (Evista)
- Hormone Replacement Therapy
 - Recommended only in women with vasomotor symptoms

Recommendation B

Case Presentation: Follow-up

- BGs well-controlled on metformin/pioglitazone, off insulin
- 3rd triamcinolone injection, BGs 400 mg/dL
- Dizziness, started on steroids
- Started on risedronate, Ca⁺⁺/Vit D

Conclusions

- Endocrine problems may complicate the care of HIV-infected patients
- Problems may be inter-related and not always clinically apparent
- High index of suspicion is required
- Causes of adrenal insufficiency shifted in HAART era. Watch out for steroid-HAART interactions causing adrenal suppression
- Slow tapers may be necessary with prolonged steroid use
- Reduced bone mineral density is common in HIV
- Clinical significance has not yet been established