

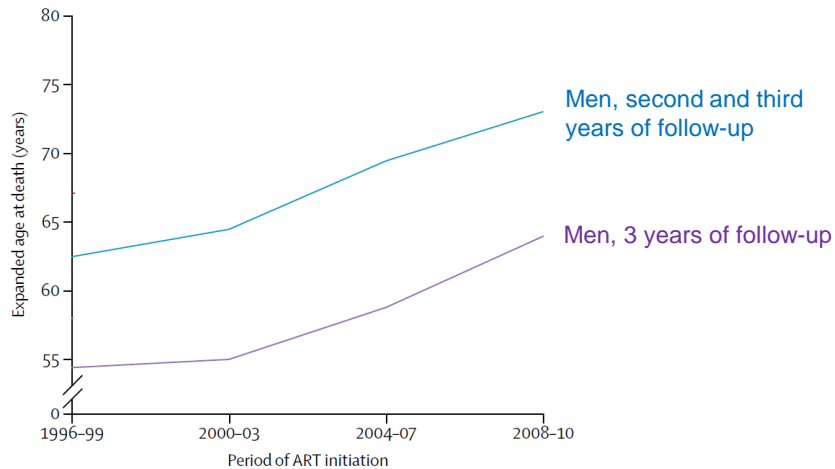
# Co-morbidities in HIV-patients: Hit hard, hit early?!

Professor Georg Behrens  
Department for Clinical Immunology and Rheumatology  
Hannover Medical School, Germany



## Life expectancy among PLHIV continues to increase over time

Expected age at death starting ART aged 20 years, by period of initiation\*

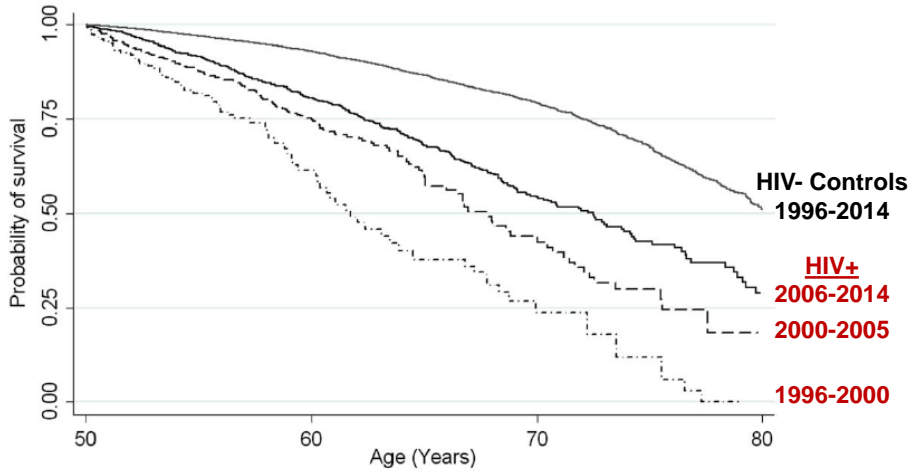


ART Collaboration. Lancet HIV 2017; May 10 S2352-3018(17)30066-8.

\*Estimates of life expectancy were based on mortality during the first 3 years of follow-up and the second and third years of follow-up.

# 10y decreased life expectancy in older HIV+ adults in modern ART era

Denmark

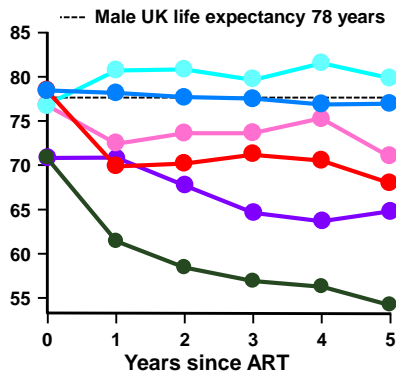


Legarth et al. JAIDS, 2016

# Ageing with HIV – with ARV therapy

## Expected age at death\*

Men

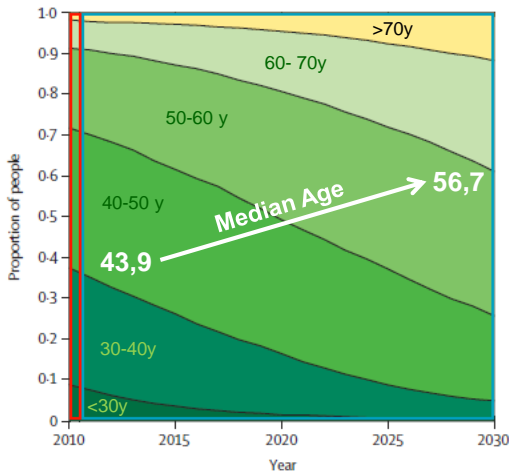


Viral load  $\leq 400$  copies/ml    ● CD4  $\geq 350$     ● CD4 200–349    ● CD4  $< 200$   
 Viral load  $> 400$  copies/ml    ● CD4  $\geq 350$     ● CD4 200–349    ● CD4  $< 200$

May M et al. AIDS 2014;28:1193–1202

\* Expected age at death for a person aged 35 years with different durations of ART according to current CD4 count and viral load suppression

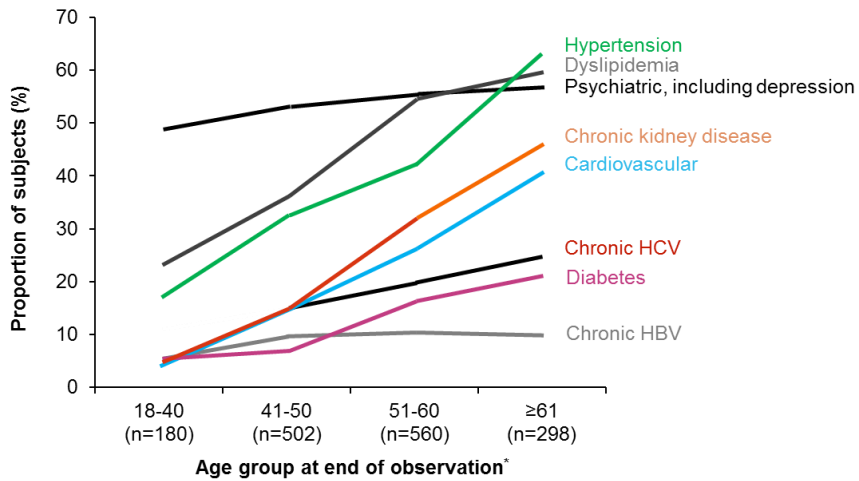
# Projected age distribution of HIV-positive patients in the Netherlands



Patient's age	2010	2030
> 50 years	28%	73%
> 60 years	8%	39%

Smit M et al. Lancet Infect Dis 2015;15:810–818

# Non-AIDS illness burden in ageing PLWHIV



Disproportionately greater increases in prevalence of hypertension, dyslipidemia, CKD and CVD with ageing in PLWHIV<sup>1</sup>

Palella FJ et al. CROI 2017. Seattle, WA. #663 HOPS cohort, 1997 to 2015

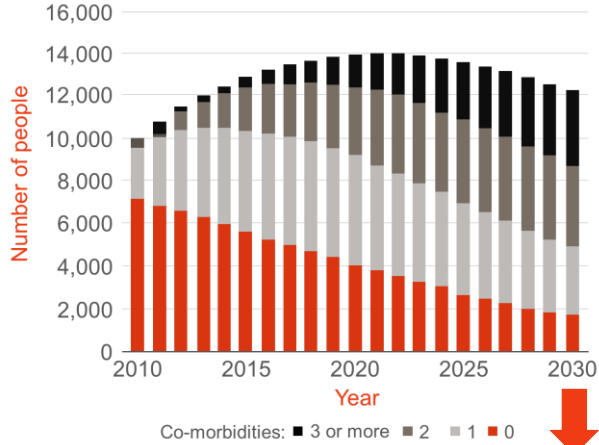
# Predicted burden of NCDs in PLWHIV 2010–2030\*

Proportion of PLWHIV with ≥1 NCD predicted to increase

- 2010 29%
- 2030 in 84%

Driven by

- **CVD** in 78%
- **Diabetes** in 17%
- **Malignancies** in 17%



**78%  
CVD**

Smit M et al. Lancet Infect Dis 2015;15(7):810–8



Diagnosed      On ART      <50 copies      Good health

**90**      **90**      **90**      **90**





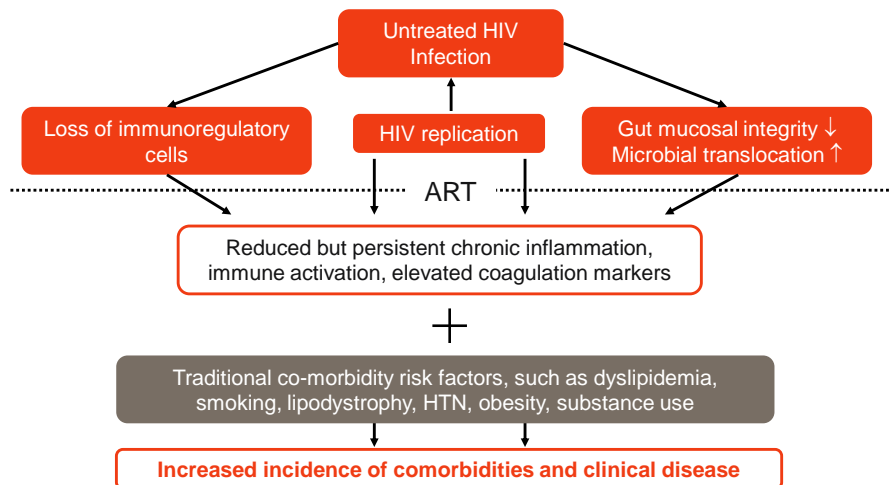
## Prevention & Management of Co-Morbidities in HIV-positive Persons (Part III)

Largest section  
~ 60 pages

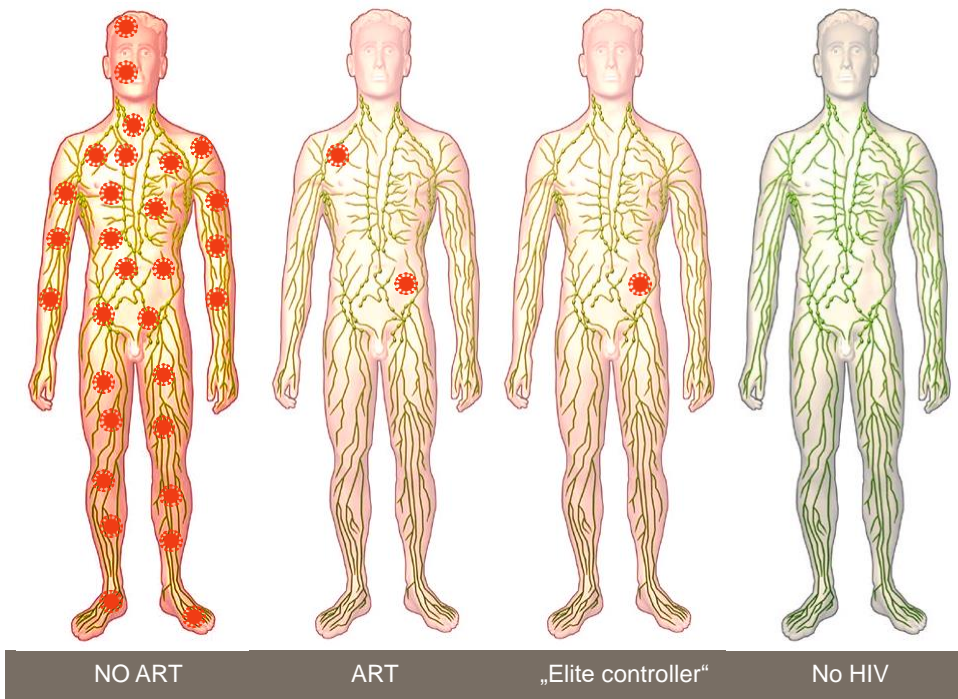
New chapters:

- Non-alcoholic fatty liver disease (NAFLD)
- Chronic obstructive pulmonary disease (COPD)
- Pharmacotherapy in the elderly
- Solid organ transplantation

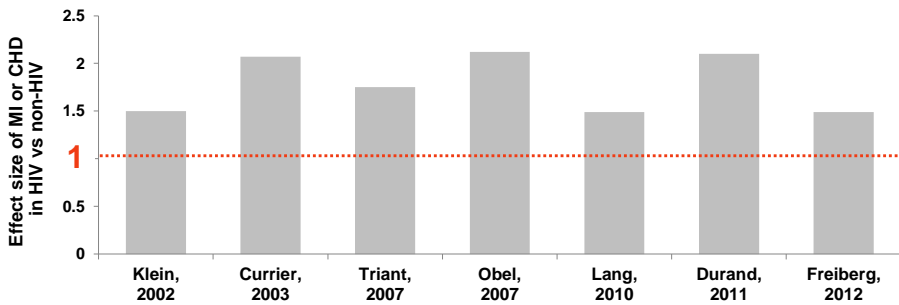
Chronic inflammation is associated with increased risk for co-morbidities in HIV+ patients



Deeks SG. Annu Rev Med. 2011;62:141-155.



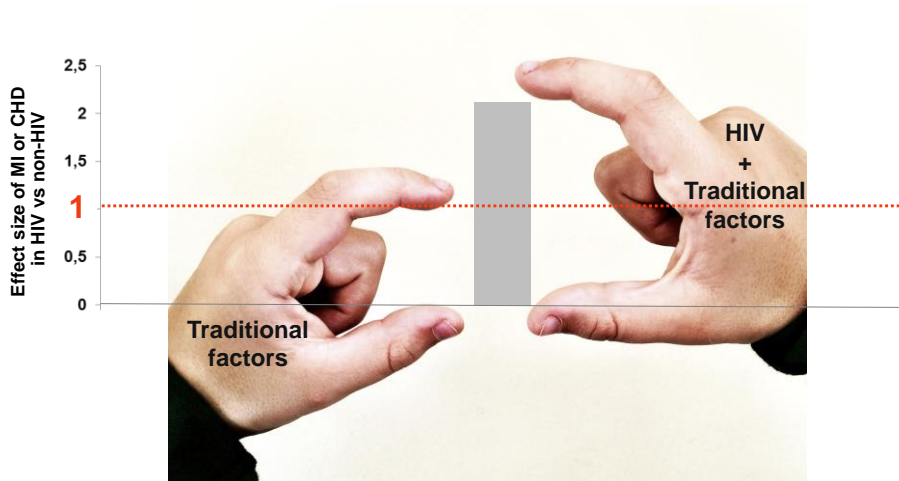
**CVD risk in HIV-positive patients is beyond that predicted by traditional risk factors**



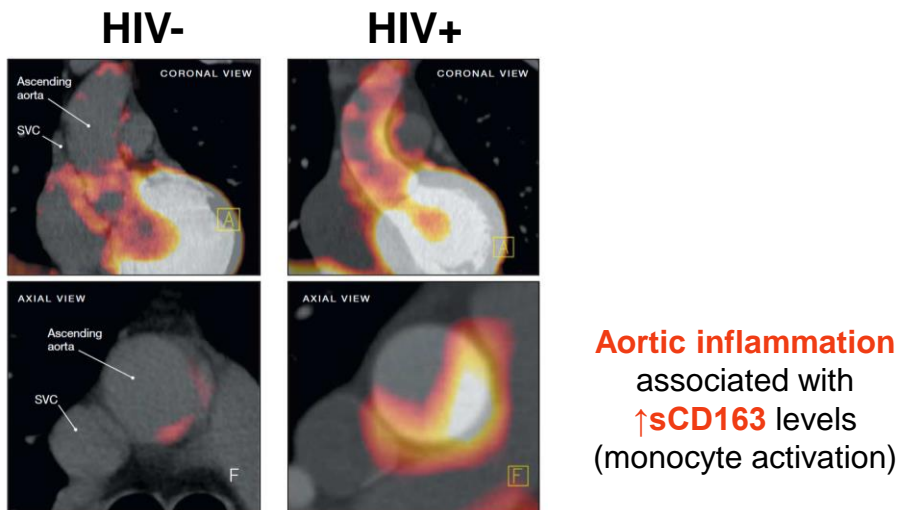
**Risk of heart disease is 1.5–2 times higher in HIV-positive patients, even after controlling for traditional risk factors**

Grinspoon S. CROI 2015. Seattle, WA. Oral #O134

## CVD risk in HIV-positive patients is beyond that predicted by traditional risk factors

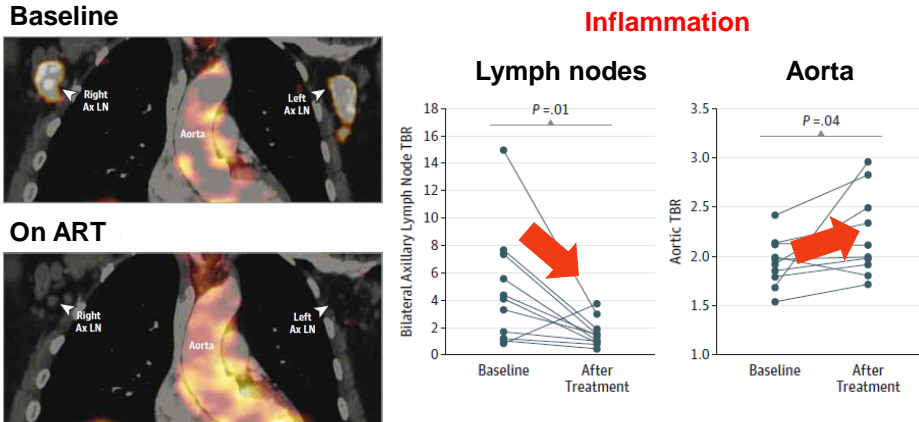


## Increased arterial inflammation in HIV



Subramanian et al JAMA 2012

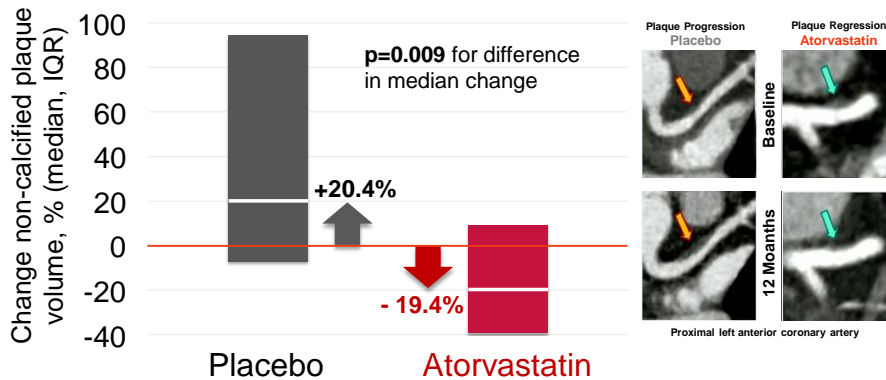
# Arterial inflammation not directly driven by HIV (PET/CT)



Zanni et al JAMA Cardiol 2016

# CVD and HIV: Lipid-lowering therapies in patients with subclinical coronary plaques

N=40 PLWHIV, Atorvastatin versus placebo; 1-year double-blind trial  
 Mean Age = 50y, non-calcified plaque by coronary CT angiography, LDL <130 mg/dL



Lo J et al. Lancet HIV 2015;2:e52-63, Longenecker C et al. CROI 2015; Seattle WA. Oral #137








## Immune cell activation and systemic inflammation in MSM with HIV

	MSM HIV pos.	Healthy Donors
T cell activation	+++	-
T cell exhaustion	+++	-
sCD163	+++	-
FABP	+++	-
Monocytic activation markers	+++	-

Kootstra N et al. EACS Online Library, Oct. 22, 2015; 114943; Booman T et al. Open Forum Infect Dis. 2017 May 25;4(3):ofx108.

## NRTI options are limited and not always guideline recommended

Treatment considerations	TDF/FTC	ABC/3TC
 *High viral load <sup>1,2</sup>	Acceptable	Caution Acceptable**
 High CVD risk <sup>1,2</sup>	Acceptable	Caution
 Renal impairment <sup>2</sup>	Caution	Acceptable
 Decrease in BMD <sup>2,3</sup>	Caution	Acceptable
 HLA-B*5701 positive <sup>1,2</sup>	Acceptable	Avoid

<sup>1</sup> >100,000 copies/mL; BMD: bone mineral density; CVD: cardiovascular disease  
<sup>2</sup> \*\* No viral load restriction for DTG/ABC/3TC use, according to May 2014 DHHS guidelines<sup>2</sup>

1. EACS Guidelines 2013; Available at: [http://www.eacsociety.org/Portals/0/Guidelines\\_Online\\_131014.pdf](http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf) (accessed Mar 2014). 2. DHHS Guidelines 2014; Available at: [www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf](http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf) (accessed May 2014); 3. Thompson MA, et al. JAMA 2012;308:387-402.

# NRTI options without limitations?

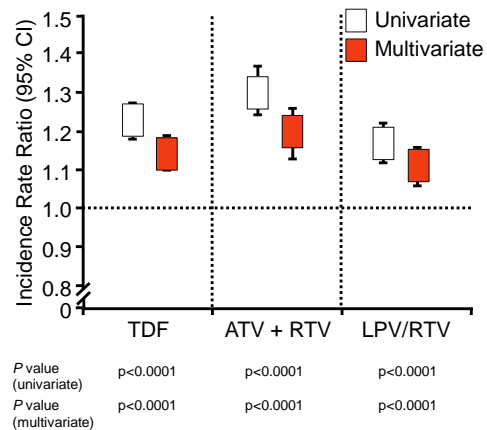
Treatment considerations	TAF/FTC	3TC only?
<b>*High viral load<sup>1,2</sup></b>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>
<b>High CVD risk<sup>1,2</sup></b>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>
<b>Renal impairment<sup>2</sup></b>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>
<b>Decrease in BMD<sup>2,3</sup></b>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>
<b>HLA-B*5701 positive<sup>1,2</sup></b>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>	<span style="background-color: #27ae60; color: white; padding: 2px 10px; border-radius: 5px;">Acceptable</span>



# D:A:D: Cumulative exposure to ARVs associated with increased CKD\* risk

CKD Risk by Yrs of ARV Exposure, Incidence Rate Ratio* (95% CI)		
Drug	1 Yr	5 Yrs
TDF	1.14 (1.10-1.19)	1.94 (1.57-2.39)
ATV + RTV	1.20 (1.13-1.26)	2.44 (1.86-3.21)
LPV/RTV	1.11 (1.06-1.16)	1.66 (1.32-2.09)

\*Multivariate analysis. For each value, P < .0001



\*CKD: Chronic kidney disease

Mocroft A, et al. Lancet HIV. 2016;3:e23-e32.

## Maintenance of HIV therapy

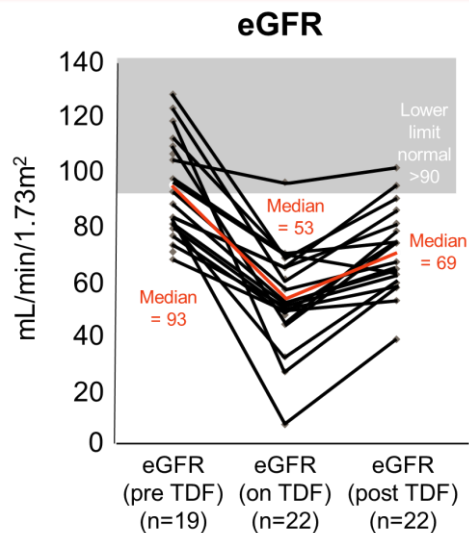
### Reactive



### Proactive

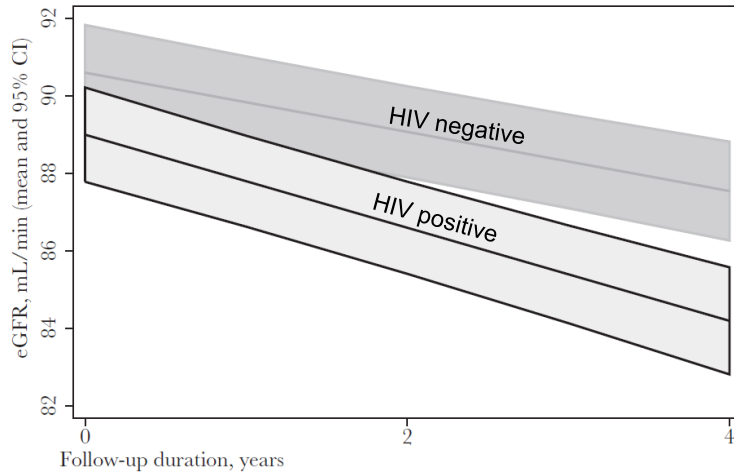


## Case series of 22 HIV-patients with TDF-associated proximal renal tubulopathy



Woodward CLN et al. HIV Medicine 2009

## Faster progression of CKD in HIV-infected individuals as compared to HIV neg. controls

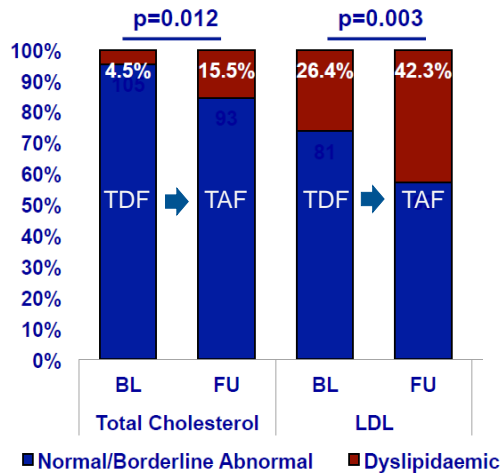


AGE<sub>hIV</sub>

Kooij KW et al. JID 2017

Mixed model adjusted for age, sex, beinf from African descent, hypertension, baseline CVD, cigarette smoking, chronic hepatitis C, T2D, dyslipidemia and their interaction with time

## Dyslipidemia following switch from TDF to TAF



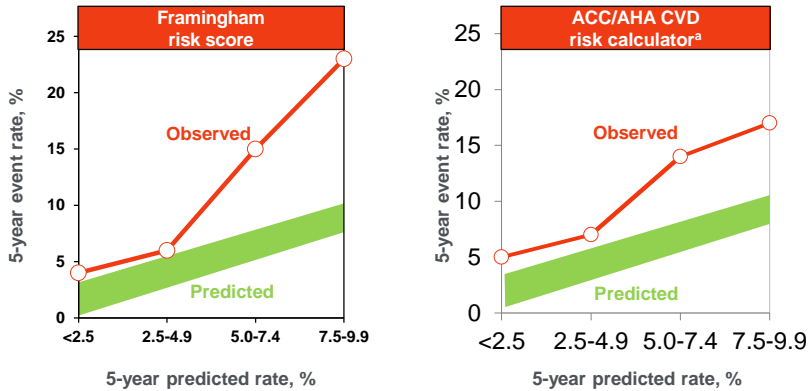
n=110, dyslipidemia defined as per NCEP ATP III guidelines

HDL cholesterol and triglycerides: no changes

Lacey A et al. EACS 2017

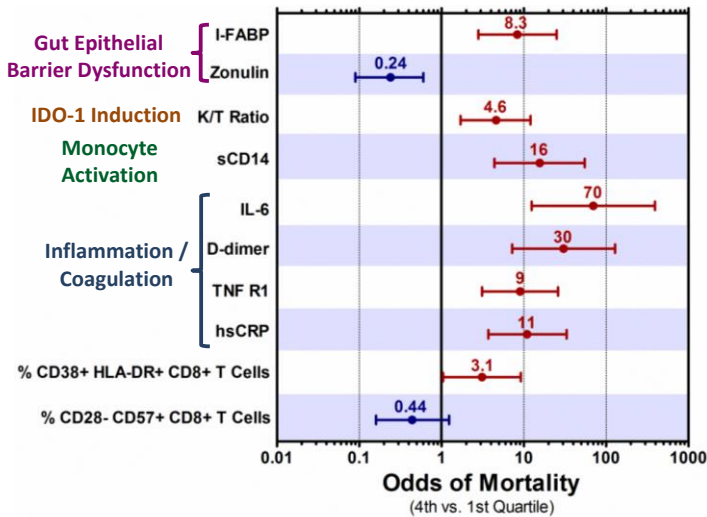
## CVD risk prediction developed for the general population underestimate CVD risk in HIV+ patients

Observed vs predicted 5-year CVD outcomes in partners healthcare system



1. Regan S et al. CROI 2015. Seattle, WA. #751; 2. Thompson-Paul A et al. CROI 2015. Seattle, WA. #747

## Innate immune activation predict mortality during suppressive ART



Hunt, JID, 2014 (see also: Sandler, JID, 2011; Tenorio, JID 2014)

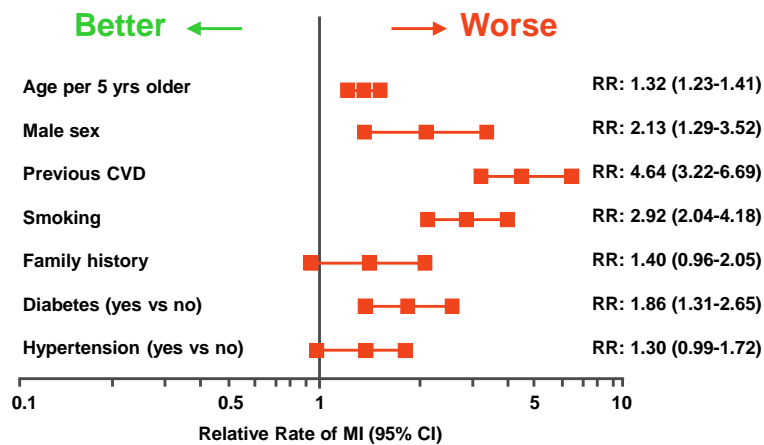
## If cytokines were colours,...



...what would be the right mixture?

Paul Cézanne

## D:A:D: Traditional risk factors for CVD

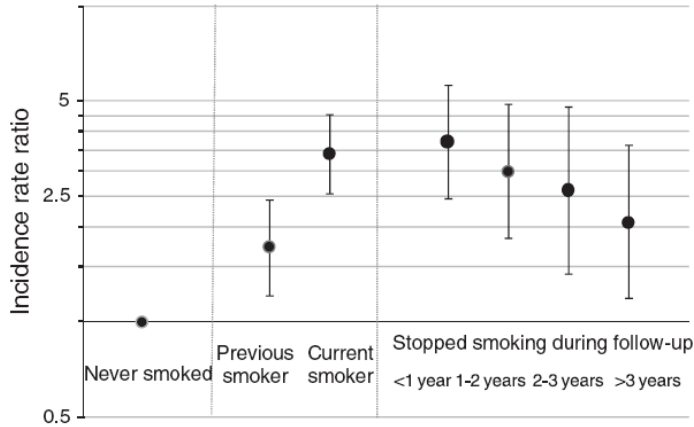


Multivariable Poisson model adjusted for age, sex, BMI, HIV risk, cohort, calendar year, race, family history of CVD, smoking, previous CVD event, TC, HDL, hypertension, diabetes.

Friis-Møller N et al. *N Engl J Med.* 2007;356:1723-1735.

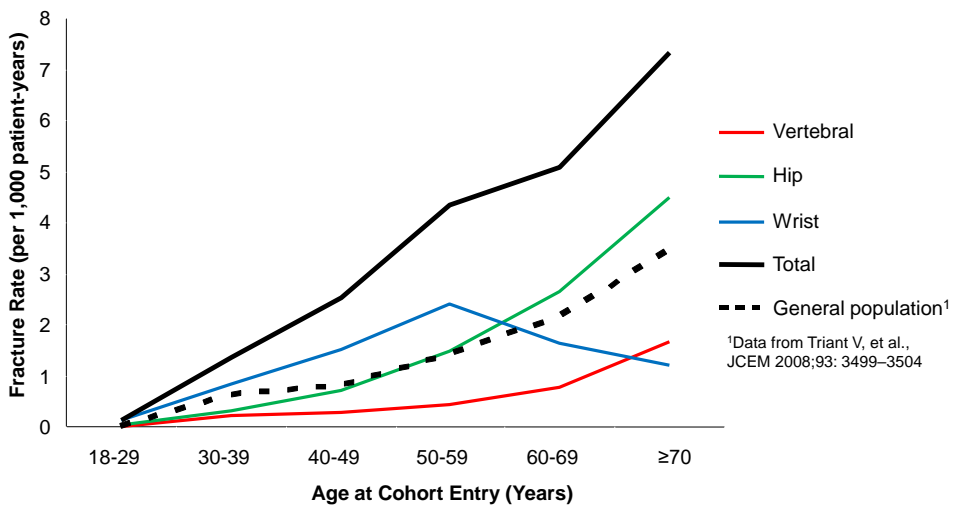
# Stop smoking! D:A:D

Myocardial infarction relative risk ratios



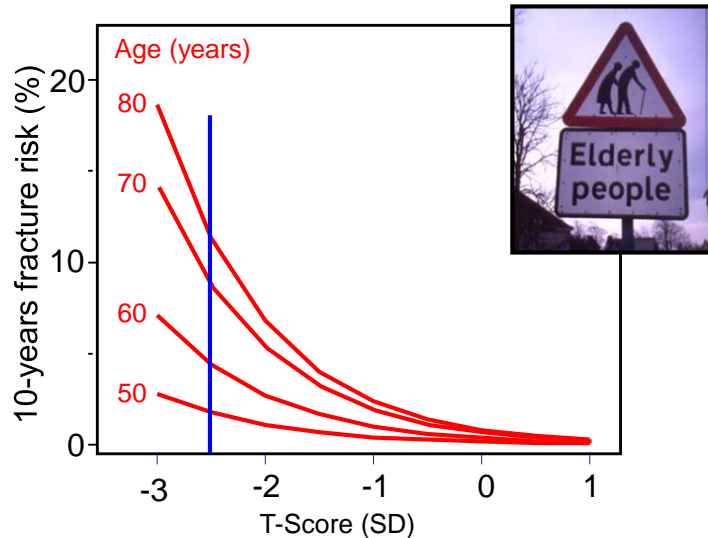
Petoumenos et al. HIV Medicine 2011

# Age-adjusted rates of osteoporotic fractures in HIV patients



Bozette et al. 2011

## Age is an important factor for osteoporotic fractures



Kanis JA et al Osteoporosis Int 2002;13:527-536

## Multi-morbidity and frailty

### Concept of **multi-morbidity**:

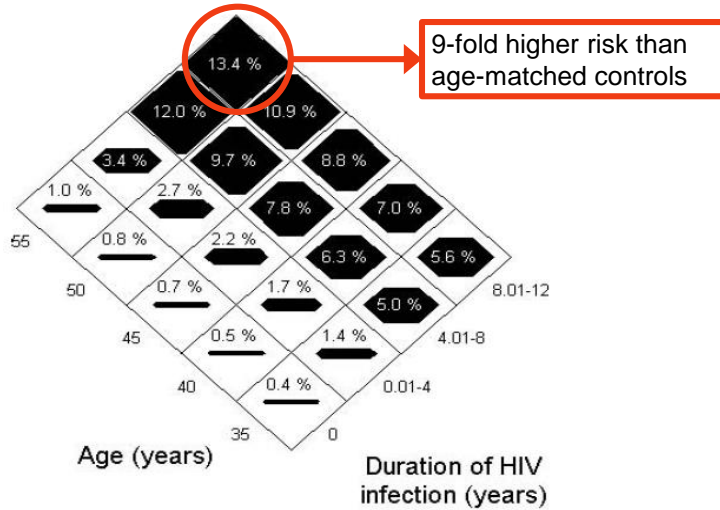
- Total is greater than sum of parts

### **Frailty phenotype**:

- 3 of 5 (weight loss, exhaustion, weakness, slowness, and low physical activity)
- associated with higher mortality in HIV



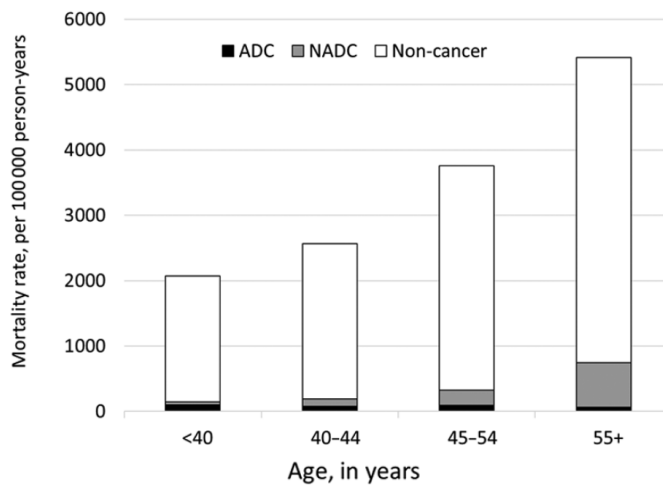
## Frailty increases with age and time with HIV



Desquilbet, et al. J Gerontol Med Sci 2007;62A:1279-86

## Cancer-attributable mortality in HIV-patients on ART (North America, 1995-2009)

10% of death attributable to cancer in patients on ART

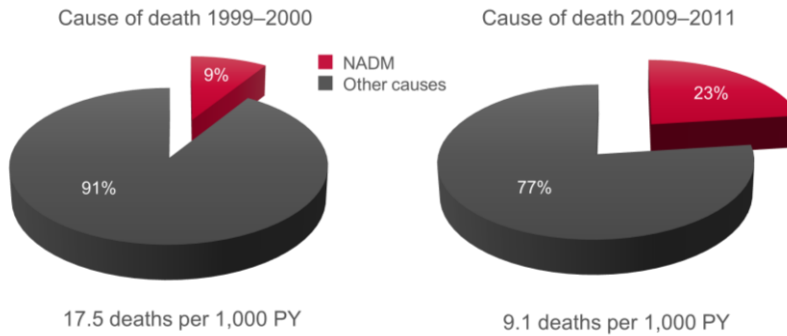


Engels et al. Clin Infect Dis 2017

N = 46,956

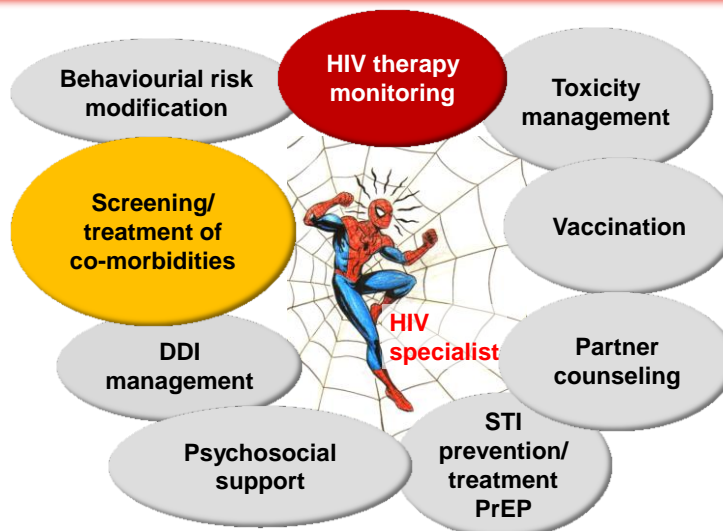
## What's killing the D:A:D cohort?

### D:A:D cohort (49,731 PLWH)

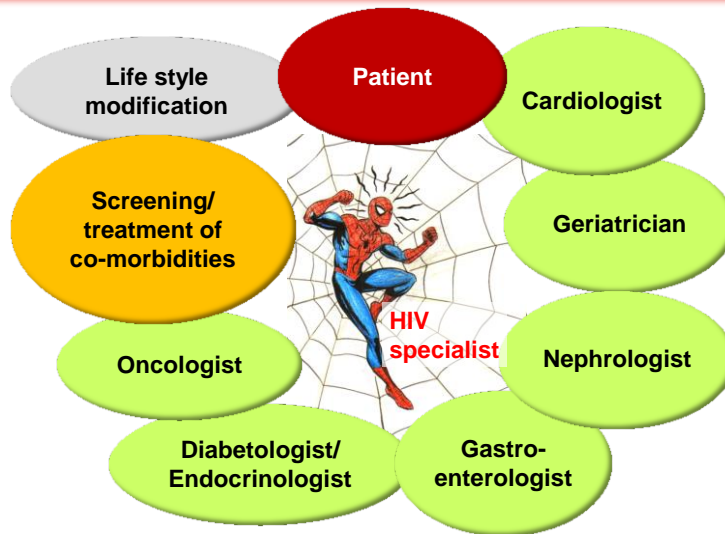


Worm SW. BMC Infect Dis 2013;13:471

## „Job description“ of HIV physicians

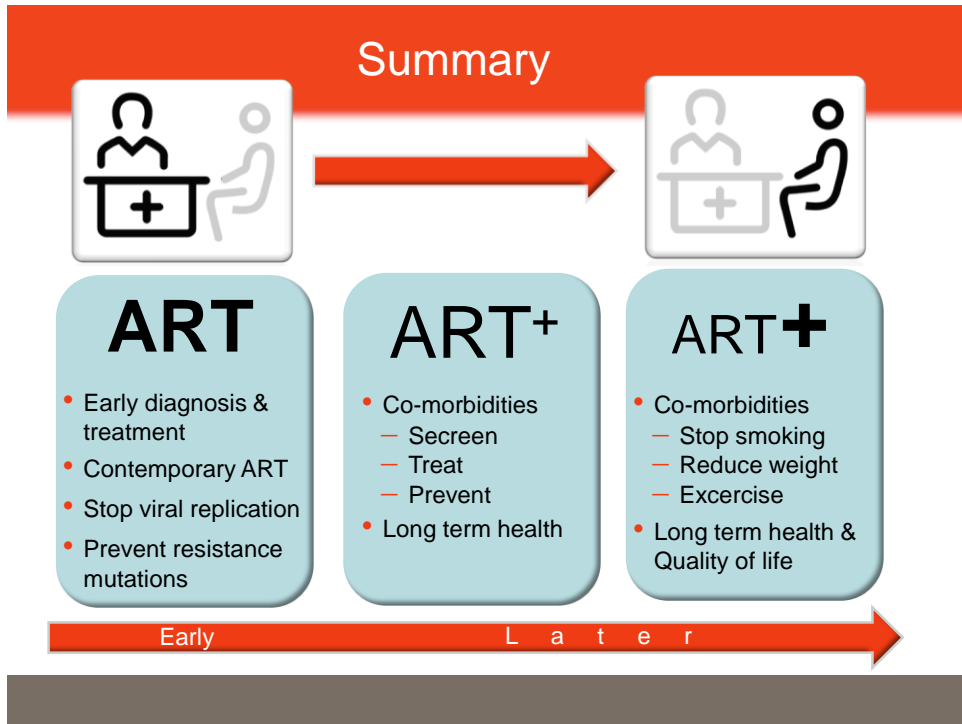


## „Job description“ of HIV physicians



## Co-morbidities in HIV patients: Hit hard, hit early????

- **Co-morbidities** are increasingly important in HIV medicine: (For physicians, patients, health care system, ...)
- Which co-morbidities are **most relevant**?
- **Guidelines** (EACS) aim to help
- **Individualized therapy** more important for co-morbidity treatment, less for ART?
- **Interventional trials**: clinical endpoints / patient-reported outcomes / different regions of the world



## Outlook

Diagnosed	On ART	<50 copies	Good health	Life expectancy
<b>90</b>	<b>90</b>	<b>90</b>	<b>90</b>	<b>90</b>