

The purpose

- What are some of the comorbidities

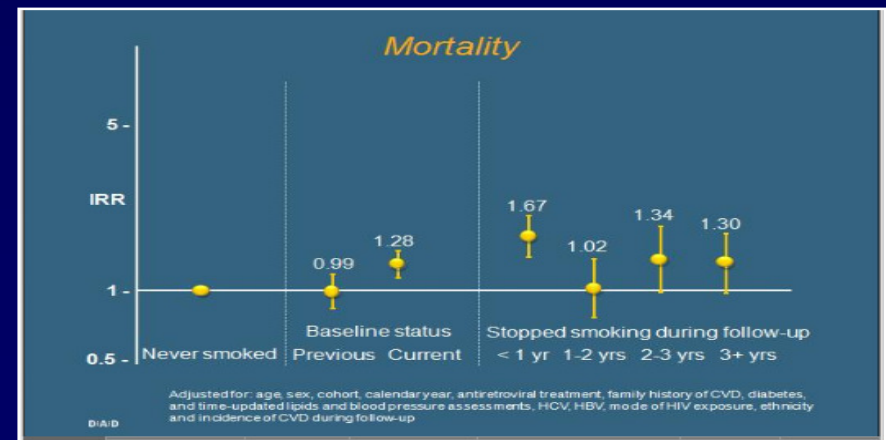
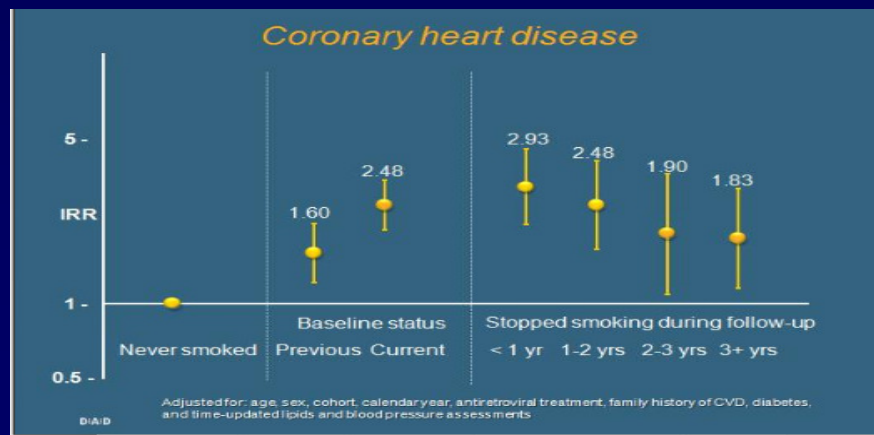
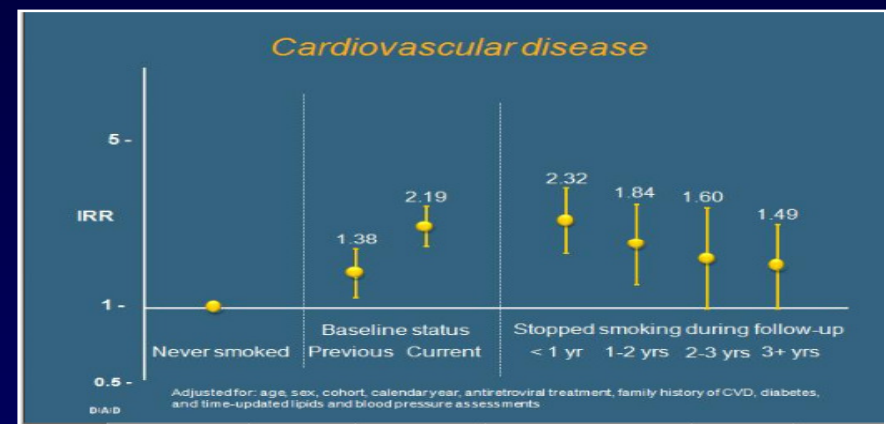
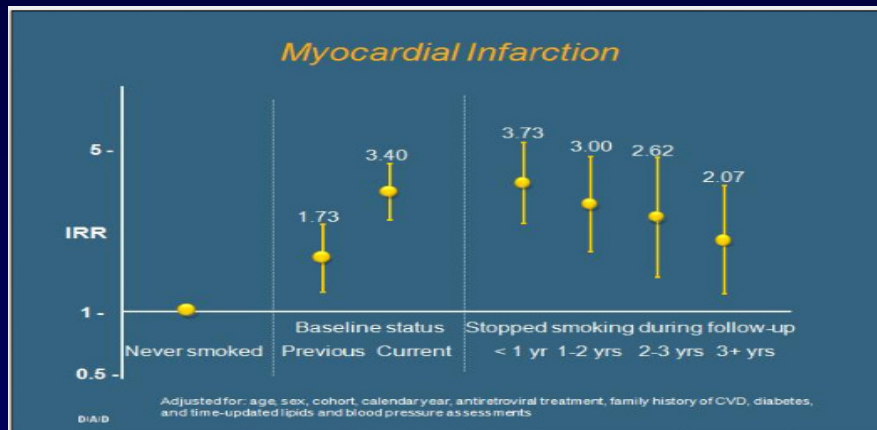
- MORE IMPORTANTLY ARE THEY REALLY RELATED TO HIV AT ALL

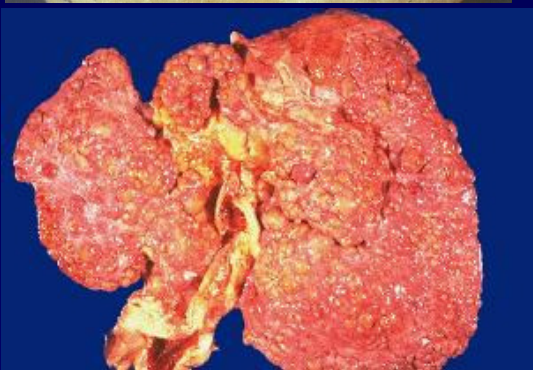
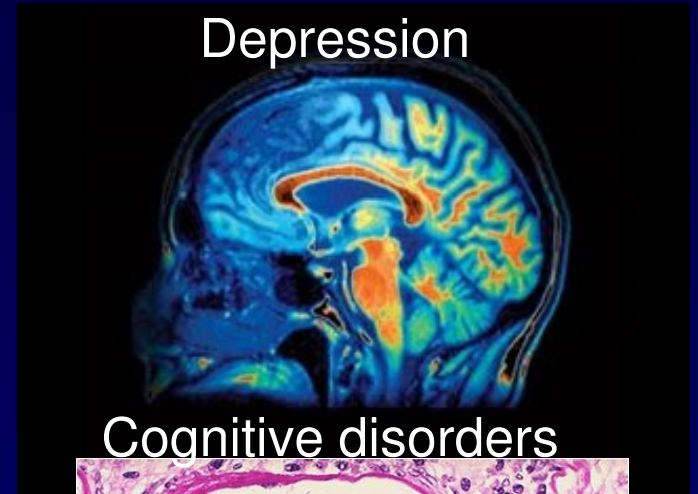
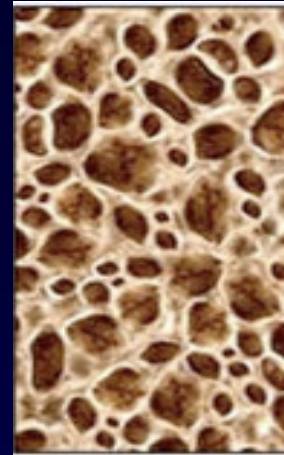
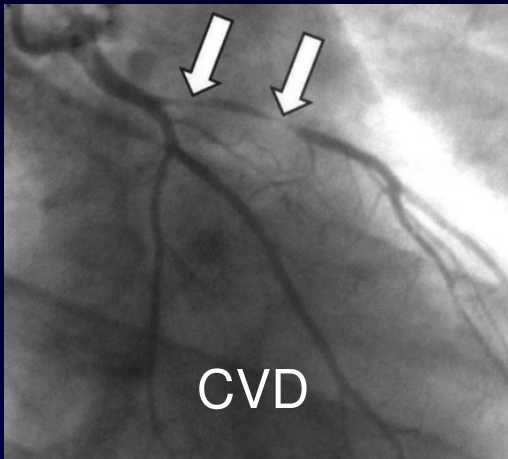
The answer

- Comorbidities exist need to be handled
- BUT relationship with HIV enormous implications for when and how to treat

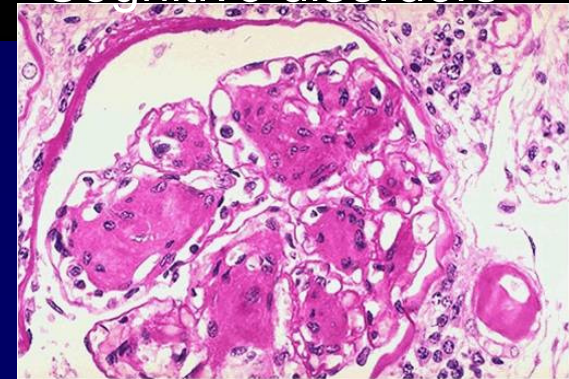
Potential clinical benefits for smoking cessation in HIV patients

- >27,500 HIV-positive patients in the D:A:D study
- Rates of CVD before and after smoking cessation





Chronic liver disease



Chronic renal disease

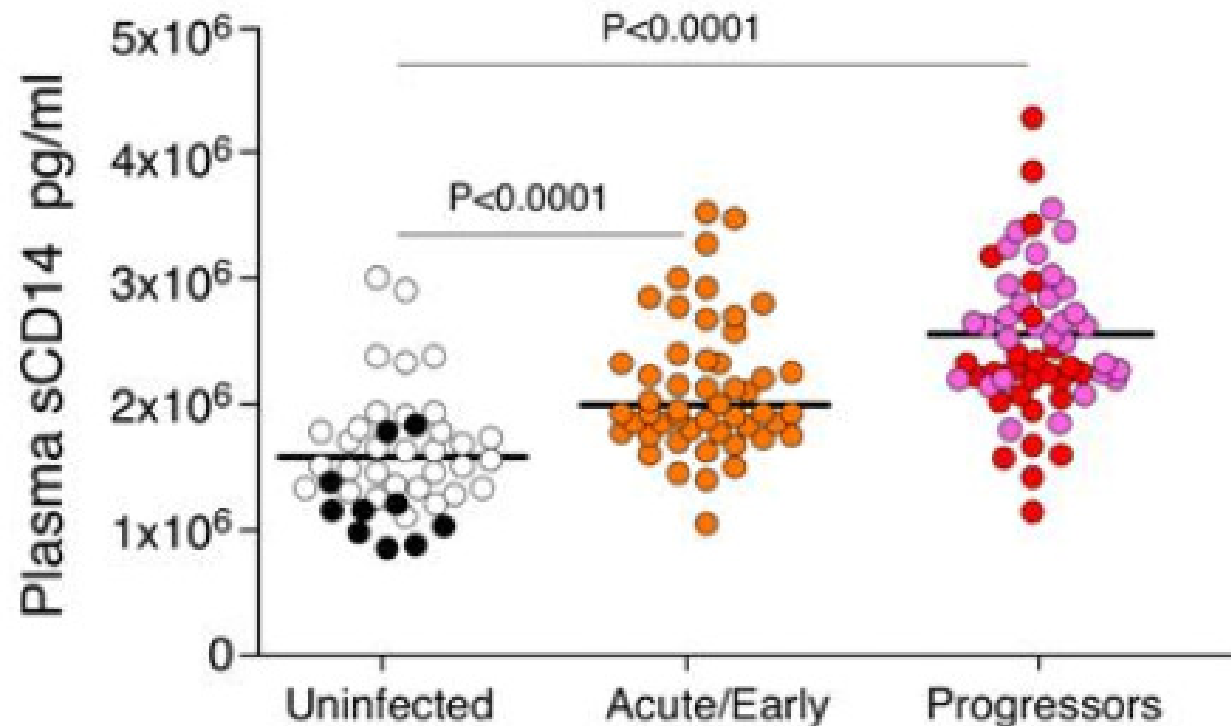
CAUSATION

\neq

ASSOCIATION

Is LPS Causing Immune Activation In Vivo?

- LPS-stimulated monocytes secrete sCD14 and shed surface CD14



Raised plasma sCD14 indicates chronic in vivo stimulation of monocyte/macrophages by LPS

Causation

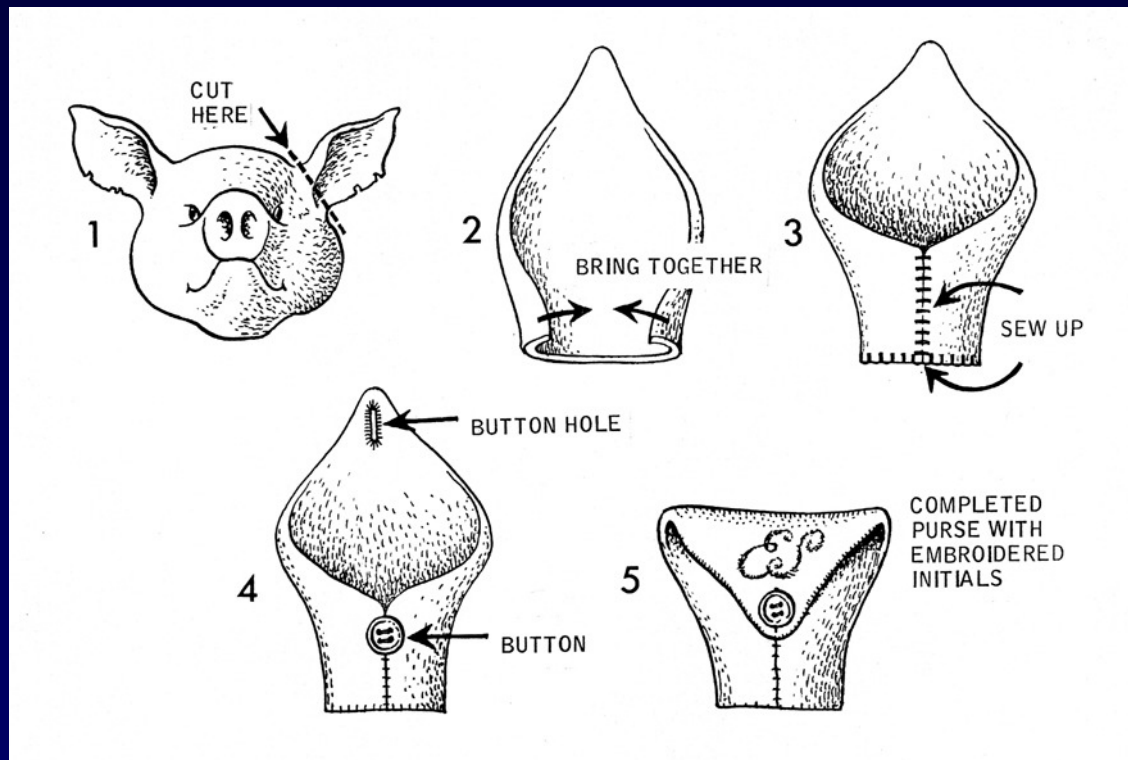
? degree of correlation

? effects of eradication

Biological plausibility

Cohort Studies

- How to make a silk purse out of a sow's ear

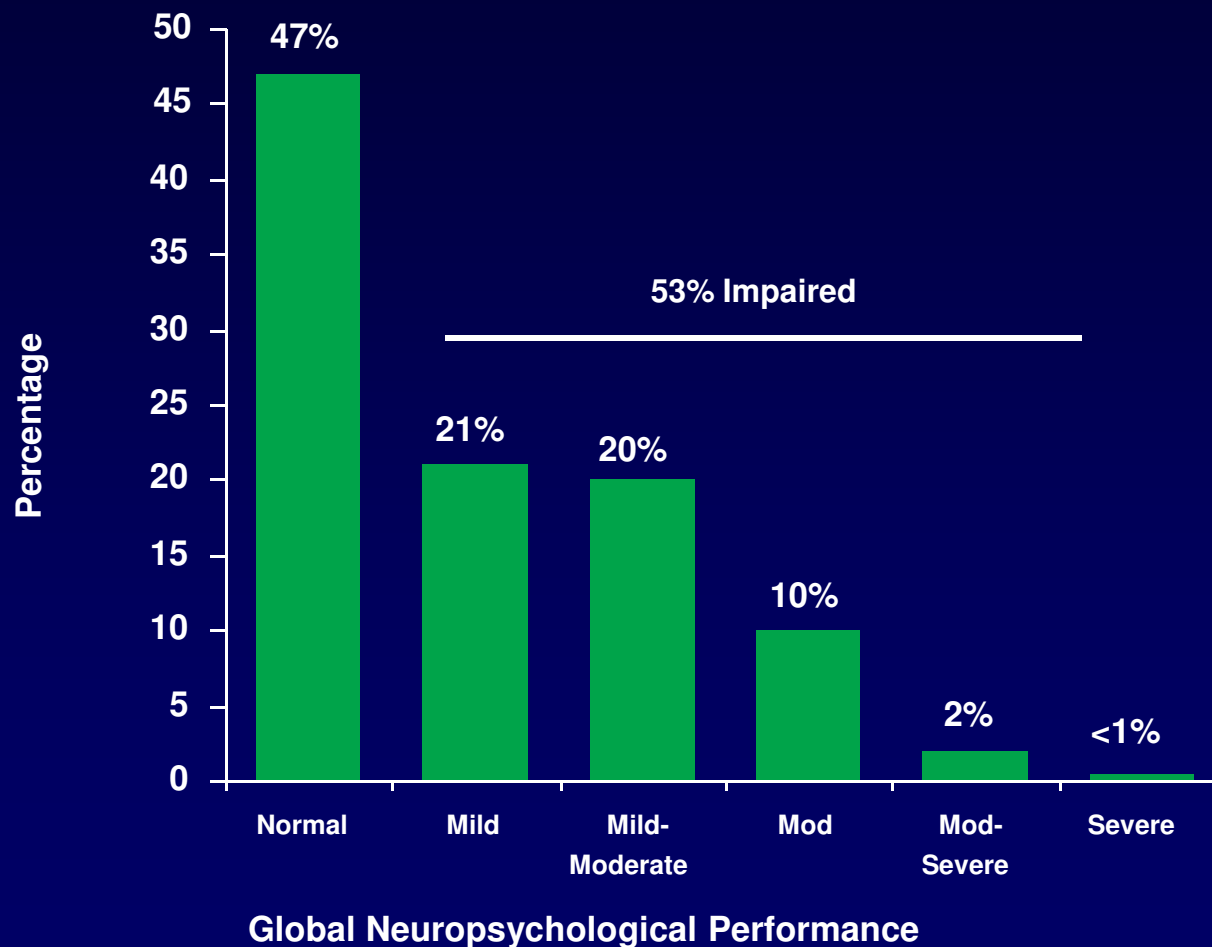


Many hidden biases

Cohort studies

1. Channelling biases
2. Missing events
3. Lead/lag time

CHARTER study: high prevalence of neurocognitive impairment



Incidence and impact on mortality of severe neuro-cognitive disorders in persons with and without HIV: a Danish nationwide cohort study

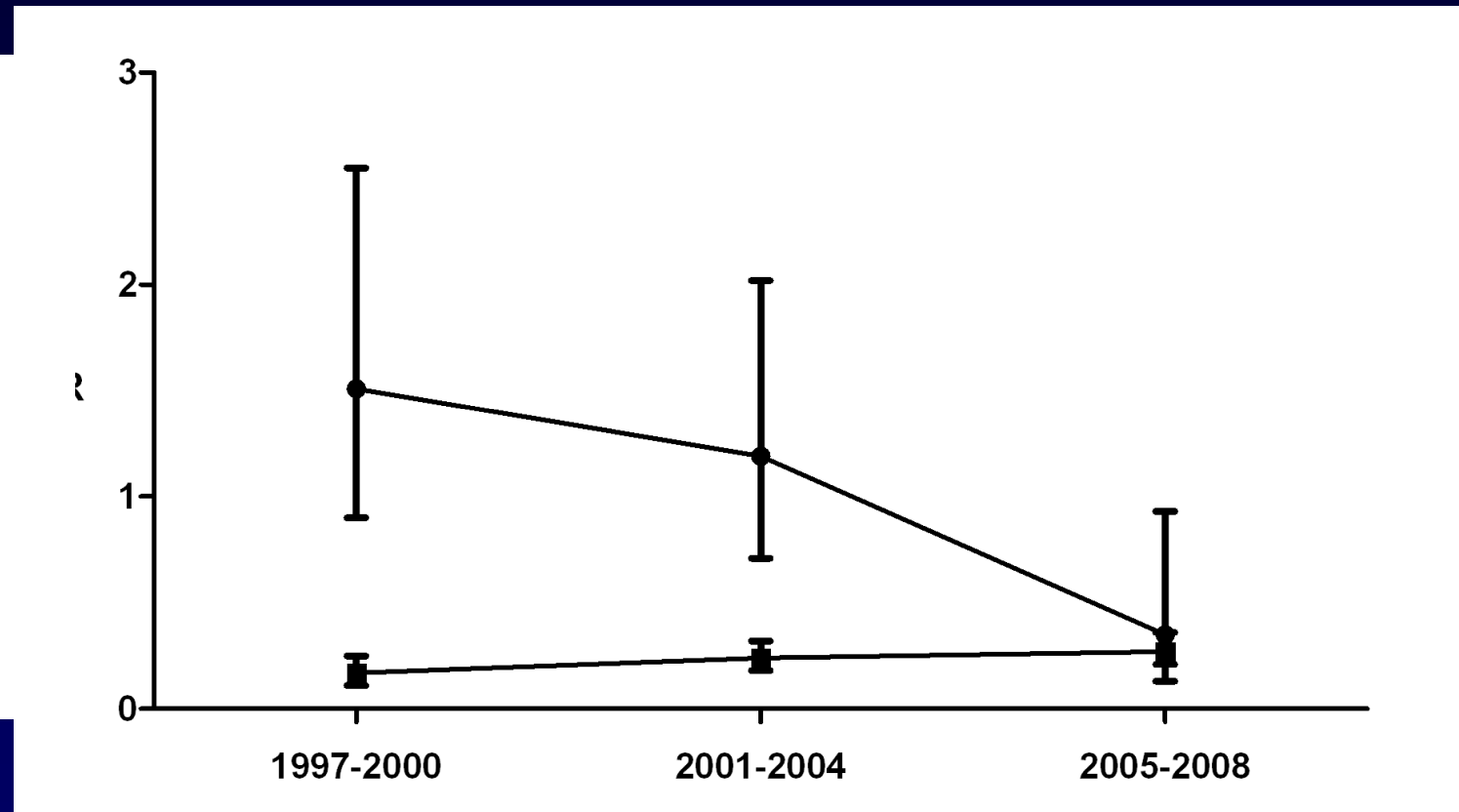
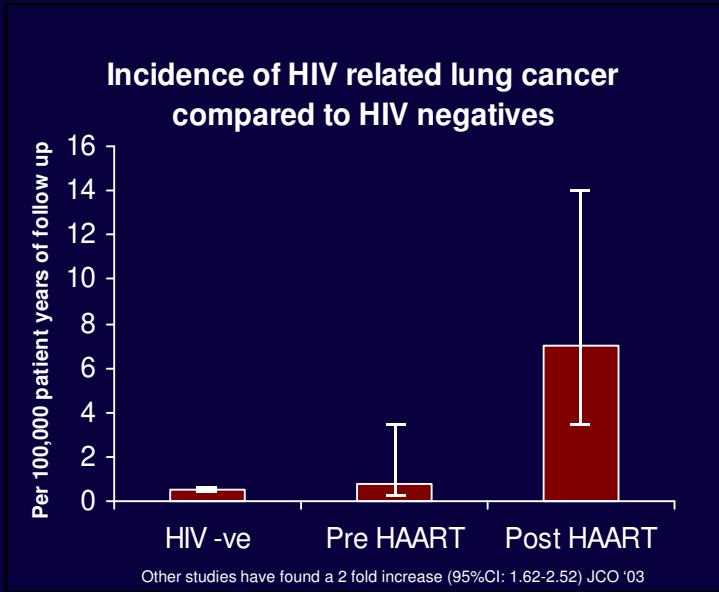
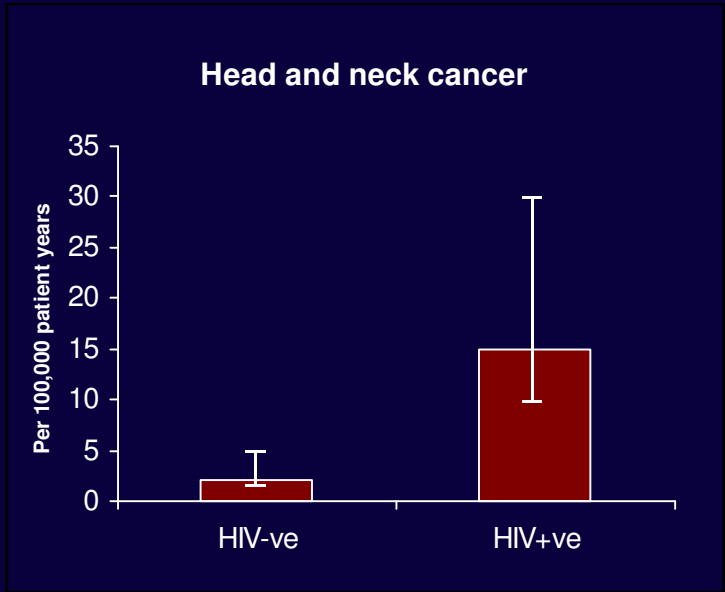
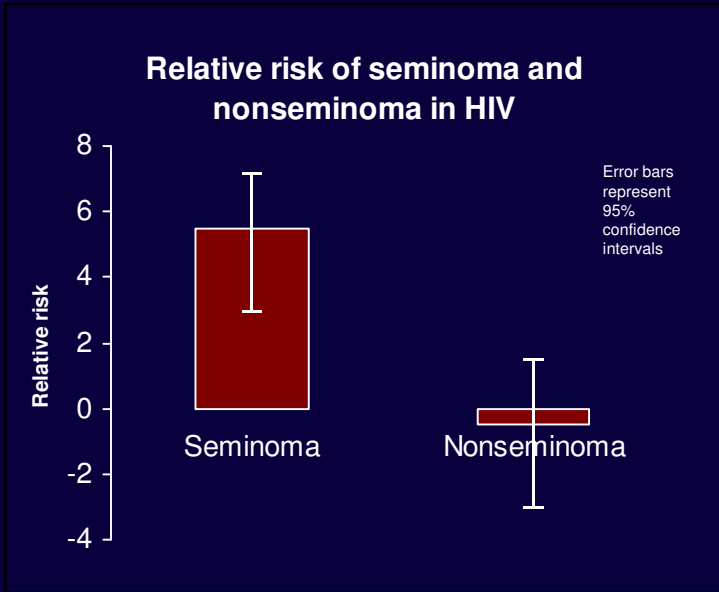
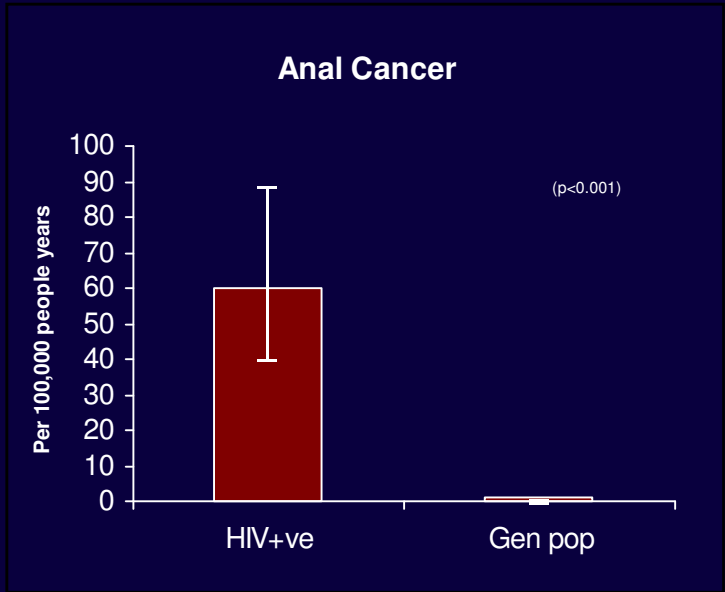


Figure 1: Incidence rates (IR) (per 1000 PYR, 95% confidence intervals) for severe neuro-cognitive disorders in HIV-infected patients (filled circles) and population controls (squares) by time periods; 1997-2000, 2001-2004 and 2005-2008.

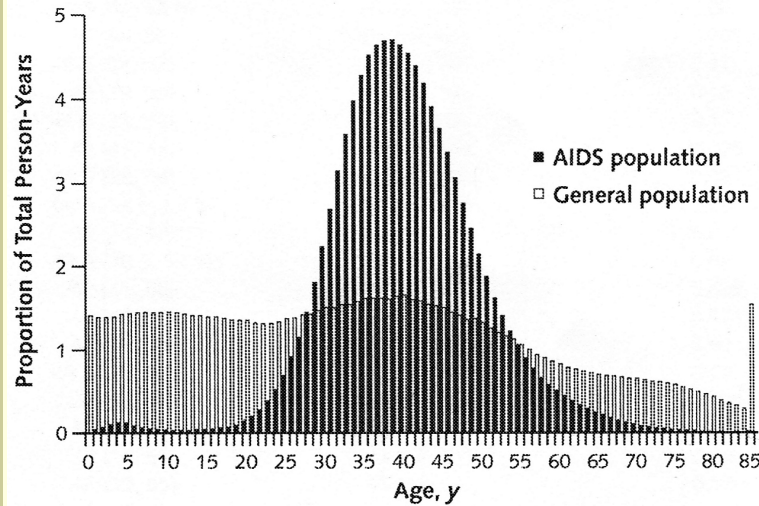
Our hand study

- Cross section on art frequency of “hand” same as general
- Population driven by anxiety

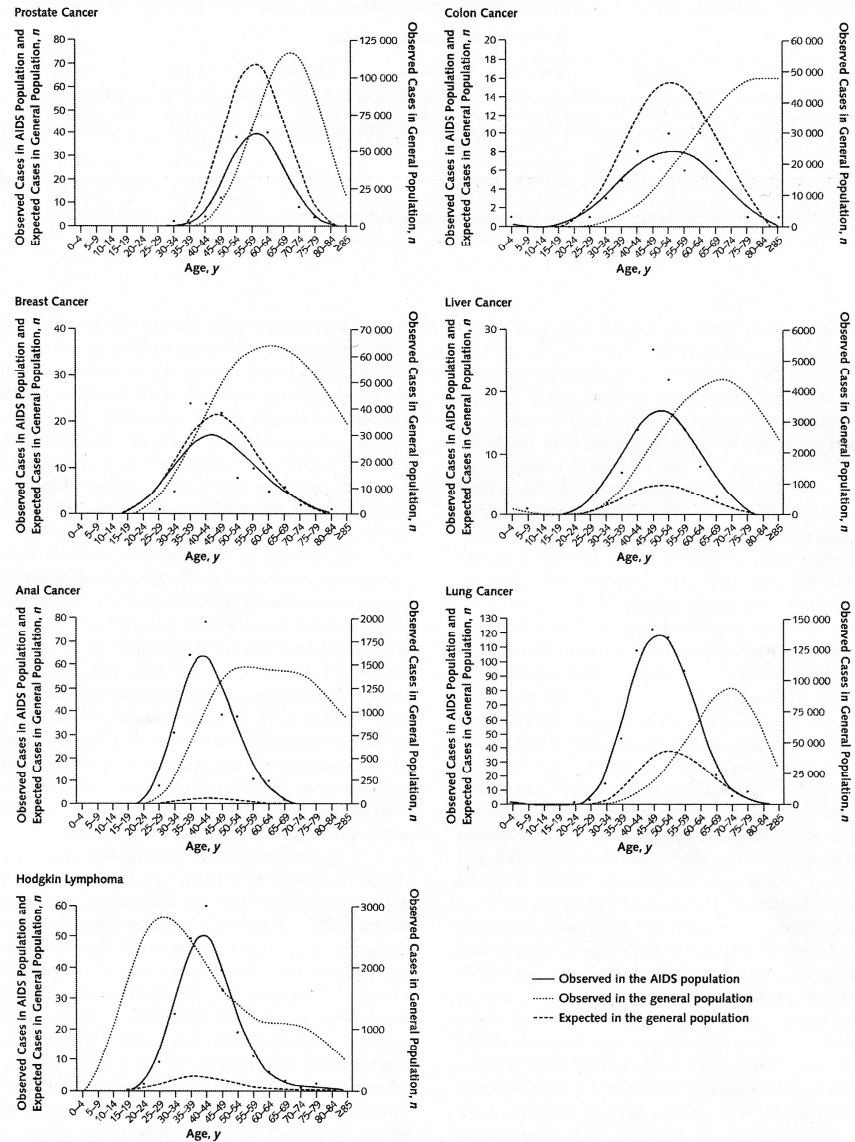
- longitudinal on art tendency to improve



Cancer in the AIDS population

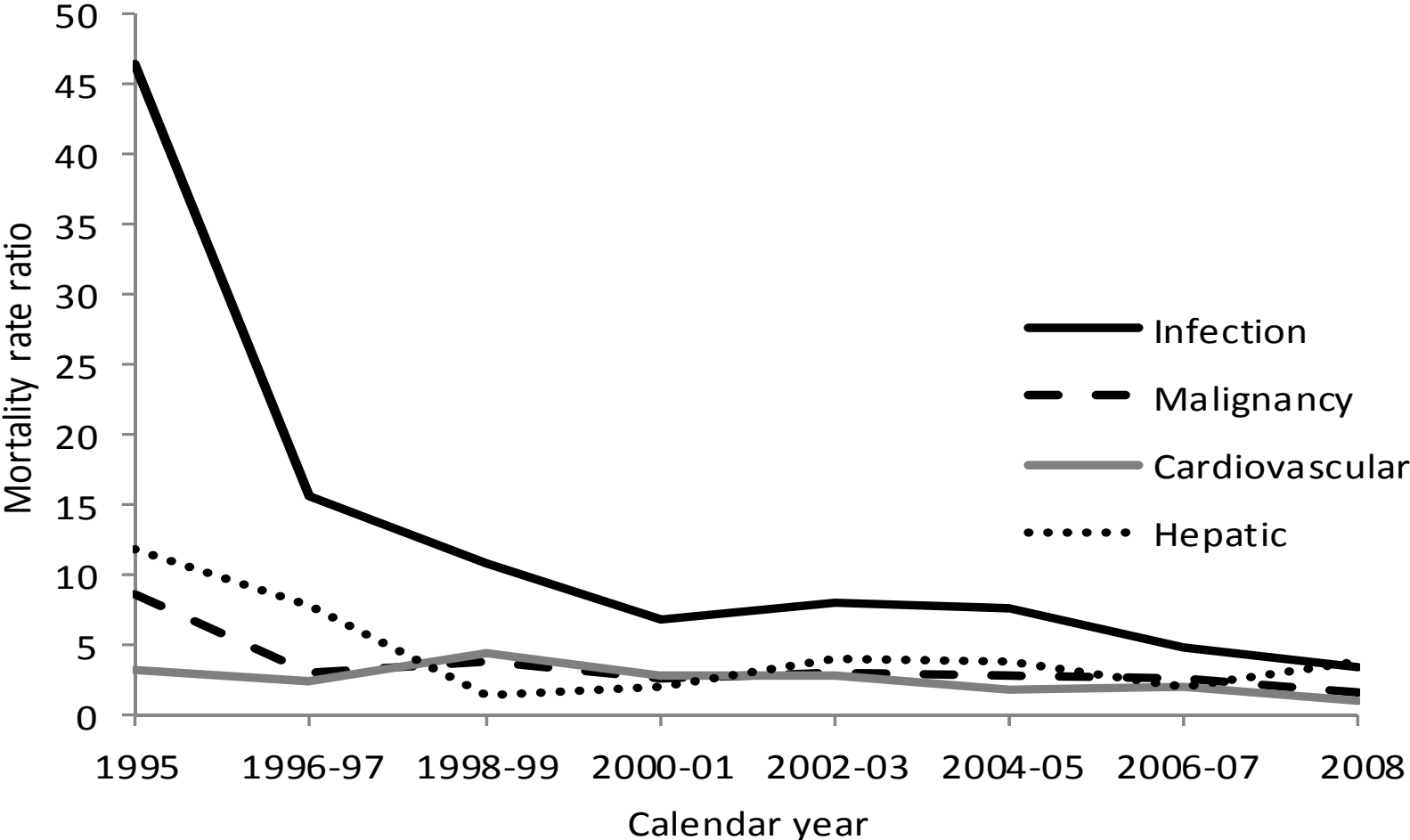


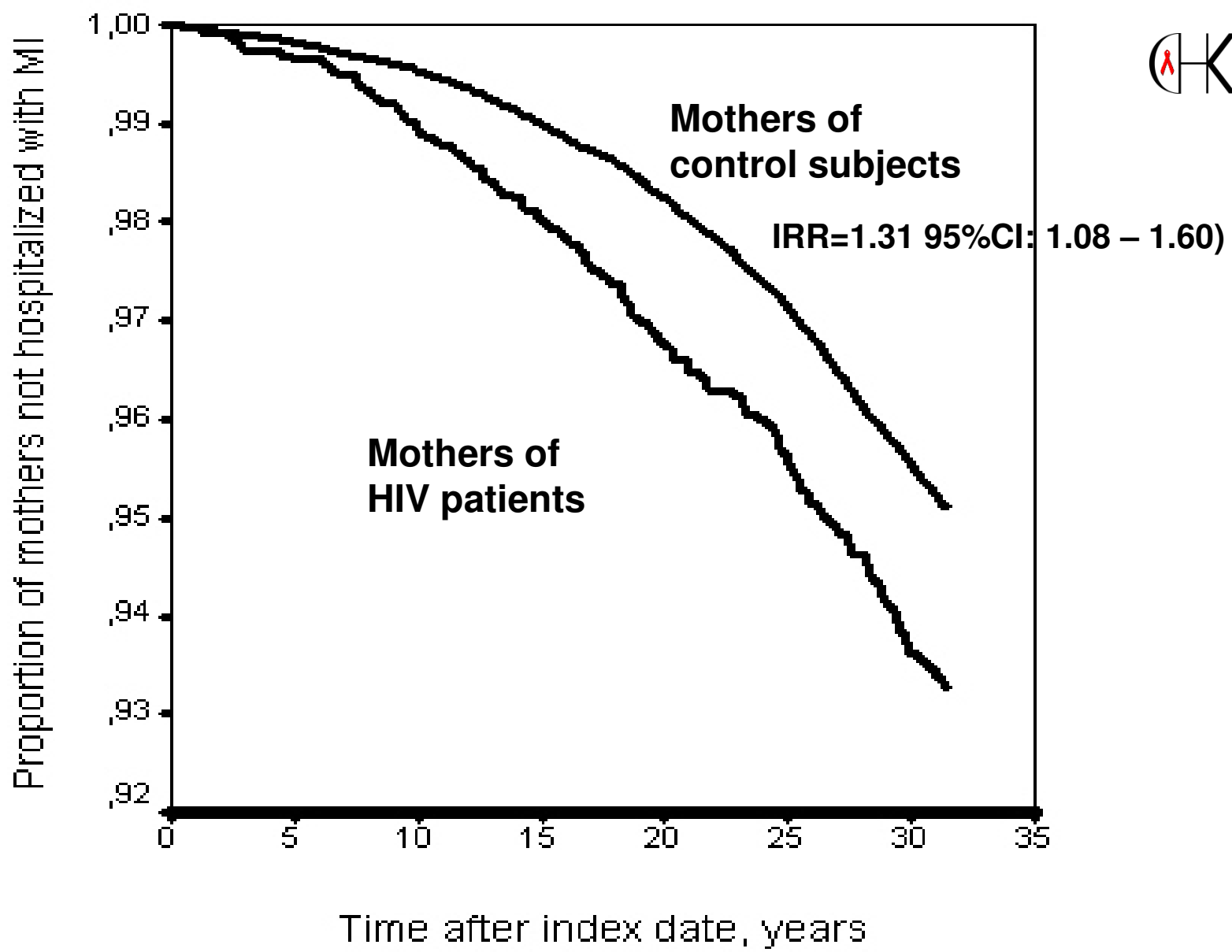
Follow-up time at risk for cancer in both the AIDS and general populations, by age, for regions covered by the HIV/AIDS Cancer Match Study (1996 to 2007).



Points represent cases of cancer observed among persons with AIDS.

Causes of death among Danish HIV patients compared to population controls in the period 1995-2008





Rasmussen et. al, BMC Infectious Diseases, 2011

Proper controls

- HIV indigent risk takers drug alcohol users
- Controls @ high risk of hiv but negative

BMD in Iprex

- 2045 individuals baseline DEXA
- Z score > -2 in 12%
- In San Fran osteoporosis 4.5% poppers

Life expectancy at birth (men)

Do they die of premature ageing in Glasgow or is it something different?

Which group of “normal Population would you choose to compare with your HIV population

Glasgow (deprived area)	54
Australian Indigenous	59
India	61
Philippines	65
Lithuania	66
US	75
UK	76
Australian average	77
Glasgow (affluent area)	82

Untangling HIV from comorbidities



When did it all Start?

Non-HIV outcomes – SMART Trial

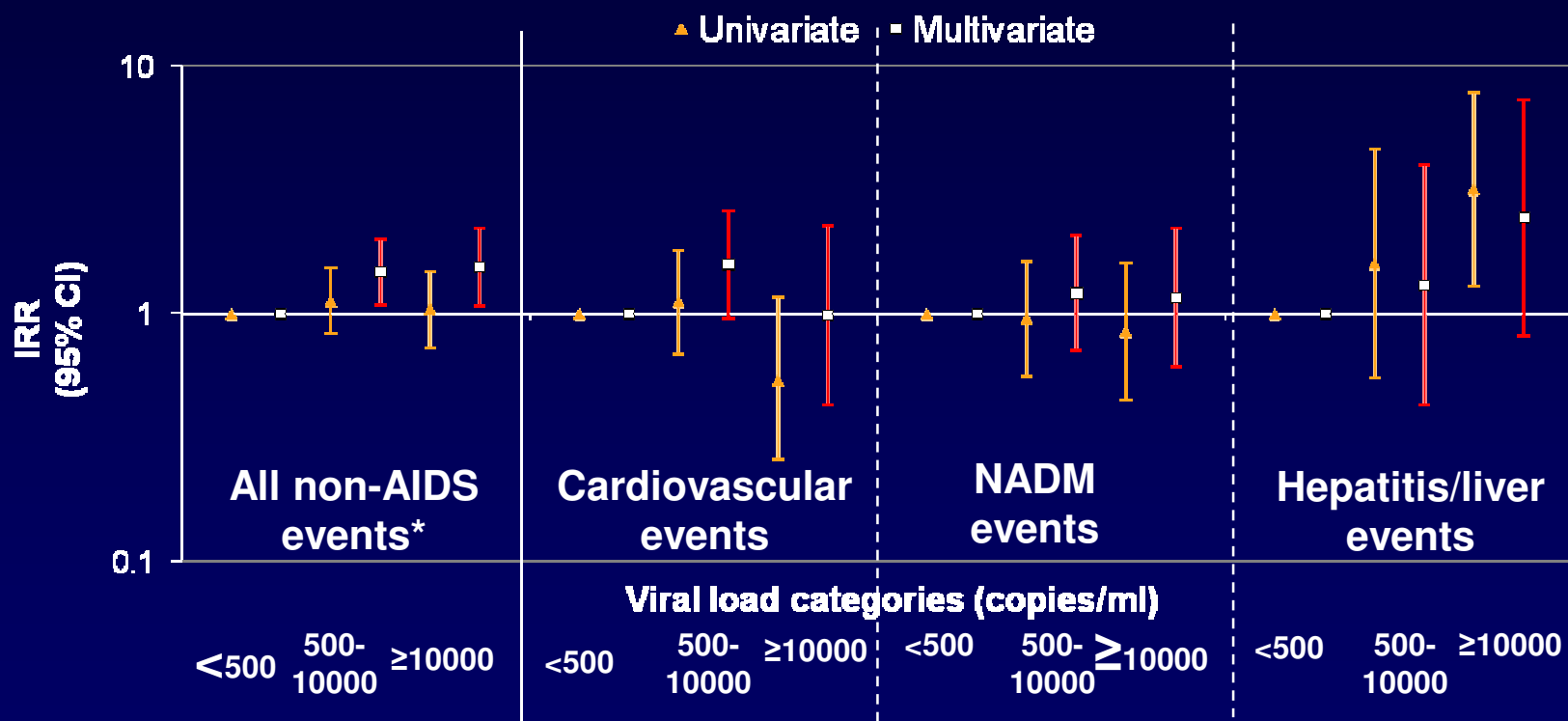
- Risk of serious non-AIDS events in subset of patients in SMART trial
- 477 patients were ART-naïve or had been off ART for ≥ 6 months

Number of events		Hazard ratio: deferred vs immediate ART (95% CI)	P-value
Deferred ART	Immediate ART		
12	2	7.02 (1.57-31.4)	0.01

Untangling HIV comorbidities

- The consequences of:
 - HIV viraemia
 - Immunodeficiency
 - Inflammation
 - HAART

Now what about the Incidence ratios for non-AIDS events



*Also adjusted for peak viral load, age, HIV exposure group, region of Europe, hepatitis B and C status, diabetes, hypertension, smoking status, on cART, prior AIDS and CD4 count

Reekie J. *AIDS* 2011;25:2259-68.

Untangling HIV comorbidities

CD4 count

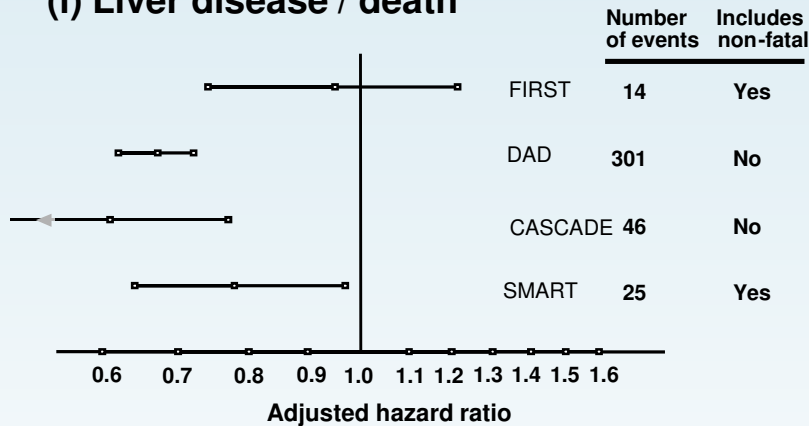
- **HIV comorbidities**

What is the association with

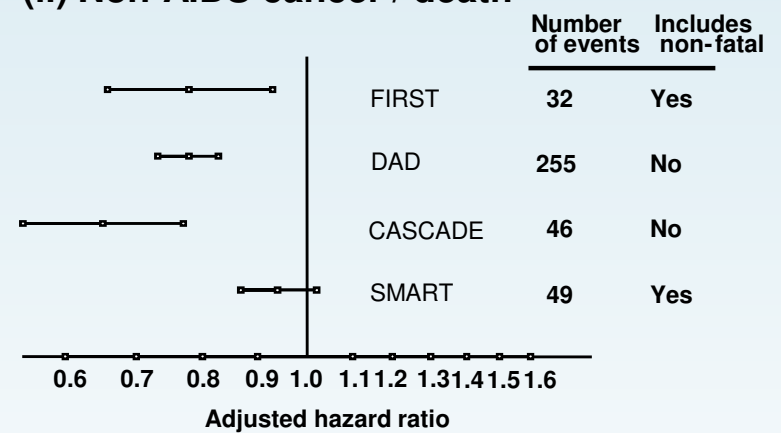
- current CD4 count

Serious non-AIDS events and latest CD4 (adjusted hazard ratio /100 cells/mm³ higher)

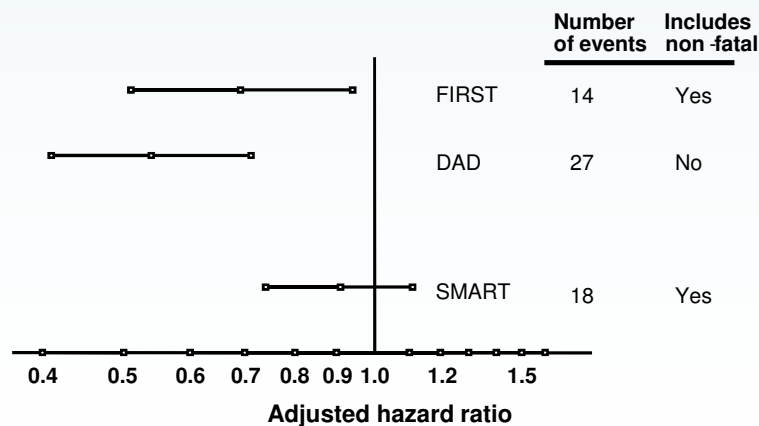
(i) Liver disease / death



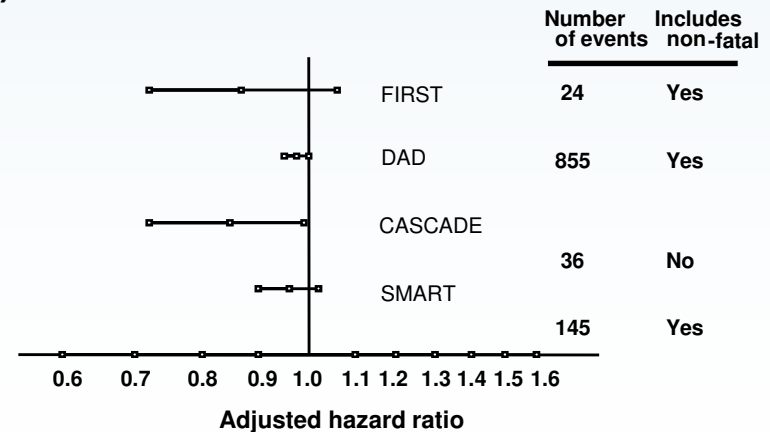
(ii) Non-AIDS cancer / death



(iii) Renal disease / death



(iv) Cardiovascular disease / death



Association Between Current CD4+ Cell Count and Non-AIDS Complications

Study	Non-AIDS Cancer/Death	Renal Disease/Death	CVD Events/Death	Liver Disease/Death
FIRST	Yes	Yes	Trend	No
D:A:D	Yes	Yes	Trend	Yes
CASCADE	Yes	NA	Yes	Yes
SMART	Trend	Trend	Trend	Yes

But is there a threshold for these events?

Impact of cART on non-AIDS events – Johns Hopkins HIV Clinical Cohort

CD4 count	Events/pyrs	Non-infectious comorbidity(/100 pyrs)	IRR (95% CI)	P-value
≤200			0.53 (0.42-0.67)	0.001
HAART	125/1029	1.2		
No HAART	400/1495	2.7		
201-350			0.5 (0.41-0.81)	0.002
HAART	64/1022	0.6		
No HAART	151/1172	1.3		
>350			0.78 (0.52-1.15)	0.16
HAART	103/2023	0.5		
No HAART	185/2386	0.8		

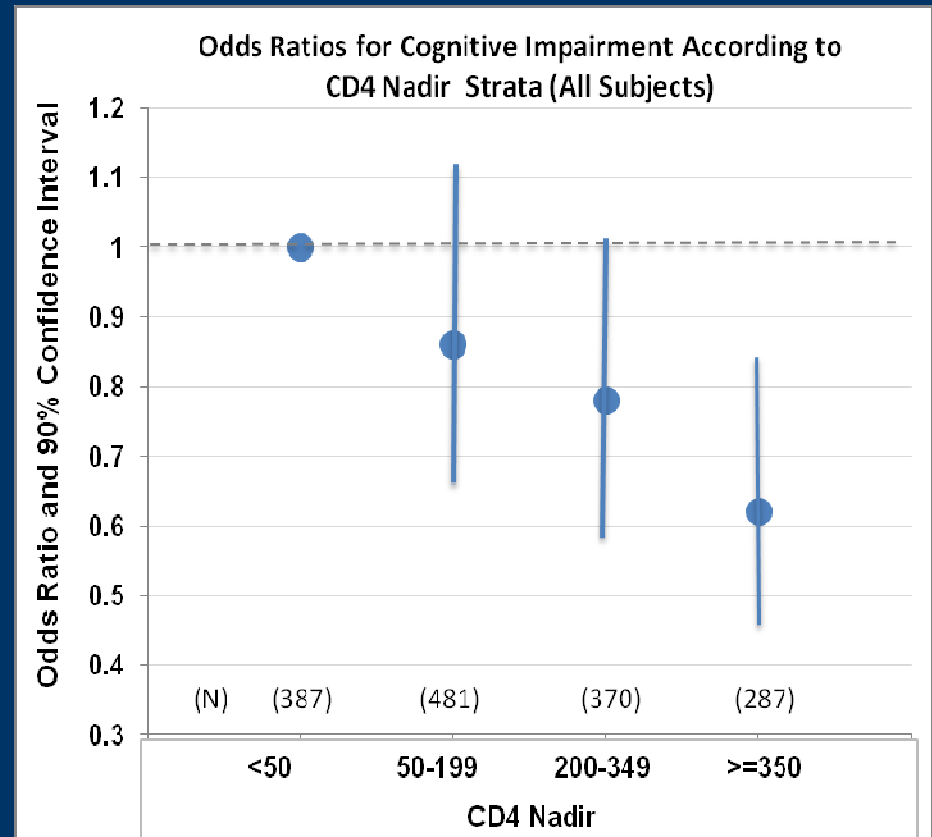
CD4 nadir and NADM – D:A:D Study

Factor		RR	95% CI	P-value
Latest CD4 count	Per 50 cells/mm ³	0.97	0.95, 0.98	0.0001
Nadir CD4 count	<100 cells/mm³	1.22	1.03, 1.44	0.02
Duration of immunosuppression (<200)	Per year	1.04	1.02, 1.05	0.0001

Worm S. Abstract 130, 19th CROI, March 5-8, 2012, Seattle.

CD4 nadir and neurocognitive impairment

- 1525 HIV+ve patients,
- CD4 nadir: 172 (48, 297) cells/ml, current CD4 count: 420 (262, 603) cells/mm³
- Nadir CD4 count determined by self-report
- CHARTER analysis suggest significant impact of nadir <350
 - Data too limited to test higher nadirs

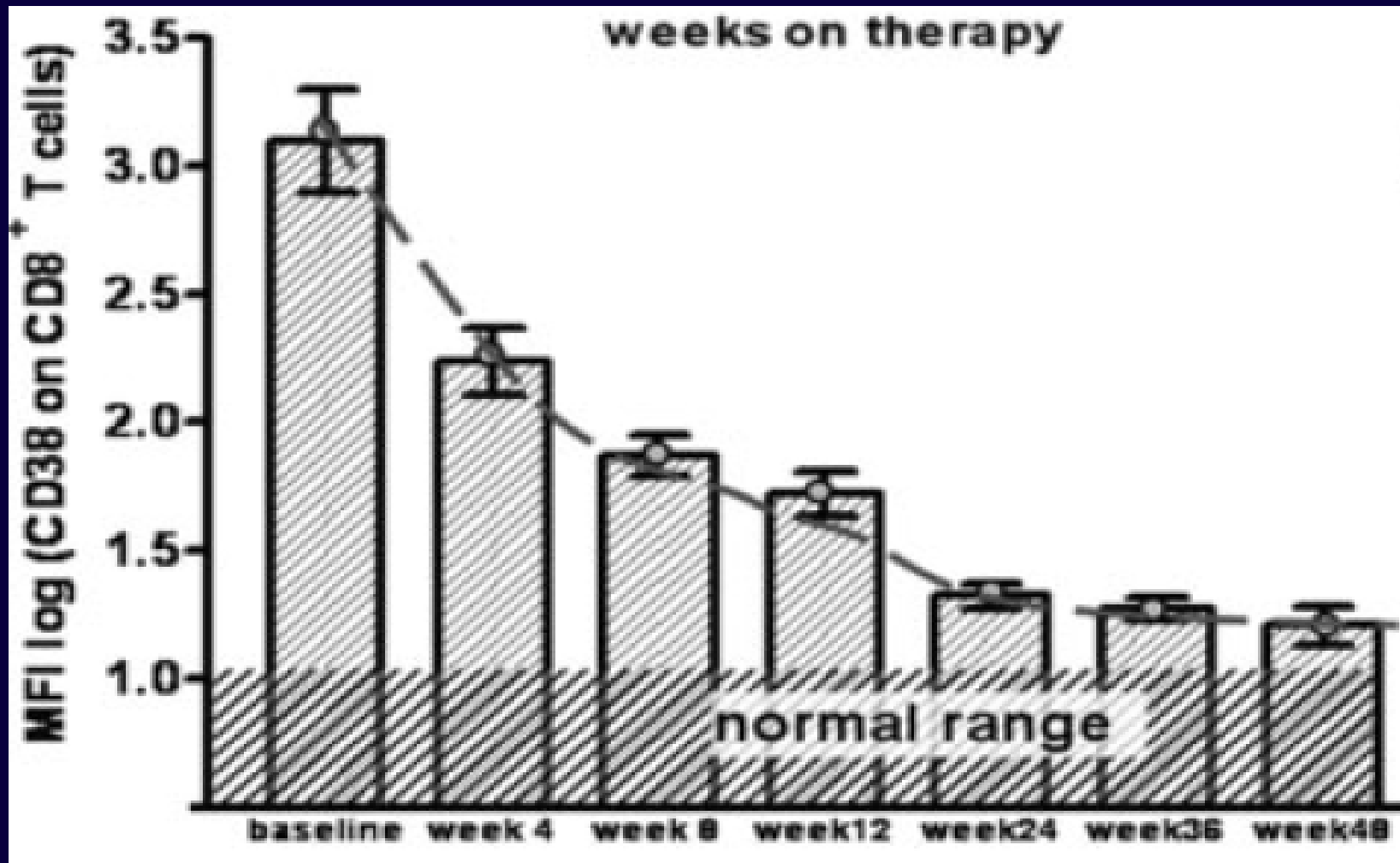


CROI 2010, Poster 429,
Ellis, et al

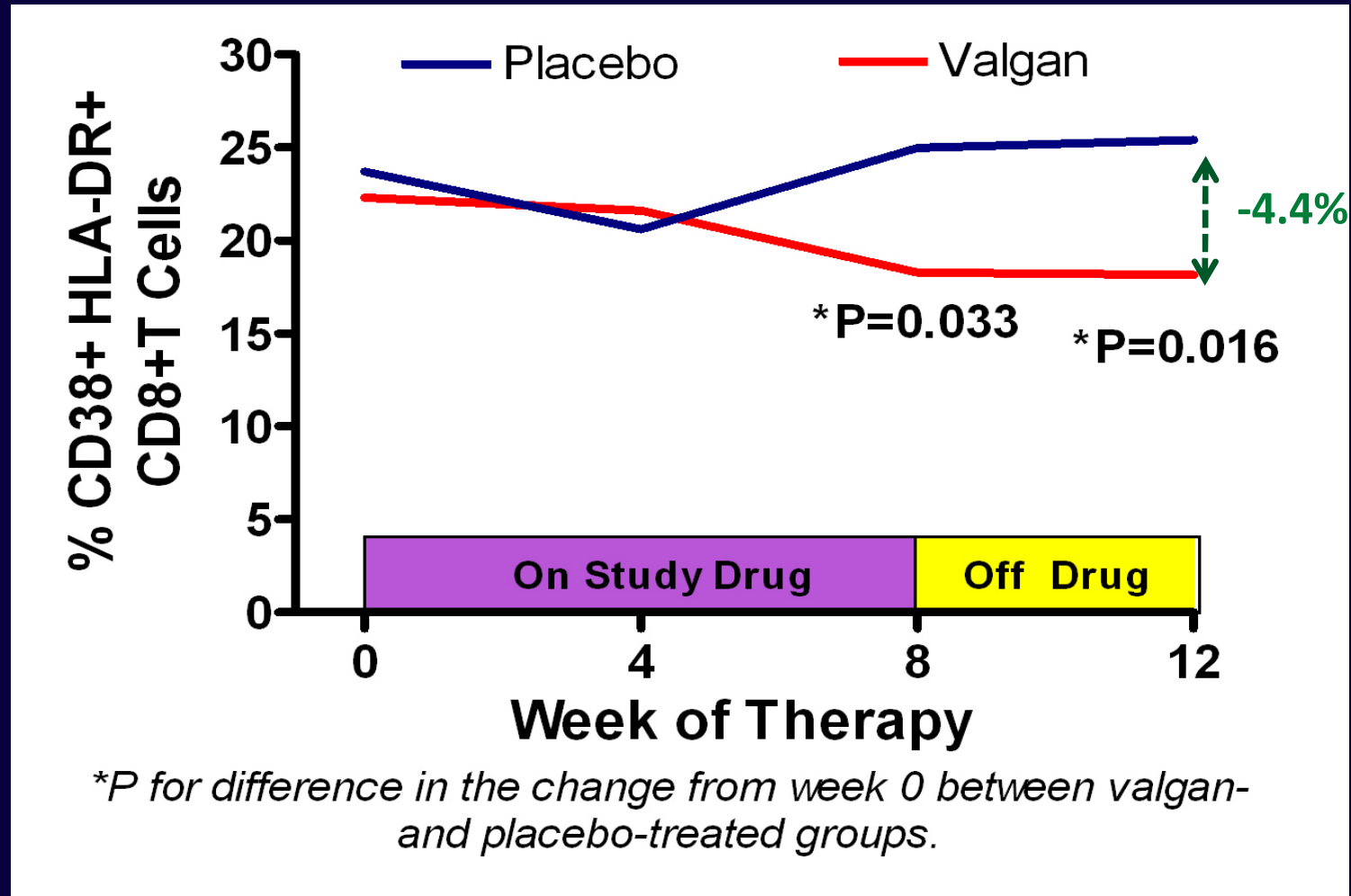
Other Mechanisms of Non –AIDS comorbidities

Inflammation

Alteration in immune activation after ART



Valgancyclovir Decreases CD8 Activation Significantly More Than Placebo



SMART: Inflammatory markers associated with mortality

Biomarker	All-cause mortality	
	Unadjusted OR	p value
hs-CRP	2.0 (1.0–4.1)	0.05
IL-6	8.3 (3.3–20.8)	<0.0001
D-dimer	12.4 (4.2–37.0)	<0.0001

- 85 cases and 170 matched controls
- OR compared top quartile with bottom quartile

OR=odds ratio; DC=drug conservation

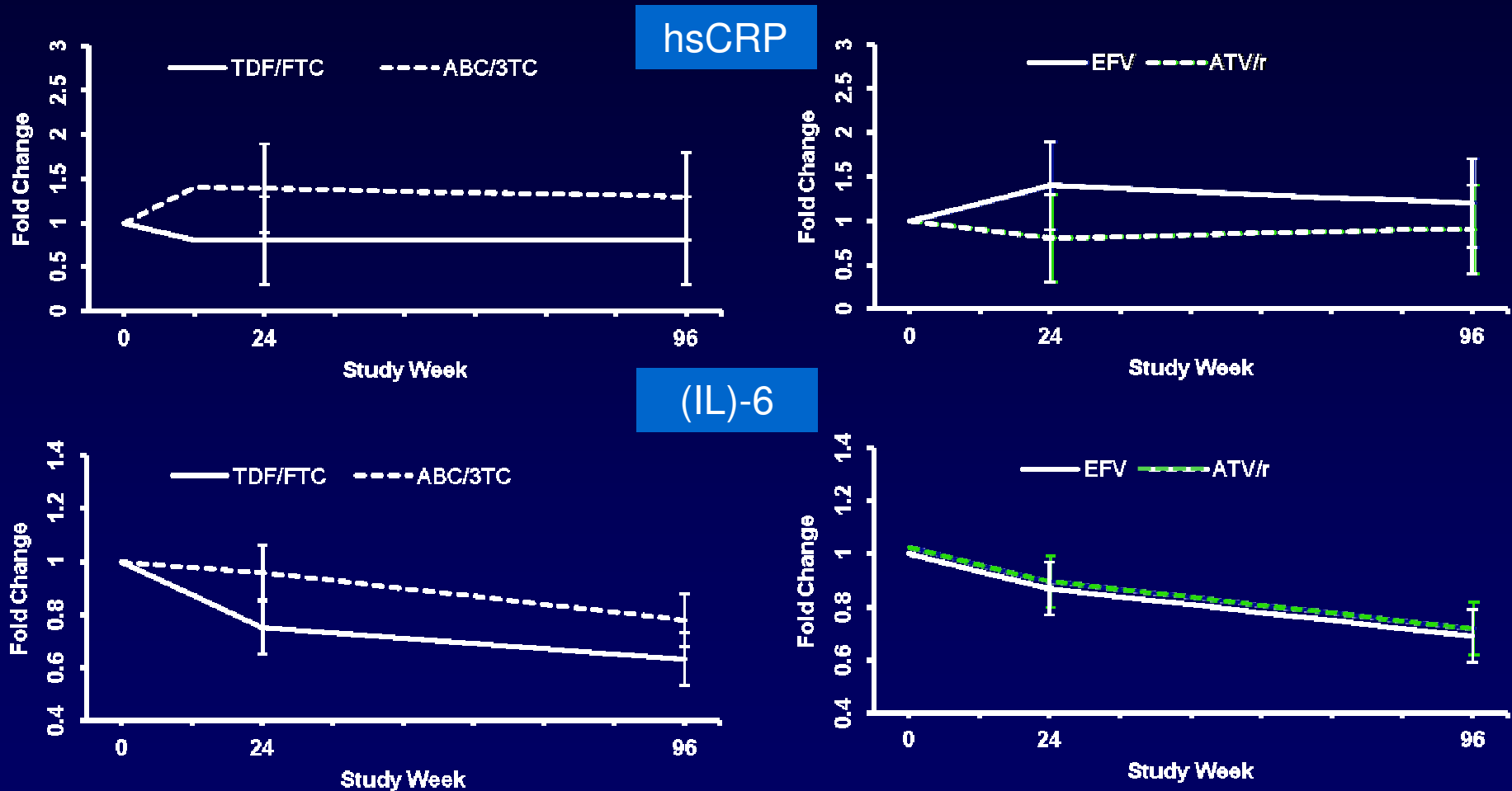


Baseline Blood Levels (median, interquartile range)

	Rosuvastatin (N = 8901)		Placebo (n = 8901)	
hsCRP, mg/L	4.2	(2.8 - 7.1)	4.3	(2.8 - 7.2)
LDL, mg/dL	108	(94 - 119)	108	(94 - 119)
HDL, mg/dL	49	(40 - 60)	49	(40 - 60)
Triglycerides, mg/L	118	(85 - 169)	118	(86 - 169)
Total Cholesterol, mg/dL	186	(168 - 200)	185	(169 - 199)
Glucose, mg/dL	94	(87 - 102)	94	(88 - 102)
HbA1c, %	5.7	(5.4 - 5.9)	5.7	(5.5 - 5.9)

All values are median (interquartile range). [Mean LDL = 104 mg/dL]

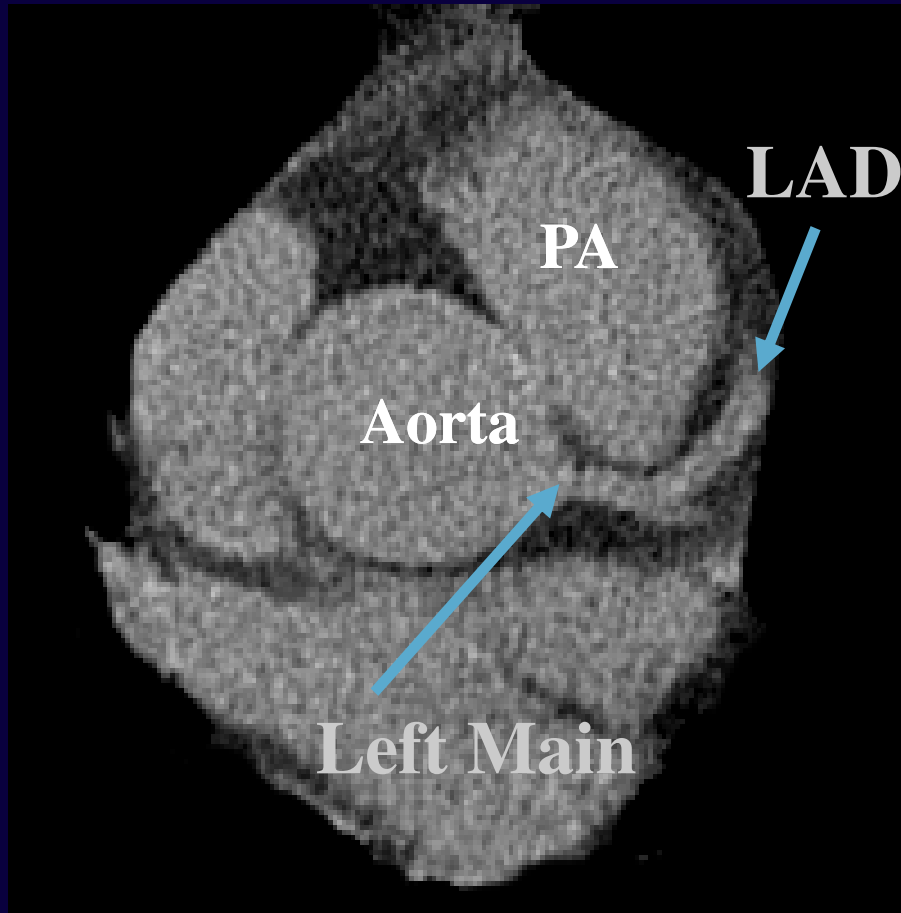
So does treatment improve things? ACTG 5224s Biomarker Results: hsCRP and IL-6



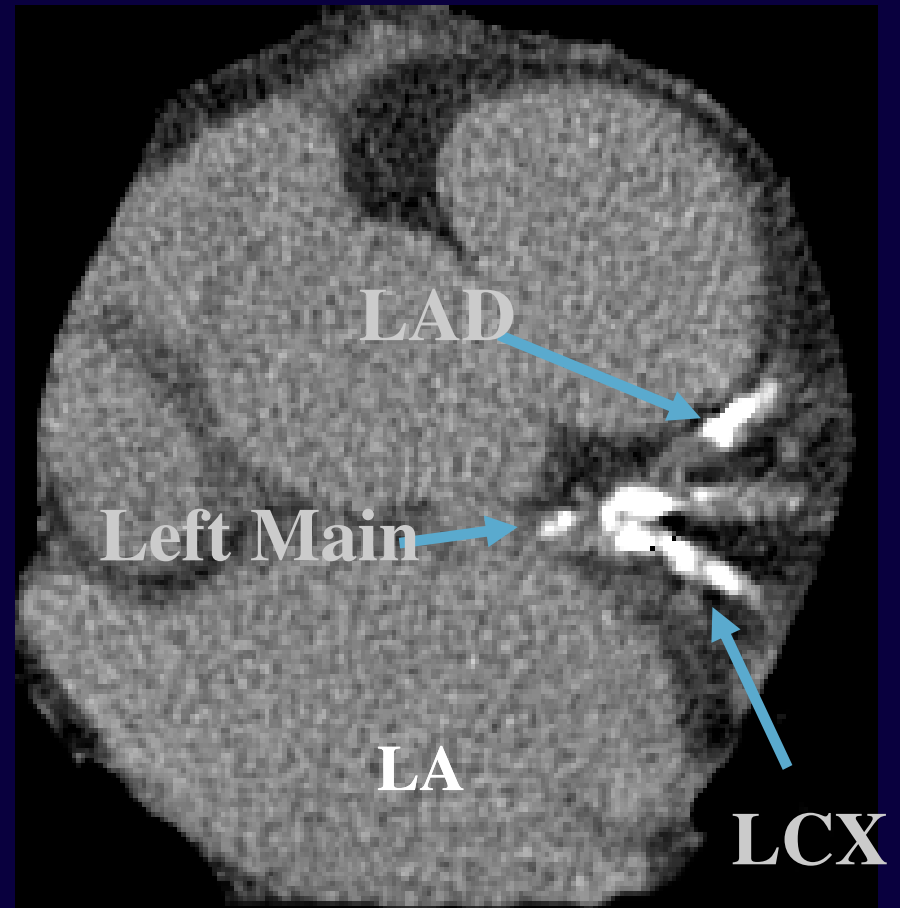
Conclusion: Small differences between the ARVs studied are unlikely to be of clinical significance.
hsCRP=high-sensitivity C-reactive protein; IL-6=interleukin-6

But are we missing subclinical disease? Coronary Artery Calcium

No Calcification



Severe Calcification



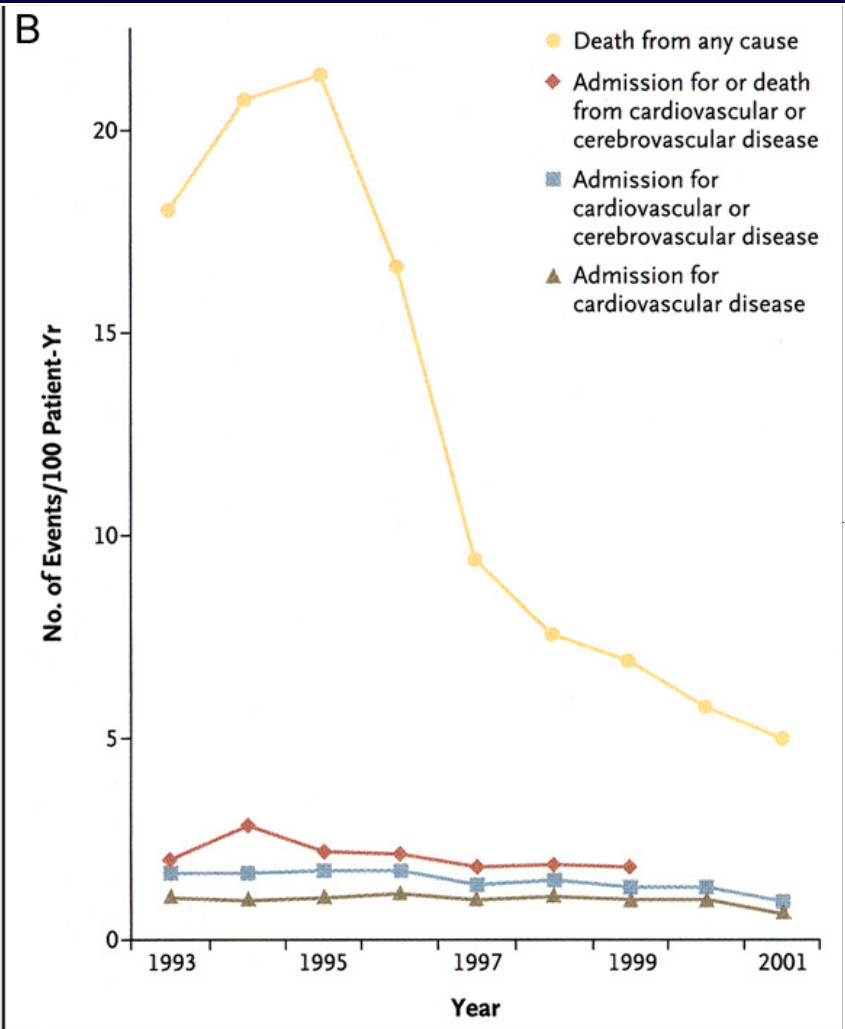
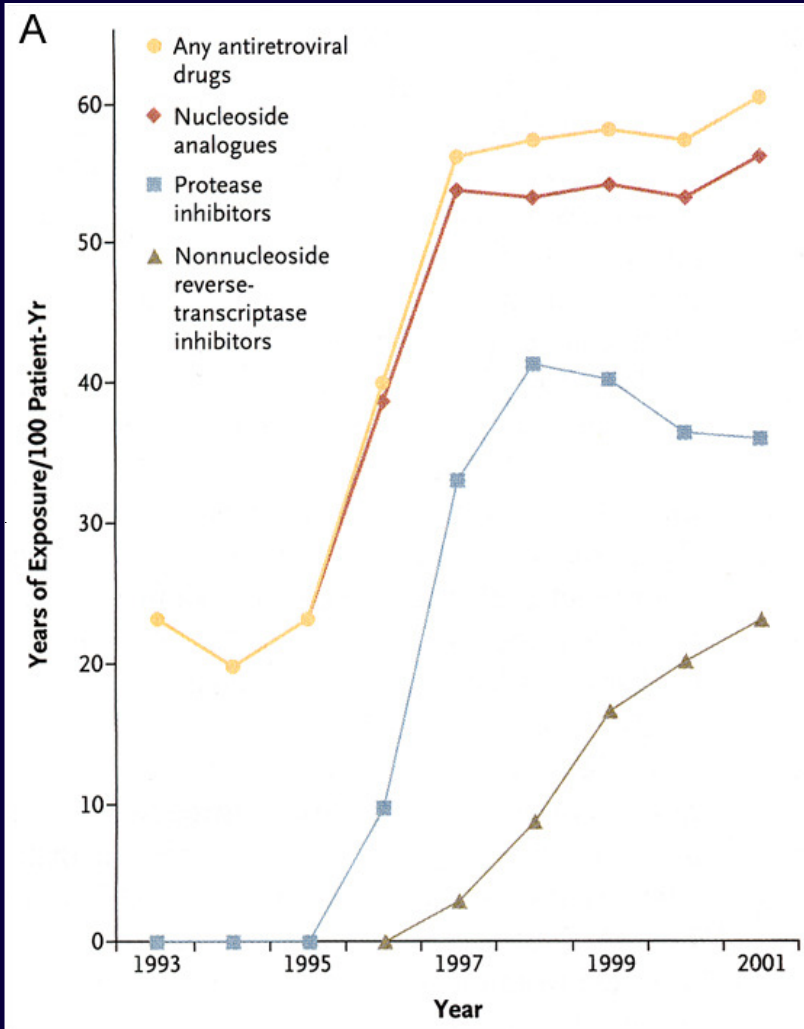
MACS: Subclinical atherosclerosis

Cross sectional analysis results

- Similar prevalence of CAC among HIV+ and HIV- men, after adjusting for CVD risk factors
- Among men with CAC, the extent of CAC is lower in HAART treated men than HIV- men
- Carotid IMT and plaque do not differ between HIV+ and HIV- men

Kingsley LA et al. *AIDS* 2008;22(13):1589-99.

Kaplan RC et al. *AIDS*. 2008 Aug 20;22(13):1615-24.



So you are still convinced of the association Co morbidities and HIV- What the studies show

- **CVD**
 - Million patient study AMI increased in HIV + RR 1.75(1.5-2.0)
 - *Triant 2007*
- **Bone**
 - Increase in fracture risk HIV + vs HIV- matched age ethnicity geography
 - *2011*
- **Brain**
 - In patients well controlled on HAART Asymptomatic NCI 19% -*Garvey 2011*
- **Cancer**
 - Anus, lung and Hodgkins are associated with HIV -*Shiels 2010*

- **CVD** **different conclusions!**

- Million patient study AMI increased in HIV + RR 1.75(1.5-2.0)
- **Not controlled for smoking, coinfection, comorbidities and recreational drugs and other behaviours- *Triant 2007***

- **Bone**

- Increase in fracture risk HIV + vs HIV- matched age ethnicity geography
- **But once other fracture risk factors and BMI included in analysis the risk disappeared-*Womack 2011***

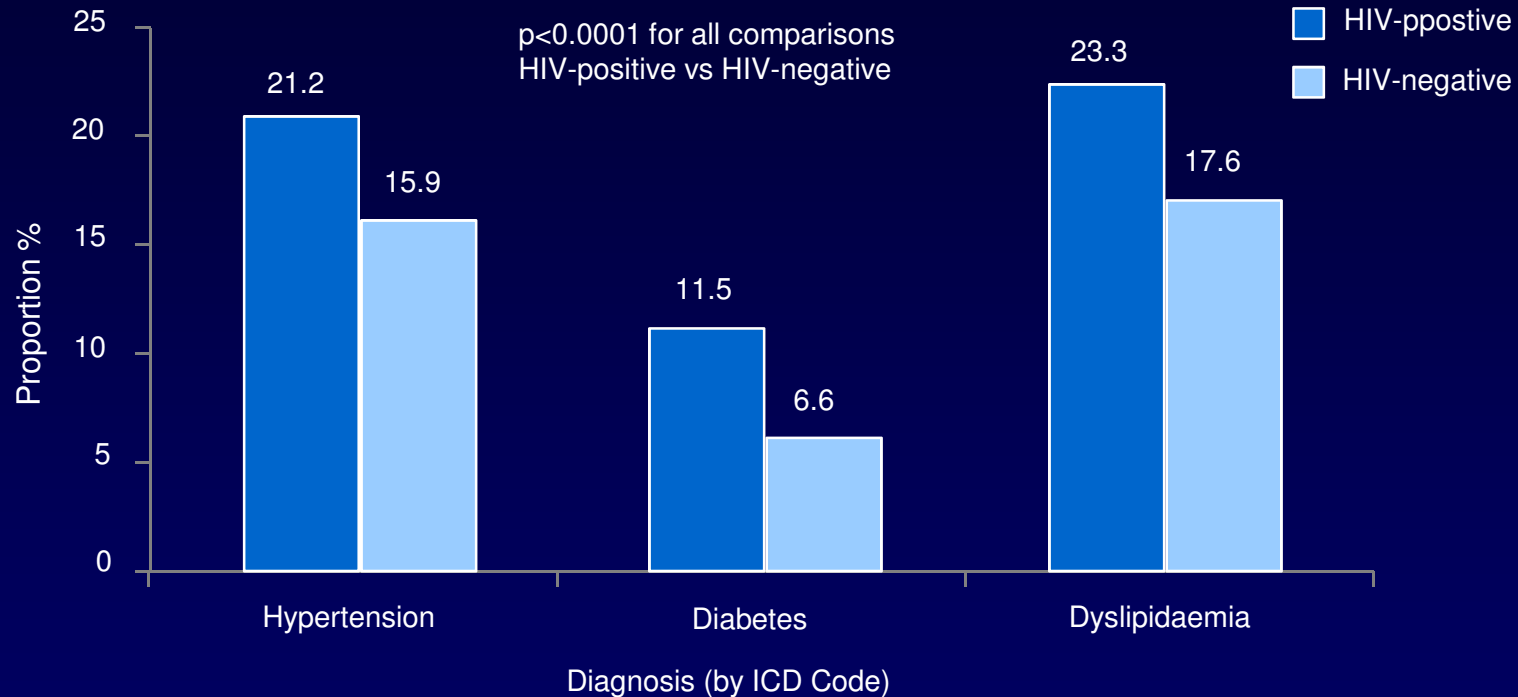
- **Brain**

- In patients well controlled on HAART Asymptomatic NCI 19% **comparable to normal population-*Garvey 2011***

- **Cancer**

- **Once account for age distributions bias compared with population only anus lung and Hodgkins are associated with HIV all have been linked to smoking or viral**

But look at Traditional CVD risk factors



HIV-negative (N= 1,044,589) 165,665
HIV-positive (N= 3,851) 818

68,565
443

184,291
896

Significantly higher proportions of hypertension, diabetes and dyslipidaemia in HIV-positive vs HIV-negative patients (p<0.0001 for all)

CVD=cardiovascular disease; ICD=international classification of disease

What is ageing?

- Ageing is the accumulation of **inflammatory** events that eventually result in organ failure and death.
- Increase in biomarkers:
 - *Interleukin-6*
 - *TNF- α*
 - *β 2-microglobulin*
 - *C-reactive protein*
 - *Erythrocyte sedimentation rate*
 - *TH1 lymphocyte%*
 - *etc.*

Age, HIV and the immune system

HIV

CD4 lymphopaenia

Inverted CD4:CD8 ratio

Reduced thymic output

Reduced naïve cells

Shorter telomeres of CD8
cells

Age

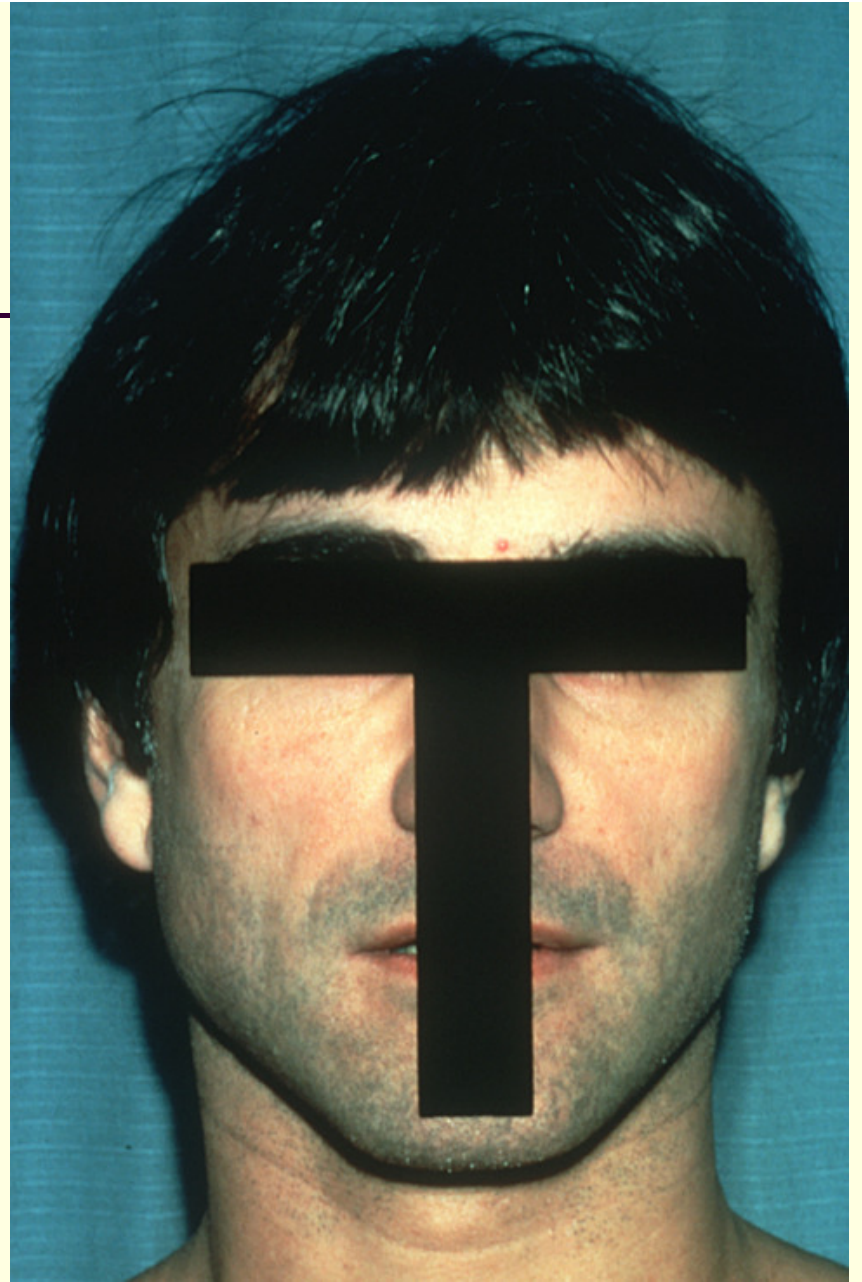
CD4 lymphopaenia

Inverted CD4:CD8 ratio

Reduced thymic output

Reduced naïve cells

Shorter telomeres of CD8
cells



Ageing and HIV –is it premature?

The problem is the choice of control group who are compared to the HIV positive group

HIV positive persons are not usually comparable to a normal population as they have one or more factors that confound comparisons

e.g.

More smoking

More recreational drugs

More infectious diseases

They are from poorer economic strata

More psychological problems etc

Conclusions

Co morbidities, Ageing and HIV

Co morbidities will Increase as the HIV population ages

Need good studies that can cut the Gordian Knot of cause and effect

While we are busy measuring we should be busy intervening where we can !!

Conclusions

**Reassure patients:
primarily a lifestyle issue - treatment**

**Caveat: may need to treat before irreversible
changes**

Age

Death be not proud though some have called thee mighty and
dreadful for thou art not so.