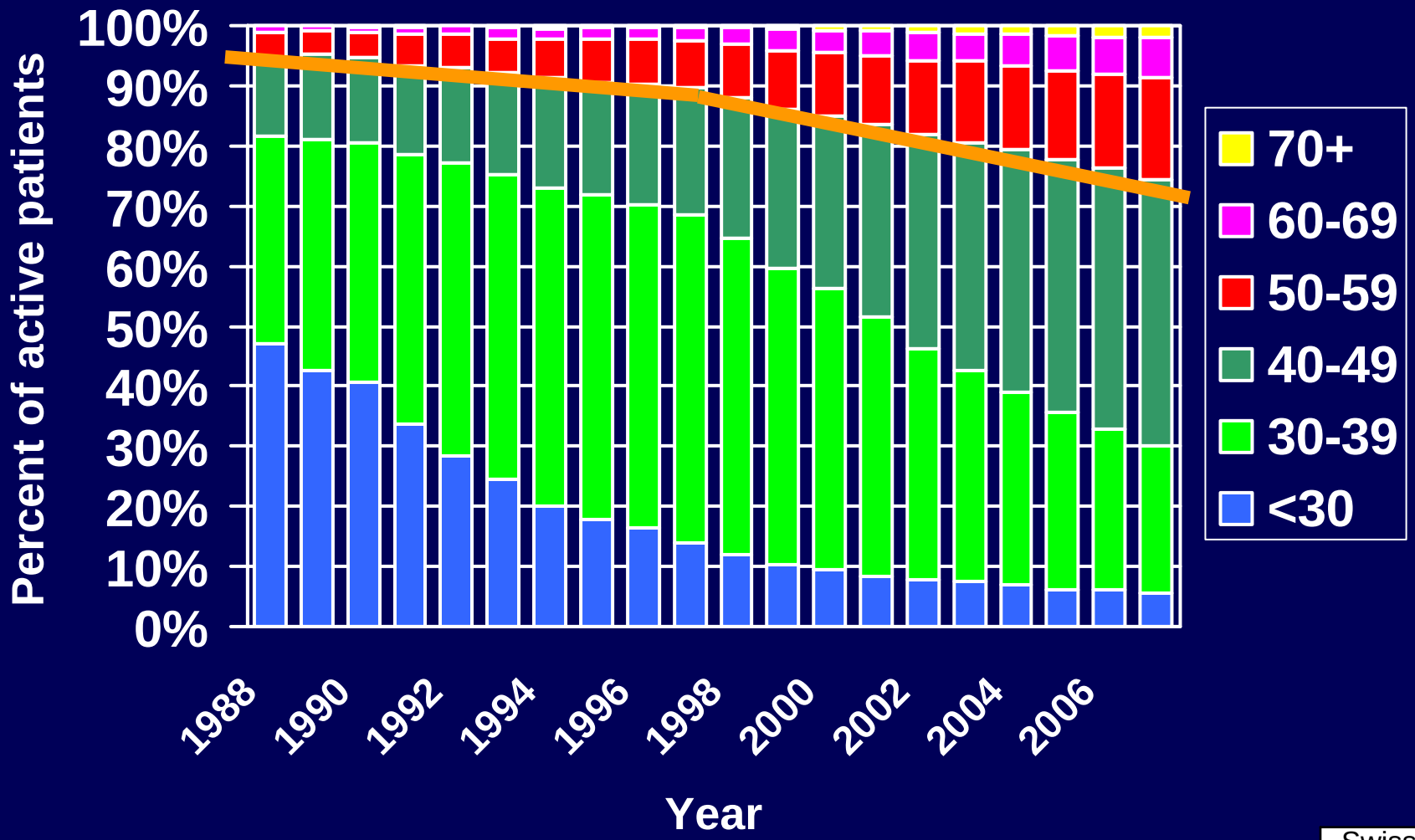
Current issues in co-morbidities and complications

Cristina Mussini

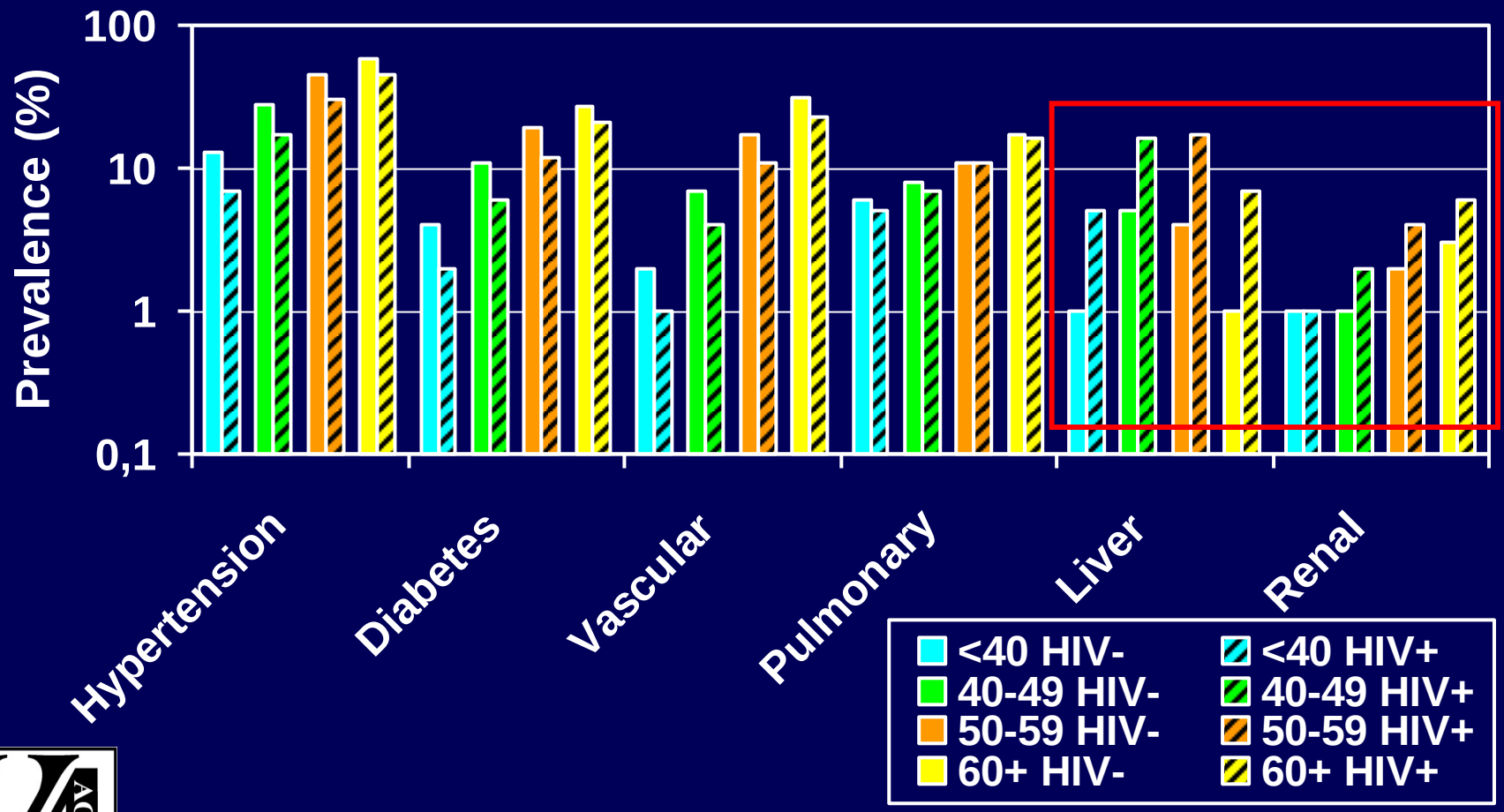
Age distribution of HIV infected individuals in Switzerland from 1988-2007



Source : SHCS 12/2007

Swiss HIV Cohort Study

Medical comorbidities among 66,840 HIV- and 33,420 HIV+ veterans

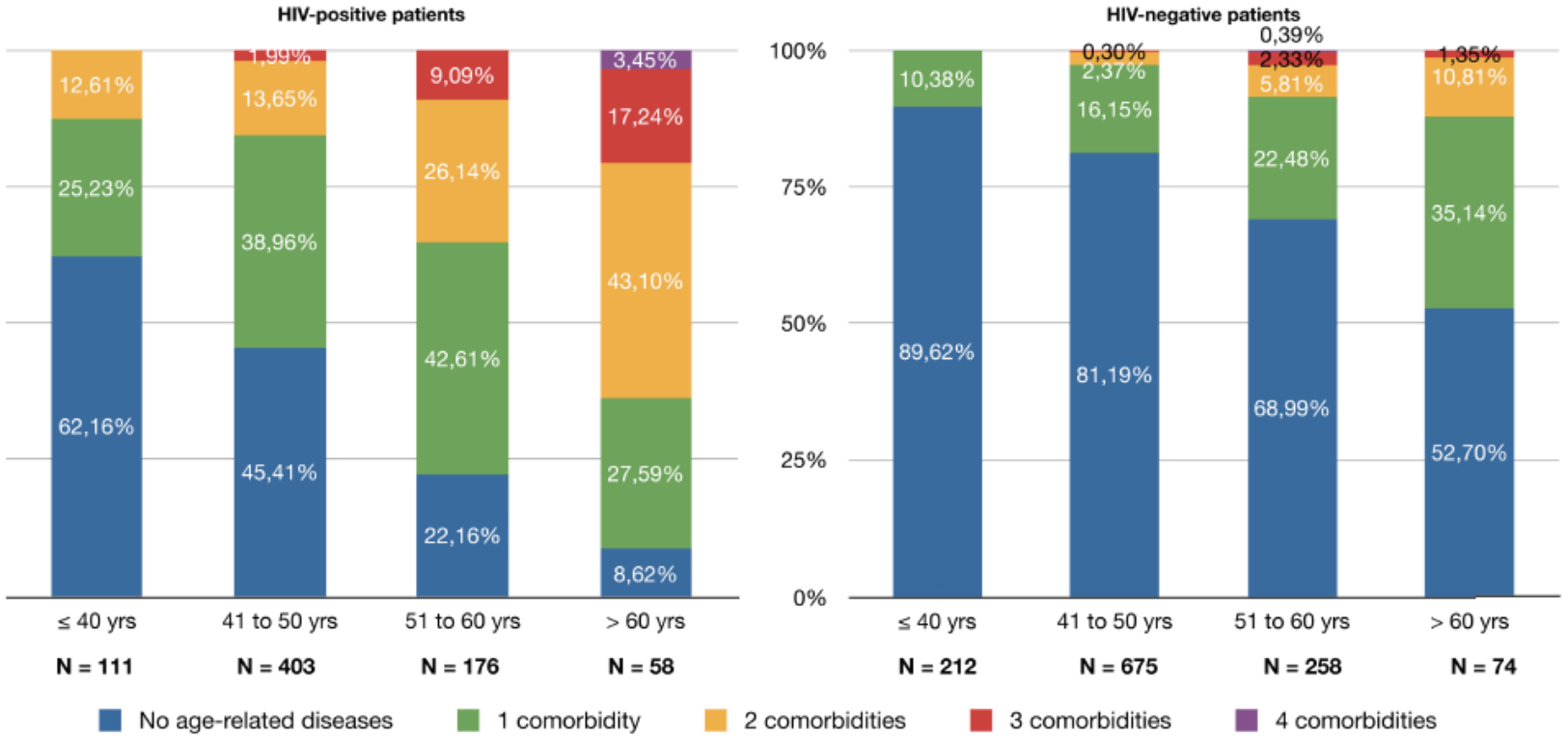


(Goulet, CID 2007)

VETERANS AGING COHORT STUDY

Prevalence of Poly-pathology is More Common in HIV Infected Patients than in HIV Negative Controls in Any Age Strata

Poly-patology prevalence in cases and controls, stratified by age categories.



The following co-morbidities were analysed: Hypertension, Type 2 Diabetes, Cardiovascular Disease and Osteoporosis.

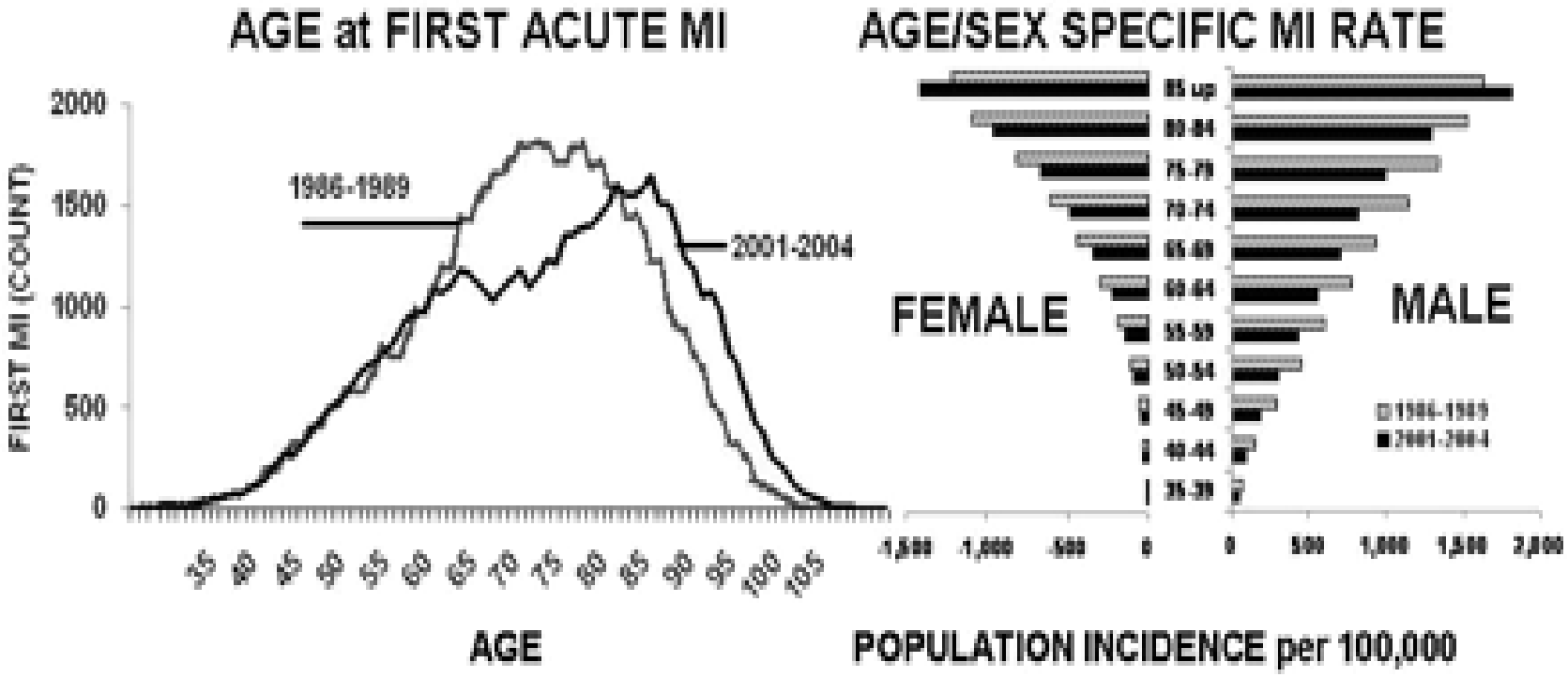
Pp prevalence was higher in cases than controls in all age strata (all p-values <0.001). Pp prevalence seen cases aged 41-50 was similar to that observed among controls aged >60 controls (p=0.282).

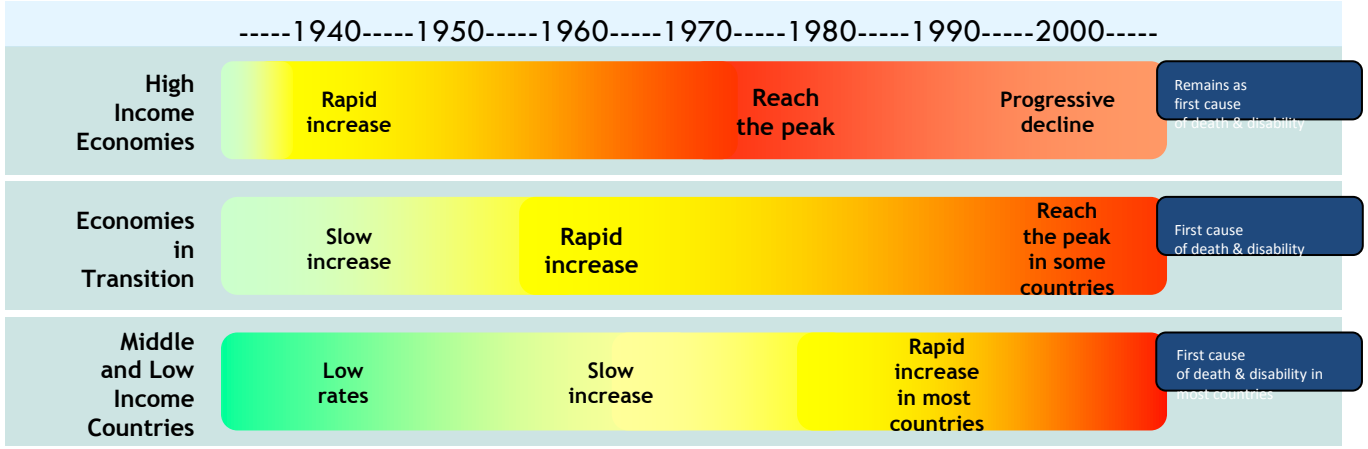
Guaraldi G. et al. CID 2011

Comorbidities to Consider When Deciding When to Initiate HAART

- Cardiovascular disease
- Bone health
- Renal impairment
  - HIV-associated nephropathy
- Hepatic dysfunction
  - HCV/HBV coinfection
- Psychiatric disease including HAND

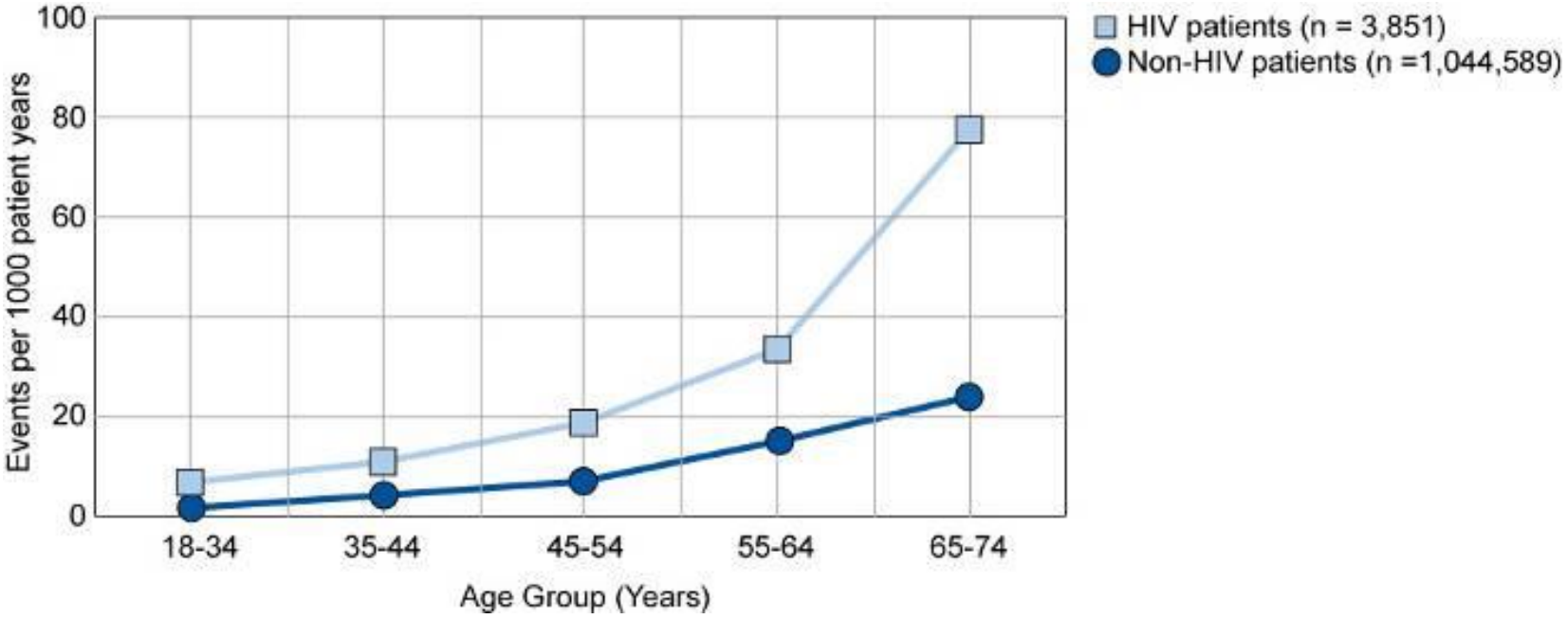
Epidemiology: trends in the general population





Epidemiology: HIV

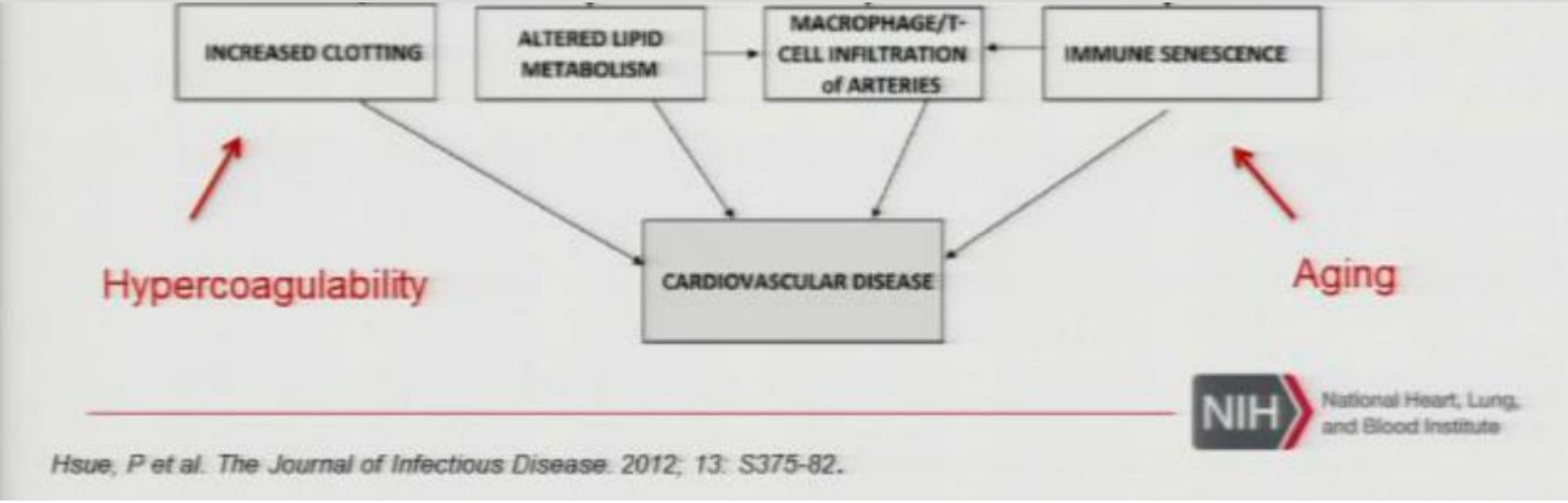
- Acute MI rates between HIV and non-HIV patients were significantly different
  - with a relative risk of 1.75 (95% CI: 1.51–2.02; p<0.0001), adjusting for age, gender, race, hypertension, diabetes and dyslipidaemia



Adapted from: Triant VA, et al.
J Clin Endocrinol Metab 2007;92:2506–12

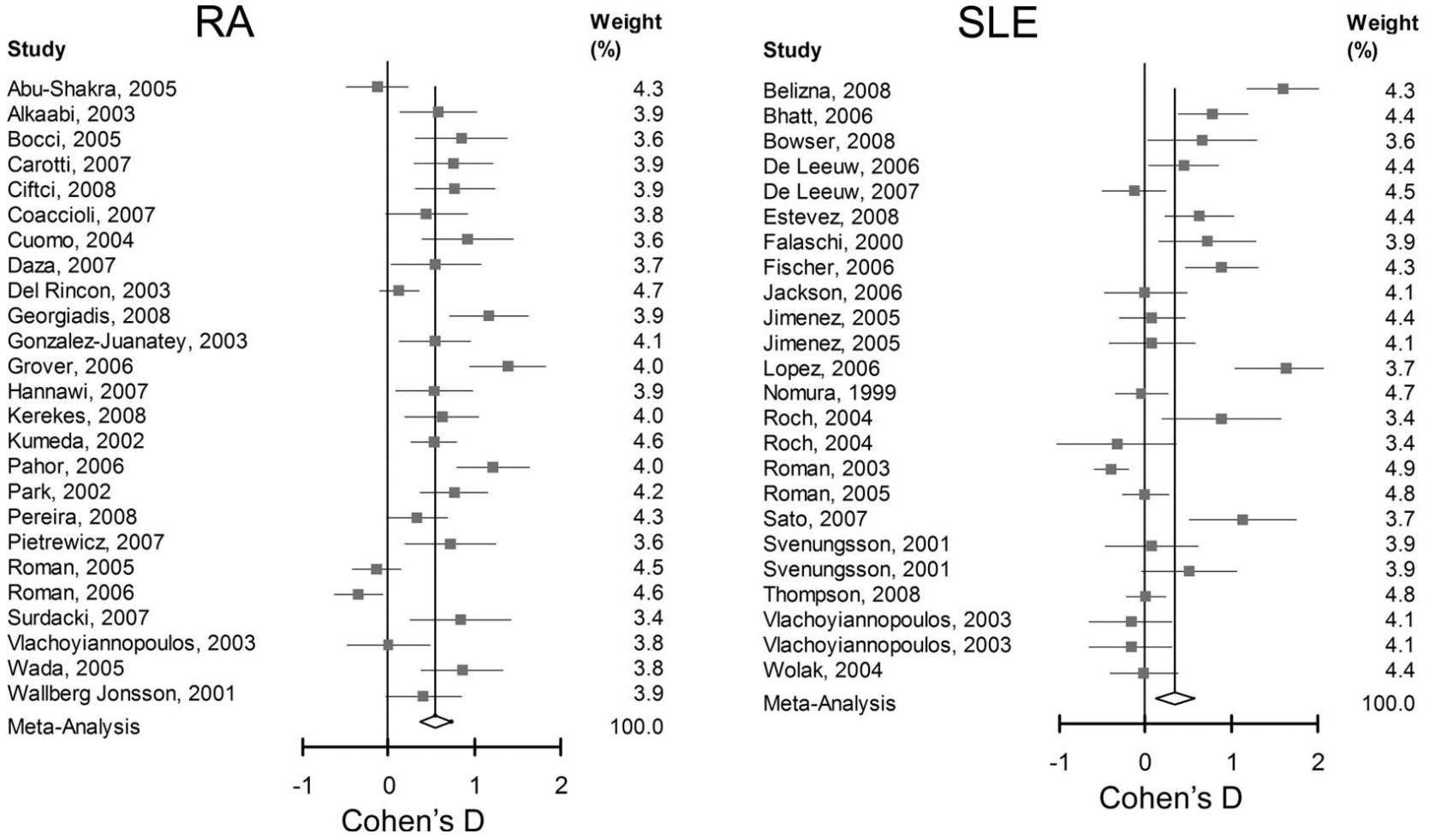
CVD Risk: are patients with HIV any different?

Major risk factors for CVD in HIV are similar to those without HIV



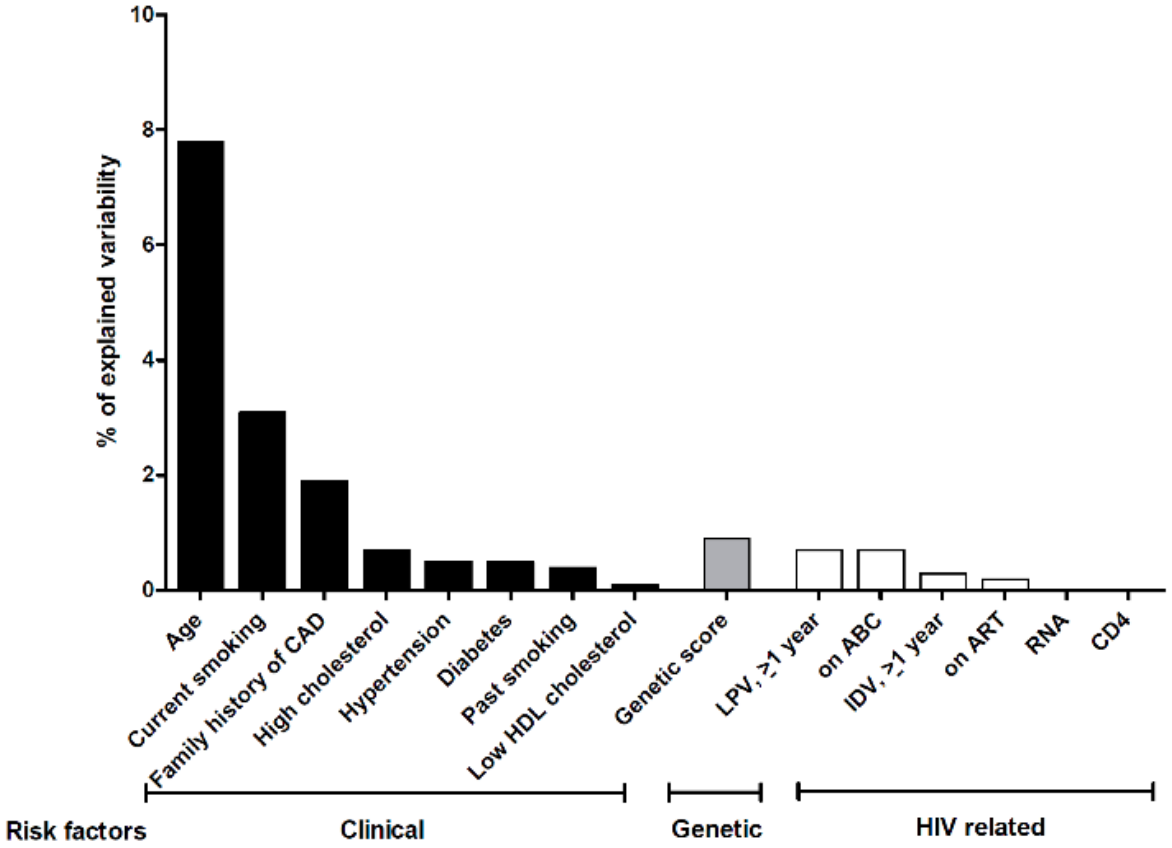
Hsue, P et al. The Journal of Infectious Disease. 2012; 13: S375-82.

Meta-analysis showing the effect size (Cohen's D) of the difference in CIMT between patients with rheumatic disease and control subjects.



Tyrrell et al Arterioscler Thromb Vasc Biol. 2010;30:1014-26.

Contribution of genetic background, traditional risk factors and HIV-related factors to coronary artery disease events in HIV-positive persons



571 pts with a first CAD event and 1304 controls

A genetic risk score built from 23 CAD-associated SNPs obtained by a Metabochip (196,725 SNPs from gene regions associated with multiple metabolic/cardiovascular traits)

In the setting of HIV infection, the effect of an unfavorable genetic background was similar to traditional CAD risk factors and certain adverse antiretroviral exposures.

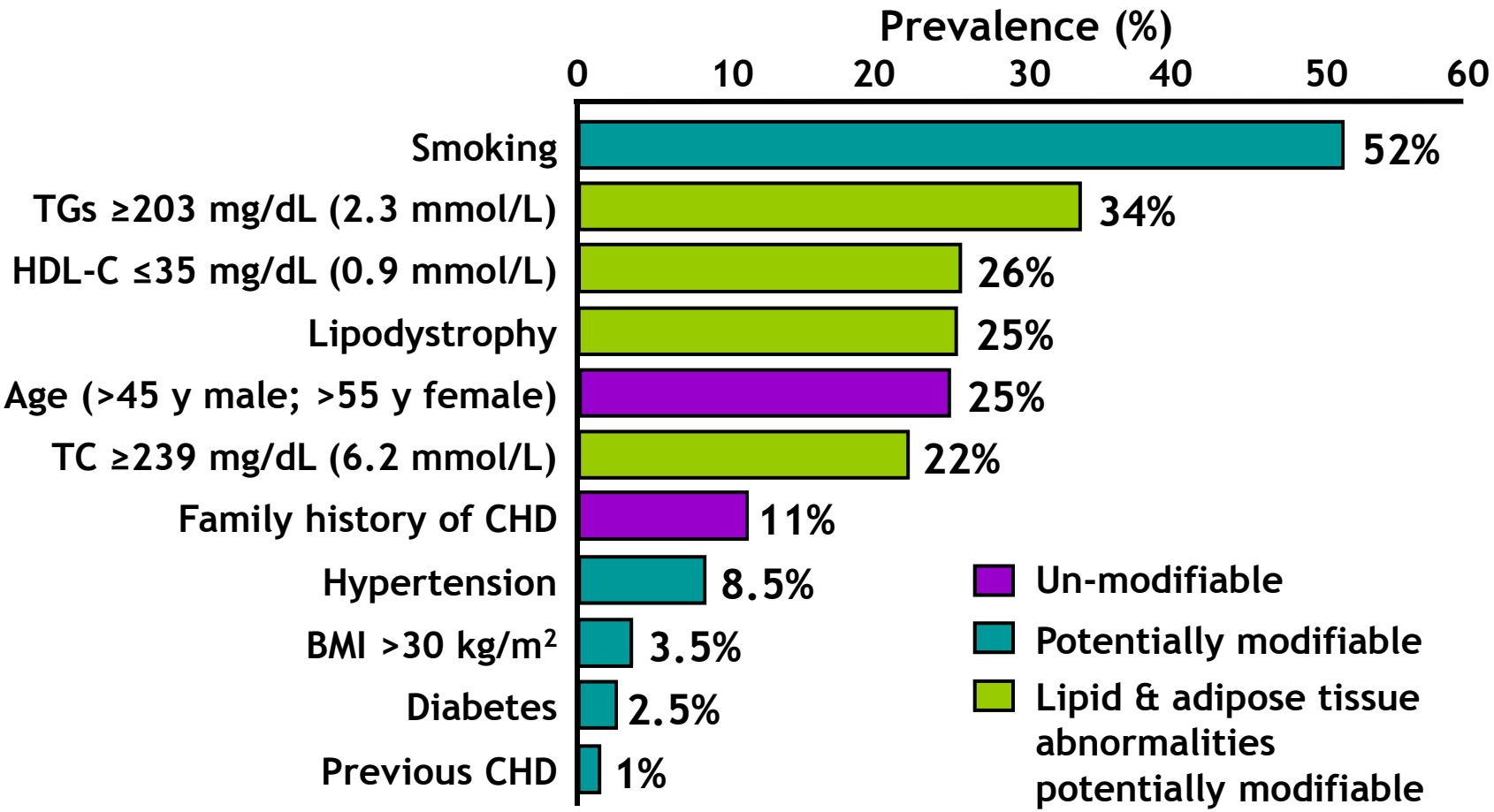
the MAGNIFICENT Consortium, CID 2013

D:A:D: Study:impact of Traditional Risk Factors for CVD

	Adjusted RR (95%CI)	*P* Value
Age (each add'l 5 yr)	1.39 (1.31-1.46)	<.001
Family history	1.56 (1.10-2.236)	.01
Prior CVD	4.30 (3.06-6.03)	<.001
Current smoker	2.83 (2.04-3.93)	<.001
cART (each yr)	1.16 (1.10-1.23)	<.001

DAD Study Group. N Engl J Med 2007;356:1723-35.

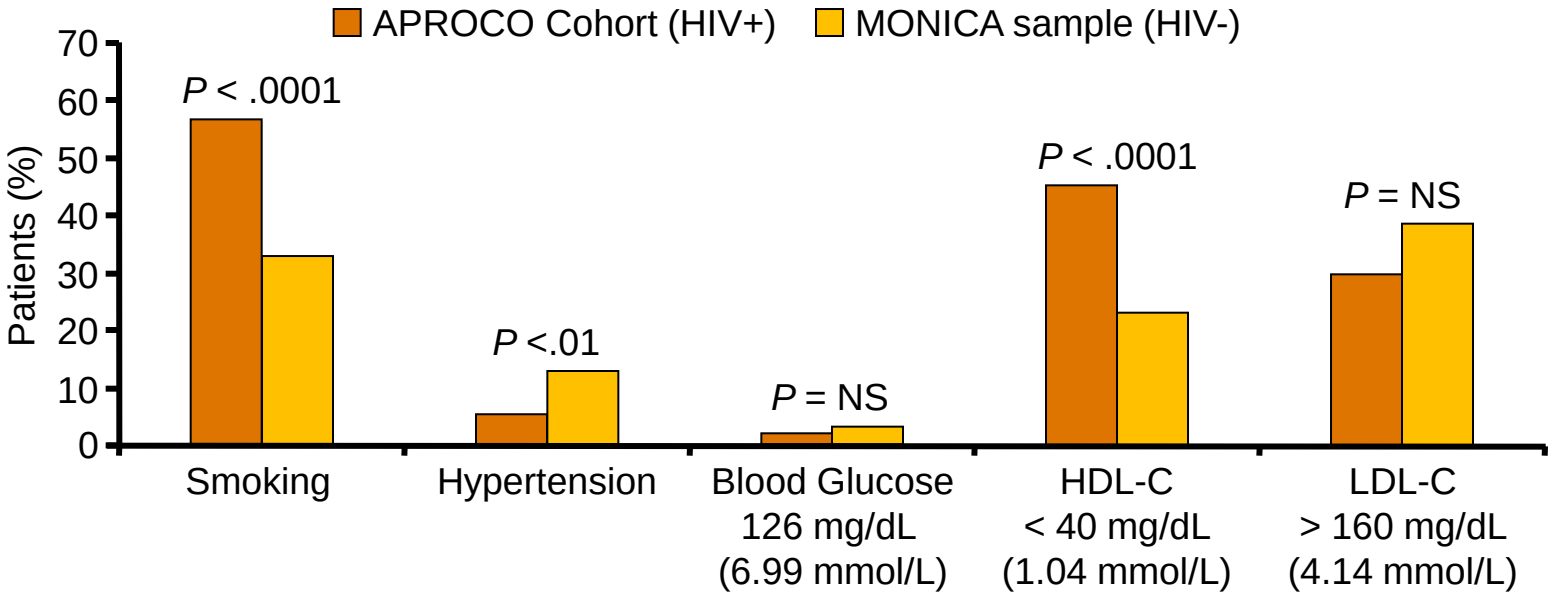
CV risk factors in an HIV-infected population: the DAD study



CHD: coronary heart disease; BMI: body mass index; DAD: Data Collection of Adverse Events

Friis-Moller N *et al*. *AIDS* 2003;17:1179–1193

Smoking incidence is increased in HIV-infected patients versus the general population



- 223 HIV+ men and women on PI-based regimens vs 527 HIV- male subjects
- HIV+ patients had lower HDL and higher TG
- No difference in total cholesterol
- Predicted risk of CHD > in HIV+ men (RR: 1.2) and women (RR: 1.6); *P* < .0001

Savès M, et al. Clin Infect Dis. 2003;37:292-298.

Elevated systolic BP is associated with relative risk of acute MI among in HIV+ patients

- Also at pre-hypertensive levels

Rates and risk of acute MI (AMI) by SBP categories and stratified by HIV status

	HIV uninfected[a]			HIV infected[b]			HIV infected[c]
SBP (mmHg) categories [hypertension status]	**# of AMIs (N)**	**AMI rate (95% CI)**	**HR (95% CI)**	**# of AMIs (N)**	**AMI rate (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
<120; no BP meds [no hypertension]	25 (45591)	0.73 (0.49–1.08)		23 (33570)	0.95 (0.63–1.42)		**1.14 (0.64–2.03)**
120–139, no BP meds [pre-hypertension]	83 (123896)	0.88 (0.71–1.09)	**1.10 (0.70–1.74)**	74 (62241)	1.52 (1.21–1.91)	**1.65 (1.02–2.64)**	**1.88 (1.19–2.99)**
<140; on BP meds [controlled hypertension]	34 (30542)	1.44 (1.03–2.02)	**1.22 (0.71–2.09)**	30 (11910)	3.73 (2.61–5.34)	**2.76 (1.57–4.86)**	**3.11 (1.79–5.41)**
≥140 on/no BP meds [uncontrolled hypertension]	94 (82251)	1.44 (1.18–1.77)	**1.39 (0.88–2.22)**	80 (32219)	3.24 (2.60–4.03)	**2.80 (1.73–4.55)**	**3.18 1.99–5.07)**

[a]**Model 1 (HIV uninfected veterans only):** hazard ratios were adjusted for age, race/ethnicity, diabetes, dyslipidemia, smoking, hepatitis C, body mass index, renal disease, cocaine and alcohol use
[b]**Model 2 (HIV infected veterans only):** hazard ratios adjusted for covariates in model 1
[c]**Model 3 (HIV infected veterans are compared to the relevant group of uninfected veterans with SBP <120 mmHg):** hazard ratios were adjusted for all covariates listed in model 1
AMI rates shown are per 1000 person years

Armah K, et al. CROI 2012; Abs 120

Increased rates of diabetes in HIV+ women

- 752 HIV+ US women (≥6 months of ART) participating in 2 CDC studies (HOPS and SUN cohorts) 2003–2006
- Diabetes was associated with older age, Hispanic race/ethnicity, body mass index ≥30 kg/m^2, hepatitis C virus infection and PI use

Diabetes amoung HAART-experienced HIV-infected women, HOPS and SUN studies, 2003-2006

Charateristic	Black (n=414)	White (n=219)	Hispanic (n=119)	Overall *P* value
Age, years, median (IQR)	41 (34, 47)	42 (38,48)	43 (37, 49)	0.003
Years of HAART, median (IQR)	35 (2.1, 5.7)	5.3 (3.4, 7.4)	4.5 (2.4, 6.5)	<0.001
Diabetes, % (CI)*	13.5 (10.4-17.2)	11.0 (7.2-15.9)	22.7 (15.5-31.3)	0.011
Impaired glucose control, % (CI)*	6.0 (4.0 – 8.8)	7.8 (4.6-12.1)	8.4 (4.1-14.9)	0.563

* Each condition defined by diagnosis, treatment, or laboratory results, including, for diabetes: fasting glucose > 125mg/Dl or two random glucose measurements > 200mg/dL or two hemoglobin AIC (HGBAIC) measurements ≥7.0%; for impaired glucose control (excluding diabetes); fasting glucose 110-125mg/dL or two random glucose measurements 140-200mg/gL or single HGBAIC ≥6.5% (without normal glucose). IQR, interquartile range

Buchacz K, et al. 18th CROI 2011. Abstract 786

ARV impact on CVR

EVIDENCES:

1. Epidemiology: association with observational data or RCT

2. Metabolic: Dislipidemia, HCY

3. Inflammatory: Soluble biomarkers, Immune-activation, CRP, IL6 Cystatine C, LPS, D-Dimer

4. Endothelial dysfunction: FMD, ADMA, Circulating Endothelial Cells, Endothelial precursor Cells

Changes in lipid levels during ART are drug specific NOT class specific

ARV class	Drug	Effect			
		Total cholesterol	Triglycerides	HDL-C	LDL-C
NNRTIs	Nevirapine	↑	↓	↑	↑
	Delavirdine	↑	↑	↑	No change
	Efavirenz	↑	↑	↑	↑
	Etravirine	↑	↑	↑	No change
	Rilpivirine	**No change**	**No change**	**No change**	**No change**
NRTIs	Stavudine	↑	↑	↓	↑
	Zidovudine	↑	↑	↑	No change
	Lamivudine	↑	↑	↑	No change
	Abacavir	No change	No change	↓	No change
	Abacavir/lamivudine	↑	↑	↑	No change
	Abacavir/lamivudine/zidovudine	↑	↑	↑	No change
	Didanosine	No change	↑	↓	No change
	Emtricitabine	↑	↑	↑	No change
	Tenofovir	**No change**	**No change**	**No change**	**No change**
IIs	**Raltegravir**	**No change**	**No change**	**No change**	**No change**
PIs	Indinavir*	↑	↑	No change	↑
	Nelfinavir	↑	No change	No change	↑
	Saquinavir*	↑	↑	↓	↑
	Lopinavir/ritonavir	↑	↑	No change	↑
	Fosamprenavir*	↑	↑	No change	↑
	Atazanavir*	No change	No change	No change	No change
	Atazanavir/ritonavir	↑	↑	No change	↑
	Tipranavir/ritonavir	↑	↑	No change	↑
	Darunavir/ritonavir	↑	↑	No change	↑
	Ritonavir (full dose)	↑	No change	No change	↑
Fusion/entry inhibitors	**Enfurvitide**	**No change**	**No change**	**No change**	**No change**
	Maraviroc	**No change**	**No change**	**No change**	**No change**

*Effects shown are for ritonavir-boosted drugs

Adapted from: Martin A, Emery S. Exp Rev Clin Pharmacol 2009;2:381–90

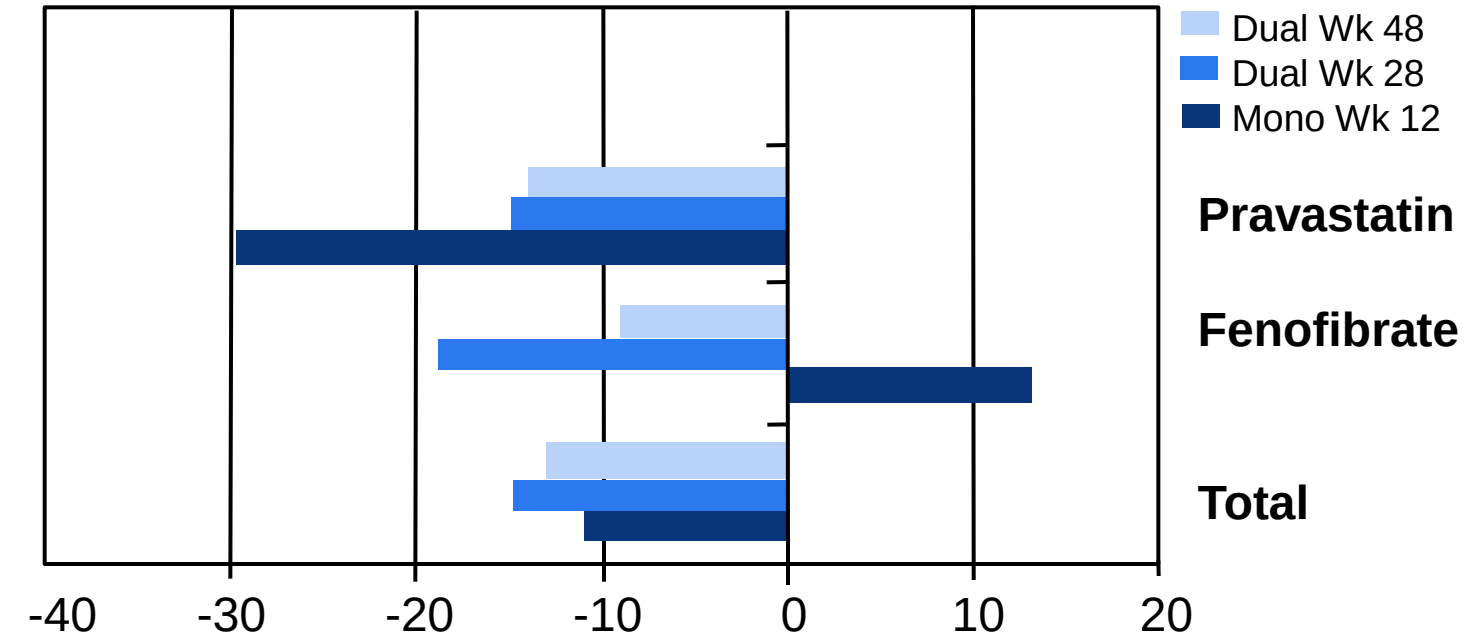
Elevated triglycerides and risk of myocardial infarction in HIV-positive persons

Signe W. Worm[a], David A. Kamara[b], Peter Reiss[c], Ole Kirk[a], Wafaa El-Sadr[d], Christoph Fux[e], Eric Fontas[f], Andrew Phillips[b,c], Antonella D'Arminio Monforte[g], Stephane De Wit[h], Kathy Petoumenos[i], Nina Friis-Møller[a], Patrick Mercie[j], Jens D. Lundgren[a] and Caroline Sabin[b]

AIDS 2011, **25**:1497–1504

Poor response to lipid-lowering agents in HIV-infected patients

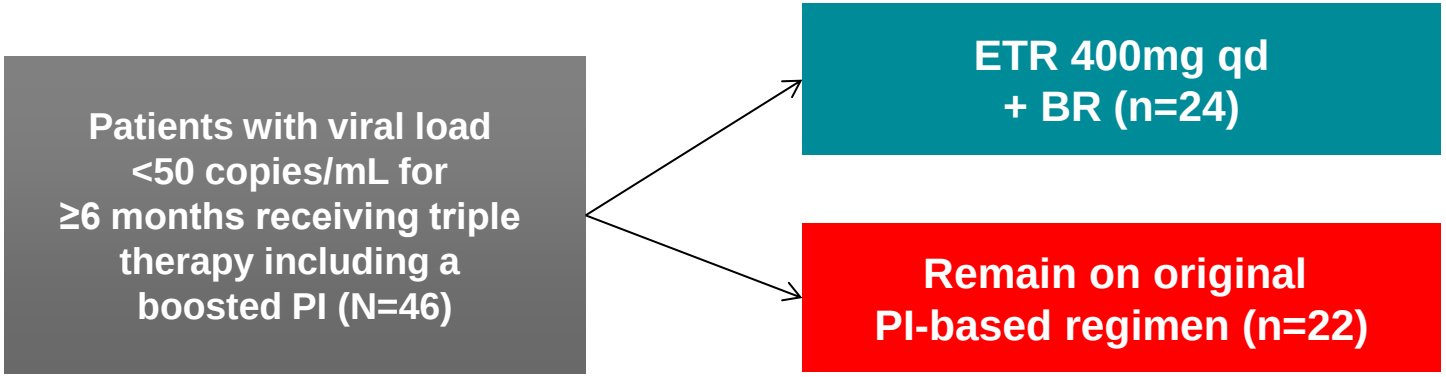
- Fenofibrate plus pravastatin for HIV-related dyslipidemia does not NCEP targets for lipid levels



LDL (mg/dl): median change by initial randomized treatment

Aberg et al AIDS Res Hum Retroviruses 2005;757–767

ETRA switch: switching from a boosted PI to an NNRTI may improve lipid profile



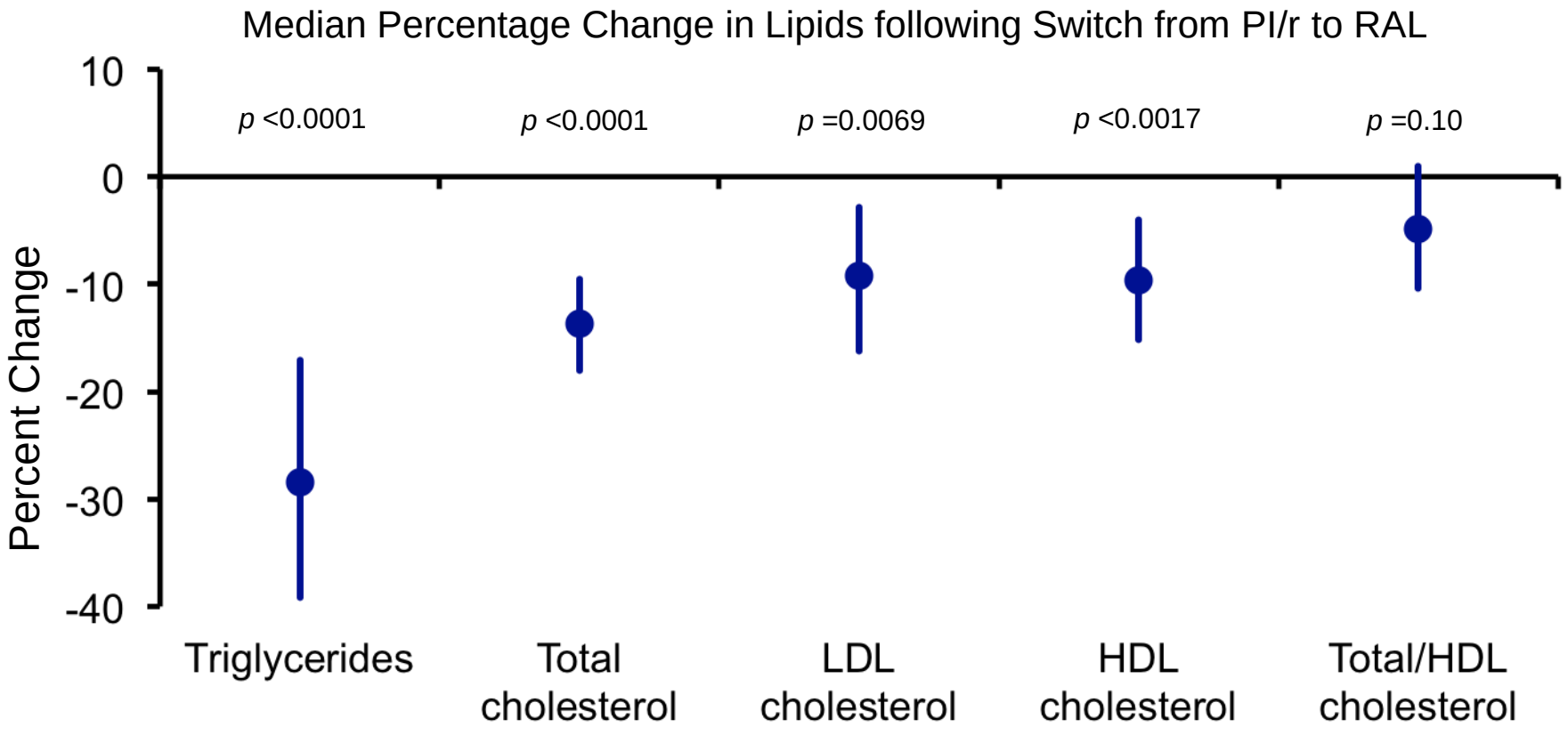
	Mean change in lipid parameters at Week 24 (mg/dL)	
Parameter	**Switch to ETR**	**Remain on PI/r**
Total cholesterol	–20*	+22
HDL cholesterol	–4†	–2
LDL cholesterol	+11	–8
Triglycerides	–61†	+18

*p=0.037 vs. baseline; †p=0.004 vs. baseline

BR, background regimen

Echeverria P, et al. ICAAC 2011. Abstract H2-785

SPIRAL: PI/r to Raltegravir Switch Improves Lipids



Conclusion: PI/r to RAL switch results in significantly improved lipids, but no change in Total/HDL cholesterol ratio.

Martinez E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 834.

ATADAR Study Design

Martinez E, et al.
Poster 772

HIV +, stratified according to total-to-HDL cholesterol ratio <4,5 or ≥4,5 (n=180)

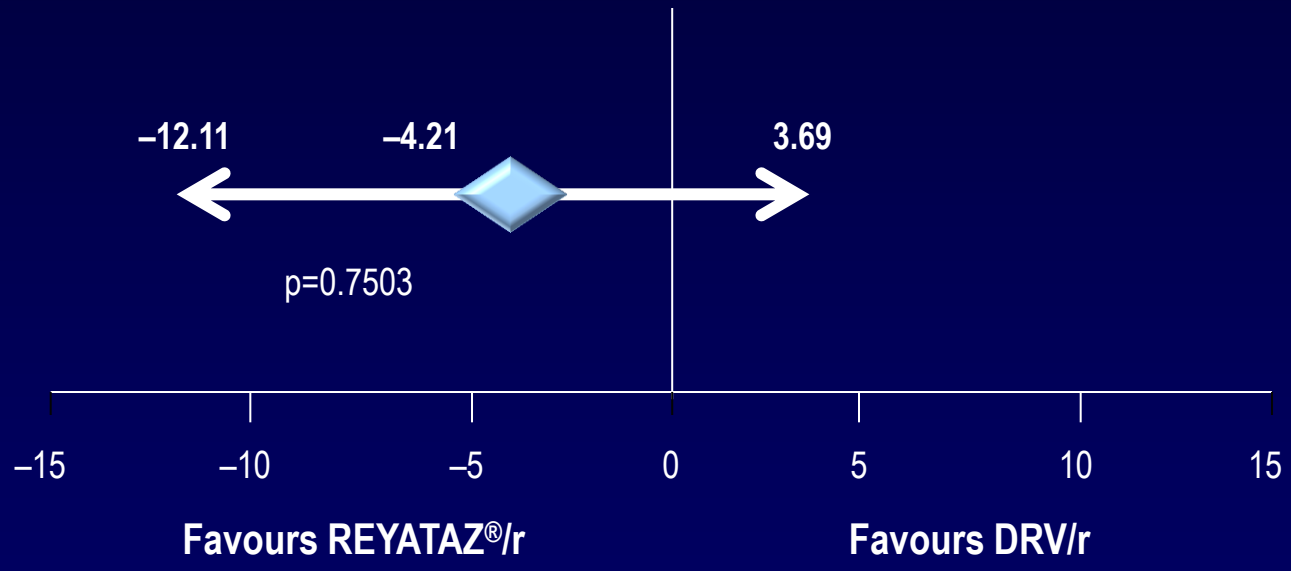
→ **ATV/r plus TDF/FTC (n=91)**

→ **DRV/r plus TDF/FTC (n=89)**

- Inclusion Criteria
  - Age ≥18y, clinically stable, ART-naïve, plasma HIV-1 RNA >1000 copies/mL
- Exclusion Criteria
  - AST/ALT ≥5 UNL, creatinine ≥2 UNL, diabetes mellitus, BMI ≥30 kg/m^2, drugs affecting lipid or glucose metabolism <1month, AIDS events requiring parenteral therapy, hypersensitivity/contraindication to study drugs, pregnancy/lactation at inclusion or expectancy to become pregnant during follow-up

ATADAR: Trend in total cholesterol changes at 24 weeks favours REYATAZ®/r[1]

ATADAR: 24-week estimated difference[a] (95% CI) in absolute change of total cholesterol (mg/dL)[1]

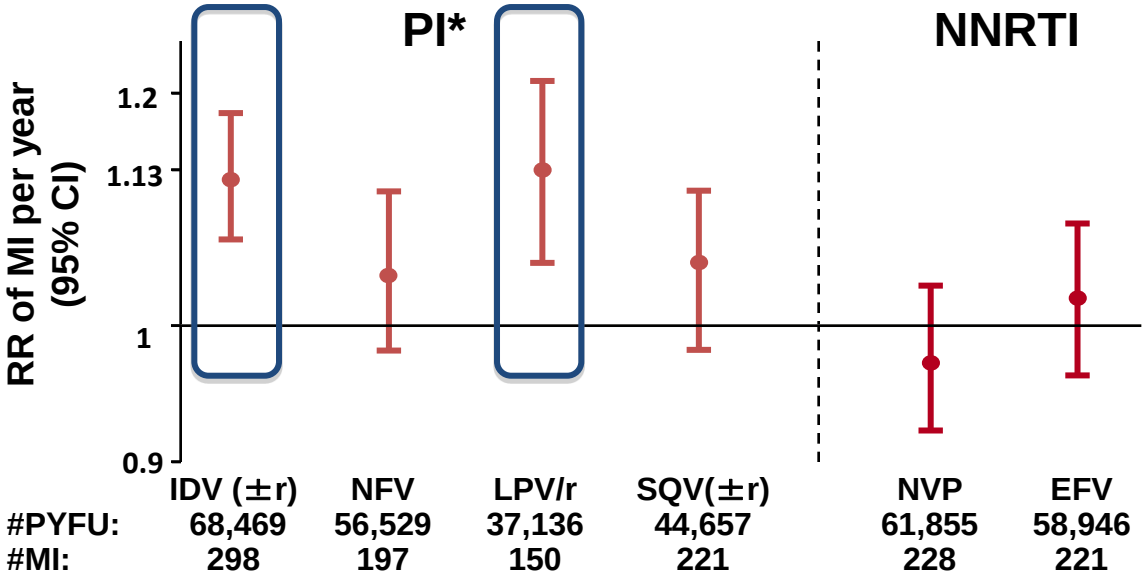


- 1. Adapted from Martínez E, *et al.*. HIV11 2012, oral presentation O423

[a] REYATAZ®/r minus DRV/r

Previous findings from D:A:D: Possible association between cumulative use of PIs and MI

Risk of MI by cumulative PI/NNRTI exposure[1,2]



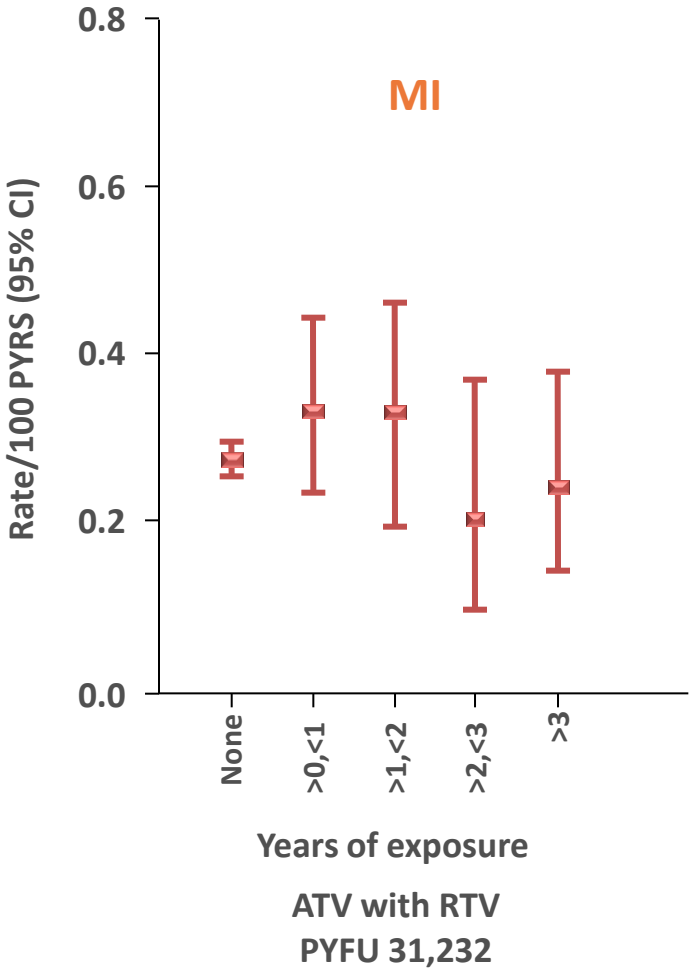
*Approximate test for heterogeneity: p=0.02

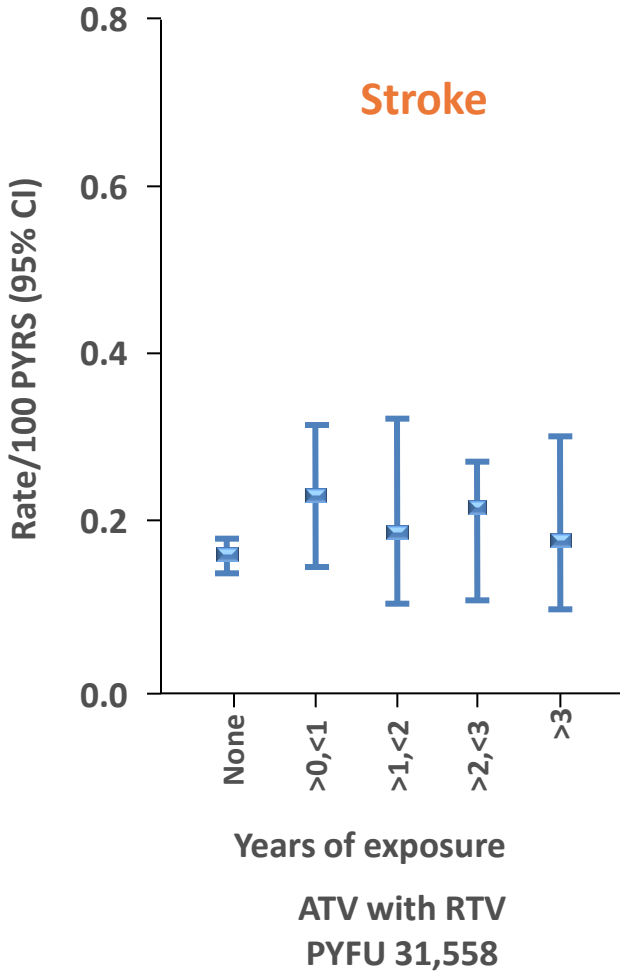
MI cases: n=580
Controls: n=32,728

1. Lundgren JD, et al. CROI 2009; Oral presentation 44LB.

D:A:D: MI and stroke rates do not increase with prolonged exposure to ATV/r

Rate of MI:
• No ATV exposure: 0.28 (95% CI 0.26 to 2.30)/ 100 PYFU
• >3 years' ATV exposure: 0.20 (0.12 to 0.32)/100 PYFU
Rate of stroke:
• No ATV exposure: 0.17 (0.16 to 0.19)
• >3 years' ATV exposure: 0.17 (0.10 to 0.27)/100 PYFU





d'Arminio Monforte A, et al. CROI 2012; Poster 823.

Improved glucose tolerance with ATV/r vs LPV/r

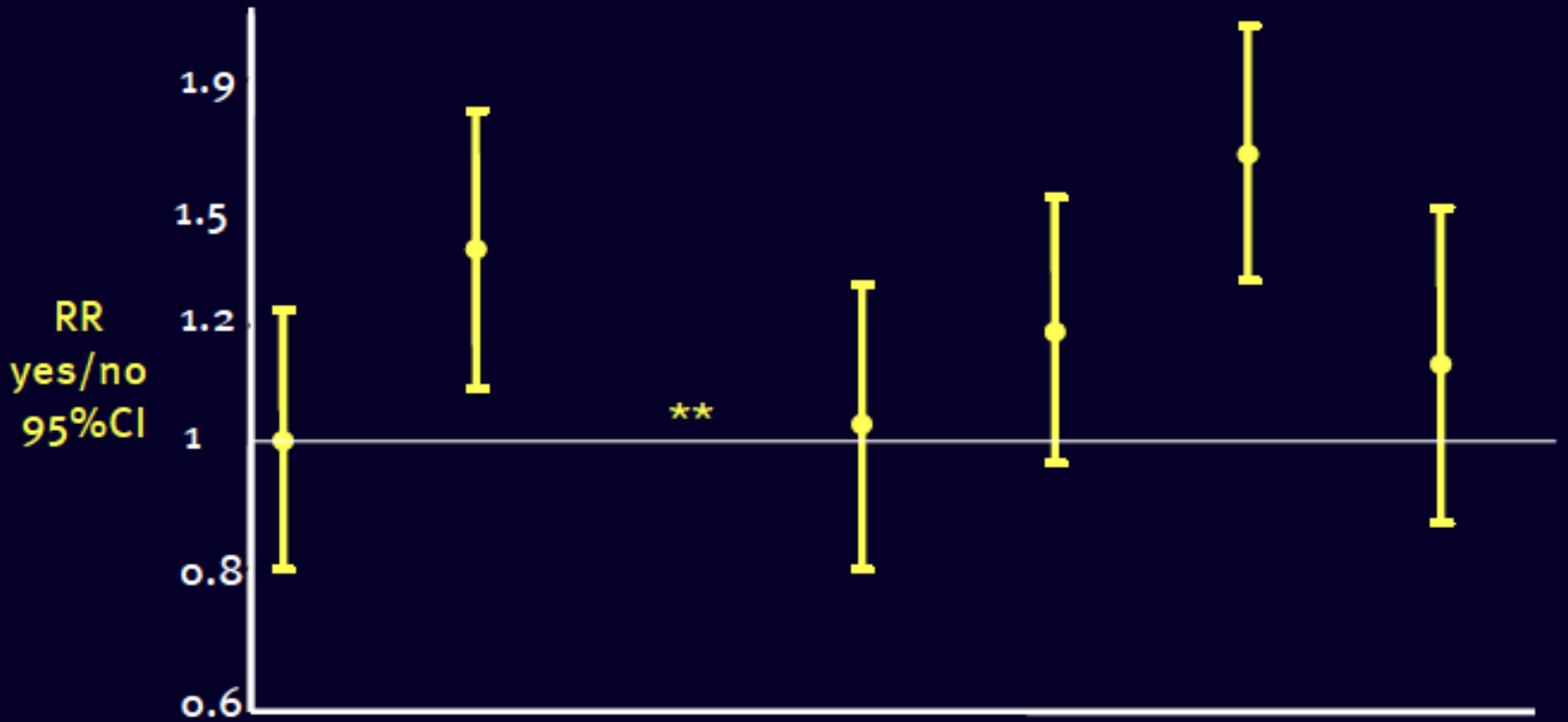
- Randomised, non-blinded comparison of continuing LPV/r (n=7) therapy vs switching to ATV/r (n=5) in HIV+ patients (20% women)*

	ATV/r		LPV/r		Net difference between groups
Glucose parameter (mean±SEM)	Baseline	6 months	Baseline	6 months	p value
Muscle glucose uptake (µmol/kg/min)	13.0 ± 4.9	26.7 ± 5.7	26.7 ± 5.9	24.4 ± 7.9	0,035
Fasting glucose (mg/dL)	87 ± 3	84 ± 3	87 ± 4	90 ± 8	0.002
M/I LBM (µmol/kg/min per µu/mL insulin × 100)	60.7 ± 20.1	39.0 ± 7.9	105.7 ± 41.9	49.2 ± 8.5	0,12

M/I LBM=insulin-stimulated glucose disposal (M) for the interval between 100-120 minutes. M was indexed to fat-free mass (M/LBM, µmol·kg FFM^{-1}·min^{-1}) and corrected for insulin (M/I)
*Inclusion criteria: fasting insulin ≥ 15 µU/mL, total cholesterol ≥ 200 mg/dL, triglycerides ≥ 150 mg/dL or treatment with lipid lowering medication. Insulin-stimulated thigh muscle glucose uptake measured by Positron Emission Tomography (PET)

Stanley TL, et al. AIDS 2009;23:1349–57

NRTIs and risk of MI: recent* exposure to each drug



	ZDV	ddI	ddC	d4T	3TC	ABC	TDF
#PYFU:	138,109	74,407	29,676	95,320	152,009	53,300	39,157
#MI:	523	331	148	405	554	221	139

DAID

* recent use= current or within the last 6 months; **: not shown (low number of patient currently on ddC)

ABC and risk of myocardial infarction

2008

D:A:D

- **Increased risk of MI with recent exposure to ABC, ddI[1]**

2010

D:A:D

- **Increased risk of MI with recent exposure to ABC[2]**

2011

FDA meta-analysis[3]

- **No association between MI and ABC use**

2011

French Hospital Database[4]

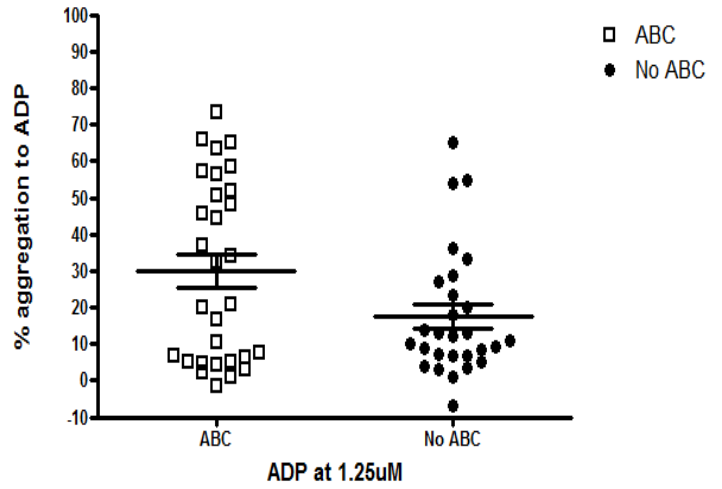
- **Recent ABC initiation associated with increased risk of MI in overall sample but NOT in the subset who did not use cocaine/IV drugs**

MI = myocardial infarction

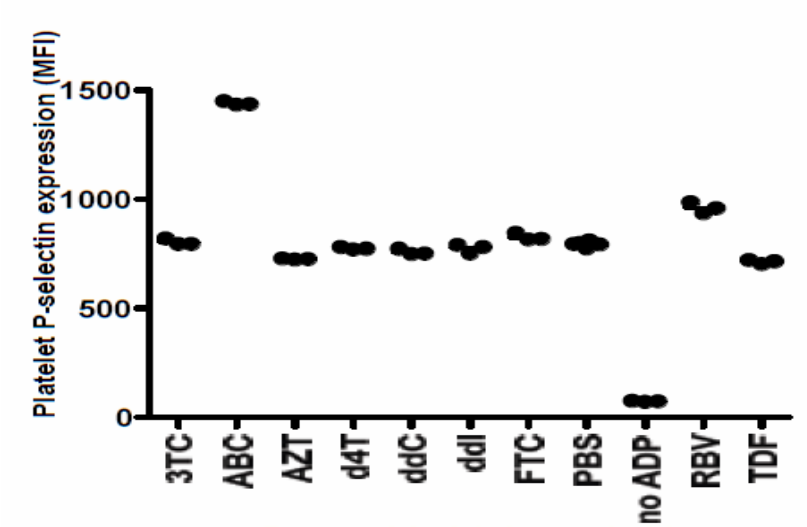
1. D:A:D Study Group. Lancet 2008;371:1417–26. 2. Worm SW, et al. J Infect Dis. 2010;201:318–30; 3. Ding X, et al. CROI 2011; Poster 808; 4. Lang S, et al. Arch Intern Med. 2010;170:1228–38.

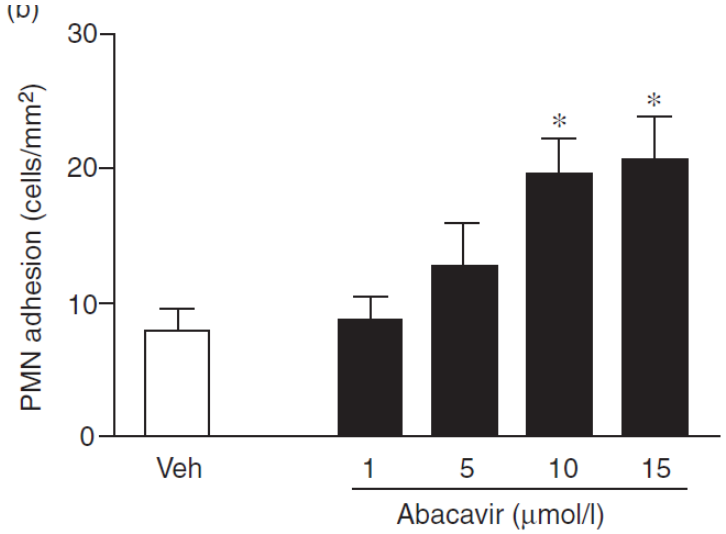
Increased platlet reactivity in HIV infected patients recheiving Abacavir containing ARV therapy

Increased platelet aggregation



Induction of P-selectin

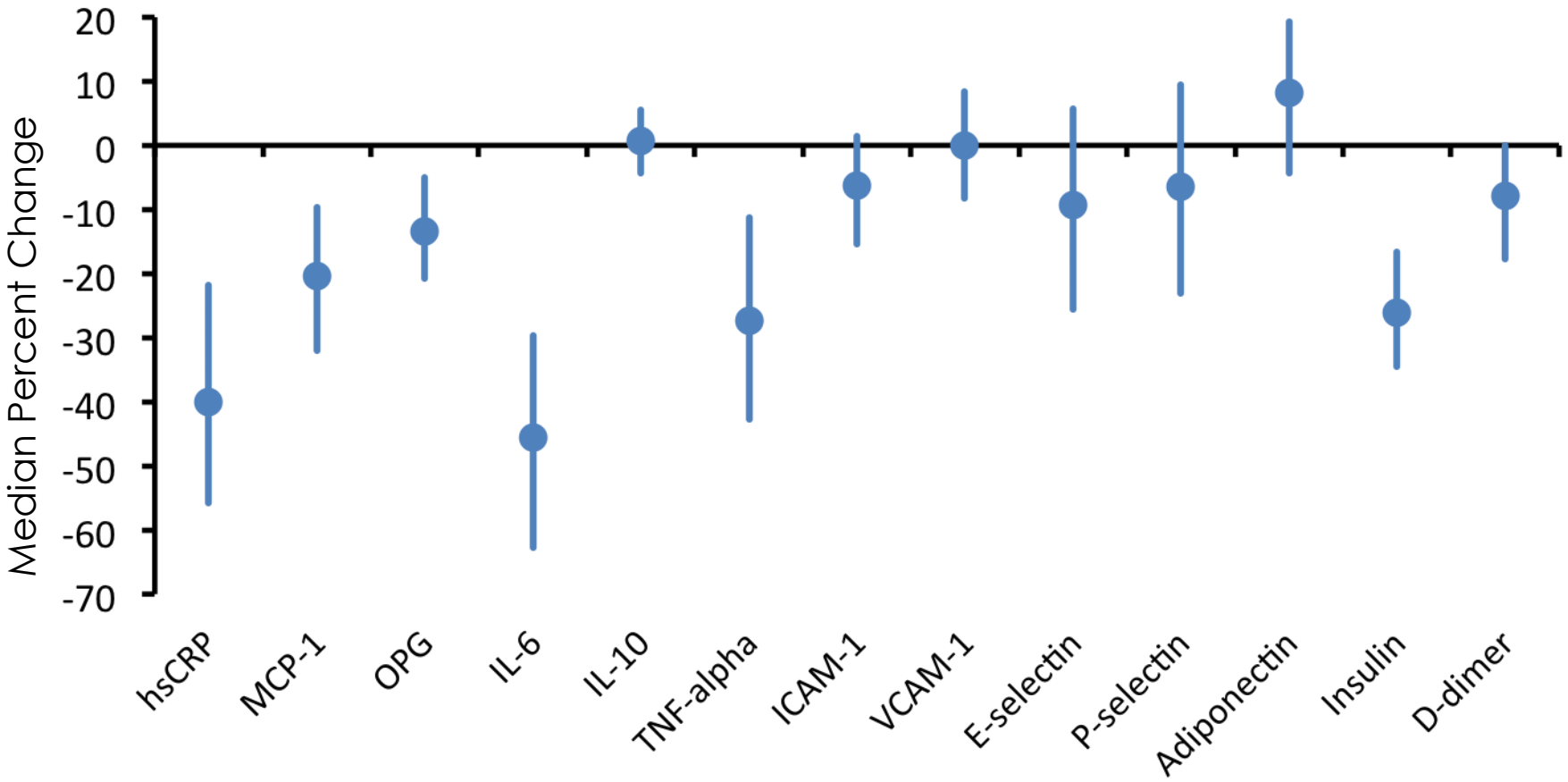




Increased neutrophil and PBMC adhesion to endothelium

Satchell et al, CROI 2009
Baum et al, CROI 2010; de Pablo C et al, AIDS 2010

SPIRAL:
Biomarker Changes after PI/r to Raltegravir Switch

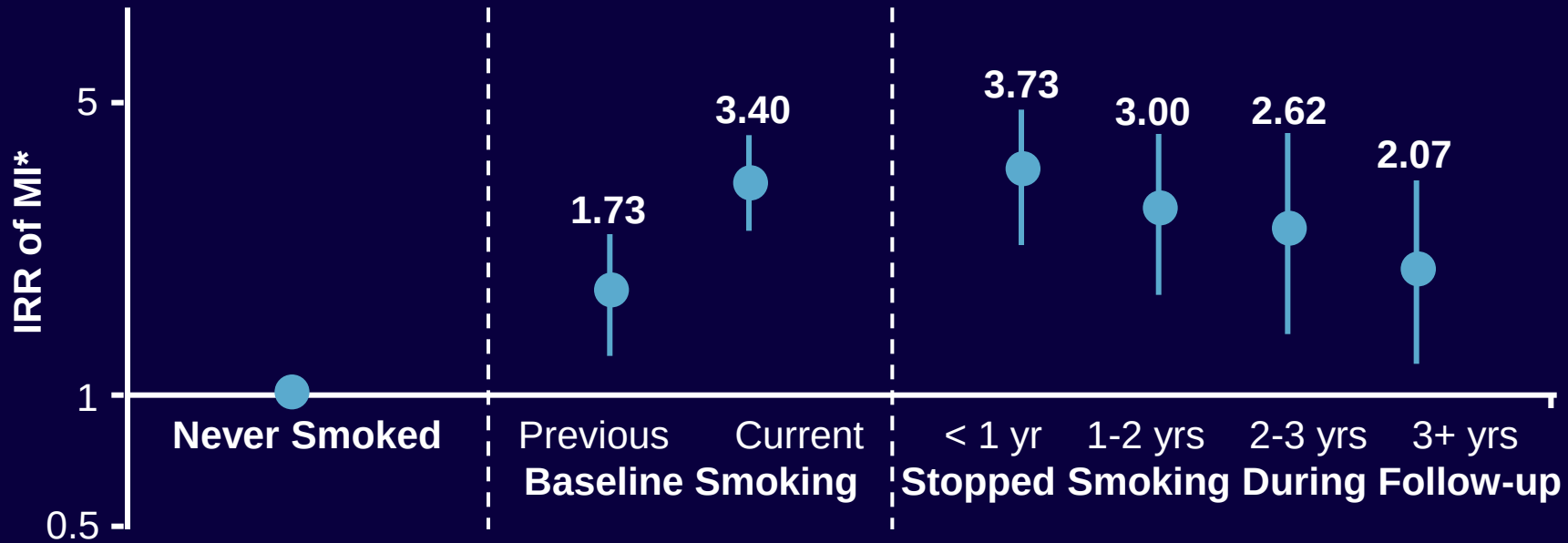


Conclusion: Switch to RAL from PI/r results in improved inflammatory and clotting markers and insulin sensitivit but not markers of vascular function.

Monocyte chemoattractant protein-1 (MCP-1), osteoprotegerin (OPG), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-a), intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1)

D:A:D Study: Smoking Cessation Reduces Risk of CVD in HIV-Infected Patients

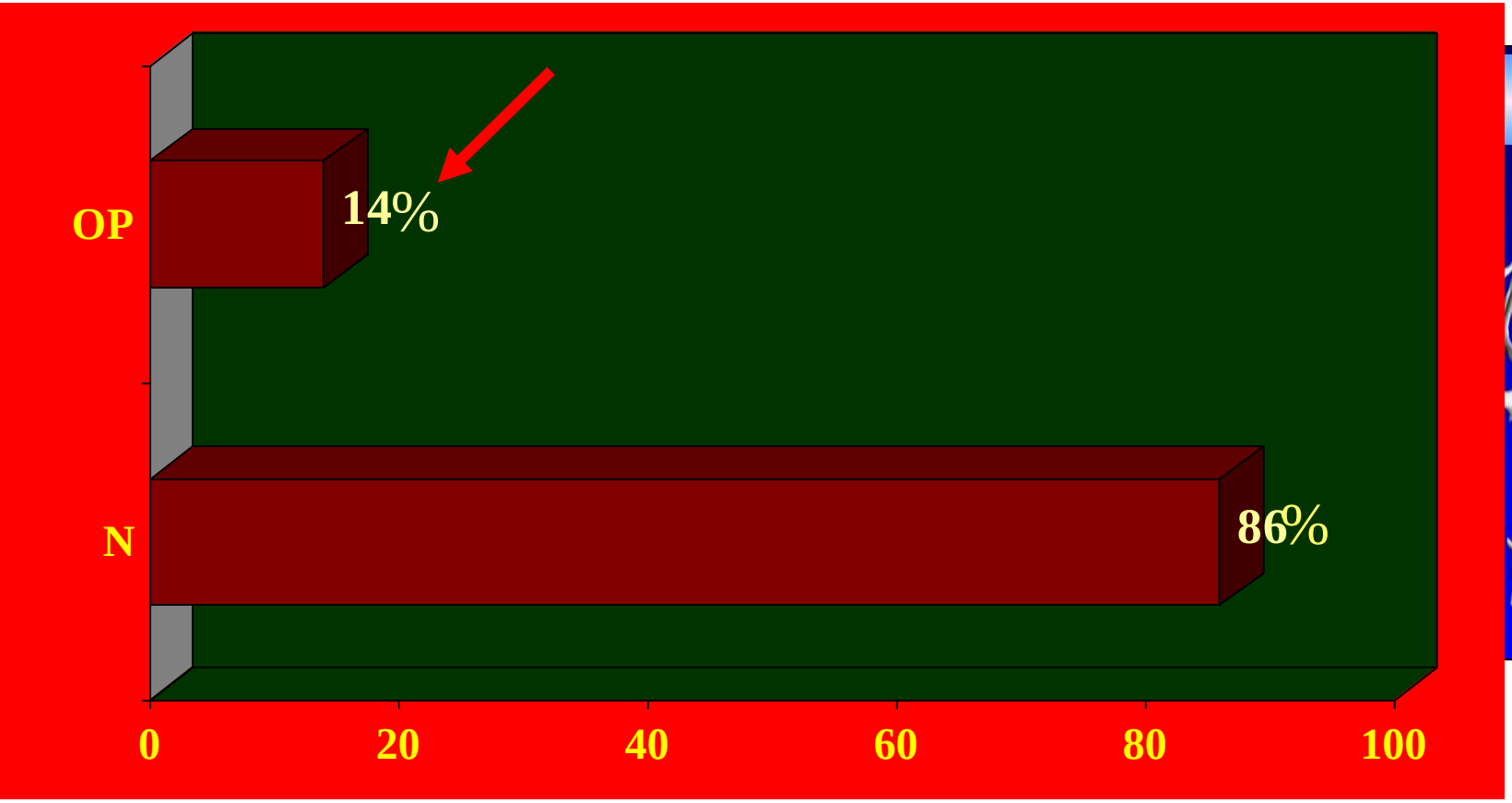
- Cessation of tobacco smoking reduced risk of MI, coronary heart disease, and CVD in HIV-infected patients
  - No association of time since smoking cessation and mortality risk



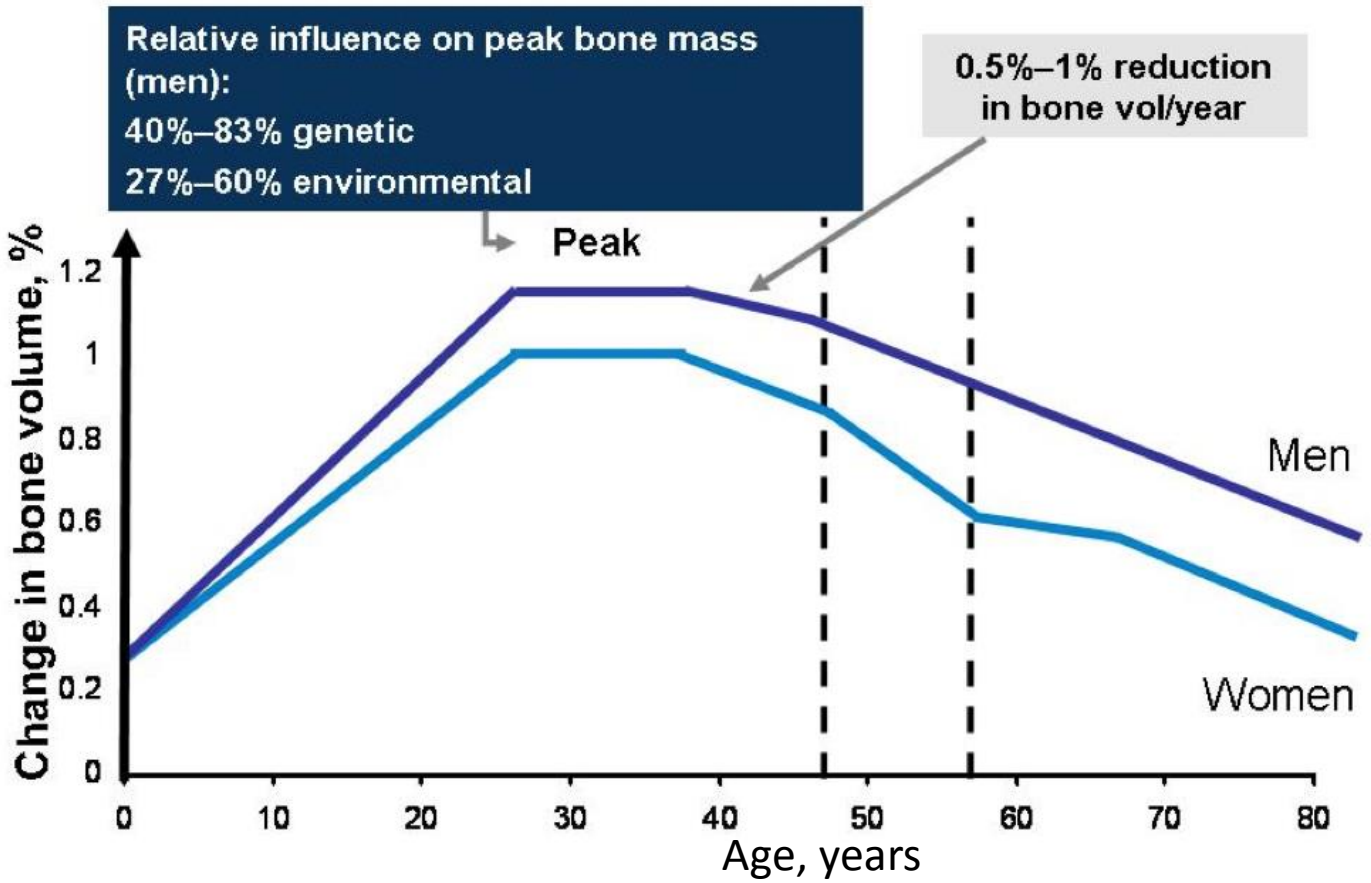
*Adjusted for: age, cohort, calendar yr, antiretroviral treatment, family history of CVD, diabetes, time-updated lipids and blood pressure assessments.

Petoumenos K, et al. CROI 2010. Abstract 124. Reproduced with permission.

Osteoporosis in Italy (>45 years old)

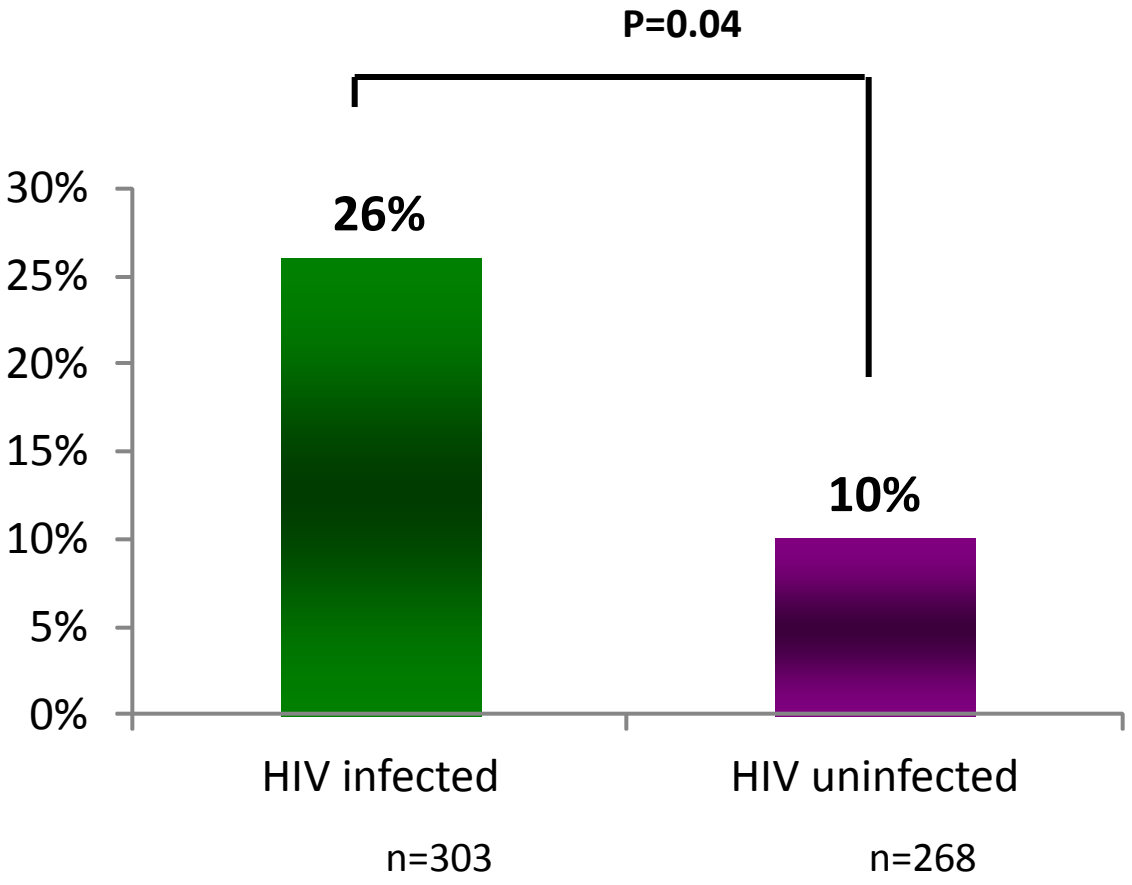


BMD decreases with age



Orwoll ES, Klein RF, Endocr Rev, 1995: 16: 87-118

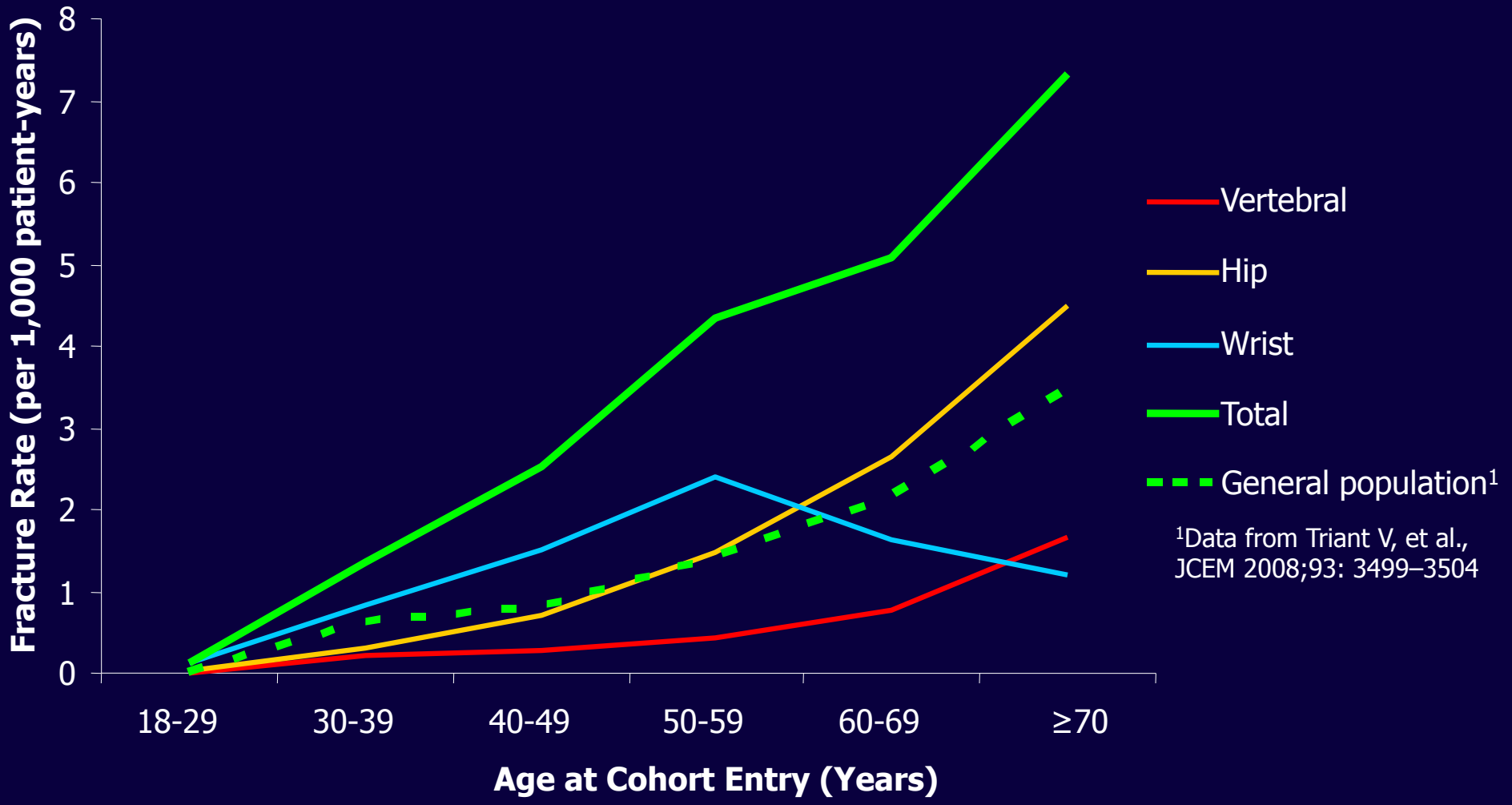
Menopause in HIV+ women
Early menopause *(< 40 aa)*



Women living with HIV were 73% more likely to experience early onset of menopause, compared with HIV-uninfected women (P=0.024) (46 *vs* 47)

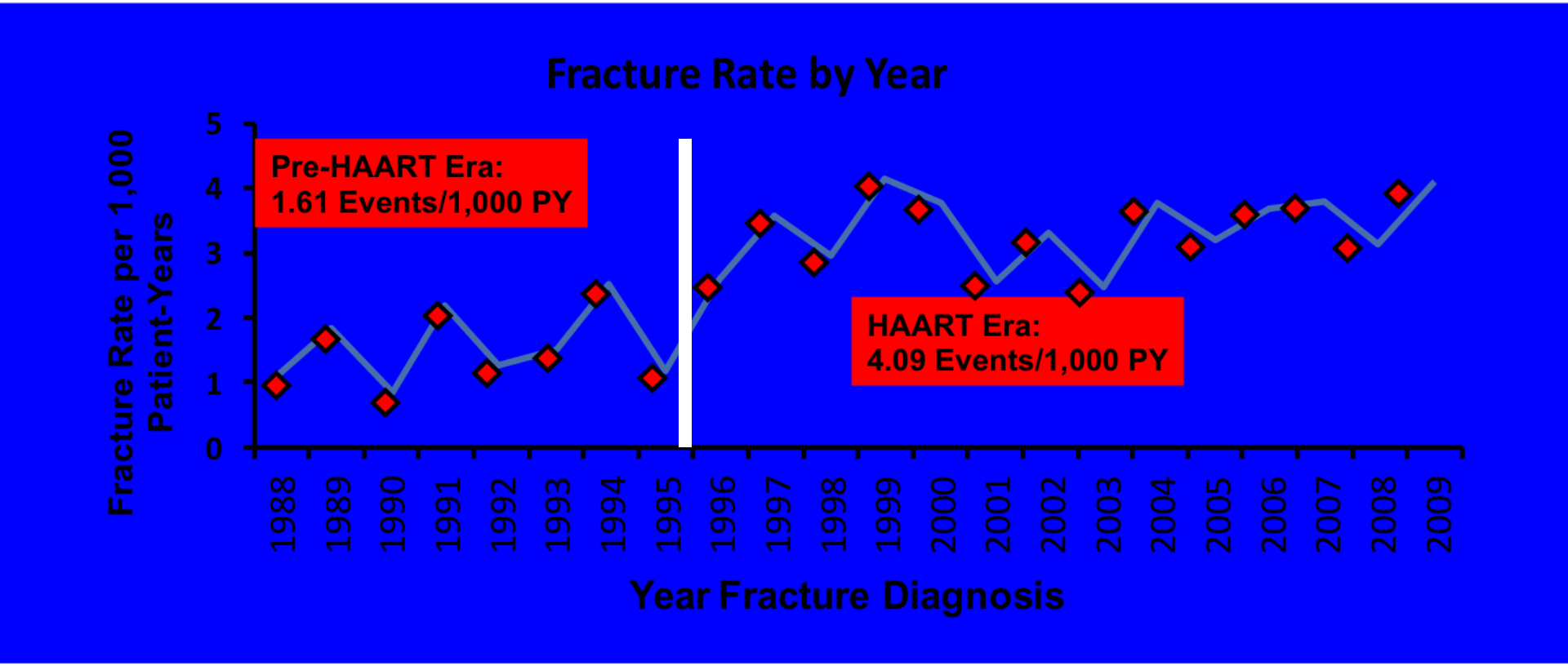
Schoenbaum et al . Clin Infect Dis 2005.

Age-adjusted Rates of Osteoporotic Fractures (Entire Cohort)



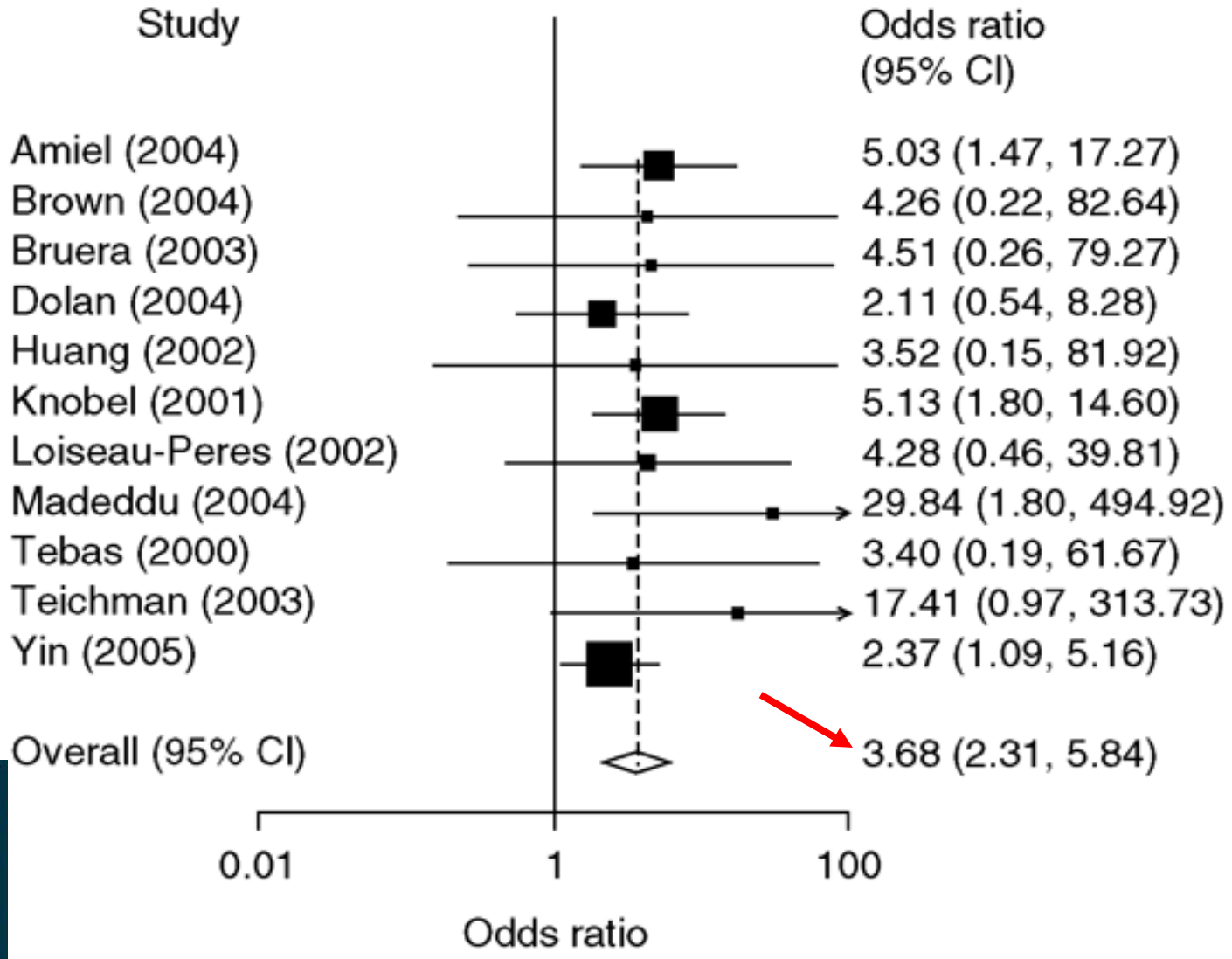
Fracture Rate by Year

- VA Cohort (N=56660; 951 with fracture)
- Higher proportion of patients on effective treatment
- Increased survival and increased fracture rates



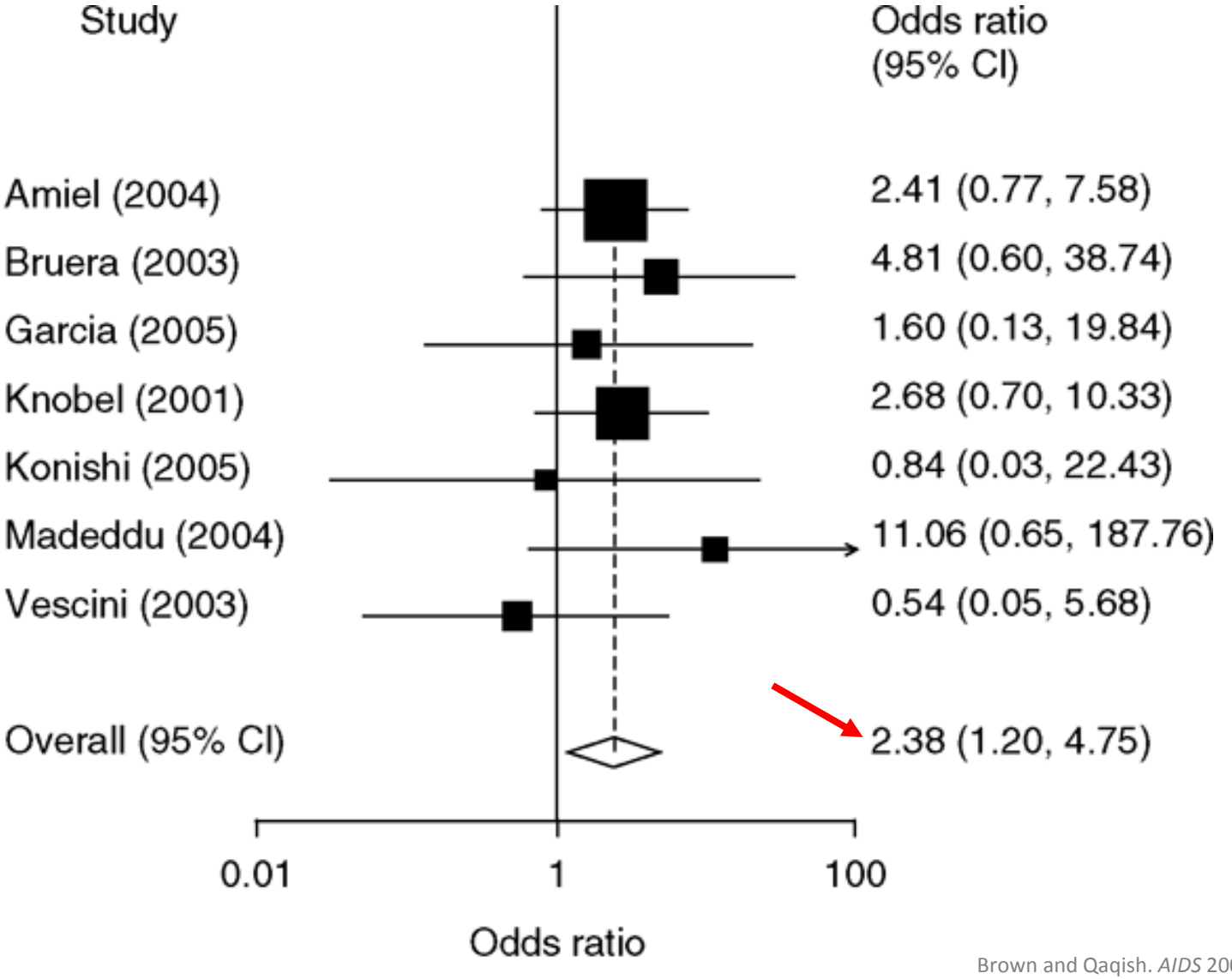
Bedimo R. et al, AIDS. 2012 Feb 1.

Odds of osteoporosis in HIV-infected patients compared with HIV-uninfected controls



Brown and Qaqish. *AIDS* 2006;20:2165-74

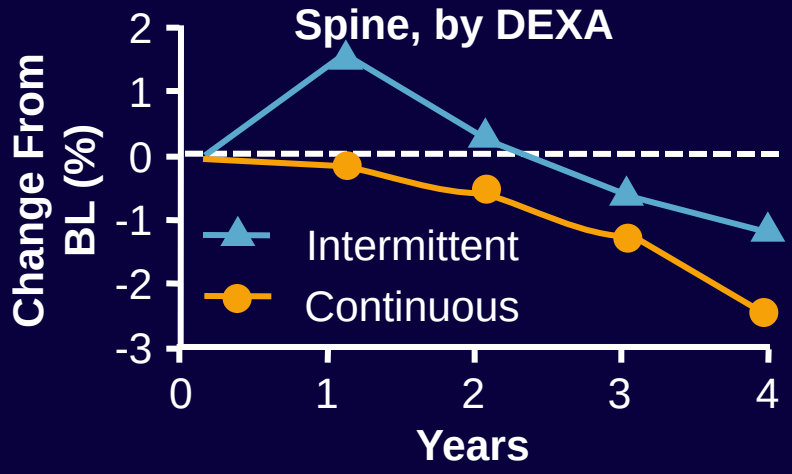
Odds of osteoporosis in HIV-infected patients on ART compared with ART-naïve patients



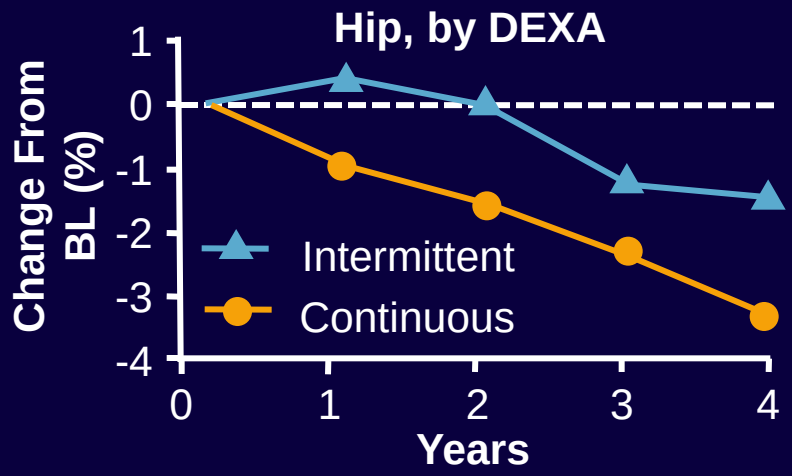
Brown and Qaqish. *AIDS* 2006;20:2165-74

SMART: BMD Loss With Continuous vs Intermittent ART

- Continuous ART associated with significantly larger BMD decline than intermittent ART; only observed disadvantage of continuous treatment in study
  - By year, differences in BMD between arms are statistically significant only in the first 1-2 years of follow-up; few patients included in analysis in Years 3-4



n =	112	88	54	10
n =	96	77	47	15
Est diff:	1.7	0.8	0.5	2.1
P values:	.003	.26	.64	.40



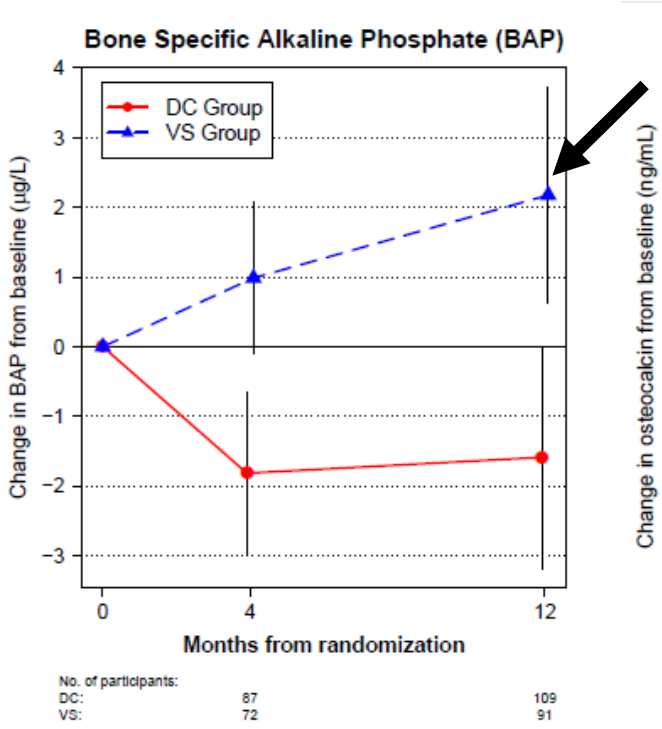
n =	109	86	51	9
n =	95	75	47	15
Est diff:	1.3	1.7	1.0	2.5
P values:	.002	.005	.27	.21

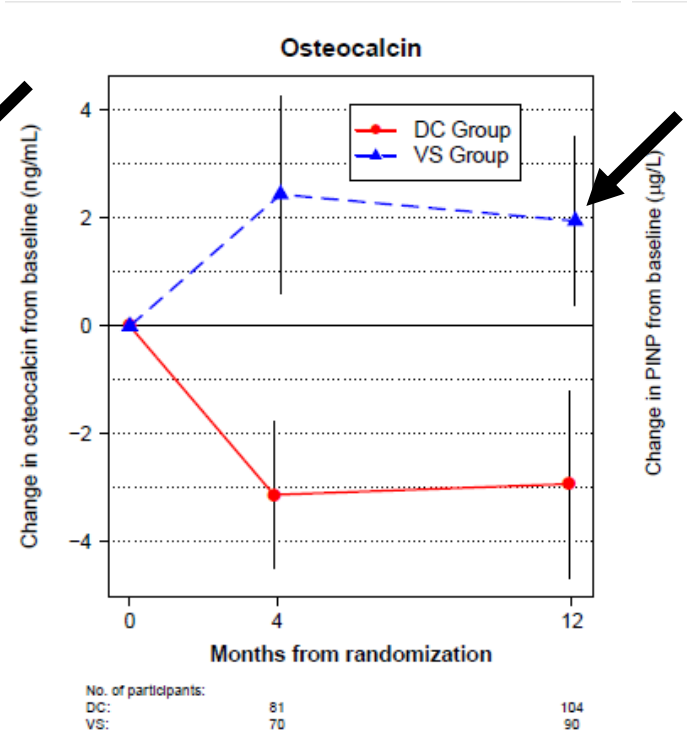
Grund B. AIDS. 2009 July 31; 23(12): 1519–1529

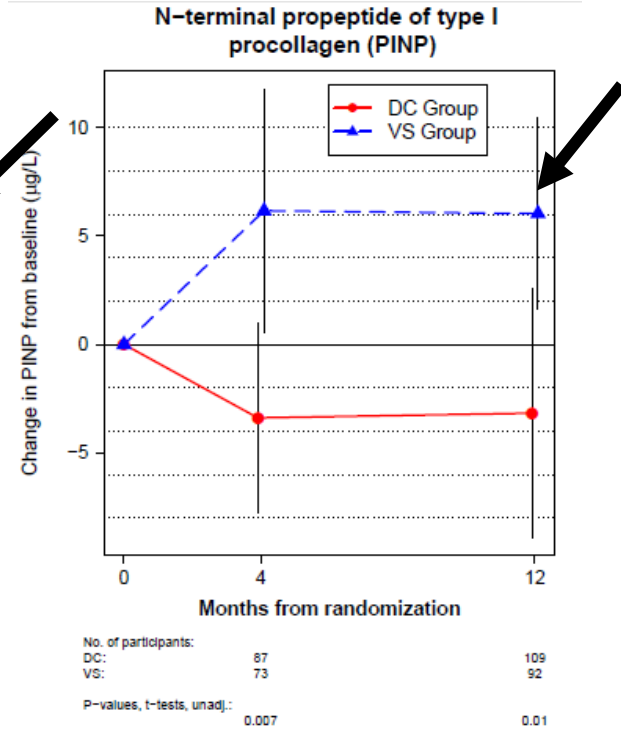
Bone turnover markers in SMART

Changes in bone formation markers

Bone ALP | Osteocalcin | P1NP







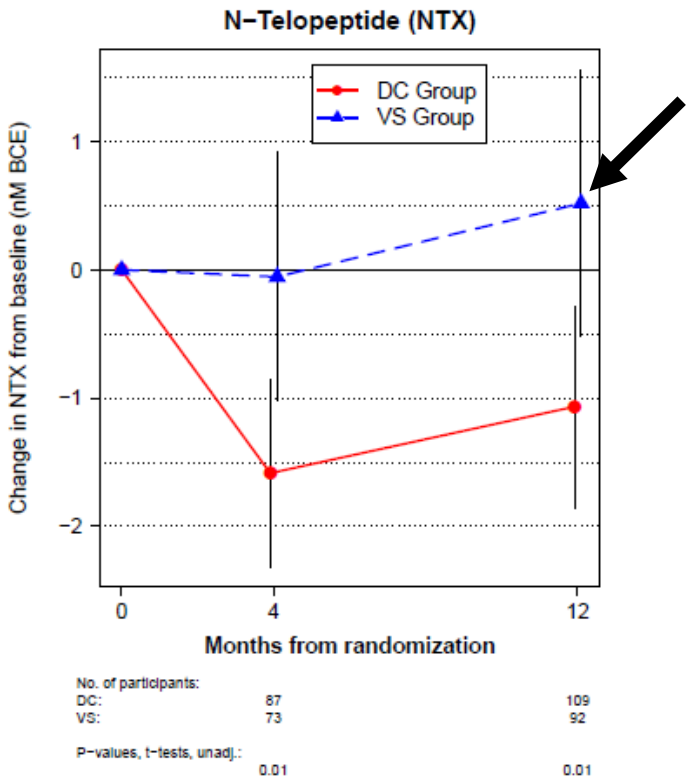
P <0.001 <0.001 <0.001 <0.001 0.007 0.01

J. Hoy et al. J Bone Miner Res. 2013 Jan 8

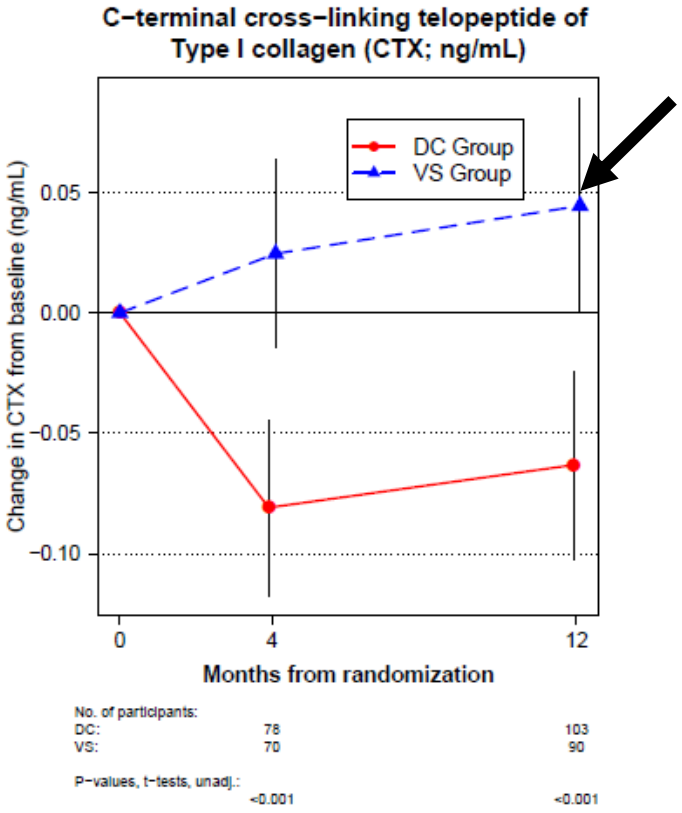
Bone turnover markers in SMART

Changes in bone resorption markers

N-telopeptide



C-telopeptide



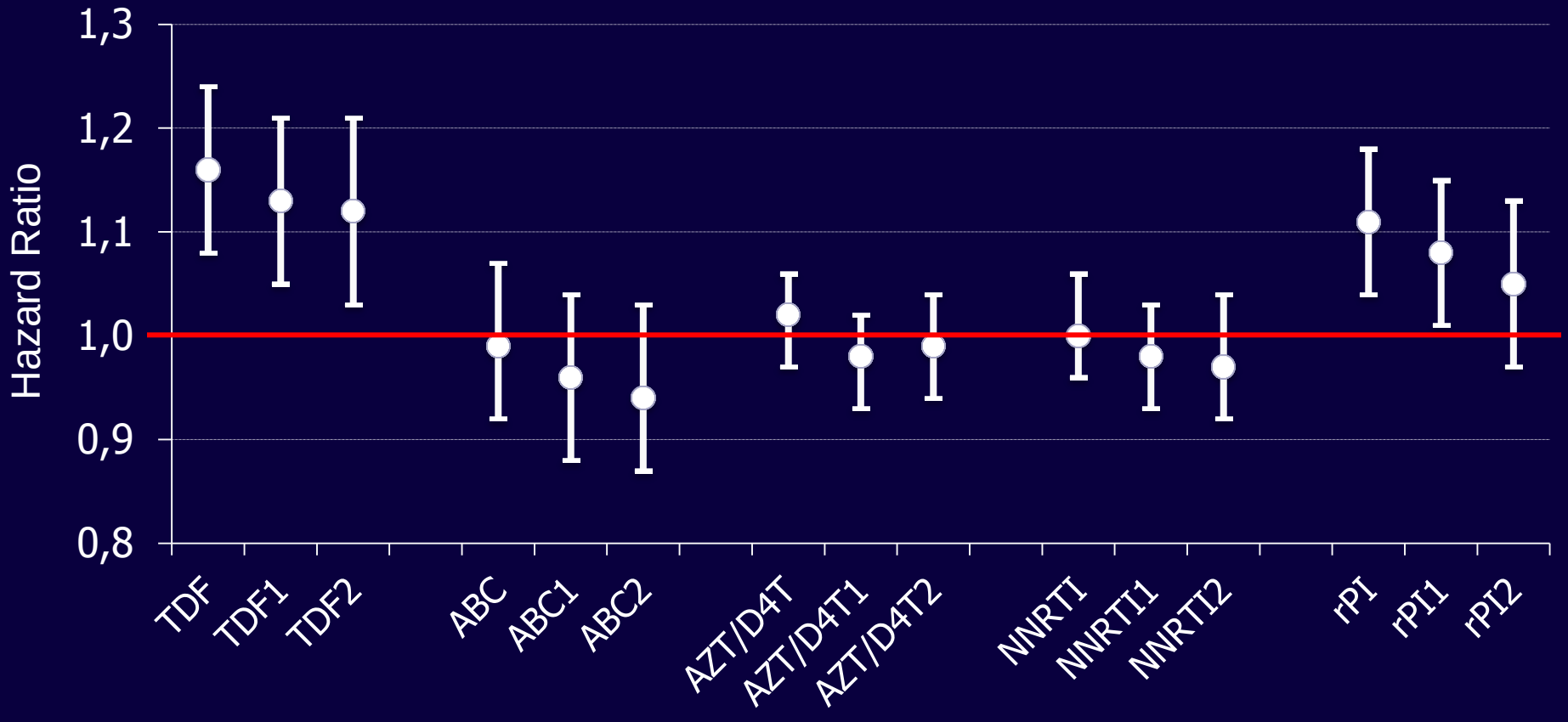
P	0.01	0.01	<0.001	<0.001

J. Hoy et al. J Bone Miner Res. 2013 Jan 8

BMD Loss with ART-initiation: ~2-6% at 48-96 weeks

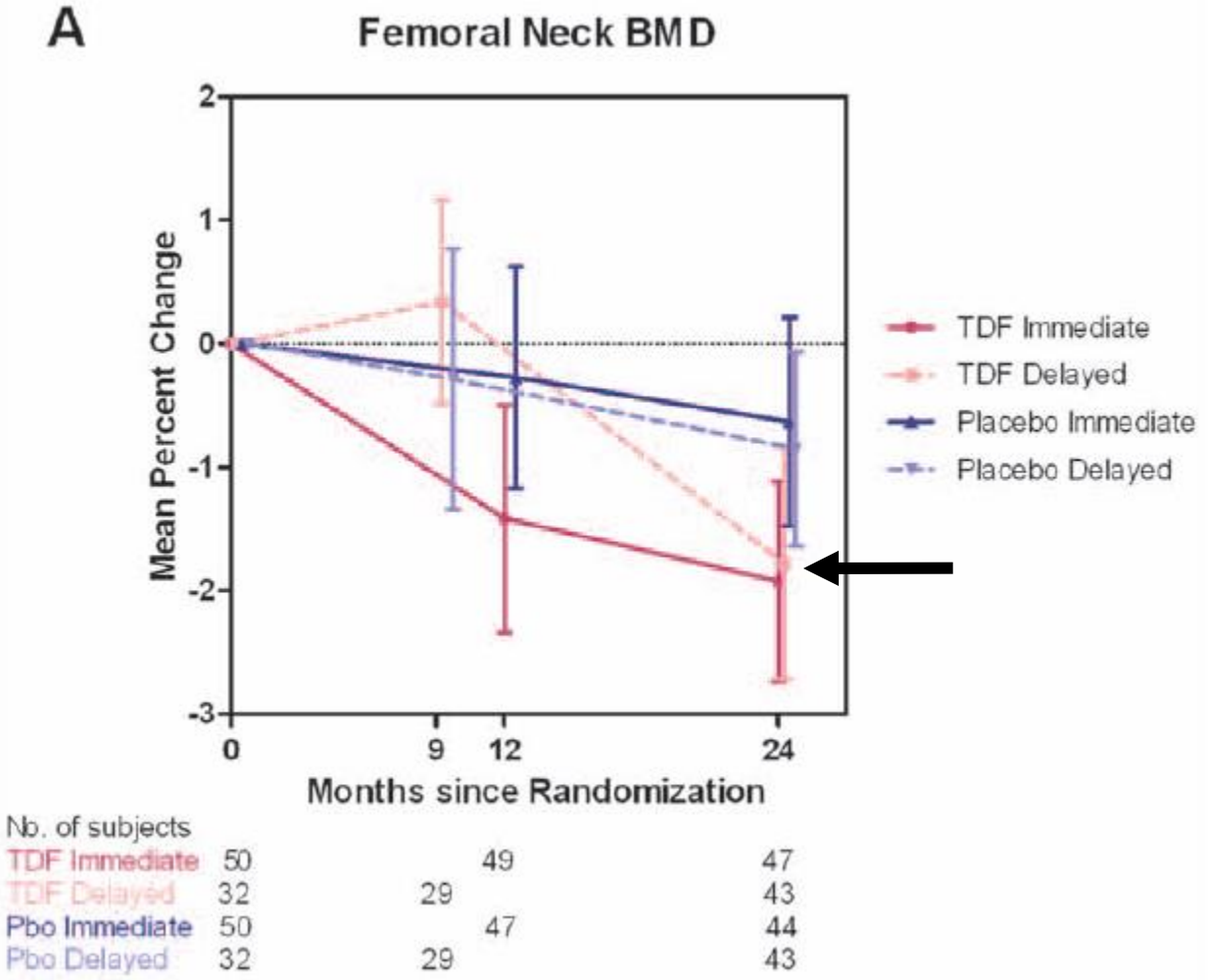
Author, y	N	Wks	ART-type	Study outcomes
Gallant, 2004	602	144	TDF vs. d4T	Spine :TDF-2.2% ; d4T:-1.0% Hip : TDF: -2.8%; d4T:-2.4%
Tebas, 2007	157	96	NFV vs EFV	2.5% decrease in total BMC
Bonnet, 2007	74	36	PI vs non-PI	0.8% decrease in lumbar BMD
Brown, 2009	106	96	LPV/r vs AZT/3TC/EFV	2.5% loss in total BMD
Duvivier, 2009	71	48	PI vs Non-PI	Spine: -4.1% , Hip: -2.8%
van Vonderen, 2009	50	104	AZT/3TC/LPV/r v NVP/LPVr	Fem Neck: -6.3% v -2.3% Spine: -5.1 v -2.6 %
Moyle, 2009	385	48	TDF v ABC	Hip: ABC:-1.9%; TDF: -3.6% Spine: ABC: -1.6%; TDF -2.4%
McComsey, 2010	258	96	TDF v ABC ATV/r vs EFV	Hip: ABC:-2.2%; TDF: -4.0% Spine: ABC: -1.8%; TDF -3.8% Hip: ATV/r:-3.5%; EFV: -3.5% Spine: ATV/r:-3.0%; EFV: -2.0%
Huang, 2010	753	96	TDF v AZT v d4T LPV/r v EFV	Total BMD: TDF: -3%; v AZT: -1.75% v d4T: -2%Difference LPV/r vs EFV: -0.5%
Qaqish, 2011	160	96	LPV/r+RAL v LPV/r+TDF/FTC	Total BMD: +0.68 v -2.5%
Tebas, 2011	349	96	RPV vs EFV (+NRTI)	Total BMD: -1.5% vs -1.5%
Moyle, 2011	224	96	ATV/r v LPV/r (+TDF/FTC)	Total BMD: -3% v -4%

Antiretroviral Exposure and Risk of Osteoporotic Fractures: HAART Era



MV Model 1: Controlling for CKD, age, race, tobacco use, diabetes and BMI;
MV Model 2: Controlling for Model 1 variables + concomitant exposure to other ARVs.

TDF monotherapy *in vivo*



Liu AY. Et al, PLoS ONE 6(8): e23688. doi:10.1371/journal.pone.0023688 (2011)

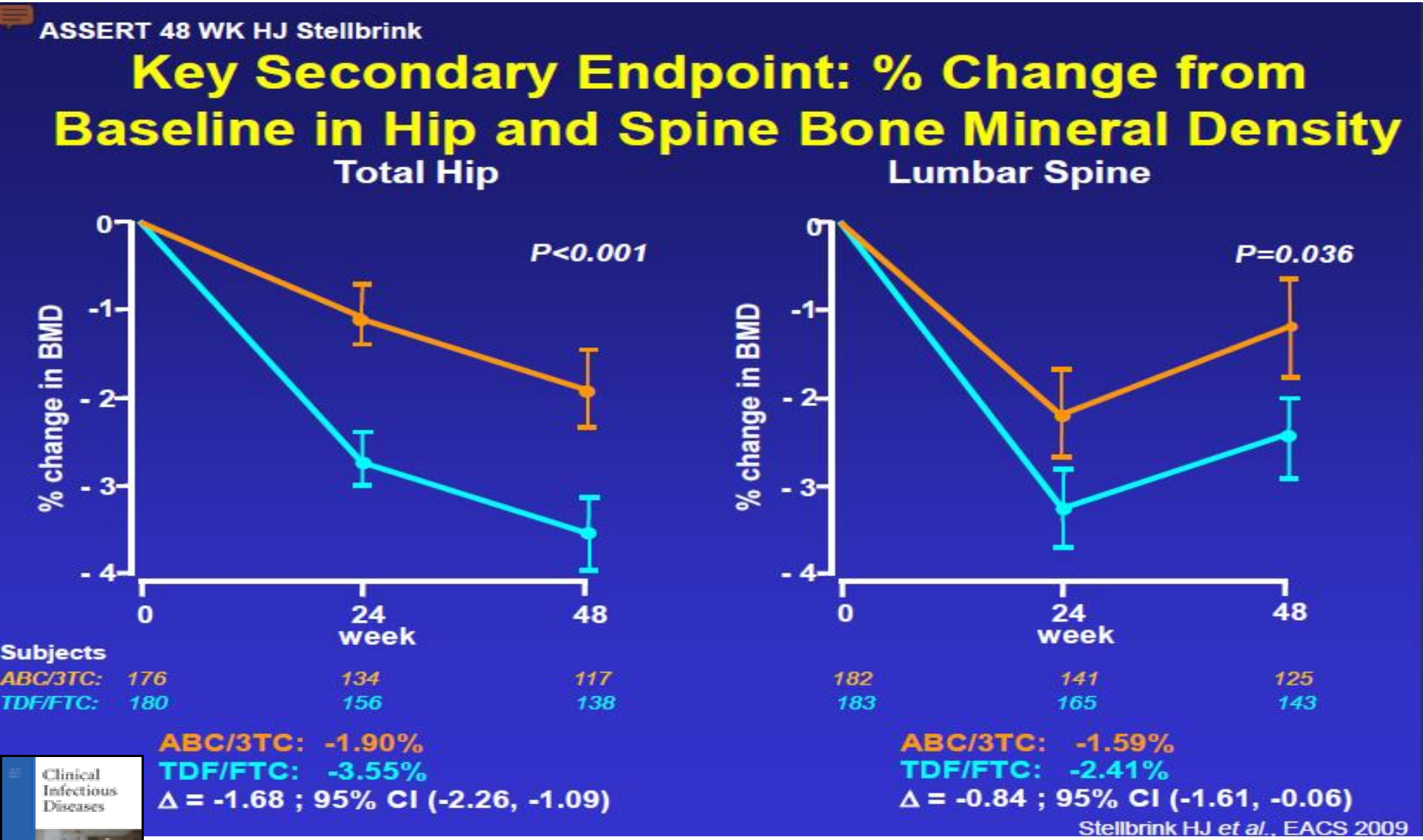
The iPrEX bone study

In this analysis of bone health, about 10% of HIV-negative MSM in the study had reduced bone mineral density *before* they were exposed to Truvada. This is about five times greater than would be expected. This finding calls for further study of HIV-negative MSM to better understand factors associated with reduced bone mineral density.

Overall, tenofovir's effect on bone mineral density was small and not linked to a statistically increased risk for fractures. However, it is noteworthy that in a substantial subset of men who received tenofovir, decreases of more than 3% in bone mineral density were detected over the course of the study.

The findings from iPrEX suggest that reduced bone mineral density may be an unrecognized problem among other men who are at high risk for HIV. A recent Dutch study may have suggested something similar

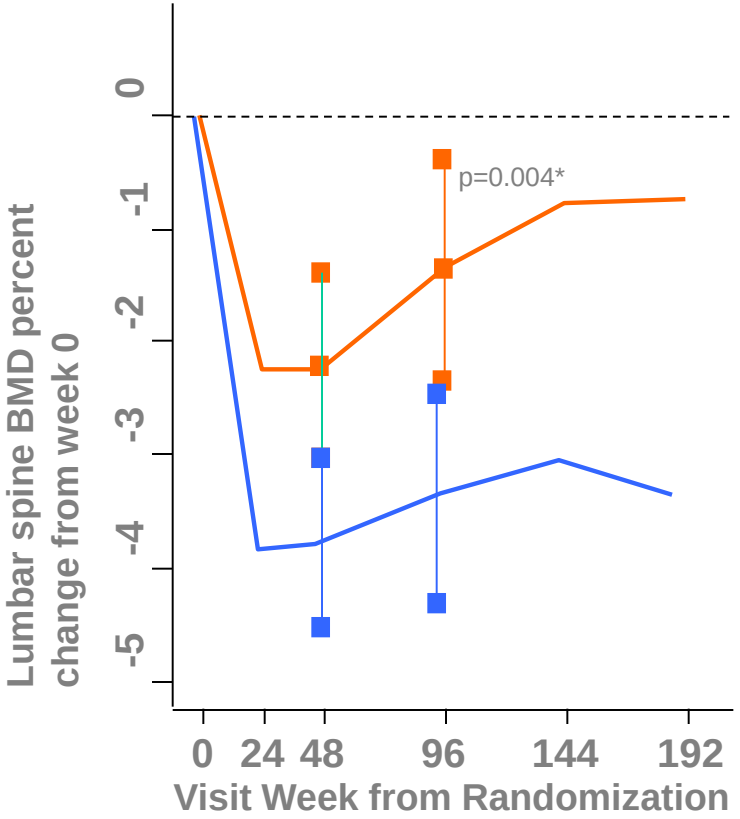
The ASSERT Study

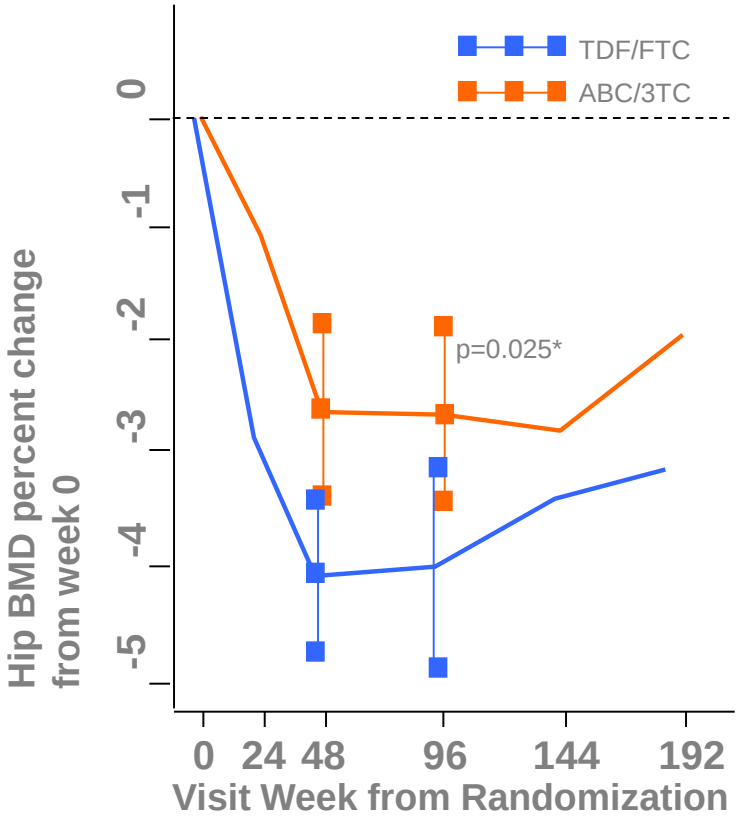


Stellbrink HJ et al. Clin Infect Dis. 2010 Oct 15;51(8):963-72

ACTG A5224s

ACTG 5224s Study





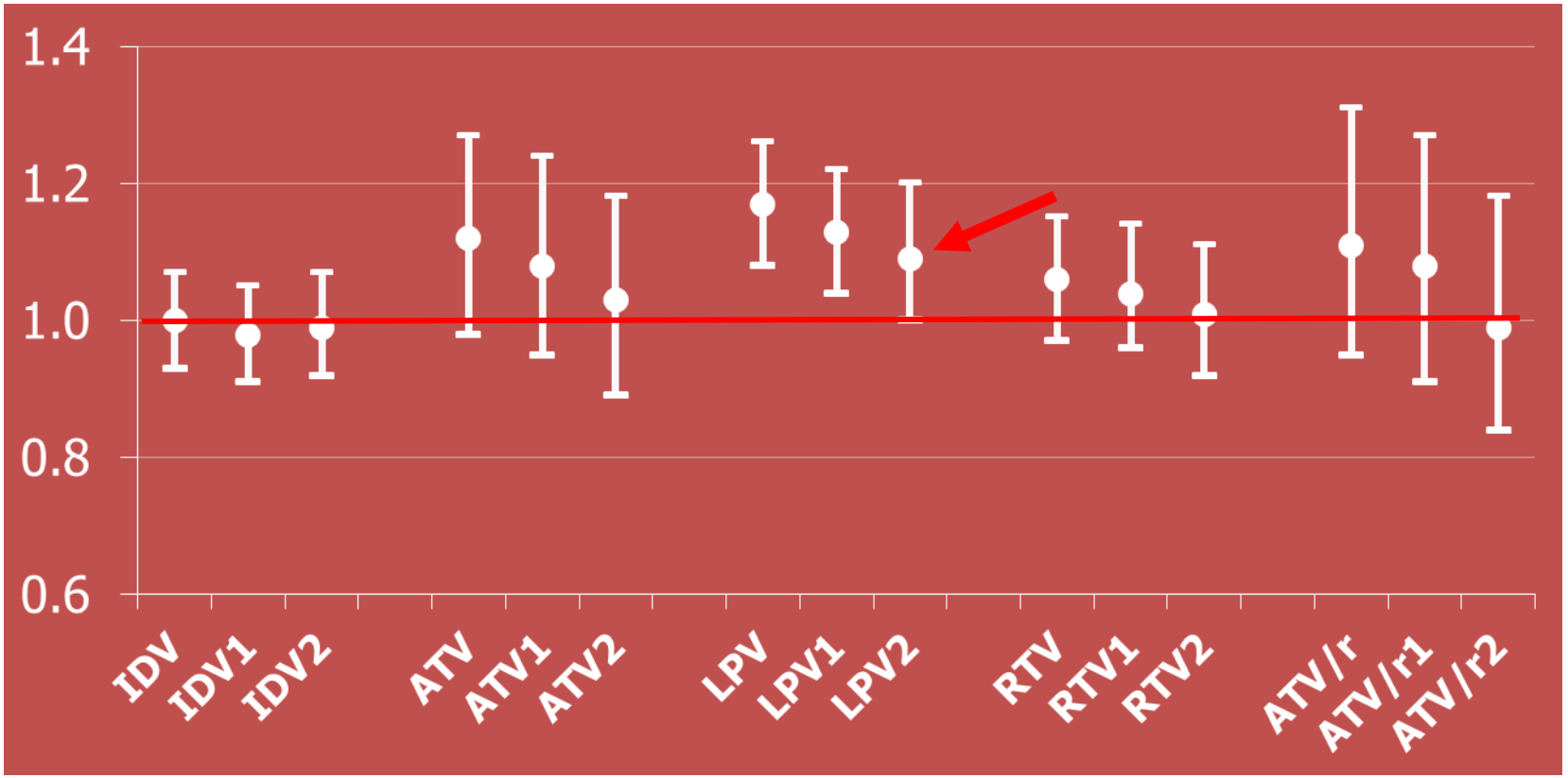
No. of subjects						
TDF/FTC	128	111	106	97	87	53
ABC/3TC	130	122	106	101	80	53

No. of subjects						
TDF/FTC	126	109	105	96	85	53
ABC/3TC	128	119	104	99	79	54

*linear regression

McComsey G, et al. Journal of Infectious Diseases 2011;203:1791–801

Exposure to Specific Protease Inhibitors and Risk of Osteoporotic Fractures

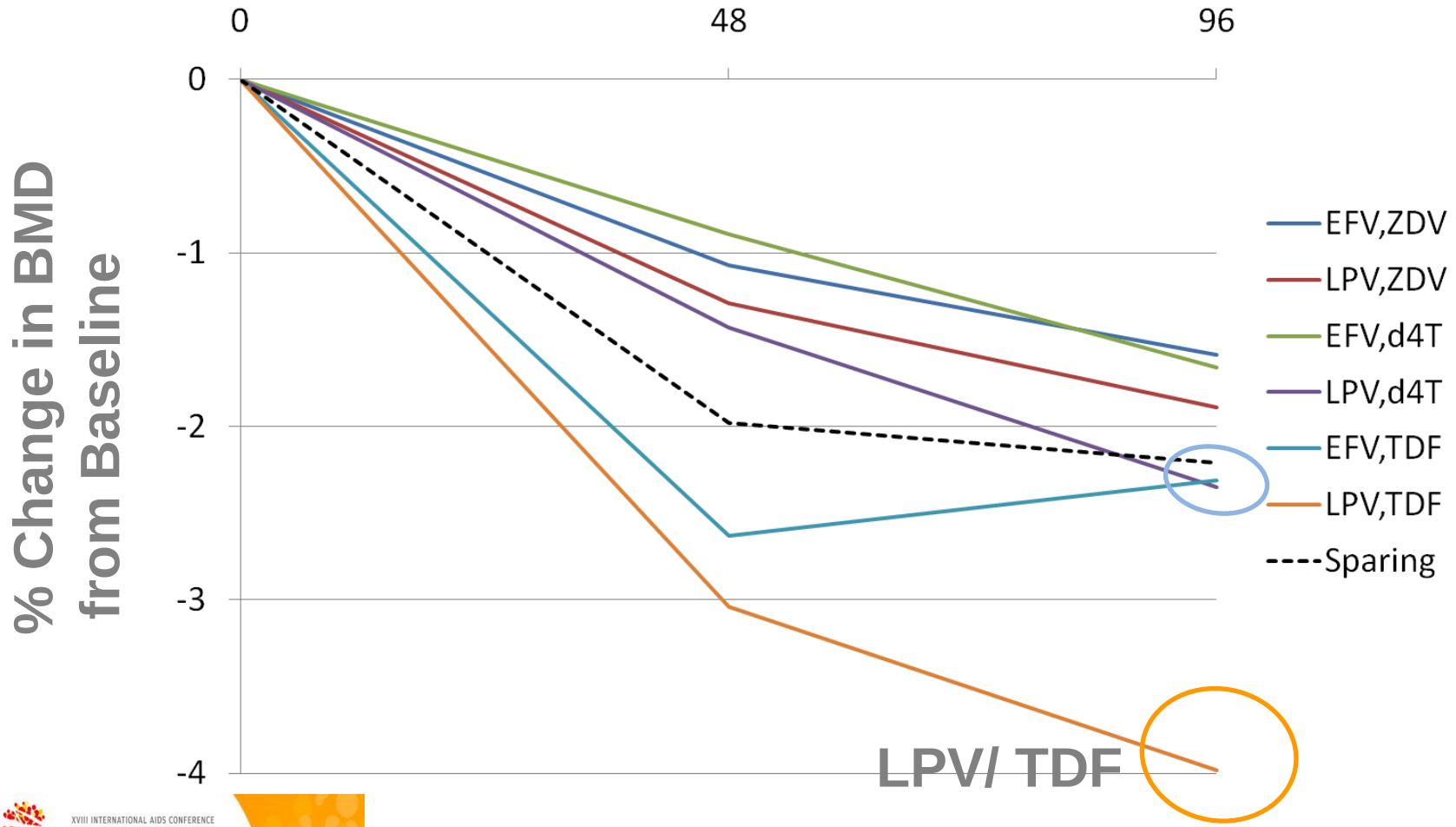


MV Model 1: Controlling for CKD, age, race, tobacco use, diabetes and BMI;
MV Model 2: Controlling for Model 1 variables + concomitant exposure to other ARVs.

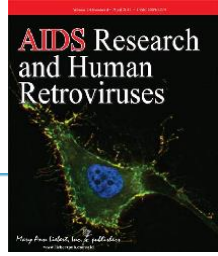
Bedimo R. et al, AIDS. 2012 Feb 1.

ACTG 5142: BMD at Wk 96

Observed Changes (as treated)

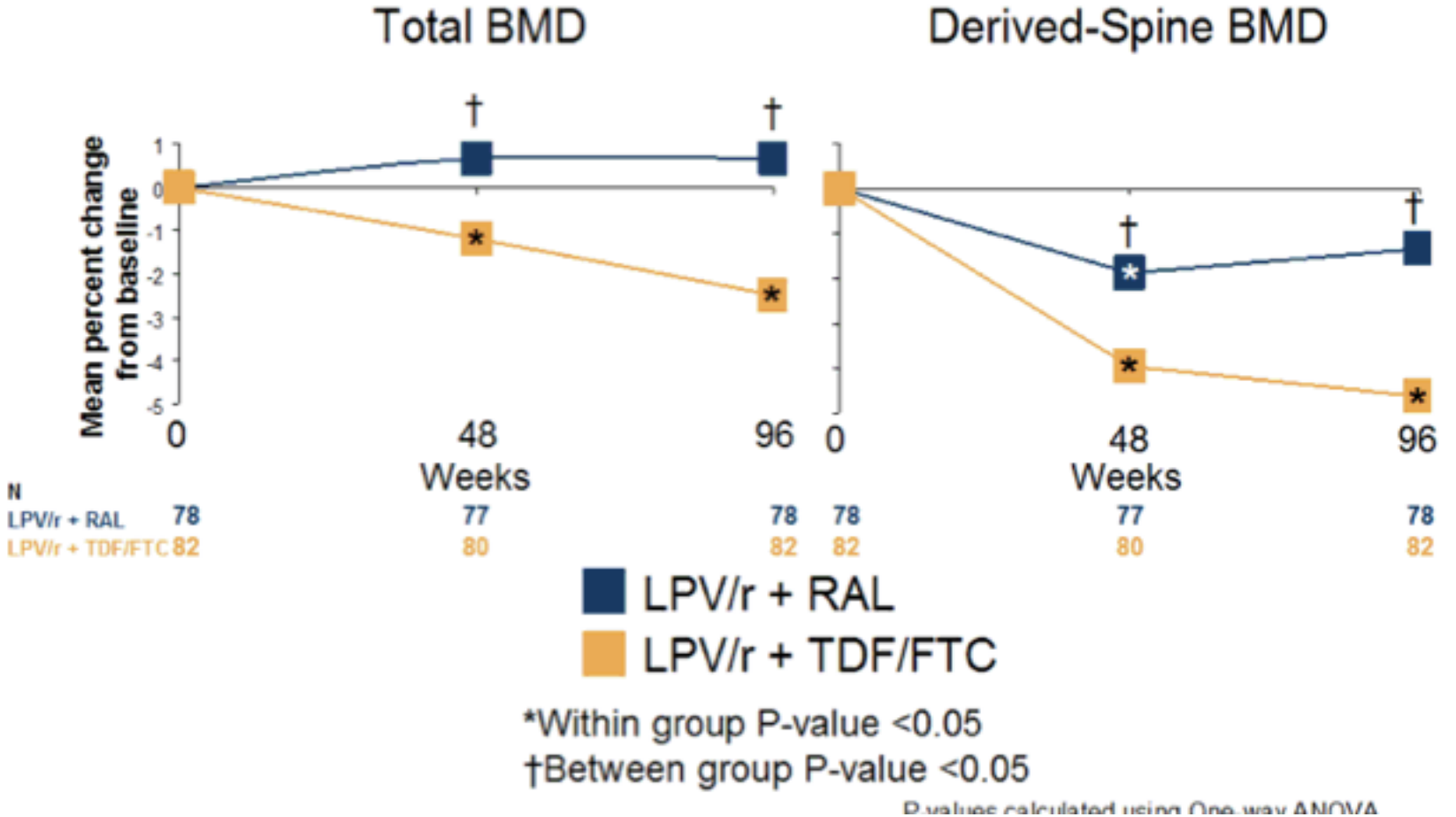


Huang J. WAIDS 2010. Vienna. WEAB0304



PROGRESS: BMD at Wk 96

Mean Percent Changes in Bone Mineral Density Analyzed Using DXA through 96 Weeks of Treatment



Reynes J. AIDS Res Hum Retroviruses 2012 Aug 3

Improved Low Bone Mineral Density and Bone Turnover Markers with Switch from Tenofovir to Raltegravir in Virologically Suppressed HIV-1+ Adults at 48 Weeks: The TROP Study

Mark Bloch[1*], Winnie Tong[2], Jennifer Hoy[3], Robyn Richardson[2], David Baker[4], Andrew Carr[2]

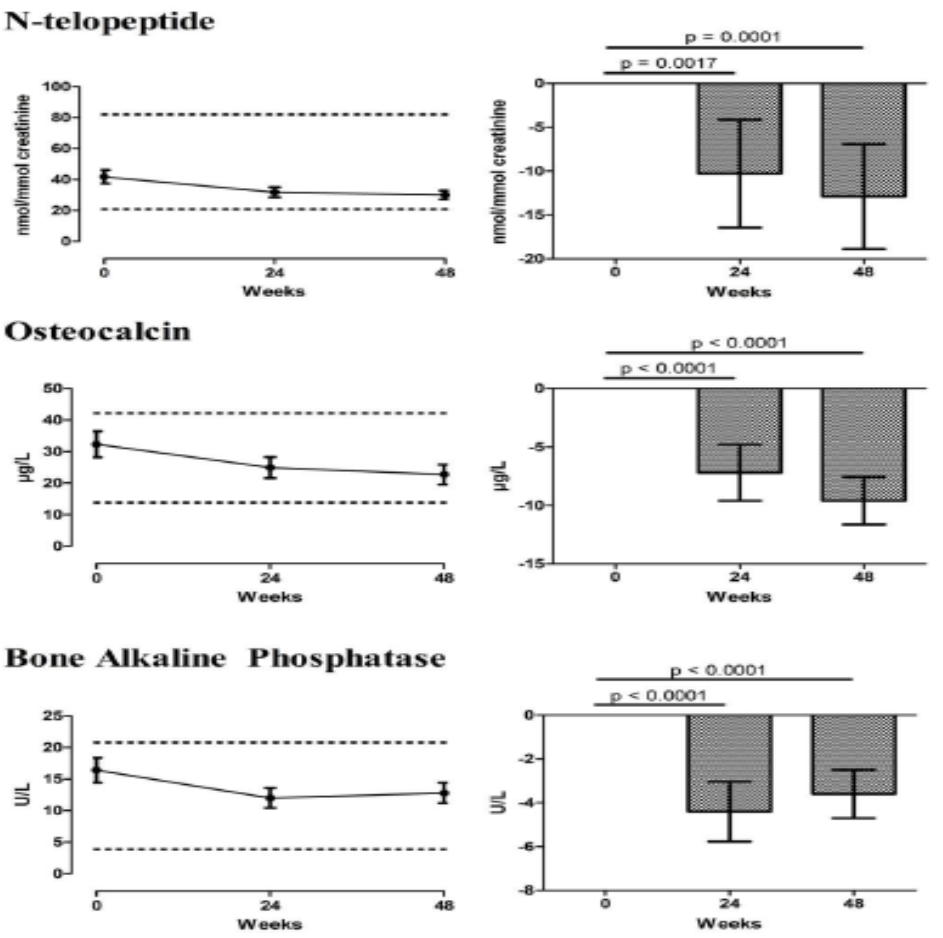
[1]Holdsworth House Medical Practice, Sydney, [2] St Vincent's Centre for Applied Medical Research, St Vincent's Hospital, Sydney, [3]The Alfred Hospital and Monash University, Melbourne, [4]East Sydney Doctors, Sydney, Australia.

Table 2: Bone Mineral Density at 24 and 48 Weeks

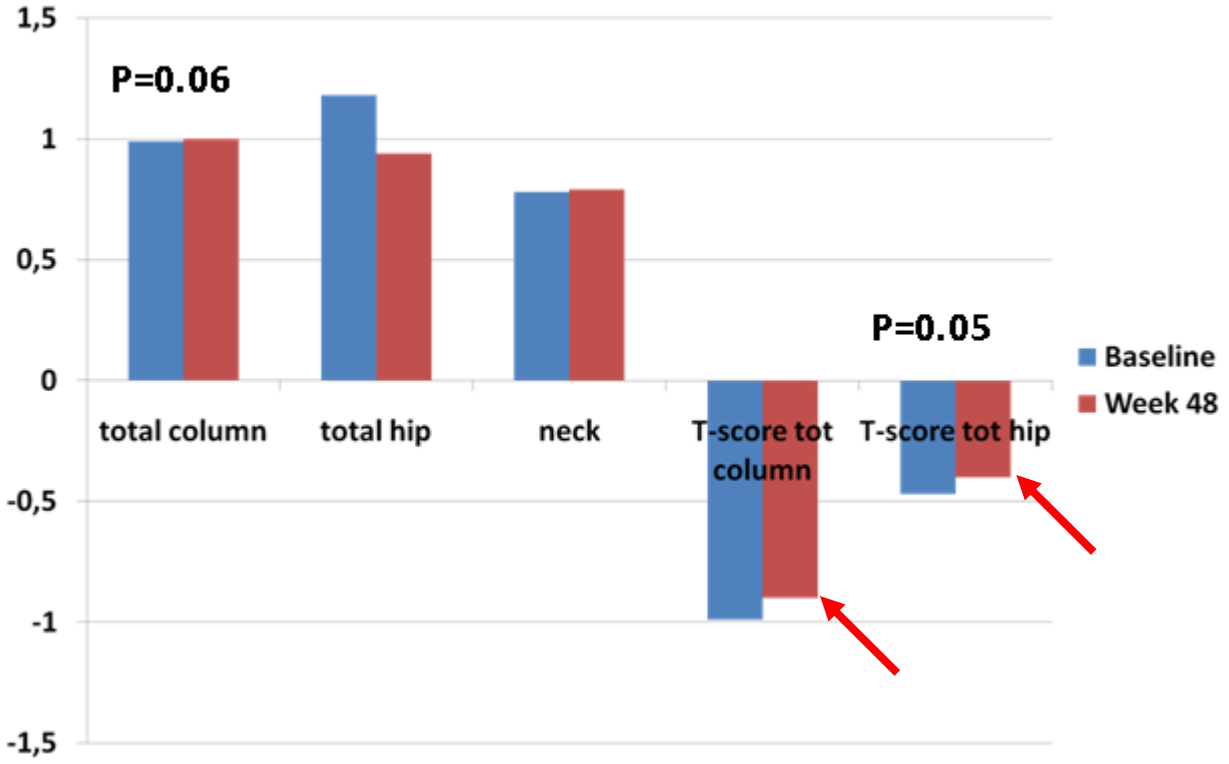
CROI 2012 SEATTLE Washington State Convention Center March 5-8, 2012

	Mean % Change from Baseline [95% CI]			
	Week 24	P	Week 48	P
Spine	1.5 [0.5, 2.5]	0.0038	3.0 [1.9, 4.0]	<0.0001
Left hip				
Total hip	1.4 [0.8, 2.0]	0.0001	2.5 [1.6, 3.3]	<0.0001
Femoral neck	1.5 [0.3, 2.7]	0.0131	2.1 [0.9, 3.2]	0.0011
Right hip				
Total hip	0.6 [−0.3, 1.5]	0.1902	2.7 [1.9, 3.5]	<0.0001
Femoral neck	0.4 [−0.9, 1.7]	0.5402	2.3 [1.2, 3.5]	0.0001

Figure: Changes in Bone Turnover Markers



ATLAS Study: modification of BMD over 48 weeks (mean values)



Di Giambenedetto S. Journal of Antimicrobial Chemotherapy, January 30, 2013

Combined Analysis of ART-initiation Studies in the ACTG

Baseline CD4 (cells/ul)	Estimated Mean 96-week % Total BMD Change (95% Confidence Interval)	P-value
<50	-2.3 (-3.4, -1.3)	<0.001
50-199	-0.8 (-1.8, 0.2)	
200-349	-0.7 (-1.6, 0.3)	
350-499	-0.6 (-1.7, 0.4)	

CD4 500 = reference; adjusted for age, sex, race, BMI, baseline VL, PI use, TDF use

(n=796)

Grant P, CROI 2013 # 823

Low CD4 Count Is Associated With an Increased Risk of Fragility Fracture in HIV-Infected Patients

Michelle K. Yong, MBBS, FRACP, MPH, Julian H. Elliott, MBBS, FRACP, PhD,*†‡*
Ian J. Woolley, MBBS, FRACP, DTMH,‡ and Jennifer F. Hoy, MBBS, FRACP*‡*

Conclusion: This is the largest clinical study to date of fragility fractures occurring in an HIV-infected population. The study found that risk of fracture was strongly associated with a low CD4 cell count, use of corticosteroids, and anti-epileptic medications. There were no associations between fracture risk and viral load, use of class, or duration of antiretroviral agent.

Key Words: CD4, fracture, HIV, osteoporosis, osteopenia

(*J Acquir Immune Defic Syndr* 2011;57:205–210)

ELSEVIER

Journal of Orthopaedic Research 20 (2002) 1185–1189

Journal of Orthopaedic Research

www.elsevier.com/locate/orthres

Tenofovir treatment at 30 mg/kg/day can inhibit cortical bone mineralization in growing rhesus monkeys (*Macaca mulatta*)

Alesha B. Castillo [a,*], Alice F. Tarantal [b,c], Mitchell R. Watnik [d], R. Bruce Martin [a]

[a] *Orthopaedic Research Laboratories, Sch* ... *Center, 4635 Second Avenue, Suite 2000,*

[b] *California Region* ... *, CA 95616, USA*

[c] *Department of Pe* ... *, CA 95616, USA*

[d] *Statistical Laborator* ... *Davis, CA 95616, USA*

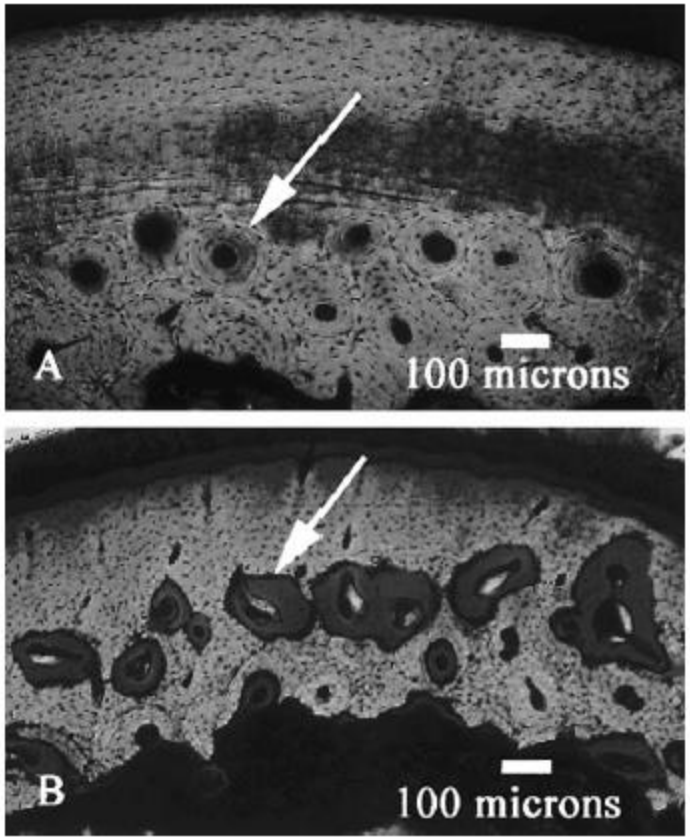


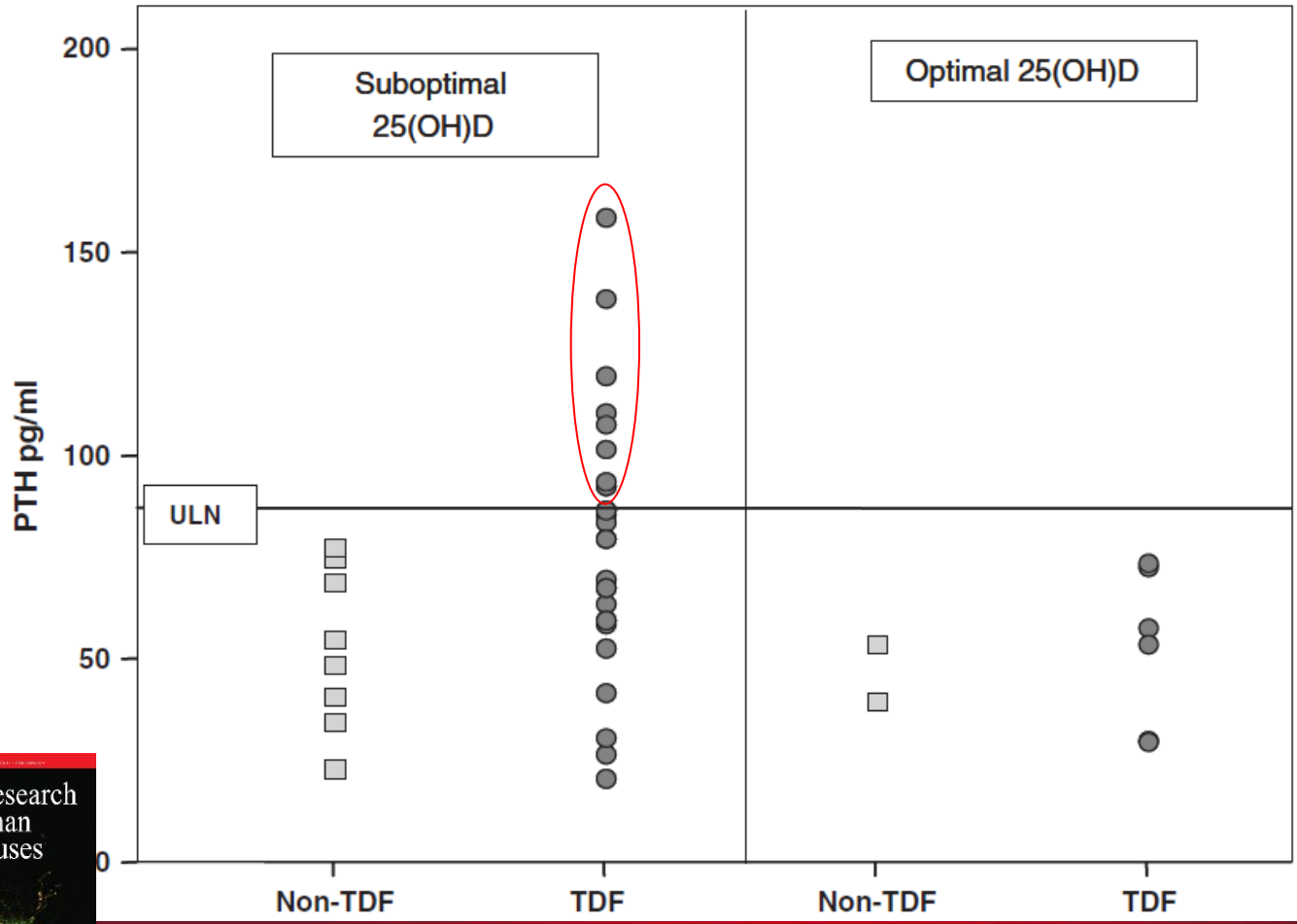
Fig. 1. Photomicrographs of tibial cross-sections stained with basic fuchsin (A) 11.5-month-old control specimen showing normal and healthy cortical bone (B) 16-month-old tenofovir-treated/uninfected specimen showing completely unmineralized secondary osteons, which are stained more darkly than the surrounding bone (magnification = 90×).

TURN the FUTURE

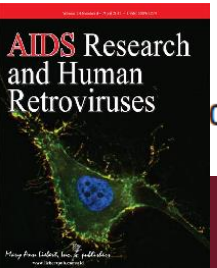
Short Communication: Inadequate Vitamin D Exacerbates Parathyroid Hormone Elevations in Tenofovir Users

Kathryn E. Childs,[1] Sarah L. Fishman,[2] Catherine Constable,[2] Julio A. Gutierrez,[2] Christina M. Wyatt,[3] Douglas T. Dieterich,[2] Michael P. Mullen,[1] and Andrea D. Branch[2]

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 26, Number 8, 2010



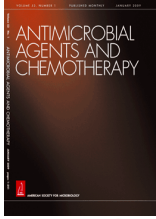
Vitamin D status and PTH in a group of 45 HIV-infected men on ART



High prevalence of renal disease in the HIV-infected population

- **32%** of patients have urinary abnormalities[1]
- **28%** had a serum creatinine > 120 μM[2]
- Up to **30%** have or develop a creatinine clearance < **90** ml/min[3]
- **18%** proteinuria > 1 g/L[4]

*1. Szczech LA, et al. Kidney Int 2002; **61**:195–202*
*2. Jones R, et al. J AIDS 2004; **37**:1489–1495*
*3. Gallant JE, et al. JAMA 2004; **292**:191–201*
*4. Gardner LI, et al. J AIDS 2003; **32**:203–209*



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2004, p. 1469–1487 Vol. 48, No. 5
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.5.1469–1487.2004

Biological Effects of Short-Term or Prolonged Administration of 9-[2-(Phosphonomethoxy)Propyl]Adenine (Tenofovir) to Newborn and Infant Rhesus Macaques

Koen K. A. Van Rompay,[1]* Laurie L. Brignolo,[1] Dennis J. Meyer,[2]† Christopher Jerome,[3] Ross Tarara,[1] Abigail Spinner,[1] Marta Hamilton,[2]‡ Linda L. Hirst,[1] David R. Bennett,[1] Don R. Canfield,[1] Trish G. Dearman,[1] Wilhelm Von Morgenland,[1] Phil C. Allen,[1] Celia Valverde,[1] Alesha B. Castillo,[4] R. Bruce Martin,[4] Valerie F. Samii,[5]

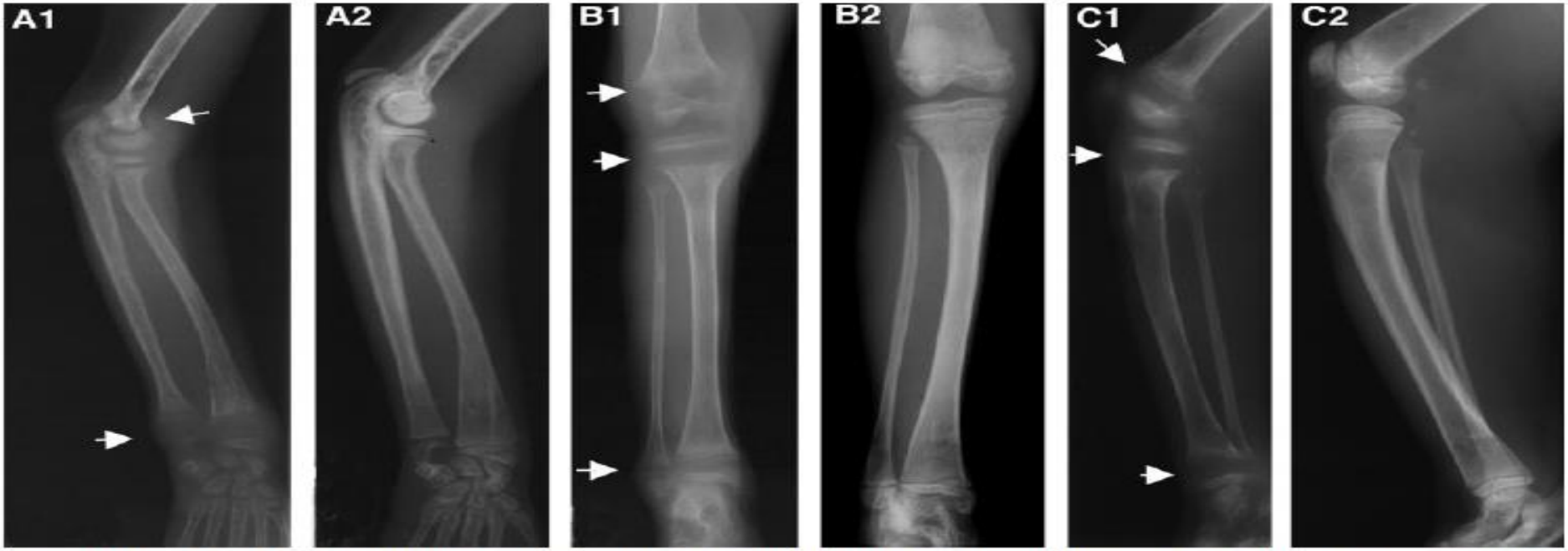
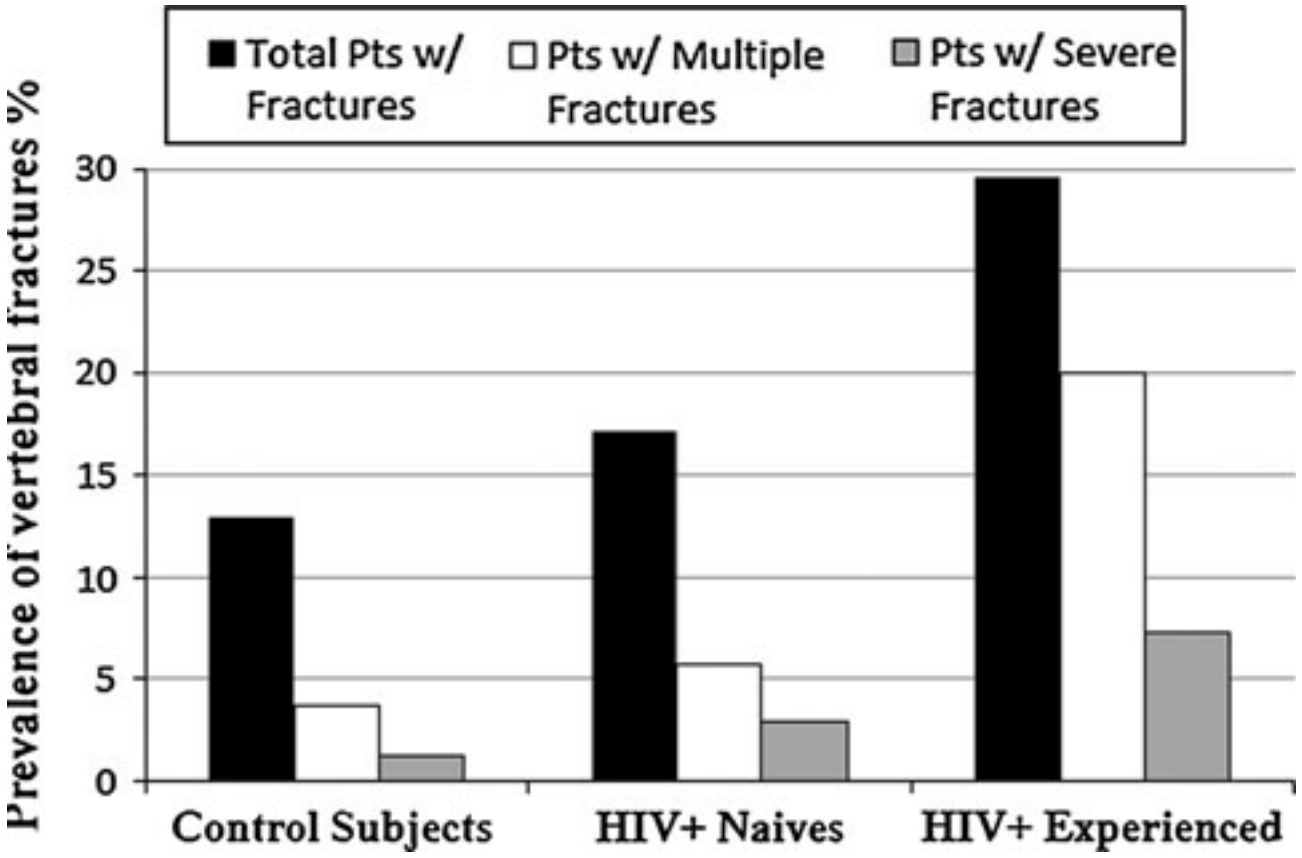
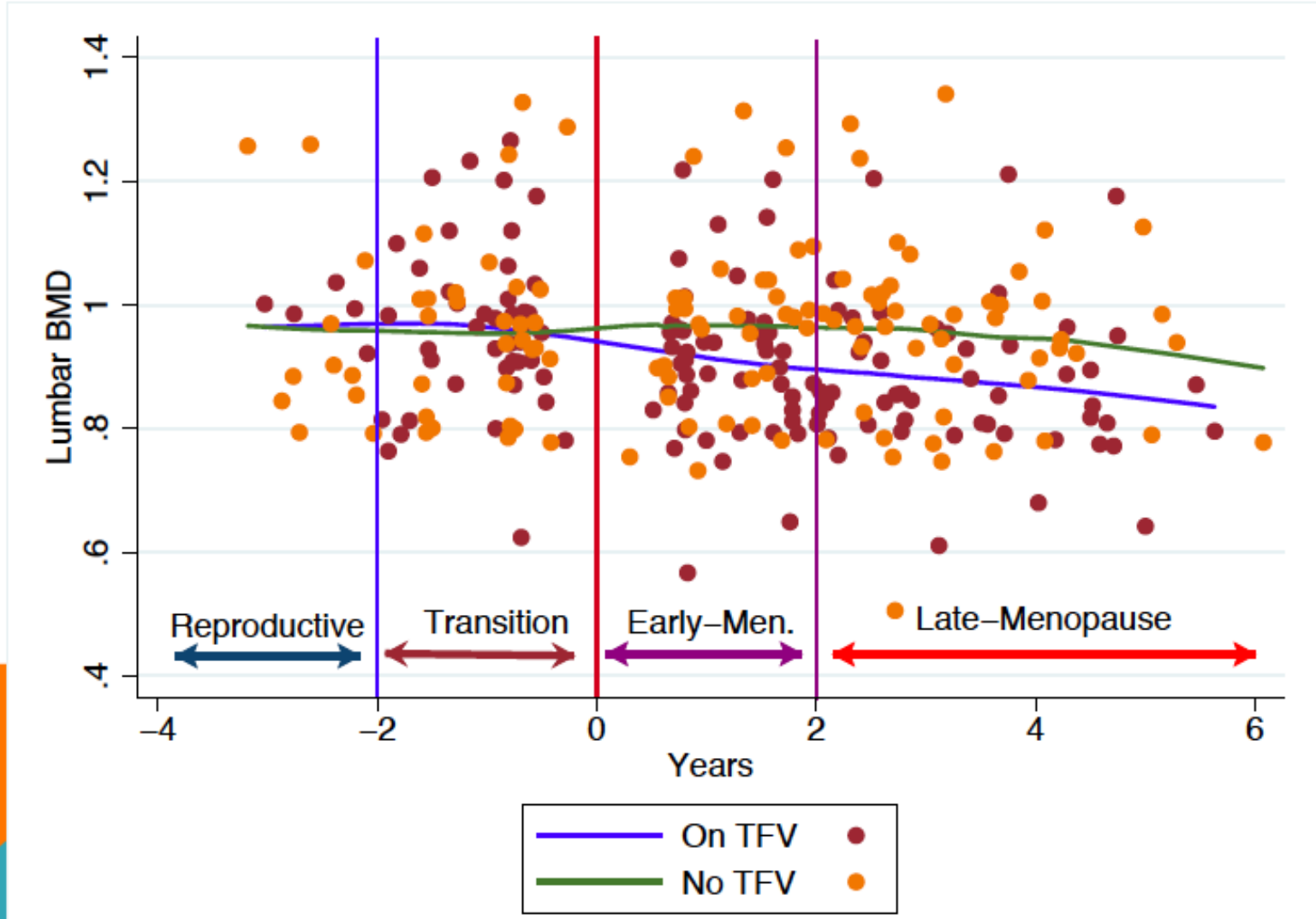


FIG. 1. Induction and reversibility of bone changes following chronic high-dose PMPA treatment. Animal 29003 was started on chronic high-dose PMPA treatment (30 mg/kg per day subcutaneously) at 3 weeks of age for a duration of 21 months. (A) Lateral view of right arm; (B) anterior-posterior view of left leg; (C) lateral view of right leg. For each of these three sets (A to C), the number 1 radiographs were taken at the end of the 21 months of PMPA treatment. Notice the reduced bone opacity and the abnormally widened growth plates (arrows). The number 2 radiographs are from the same animal and were obtained 5 months after PMPA treatment was stopped. Notice the improved bone opacity and normalization of the growth plates.



Torti C et al. Endocrine. 2012;41:512-7

Lowess smoothing curves were drawn to analyze impact of menopause and TDF on lumbar BMD.



Multivariable regression analysis for BMD prediction

	Transitional period			Early-menopause			Late-menopause		
	ß	95% C.I.	p-value	ß	95% C.I.	p-value	ß	95% C.I.	p-value
Years to (from*) menopause	-0.01	-0.03; 0.01	0.407	-0.01	-0.02; -0.01	< 0.001	-0.01	-0.02; -0.003	0.009
Baseline lumbar BMD	0.0002	-0.001; 0.003	0.078	0.0002	-0.0001; 0.0004	0.074	0.90	0.70; 1.09	< 0.001
PTH	-0.0005	-0.001; 0.0004	0.280	0.0001	-0.0004; 0.0002	0.535	-0.0001	-0.0002; 0.0002	0.800
BMI	0.003	-0.005; 0.010	0.489	0.004	-0.001; 0.010	0.142	0.008	0.002; 0.014	0.010
VitD supplement.on	-0.003	-0.05; 0.04	0.865	0.008	-0.010; 0.026	0.392	0.03	0.001; 0.054	0.038
TDF current exposure	-0.03	-0.07; 0.01	0.125	-0.03	-0.05; -0.01	0.012	-0.04	-0.09; 0.01	0.129

Chronic Kidney Disease Associated With Increased Risk of MI

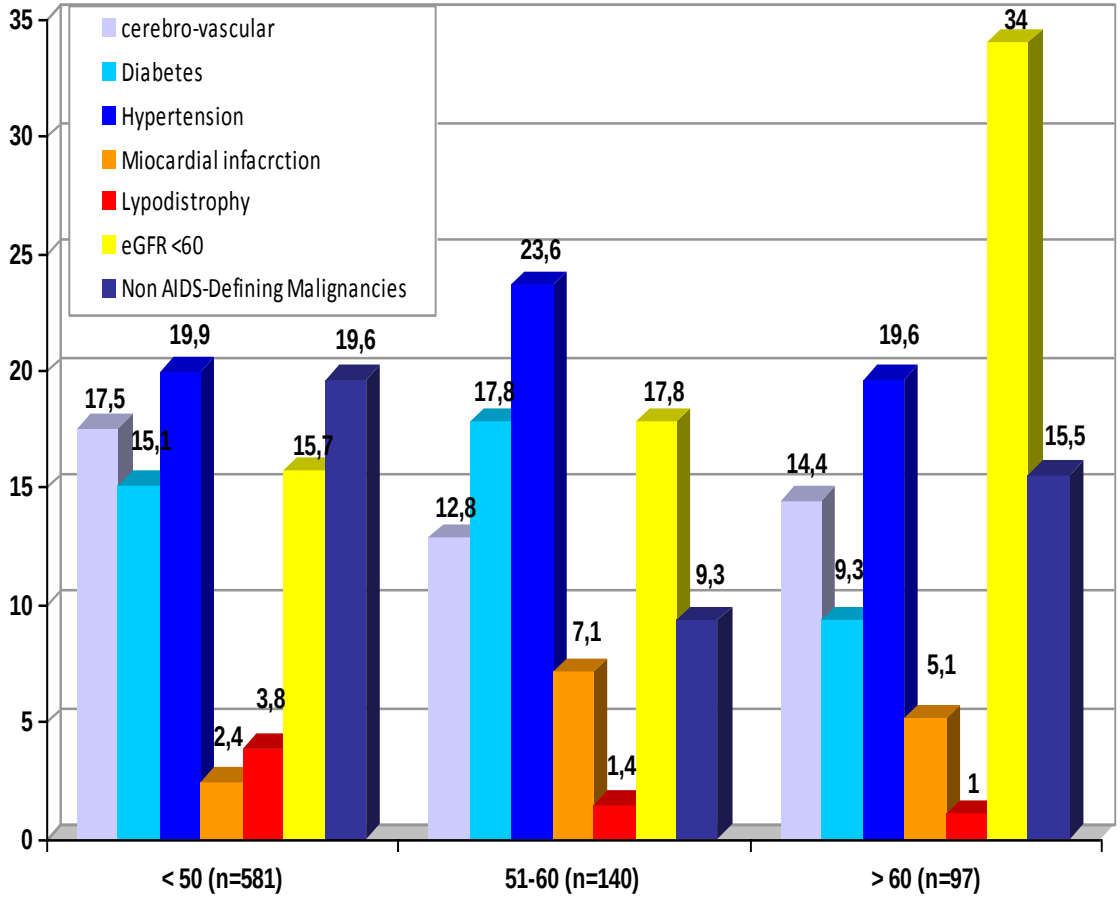
Estimated GFR, mL/min/1.73 m^2	MI			CVA		
	Rate per 1000 Pt-Yrs	Unadjusted HR	*P* Value	Rate per 1000 Pt-Yrs	Unadjusted HR	*P* Value
▪ < 60	11.33	3.85	< .0001	30.58	2.95	.002
▪ 60-89	3.89	1.33	.048	12.57	1.28	< .0001
▪ ≥ 90	2.92	Ref	--	9.74	Ref	--

- Pts with CKD significantly more likely to receive ABC vs TDF
  - 12.3% vs 7.2%; *P* < .0001
- CKD (eGFR < 60 mL/min/1.73 m^2) associated with higher risk of MI and CVA after adjustment for last ART regimen
  - HR for MI: 3.16 (95% CI: 2.35-4.26)
  - HR for CVA: 2.27 (95% CI: 1.88-2.74)
- HCV not associated with MI or CVA

Bedimo R, et al. IAS 2009. Abstract MOAB202.

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

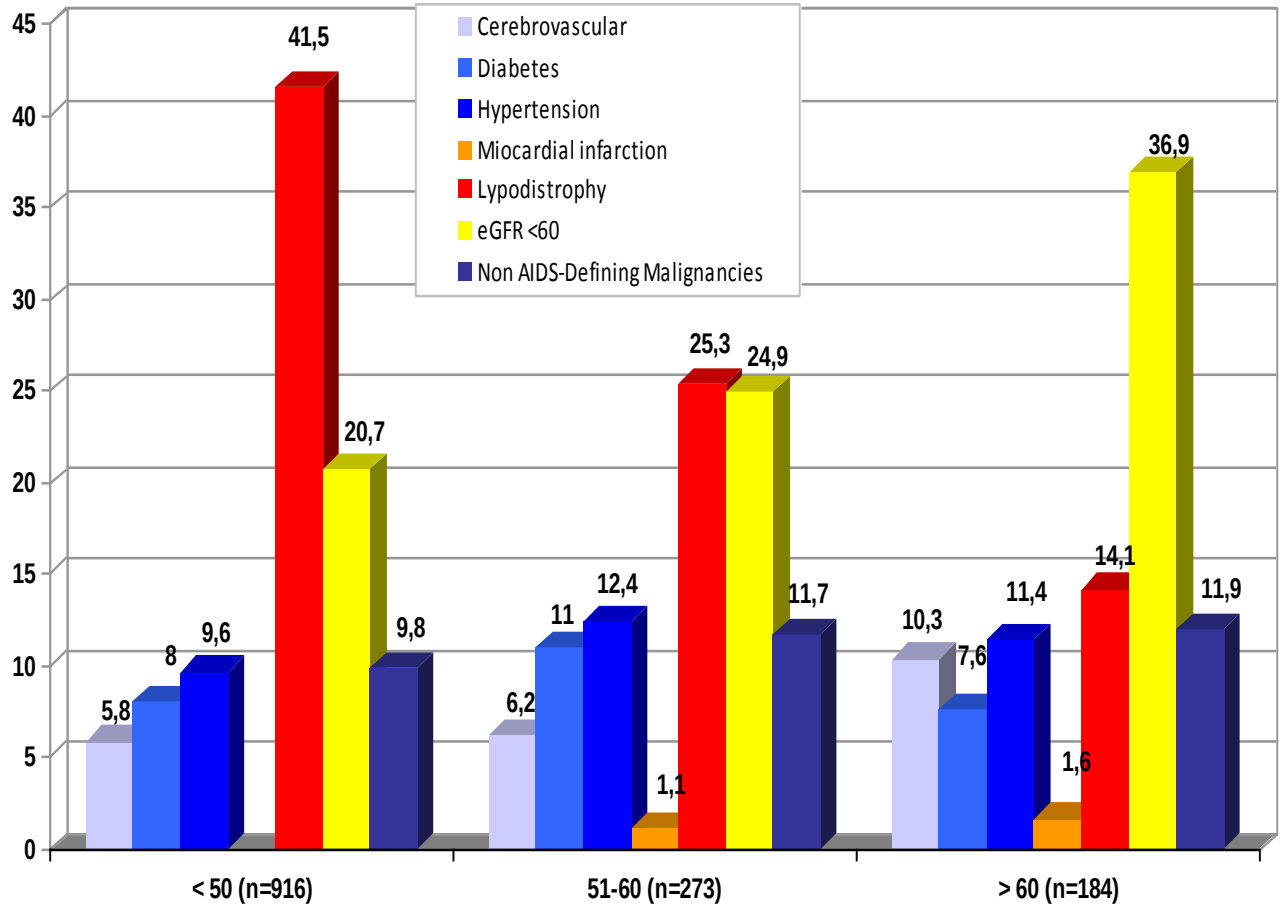
Icona: prevalence of different non-AIDS related comorbidities according to age **in naive patients**



ICONA Foundation. Internal data

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

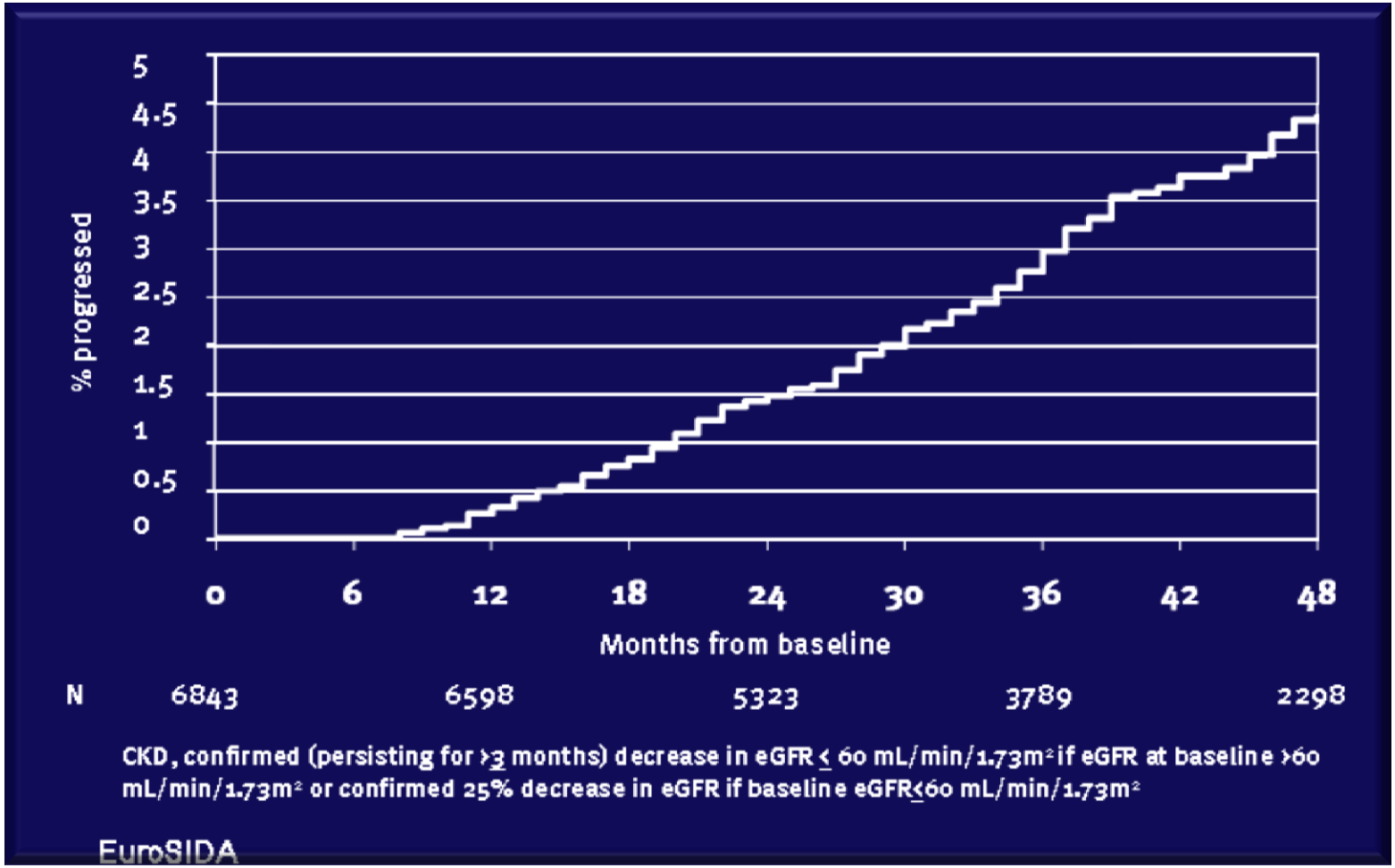
Icona: prevalence of different non-ADS related comorbidities according to age in **ART-treated patients**



ICONA Foundation. Internal data

EuroSIDA Study: Risk for Chronic Kidney Disease

EuroSIDA: Kaplan-Meier Progression to CKD

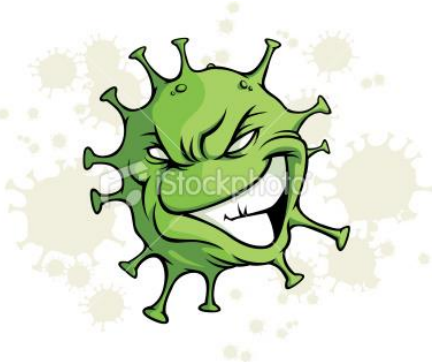


Kirk, O et al. 17th CROI 2010. Abstract 107LB

Classic risk factors:

age
high blood pressure
diabetes

Genetic



Virus

Drugs

At 65 years old glomerular filtration is reduced by about 30% and each subsequent year reduces it by an additional 1-2%

Brenner and Rector's The Kidney, 9th Edition

Factors associated to Chronic Kidney Disease in an Urban HIV Infected Population

Table 5. Multivariate Analysis

Variables	OR	95% CI	*P* Value
Age 50 years	1.05	0.60–1.85	0.86
Race (AA vs other)	2.24	1.33–3.76	0.002
Years of HIV	1.05	1.01–1.11	0.03
AIDS diagnosis	1.73	0.49–6.15	0.40
CD4 <200 cells/mm^3 at GFR	1.21	0.65–2.26	0.54
CD4 Nadir <200 cells/mm^3	1.85	0.54–6.38	0.33
Ever on antiretroviral therapy	1.04	0.39–2.73	0.94
HTN only	2.35	1.30–4.23	0.005
HTN and diabetes	6.37	2.48–16.36	<0.001
Ever on tenofovir	1.31	0.70–2.45	0.40
Ever on indinavir	1.69	0.97–2.94	0.06

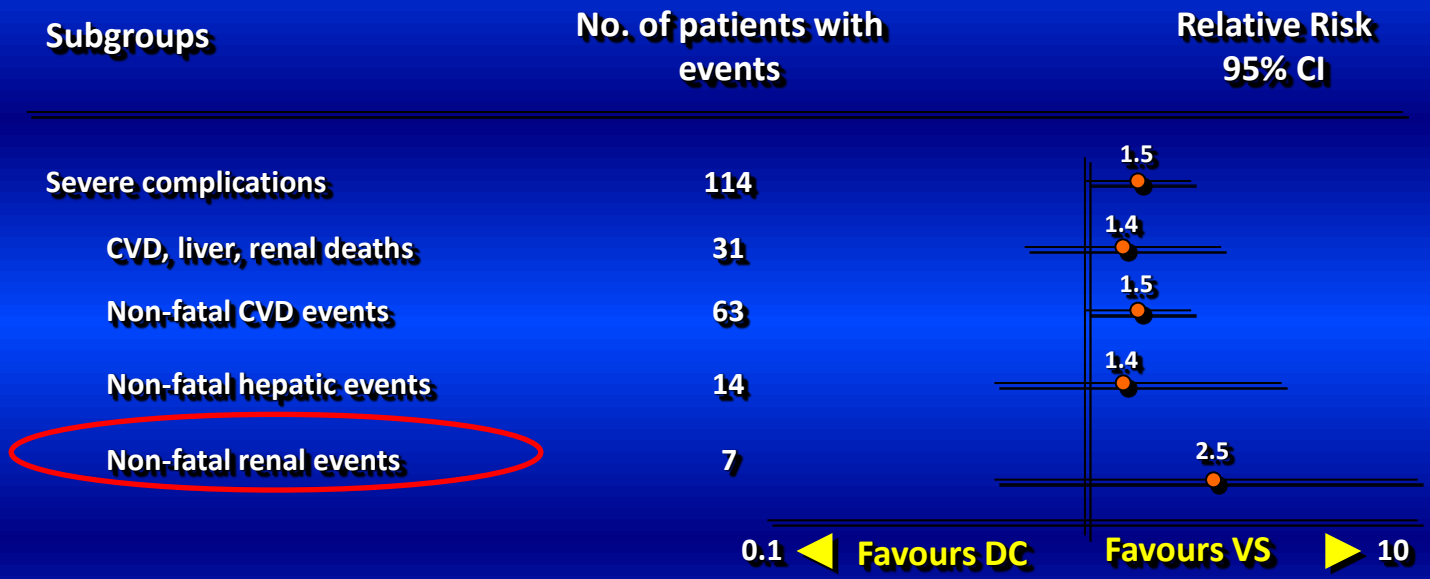
OR denotes odds ratio; CI, confidence interval; AA, African American; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; GFR, glomerular filtration rate; HTN, hypertension.

Sanjay K et al., Am J Med Sci 2008;335(2):89–94

SMART Study: Short-term CD4+ guided episodic use of ART is inferior to continuous therapy

- CD4+ guided drug conservation (DC) strategy was associated with significantly greater disease progression or death compared with continuous viral suppression (VS): RR 2.5 (95% CI: 1.8–3.6; $p<0.001$)
- Includes increased CVD-, liver- and renal-related deaths and non-fatal CVD events

Severe complications endpoint and components



EuroSIDA Study: Risk for Chronic Kidney Disease

Analysis of patients with ≥3 creatinine measurements + body weight (2004)

6,842 patients with 21,482 person-years of follow-up

Definition of CKD (eGFR by Cockcroft-Gault)

If baseline eGFR ≥60 mL/min/1.73 m^2, fall to <60

If baseline eGFR <60 mL/min/1.73 m^2, fall by 25%

225 (3.3%) progressed to CKD

	Univariable			Multivariable		
	IRR/year	95% CI	P-value	IRR/year	95% CI	P-value
Tenofovir	1.32	1.21-1.41	<0.0001	1.16	1.06-1.25	<0.0001
Indinavir	1.18	1.13-1.24	<0.0001	1.12	1.06-1.18	<0.0001
Atazanavir	1.48	1.35-1.62	<0.0001	1.21	1.09-1.34	0.0003
Lopinavir/r	1.15	1.07-1.23	<0.0001	1.08	1.01-1.16	0.030

Risk factors for CKD on TDF: age, HTN, HCV, lower eGFR, lower CD4+ count

Mocroft A et al., AIDS. 2010;24:1667-78.

Association of tenofovir exposure with kidney disease risk in HIV infection

Rebecca Scherzer[a], Michelle Estrella[b], Yongmei Li[a], Steven G. Deeks[c], Carl Grunfeld[a] and Michael G. Shlipak[a]

AIDS 2012, **26**:000–000

Table 3. Association of cumulative tenofovir (in different time ranges) with risk[a] of kidney disease outcomes.

Outcome Category of exposure[b]	Hazard Ratio (95% CI)	P Value
Proteinuria		
Tenofovir <0.5 years	1.72 (1.50–1.96)	<0.0001
Tenofovir 0.5–1 years	1.59 (1.36–1.86)	<0.0001
Tenofovir 1–3 years	1.68 (1.44–1.95)	<0.0001
Tenofovir >3 years	2.17 (1.48–3.20)	0.0001
Rapid Decline[c]		
Tenofovir <0.5 years	1.35 (1.16–1.56)	0.0001
Tenofovir 0.5–1 years	1.59 (1.38–1.84)	<0.0001
Tenofovir 1–3 years	1.23 (1.07–1.42)	0.0042
Tenofovir >3 years	1.04 (0.66–1.63)	0.88
CKD		
Tenofovir <0.5 years	1.30 (0.91, 1.86)	0.15
Tenofovir 0.5–1 years	1.85 (1.35, 2.53)	0.0001
Tenofovir 1–3 years	1.69 (1.26, 2.27)	0.0005
Tenofovir >3 years	1.56 (0.73, 3.36)	0.25

[a]All estimates based on multivariable adjusted time-dependent Cox models described in Table 2.
[b]Reference is versus 0 years.
[c]Rapid decline in kidney function was defined as an annual decline of 3 ml/min/1.73m^2 or more for two consecutive years.

Aquitaine Cohort: TDF Use, Alone or With Concomitant PI, Associated With CKD

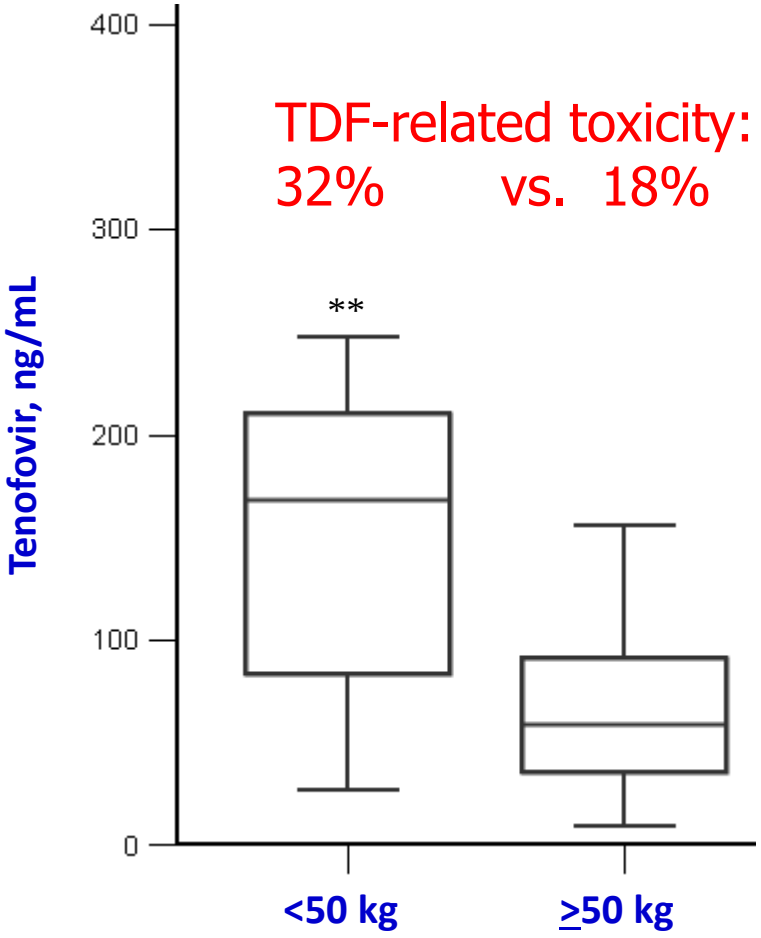
- 2693 HIV-infected patients with baseline CrCl > 60 mL/min/1.73 m^2 followed from 2004-2008
- 86 cases of incident CKD during follow-up
  - Among patients with CKD, 96% had baseline CrCl < 90 mL/min/1.73 m^2 and 90% had ≥ 3 traditional risk factors*

Association With CKD (Multivariate Analysis)	Risk Ratio (95% CI)
TDF use (adjusted for other risk factors)	2.5 (1.5-4.1)
▪ Without ≥ 6 months of concomitant PI†	1.8 (1.0-3.3)‡
▪ With ≥ 6 months of concomitant PI†	3.5 (2.1-6.1)‡

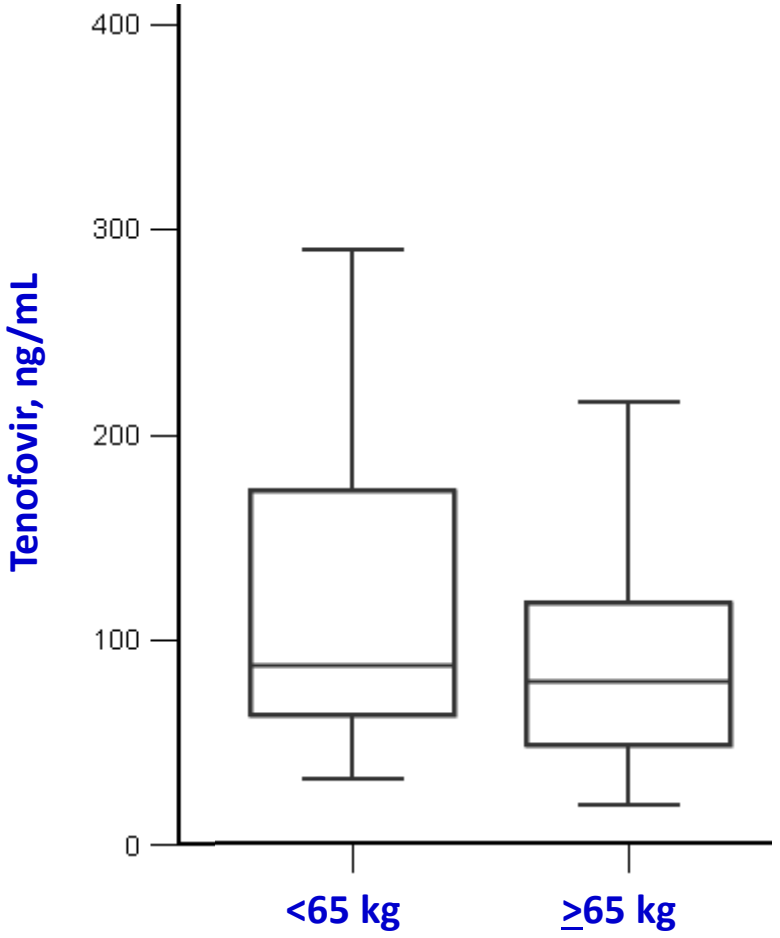
*Other variables associated with increased CKD: female sex, older age, diabetes, hyperlipidemia, preexisting mild renal dysfunction (CrCl 61-89 mL/min/1.73 m^2), and low CD4+ cell count.
†PIs used: ATV 41%, LPV 35%, FPV 11%, SQV 4%.
‡PI vs without PI: $P = .02$.

Morlat P, et al. IAS 2011. Abstract WEPDB0104.

Distribution of TDF concentrations according to gender and body weight



Females



Males

- Gervasoni et al, CROI 2013-

Renal toxicity associated with indinavir (and atazanavir)

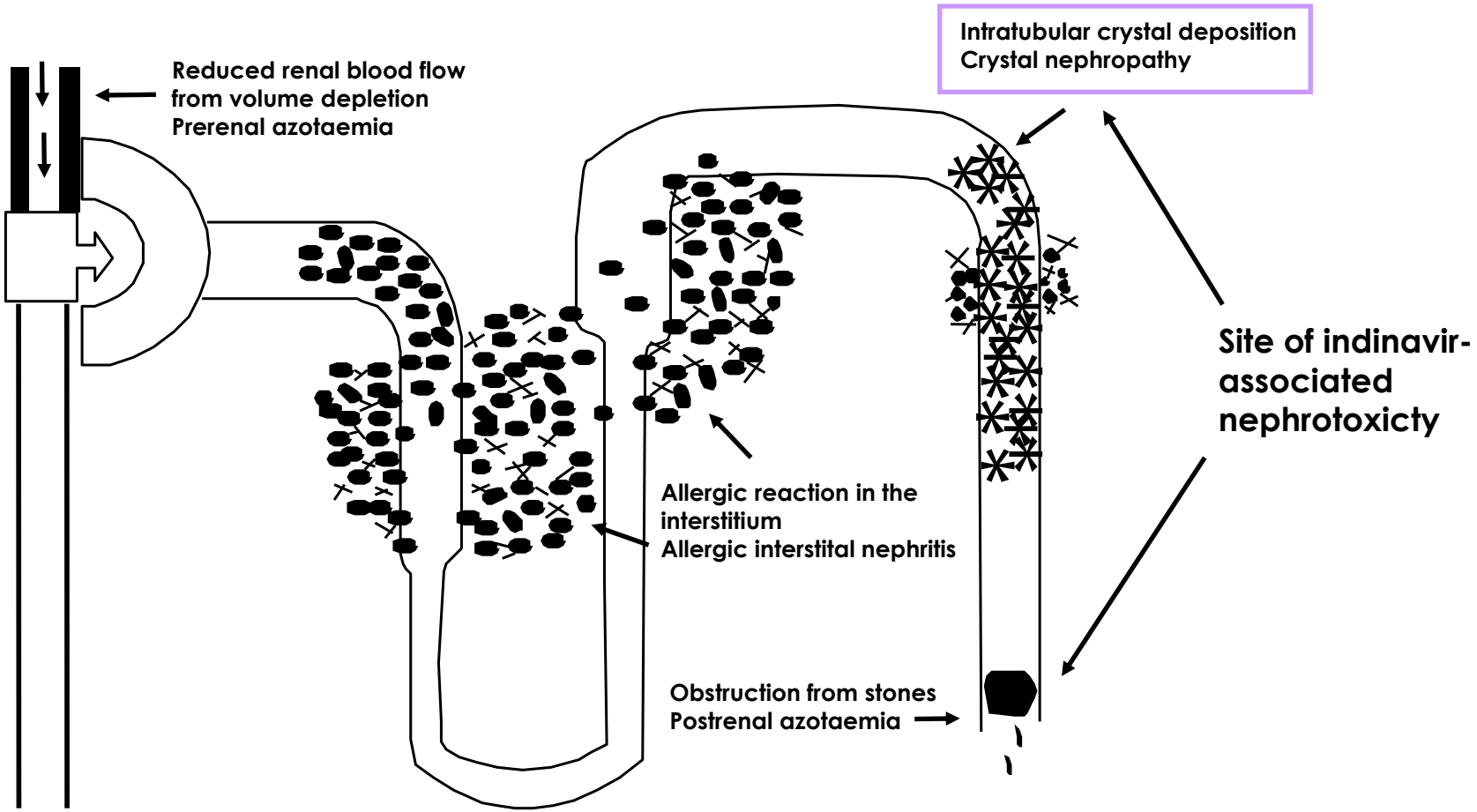
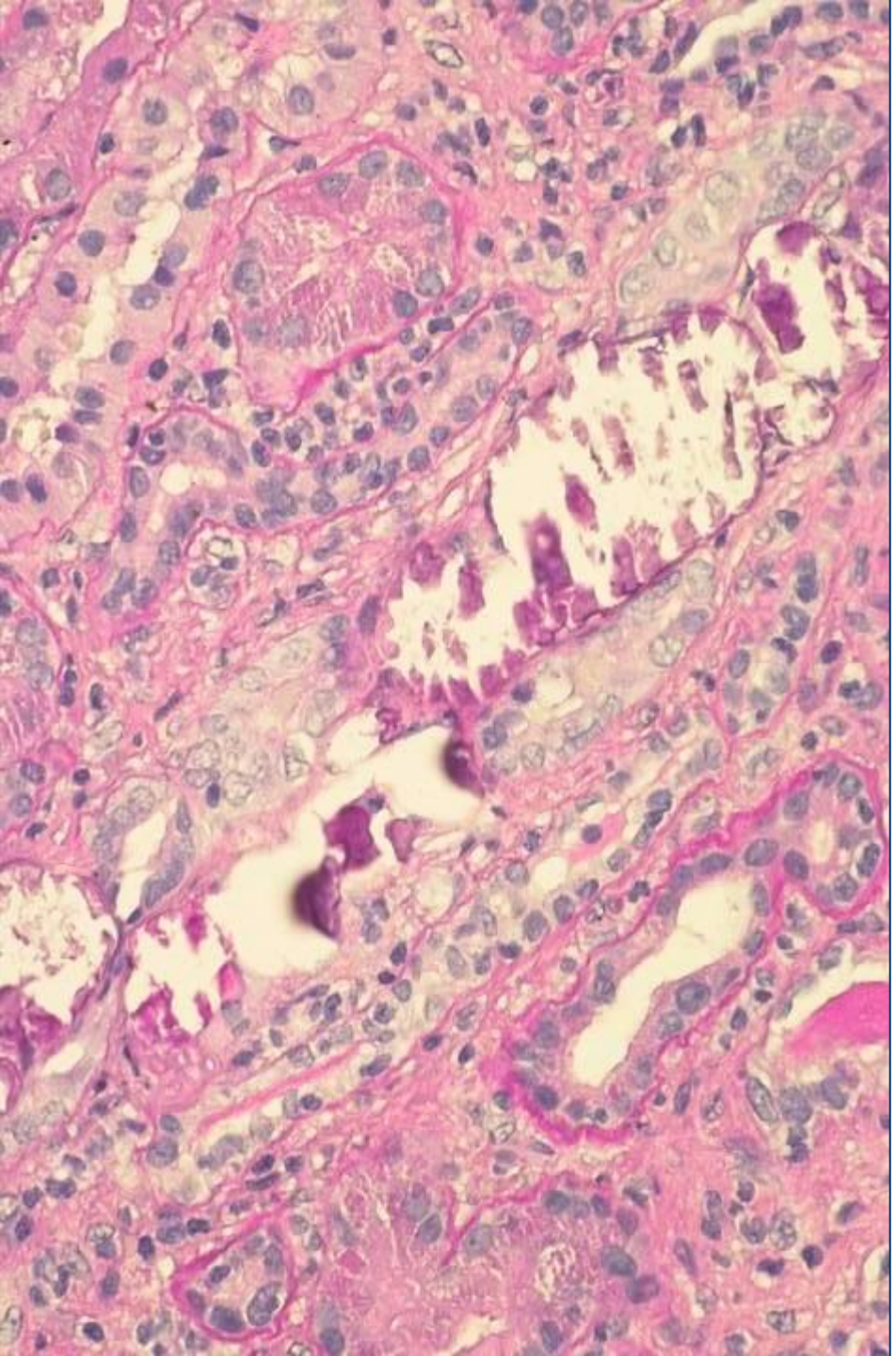


Illustration adapted from: Reilly RF & Perazella M. Nephrology in 30 days. McGraw-Hill, 2005



ATV/r and nephrolithiasis

- Cases of nephrolithiasis were reported during post-marketing surveillance in HIV-infected patients receiving ATV therapy[1]
  - As these adverse drug events are obtained voluntarily from a population of unknown size, the ability to make reliable estimates in frequency or establish a causal relationship with drug exposure is not always possible
  - Low overall prevalence in a retrospective case series published (< 1%)[2]
- Nephrolithiasis has been rarely reported in clinical trials
  - < 1% in CASTLE Study in both, ATV/r and LPV/r arms[3]
- The mechanism of the development of kidney stones composed of ATV or ATV metabolites in patients receiving ATV is unknown[2]
  - ATV is metabolised and excreted mainly through the liver
  - Stone composition analysis has not consistently reported presence of ATV

1. Chan-Tack et al. AIDS 2007;21:1215–8. 2. Couzigou et al. Clin Infect Dis. 2007;45:e105.
3. Molina et al. J Acquir Immune Defic Syndr 2010;53:323–32.

PIs and nephrolithiasis

PI	Nephrotoxicity	References
IDV	Urolithiasis, interstitial nephritis, acute renal failure, papillary necrosis, nephrogenic DI	Gagnon et al. 2000; Kopp et al. 1997; Balani et al. 1995; Dieleman et al. 2002; Sarcletti et al. 2000; Van Rossum et al. 2002; Kopp et al. 2002; Dieleman et al. 2001; Hanabusa et al. 1999.
NFV	Urolithiasis	Engeler et al. 2002
APV	Urolithiasis	Feicke et al. 2008
SQV	Urolithiasis	Green et al. 1998
LPV/r	Urolithiasis	Doco-Lecompte et al. 2004
ATV	Urolithiasis, AIN	Chang 2006; Pacanowski et al. 2006
DRV	Urolithiasis	Rockwood N, et al. 2011[1]

Adapted from Jao et al. Adv Chronic Kidney Dis 2010;17:72–82. 1. Rockwood et al. IAS 2011: abstract TUPE249.

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Journal of Antimicrobial Chemotherapy

High levels of atazanavir and darunavir in urine and crystalluria in asymptomatic patients

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[1]Infectious Diseases Department, St Louis Hospital, APHP and Sorbonne Paris Cité, University Paris Diderot, Paris, France; [2]Biochemistry Department, Tenon Hospital, University Pierre et Marie Curie, Paris, France; [3]Biostatistics Department, St Louis Hospital, APHP and Sorbonne Paris Cité, University Paris Diderot, Paris, France; [4]Pharmacology Department, St Louis Hospital, APHP and Sorbonne Paris Cité, University Paris Diderot, Paris, France; [5]INSERM U941, FR-75010 Paris, France

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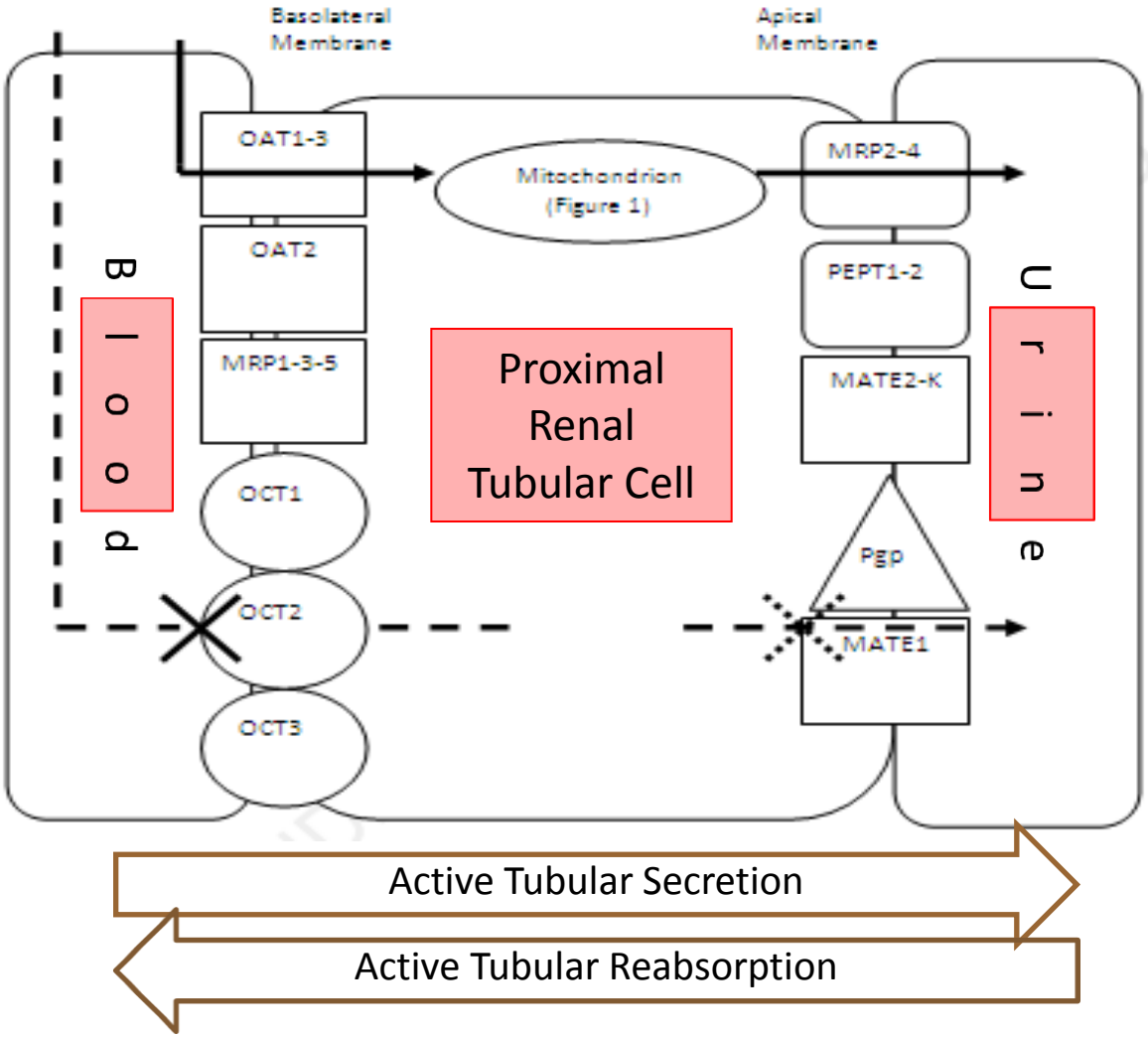
Objectives: Atazanavir has been associated with kidney stones and renal failure. We measured urine and plasma concentrations of recent protease inhibitors (PIs) and searched for PI crystals in the urine of asymptomatic patients.

Methods: A cross-sectional analysis of HIV-infected patients taking ritonavir-boosted atazanavir 300 mg/day (ATV300/r), unboosted atazanavir 400 mg/day (ATV400), ritonavir-boosted darunavir at either 800 mg/day (DRV800/r) or 1200 mg/day (DRV1200/r) or ritonavir-boosted lopinavir 800 mg/day was performed. Plasma and urine were collected and PI levels measured using HPLC. Crystals were detected and identified in urine using polarized microscopy.

Results: PI levels were measured in 266 patients, 142 of whom were assessed for urinary crystals. Their mean age was 46 years. The mean duration of HIV infection was 10.5 years and the mean duration of the current PI-containing regimen was 22.5 months. The mean CD4 cell count was 494 cells/mm^3; 74% showed controlled HIV replication. Median urinary PI levels were 22.3, 14.3, 26.9 and 29.7 mg/L for ATV300/r, ATV400, DRV800/r and DRV1200/r, respectively, significantly higher than plasma levels, which were all <5 mg/L ($P<0.001$). In contrast, median urinary lopinavir concentrrations did not significantly differ from plasma concentrations (4.2 and 6.4 mg/L, respectively; $P=0.7$) and were significantly lower than those of other PIs ($P<0.001$). Atazanavir crystals were found in 7/78 patients receiving ATV300/r (8.9%; 95% CI=2.6%–15.2%) and darunavir crystals were found in 4/51 patients receiving darunavir (7.8%; 95% CI=0.4%–15.2%). Longer exposure to atazanavir was the only risk factor associated with the presence of atazanavir crystalluria ($P=0.04$).

Conclusions: Unlike lopinavir, atazanavir and darunavir reached high concentrations in urine. Urinary crystals were found in a few patients receiving ritonavir-boosted atazanavir or darunavir and may favour nephrolithiasis.

Renal Tubular Transporters



Tenofovir

DTG inhibition

COB inhibition

Creatinine

OCT2:	Cimetidine
	Trimethoprim
	Quinidine
	Dolutegravir
OAT1-3:	Probenecid
PGP:	Quinidine
MATE-1:	Cimetidine
	Chloroquine
	Cobicistat

Urinary Creatinine is secreted by tubule at approximately 10% of total amount

Creatinine is an endogenous substrate of OCT2 (uptake in tubule cells)[1]

Creatinine efflux in urine seems mediated by MATE1 and MATE2-K[2]

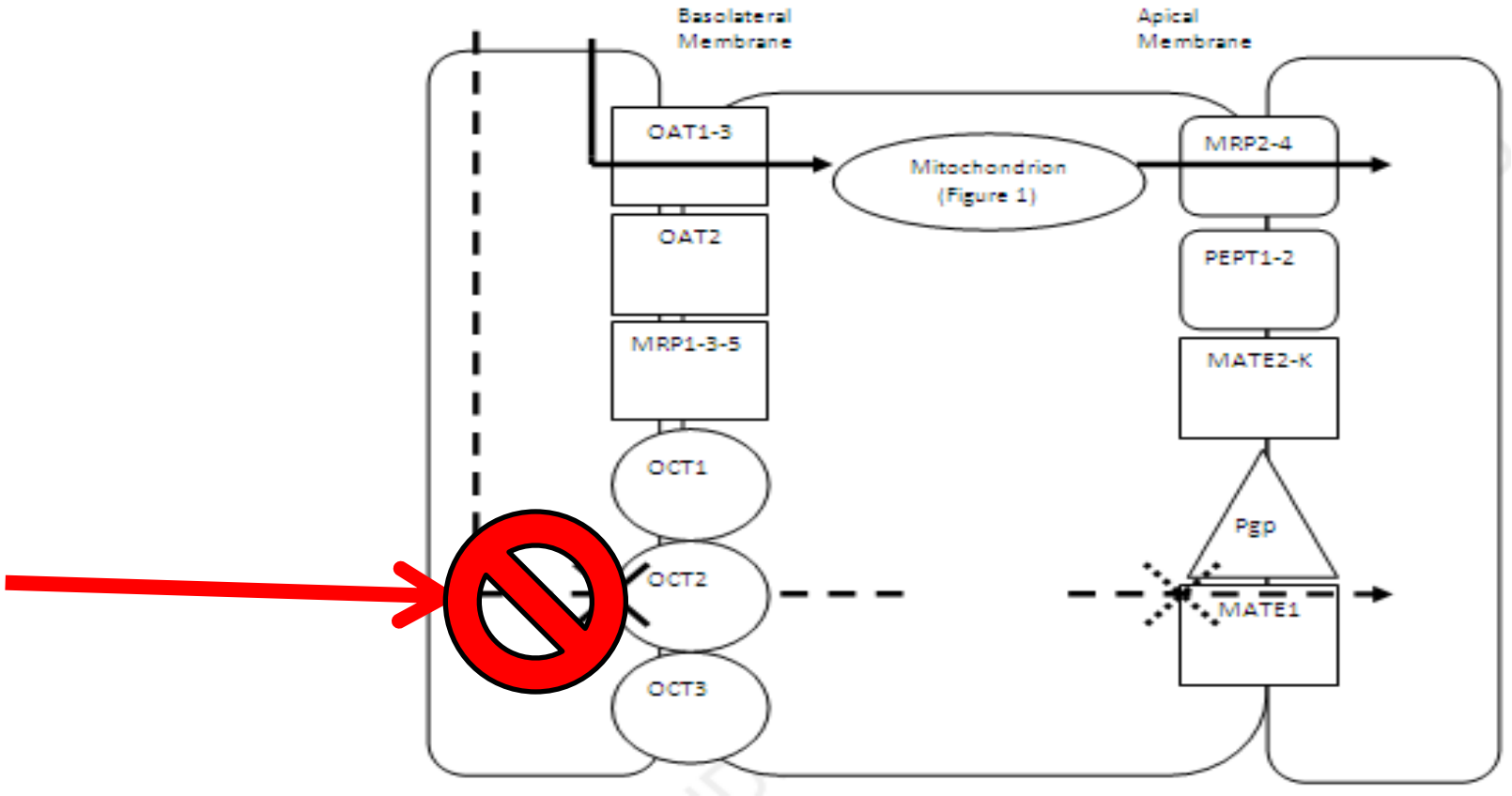
1.Urakami Yet al., Pharm Res 2004;21(6):976-981; 2. Imamura Y et al., Clin. Pharmacol. Ther 2001;89:81-88

Co-administration of cobicistat and tenofovir (Stribild) results in an increase of the AUC and Cmax of tenofovir between 25-30%, probably via an inhibitory effect on p-gp mediated transport of tenofovir in the gut.

In 2013 EMA has approved the use of this quad pill, with the warning of not use in patients with creatine clearance <70 ml/min per m^2.
It is recommended that Stribild is not initiated in patients with creatine clearance <90 ml/min per m^2 unless, after review of the available treatment options, it is considered the preferred treatment for the individual patient
[Stribild SPC – EMA 2013].

Recently, in a revision of ECHO and THRIVE studies, an inhibitory effect of rilpivirine on OCT2 system has been suggested

Cohen C. et al., AIDS 2013;27:939-950



eGFR formulas

1. **Cockroft-Gault** (estimated creatinine clearance):
   – (140 – Age) * body weight * 0.85 [*if female*] / 72 * SCr

2. **MDRD**:
   – $186 \times S\ Cr^{-1.154} * Age^{-0.203} * 0{,}742$ [*if female*] *1,21 [*if black*]

3. **CKD-EPI**[†]:
   – $141 * \min(SCr/\kappa, 1)^{\alpha} * \max(SCr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [*if female*] * 1.159 [*if black*]

   – κ = 0.7 *female*; 0.9 *male*
   – α = - 0.329 *female* - 0.411 *male*

[†]The Scr should be measured with a IDMS traceable method

1. Cockcroft DW, Gault MH Nephron 1976;16(1):31-34
2. Levey AS et al. Ann Intern Med 1999;130:461-

Assessment of proteinuria

- Dipstick (screening)(0 – 4+, 0 - > 300 mg/dl)
- Quantitative total proteins on collected urine (g/24 hr)
    - Normal < 0.3 g/24 hr
- Protein/Creatinine ratio (PCR) on spot urine sample
    - Normal < 0.2 g/g
- Albumin/Creatinine ratio (ACR) on spot urine sample
    - Normal < 30 mg/g

NKF - Am J Kidney Dis, 2002;39(2) Suppl 1:S76-S110

Quality of proteinuria

- **Glomerular Proteinuria** : mainly represented by albumin

- **Tubular Proteinuria** : a few albumin, but other low molecular weight proteins

Renal Complications in HIV Disease: Between Present and Future

Qualitative assessment for risk of kidney disease

- Race
- Family history of kidney disease
- CD4+ lymphocyte count*
- HIV RNA level*
- History of use of nephrotoxic drugs
- Comorbidities*
  - Diabetes mellitus
  - Hypertension
  - Hepatitis coinfection

Screening at diagnosis

- Proteinuria
  [dipstick in morning urine sample] — abnormal values ≥ 1+
- Hematuria
  [dipstick in morning urine sample]
- Serum creatinine
  [estimate creatinine clearance or eGFR calculation with appropriate formula†]
- Serum Phosphate — abnormal value < 2.5 mg/dl

Maggi P et al., AIDS Reviews. 2012:14:37-53

Renal Complications in HIV Disease: Between Present and Future

Abnormal values

- Proteinuria
  Evaluation of spot urine protein/creatinine ratio [uP/uCr] or 24h urine. If confirmed refer to nephrologist for evaluation
- Hematuria
  refer to nephrologist for evaluation
- eGFR < 69 ml/min/1.73 m^2
  monitor every 3-4 months
- eGFR < 60 ml/min/1.73 m^2
  refer to nephrologist for evaluation
- eGFR declining over time
  refer to a nephrologist for evaluation
- Serum phosphate < 2.5 mg/dl
  refer to nephrologist for evaluation

If eGFR < 80 ml/min/1.73m^2 adjust drug dosage, accordingly with table 2

Normal values

- Monitor annually in ART-naive patients
- Repeat before starting ART, after 4 weeks and monitor annually
- If TDF-based ART: after 2, 4 and 12 weeks, then monitor every 6 months

Maggi P et al., AIDS Reviews. 2012:14:37-53

Health professionals need to cooperate, communicate, and integrate care in teams to ensure that care is continuous and reliable

Institute of Medicine (2003). Health Professions Education: A Bridge to Quality