Update on HIV, Ageing and Multimorbidity

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HMRG HIV Molecular Research Group

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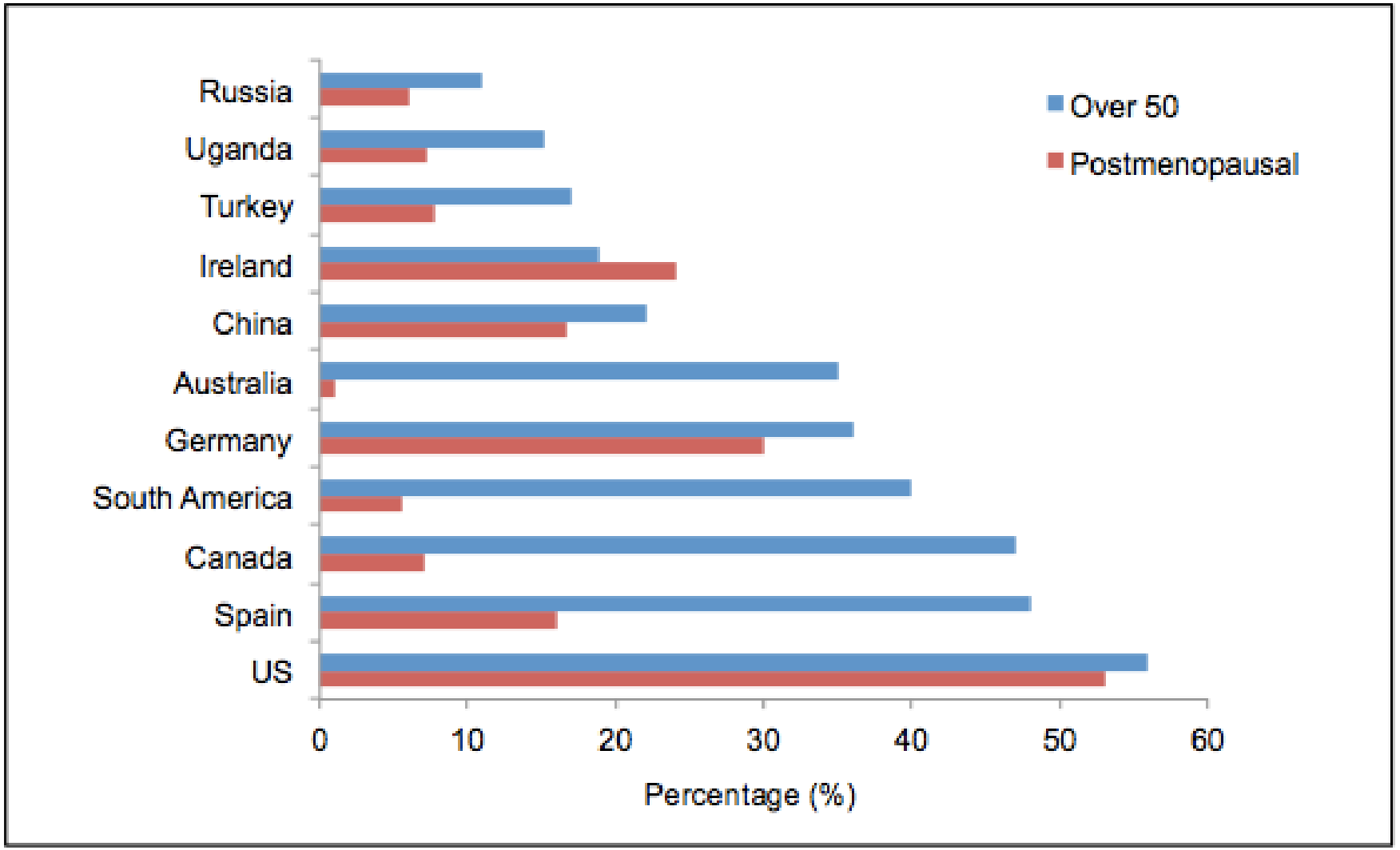
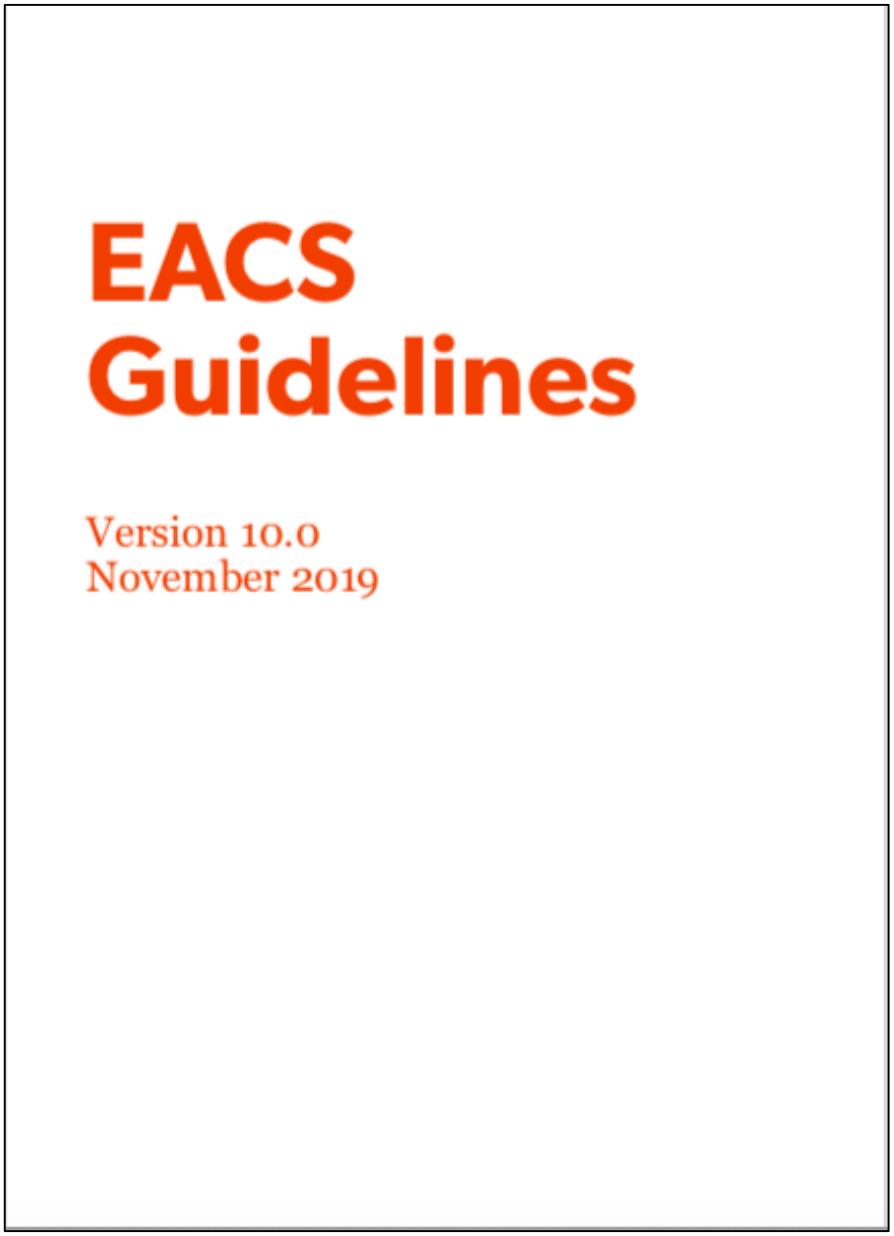
Ageing and HIV



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



90 pages of guidelines targeted at management of co-morbidities.

EACS Guidelines

Version 10.0
November 2019

90 pages of guidelines targeted at management of co-morbidities.

The POPPY Study

Prospective, multi-centre cohort study
Comprises 3 groups:

PLWH ≥50 years

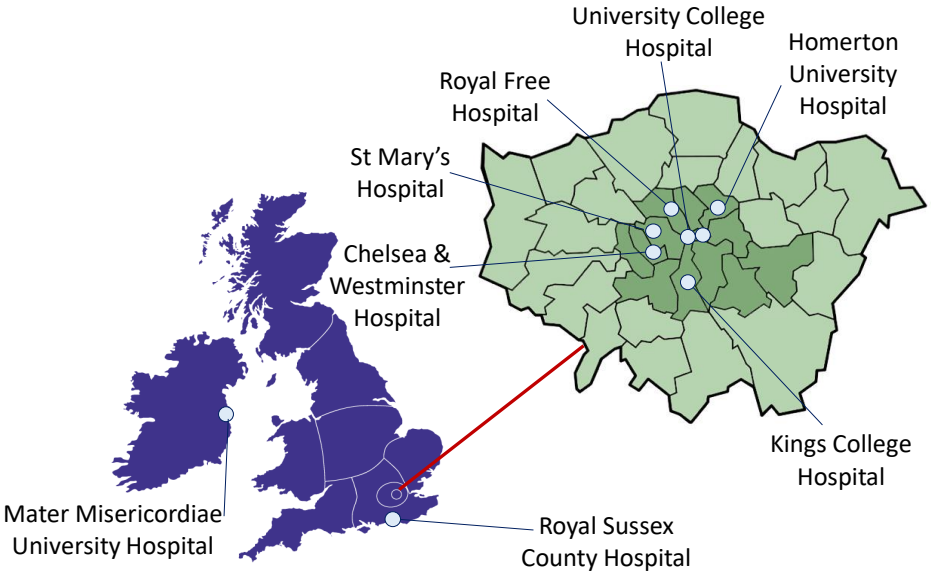
white/black African ethnicity
acquired HIV via sexual routes

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)



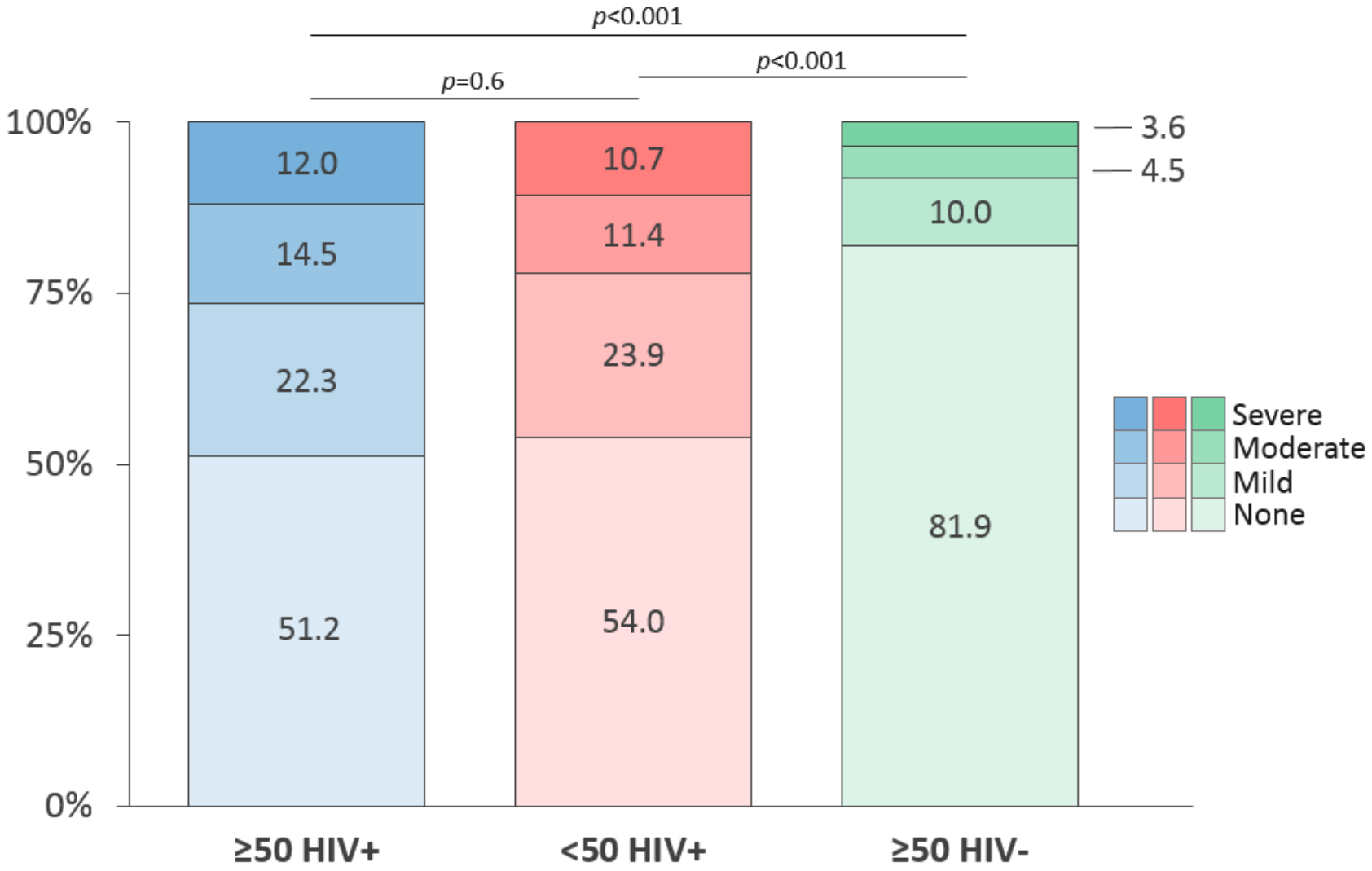
The POPPY Study

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

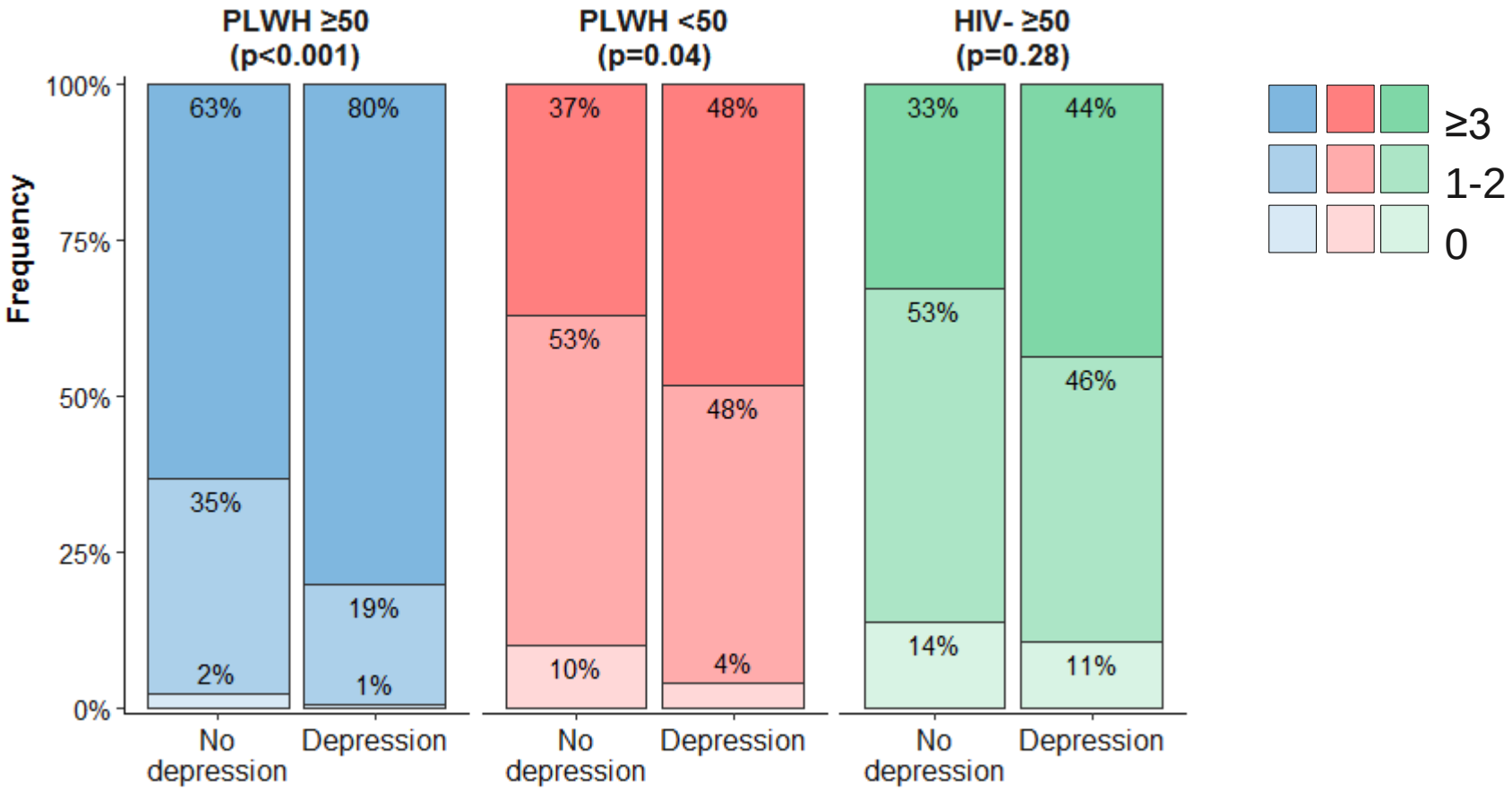
Prevalence of depressive symptoms



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

POPPY - depression

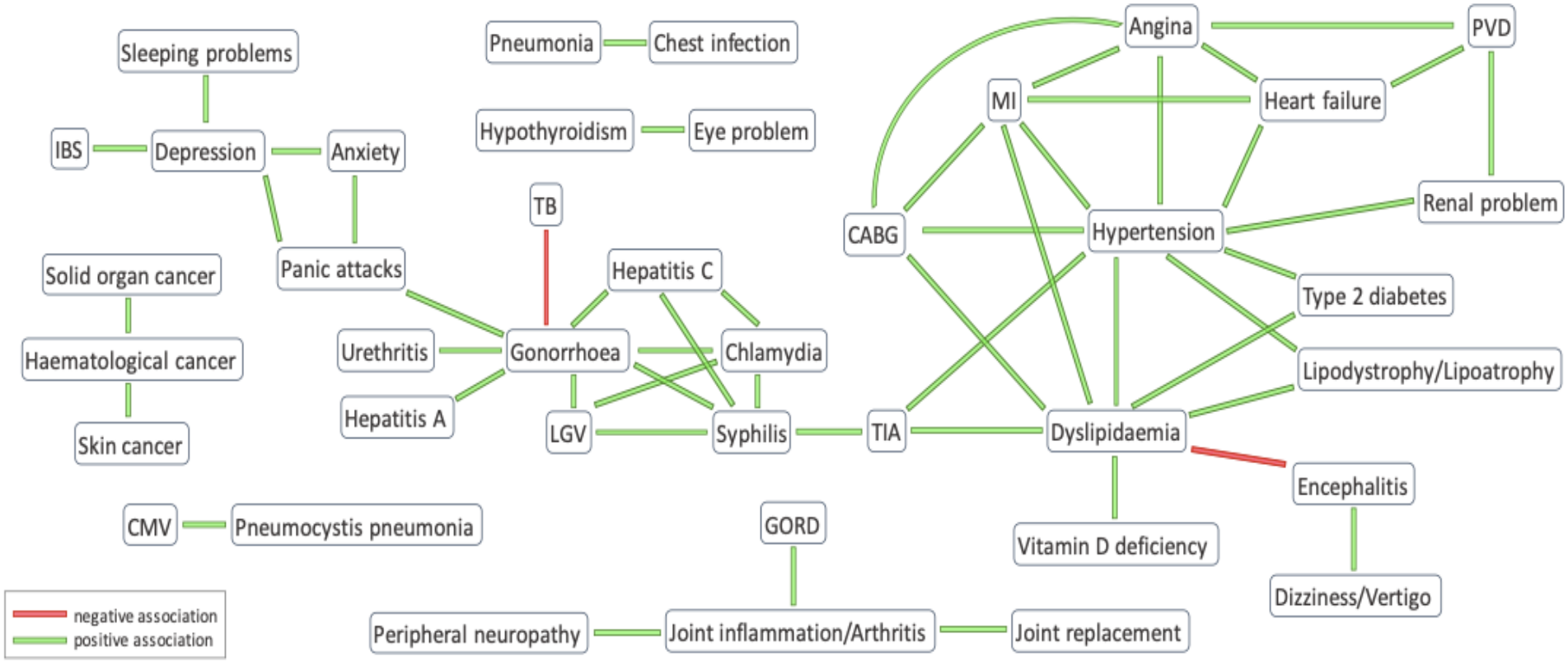
Association of depressive symptoms with comorbidities*



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

‘Mapping’ ageing in PLWH

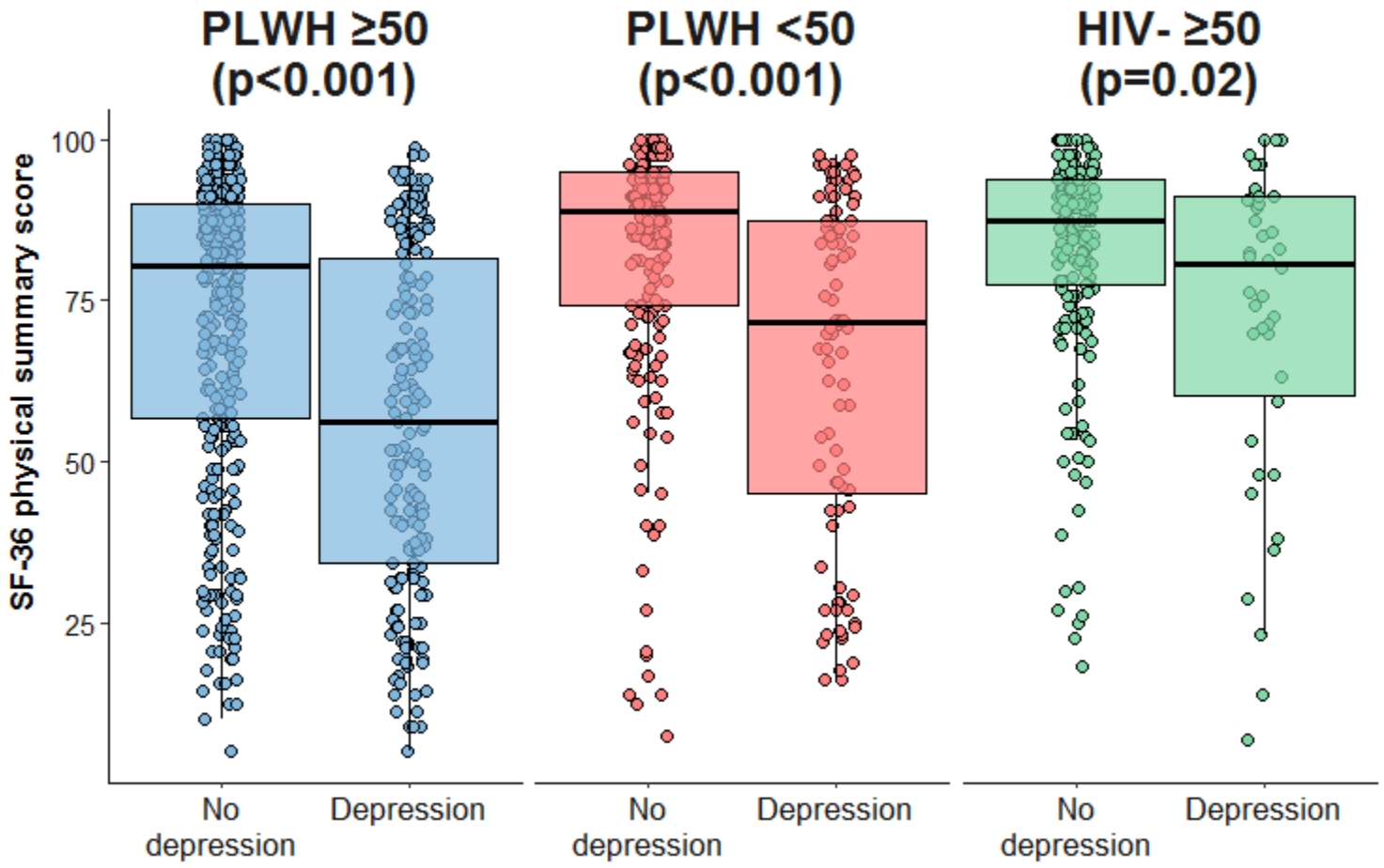
Certain co-morbidities cluster in PLWH
POPPY study and the AGE$_h$IV cohort study



De Francesco D *et al*. *OFID* 2018.

POPPY – depression and QOL

Association of depressive symptoms with physical 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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Mater Misericordiae
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

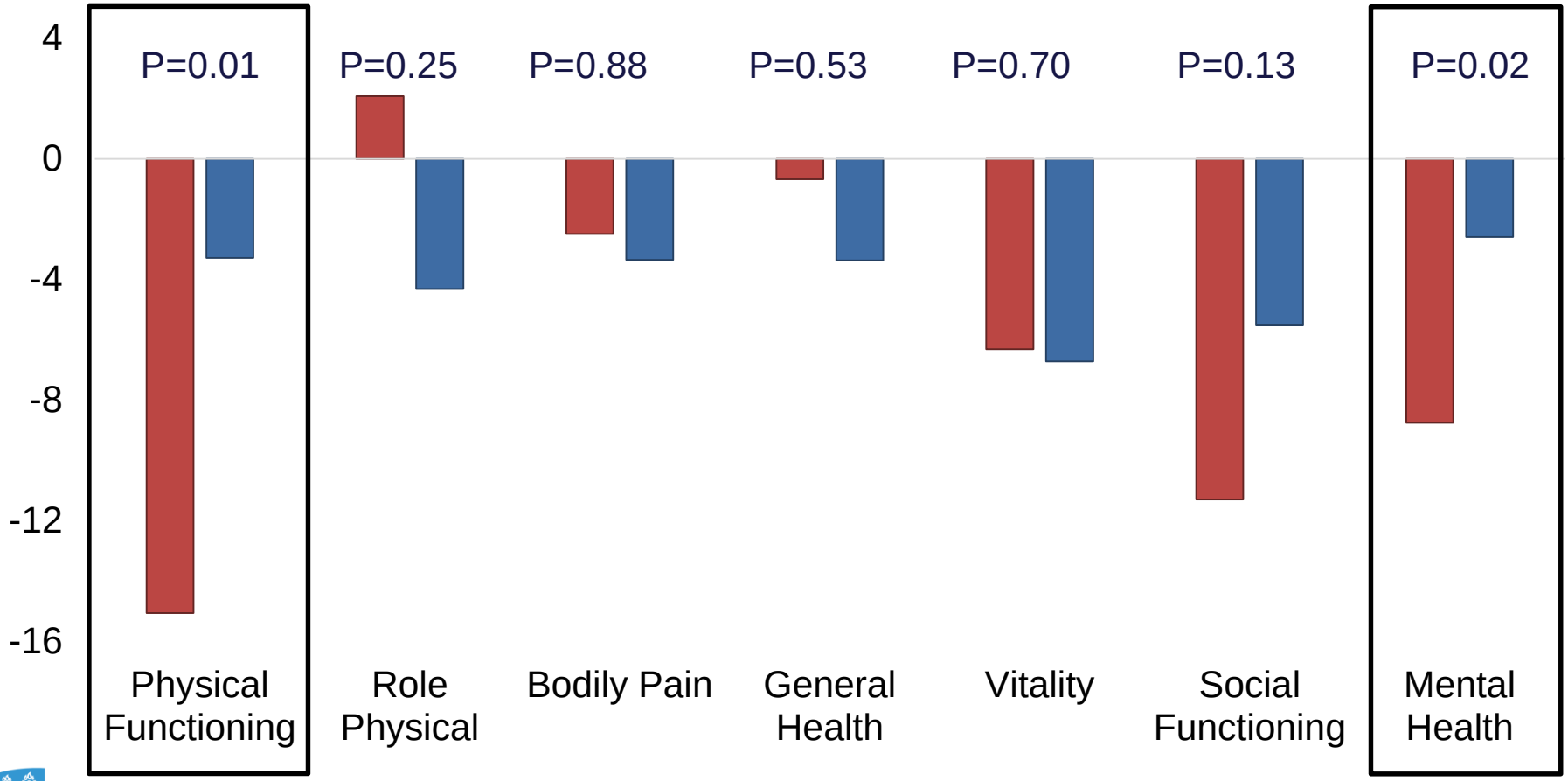
Physical Health

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.

Mental health and ageing in HIV

- 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

Mental health and ageing in HIV

Depression: Screening and Diagnosis

Significance

- Higher prevalence of depression reported in HIV-positive persons (20-40% versus 7% in general population)
- Significant disability and poorer HIV treatment outcomes associated with depression

Screening and diagnosis

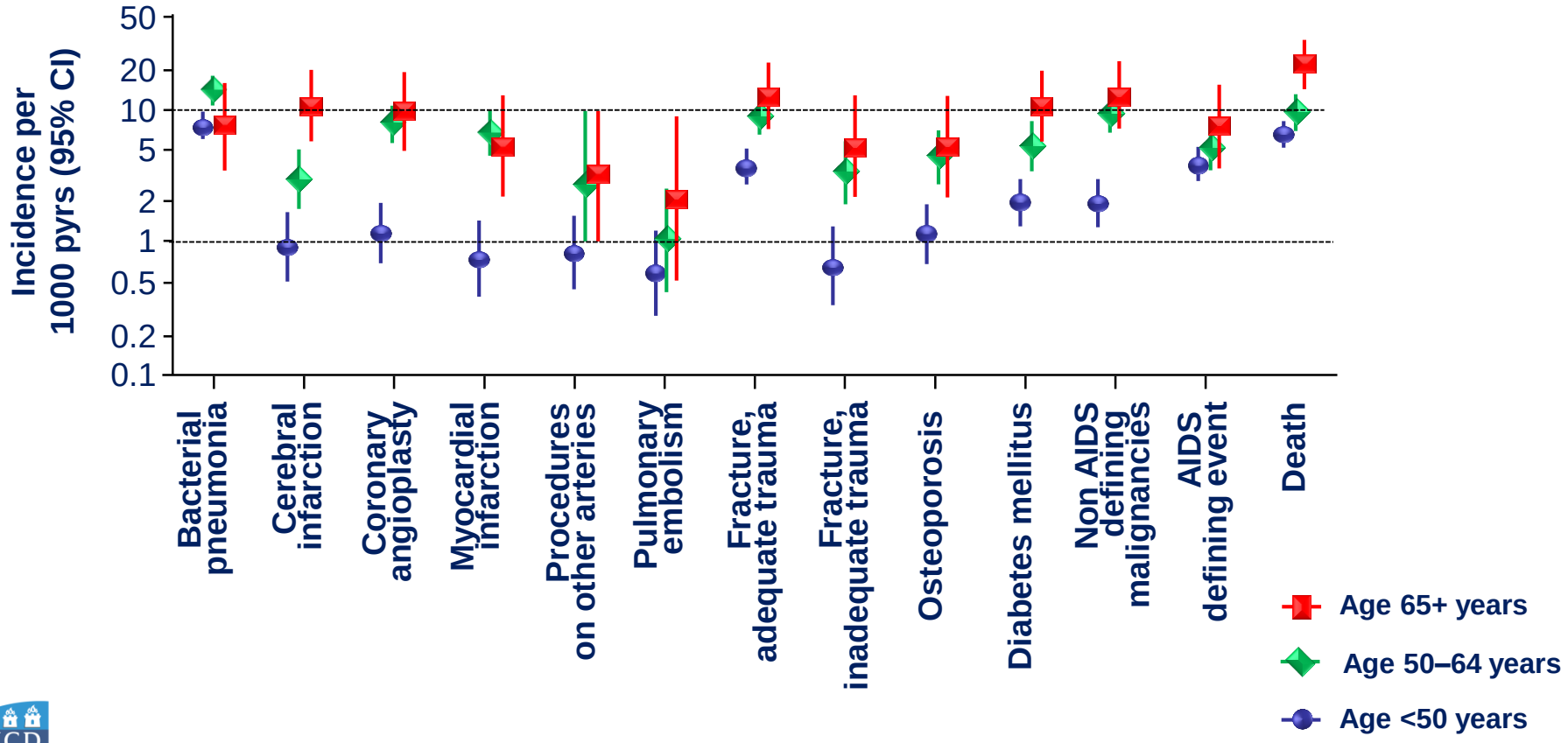
Who?	How to screen?	How to diagnose?
Screening of all HIV-positive persons recommended in view of the high prevalence of depression **Populations at particularly high risk** • Positive history of depression in family • Depressive episode in personal history • Older age • Adolescence • Persons with history of drug addiction, psychiatric, neurologic or severe somatic co-morbidity • Use of EFV • Use of neurotropic and recreational drugs • As part of investigation of neurocognitive impairment, see page 74	• Screen every 1-2 years • Two main questions: 1. Have you often felt depressed, sad or without hope in the last few months? 2. Have you lost interest in activities that you usually enjoy? • Specific symptoms in men: – Stressed, burn out, angry outbursts, coping through work or alcohol • Rule out organic cause (such as hypothyroidism, hypogonadism, Addison's disease, non-HIV drugs, vitamin B12 deficiency)	**Symptoms – evaluate regularly** **A.** At least 2 weeks of depressed mood OR **B.** Loss of interest OR **C.** Diminished sense of pleasure **PLUS 4 out of 7 of the following:** 1. Weight change of ≥ 5% in one month or a persistent change of appetite 2. Insomnia or hypersomnia on most days 3. Changes in speed of thought and movement 4. Fatigue 5. Feelings of guilt and worthlessness 6. Diminished concentration and decisiveness 7. Suicidal ideation or a suicide attempt[i]

i EFV has been associated with a higher risk of suicidal ideation

http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

Ageing with HIV: Clinical consequences

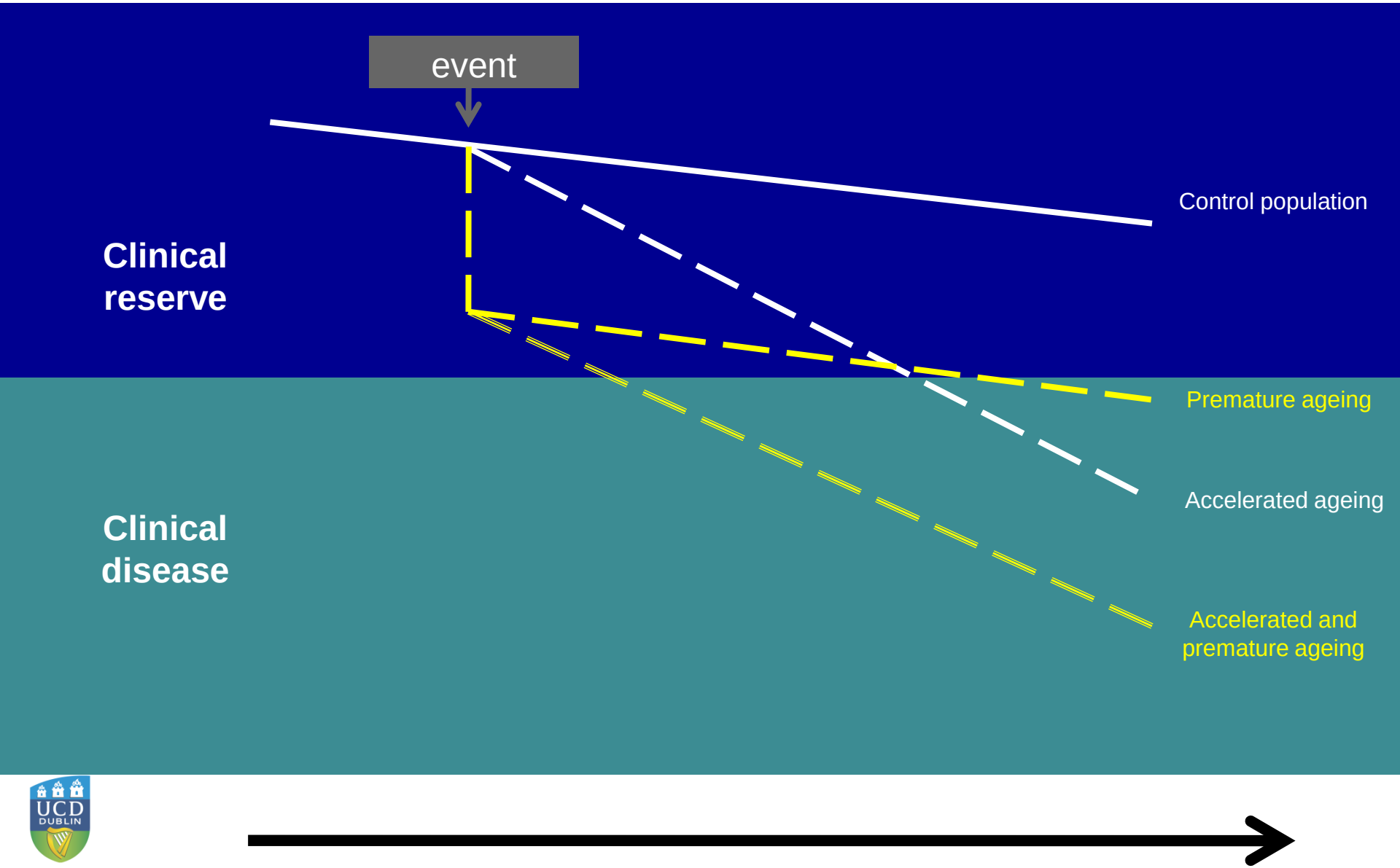
Swiss HIV Cohort Study: Incidence of clinical events between January 1, 2008, and June 30, 2010 stratified by age



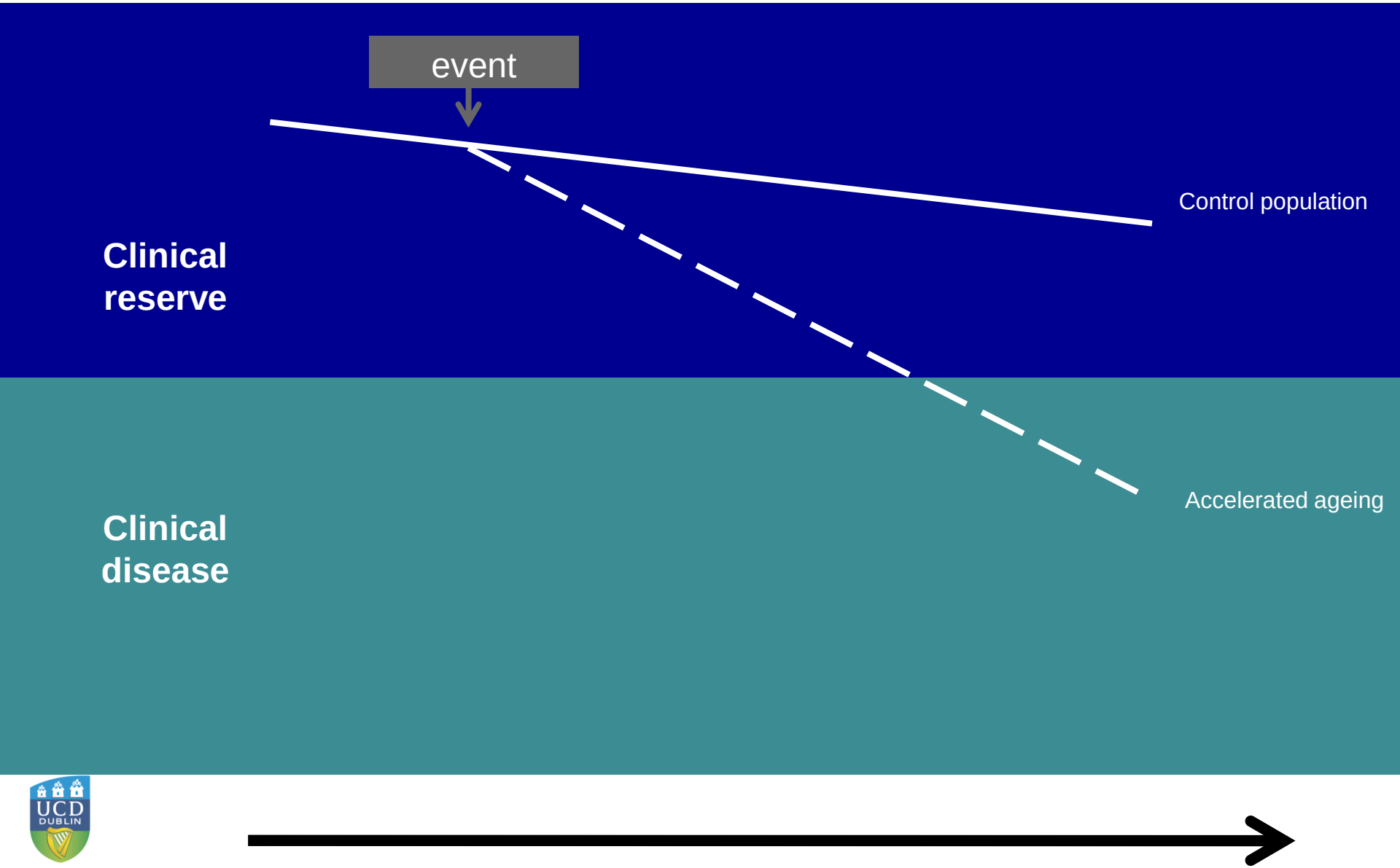
CI, confidence interval; pyrs, person-years

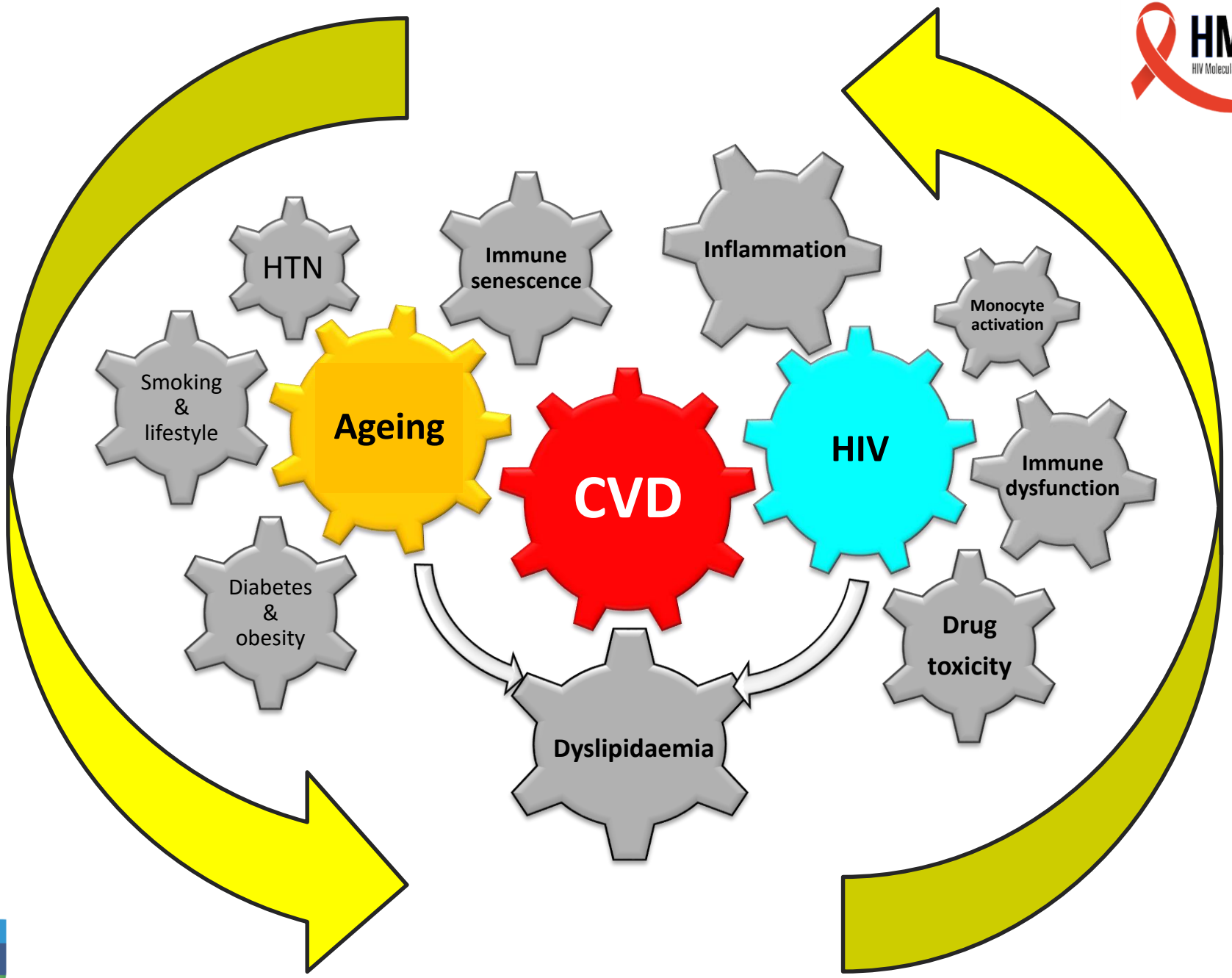
Adapted from Hasse B, et al. Clin Infect Dis 2011;53(11):1130-1139.

Premature vs accelerated ageing



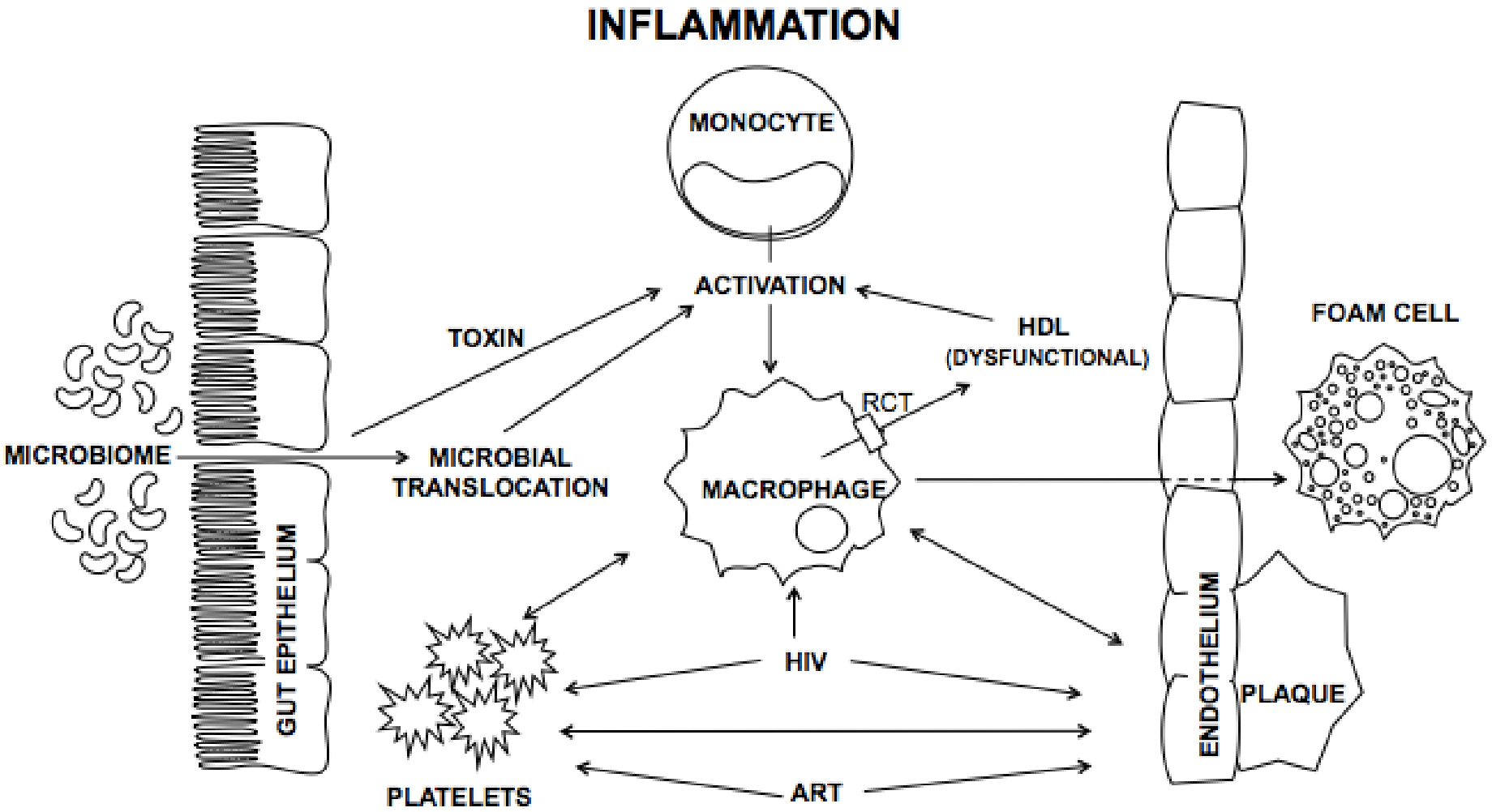
Premature vs accelerated ageing





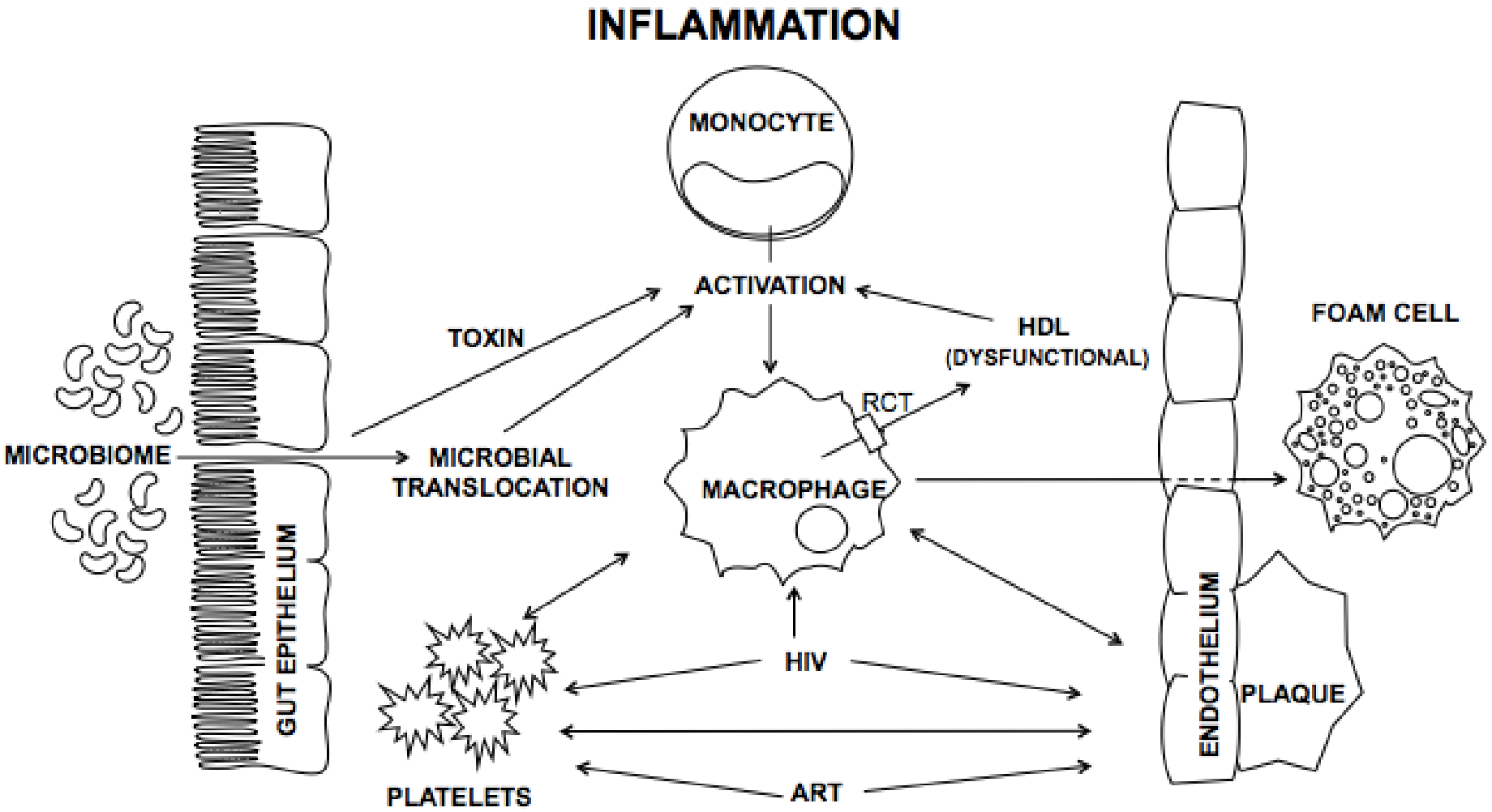
J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

HIV & '*Inflammaging*'



McGettrick et al. 2017

HIV & '*Inflammaging*'

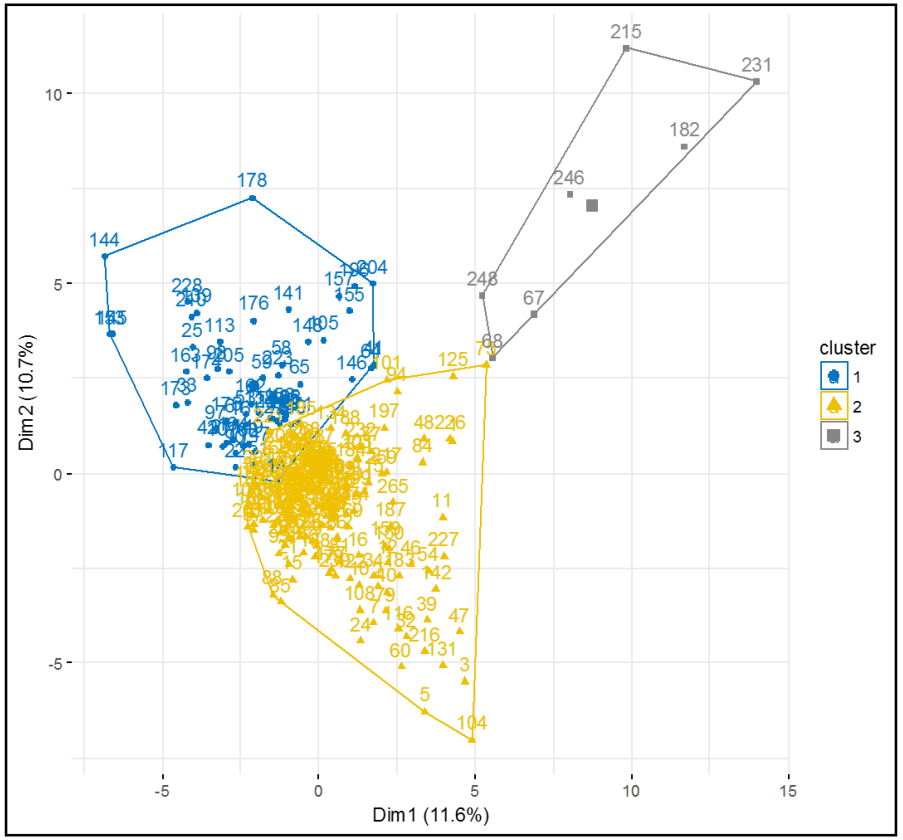


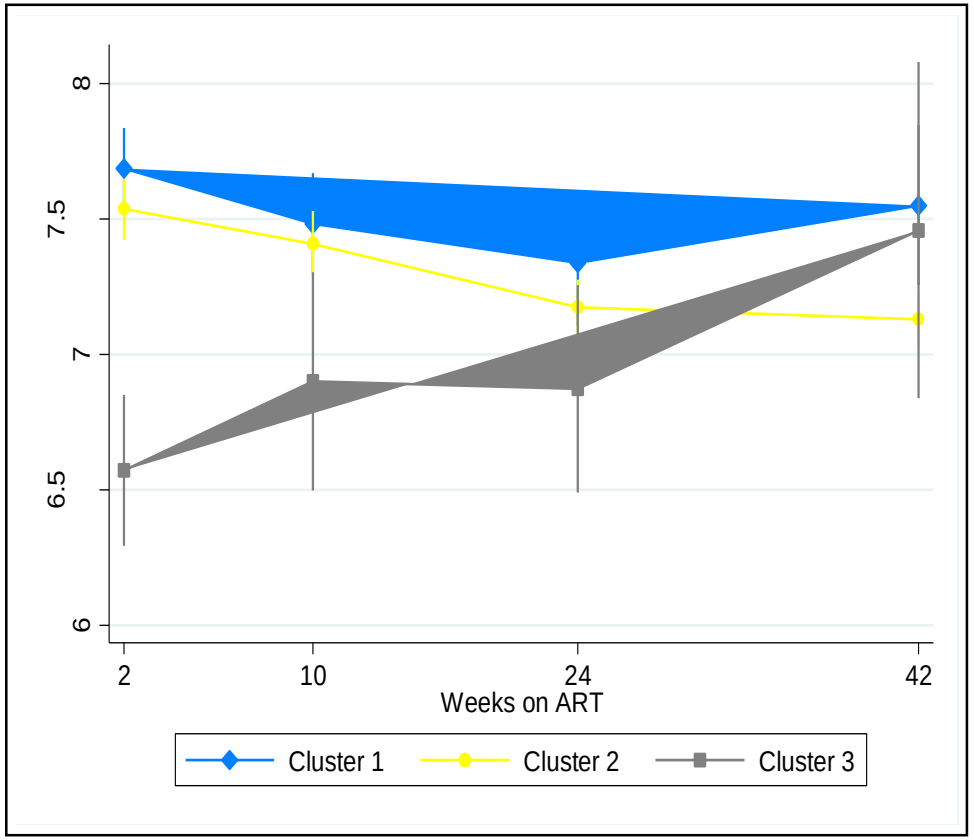
McGettrick et al. 2017

HIV & '*Inflammaging*' – biological mapping

N= 260 African PLWH

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





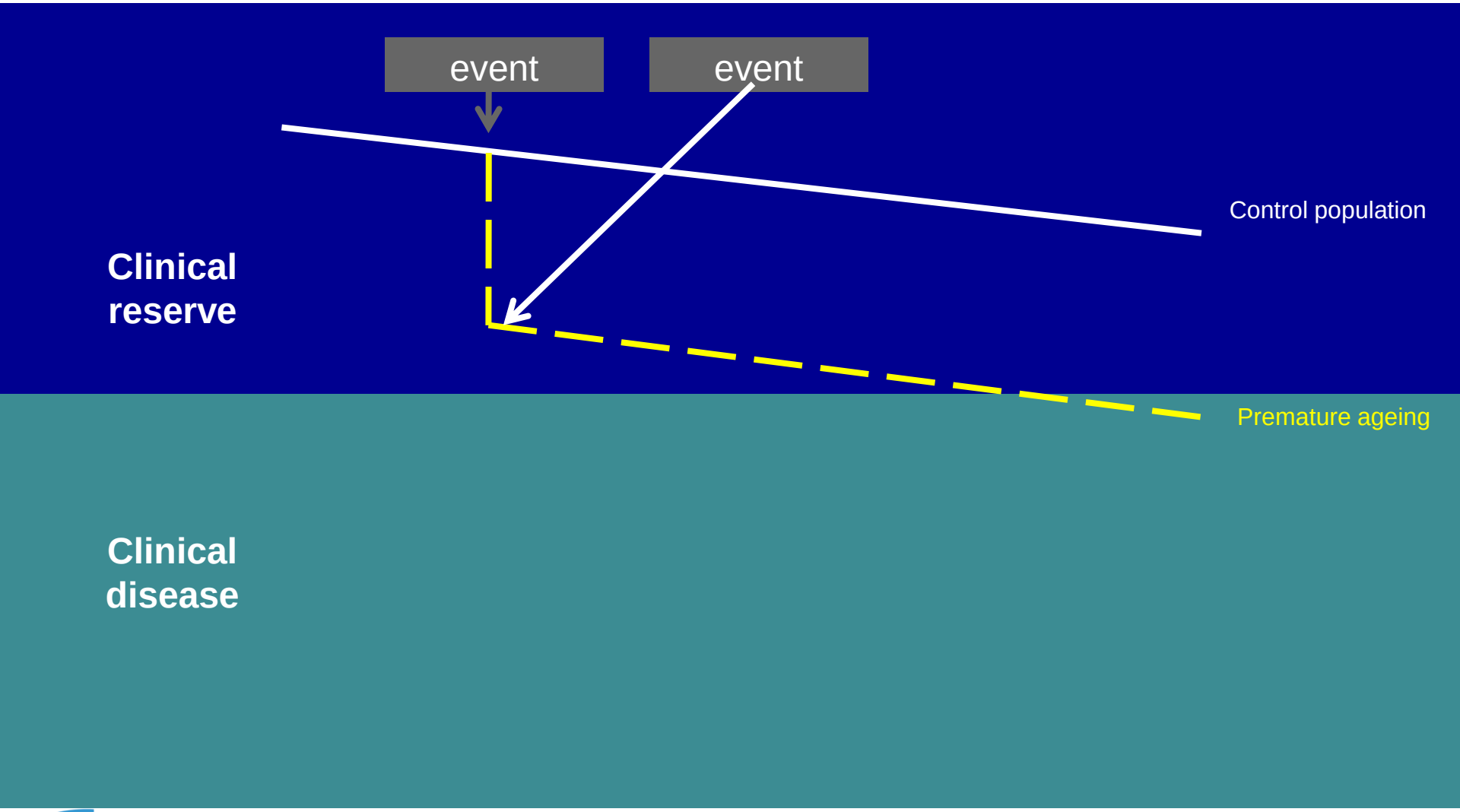
Kenny C. et al. CROI. 2019. Abstract 646.

HIV & CVD – monitoring is key!

CO-MORBIDITIES						
Haematology	FBC	+	+	3-12 months		
	Haemoglobinopathies	+			Screen at risk persons	
	G6PD	+			Screen at risk persons	
Body Composition	Body-mass index	+	+	Annual		41
Cardiovascular Disease	Risk assessment (Framingham score[iii])	+	+	2 years	Should be performed in all men > 40 years and women > 50 years without CVD	42
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
Hypertension	Blood pressure	+	+	Annual		43-45
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	48
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)	46-47
Pulmonary Disease	Respiratory symptoms and risk factors[xii]	+	+	Annual	If severe shortness of breath is reported with preserved spirometry, echocardiography may be performed to rule out heart failure and/or pulmonary hypertension	75
	Spirometry			As indicated	Spirometry should be performed in all symptomatic persons[xii]	
Liver Disease	Risk assessment[v]	+	+	Annual		56-61
	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)	57-58, 81, 84
	Hepatic ultrasound			6 months	Persons with liver cirrhosis[xiii]	58, 81, 84
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]	52-55
	eGFR (CKD-EPI)[vii]	+	+	3-12 months		
	Urine dipstick analysis[viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min or rapid decline in eGFR [xiv], 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		49, 51
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons (see page 49 for details)	
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons	50

http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

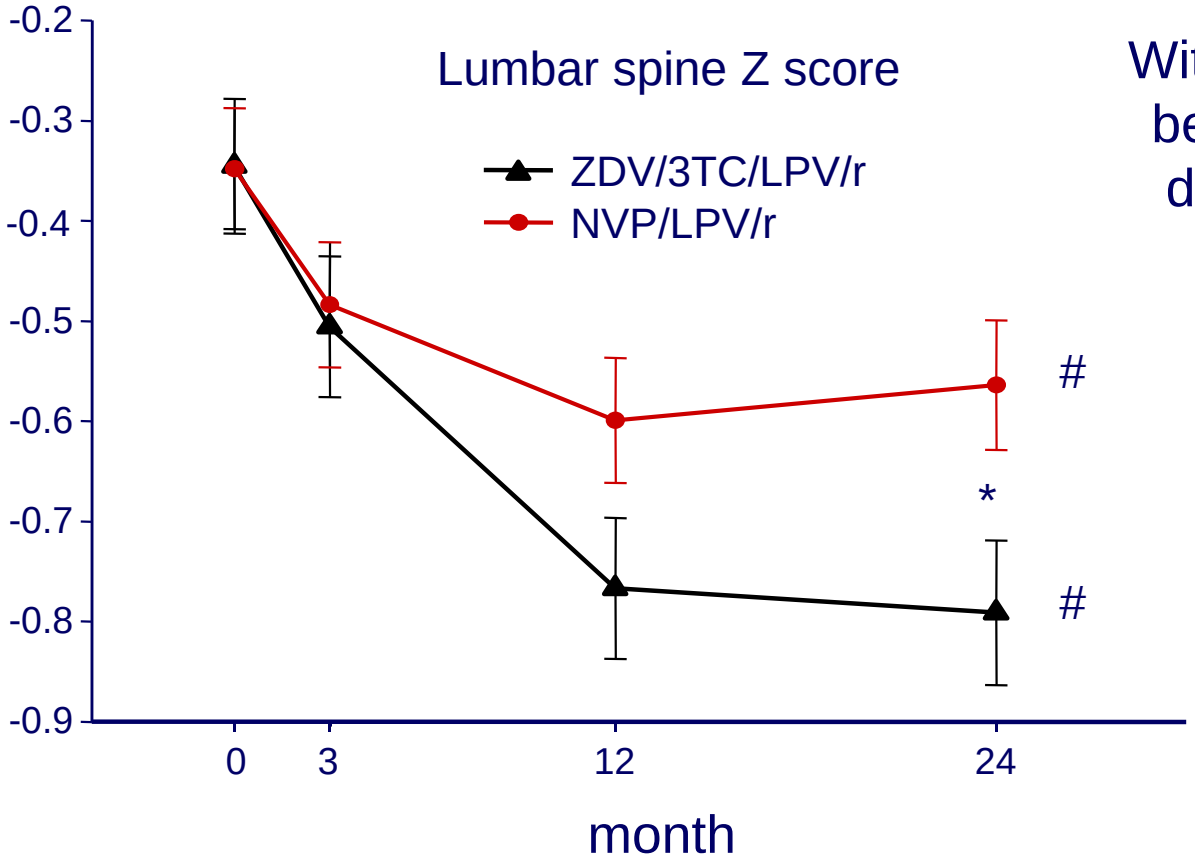
Premature vs accelerated ageing



Bone Disease

ART initiation is associated with bone loss

Greater loss in BMD with ART containing NRTI



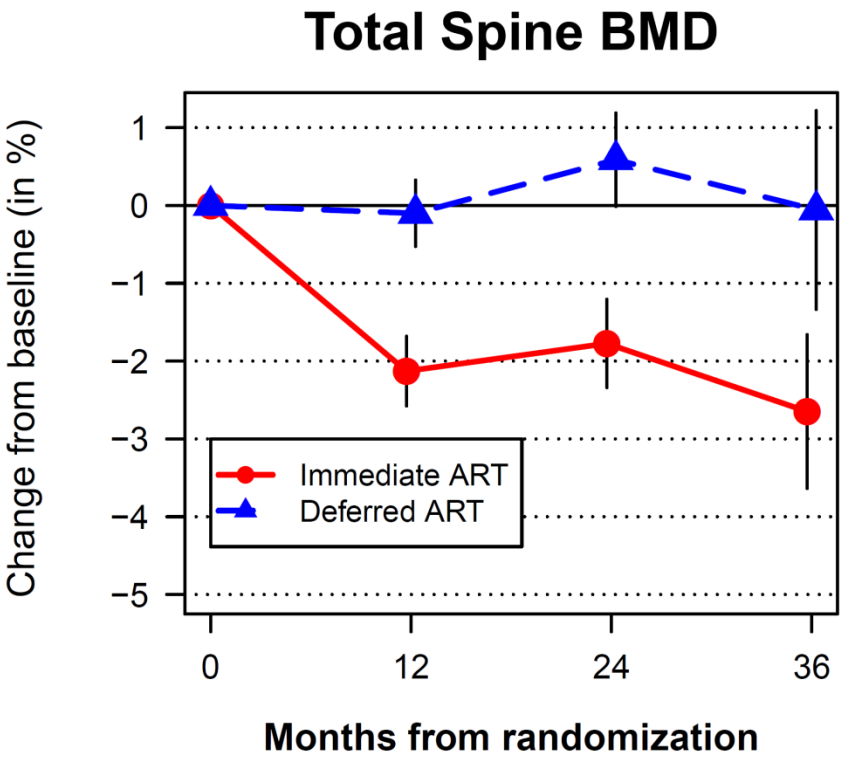
Within group and between-group differences all $P<0.05$

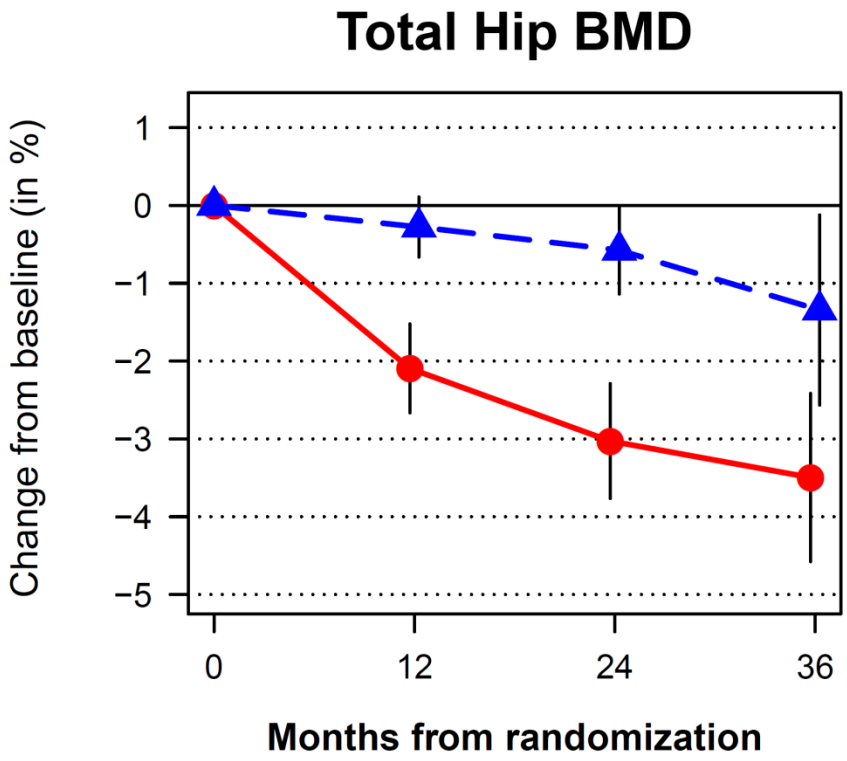
Changes in BMD accompanied by increases in markers of bone turnover

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





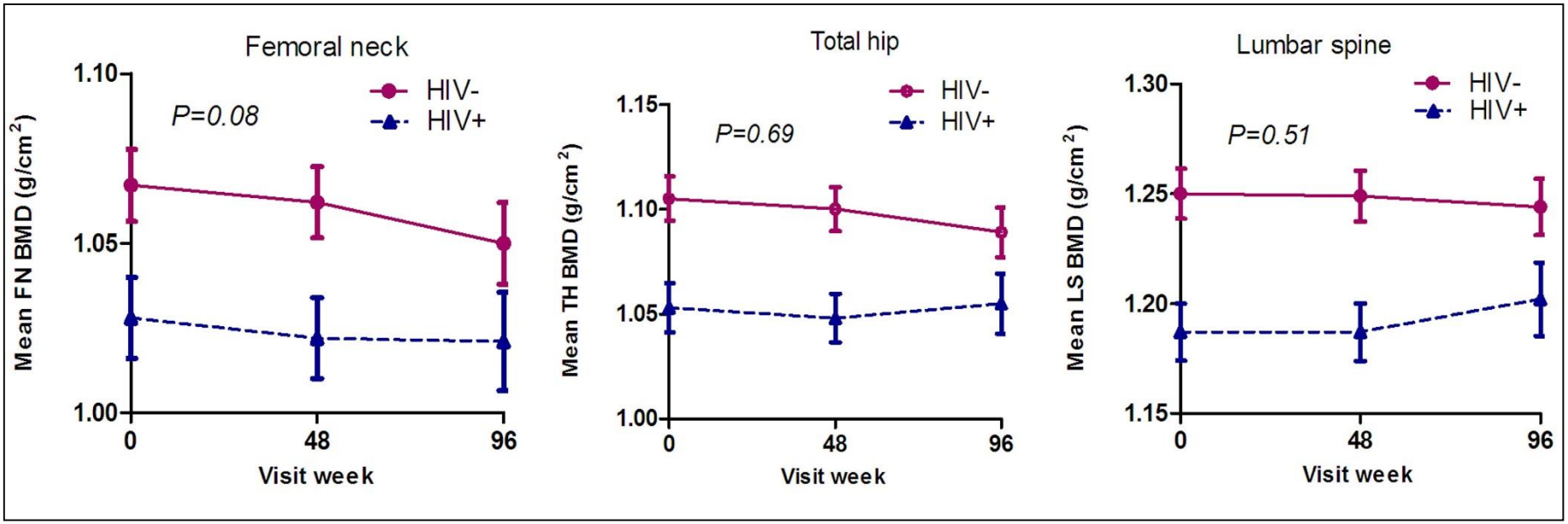
Estimated Mean Diff (95% CI)
-2.2% (-2.8, -1.6), p<0.001

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 BMD – long-term follow-up

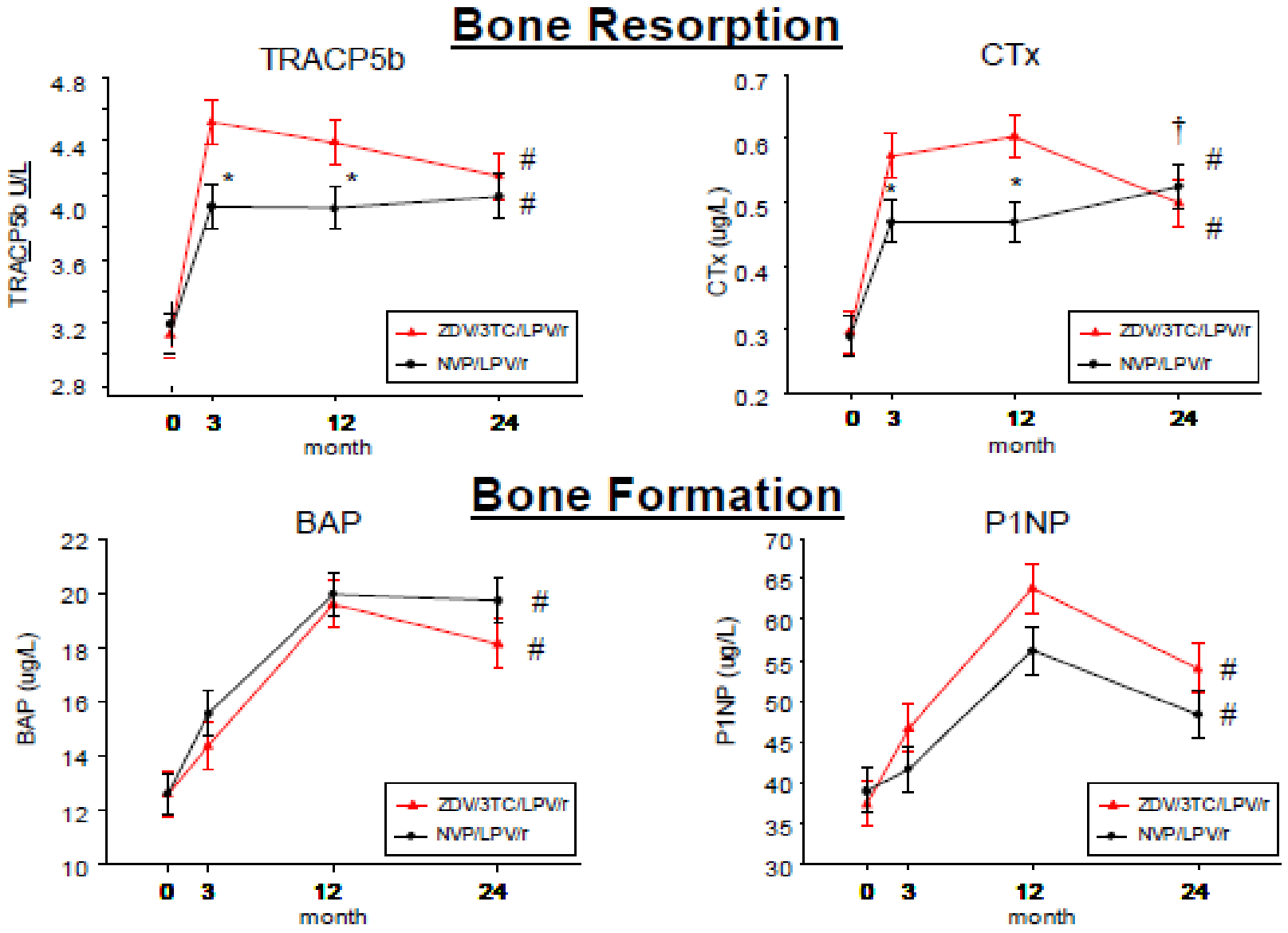
HIV UPBEAT Study. *N*= 384. 3 year follow-up.
HIV+, *N*=120, 88% on ART.



- 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

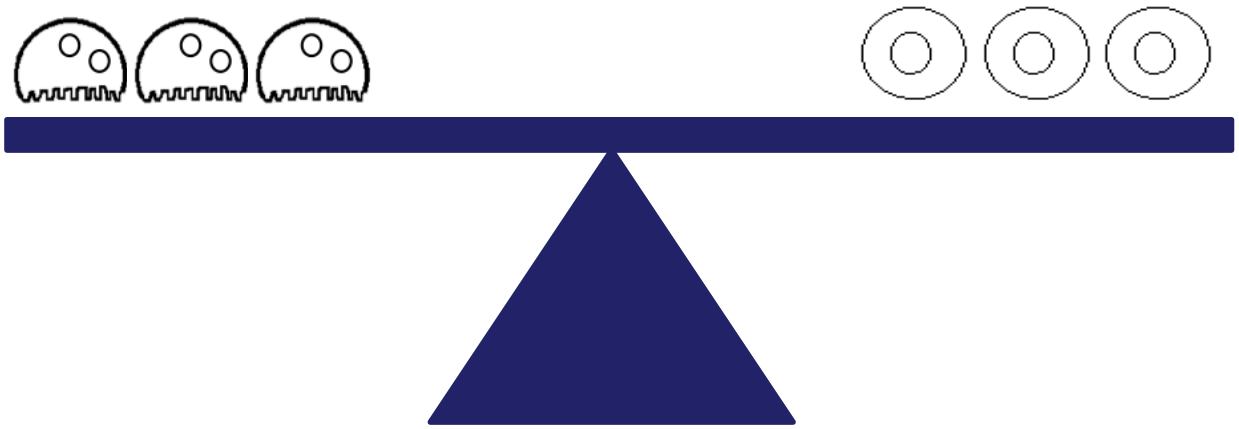
Tinago W et al. AIDS 2017, Mar 13;31(5):643-652

ART initiation and Bone Turnover



Van Vonderen et al. CROI 2011, abstract 833

ART initiation and Bone Turnover



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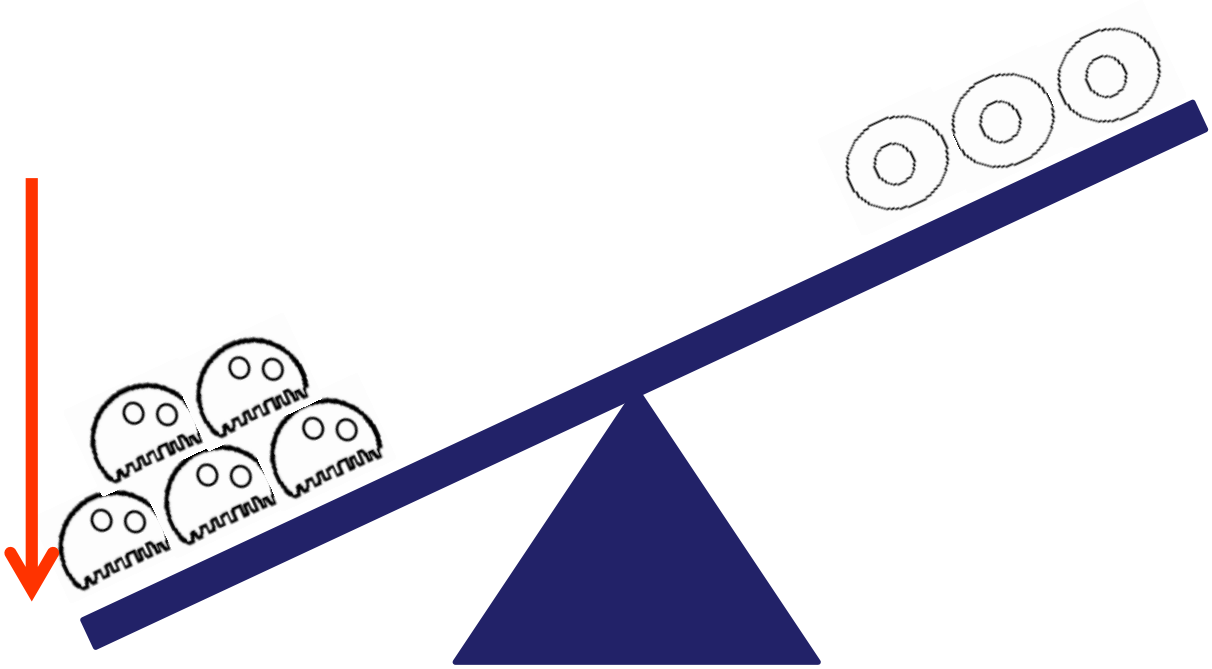
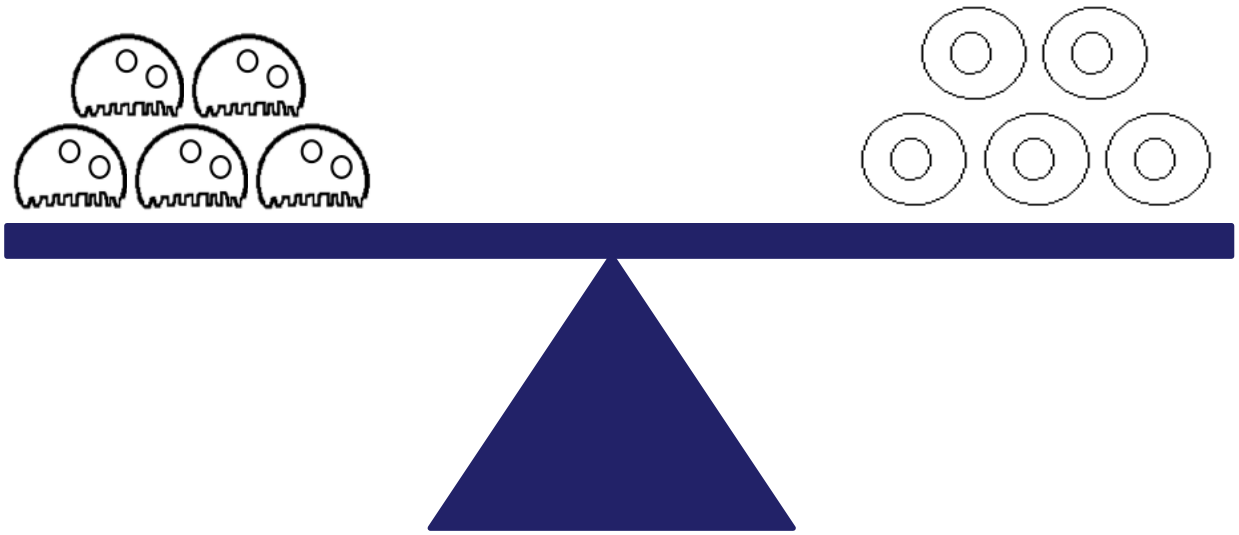


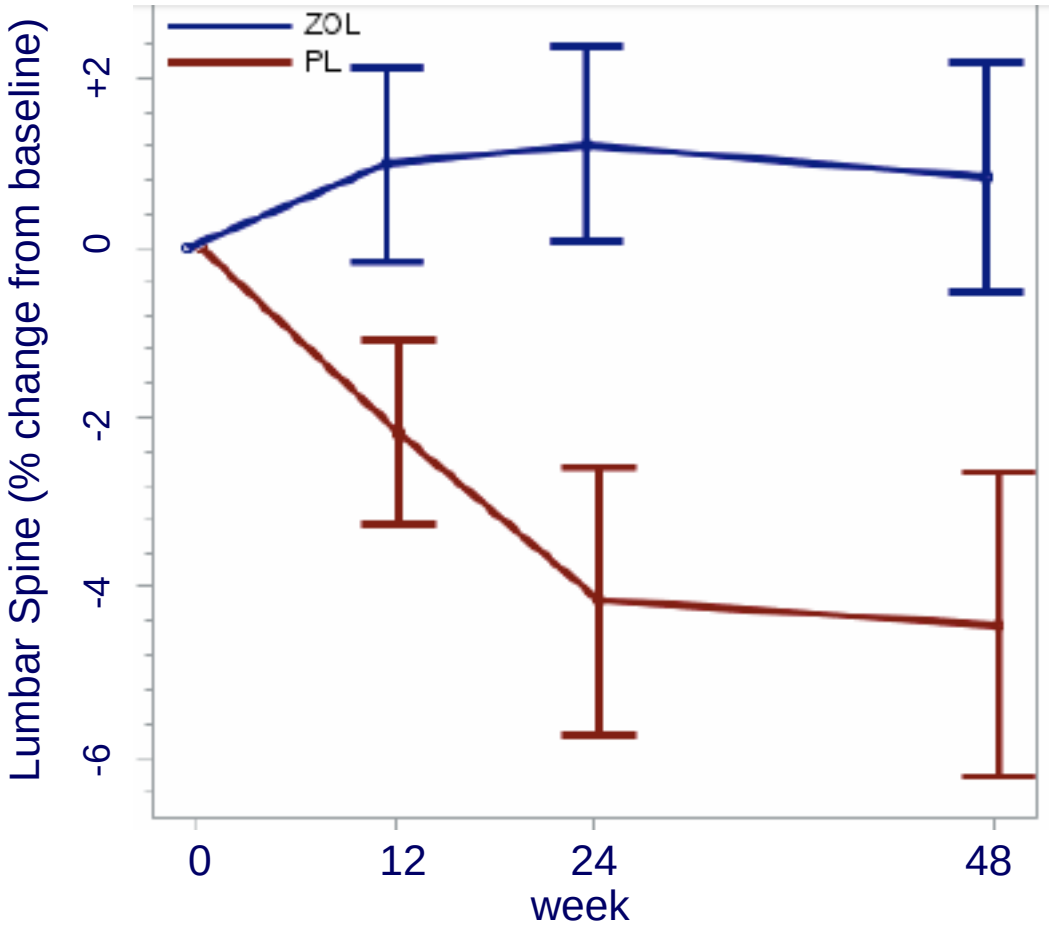
ART initiation and Bone Turnover



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

Approach to low BMD in HIV….

Bone Disease: Screening and Diagnosis

Condition	Characteristics	Risk factors	Diagnostic tests
Osteoporosis • Postmenopausal women and men aged ≥ 50 years with BMD T-score ≤ -2.5 • Premenopausal women and men aged < 50 years with BMD Z-score ≤ -2 and fragility fracture	• Reduced bone mass • Increased incidence of fractures in HIV-positive persons • Asymptomatic until fractures occur Common in HIV • Up to 10-15% prevalence of osteoporosis • Aetiology multifactorial • Loss of BMD observed with ART initiation • Greater loss of BMD with initiation of certain ARVs[i]	Consider classic risk factors[iii] and estimate fracture risk using FRAX. Consider DXA in any person with ≥ 1 risk of:[iii] 1. Postmenopausal women 2. Men ≥ 50 years 3. Those between 40-50 years with high fracture risk (> 20% 10-year major osteoporotic fracture risk based on FRAX assessment without DXA) 4. History of low impact fracture 5. High risk for falls[iv] 6. Clinical hypogonadism (symptomatic, see Sexual Dysfunction) 7. Oral glucocorticoid use (minimum 5 mg/qd prednisone equivalent for > 3 months) Preferably perform DXA in those with above risk factors prior to ART initiation. Assess effect of risk factors on fracture risk by including DXA results in the FRAX® score (http://www.shef.ac.uk/FRAX) • Only use if > 40 years • May underestimate risk in HIV-positive persons • Consider using HIV as a cause of secondary osteoporosis[v]	**DXA scan** **Rule out causes of secondary osteoporosis if BMD low**[vi] **Lateral spine X-rays** (lumbar and thoracic) if low spine BMD, osteoporosis on DXA, or significant height loss or kyphosis develops. (DXA-based vertebral fracture assessment can be used as an alternative to lateral spine X-ray).

http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

Approach to low BMD in HIV….

Bone Disease: Screening and Diagnosis

Condition	Risk factors	Diagnostic tests
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Consider DXA in any person with ≥ 1 risk of:[iii]

1. Postmenopausal women
2. Men ≥ 50 years
3. Those between 40-50 years with high fracture risk (> 20% 10-year major osteoporotic fracture risk based on FRAX assessment without DXA)
4. History of low impact fracture
5. High risk for falls[iv]
6. Clinical hypogonadism (symptomatic, see Sexual Dysfunction)
7. Oral glucocorticoid use (minimum 5 mg/qd prednisone equivalent for > 3 months)

Preferably perform DXA in those with above risk factors prior to ART initiation. Assess effect of risk factors on fracture risk by including DXA results in the FRAX® score (http://www.shef.ac.uk/FRAX)

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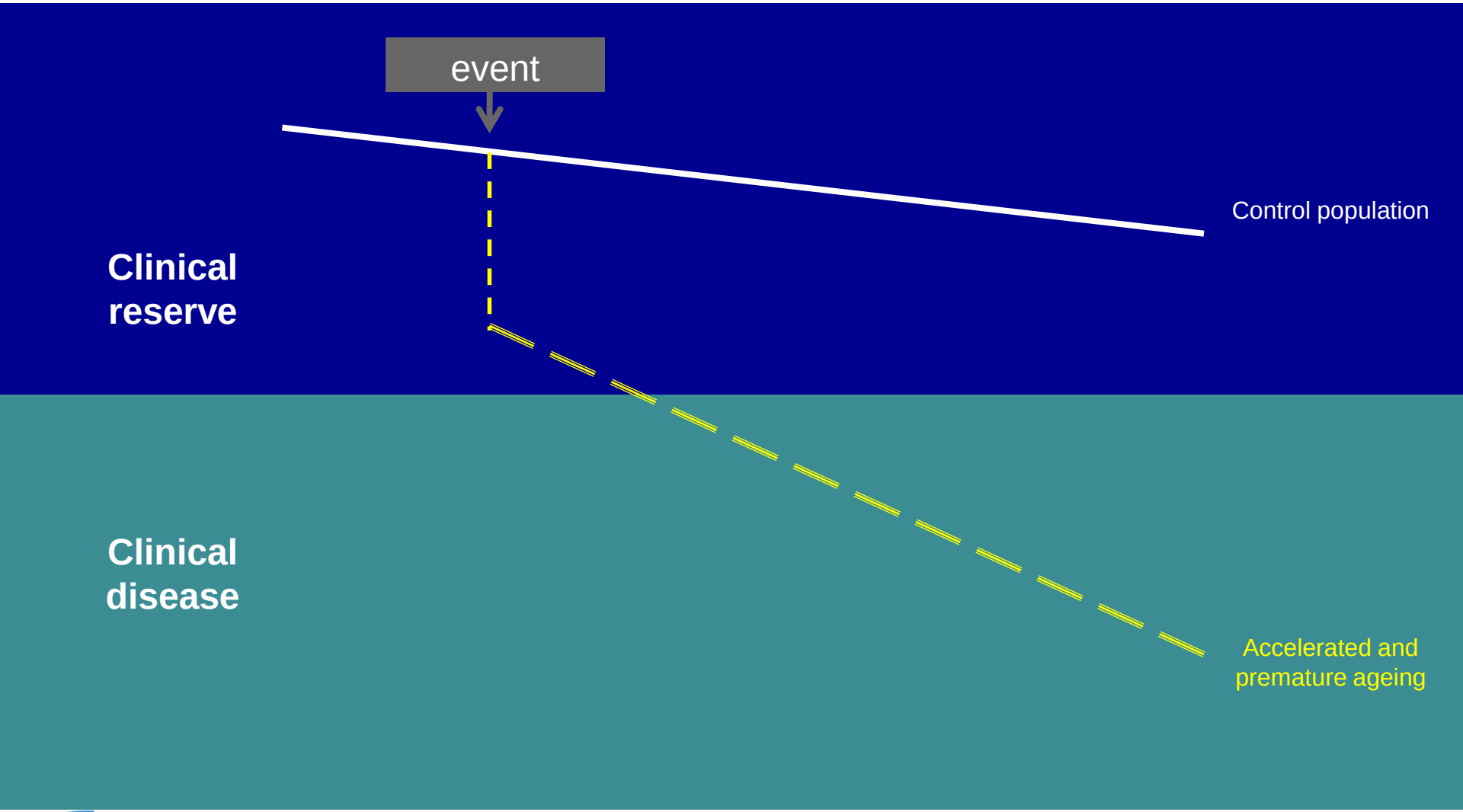
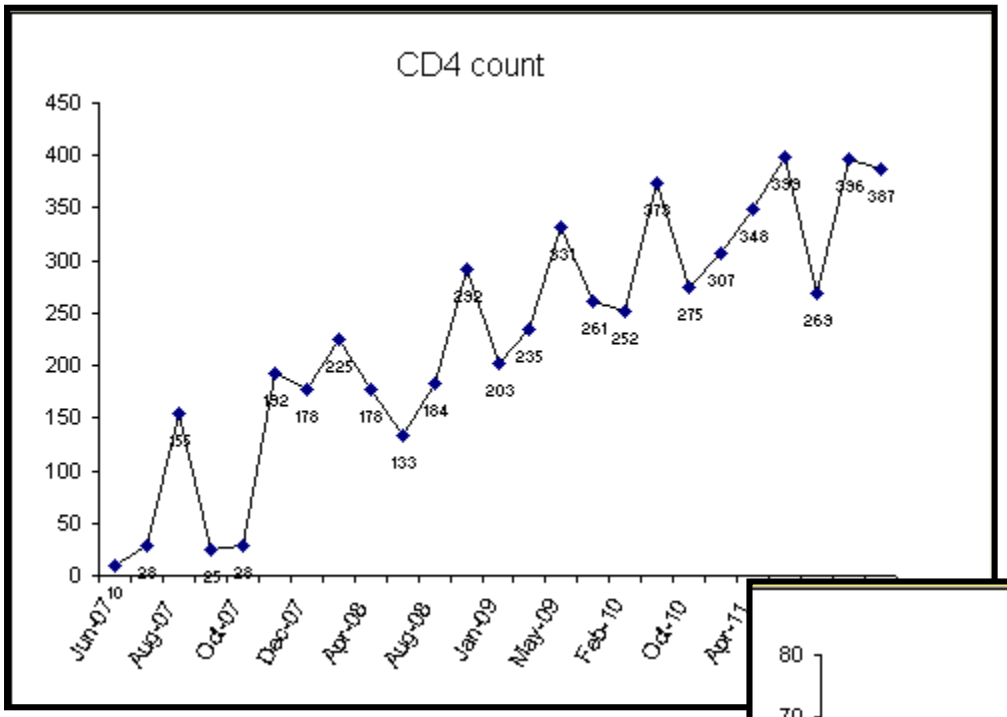
Premature vs accelerated ageing

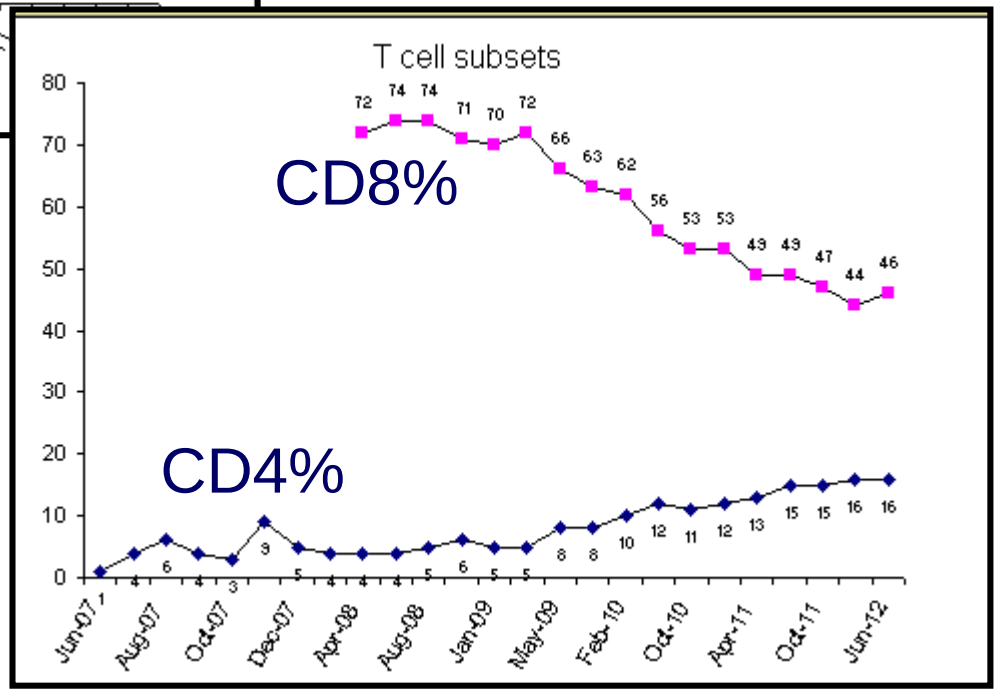


Inflammation and Immune Dysfunction



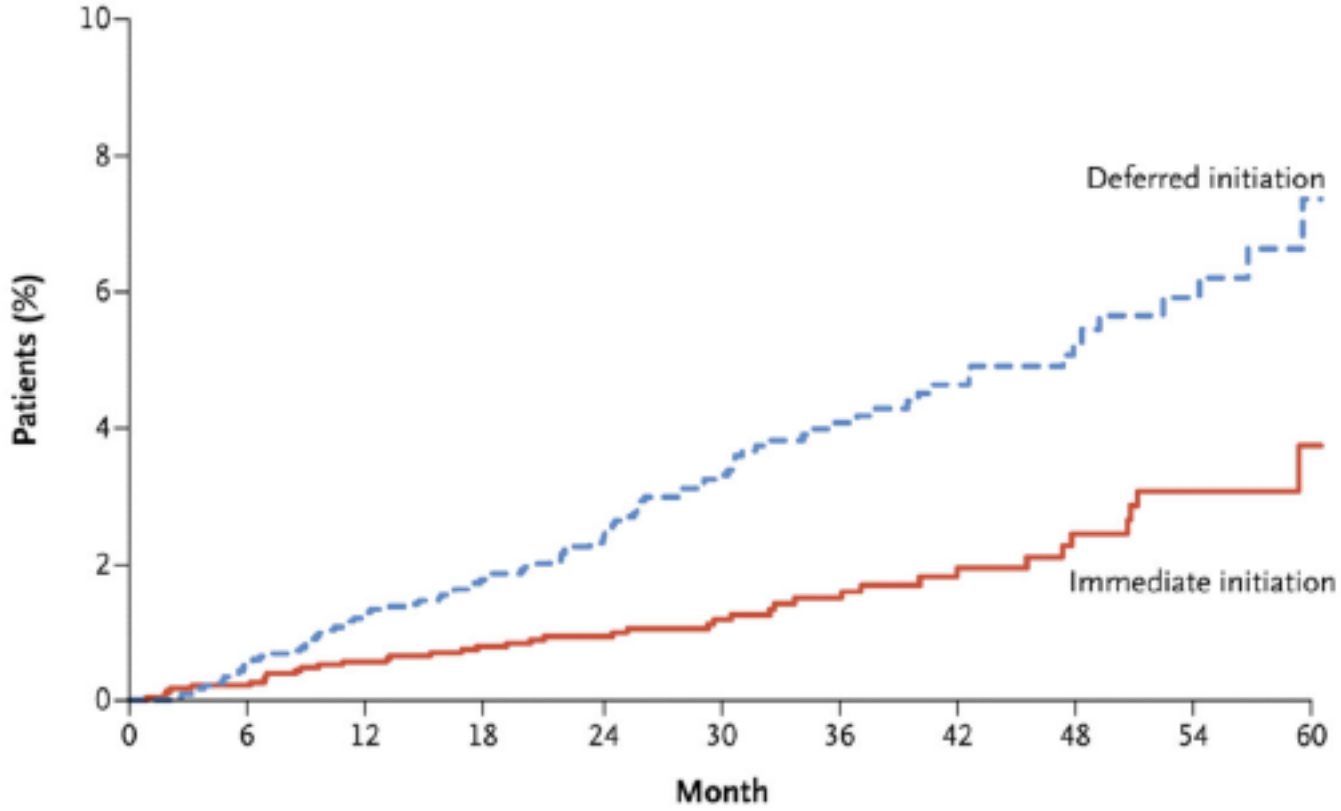
Does it matter…..

….that we don't know if it matters?



Early ART – START Study

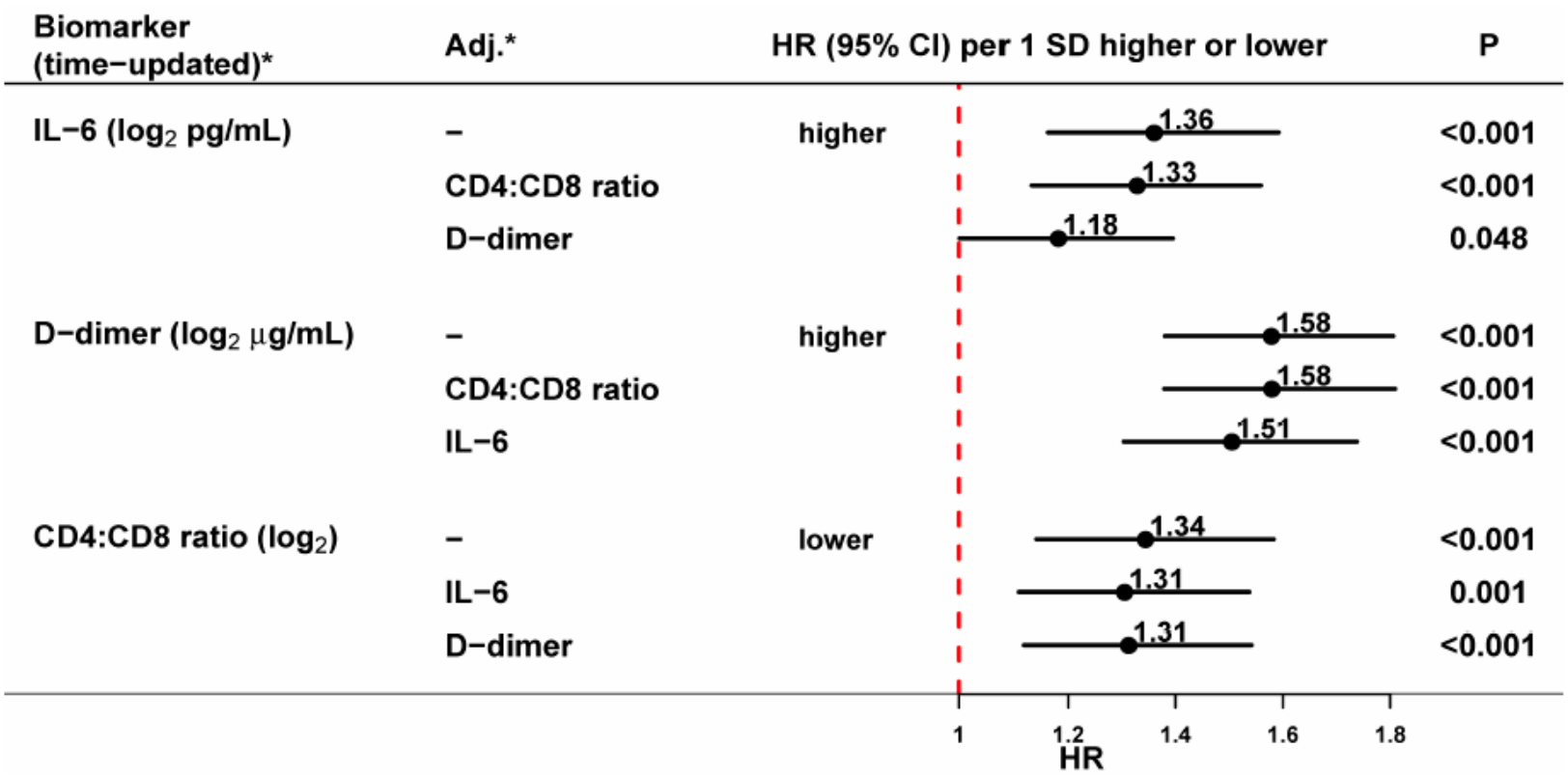
Randomised trial. HIV-1, CD4>500 cells/mm^3
Immediate versus deffered (CD4<350) ART.
N=4685. Endpoint of serious AIDS or non-AIDS event or death.



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

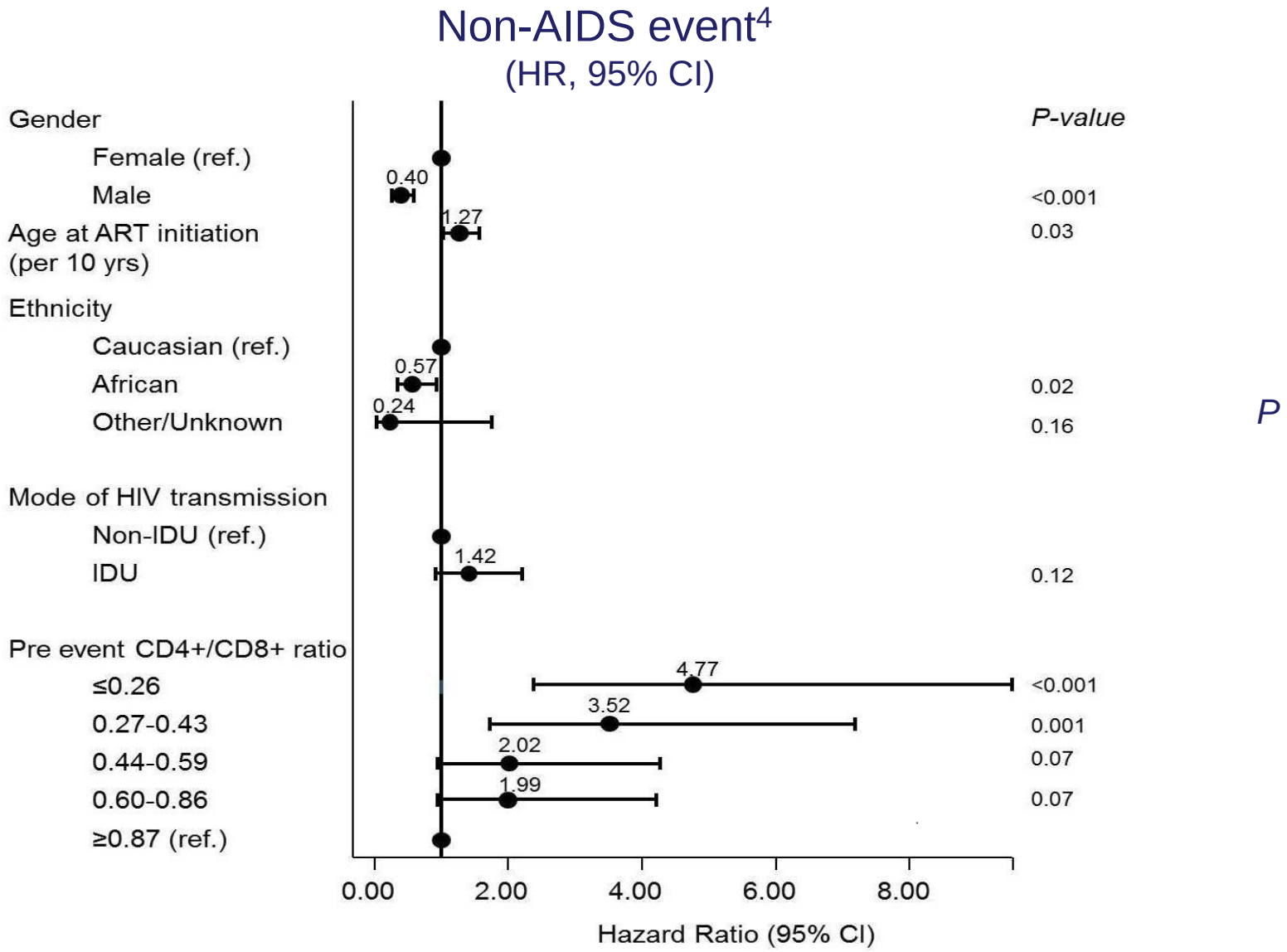


START

† *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.*

Biomarkers and outcome – CD4:CD8 ratio



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Immunosenescence in HIV is associated with CMV serostatus and lower CD4:CD8 ratio

Tara McGinty,[1,2] Sarah Miles,[1] Willard Tinago ,[1] Caroline A. Sabin,[3] Alan Landay,[4] Jeffrey Martinson,[4] Charlotte Prior, [2] Brenda Doak,[2] Cillian DeGascun,[5] Deirdre Burke,[5] Alan Macken,[1] Gerard Sheehan,[1,2] John Lambert ,[1,2] Aoife G. Cotter,[1,2] Patrick W.G. Mallon[1,2] on behalf of the HIV UPBEAT (Understanding the Pathology of Bone Diseases in HIV-infected Subjects) Study Group.

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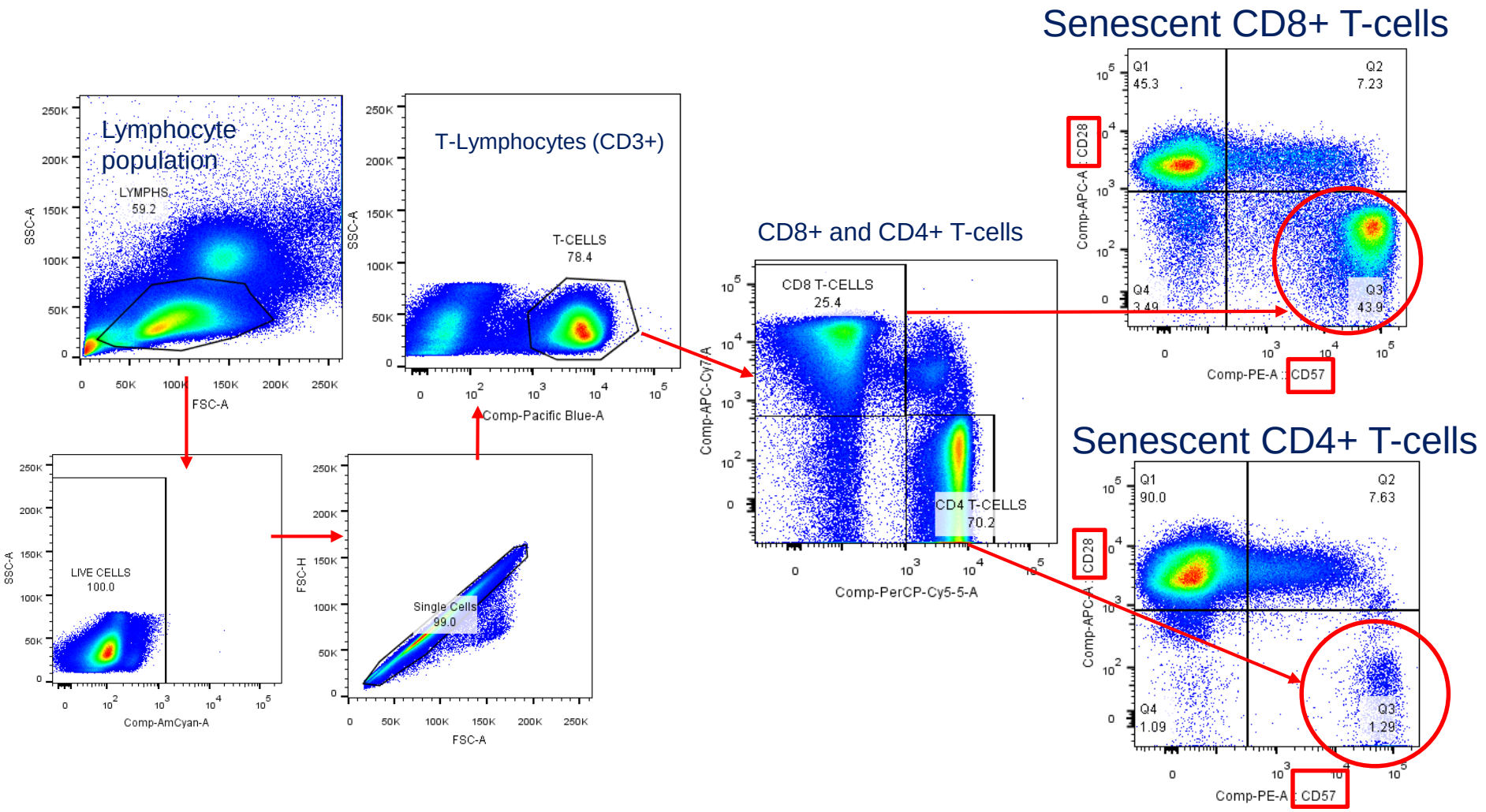
Immunosenescence – HIV UPBEAT



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Immunosenescence – HIV UPBEAT

	HIV - positive n= 107	HIV - negative n= 112	P
Male n (%)	71(68.9%)	54 (48.2%)	0.002
Age (years)	47 [39.4, 52.8]	50 [43.8, 55.9]	0.007
Caucasian ethnicity n (%)	69 (64.6%)	95 (83.3%)	0.008
BMI (kg/m^2)	26 [23,29]	27 [24,30]	0.012
Current smoker n (%)	30 (28%)	17 (14.9%)	0.020
Alcohol Use n(%)	64(59.8%)	96(85.7%)	<0.001
CMV IgG+ n(%)	96 (89.7%)	43(40%)	<0.001
CMV IgG avidity index	172[48, 223]	0.5[0.3, 59]	<0.001
%CD4+ senescent T-cells	4.21 [1.37, 7.64]	0.51 [0.12,2.10]	<0.001
%CD8+ senescent T-cells	34.1 [21,45.40]	22.65 [14.43, 35.03]	<0.001
CD4:CD8 Ratio	0.89[0.65,1.19]	2.37 [1.63,3.18]	<0.001
IRP+	25 (23%)	1 (0.9%)	<0.001

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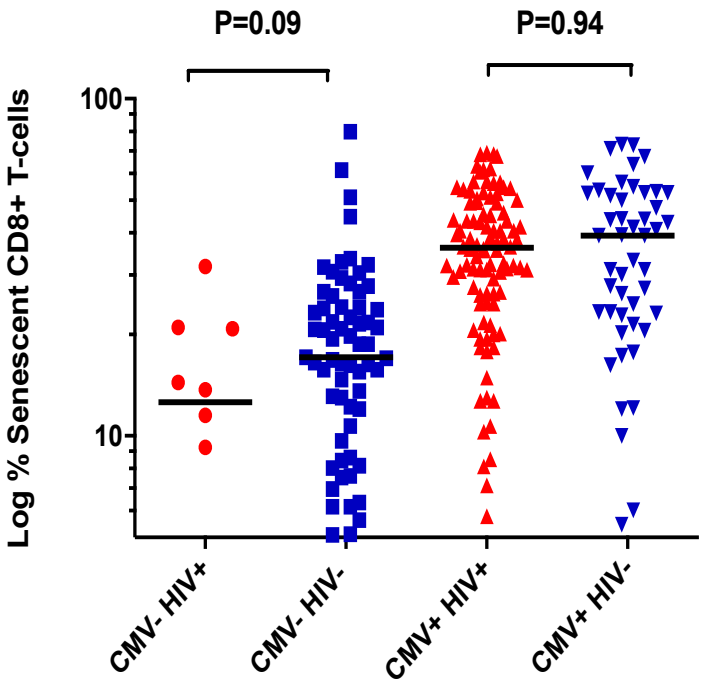
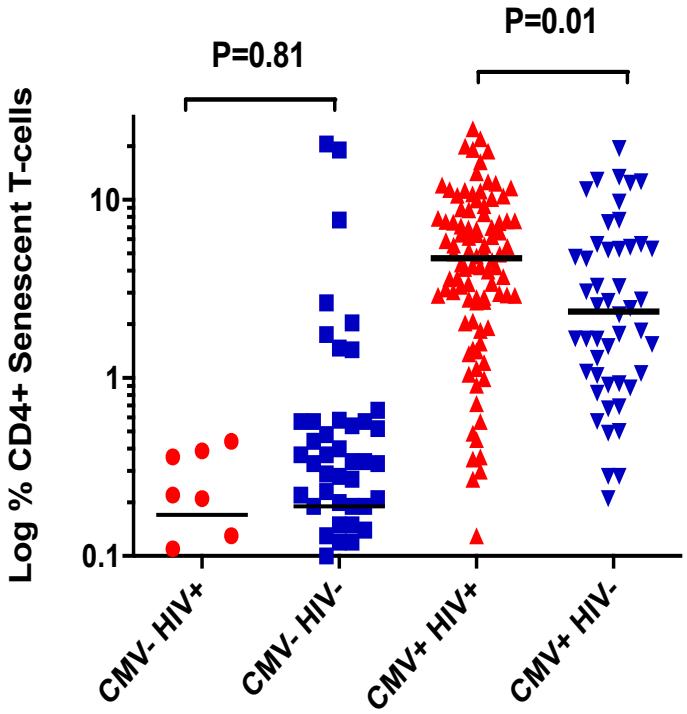
Immunosenescence – HIV UPBEAT

Senescence stratified according to HIV status and CMV status

%CD8+ CD28- CD57+ T-cells by CMV and HIV serostatus



%CD4+ CD28- CD57+ T-cells by CMV and HIV serostatus



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Immunosenescence – HIV UPBEAT

Multivariable Models : Predictors of CD8+ T-cell senescence

Effect on CD8+ T-cell senescence	(i) ME	95% CI	P	(ii) ME	95% CI	P	(iii) ME	95% CI	P
HIV+ vs HIV -	-0.087	-0.312; 0.138	0.45	-0.053	-0.245; 0.139	0.59	-0.328	-0.541; -0.116	0.003
CD4:CD8 ratio (log)	-0.392	-0.529; -0.256	<0.001	-	-	-	-0.313	-0.437; -0.189	<0.001
CMV IgG+ vs CMV IgG-	-	-	-	0.803	0.6; 1.005	<0.001	0.717	0.522; 0.913	<0.001

*Adjusted for age, gender, Ethnicity and smoking status

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Immunosenescence – HIV UPBEAT

Multivariable Models : Predictors of CD4+ T-cell senescence

Effect on CD4+ T-cell senescence	(i) ME	95% CI	P	(ii) ME	95% CI	P	(iii) ME	95% CI	P
HIV+ vs HIV-	0.665	0.075; 1.256	0.03	0.422	-0.022; 0.866	0.062	-0.206	-0.698; 0.287	0.41
CD4:CD8 ratio (log)	-0.999	-1.357; -0.642	<0.001	-	-	-	-0.713	-1.001; -0.425	<0.001
CMV IgG+ vs CMV IgG-	-	-	-	2.786	2.317; 3.254	<0.001	2.591	2.139; 3.043	<0.001

*Adjusted for age, gender, Ethnicity and smoking status

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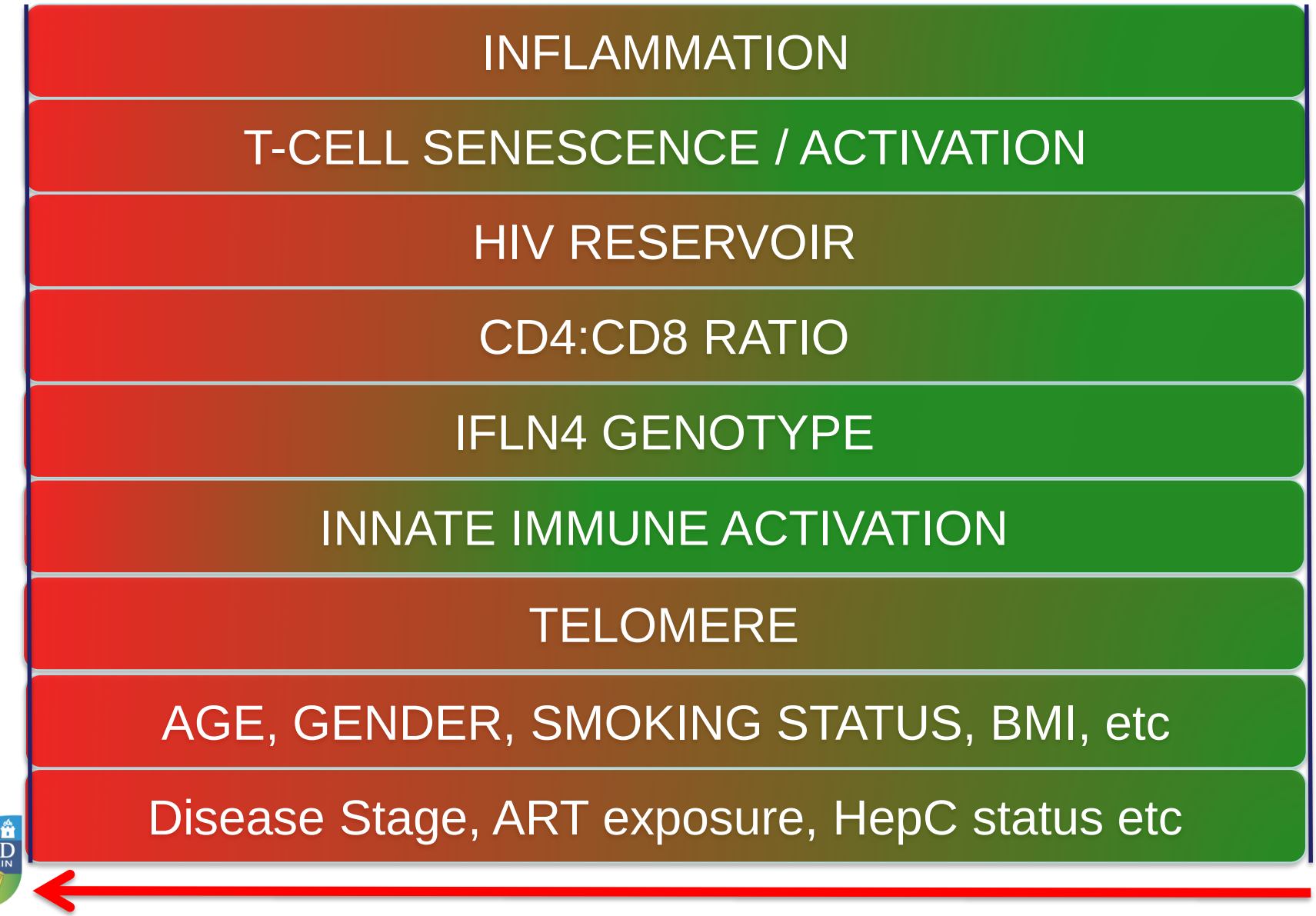
Biological phenotype of Ageing



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- Aoife McDermott
- Aoife Lacey

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