Looking Beyond HIV: The Factors to Consider with an Ageing Population

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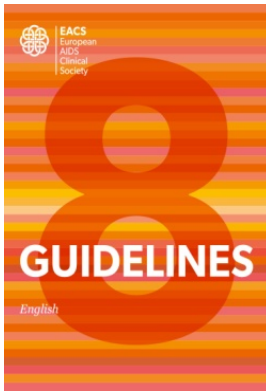
Lene Ryom
MD PhD
Assistant EACS Guidelines Coordinator
CHIP, Rigshospitalet, Department of Infectious Diseases, University of Copenhagen, Denmark



Outline

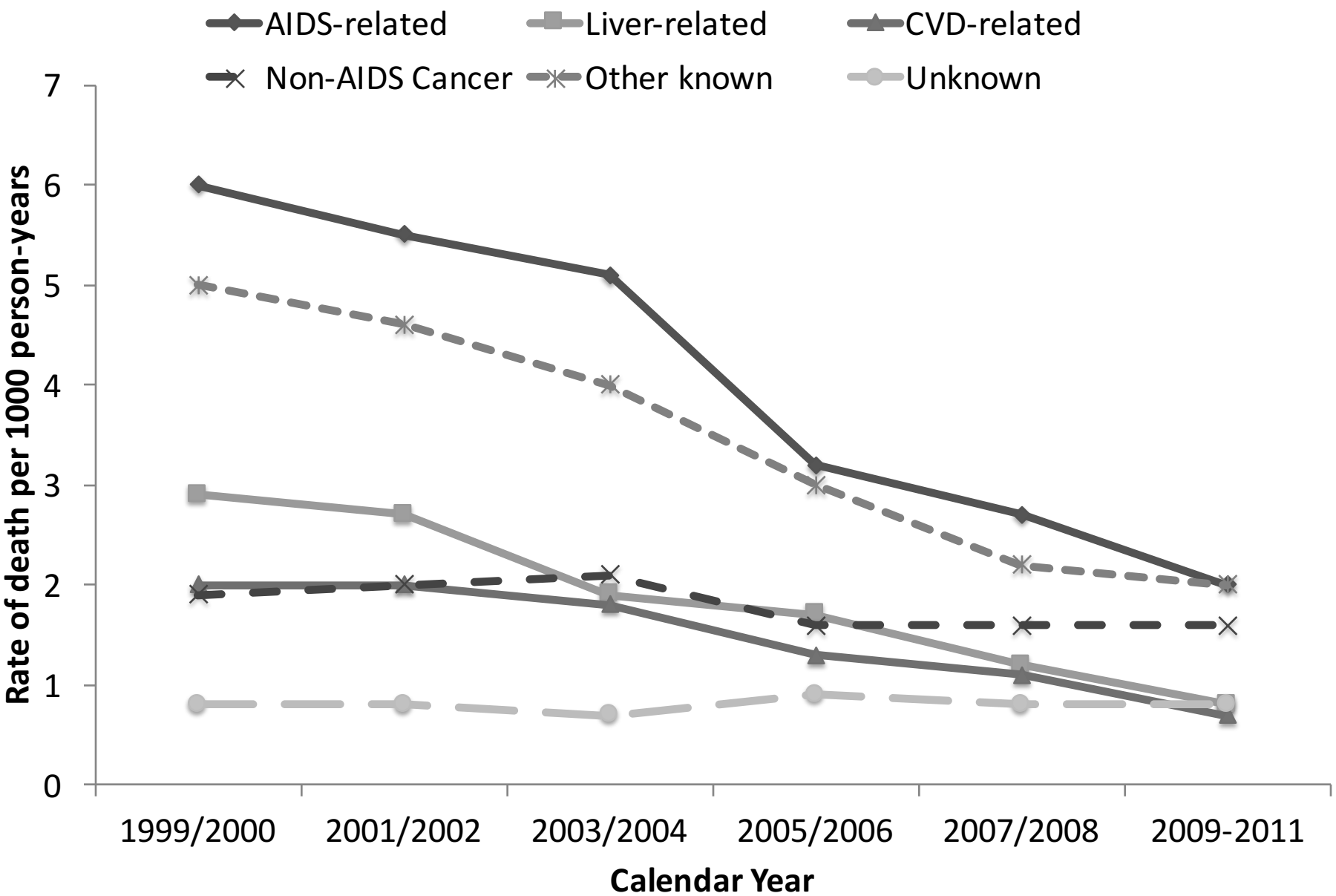
- Survival rates and age-distibution of the HIV-positive population

- How frequent are comorbidities in HIV-positive persons?
- Which specific comorbities?
- What potential mechanisms?

- Impact of ART and other drugs on comorbidities
  - Adverse drug effects
  - Polypharmacy
  - Drug-drug interactions

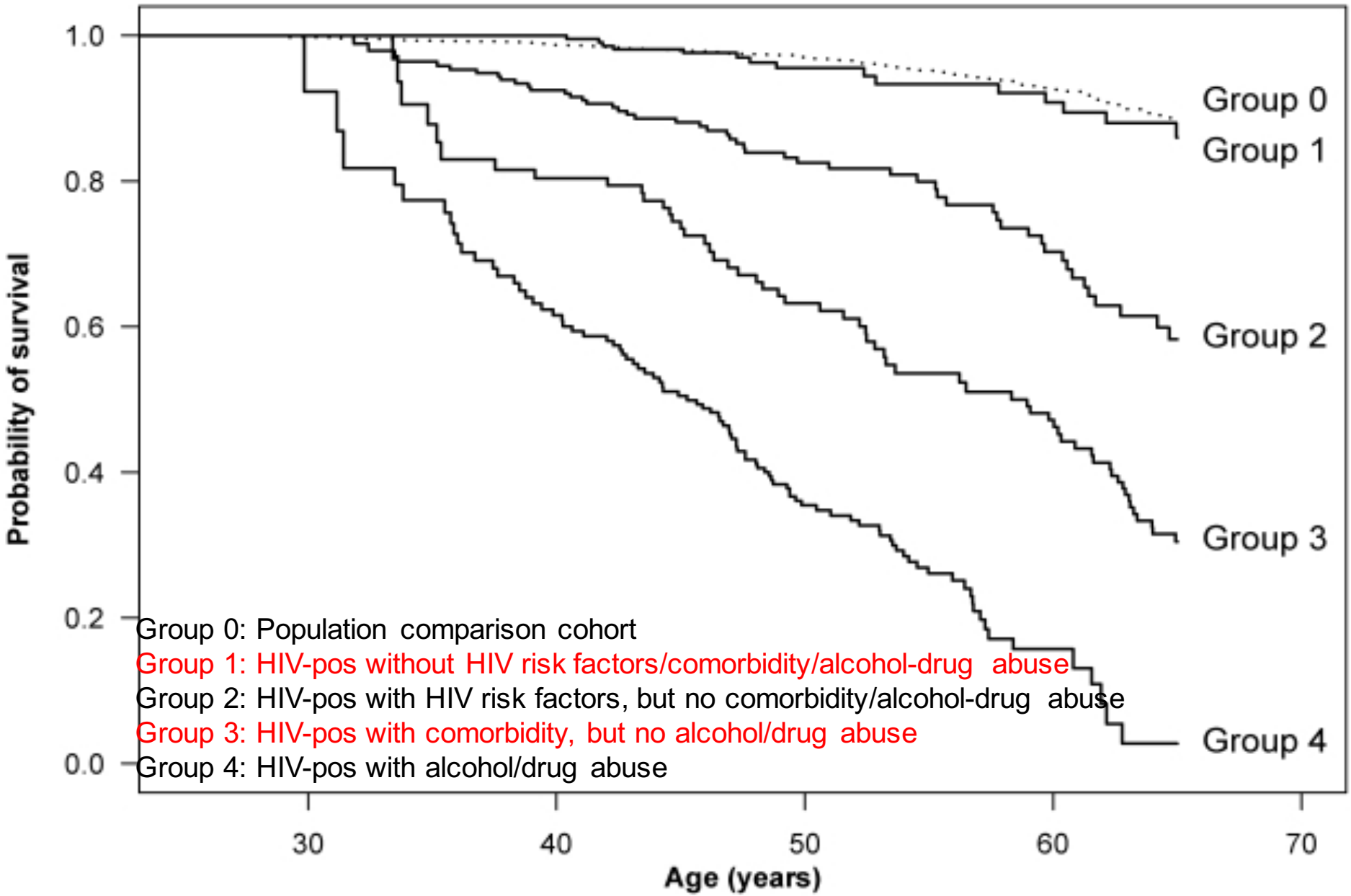
- What to do?
  - EACS guidelines/multidiciplinary approach
  - Impact of specific interventions

Time Trends of Mortality Rates in HIV-positive Persons



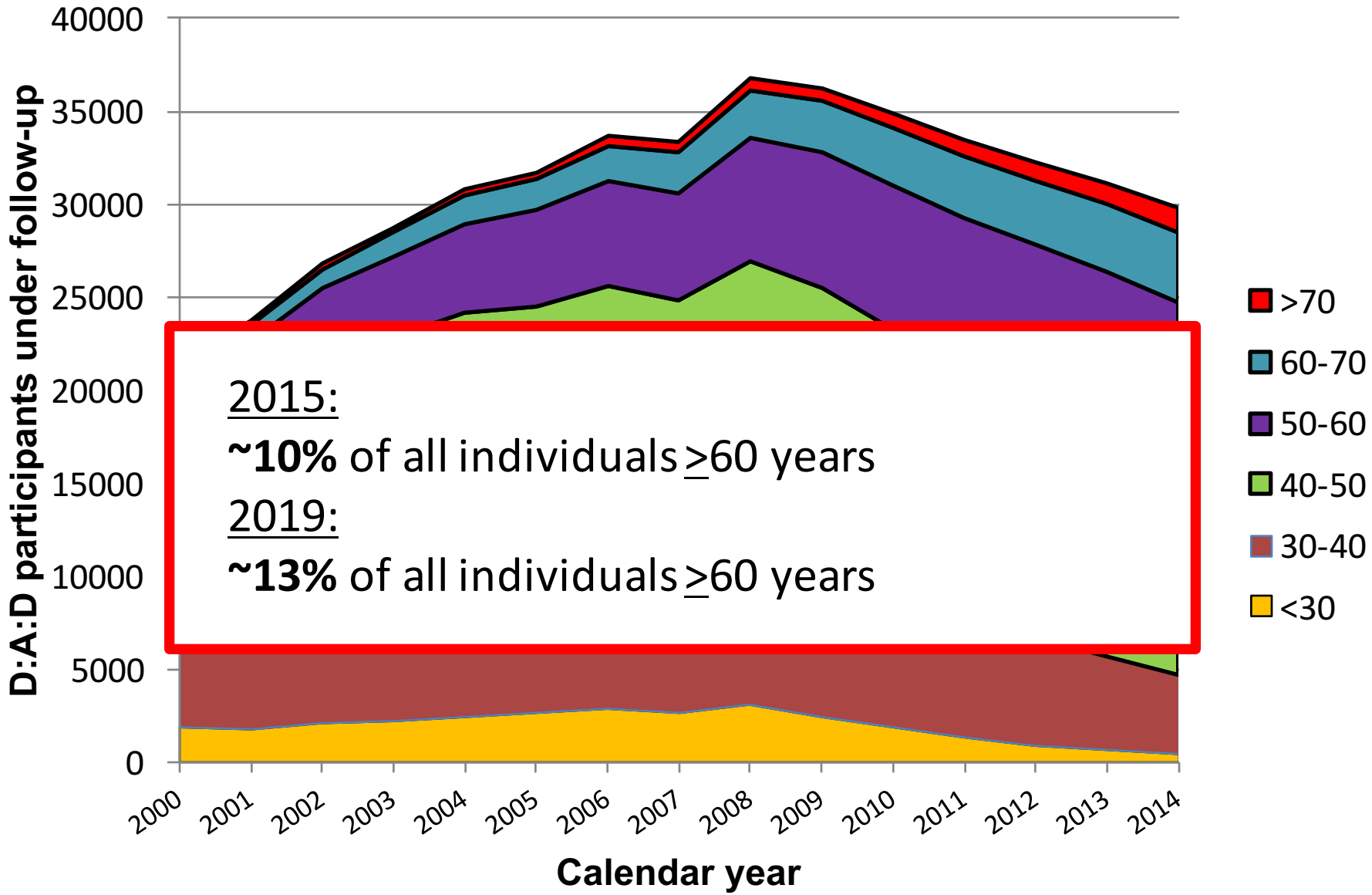
Smith C. et al. for D:A:D, Lancet 2014, Jul 19;384(9939):241-8.

Survival Rates in HIV-Positive vs. Negative Persons



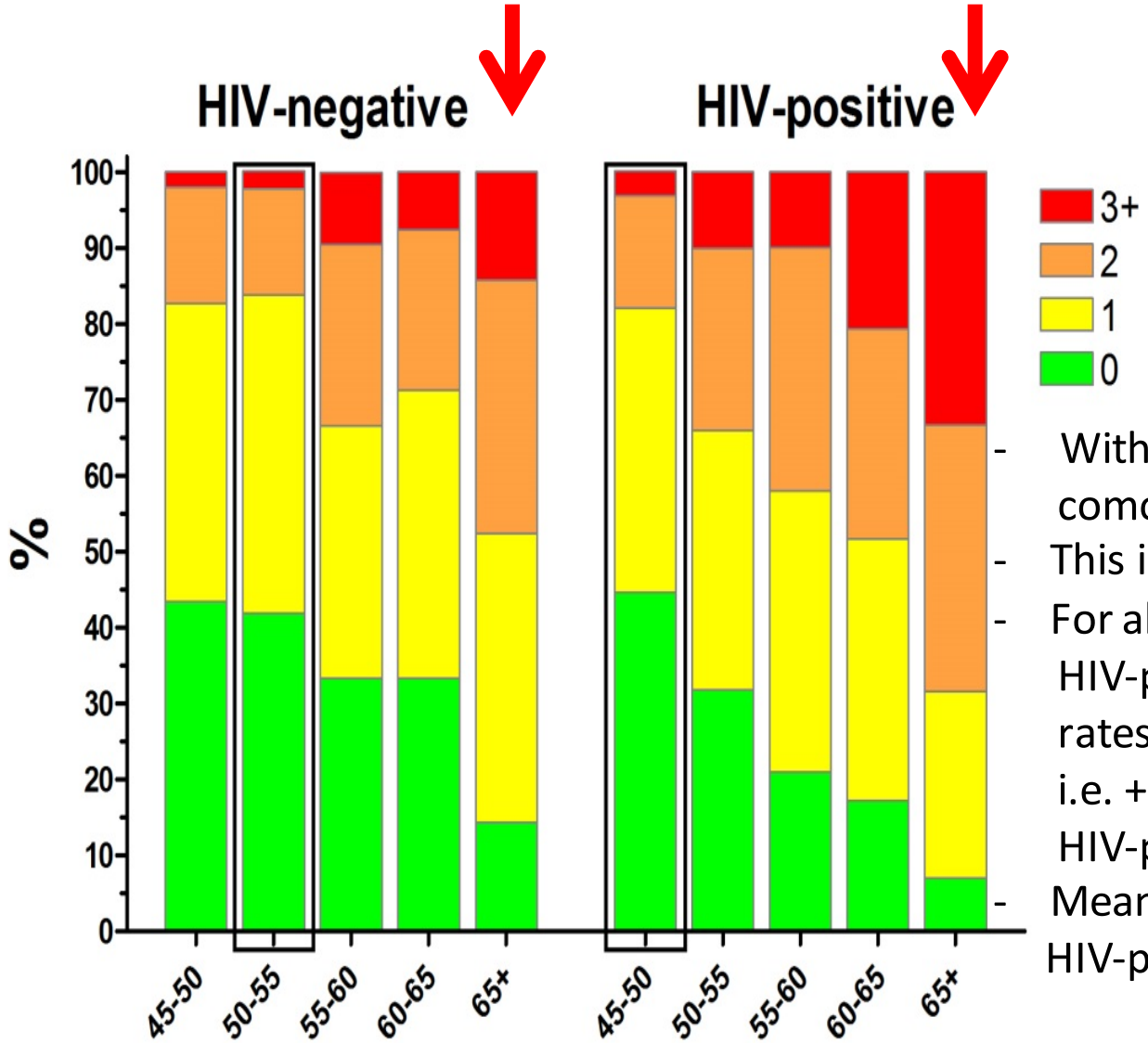
Obel N. et al. for the Danish HIV Cohort, Plos One 2011

Age Distribution of D:A:D Study Participants



D:A:D Merger 16 dataset, unpublished data

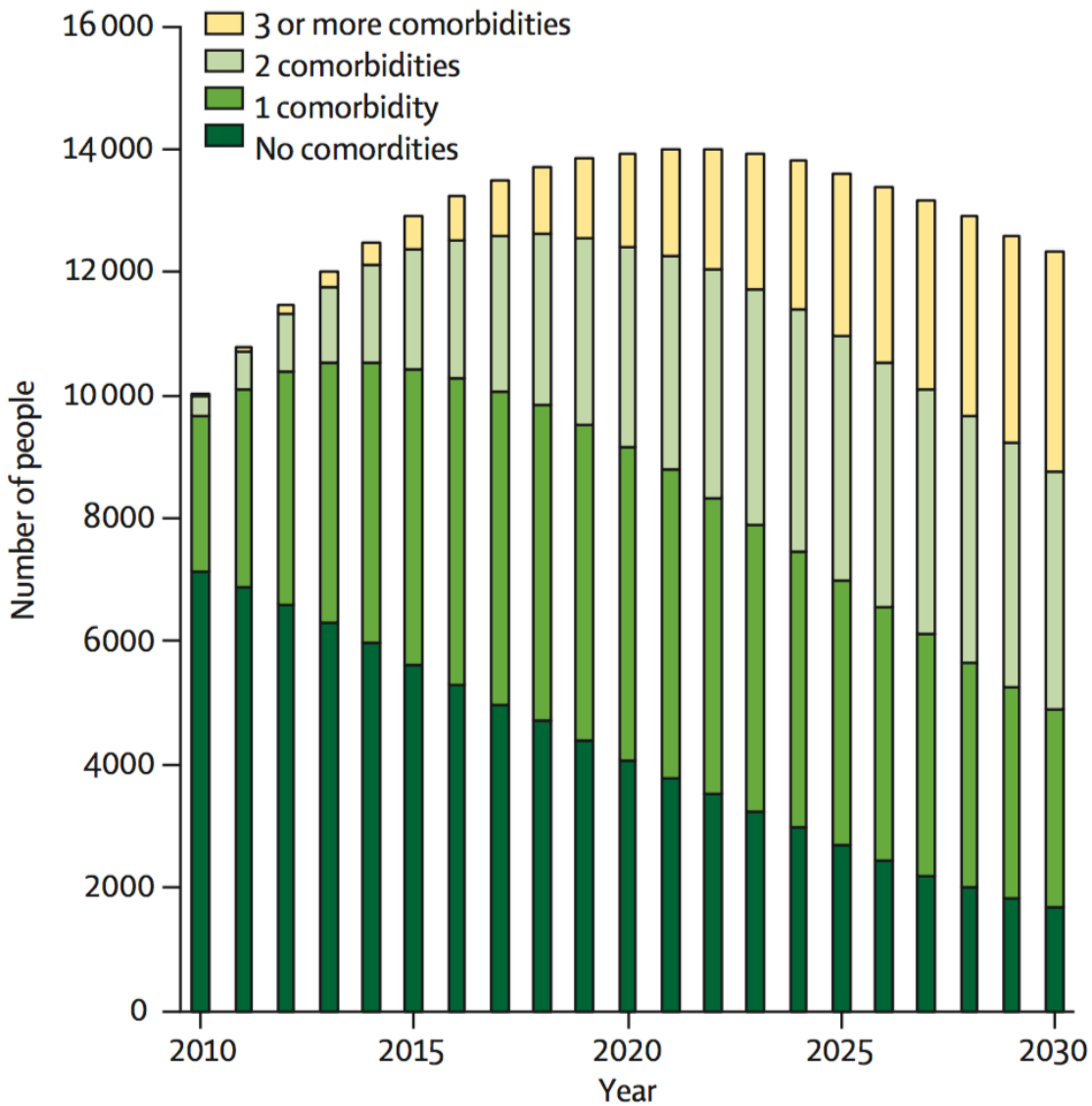
Comorbidities and Ageing



- With increasing age the number of comorbidities also increase
- This is not specific for HIV-pos pers.
- For all age-groups >45 years HIV-pos pers. have higher comorbidity rates compared to HIV-neg i.e. +65yrs: >30% +3 comorbidities HIV-pos vs. 15% in HIV-neg pers.
- Mean number of comorbidities: HIV-pos 1.3 vs. HIV-neg 1.0 pers.

Schouten J. et al. for Age HIV, Clin Infect Dis 2014;**59**:1787-97.

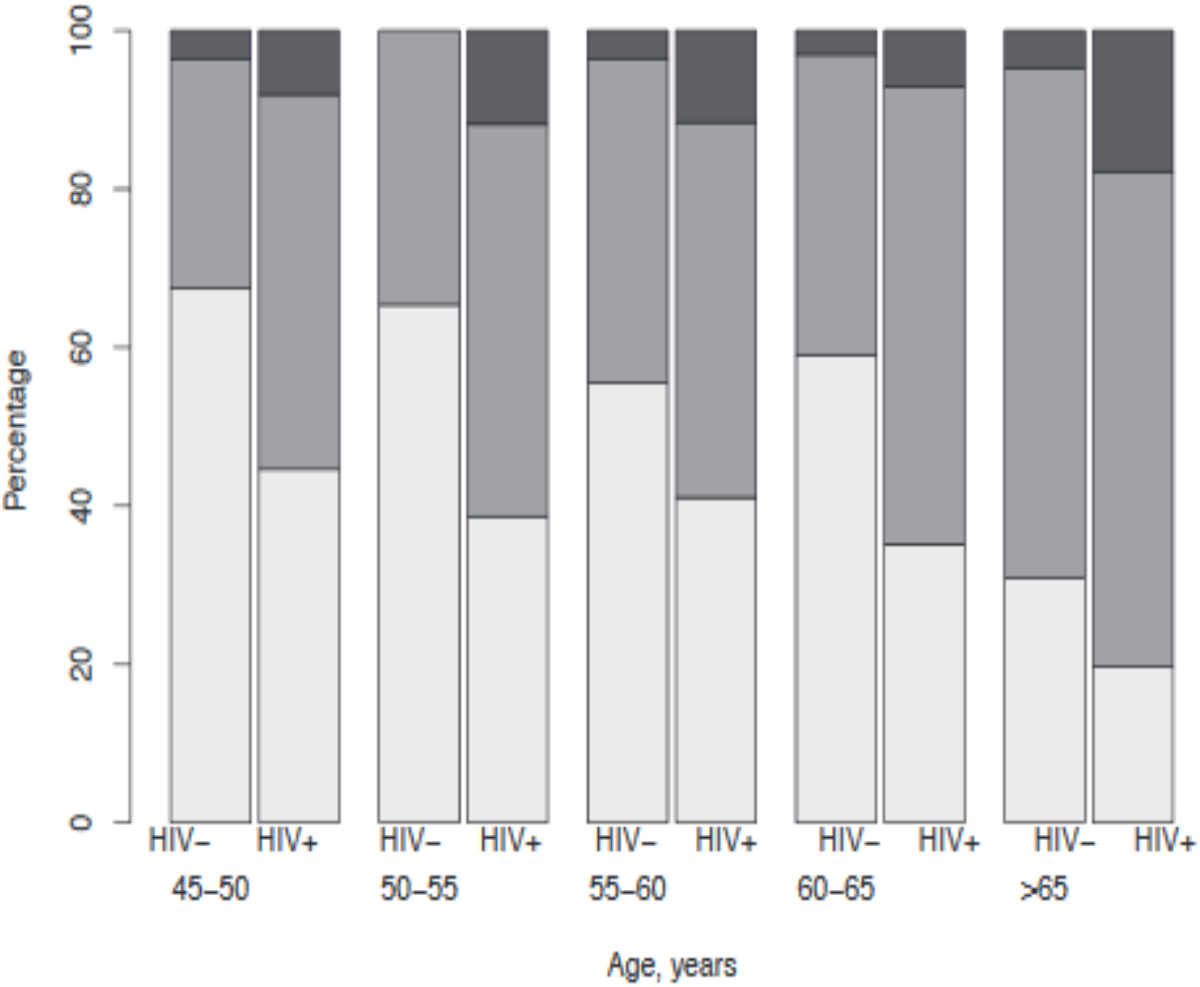
Future Projected Comorbidity Rates



	2010	2030
≥1 comorbidity	29%	84%
≥3 comorbidities	0.3%	28%

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

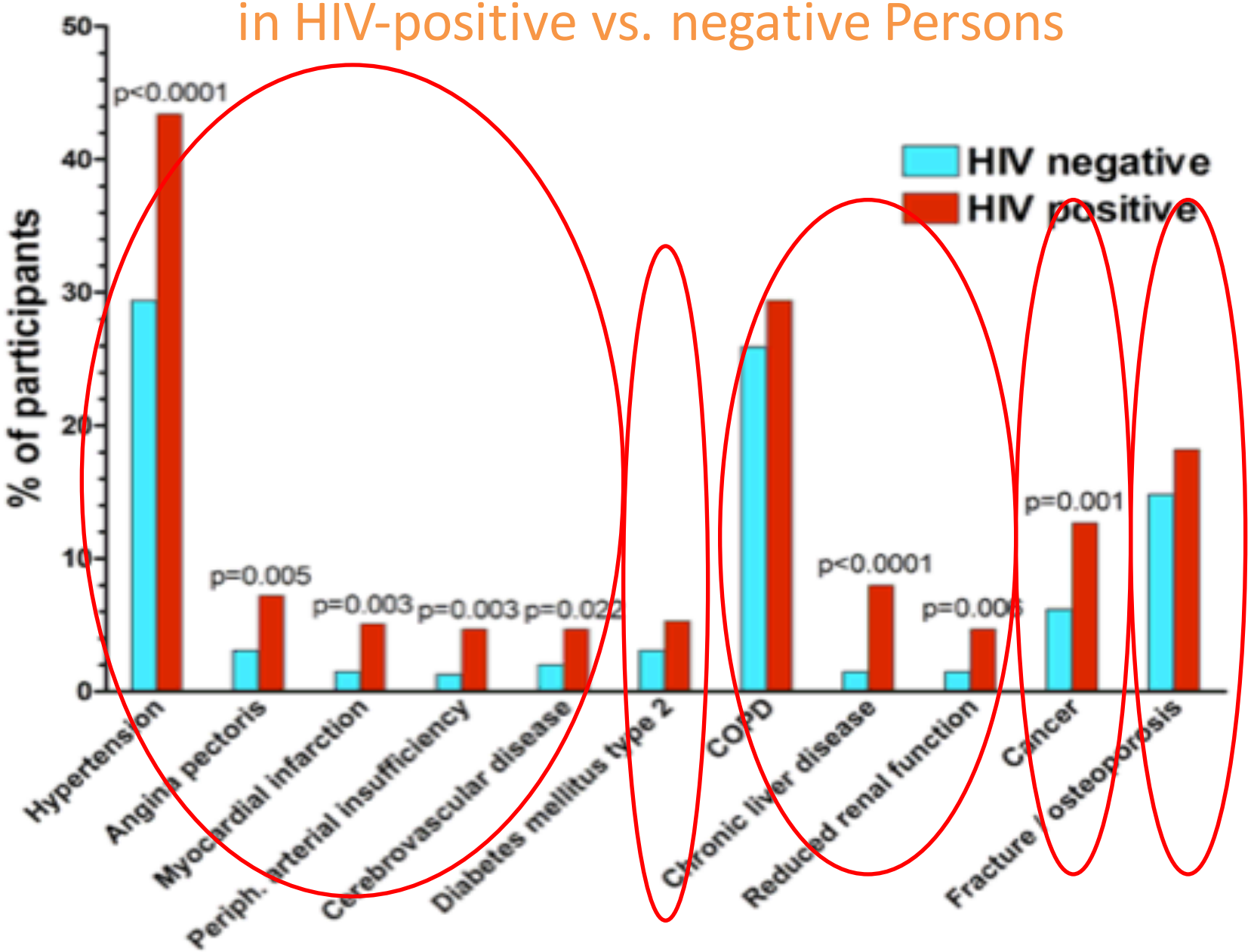
Frailty by Age in HIV-positive and Negative Persons



- Increased multisystem vulnerability with inability to cope with everyday /acute stressors
- low grip strength
- low energy
- slowed waking speed
- low physical activity
- unintentional weight loss
- HIV-pos pers. are at higher frailty (10.6 vs. 2.7%) and pre-frailty risk (50.7 vs. 36.3%) than HIV-negative pers. ($p < 0.001$) for all age groups >45 years

Kooij K. for Age HIV, AIDS 2016 Jan;30(2):241-50

Distribution of Comorbidities in HIV-positive vs. negative Persons



Schouten J et al. for Age HIV, IAS 2012

Depression

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 treatment outcomes associated with depression

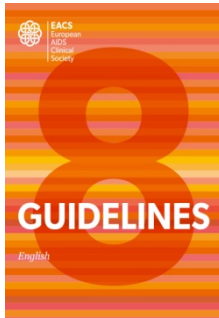
Screening and diagnosis		
Who?	**How to screen?**	**How to diagnose?**
Screening of all HIV-positive persons recommended in view of the high prevalence of depression **Populations at particular high risk** • Positive history of depression in family • Depressive episode in personal history • Older age • 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 64	• Screen every 1-2 years • Two main questions: 1. Have you often felt sad or without hope i months? 2. Have you lost inter ties that you usually e • Specific symptoms in – Stressed, burn out outbursts, coping t or alcohol • Rule out organic caus hypothyroidism, hypo Addison's disease, n vitamin B12 deficienc	Symptoms – evaluate regularly

Screening and diagnosis

Who?

Screening of all HIV-positive persons recommended in view of the high prevalence of depression

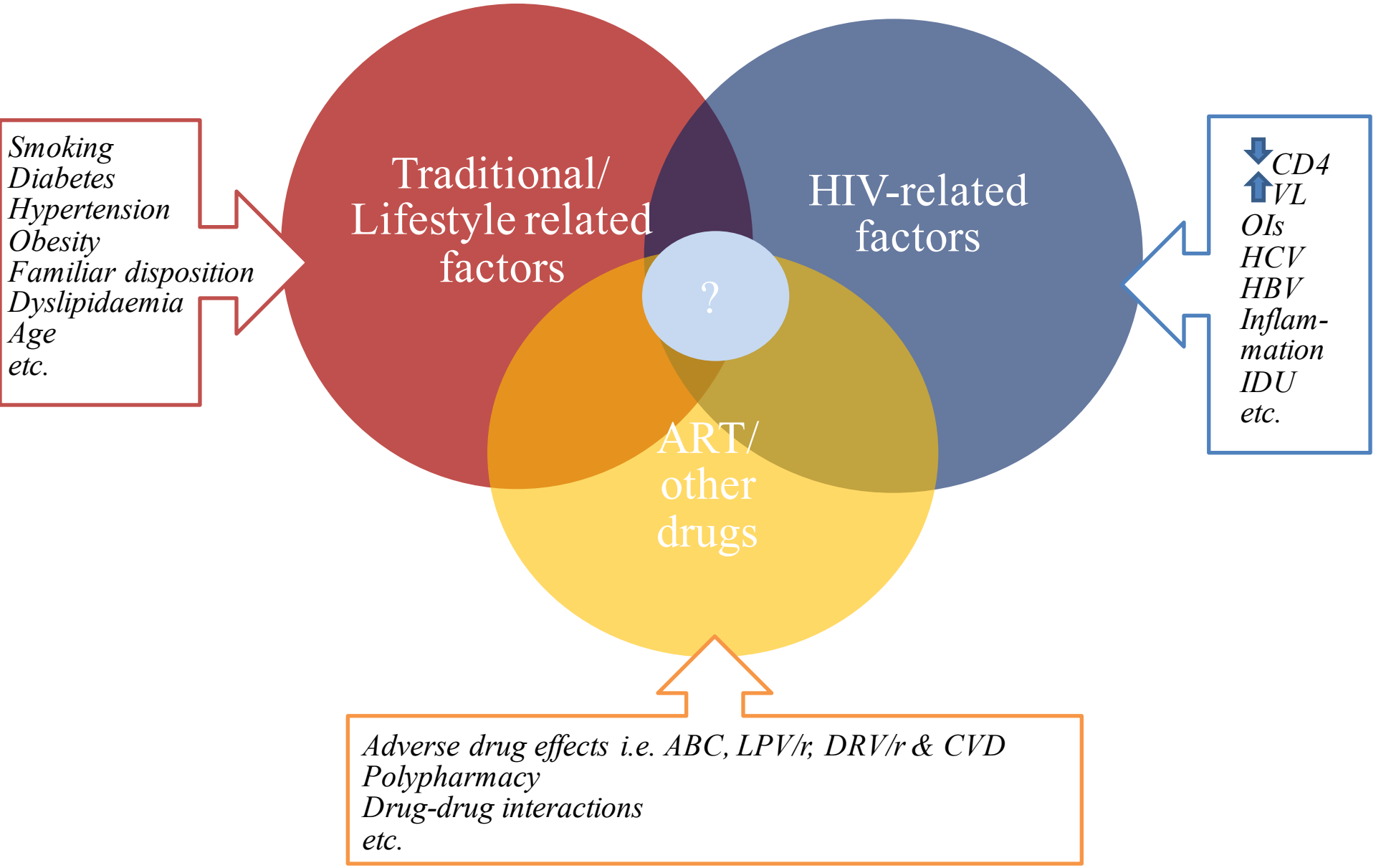
i EFV has been associated with a higher risk of suicidal ideation



Disease Clusters in HIV

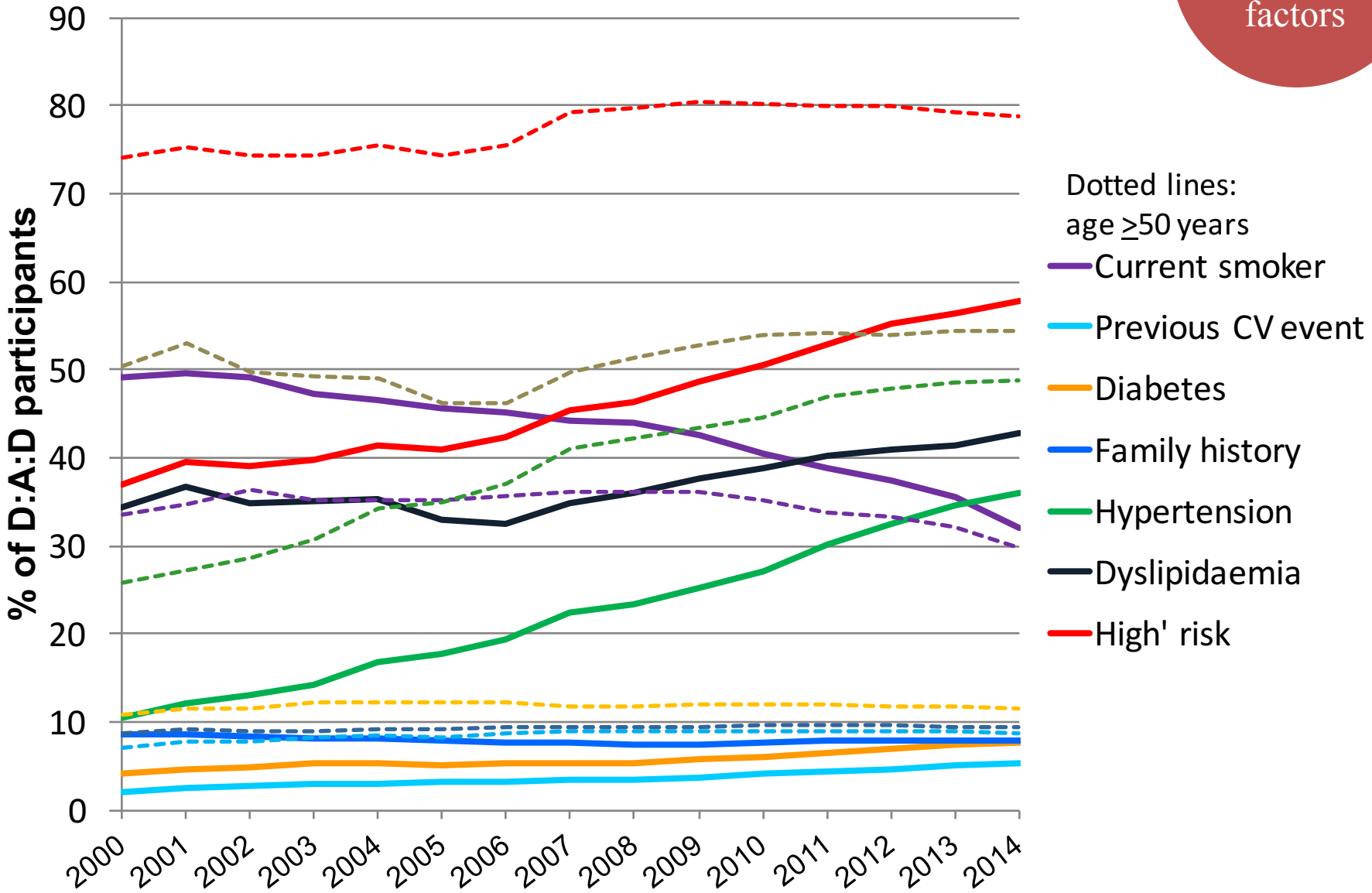
- HIV, depression and pain
- HIV, depression and non-adherence
- HIV and hypertension
- HIV, hypertension and pain treatment
- HIV, depression, hypertension, non-adherence and mental disorders
- HIV and cardiovascular risk factors such as dyslipidemia and hypertension
- HIV and drug dependency, addiction and hepatitis

Mechanism?
Factors Associated with Comorbidities



Changes over Time in the Prevalence of Traditional CVD Risk Factors

Traditional/ Lifestyle related factors



D:A:D Merger 16 dataset, unpublished data

Comparison of Aterosclerotic Lesions in HIV-Positive and Negative Pers. with Acute Coronary Syndrome

?

Angiographic characteristics

Variable	HIV-Infected (n = 48)	Non-HIV-Infected (n = 48)	Non-HIV-Infected Diabetic (n = 48)	p Value	
				HIV-Infected vs Non-HIV-Infected	HIV-Infected vs Non-HIV-Infected Diabetic
Number of narrowed coronary arteries				0.008[§]	0.01[§]
0	0 (0%)	3 (6%)	4 (8%)		
1	34 (71%)	30 (63%)	21 (44%)		
2	5 (10%)	13 (27%)	13 (27%)		
3	9 (19%)	2 (4%)	10 (21%)		
Number of lesions	2.1 ± 0.2	1.6 ± 0.2	2.2 ± 0.3	0.12*	0.77*
Type of lesion[†]				<0.0001[§]	0.005[§]
A	3 (9%)	0 (0%)	2 (5%)		
B1	18 (53%)	2 (6%)	6 (16%)		
B2	10 (30%)	25 (76%)	22 (60%)		
C	3 (9%)	6 (18%)	7 (19%)		
Number of patients with type B2/C or higher lesions	13 (38%)	31 (94%)	29 (78%)	<0.0001[§]	0.001[§]
Length of stenosis[†] (eyeballing) (mm)	14.3 ± 1.3	13.6 ± 1.1	17.1 ± 1.3	0.86*	0.08*
Length of total stenoses (mm)	20.5 ± 2.4	15.3 ± 1.9	24.9 ± 3.0	0.07*	0.29*
Length of stent segment[†] (mm)	19.0 ± 1.5	18.7 ± 1.2	21.1 ± 1.6	0.93*	0.29*
Procedural characteristics[‡]					
Number of lesions dilated	1.34 ± 0.65	1.26 ± 0.57	1.57 ± 0.90	0.62*	0.32*
Percutaneous coronary intervention	39 (81%)	30 (64%)	35 (73%)		
Balloon angioplasty	4 (8%)	4 (9%)	2 (4%)		
Coronary artery bypass graft	4 (8%)	4 (9%)	6 (13%)		

Knudsen A et al, Am J. Cardiol. 2013

Immune Suppression

HIV-related factors

Risk factors for End-Stage Renal Disease (ESRD)

Risk Factors	Multivariate-Adjusted Model[a] HR (95% CI)	*P*
CD4 count		
>350 cells/μL	1.00 (reference)	—
200-350 cells/μL	0.92 (0.65-1.29)	0.6
<200 cells/μL	1.54 (1.17-2.02)	0.002

Jotwani for the VA cohort, Am J Kidney Dis 2011

Markers of Inflammation/Coagulation Activation and CVD Rates

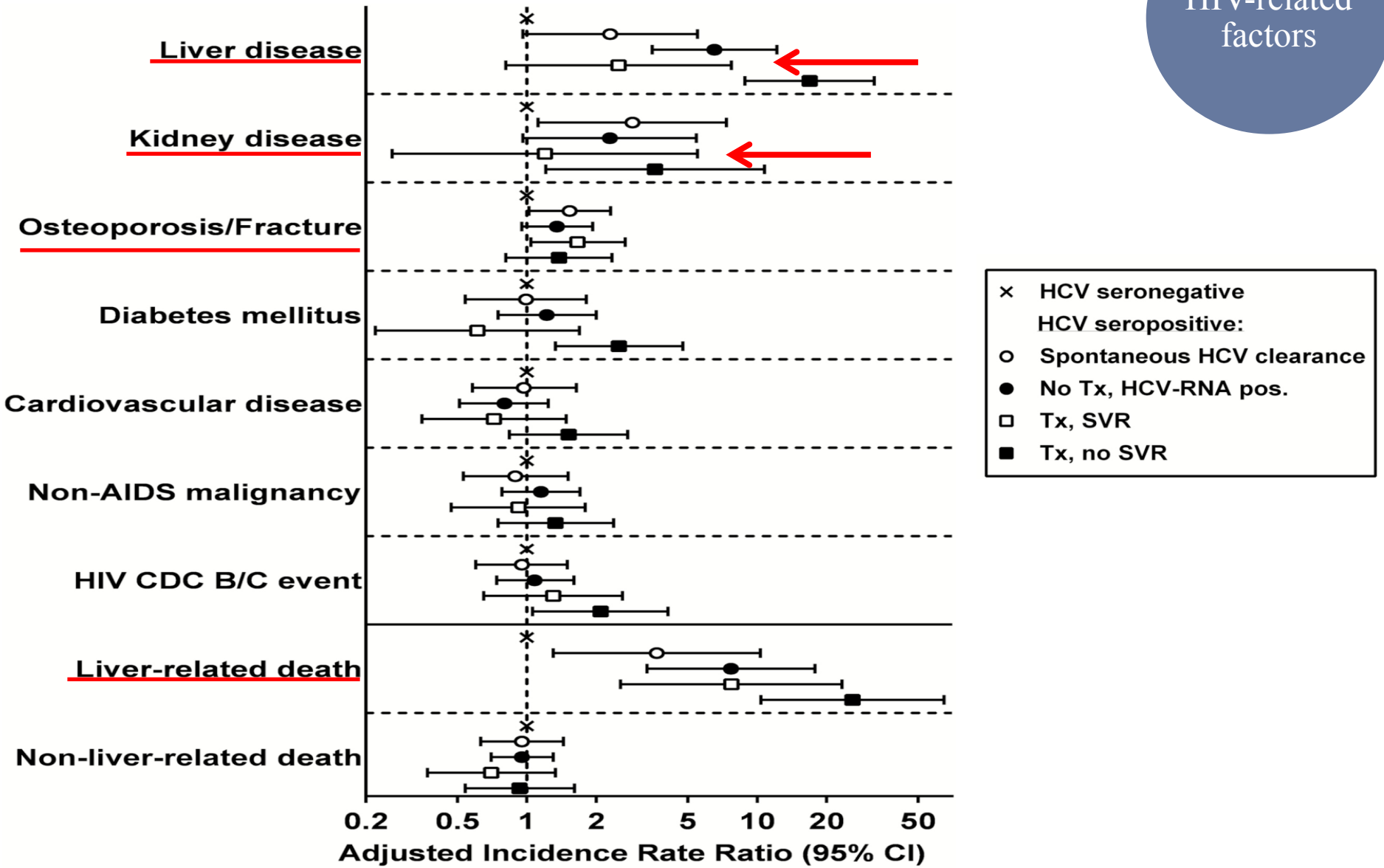
HIV-related factors

	No Event*	Fatal CVD†	Nonfatal CVD‡	*P* Value§
Baseline characteristics, n	9476	74	214	
Age (y), median (IQR)	42 (36 to 48)	48 (41 to 54)	49 (42 to 54)	0.76
Sex (% female)	22	14	8	0.21
Race (% black)	19	23	16	0.20
BMI (kg/m^2), median (IQR)	24.3 (22.1 to 27.0)	24.0 (22.1 to 27.0)	24.3 (22.1 to 27.1)	0.58
CD4$^+$ cell count, (cells/mm^3) median (IQR)	487 (367 to 669)	409 (331 to 644)	469 (356 to 633)	0.63
HIV-RNA<500 copies/mL, %	77	74	77	0.64
Earlier AIDS event, %	26	39	29	0.10
IL-6, (pg/mL) median (IQR)	1.8 (1.2 to 2.8)	3.1 (1.9 to 4.5)	2.3 (1.5 to 3.5)	0.01‖
% highest tertile (<1.88)#	20	45	28	
% middle tertile (1.88≤x<3.14)#	27	31	36	
% lowest tertile (≥3.14)#	52	24	36	0.02¶
D-dimer, (μg/mL) median (IQR)	0.24 (0.15 to 0.37)	0.35 (0.24 to 0.61)	0.27 (0.17 to 0.45)	0.006‖
% highest tertile (<0.22)	21	45	29	
% middle tertile (0.22≤x< 0.41)	31	32	34	
% lowest tertile (≥0.41)	47	23	37	0.03¶
hsCRP, (μg/mL) median (IQR)	1.6 (0.7 to 3.6)	3.1 (1.1. to 7.5)	2.2 (1.1 to 5.6)	0.26‖
% highest tertile (<1.55)	21	39	31	
% middle tertile (1.55≤x<4.17)	29	32	34	
% lowest tertile (≥4.17)	50	28	35	0.49¶
IL-6 and D-dimer score median (IQR)	−0.02 (−0.60 to 0.61)	0.85 (0.20 to 1.36)	0.30 (−0.20 to 0.89)	0.003
% highest tertile (<1.04)	19	51	27	
% middle tertile (1.04≤x<1.75)	28	26	36	
% lowest tertile (≥1.75)	53	23	37	0.001¶

AD Norbell et al for ESPRIT, SILCAT, SMART, J. AM Heat Ass 2014

HCV Co-infection

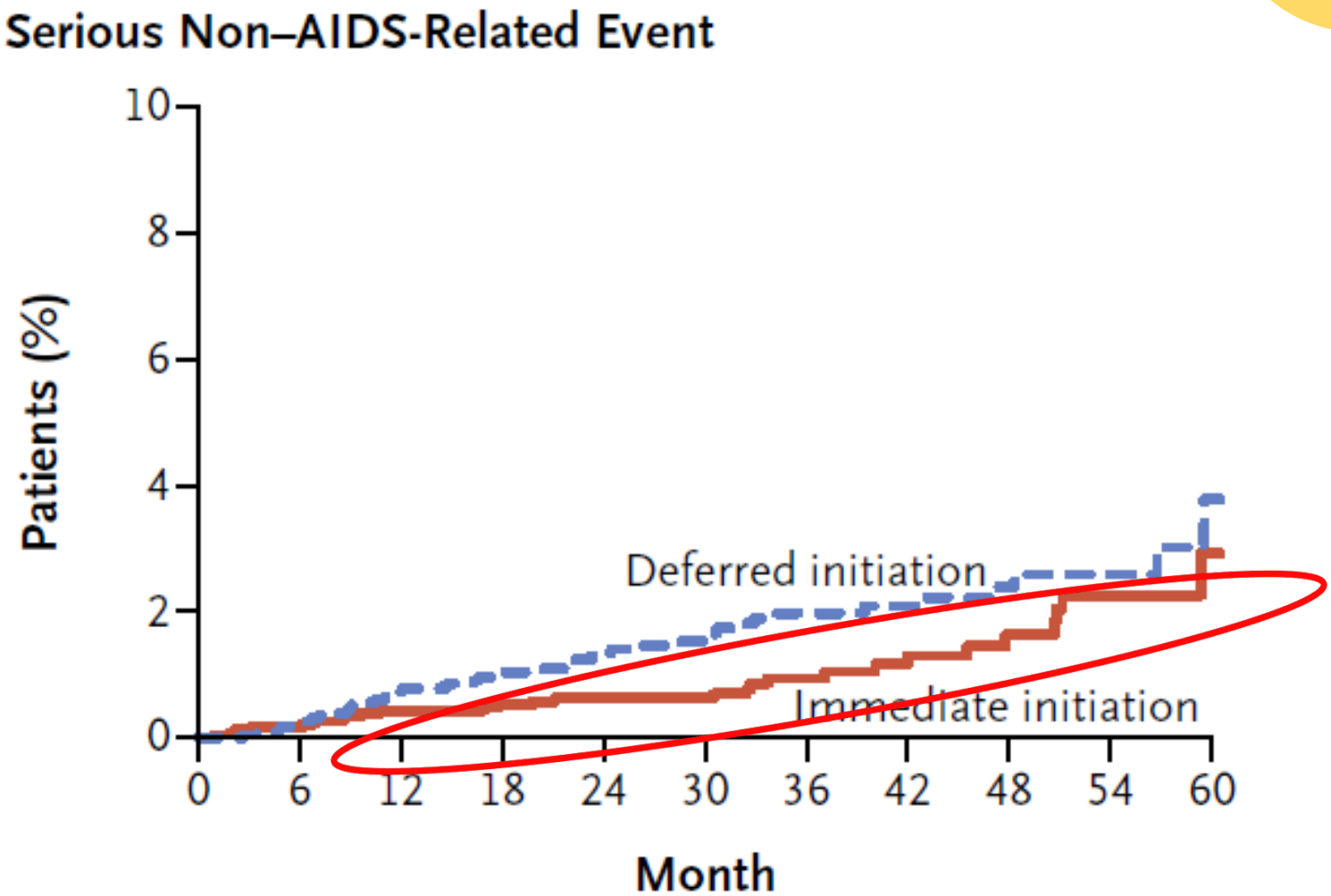
HIV-related factors



Kovari J et al. for the SWISS HIV Cohort, Clin Infect Dis. 2016;64(4):490-497.

Progression to Serious Non-AIDS-Related Events in START

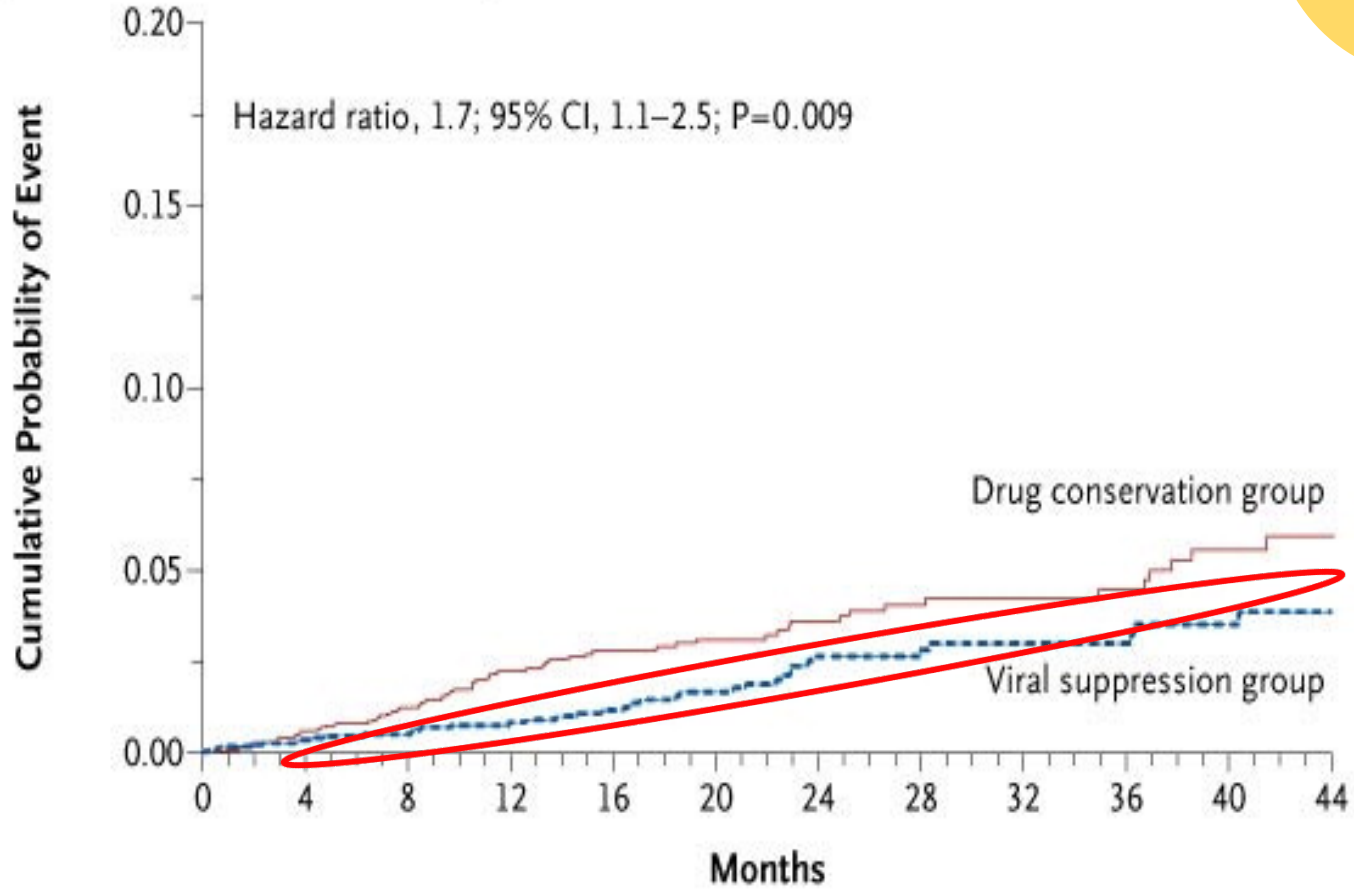
ART/
other drugs



Lundgren JD el al. for START, N Engl J Med 2016

Progression to Serious Non-AIDS-Related Events in SMART

ART/
other drugs



No. at Risk

Drug conservation	2720	2070	1663	1292	1041	867	693	543	443	375	273	157
Viral suppression	2752	2077	1692	1307	1070	899	713	563	462	380	282	165

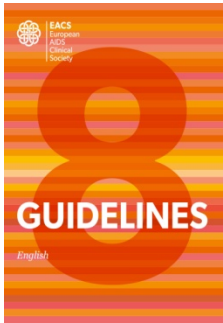
El-Sadr W el al., for SMART, N Engl J Med 2006

Adverse Effects of ARVs & Drug Classes

Bold: Frequent effects
Red: Severe effects
Black: Neither Frequent nor Severe[1]

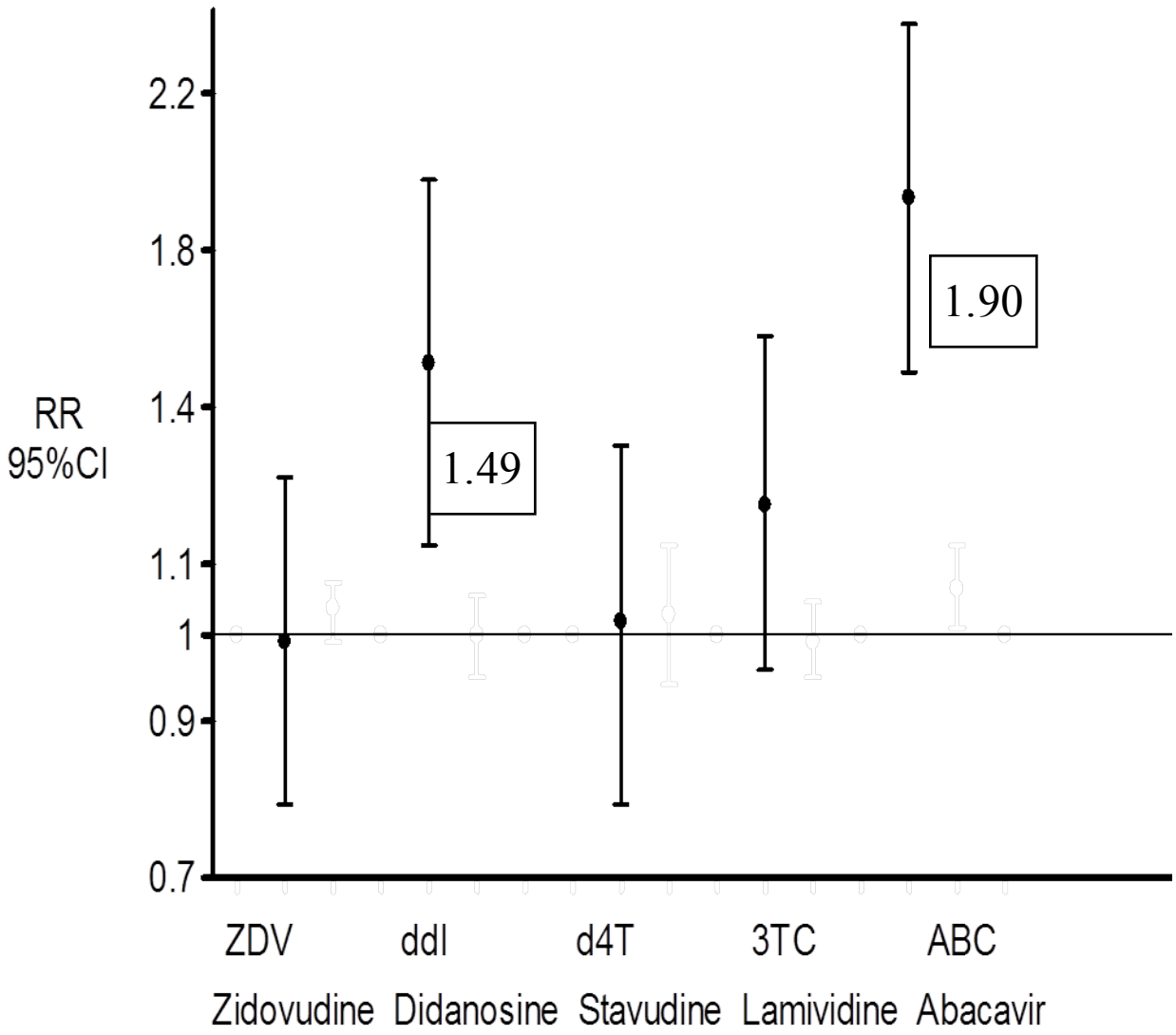
ART/ other drugs

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genito-urinary	Nervous	Body fat	Metabolic	Other
NRTIs										
ABC	Rash*	Nausea* Diarrhoea*		IHD						*Systemic hypersensitivity syndrome (HLA B*5701 dependent)
ZDV[6]	Nail pigmen-tation	Nausea	Steatosis		Myopathy, Rhabdomy-olysis			**Lipoatrophy**	Dyslipi-daemia, Hyperlacta-taemia	Anaemia
d4T[6]		Pancreatitis	**Steatosis**				**Peripheral neuropathy**		**Dyslipi-daemia,** Hyperlacta-taemia	
ddI[6]			Steatosis, Liver fibrosis	IHD					Hyperlacta-taemia	
3TC										
FTC										
TDF[6]					↓ BMD, Osteomalacia ↑ Fractures risk	↓ eGFR, Fanconi syndrome				
TAF[6]										
NNRTIs										
EFV	Rash		Hepatitis				**Depression, Sleep disturbances, Headache,** Suicidal ideation		**Dyslipi-daemia,** Gynaeco-mastia	**↓ plasma 25(OH) vitamin D,** Teratogenesis
ETV	Rash									
NVP	Rash*		Hepatitis*							*Systemic hypersensitivity (CD4 count-and gender-depend-ent)
RPV	Rash		Hepatitis			↓ eGFR[6]	Depression, Sleep disturbances, Headache			
PIs										
ATV[6]			**Hyperbilirubinaemia,** Jaundice, Choleithiasis			↓ eGFR, Nephrolithiasis			Dyslipi-daemia	
DRV[6]	Rash					Nephrolithiasis			Dyslipi-daemia	
FPV[6]	Rash			IHD					**Dyslipi-daemia**	
IDV[6]	**Dry skin,** Nail dystrophy	**Nausea and Diarrhoea**[4]	Jaundice	IHD		**Nephrolithiasis**		**↑ Abdominal fat**	**Dyslipi-daemia,** Diabetes	



Recent ARV Use and Incidence of MI

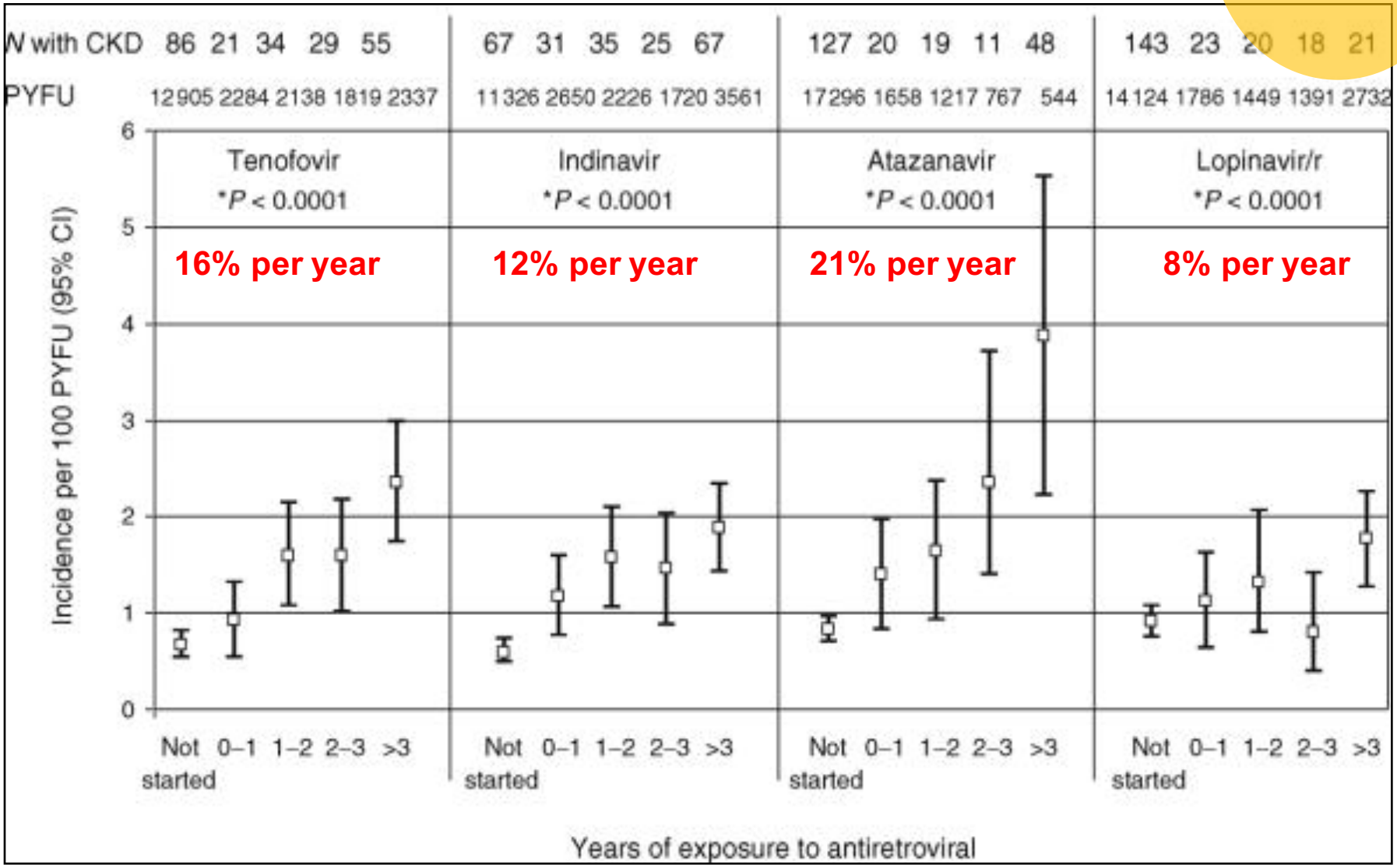
ART/
other drugs



Sabin C. et al for D:A:D Lancet April 2008 & BMC Med. 2016

Cumulative (/year) ARV Use and incidence of CKD

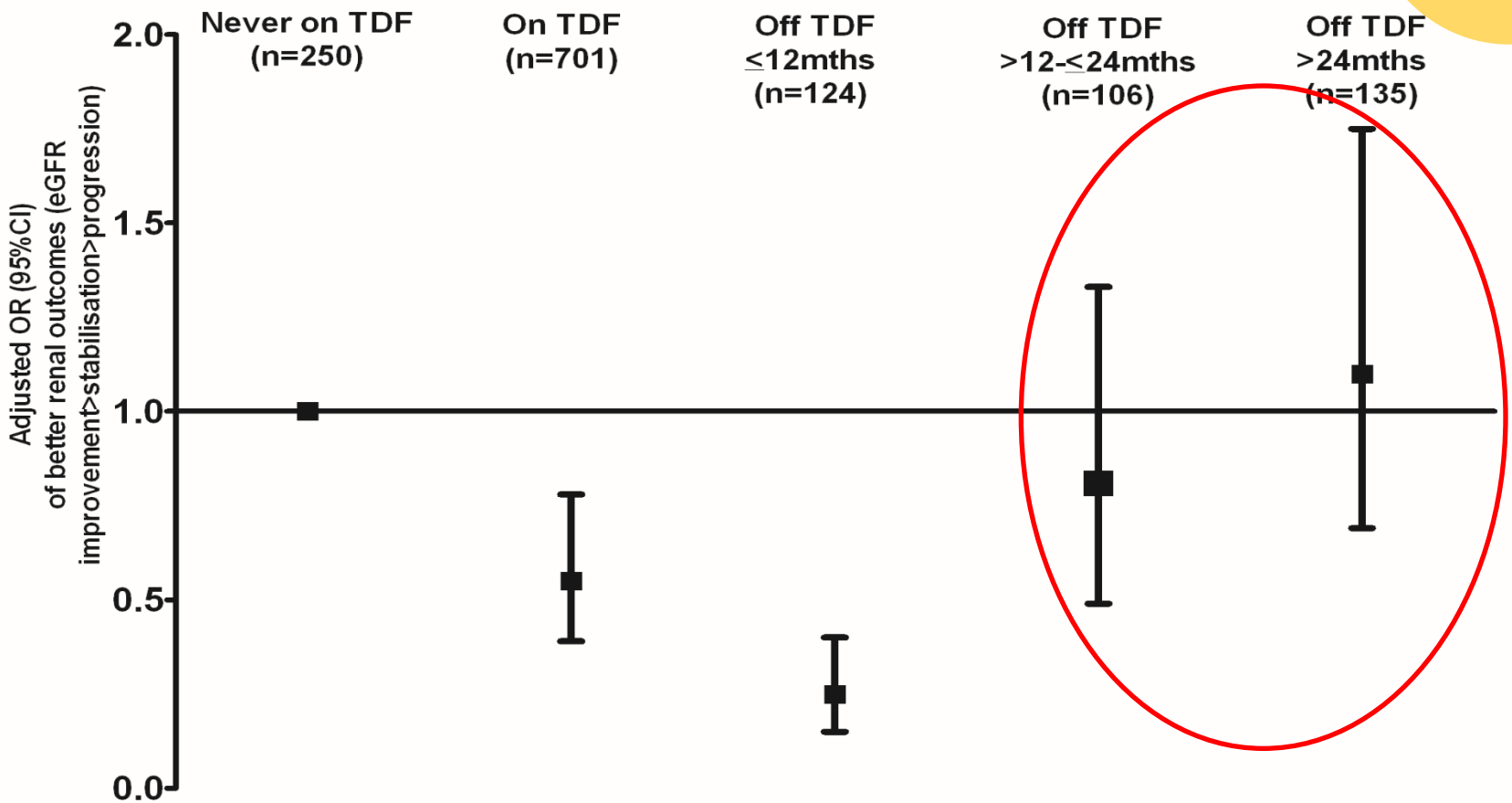
ART/
other drugs



Mocroft A et al. for EuroSIDA AIDS 2010

Reversability of ART-nephrotoxicity

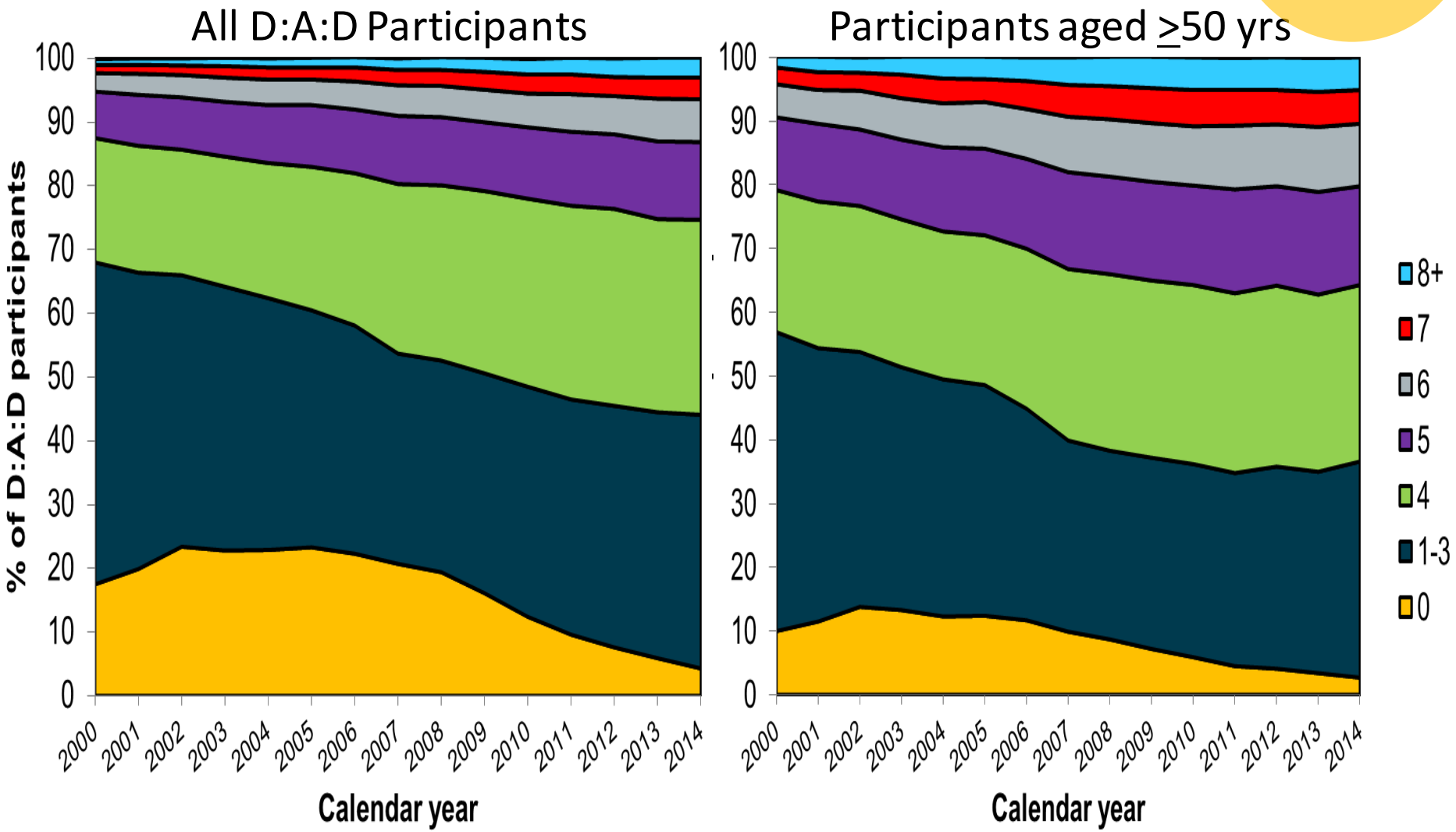
ART/
other drugs



Ryom L for D:A:D, *In press* AIDS

Polypharmacy

ART/
other drugs



D:A:D Merger 16 dataset, unpublished data

Polypharmacy
Commonly Used non-ARV Drugs

ART/
other drugs

Table 2. Treatment Characteristics of 8444 HIV-Seropositive Cohort Participants, Stratified by Age

Variables	Total	Age group <50 years	50–64 years	≥65 years	*P* value[a]
Non-ART medication, no. (%)					
Antihypertensives (not ACE inhibitors)	831 (9.8)	323 (5.6)	367 (16.4)	141 (31.3)	<.001
Antihypertensives (ACE inhibitors)	935 (11.1)	355 (6.2)	432 (19.4)	148 (32.9)	<.001
Lipid-lowering agents	1071 (12.7)	356 (6.2)	527 (23.6)	188 (41.8)	<.001
Oral antidiabetics	179 (2.1)	51 (0.9)	87 (3.9)	41 (9.1)	<.001
Insulin	116 (1.4)	40 (0.7)	50 (2.2)	26 (5.8)	<.001
Antiplatelet drugs	488 (5.8)	121 (2.1)	237 (10.6)	130 (28.9)	<.001
Antidepressants	846 (10.0)	560 (9.7)	251 (11.2)	35 (7.8)	.659

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; VL, viral load; PI, Protease inhibitor, NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; ACE, Angiotensin-converting enzyme.

[a] Test for trend across age groups.

Hasse B et al., for the Swiss cohort, study, Clin Infec Dis 2011 Dec;53(11):1130-9

Drug-drug Interactions

ART/
other drugs

Drug-drug Interactions between ARVs and Non-ARVs[i]

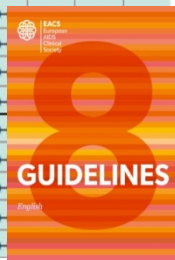
	Non-ARV drugs	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Cardiovascular drugs	atorvastatin	↑	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	fluvastatin	↔	↑	↔	↔	↑	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	pravastatin	↔	↑	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	rosuvastatin	↑213%	↑	↑48%	↑107%	↔	↔	↔	↔	↔	↔	↑38%	↔	↔	↔	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	amlodipine	↑[iii]	↑	↑	↑[iii]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[iii]	↑	↑	↑[iii]	↓69%	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑[iii]	↑	↑	↑[iii]	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑[iii]	↑	↑	↑[iii]	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	E	E	↔
	warfarin	↑ or ↓	↑	↓	↓	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔

Drug-drug Interactions between Anticoagulants/Antiplatelet agents and ARVs

		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Anticoagulants	acenocoumarol	↓	↔	↓	↓	↓	↑	↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
	apixaban	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	dabigatran	↑	↑	↑	↑?	↔	↔	↔	↑?	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	dalteparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	edoxaban	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	enoxaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fondaparinux	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	heparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenprocoumon	↑or↓[a]	↑	↑or↓	↑or↓	↓	↑or↓	↓	↔	↔	↔	↑or↓	↔	↔	↔	↔	↔	↔	↔
	rivaroxaban	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	warfarin	↑or↓[a]	↑	↓	↓	↑or↓	↑	↑or↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
Antiplatelet agents	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	[b]	↔
	clopidogrel	↓[c]	↓[c]	↓[c]	↓[c]	↑[d]	↓[c]	↑[d]	↔	↔	↔	↓[c]	↔	↔	↔	↔	↔	↔	↔
	dipyridamole	↓[e]	↔	↓	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	prasugrel	↓[f]	↓[f]	↓[f]	↓[f]	↔	↔	↔	↔	↔	↔	↓[f]	↔	↔	↔	↔	↔	↔	↔
	ticagrelor	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔

Drug-drug Interactions between Antihypertensives and ARVs

	antihypertensives	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	RAL	ABC	FTC	3TC	TDF	ZDV
ACE inhibitors	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↓	↓	↓	↓	↓	↓	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	losartan	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↑[b]	↑[b]	↔	↔	↔	↔	↔	↔	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↔[d]	↔	↔	↔	↔[d]	↔[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bisoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	carvedilol	↑↓[d]	↑↓	↑↓	↑↓	↑↓[d]	↑↓[d]	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	propanolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Calcium channel blockers	amlodipine	↑[c]	↑	↑	↑80%	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[c]	↑	↑	↑	↑	↑[c]	↓69%	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
	felodipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	lacidipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔

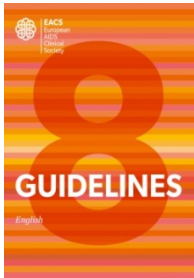


www.hiv-druginteractions.org

EACS Guidelines V8.2 Jan 2017 www.eacssociery.org

What To Do About The Co- & Multimorbidities?

- Requires a multidisciplinary approach
- Systematic screening and management
- Recommendations are available in the EACS Guidelines
  http://www.eacsociety.org/files/guidelines_8.1-english.pdf



	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment
CO-MORBIDITIES					
Haematology	FBC	+	+	3-12 months	
	Haemoglobinopathies	+			Screen at risk persons
	G6PD	+			Screen at risk persons
Body composition	Body-mass index	+	+	Annual	
Cardiovascular disease	Risk assessment (Framingham score[iii])	+	+		Should be performed in all men > 40 years and women > 50 years without CVD
	ECG	+	+/-	Annual	Consider baseline ECG prior to starting ARVs associated with potential conduction problems
Hypertension	Blood pressure	+	+	Annual	
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)
Glucose	Serum glucose	+	+	6-12 months	Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL)
Pulmonary disease	CXR	+/-		As indicated	Consider CXR if prior history of pulmonary disease
	Spirometry			As indicated	Screen for COPD in at risk persons[xii]
Liver disease	Risk assessment[v]	+	+	Annual	
	ALT/AST, ALP, Bilirubin	+	+	3-12 months	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs
Renal disease	Risk assessment[vi]	+	+	Annual	More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs[ix]
	eGFR (aMDRD)[vii]	+	+	3-12 months	
	Urine Dipstick analysis[viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min. If proteinuria ≥ 1+ and/or eGFR< 60 mL/min perform UP/C or UA/C[vii]
Bone disease	Bone profile: calcium, PO^4, ALP	+	+	6-12 months	
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons
Neurocognitive impairment	Screening questionnaire	+	+	2 years	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 61 for further assessment.
Depression	Questionnaire	+	+	1-2 years	Screen at risk persons
Cancer	Mammography			1-3 years	Women 50-70 years
	Cervical PAP			1-3 years	Sexually active women
	Anoscopy and PAP (MSM)			1-3 years	Evidence of benefit not known
	Ultrasound and alpha-foetoprotein			6 months	Controversial/Persons with cirrhosis and with HBV irrespective of fibrosis stage
	Others				Controversial

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment
CO-MORBIDITIES					
Haematology	FBC	+	+	3-12 months	
	Haemoglobinopathies	+			Screen at risk persons
	G6PD	+			Screen at risk persons
Body composition	Body-mass index	+	+	Annual	
Cardiovascular disease	Risk assessment (Framingham score[iii])	+	+		Should be performed in all men > 40 years and women > 50 years without CVD
	ECG	+	+/-	Annual	Consider baseline ECG prior to starting ARVs associated with potential conduction problems
Hypertension	Blood pressure	+	+	Annual	
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)
Glucose	Serum glucose	+	+	6-12 months	Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL)
Pulmonary disease	CXR	+/-		As indicated	Consider CXR if prior history of pulmonary disease
	Spirometry			As indicated	Screen for COPD in at risk persons[xii]
Liver disease	Risk assessment[v]	+	+	Annual	
	ALT/AST, ALP, Bilirubin	+	+	3-12 months	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs
Renal disease	Risk assessment[vi]	+	+	Annual	More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs[ix]
	eGFR (aMDRD)[vii]	+	+	3-12 months	
	Urine Dipstick analysis[viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min, If proteinuria ≥ 1+ and/or eGFR< 60 mL/min perform UP/C or UA/C[vii]
Bone disease	Bone profile: calcium, PO^4, ALP	+	+	6-12 months	
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons
Neurocognitive impairment	Screening questionnaire	+	+	2 years	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 61 for further assessment.
Depression	Questionnaire	+	+	1-2 years	Screen at risk persons
Cancer	Mammography			1-3 years	Women 50-70 years
	Cervical PAP			1-3 years	Sexually active women
	Anoscopy and PAP (MSM)			1-3 years	Evidence of benefit not known
	Ultrasound and alpha-foetoprotein			6 months	Controversial/Persons with cirrhosis and with HBV irrespective of fibrosis stage
	Others				Controversial

Prevention of CVD

Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated[i]. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in persons with a history of CVD.

CVD & renal, bone, liver etc.:
- Assess risk: consider using risk scores
- Identify: key risk factors
- Modify: were relevant/possible

Assess CVD risk in next 10 years[i]

↓

Advise on diet and lifestyle in all persons

Consider ART modification if 10-year CVD risk ≥ 20%[ii]

↓

Smoking (see page 29) → Identify key modifiable risk factors[iii]

↓

Blood Pressure

↓

Drug treatment if: SBP ≥ 140 or DBP ≥ 90 mmHg (especially if 10-year CVD risk ≥ 20%)

↓

Target	
If diabetic or prior CVD or CKD + proteinuria	Others
SBP < 130	< 140
DBP < 80	< 90

↓

Treatment (see page 31-33)

Coagulation

↓

Drug treatment if: established CVD or age ≥ 50 and 10-year CVD risk ≥ 20%

↓

Target - N/A

↓

Consider treating with acetylsalicylic acid 75-150 mg[vi]

Glucose

↓

Confirm DM and treat with drugs

↓

Target
HbA1C < 6.5-7.0%

↓

Treatment (see page 35)

Lipids

↓

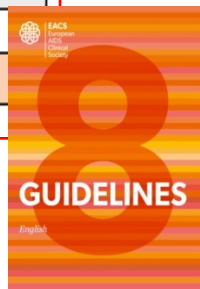
Drug treatment[iv] if: established CVD or type 2 diabetes or 10-year CVD risk ≥ 20%

↓

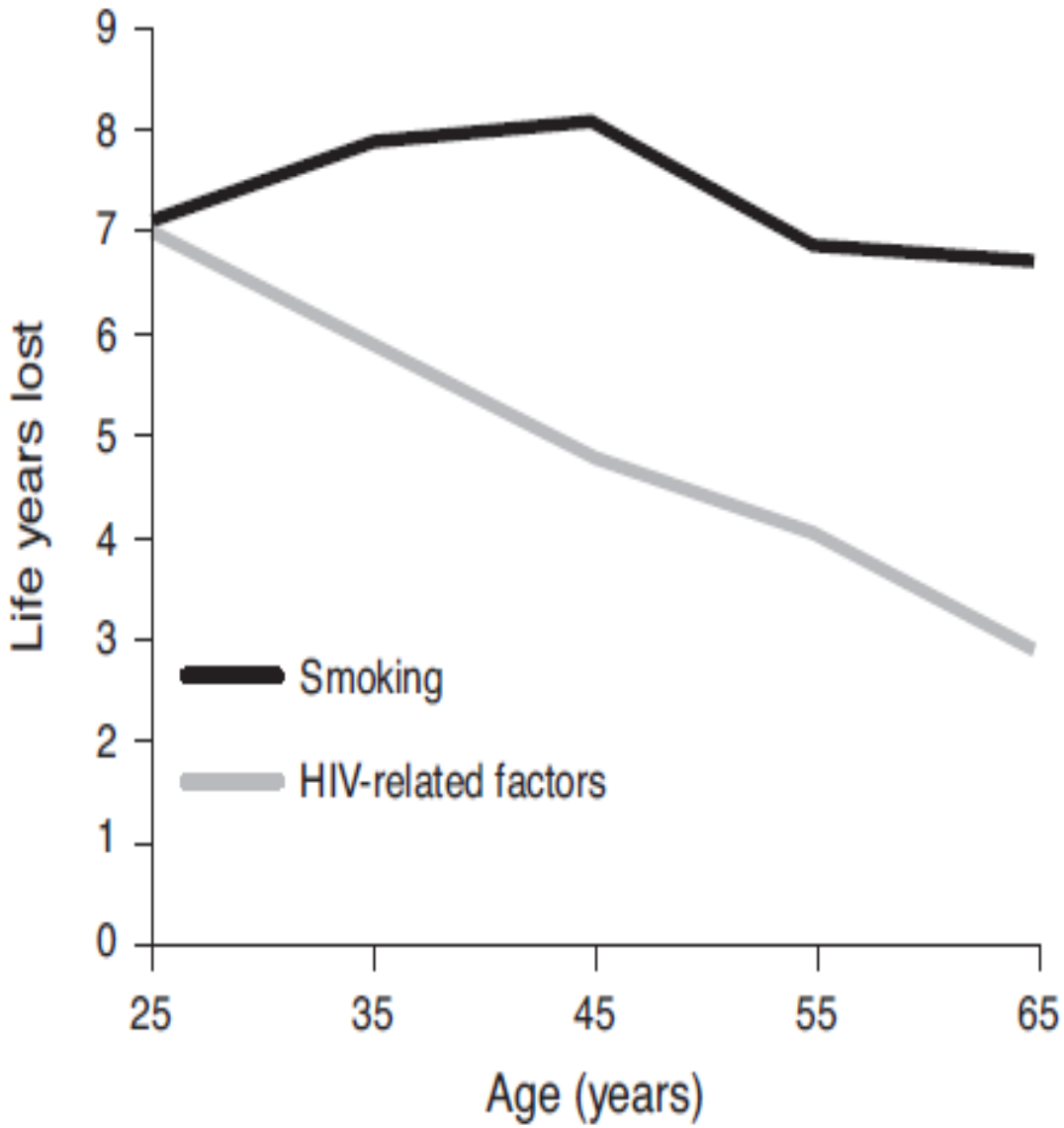
Target[v]		
	Optimal	Standard
TC	≤ 4 (155)	≤ 5 (190)
LDL	≤ 2 (80)	≤ 3 (115)

↓

Treatment (see page 36)



Smoking and Loss of Life Years in HIV-positive Persons



Helleberg M et al. for the Danish HIV cohort, AIDS 2015;**29**:221-9.

Modifying CVD Risk at Age 50 Years

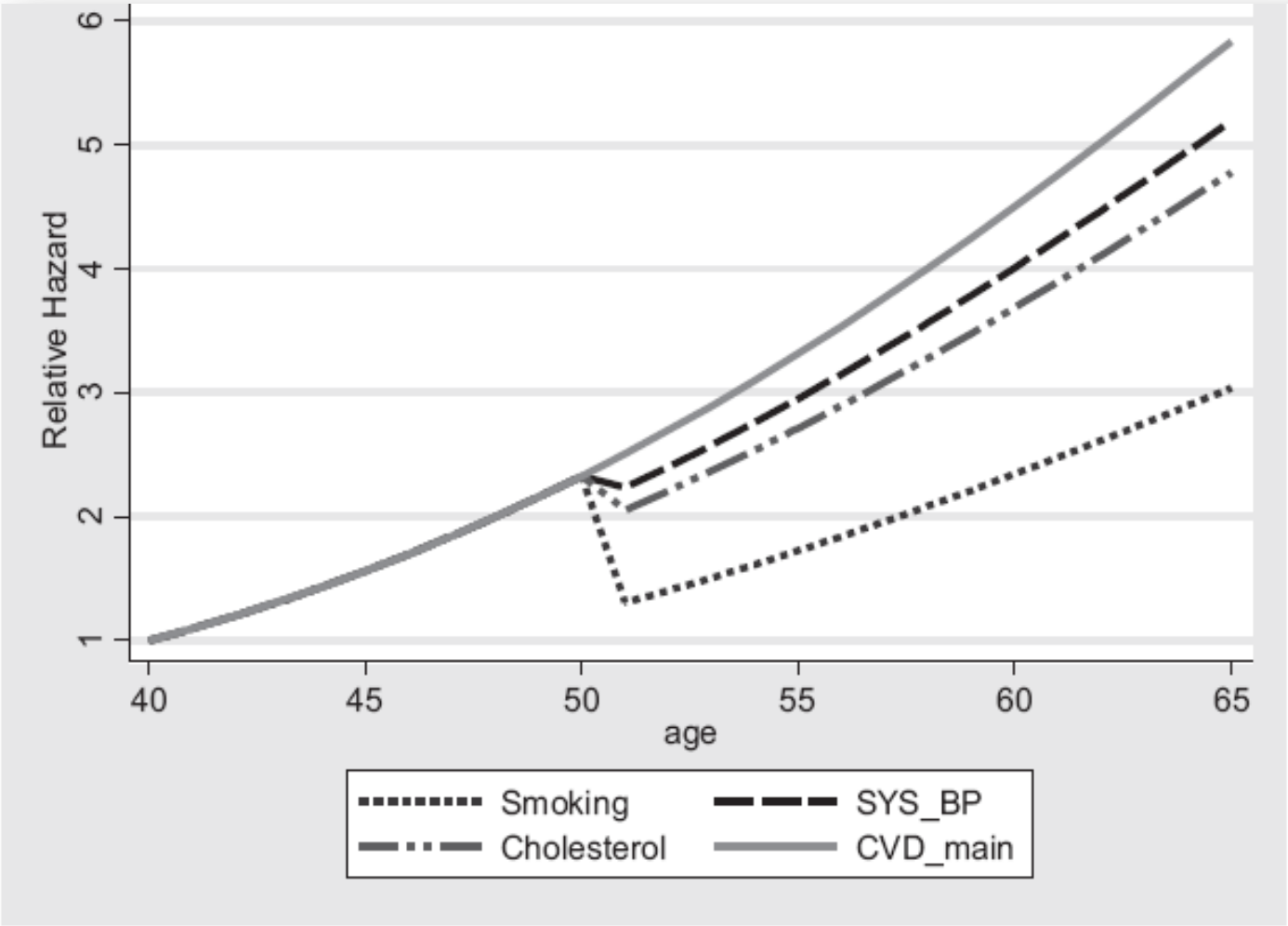


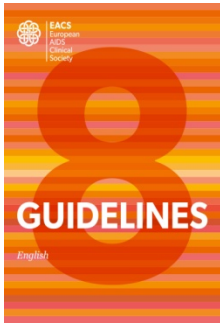
Fig. 3 Relative risk of cardiovascular disease (CVD) from age 40 years including stopping smoking, reducing cholesterol (by 1 mmol/L) or reducing systolic blood pressure (SYS_BP) (by 10 mmHg) at age 50 years.

Petoumenos K et al. for D:A:D, *HIV Med* 2014;**15**:595-603.

Time Trends in Short-term Survival after MI in HIV-positive Persons

	Year of MI				
	99-02	03-04	05-06	07-08	09-11
% dying in first month after MI	26.4	24.7	19.8	16.4	8.2
OR dying in first month after MI (/later year) (95% CI)					
Unadjusted	0.88 [0.83, 0.94]				
Adjusted for baseline characteristics	0.88 [0.83, 0.94]				
Additionally adjusted for use of invasive procedures and/or medications in the first month post-MI	1.02 [0.94, 1.10]				

Hatleberg C et al for D:A:D AIDS, 2016, Jun 19;30(10):1583-9

Conclusions

- With improvements in ART the HIV-positive population is ageing with increasing rates of several comorbidities contributing to excess morbidity & mortality
- The underlying mechanistics of these comorbidities and their interactions are complex- multiple potential contributing factors
- Determination of the relative contribution of different risk factors on individual comorbidities can be challenging, but is important for targeted interventions
- A multidisciplinary effort is required and guidance is available i.e. in the EACS guidelines
- Be aware of polypharmacy, drug-drug interactions and adverse drug effects
- Focus on continued regular and systematic risk assessments, identification and management of modifiable risk factors
- Interventions for CVD seem to works! Need evaluation of Interventions for other comorbidities in elderly HIV-positive individuals