Comorbidities

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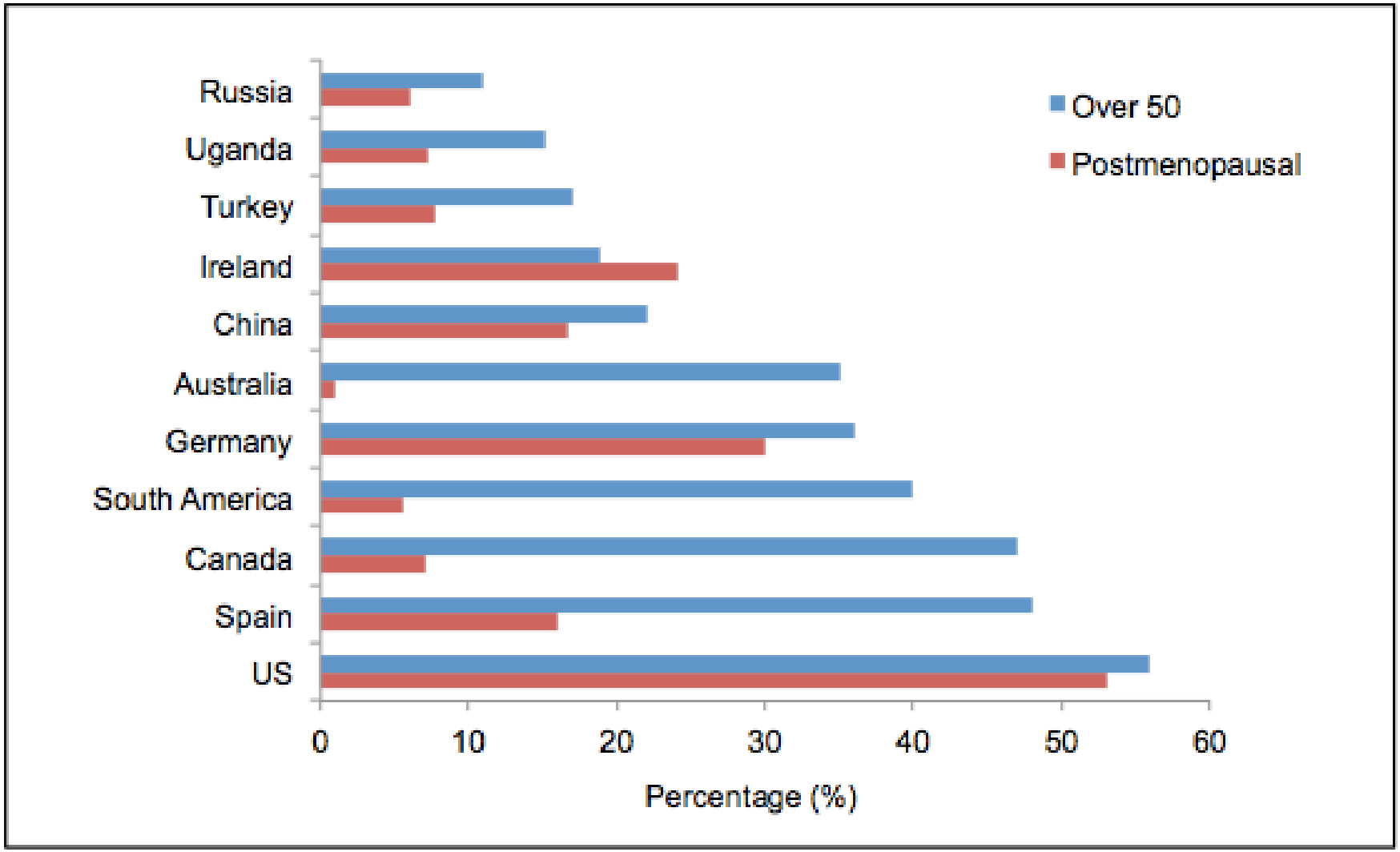
HMRG HIV Molecular Research Group

Scoil an Leighis agus laíocht An Leighis UCD

Misericordia

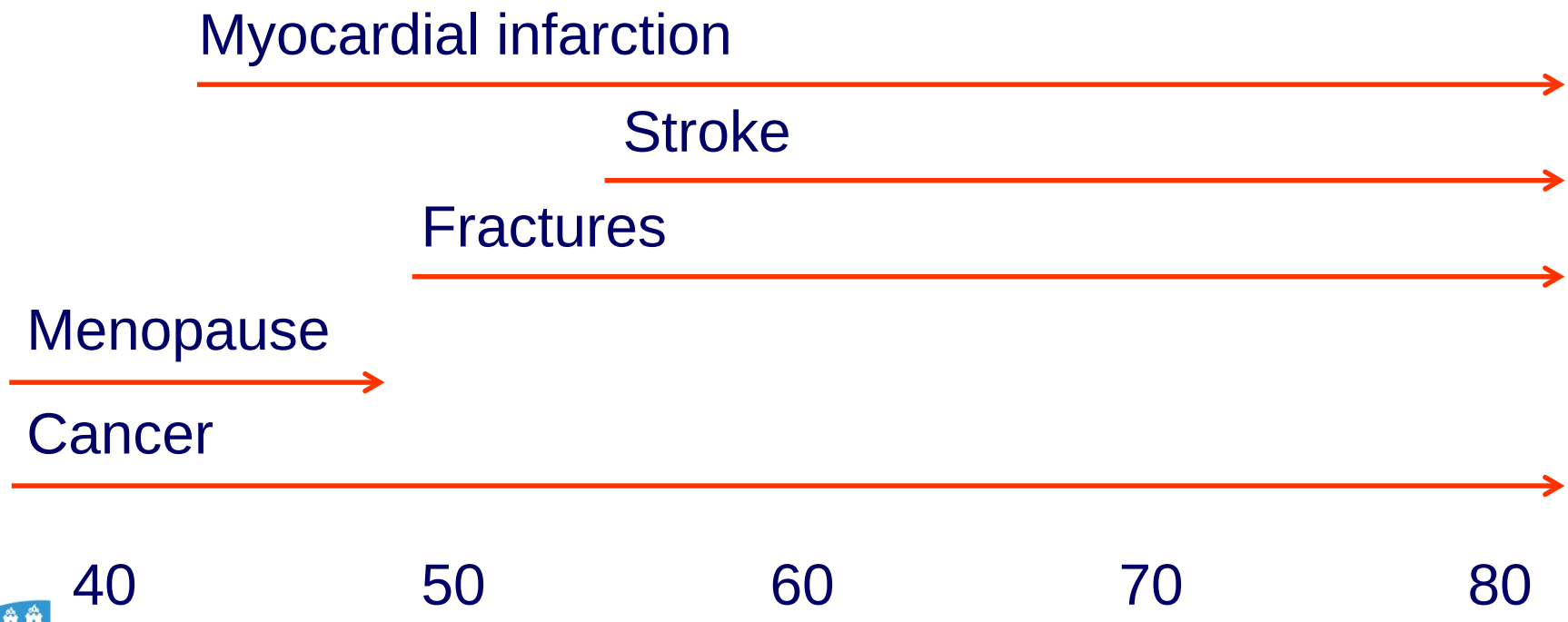
Ageing and HIV



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

Health challenges arising from ageing

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



Mallon personal communication May 2018

The POPPY Study

Prospective, multi-centre cohort study
Comprises 3 groups:

PLWH ≥50 years

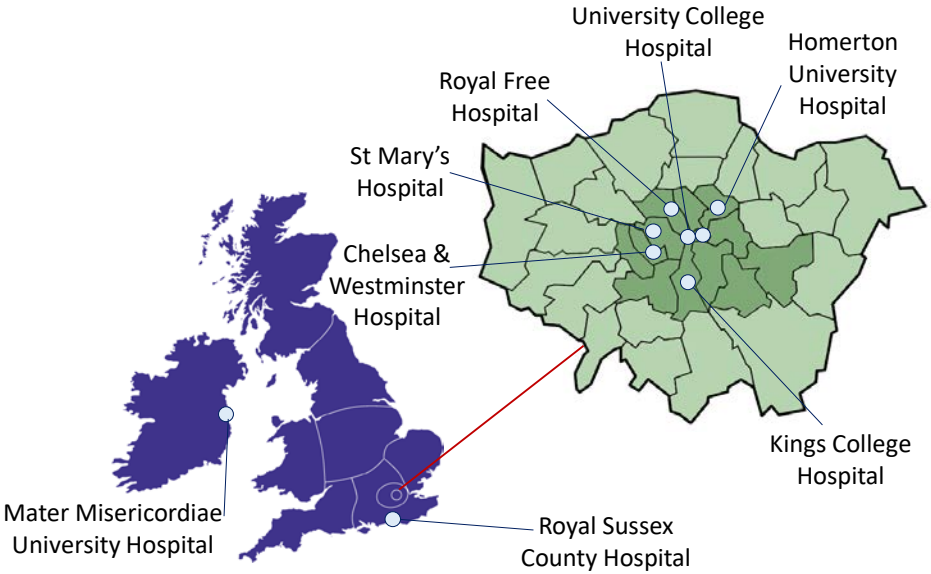
white/black African ethnicity
acquired HIV via sexual routes

PLWH ≤50 years

frequency matched on age, gender, ethnicity, sexuality and location (in/out London)

HIV-negative ≥50 years

frequency matched on age, gender, ethnicity, sexuality and location (in/out London)



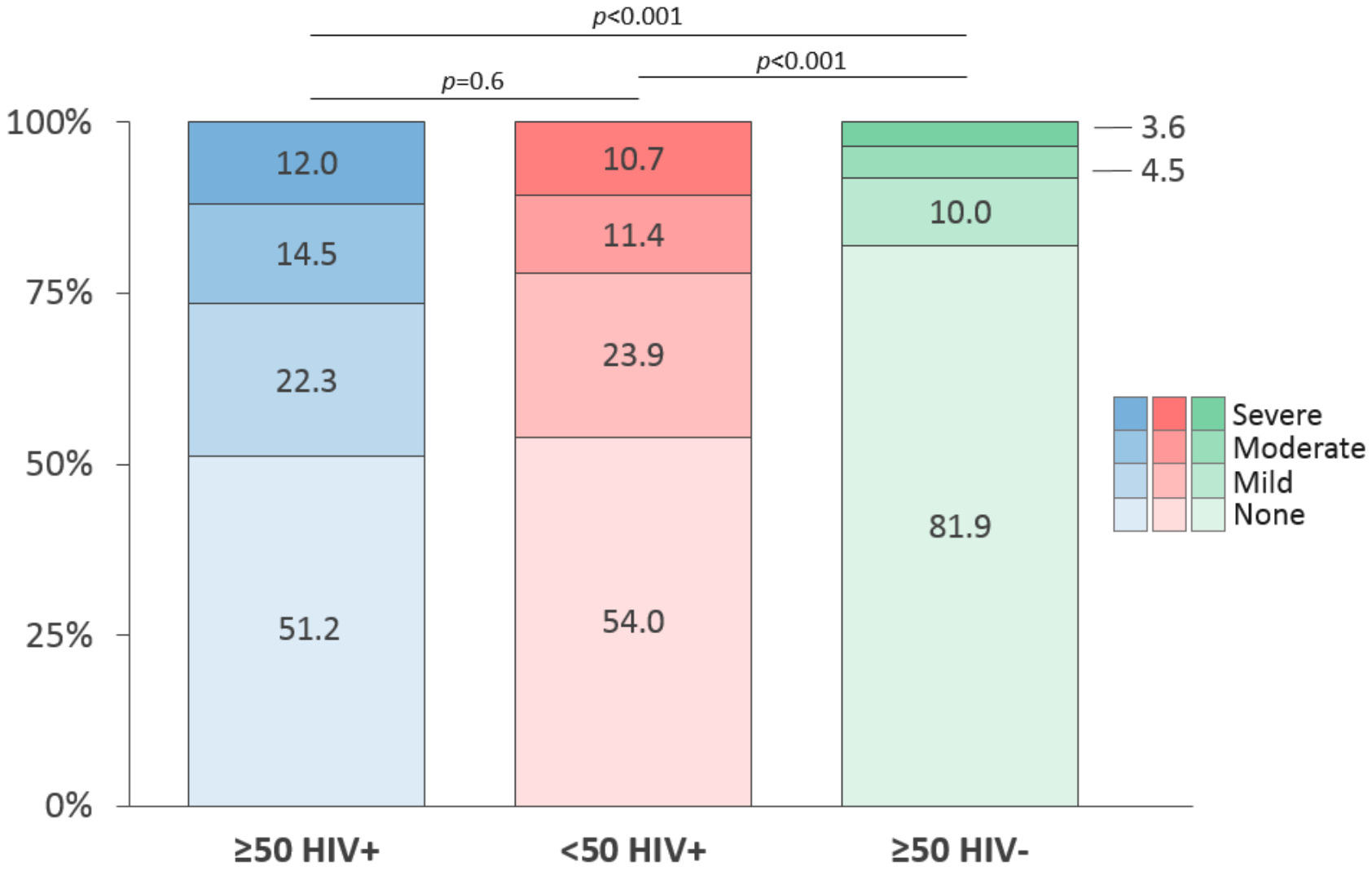
The POPPY Study

Baseline characteristics

	Older HIV+ (N=649) n(%)		Younger HIV+ (N=353) n(%)		Older HIV- (N=291) n(%)	
Sex						
Male	573	(88.3)	282	(79.9)	183	(62.9)
Female	76	(11.7)	71	(20.1)	108	(37.1)
Race						
White	562	(86.6)	280	(79.3)	260	(89.4)
Black African	87	(13.4)	73	(20.7)	31	(10.7)
Mode of infection/sexuality						
MSM / homosexual	515	(79.4)	252	(71.4)	133	(45.7)
Heterosexual	134	(20.7)	101	(28.6)	158	(54.3)
Body mass index (kg/m^2)	26	(16, 46)	25	(15, 43)	27	(18, 59)

POPPY - depression

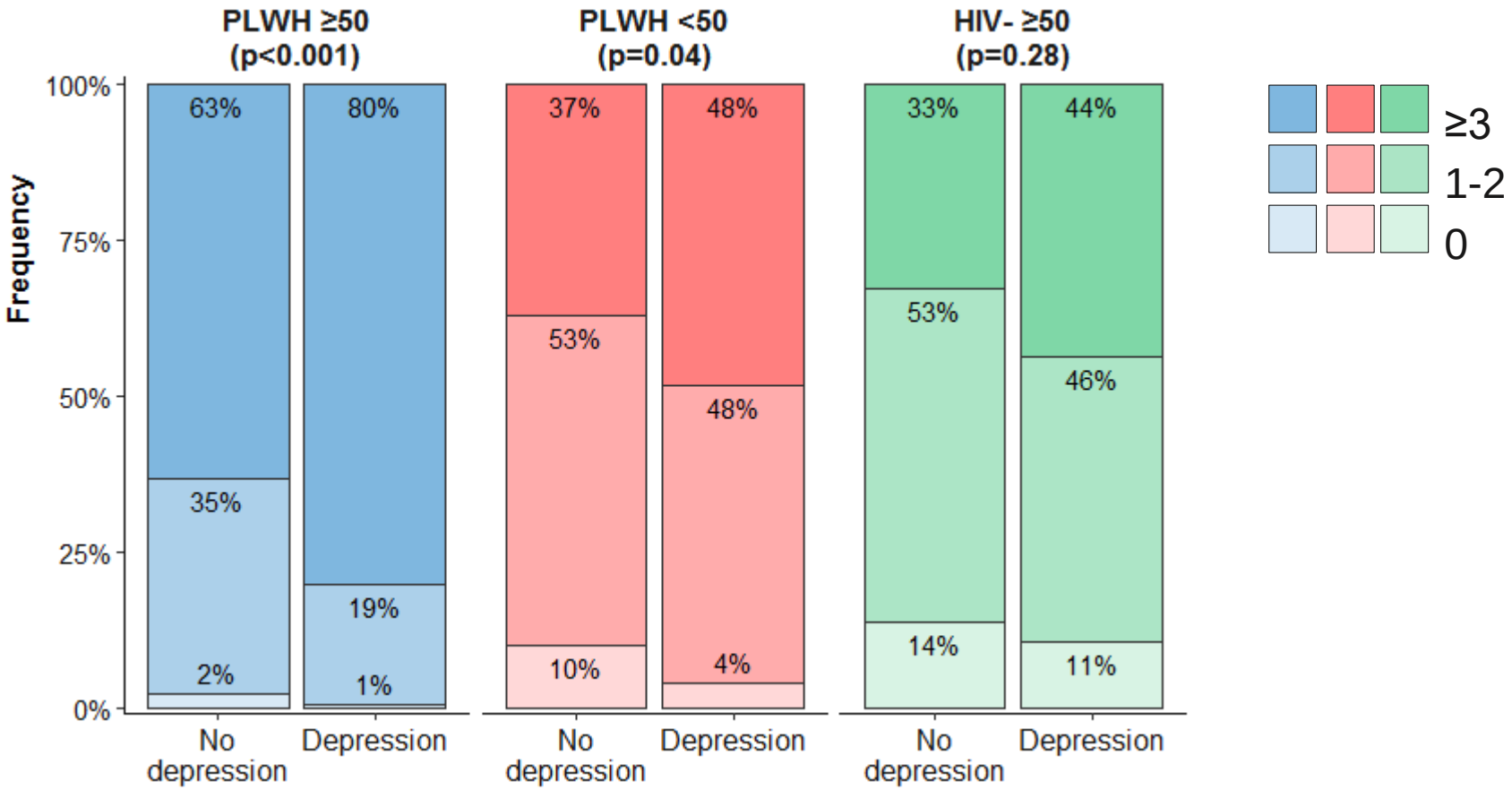
Prevalence of depressive symptoms



J Int AIDS Soc 19(8Suppl 7): 21487, O215

POPPY - depression

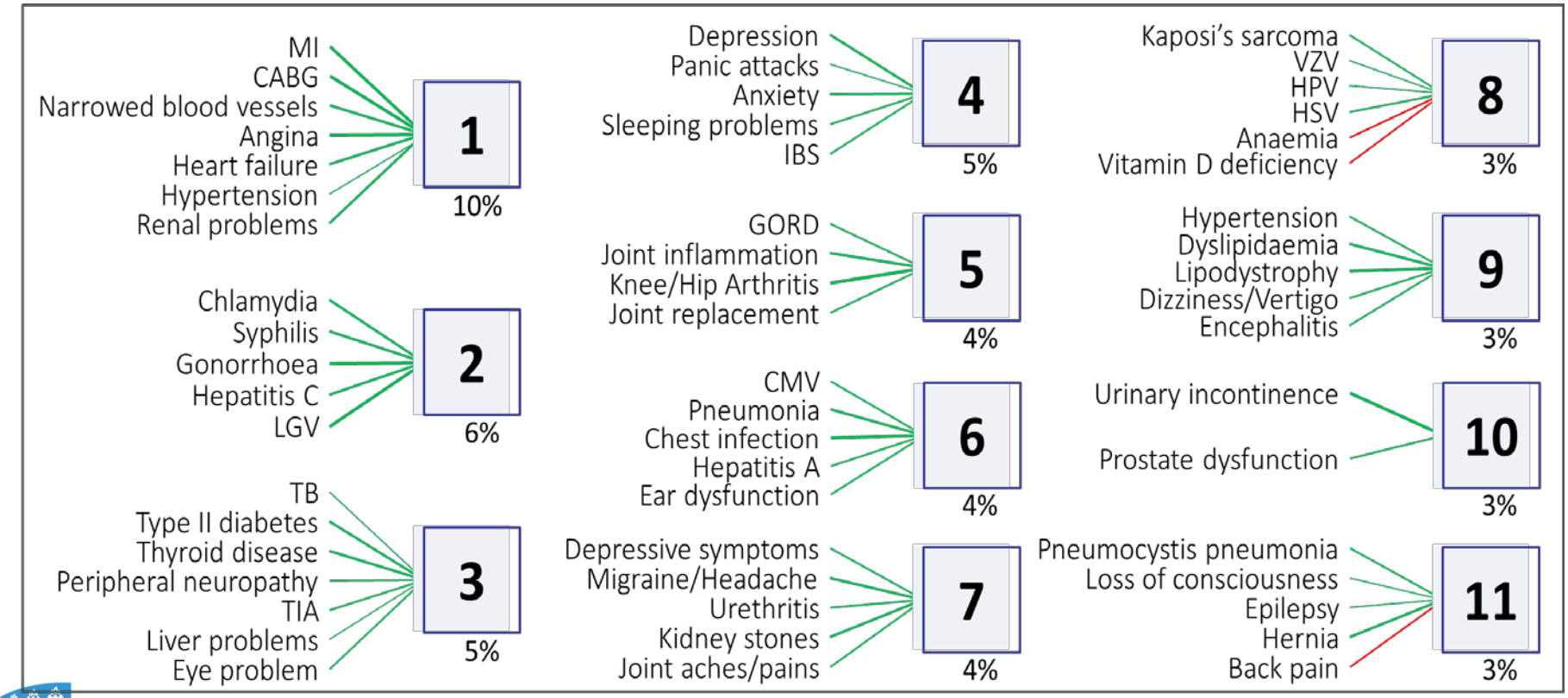
Association of depressive symptoms with comorbidities*



*between diabetes mellitus, CVDs, chest problems, Hepatitis B and C, AIDS events neurological problems, genitourinary problems, cancer, STDs, joint problems

Clustering of co-morbidities

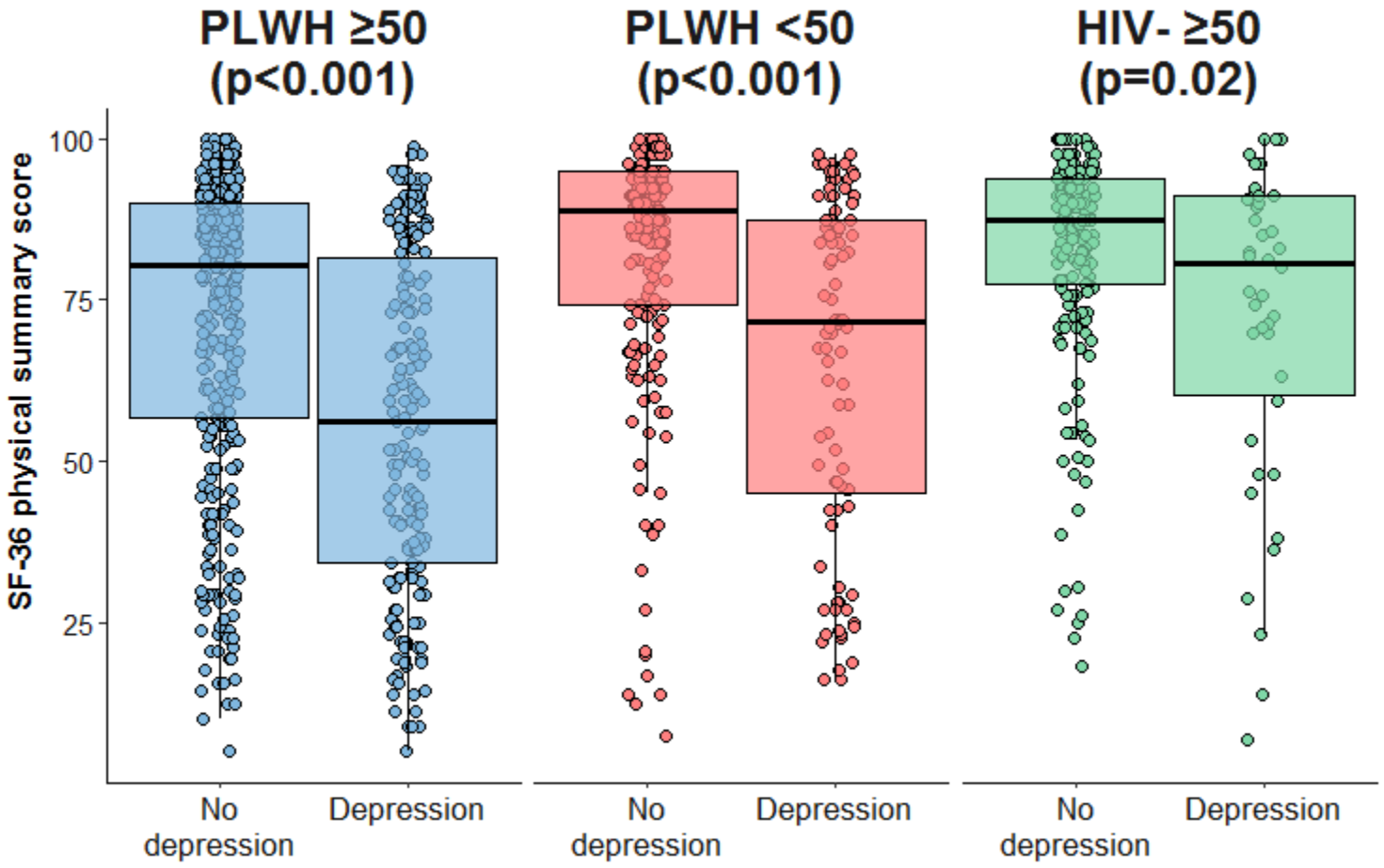
Comorbidities associated with each component extracted by the PCA with a positive (in green) or negative (in red) correlation greater than 0.4



D De Francesco et al, EACS 2017

POPPY – depression and QOL

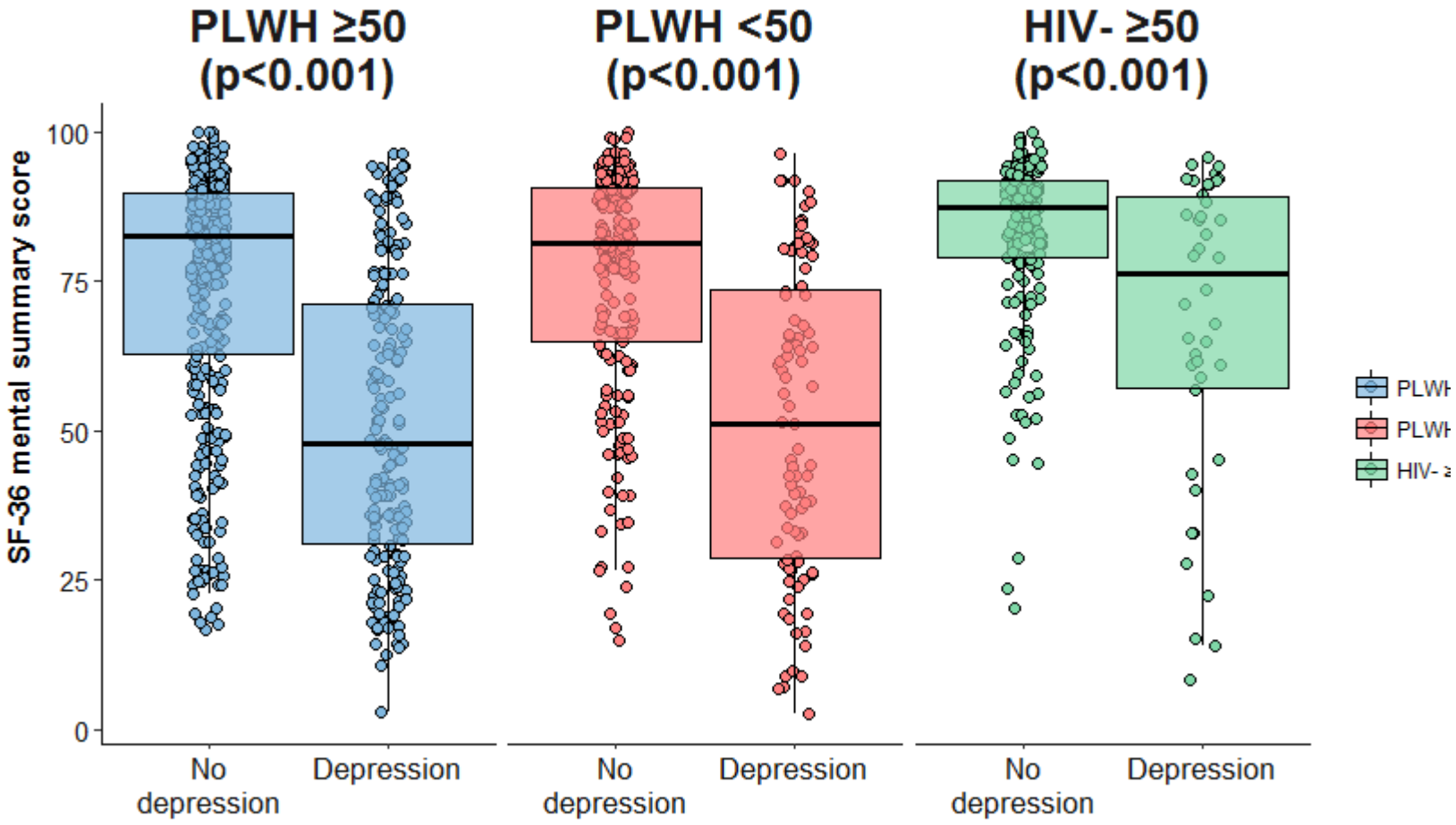
Association of depressive symptoms with physical health (SF-36)



D De Francesco et al 2017

POPPY – depression and QOL

Association of depressive symptoms with mental health (SF-36)



D De Francesco et al 2017

Longitudinal analysis of Quality of Life (QoL) in HIV-positive and HIV-negative subjects enrolled to the UPBEAT cohort study after 5 years of follow-up

E. Alvarez[1], A.G. Cotter[1,2], C.A. Sabin[3], T. McGinty[1], S. Babu[1], R. Chen[4], A. Macken[1], J.J. Brady[2], E. Kavanagh[2], G. McCarthy[2], J. Compston[5], P.W.G. Mallon[1,2], HIV UPBEAT Study Group

[1]HIV Molecular Research Group, University College Dublin School of Medicine, Dublin, Ireland, [2]Mater Misericordiae University Hospital, Dublin, Ireland, [3]Institute of Global Health, University College London, London, UK, [4]Medical College of Wisconsin, USA, [5]Department of Medicine, School of Clinical Medicine, Addenbrooke's NHS Trust, University of Cambridge, UK

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University Hospital

QOL & HIV – UPBEAT Study

'Understanding the Pathology of Bone Disease in HIV-infected Individuals': Prospective cohort of HIV-positive and HIV-negative subjects from similar demographic backgrounds in Ireland with over 5 years of follow-up

QoL assessments:

Vigorous / Moderate activities Lift or carry groceries Climb flights of stairs Bend, Kneel Walk a mile / several blocks Bathe / Dress	Physical Functioning
Cut down time / Accomplished less Limited in kind of activities Difficulty in performing activities	Role Physical
Bodily pain: magnitude Bodily pain: interference	Bodily Pain
General health rating Health perception	General Health
Full of pep / Energy Worn out / Tired	Vitality
Interference: extent Interference: time	Social Functioning
Cut down time Accomplished less Less careful	Role emotional
Nervous / Down in dumps Blue / Sad Peaceful / Happy	Mental Health

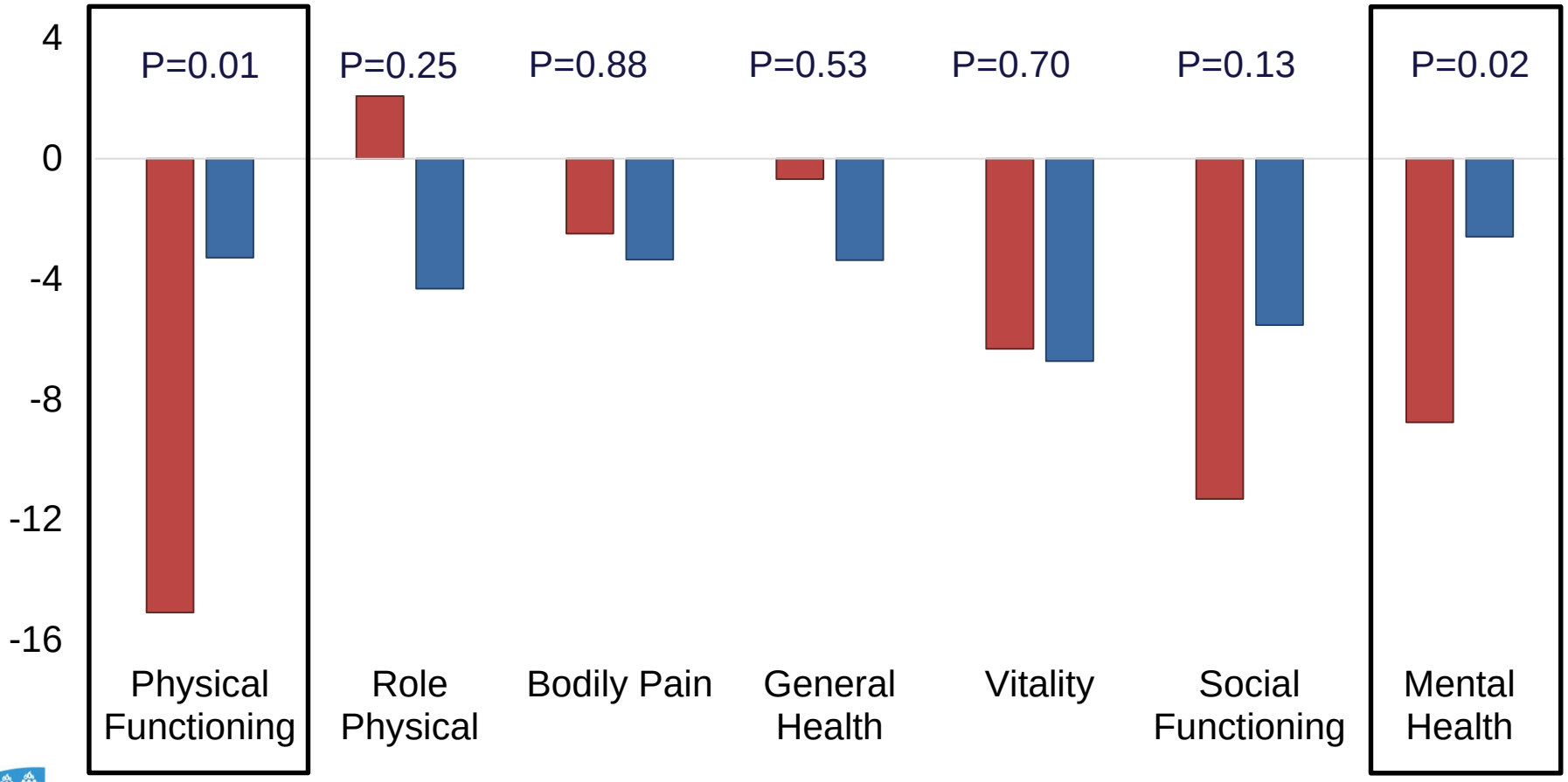
Physical Health

Mental Health

Alvarez E et al. 19th ADRLH Madrid 2017. Abstract 72.

UPBEAT – changes in QOL subdomains

- Absolute mean change in QoL sub-domain scores HIV+ HIV-



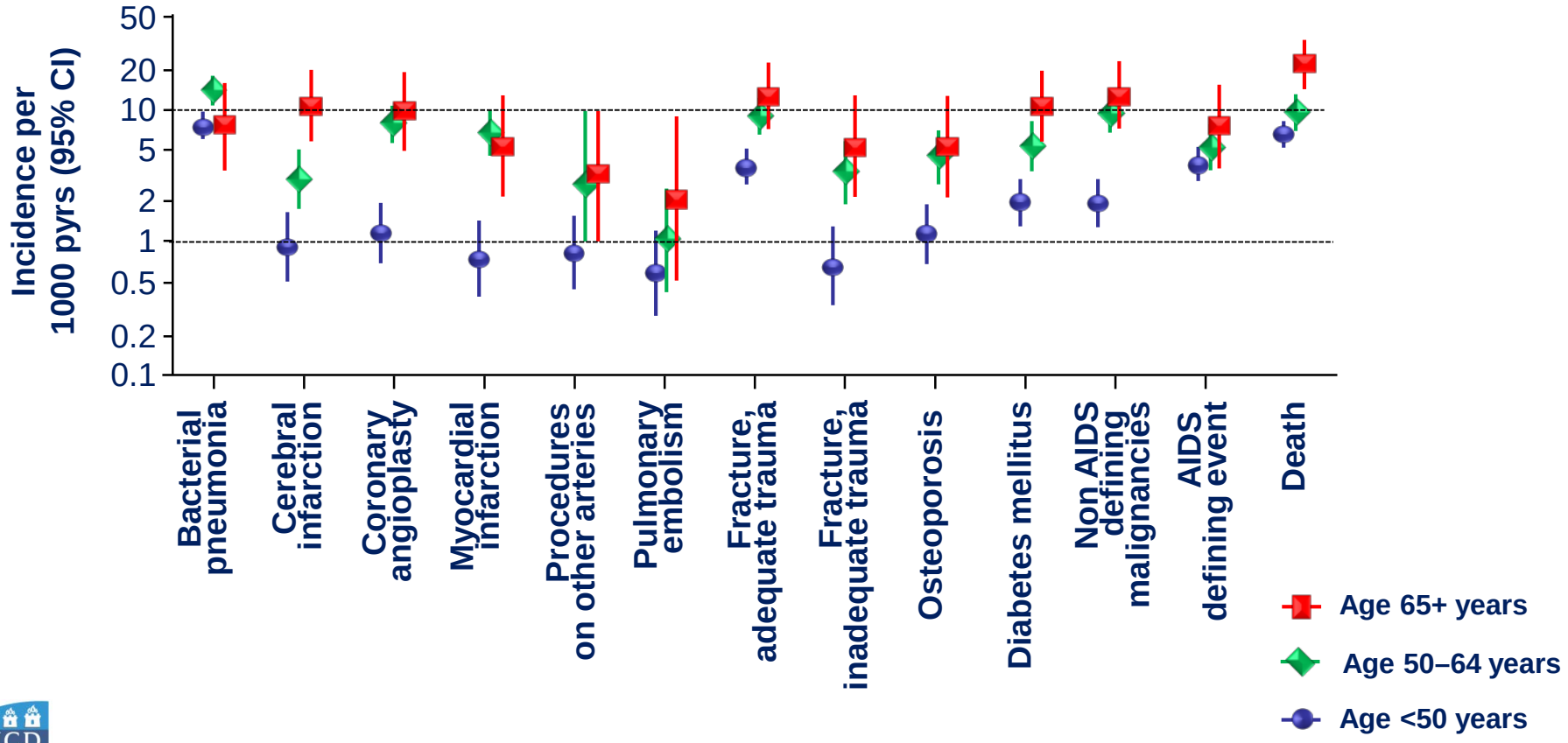
Alvarez E et al. 19th ADRLH Madrid 2017. Abstract 72.

Summary (1)

- Mental health and depression commoner in older PLWH
- Associations between mental health and prevalence of other co-morbidities in older PLWH
- Clustering of co-morbidities suggests a ‘risk profile’
- Consistent with this is greater declines in **physical functioning** and **mental health** sub-domains of QoL over 5 years in HIV UPBEAT
- Changes in estimated QOL result in **significant age-adjusted reductions in QALY**

Ageing with HIV: Clinical consequences

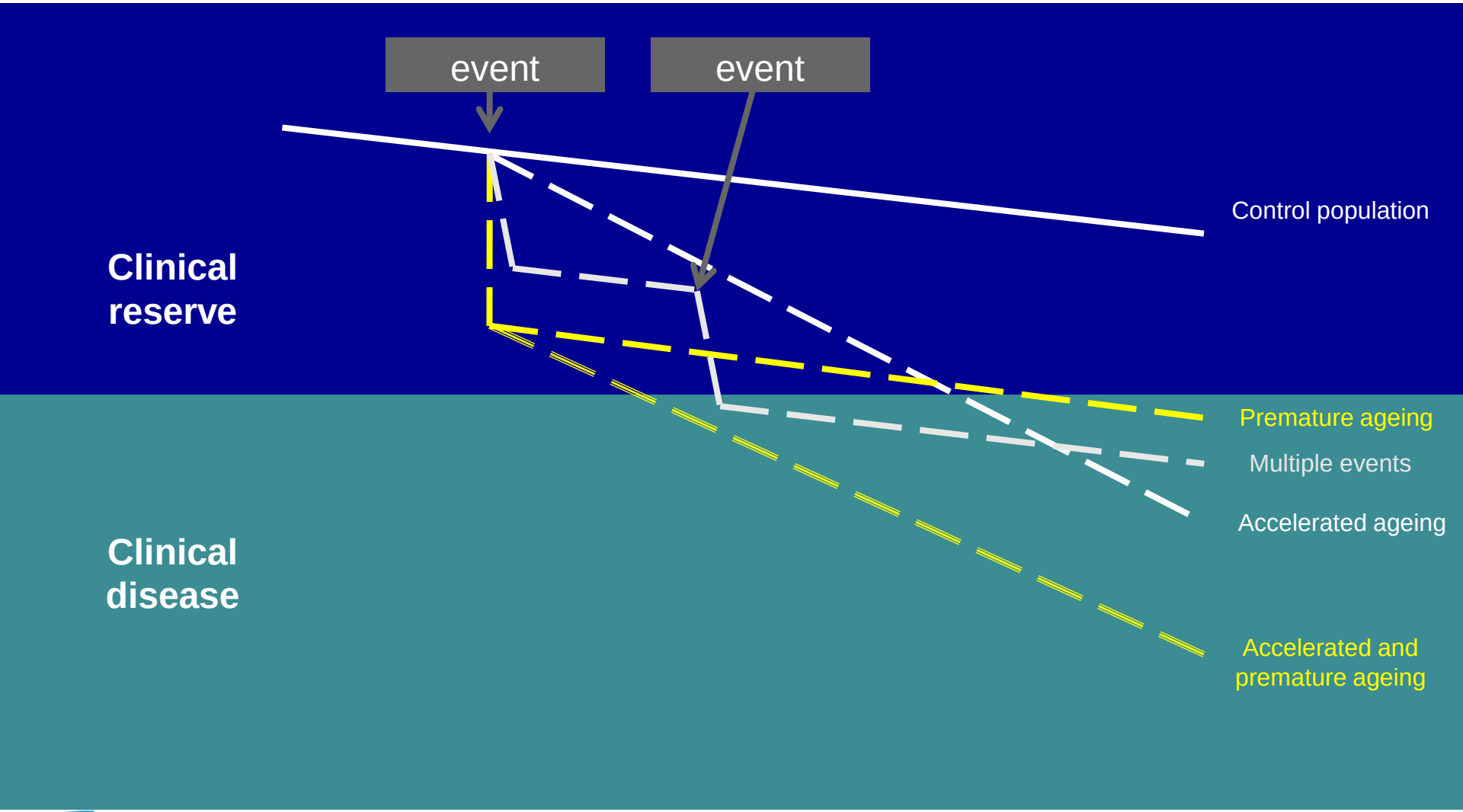
Swiss HIV Cohort Study: Incidence of clinical events between January 1, 2008, and June 30, 2010 stratified by age



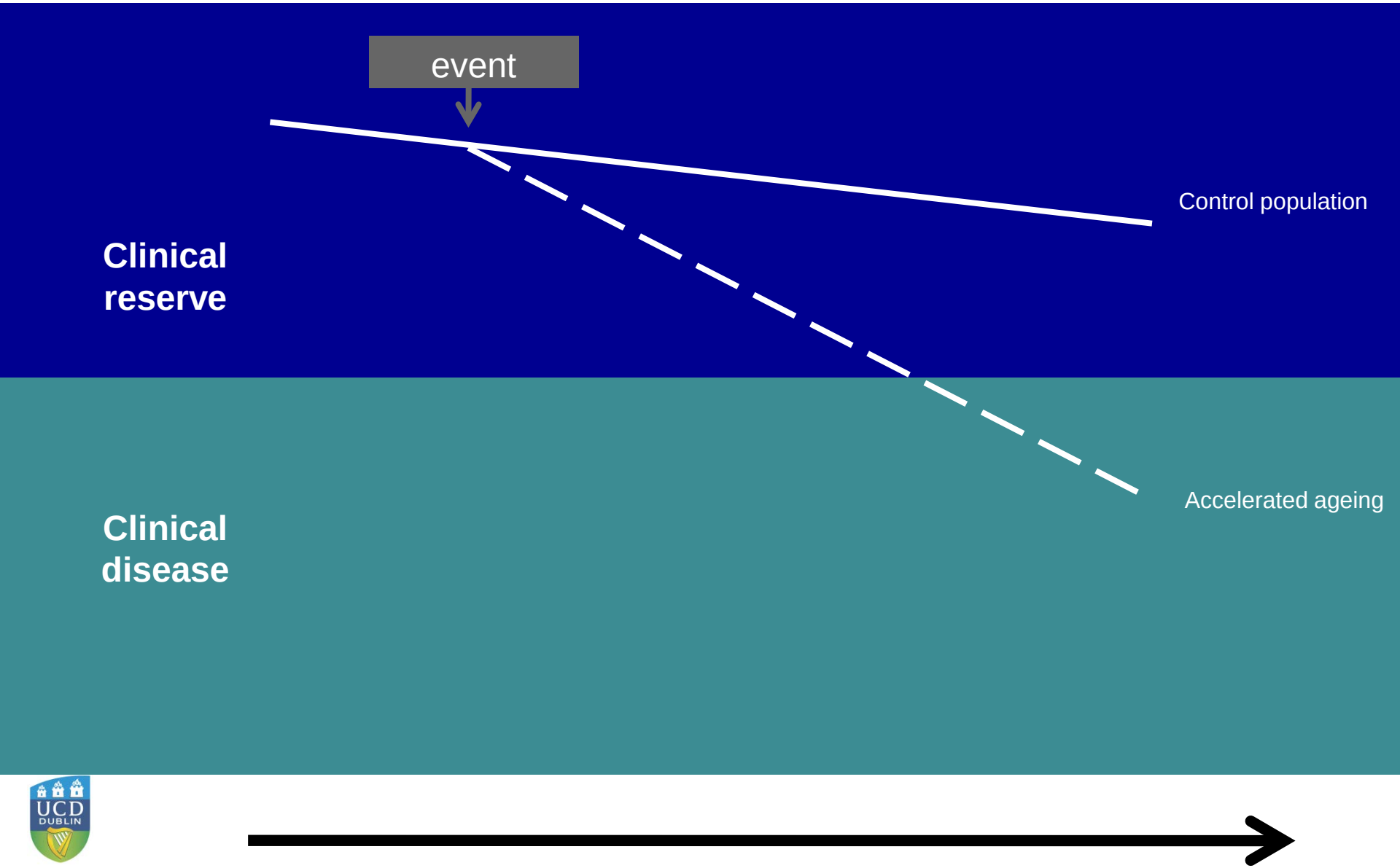
CI, confidence interval; pyrs, person-years

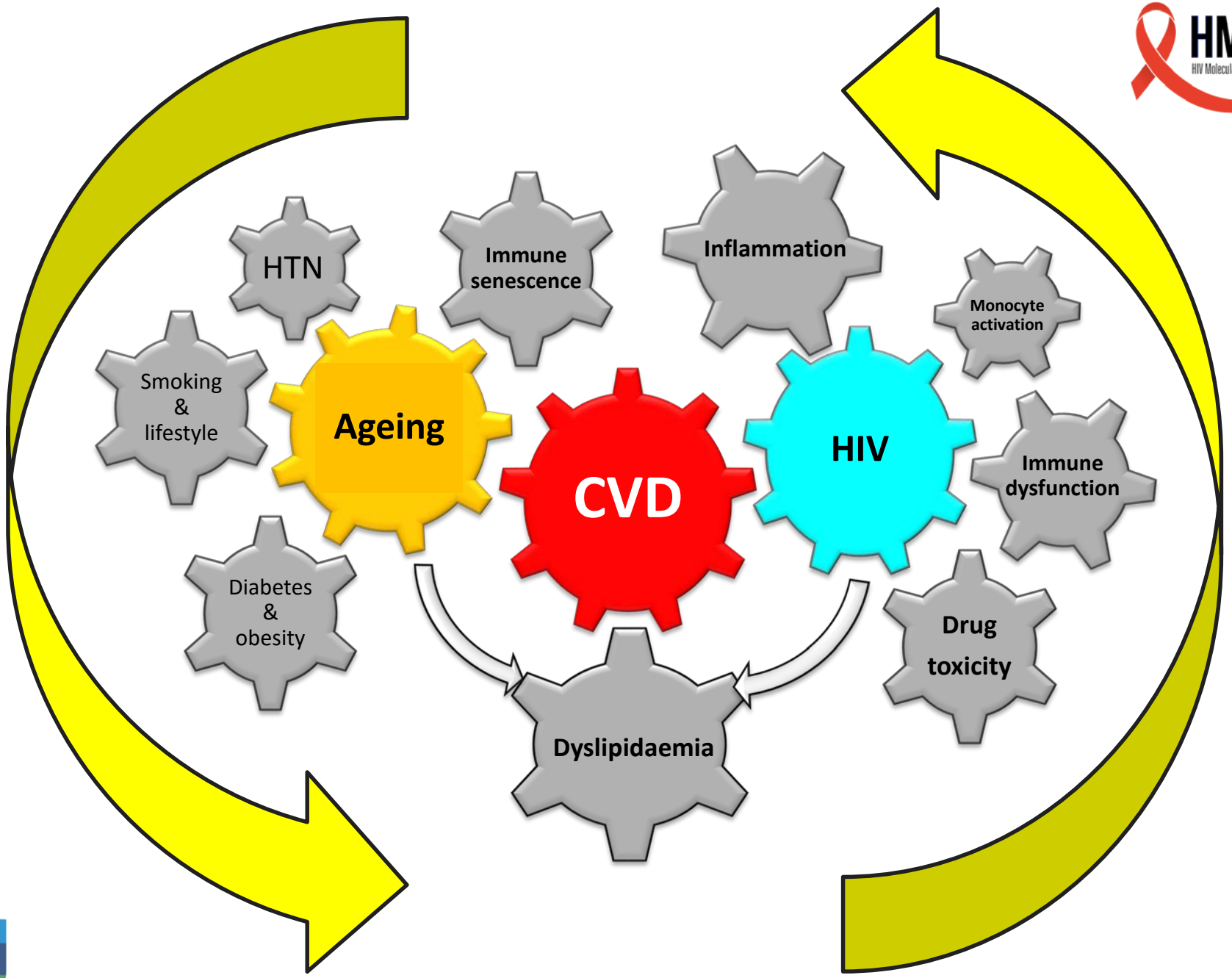
Adapted from Hasse B, et al. Clin Infect Dis 2011;53(11):1130-1139.

Premature vs accelerated ageing



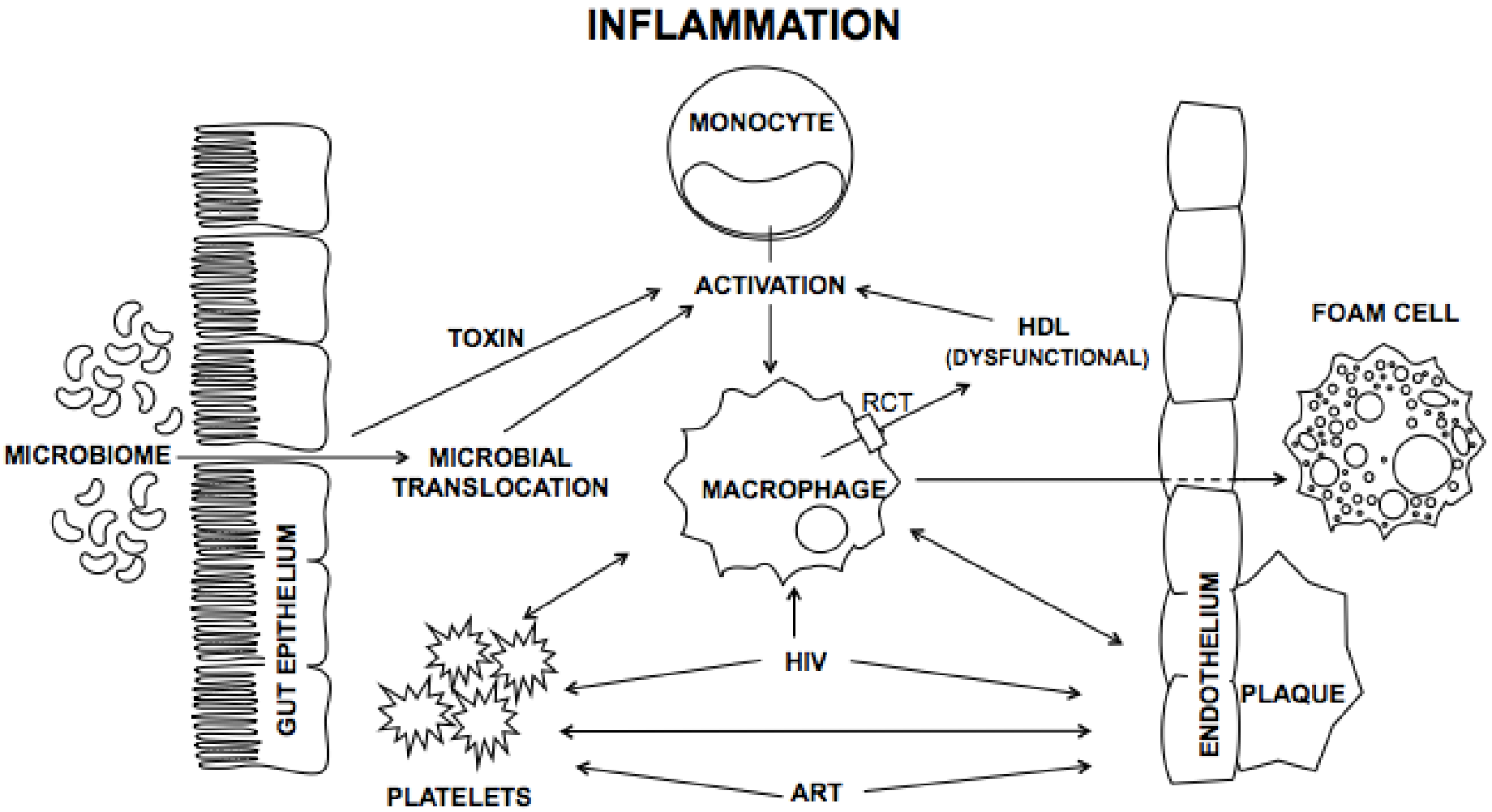
Premature vs accelerated ageing





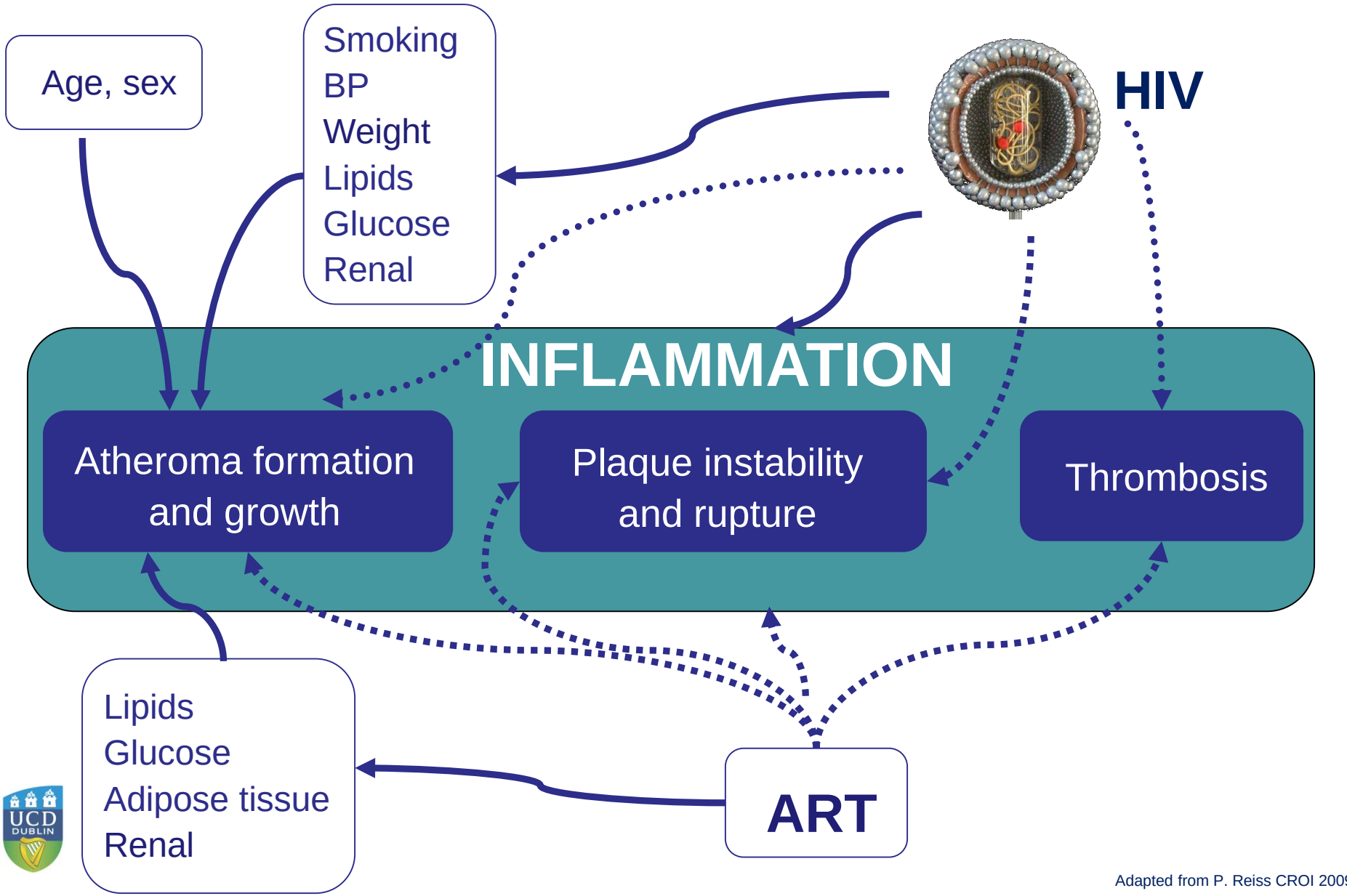
J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

HIV & '*Inflammaging*'



McGettrick et al. 2017

CVD in HIV – role of inflammation



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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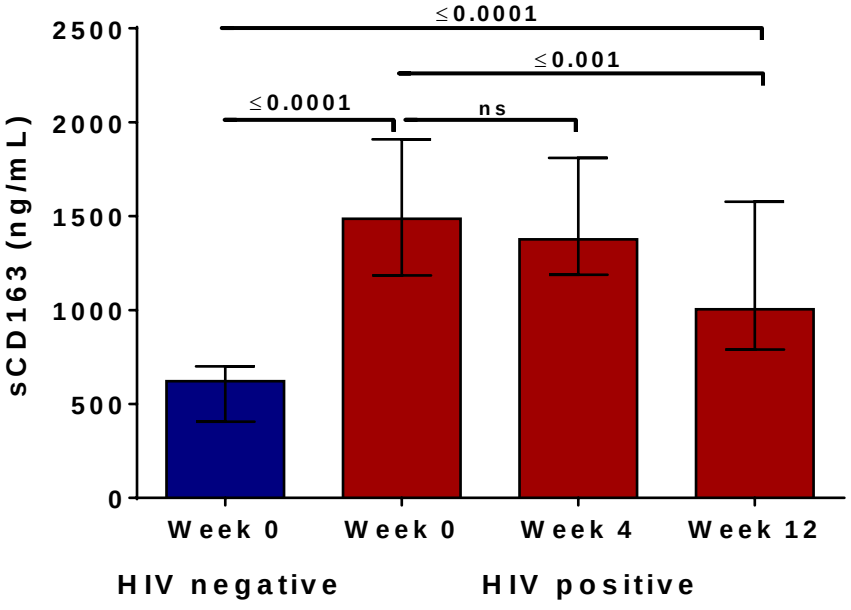
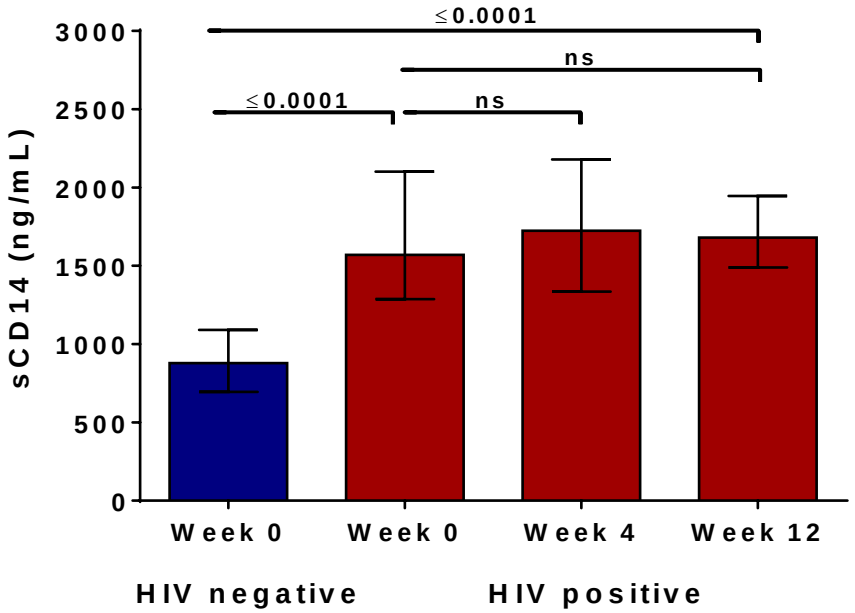
Markers of monocyte activation

- 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



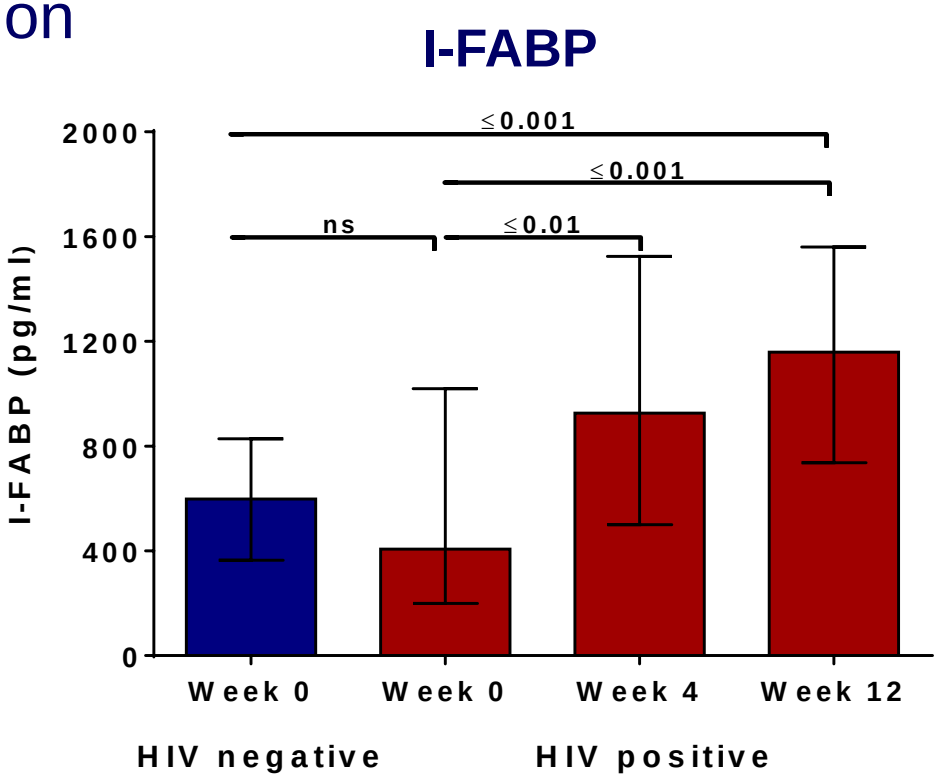
sCD14 baseline comparison and post ART initiation in HIV



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

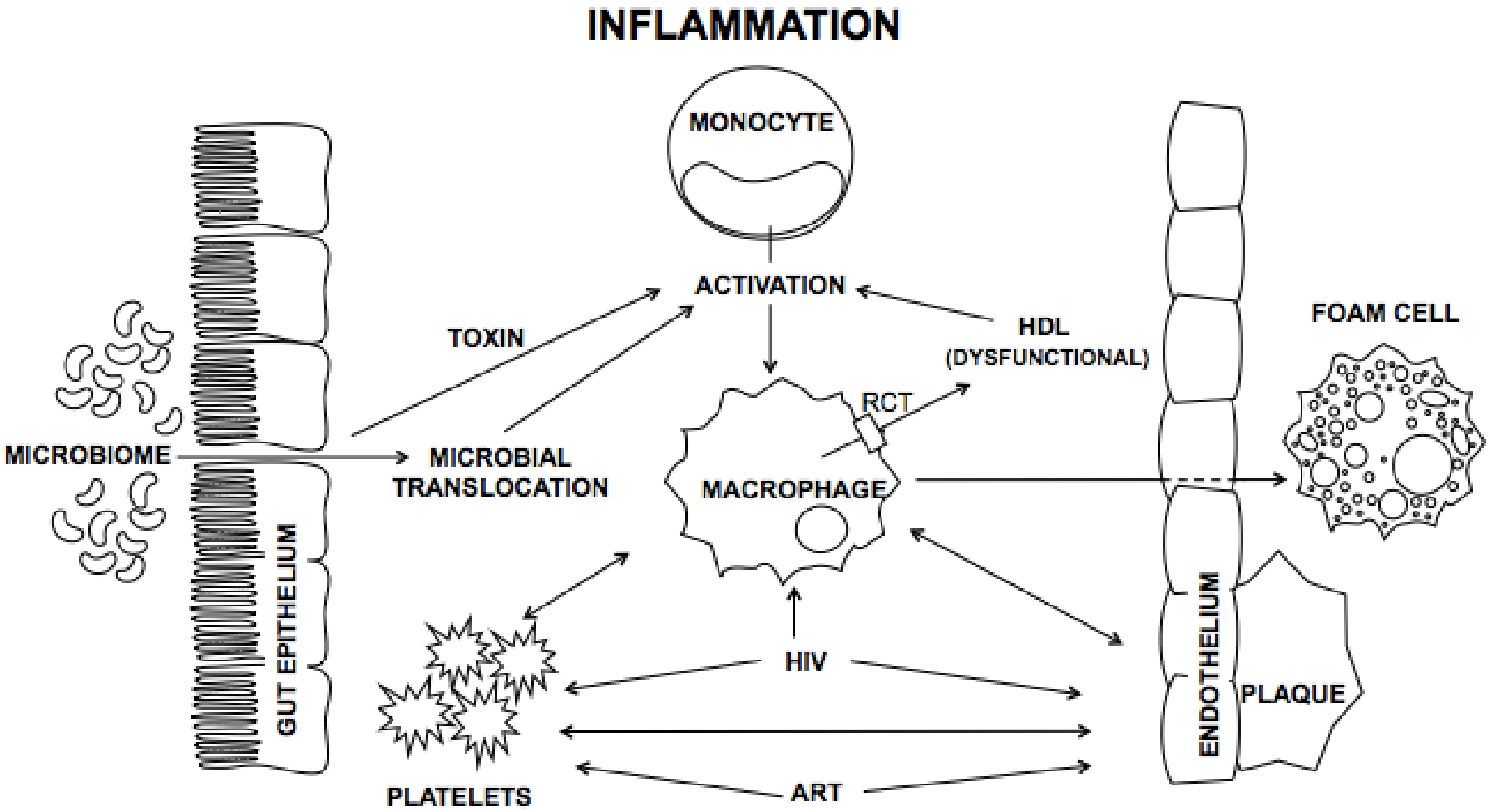
Marker of gut epithelial barrier dysfunction

- 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 & '*Inflammaging*'

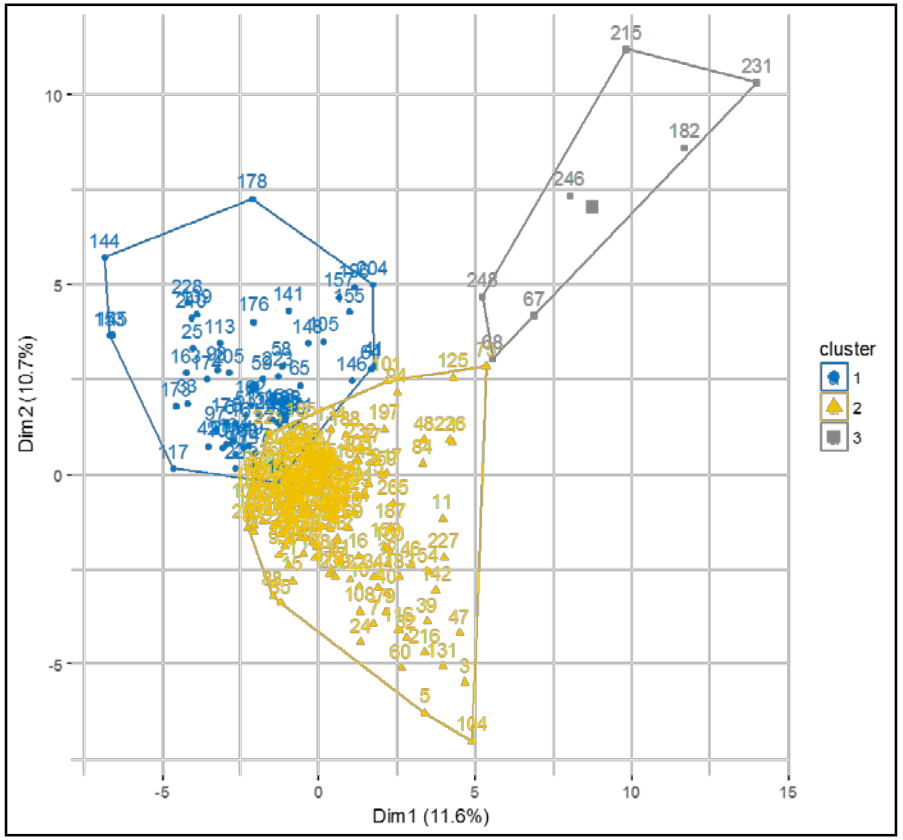


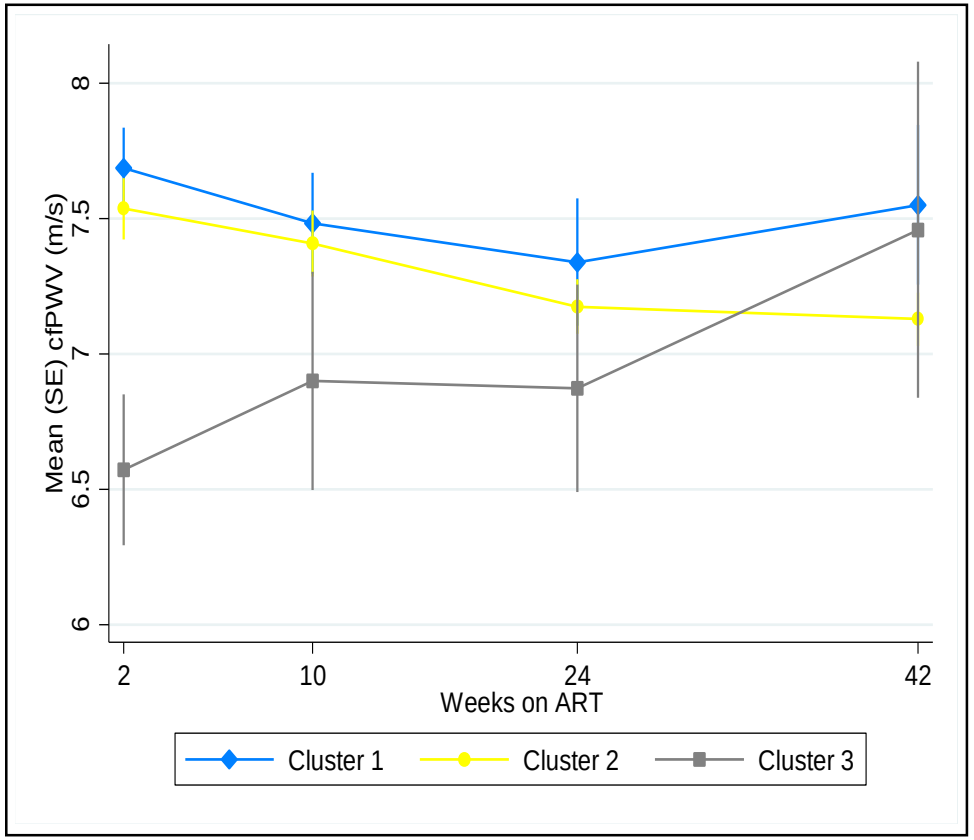
McGettrick et al. 2017

HIV & '*Inflammaging*' – biological mapping

N= 260 African PLWH

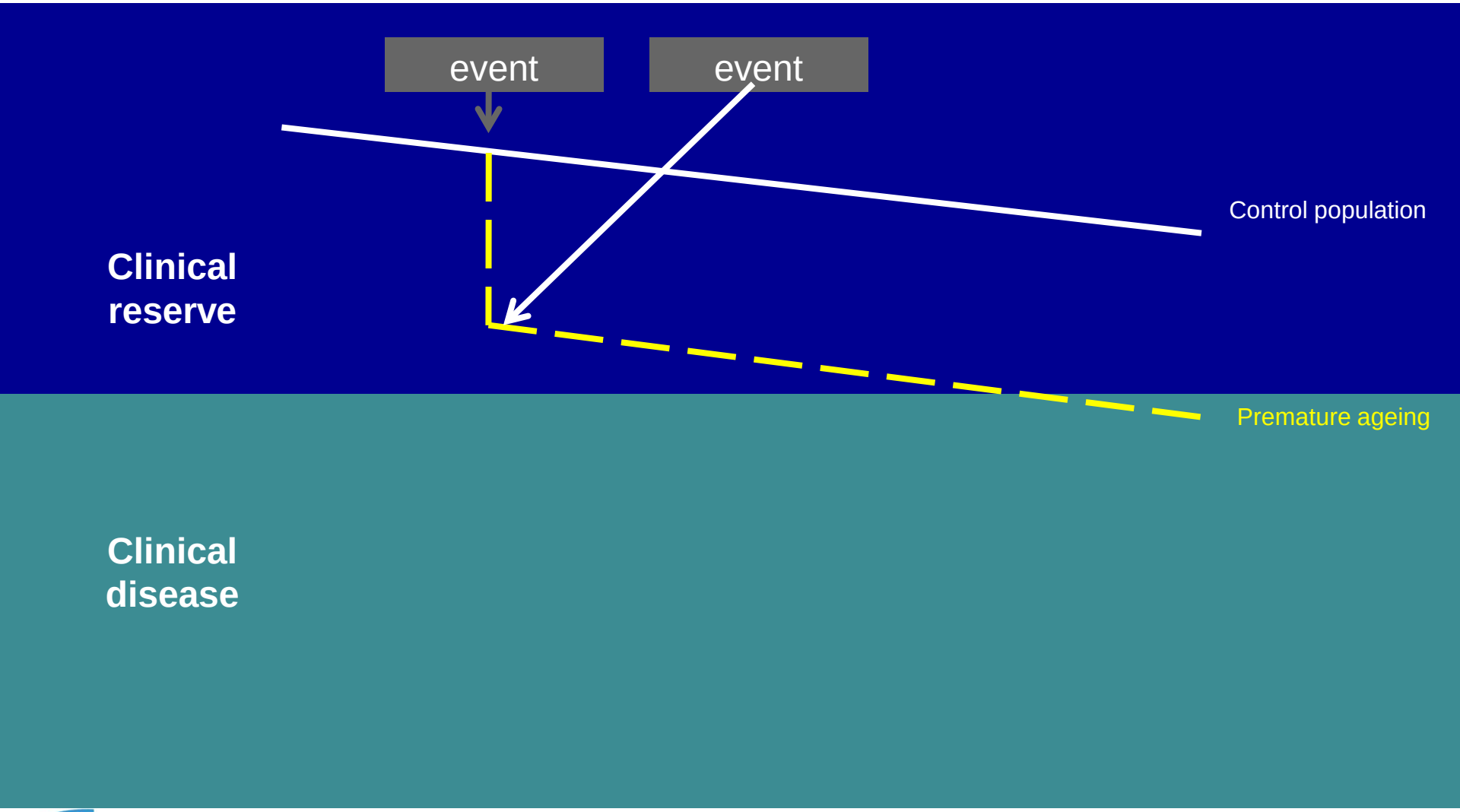
22 immunological and inflammatory parameters compared with change in pulse wave velocity (PWV) after ART initiation





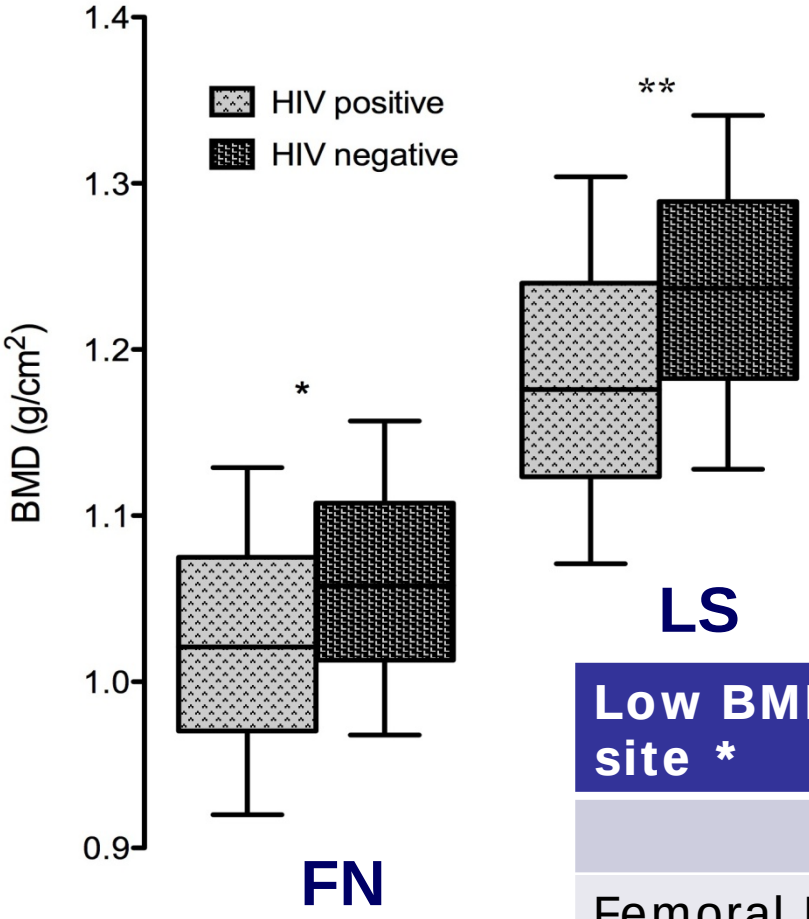
Kenny C. et al. Unpublished data. 2018.

Premature vs accelerated ageing



Bone Disease

HIV UPBEAT



Femoral neck (FN) between group **P*=0.003

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

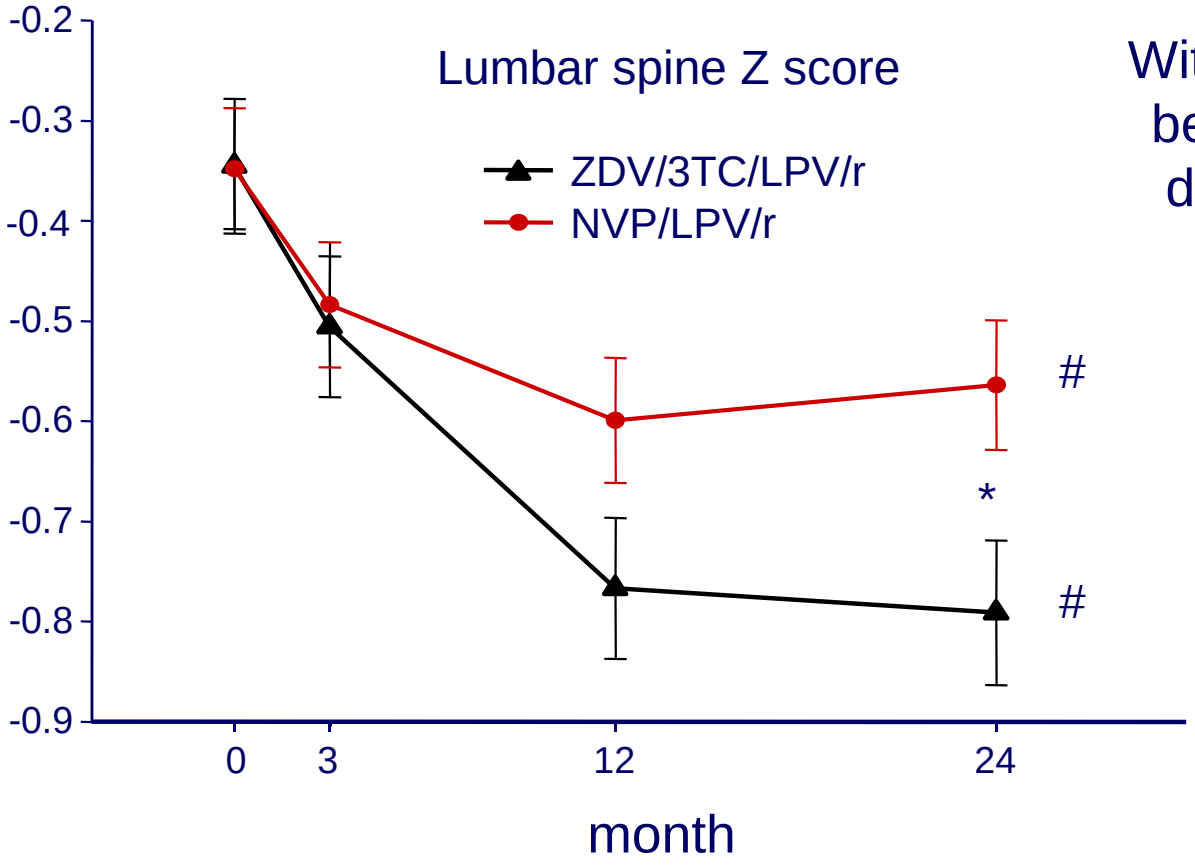
Low BMD by site *	HIV+ (N=210)	HIV- (N=264)	
	n (%)	n (%)	P
Femoral Neck	50 (23.8)	31 (11.7)	0.001
Lumbar Spine	51 (24.3)	33 (12.5)	0.001

*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

ART initiation is associated with bone loss

Greater loss in BMD with ART containing NRTI



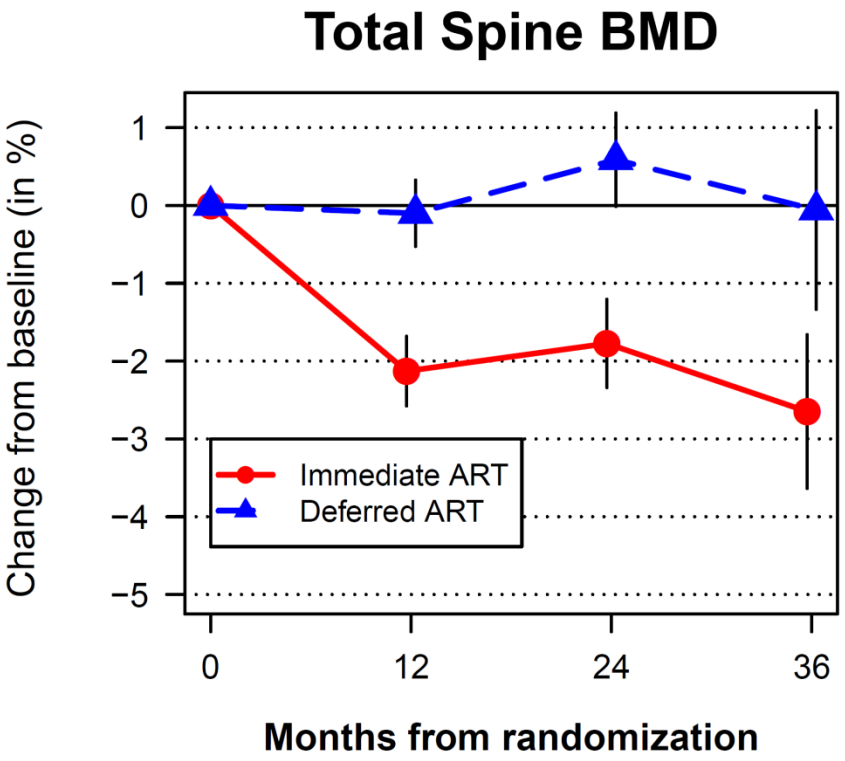
Within group and between-group differences all $P<0.05$

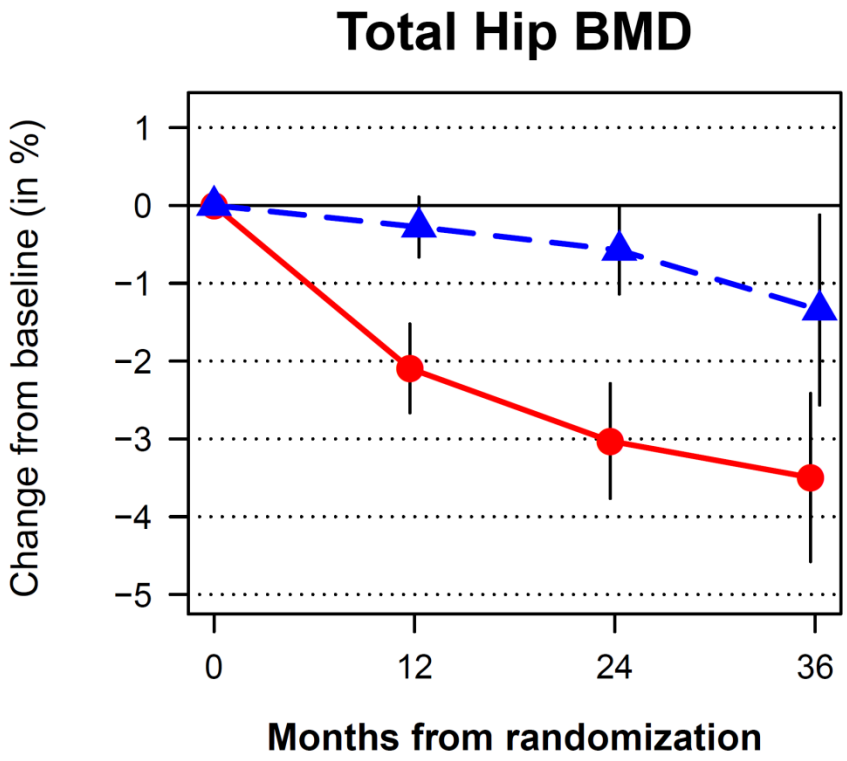
Changes in BMD accompanied by increases in markers of bone turnover

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

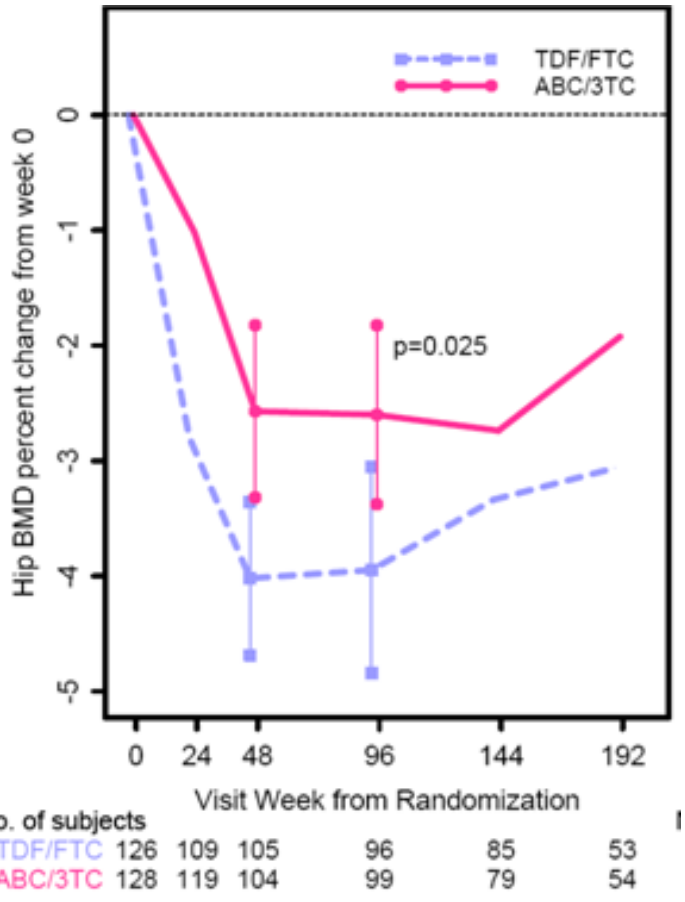
Estimated Mean Diff (95% CI)
-2.1% (-2.8, -1.4), p<0.001

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

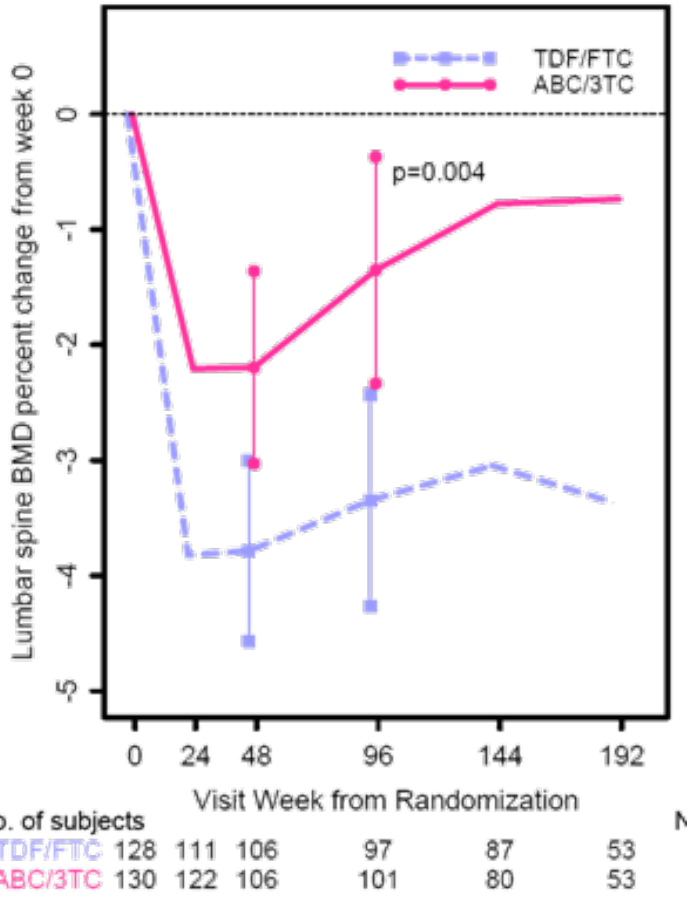
ART and bone loss - ABC/3TC vs TDF/FTC

A5224s: Metabolic Substudy of A5202

Hip



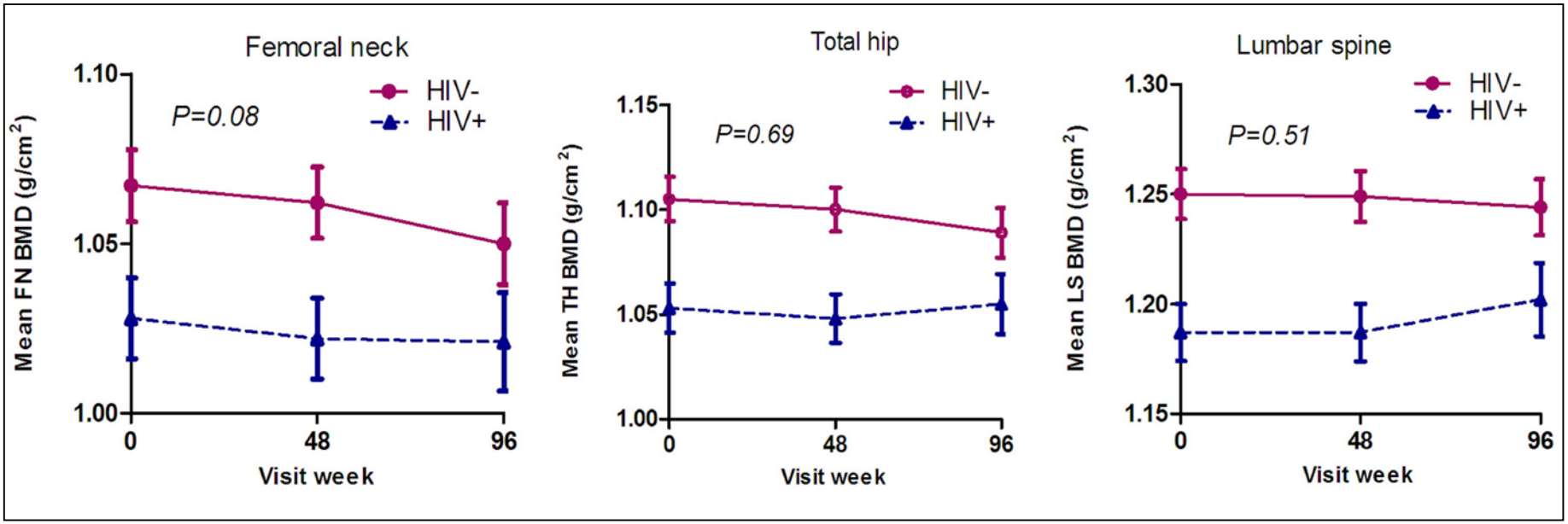
Lumbar Spine



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

ART and BMD – long-term follow-up

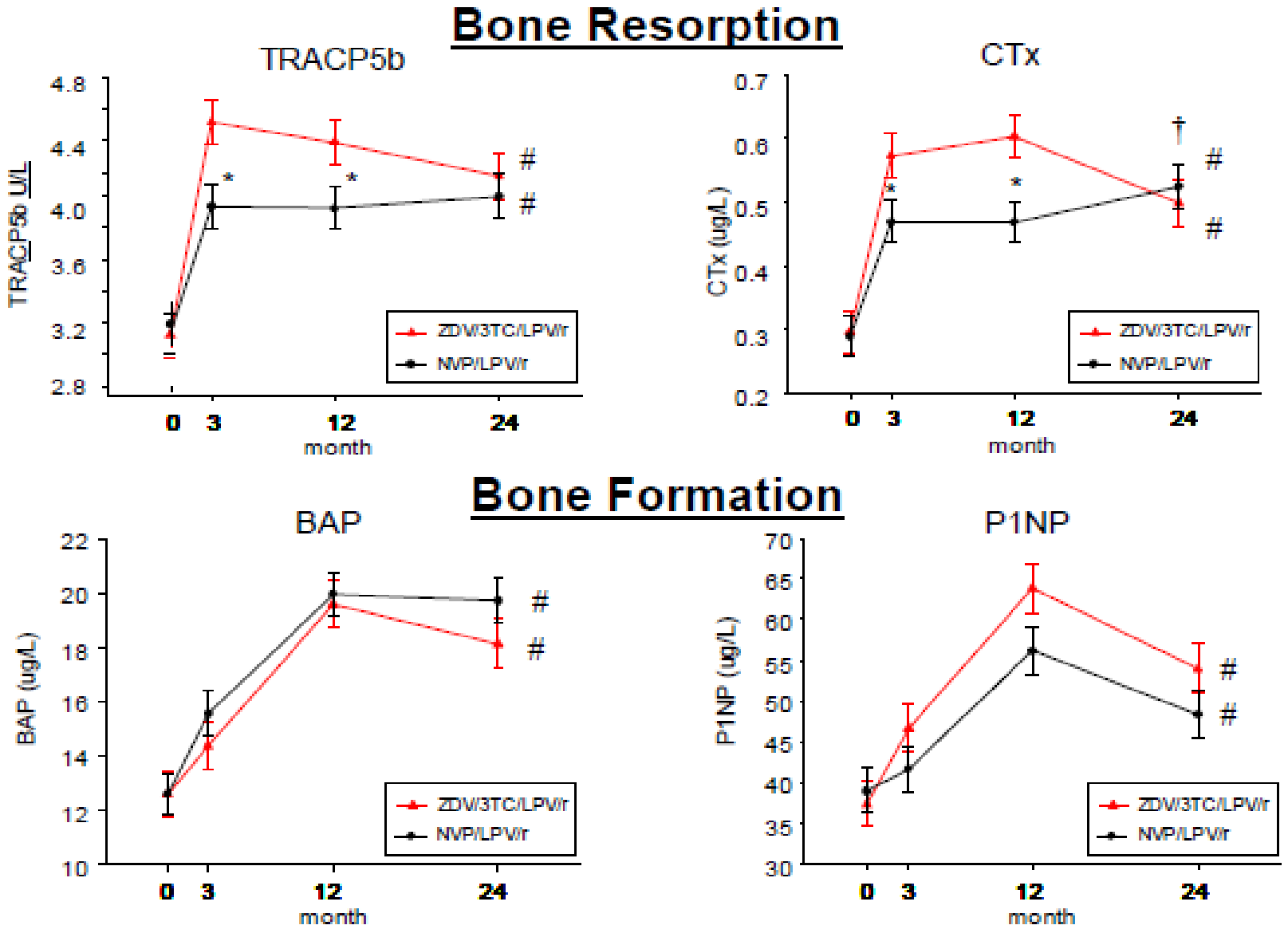
HIV UPBEAT Study. *N*= 384. 3 year follow-up.
HIV+, *N*=120, 88% on ART.



- 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

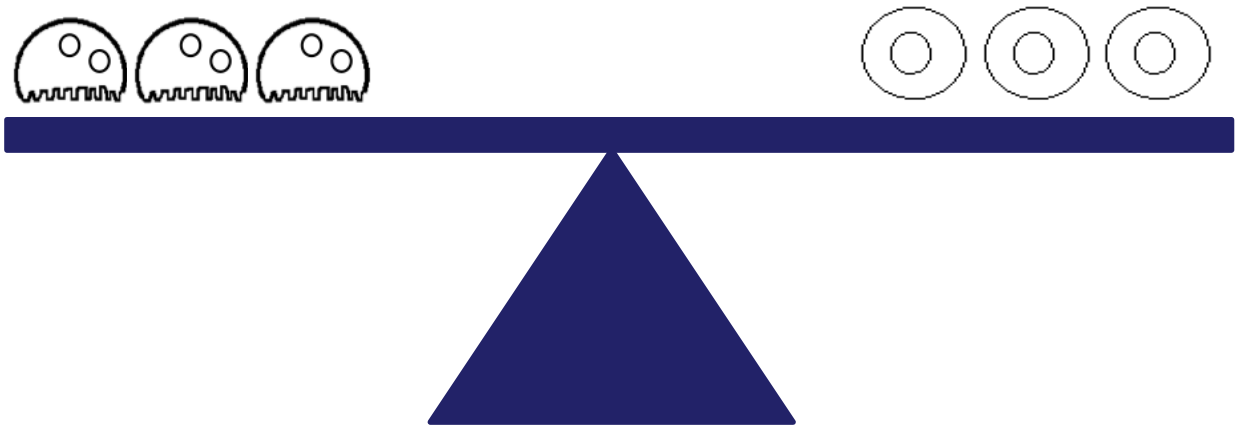
Tinago W et al. AIDS 2017, Mar 13;31(5):643-652

ART initiation and Bone Turnover

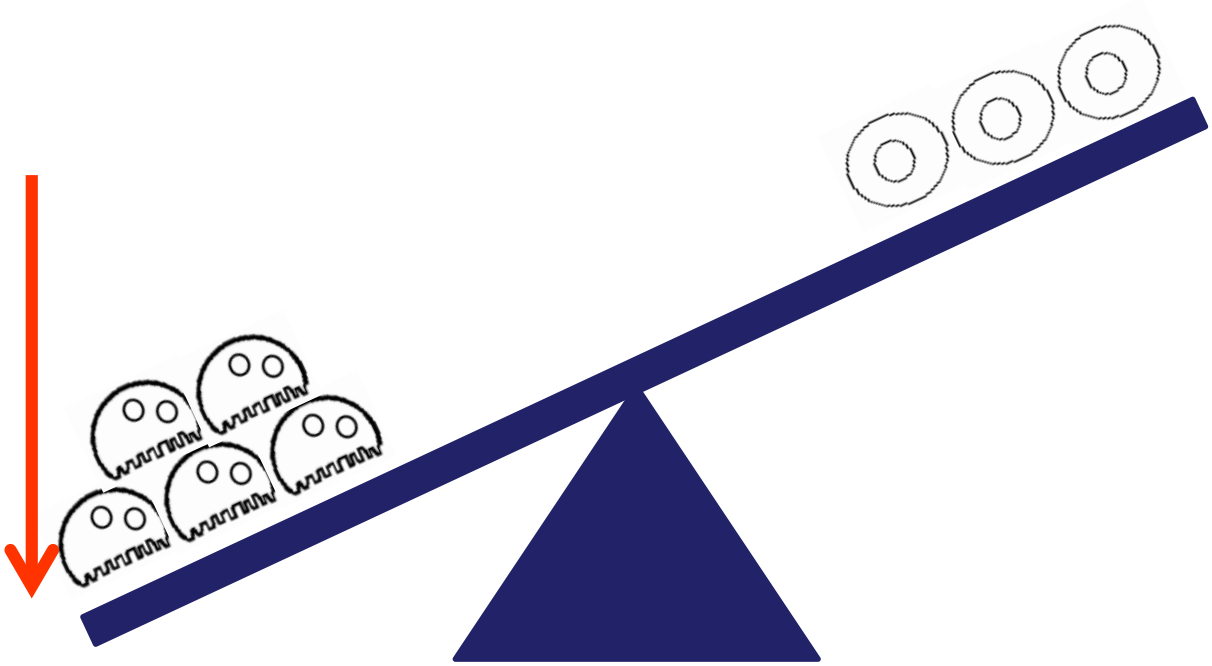


Van Vonderen et al. CROI 2011, abstract 833

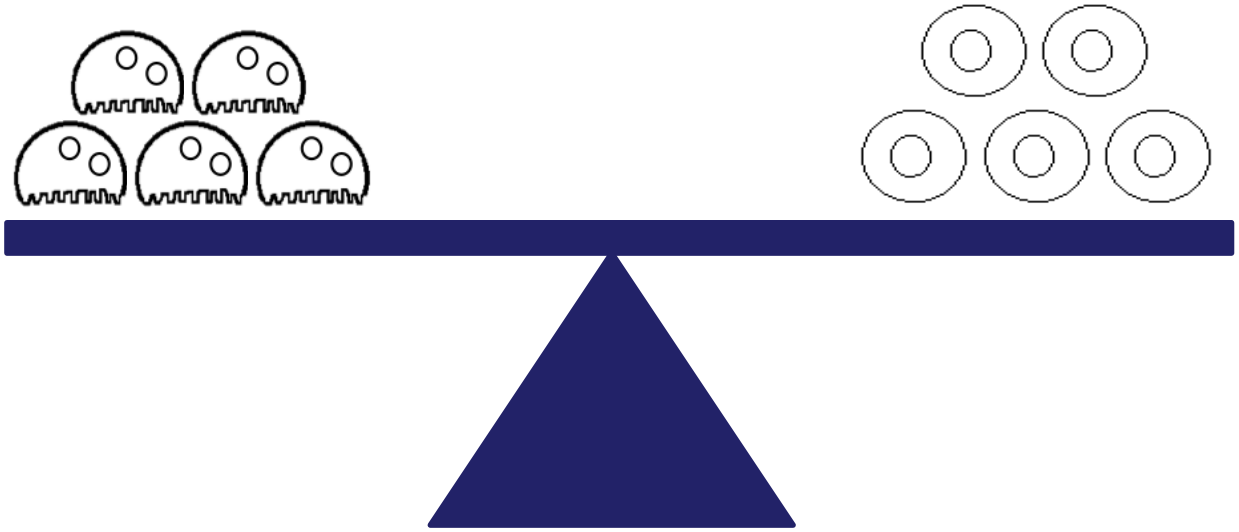
ART initiation and Bone Turnover



ART initiation and Bone Turnover



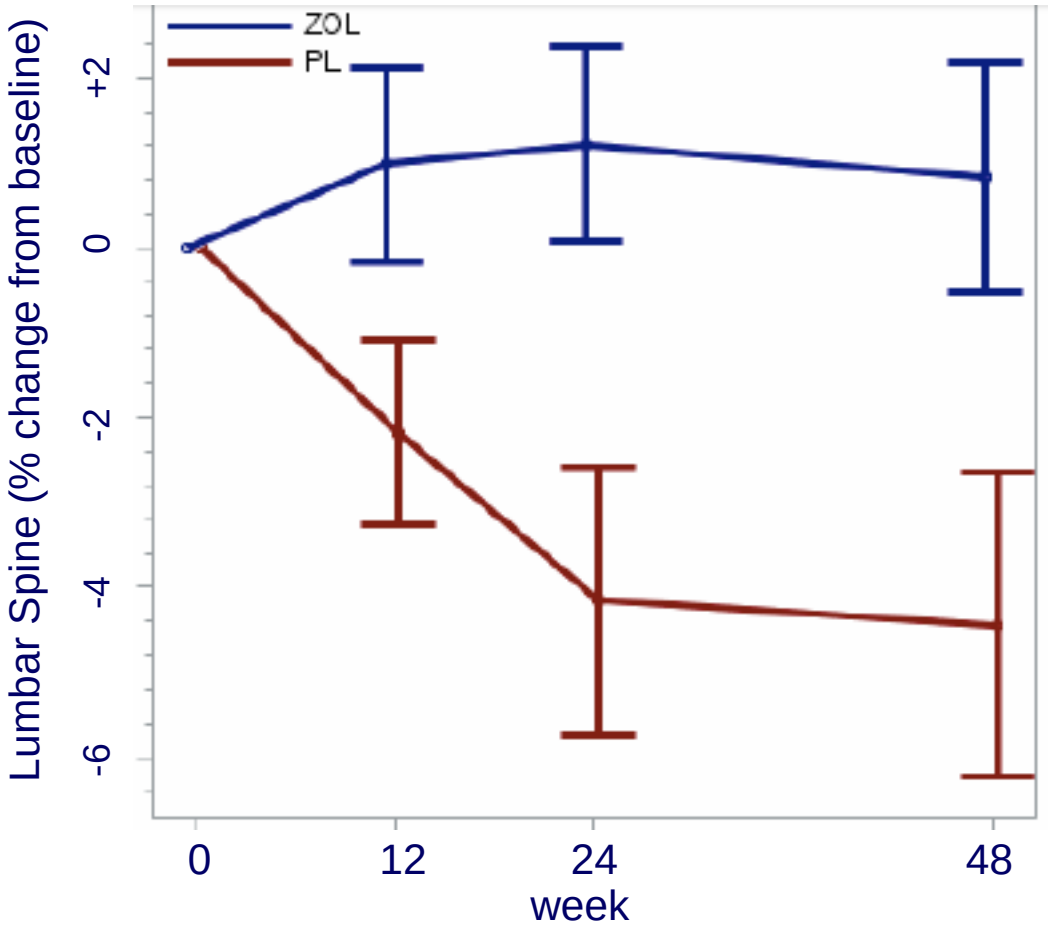
ART initiation and Bone Turnover



BMD loss with ART initiation *is* avoidable!

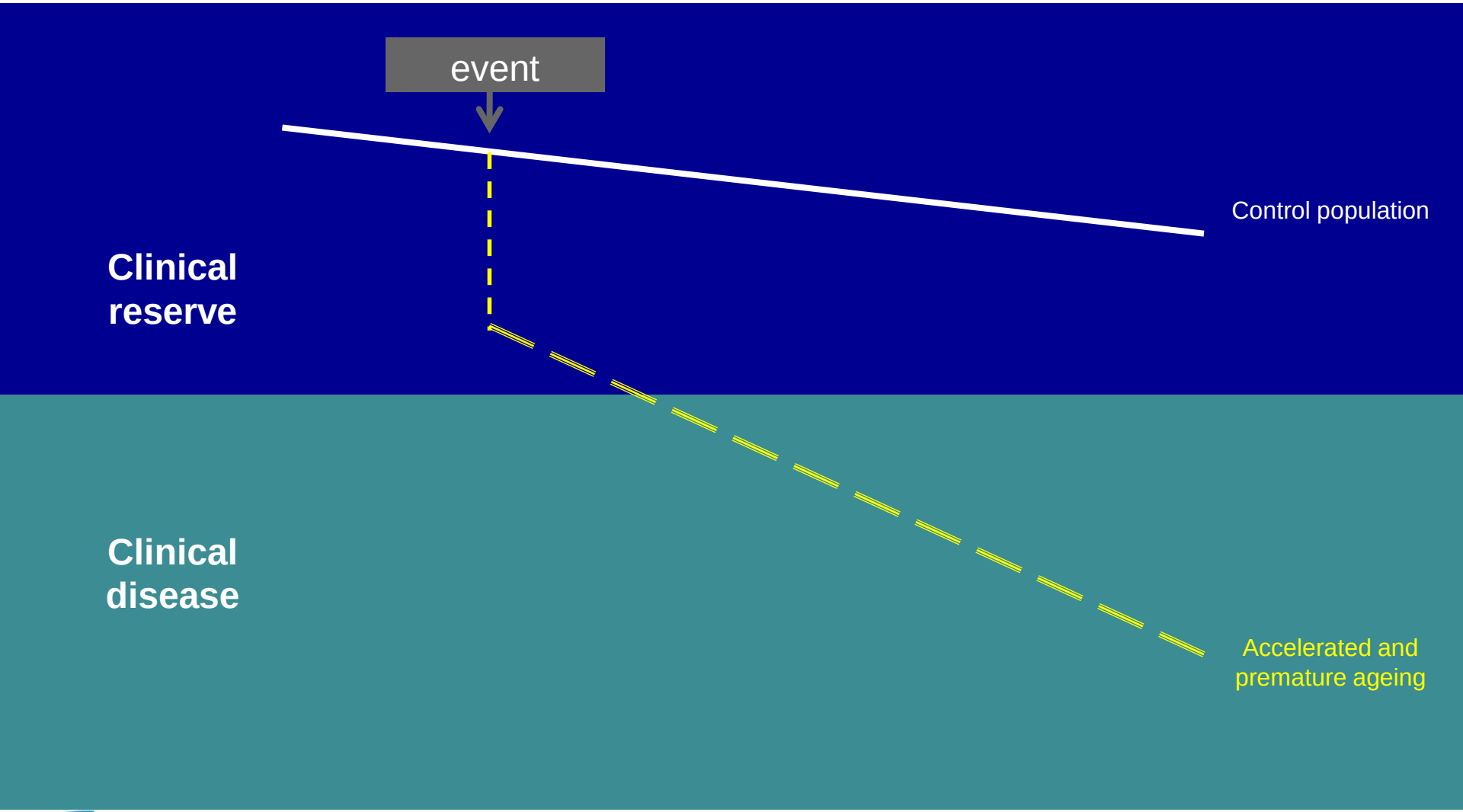
N=63, ART naïve, >30 yrs, TDF/FTC/ATVr

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

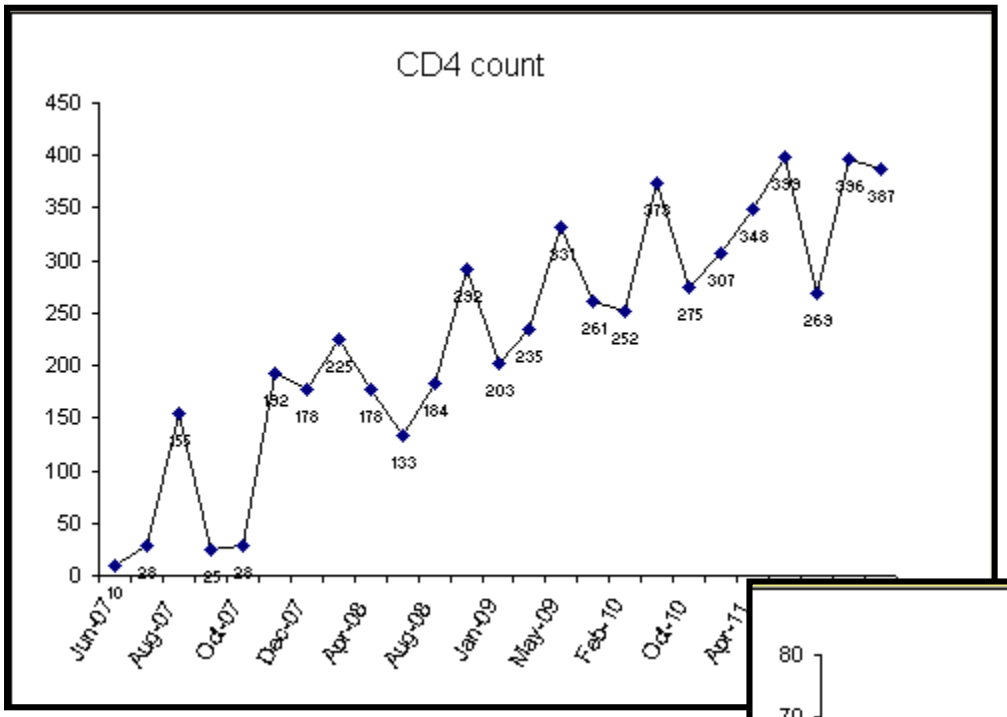


Ofotokun I et al. CROI 2016

Premature vs accelerated ageing

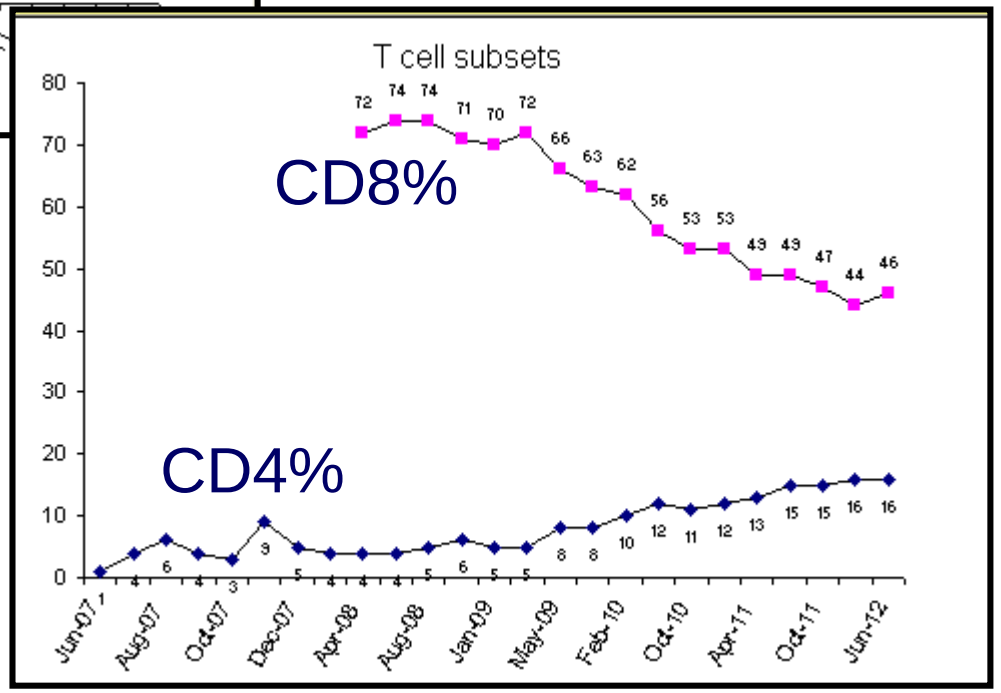


Inflammation and Immune Dysfunction



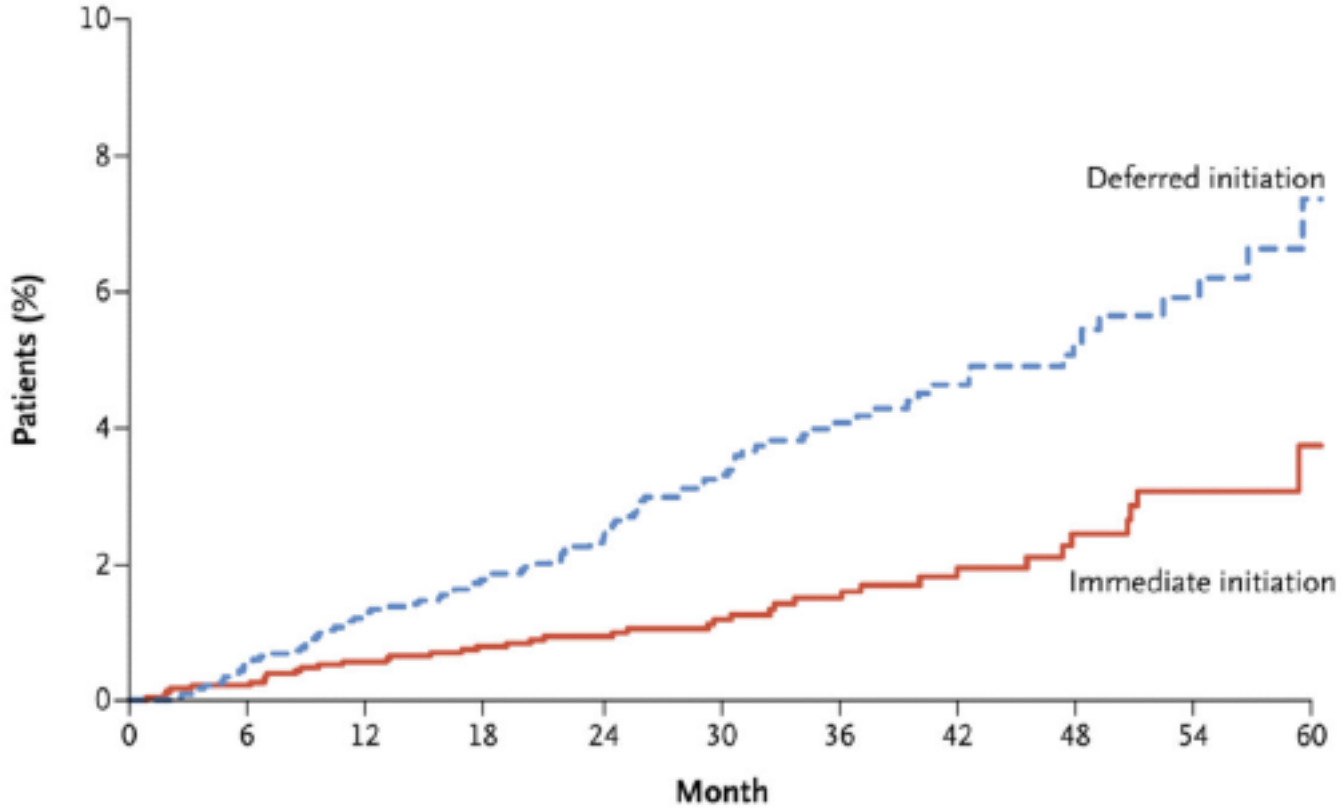
Does it matter…..

….that we don't know if it matters?



Early ART – START Study

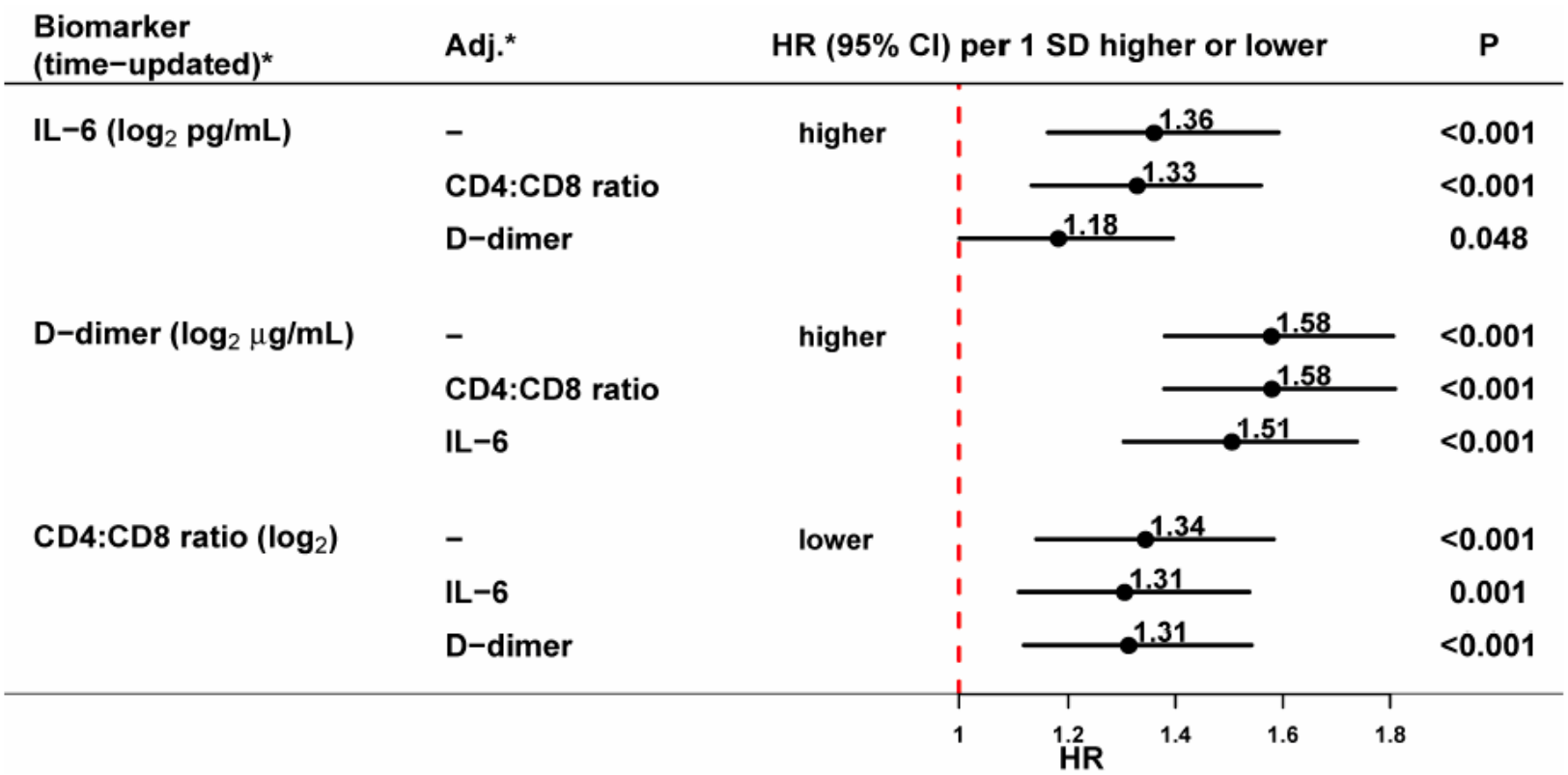
Randomised trial. HIV-1, CD4>500 cells/mm^3
Immediate versus deffered (CD4<350) ART.
N=4685. Endpoint of serious AIDS or non-AIDS event or death.



HR 0.43 (95% CI 0.3, 0.62, P<0.001)

The INSIGHT START Study Group NEJM 2015 Aug 27;373(9):795-807

Clinical Event Risk† by Latest Biomarker Level - 2



START

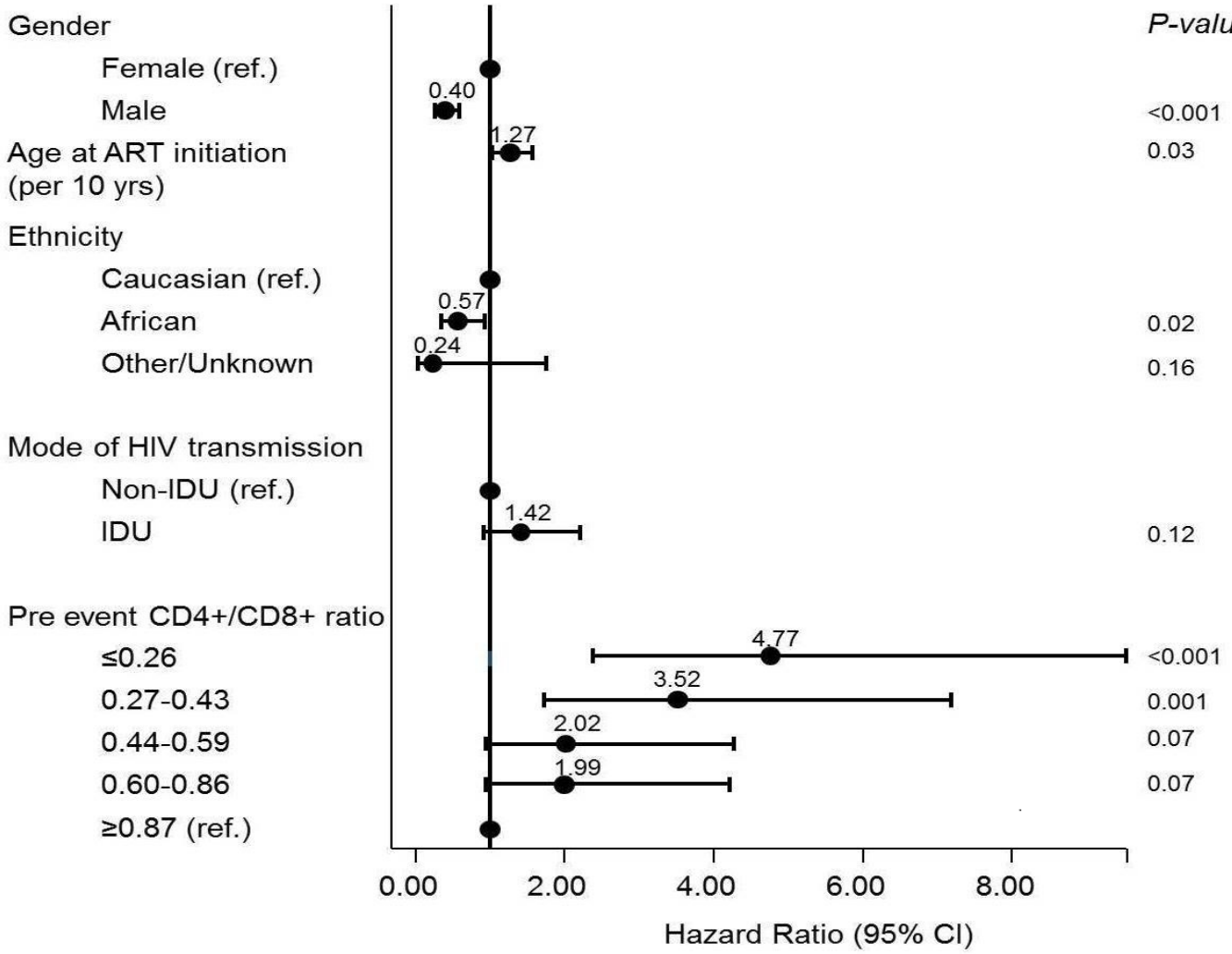
† *Primary outcome: AIDS, serious non-AIDS or death*

**Latest levels of biomarkers at baseline and Month 8. All models are also adjusted for treatment group.*

insight

Biomarkers and outcome – CD4:CD8 ratio

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



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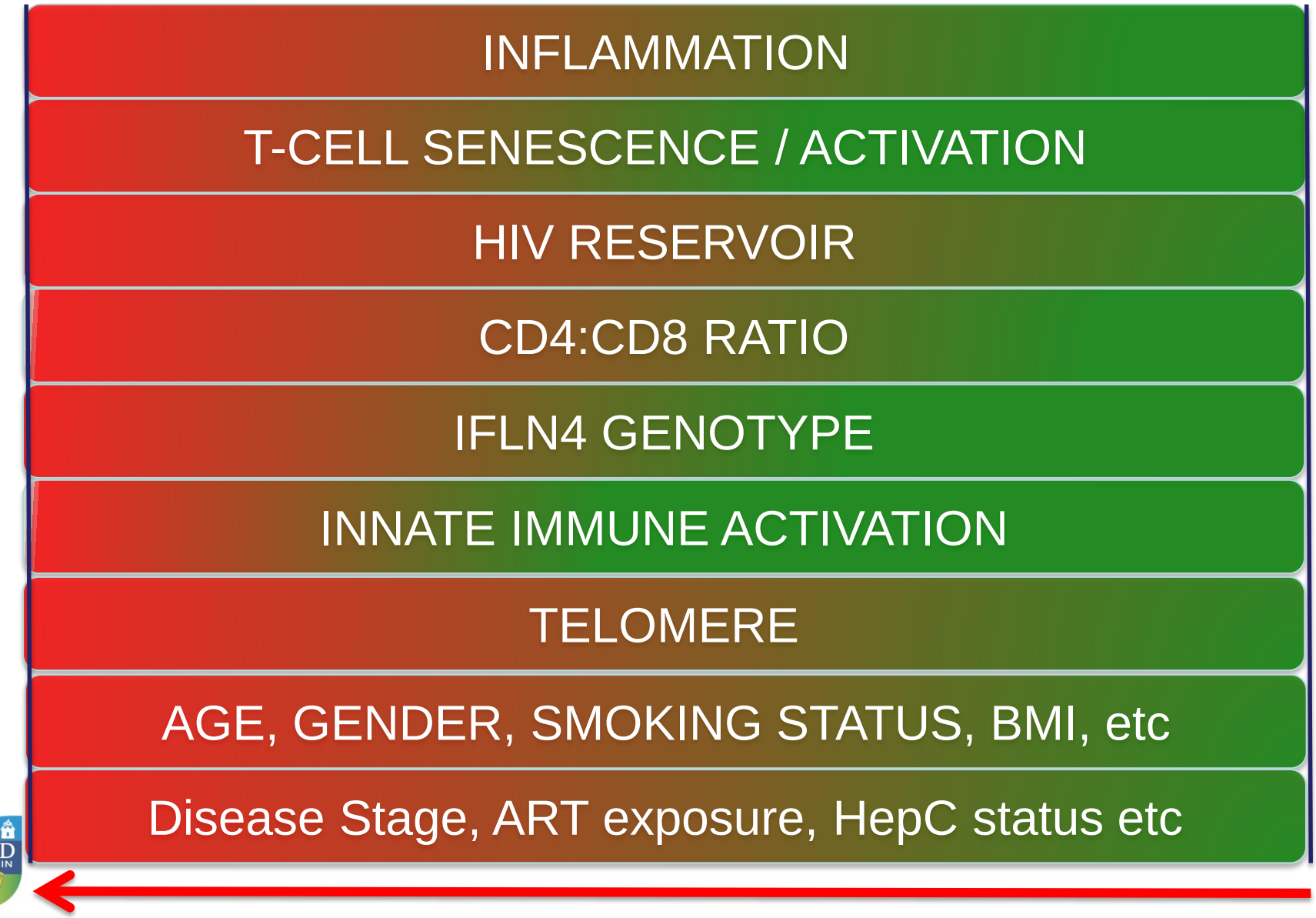
Biological phenotype of Ageing

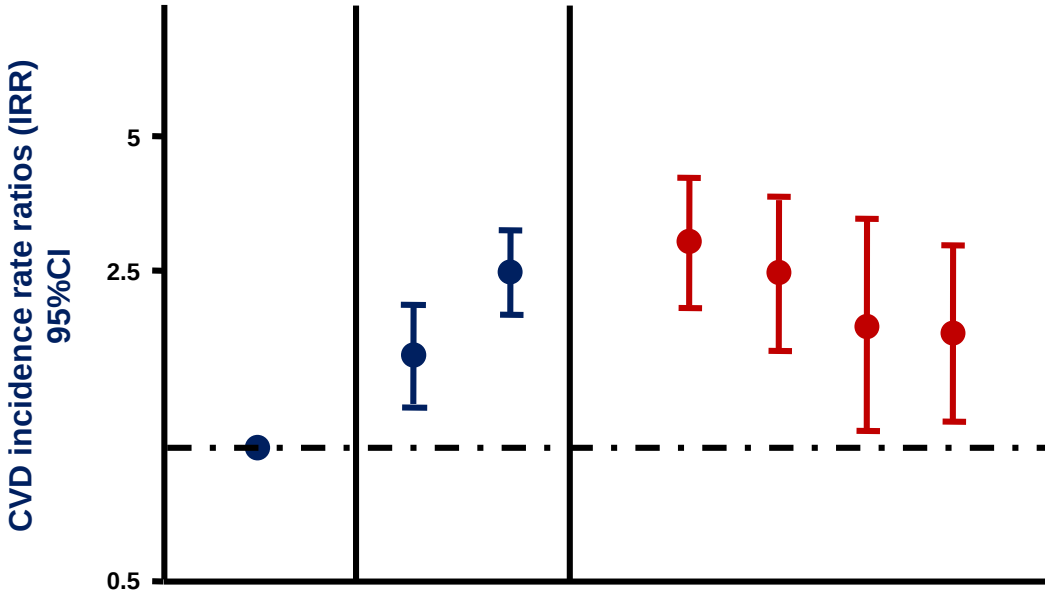


Monitoring for co-morbidities

- 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 - ?CD4:CD8 ratio?
  - Annual / Birthday checks
  - Understand healthy versus unhealthy change
  - 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	

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