# Co-morbidities 1

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# Ageing with HIV

## Survival living with HIV on ART in 2012

- *N*=3280 on continuous ART from SMART and ESPRIT trials
- 80% male, 61% MSM (no IDU), 43 years
- CD4 >350 and suppressed HIV RNA
- 62 deaths - mortality rate 5.02/1000 PY (95% CI 3.85, 6.43)
- Standardised mortality ratios (SMR) compared to the Human Mortality Database

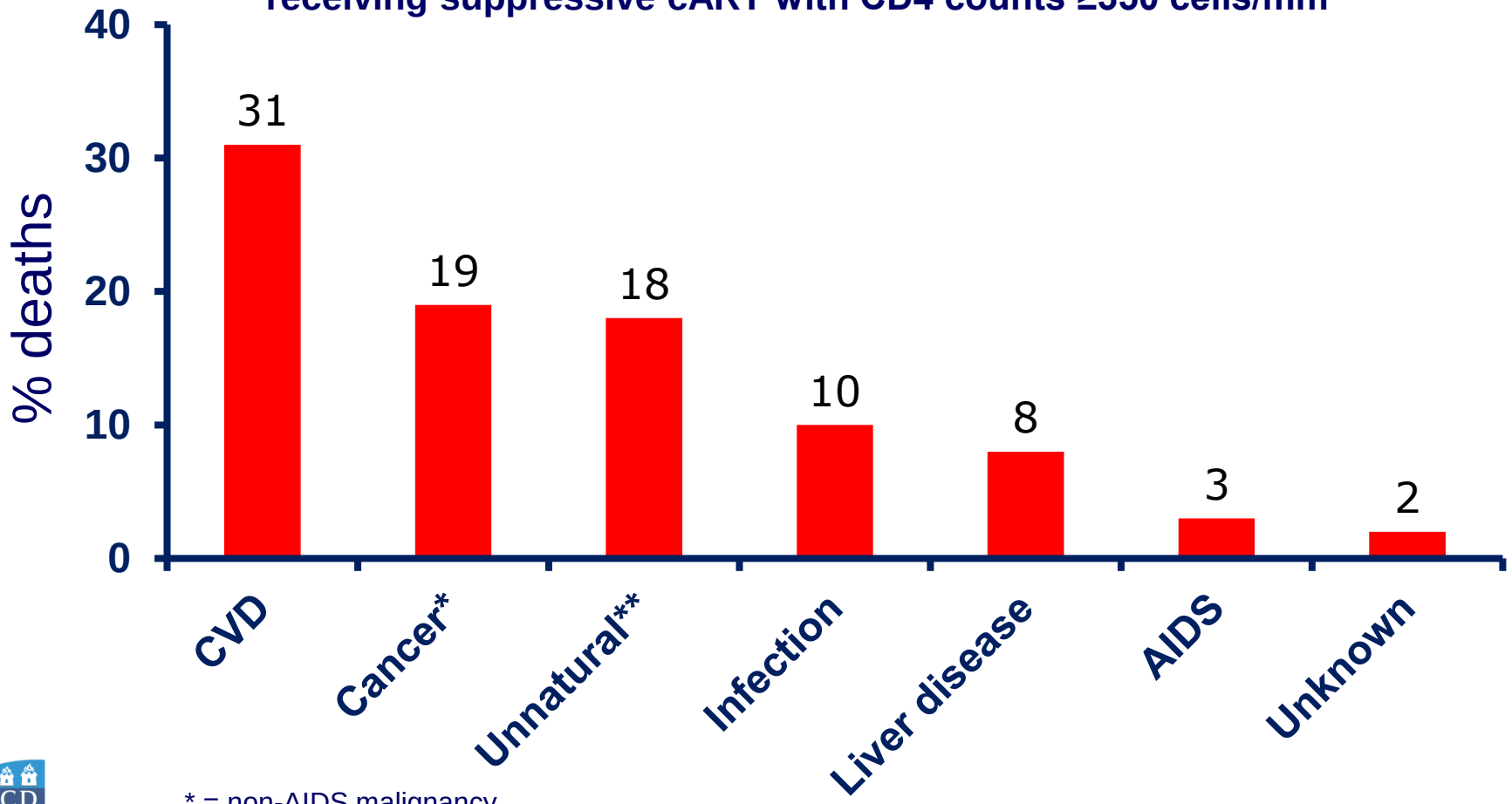
| CD4 (cells/mm3) | 350-500 | >500 |
|---|---|---|
| SMR (95% CI) | 1.77 (1.17, 2.55) | **1.00** (0.69, 1.4) |

Rodger A. et al. AIDS 2013;27(6):973-9

# Mortality in treated HIV

## Causes of death in a **successfully ART-treated** population:

**SMART/ESPRIT: causes of death in N=3,280 HIV-infected persons receiving suppressive cART with CD4 counts ≥350 cells/mm$^3$**




* = non-AIDS malignancy

** = accident, suicide or violent death

Rodger A. et al. CROI 2012. Abstract 638.

# Ageing with HIV

- Immune dysfunction associated with ageing
- Bone disease
- Cardiovascular disease
- Renal disease
- Neurocognitive impairment

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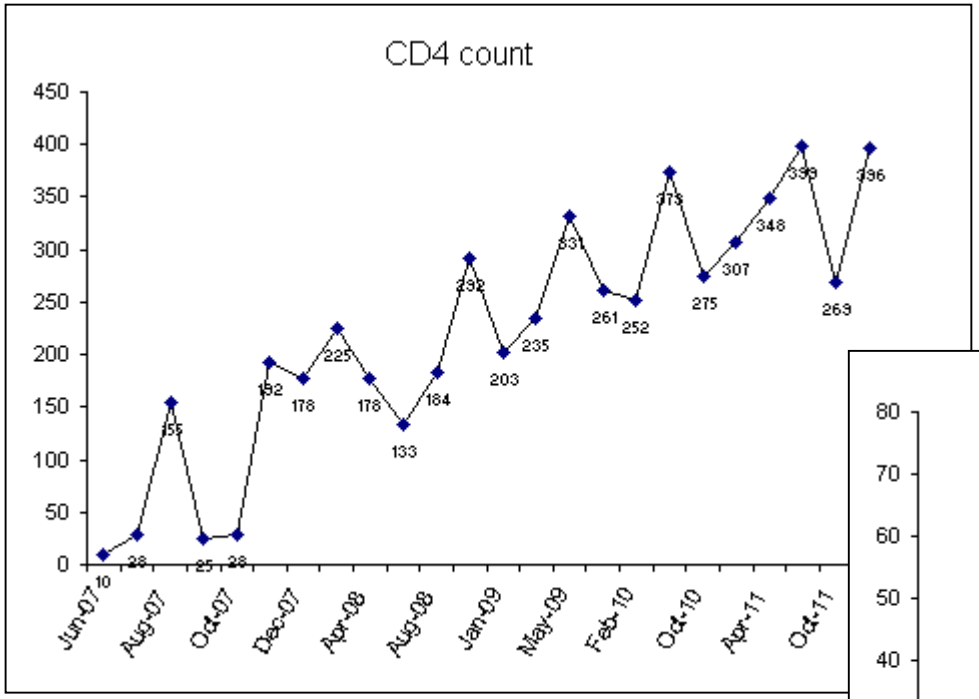
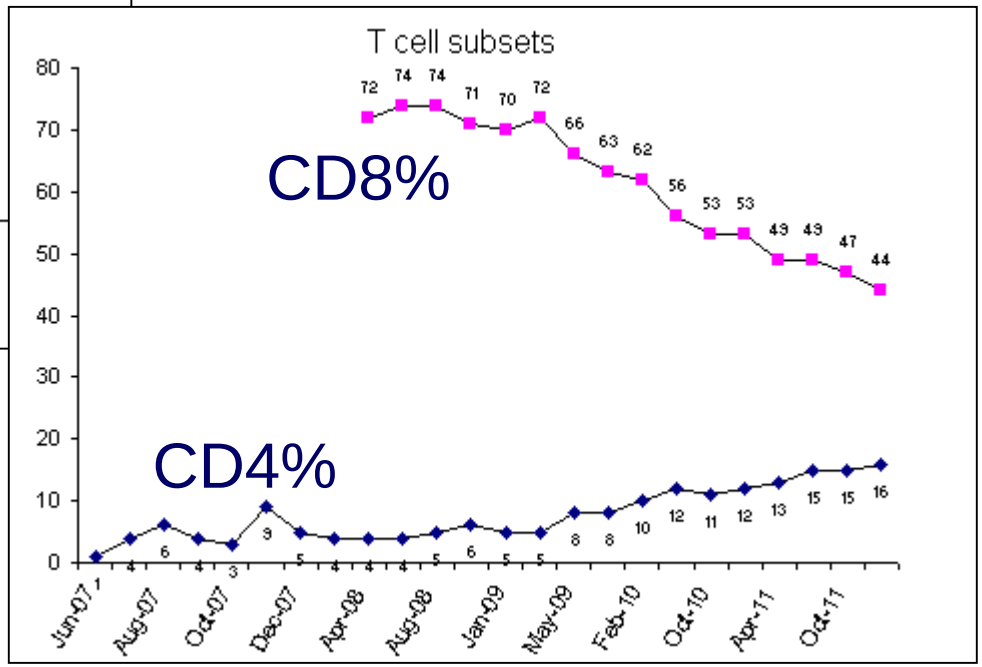
# Ageing with HIV – the immune system

## Similar immunologic changes in ageing and HIV infection

| Outcome | Uninfected aged > 70 years | HIV-infected, untreated | HIV-infected long-term treated (5-10 years) |
|---|---|---|---|
| CD4/CD8 cell ratio | Low | Low | Low |
| Naïve/memory cell ratio | Low | Low | Low? |
| T cell proliferative potential | Low | Low | Low? |
| CD28-CD8+ T cells | High | High | Unknown |
| CD57+ T cells | High | High | Unknown |
| T cell repertoire | Reduced | Reduced | Reduced? |
| IL-6 levels | Increased | Increased | Increased? |
| T cell activation | Unclear | Increased | Increased? |
| Thymus function | Reduced | Reduced | Unknown |
| Response to vaccines | Reduced | Reduced | Reduced? |

- Adapted from Deeks S. Annu Rev Med 2011;62:141-155.


CD4 count
450
400
350
300
250
200
150
100
50
0
10
28
155
25
28
192
178
225
178
133
184
292
203
235
331
261
252
373
275
307
348
399
269
396
Jun-07
Aug-07
Oct-07
Dec-07
Apr-08
Aug-08
Jan-09
May-09
Feb-10
Oct-10
Apr-11
Oct-11


T cell subsets
CD8%
CD4%
80
70
60
50
40
30
20
10
0
72
74
74
71
70
72
66
63
62
56
53
53
49
49
47
44
4
6
4
3
9
5
4
4
4
5
6
5
5
8
8
10
12
11
12
13
15
15
16
Jun-07
Aug-07
Oct-07
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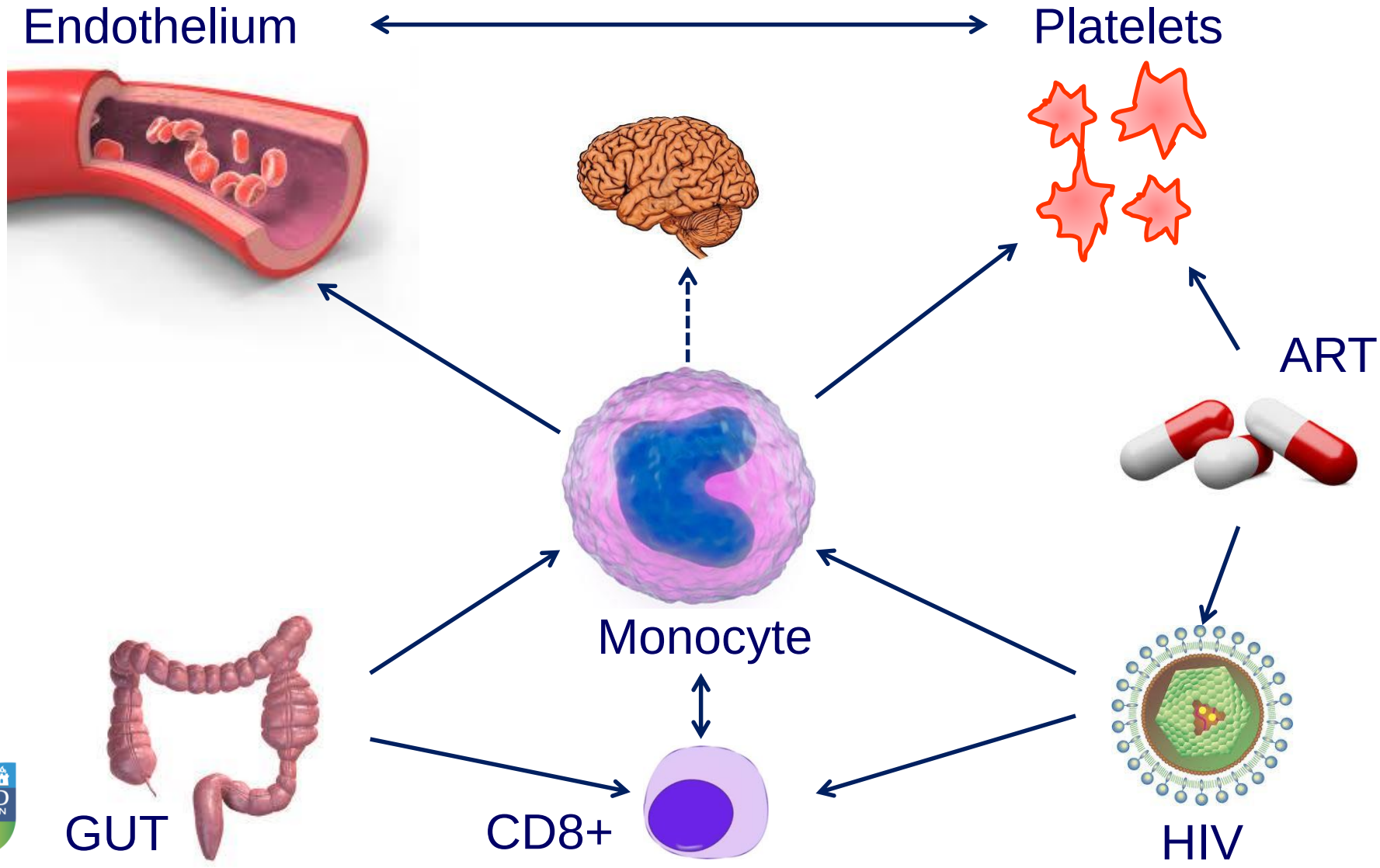
Feb-10
Oct-10
Apr-11
Oct-11

# HIV, inflammation and co-morbidities



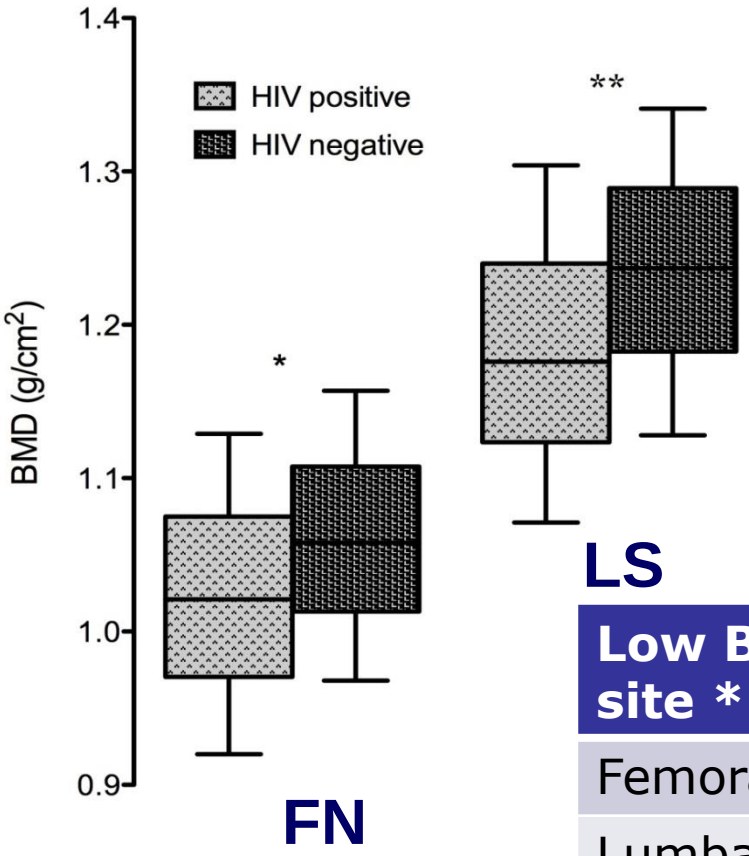
# Ageing with HIV

- Immune dysfunction associated with ageing
- Bone disease
- Cardiovascular disease
- Renal disease
- Neurocognitive impairment

# Is HIV a risk factor for low BMD?

HIV UPBEAT Study – prospective cohort

HIV+ (N=210) & HIV- (N=264) similar demographic background




Femoral neck (FN) between group

**P*=0.003

Lumbar spine (LS) between group **

*P*=0.001

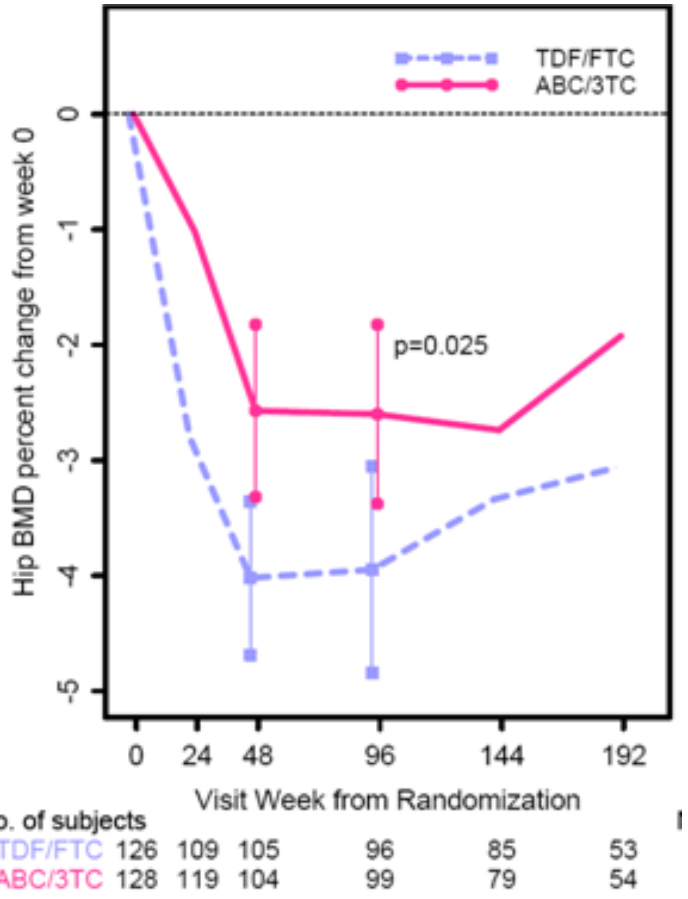
| Low BMD by site * | HIV+ (N=210) | HIV- (N=264) | P |
|---|---|---|---|
| Femoral Neck | 50 (23.8) | 31 (11.7) | 0.001 |
| Lumbar Spine | 51 (24.3) | 33 (12.5) | 0.001 |

*Z-score ≤ -2.0 in those aged <40 years or
T-score of ≤ -1.0 in those aged ≥ 40 years

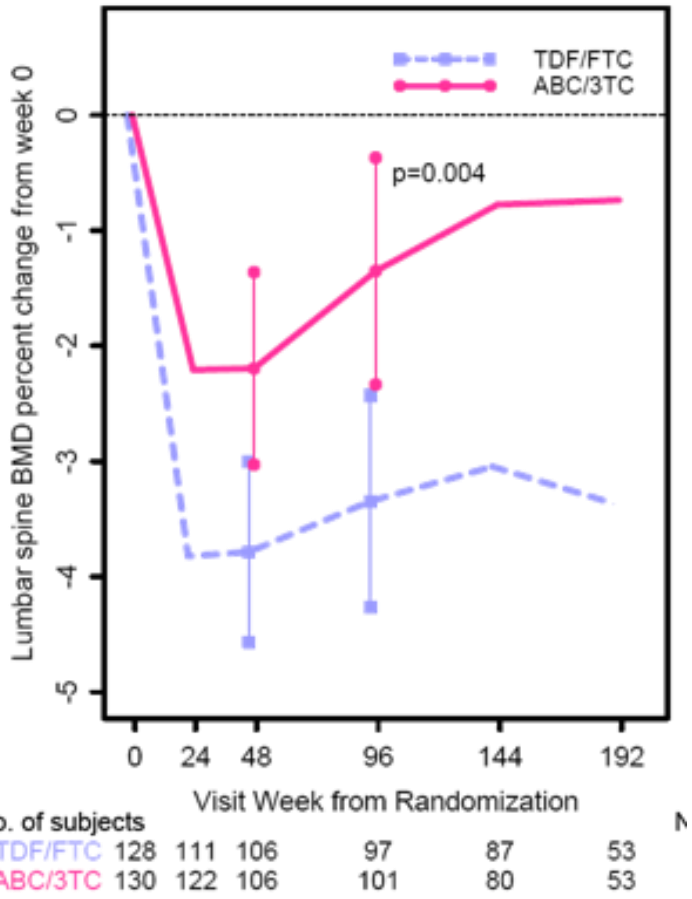
Cotter AG et al. 20th AIDS 28 (14), 2051-2060

# ART and loss of BMD – 1st line ART

## Hip



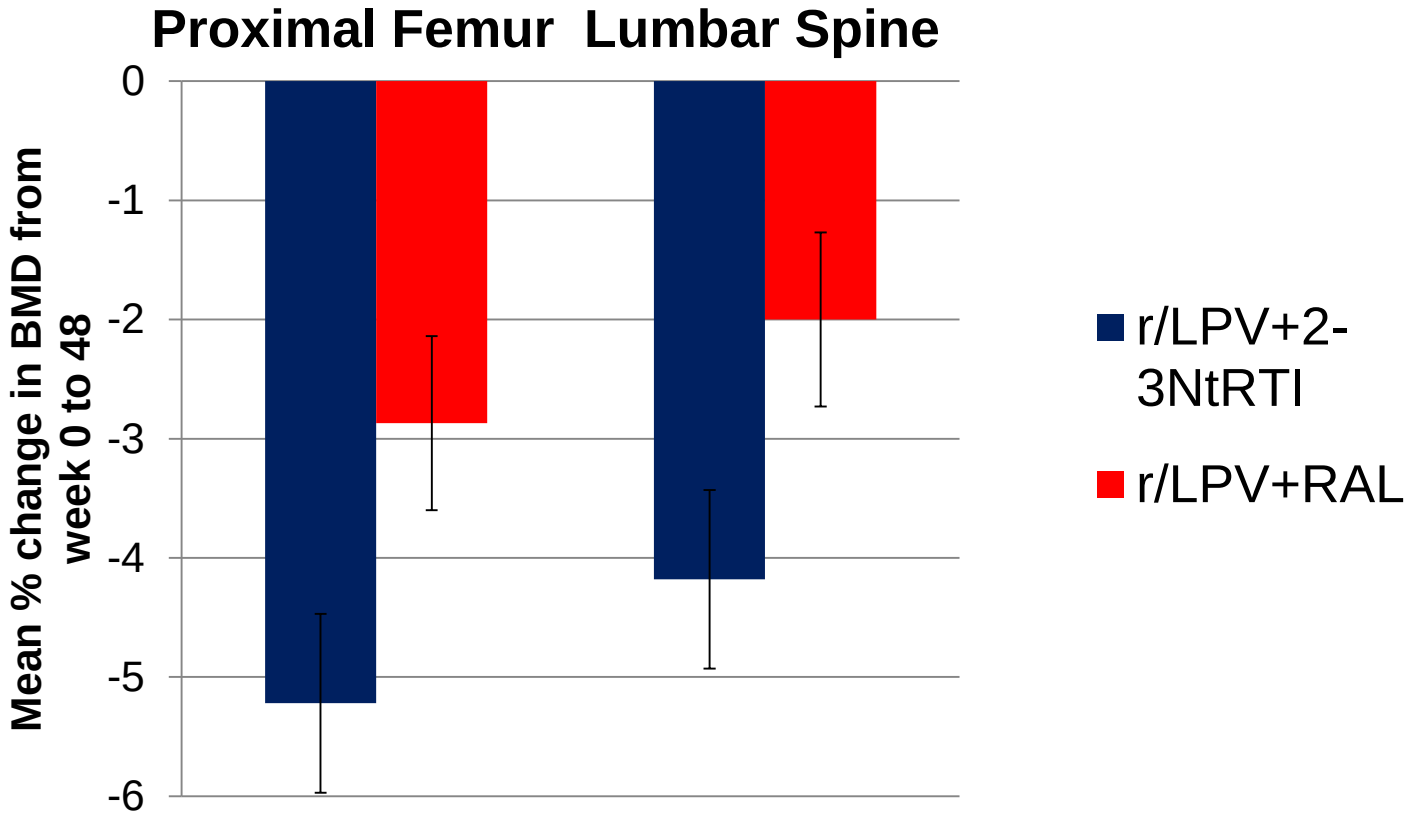

## Lumbar Spine




McComsey GA et al. CROI 2010

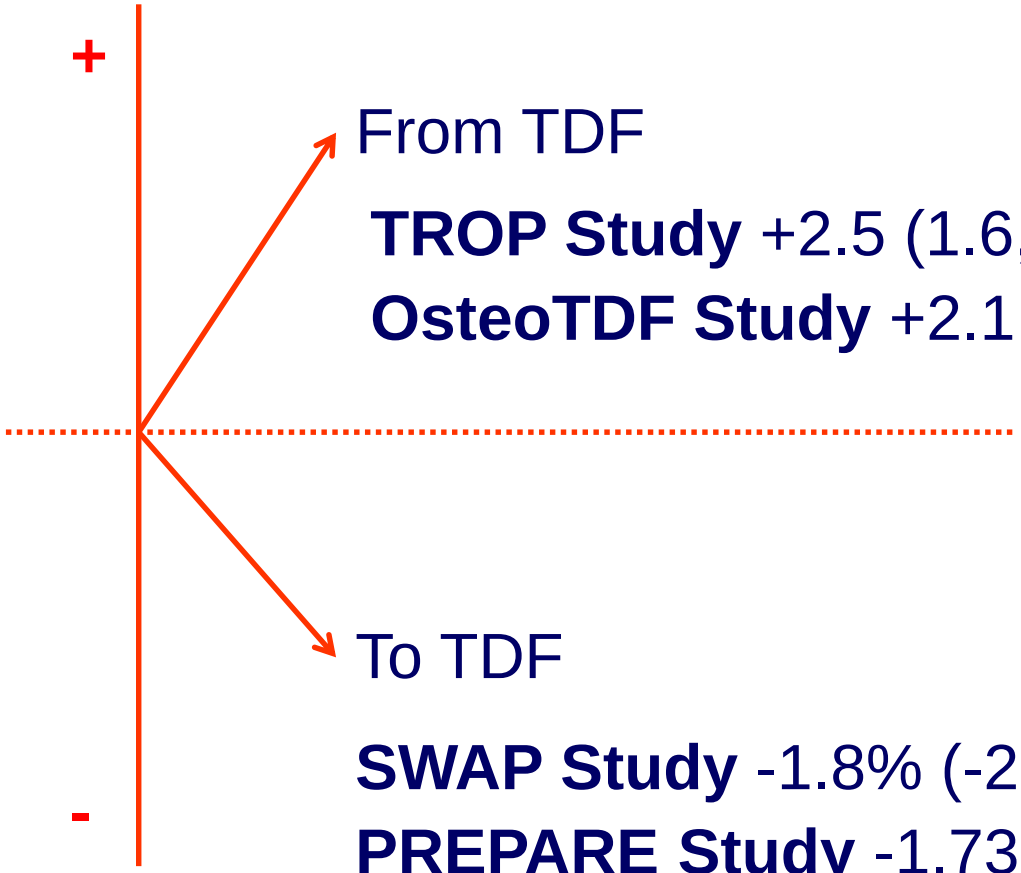
# ART and loss of BMD - 2nd Line ART

N=210, age 38.8 yrs, 47.6% male, 51% Asian, 43% African,
Failing first-line NNRTI-based ART
Randomised RAL/LPVr versus LPVr / NRTI




Martin A *et al. AIDS* 2013;27:2403-2411

# ART and loss of BMD - switching ART




From TDF

**TROP Study** +2.5 (1.6, 3.3)% BMD gain at hip

**OsteoTDF Study** +2.1 (-0.6, 4.7)% BMD gain at hip

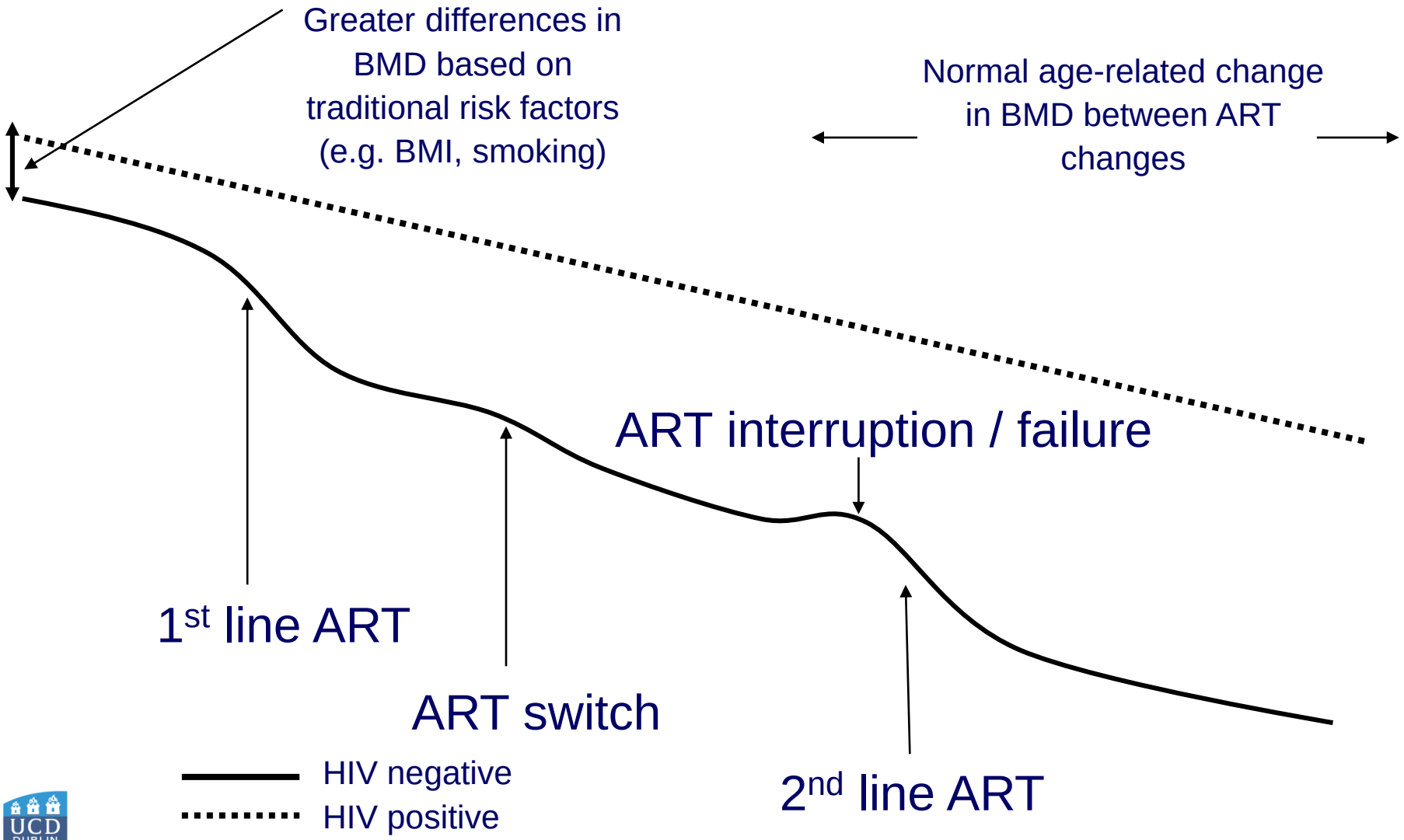
To TDF

**SWAP Study** -1.8% (-2.6, -1.1)% BMD loss at hip

**PREPARE Study** -1.73 (2.76)% BMD loss at hip

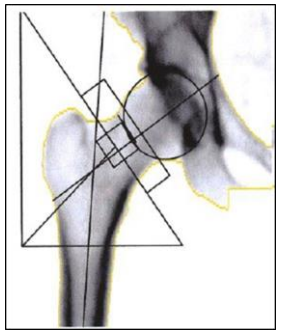
Bloch M. et al. CROI 2012. Abstract 878. Negredo E. et al. CROI 2013. Paper #824 Rasmussen TA et al. PLoS One 2012;7 (3) Cotter AG et al. JCEM 2013;09(4):1659-66

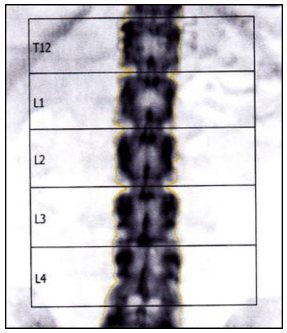
# ART and BMD loss




Mallon PWG. Current Opinion in HIV and AIDS 2014. *In Press.*

# Bone health and HIV






| | N | HIV+ | % male | Fractures | Association between fracture and HIV |
|---|---|---|---|---|---|
| USA[1] | 119,318 | 33% | 100 | 1615 | HR 1.24 (1.11, 1.39) |
| Denmark[2] | 31,836 | 5,306 | 76 | 806 | IRR 1.5 (1.4-1.7) |
| Canada[3] | 540 | 138 | 0 | - | OR 1.7 (1.1, 2.6) |
| USA[4] | 559 | 328 | 100 | 33 | No difference in fracture rates |
| Spain[5] | 1,118,156 | 2,489 | - | 24,457 (HIV+ 49) | HR 4.7 (2.44, 9.5) hip |

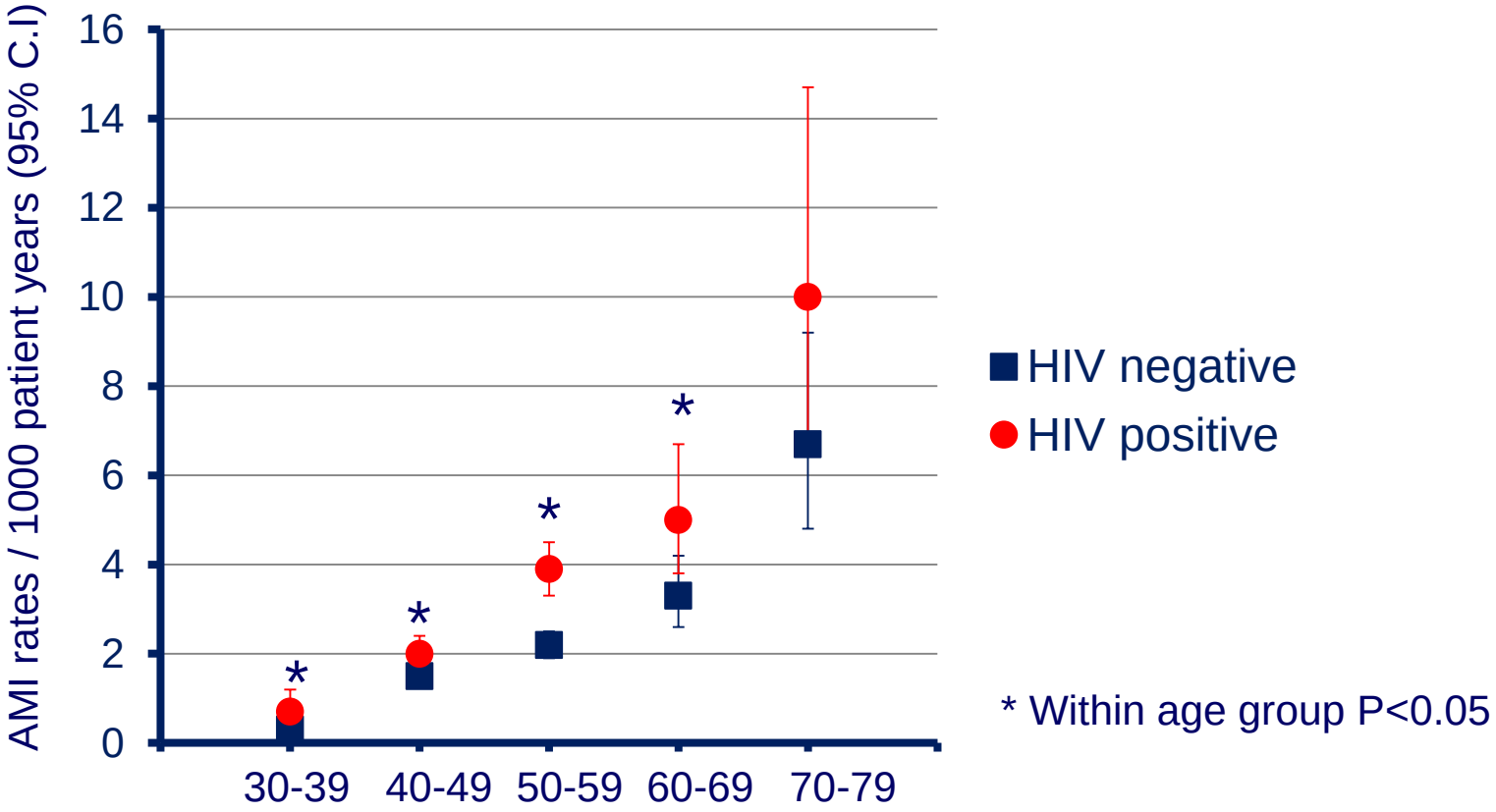
1. Womack JA et al. PLoS One 2011; 6(2):e17217 2. Hansen AE et al. AIDS 2012; 26(3):285-93. 3. Prior J et al. Osteoporosis Int 2007; 18:1345-1353. 4. Arnsten JA et al. AIDS 2007; 21(5):617-623. 5. Guerri-Fernandez R et al. JBMR 2013; 28(6):1259-1263

# Ageing with HIV

- Immune dysfunction associated with ageing
- Bone disease
- Cardiovascular disease
- Renal disease
- Neurocognitive impairment

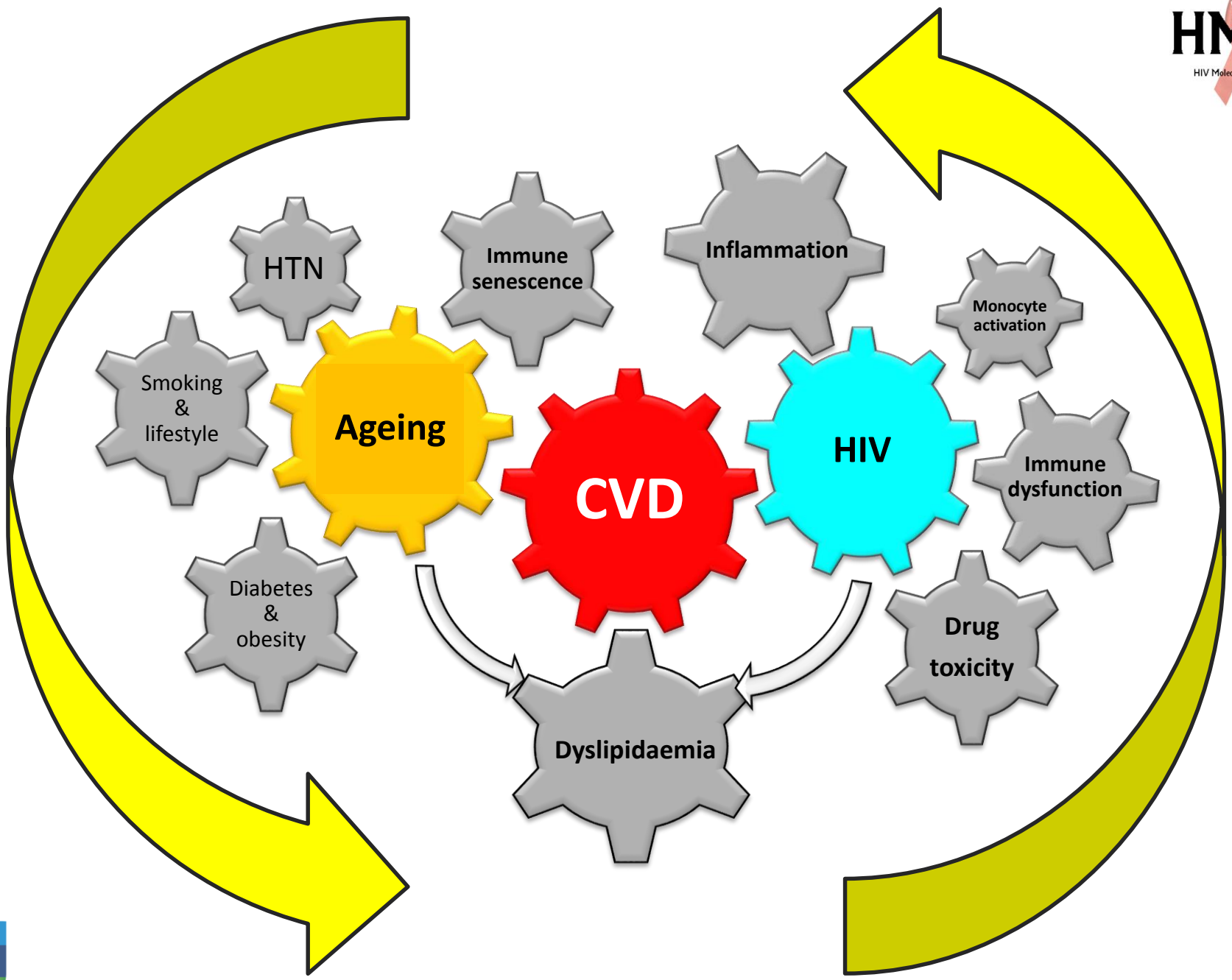
# HIV and CVD – incidence of MI

## AMI is more common in HIV-positive than HIV-negative populations

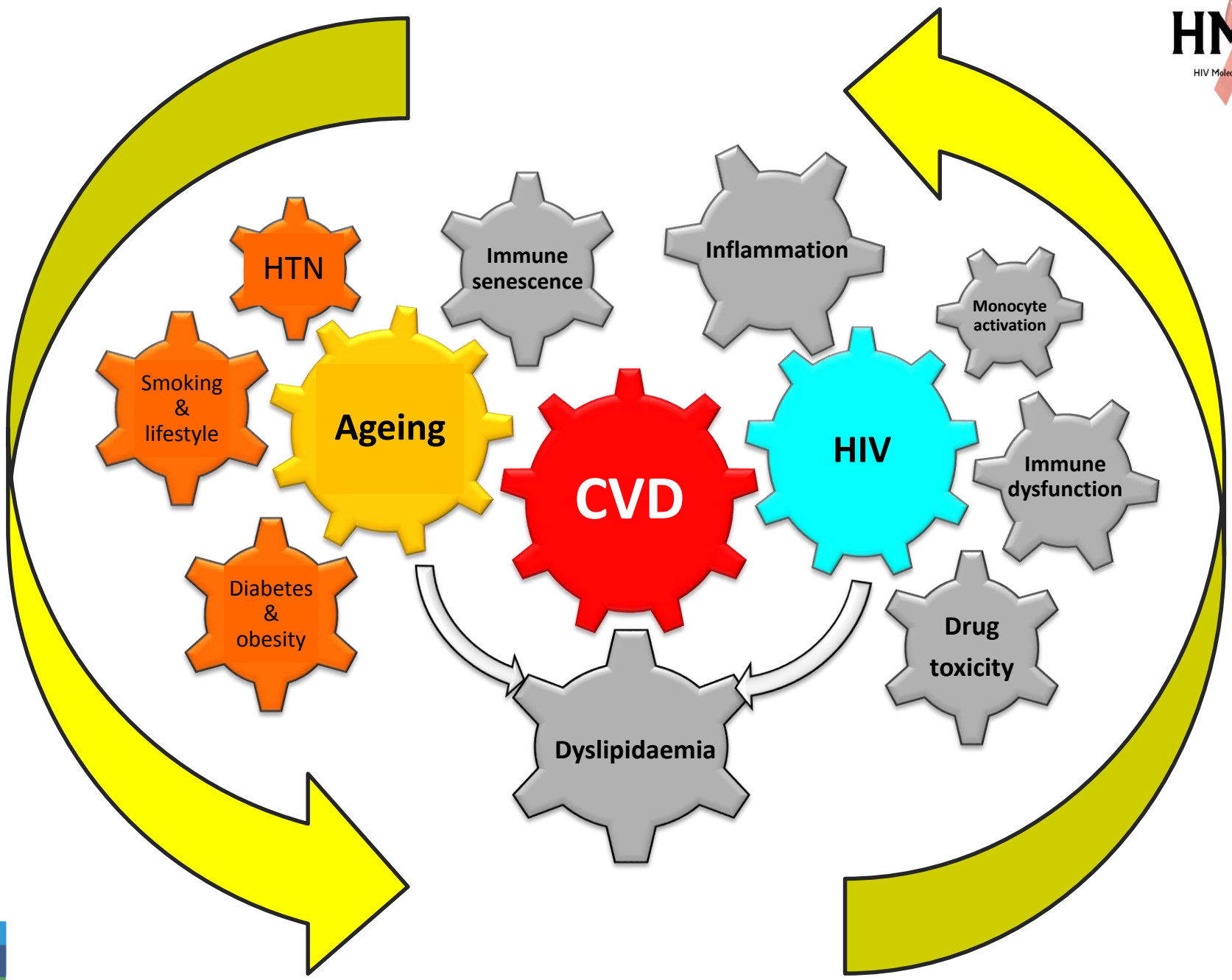



AMI=acute myocardial infarction; CI=confidence interval.

Freiberg MS, et al. JAMA Int Med. 2013; 173(8):614-22, Mallon PW. JAMA Int Med 2013; 173(8):622-3.




J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

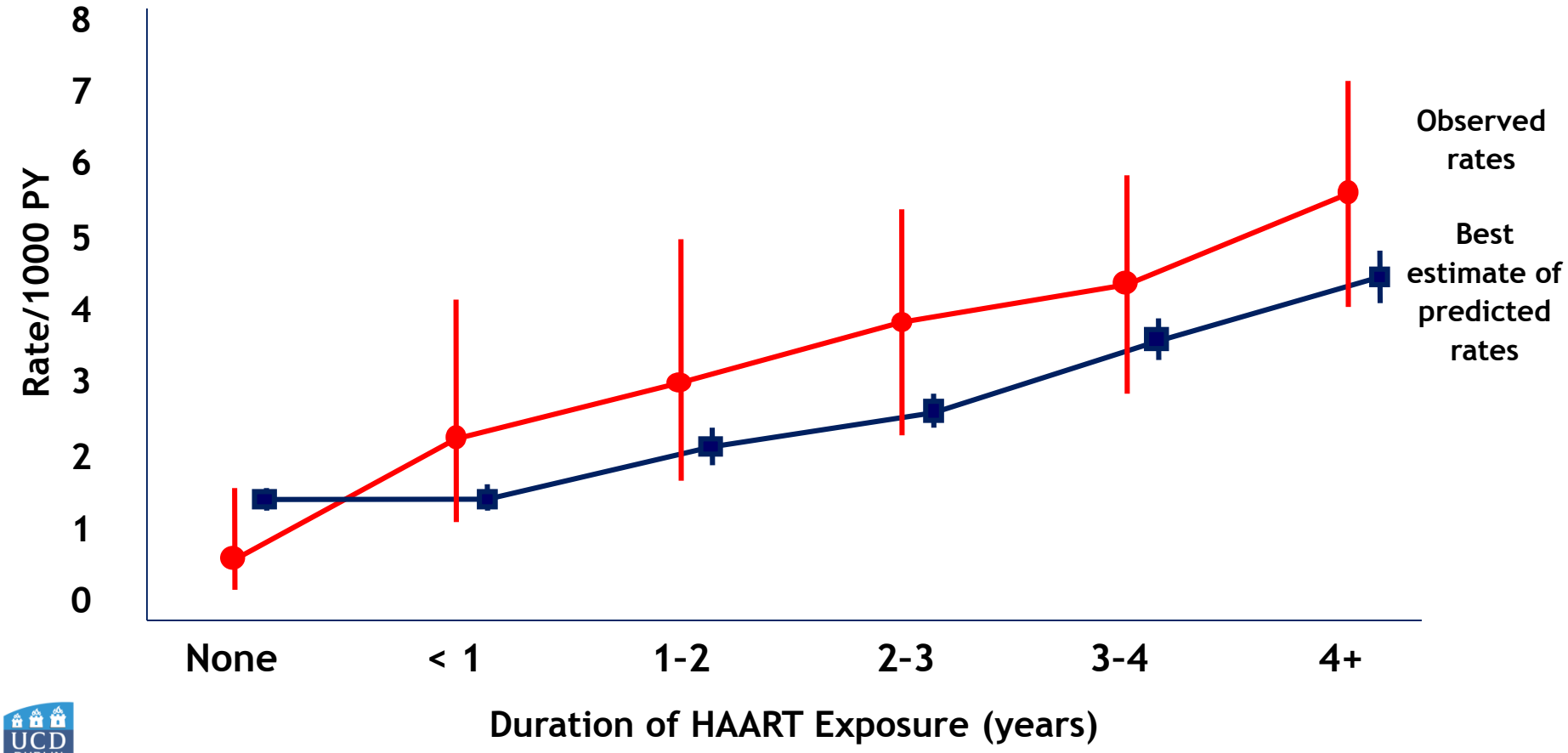



J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

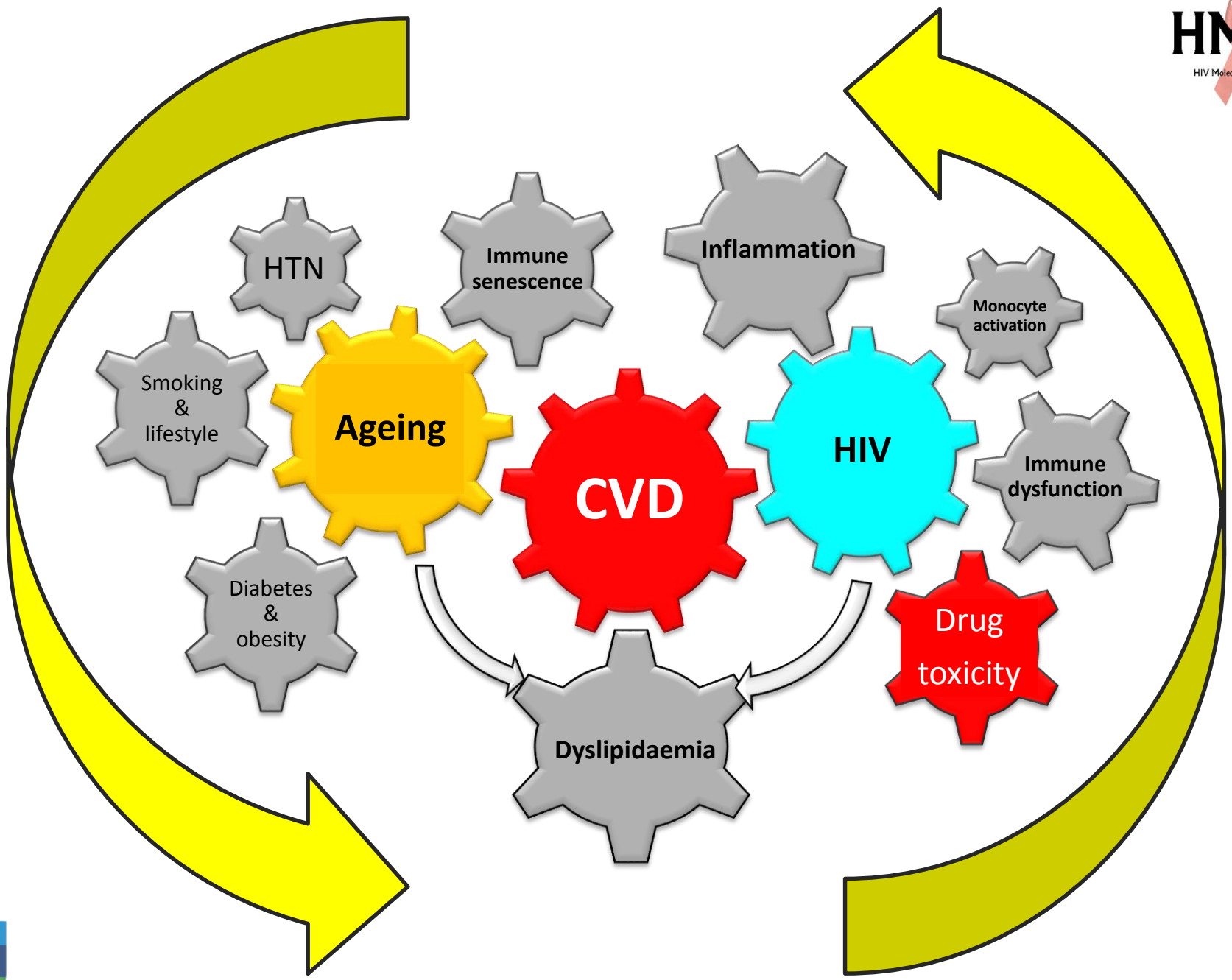
# HIV and MI – role of traditional risk factors

## Framingham risk assessment may underestimate MI risk in HIV

### Observed and predicted MI rates according to ART exposure (D:A:D Study)



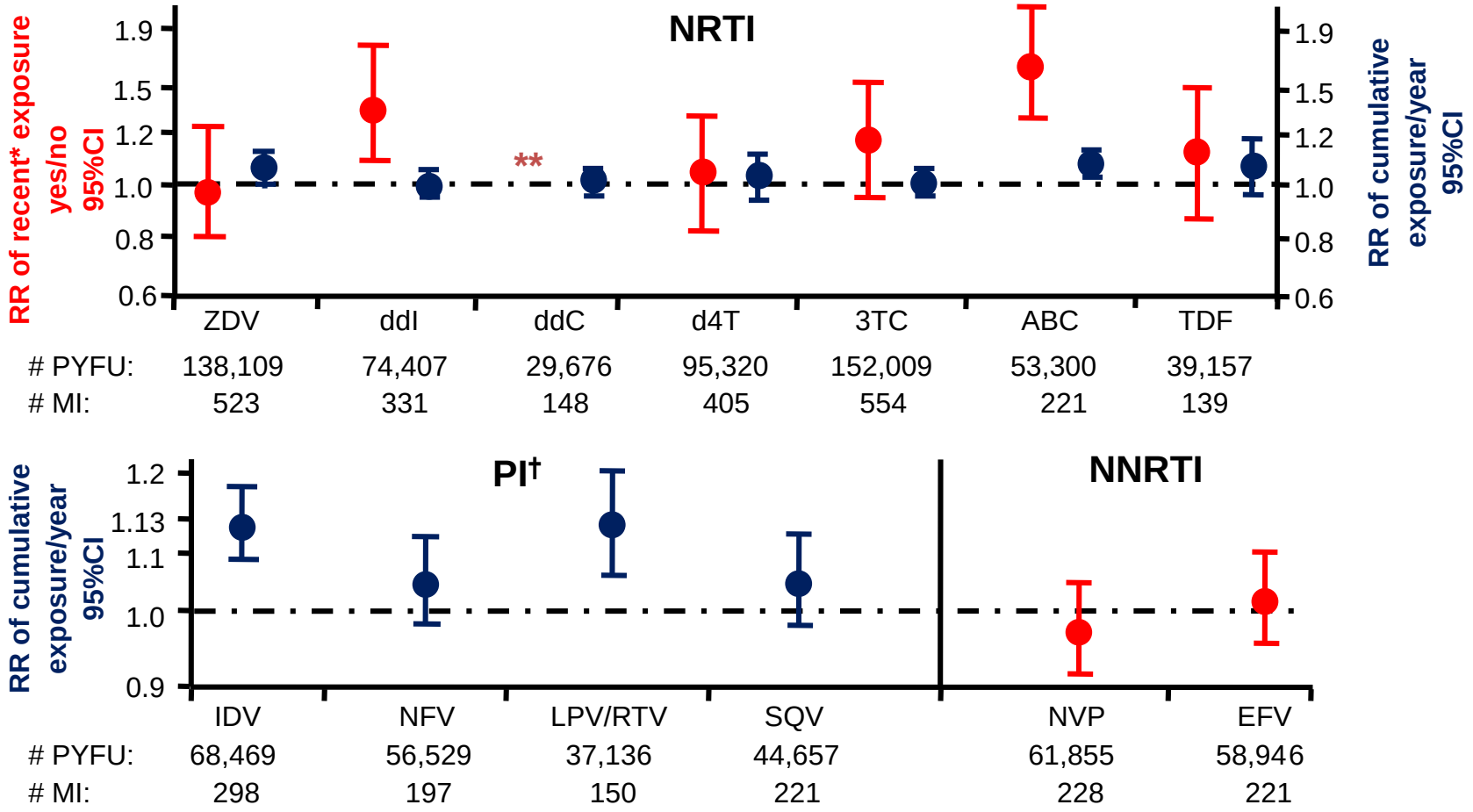

Law MG, et al. HIV Med 2006;7:218-230.




J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

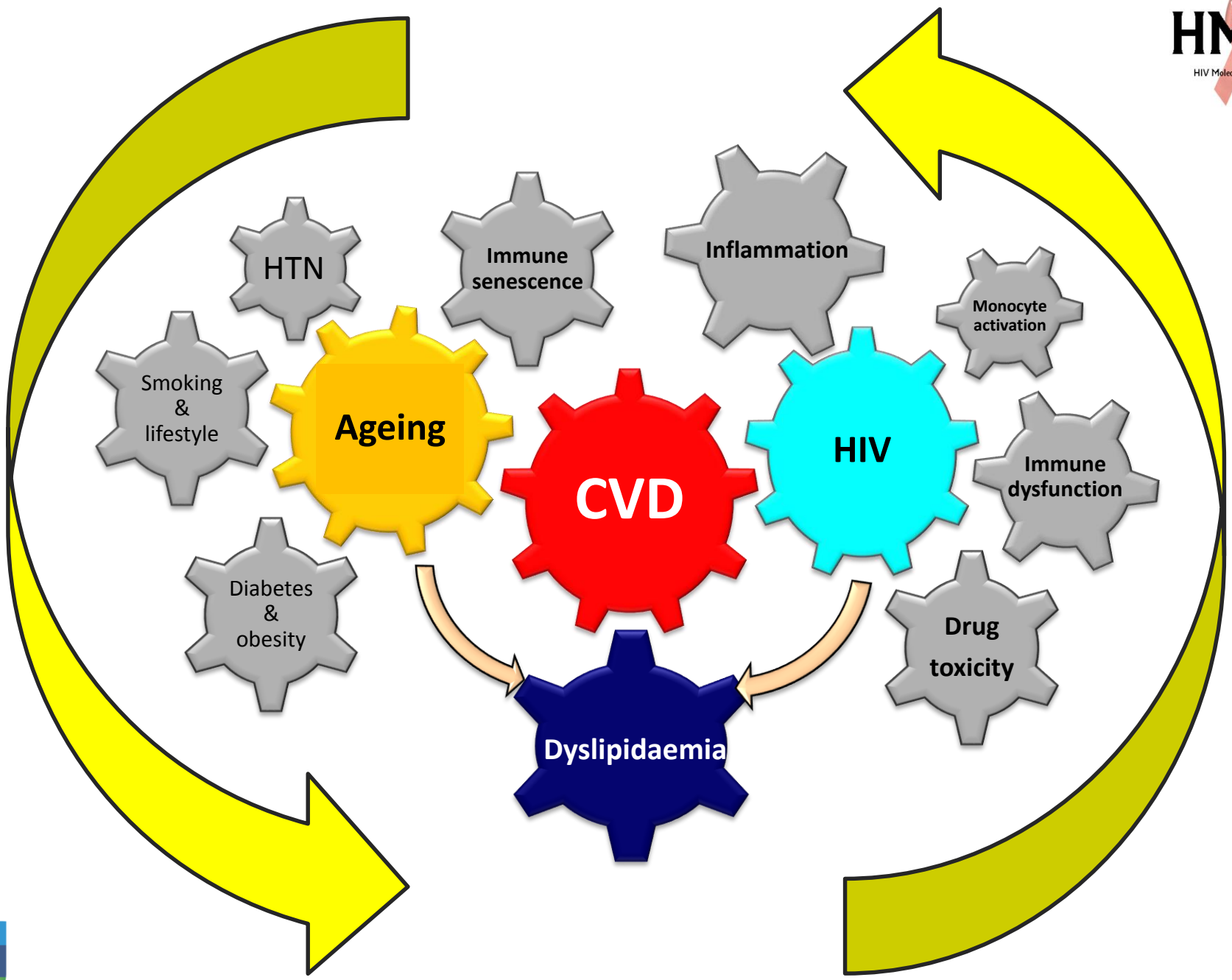
# Cardiovascular events: Do drugs matter?

## D.A.D: MI risk is associated with **recent** and/or **cumulative** exposure to specific NRTIs and PIs



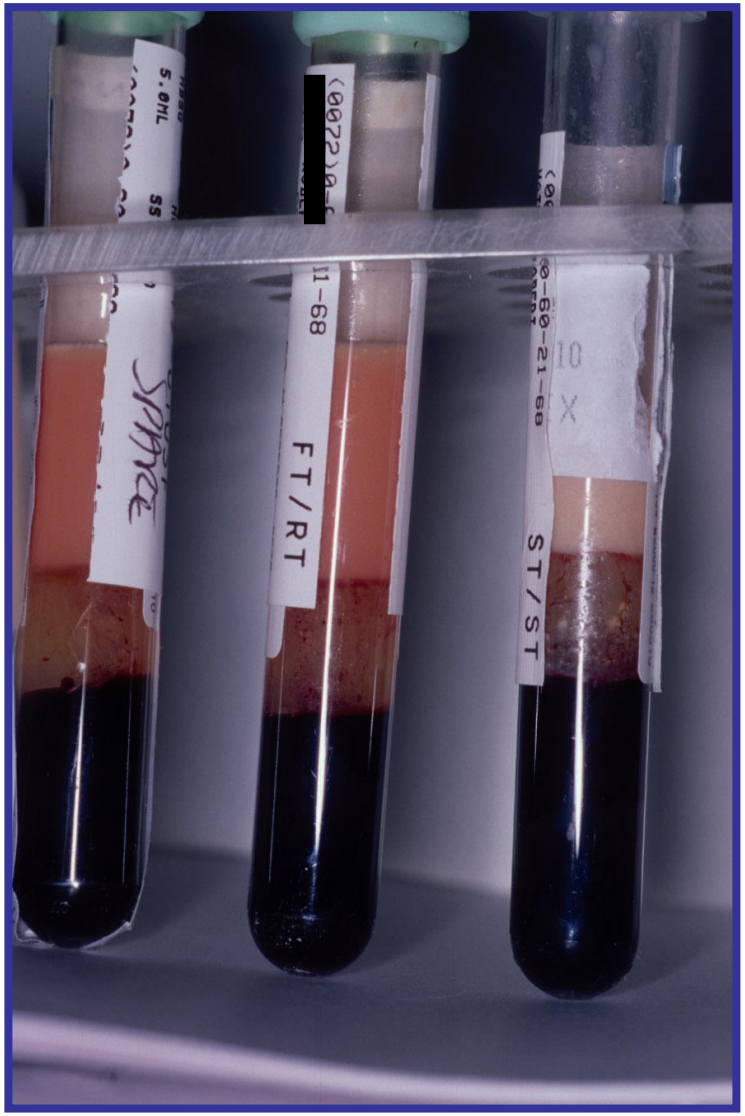

*Current or within past 6 months; †Approximate test for heterogeneity: p=0.02; **not shown due to low number of patients receiving ddC.
CVD=cardiovascular disease; MI=myocardial infarction; RR=relative risk; PYFU=patient years of follow up.

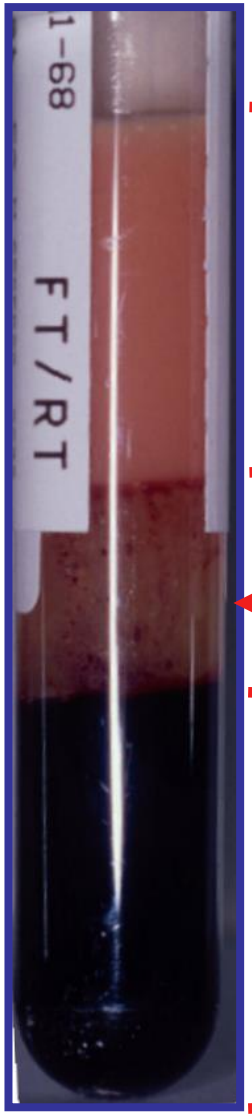
Adapted from Lundgren JD, et al. CROI 2009. Oral presentation 44LB.




J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

# Dyslipidaemia – the '*legacy*'




Plasma

Gel

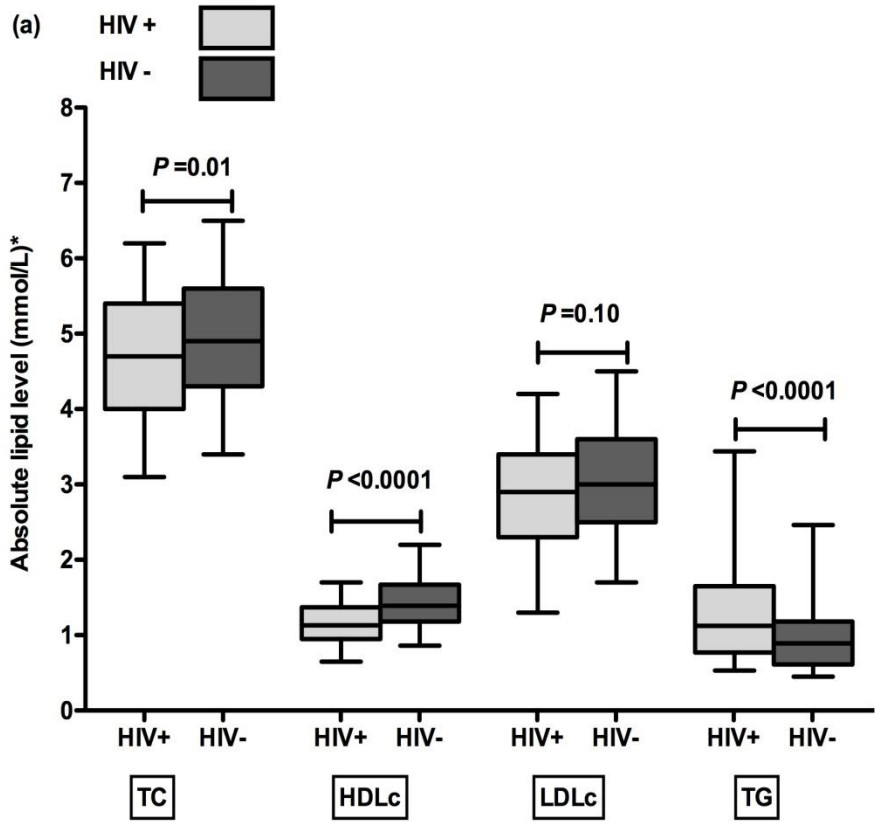
Cells

**Cholesterol**
**19 mmol/L**

**Triglycerides**
**94.4 mmol/L**

# Dyslipidaemia in HIV UPBEAT

| | HIV- (N=259) | HIV+ (N=190) | *P* |
|---|---|---|---|
| Age | 41 (34, 48) | 38 (33, 46) | 0.08 |
| Male gender | 42.9% | 61.6% | <0.0001 |
| Smokers | 36.3% | 16.2% | 0.0001 |

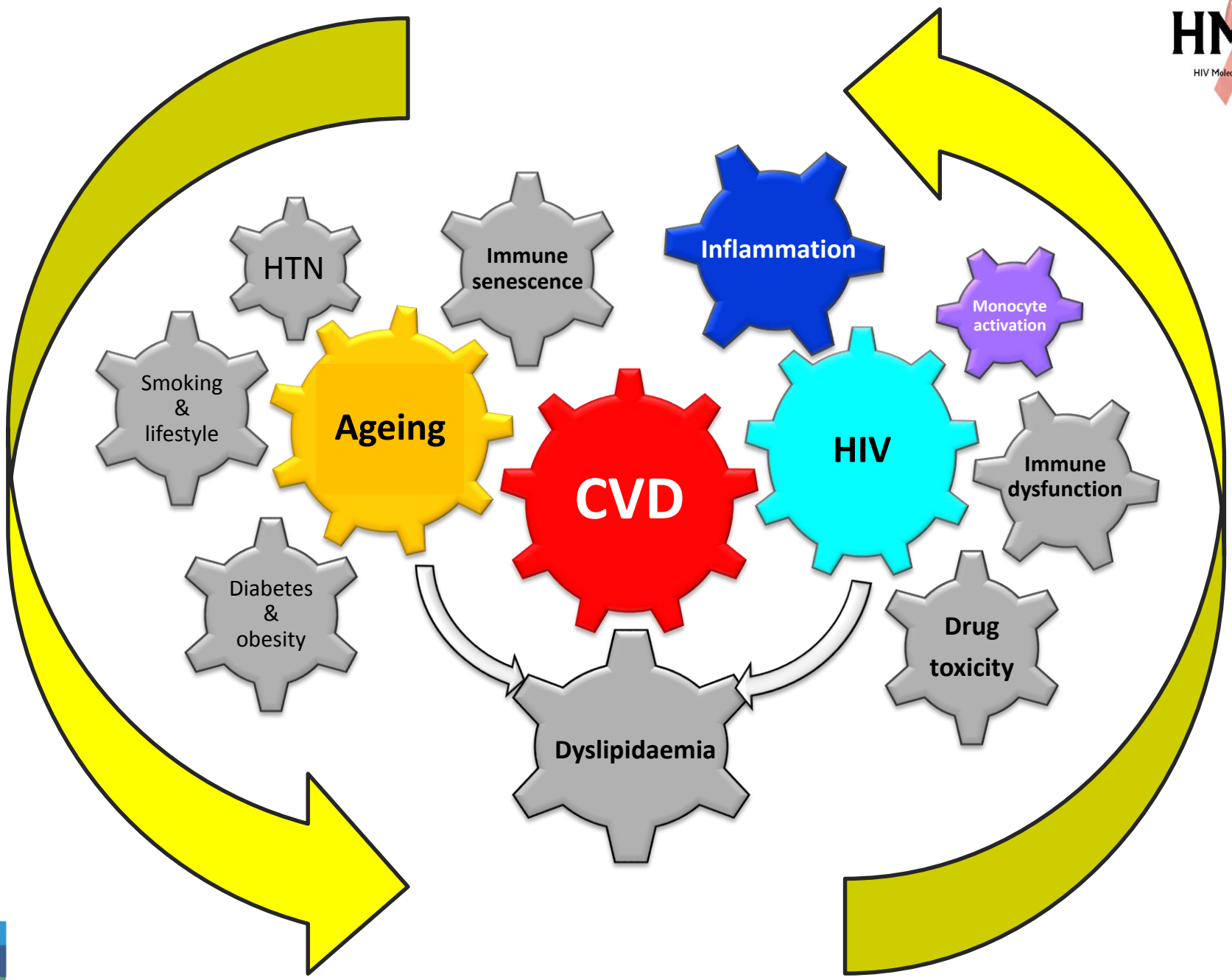



Differences in HDL and TG, but not LDL, remained significant in fully adjusted analyses

| | HDL <1mmol/L* |
|---|---|
| HIV+ | 35.2% |
| HIV- | 11.4% |

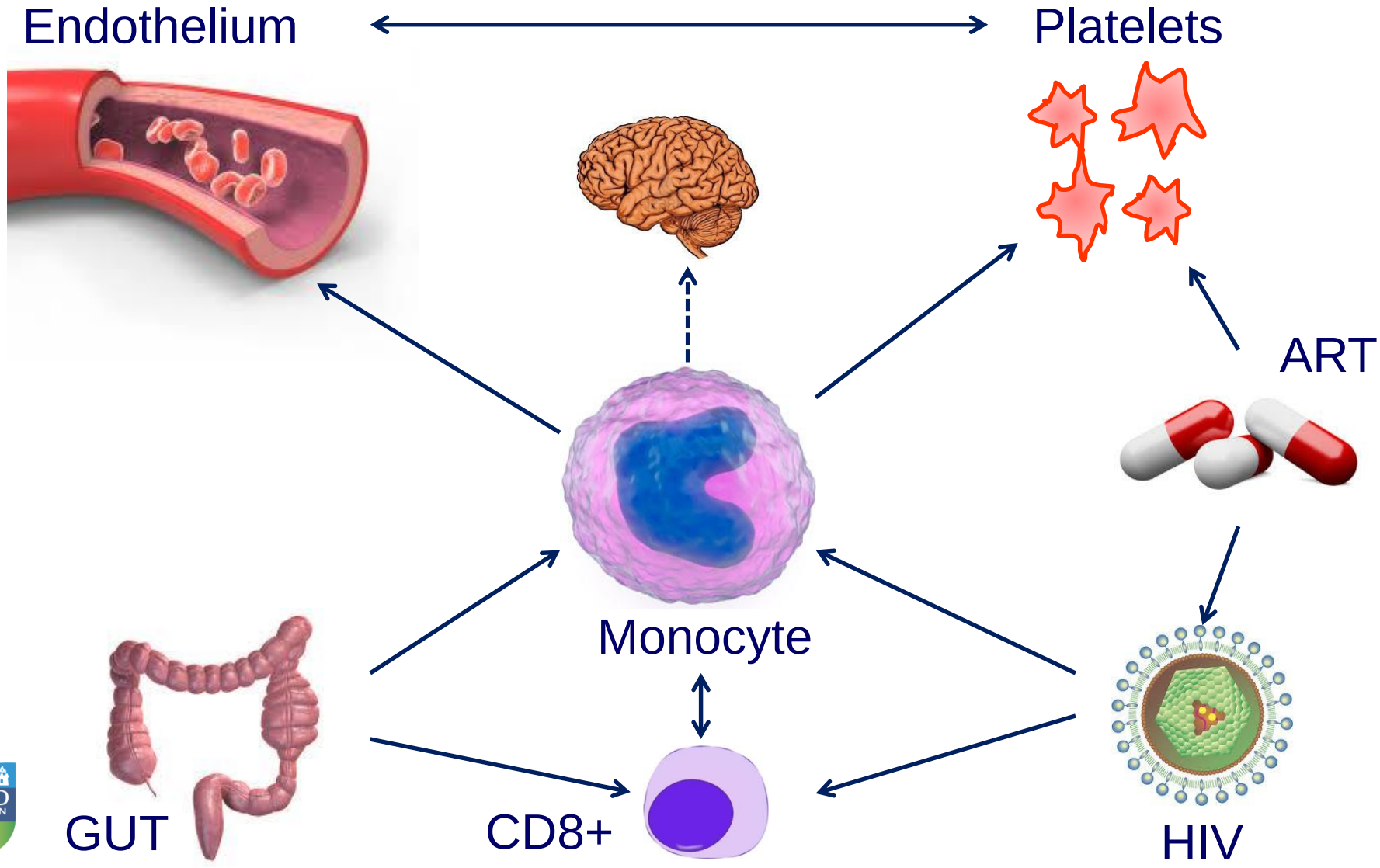
(P<0.0001) (* <40mg/dl)

Cotter AG et al. 14th EACS Conference, Brussels. Abstract # PE11/28




J O'Halloran, Future Virology 2013 Oct; 8(10):1021-1034

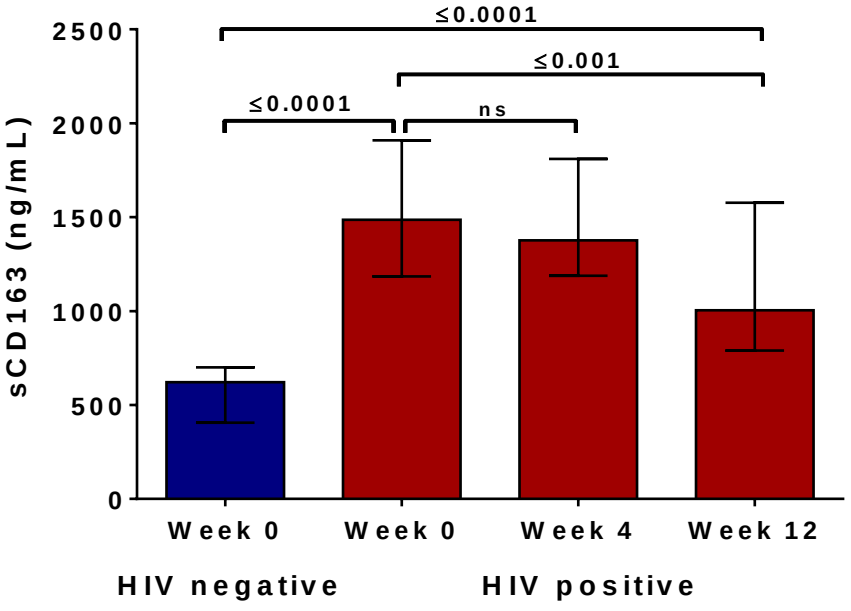
# HIV, CVD and inflammation



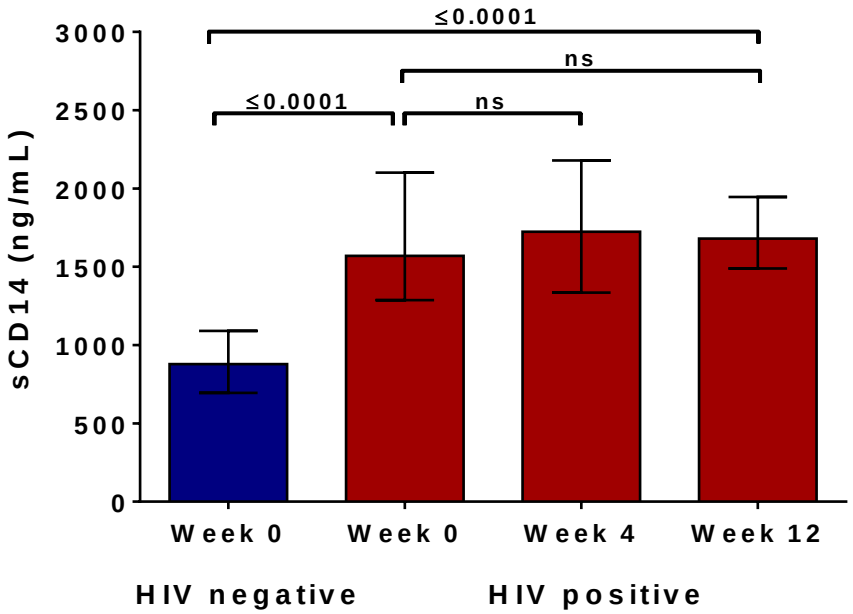
# Markers of monocyte activation

- Both sCD14 & sCD163 were significantly higher in untreated HIV+ subjects compared to HIV- controls
- ART initiation resulted in significant reductions in sCD163
- No effect on sCD14 with ART initiation

**sCD163 baseline comparison and post ART initiation in HIV**

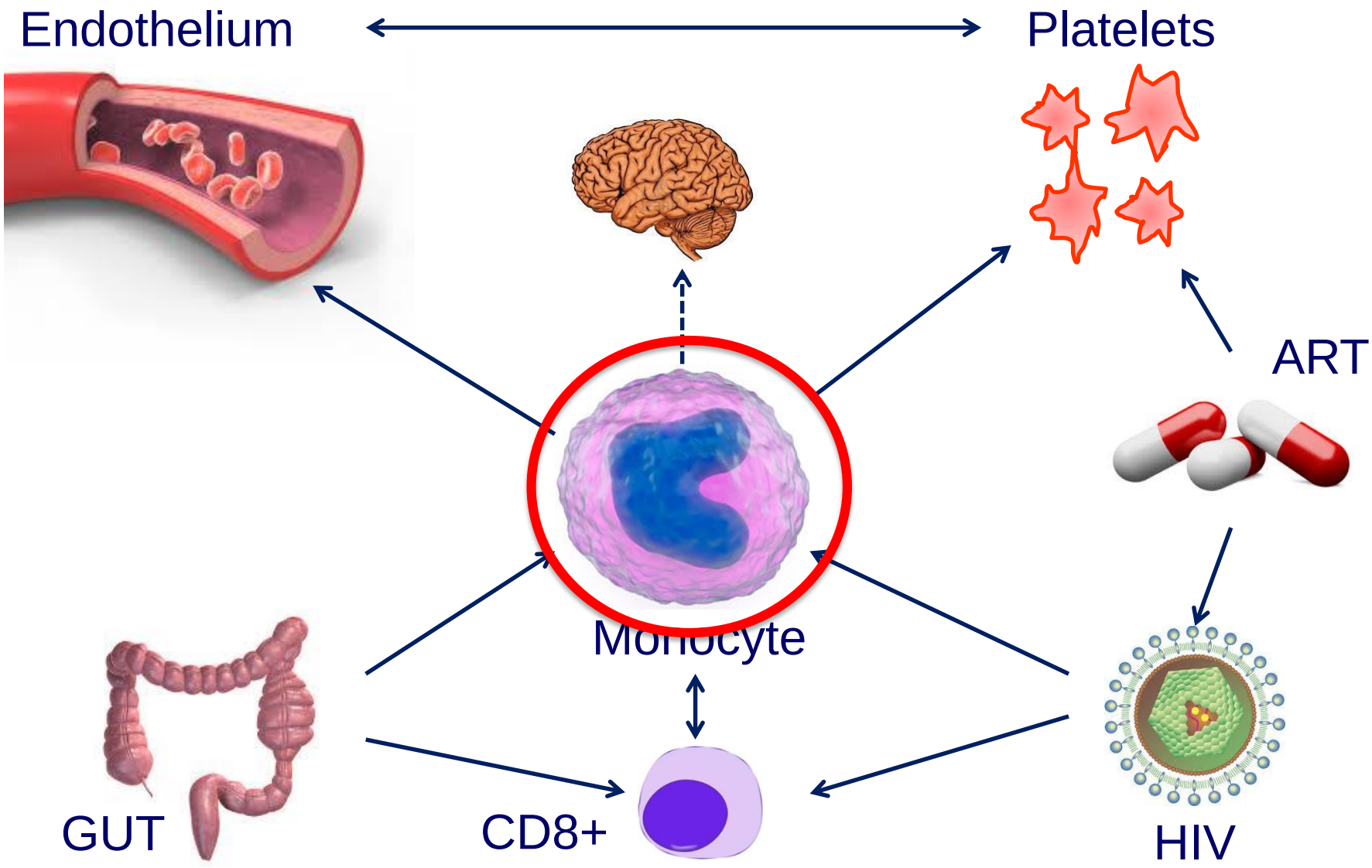



**sCD14 baseline comparison and post ART initiation in HIV**



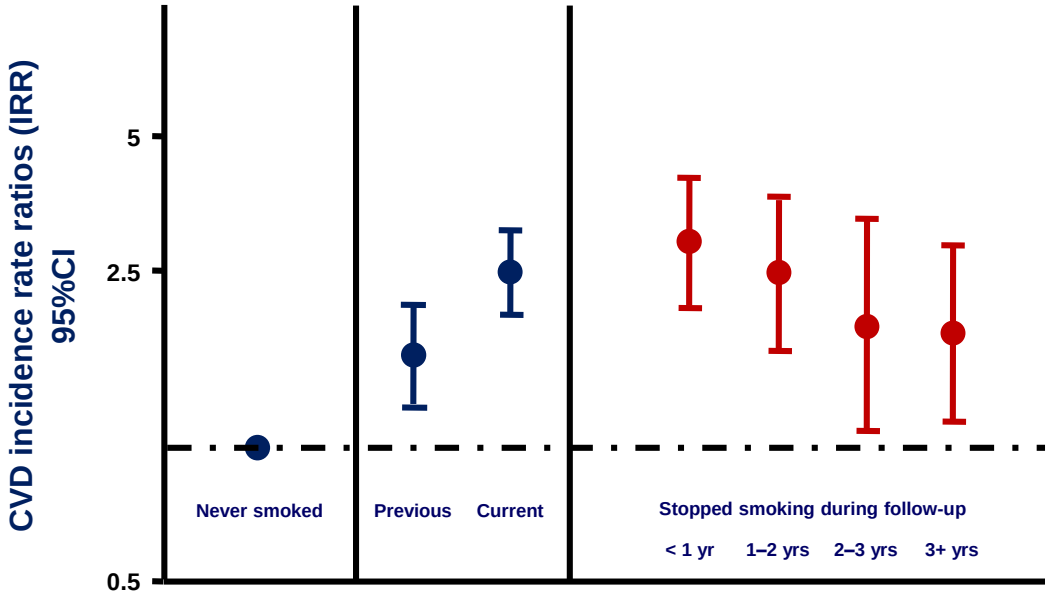

O'Halloran J et al. HIV Medicine 2015. *In Press*

# HIV, CVD and inflammation



# Reducing risk of MI – what works?

## D:A:D - risk of CVD events decreases by nearly 30% after stopping smoking for > 3 years




- 746 CVD events reported during 151,717 person years of follow up, yielding overall crude rates (and 95% CI) per 1,000 person years of 4.92 (4.57, 5.28)

- Compared to current smokers, the risk of CVD among patients who stopped smoking for more than 3 years was **reduced by approximately 30% (IRR (95% CI): 0.74 (0.48, 1.15)**

Adapted from Petoumenos K, et al. HIV Med 2011;12:412–21.

# Ageing with HIV

- Immune dysfunction associated with ageing
- Bone disease
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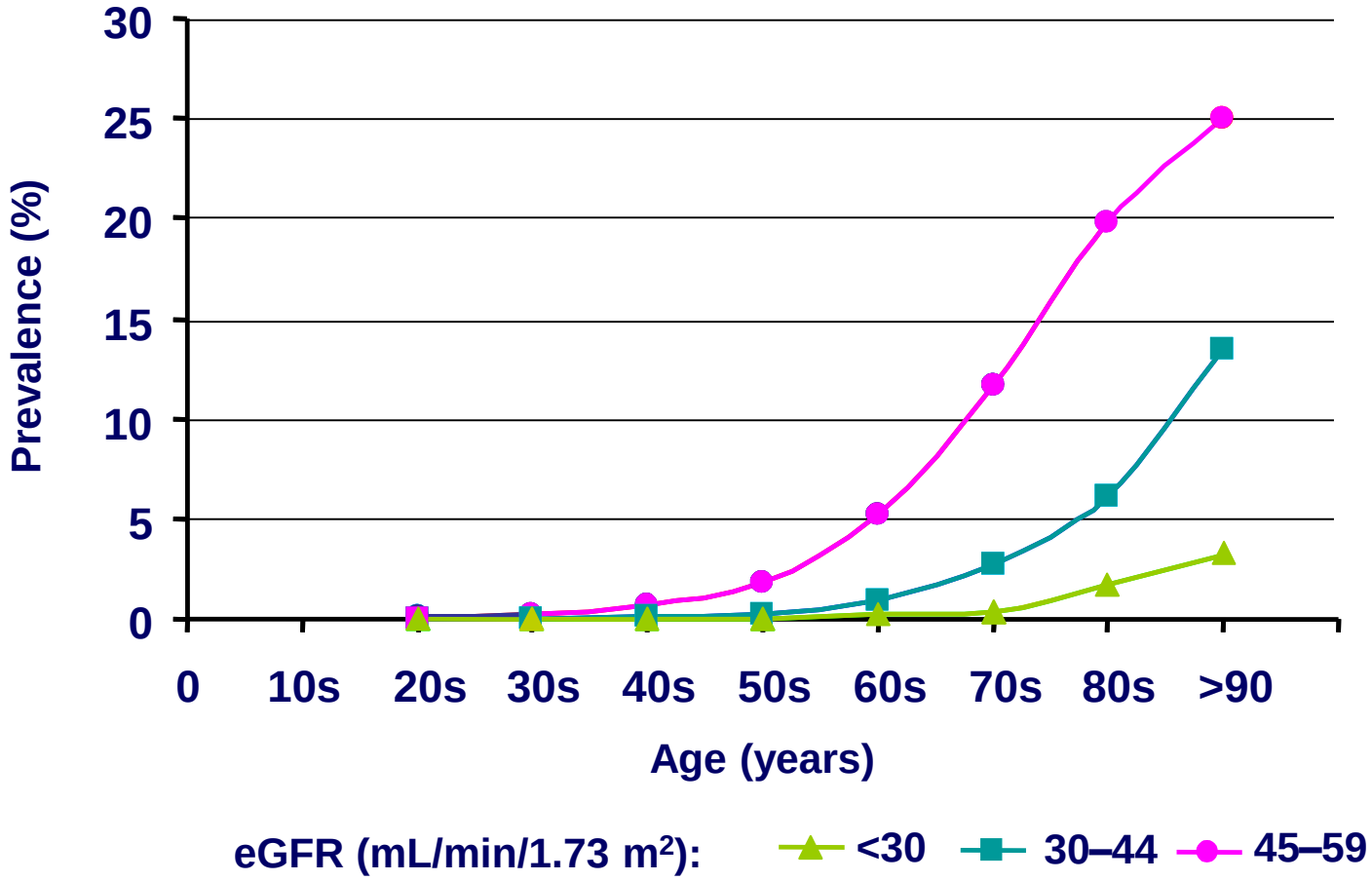
- Neurocognitive impairment

# Prevalence of CKD increases with age

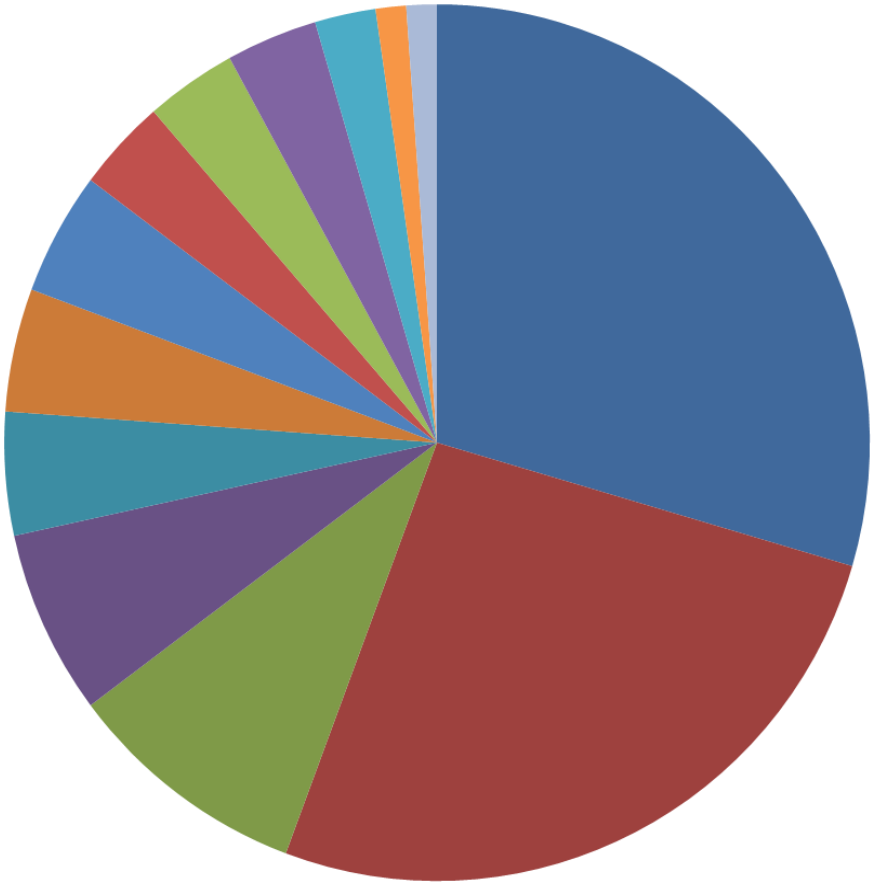


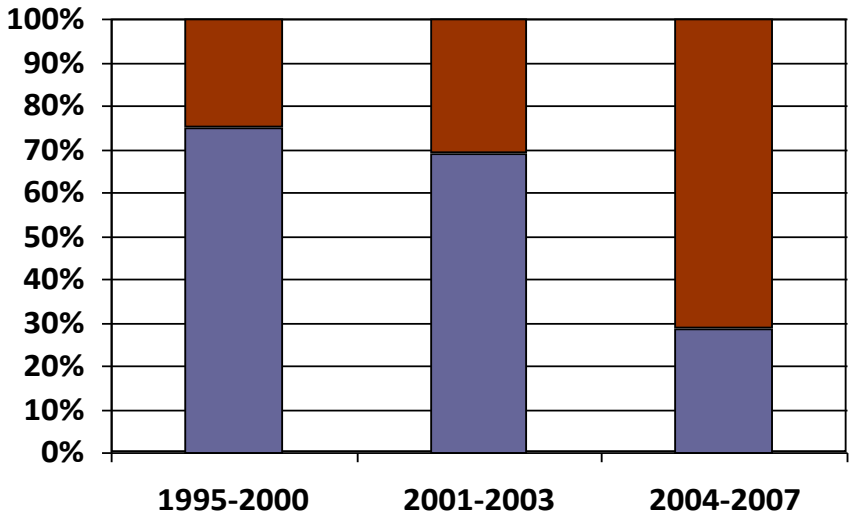

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate

Created from Hallan SI, et al. BMJ. 24 October 2006

# Types of renal disease in HIV

## Histologic glomerular lesions

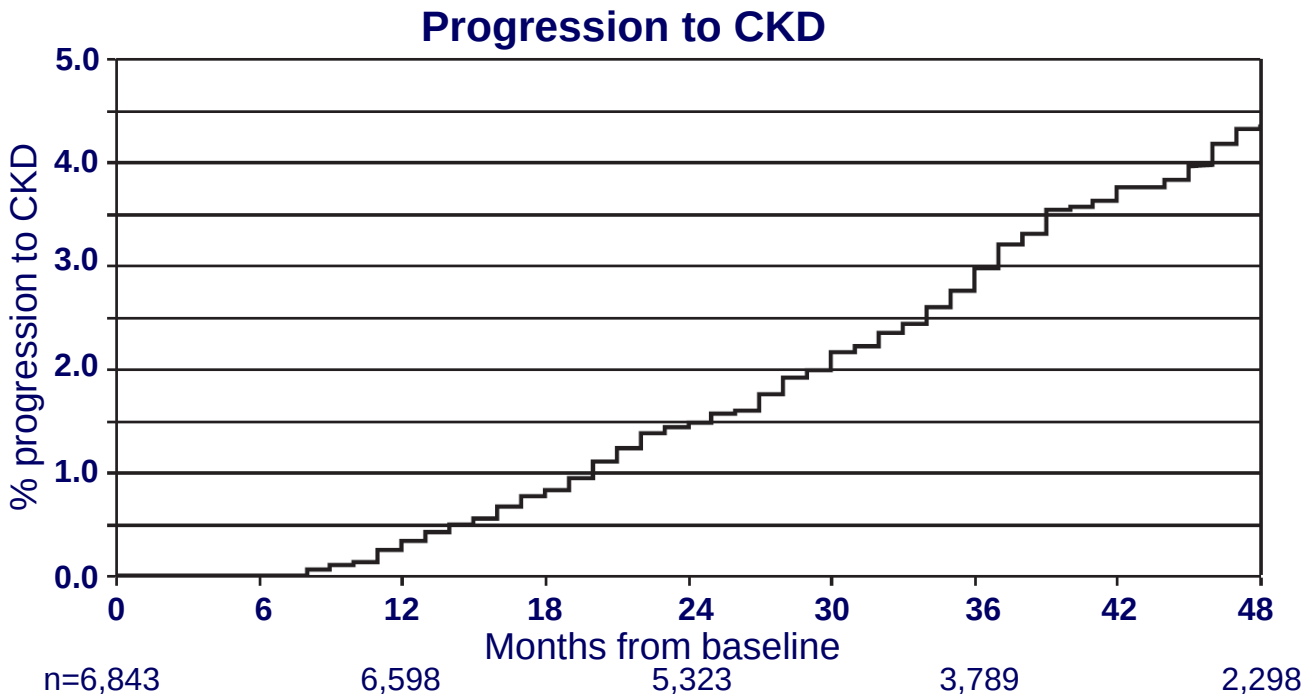



Flateau, C et al. IAC 2010

# HIV and Kidney - EuroSIDA

- N=6,843 (consecutive weights and creatinine recorded)
- Recruited from 2004 to 2005
- Median follow up 3.7 years (IQR 2.8–5.7)
- CKD (eGFR<60 mL/min/1.73m$^2$ or 25% decline)
- 225 (3.3%) progressed to CKD
- Incidence 1.05 per 100 PYFU

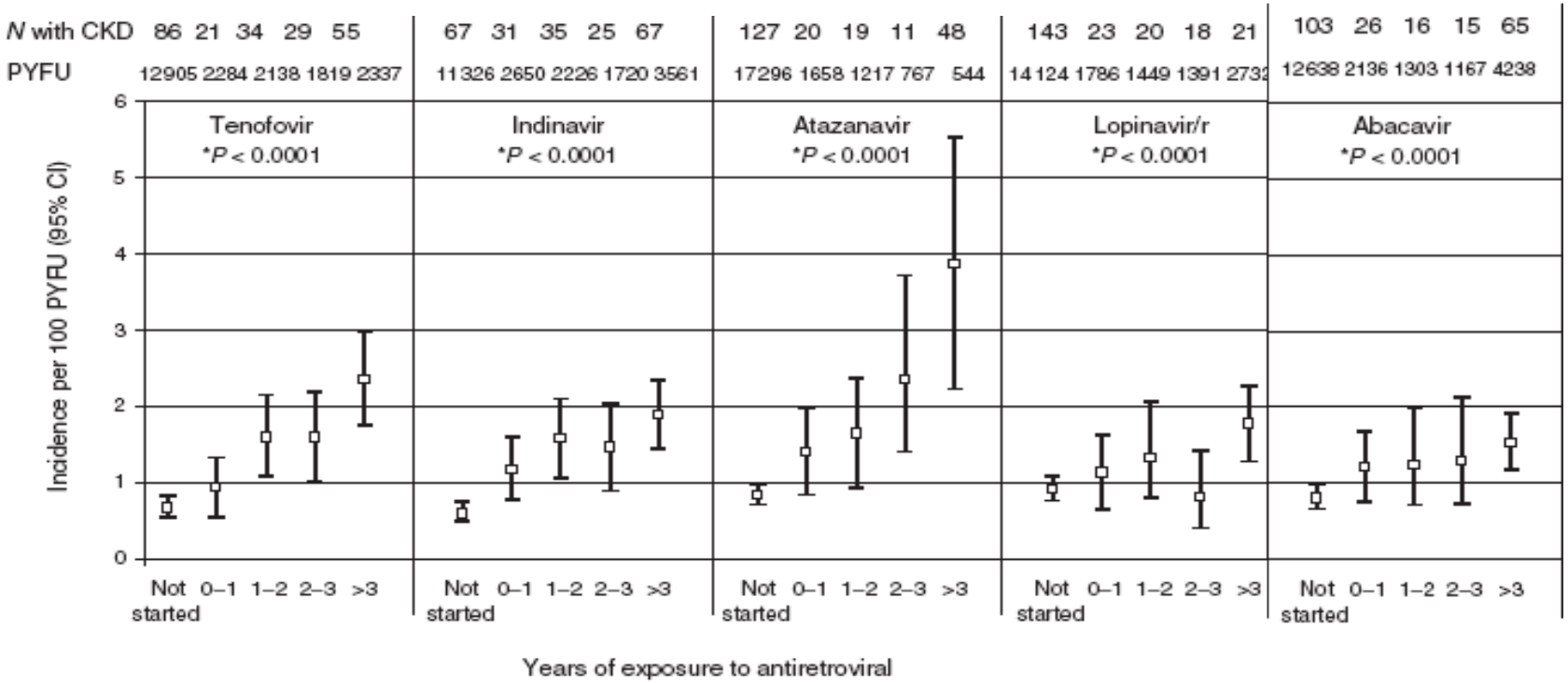



IQR=interquartile range.

Adapted from Mocroft A, et al. AIDS 2010;24:1667–78.

# HIV and Kidney - EuroSIDA

| Drug | IRR | 95% CI |
|---|---|---|
| TDF | 1.16 | 1.06–1.25 |
| IDV | 1.12 | 1.06–1.18 |
| ATV | 1.21 | 1.09–1.34 |
| LPV/r | 1.08 | 1.01–1.16 |



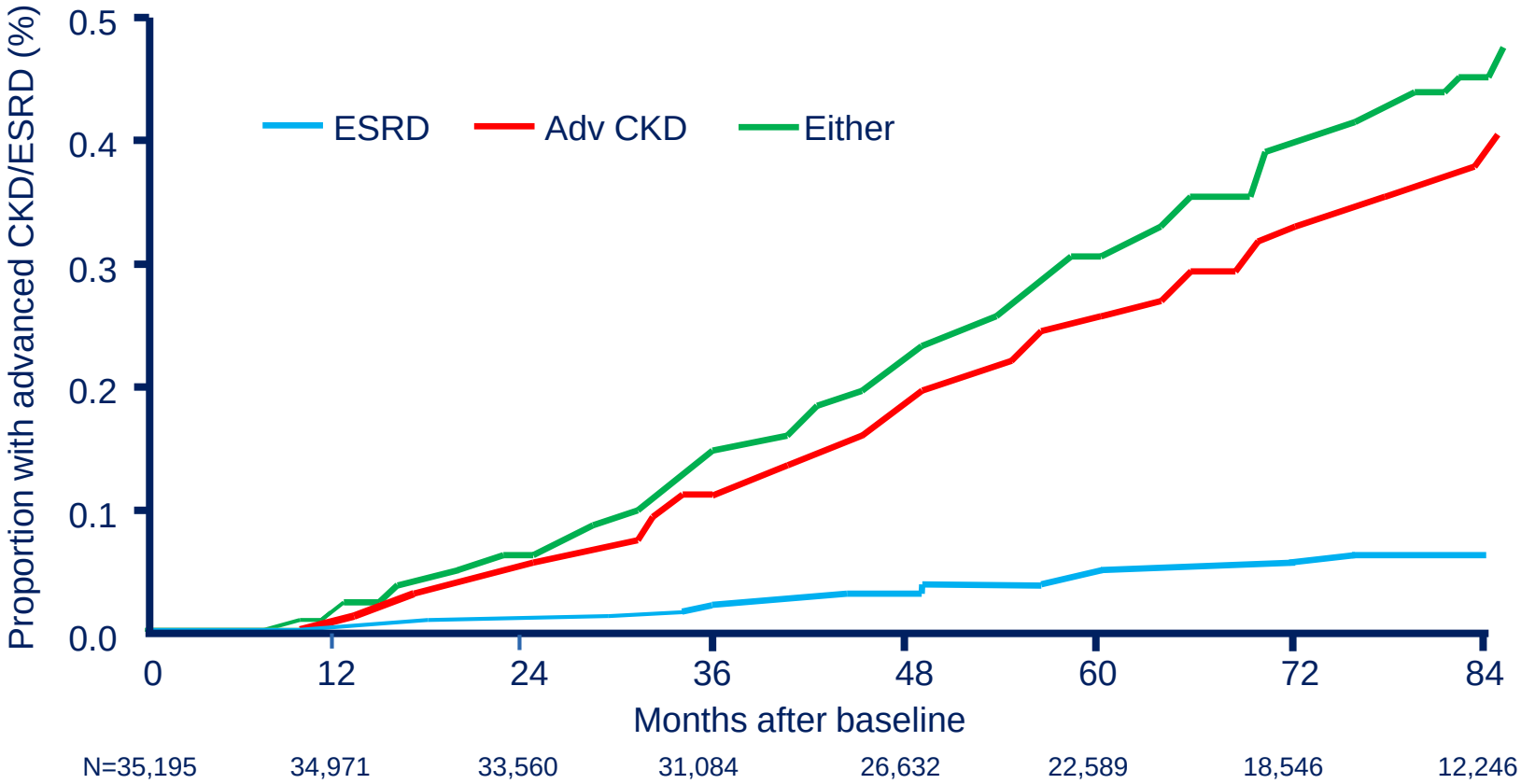

Adapted from Mocroft A, et al. AIDS 2010;24:1667–78.

# HIV and Kidney – D:A:D

Kaplan-Meier progression to advanced CKD/ESRD

CKD = eGFR ≤30ml/min for ≥3 months

ESRD = dialysis for ≥3 months or renal transplantation

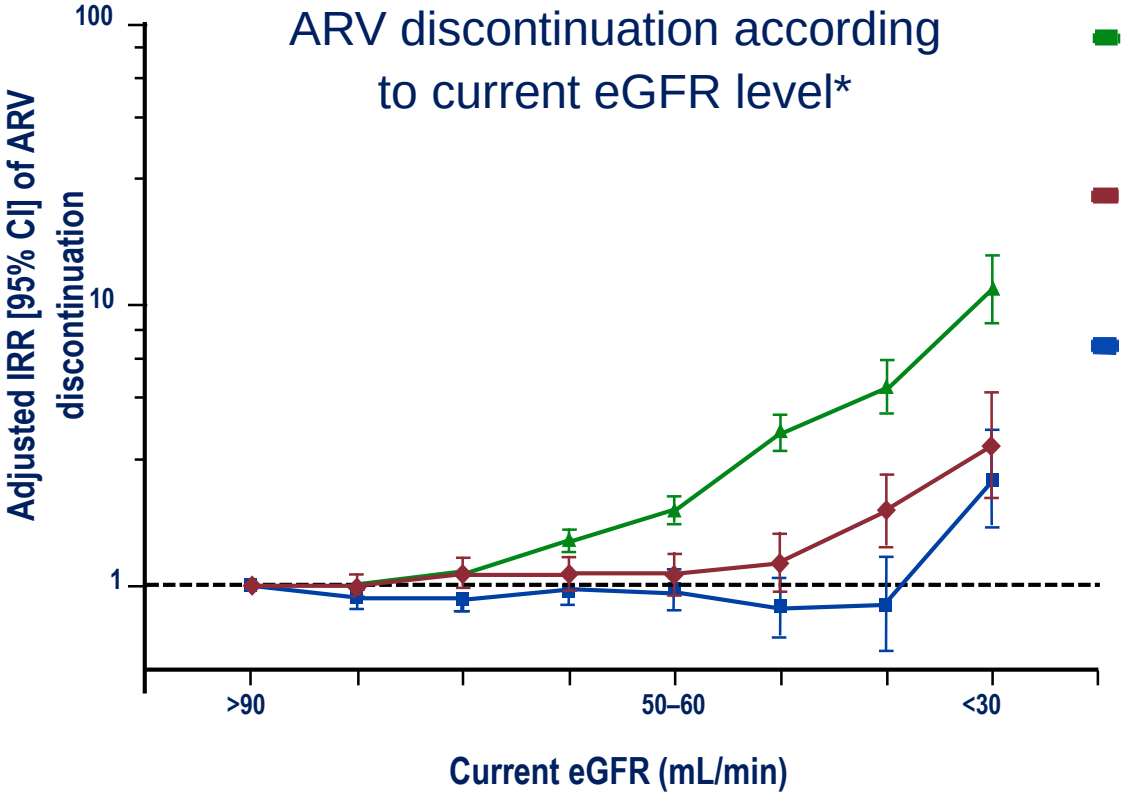



ESRD=end-stage renal disease.

Ryom L, et al. CROI 2013. Poster 810.

# HIV and Kidney – D:A:D

## ARV discontinuation increases significantly with eGFR decline



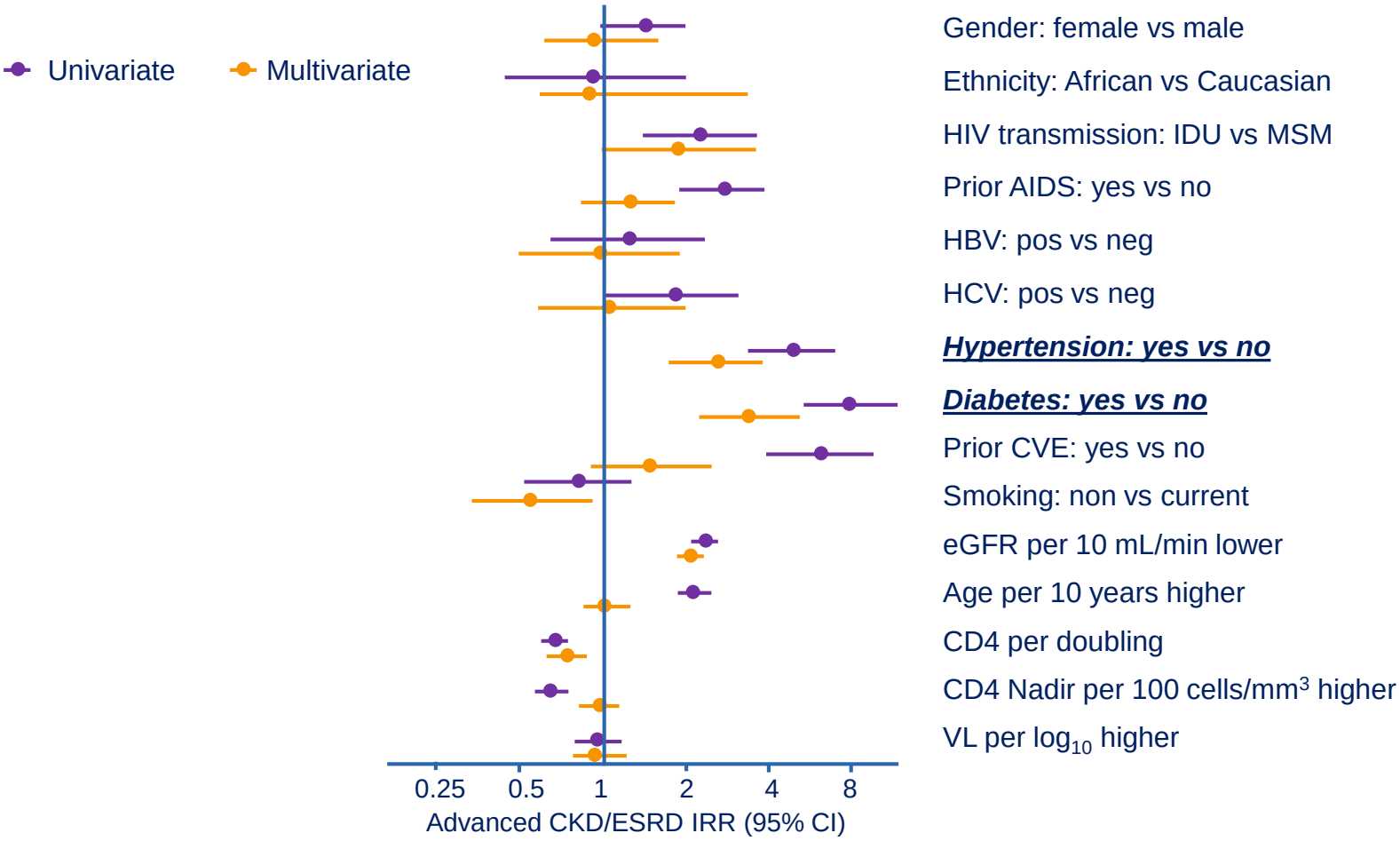

- **TDF: 21,899 patients on TDF at baseline or start during follow up. 9,141 stop during 63,698 PY**
- **ATV/r: 7,857 patients on ATV/r at baseline or start during follow up. 4,709 stop during 19,371 PY**
- **LPV/r: 8,038 patients on LPV/r at baseline or start during follow up. 5,387 stop during 20,449 PY**

*Same pattern for ATV and other PI/r as for LPV/r. Models adjusted for CD4 nadir, gender, ethnicity, HIV transmission risk, enrolment cohort and prior AIDS (all at baseline) and HBV, HCV, smoking status, hypertension, diabetes, CV events, age and CD4 as time-updated values.

Ryom L, et al. CROI 2013. Poster 810.

# HIV and Kidney – D:A:D

## Non-ARV predictors of advanced CKD/ESRD




Gender: female vs male

Ethnicity: African vs Caucasian

HIV transmission: IDU vs MSM

Prior AIDS: yes vs no

HBV: pos vs neg

HCV: pos vs neg

***Hypertension: yes vs no***

***Diabetes: yes vs no***

Prior CVE: yes vs no

Smoking: non vs current

eGFR per 10 mL/min lower

Age per 10 years higher

CD4 per doubling

CD4 Nadir per 100 cells/$mm^3$ higher

VL per $log_{10}$ higher

Poisson regression model adjusted for gender, ethnicity, HIV transmission group, enrolment cohort, prior AIDS, HBV status*, HCV status*, hypertension*, smoking status*, diabetes*, CVE*, baseline year, eGFR, age, current CD4 count*, CD4 Nadir, HIV-1 viral load*, and use of TDF, ATV/r, LPV/r, other PI/r, and INI.

*Time-updated.

CVE=cardiovascular event.

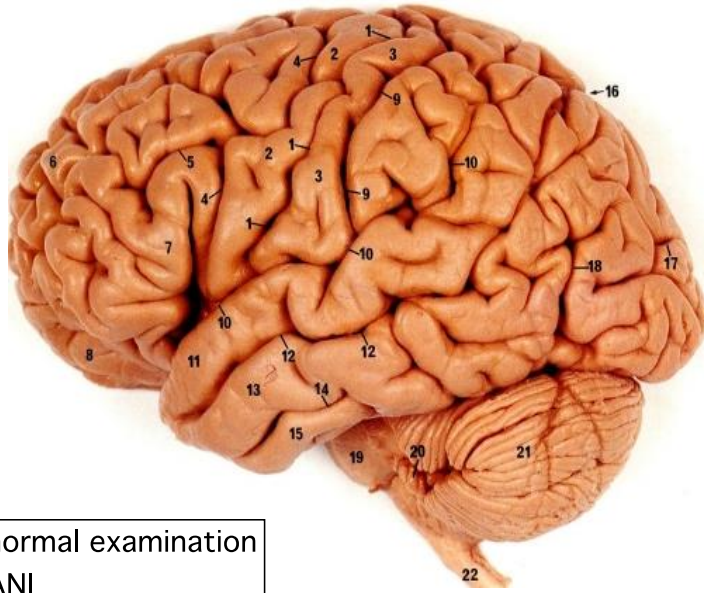
Ryom L, et al. CROI 2013. Poster 810.

# Ageing with HIV

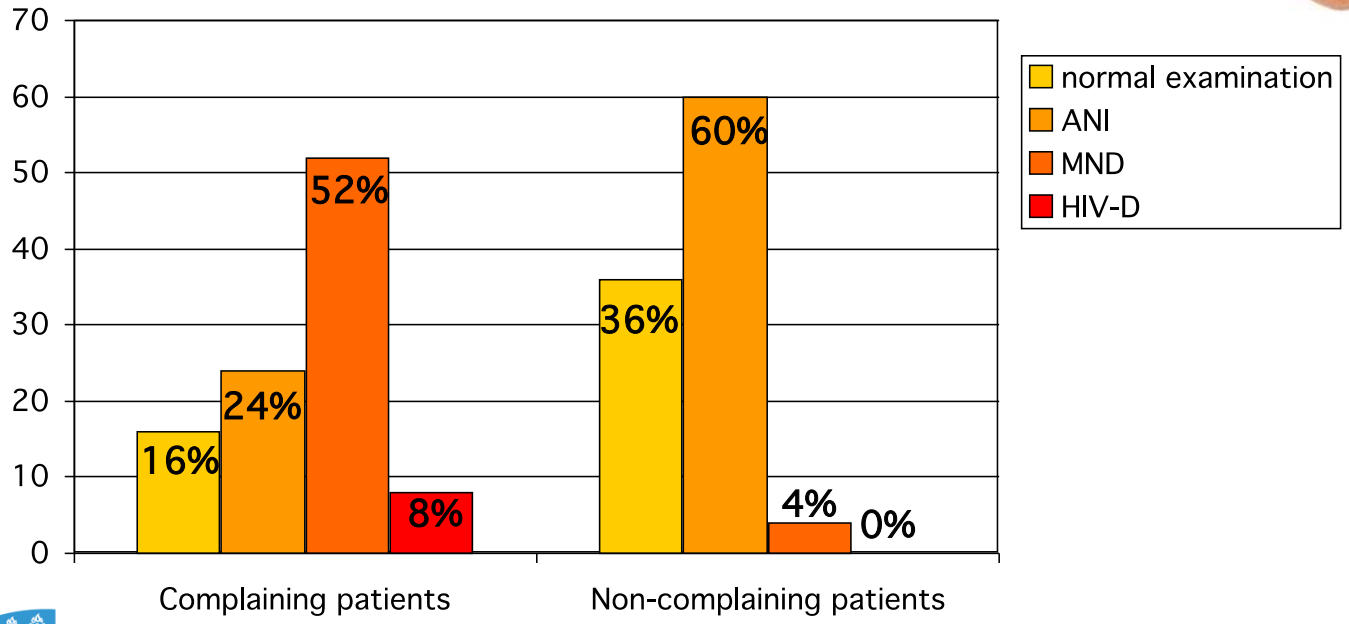
- Immune dysfunction associated with ageing
- Bone disease
- Cardiovascular disease
- Renal disease
- Neurocognitive impairment

# HIV-associated neurocognitive disorders

- Asymptomatic
- Mild
- Symptomatic (dementia)

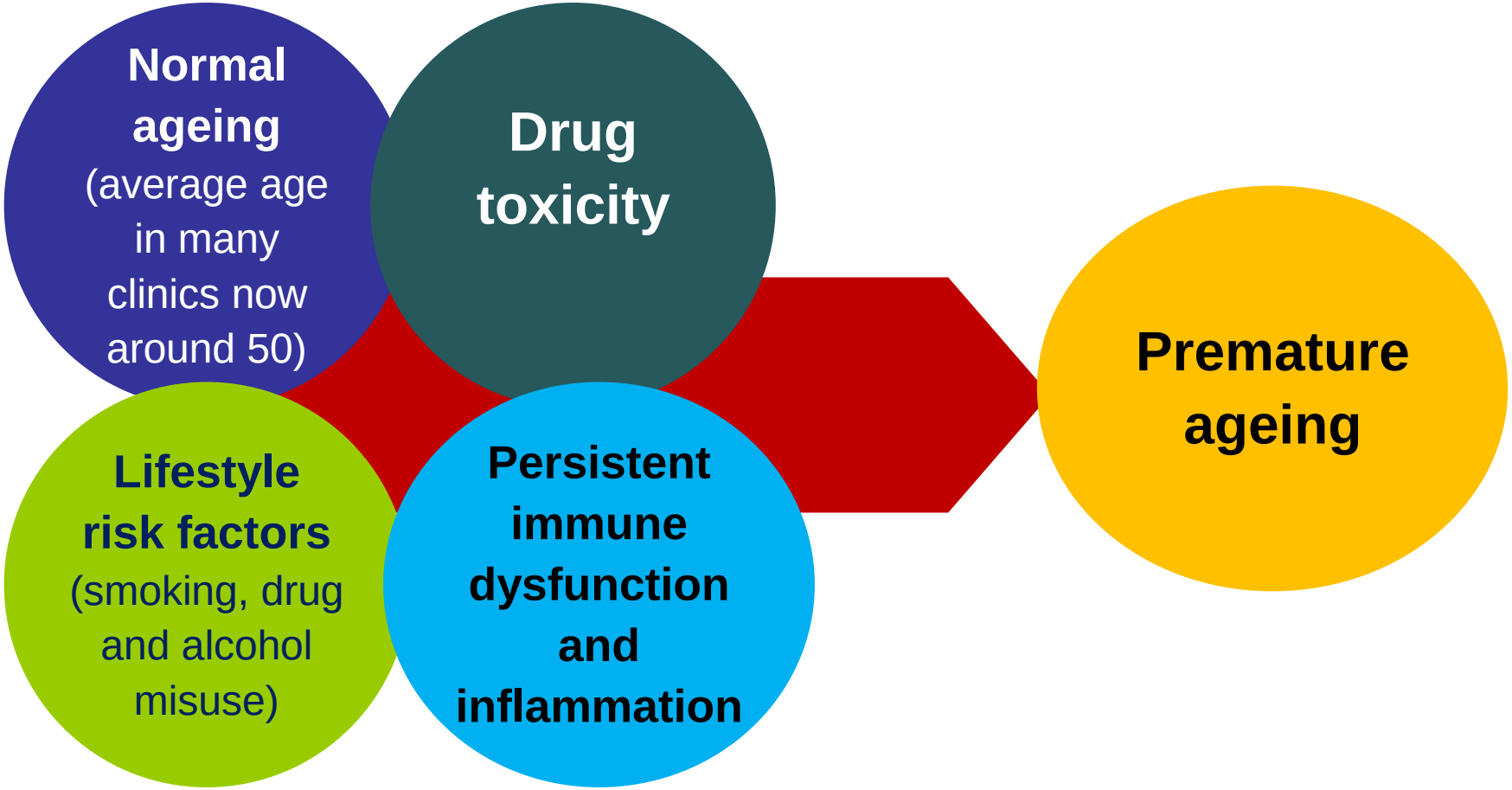


- Prevalence 20-50%




Sacktor Neurology 01; McArthur J Neuroimmunol 04; Woods Neuropsychol Rev 09; Robertson AIDS 2007; Cysique J Neurovirol 2007, etc.

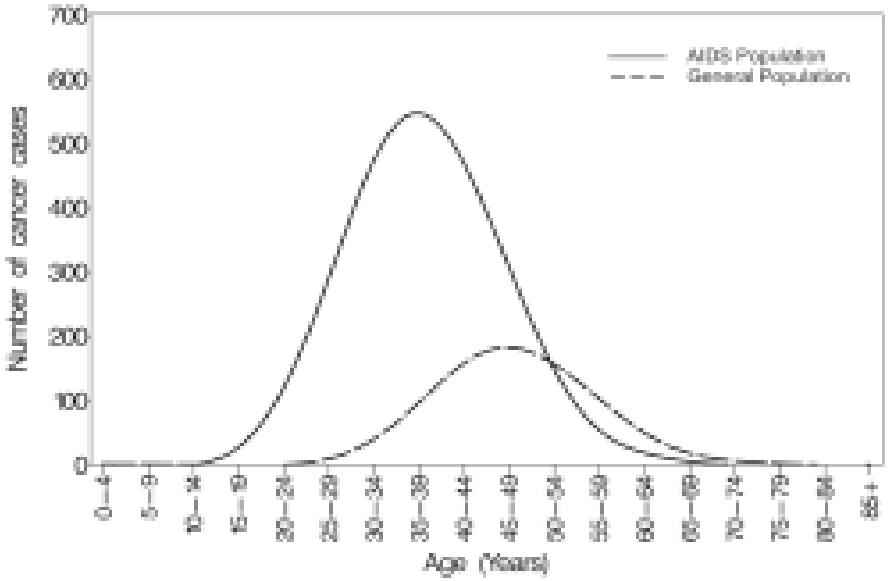
# HIV and 'Premature Ageing'

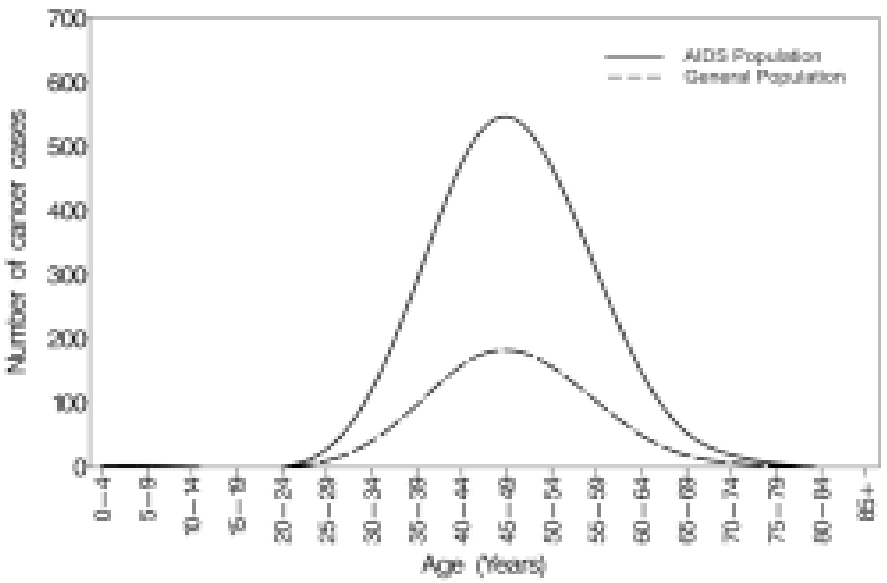



Adapted from Deeks SG, Phillips AN. *Br Med J* 2009;**338**:a3172

# HIV and Ageing

## '***Accelerated*** or ***accentuated***?'




A. Accelerated and Accentuated risk: Cancer occurs earlier in persons with HIV than uninfected comparators, and more frequently

B. Accentuated risk: Cancer occurs at the same ages in the HIV-infected population, but more often than among comparators

Shiels MS, et al. Ann Intern Med 2010:153:452-460.


Personal communication Giovanni Guaraldi, October 2012

# Nucleoside Reverse Transcriptase Inhibitors

| Class | Purine | | Pyrimidine | |
|---|---|---|---|---|
| Endogenous nucleotide | adenosine | guanosine | cytosine | thymidine |
| Synthetic NRTI analogues | didanosine (ddI) | abacavir (ABC) (carbovir) | zalcitabine (ddC) | zidovudine (AZT) |
| | adefovir (PMEA) | | lamivudine (3TC) | stavudine (d4T) |
| | tenofovir disoproxil fumarate (TDF) | | emtricitabine (FTC) | |

# Monitoring for co-morbidities

- Time consuming!!
- Difficult to implement in busy clinics
- Aim for broad screening at presentation
- Thereafter, use risk assessment to target monitoring
  - Older PLWH
  - Threshold testing
  - Annual / Birthday checks
  - Research….

| | Assessment | At HIV diagnosis | Prior to starting ART | Follow-up frequency | Comment | See page |
|---|---|---|---|---|---|---|
| **CO-MORBIDITIES** | | | | | | |
| **Haematology** | FBC | + | + | 3-12 months | | |
| | Haemoglobinopathies | + | | | Screen at risk persons | |
| | G6PD | + | | | Screen at risk persons | |
| **Body composition** | Body-mass index | + | + | Annual | | 33 |
| **Cardiovascular disease** | Risk assessment (Framingham score[iii]) | + | + | 2 years | Should be performed in all men > 40 years and women > 50 years without CVD | 34 |
| | ECG | + | +/- | As indicated | Consider baseline ECG prior to starting ARVs associated with potential conduction problems | |
| **Hypertension** | Blood pressure | + | + | Annual | | 35-36 |
| **Lipids** | TC, HDL-c, LDL-c, TG[iv] | + | + | Annual | Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake) | 40 |
| **Glucose** | Serum glucose | + | + | Annual | Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL) | 38-39 |
| **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 | | 48-50 |
| | ALT/AST, ALP, Bilirubin | + | + | 3-12 months | More frequent monitoring prior to starting and on treatment with hepatotoxic drugs | |
| | Staging of liver fibrosis | | | 12 months | In HCV and/or HBV co-infected persons (e.g. FibroScan, serum fibrosis markers) | 67, 71 |
| | Hepatic ultrasound | | | 6 months | In HCV co-infected persons with liver cirrhosis Child Pugh class A or B and Child Pugh class C awaiting liver transplantation; and in HBV co-infected persons irrespective of fibrosis stage | 67, 71 |
| **Renal disease** | Risk assessment[vi] | + | + | Annual | More frequent monitoring if eGFR < 90mL/min, CKD risk factors present[vi] and/or prior to starting and on treatment with nephrotoxic drugs[ix] | 44-45 |
| | eGFR (CKD-EPI)[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[viii] | |
| **Bone disease** | Bone profile: calcium, $PO_4$, ALP | + | + | 6-12 months | | 41, 43 |
| | Risk assessment[x] (FRAX®[xi] in persons > 40 years) | + | + | 2 years | Consider DXA in specific persons (see page 41 for details) | |
| **Vitamin D** | 25(OH) vitamin D | + | | As indicated | Screen at risk persons | 42 |
| **Neurocognitive impairment** | Screening questionnaire | + | + | As indicated | Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 66 for further assessment. | 66 |
| **Depression** | Questionnaire | + | + | As indicated | Screen at risk persons | 62-64 |
| **Cancer** | Mammography | | | 1-3 years | Women 50-70 years | 32, 50 |
| | 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 persons with HBV irrespective of fibrosis stage | |
| | Others | | | | Controversial | |

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# QUESTIONS?

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