

HIV and Ageing

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How the UK NHS has aged me!



The great success story - HAART

- Decreased mortality since the introduction of HAART
- Decreased incidence of HAART failure through improved treatment options
- Improved survival benefits of HIV care
- Decreased incidence of AIDS cases and death, increased number of people living with AIDS

But ...

The ageing HIV +ve population is developing a different disease spectrum with high proportion of cardiovascular and malignant disease. Diseases of old age, such as dementia, balance disorders combined with high personal needs profiles will become major problems in the foreseeable future.

HIV and ageing: Key questions

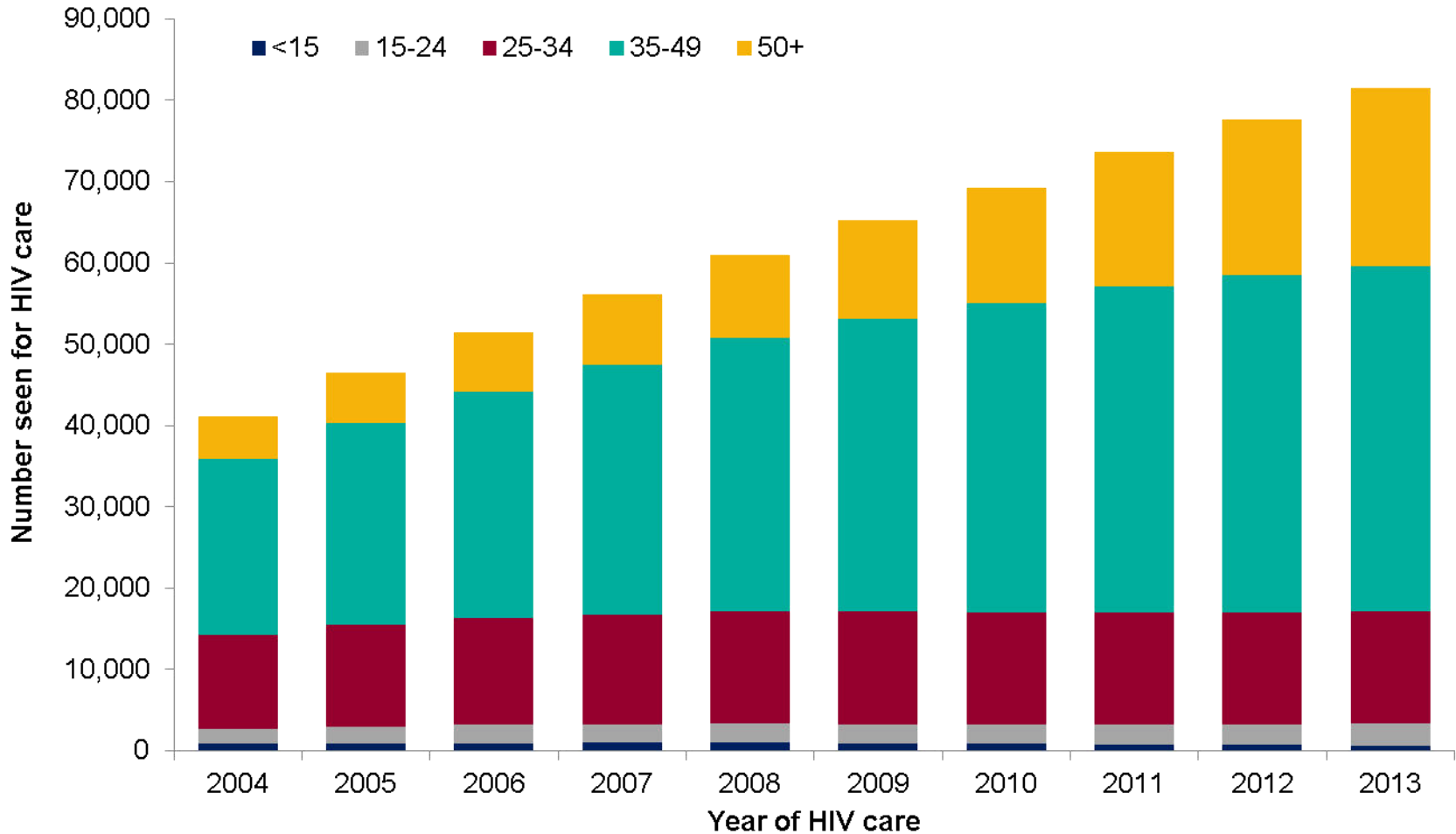
1. Why do we age?
2. How and when do we age?
3. What is healthy ageing?
4. Can we prevent ageing?
5. What are the aims of medical intervention?
6. How does ageing affect patients with HIV?
7. What lies ahead in the future?

Epidemiology

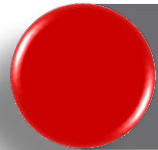
Section 1



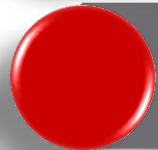
HIV diagnosed persons seen for HIV care by age group: United Kingdom, 2004-2013



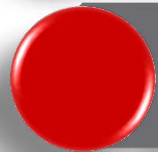
A number of factors influence the rate of new infections in the over 50s age group



This age group is the least likely to practice safe sex^{1,2}



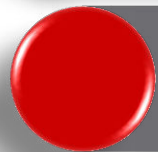
Late-life changes in the reproductive tract and immune system may enhance their susceptibility to HIV acquisition¹



Physicians are less likely to recommend HIV testing to older patients²⁻⁴



Asymptomatic older HIV-infected individuals are less likely to seek testing and medical care^{2,5}



Symptomatic older HIV-infected individuals are more likely to attribute symptoms to other illnesses or to ageing⁶

HIV & immunosenescence

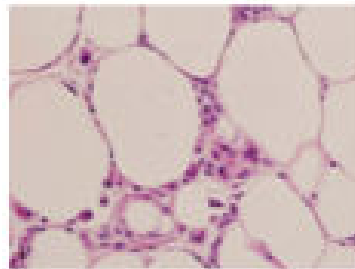
Section 2

HIV-infected patients exhibit many of the immune characteristics found in older uninfected patients

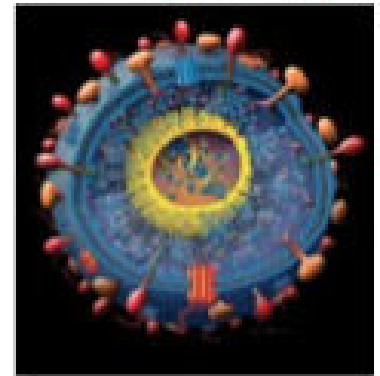
	Elderly* uninfected patients	Untreated HIV infection
Inverted CD4/CD8 ratio	✓	✓
↑ CD28 ⁻ , CD8 ⁺ , CD57 ⁺ T cells	✓	✓
↑ CMV-specific CD8 cells	✓	✓
↓ IL-2, ↑ IFN- γ (CD8 ⁺ T cells)	✓	✓
↑ IL-6	✓	✓
↓ Thymic output	✓	✓
↓ Naive/memory T cells	✓	✓
↓ T cell proliferation	✓	✓
↑ T cell activation	~	✓
↓ T cell repertoire	✓	✓
↓ Telomeres for T cells	✓	✓

* Defined as ≥ 70 years in ref 2

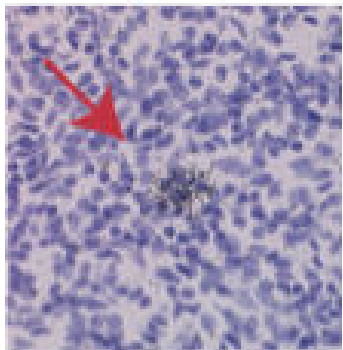
HIV-associated fat Metabolic syndrome



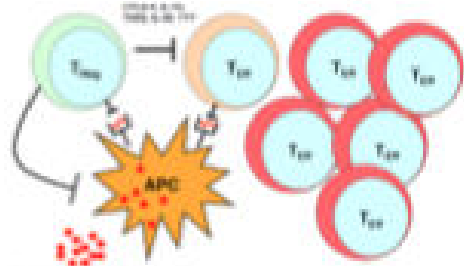
CMV Excess pathogens



HIV production HIV replication

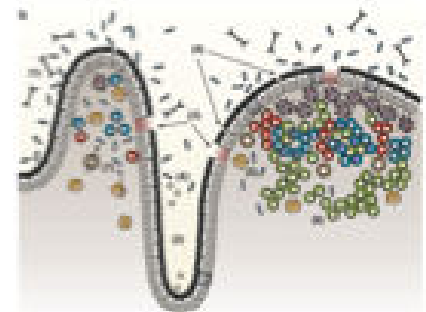


Loss of regulatory cells



Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Microbial translocation



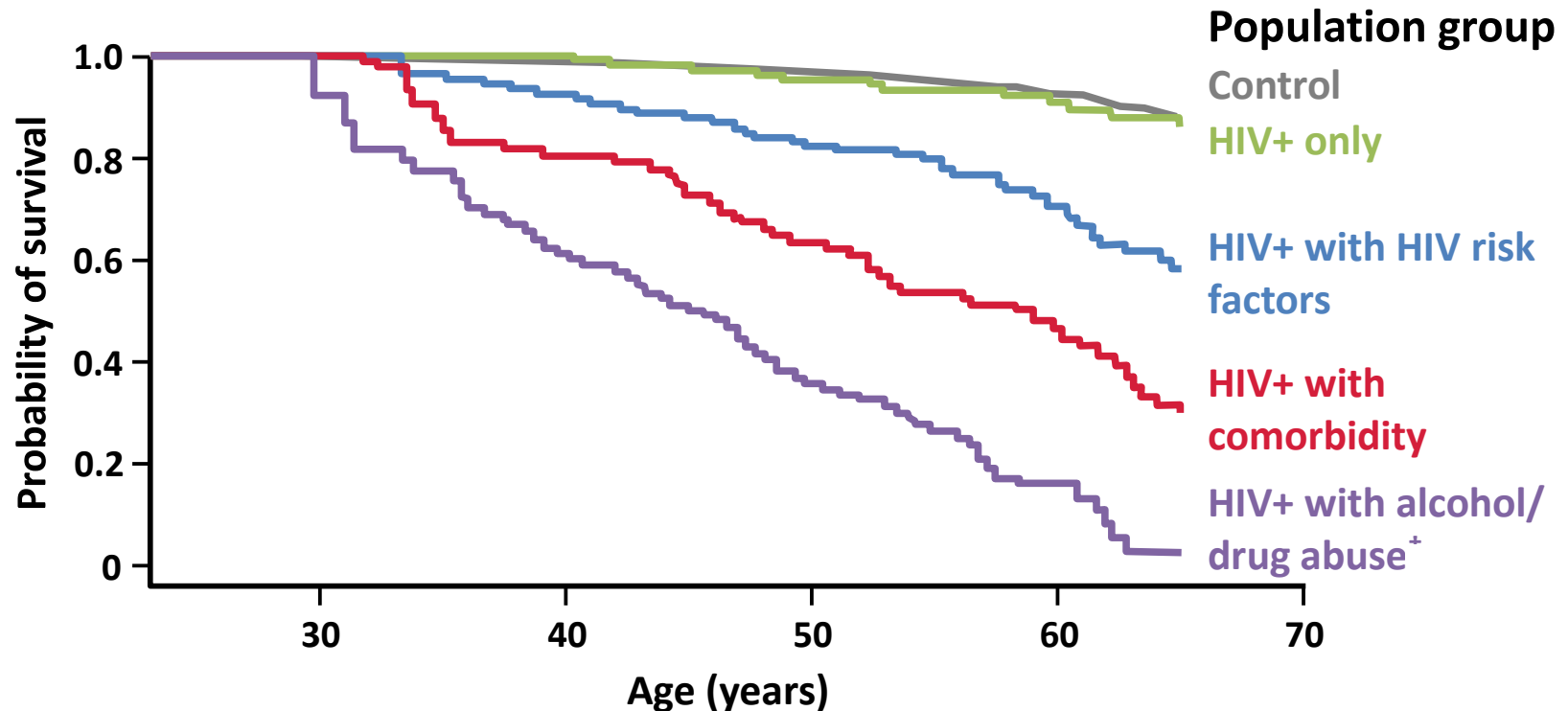
**Co-morbidities
Aging**

Age and co-morbidities in HIV infection

Section 3

Age at diagnosis, co-morbidities and life expectancy

Danish population-based cohort of 2,267 HIV-infected patients starting on HAART and a comparison cohort of 9,068 from the general population on date of birth and gender between 1998–2009



Although the risk of death was increased in HIV-infected patients on HAART compared with the general population; mortality was associated mainly with HIV- and non-HIV-associated risk factors, which are identifiable prior to or in the initial phase of HAART treatment

Prevalence of comorbidities in patients with HIV vs uninfected controls

Comorbidity by age	Patients with HIV (n=2,584)	Uninfected controls	p value
Cardiovascular disease[†]			
≤40 years	0.91%	0.24%	0.049
41–50 years	2.26%	0.64%	<0.001
51–60 years	5.97%	2.65%	0.002
>60 years	16.18%	5.88%	0.076
Renal failure[‡]			
≤40 years	3.28%	0.06%	<0.001
41–50 years	5.22%	0.15%	<0.001
51–60 years	9.07%	0.29%	<0.001
>60 years	24.26%	0.49%	<0.001
Bone fracture			
≤40 years	10.77%	0.73%	<0.001
41–50 years	15.20%	0.93%	<0.001
51–60 years	14.82%	1.33%	<0.001
>60 years	12.50%	2.45%	<0.001

[†]Cardiovascular disease included myocardial infarction, stroke, angina pectoris, coronary artery bypass grafting, and angioplasty diagnoses

[‡]Renal failure defined as CrCl <60 mL/min, chronic kidney disease Grade 3.

HIV-associated Cognitive Impairment

Cognition Memory loss

Concentration

Mental slowing

Comprehension



Behavior

Apathy

Depression

Agitation, Mania

Motor

Unsteady gait

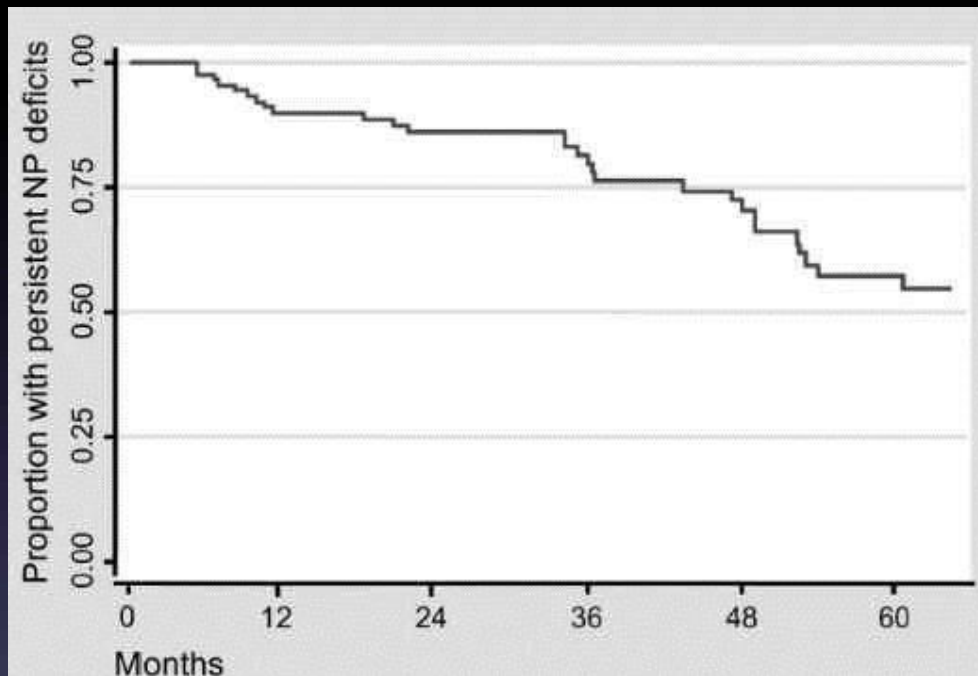
Poor
coordination

Tremor

Controversy

“I don't see cognitive impairment in my patients who are adherent to medications.”

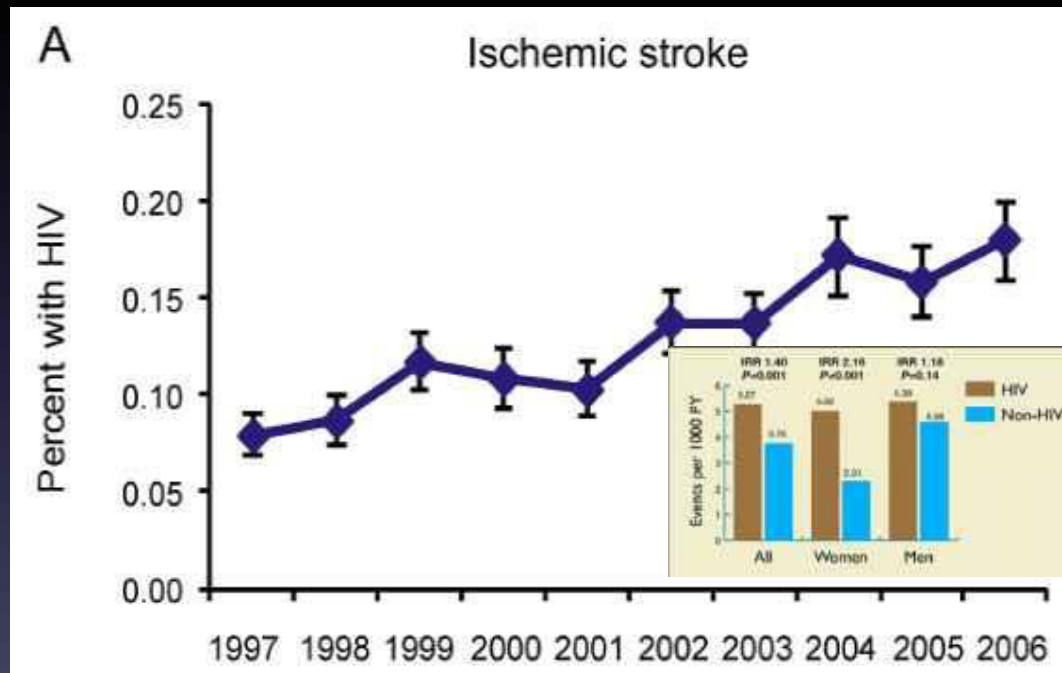
Persistent Cognitive Deficits



n = 94 Neuropsychologic
impairment = (a)-1 SD on
two tests or
(b)-2 SD on one test out

>50% probability of persistent neuropsychological deficits despite 5 years of cART

Increasing Frequency of Ischemic Stroke in HIV



Ovbagle and Nath 2011 Neurology & Chow et al 2011 JAIDS

HIV status and the risk of ischemic stroke among men

Table 3 Rates of stroke (95% CI) per 1,000 person-years stratified by age

Age, y	HIV+	HIV-	p Value (comparison by HIV status)	Overall
<50	1.70 (1.42-2.04)	1.09 (0.93-1.28)	<0.01	1.30 (1.15-1.46)
50-64	3.79 (3.27-4.39)	3.11 (2.79-3.46)	0.03	3.32 (3.04-3.62)
≥65	8.54 (6.33-11.51)	7.94 (6.43-9.79)	0.69	8.13 (6.84-9.65)

- HIV infection is associated with an increased ischemic stroke risk among HIV-infected compared with demographically and behaviorally similar uninfected male veteran
- Compared with uninfected veterans, HIV-infected veterans were at highest risk of incident ischemic stroke with a:
 - CD4 count <200 cells/mm³ (HR = 1.66, 95% CI 1.30–2.12)
 - or HIV-1 RNA ≥500 copies/mL (HR = 1.36, 95% CI 1.15–1.63)
- Mean (SD) age at stroke event was 57.2 (9.8) and 58.4 (9.3) years

HIV protease inhibitor exposure predicts cerebral small vessel disease

Virawudh Soontornniyomkij^{a,b}, Anya Umlauf^a, Sandra A. Chung^a,
Megan L. Cochran^a, Benchawanna Soontornniyomkij^b, Ben Gouaux^a,
Will Toperoff^a, David J. Moore^{a,b}, Eliezer Masliah^{a,c,d}, Ronald J. Ellis^{a,d},
Igor Grant^{a,b} and Cristian L. Achim^{a,b,c}

Mild

Moderate

Severe

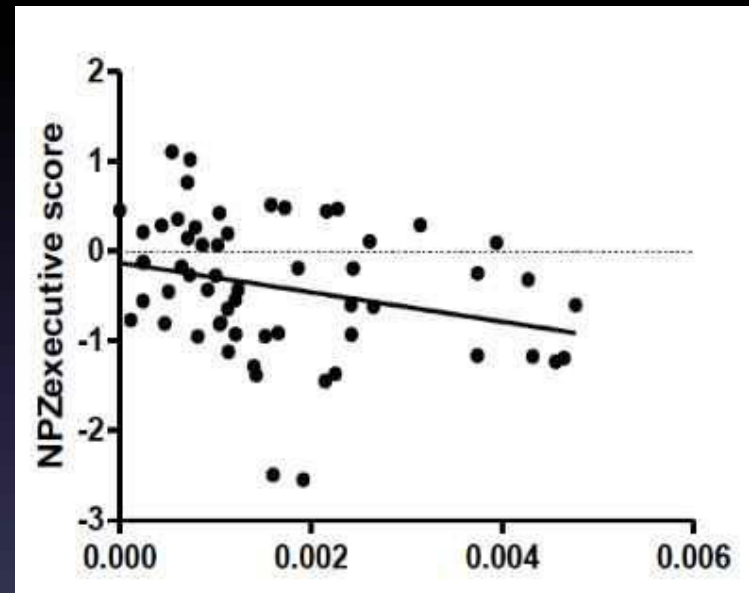
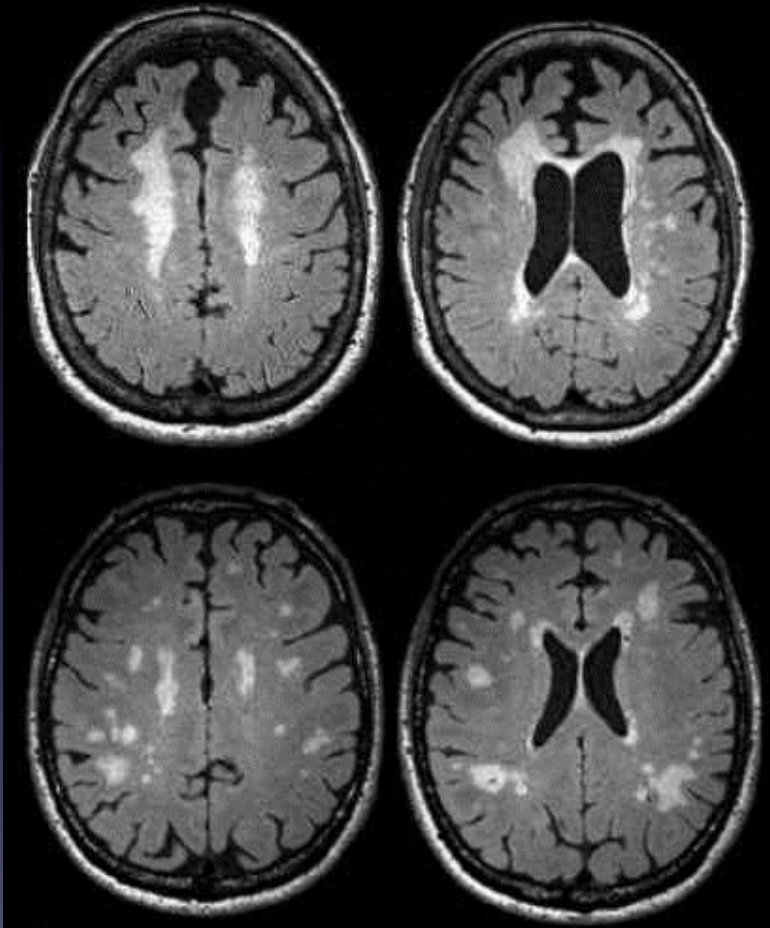


- Autopsy series in the US between 1999 to 2011
- Associated with PI use; ? Legacy effect

50 % of cases

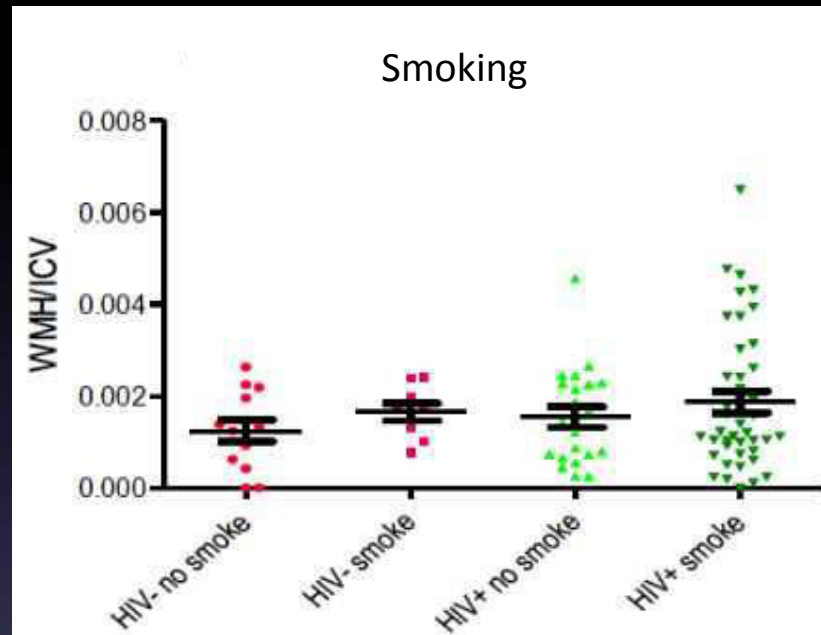
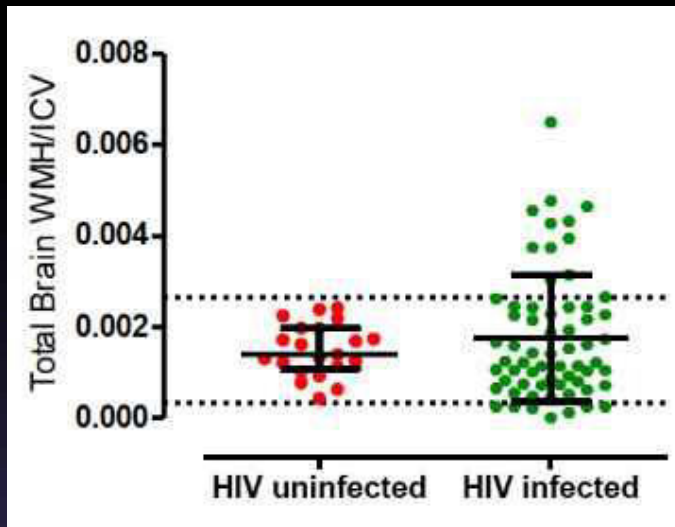
Soontornniyomkij et al AIDS 2014

White Matter Injury

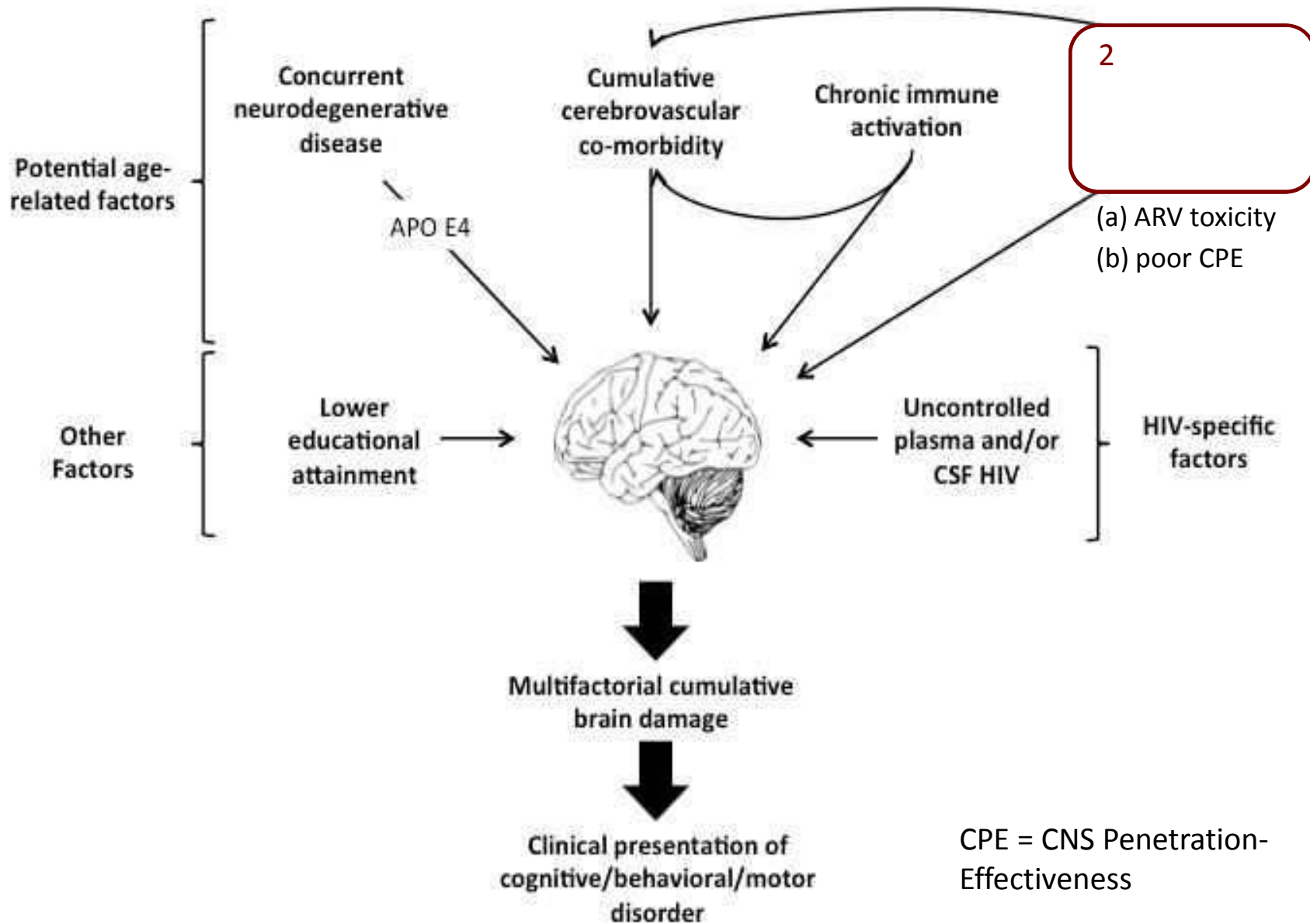


Subjects over the age of 60 in the US who are living with HIV as a chronic illness

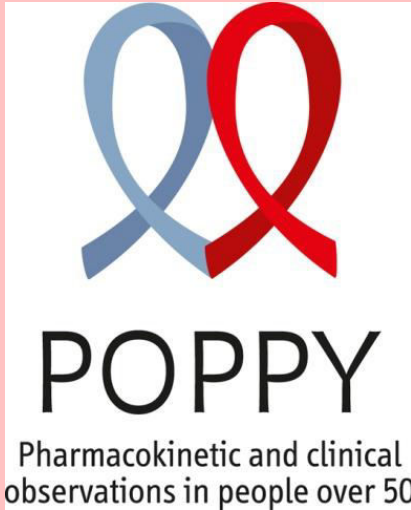
White Matter Lesions



- Higher white matter lesion volume in HIV compared to age-matched controls
- Smoking impacts total WML volume in HIV



Cohort studies



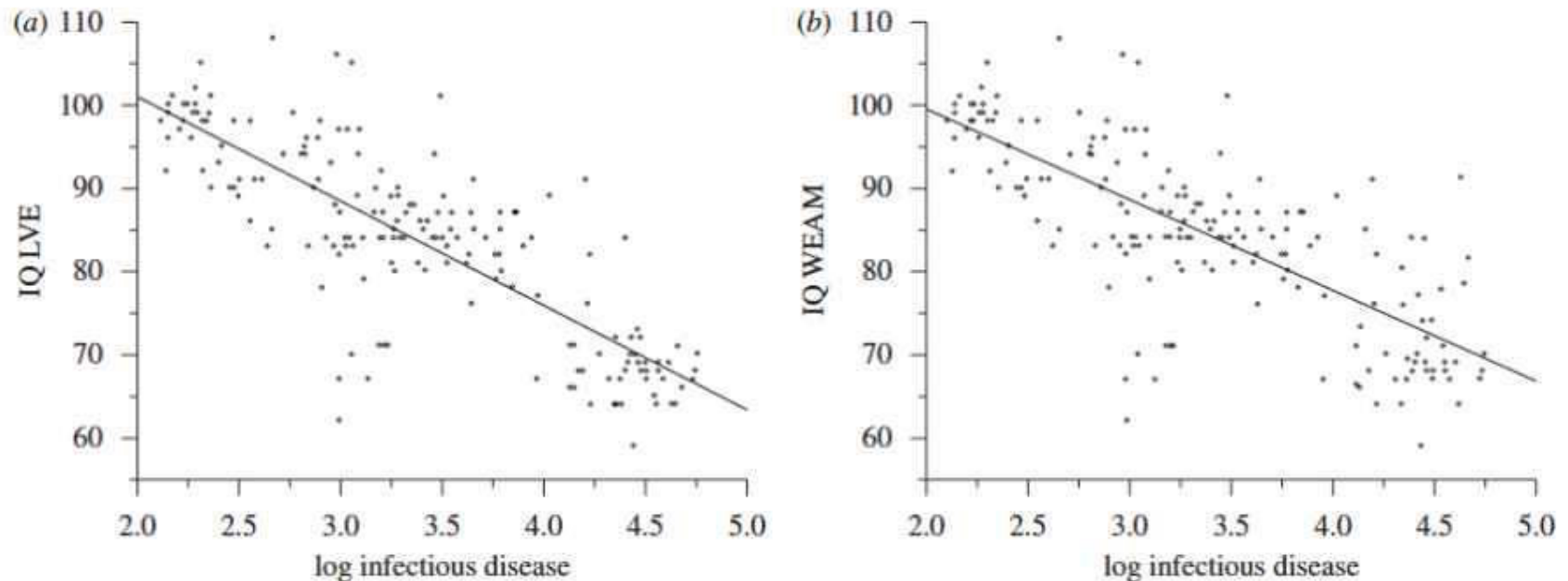
POPPY:
'Pharmacokinetic
and Clinical
Observations in
People over Fifty'



- COBRA: a neurology sub-study of POPPY and AGE_hIV
- Detailed assessment of cognitive function
 - CSF examination
 - Detailed neuroimaging

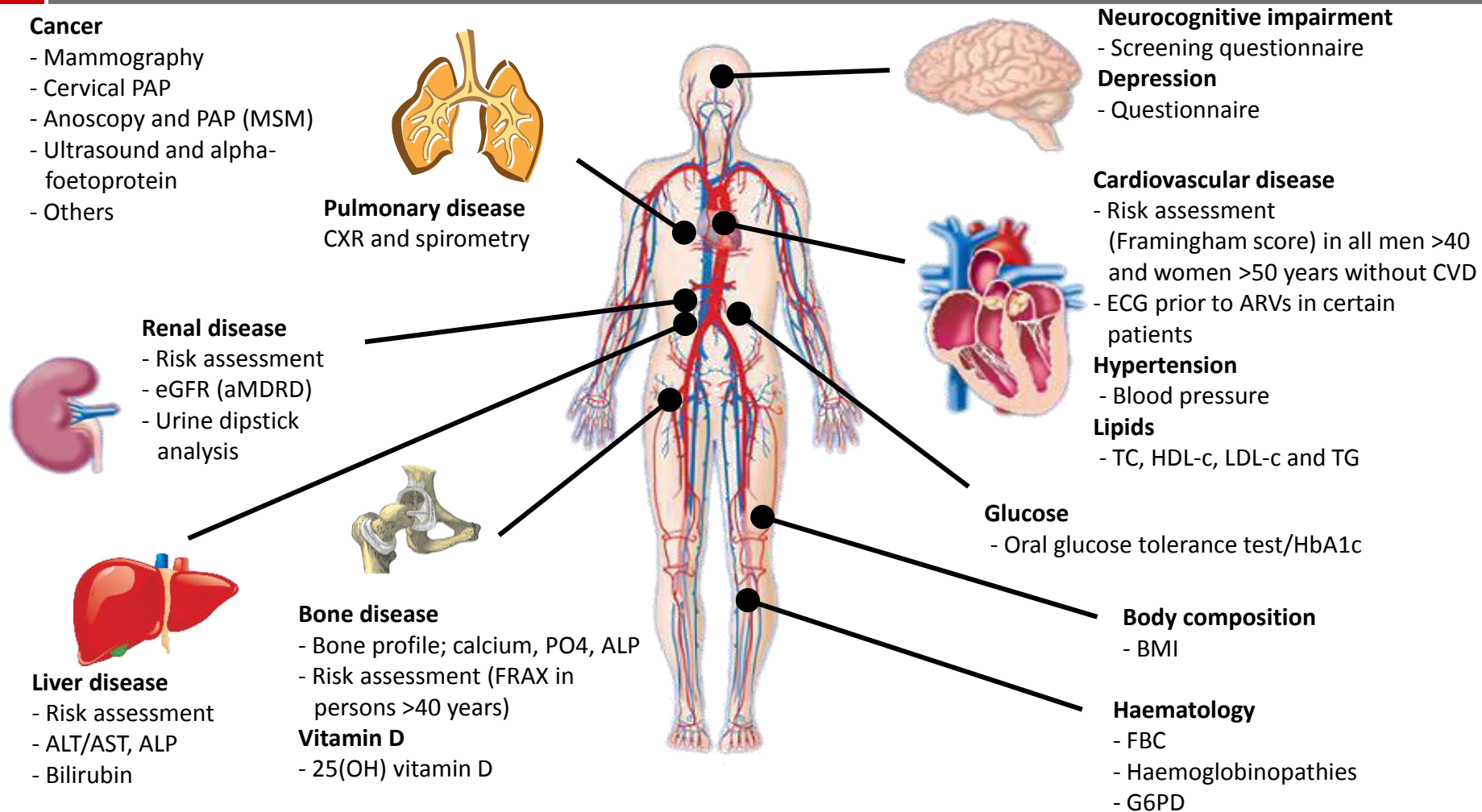
Parasite prevalence and the worldwide distribution of cognitive ability

Christopher Eppig*, Corey L. Fincher and Randy Thornhill



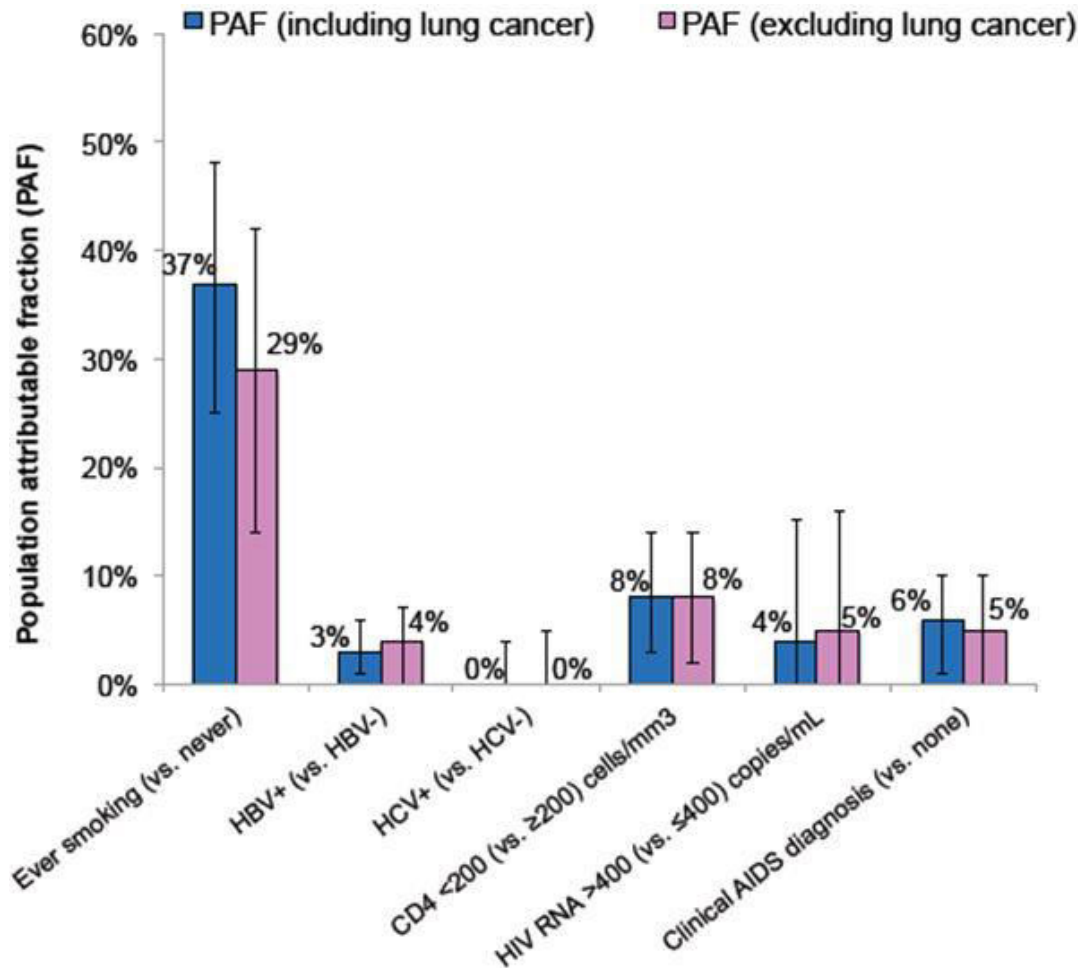
Hypothesized influence of competing metabolic demands during neurodevelopment

Accelerated or augmented risk for HANA*



*See guidelines for detail on follow-up frequency, subgroups to be screened and further information
HANA, HIV-associated non-AIDS

Avoiding smoking could prevent 37% of non-AIDS cancers in adults with HIV



- Population attributable fraction (PAF) and 95% confidence interval for smoking and HIV-related risk factors, non AIDS defining cancers (NADC) with and without lung cancer
- The PAF of smoking declines from 37% to 29% when lung cancers are removed from NADC outcome. Regardless, smoking has a higher PAF than any of the HIV-related risk factors

The Effect of Physical Activity on Cardio-metabolic Health and Inflammation in HIV

	Carotid IMT (mean bulb)		Carotid Distensibility		FMD (hyperemic VTI)	
	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value
Physical Activity	-0.001	<0.0001	0.839	<0.0001	0.001	<0.001
Age	0.010	<0.0001	-0.552	<0.0001	-0.005	<0.001
sex	-0.001	0.99	3.819	<0.0001	0.014	0.545
Race	-0.026	0.326	-2.039	0.019	-0.590	0.003
CD4 Nadir	<0.0001	0.110	0.001	0.247	<-0.0001	<0.001
ARV duration	-0.001	<0.0001	-0.008	0.020	<-0.0001	0.076
STATIN Group						
	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value
Physical Activity	-0.001	<0.0001	0.0836	<0.0001	0.001	0.460
Age	0.011	<0.0001	-.0567	<0.0001	-0.005	<0.0001
sex	-0.001	0.943	4.078	<0.0001	0.013	0.788
Race	-0.231	0.413	-1.881	0.021	-0.050	<0.0001
CD4 Nadir	-0.001	0.228	0.001	0.606	-0.001	0.001
ARV duration	-0.001	<0.0001	-0.008	0.065	-0.001	0.304
statin	0.403	<0.0001	0.527	0.269	0.038	0.444

Physical activity associated with markers of vascular health at all time points

Factors associated with frailty among HIV-positive individuals on HAART

■ HIV-related measures^{1,4,6}

- Longer time since diagnosis
- Lower current CD4 count
- Lower nadir CD4 count
- Low CD4/CD8 ratio
- Detectable viral load
- Protease inhibitor-containing HAART regimen

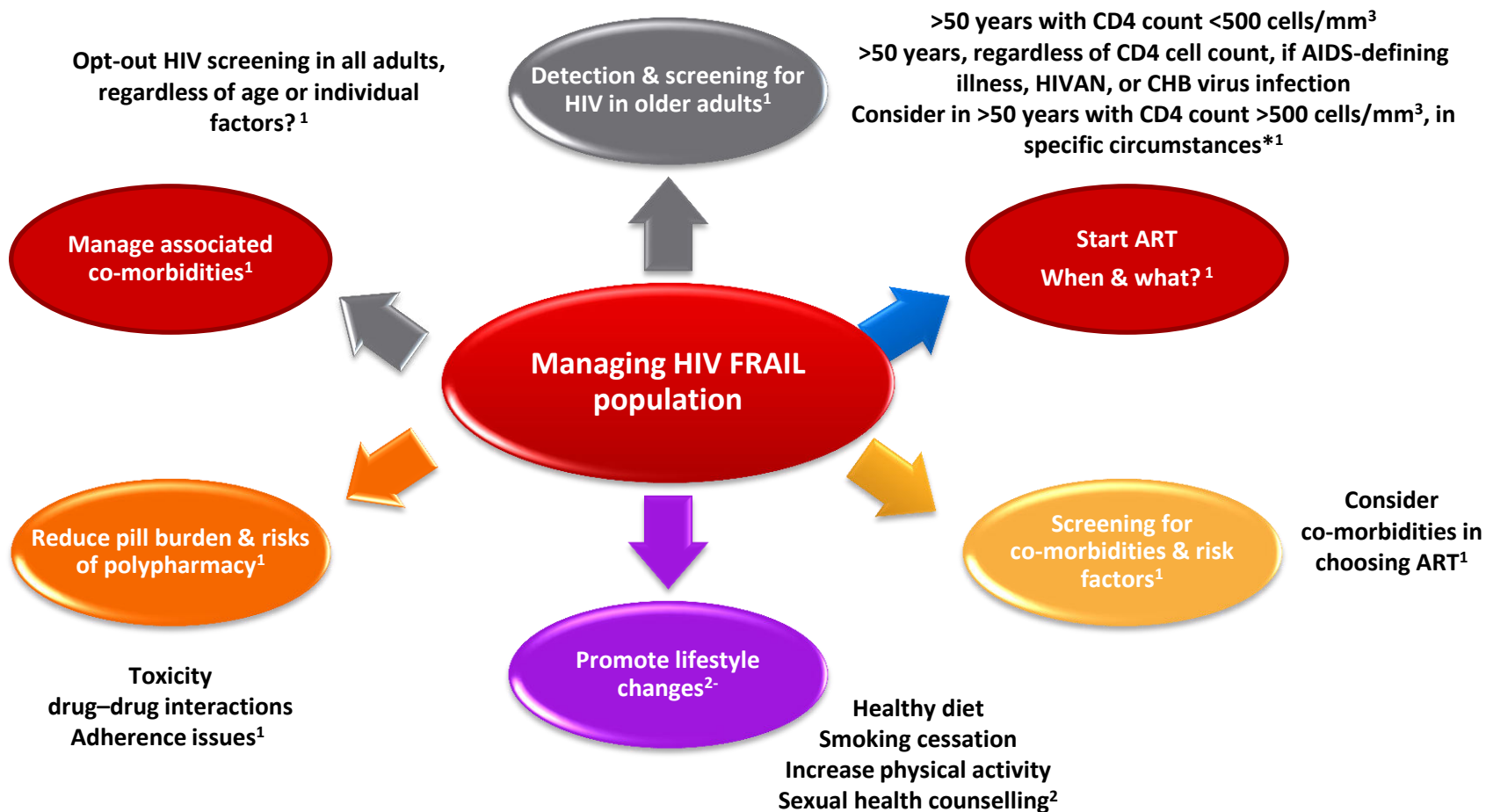
■ Co-morbidities^{2,3,5,7}

- Hepatitis C co-infection
- Low BMI
- High BMI
- Lipodystrophy
- Depressive symptoms
- Cognitive impairment
- Inflammation
- Weak upper and lower extremities

■ Social factors³

- Lower education
- Current unemployment
- Low income in past year

How to manage pre-frail or frail HIV patients?



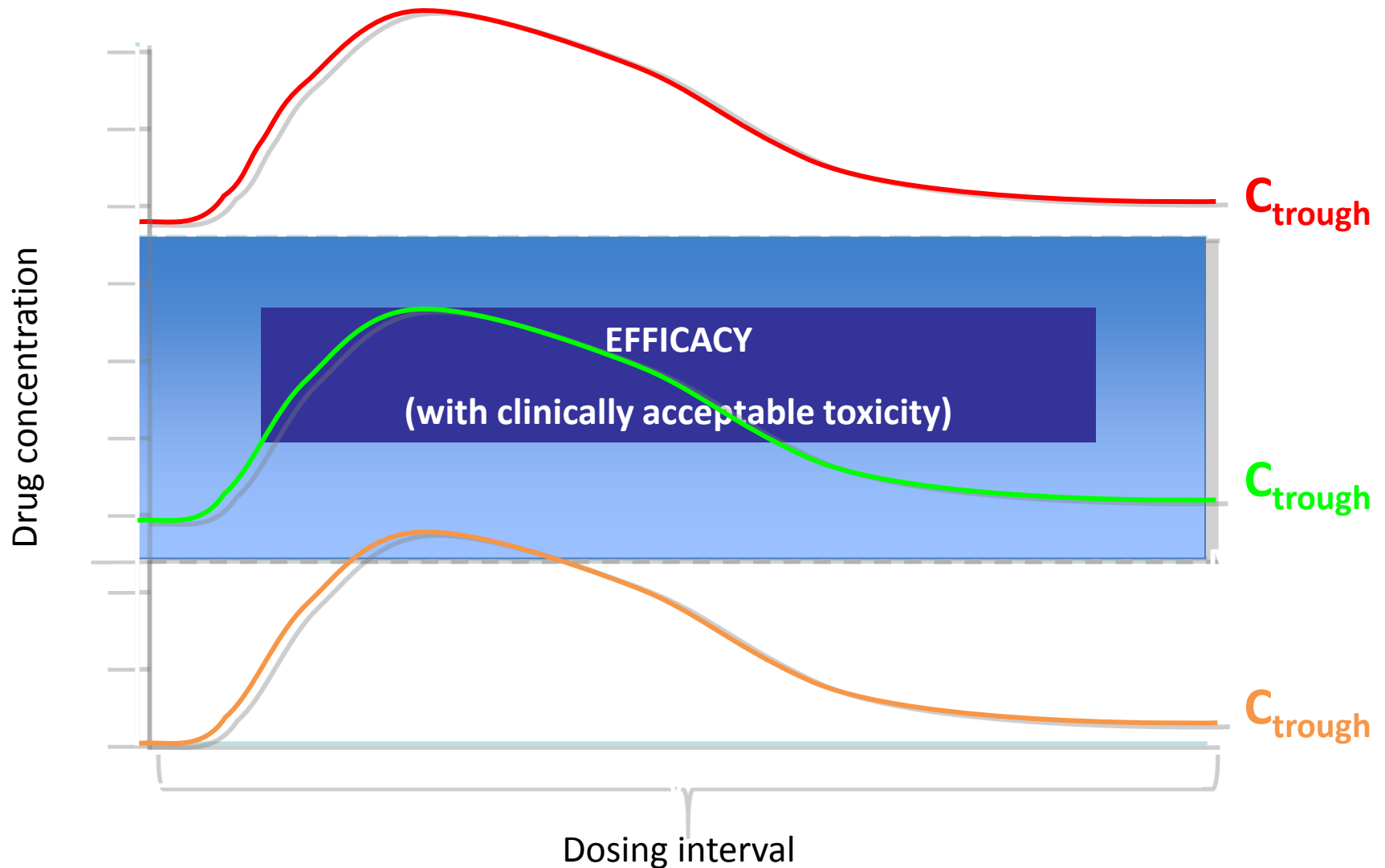
*if plasma HIV RNA levels >50,000 copies/ml, greater than 100-point decline in CD4 count in prior 12 months, or risk factors for CVD

1. The HIV and Aging Consensus Project: Recommended Treatment Strategies for Clinicians Managing Older Patients with HIV 2011. Available at: <http://www.aahivm.org/hivandagingforum>. Accessed April 2012; 2. Fitch K et al. *AIDS* 2006;20:1843–1850

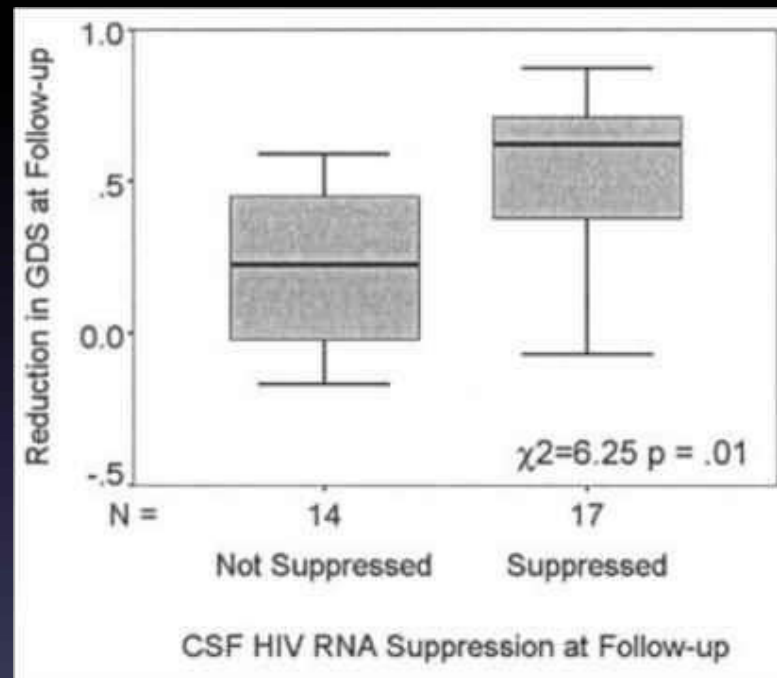
Pharmacology of ageing and antiretroviral therapy

Section 5

Ageing increases variability in PK



CSF viral load and cognition

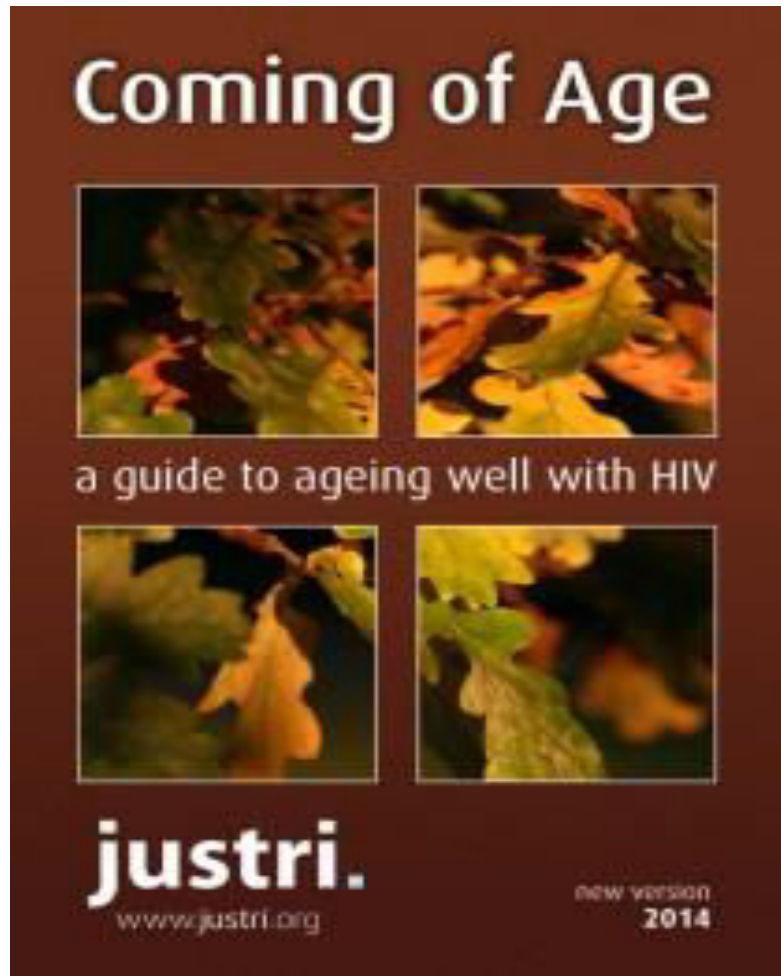


Improved control of CSF HIV RNA relates to greater improvements in cognitive performance.

Management of Older HIV-Infected Patients

- Choice of antiretroviral therapy
 - Avoidance of metabolic or other toxicities
- ↑ Need for primary care and health review
 - Fasting lipids/glucose, renal function, bone disease
 - Cancer screening
- Poly-pharmacy considerations
 - Drug-drug interactions
 - Adherence
- Earlier initiation of antiretroviral therapy? START study

A patient guide to ageing well with HIV



Designed for patients & those
who care for them

online at

www.justri.org

Also many slide presentations
on ageing at

www.justrislide.com

Summary: HIV and ageing

- The number of HIV-infected persons aged 50 and over is increasing
- Morbidity associated with normal ageing may be enhanced by HIV infection and/or ART
- Clinicians should be aware of the challenges associated with management of an older HIV patient:
 - Older patients may present with more advanced HIV disease
 - Immunological response in ageing patients is less robust than in younger patients
 - Choice of initial and subsequent ART should take co-morbidities into consideration
- Primary health care considerations in HIV patients should include screening and management of age-related co-morbidities

Come visit us



Be diligent, think laterally and care



Ah the passage of time.....

