Management and Prevention of Co-morbidities

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HMRG
HIV Molecular Research Group

Scoil an Leighis agus Eolaíocht An Leighis UCD

Disclosures

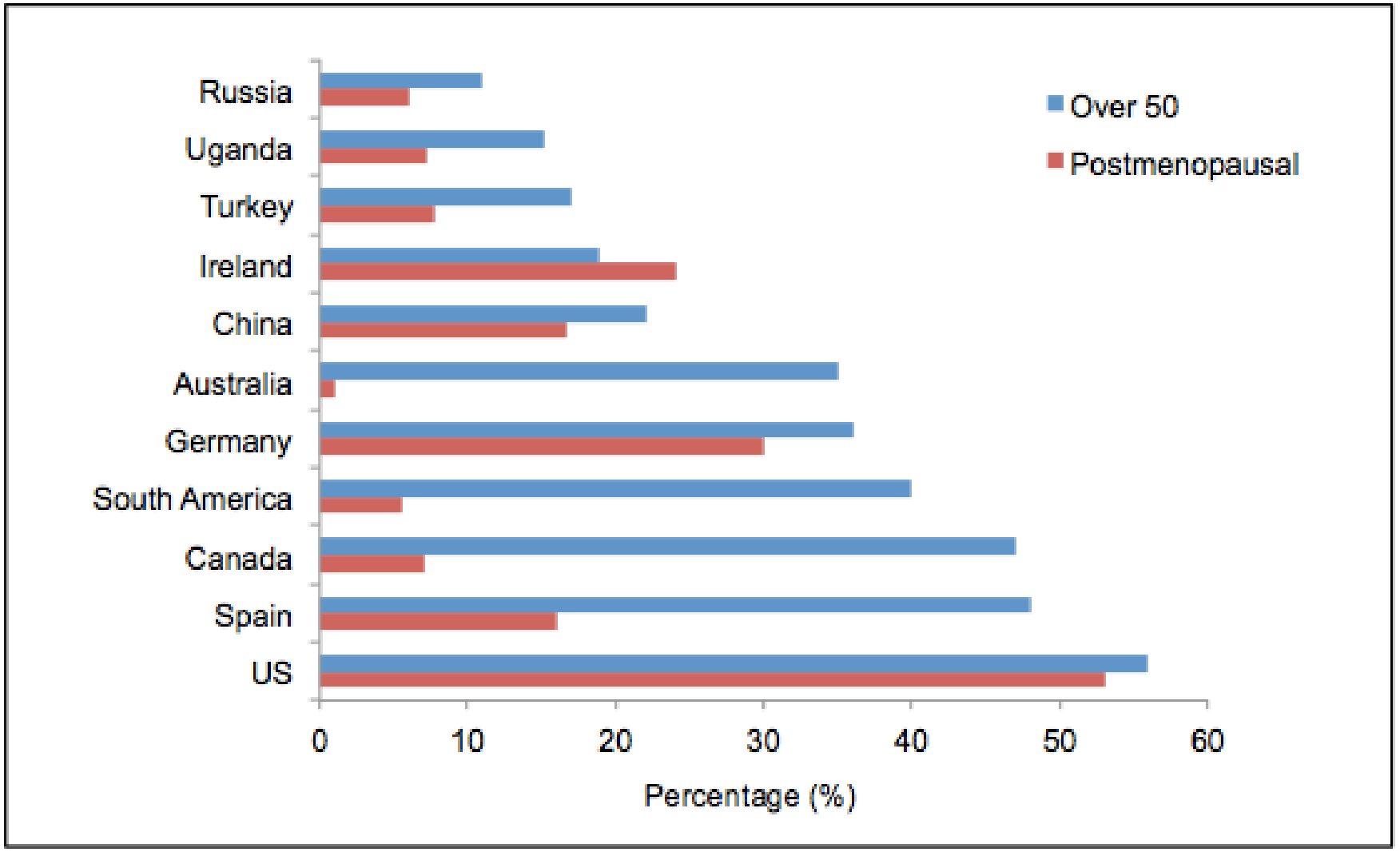
Speaker Bureau / Honoraria:

ViiV Healthcare, Merck Sharpe and Dohme, Gilead, Janssen Cilag (Tibotec), Bristol Myers Squibb

Research funding / educational grants:

- GlaxoSmithKline
- Gilead Sciences
- Bristol Myers Squibb
- Janssen Cilag (Tibotec)
- Merck Sharpe and Dohme
- Science Foundation Ireland
- Health Research Board (Ireland)
- Molecular Medicine Ireland
- Wellcome Trust
- NIH

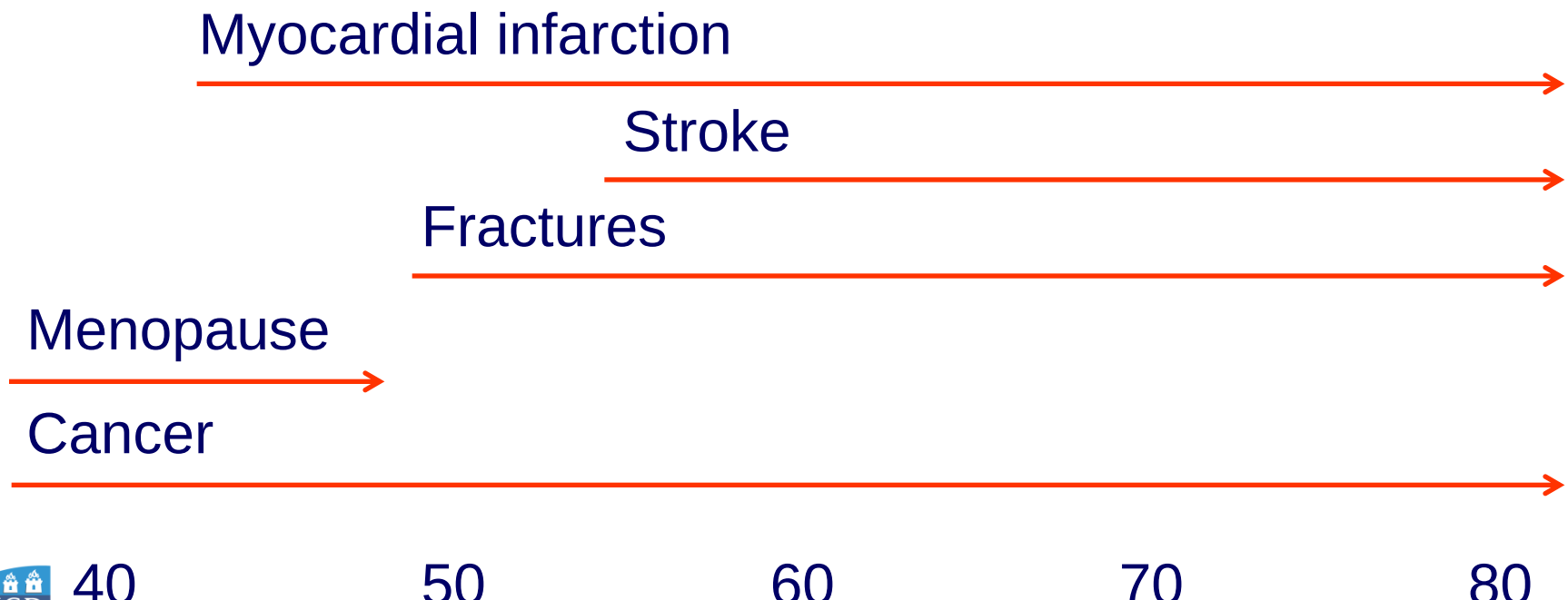
Ageing and HIV



Alvarez-Barco E et al. Curr Opin HIV AIDS. 2016.

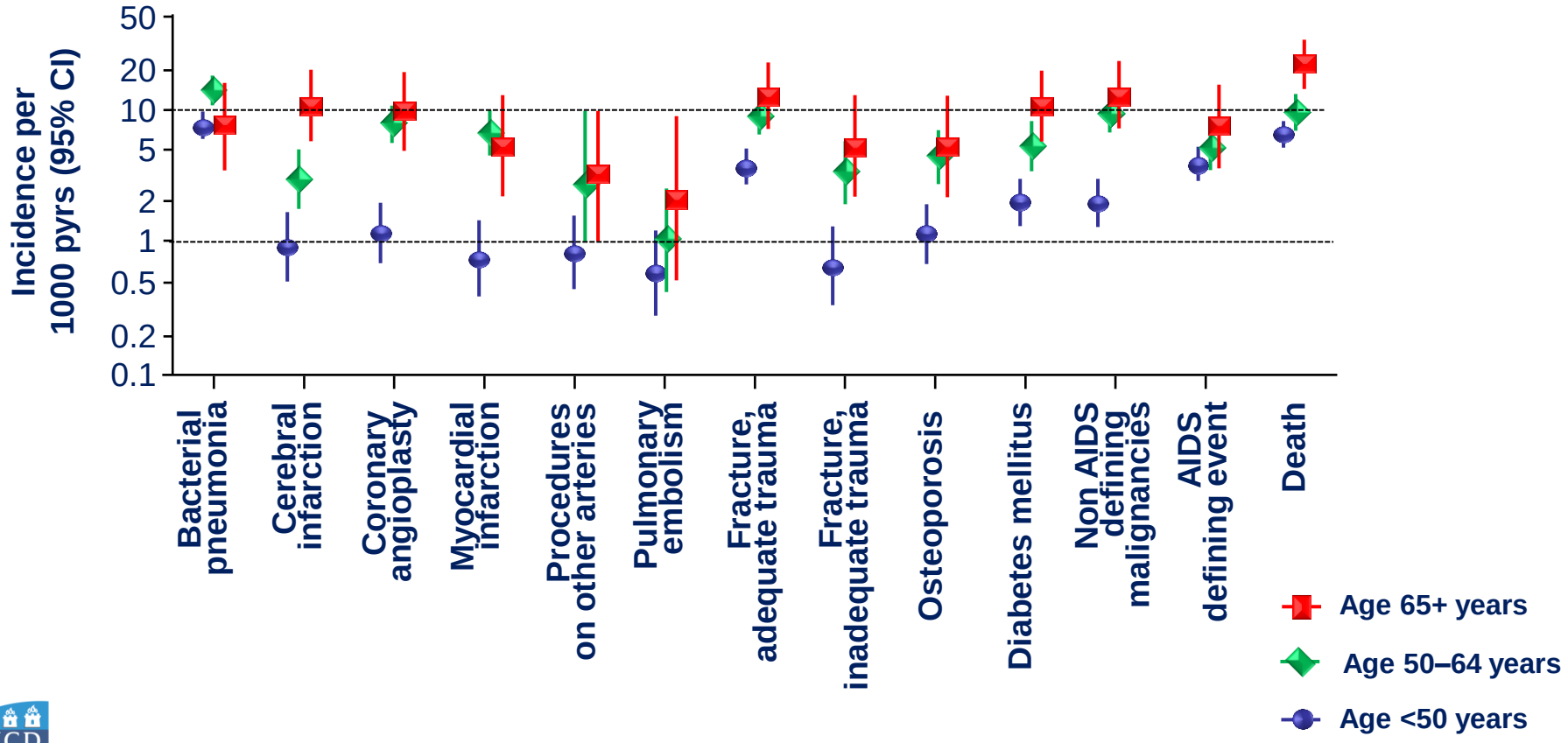
Health challenges arising from ageing

…immune dysfunction – ‘premature ageing’
…end-organ dysfunction (renal / liver / bone)
…polypharmacy…
…socioeconomic factors….retirement…unemployment



Ageing with HIV: Clinical consequences

Swiss HIV Cohort Study: Incidence of clinical events between January 1, 2008, and June 30, 2010 stratified by age



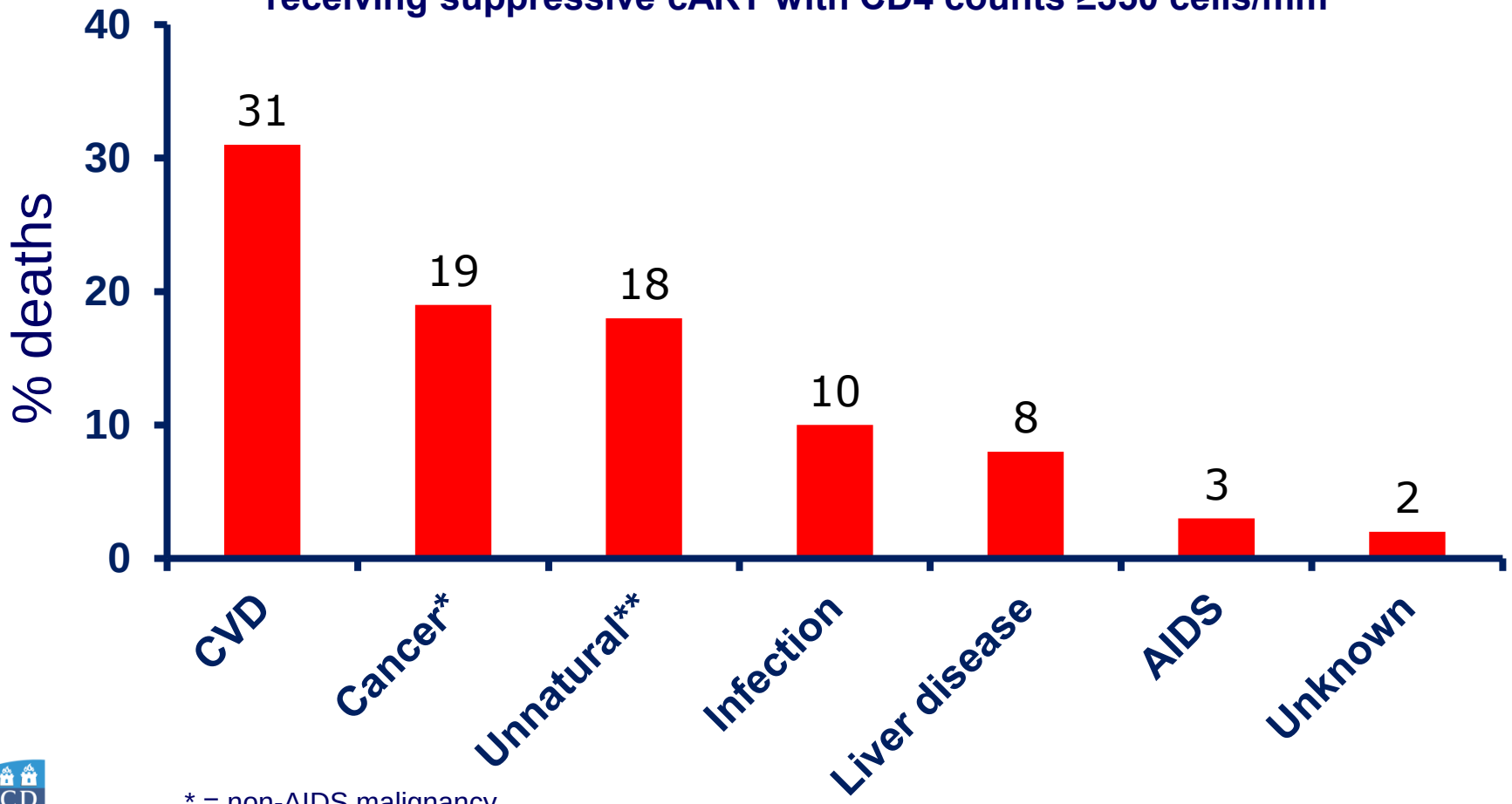
CI, confidence interval; pyrs, person-years

Adapted from Hasse B, et al. Clin Infect Dis 2011;53(11):1130-1139.

Mortality in treated HIV

Causes of death in a **successfully ART-treated** population:

SMART/ESPRIT: causes of death in N=3,280 HIV-infected persons receiving suppressive cART with CD4 counts ≥350 cells/mm^3



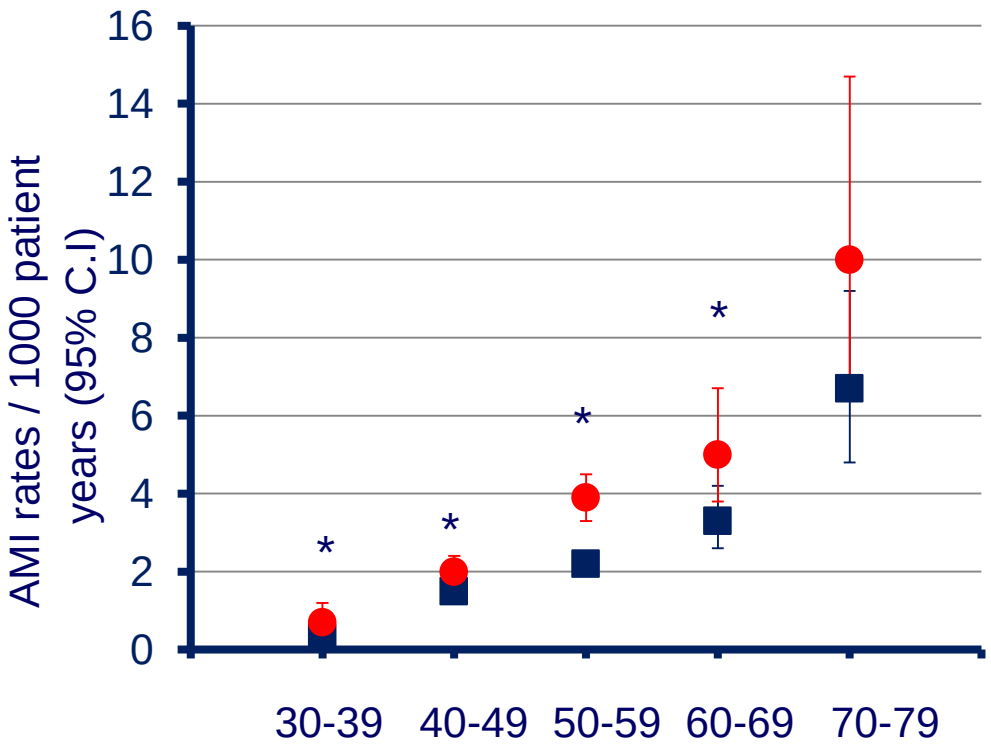
* = non-AIDS malignancy

** = accident, suicide or violent death

Rodger A. et al. CROI 2012. Abstract 638.

HIV and CVD – incidence of MI

AMI is more common in HIV-positive than HIV-negative populations[1]

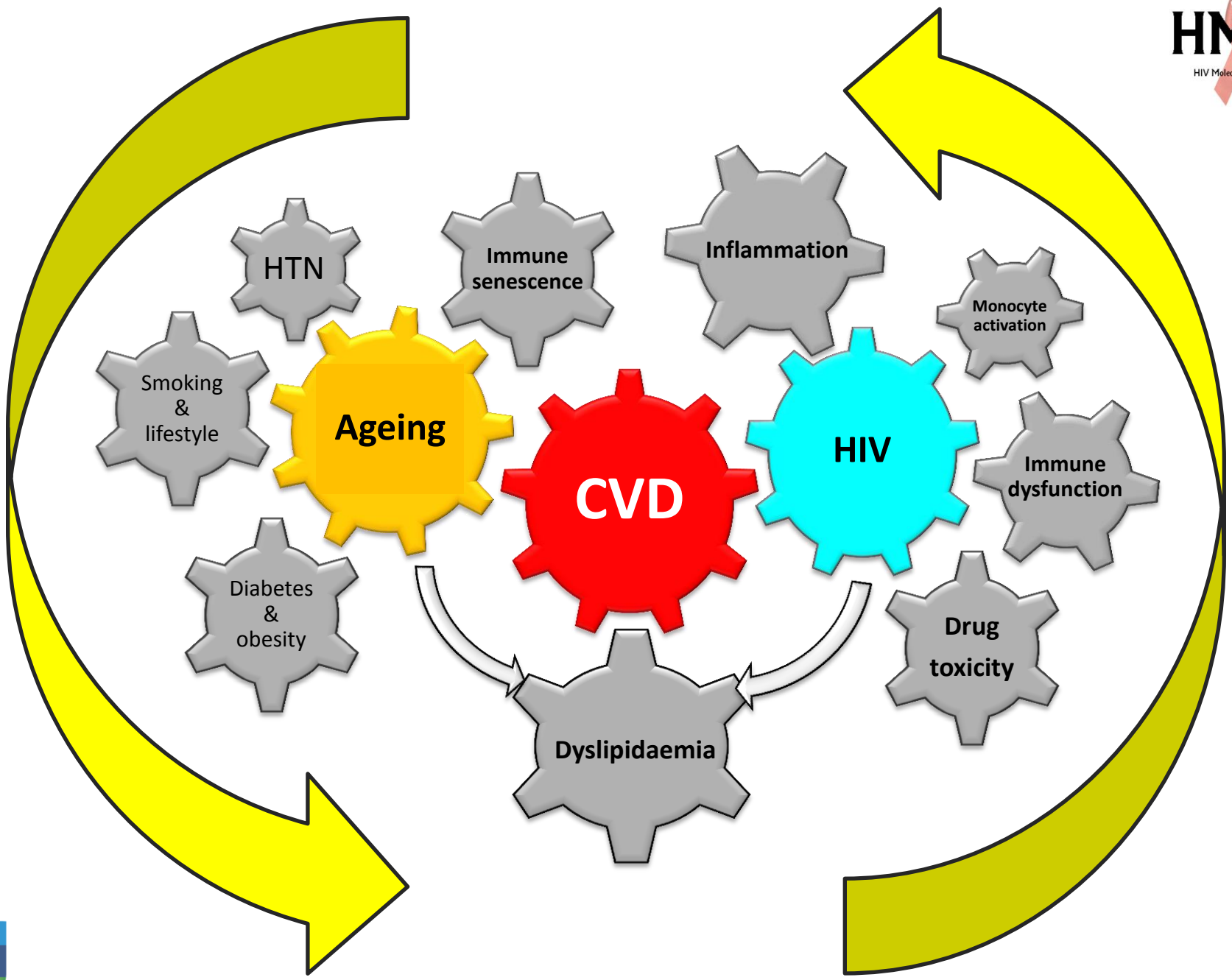


AMI=acute myocardial infarction; CI=confidence interval.

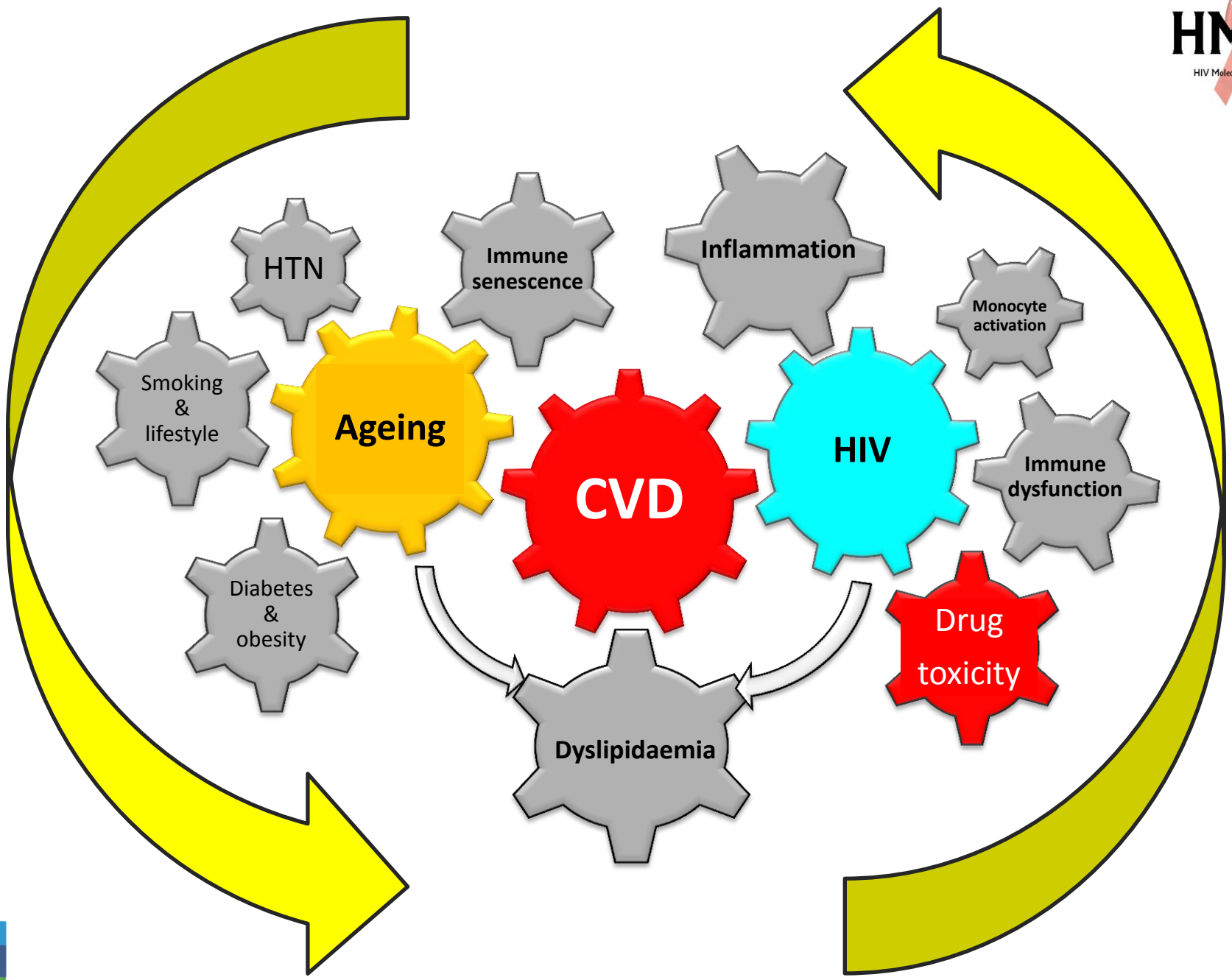
* Within age group P<0.05

RR of MI with age not different between HIV and the general population risk estimates[2]

1. Freiberg MS, et al. JAMA Int Med. 2013; 173(8):614-22, 2. Petoumenoa K et al. HIV Med 2014. May 19.



J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034



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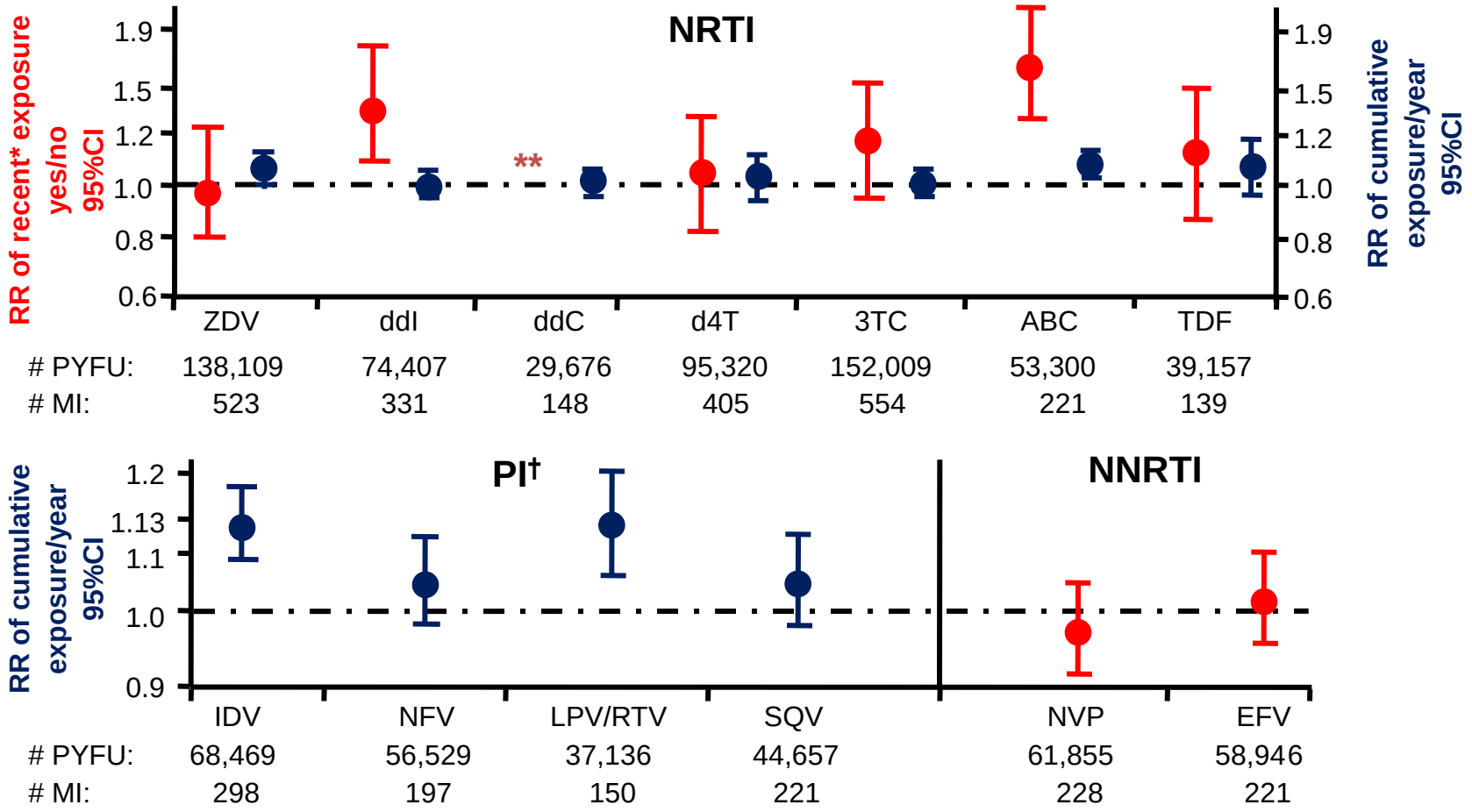
J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

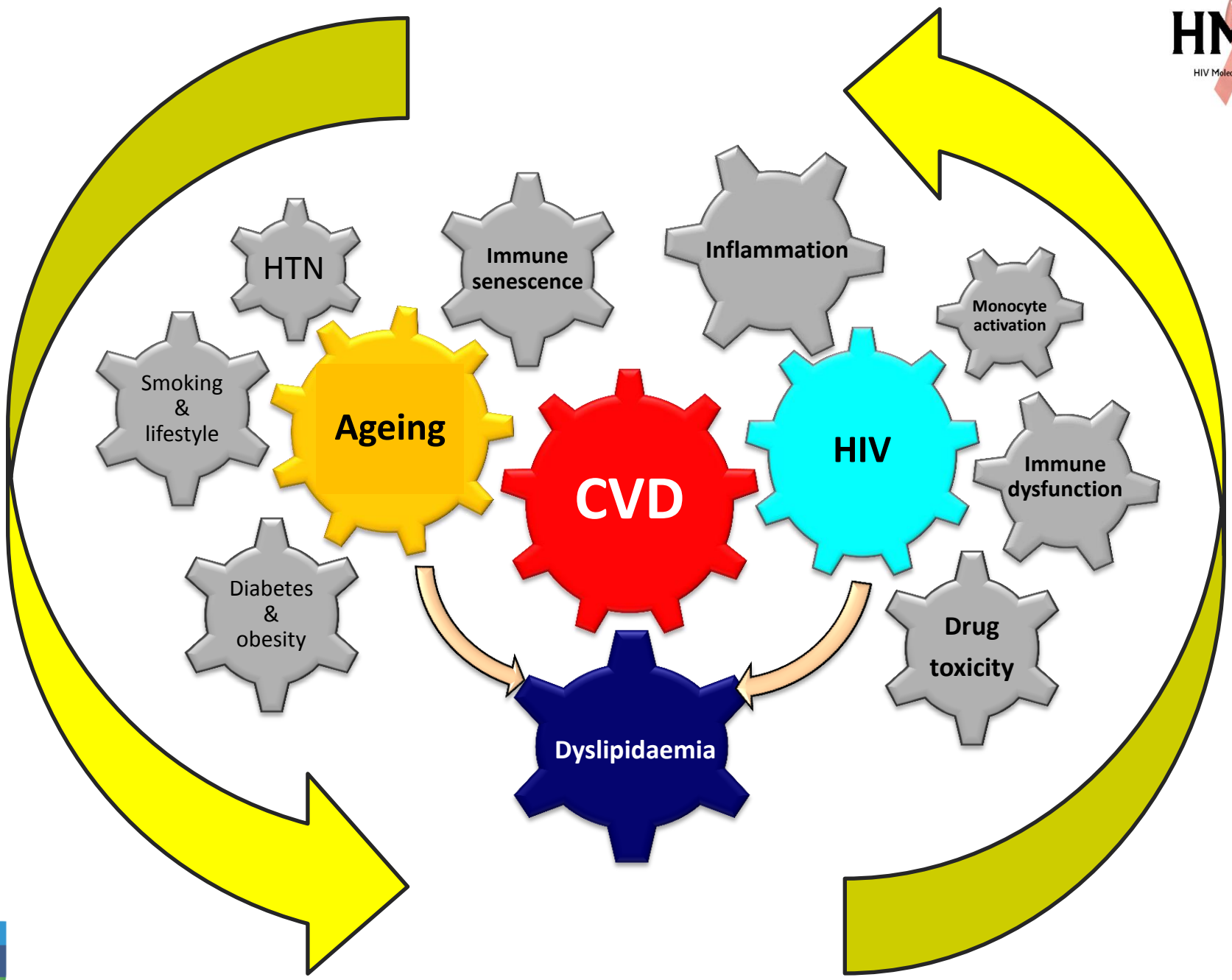
Cardiovascular events: do drugs matter?

D.A.D: MI risk is associated with **recent** and/or **cumulative** exposure to specific NRTIs and PIs



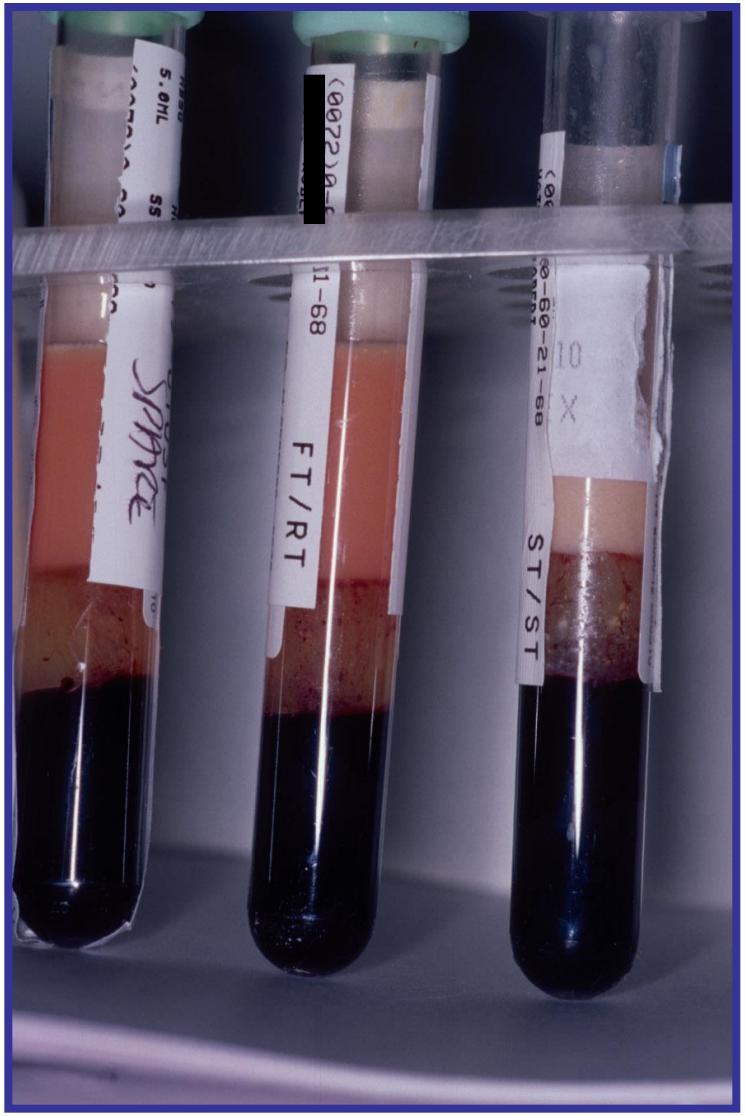
*Current or within past 6 months; †Approximate test for heterogeneity: P=0.02; **not shown owing to low number of patients receiving ddC.
CVD=cardiovascular disease; MI=myocardial infarction; RR=relative risk; PYFU=patient years of follow up.

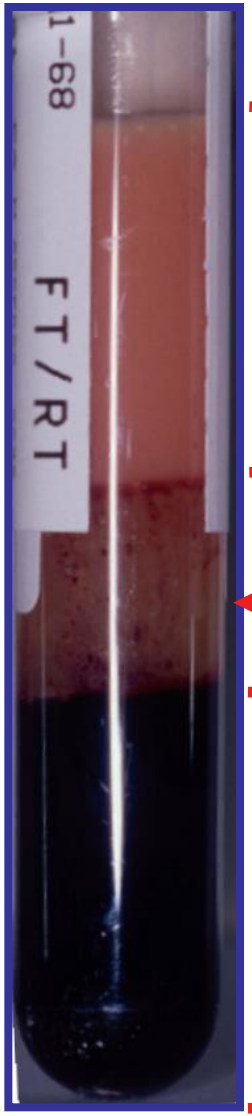
Adapted from Lundgren JD, et al. CROI 2009. Oral presentation 44LB.



J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

Dyslipidaemia – the '*legacy*'





Plasma

Gel

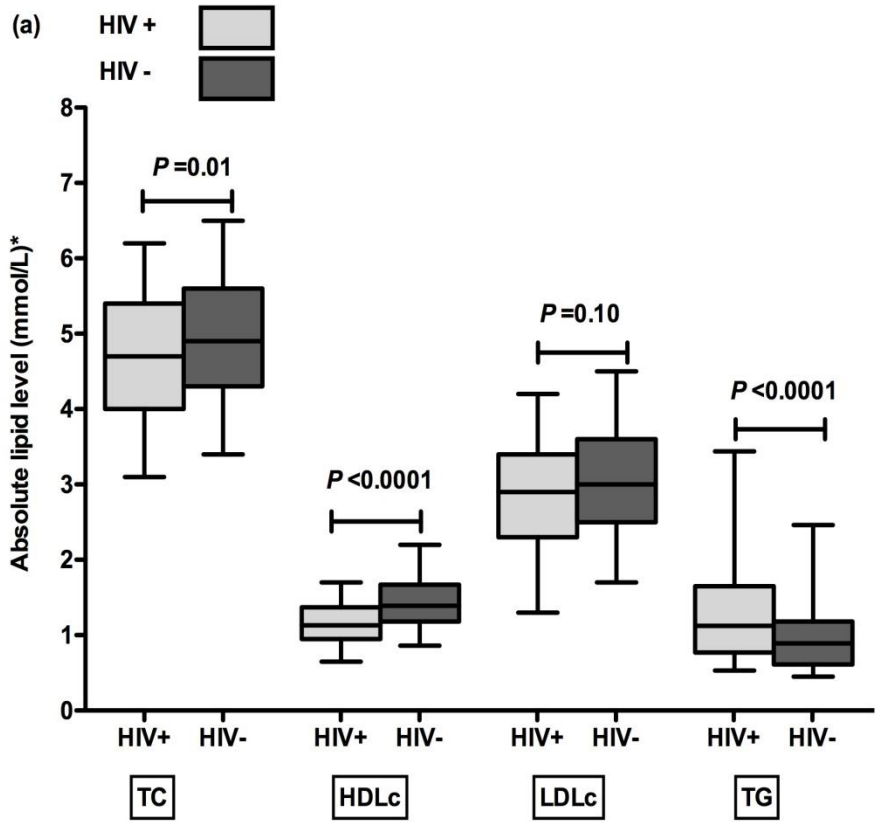
Cells

Cholesterol 19mmol/L

Triglycerides 94.4mmol/L

Dyslipidaemia in HIV UPBEAT

	HIV- (N=259)	HIV+ (N=190)	P
Age	41 (34, 48)	38 (33, 46)	0.08
Male gender	42.9%	61.6%	<0.0001
Smokers	36.3%	16.2%	0.0001

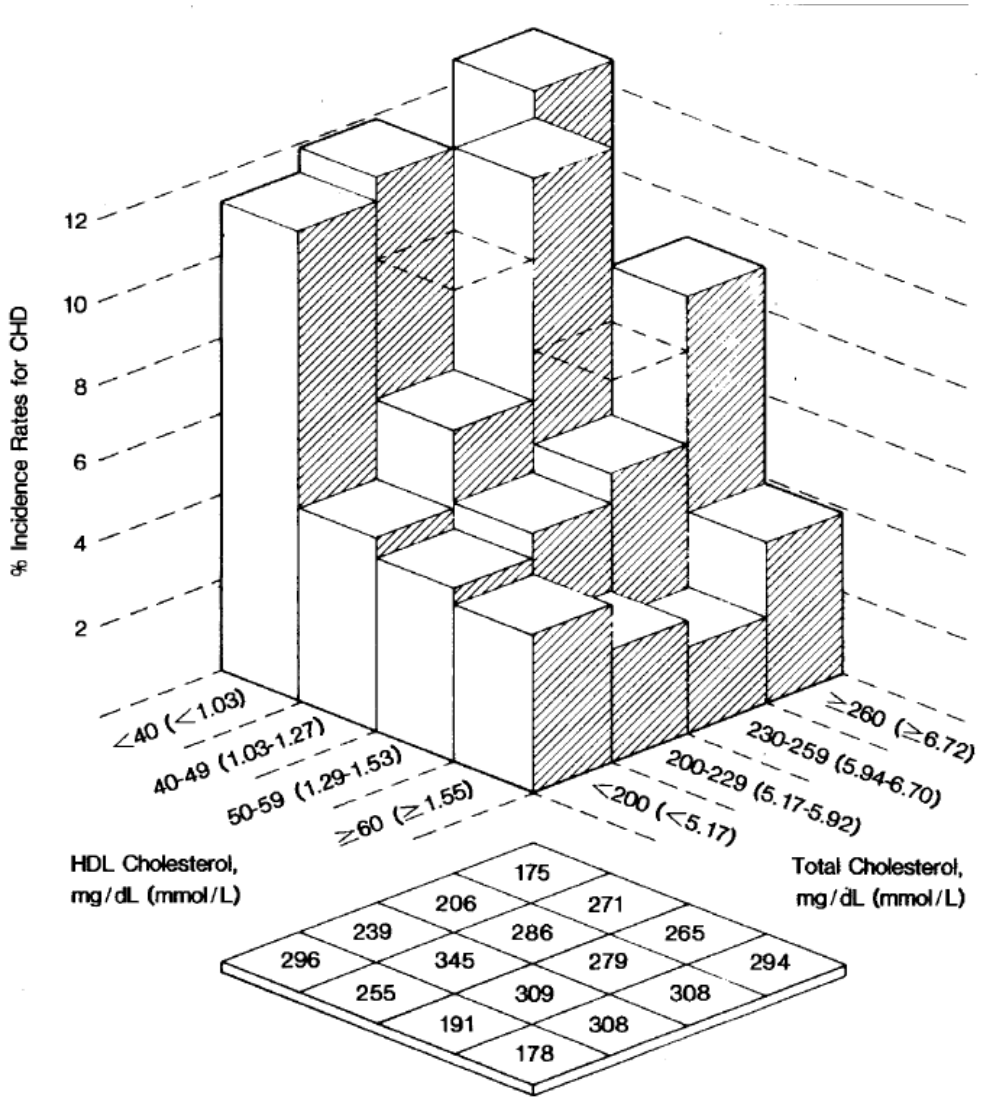


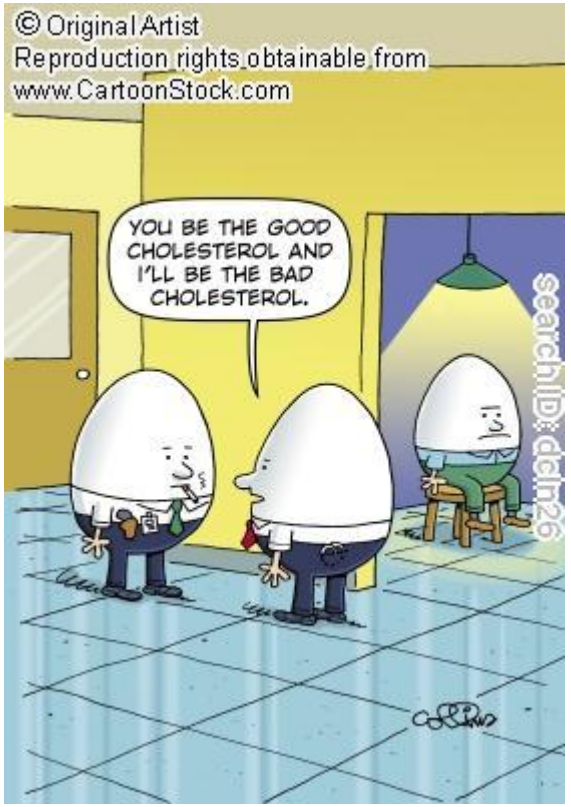
Differences in HDL and TG, but not LDL, remained significant in fully adjusted analyses

	HDL <1mmol/L*
HIV+	35.2%
HIV-	11.4%

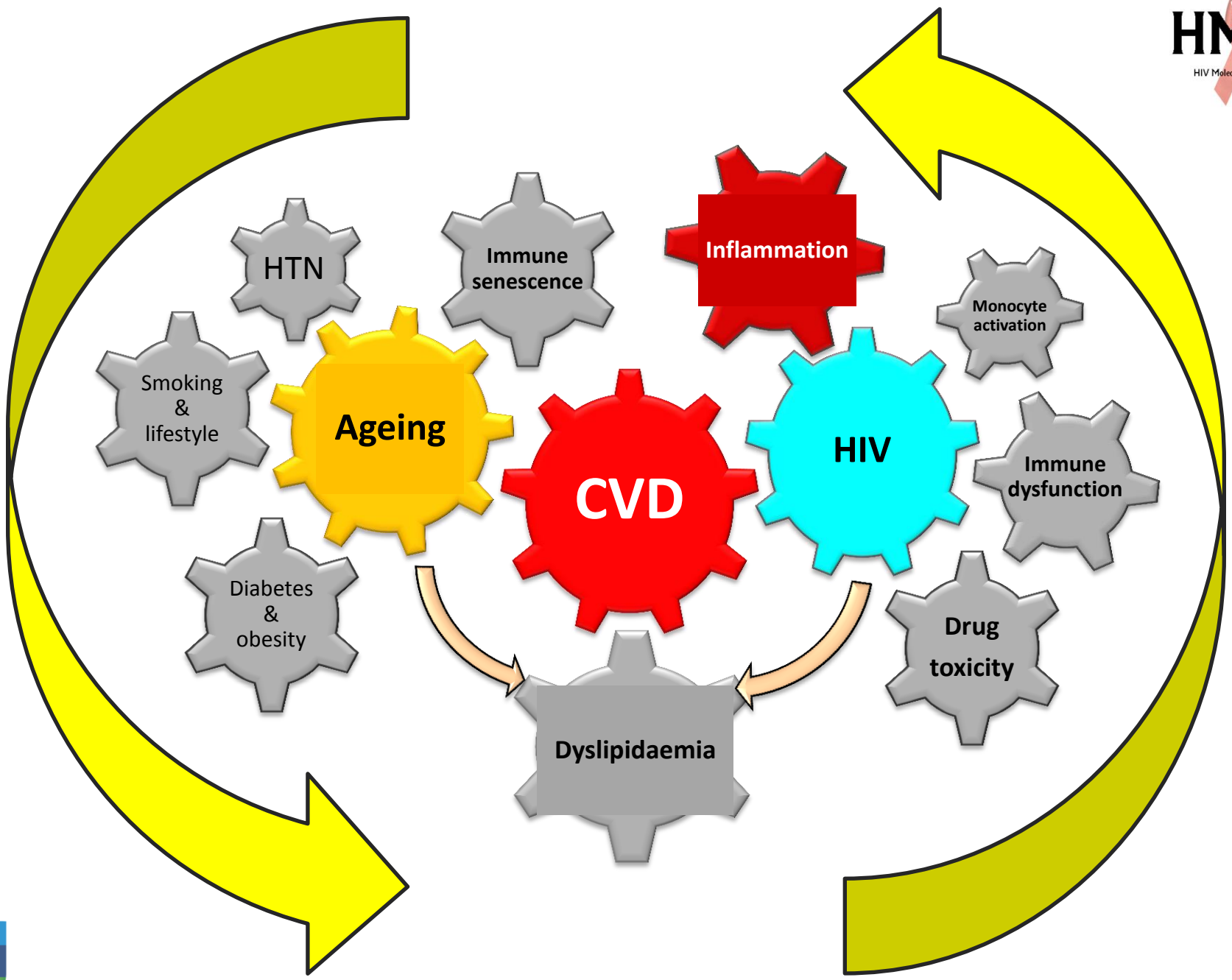
(P<0.0001) (*<40mg/dl)

HDL – *'good cholesterol'*



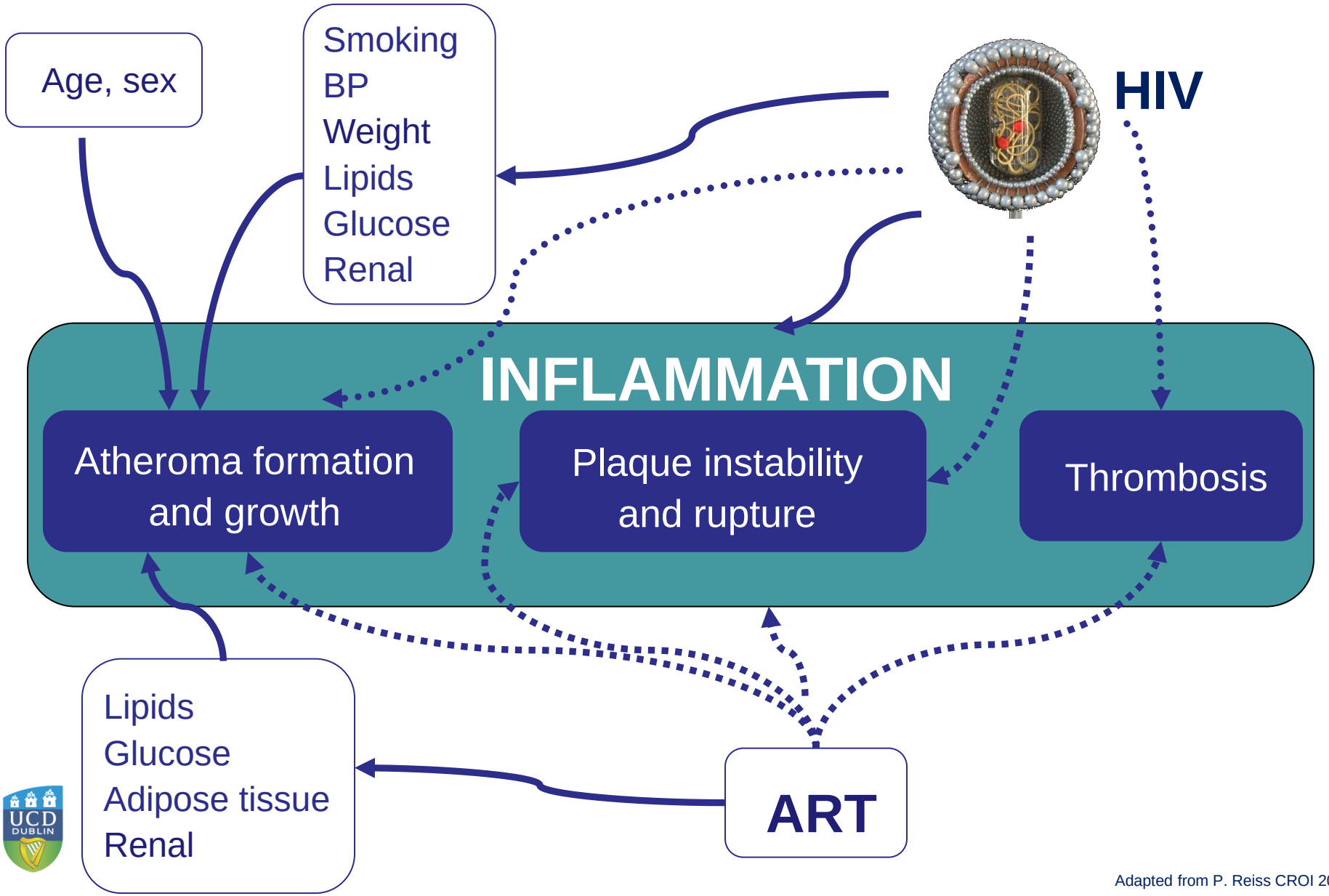


Castelli et al. JAMA 1986;256:2835-2838



J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

MI in HIV



Adapted from P. Reiss CROI 2009

Effect of initiating antiretroviral therapy on markers of monocyte activation, endothelial dysfunction and platelet activation in HIV-1 infection

JA O'Halloran[1, 2], E Dunne[3], MMP Gurwith[1], JS Lambert[1, 2], GJ Sheehan[2], ER Feeney[1], A Pozniak[4], P Reiss[5], D Kenny[3], PWG Mallon[1, 2]

[1]HIV Molecular Research Group, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland
[2]Department of Infectious Diseases, Mater Misericordiae University Hospital, Dublin, Ireland
[3]Cardiovascular Biology Group, Royal College of Surgeons in Ireland, Dublin, Ireland
[4] HIV Directorate, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom
[5] University of Amsterdam, Academic Medical Center, Department of Global Health and Stichting HIV Monitoring, Amsterdam, Netherlands

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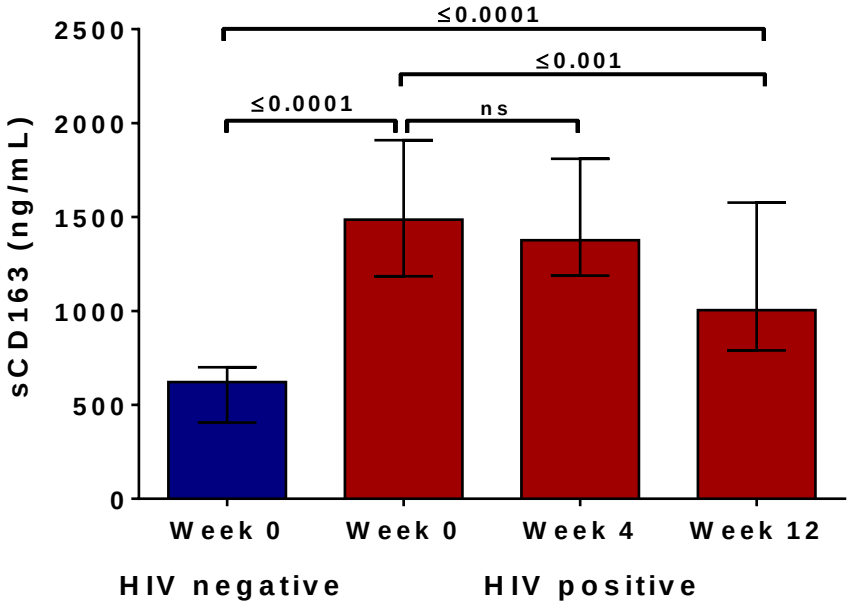
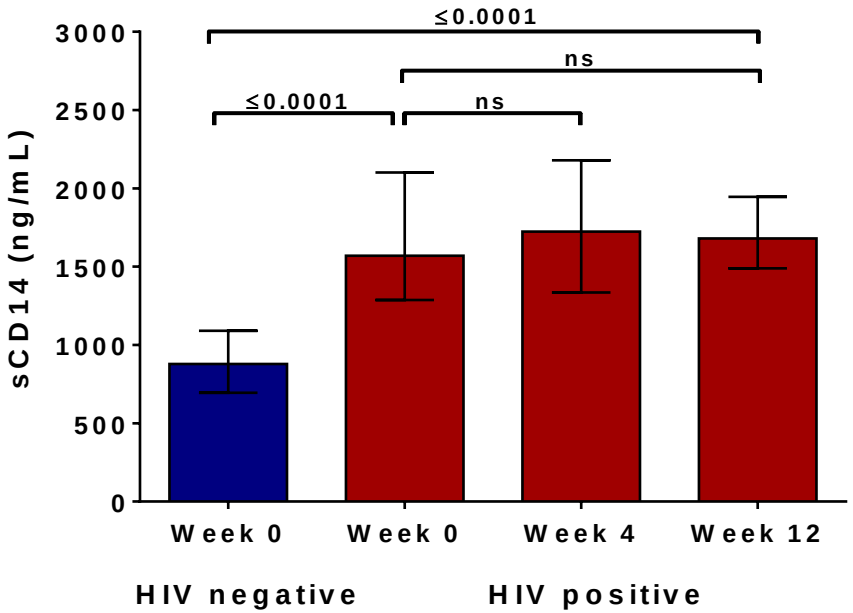
Markers of monocyte activation

- Both sCD14 & sCD163 were significantly higher in untreated HIV+ subjects compared to HIV- controls
- ART initiation resulted in significant reductions in sCD163
- No effect on sCD14 with ART initiation

sCD163 baseline comparison and post ART initiation in HIV



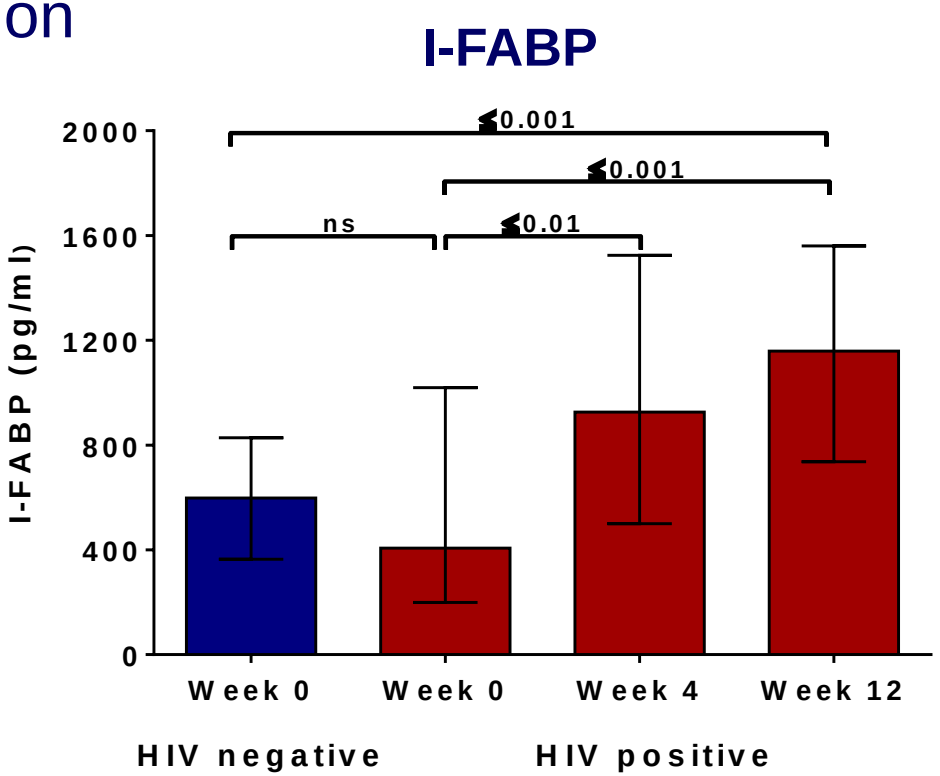
sCD14 baseline comparison and post ART initiation in HIV



O'Halloran J et al. *HIV Med*. 2015 Jun 25. doi: 10.1111/hiv.12270

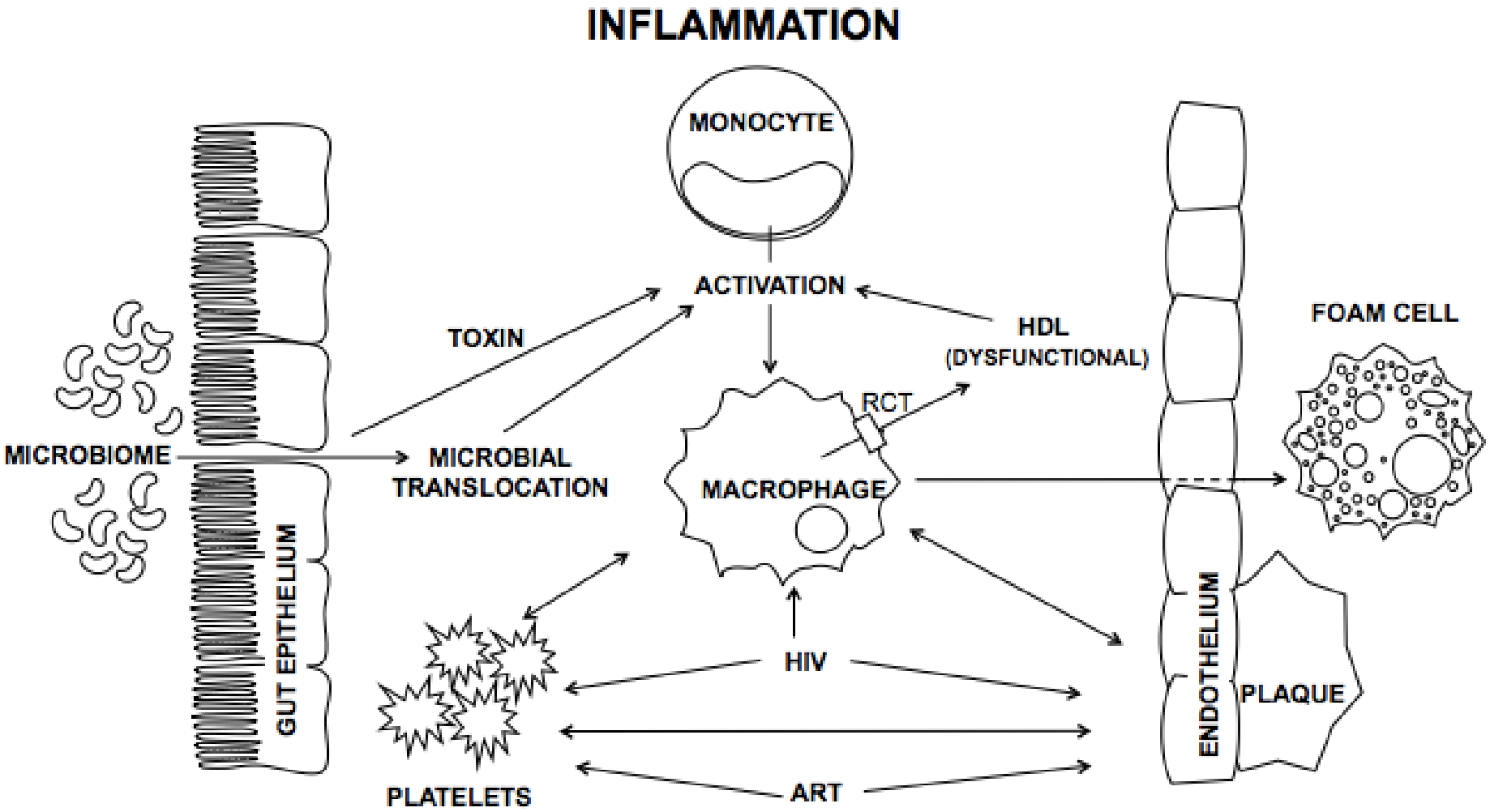
Marker of gut epithelial barrier dysfunction

- To explore persistent elevatations in sCD14 despite ART
- Measured I-FABP – measure of microbial gut translocation
- No significant between-group difference in pre-ART I-FABP
- I-FABP significantly increased, rather than decreased post ART initiation



O'Halloran J et al. HIV Medicine *HIV Med*. 2015 Jun 25. doi: 10.1111/hiv.12270

HIV and '*Inflammaging*'



Future research to understand risk

Randomized Trial to Prevent Vascular Events in HIV

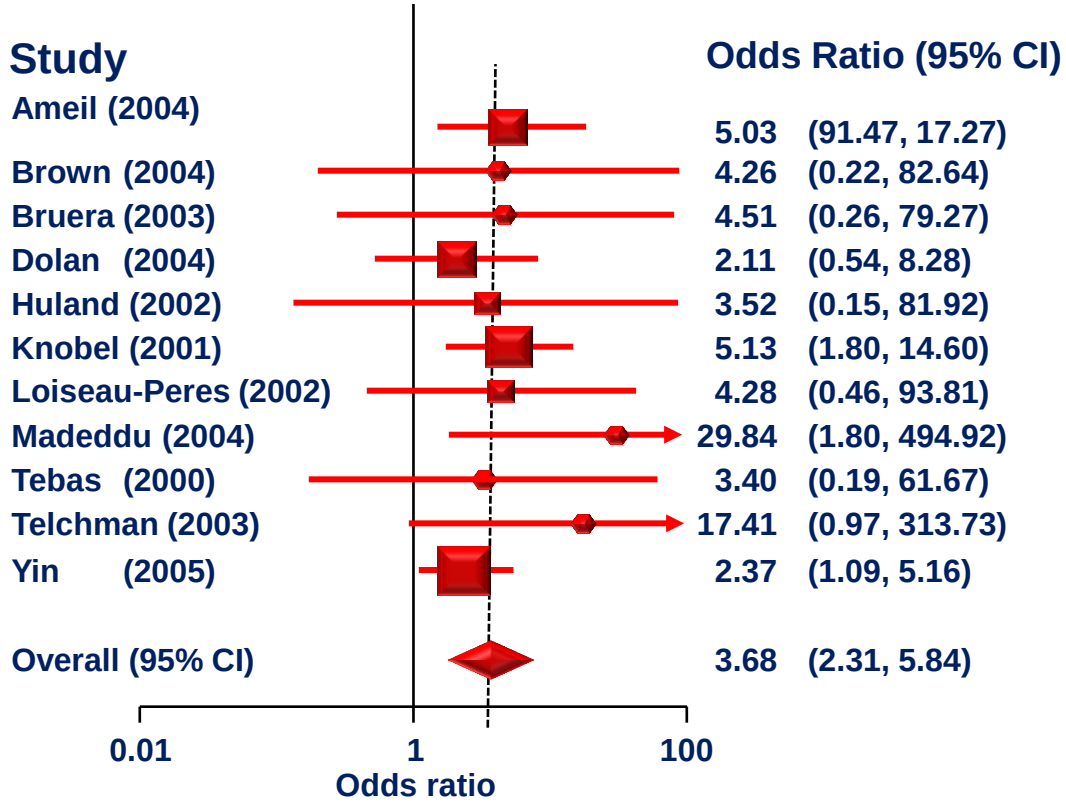
'Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults'

- NHLBI / NIAID 'A5332'
- Pitavastatin 4mg vs placebo
- *N*=6,500, HIV+ on ART, age >40 yrs, ASCVD risk <7.5%
- 1º endpoint time to CVD event
- 2º endpoints include non-calcified plaque, inflammation (sCD163)

http://reprievetrial.org/overview/ https://clinicaltrials.gov/ct2/show/NCT02344290
Accessed Sept 2015

Bone disease and HIV – role of inflammation

Meta-analysis: Prevalence of osteoporosis in HIV-infected patients is > 3.5 times greater than in uninfected controls[1]



- Decrease in BMD more pronounced with PI-containing regimens (LPV/r or IDV/r) compared with regimens consisting of an NNRTI and two NRTIs[2]
- Specific association between NRTIs, especially TDF, and Fanconi syndrome[3]

Odds ratio = odds of osteoporosis (T-score ≤ -2.5) in HIV-infected patients vs HIV-uninfected controls.

1. Figure adapted from Brown TT, et al. AIDS 2006:20;2165–74
2. Duvivier C, et al. AIDS 2009; 27:817–24, 3. Woodward CL, et al. HIV Medicine 2009;10:482–7

Is HIV a risk factor for low BMD?

- HIV UPBEAT Study
- Prospective cohort (3 annual visits)
- HIV+ and HIV- from similar demographic backgrounds
- Demographic, socio-economic, medical history
- Bone health, fracture history, falls and QOL questionnaire
- Fasting bloods (FBC, U&E, LFTs, Bone, PTH, 25(OH)D, TFTs, lipids, glucose, hepatitis / HIV serology)
- Dual X-ray Absorptiometry scan – total body composition, densitometry at femoral neck (FN), total hip (TH) and lumbar spine (LS)

Cotter AG et al. AIDS. 2014; 28(14):2051-60

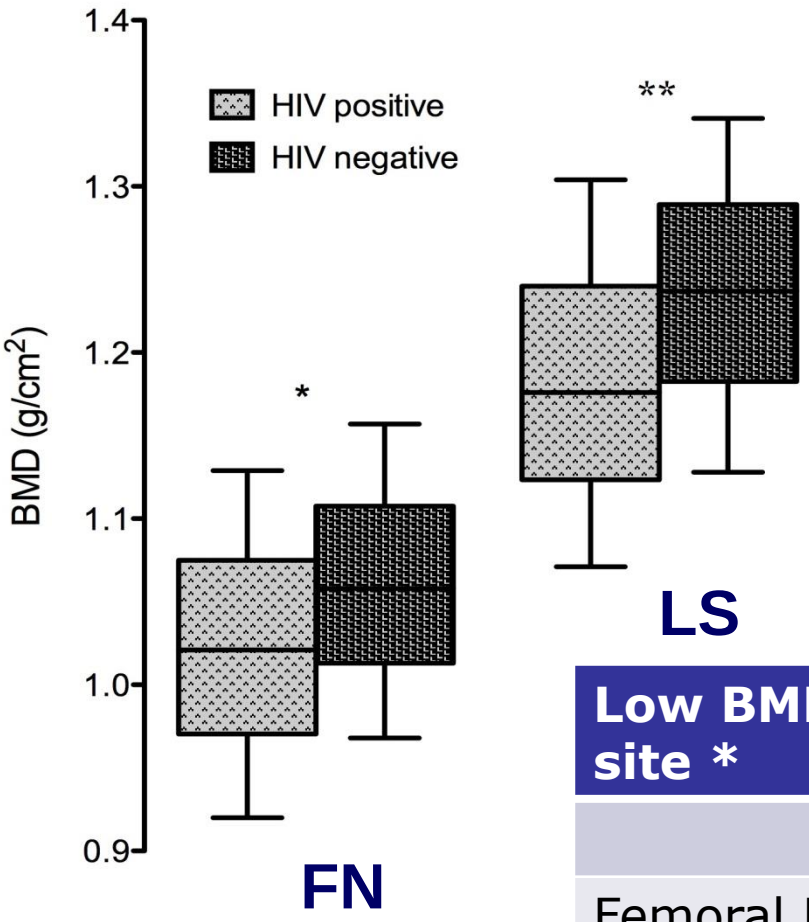
HIV UPBEAT

	HIV+ (n=210)	HIV- (n=264)	
	N (%)	N (%)	*P*
Male	123 (58.6)	115 (43.6)	0.001
Age (years)*	39 (33, 46)	42 (34, 49)	0.03
African ethnicity	83 (39.5)	65 (24.6)	0.001
BMI (kg/m^2)*	26 (23, 30)	27 (24, 30)	0.05
HBV Sag+	6 (3.0)	4 (1.5)	0.22
HCV ab+	34 (18.1)	3 (1.2)	<0.0001
Smoker	73 (34.8)	44 (16.7)	<0.0001
Ex-IVDU	29 (13.8)	2 (0.8)	<0.0001
Third level education	97 (46.2)	175 (66.3)	
Undisclosed education level	20 (9.5)	6 (2.3)	<0.0001

* Median (IQR)

Cotter AG et al. AIDS. 2014; 28(14):2051-60

HIV UPBEAT



Femoral neck (FN) between group *P=0.003

Lumbar spine (LS) between group ** P=0.001

Low BMD by site *	HIV+ (N=210)	HIV- (N=264)	
	n (%)	n (%)	P
Femoral Neck	50 (23.8)	31 (11.7)	0.001
Lumbar Spine	51 (24.3)	33 (12.5)	0.001

*Z-score ≤ -2.0 in those aged <40 years or
T-score of ≤ -1.0 in those aged ≥ 40 years

Cotter AG et al. AIDS. 2014; 28(14):2051-60

HIV UPBEAT

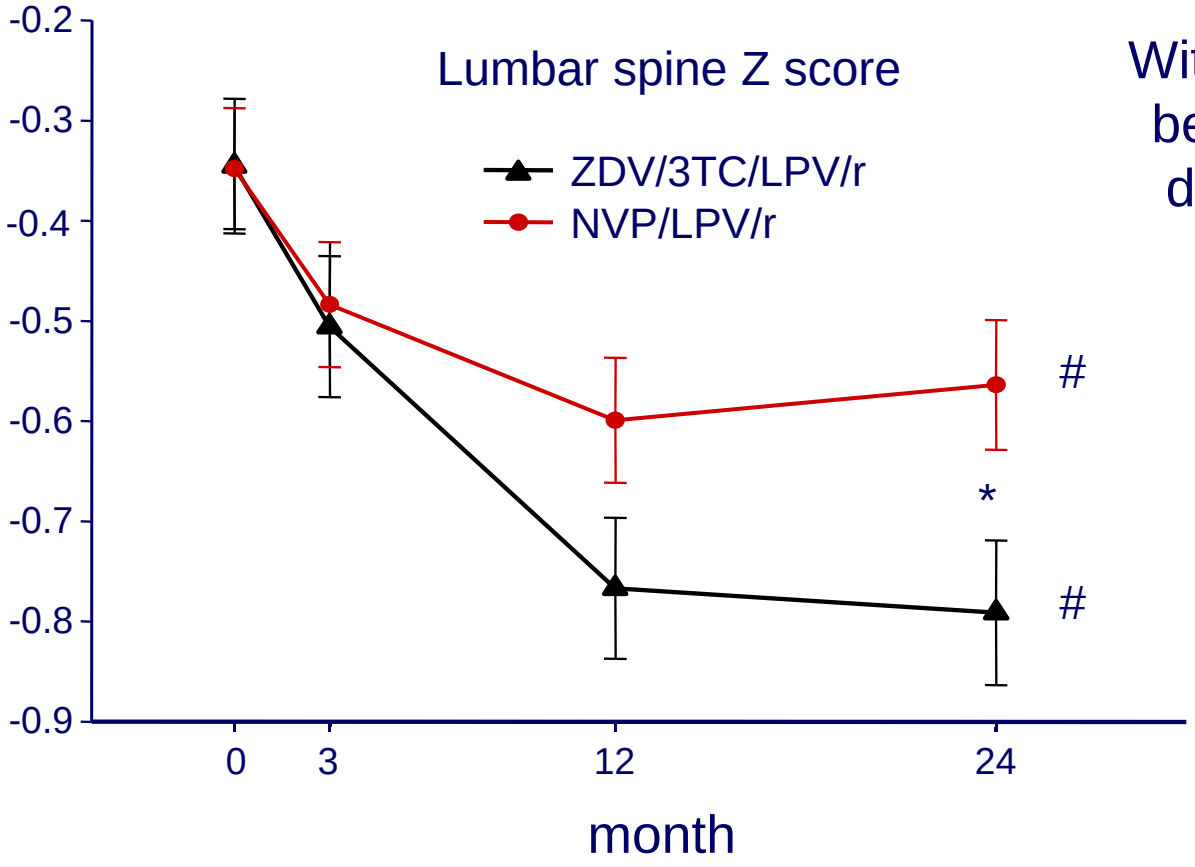
In multivariate analyses, HIV remains an independent predictor of lower BMD

	Effect on Femoral neck BMD	95% C.I.	*P*-value
HIV+ vs HIV-	**-0.041**	**-0.070, -0.012**	**0.01**
Male vs female	0.075	0.048, 0.102	<0.0001
Age (per 5 year increase)	-0.016	-0.023, -0.010	<0.0001
African vs non-African	0.077	0.045, 0.110	<0.0001
Third level vs 1st/2nd education	0.022	-0.005, 0.048	0.11
Undisclosed vs 1st/2nd level education	-0.012	-0.053, 0.077	0.72
B.M.I. (per 10/kg/m^2 increase)	0.088	0.063, 0.113	<0.0001
Alk phos (per 5 IU/L increase)	-0.005	-0.008, -0.003	<0.0001

Cotter AG et al. AIDS. 2014; 28(14):2051-60

ART initiation is associated with bone loss

Greater loss in BMD with ART containing NRTI



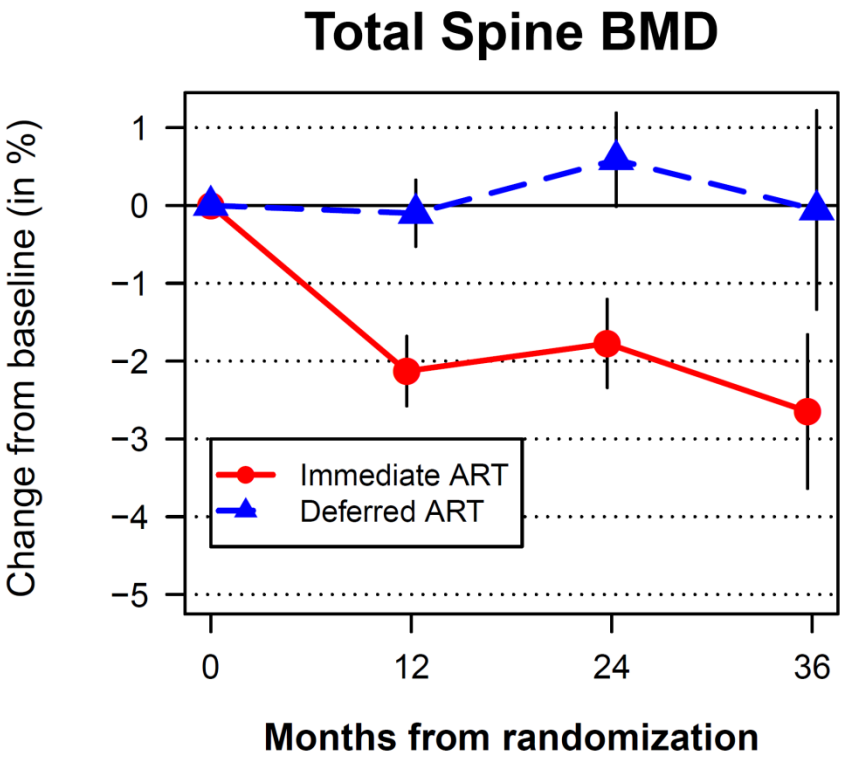
Within group and between-group differences all $P<0.05$

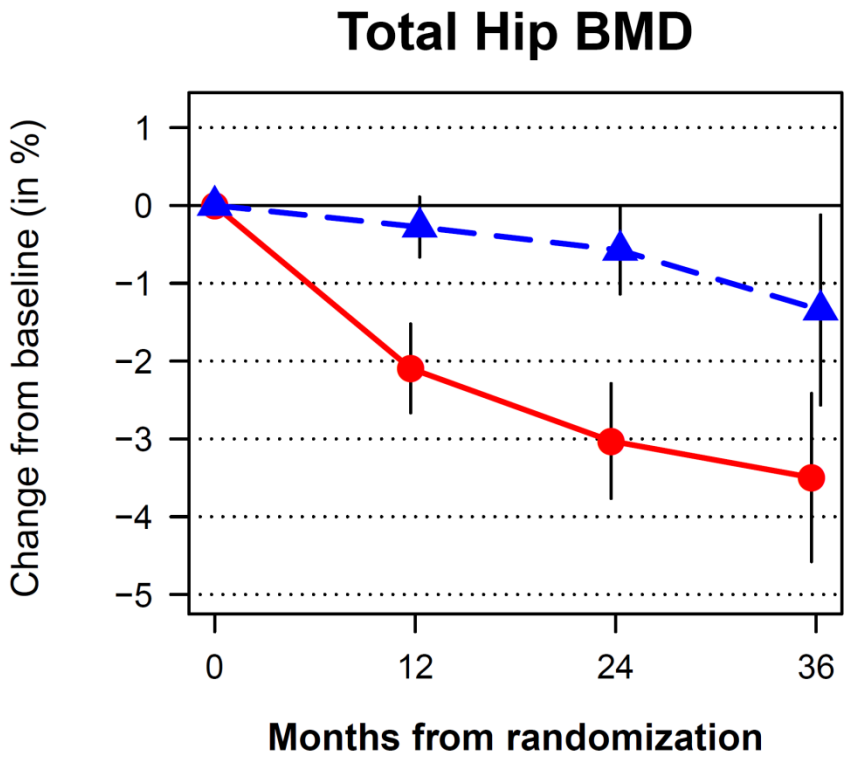
Changes in BMD accompanied by increases in markers of bone turnover

von Voderen M. et al. AIDS 2009; 23(11): 1367-1376

This isn't a re-setting of bone metabolism!

Change in bone mineral density on ART versus off ART





Estimated Mean Diff (95% CI)
-2.2% (-2.8, -1.6), p<0.001

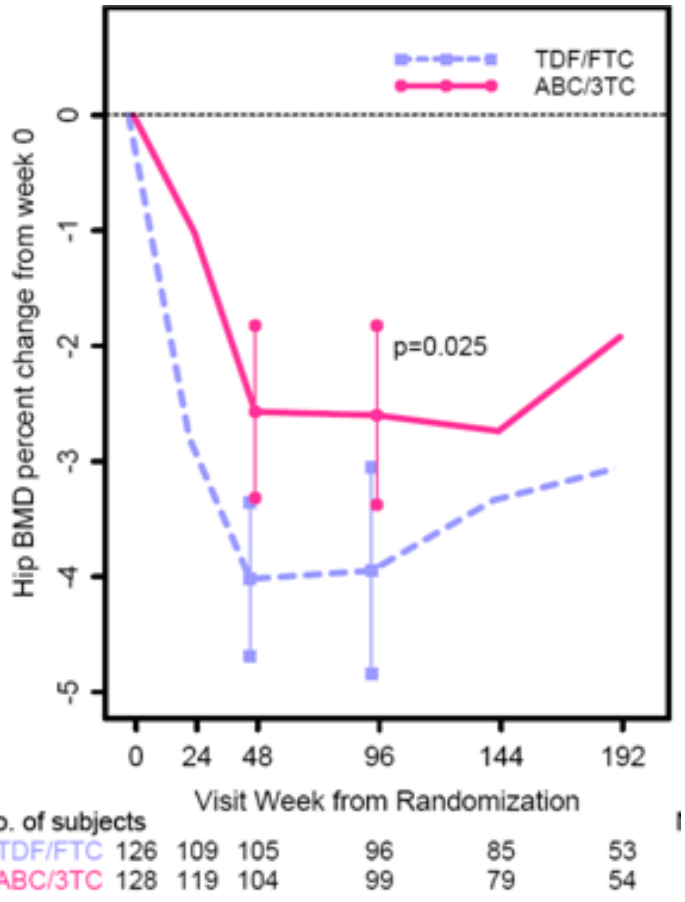
Estimated Mean Diff (95% CI)
-2.1% (-2.8, -1.4), p<0.001

Hoy JF. et al. 15th EACS 2015; Abstract ADRLH-62

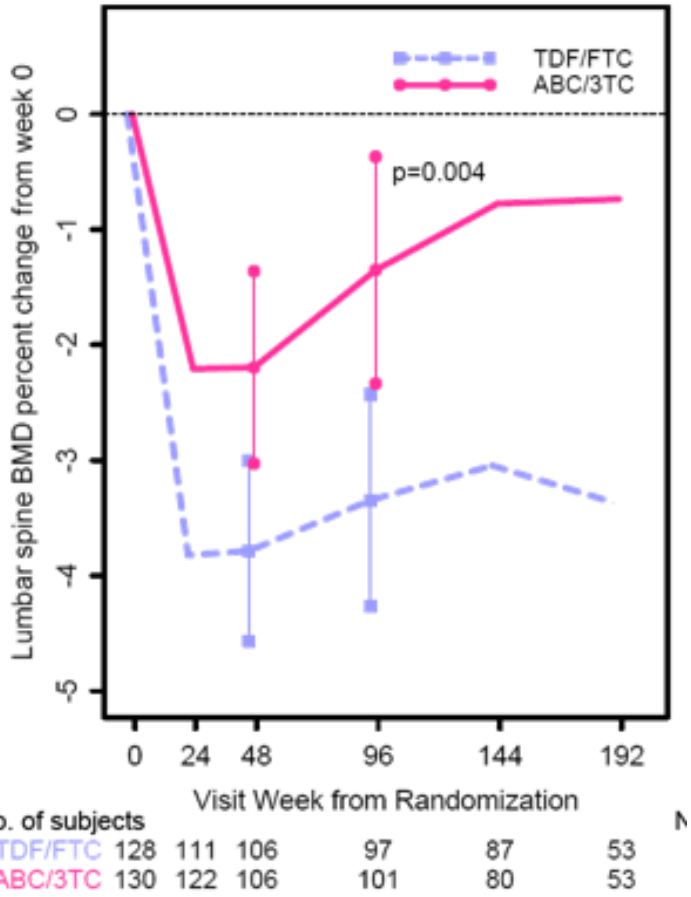
ART and bone loss - ABC/3TC vs TDF/FTC

A5224s: Metabolic Substudy of A5202

Hip



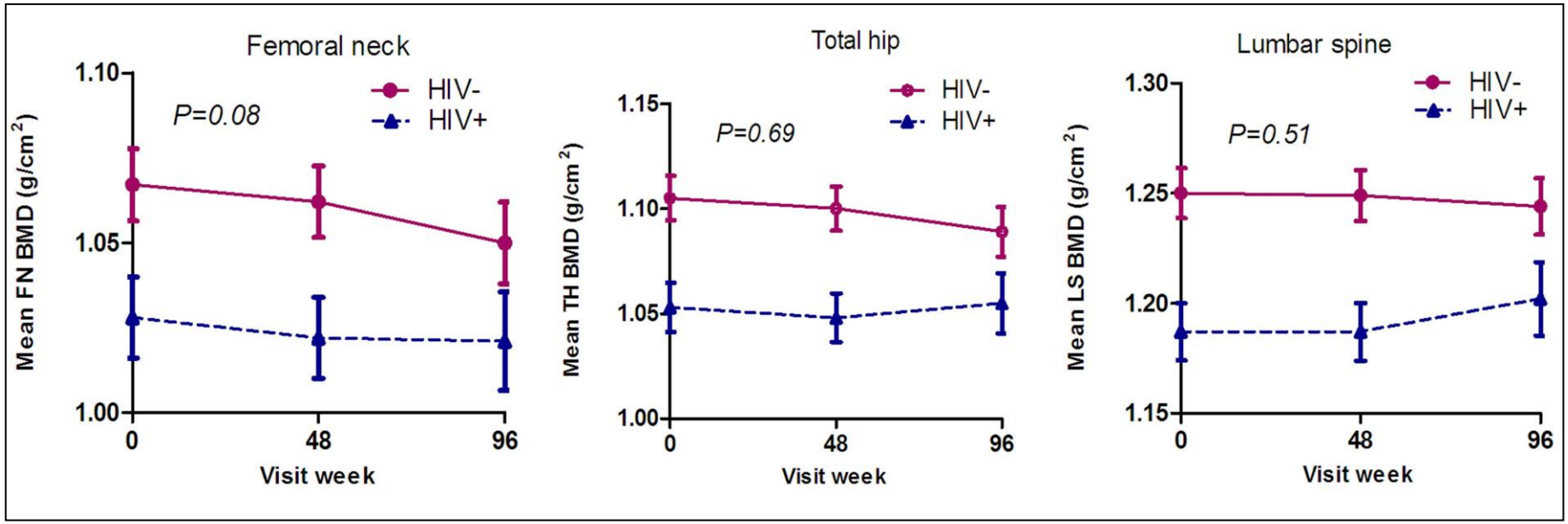
Lumbar Spine



McComsey GA et al. JID. 2011;203(12):1791-801.

ART and BMD – long-term follow-up

HIV UPBEAT Study. *N*= 384. 3 year follow-up.
HIV+, *N*=120, 88% on ART.

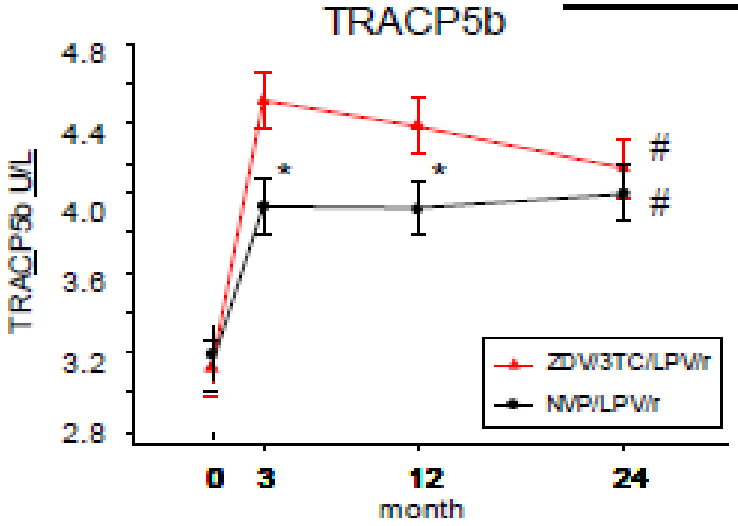


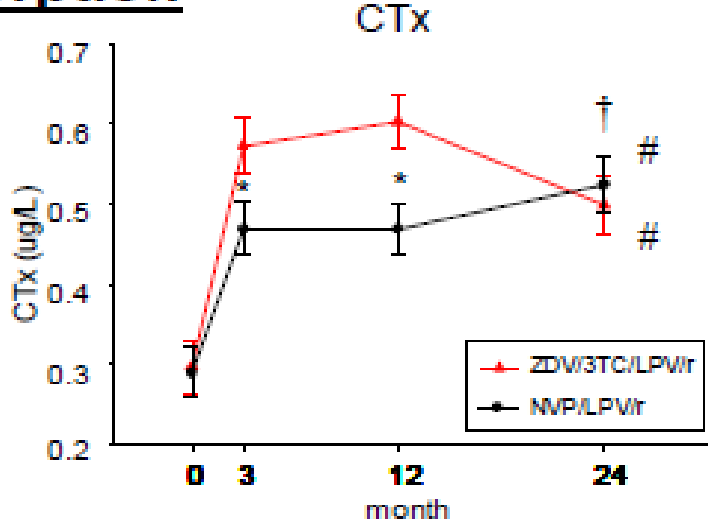
- No significant differences in rate of BMD decline in HIV+ vs HIV-
- Starting ART in previous 3/12 or not on ART both associated with greater BMD decline
- No association between specific ART and BMD decline

Tinago W et al. AIDS 2017, Mar 13;31(5):643-652

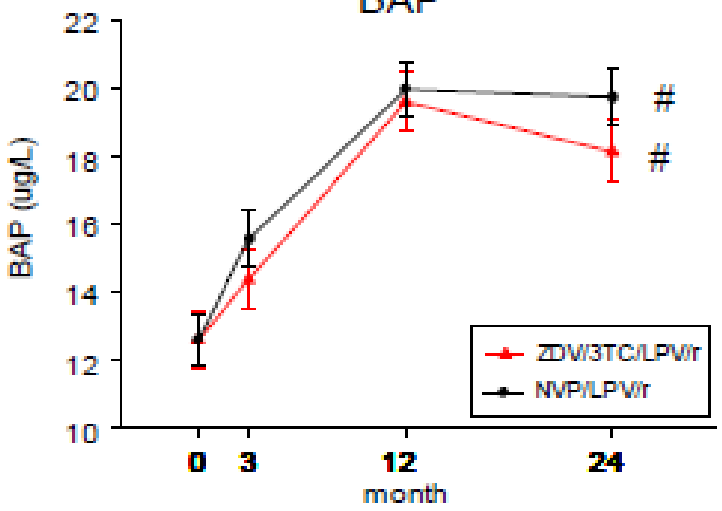
ART initiation and Bone Turnover

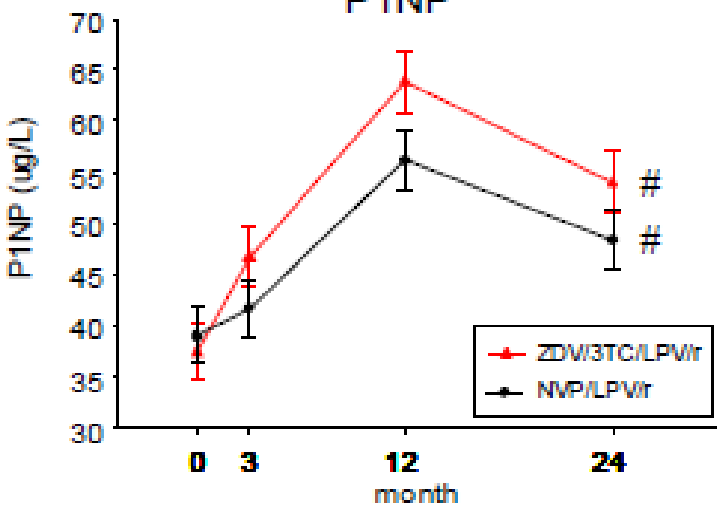
Bone Resorption





Bone Formation



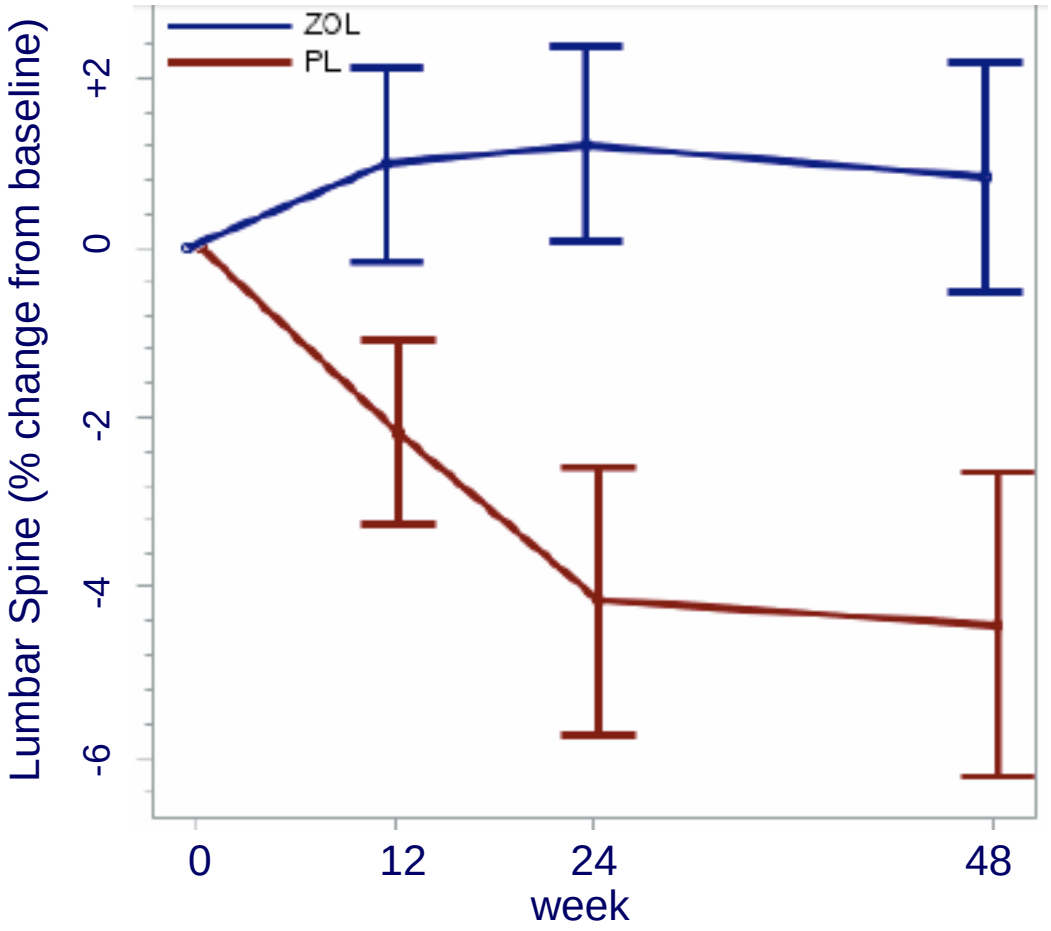


Van Vonderen et al. CROI 2011, abstract 833

BMD loss with ART initiation *is* avoidable!

N=63, ART naïve, >30 yrs, TDF/FTC/ATVr

Single dose zoledronic acid 5mg IV (N=34) vs placebo (N=29)



Ofotokun I et al. CROI 2016

Strategies to avoid bone loss

APART
ALENDRONATE FOR PREVENTION OF ART-ASSOCIATED BONE LOSS

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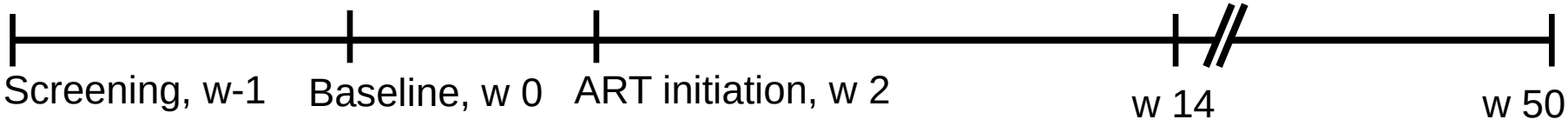
Alendronate for Prevention of ART-associated Bone Loss (APART)

- Multi-centre, prospective, randomised, double-blind, placebo-controlled trial
- Randomisation stratified by site, gender, Caucasian ethnicity and use of PI
- 80 HIV-1 positive, ARV naïve adults requiring initiation of ART



Arm 1: Alendronate 70 mg weekly

Arm 2: Placebo to alendronate 70 mg weekly

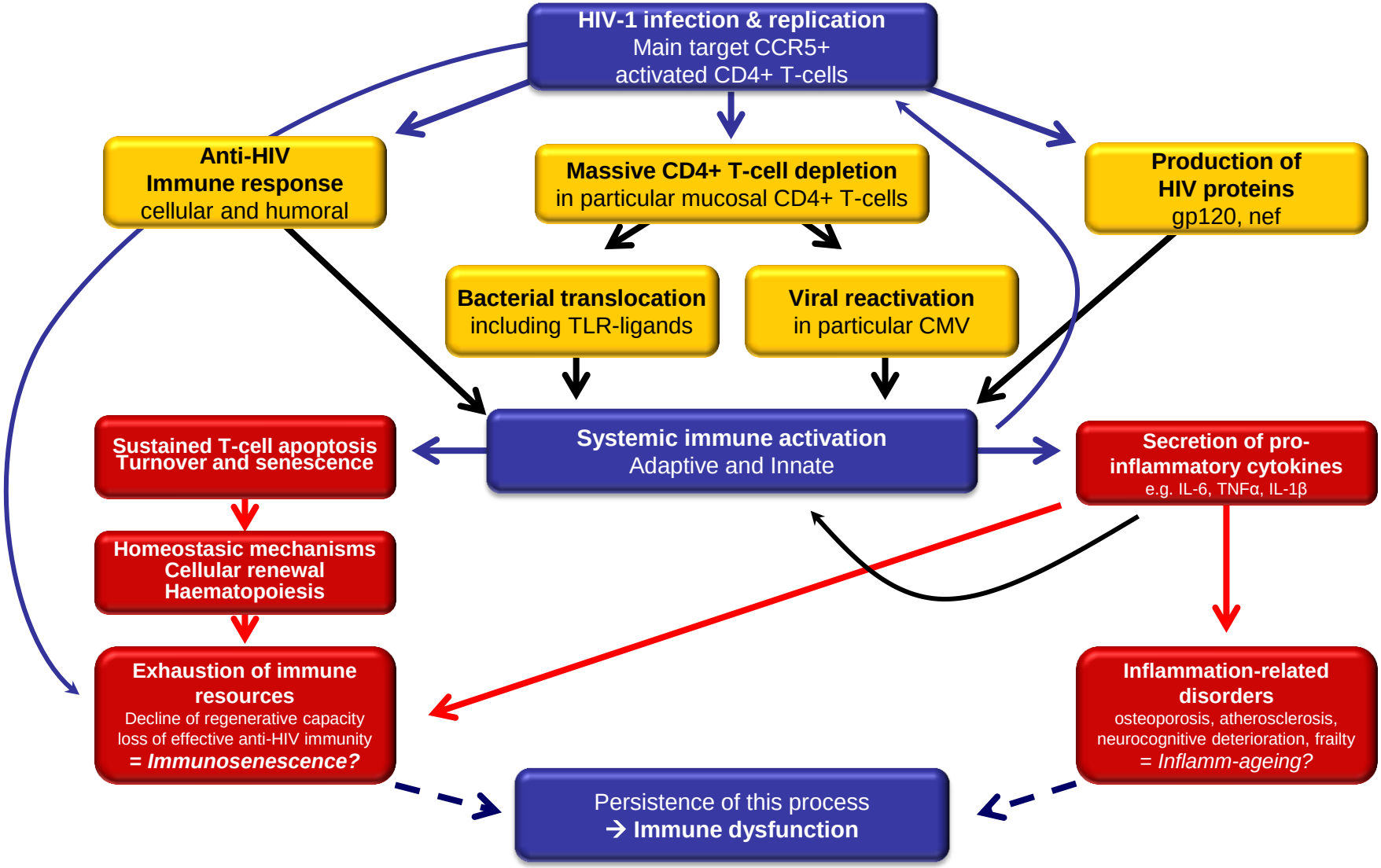
Calcichew D3 forte twice daily

TDF/FTC

HRB
Health Research Board

UCD
DUBLIN

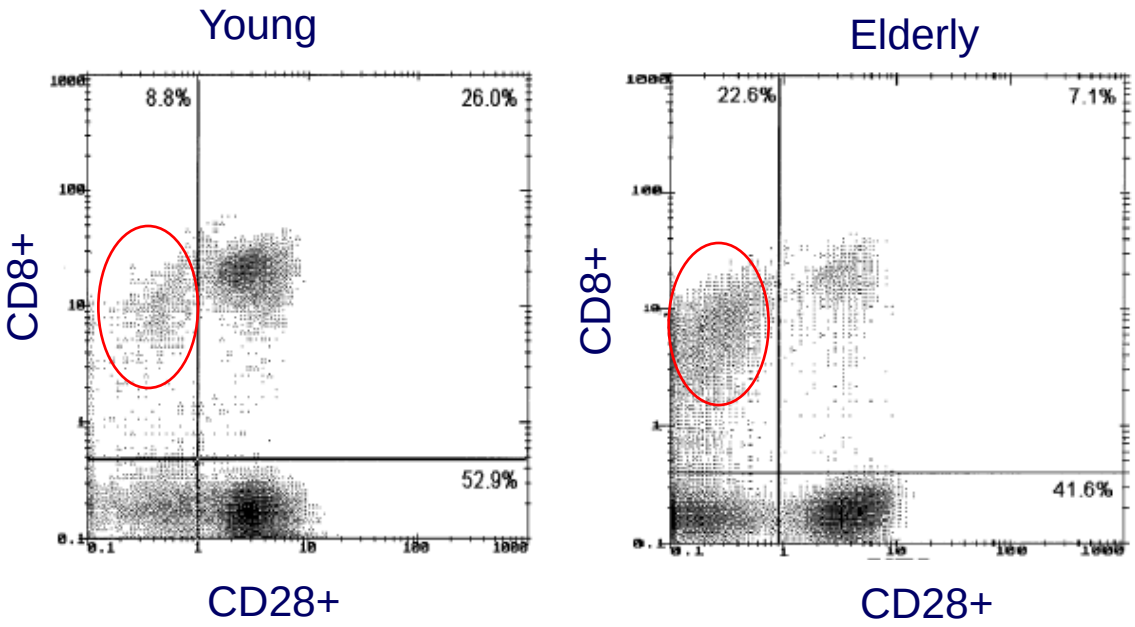
HIV is a disease of immune activation

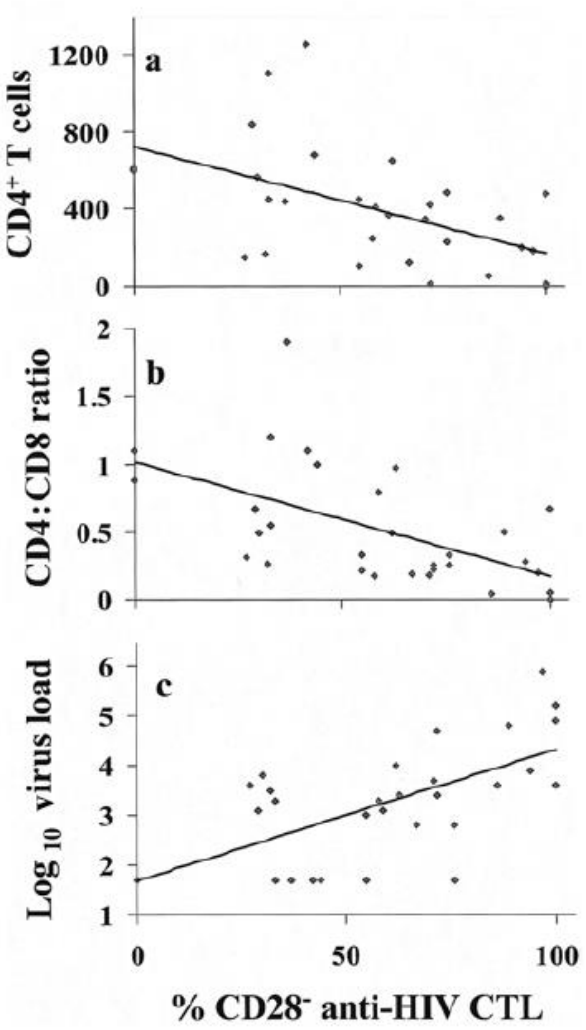


Adapted from Appay V and Sauce D. J Pathol 2008;214:231-241.

HIV, Ageing and Immune Function

- CD8+CD28- increase with age
- Increased CD8+CD28- in HIV+
- Thought to be ‘end-stage’ T-cells
- Less responsive to stimulus





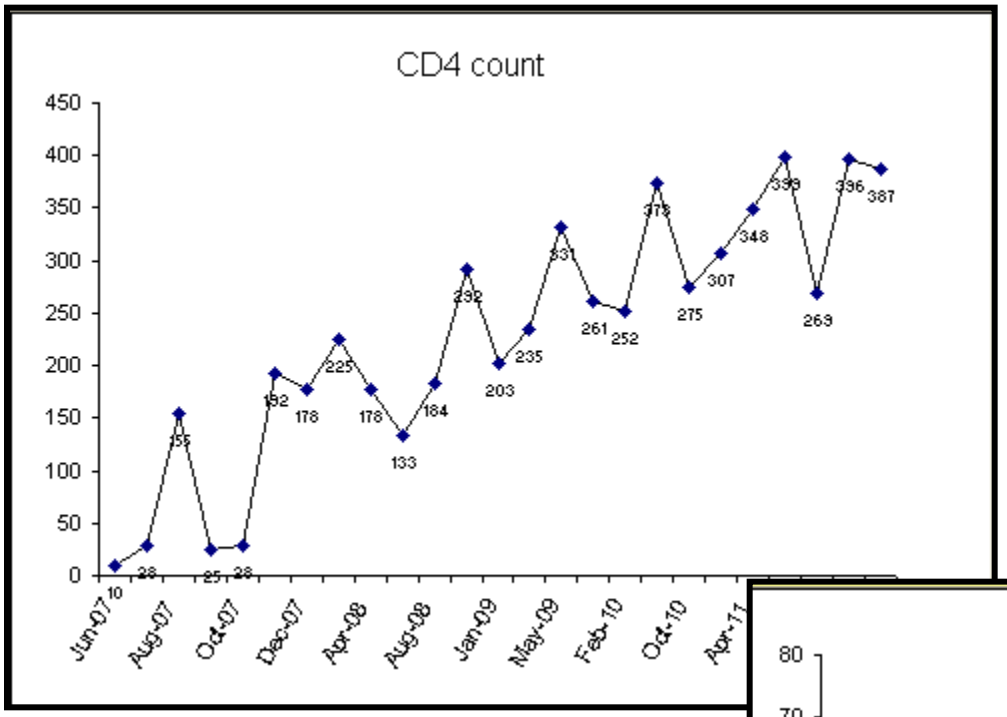
Boucher N, et al. *Exp Gerontol* 1998;33(3):267-282. Gamberg J, et al. *Immunol Cell Biol* 2004;82,38-46.

Ageing with HIV – the immune system

Similar immunologic changes in ageing and HIV infection

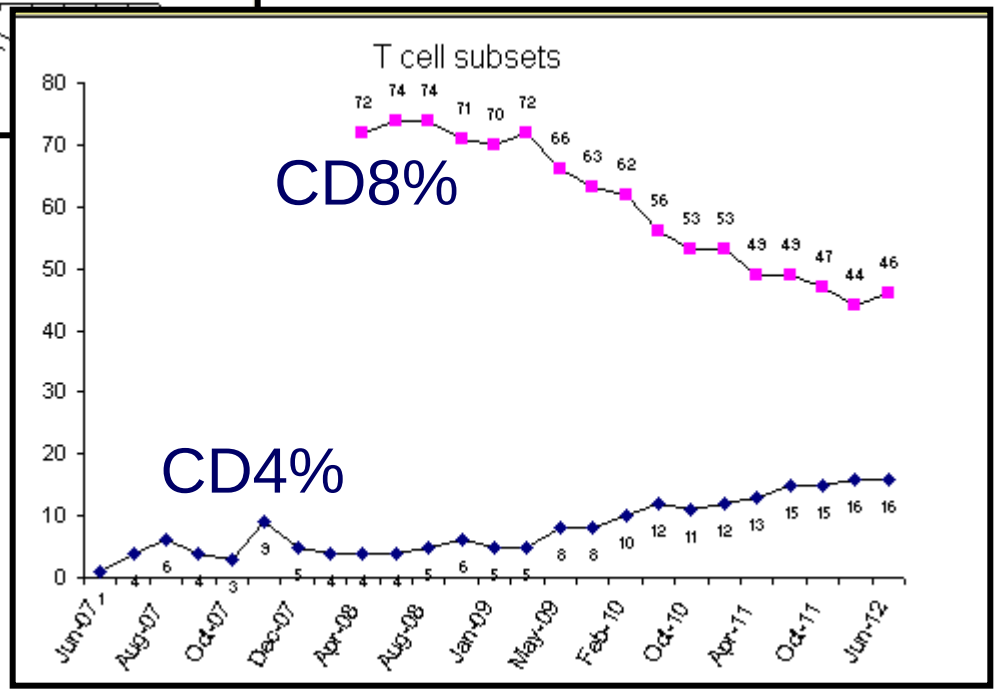
Outcome	Uninfected aged > 70 years	HIV-infected, untreated	HIV-infected long-term treated (5-10 years)
CD4/CD8 cell ratio	Low	Low	Low
Naïve/memory cell ratio	Low	Low	Low?
T cell proliferative potential	Low	Low	Low?
CD28-CD8+ T cells	High	High	Unknown
CD57+ T cells	High	High	Unknown
T cell repertoire	Reduced	Reduced	Reduced?
IL-6 levels	Increased	Increased	Increased?
T cell activation	Unclear	Increased	Increased?
Thymus function	Reduced	Reduced	Unknown
Response to vaccines	Reduced	Reduced	Reduced?

- Adapted from Deeks S. Annu Rev Med 2011;62:141-155.



Does it matter…..

….that we don't know if it matters?



Biomarkers and outcome – CD4:CD8 ratio

- Increasing interest in relationship between CD4:CD8 ratio normalisation (>1) and outcome[1]
- ICONA Cohort (N=3236) analysis 1997-2013[2]
- 14% normalised during follow-up

Risk of non-AIDS events

CD4:CD8 ratio	Estimate (per 1000 years FU)	95% CI
<0.3	4.2	(3.4-5.3)
0.3-0.45	2.3	(2.1-2.5)
>0.45	2.2	(1.7-2.9)

*by Poisson Regression

1. Serrano-Villar S et al. PLoS Pathog 2014:10(5): e1004078. doi:10.1371/journal.ppat.1004078
2. Mussini C et al. Lancet HIV 2015;2(3):e98-e106

Biomarkers and outcome – CD4:CD8 ratio

MMUH ID Cohort Study
550 PLWH started ART since Jan 2001
135 first time NADE / 2557 PYFU (5.3 /100 PYFU)

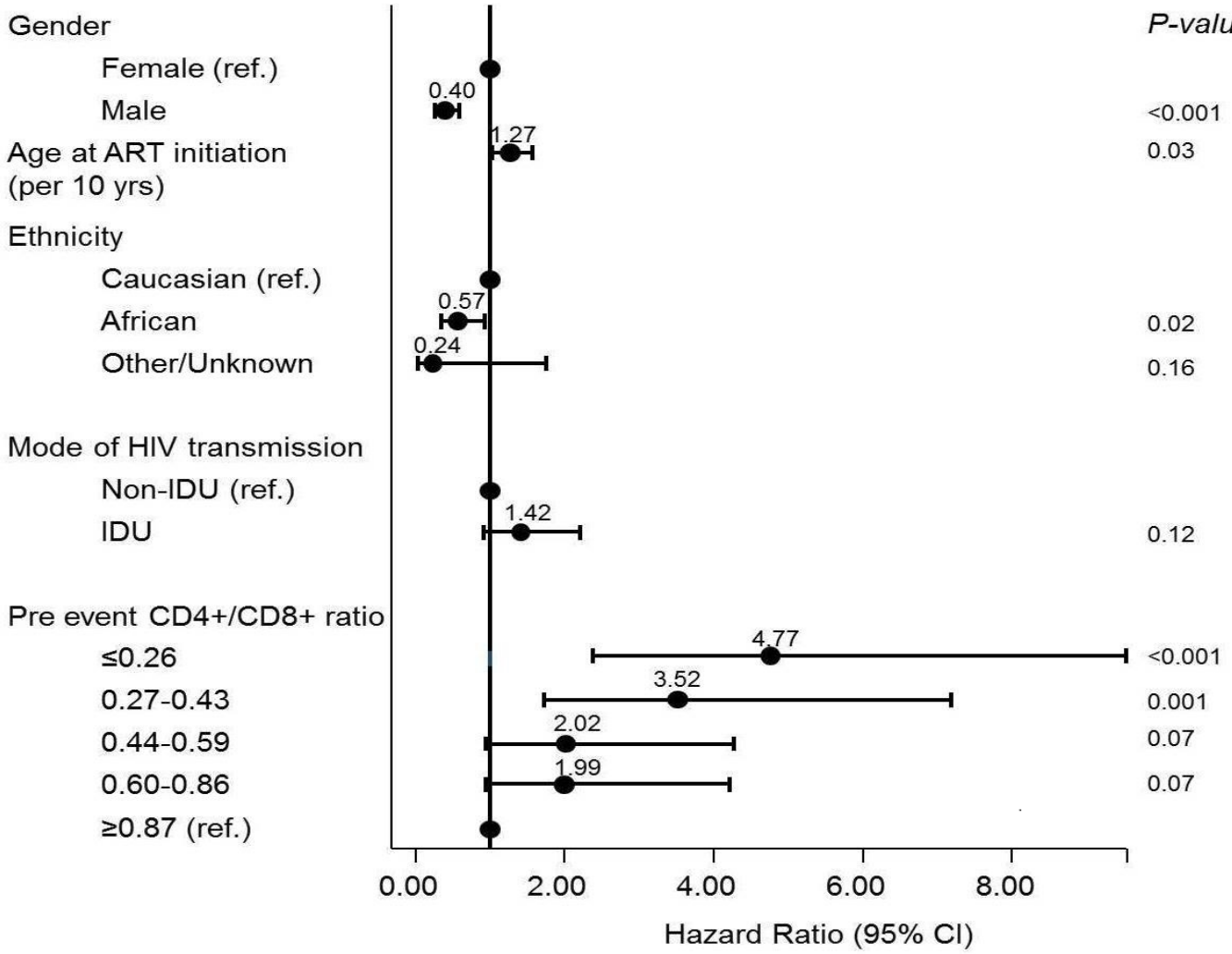
	N=550
Male	317 (58%)
Age at ART initiation	34 (29-40)
Caucasian	299 (54%)
HIV transmission risk	
- Heterosexual	279 (51%)
- MSM	114 (21%)
- IDU	131 (24%)
CD4+ current	545 (389-717)
CD4+ nadir	187 (80-284)
CD4:CD8 ratio current	0.7 (0.39-0.92)

44% PI
44% NNRTI
11% InSTI

McGettrick P et al. CROI 2016 Abstract 710

Biomarkers and outcome – CD4:CD8 ratio

Non-AIDS event[4]
(HR, 95% CI)



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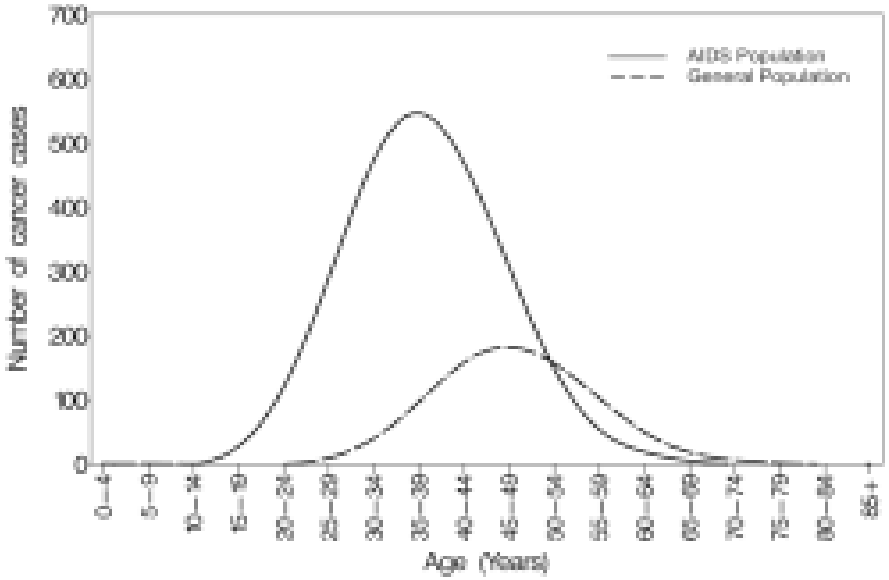
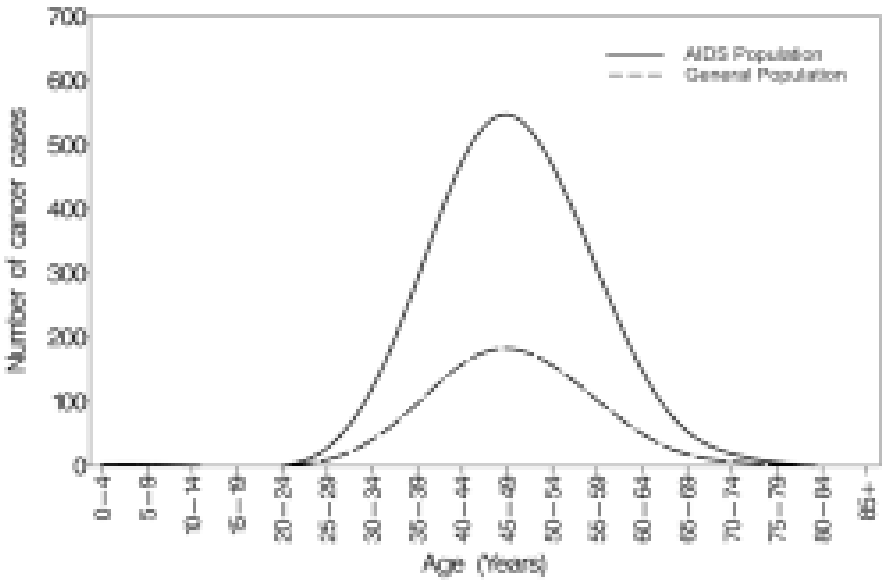
HIV and Ageing

'***Accelerated*** or ***accentuated***?'





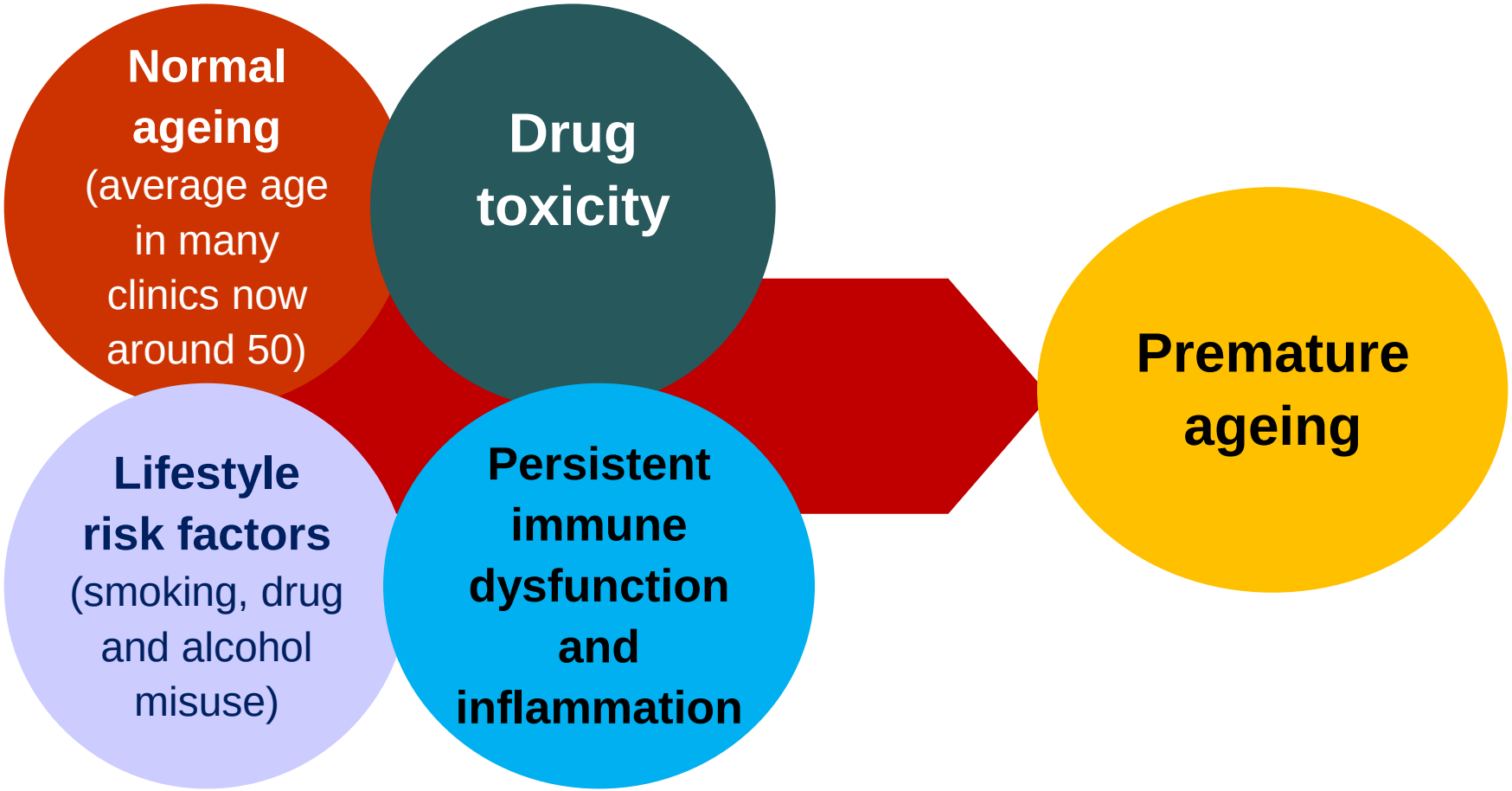
A. Accelerated and Accentuated risk: Cancer occurs earlier in persons with HIV than uninfected comparators, and more frequently

B. Accentuated risk: Cancer occurs at the same ages in the HIV-infected population, but more often than among comparators

Shiels MS, et al. Ann Intern Med 2010:153:452-460.

HIV and 'Premature Ageing'

Medicalisation or '*Disease Mongering*'



Adapted from Deeks SG, Phillips AN. *Br Med J* 2009;**338**:a3172

HIV and Ageing - cancer

Study compared age at cancer onset for 26 different cancer diagnoses

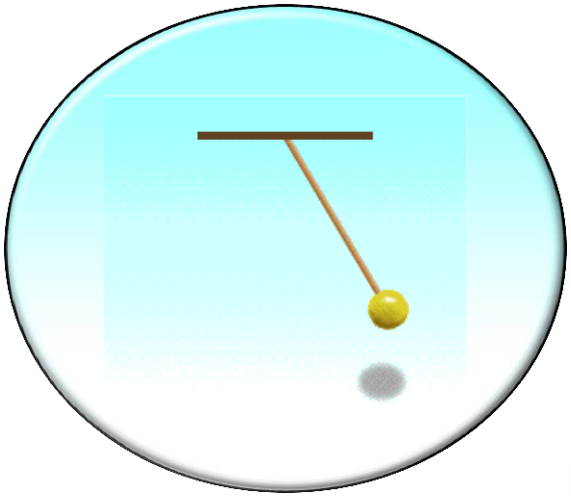
No real difference in age at onset for 18 cancers ($p<.05$)

Differences for remaining cancers were ≤ 5 years

Cancer	AIDS Patients	HIV Uninfected	Age-Adjusted HIV Uninfected	Apparent Difference (Yrs)	Real Difference (Yrs)
Renal	46	69	51	-23	-5
Anal	50	62	54	-12	-4
Larynx	48	65	52	-17	-4
Lung	50	70	54	-20	-4
Ovarian	42	63	46	-21	-4
Testicular	35	34	38	+1	-3
Hodgkin lymphoma	42	37	40	+5	+2
Myeloma	47	70	52	-23	-5

Adapted from Justice A. CROI 2012. Abstract 175; Adapted from Shiels MS, et al. Ann Intern Med 2010:153:452-460.

When to Start HIV Treatment



Late clinical stages

Early clinical stages

< 200

> 500

200

350

Any viral load

High viral load

CD4

DRUG SAFETY

AGE

Adapted from Schechter M, *JID* 2004;**190**:1043-1045

HIV and Ageing

Is there a ***'legacy'*** cohort?

- Mitochondrial toxicity
- Extreme dyslipidaemia
- Insulin resistance/DM
- Higher CVD risk?

Personal communication Giovanni Guaraldi, October 2012

Biological phenotype of Ageing

HMRG
HIV Molecular Research Group

HIV CURE

HIV CO-MORBIDITIES

- INFLAMMATION
- T-CELL SENESCENCE / ACTIVATION
- HIV RESERVOIR
- CD4:CD8 RATIO
- IFLN4 GENOTYPE
- INNATE IMMUNE ACTIVATION
- TELOMERE
- AGE, GENDER, SMOKING STATUS, BMI, etc
- Disease Stage, ART exposure, HepC status etc

UCD DUBLIN

Future research in HIV and ageing

'Pharmacokinetic and Clinical Observations in People over Fifty'

POPPY

Pharmacokinetic and clinical observations in people over 50

UK and Ireland

agehiv cohort study

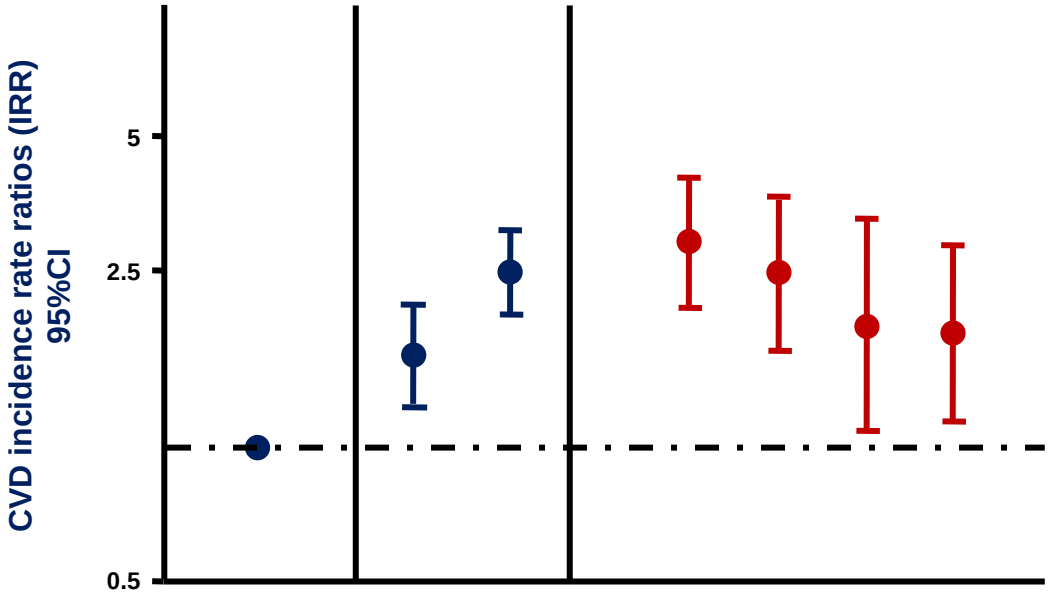
The Netherlands

Monitoring for co-morbidities

- Time consuming!!
- Difficult to implement in busy clinics
  - Consistency…….doctors….?
  - Be good at the basics – blood pressure / weight / smoking
- Aim for broad screening at presentation
- Thereafter, use risk assessment to target monitoring
  - Older PLWH
  - Threshold testing
  - Annual / Birthday checks
  - Research….

Reducing risk of comorbidities

D:A:D - risk of CVD events decreases by nearly 30% after stopping smoking for > 3 years



- 746 CVD events reported during 151,717 person years of follow up, yielding overall crude rates (and 95% CI) per 1,000 person years of 4.92 (4.57, 5.28)

- Compared to current smokers, the risk of CVD among patients who stopped smoking for more than 3 years was **reduced by approximately 30% (IRR (95% CI): 0.74 (0.48, 1.15)**

Adapted from Petoumenos K, et al. HIV Med 2011;12:412–21.

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
CO-MORBIDITIES						
Haematology	FBC	+	+	3-12 months		
	Haemoglobinopathies	+			Screen at risk persons	
	G6PD	+			Screen at risk persons	
Body composition	Body-mass index	+	+	Annual		33
Cardiovascular disease	Risk assessment (Framingham score[iii])	+	+	2 years	Should be performed in all men > 40 years and women > 50 years without CVD	34
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
Hypertension	Blood pressure	+	+	Annual		35-36
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	40
Glucose	Serum glucose	+	+	Annual	Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL)	38-39
Pulmonary disease	CXR	+/-		As indicated	Consider CXR if prior history of pulmonary disease	
	Spirometry			As indicated	Screen for COPD in at risk persons[xii]	
Liver disease	Risk assessment[v]	+	+	Annual		48-50
	ALT/AST, ALP, Bilirubin	+	+	3-12 months	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs	
	Staging of liver fibrosis			12 months	In HCV and/or HBV co-infected persons (e.g. FibroScan, serum fibrosis markers)	67, 71
	Hepatic ultrasound			6 months	In HCV co-infected persons with liver cirrhosis Child Pugh class A or B and Child Pugh class C awaiting liver transplantation; and in HBV co-infected persons irrespective of fibrosis stage	67, 71
Renal disease	Risk assessment[vi]	+	+	Annual	More frequent monitoring if eGFR < 90mL/min, CKD risk factors present[vi] and/or prior to starting and on treatment with nephrotoxic drugs[ix]	44-45
	eGFR (CKD-EPI)[vii]	+	+	3-12 months		
	Urine dipstick analysis[viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min, if proteinuria ≥ 1+ and/or eGFR < 60 mL/min perform UP/C or UA/C[viii]	
Bone disease	Bone profile: calcium, PO_4, ALP	+	+	6-12 months		41, 43
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons (see page 41 for details)	
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons	42
Neurocognitive impairment	Screening questionnaire	+	+	As indicated	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 66 for further assessment.	66
Depression	Questionnaire	+	+	As indicated	Screen at risk persons	62-64
Cancer	Mammography			1-3 years	Women 50-70 years	32, 50
	Cervical PAP			1-3 years	Sexually active women	
	Anoscopy and PAP (MSM)			1-3 years	Evidence of benefit not known	
	Ultrasound and alpha-foetoprotein			6 months	Controversial; persons with cirrhosis and persons with HBV irrespective of fibrosis stage	
	Others				Controversial	

Discussion