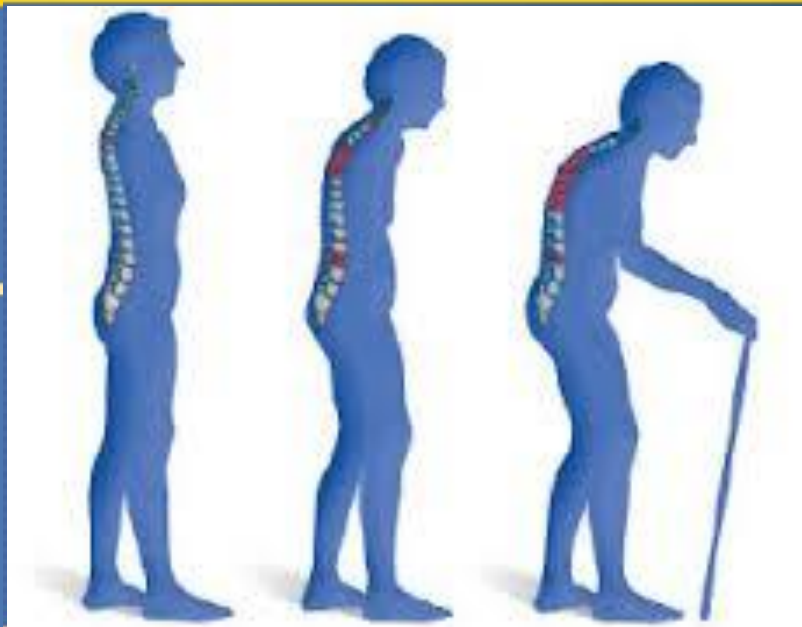# HIV and Metabolic Cases

Amita Gupta MD, MHS
Associate Professor of Medicine & International Health
Deputy Director Johns Hopkins Center for Clinical Global Health

Disclosures

None

Receive grant funding from NIH, US CDC, Indian government, Gates, Mylan, Gilead Foundation and Ujala Foundation

Bones

Case: Ms. AG

- 58 year old Black female
- History of treated pulmonary TB
- Social History
  - Smokes cigarettes 1ppd
  - Drinks: 2-3 beers "most days"
    - Sometimes also wine on weekends
  - Exercise: none
  - Stable home environment

Case; Ms AG

- FH:
  - *"All the women are hunched over"*
  - *"All the men die of heart attacks before age 60"*
- PE: unremarkable
  - BMI = 21 kg/m^2
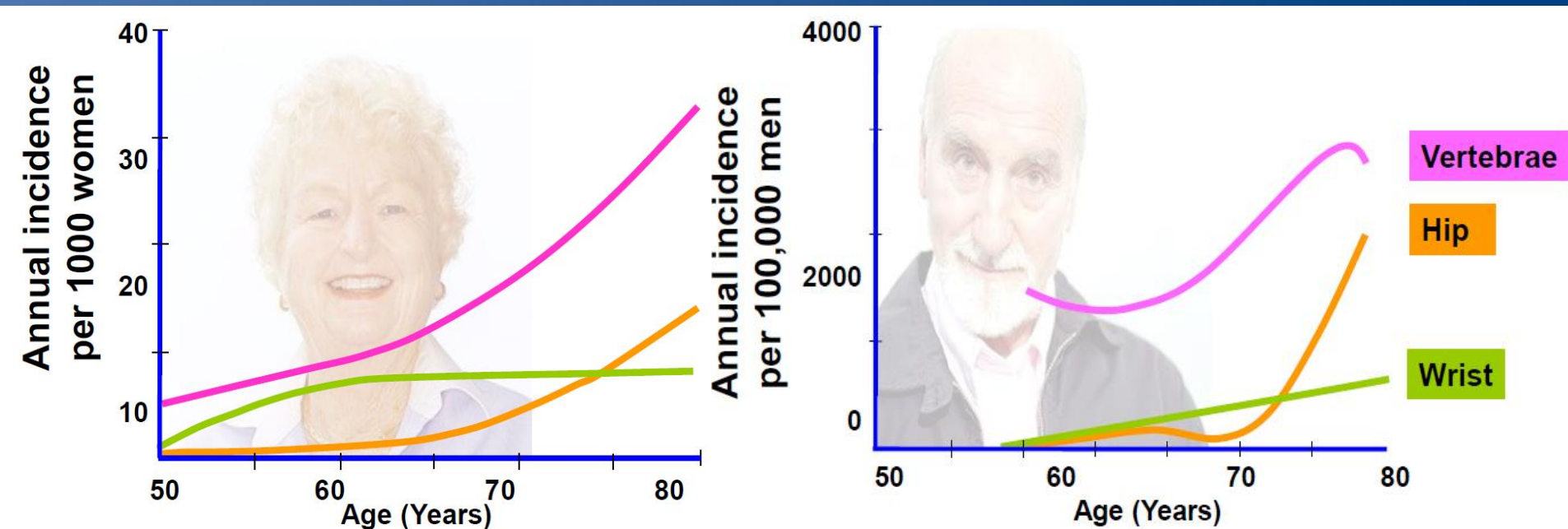
Case: Ms AG

- Labs
  - CD4 = 333 cell/mm^3
  - VL: 195, 000 cells/mL
  - Hep B negative
  - TC: 288 mg/dL
    - LDL: 220, HDL 31, TG 183
- She is ready and able to start HAART

Audience: Particularly worried about her bones, you recommend:

1. TDF/FTC/EFV
2. TDF/FTC + RAL
3. TDF/FTC + LPV/r
4. TDF/FTC + ATV/r
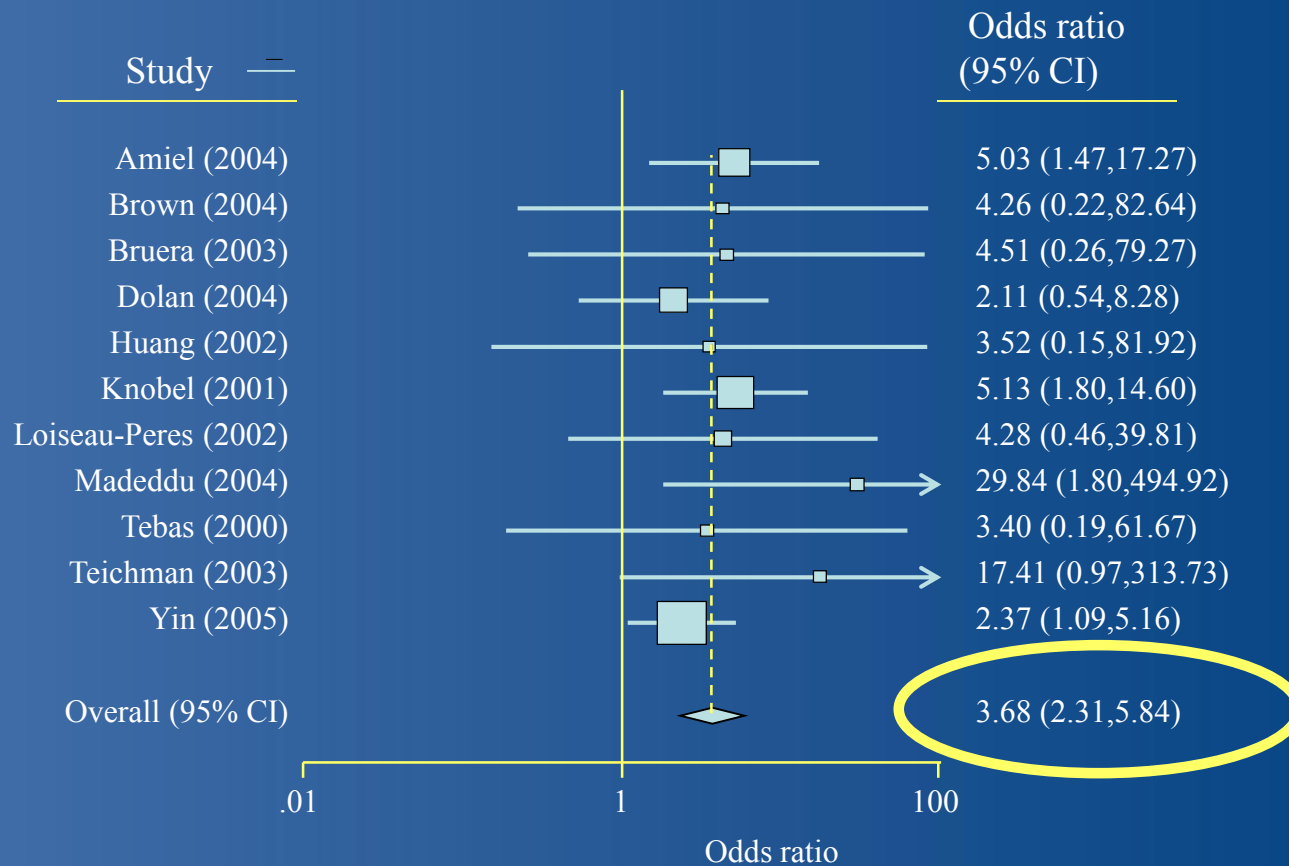5. ABC/3TC + EFV
6. Something else
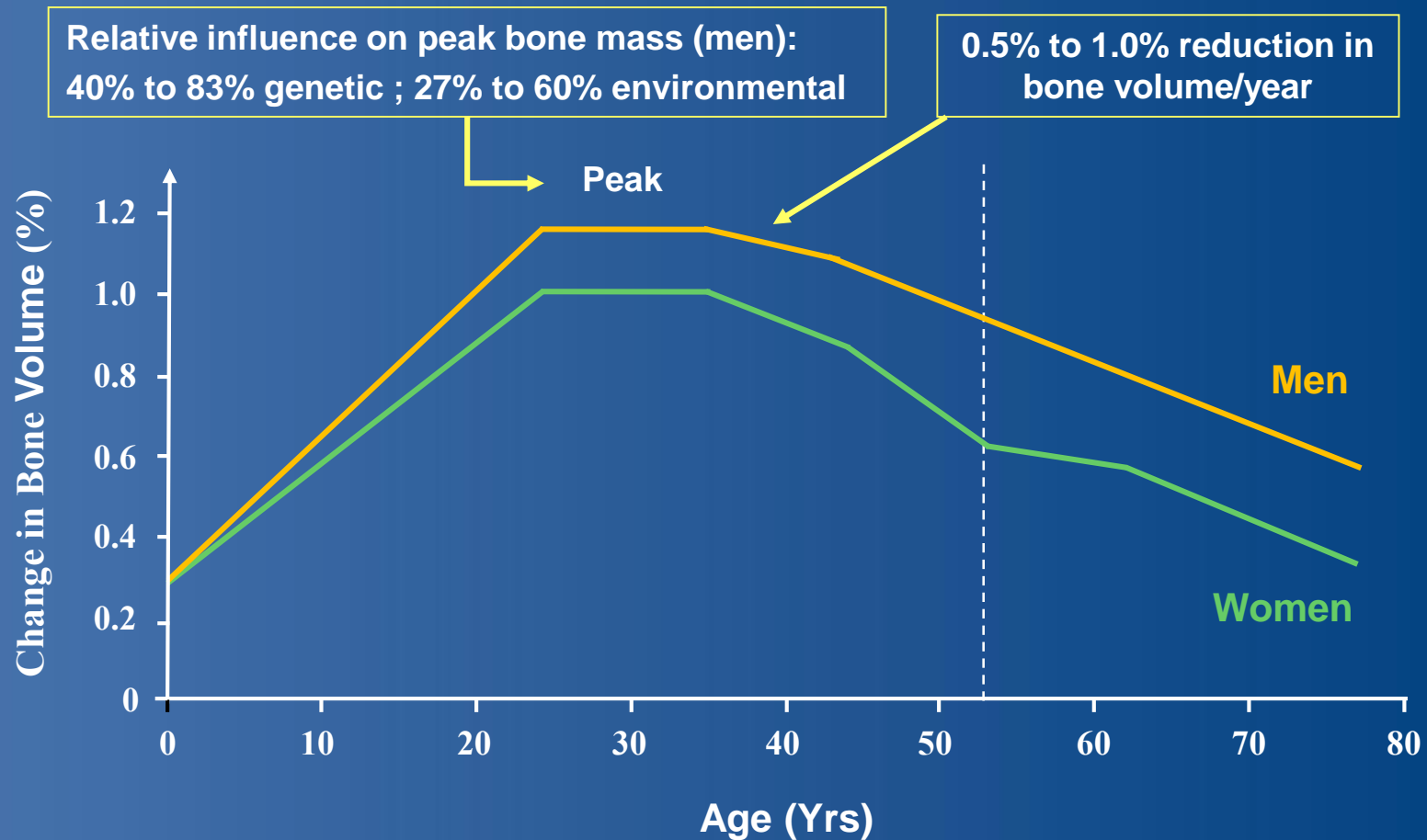
Fragility Fractures in Women and Men over 50 years

Wasnich RD, Osteoporos Int 1997;7 Suppl 3:68-72 Images from the National Osteoporosis Foundation

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

JOHNS HOPKINS
MEDICINE

Overall prevalence of osteoporosis in HIV-infected patients 15%

Study	Odds ratio (95% CI)
Amiel (2004)	5.03 (1.47,17.27)
Brown (2004)	4.26 (0.22,82.64)
Bruera (2003)	4.51 (0.26,79.27)
Dolan (2004)	2.11 (0.54,8.28)
Huang (2002)	3.52 (0.15,81.92)
Knobel (2001)	5.13 (1.80,14.60)
Loiseau-Peres (2002)	4.28 (0.46,39.81)
Madeddu (2004)	29.84 (1.80,494.92)
Tebas (2000)	3.40 (0.19,61.67)
Teichman (2003)	17.41 (0.97,313.73)
Yin (2005)	2.37 (1.09,5.16)
Overall (95% CI)	3.68 (2.31,5.84)

Odds ratio

BMD Decreases With Age

Relative influence on peak bone mass (men): 40% to 83% genetic ; 27% to 60% environmental

0.5% to 1.0% reduction in bone volume/year

Peak

Men

Women

Change in Bone Volume (%)

Age (Yrs)

Orwoll ES et al. *Endocr Rev*. 1995;16(1):87-116.

Osteoporosis in HIV-Positive Patients

- Osteoporosis and fractures are common in HIV-positive patients and will increase with aging

- Risk factors include
  - Pre-ART HIV disease severity ↓ CD4, ↑ HIV-1 RNA
  - ART (TDF, certain PIs, any ART initiation)
  - Traditional: smoking, alcohol, HCV, low T, low weight

- Screening: dual-energy x-ray absorptiometry should be considered in all HIV-positive postmenopausal women and in men aged older than 50 yrs (US)

McComsey G, et al. Clin Infect Dis. 2010;51:937-946

Specific ARV

- TDF > other NRTIs

- PI vs other 3rd drug: data mixed/limited
  - vs EFV: Effect seen at spine, but not hip (A5224s)

- Recent trial A5257 compared ATV vd DRV vs RAL with TDF/FTC backbone
  - RAL better than PIs

ACTG 5257 (sub-study 5260s) : BMD through week 96


Change in BMD Over 96 Weeks
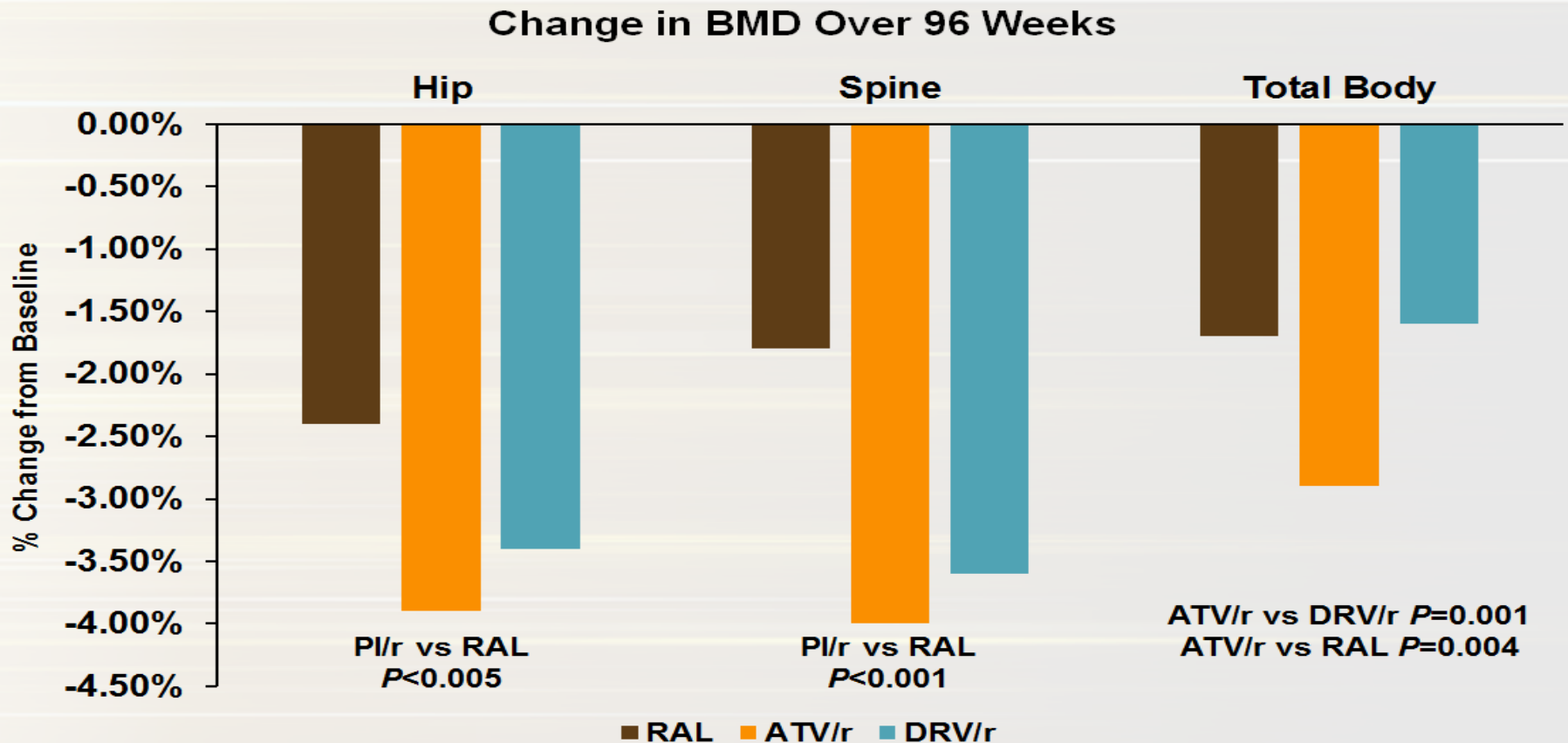
Case: Ms AG

- You start her on TDF/FTC+EFV
- She gets enrolled into a study where they are measuring Vitamin D
- Vitamin D is 20 ng/mL

Audience: What should you consider next?

- A) continue her ART
- B) initiate Vitamin D at 400 IU/daily
- C) initiate Vitamin D at 50,000 IU/daily
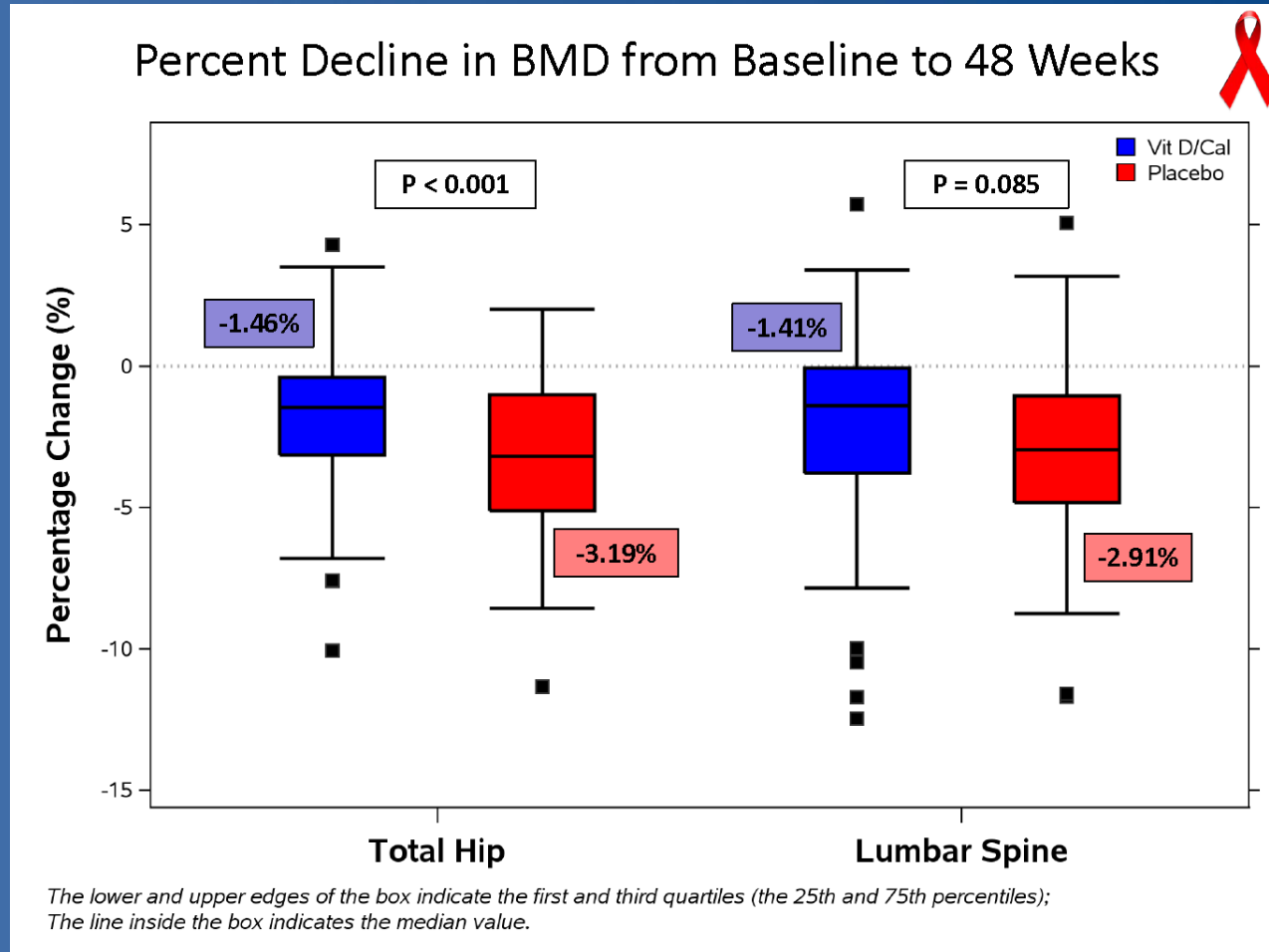- D) initiate Vitamin D 2000 IU+ Calcium supplement

EFV associated with decrease in Vitamin D: A5175
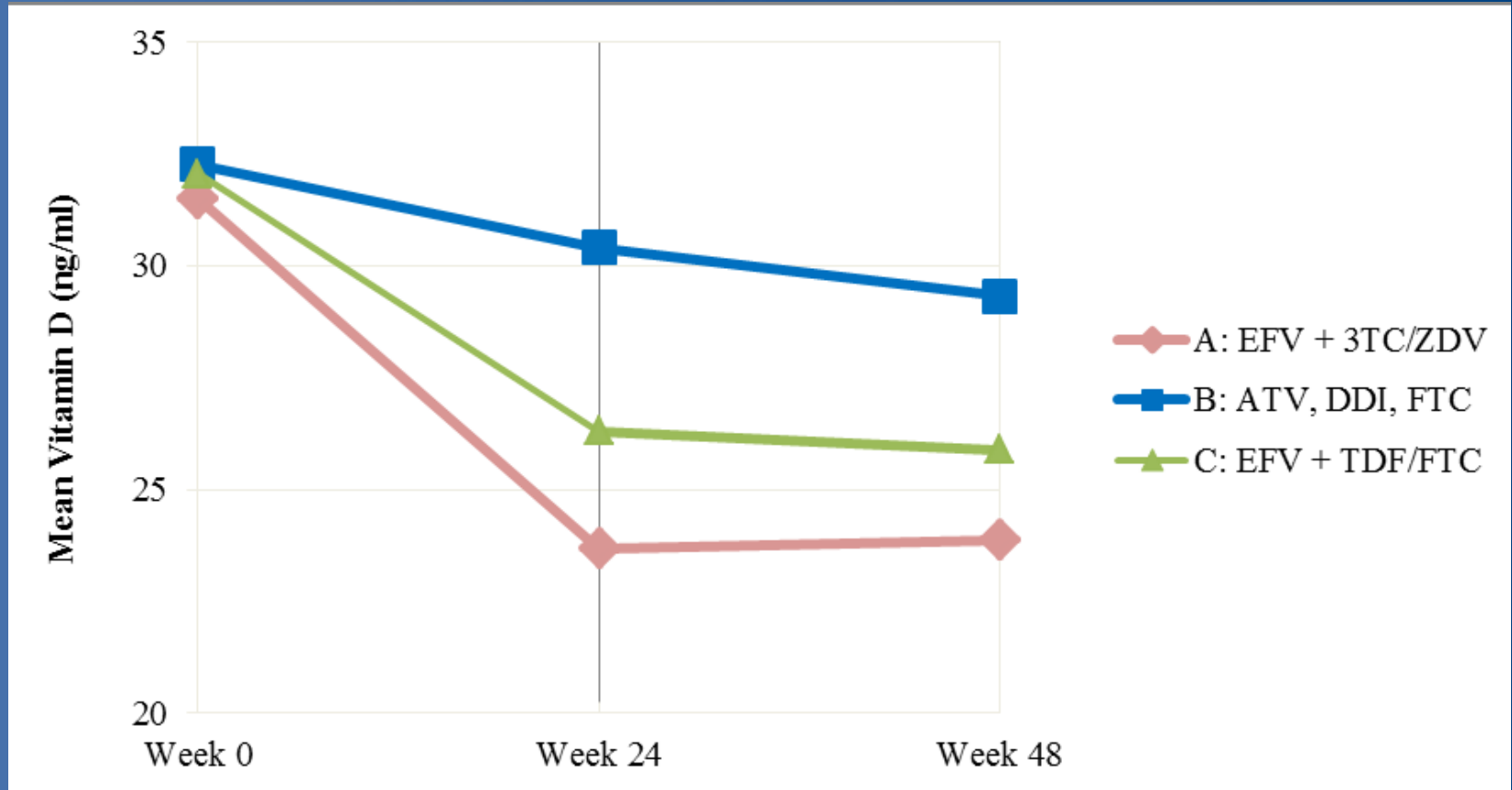
Calcium and Vitamin D: ACTG 5280

- Randomized, double-blind trial
  - patients initiating TDF/FTC/EFV
  - baseline vitamin D 10-75 ng/mL
- Intervention:
  - Vitamin D3 4000 IU/day
  - Calcium carbonate 1000 IU/day

High Dose Vitamin D and Calcium Attenuates Bone Loss with Initiation of TDF/FTC/EFV

Percent Decline in BMD from Baseline to 48 Weeks

Total Hip: P < 0.001 — Vit D/Cal: -1.46%, Placebo: -3.19%

Lumbar Spine: P = 0.085 — Vit D/Cal: -1.41%, Placebo: -2.91%

Percentage Change (%)

The lower and upper edges of the box indicate the first and third quartiles (the 25th and 75th percentiles);
The line inside the box indicates the median value.

Overton, CROI, 2014

Bones Summary

- Good health maintenance:
    - Calcium
    - Vitamin D supplement (600-1200 IU)
    - Stop cigarettes
    - Decrease alcohol ($\leq$ 2/day)
    - Weight bearing exercise
- Consider DXA scan
- Think about ARV selection

4: Lipids + CVD

Case: Mr. JW

- 54 yo Black male
- PMH:
  - CAD
    - 1 drug eluting stent (2012)
  - HTN
  - Hyperlipidemia
  - (No DM)

Case: Mr JW

- SH:
  - Former 1.5 ppd smoker (quit 2012)
  - 1 glass red wine, 4 times a week
  - No drugs
  - Exercises "occasionally"
- FH: CAD

Case: Mr JW

- PE: unremarkable
- Meds (all once daily)
    - Aspirin 81 mg
    - Lisinopril 40 mg
    - Atorvastatin 80 mg
    - Metoprolol XL 100 mg
    - herbal supplement

Case: Mr JW

- He is found to be HIV positive
- Labs
  - CD4 = 522 cell/mm^3
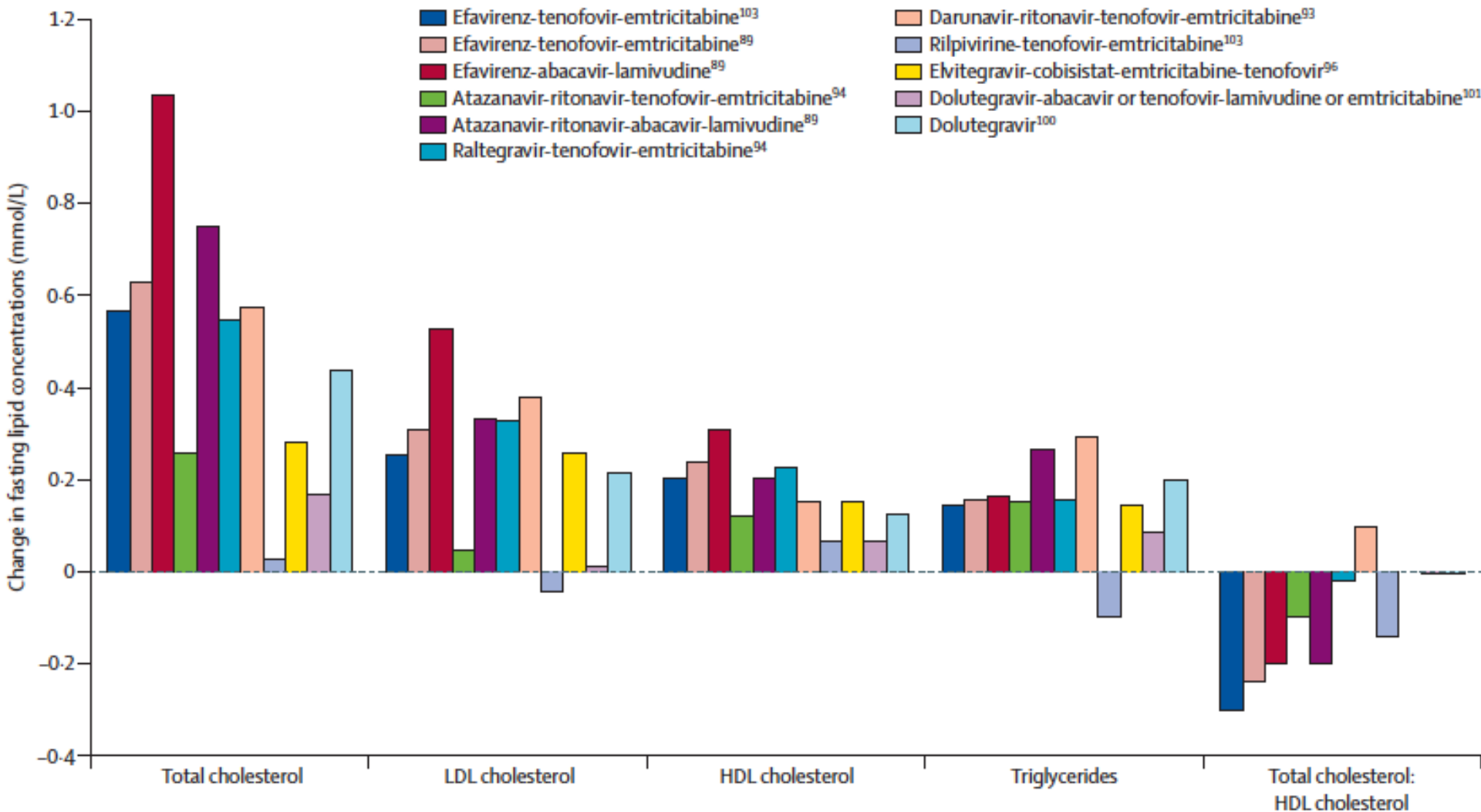 - VL: 88, 000 cells/mL
  - Hep A+ B nonimmune

Audience: Given his CVD, you recommend

1. TDF/FTC/EFV
2. DRV/r + RAL
3. DRV/r + TDF/FTC
4. ABC/3TC + ATV/r
5. ABC/3TC + DTG
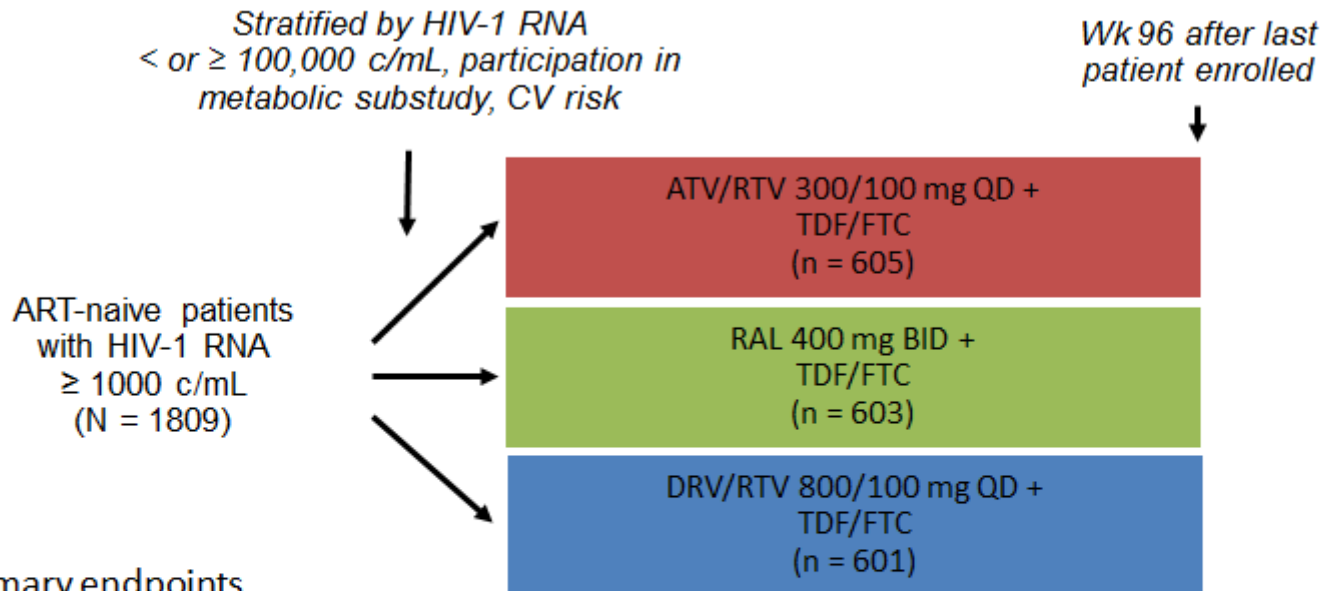6. None: He doesn't need to start HAART

ART effect on Lipids

Legend:
- Efavirenz-tenofovir-emtricitabine[103]
- Efavirenz-tenofovir-emtricitabine[89]
- Efavirenz-abacavir-lamivudine[89]
- Atazanavir-ritonavir-tenofovir-emtricitabine[94]
- Atazanavir-ritonavir-abacavir-lamivudine[89]
- Raltegravir-tenofovir-emtricitabine[94]
- Darunavir-ritonavir-tenofovir-emtricitabine[93]
- Rilpivirine-tenofovir-emtricitabine[103]
- Elvitegravir-cobisistat-emtricitabine-tenofovir[96]
- Dolutegravir-abacavir or tenofovir-lamivudine or emtricitabine[101]
- Dolutegravir[100]

Y-axis: Change in fasting lipid concentrations (mmol/L)

X-axis categories: Total cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides, Total cholesterol: HDL cholesterol

(1) ACTG 5257:
ATV/r, RAL, DRV/r with TDF/FTC

Stratified by HIV-1 RNA
< or ≥ 100,000 c/mL, participation in
metabolic substudy, CV risk

Wk 96 after last
patient enrolled

ART-naive patients
with HIV-1 RNA
≥ 1000 c/mL
(N = 1809)

ATV/RTV 300/100 mg QD +
TDF/FTC
(n = 605)

RAL 400 mg BID +
TDF/FTC
(n = 603)

DRV/RTV 800/100 mg QD +
TDF/FTC
(n = 601)

- Primary endpoints
  - **Virologic failure:** time to HIV-1 RNA > 1000 c/mL (at Wk 16 or before Wk 24) or > 200 c/mL (at or after Wk 24)
  - **Tolerability failure:** time to discontinuation of randomized component for toxicity
- Composite endpoint: the earlier occurrence of either VF or TF in a given participant
- Switch of regimens allowed for tolerability
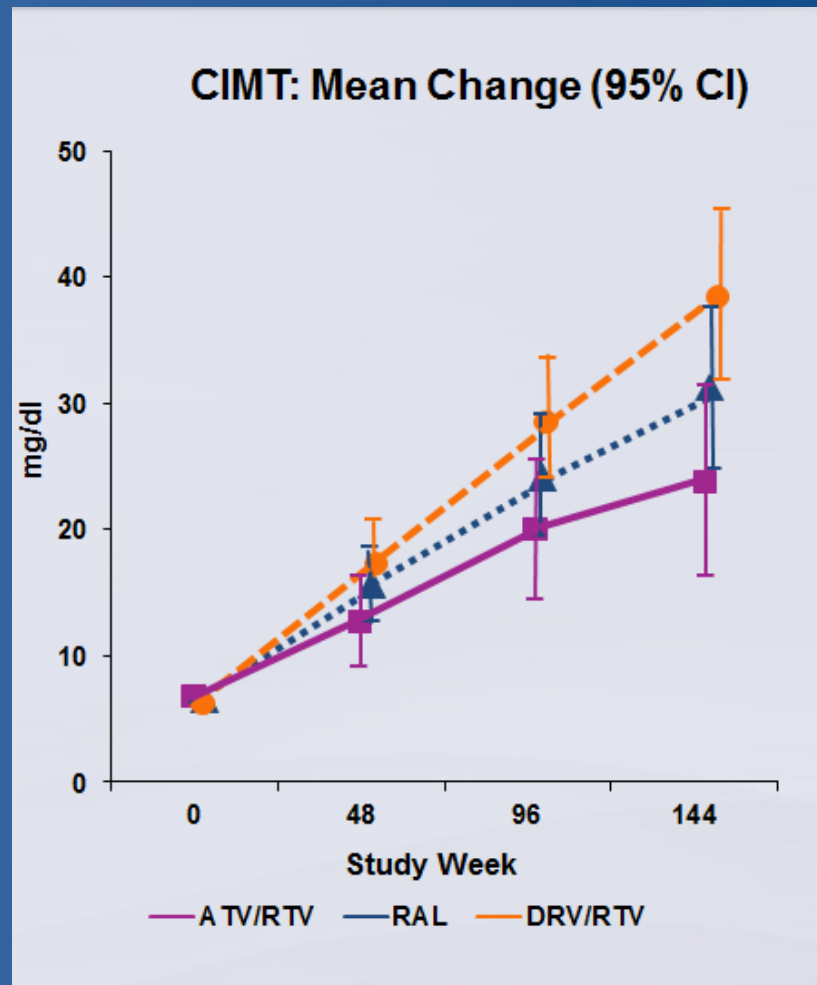
Landovitz R, et al. CROI 2014. Abstract 85.

Landovitz R, et al. CROI 2014. Abstract 85.

ACTG 5257: Lipids at week 96

- DRV/r or ATV/r PI-containing regimens (vs. RAL)
  - significantly greater ⬆
    - TC
    - LDL-C
    - TGs
  - Lipids remained stable or ⬇ in RAL arm
  - Lipids changes in boosted PI arms similar

Ofotokun I, et al. CROI 2014. Abstract 746.

ACTG 5257: Lipid Changes at 96 Weeks

Ofotokun I, et al. CROI 2014. Abstract 746.
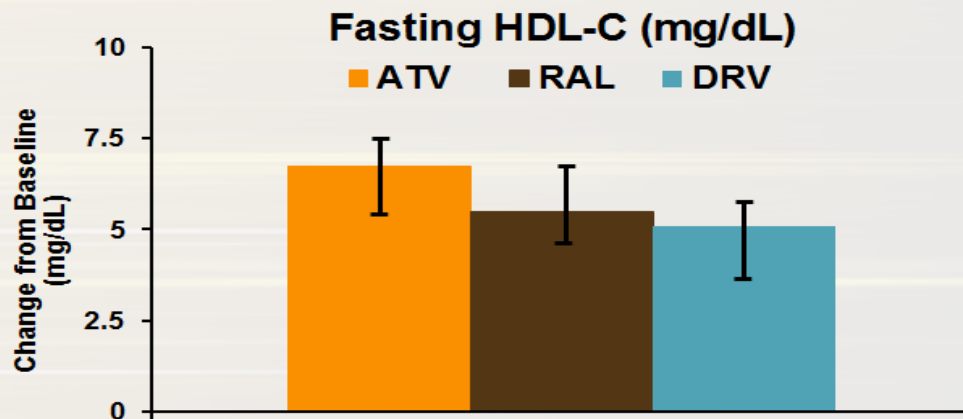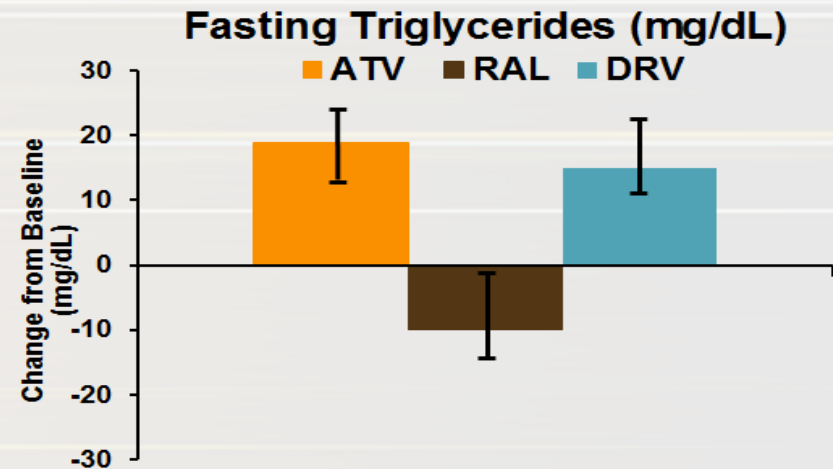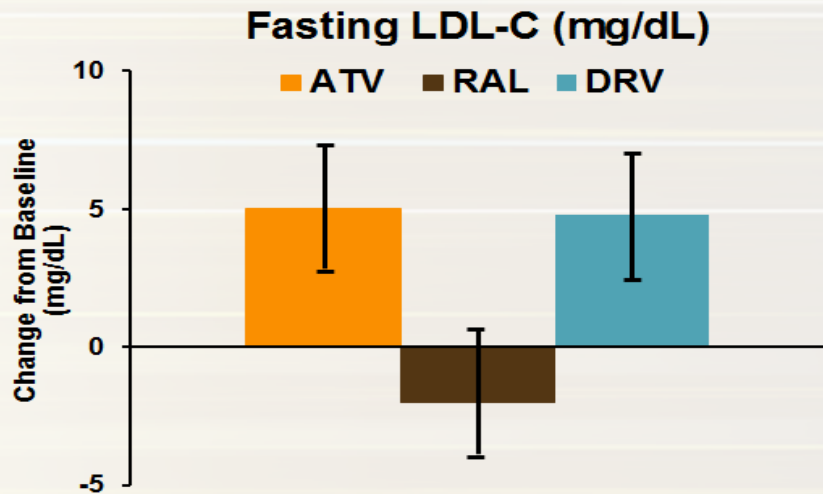
ACTG 5257: Carotid Intima-Media Thickening (IMT)

Stein J et al, *J Am Coll Cardiol*. 2014;63(12_S):. Abstract A1322

What did we learn about lipids?

- Its not straight forward
- RAL better than PIs (provided:+TDF/FTC)
  - TC, LDL, TG
- Carotid IMT seems to worsen in all ARV
  - Didn't necessarily follow lipids
- With PIs, TDF/FTC is better than RAL
  - TC, LDL
    - But worse HDL, no difference in ratio

JOHNS HOPKINS
MEDICINE

What did we learn about lipids? (STRATEGY trials)

- EVG compared to PIs
  - Better for TG
- EVG compared to EFV
  - Better for LDL
  - Worse for HDL

Pozniak CROI 2014; Arribas CROI 2014

Bottom line

- TDF is better for lipids than other nRTIs
- With TDF: Integrase inhibitors seem better
- NNRTI: neutral overall (increase LDL, TG, HDL eith EFV but not total:HDL ratio)
- PIs
  - Use clinical judgment about entire patient
    - between ATV and DRV

Case: Mr JW

- He did not tolerate EFV and was switched to LPV/r+TDF/FTC
- 1 year later his LDL increased to 190mg/dL and his TG was 240

What would you do next?

- a) switch his LPV/r to ATV/r
- b) start simvistatin
- c) start atorvastatin
- d) both a and c
- c) not sure

Guidance based on ATP III

Risk Category	Goal LDL	Initiate Lifestyle Modification (LDL mg/dL)	Initiate Drug Therapy (LDL mg/dL)
High risk: Known CAD or CAD equivalent	<100 or <70	Any LDL	>100 consider >70
Moderately high risk: 2+ risk factors (10-20% 10 yr risk*)	<130 or <100	Any LDL	>=130 consider >100
Moderate risk: 2+ risk factors (10yr risk < 10%*)	<130	>=130	>=160
Lower risk: 0-1 risk factor(s)	<160	>=160	>=190

Statins and ART

Statin type	Approach
Pravastatin	start 20mg (max 80mg)
Atorvastatin	start 10mg (max 80mg; but most on ART max 40mg)
Rosuvastatin	start 5mg (max 40mg)
Lovastatin and Simvistatin	AVOID

Fibric acids for high TG >500	gemfibroxil 600mg BID or fenofribate 48-145mg qd
Niacin	an option but can worsen insulin resistance

Lipid-Lowering Therapy in HIV

Concomitant use of 2 to 3 lipid-modifying agents with HAART commonly seen

	Primary option	Alternative
Elevated LDL-C or non-HDL-C, and triglycerides 200-500 mg/dL	• Atorvastatin • Pravastatin • (Rosuvastatin)	• Fluvastatin • Fibrate
Triglycerides > 500 mg/dL	• Fibrate	• Niacin • Prescription omega-3 fish oils

Dubé MP, et al. *Clin Infect Dis.* 2003;37:613-627.[17]

CV Summary

- Standard risk factors still dominate
    - Stop Smoking
    - Control HTN
    - Watch for and control DM
    - Exercise
    - TREAT Lipids
- Consider ARVs that may be better
    - TDF seems to lower lipids
    - INSTIs seem to have better lipid profiles

CV Summary

- Add Aspirin when appropriate
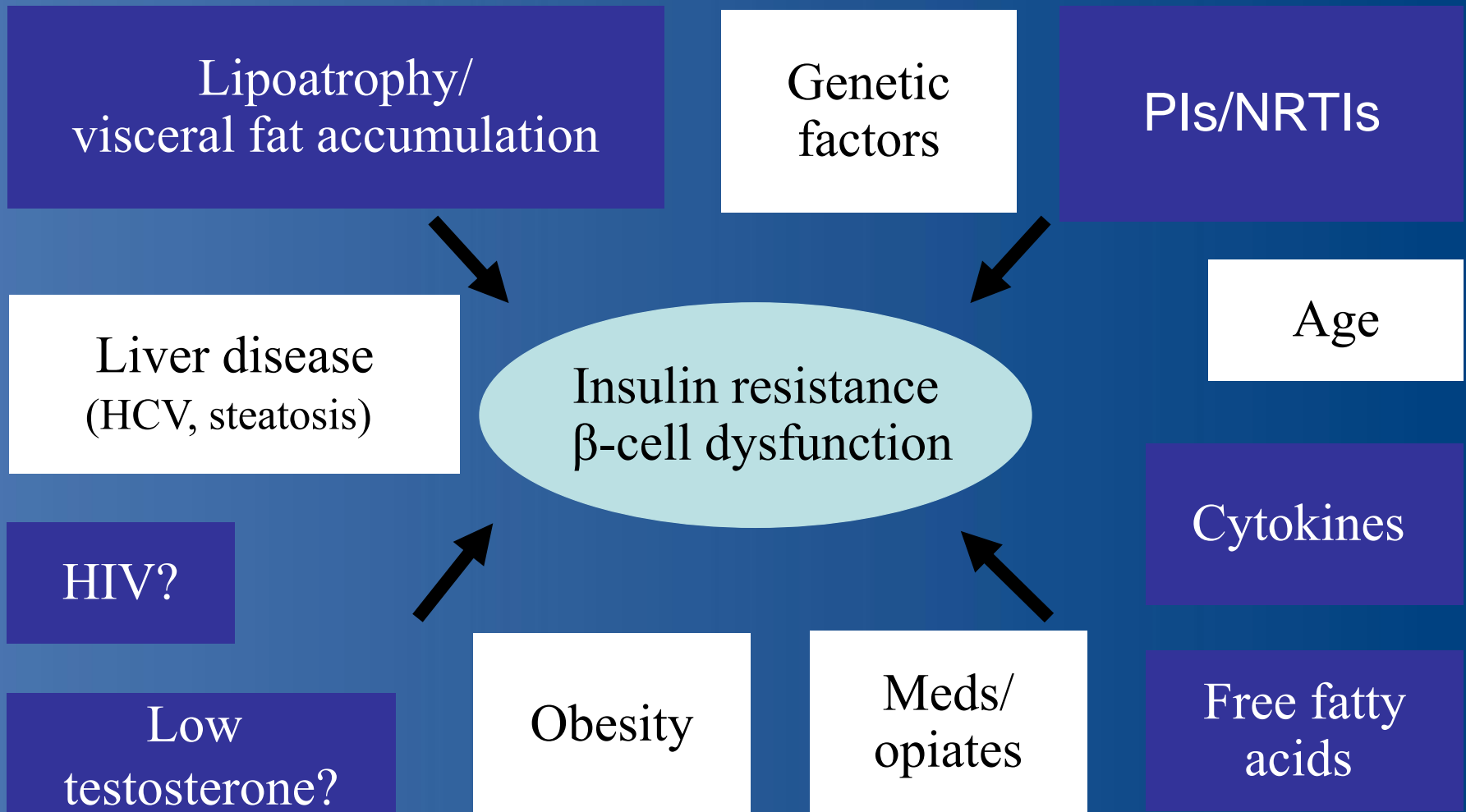- Proper diet
- Exercise
- (Enjoy a drink)

Case: Mr JW

- Mr JW now complains of polydipsia, polyphagia and fatigue for the past 2 months

What should you do next?

- a) send a HgBA1c
- b) send a fasting sugar
- c) have him do a oral glucose tolerance test
- d) send a random blood sugar

Multiple Factors May Contribute to Diabetes in HIV

Lipoatrophy/
visceral fat accumulation

Genetic
factors

PIs/NRTIs

Liver disease
(HCV, steatosis)

Insulin resistance
β-cell dysfunction

Age

HIV?

Cytokines

Low
testosterone?

Obesity

Meds/
opiates

Free fatty
acids

ADA Definitions of Diabetes: 2013

1. HbA1c ≥ 6.5%* *or*

2. Fasting plasma glucose ≥ 126 mg/dL* *or*

3. Plasma glucose ≥ 200 mg/dL when measured 2 hrs after 75-g oral glucose tolerance test * *or*

4. Random plasma glucose ≥ 200 mg/dL with polyuria and polydipsia

*Should be confirmed on repeat testing.

DA Guidelines 2013.

HbA1c Underestimates Glycemia in HIV-Infected Persons

- Prospective cross-sectional study of 100 HIV-infected adults with type 2 diabetes (77%) or fasting hyperglycemia (23%)

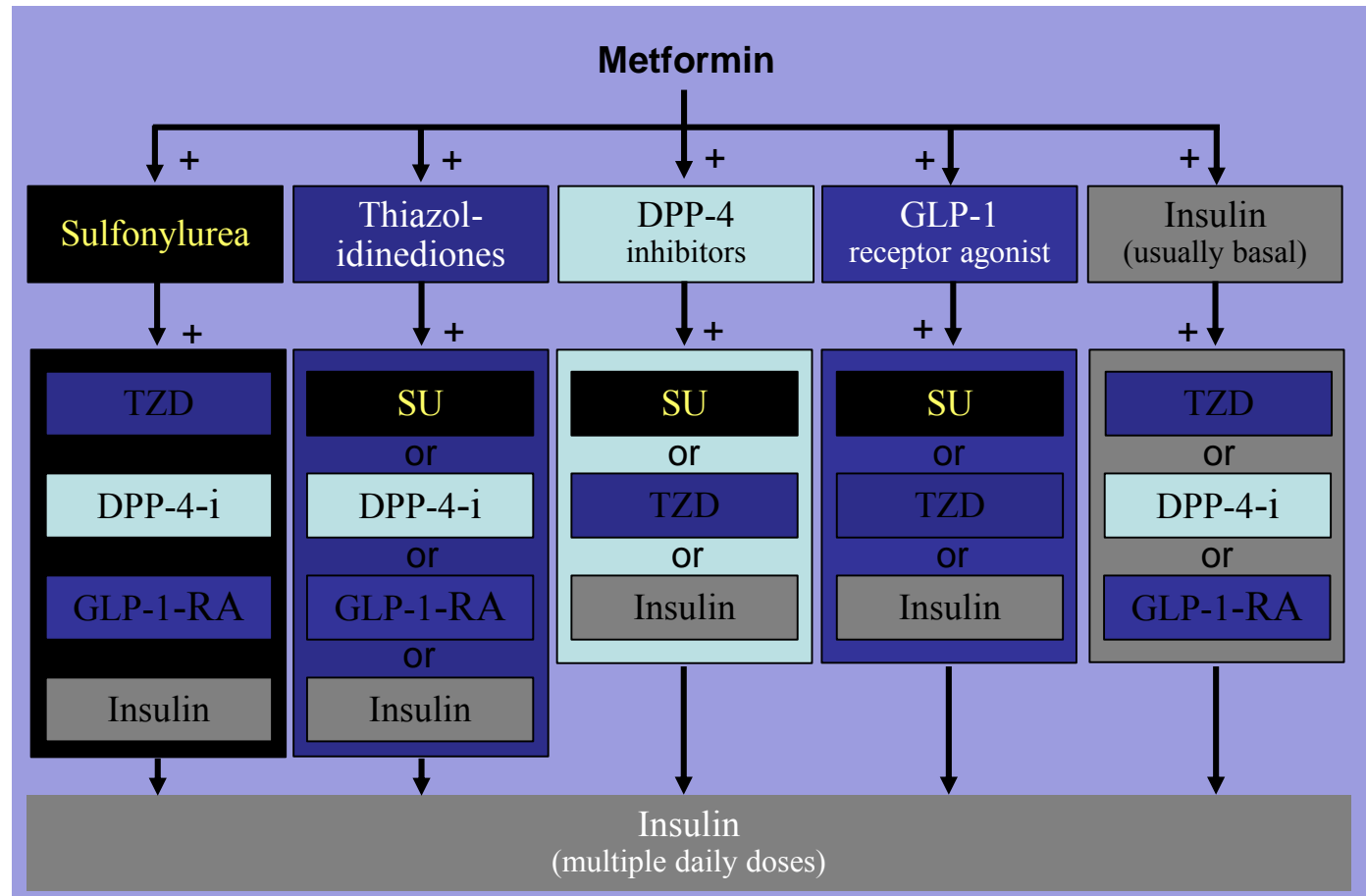Kim PS, et al. Diabetes Care. 2009;32:1591-1593.
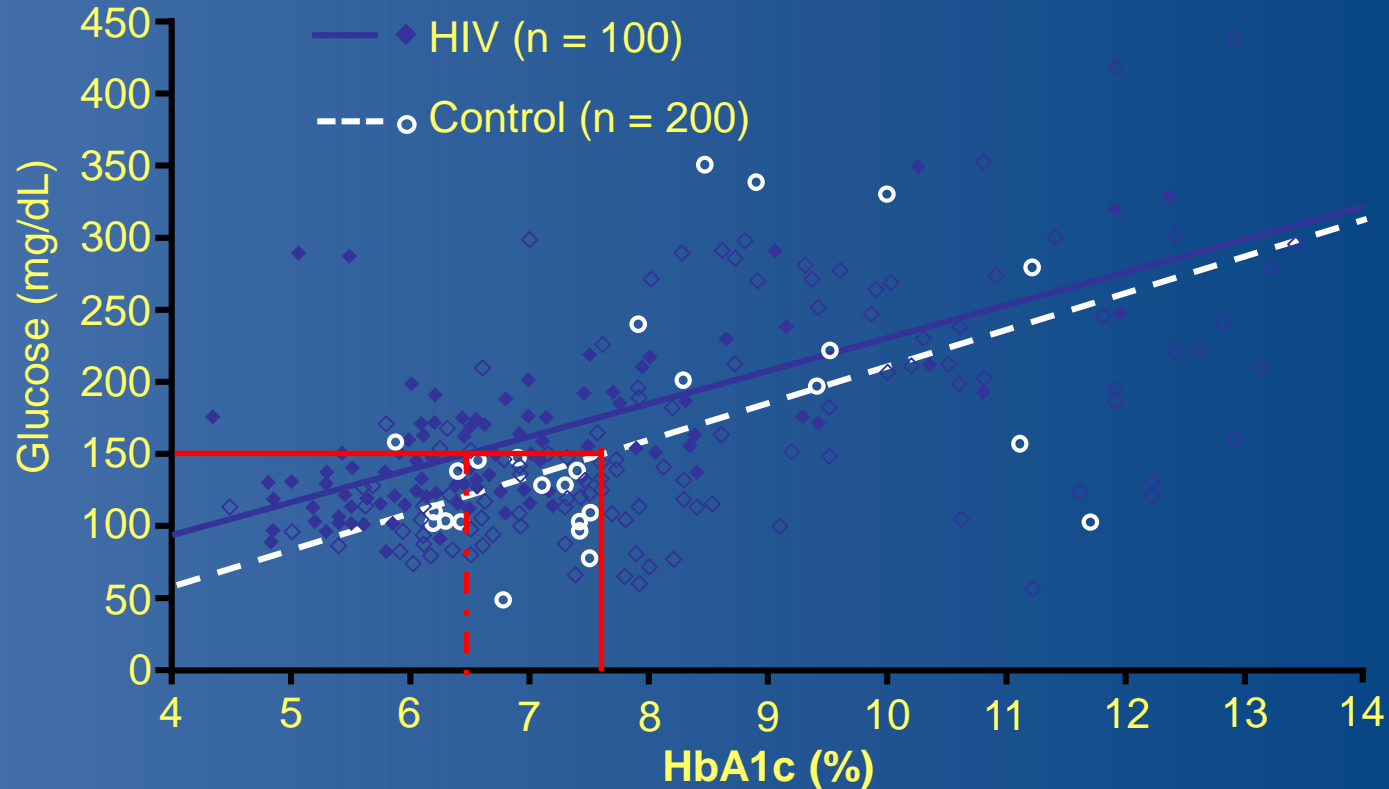
Diabetes Screening

- How?
  - Fasting glucose
  - If 100-125 mg/dL, consider 75-g OGTT
- When?

  HIVMA/IDSA:

  - Fasting glucose every 6-12 mos in all patients
  - Consider testing 1-3 mos after starting or modifying ART

Aberg JA, et al. Clin Infect Dis. 2009;49:651-681.

Inzucchi SE, et al. Diabetes Care. 2012;35:1364-1379.

HbA1c Goal for the Prevention of Diabetes Complications

< 7%

Individualization is key:

Tighter control (HbA1c 6.0% to 6.5%): younger, healthier

Looser control (HbA1c 6.5% to 8.0%+): older, hypoglycemia prone, comorbidities

Should HbA1c goal be lower in HIV-positive patient if it underestimates glycemia?

Inzucchi SE, et al. Diabetes Care. 2012;35:1364-1379.

Acknowledgements

- Todd Brown (Johns Hopkins University)
- Joe CoFrancesco (Johns Hopkins University)
- Moderator and copanelists
- HIVSAC organizers

THANK YOU!