

Dispelling the myths: HIV, ageing and the changing causes of morbidity

Caroline A Sabin

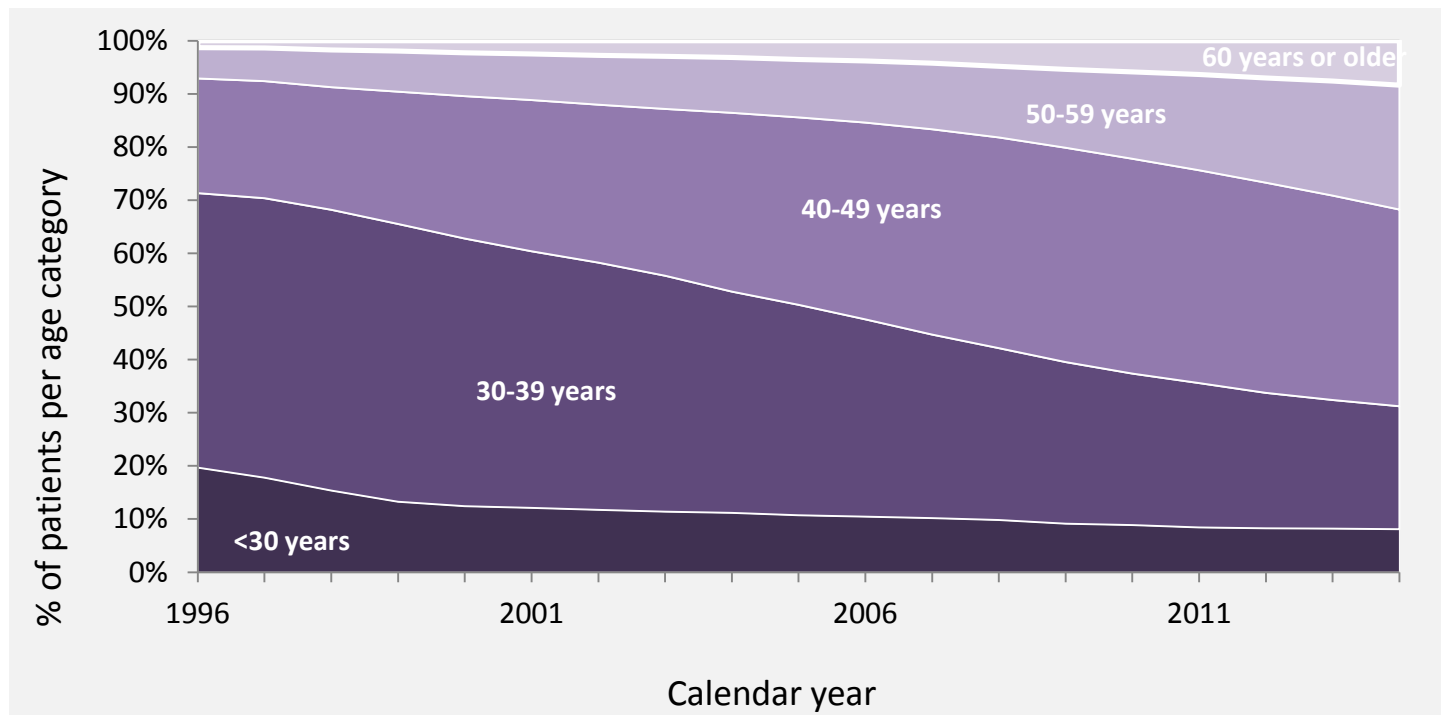
Centre for Clinical Research, Epidemiology, Modelling and Evaluation
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Disclosures

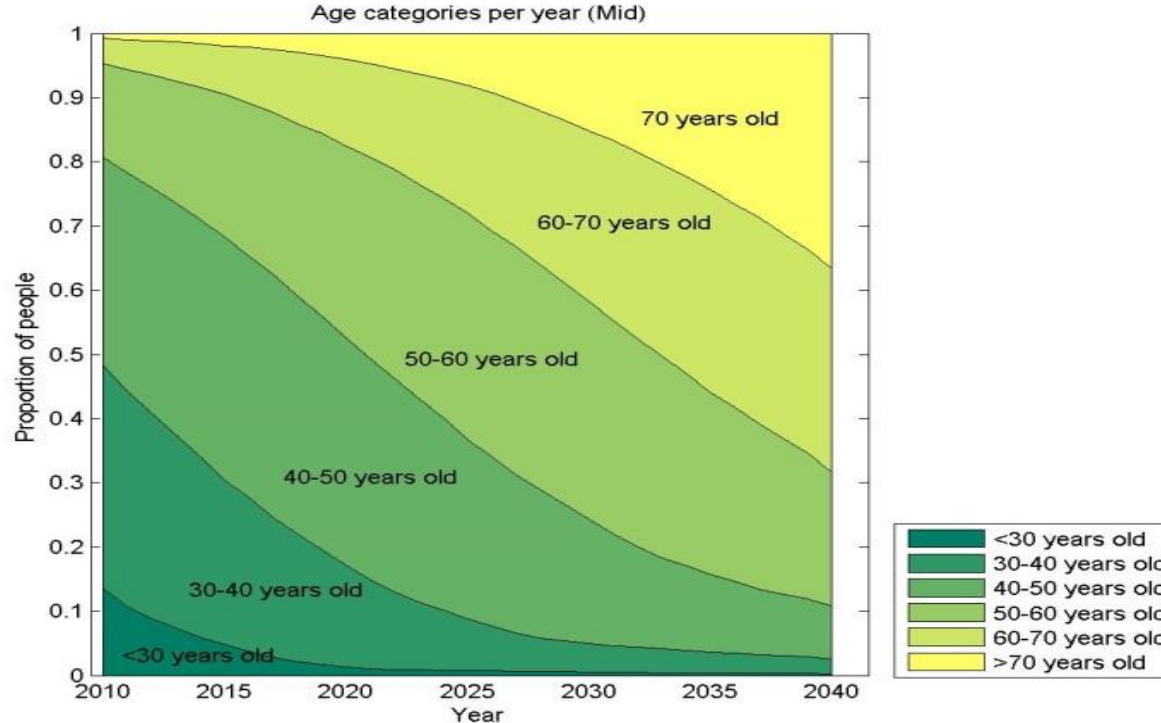
I have received funding for membership of Data Safety and Monitoring Boards, Advisory Boards, Speaker Panels and for preparation of educational materials from the following:

- Gilead Sciences
- ViiV Healthcare
- Janssen-Cilag

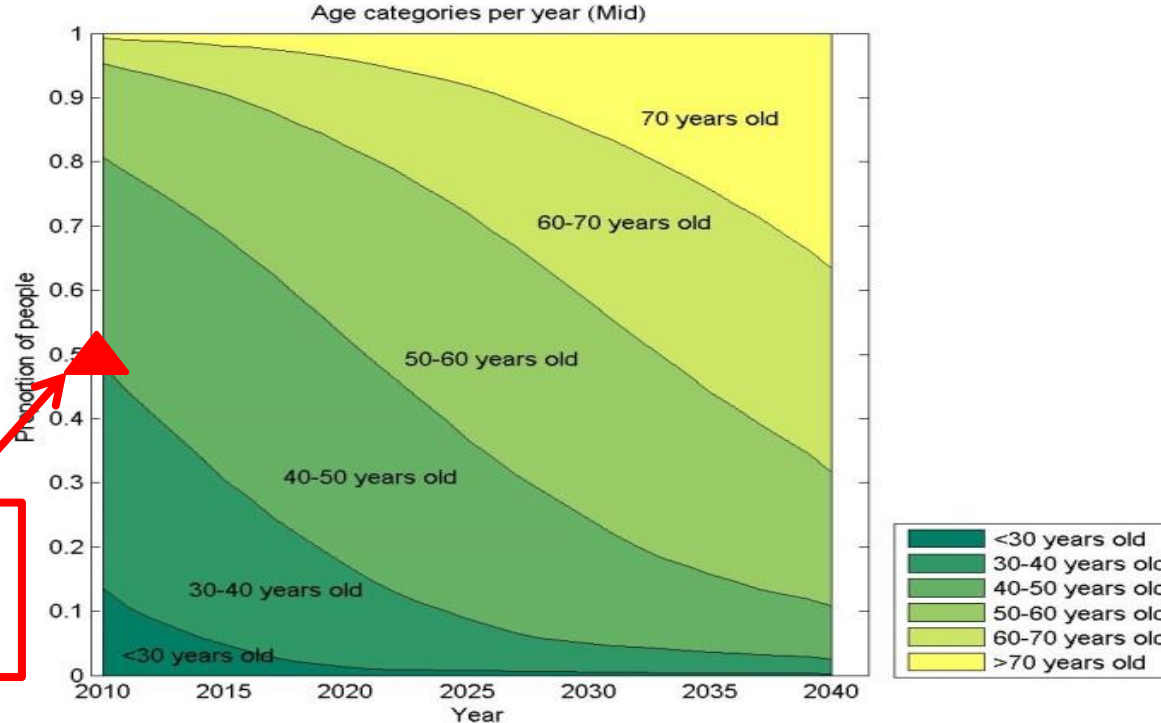
Age of UK CHIC participants



Future projections

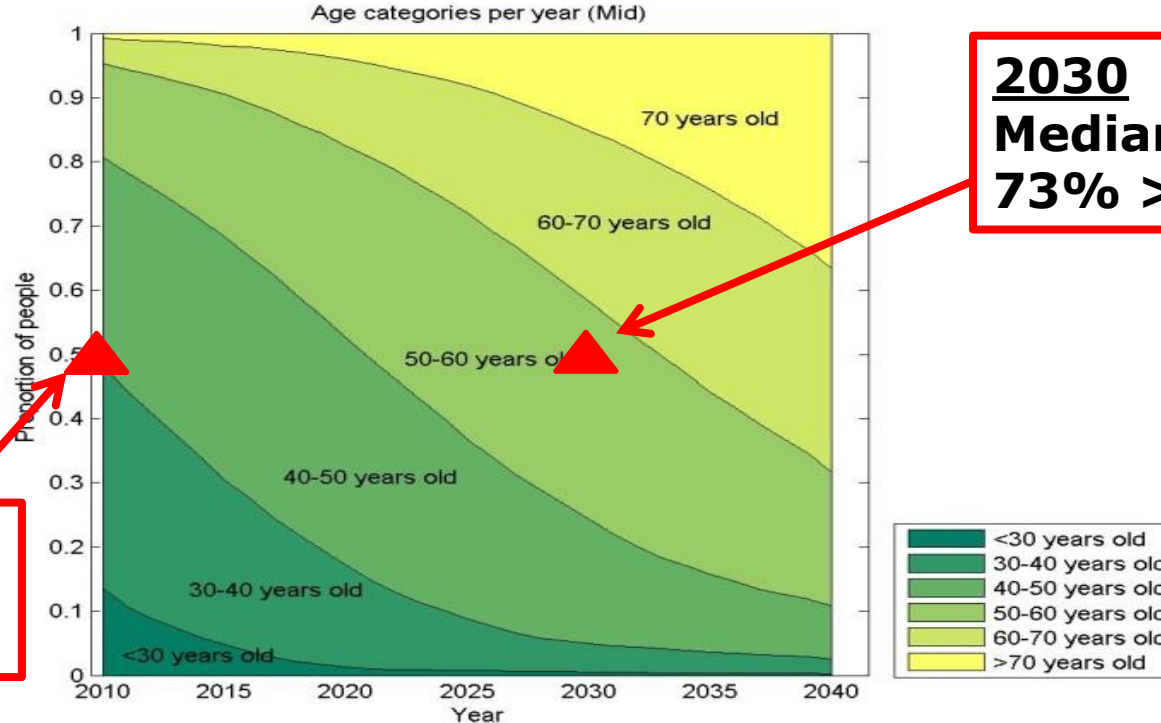


Future projections



2010
Median age: 44
28% >50 years

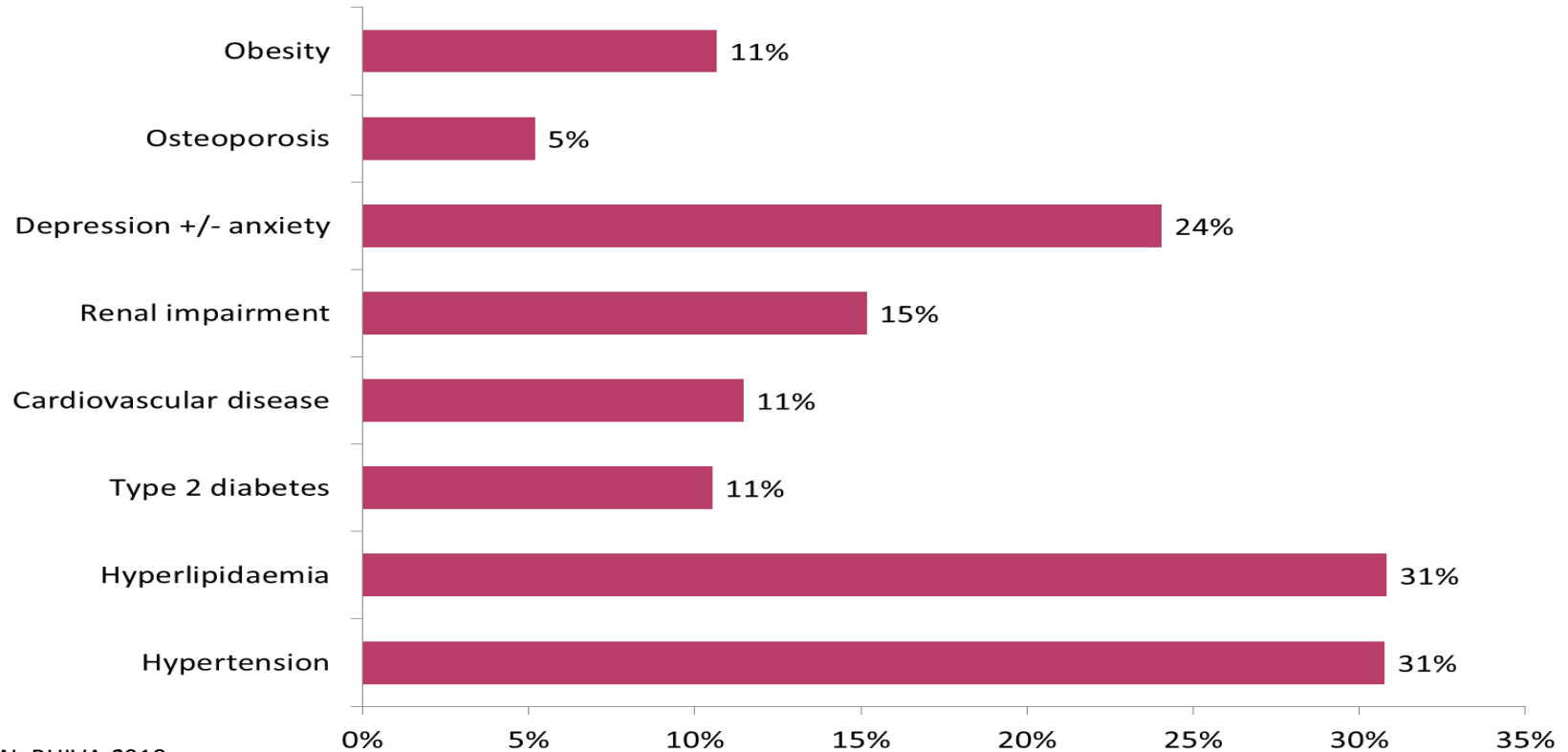
Future projections



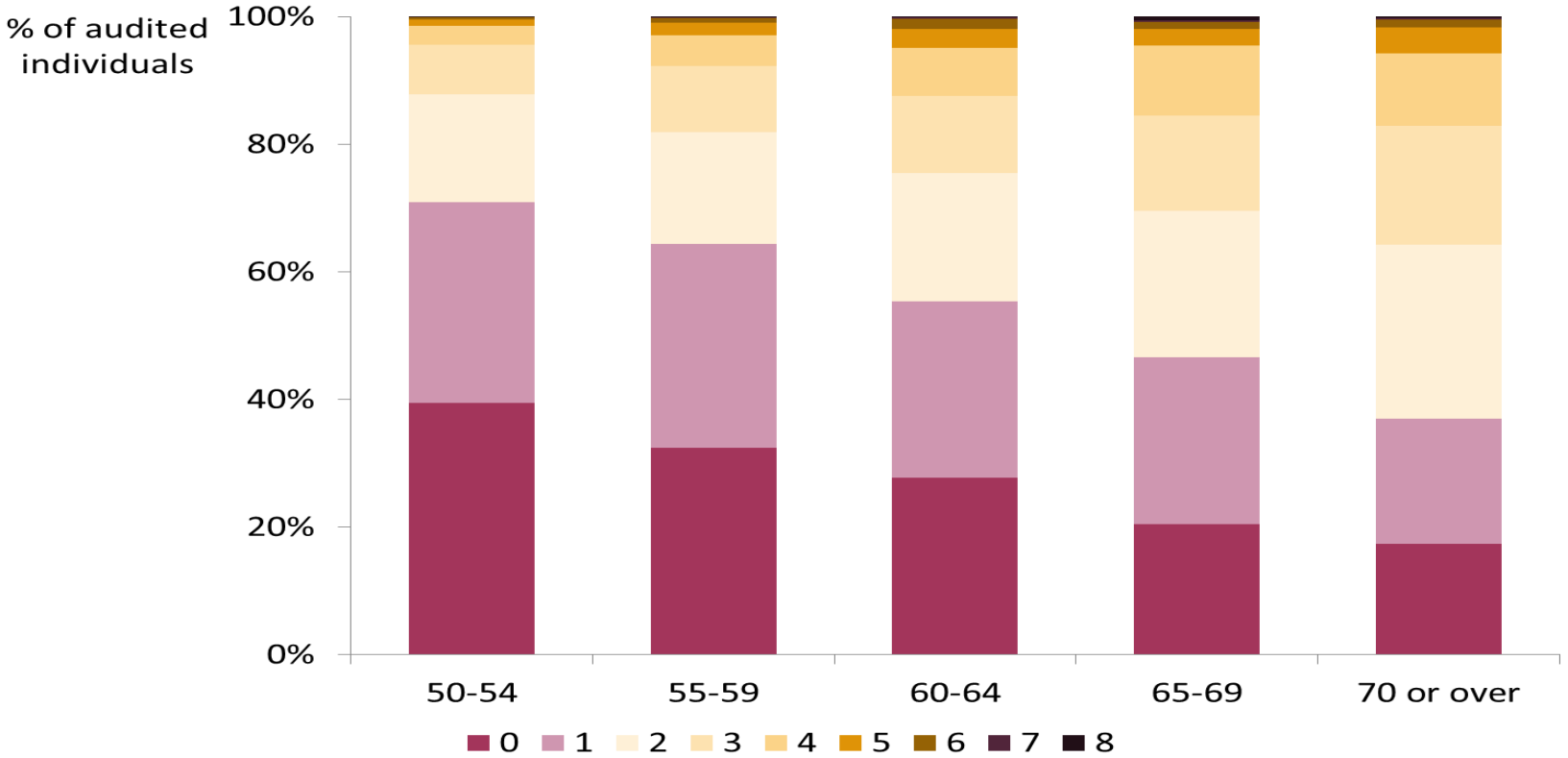
2010
Median age: 44
28% >50 years

2030
Median age: 57
73% >50 years

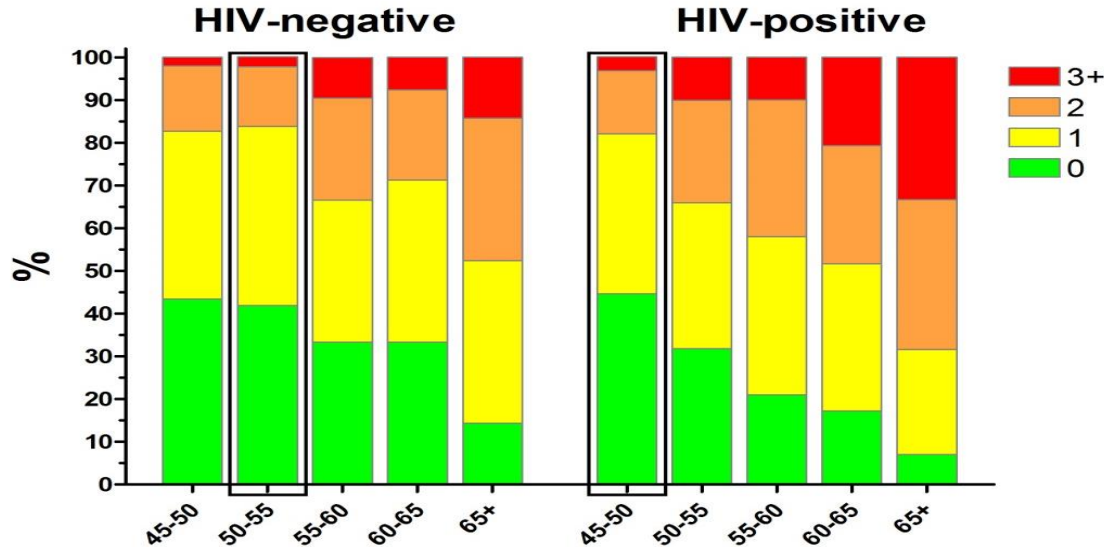
Reported prevalence of common co-morbidities



Age vs. number of common co-morbidities



Co-morbidities



Mean number of comorbidities:
 HIV-positive: 1.3
 HIV-negative: 1.0

Raised rates of:
 Hypertension
 MI
 Peripheral arterial disease
 Impaired renal function

Beliefs about ageing

- Literature abundant with studies reporting that HIV causes ‘premature ageing’ or that co-morbidities occur at an earlier age in PLWH

Beliefs about ageing

- Literature abundant with studies reporting that HIV causes ‘premature ageing’ or that co-morbidities occur at an earlier age in PLWH



The screenshot shows a web browser displaying a page from Medical News Today. The URL in the address bar is <http://www.medicalnewstoday.com/articles/299374.php>. The page features a navigation menu with 'NEWSLETTER' and the site logo 'MEDICALNEWS TODAY'. Below the navigation is an advertisement for 'Elevate Your Miami Escape' by Trump, with the text 'Enjoy our all new luxurious accommodations and savor some incredible savings.' The main article title is 'HIV infection associated with premature aging', written by Yvette Brazier and published on Friday, 22 April 2016. The article text begins with 'While combination antiretroviral therapy can enable people with HIV to enjoy many more years of life than they might previously have expected, the same patients appear to be prone to losing an average of 5 years of life due to premature aging.' A partial advertisement for 'THE UK #1 LE LIGHTIN SPECIAL' is visible on the right side of the page.

Beliefs about ageing

- Literature abundant with studies reporting that HIV causes ‘premature ageing’ or that co-morbidities occur at an earlier age in PLWH

The image displays two overlapping browser screenshots. The background screenshot is from Medical News Today, dated Friday 22 April 2016, with the headline "HIV infection associated with prema...". The foreground screenshot is from AIDSmap.com, dated 20 October 2011, with the headline "Diseases of ageing occurring 10 to 15 years earlier in patients with HIV".

Medical News Today Article (Background):
URL: <http://www.medicalnewstoday.com/articles/30774.php>
Headline: HIV infection associated with prema...
By Yvette Brazier | Published Friday 22 April 2016

AIDSmap.com Article (Foreground):
URL: <http://www.aidsmap.com/Diseases-of-ageing-occurring-10-to-15-years-earlier-in-patients-with-hiv>
Headline: Diseases of ageing occurring 10 to 15 years earlier in patients with HIV
Author: Michael Carter
Published: 20 October 2011
Text: The diseases of ageing develop earlier in patients with HIV than in the general population, Italian investigators report in the online edition of *Clinical Infectious Diseases*.
*Our findings suggest that an aggressive approach to the screening, diagnosis, and treatment of...

Beliefs about ageing

- Literature abundant with studies reporting that HIV causes ‘premature ageing’ or that co-morbidities occur at an earlier age in PLWH
- Search continues for biological mechanisms that drive this apparent increased risk
 - Residual inflammation / ‘Inflammageing’?
 - Altered gut microbiota?
 - Mitochondrial dysfunction?
 - Immunosenescence?

Beliefs about ageing

- Literature abundant with studies reporting that HIV causes 'premature ageing' or that co-morbidities occur at an earlier age in PLWH

In our rush to establish mechanisms, have we forgotten the basic rules of epidemiology?

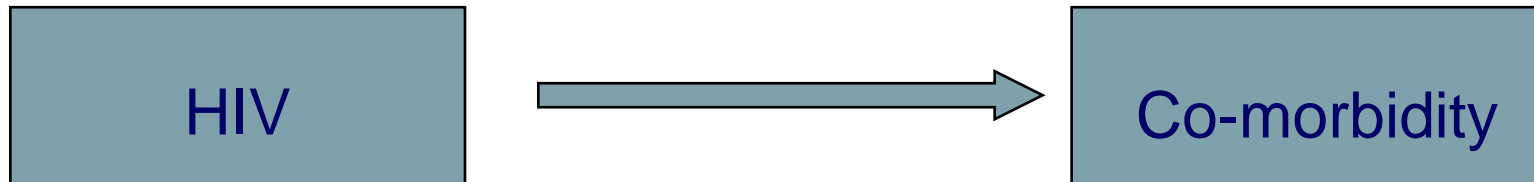
- Residual inflammation / inflammageing?
- Altered gut microbiota?
- Mitochondrial dysfunction?
- Immunosenescence?

Confounding

- PLWH have very different characteristics to the general population, including increased risk of:
 - sexually transmitted infections
 - viral coinfections
 - smoking
 - recreational drug use, etc.
- Could these other factors confound associations with co-morbidities and/or bio-markers?

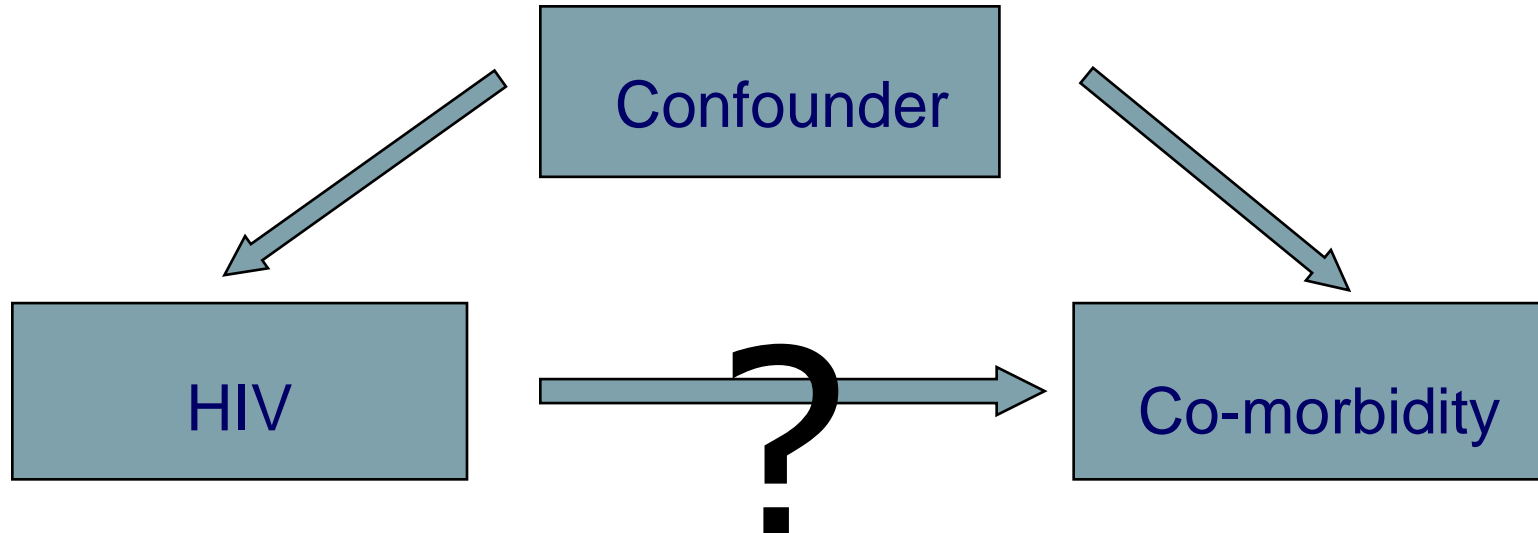
Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome



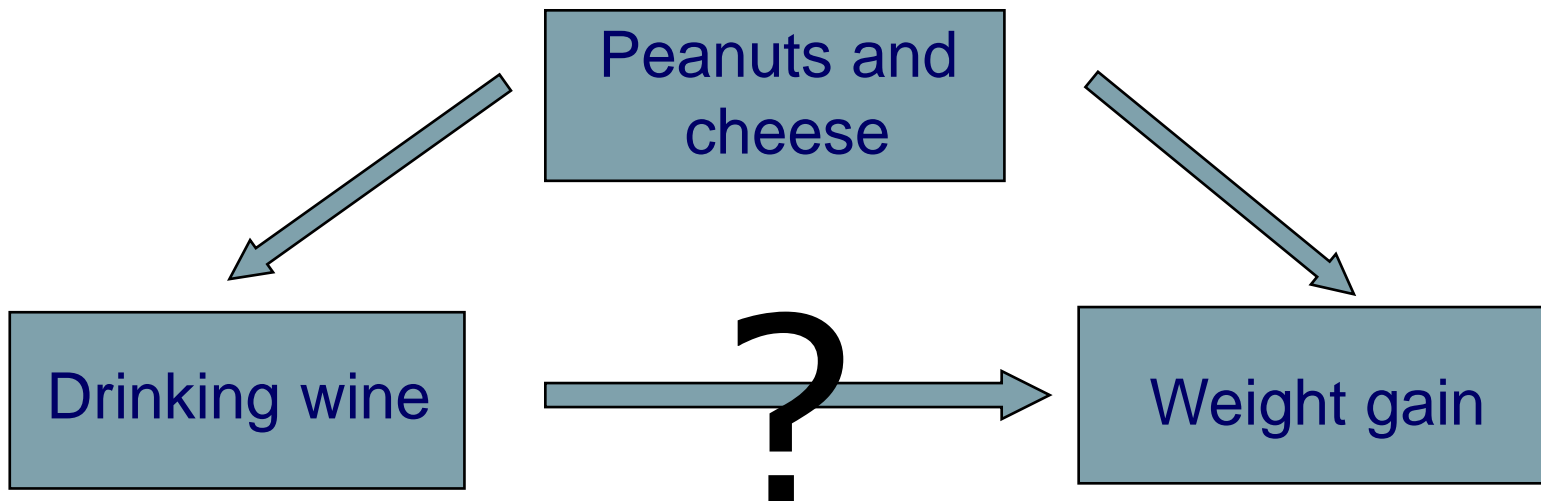
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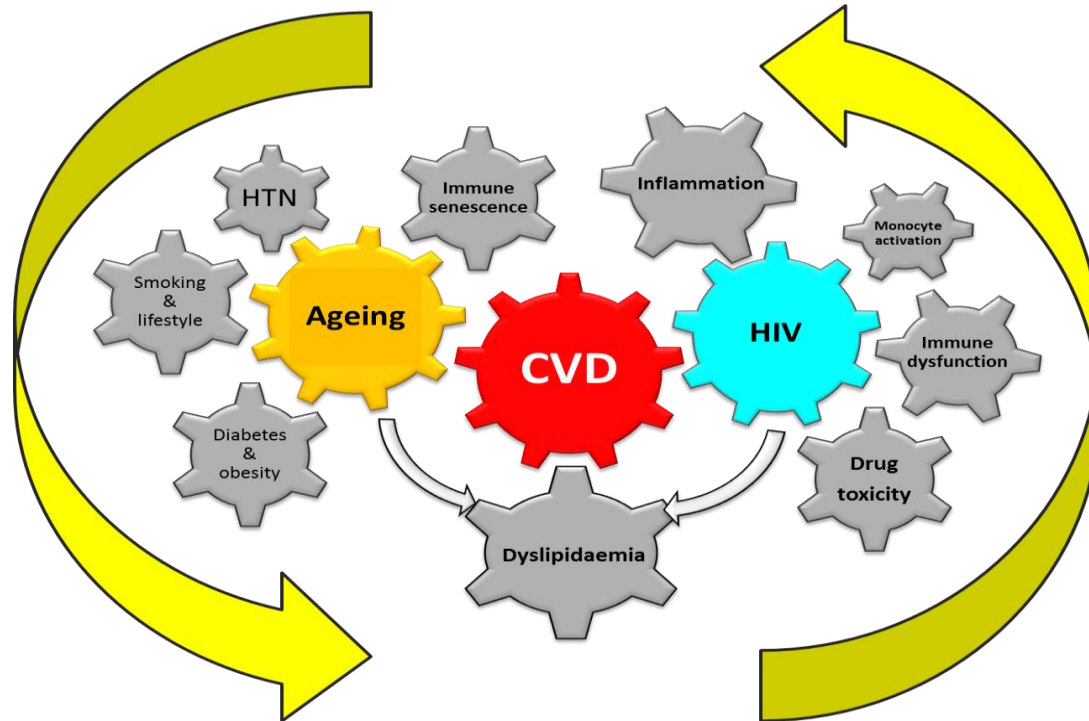


Bias due to confounding

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Co-morbidities are often multi-factorial



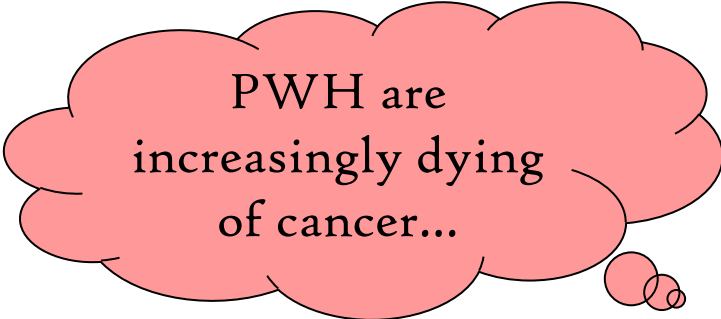
Confounding

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 - sexually transmitted infections

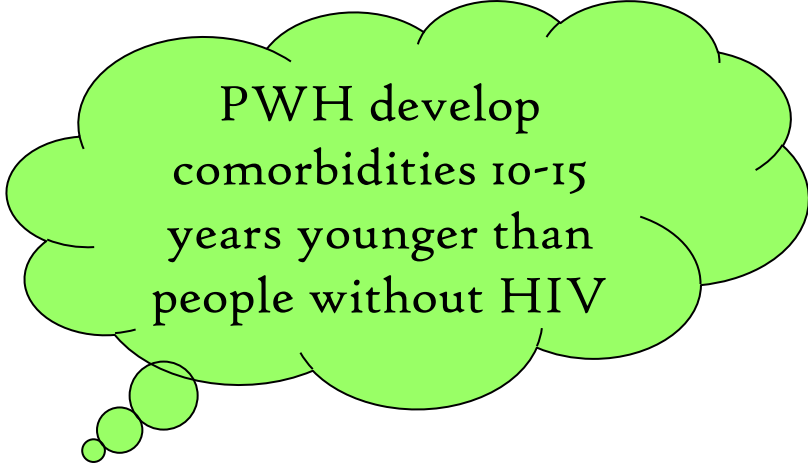
Does HIV really cause premature ageing – or is this simply a result of unmeasured confounding?

- Could these other factors confound associations with co-morbidities and/or bio-markers?

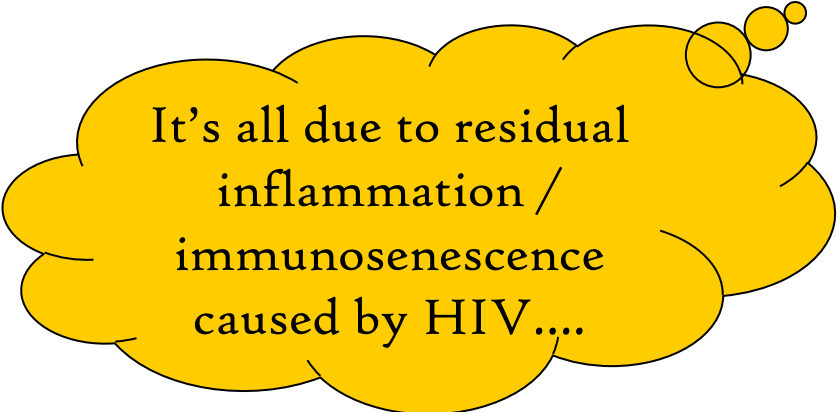
What is being said?



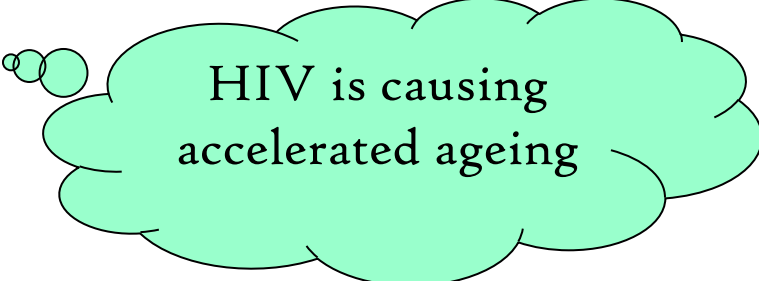
PWH are increasingly dying of cancer...



PWH develop comorbidities 10-15 years younger than people without HIV

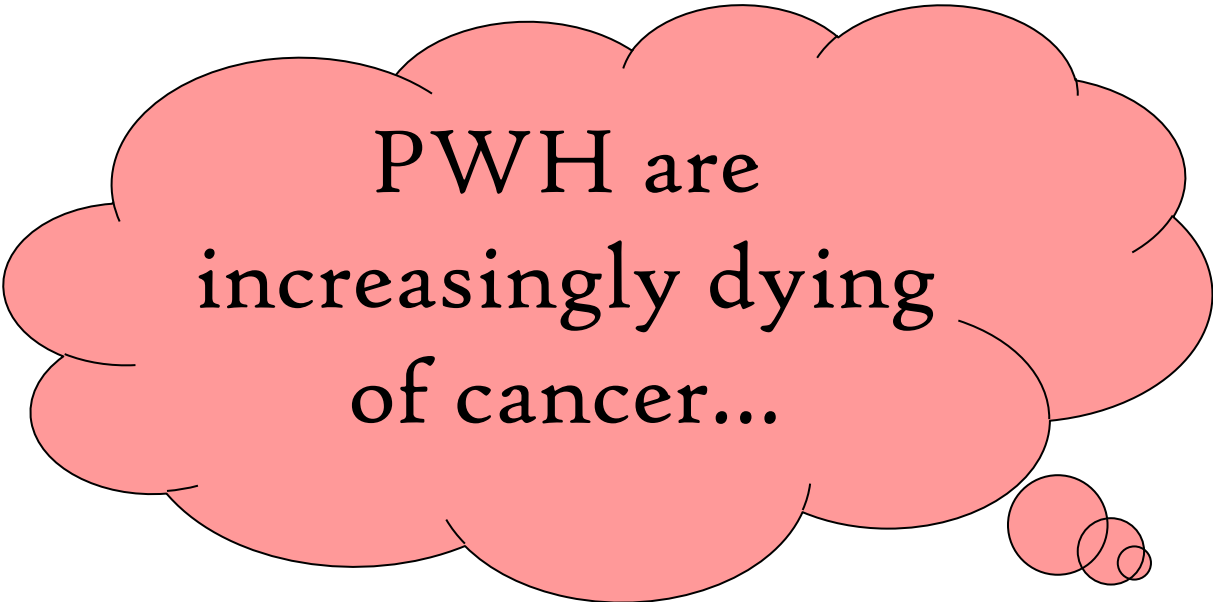


It's all due to residual inflammation / immunosenescence caused by HIV....



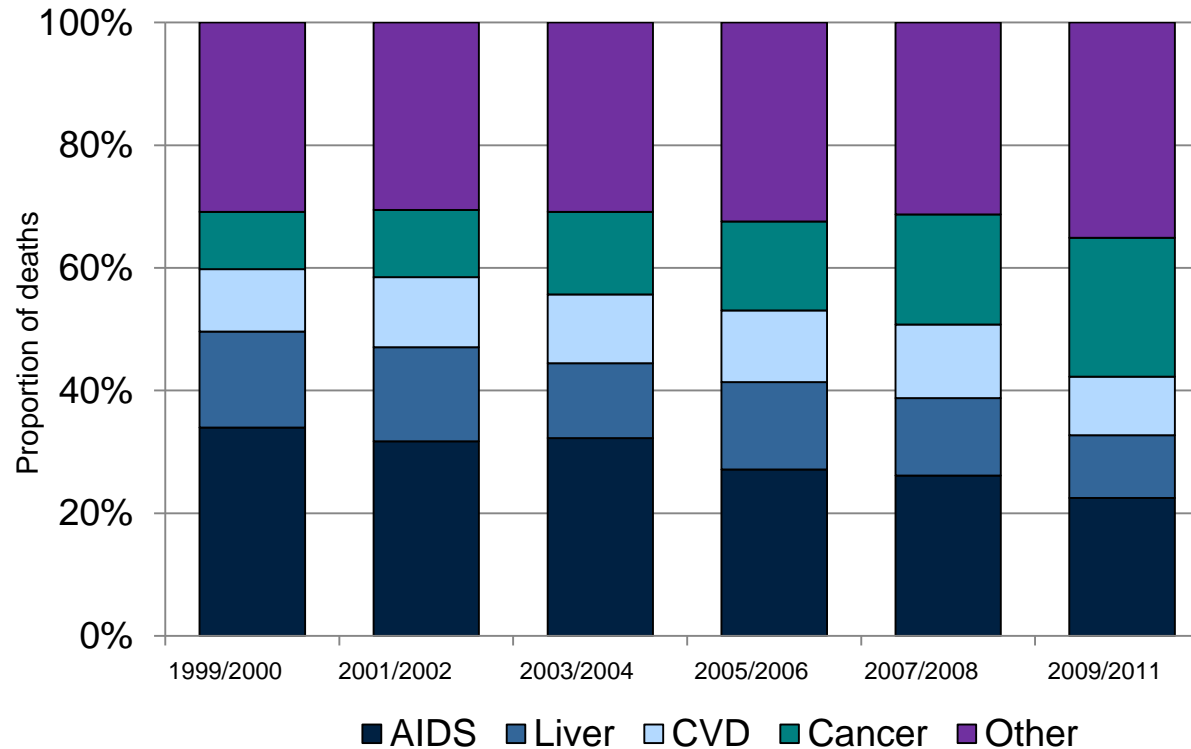
HIV is causing accelerated ageing

What is being said?

A large, light red thought bubble with a black outline, containing text. It has three smaller circles of decreasing size leading to it from the bottom right.

PWH are
increasingly dying
of cancer...

Causes of death



Deaths from cancer - Mortalité surveys

	Mortalité 2000	Mortalité 2005	Mortalité 2010	p-value ^a
Reported deaths	964	1042	728	
Cancer-related causes of death, n (%)	269 (27.9%)	344 (33.0%)	262 (36.0%)	0.003
AIDS-related, n (%)	149 (15.5%)	134 (12.9%)	68 (9.3%)	0.024
Non Hodgkin lymphoma	105 (10.9%)	103 (9.9%)	53 (7.3%) ^b	0.122
Kaposi sarcoma	40 (4.1%)	25 (2.4%)	11 (1.5%)	0.084
Cervical cancer	4 (0.4%)	6 (0.6%)	4 (0.5%)	0.848
Hepatitis-related, n (%)	17 (1.8%)	37 (3.6%)	31 (4.3%)	0.028
Hepatitis C	8 (0.8%)	27 (2.6%)	19 (2.6%)	0.021
Hepatitis B	7 (0.7%)	6 (0.6%)	10 (1.4%)	0.279
Hepatitis B and C	2 (0.2%)	4 (0.4%)	2 (0.3%)	0.732
Non AIDS/non hepatitis related, n (%)	103 (10.7%)	173 (16.6%)	163 (22.4%)	<0.001
Respiratory	50 (5.2%)	65 (6.2%)	78 (10.7%)	0.004
Lung	44 (4.6%)	53 (5.1%)	61 (8.4%)	0.040
Ear, nose and throat	6 (0.6%)	12 (1.2%)	17 (2.3%)	0.056
Digestive	6 (0.6%)	13 (1.2%)	10 (1.4%)	0.342
Pancreas	3 (0.3%)	11 (1.1%)	7 (1.0%)	0.282
Anal	6 (0.6%)	11 (1.1%)	13 (1.8%)	0.073
Skin	2 (0.2%)	10 (1.0%)	3 (0.4%)	0.065
Hodgkin's lymphoma	12 (1.2%)	9 (0.9%)	8 (1.1%)	0.473
Other hemopathies	5 (0.5%)	8 (0.8%)	7 (1.0%)	0.602
Breast	3 (0.3%)	7 (0.7%)	5 (0.7%)	0.647
Central nervous system	4 (0.4%)	6 (0.6%)	2 (0.3%)	0.530
Other and unknown ^c	12 (1.2%)	33 (3.2%)	27(3.7%)	0.029
Multiple ^d	-	-	3 (0.4%)	-

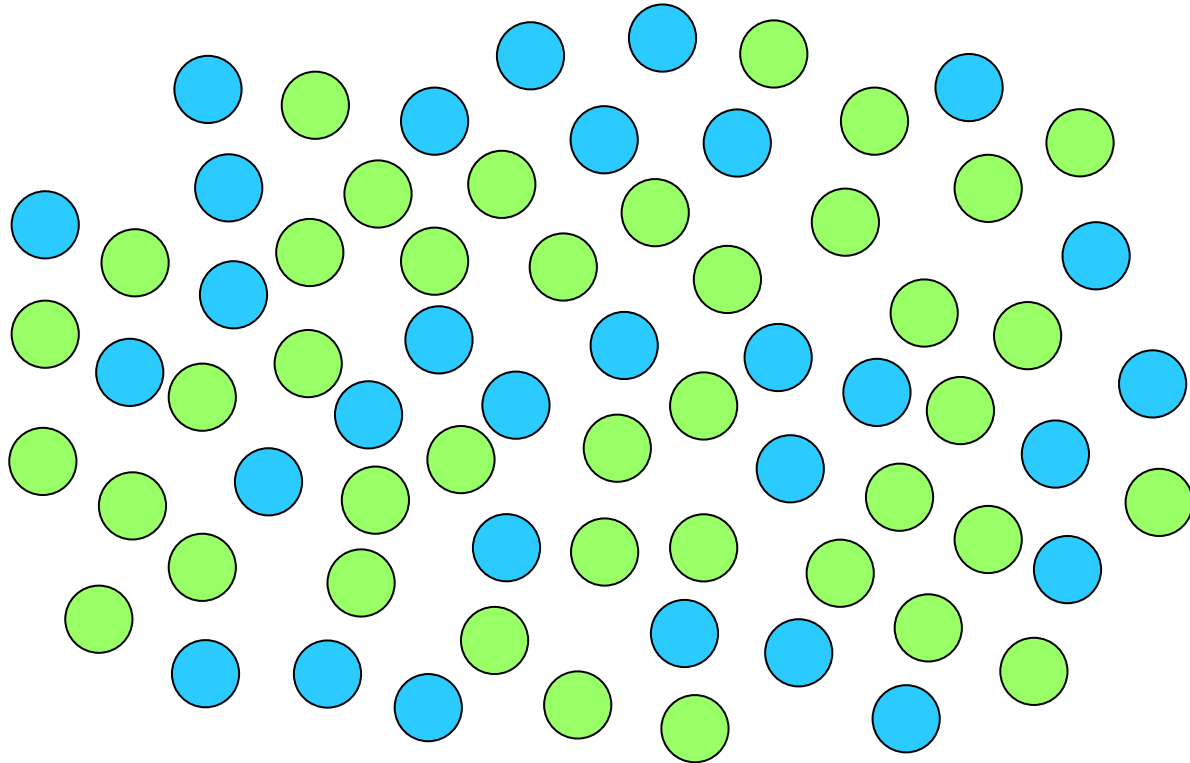
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Multiple ^d	-	-	3 (0.4%)	-

Significant increases in proportions of deaths from:

- All cancer-related causes
- Respiratory cancers
- Lung cancers
- Ear, nose & throat cancers
- Anal cancer
- Other hemopathies
- Other/unknown cancers

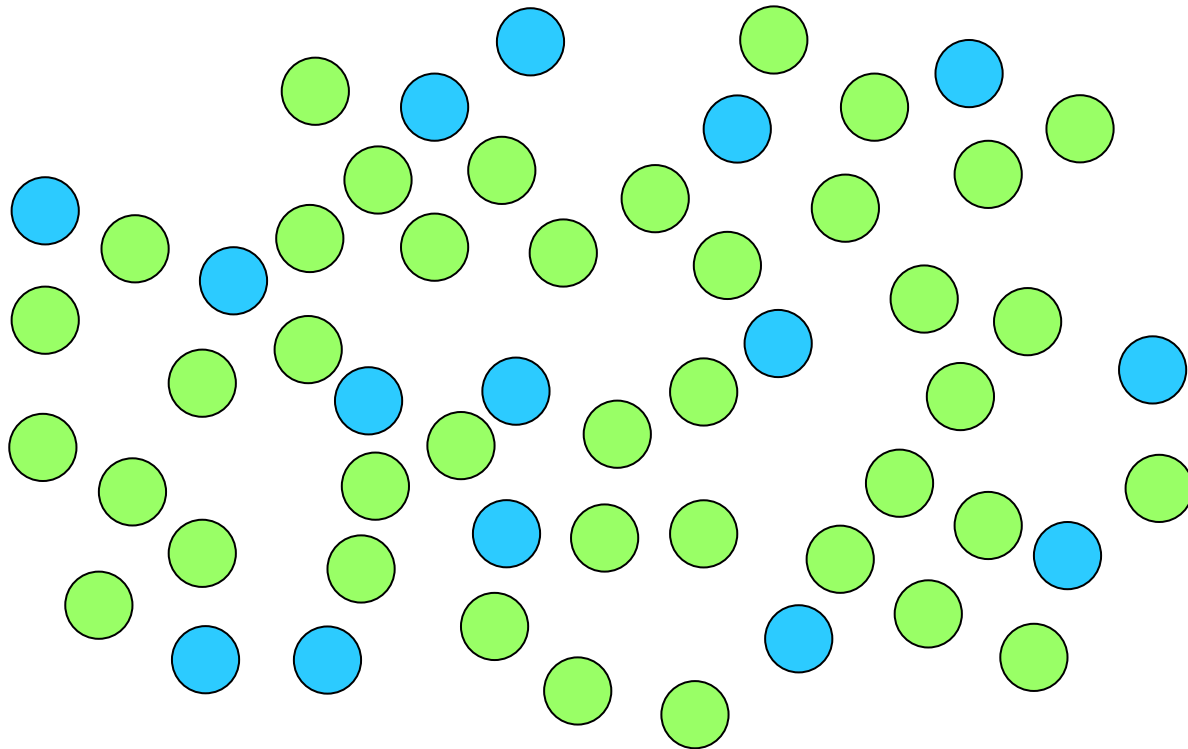
Removing a cause of morbidity



-  Deaths from HIV causes
-  Deaths from non-HIV causes

40/70 (57.1%) deaths due to non-HIV causes

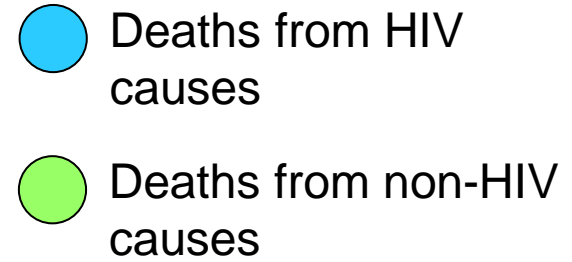
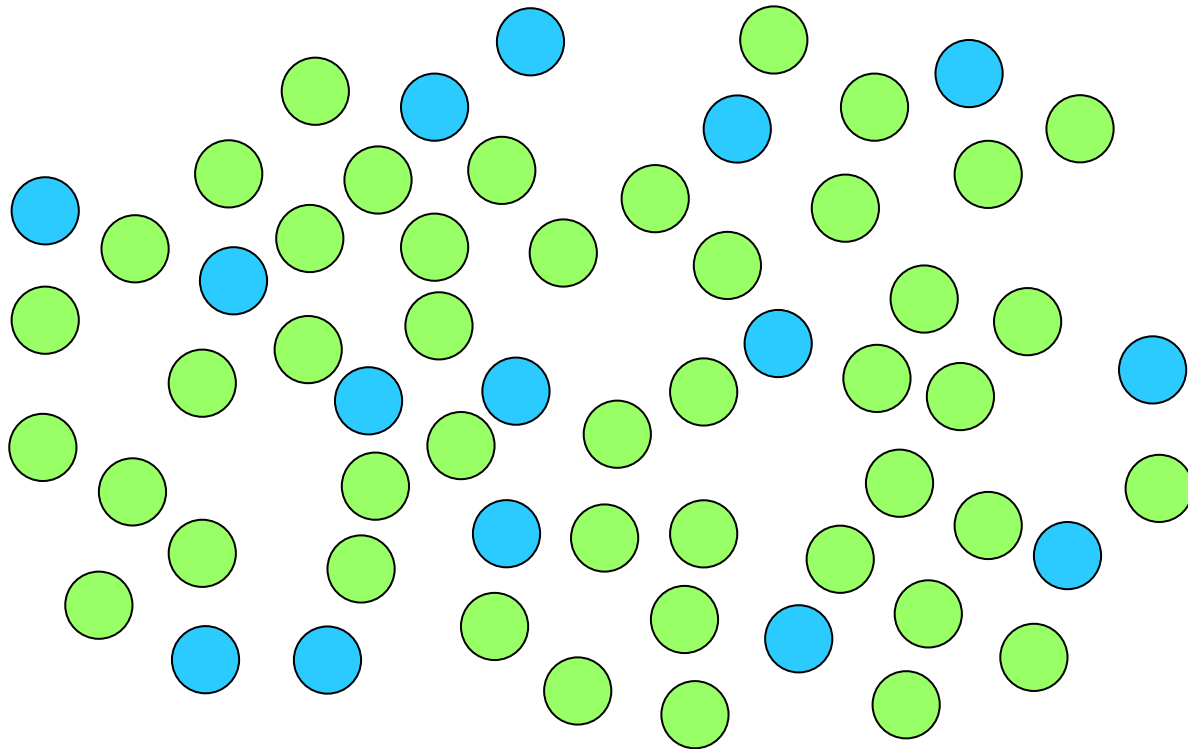
Removing a cause of morbidity



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- Deaths from non-HIV causes

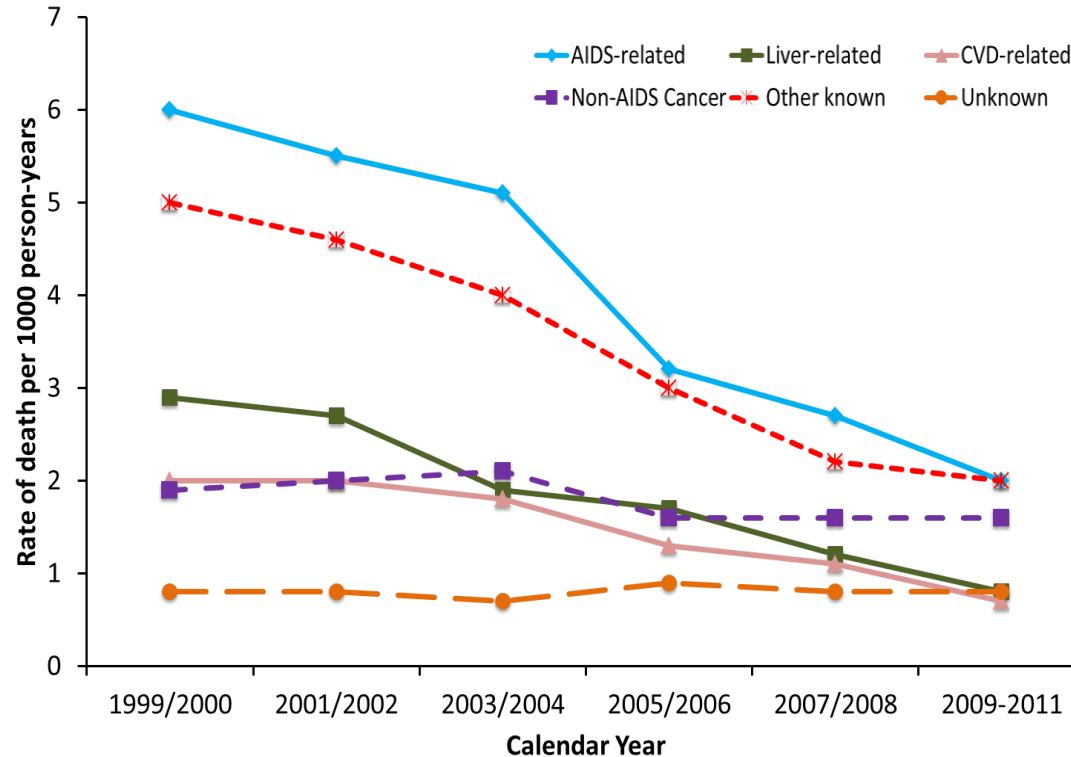
40/55 (72.7%) deaths due to non-HIV causes

Removing a cause of morbidity

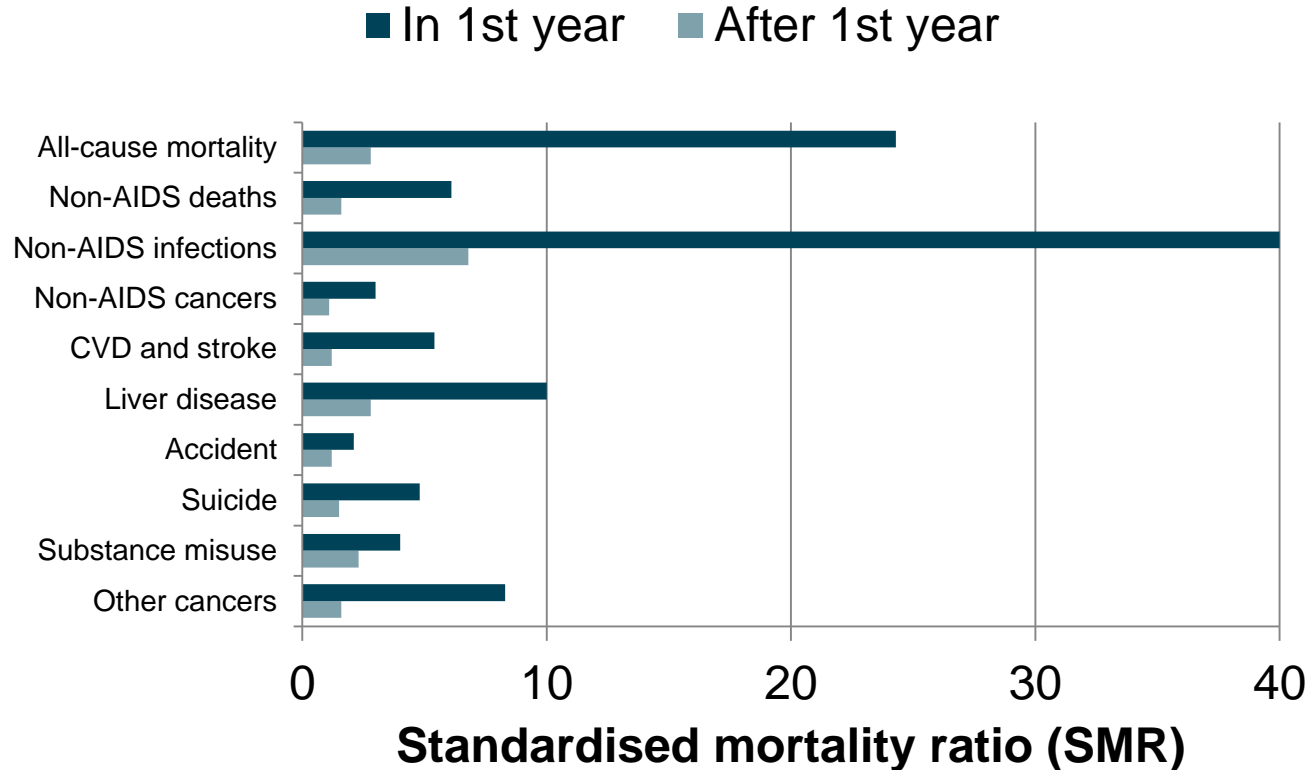


45/60 (75.0%) deaths due to non-HIV causes

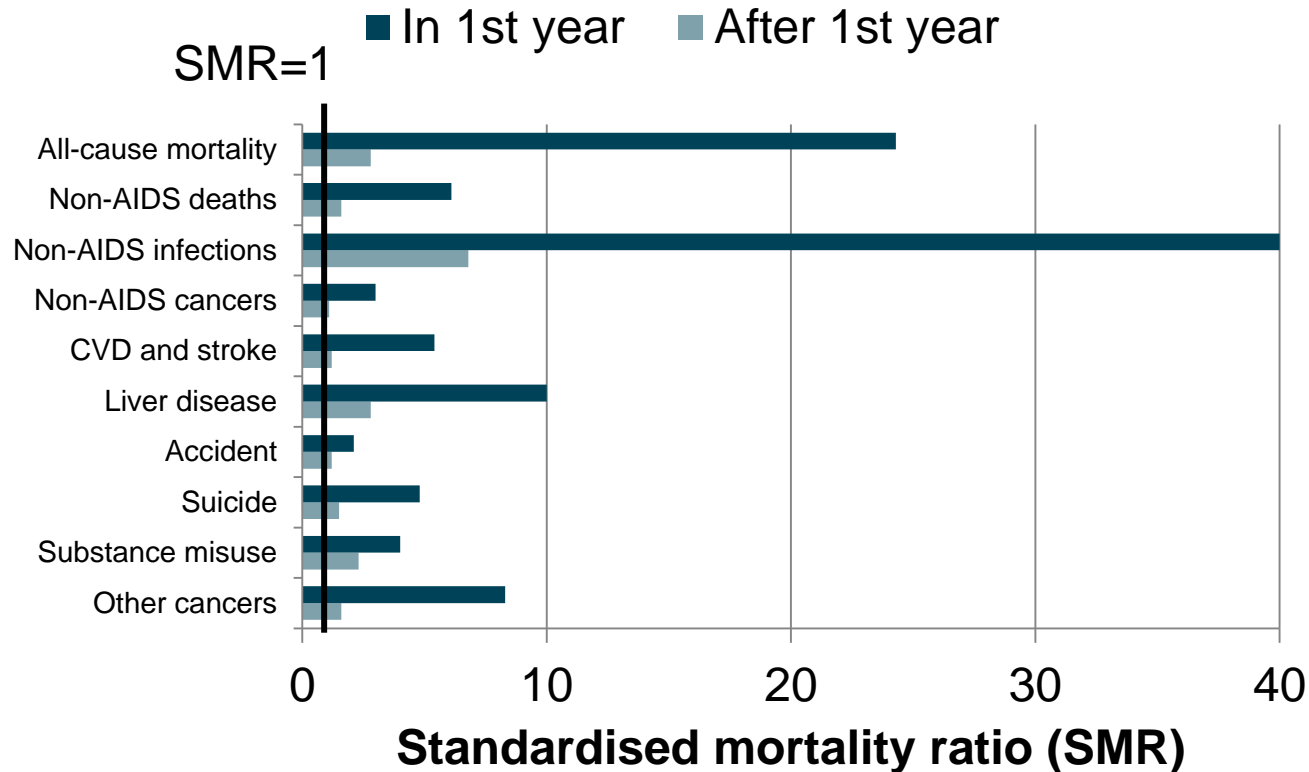
Age-standardised mortality rates



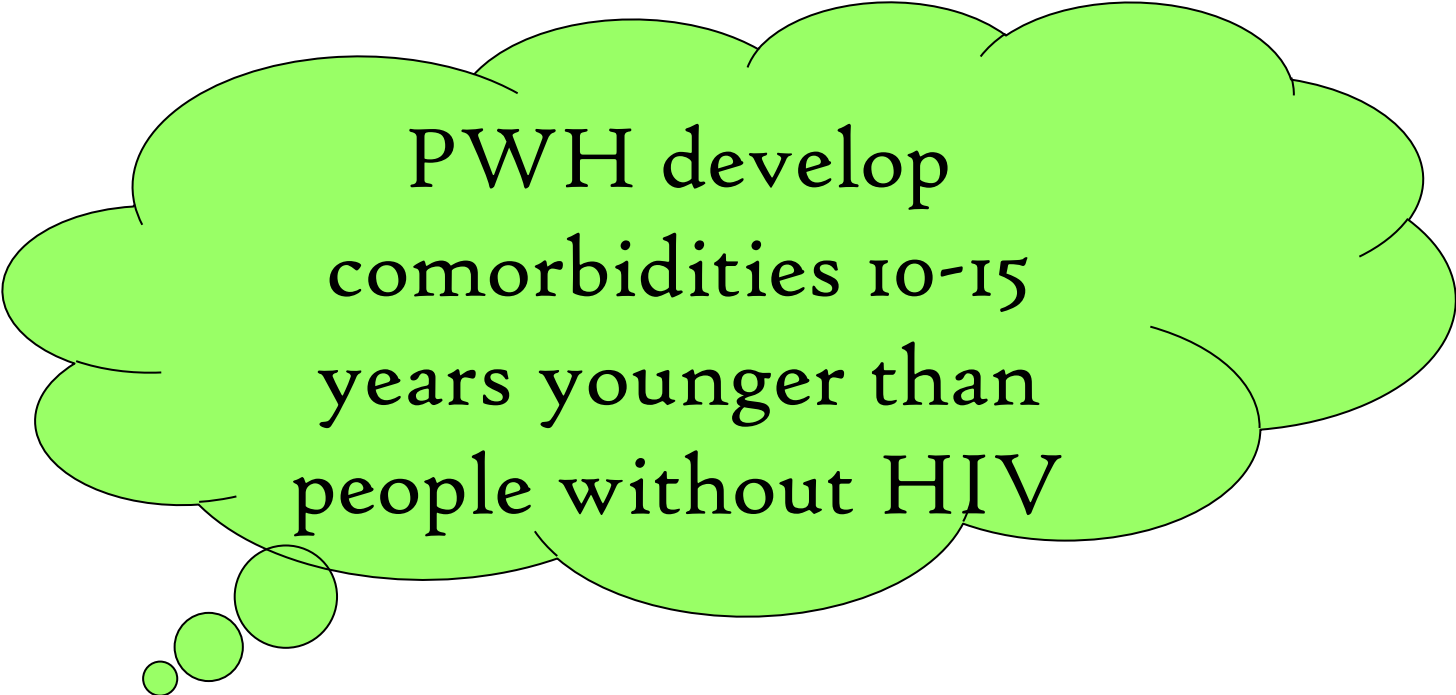
Non-AIDS mortality after HIV diagnosis



Non-AIDS mortality after HIV diagnosis



What is being said?



PWH develop
comorbidities 10-15
years younger than
people without HIV

Age at onset of co-morbidity



CHEST

Commentary

Epidemic of Lung Cancer in Patients With HIV Infection

Tiffany A. Winstone, MD; S. F. Paul Man, MD, FCCP; Mark Hull, MD; Julio S. Montaner, MD, FCCP; and Don D. Sin, MD, FCCP

Several studies have examined the risk of lung cancer in the HIV-infected population (Table 1). Approximately one-half of these studies used a case-control design, whereas the other half used a longitudinal cohort approach. **Of note, the average age at lung cancer diagnosis in this population was between 38 and 57 years. In contrast, the average age at lung cancer diagnosis in the general population is approximately 70 years.** On a discouraging note, most of the cases were discovered in stages III or IV, and the median survival of these patients was measured in months from the time of diagnosis (Table 1).

Age at onset of co-morbidity

CLINICAL SCIENCE

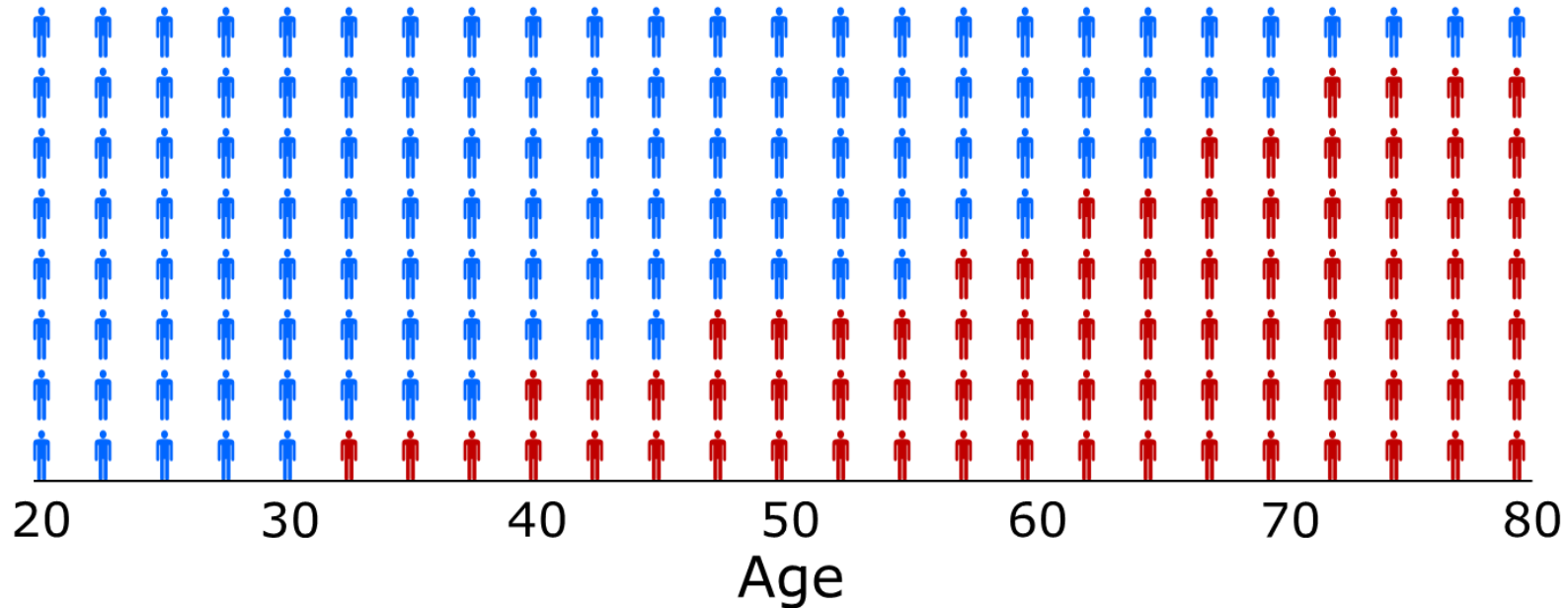
Geriatric Syndromes in Older HIV-Infected Adults

Meredith Greene, MD,† Kenneth E. Covinsky, MD, MPH,*† Victor Valcour, MD, PhD,*‡
Yinghui Miao, MD, MPH,*† Joy Madamba, BS,§ Harry Lampiris, MD,#|| Irena Stijacic Cenzer, MA,*†
Jeffrey Martin, MD, MPH,¶ and Steven G. Deeks, MD§*

In comparison, reported rates of falls and incontinence from the general population of community dwelling adults aged 65 years and older are 30% and 22% (for older men), respectively. Estimates of frailty depend on the definition, but using the Fried phenotype definition, estimates range from 7% (original Fried article) to 10%–14%. **These data suggest that HIV-infected adults may experience similar rates of geriatric syndromes at relatively younger ages** and emphasize the critical need for appropriate HIV-negative comparison groups to put these findings into further context.

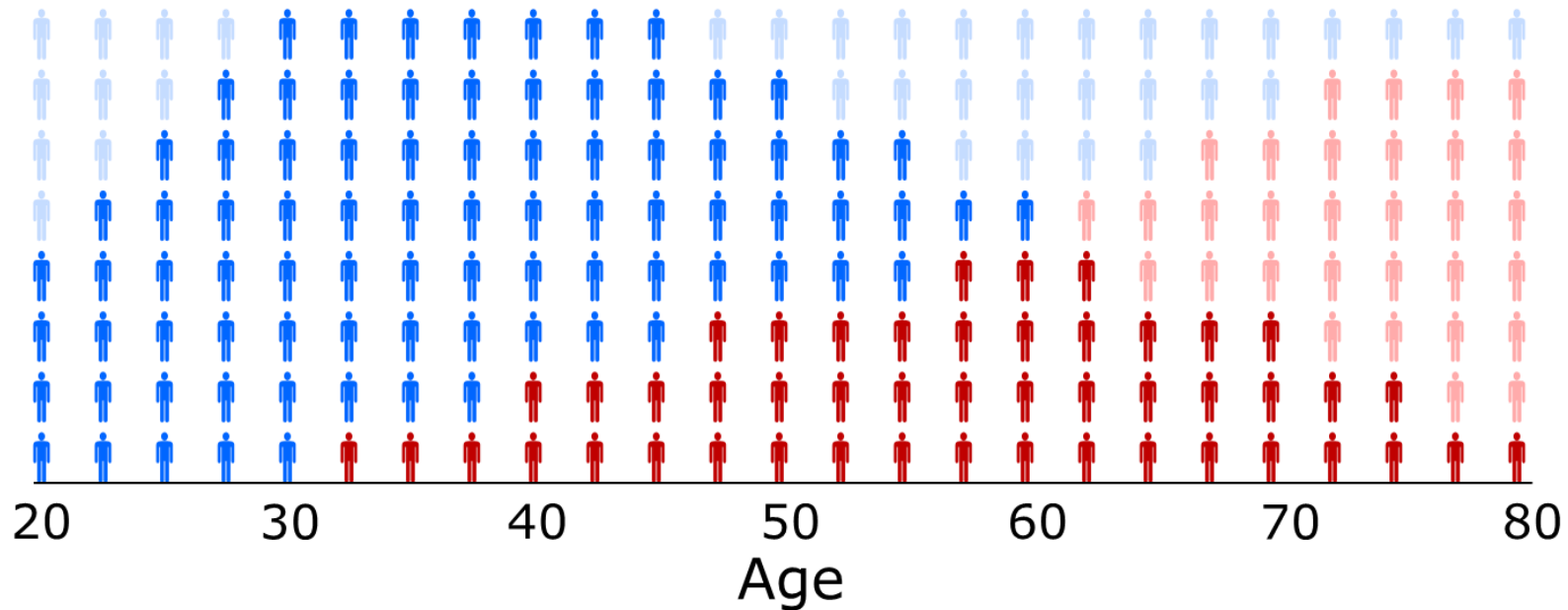
Age at onset of co-morbidity

Median age at diagnosis = 67.5 years



Age at onset of co-morbidity

Median age at diagnosis = 57.5 years

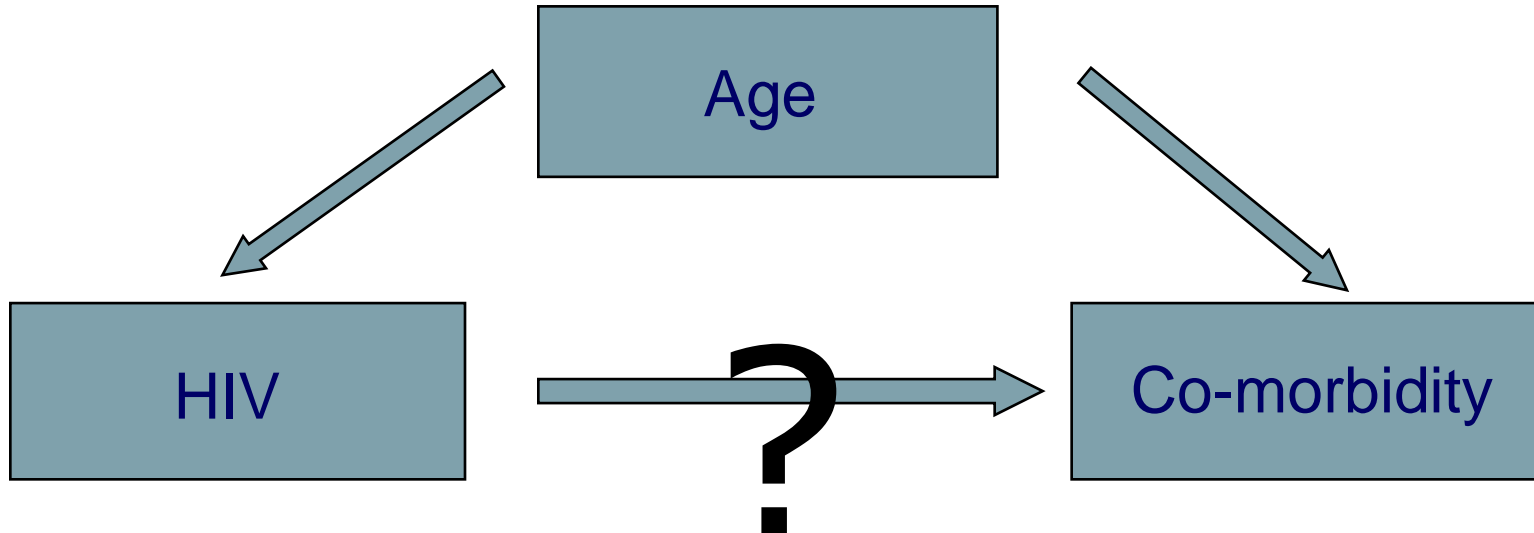


Age at onset of co-morbidity – VACS VC

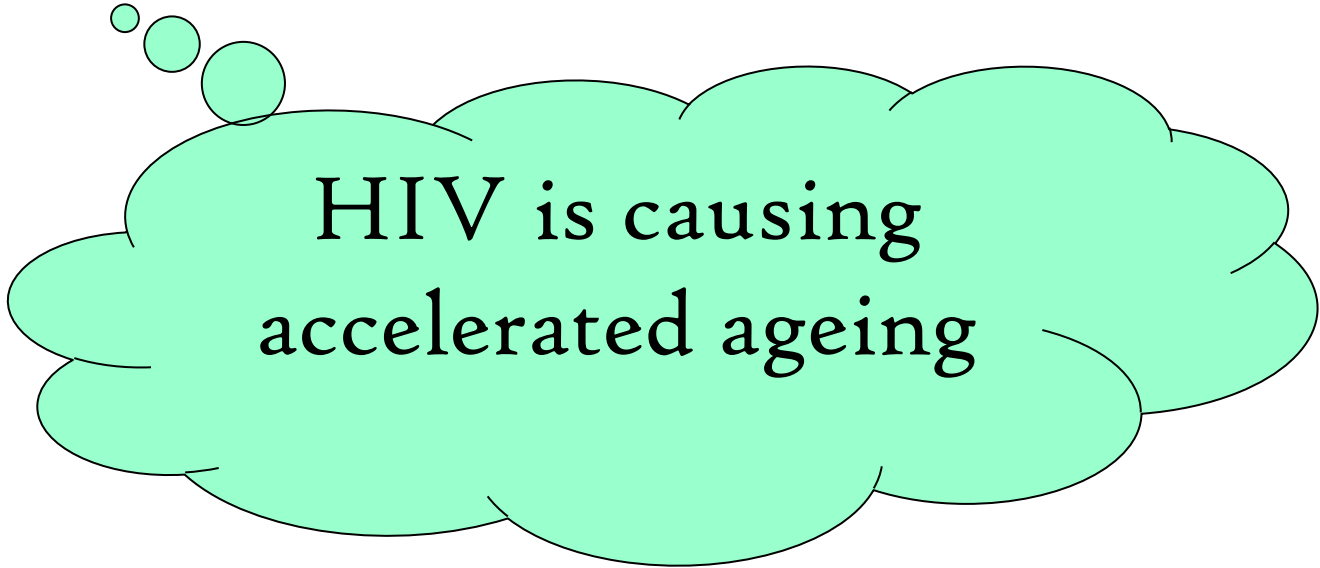
Event	No. events	Mean age diagnosis	Crude diff.	Adjusted diff.	95% CI
MI					
HIV-ve	308	56.0	0.2	-0.11	-0.59, +0.37
HIV+ve	291	56.2			
End-stage renal disease					
HIV-ve	688	59.4	-3.4	-0.46	-0.86, -0.07
HIV+ve	447	56.0			
NADC					
HIV-ve	2708	58.9	-1.1	-0.10	-0.30, 0.10
HIV+ve	1471	57.8			
HIV-associated cancers					
HIV-ve	826	58.6	-2.0	-0.22	-0.52, 0.08
HIV+ve	732	56.6			

Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome



What is being said?

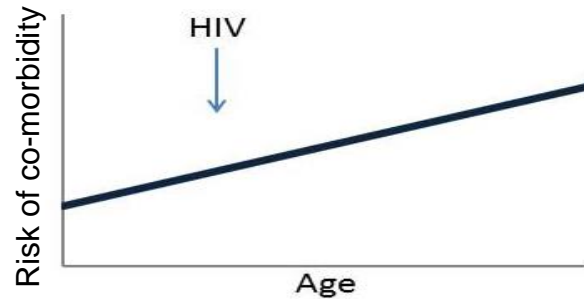


HIV is causing
accelerated ageing

Accelerated or accentuated ageing?

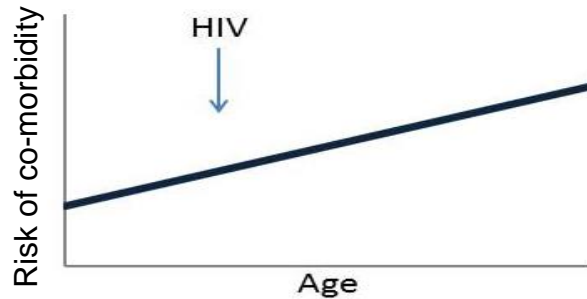
Accelerated or accentuated ageing?

a) No impact of HIV on aging



Accelerated or accentuated ageing?

a) No impact of HIV on aging

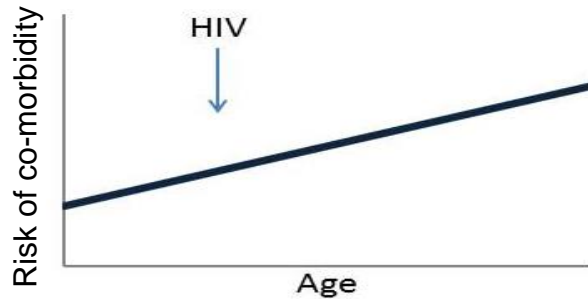


b) Accelerated aging

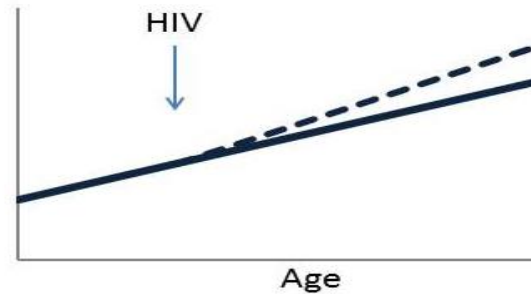


Accelerated or accentuated ageing?

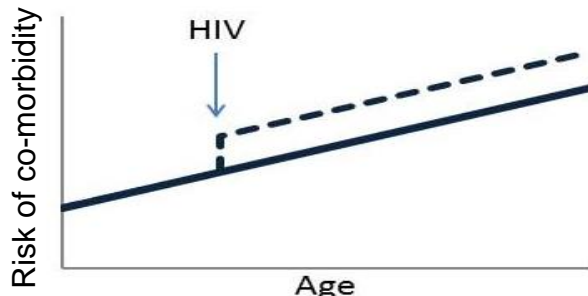
a) No impact of HIV on aging



b) Accelerated aging

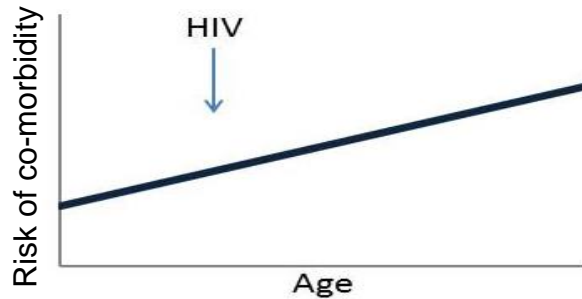


c) Accentuated aging

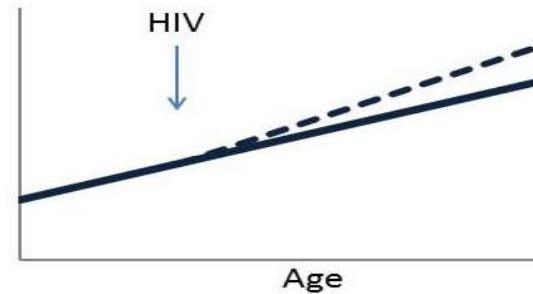


Accelerated or accentuated ageing?

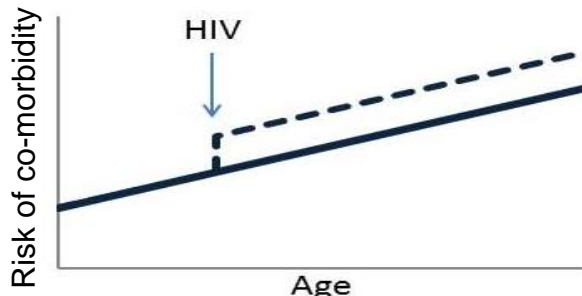
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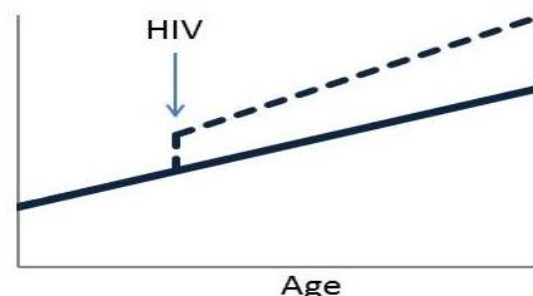
b) Accelerated aging



c) Accentuated aging



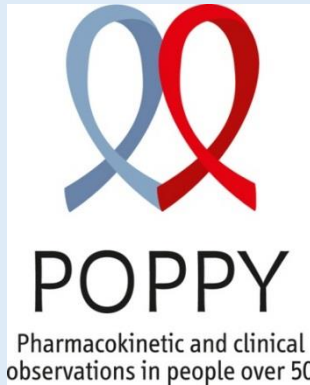
d) Accelerated AND accentuated aging



Why is this important?

- Underlying aetiology and/or mechanisms differ
- Statistical approach to test for each will differ - need to consider the 'slope' of the association with age, as well as absolute risk of event
- Studies that claim to demonstrate 'accelerated' ageing, often provide little evidence to support the statement
- Difficult to differentiate between the models with a cross-sectional study

The Co-morBidity in Relation to Aids (COBRA) Collaboration



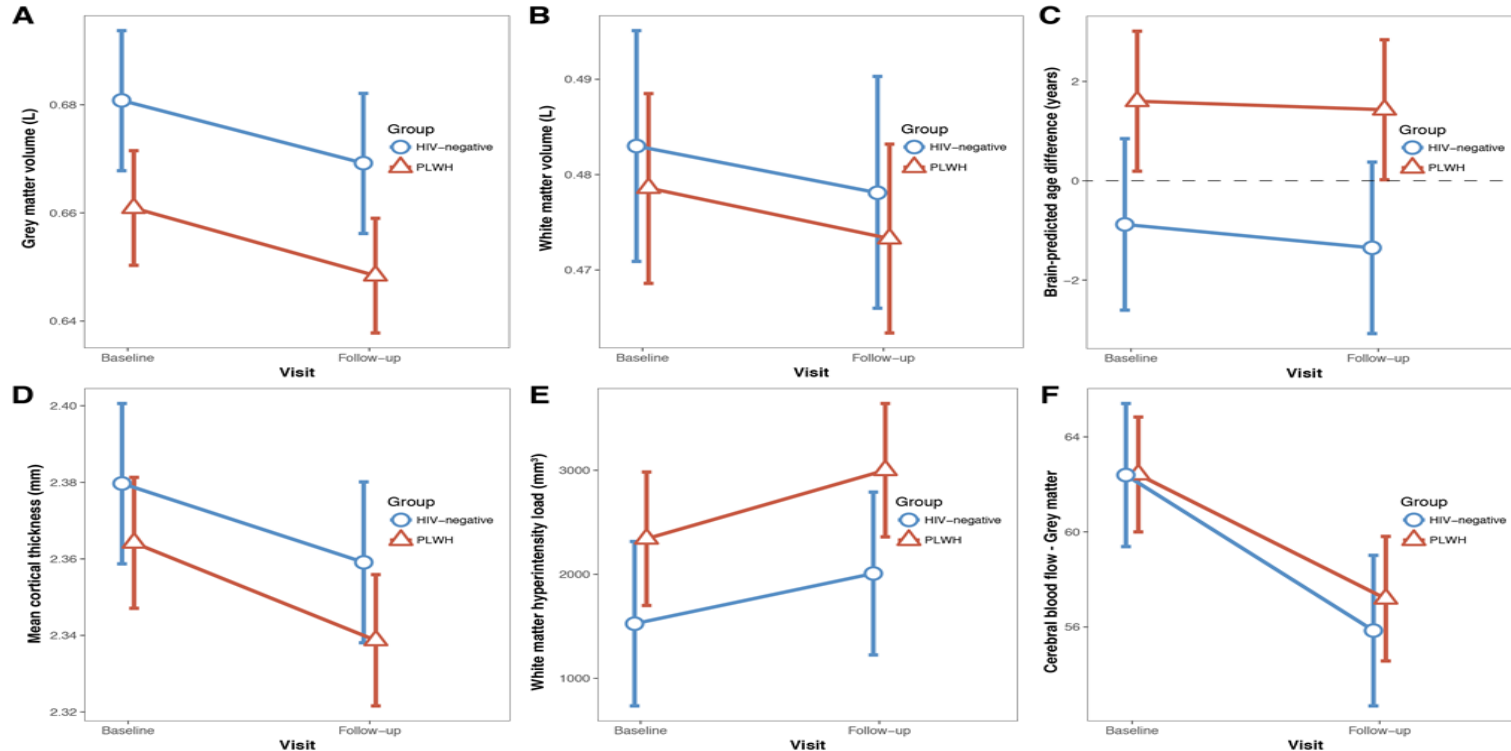
POPPY:
'Pharmacokinetic
and Clinical
Observations in
People over Fifty'



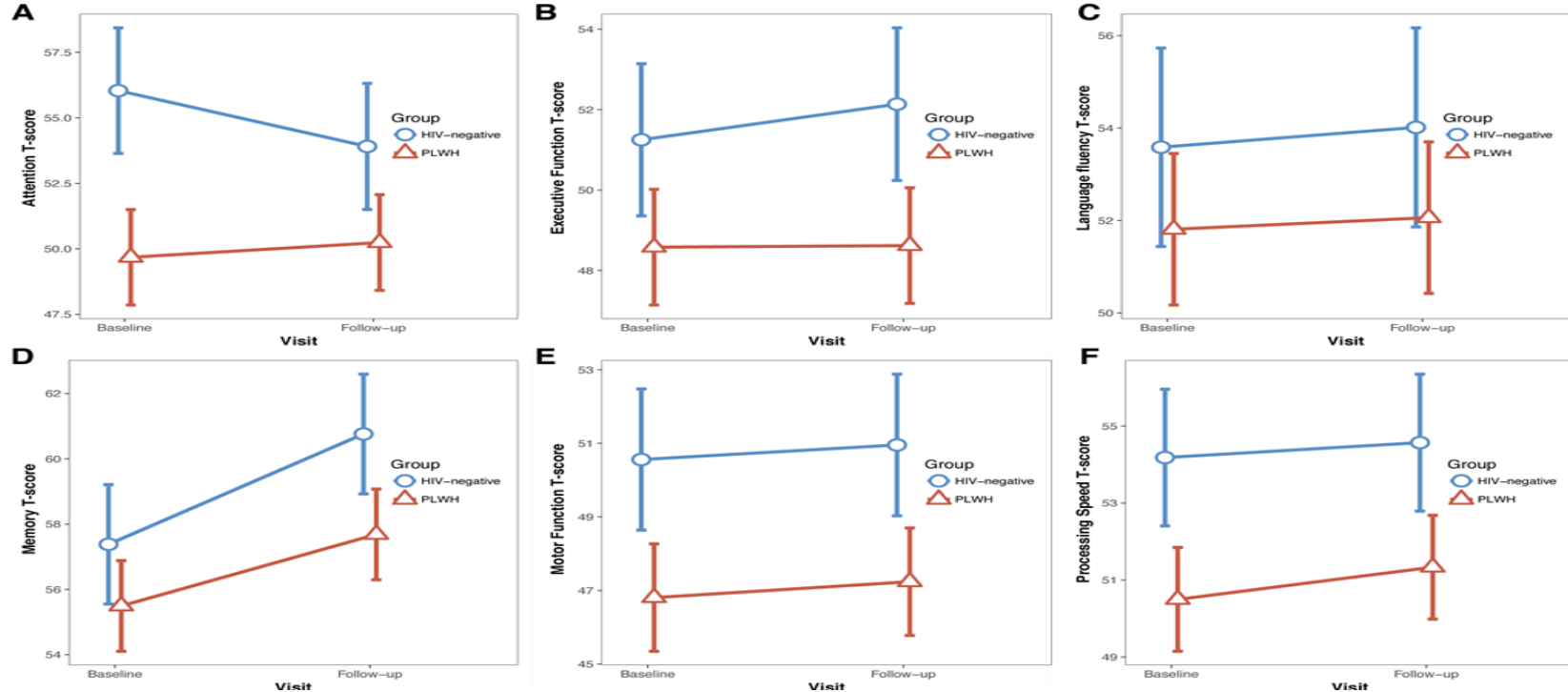
COBRA: clinical studies run as sub-studies of POPPY and AGE_hIV:

- Collecting the extra information required
- Whilst utilising the existing infrastructure

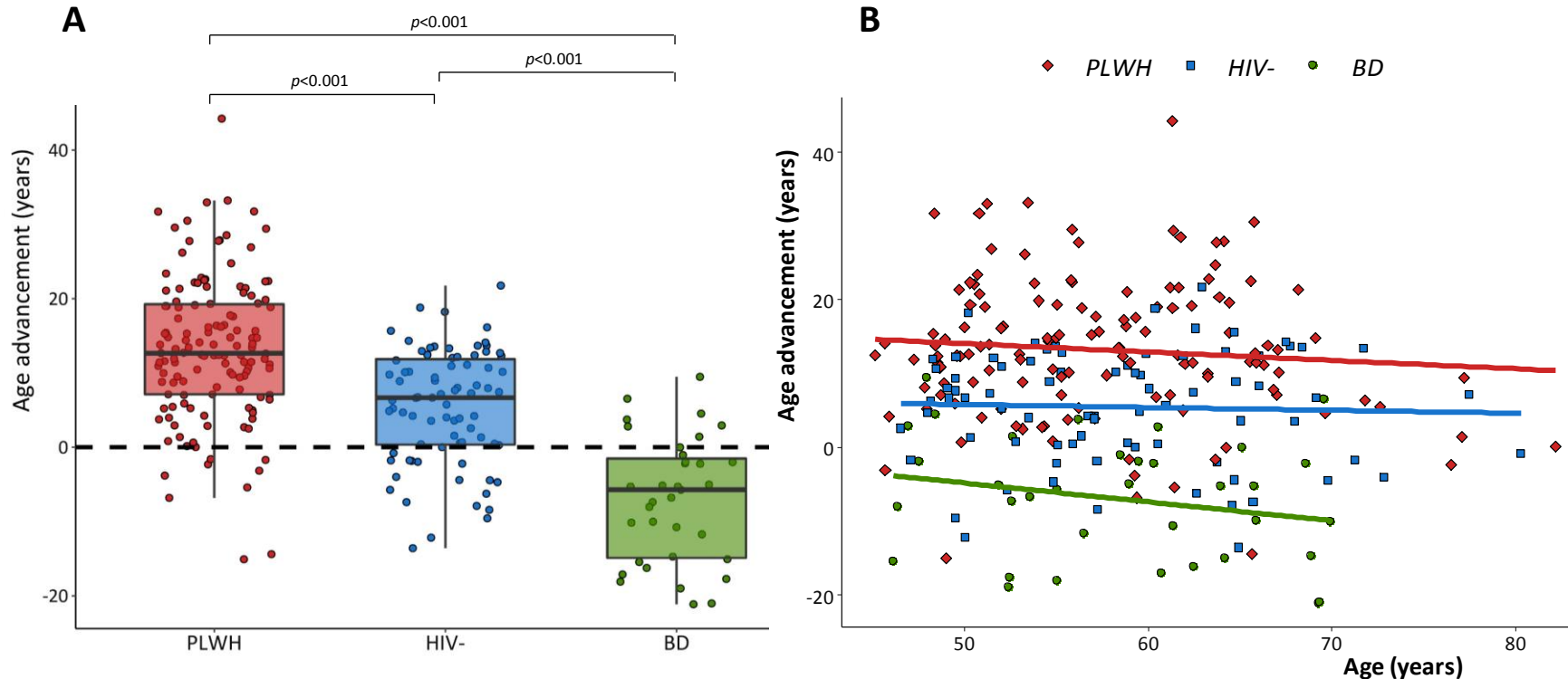
Neuroimaging results - COBRA



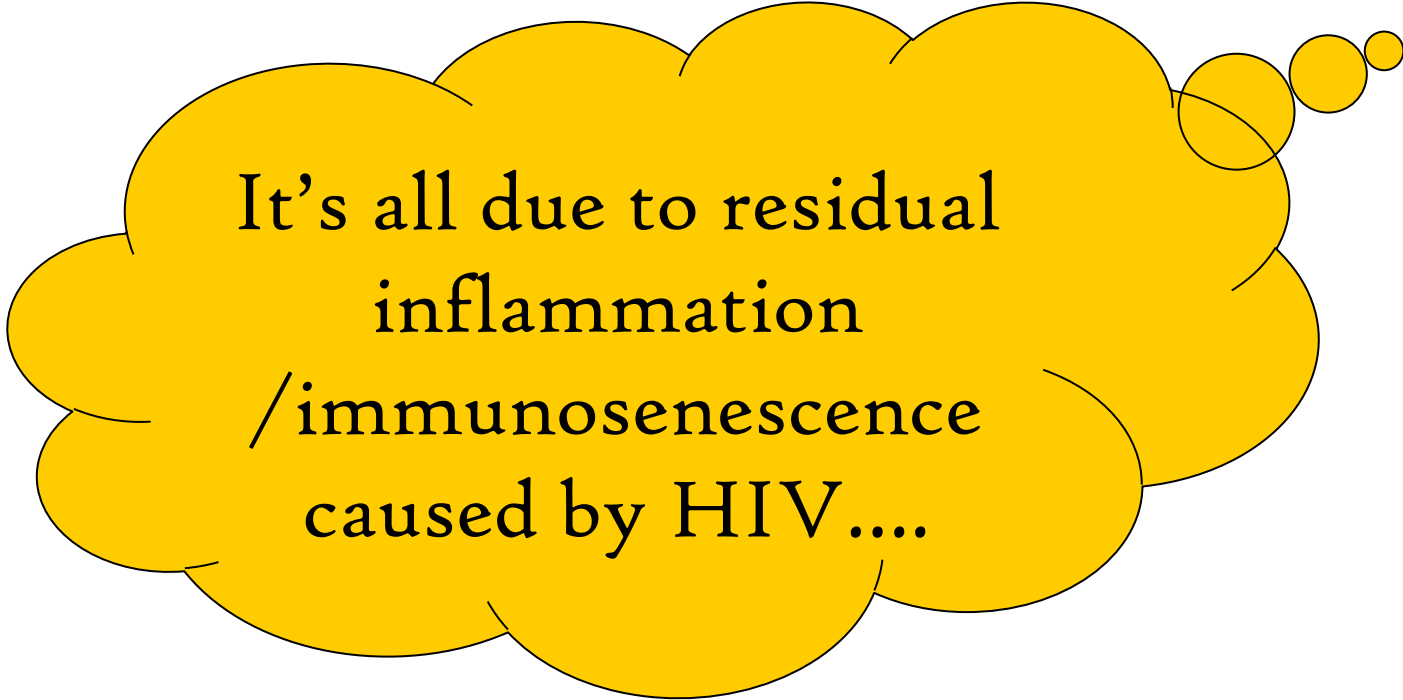
Cognitive testing results - COBRA



Bio-marker age advancement - COBRA



What is being said?



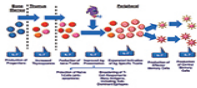
It's all due to residual
inflammation
/immunosenescence
caused by HIV....

Immunosenescence and HIV

Virulence

Journal of Clinical Virology

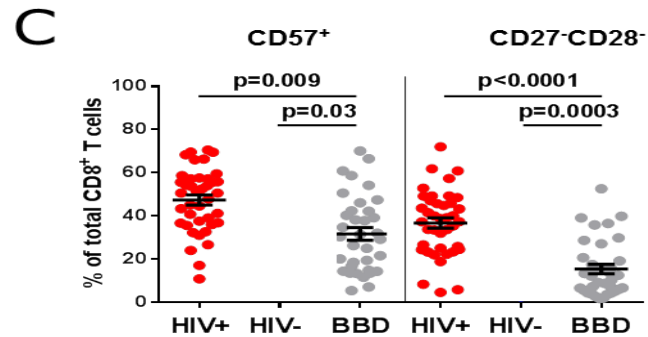
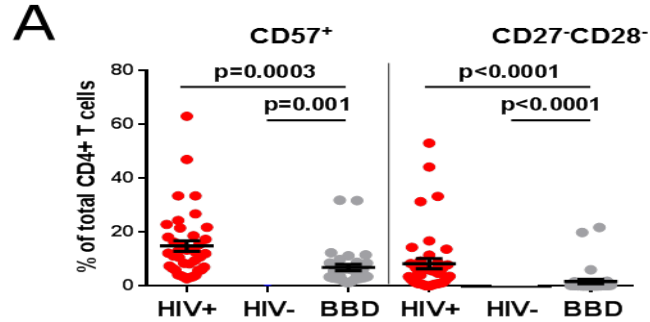
Volume 8 Number 8 2017



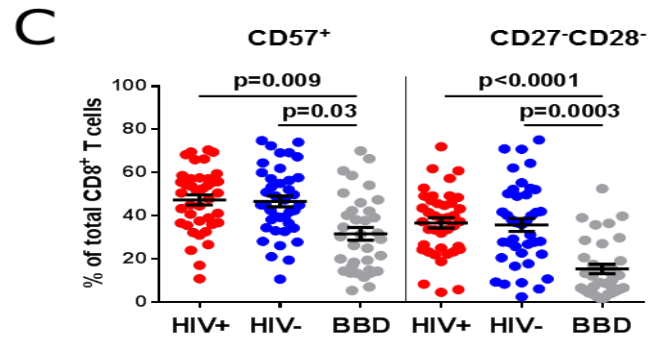
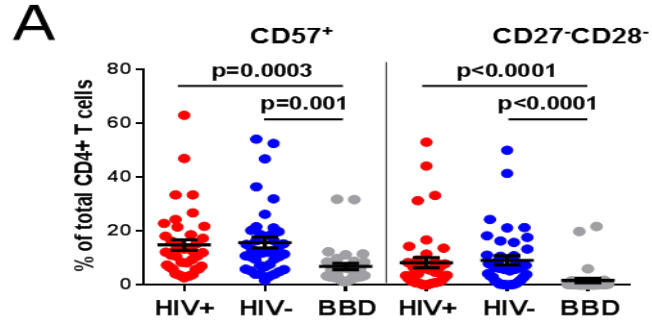
Virulence

People living with HIV (PLWH) who are treated with effective highly active antiretroviral therapy (HAART) have a similar life expectancy to the general population. Moreover, an increasing proportion of new HIV diagnoses are made in people older than 50 y. The number of older HIV infected patients is thus constantly growing and it is expected that by 2030 around 70% of PLWH will be more than 50 y old. **On the other hand, HIV infection itself is responsible for accelerated immunosenescence, a progressive decline of immune system function in both the adaptive and the innate arm**, which impairs the ability of an individual to respond to infections and to give rise to long-term immunity; furthermore, older patients tend to have a worse immunological response to HAART.

CD4 and CD8 T cell senescence



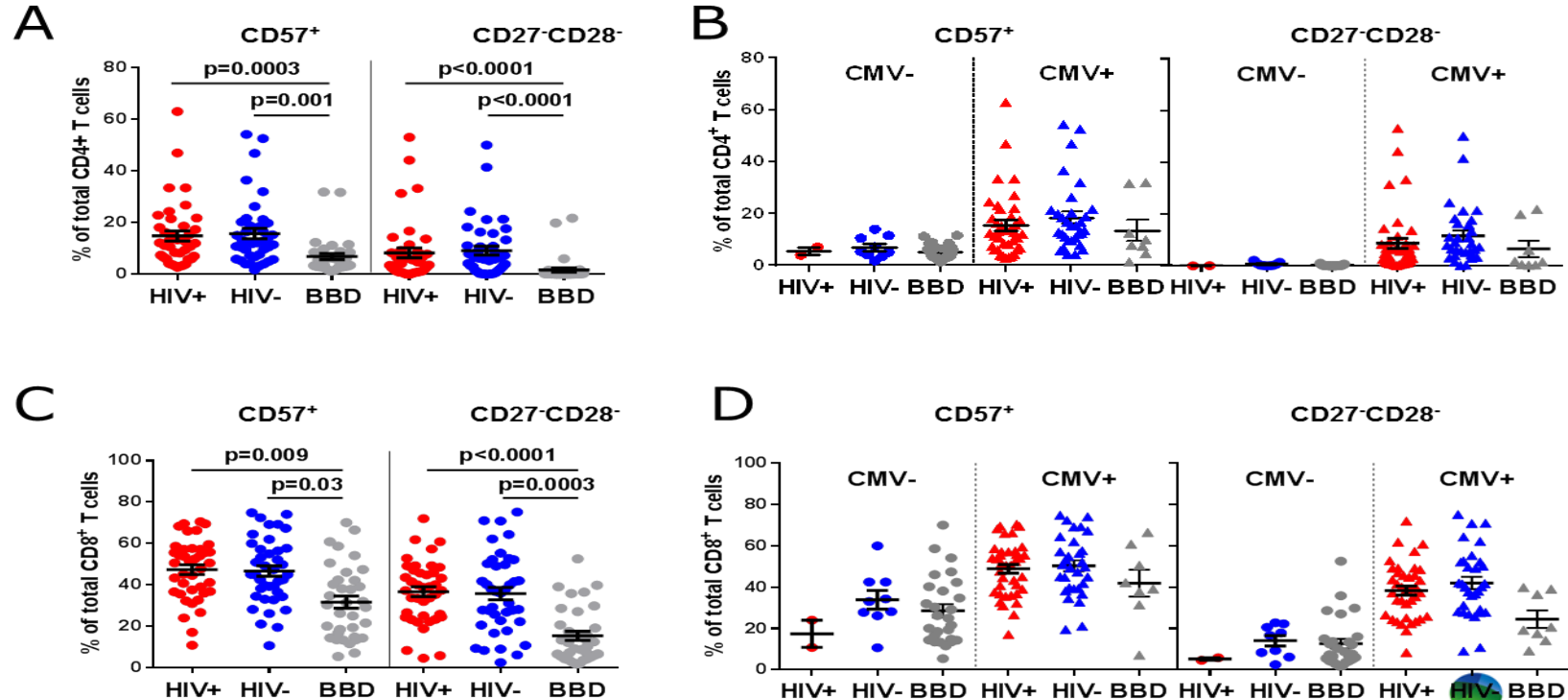
CD4 and CD8 T cell senescence



CD4 and CD8 T cell senescence

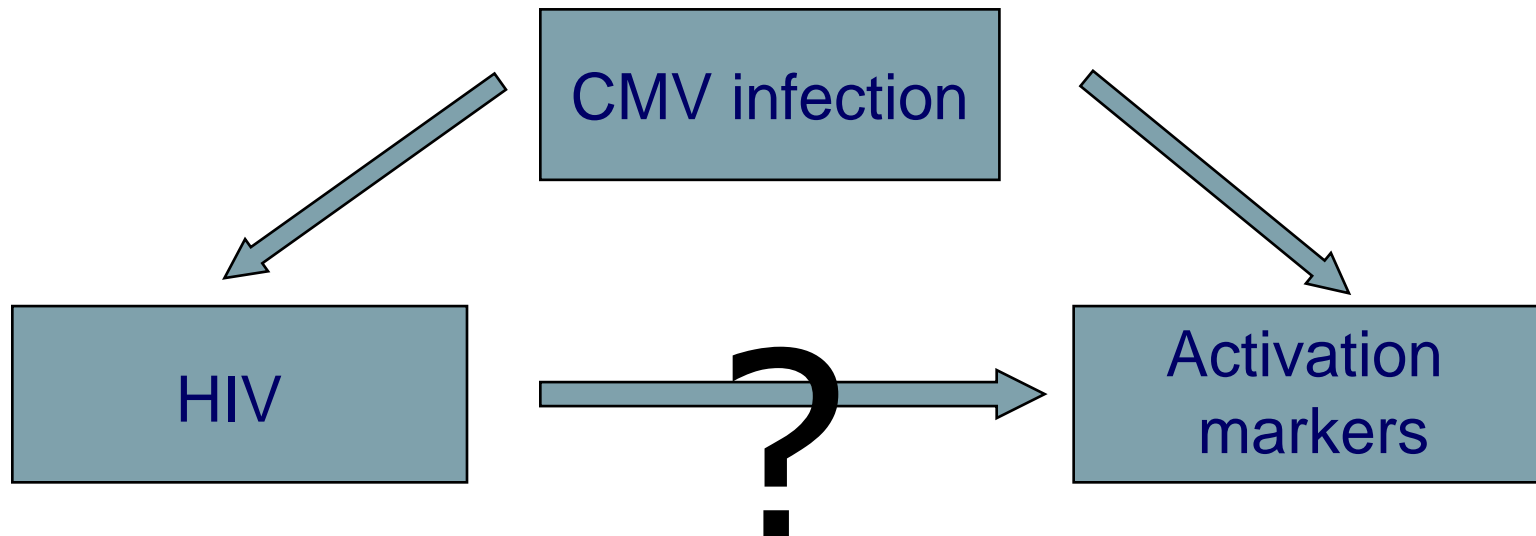
	HIV-positive	HIV-negative	Blood-bank donors
N	40	40	35
Age (yrs), median (IQR)	58 (53-63)	59 (53-64)	58 (52-65)
Male sex, %	90	92.5	51.4
African origin, %	12.5	2.5	n/a
MSM, %	80.0	75.0	n/a
CMV+ve, %	95.0	77.5	22.9
Anti-CMV IgG	50.9 (23.5-108.6)	23.9 (13.8-87.8)	11.3 (10.2-16.8)
High avidity anti-CMV IgG	30.7 (13.0-57.0)	13.3 (8.2-39.7)	10.7 (10.0-13.2)

CD4 and CD8 T cell senescence



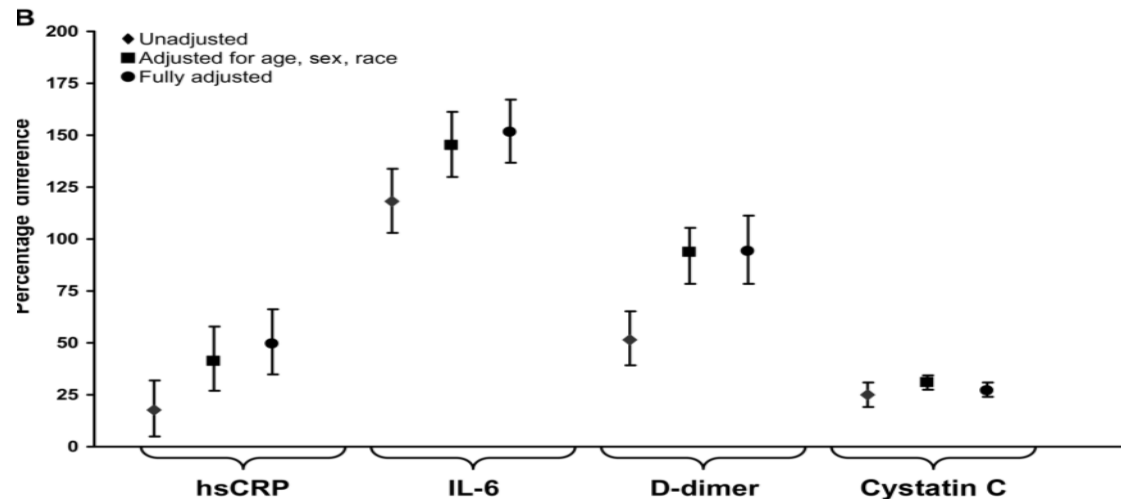
Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome

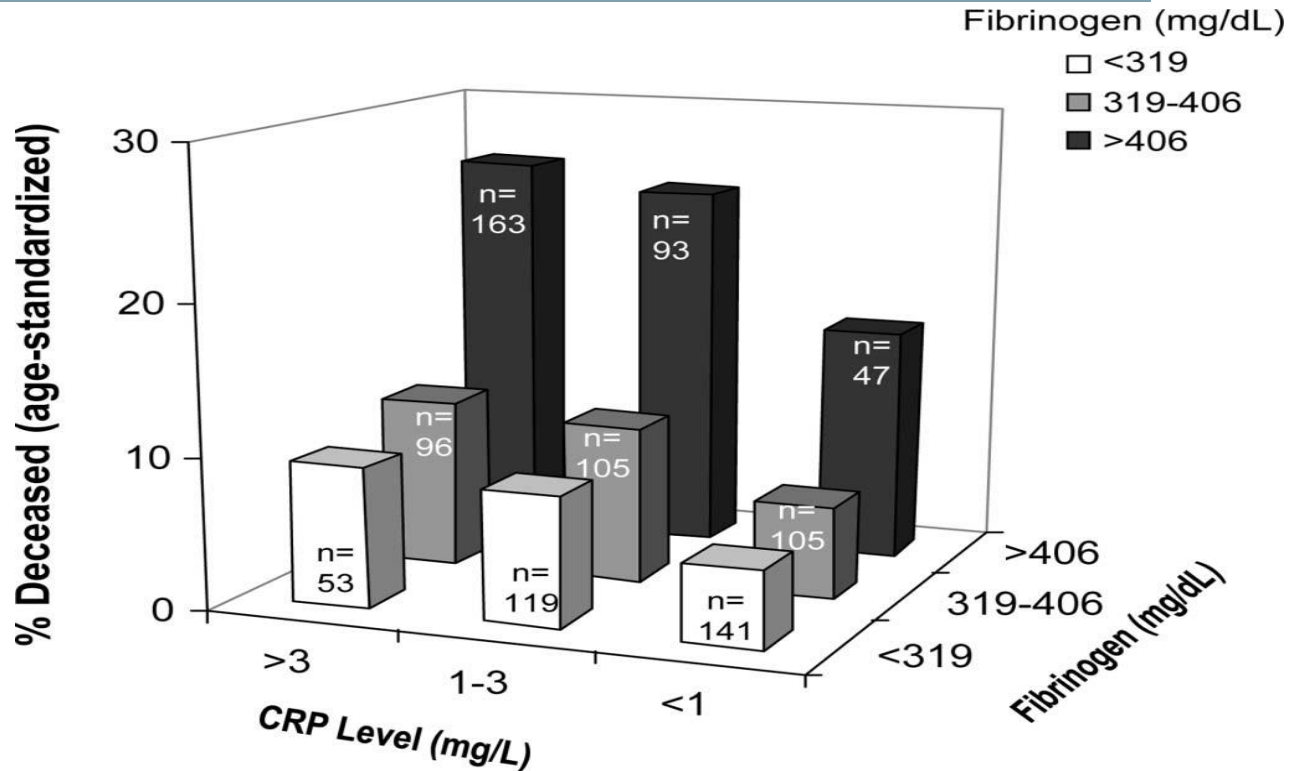


Inflammation markers - SMART

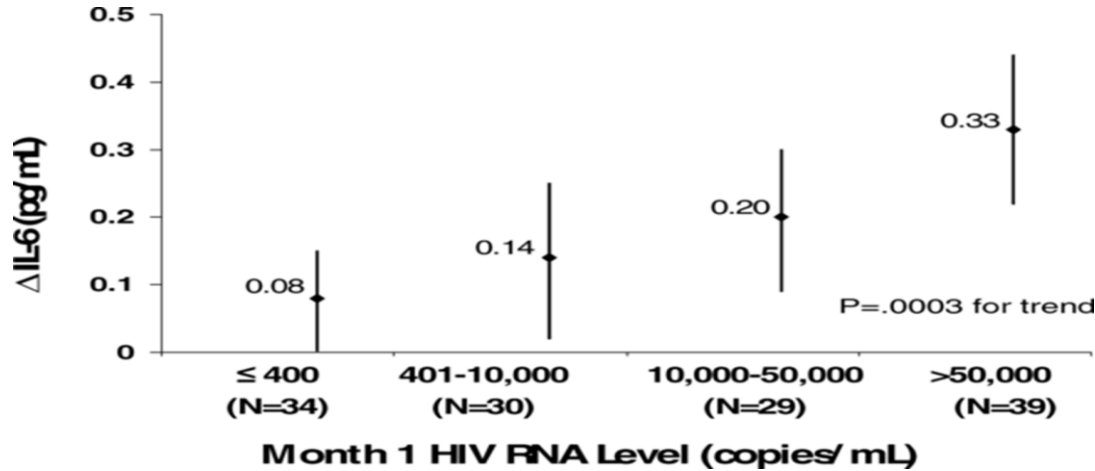
PLWH aged **45-76** years vs. participants in Multi-Ethnic Study of Atherosclerosis (MESA) study



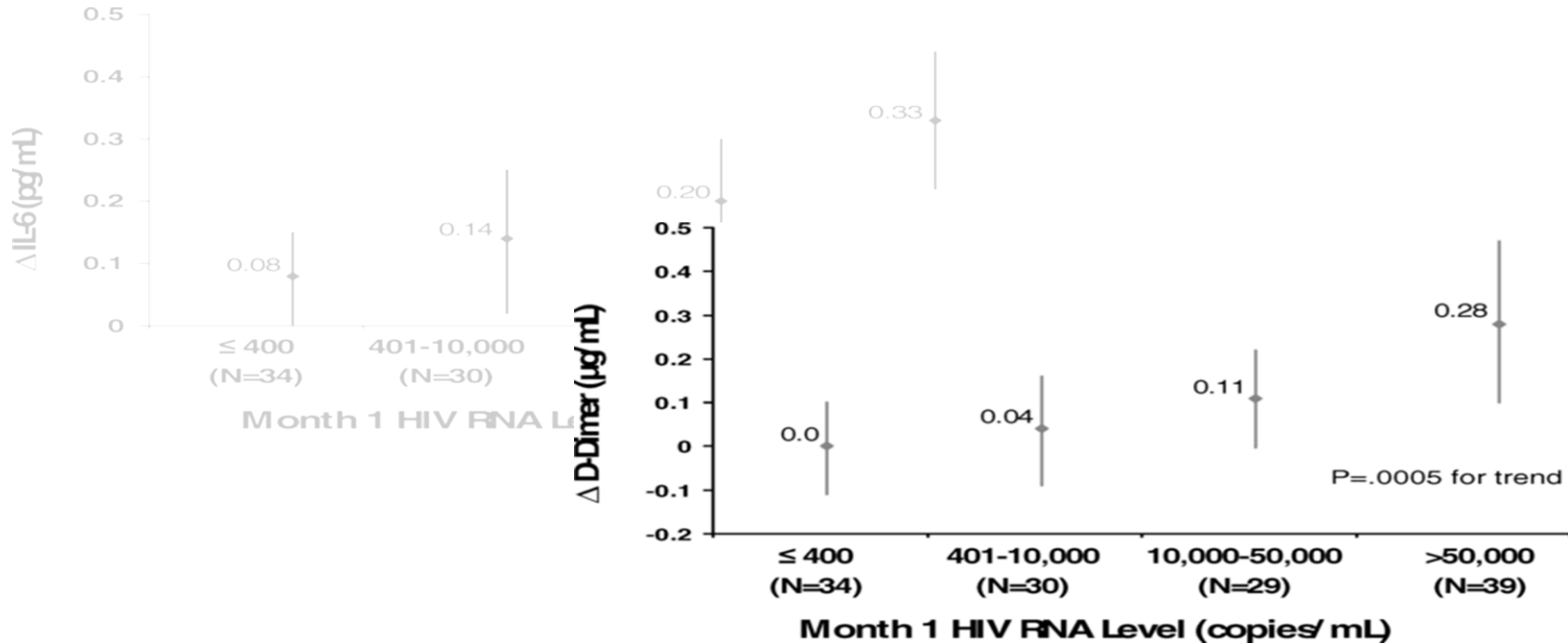
Mortality – FRAM cohort



Risk of death – SMART



Risk of death – SMART



Inflammation markers - SMART

Subset of SMART participants on ART with HIV RNA ≤ 400 copies/ml

Biomarker	Participants 33–44 years of age			Participants 45–76 years of age		
	No.	Median level (IQR)	% Diff. (<i>P</i>)	No.	Median level (IQR)	% Diff. (<i>P</i>)
hsCRP, $\mu\text{g/mL}$	140	2.13 (0.77–5.20)	40.2 (<.001)	293	2.83 (1.07–6.80)	37.8 (<.001)
IL-6, pg/mL	139	1.89 (1.15–3.42)	39.0 (<.001)	291	2.64 (1.55–4.14)	60.1 (<.001)
D-dimer, $\mu\text{g/mL}$	140	0.21 (0.15–0.46)	NA	293	0.29 (0.17–0.57)	49.1 (<.001)
Cystatin C, mg/dL	86	0.90 (0.78–0.97)	NA	130	1.00 (0.86–1.16)	20.9 (<.001)

NOTE. Data are the median level and (interquartile range [IQR]). CARDIA, Coronary Artery Development in Young Adults; Diff., difference; MESA, Multi-Ethnic Study of Atherosclerosis; NA, not available; SMART, Strategies for Management of Anti-Retroviral Therapy.

Smoking - AGE_hIV

	hsCRP		D-dimer	
	OR (95% CI)	P-value	OR (95% CI)	P-value
All participants				
Never smoker	Ref.		Ref.	
Former smoker	1.04 (0.80, 1.35)	0.79	0.92 (0.70, 1.22)	0.57
Current smoker	1.57 (1.16, 2.12)	0.004	1.36 (1.00, 1.85)	0.05
HIV-positive status	1.44 (1.13, 1.83)	0.003	0.64 (0.50, 0.83)	0.001
Current smokers only				
Cigarettes smoked per day (/10)	1.49 (1.18, 1.87)	0.001	1.30 (1.04, 1.63)	0.02
HIV-positive status	1.24 (0.78, 1.97)	0.37	0.52 (0.32, 0.84)	0.007

Smoking

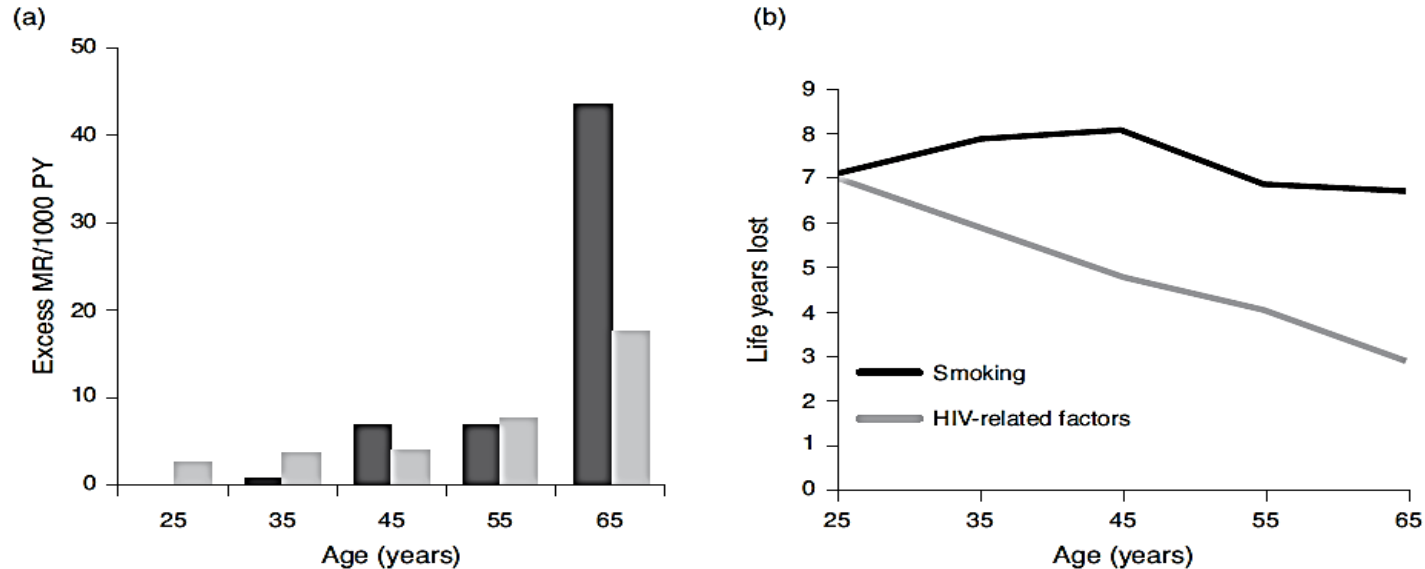


Fig. 1. Excess mortality and loss of life years. Age-specific excess mortality rates (a) and numbers of life years lost (b) in association with smoking (black bars/line) and HIV-related factors (grey bars/line) among HIV-infected men. PY, person-years.

Lifestyle factors

- In addition to smoking, several other demographic and lifestyle/behavioural factors are prevalent in PWH
 - Obesity/low exercise levels
 - Recreational drug use
 - Alcohol use
- Each is associated with raised inflammatory markers
- Each is associated with morbidity/mortality risk
- What role do these play?

Summary

- Population of people with HIV is aging:
 - - increased incidence and spectrum of age-related co-morbidities
 - - when people die, increasingly dying of non-AIDS causes
- Partly to be expected, given the age and lifestyle/demographic factors that are prevalent
- Statements about HIV and ageing are often based on poor interpretation of data and/or lack of adjustment for confounders

Summary (2)

- Whilst there may be some effect of HIV, model appears to be one of accentuated rather than accelerated ageing
- Need to focus our efforts on understanding the reasons for this – with a view to identifying appropriate interventions
- But should also continue to focus on other modifiable risk factors, as in the general population

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