The Amsterdam AGE$_h$IV Cohort Study

An overview

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- Amsterdam Institute for Global Health and Development

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Potential conflicts of interest

Over the past year, I have received funding for membership of Advisory Boards and for the preparation of educational materials from the following companies:

- Gilead Sciences
- ViiV Healthcare

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- Stichting AIDS Fonds grant nr. 2009063 & 2012033 & 2010039
- Nuts-OHRA Foundation (grant no 1003–026)
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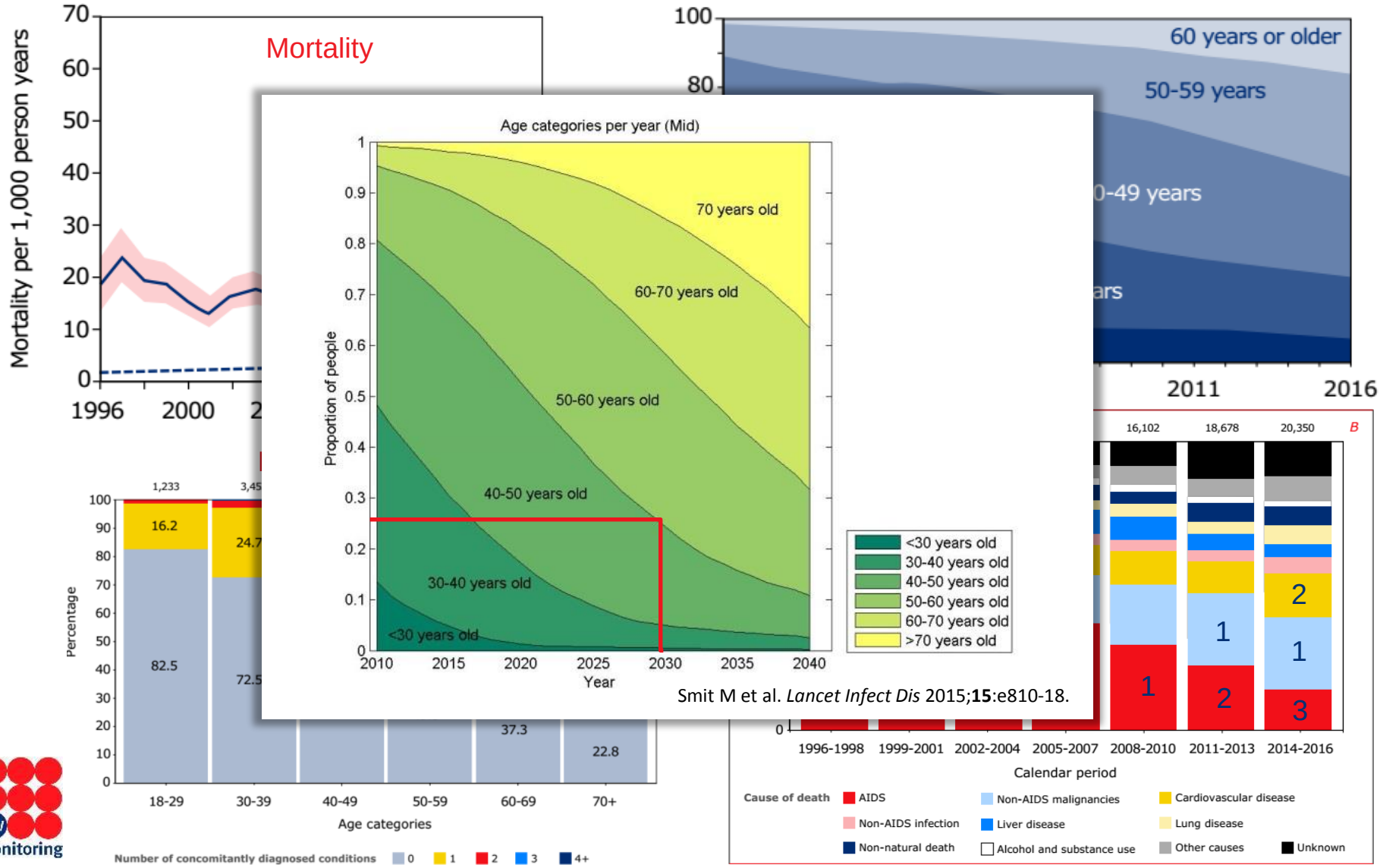
Additional unrestricted scientific grants from:

- Gilead Sciences
- ViiV Healthcare
- Janssen Pharmaceutica N.V.
- Bristol Myers Squibb
- Merck & Co

HIV Monitoring

Background



Smit M et al. *Lancet Infect Dis* 2015;**15**:e810-18.

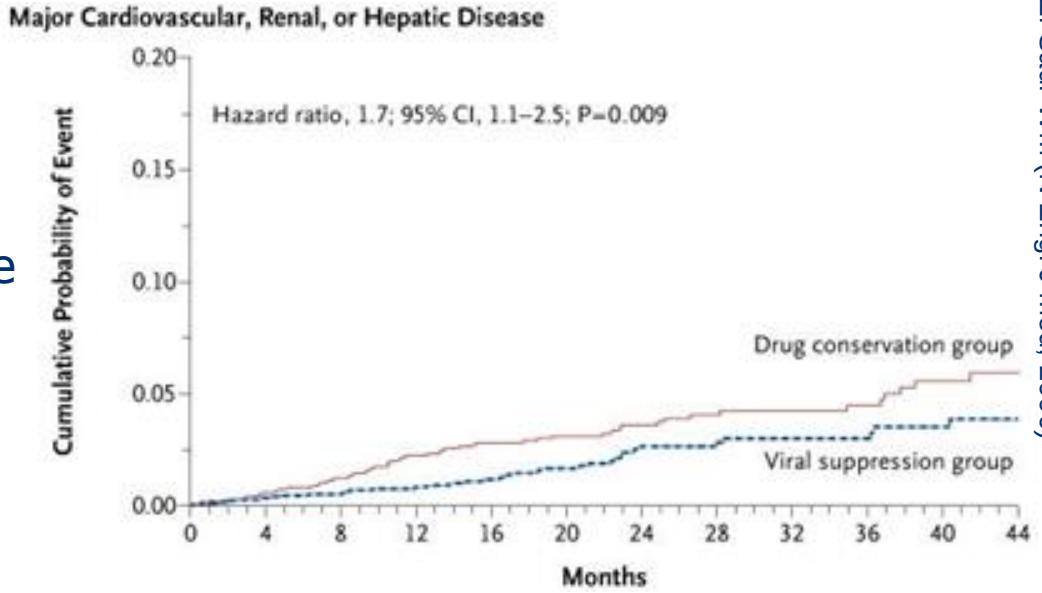
SHM Monitoring Report 2017

HIV Monitoring

Background

SMART study (2006)

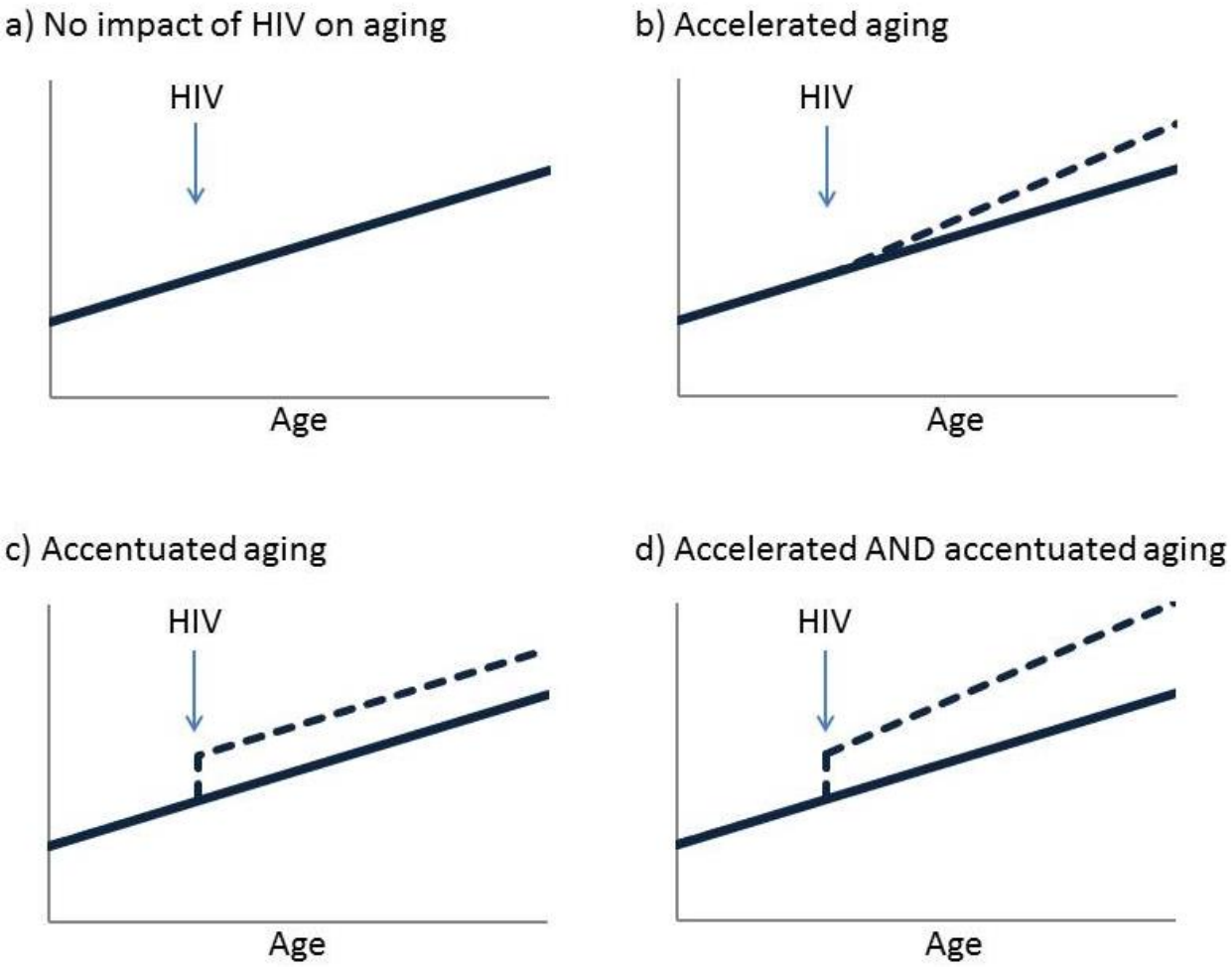
- 90% of deaths were non-AIDS-related
- Non-AIDS events were associated more with HIV replication and CD4 than with cART
- Inflammatory (hsCRP, IL-6) and coagulation (D-dimer) biomarkers were associated with increased morbidity & mortality, even in continuously treated patients, also in the long-term
- The strength of the associations in PLHIV were higher than in uninfected people
- Treating earlier might be beneficial, now confirmed for any CD4 level by START & TEMPRANO



El-Sadr WM (N Engl J Med, 2006)

Background

'accelerated / accentuated' ageing



The AGE$_h$IV cohort study

- Prevalence, incidence, and risk factors of non-AIDS comorbidities in persons ≥45 years
- Started October 2010, 2-yearly visits
- Participants:
  - HIV-1-infected: from the HIV outpatient clinic at the Academic Medical Center (Amsterdam)
  - HIV-1-uninfected: from the Amsterdam Public Health Service sexual health clinic, and the ongoing Amsterdam Cohort Studies on HIV/AIDS

Aims of the AGE$_h$IV cohort study

Are non-AIDS co-morbidities more prevalent among HIV+ versus HIV- individuals?

What are the most important risk factors for comorbidities in the context of HIV infection?

How do HIV and comorbidities influence quality of life of people living with HIV?

HIV-positive patients on cART

Highly comparable HIV-negative control group

Detailed data collection

Standardized procedures and protocols

HIV-positive and HIV-negative participants are highly comparable

HIV+	HIV-
52.9 y	52.1 y
88.1% 73.9%	85.1% 69.7%
72.2%	81.3%
32.0% 22.2 y	24.6% 15.0 y
4.8% Cannabis 13.5% Cocaine 3.7% Ecstasy 5.3%	7.3% Cannabis 11.6% Cocaine 2.9% Ecstasy 8.6%
44.3%	53.0%
SBP 135 (126-147) mmHg DBP 81 (75-89) mmHg	SBP 133 (125-143) mmHg DBP 79 (72-85) mmHg

HIV Monitoring

Characteristics of HIV+ group

HIV+

12.1 (6.2-17.1) years

95.7%
10.4 (4.4-14.5) y

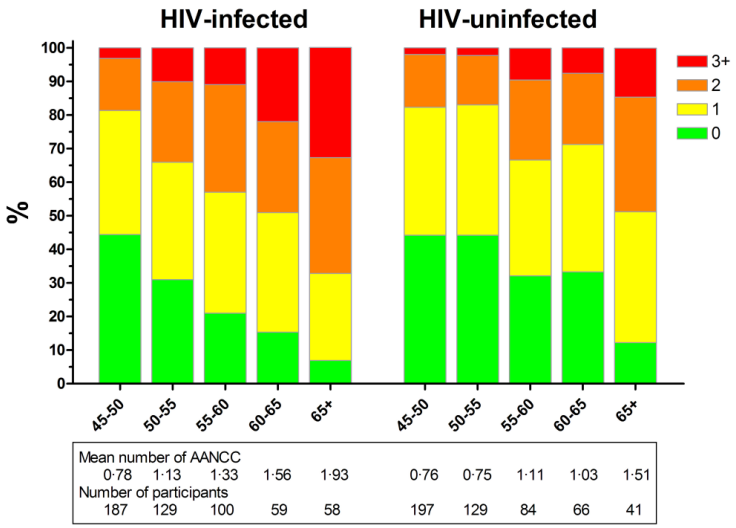
HIV-RNA <200 c/mL: 98.5%

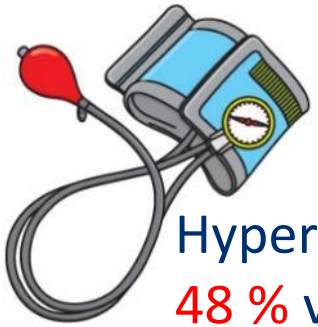
Current: 565 (435-745) cells/µL
Nadir: 180 (78-260) cells/µL

AIDS 31.3%

AGEhIV: Comorbidity burden is higher among HIV+ patients

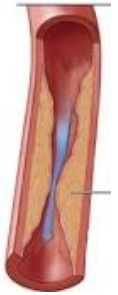
More multimorbidity

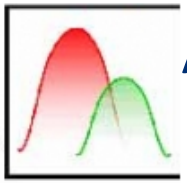




Hypertension
48 % vs. 36 %

Cardiovascular disease
10 % vs. 5 %



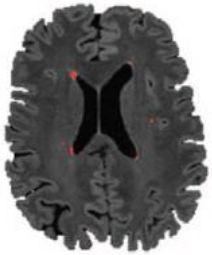


Arterial stiffness
7.9 vs. 7.7 m/s

CKD
26 % vs. 7 %

Low bone mineral density
13 % vs. 7 %

Significant liver fibrosis
38.2 % vs. 29.5 %



WM hyperintensities
1.0 vs. 0.7 mL

Frailty
10.6% vs. 2.7%

GMV 659 vs. 673 mL
FA 0.477 vs. 0.484

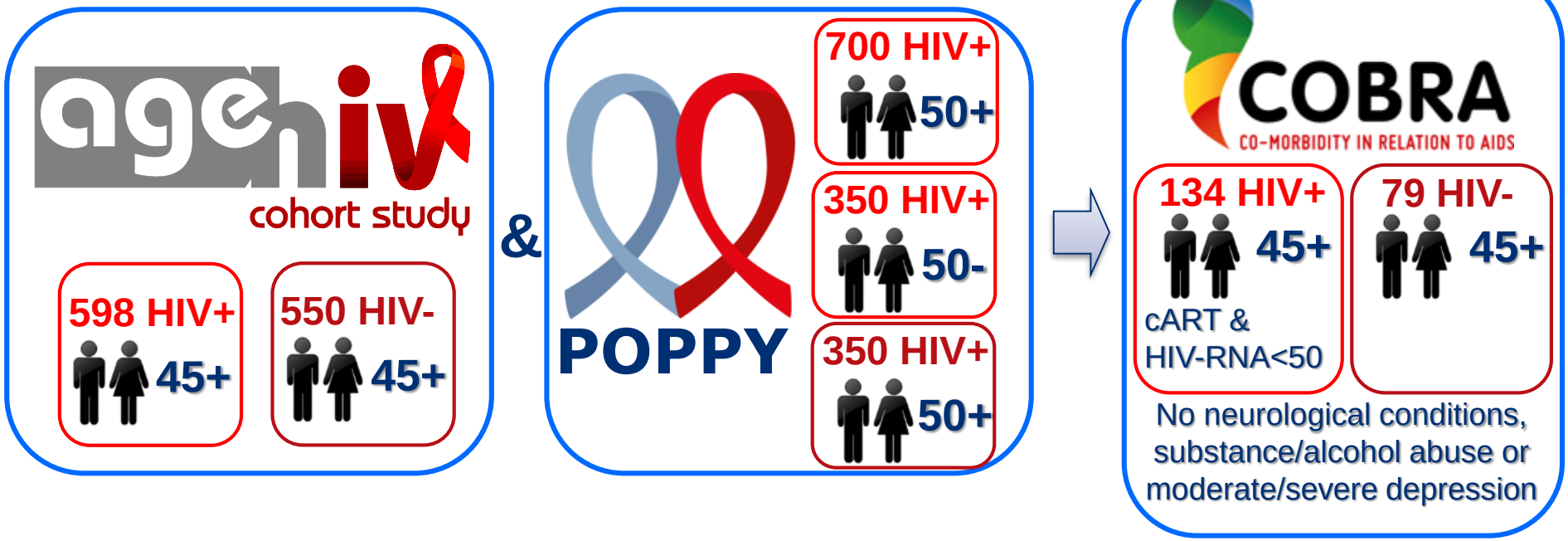
Cognitive impairment
17 % vs. 5 %

HIV Monitoring

Summary of important risk factors

	Multimor-bidity	Hyper-tension	Aortic stiffness	Liver fibrosis	Frailty	Osteo-porosis	Brain	HAND
Confounders: Older age	✓	✓	✓	✓	✓	✓	✓	✓
Confounders: Genetic background	✓	✓		✓				
Confounders: HCV	✓			✓	✓	✓		
Confounders: Smoking	✓		✓		✓	✓	✓	
Mediators: (Abdominal) obesity	✓	✓	✓		✓		✓	✓
Mediators: Inflammation	✓		✓	✓			✓	
HIV-related: 'Old fashion-ed' ART	✓	✓		✓	✓			
HIV-related: Immuno-deficiency	✓		✓	✓		✓	✓	✓

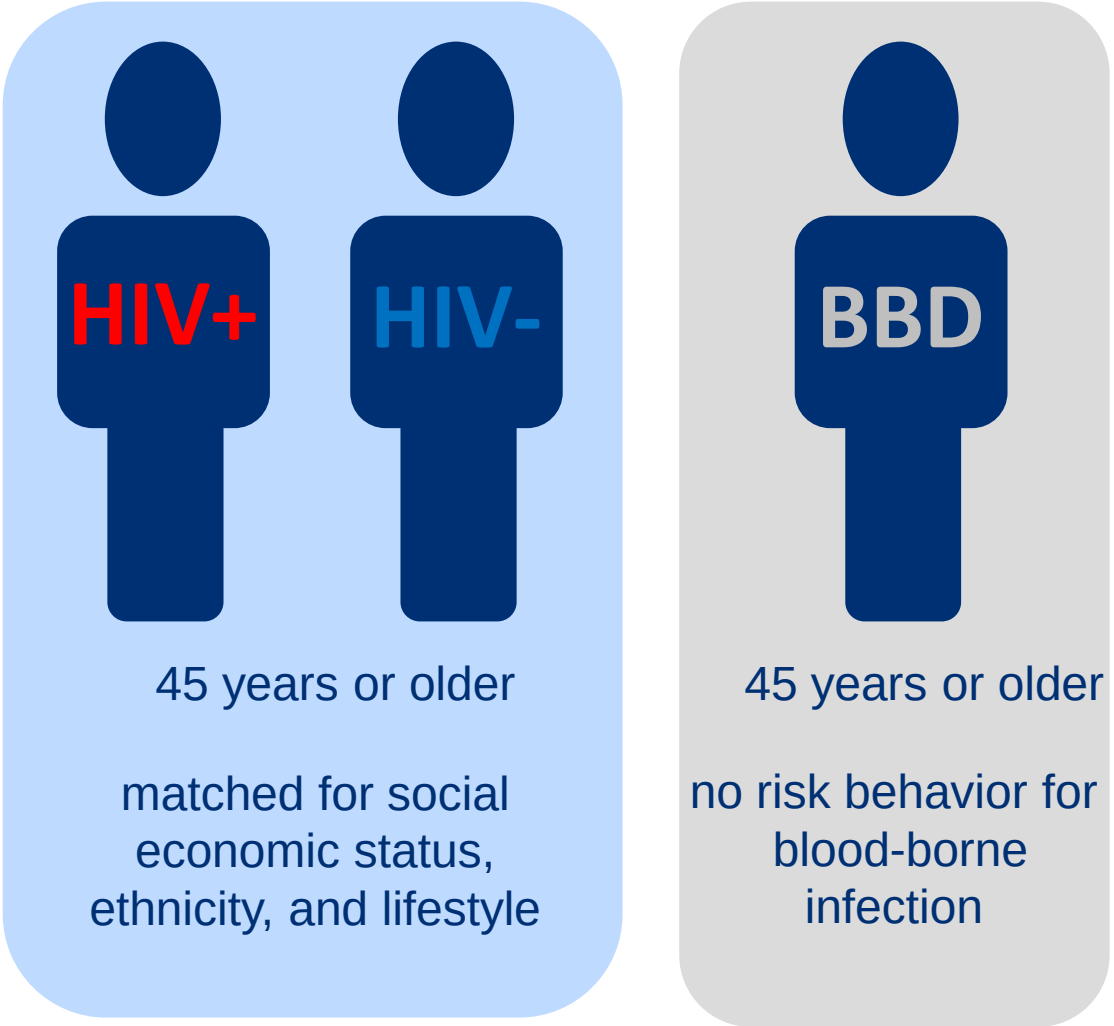
The COBRA project



HIV Monitoring

SEVENTH FRAMEWORK PROGRAMME

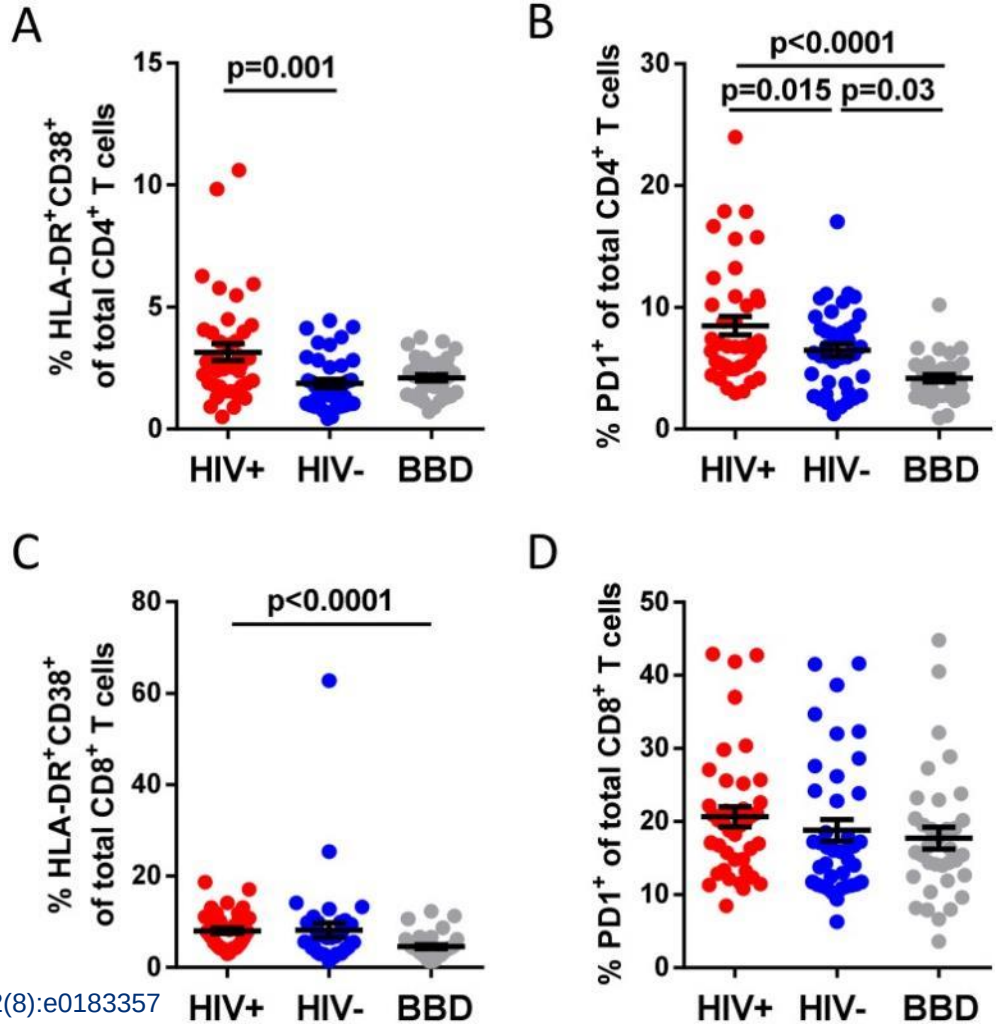
Immunological studies



Cobos Jiménez V. J Infect Dis. 2016 Apr 12.

Immunological studies

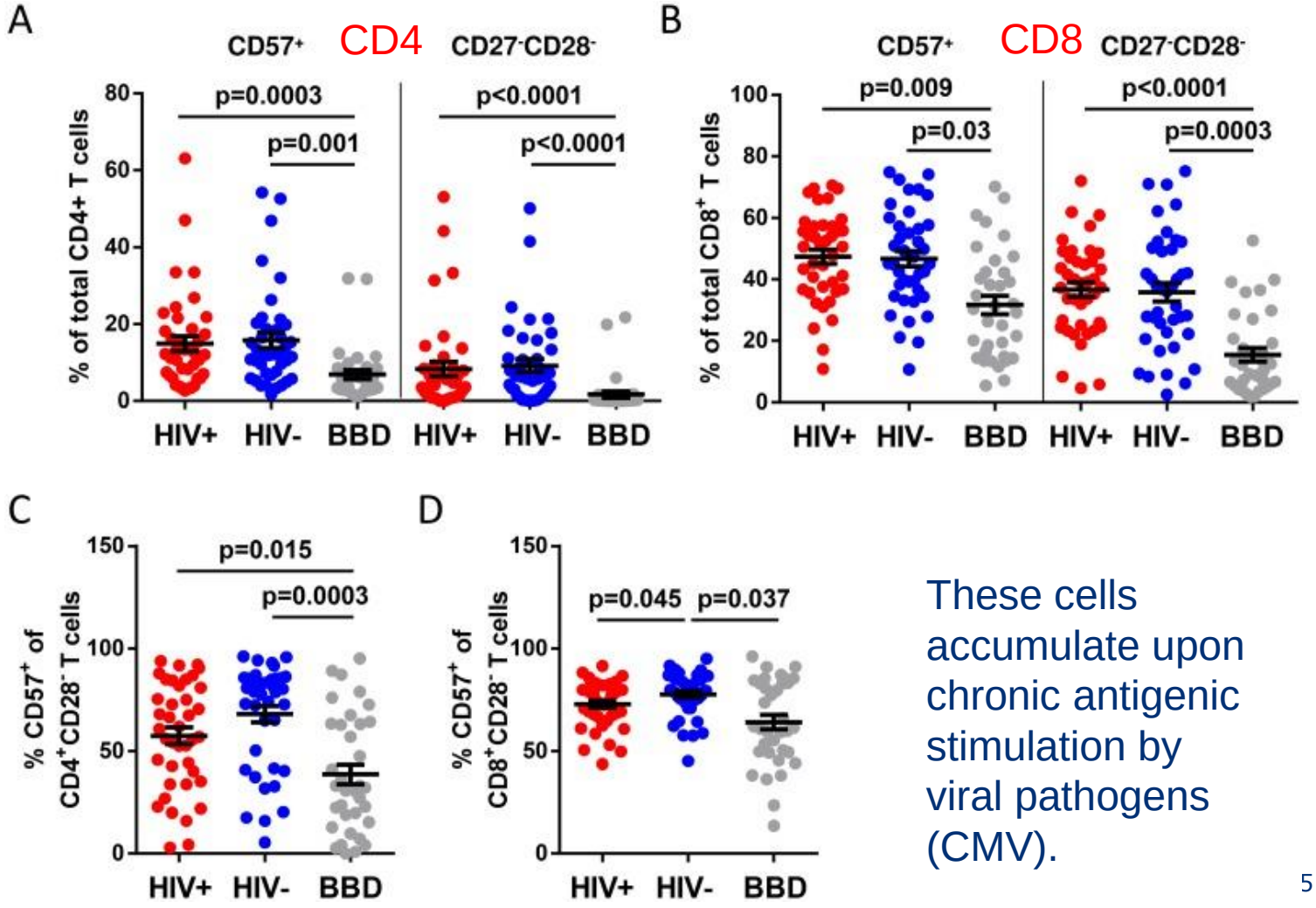
CD4 and CD8 T cell activation and exhaustion



PLoS One. 2017;12(8):e0183357

Immunological studies

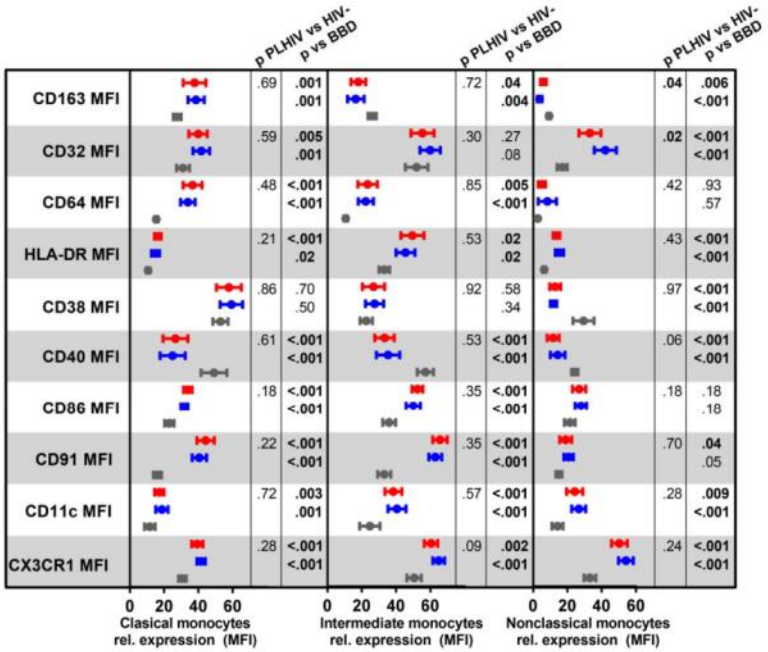
Terminally differentiated CD4 and CD8 T cells

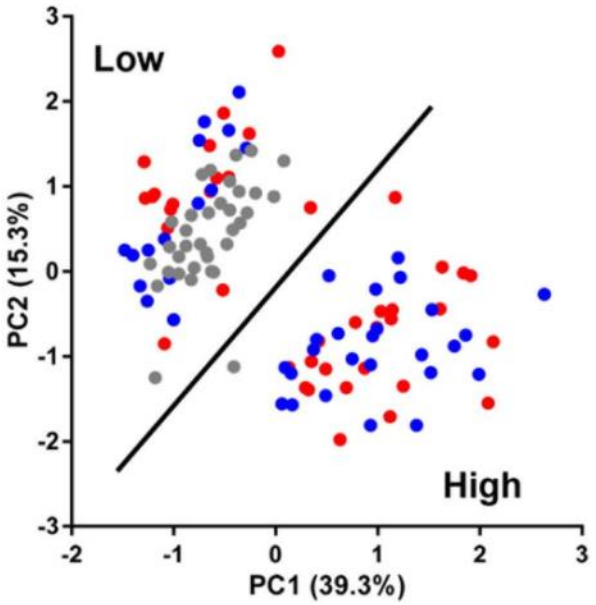


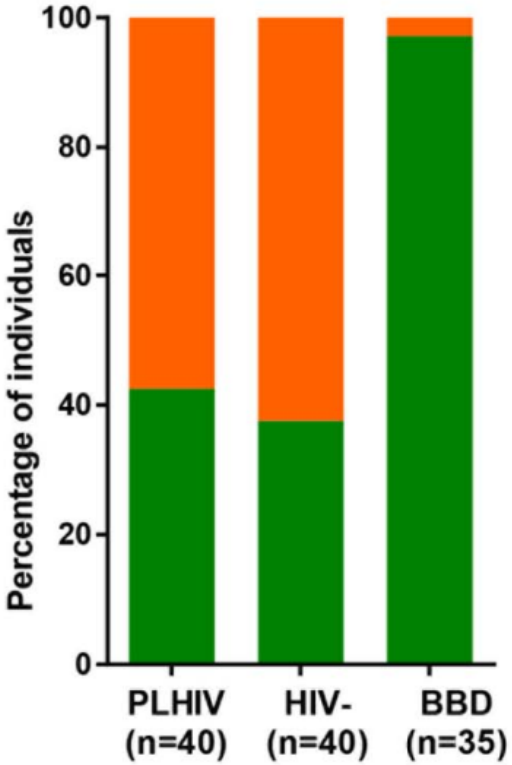
These cells accumulate upon chronic antigenic stimulation by viral pathogens (CMV).

PLoS One. 2017;12(8):e0183357

Immunological studies





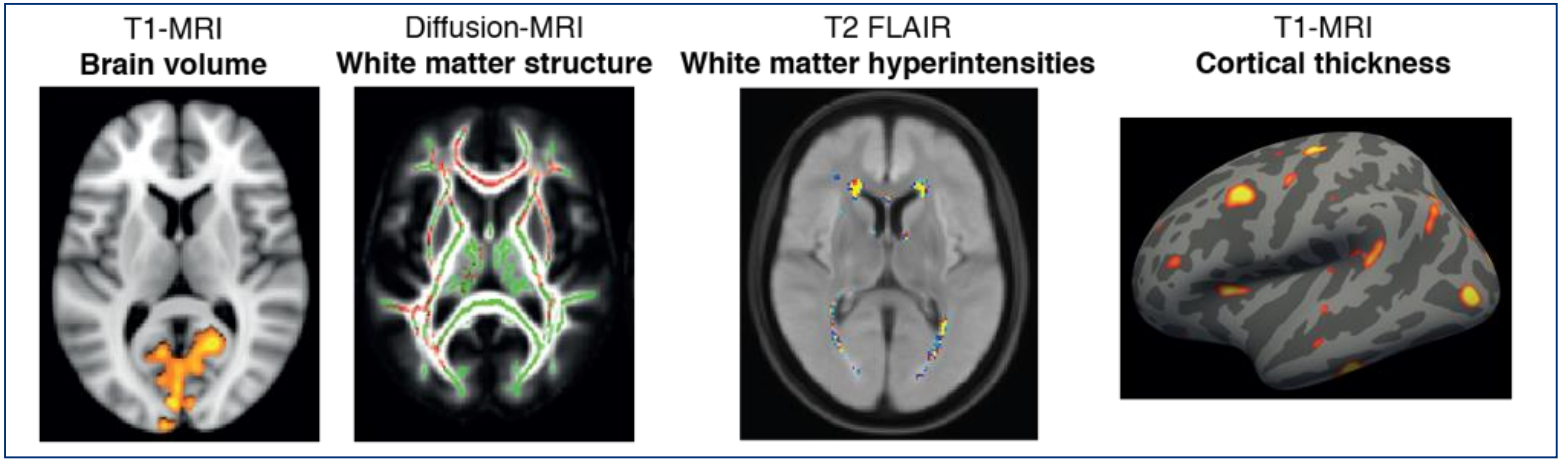


- Expression of CD163, CD32, CD64, HLA-DR, CD38, CD40, CD86, CD91, CD11c, and CX3CR1 on monocytes did not differ between PLHIV and HIV-negatives, but differed significantly from BBD.
- PCA showed 57.5% of PLHIV and 62.5% of HIV-negative had high monocyte activation compared to 2.9% of BBD.

Booijman, Open Forum Infect Dis 2017

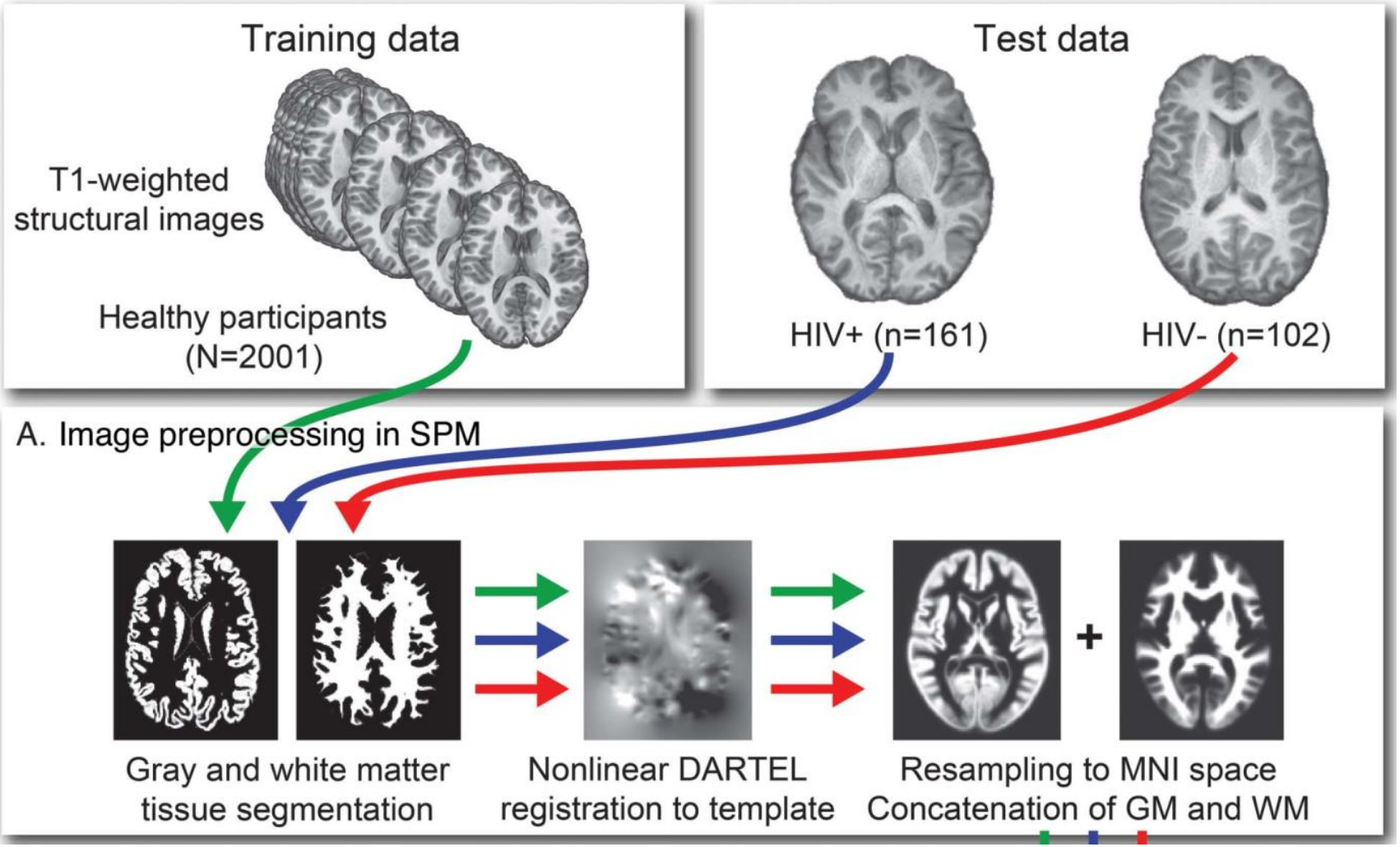
Brain imaging and neuropsychological studies

				OR (95% CI)
GDS	18.0%	vs.	3.8%	5.58 (1.86-24.1)
Frascati	18.0%	vs.	3.8%	5.58 (1.86-24.1)
MNC	19.5%	vs.	2.5%	9.36 (2.68-59.2)



Su T et al. *AIDS* 2016;**30**:311-22.
Su T et al. *AIDS* 2016;**30**:2329-39.
Cole et al. *CROI* 2017; abstract number 352LB.
Underwood J et al. *Clin Infect Dis* 2017;**65**:422-32.

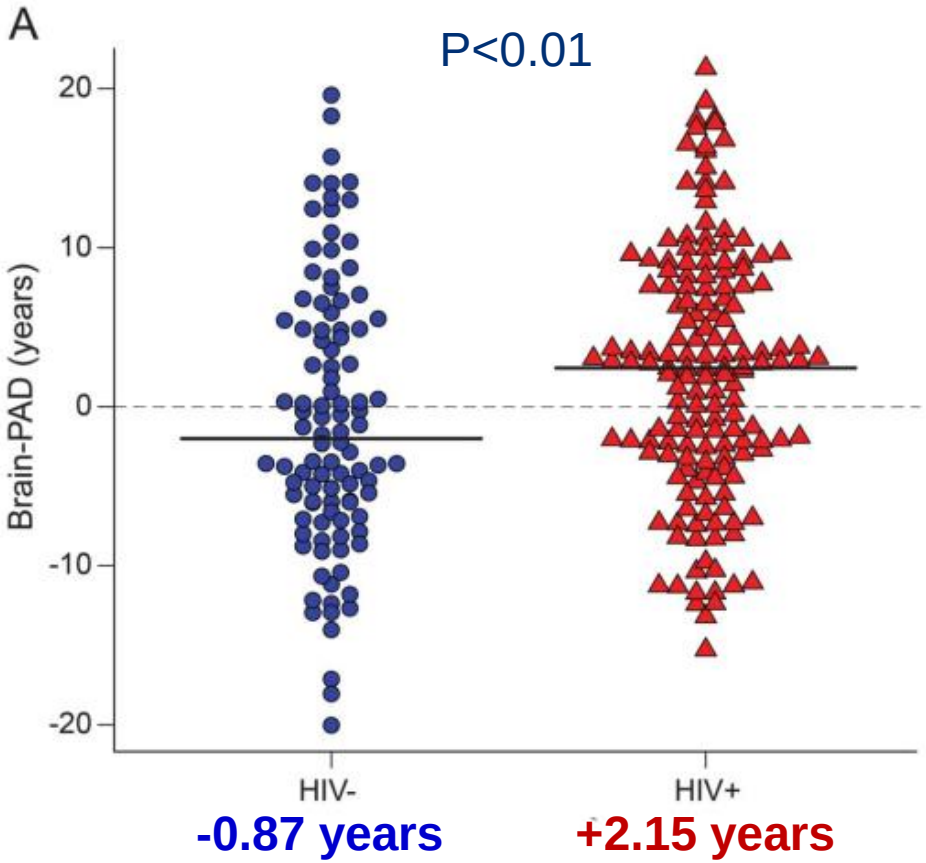
Brain age studies

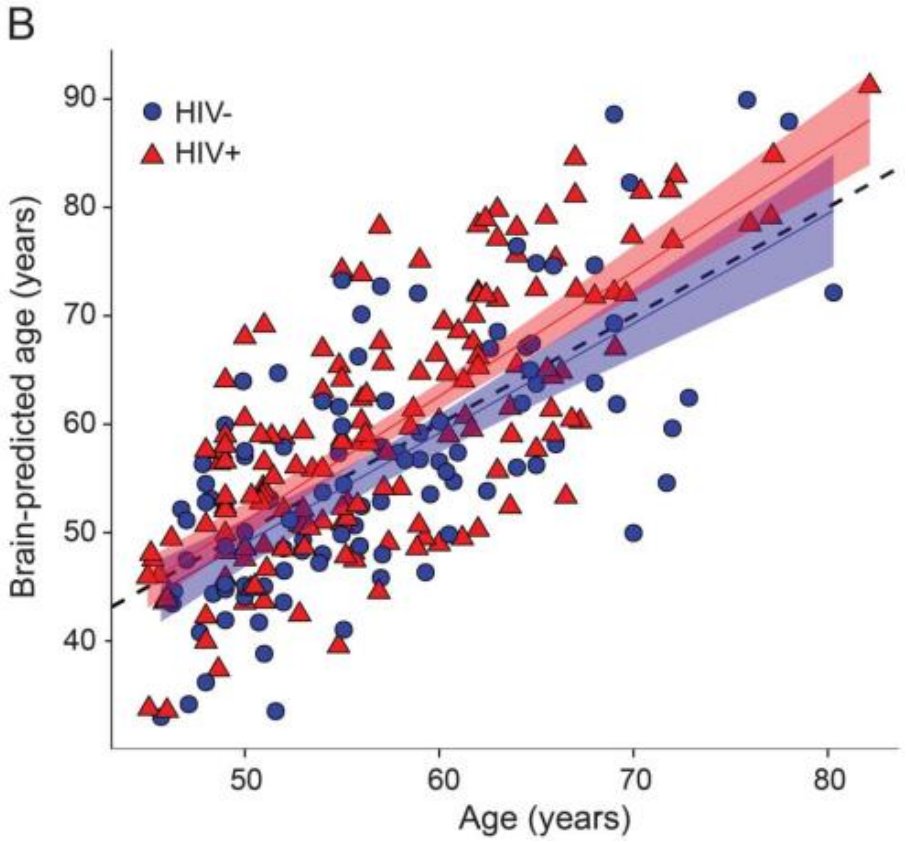


Cole *et al*. Neurology. 2017 Apr 4;88(14):1349-1357

Brain age studies

Predicted brain age vs calendar age





Cole *et al*. Neurology. 2017 Apr 4;88(14):1349-1357

Brain age studies

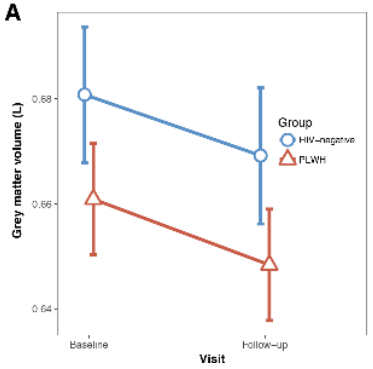
Brain-predicted age difference and neuropsychological assessment

	Main effect of brain-PAD				
Cognitive domain	b	SE	t	*p* Value	η^2 (90% CI)
Processing speed	−0.13	0.06	−2.25	0.03	0.019 (0.0–0.06)
Executive function	−0.15	0.06	−2.48	0.01	0.023 (0.0–0.07)
Language	−0.13	0.07	−1.88	0.06	0.014 (0.0–0.05)
Memory	−0.20	0.06	−3.32	<0.01	0.041 (0.01–0.08)
Attention	−0.14	0.08	−1.71	0.09	0.011 (0.0–0.04)
Motor function	−0.11	0.06	−1.73	0.09	0.012 (0.0–0.05)
Global cognition	−0.14	0.04	−3.33	<0.01	0.040 (0.01–0.09)

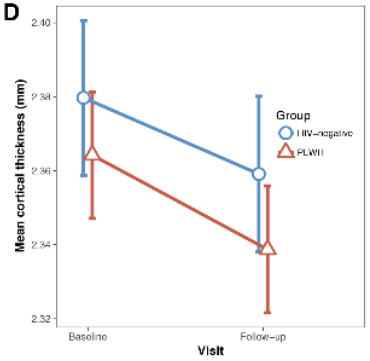
Cole *et al*. Neurology. 2017 Apr 4;88(14):1349-1357

Longitudinal brain imaging and brain age studies

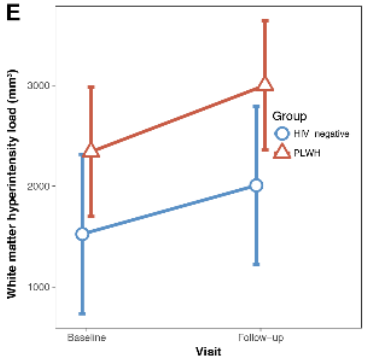
Brain Imaging Measures



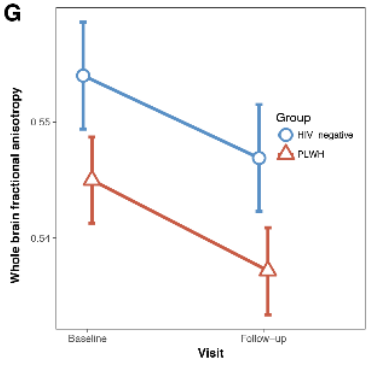
Grey matter volume



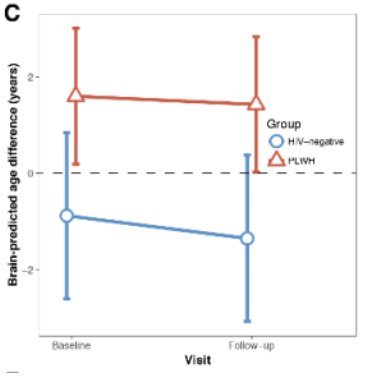
Mean cortical thickness



White matter hyperintensity load

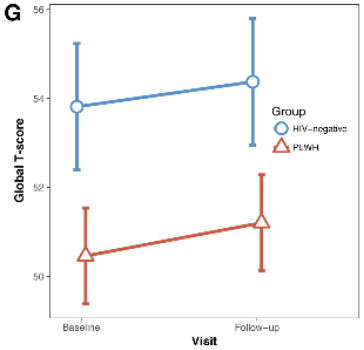


Fractional anisotropy



Brain predicted age difference

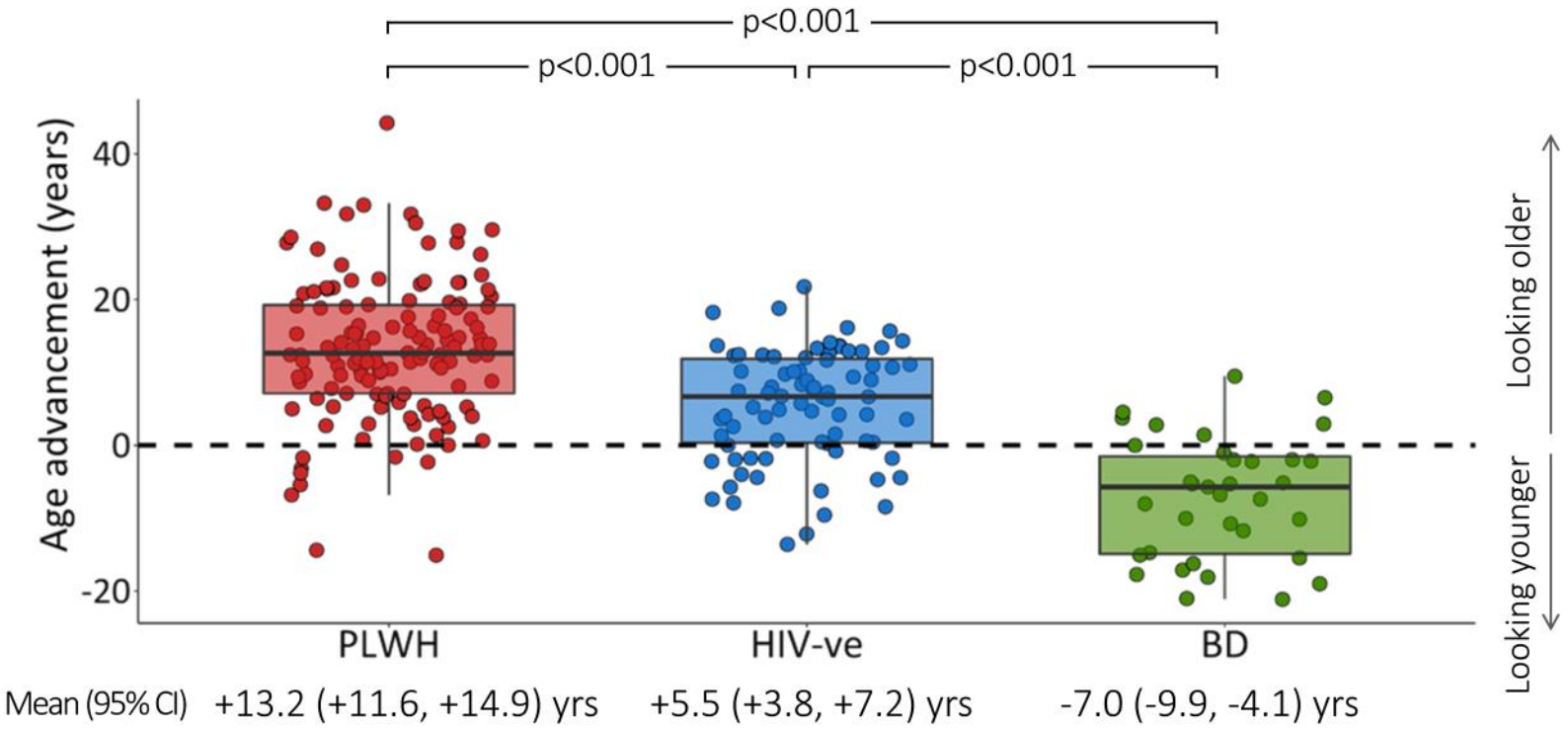
Neuropsychological assessment



Global T-score

Cole et al. *CROI* 2017; abstract number 352LB.

Accelerated ageing studies



De Francesco, et al. Poster TULBPEB19, IAS 2017

Accelerated ageing studies

Variable	rho	Regression parameter	*p*-value
HIV-duration (years)	0.18	0.26 (0.01, 0.51)	0.04
ART duration (years)	0.17	0.29 (0.01, 0.57)	0.05
Peak VL (per 1000 copies/mL)	-0.01	0.0001 (-0.002, 0.002)	0.90
$CD4^+$ T cell count (per 100 cells/µL)	-0.09	-0.39 (-1.16, 0.39)	0.33
Nadir $CD4^+$ T cell count (per 100 cells/µL)	-0.10	-0.69 (-1.84, 0.46)	0.24
$CD4^+$:$CD8^+$ ratio	-0.14	-2.78 (-6.11, 0.55)	0.10
Time with $CD4^+$ < 500 cells/µL (years)	0.11	0.21 (-0.13, 0.56)	0.22
Time with $CD4^+$ < 350 cells/µL (years)	0.15	0.43 (-0.05, 0.91)	0.08
Time with $CD4^+$ < 200 cells/µL (years)	0.18	0.87 (0.06, 1.69)	0.04

Variable		N	Difference (95% CI)	*p*-value
Prior AIDS	Yes vs No	42/92	1.59 (-1.98, 5.15)	0.38
MSM	MSM vs Non-MSM	114/20	0.48 (-2.84, 3.80)	0.77
$CD4^+$:$CD8^+$ ratio	< 1 vs ≥ 1	89/45	2.78 (-0.70, 6.26)	0.12
Chronic Hep B	Yes vs No	7/124	9.12 (1.82, 16.41)	0.01
Hepatitis C	Yes vs No	14/120	3.32 (-2.07, 8.72)	0.22
Route of transmission				0.80

De Francesco, et al. Poster TULBPEB19, IAS 2017

Conclusions -1-

- Burden of various non-AIDS co-morbidities is consistently increased in (well-treated) HIV, especially in elderly patients
- Independent associations with HIV are observed for most but not all co-morbidities
- Traditional risk factors play an important role: both as confounders and mediators of the "HIV effect"
- Longer time spent at low CD4 counts, rather than longer exposure to ART or duration of HIV infection, generally contributes most to greater co-morbidity risk
- The harmful effects of old-fashioned ART are still visible

Conclusions -2-

- Persistent inflammation and innate immune activation generally seem to additionally contribute towards risk
  - HIV, HBV, HCV, CMV, STIs
  - Inflammation & immune activation play an important role too in HIV-negative controls with similar lifestyle
- Pathogenic pathways involving effects on the biology of aging appear to be negatively affected in PLHIV, as well as (but to a lesser extent than) appropriate controls, but these findings needs further exploration
- Having an appropriate control group makes interpretation of findings in observational cohorts more robust
- Patients are still relatively young – what does the future hold in store for them?

Accelerated ageing?

- PLHIV have increased biological age based on MARK-AGE biomarker set
  - … but so did the HIV-negative controls …
  - … and there were similar rates of change in biological age in PLHIV on cART and HIV-negative controls
- Biological age and immune senescence was strongly associated with chronic viral infections, e.g. (treated) HIV
  - … but also with CMV and viral hepatitis
- Increased biological age and immune senescence need to be confirmed as risk factors for non-aids co-morbidities and mortality in prospective studies
- Many of the ageing markers are measured in immune cells, which is a compartment that is heavily affected in HIV infection
  - are changes in this compartment reflective of changes in the whole body?

Recommendations for resilient ageing

- Multimorbidity and polypharmacy are becoming more important → "geriatric-type" multidisciplinary management
- Most important interventions:
  - Optimization of ARV: toxicities, interactions
  - Screening and prompt treatment of (risk factors for) comorbidities
  - Smoking cessation and other lifestyle interventions
- Prevention and treatment of comorbidities in general the same as for general population
  - PLHIV are at increased risk because of high prevalence of risk factors and unique contribution of HIV- and ART-related factors
  - Management should be pro-active and more aggressive
- Watch out for drug-drug interactions between ARVs and co-medications, especially in the elderly and polypharmacy

CVD prevention modelling ATHENA

The impact of 4 interventions on future CVD burden was evaluated

Increasing the rate of earlier HIV diagnosis and treatment

Avoiding the use of cART regimens with increased CVD risk * (abacavir and protease inhibitors)

Achieving an increased rate of smoking cessation *

Intensified monitoring and drug treatment of hyper-tension and dyslipidaemia *

Achieving 50% vs 100% successful implementation

50% successful  100% successful

Reaching all patients in care or moderate to high risk patients only *

(predicted 5-year CVD risk ≥5%)

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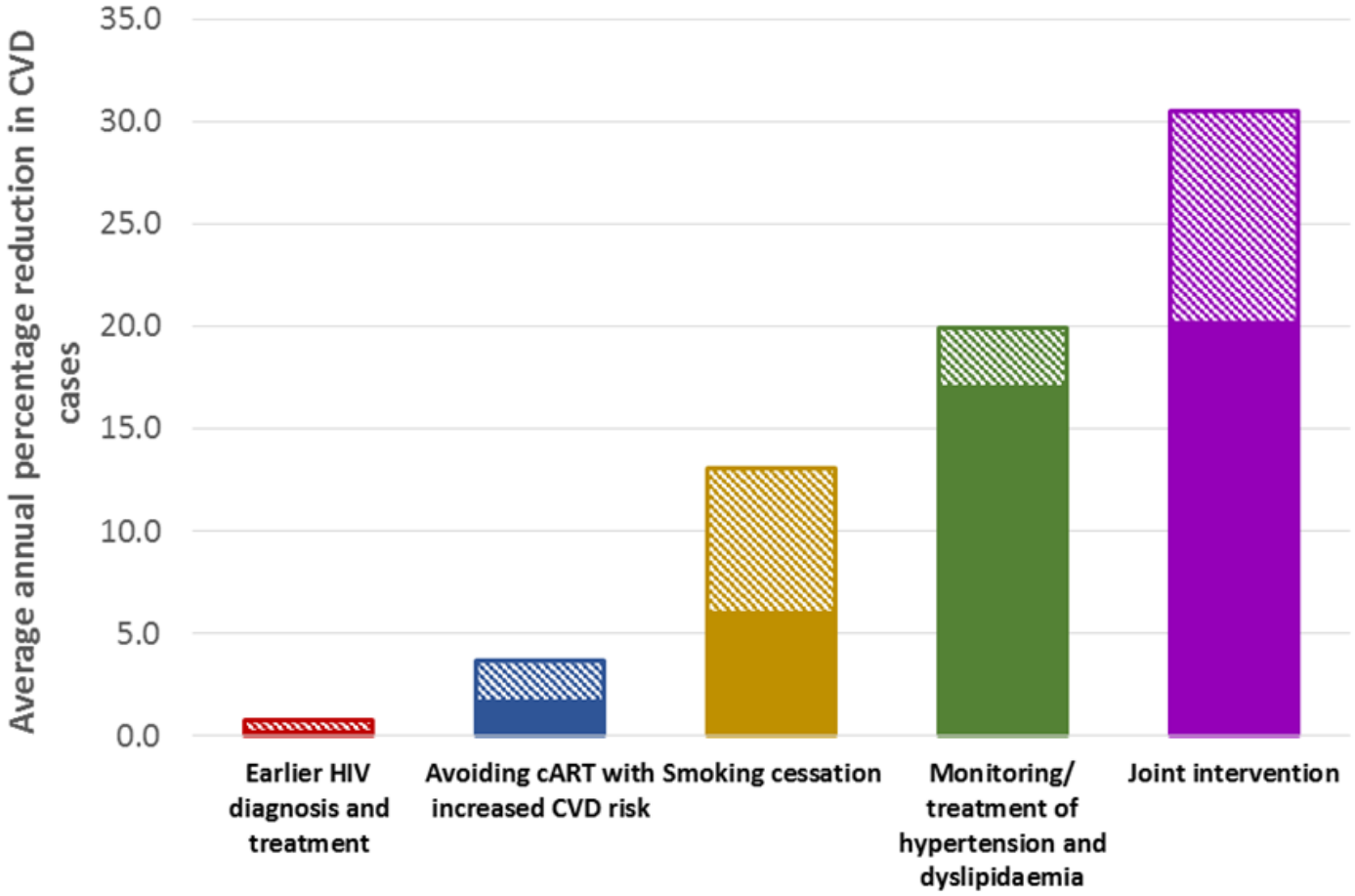
Smit *et al*. Clin Infect Dis. 2017 Oct 6

CVD prevention modelling ATHENA

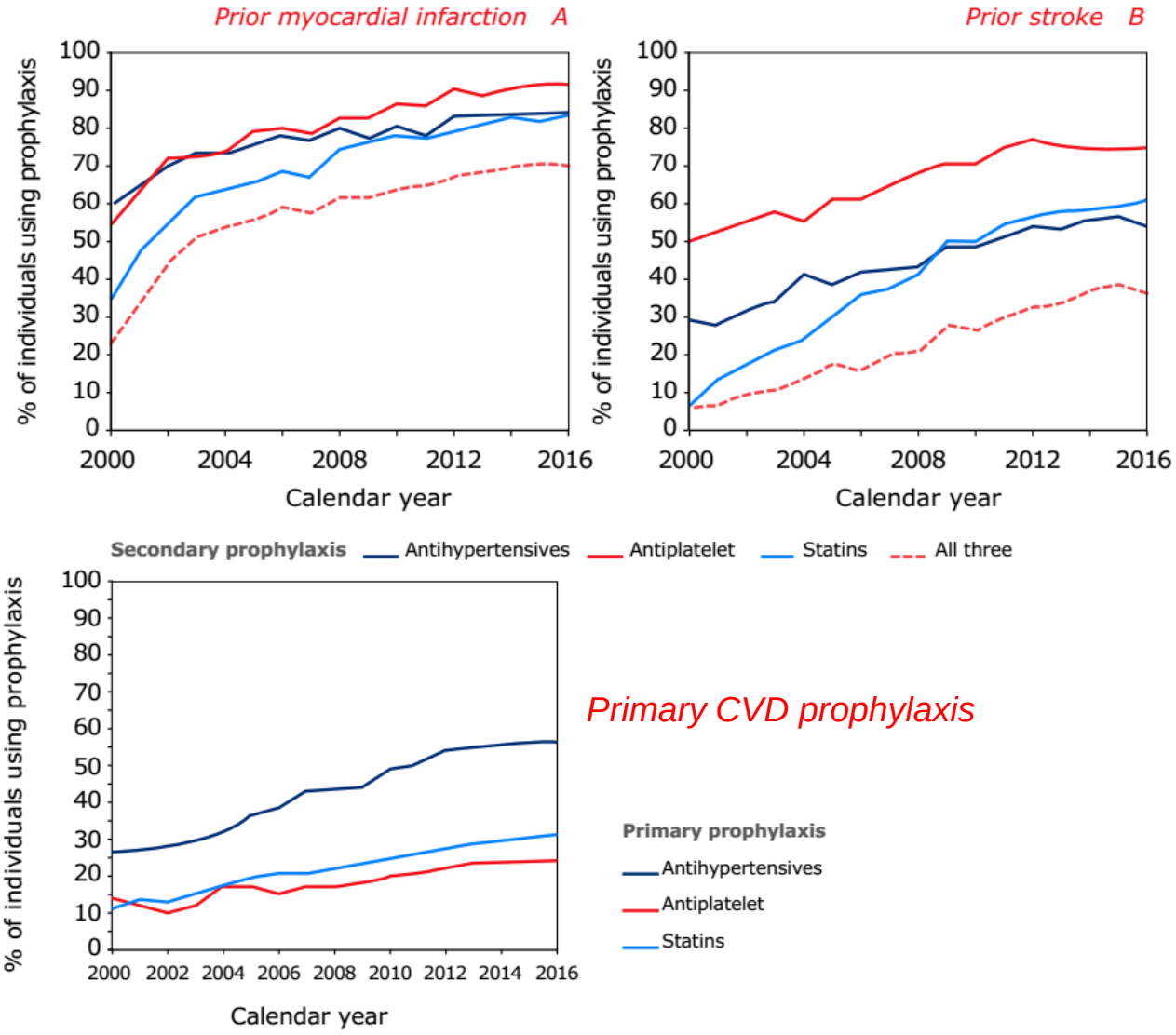
Average annual percentage of averted CVD cases



Solid areas represent percentage averted assuming 50% successful implementation and the striped area for 100% successful implementation

Smit *et al*. Clin Infect Dis. 2017 Oct 6

CVD prevention in ATHENA



AGEhIV Cohort Study Group

Scientific oversight and coordination

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Datamanagement

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Bristol Myers Squibb
Merck & Co

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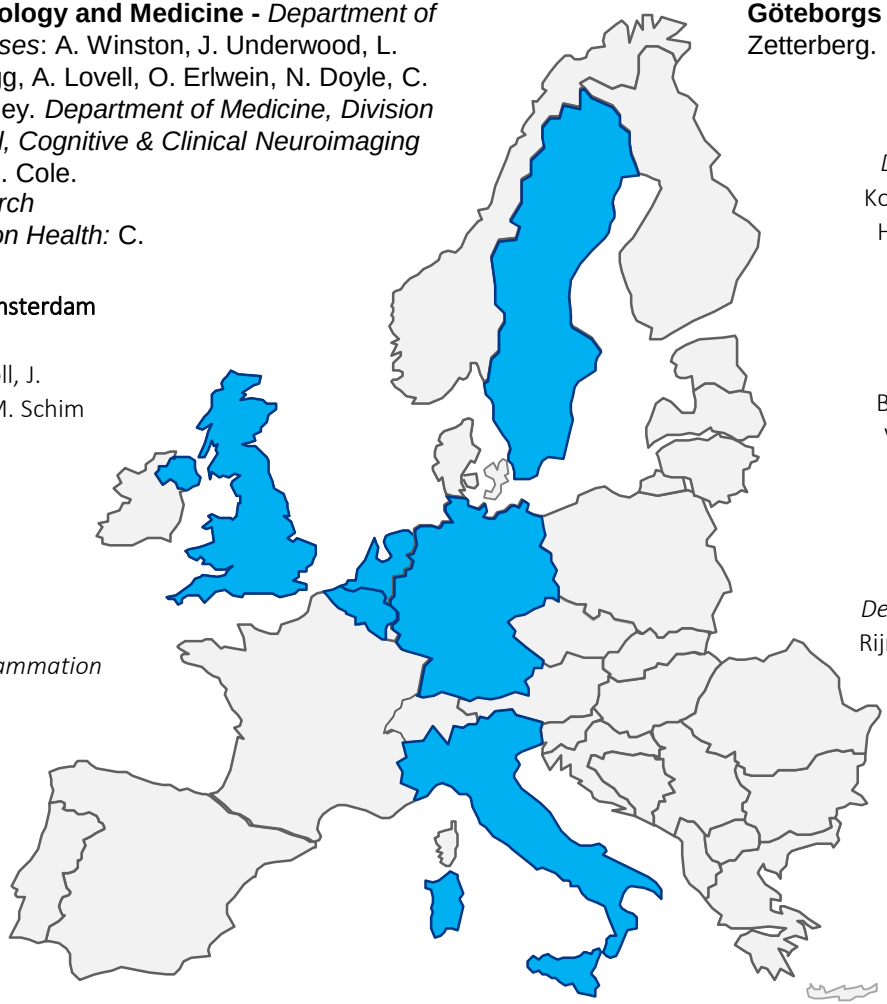

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