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COMPETING INTEREST OF FINANCIAL VALUE \geq £1,000:	
Speaker Name	Statement
Paddy Mallon	has acted in a consultancy capacity (advisory board membership) has received honoraria for presentations and/or support for attending conferences from Gilead Sciences, Bristol Myers Squibb, Merck Sharpe and Dohme, ViiV Healthcare and Janssen Cilag. Dr Mallon's institution (University College Dublin and/or the Mater Misericordiae University Hospital) has also received funding in the form of research grants from Gilead Sciences, GlaxoSmithKline (Ireland), Merck Sharpe and Dohme and Janssen Cilag.
Date	22 September 2012

Does ageing really matter in HIV?

Dr Paddy Mallon

UCD HIV Molecular Research Group

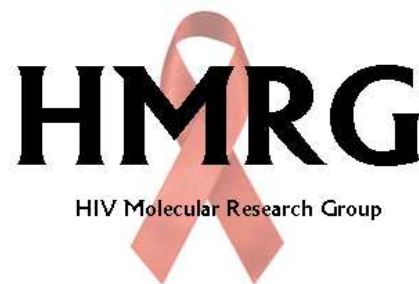
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UCD School of Medicine
& Medical Science



Scoil an Leighis agus
Eolaíocht An Leighis UCD





Sir William Osler

1849-1919

Regius Professor of
Medicine at Oxford

Geriatrician
(‘Gerontologist’)



‘The effective, most vitalizing work of the world is done between the ages of 25 and 40..’

William Osler



*'The value of
experience is not in
seeing much but in
seeing wisely'*

William Osler



Ageing with HIV

Survival living with HIV on ART in 2012

- $N=3280$ on continuous ART from SMART and ESPRIT trials
- 80% male, 61% MSM (no IDU), 43 years
- CD4 >350 and suppressed HIV RNA
- 62 deaths - mortality rate 5.02/1000 PY (95% CI 3.85, 6.43)
- Standardised mortality ratios (SMR) compared to the Human Mortality Database

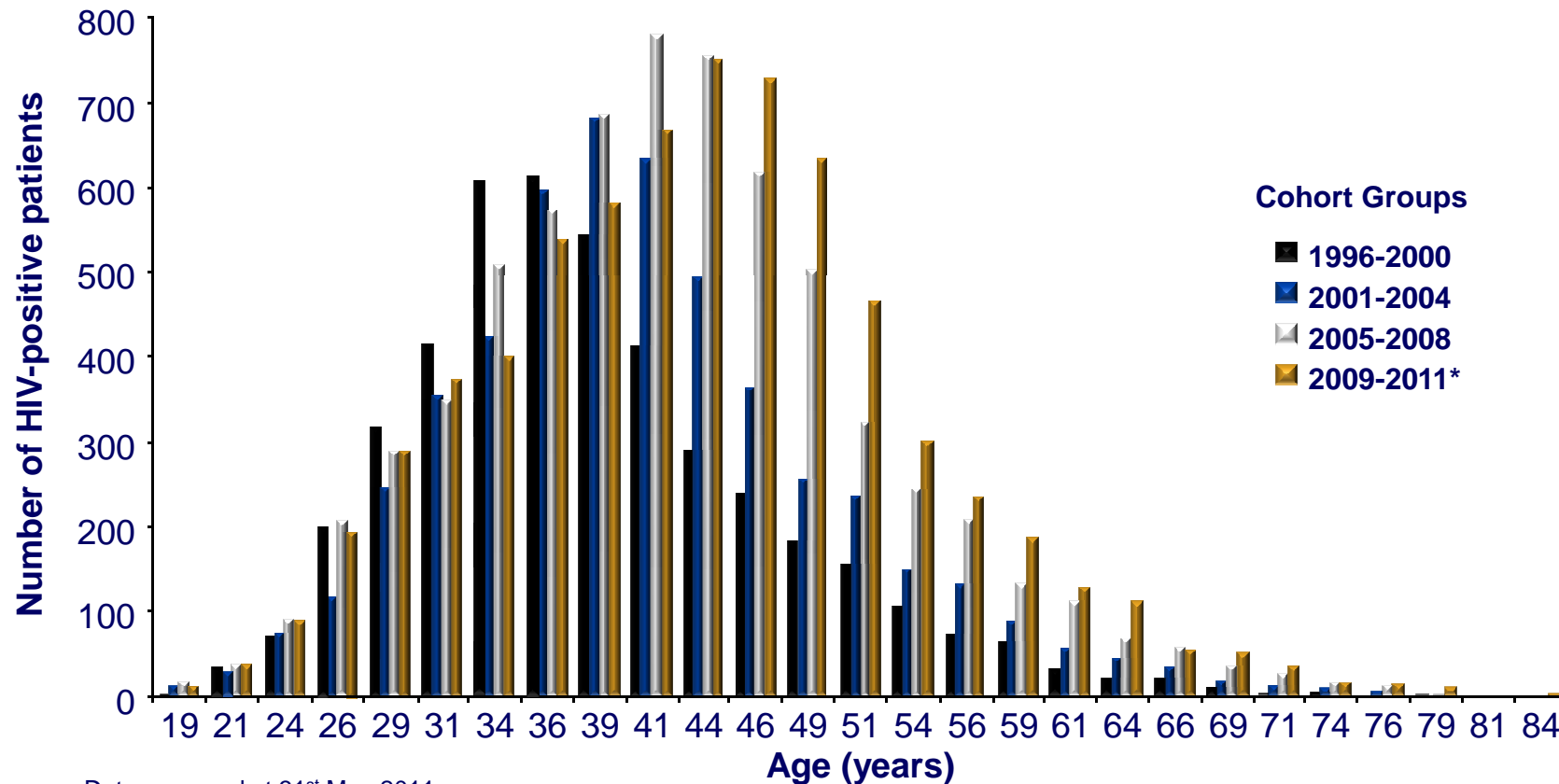
CD4 (cells/mm ³)	350-500	>500
SMR (95% CI)	1.77 (1.17, 2.55)	1.00 (0.69, 1.4)



Ageing with HIV

- In 2005, 15% of new US HIV/AIDS diagnoses were aged >50 yrs¹

Chelsea and Westminster HIV cohort n = 15,0481²



Data censored at 31st May 2011

- 1. CDC HIV/AIDS among Persons Aged 50 and Older Fact Sheet Feb 2008. Available at <http://www.cdc.gov/hiv/topics/over50/resources/factsheets/pdf/over50.pdf> Accessed April 2012;
- 2. Adapted from Mandalia S, et al. Oral Presentation. 2nd Int Workshop on HIV and Aging. 2011.

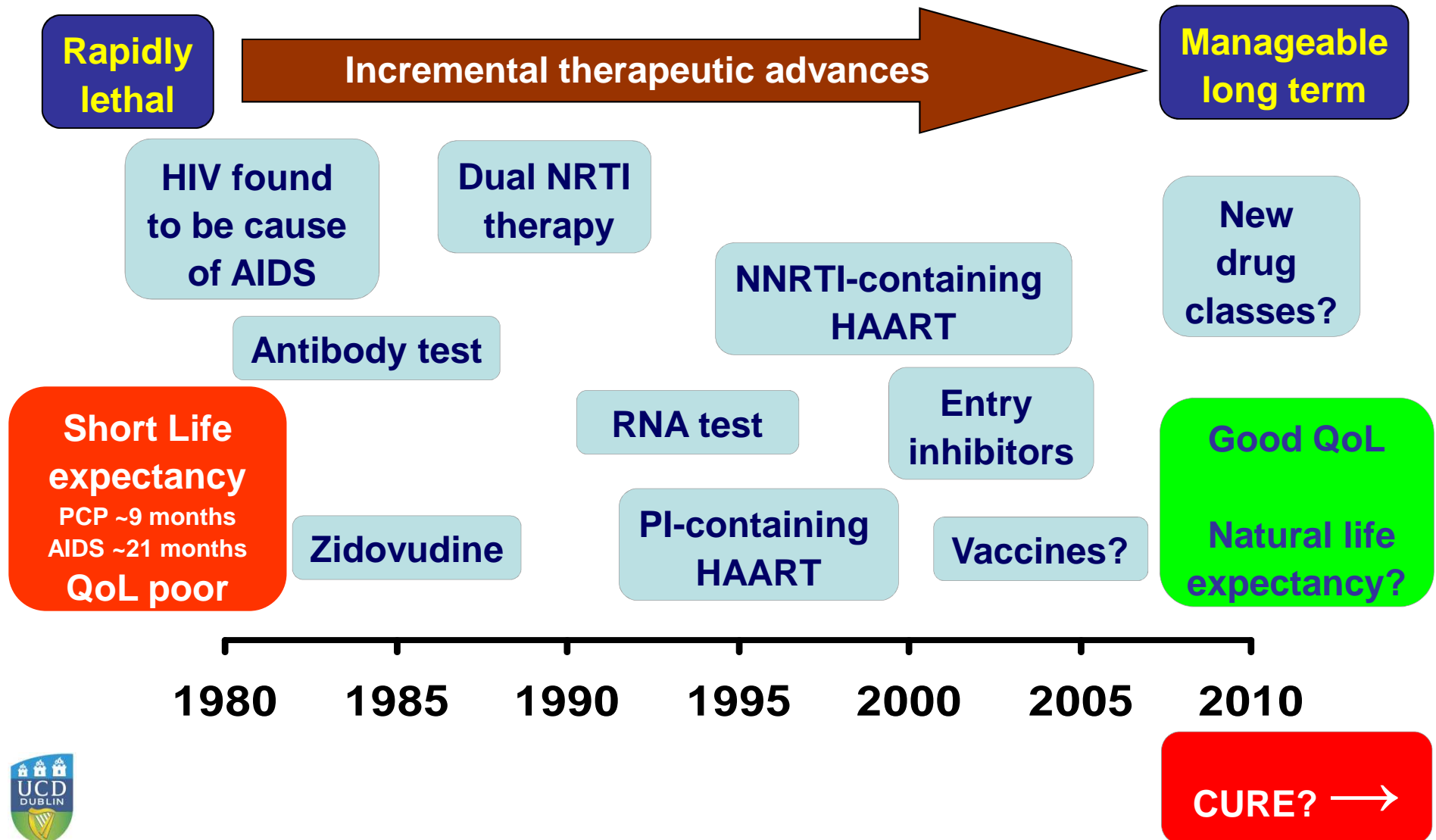




Aging with HIV should
be ***celebrated!***

Evolution of treatment for HIV infection

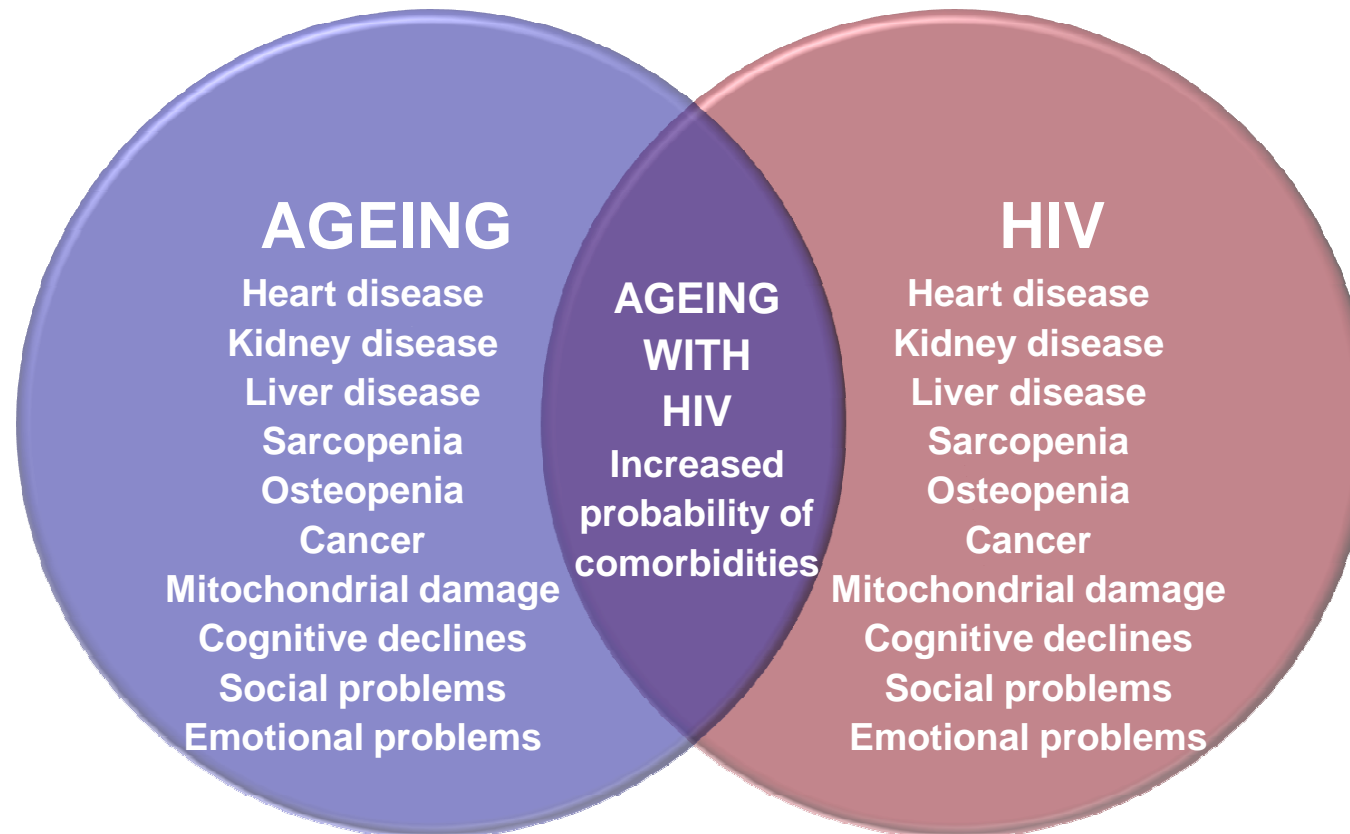
From mortality to long-term manageability



Ageing with HIV

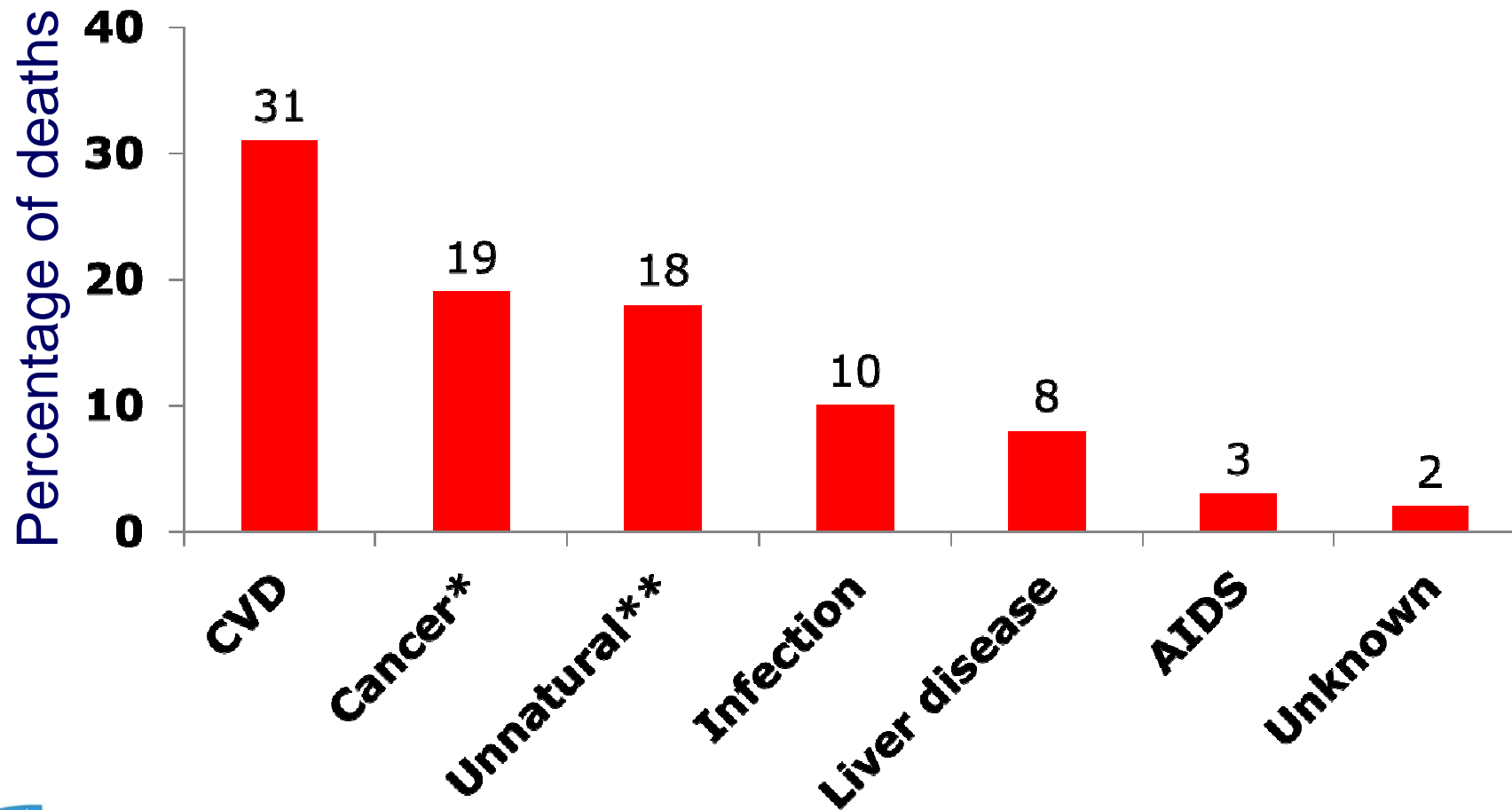


Ageing with HIV: Clinical consequences



Ageing with HIV: Clinical consequences

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

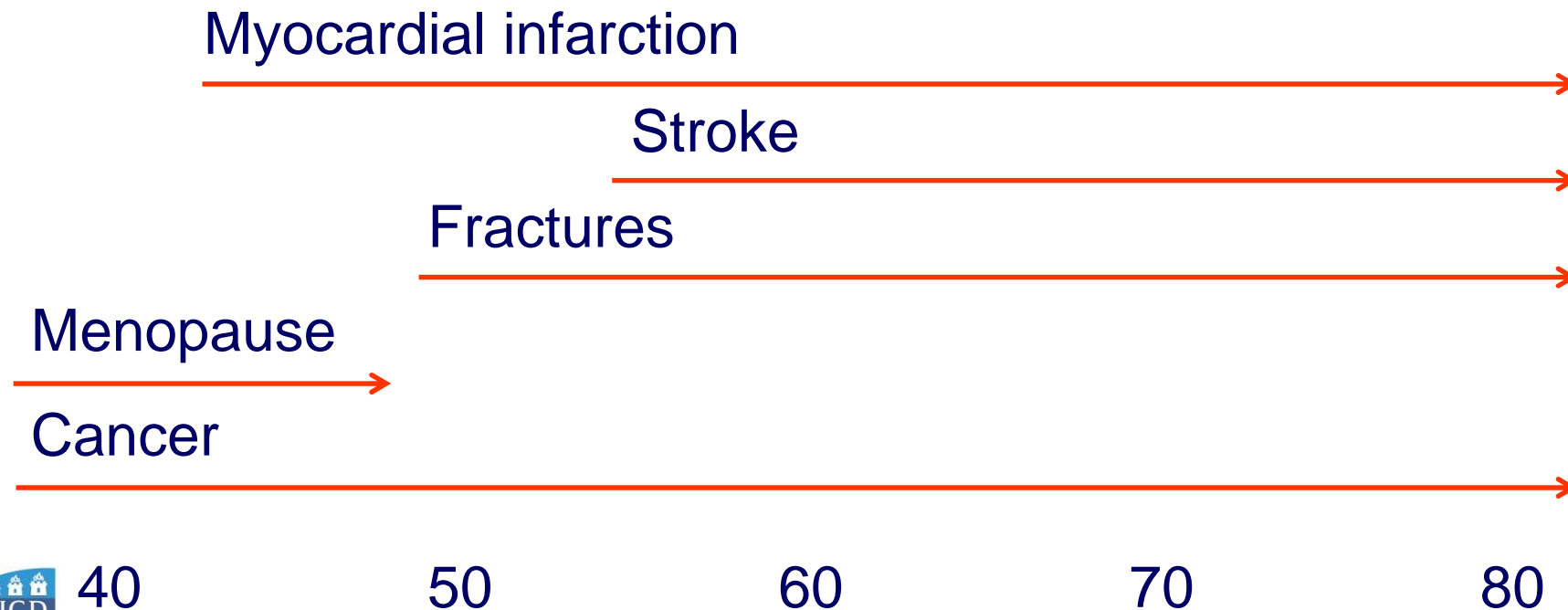


* = non-AIDS malignancy

** = accident, suicide or violent death

Health challenges arising from ageing

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



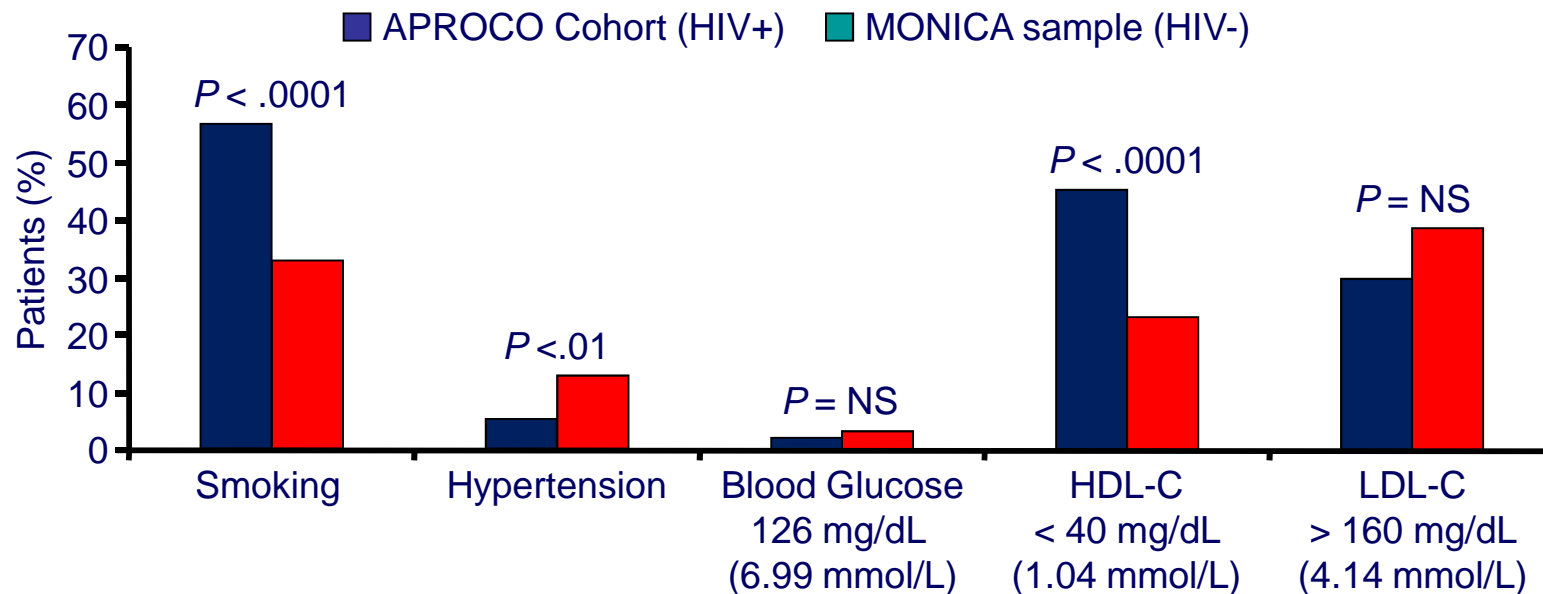
HIV and cardiovascular disease

Incidence of CVD is increased in HIV-infected persons compared with non-HIV-infected ones

References	Size	Outcome	HIV+ vs HIV-
Klein, JAIDS, '02	4,159/39,877	CAD	↑ (6.5 vs 3.8 /1000 PY)
Klein, CROI, '07	5,000/43000	CAD	↑ (4.5 vs 2.9/1000 PY)
Currier, JAIDS, '03	28,513/3 mill	CAD	↑ (only in young)
Triant, JCEM, '07	3,851/1 mill	MI	↑ (75%)
Obel, CID, '07	3,953/0.4mill	CAD	↑ (39-112%)

HIV and Ageing - CVD

CVD risk factors differ from the general population



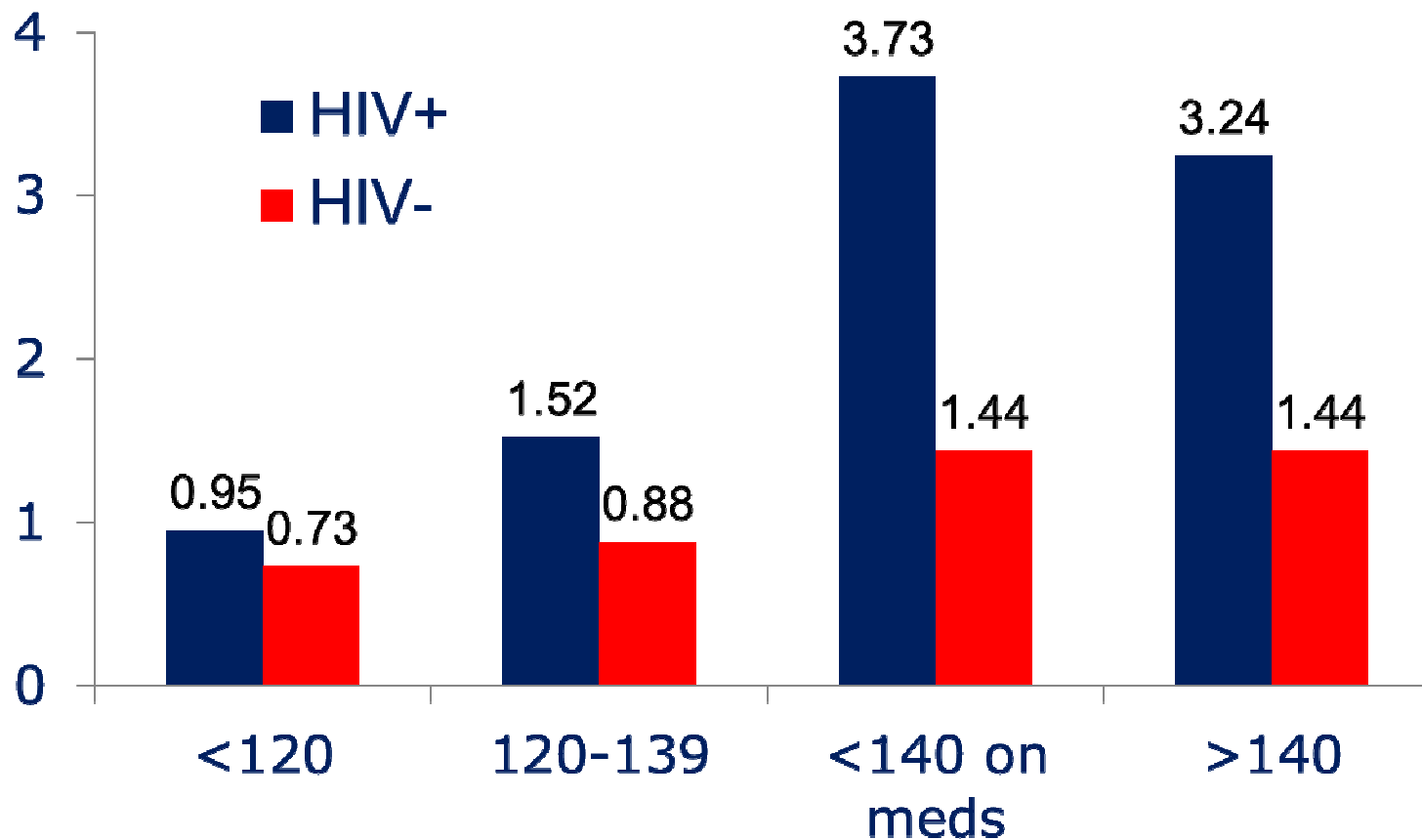
- 223 HIV+ men and women on PI-based regimens vs 527 HIV- male subjects
- HIV+ patients had lower HDL and higher TG
- No difference in total cholesterol
- Predicted risk of CHD > in HIV+ men (RR: 1.2) and women (RR: 1.6); $P < .0001$

Influence of risk factors differs with HIV

Veterans Ageing Cohort Study (N= 84,444, no baseline CVD)

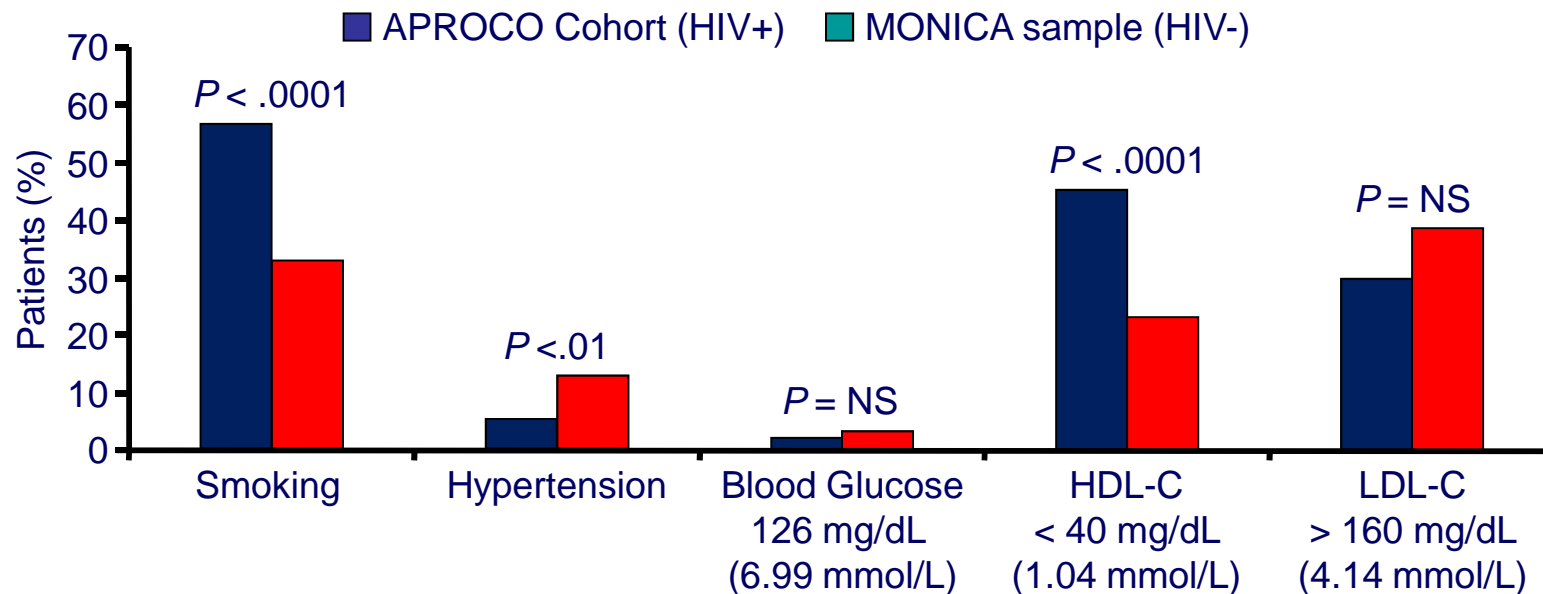
Rates and risk of acute MI (AMI) by SBP categories.

446 MI 47% in HIV+



HIV and Ageing - CVD

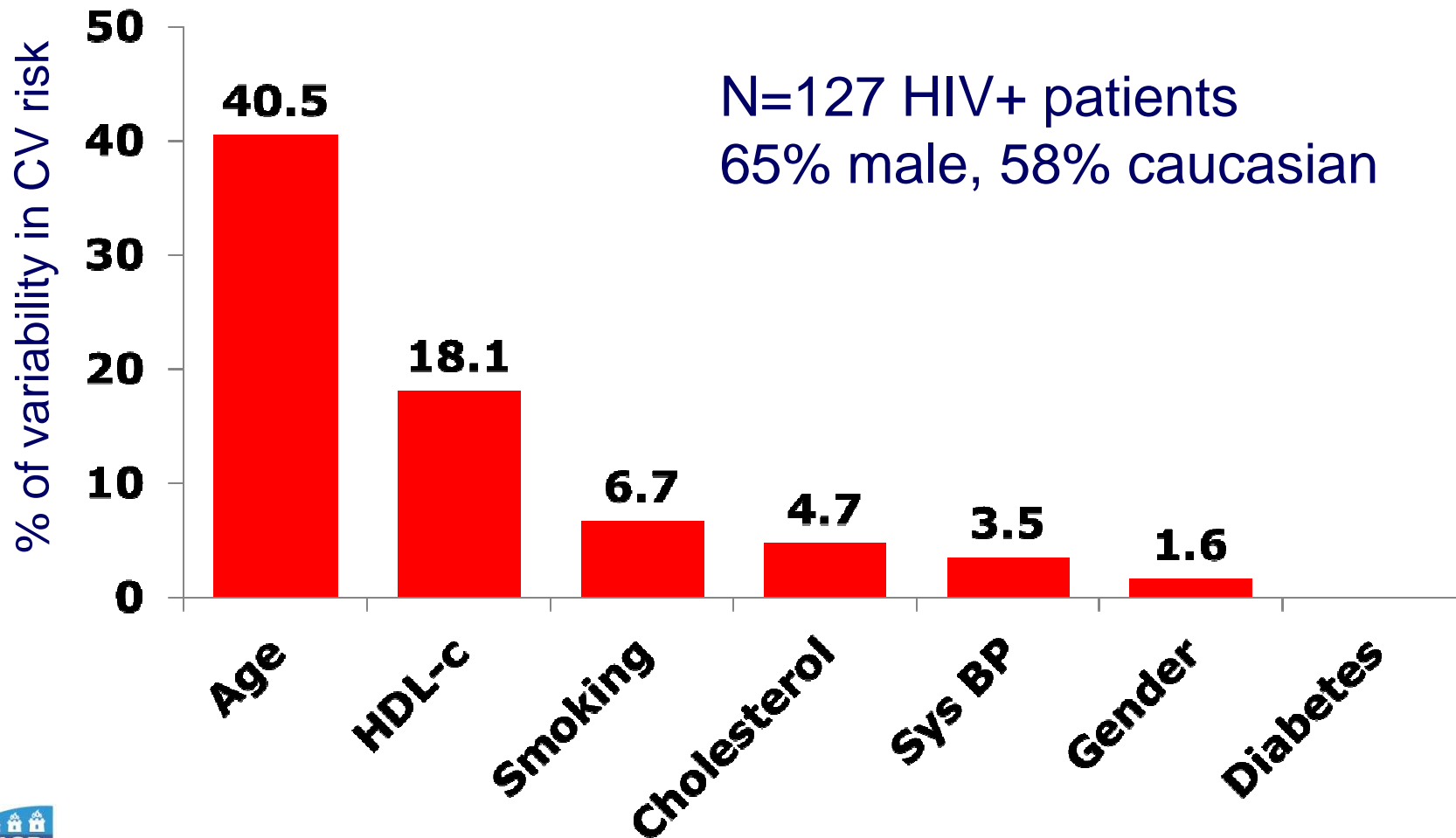
CVD risk factors differ from the general population



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HIV, HDL and CVD

- Low HDL a significant contribution to overall CVD risk¹



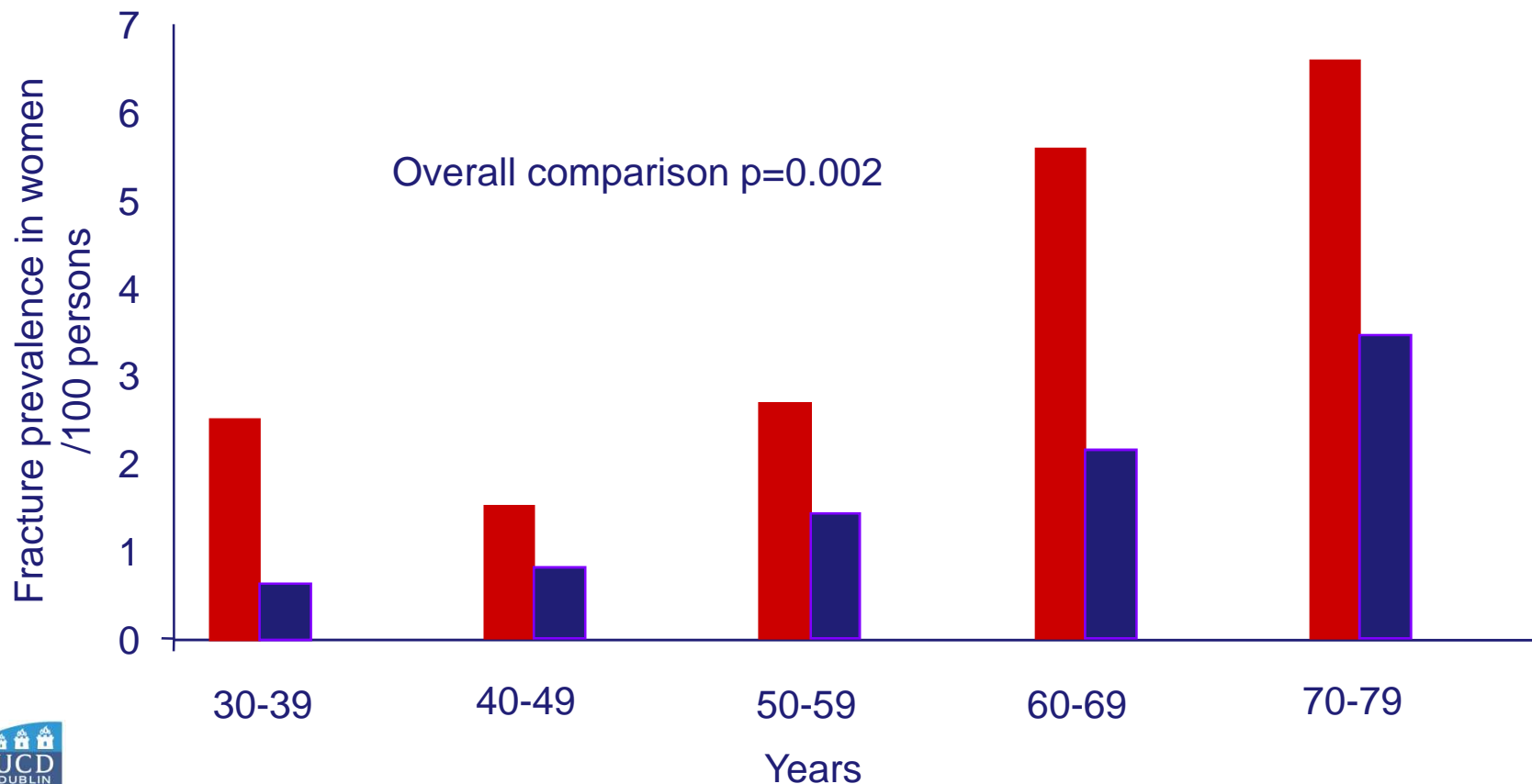
Low BMD is common in HIV+ patients

Publication	Number of patients		% ↓ BMD	
	HIV+	HIV-	HIV+	HIV-
Amiel <i>et al</i> 2004	148	81	82.5	35.8
Brown <i>et al</i> 2004	51	22	63	32
Bruera <i>et al</i> 2003	111	31	64.8	13
Dolan <i>et al</i> 2004	84	63	63	35
Huang <i>et al</i> 2002	15	9	66.6	11
Knobel <i>et al</i> 2001	80	100	87.5	30
Loiseau-Peres <i>et al</i> 2002	47	47	68	34
Madeddu <i>et al</i> 2004	172	64	59.3	7.8
Tebas <i>et al</i> 2000	95	17	40	29
Teichman <i>et al</i> 2003	50	50	76	4
Yin <i>et al</i> 2005	31	186	77.4	56

Fractures more common in HIV+ patients

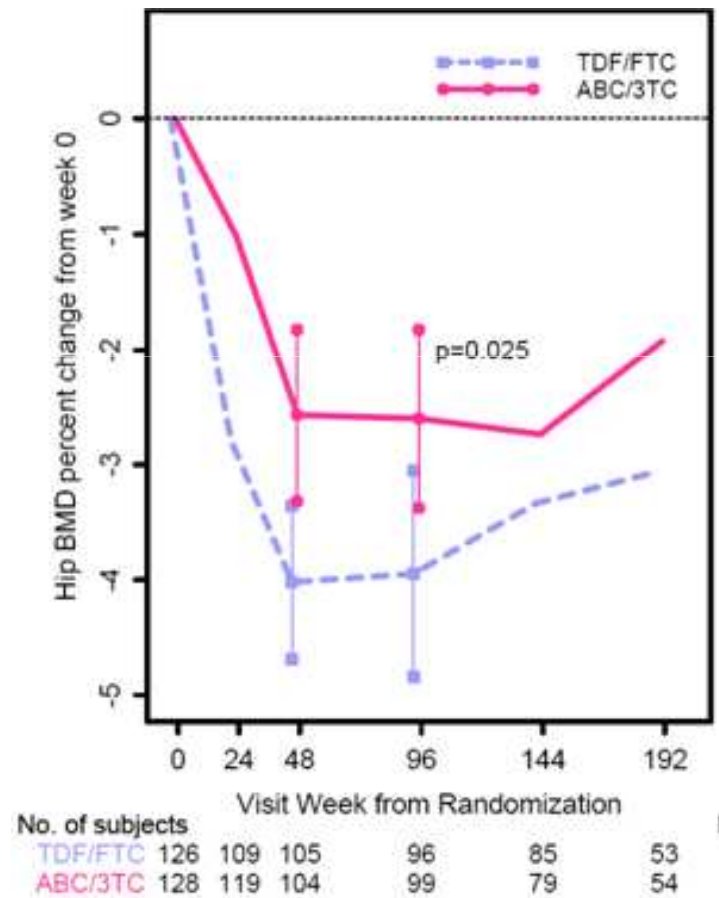
Healthcare Registry study
8,525 HIV-infected patients
2,208,792 non HIV-infected patients
Fracture rates in women demonstrated

 HIV+
 HIV-

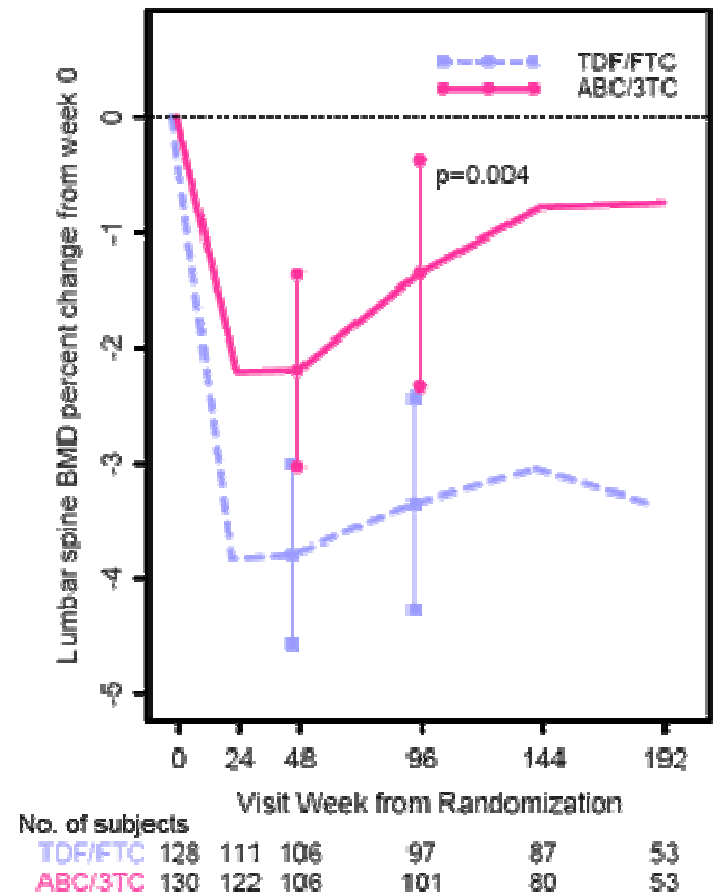


ART initiation and bone loss

Hip

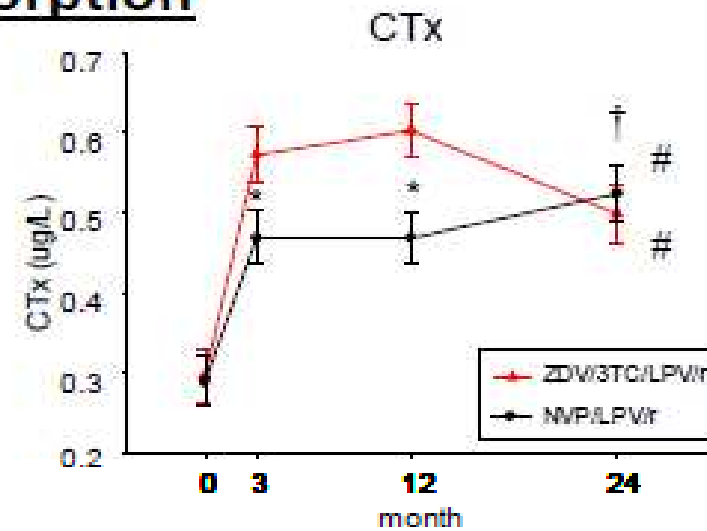
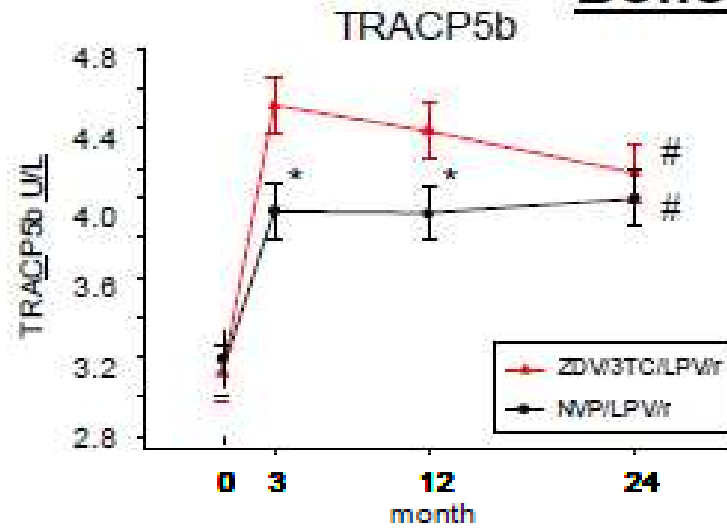


Lumbar Spine

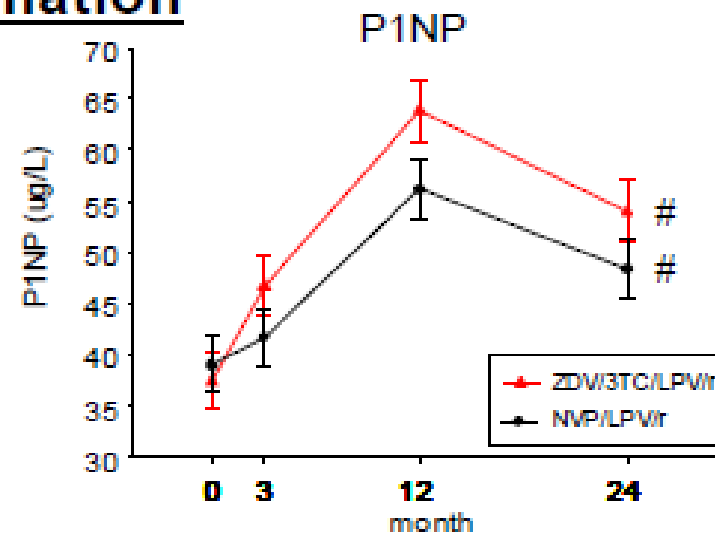
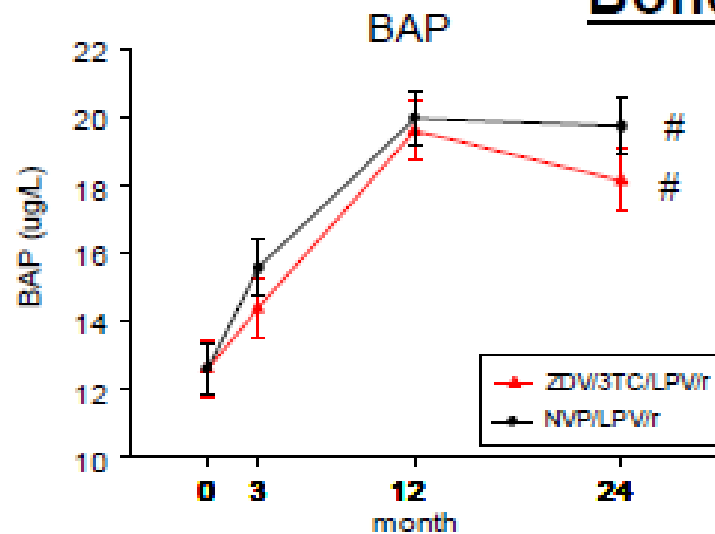


HIV and Bone Turnover

Bone Resorption



Bone Formation



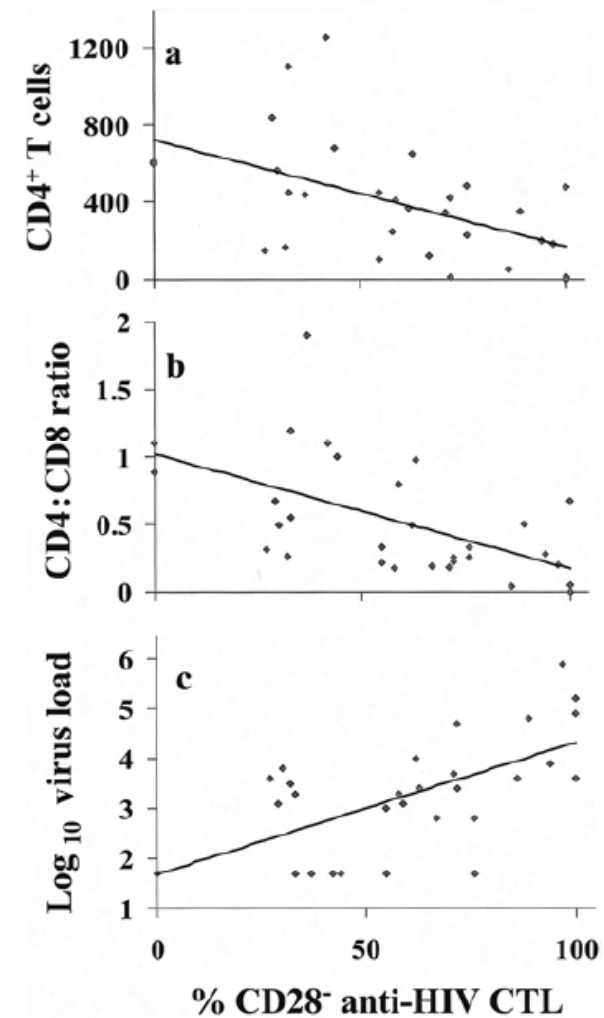
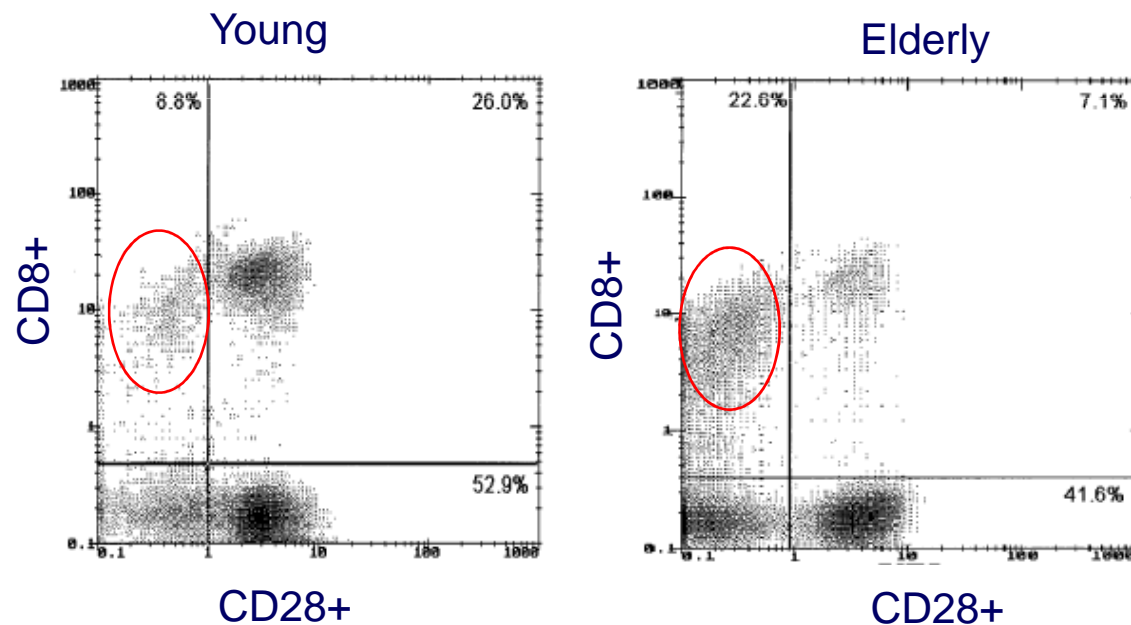
HIV, Ageing and Immune Function

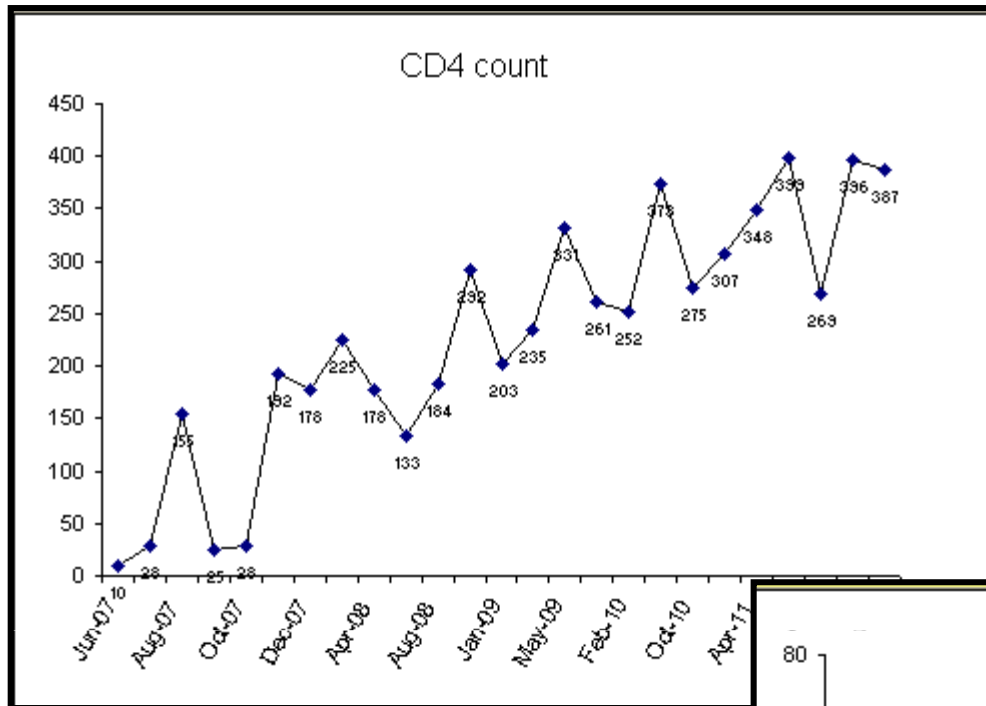
The extent to which ART prevents these changes is unclear, owing to a lack of sufficiently long-term studies

Outcome	Uninfected aged > 70 years	HIV-infected, untreated	HIV-infected long-term treated (5-10 years)
CD4/CD8 cell ratio	Low	Low	Unknown
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?

HIV, Ageing and Immune Function

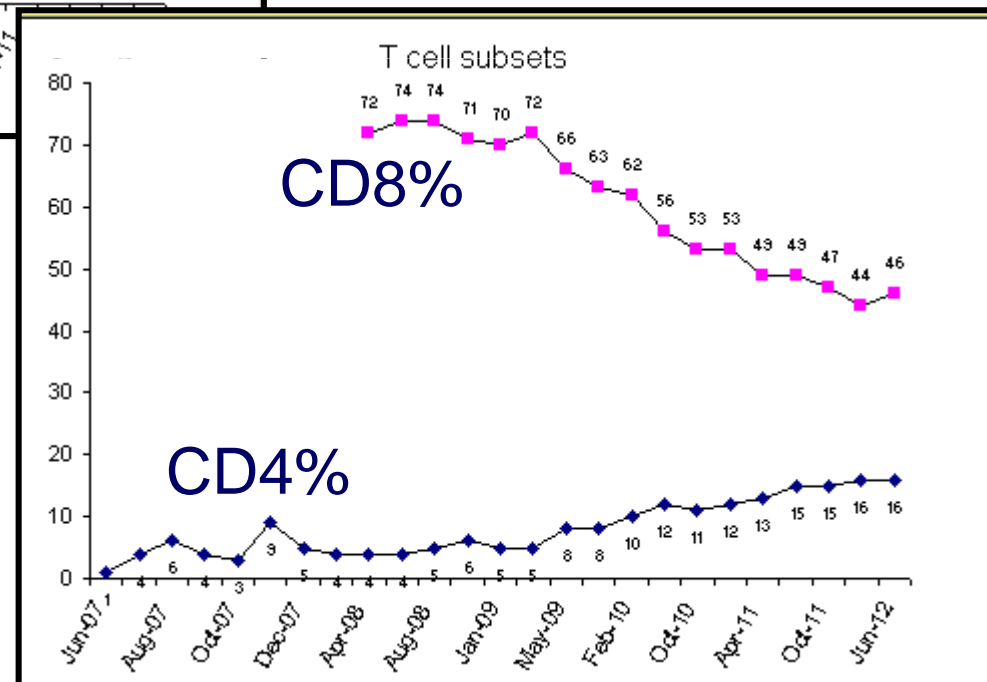
- CD8+CD28- increase with age
- Increased CD8+CD28- in HIV+
- Thought to be 'end-stage' T-cells
- Less responsive to stimulus





Does it matter.....

....that we don't know if it matters?





*'Look wise, say
nothing and grunt.
Speech was given
to conceal thought'*

William Osler



There's something to be said for not rushing into things....

HIV and Aging – ‘*Disease Mongering!*’

(....or medicalisation)

As we attempt to understand pathogenesis, we rush to translate research into guidelines / practice.

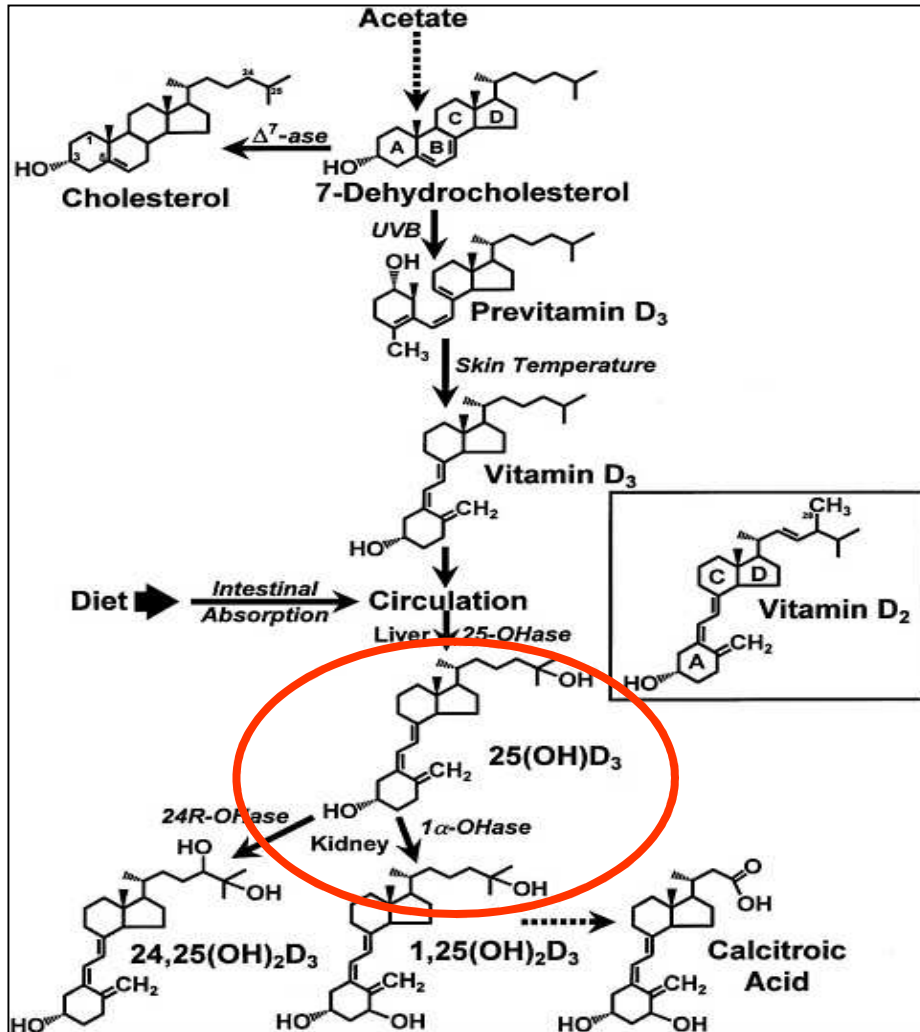
We run the risk of ‘*medicalising*’ HIV and ageing.

‘The social construction of illness is being replaced by the corporate construction of disease.’¹

‘Inappropriate medicalisation carries the dangers of unnecessary labelling, poor treatment decisions, iatrogenic illness, and economic waste...’¹

Growing old with HIV is a “natural” process – **not a disease.**

HIV and Vitamin D



‘Normal’ range = mean \pm 2 SD
20 – 37.5 nmol/L

Much debate about ‘normal’

Bone health:

Reference	nmol/L	ng/mL
Deficient	<27.5	<11
Insufficient	<37.5	<15
‘Normal’	50-75	20-30

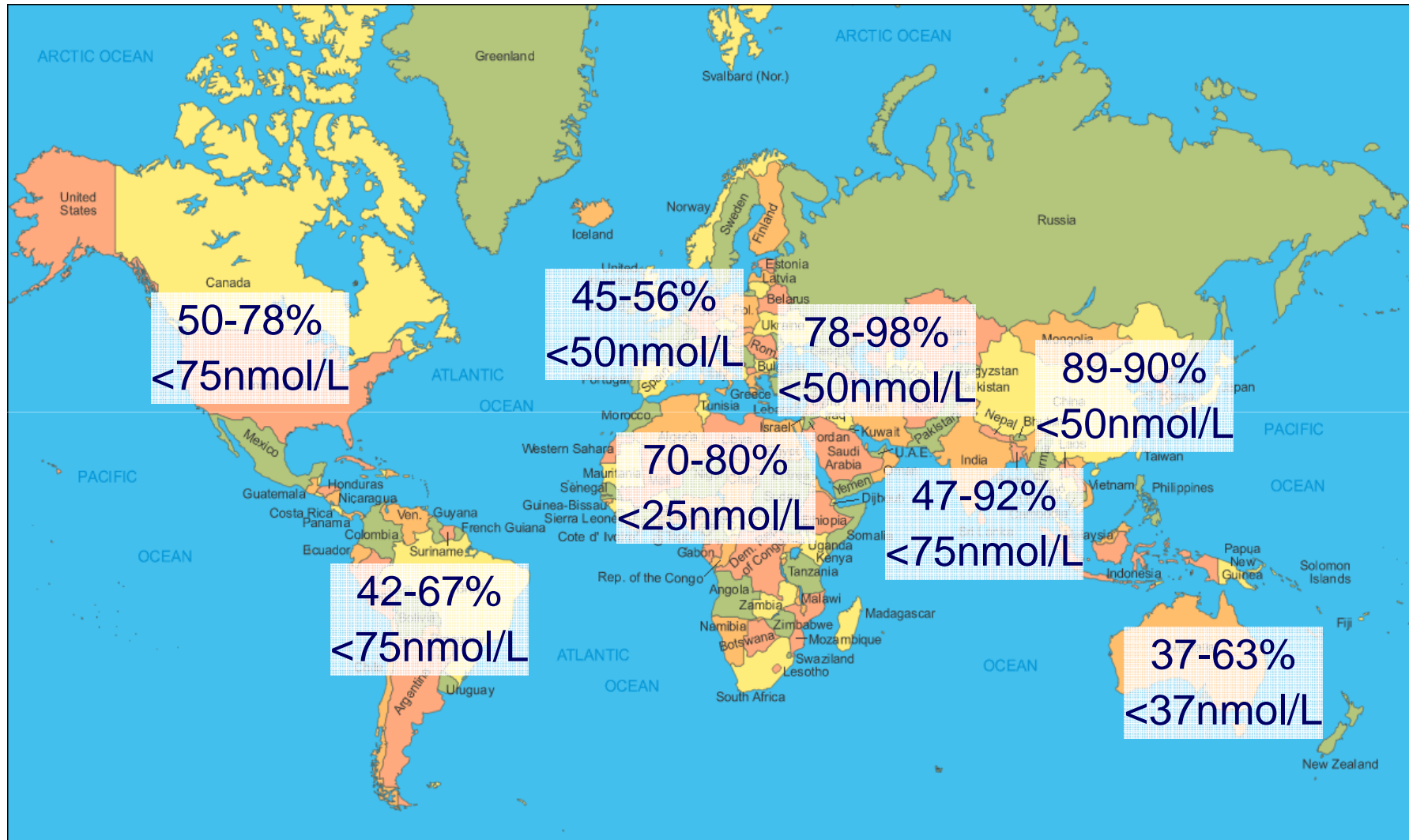
HIV and vitamin D

Study	N	% caucasian	Insufficient ($<75\text{nmol/L}$)	Deficient ($<30\text{nmol/L}$)
SUN study	672	58%	72%	-
Swiss HIV Cohort	215	80%	-	41%
ICONA	852	-	54%	7%
C&W cohort	312	-	35% ($<70\text{nmol/L}$)	21% ($<40\text{nmol/L}$)
Crutchley (USA)	200	40%	64% ($<50\text{nmol/L}$)	20% ($<27.5\text{nmol/L}$)
NYC (St Luke's)	342	-	85%	-



1. Dao, CN et al, CROI 2010 #750, 2. Fux et al. CROI 2010t #749 3. Muller N. et al. CROI 2010 #752 4. Borderi M et al CROI 2010 #751, Rashid T et al. AIDS 2010 Vienna. Crutchley et al. AIDS 2010, Vienna. Gandhi et al. AIDS 2010, Vienna.

HIV and vitamin D



HIV and vitamin D

Women’s Interagency HIV Study (WIHS).

N=1650 (71% HIV+)

23% Vit D insufficient (20-30ng/mL), 63% deficient (<20ng/mL)

	HIV+	HIV-
25(OH)D (ng/ml)	16 [10-25]	14 [9-20]

REACH cohort (US).

87% low Vit D (<37.5nmol/L)

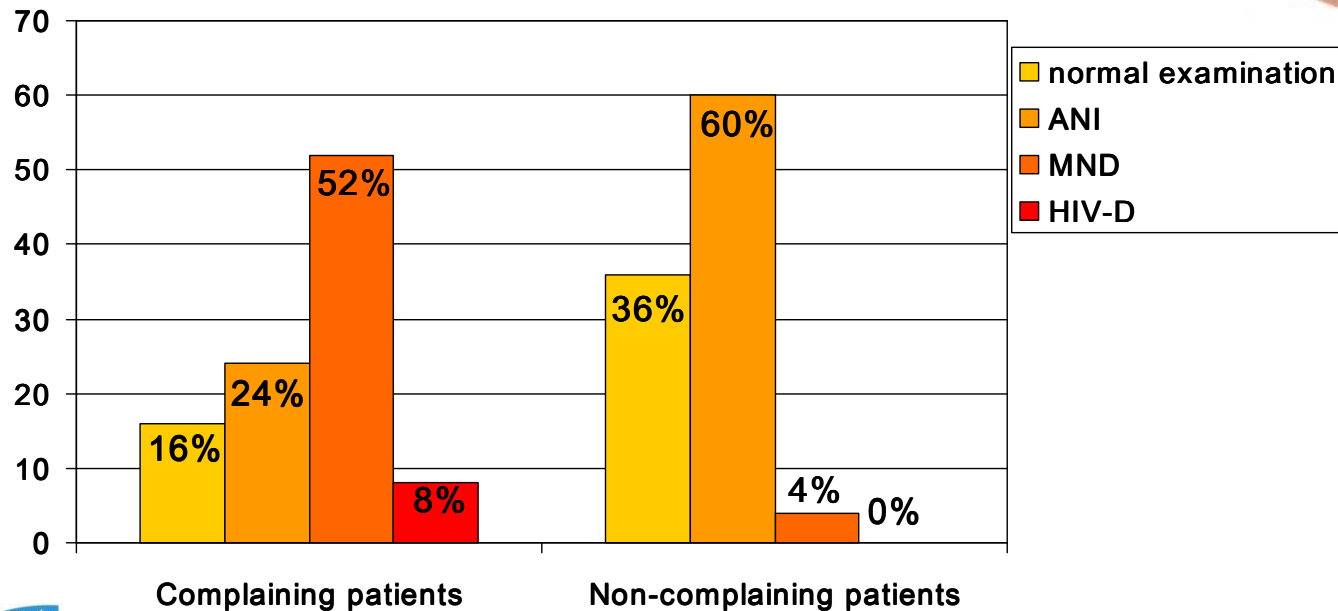
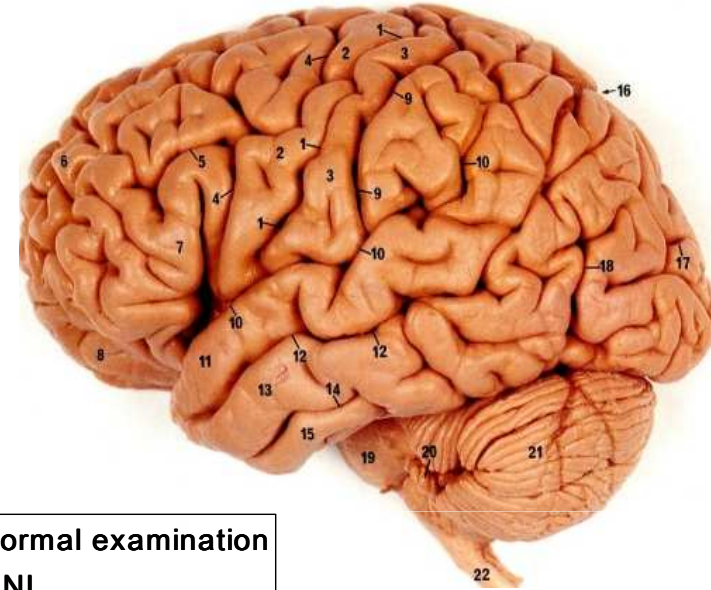
- Latitude, vitamin D intake and ETOH 3 strongest predictors of vitamin D concentrations

	HIV+	HIV-
25 (OH)D (nmol/L)	20.3 [1.1]	19.3 [1.7]

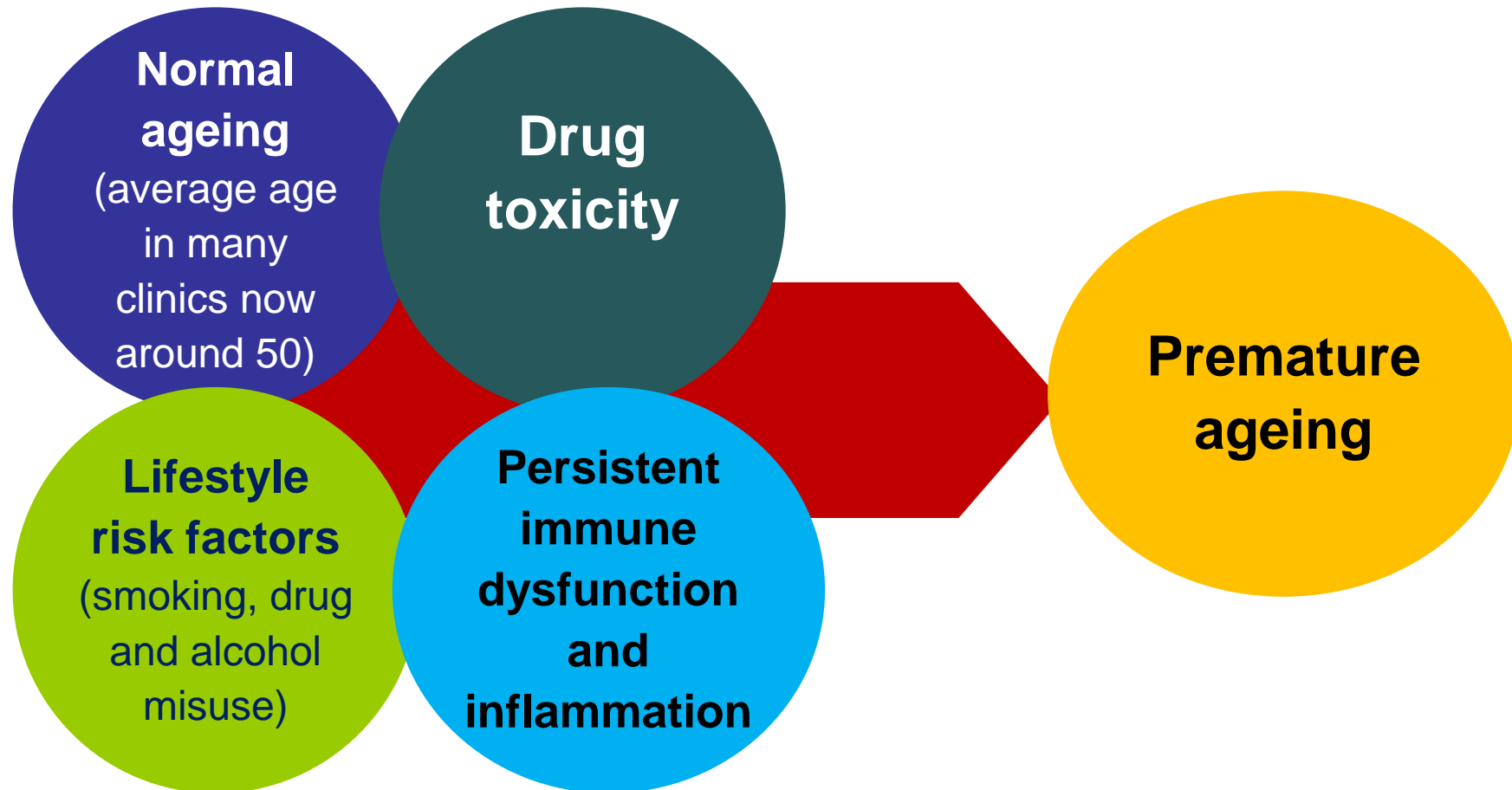


HIV-associated neurocognitive disorders

- Asymptomatic
 - Mild
 - Symptomatic (dementia)
- Prevalence 20-50%

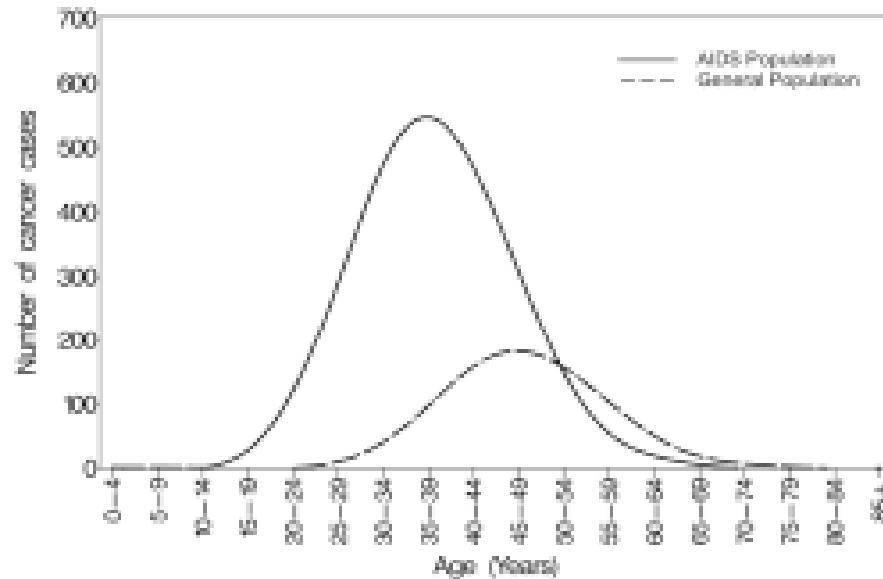


HIV and 'Premature Ageing'

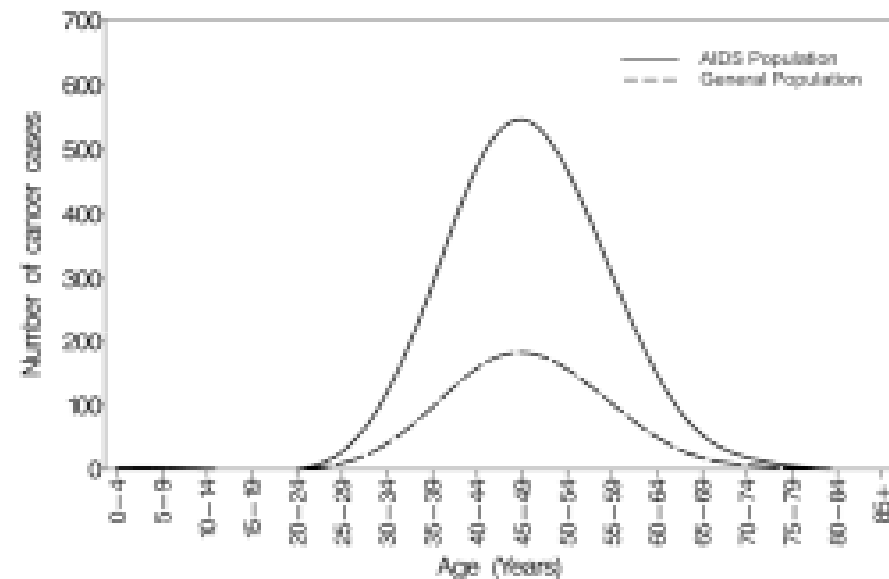


HIV and Ageing

'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

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



*‘The good physician
treats the disease;
the great physician
treats the patient
who has the
disease.’* William Osler



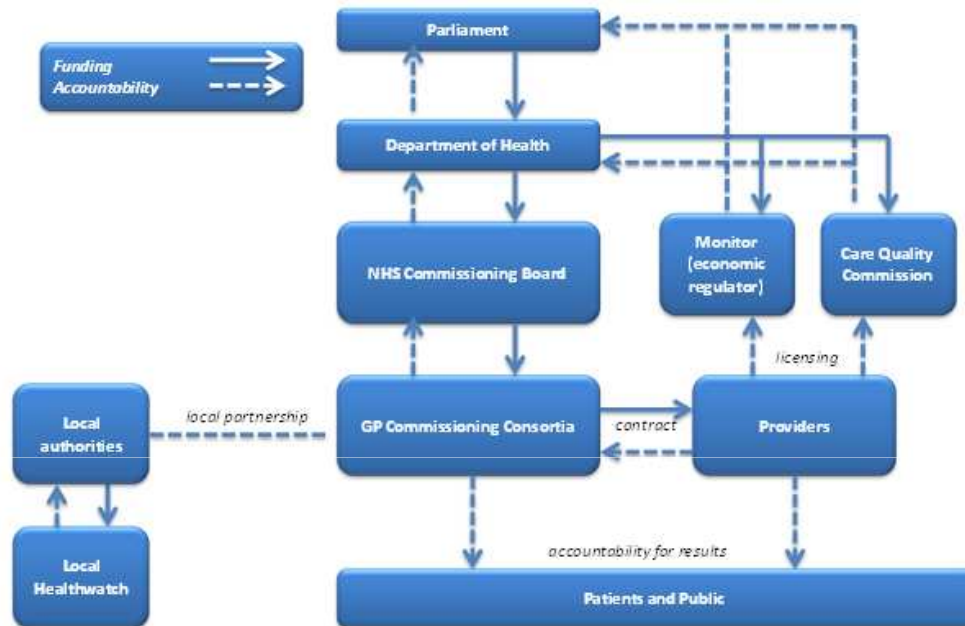
Managing the older HIV+ patient

73-year old man. Married. HIV+ 2007 (MSM)

06 / 2007	PCP, CMV gastritis
08 / 2007	Fall – subdural haematoma Skull osteomyelitis (aspergillus)
10 / 2007	DVT
06 / 2009	Urosepsis and AKI
02 / 2010	CKD (eGFR 33) secondary ↑PTH
06 / 2010	Urosepsis
11 / 2010	SCC (chest wall)
10 / 2011	Retinal haemorrhages
06 / 2012	SCC (hand and face)
09 / 2012	Prostatism - ↑PSA

NHS reforms

Latest information & comment about changes to the National Health Service in Eng



FORM GP PRESCRIPTION 1A



Patient's Name **Mr David Cameron**
 Address **10 Downing Street
 London
 SW1A 2AA**

Take one health reforms Bill. Rip it up and start again.

NHS

Date 4/2/2012



Managing the older HIV+ patient

‘...concerns..that..localisation will exacerbate inequalities and social exclusion; gains from successful national strategies and frameworks will be at risk; and the needs of **patients with less common conditions will not be identified and responded to by GP commissioners with low awareness.**’

‘Perhaps the biggest worry, though, is **whether in a localised system, new national action can be planned** to ramp up areas of poor or patchy care, like mental health, neurological or diabetes care and treatment, or **to provide better deals for children and for older people with long-term conditions.**’

Will HIV Physicians lose control over development of services for what is still a rapidly evolving and relatively poorly understood chronic disease?



*'The best
preparation for
tomorrow is to do
today's work
superbly well.'*

William Osler

HIV UpBEAT and HRB Bone studies



Largest, prospective cohort study of HIV+ and HIV- focused on bone.

'HIV UpBEAT' – pathology underlying bone disease in HIV

'HRB Bone' – natural history of changes in BMD

HIV+ and HIV- (matched for demographic background):

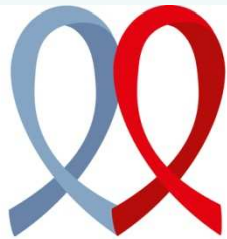
- 196 HIV+ (38.5 yrs, 61% male, 39% African origin)
- 265 HIV- (41.7 yrs, 41% male, 25% African origin)

Detailed population profiling – socioeconomic evaluation



Future research in HIV and aging

***'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



*‘We are here to add
what we can to life,
not to get what we
can from life’* William Osler





*‘The physician who
knows Syphilis
knows medicine’*

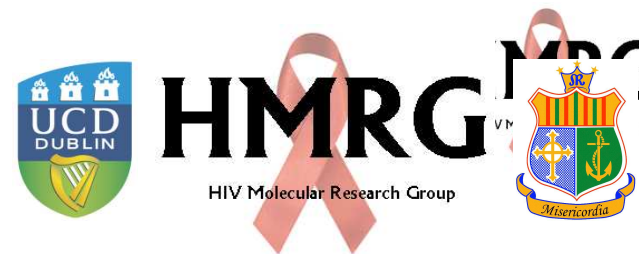
William Osler

*‘The physician who
knows HIV knows
medicine’*

Eoin Feeney



Acknowledgements



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- Ms Collette O'Connor



Speaker Bureau / Honoraria: GlaxoSmithKline, ViiV Healthcare, Merck, Gilead, Abbott, Tibotec, BMS

