# Metabolic consequences of HIV-induced inflammation

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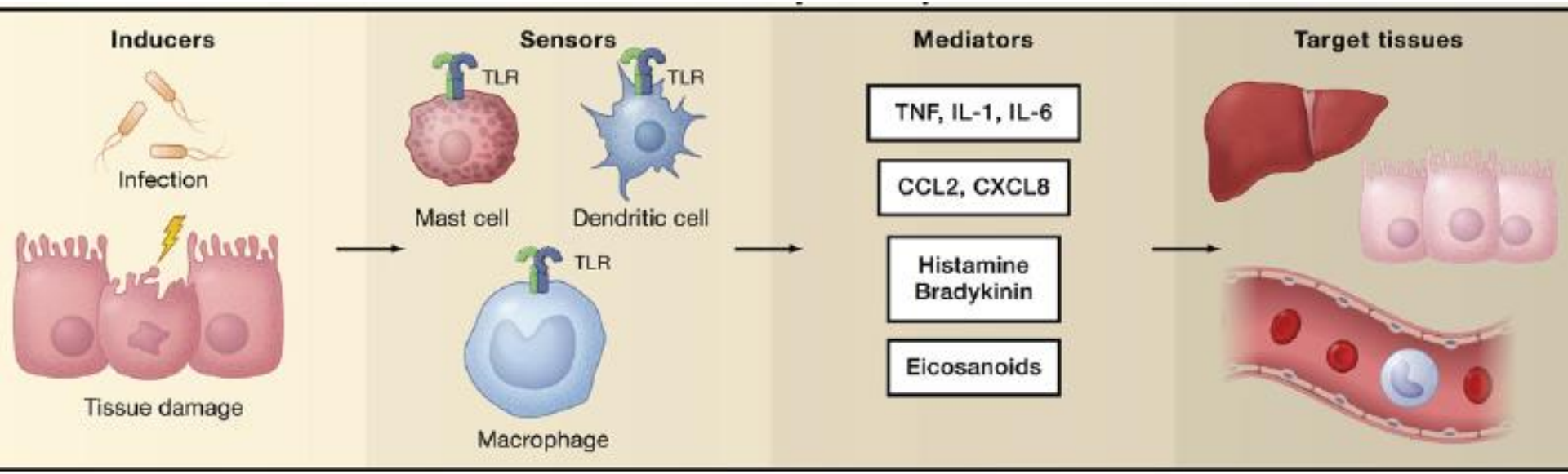
1. Pathogenesis of low-grade inflammation/immune activation
2. Impact on aging
3. Consequences on mortality and morbidity in HIV-infected patients
4. Impact of HIV drugs on metabolic parameters

# Acute inflammation pathways components




Infection → Inflammation → Host defense

Injury → Inflammation → Tissue repair

Activation of innate immunity

*R Medzhitov Cell 2010*

# Acute vs chronic inflammation

## Acute inflammation

- ✓Pathogen or wound
- ✓Several days
- ✓Eradication of the stimulus
- ✓Repair
- ✓Return to a quiescent state for immune cells
- ✓Protective response
- ✓Beneficial for the host

## Chronic inflammation

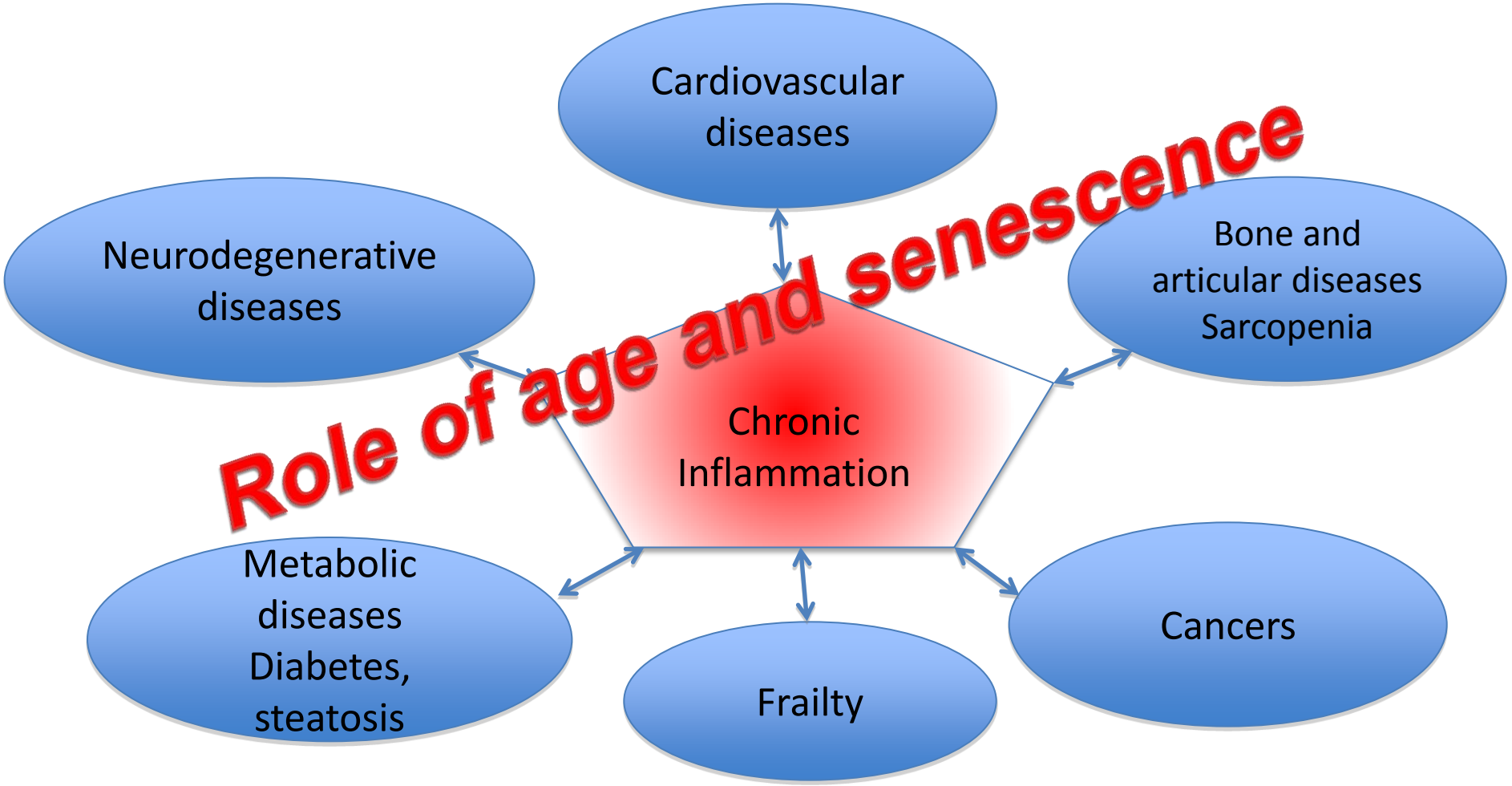
- ✓Persistence of the stimulus: pathogen, cancer antigen, auto-antigen
- ✓As HIV infection, long-term infections, auto-immune or inflammatory diseases, cancers
- ✓Deleterious for the host
- ✓Long-term consequences: CVD, cancer

*From L Weiss*

# Increased activation of the immune system

- ✓ Long-term infections: HIV, CMV..
- ✓ Intestinal bacterial products: LPS…
- ✓ Innate immunity: Tissue resident macrophages
- ✓ Acquired cellular immunity: CD4 and CD8 T lymphocytes
- ✓ Acquired humoral immunity: B lymphocytes, hypergammaglobulinemia

# Most age-related comorbidities are associated with a chronic low-grade inflammation

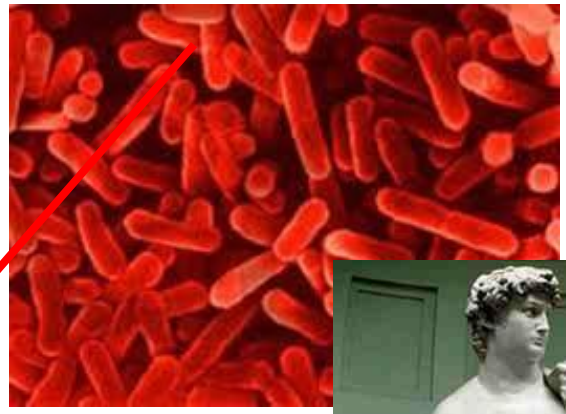


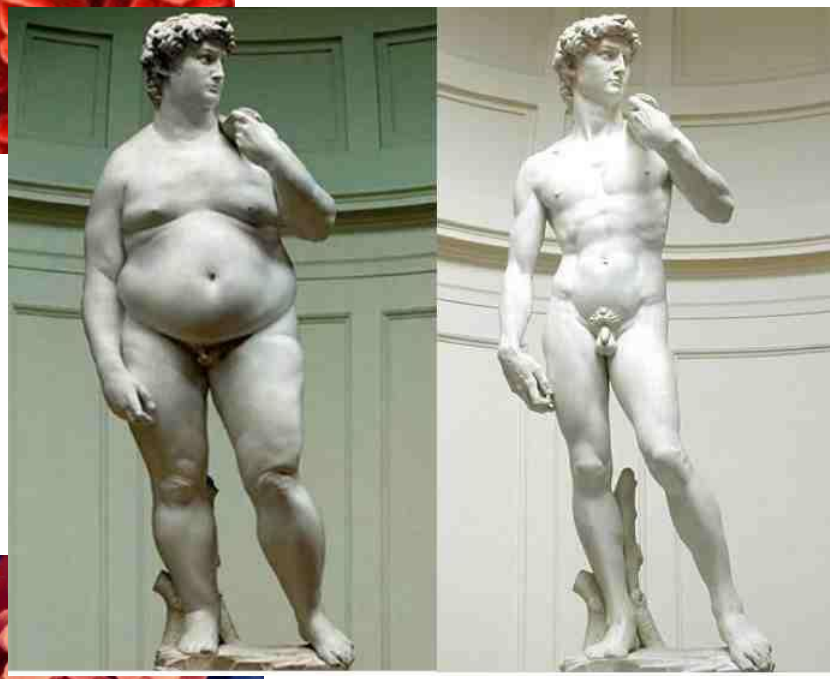

CRP< 10mg/l

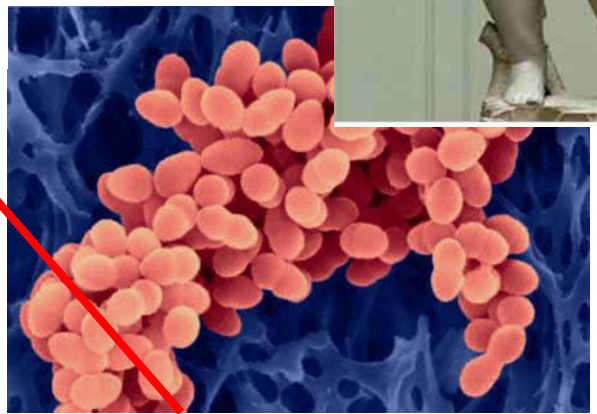
*From A Freund Trends Molecular Med 2010*

# Gut-derived inflammation and metabolic risk

# Gut microflora is involved in abdominal obesity and metabolic disorders



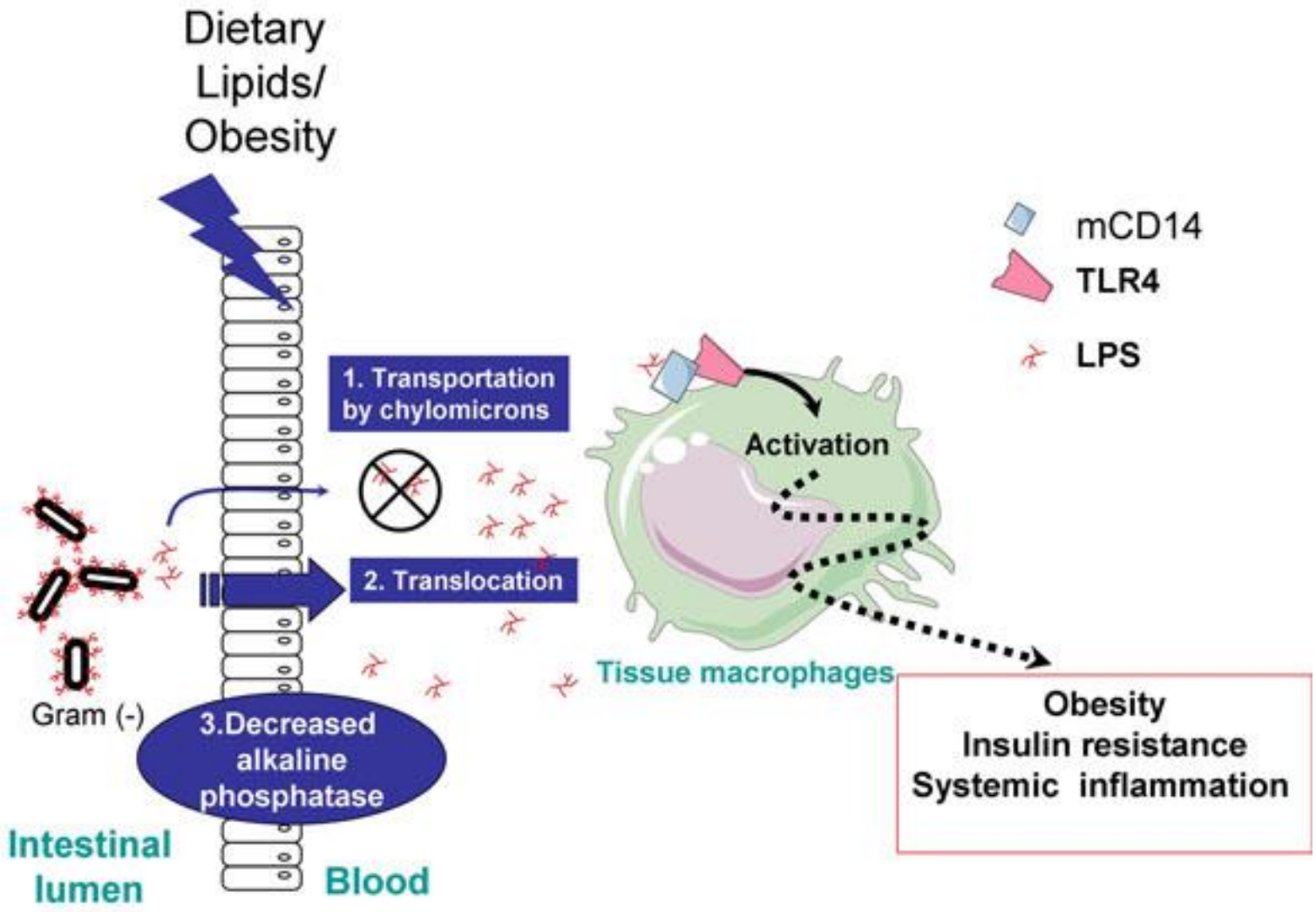




$10^{13}$ bacterias

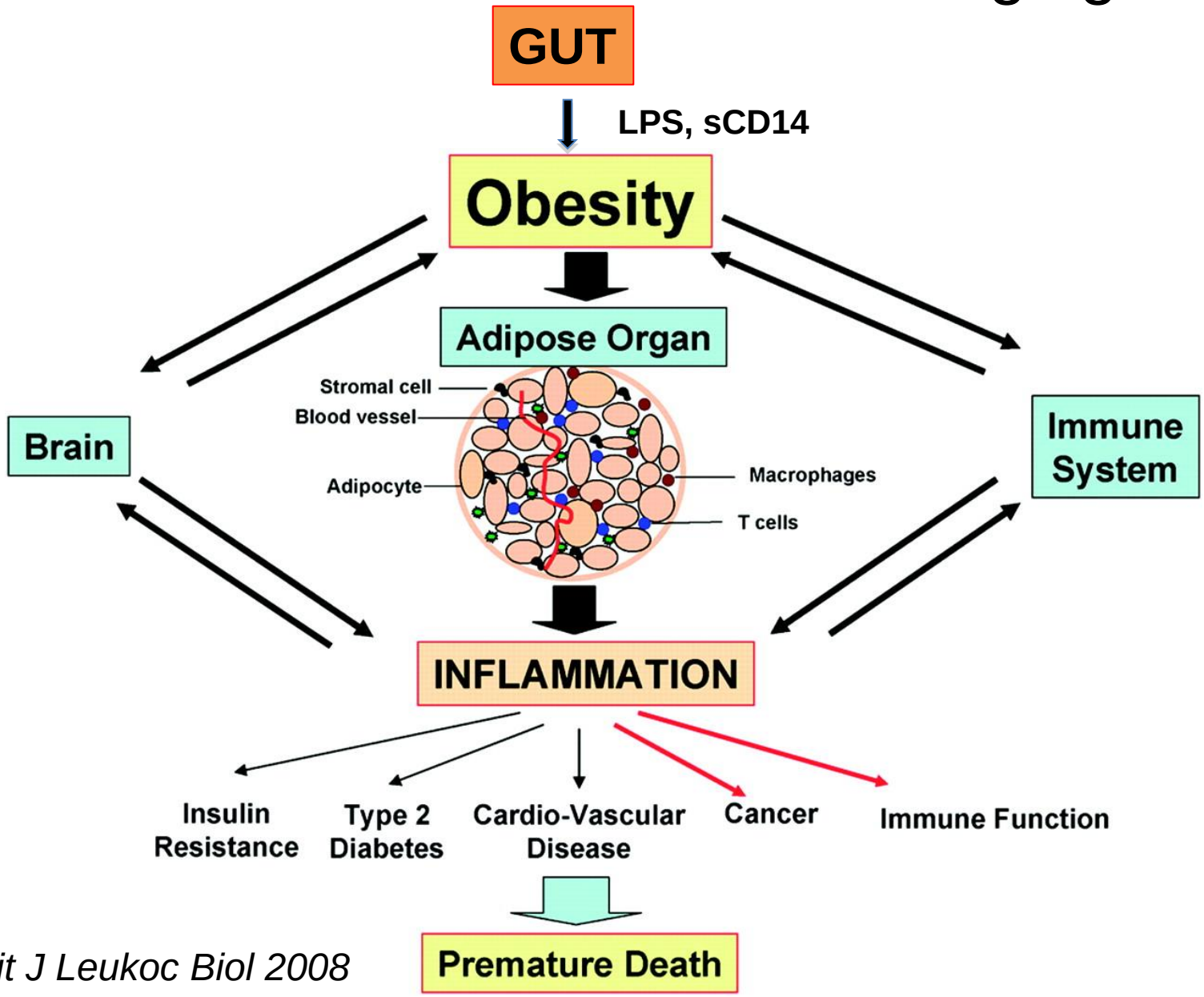
Great diversity

# Gut dysbiosis is involved in metabolic disorders



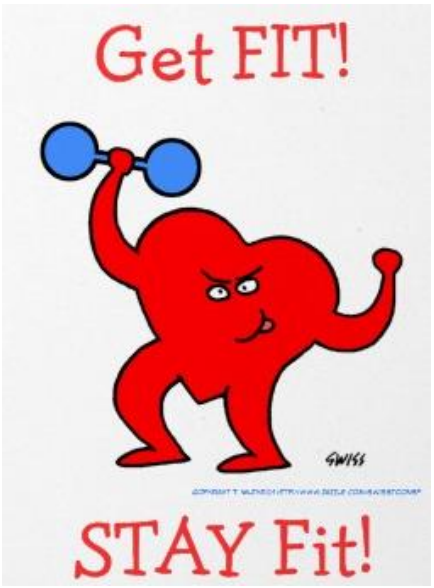

*NM Delzenne Microbial Cell Factories 2011*

# Role of gut dysbiosis and adiposity in inflammation, comorbidities and aging



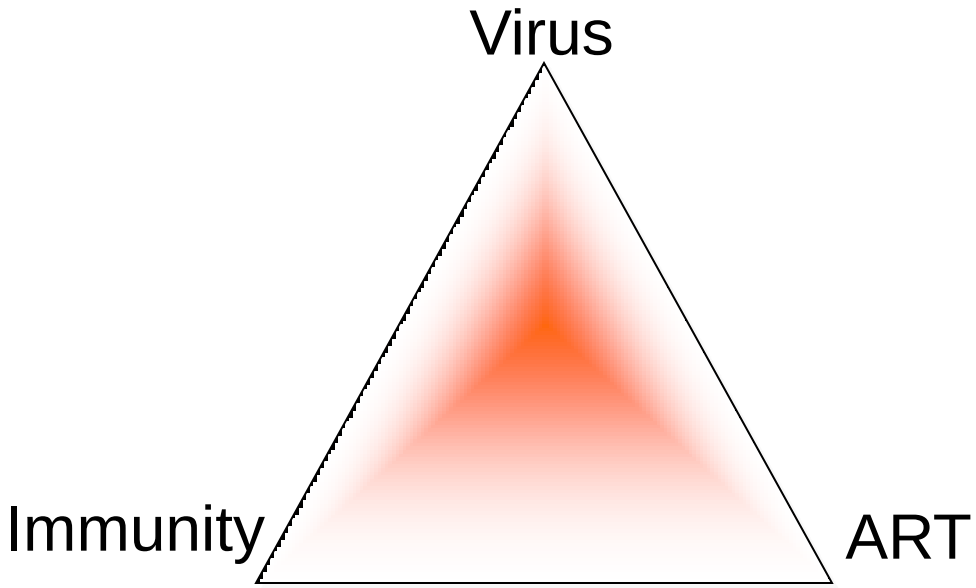

*From VD Dixit J Leukoc Biol 2008*

# Role of personal and life-style factors

# Pathogenesis of inflammation/immune activation in HIV-infected patients

- Role of chronic infection
- Role of inflammation/immune activation
- Role of immune deficiency/senescence
- Role of treatment
- Role des personal factors : age, tobacco, coinfections



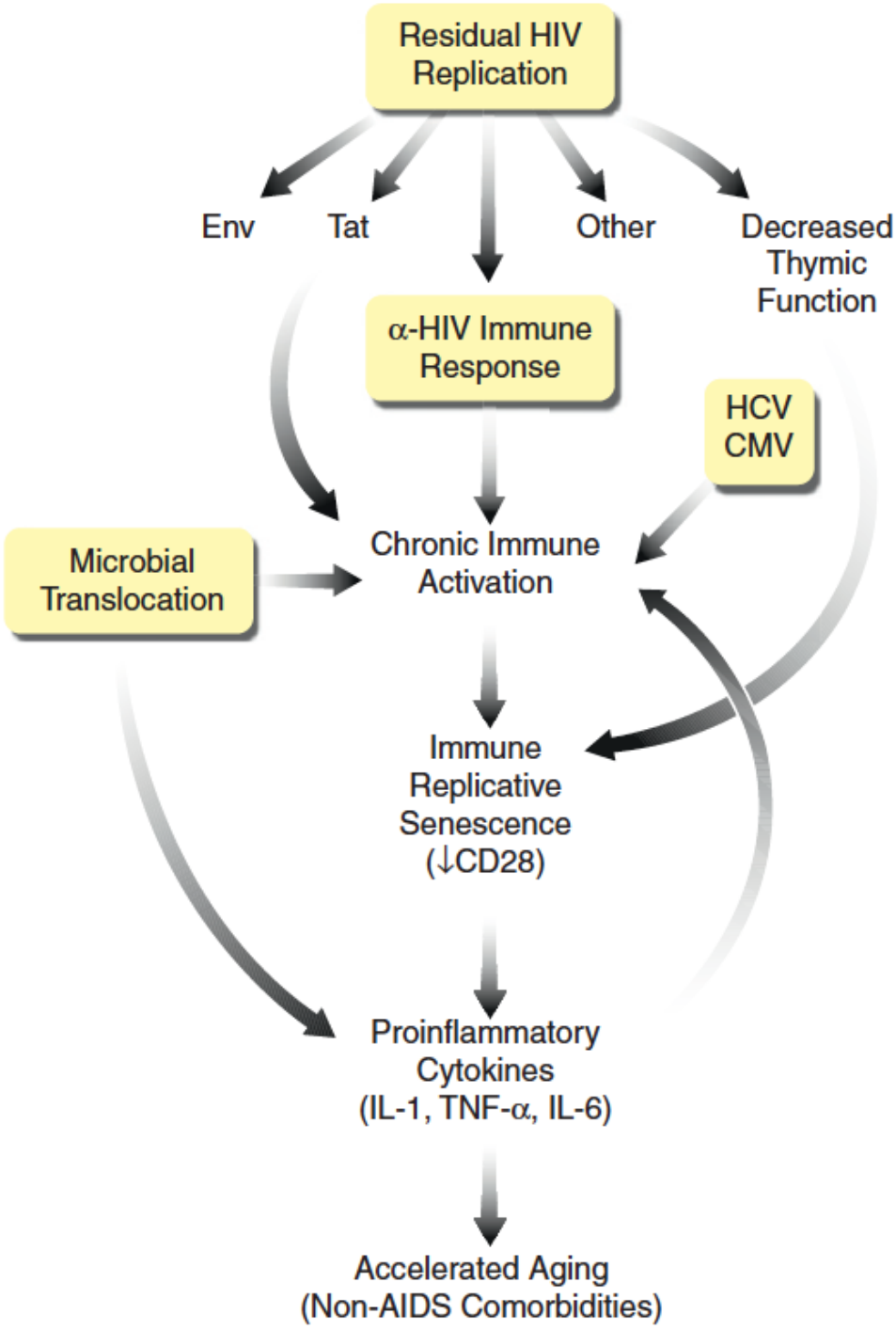
# Increased levels of proinflammatory markers in HIV-infected patients as compared to the general population

Biomarkers Levels in SMART Study Participants Receiving Antiretroviral Therapy (ART) Who Had an HIV RNA Level ≤400 Copies/mL and Percentage Differences in Levels Versus CARDIA and MESA Study Participants

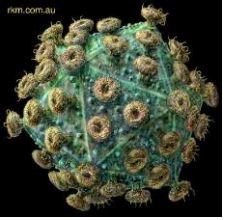
| Biomarker | Participants 33-44 years of age | | | Participants 45-76 years of age | | |
|---|---|---|---|---|---|---|
| | No. | Median level [IQR] | % Difference (*P*) | No. | Median level [IQR] | % Difference (*P*) |
| hsCRP, μg/mL | 140 | 2.13 (0.77-5.20) | 40.2 (<.001) | 293 | 2.83 (1.07-6.80) | 37.8 (<.001) |
| IL-6, pg/mL | 139 | 1.89 (1.15-3.42) | 39.0 (<.001) | 291 | 2.64 (1.55-4.14) | 60.1 (<.001) |
| D-dimer, μg/mL | 140 | 0.21 (0.15-0.46) | NA | 293 | 0.29 (0.17-0.57) | 49.1 (<.001) |
| Cystatin C, mg/dL | 86 | 0.90 (0.78-0.97) | NA | 130 | 1.00 (0.86-1.16) | 20.9 (<.001) |

*J Neuhaus CID 2010*

# Mechanisms involved

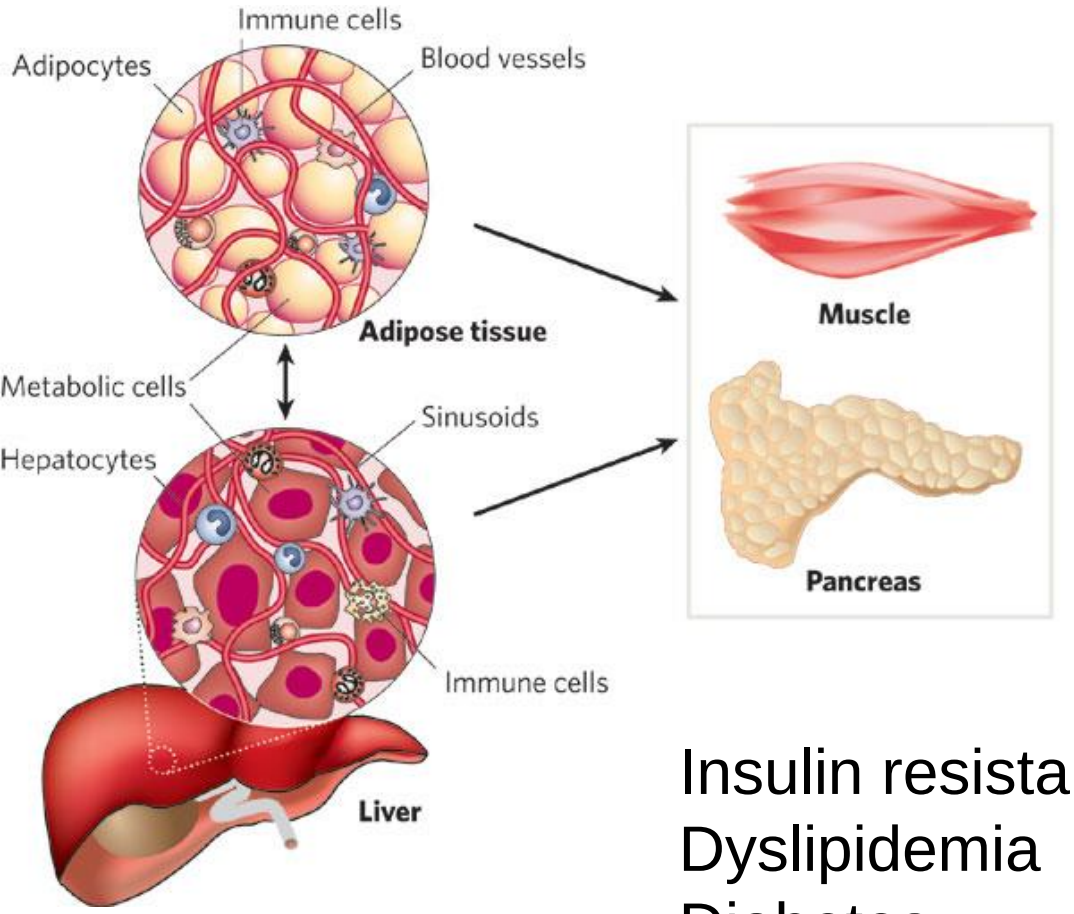



*Deeks Cur Opin Immunol 2012*



# Role of resident tissue macrophages in tissue functions: HIV reservoirs?

Resident macrophages with a M2 anti-inflammatory phenotype present in some tissues: change to a M1 pro-inflammatory phenotype when adversely stressed



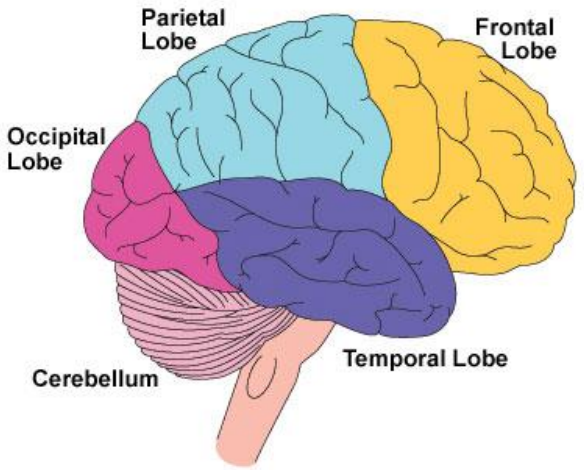

*Hotamisligil, Nature 2006*

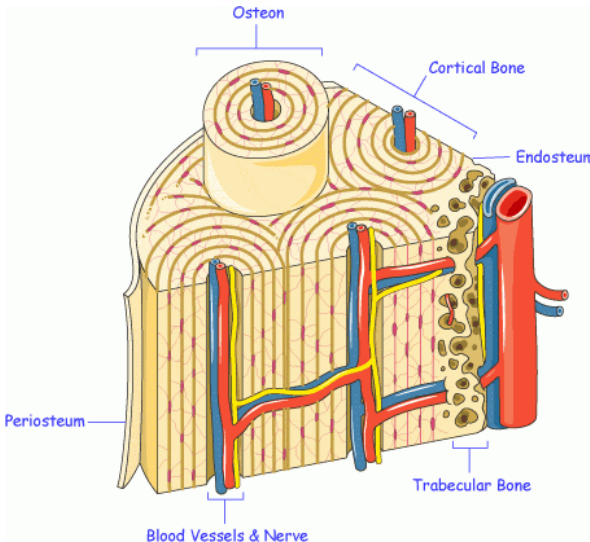
Adipose Tissue

Brain

Bone

Liver

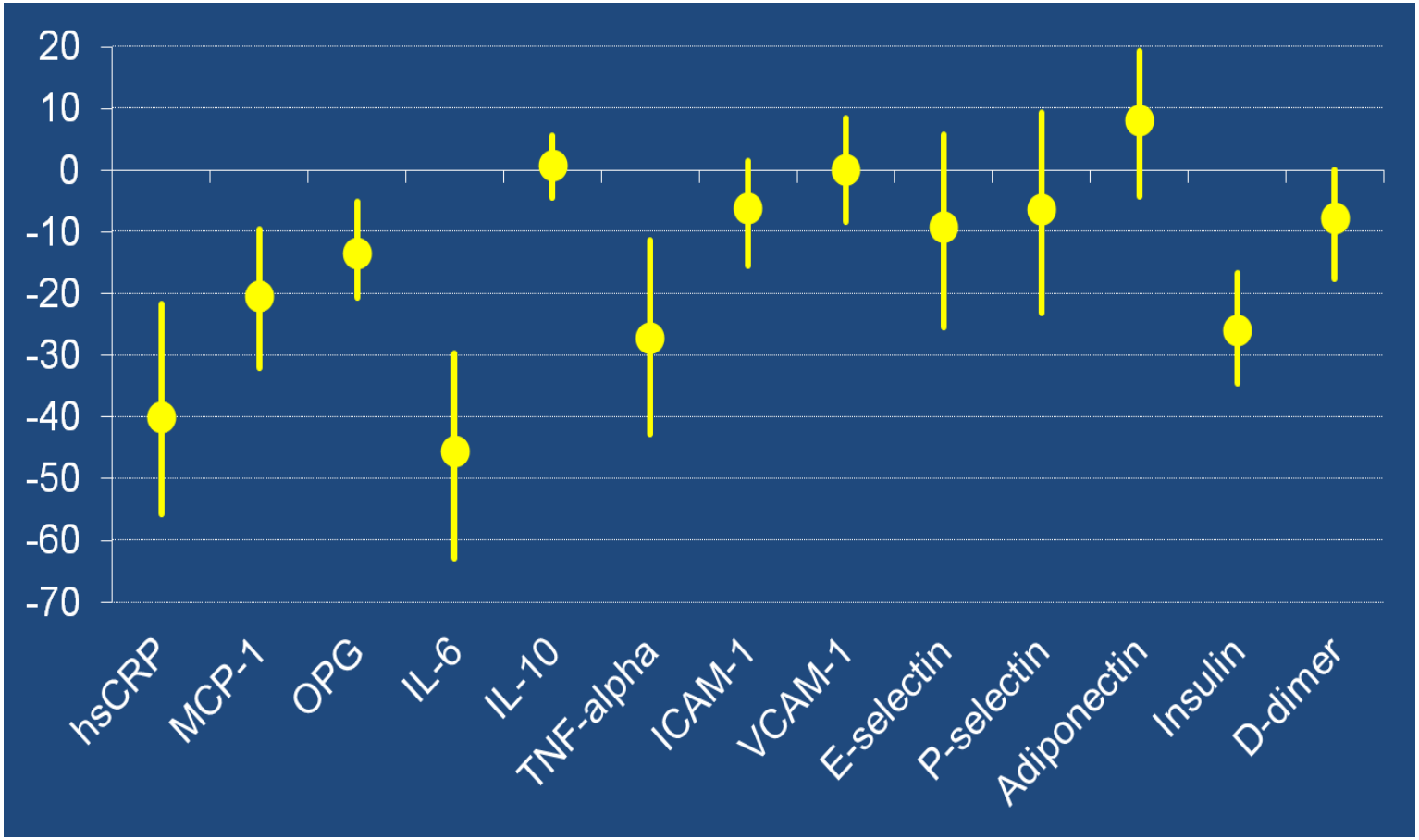



Insulin resistance
Dyslipidemia
Diabetes

# Role of ART

## Changes in inflammatory biomarkers in subjects switching from Ritonavir-Boosted PIs to Raltegravir: The SPIRAL Study.




*E Martinez CROI 2012 #834 AIDS 2013*

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# Mecanisms of aging

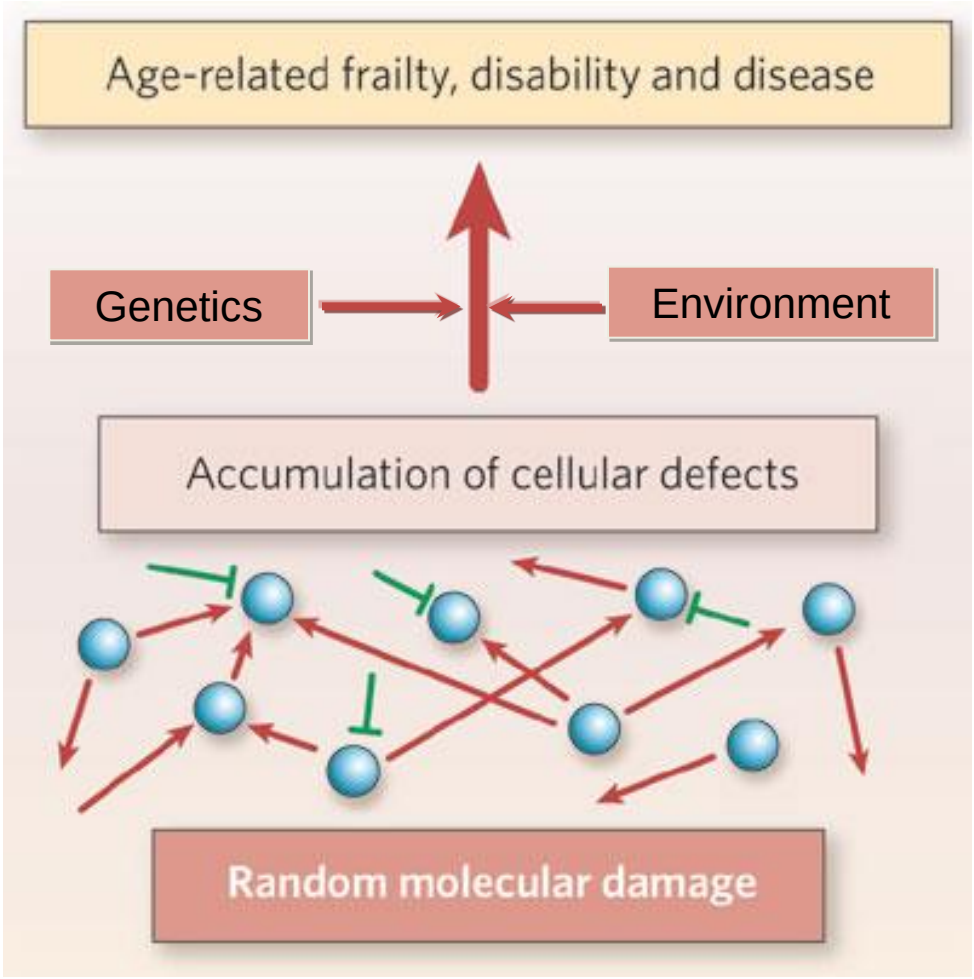
In the general population

2008- 2013

# Aging

- ✓ Complex and multifactorial physiological process
- ✓ Functional impairment of several tissues
- ✓ Decreased ability to face stress
- ✓ Increased prevalence of age-related diseases
- ✓ Naturally ending by death

# Aging




*From J Campisi 2009*

# Damages

Somatic Mutations
Germinal Mutations
Telomere shortening

Mitochondrial dysfunction leading to oxidative stress

p53, p16, p21

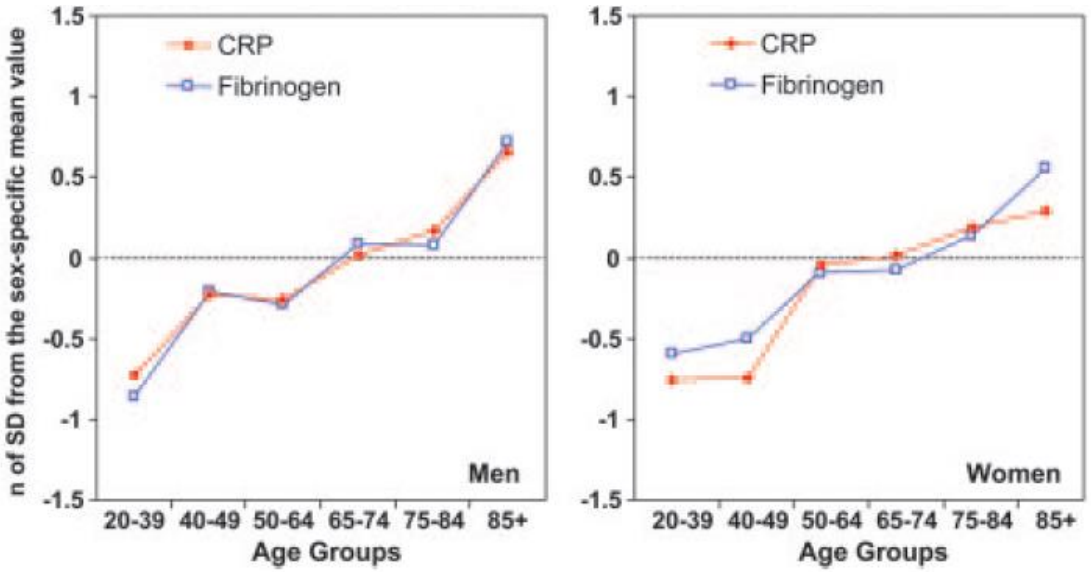
Accumulation of prelamin A

miRNA

Inflammation

*From TB Kirkwood Science, 2008;451:644*

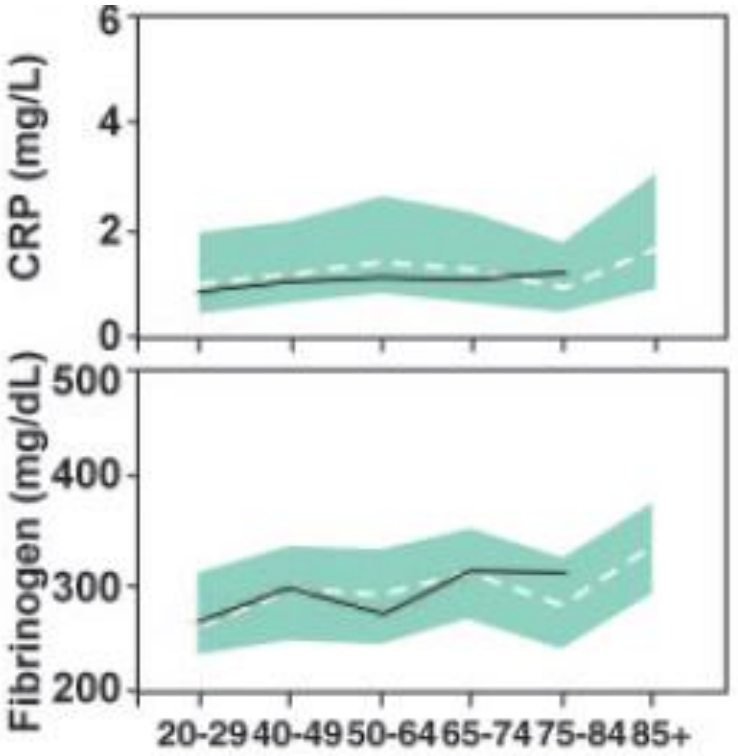
# Inflammatory Cytokines Go Up with Age




CRP and Fibrinogen go up with age

But go up much less in models which assume a low risk profile and no major co-morbidities, especially CVD

InChianti: Information on inflammatory markers, cardiovascular risk factors, and diseases was collected in 595 men and 748 women sampled from the general population (age, 20-102 years)




Ferrucci et al., *BLOOD*. 2005;105: 2294-2299

# Simple Biologically Informed Inflammatory Index of Two Serum Cytokines Predicts 10 Year All-Cause Mortality in Older Adults

Table 2. Mortality Risk of Inflammatory Phenotype in 1-, 2-, and 10-Year Cardiovascular Health Study (CHS) Cohort

| | 10-Year CHS | | | 1-Year CHS | | | 2-Year CHS | | |
|---|---|---|---|---|---|---|---|---|---|
| Variables | HR | 95% CI | | HR | 95% CI | | HR | 95% CI | |
| Log(IL-6) | 1.42 | 1.36 | 1.49 | 1.87 | 1.56 | 2.24 | 1.72 | 1.52 | 1.95 |
| Log(sTNFR1) | 1.46 | 1.39 | 1.53 | 1.98 | 1.69 | 2.32 | 1.72 | 1.52 | 1.94 |
| Log(CRP) | 1.25 | 1.19 | 1.31 | 1.63 | 1.33 | 1.98 | 1.59 | 1.39 | 1.82 |
| Log(IL-18) | 1.10 | 1.05 | 1.15 | 1.26 | 1.02 | 1.56 | 1.25 | 1.08 | 1.44 |
| Log(IL-1RA) | 1.21 | 1.15 | 1.26 | 1.44 | 1.19 | 1.73 | 1.29 | 1.13 | 1.48 |
| Age | 1.80 | 1.72 | 1.87 | 1.53 | 1.27 | 1.83 | 1.62 | 1.43 | 1.83 |
| WSS | 1.47 | 1.41 | 1.54 | 2.14 | 1.77 | 2.58 | 1.88 | 1.65 | 2.15 |
| PCS | 1.44 | 1.37 | 1.50 | 2.04 | 1.69 | 2.47 | 1.85 | 1.62 | 2.11 |
| IIS | 1.62 | 1.54 | 1.70 | 2.45 | 2.02 | 2.96 | 2.06 | 1.80 | 2.36 |
| IIS* | 1.88 | 1.77 | 2.00 | 3.21 | 2.50 | 4.11 | 2.58 | 2.16 | 3.08 |

All analyses were adjusted for age, CVD, gender, education, smoke, and body mass index (BMI; except for age-only model), and the IIS* model was only adjusted for age, education, smoking, and BMI.

IIS and IIS* was calculated as follows:

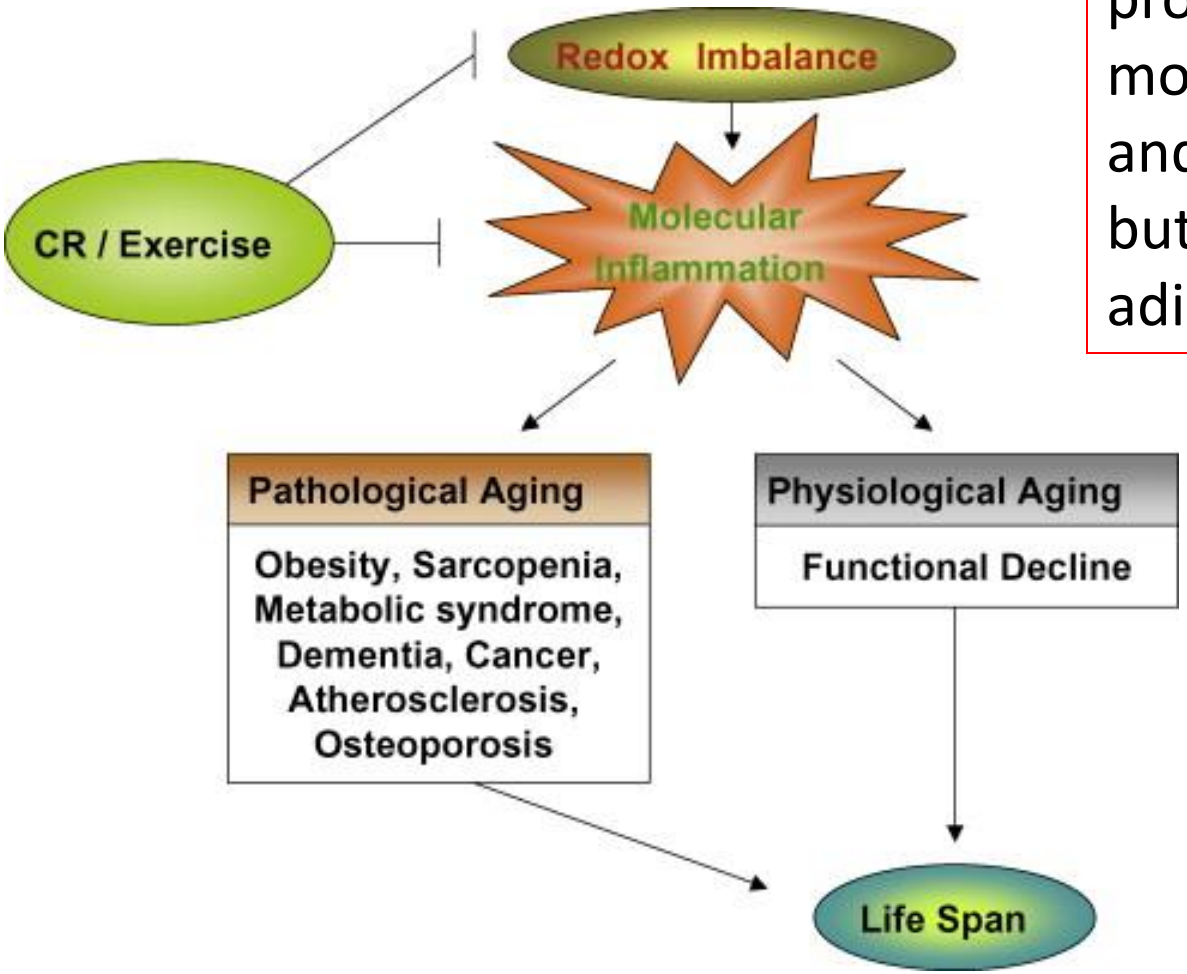
IIS = 1/3 log(IL-6) + 2/3 log(sTNFR1), for all individuals.

IIS* = 1/3 log(IL-6) + 2/3 log(sTNFR1), if female and non-CVD.
2/5 log(IL-6) + 3/5 log(sTNFR1), if male and non-CVD,
1/4 log(IL-6) + 3/4 log(sTNFR1), if female and CVD,
1/3 log(IL-6) + 2/3 log(sTNFR1), if male and CVD.

*R Varadhan J Gerontol 2013*

# « Inflammaging »

Proinflammatory cytokines produced by immune cells: monocytes/macrophages and T lymphocytes
but also endothelial cells, adipocytes, epithelial cells

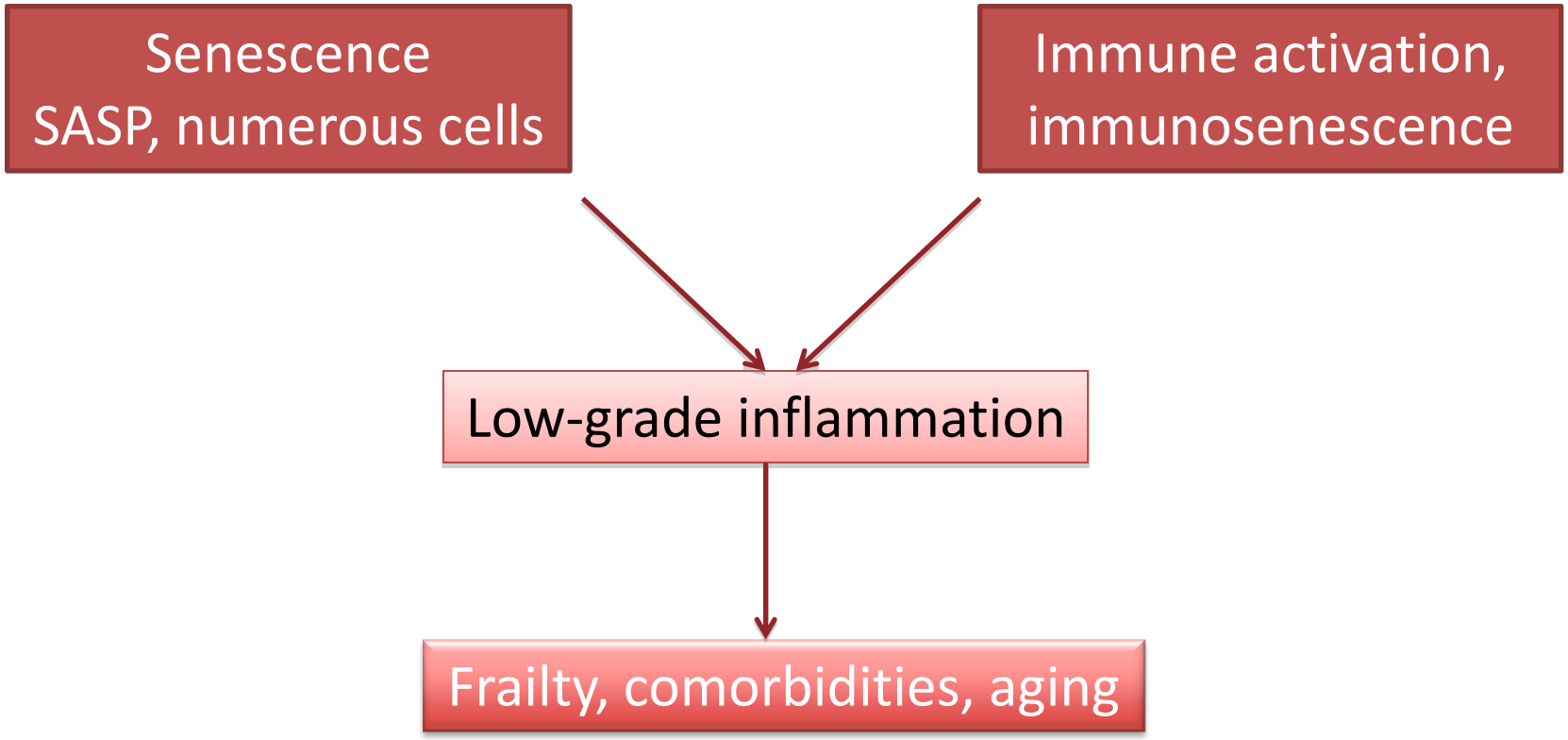




*HY Chung Aging Research Reviews 2008,9;8:18*

# Inflammation and aging

General population

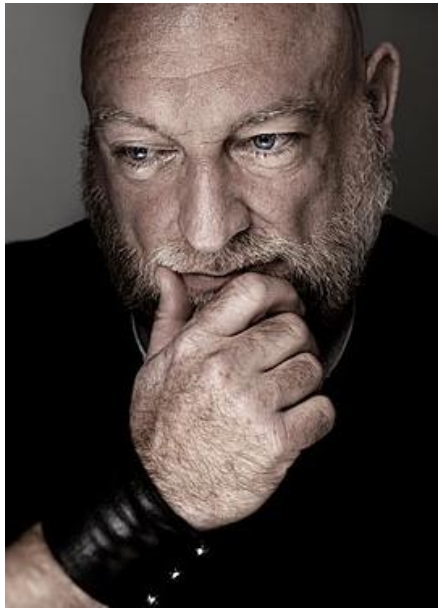


# Mecanisms of aging

## In HIV-infected patients

**Norma Martinez**.
Age: 61
HIV: 12 years
lipodystrophy,
fatigue

**Mike Weyand**. Age: 58
/ HIV: 20 years /
osteoporosis,
lipodystrophy, memory
loss

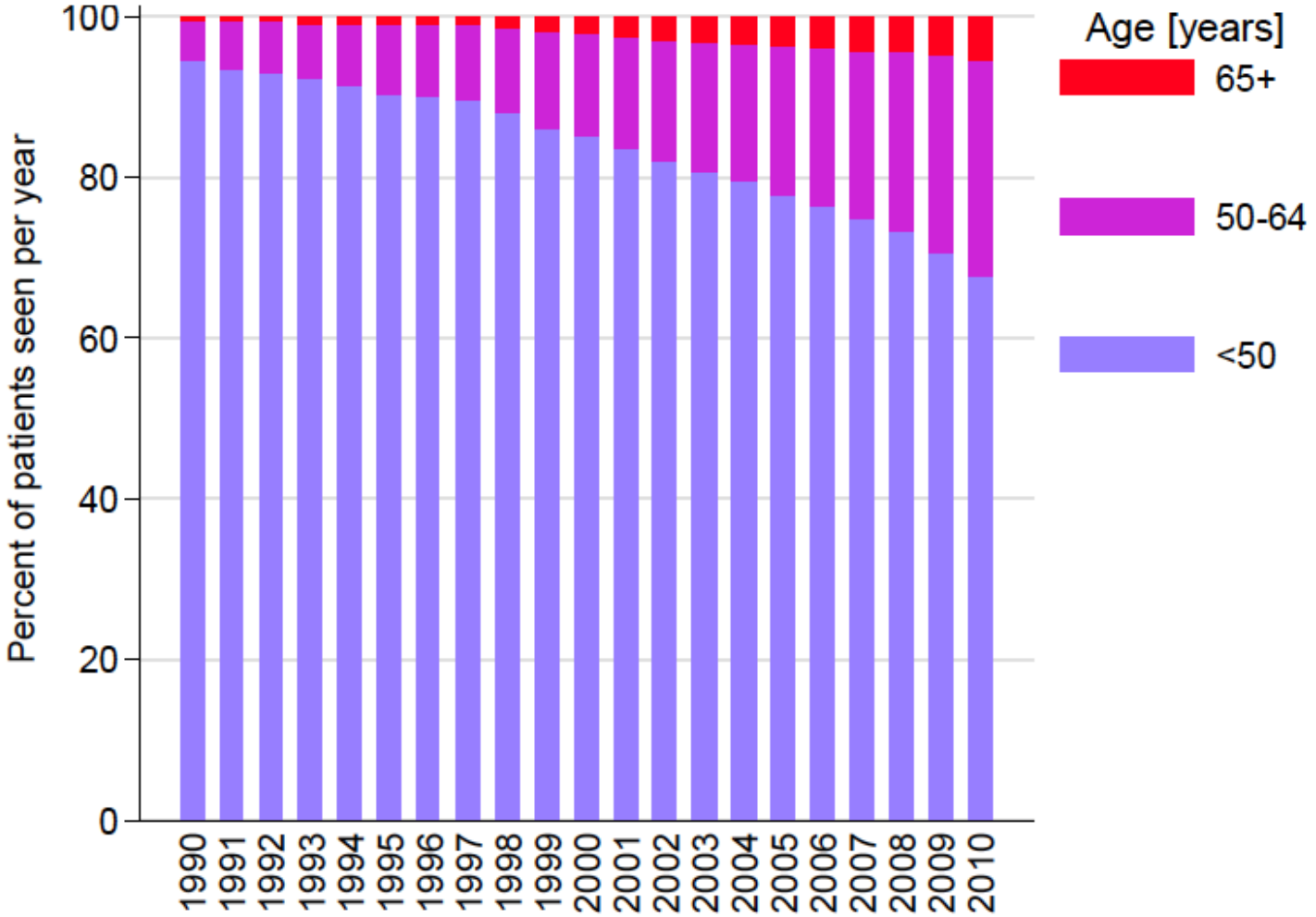


**Doug Turkington**
Age: 52
HIV: 20 years
osteoporosis, two
hip replacements

Photos *courtesy of New York Magazine, Nov 2009*

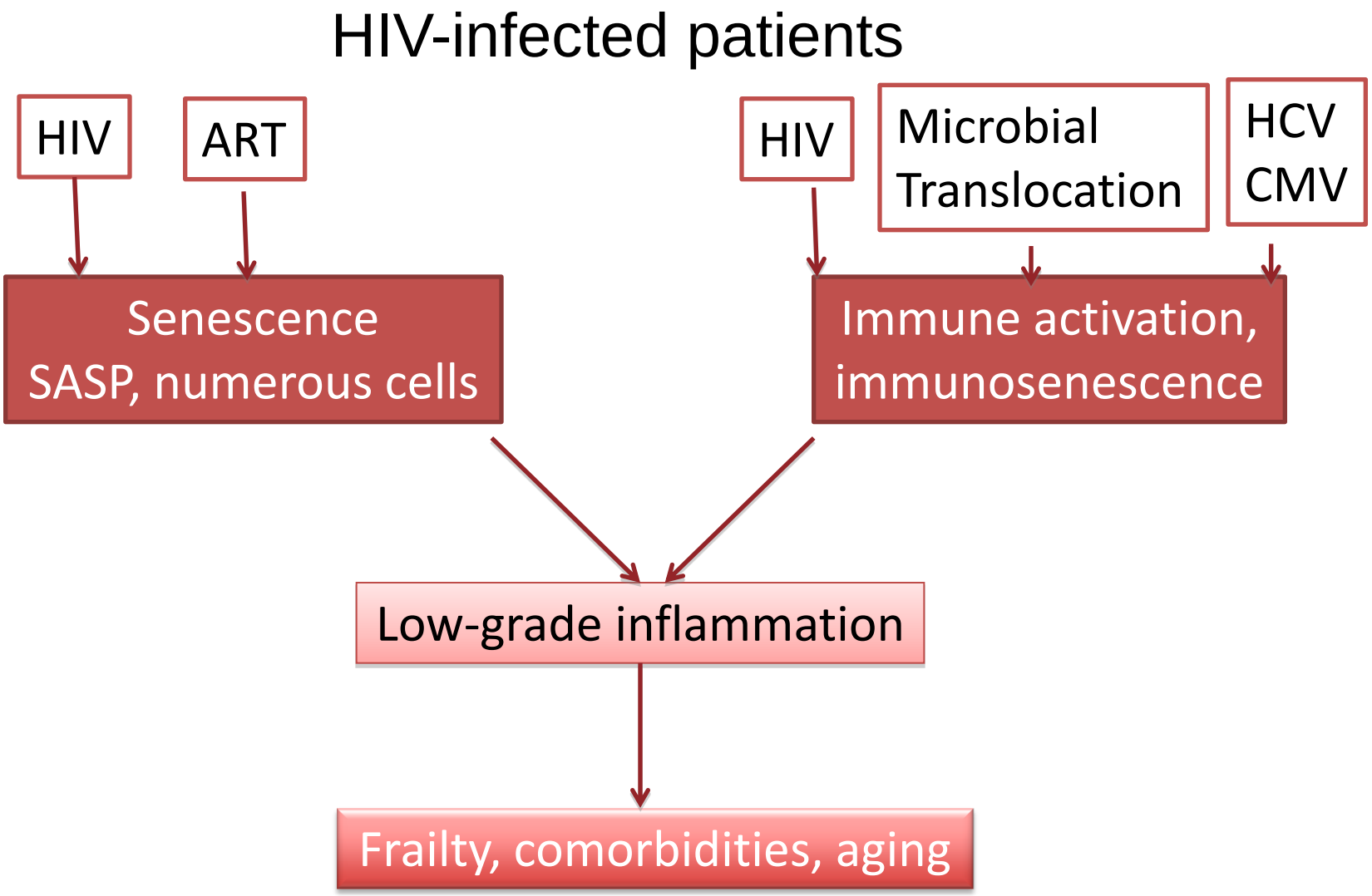
# HIV-infected patients are aging:

**Figure 1:** Age distribution among active participants of the Swiss HIV Cohort Study over time.




*B Hasse CID 2011*

# Inflammation and aging



1. Pathogenesis of low-grade inflammation/immune activation
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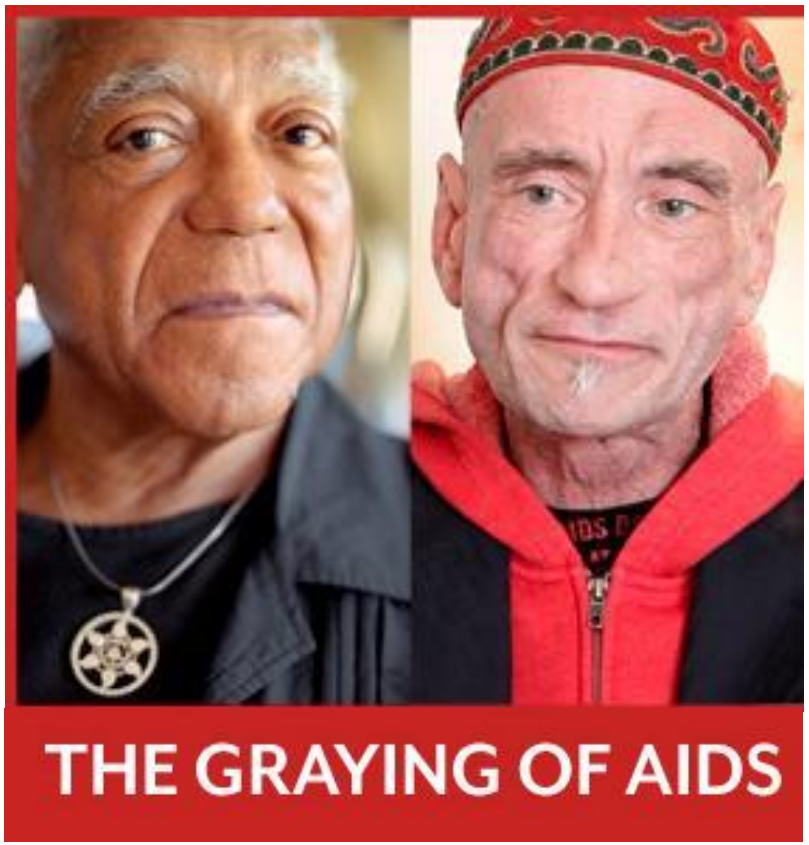
# Increased incidence of non AIDS-related comorbidities

- Neurocognitive dysfunction
- Osteoporosis
- Cardio-vascular risk and hypertension
- Kidney failure
- Frailty
- Fat redistribution and lipodystrophy
- Insulin resistance, diabetes et dyslipidemia
- Non-AIDS related cancers




Age-defining comorbidities

# Biomarkers of inflammation and coagulation are associated to mortality in the SMART study

| Sampling Point | Biomarker | Deaths, Median (25th, 75th %ile) | Controls, Median (25th, 75th %ile) | Difference (Case–Control) after $Log_{10}$ Transformation (SE) | *p*-Value[a] |
|---|---|---|---|---|---|
| Study entry[b] | hsCRP (µg/ml) | 4.26 (2.12, 7.49) | 2.14 (0.84, 5.68) | 0.21 (0.07) | 0.005 |
| | Amyloid A (mg/l) | 4.75 (2.80, 9.06) | 3.65 (1.90, 8.08) | 0.10 (0.06) | 0.11 |
| | Amyloid P (µg/ml) | 58.8 (43.1, 82.3) | 67.8 (48.8, 94.1) | −0.08 (0.03) | 0.009 |
| | IL-6 (pg/ml) | 3.80 (2.72, 7.20) | 2.31 (1.51, 3.33) | 0.29 (0.04) | <0.0001 |
| | D-dimer (µg/ml) | 0.49 (0.27, 1.16) | 0.26 (0.17, 0.45) | 0.35 (0.06) | <0.0001 |
| | F1.2 (pmol/l) | 344.0 (245.8, 565.8) | 351.4 (255.5, 533.4) | 0.01 (0.04) | 0.81 |
| Latest level[c] | hsCRP (µg/ml) | 5.26 (2.19, 19.3) | 2.00 (0.78, 4.80) | 0.47 (0.09) | <0.0001 |
| | Amyloid A (mg/l) | 6.88 (2.40, 16.7) | 3.35 (2.00, 6.75) | 0.28 (0.08) | 0.002 |
| | Amyloid P (µg/ml) | 57.7 (34.9, 78.5) | 67.3 (49.6, 88.1) | −0.09 (0.03) | 0.009 |
| | IL-6 (pg/ml) | 7.84 (3.08, 15.5) | 2.72 (1.60, 4.39) | 0.45 (0.06) | <0.0001 |
| | D-dimer (µg/ml) | 0.70 (0.34, 1.64) | 0.34 (0.22, 0.63) | 0.39 (0.07) | <0.0001 |
| | F1.2 (pmol/l) | 339.5 (260.6, 463.7) | 321.1 (218.8, 507.4) | −0.01 (0.04) | 0.93 |

- Study entry and latest levels of six biomarkers for deaths and matched controls

*Kuller PLOS Med 2008*

# Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection

**Netanya G. Sandler,[1] Handan Wand,[10] Annelys Roque,[1] Matthew Law,[10] Martha C. Nason,[3] Daniel E. Nixon,[5] Court Pedersen,[8] Kiat Ruxrungtham,[9] Sharon R. Lewin,[11,12,13] Sean Emery,[10] James D. Neaton,[6] Jason M. Brenchley,[2] Steven G. Deeks,[7] Irini Sereti,[4] and Daniel C. Douek,[1] for the INSIGHT SMART Study Group**

**Table 2. Increased Mortality in Human Immunodeficiency Virus–Infected Subjects with High Baseline sCD14 Levels**

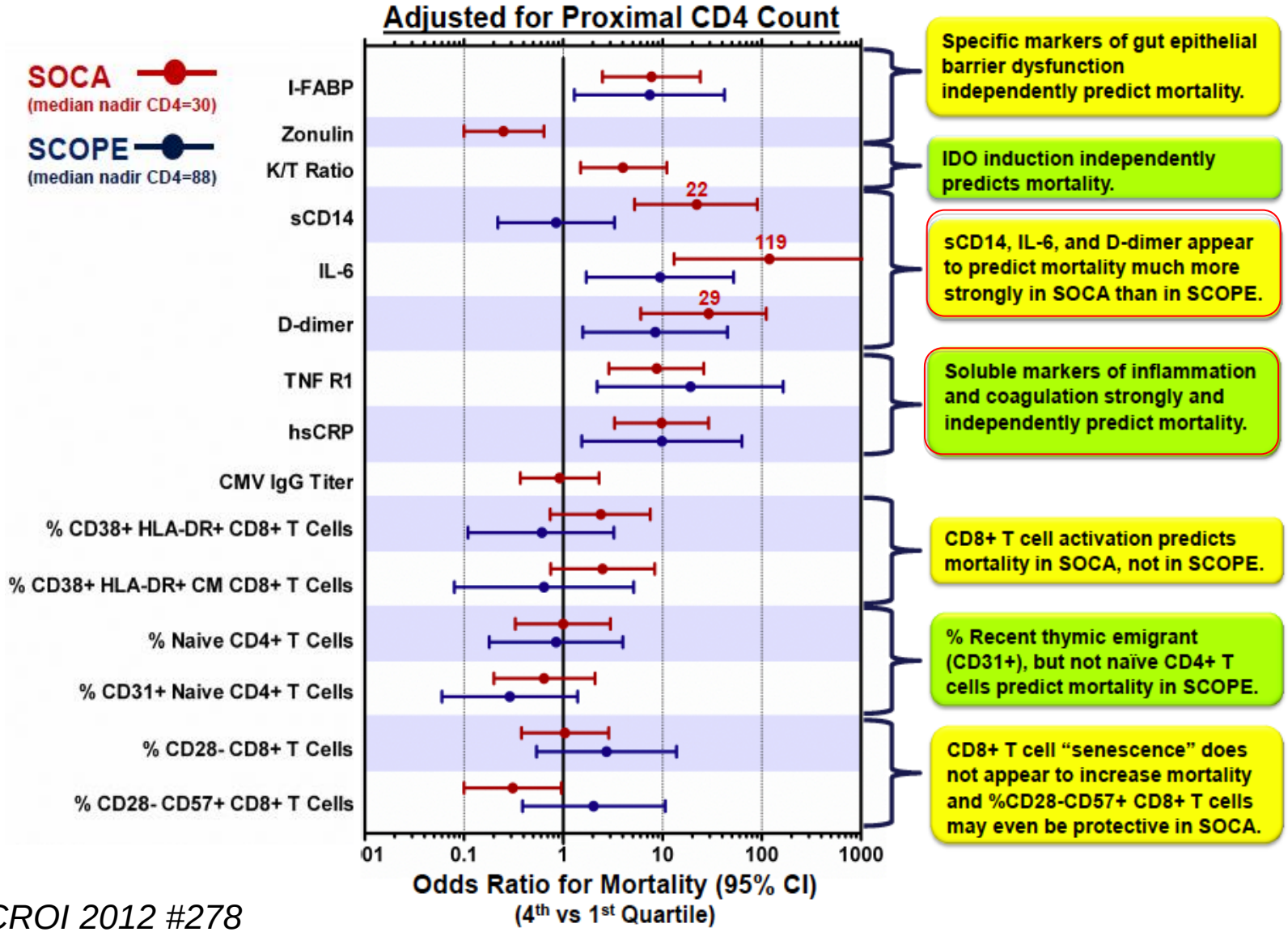
| | | 25th – 49th Percentile | | 50th – 74th Percentile | | ≥74th Percentile | |
|---|---|---|---|---|---|---|---|
| Biomarker | <25th Percentile(Reference) | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| sCD14 (×10$^6$ pg/mL) | | | | | | | |
| N (case patients/control subjects) | 10/46 | 16/39 | | 21/35 | | 27/28 | |
| Univariate | 1.0 | 2.1 (0.8–5.7) | .12 | 3.3 (1.3– 8.6) | .01 | 6.0 (2.2–16.1) | <.001 |
| Adjusted—risk factors[a] | 1.0 | 2.8 (0.8–10.0) | .10 | 2.7 (.8–9.0) | .11 | 8.0 (2.0–31.9) | .003 |
| Adjusted—inflammation[b] | 1.0 | 2.3 (0.7–8.1) | .18 | 2.9 (.9–9.4) | [illegible] | 4.1 (1.2–13.9) | .02 |

[a] Risk factors include age, race (black vs other), use of ART and human immunodeficiency virus RNA level (no ART, ART and ≤400 copies/mL, ART and >400 copies/mL), CD4+ cell count, smoking status, body mass index, prior cardiovascular disease, diabetes, use of blood pressure medication, use of lipid lowering medication, total/high-density lipoprotein cholesterol ratio, hepatitis B virus or hepatitis C virus co-infection, and treatment group (viral suppression or drug conservation).

[b] Markers of inflammation (and coagulation) include IL-6, hsCRP, SAA and D-dimer.

*NG Sandler CID 2011*

# Immune activation and inflammation predict mortality




*PW Hunt CROI 2012 #278*

# Inflammation and mortality

| | SMART/ ESPRIT | FRAM | SOCA/ SCOPE | UARTO | VACS | FIRST (pre ART) |
|---|---|---|---|---|---|---|
| | **Case control** | **Cohort** | **Cohort** | **Cohort** | **Cohort** | **Case control** |
| **T cell activation** | | | ✔ | ✔ | | |
| **CRP** | ✔ | ✔ | ✔ | | | ✔ |
| **IL-6** | ✔ | | ✔ | | | ✔ |
| **K/T IDO** | | | ✔ | ✔ | | |
| **Cystatin C** | | ✔ | | | | |
| **sCD14** | ✔ | | ✔ | | ✔ | |
| **LPS** | **No** | | | | | |
| **D-dimer** | ✔ | | ✔ | | ✔ | ✔ |
| **Fibrinogen** | | ✔ | | | | |

*S Lewin CROI2013*

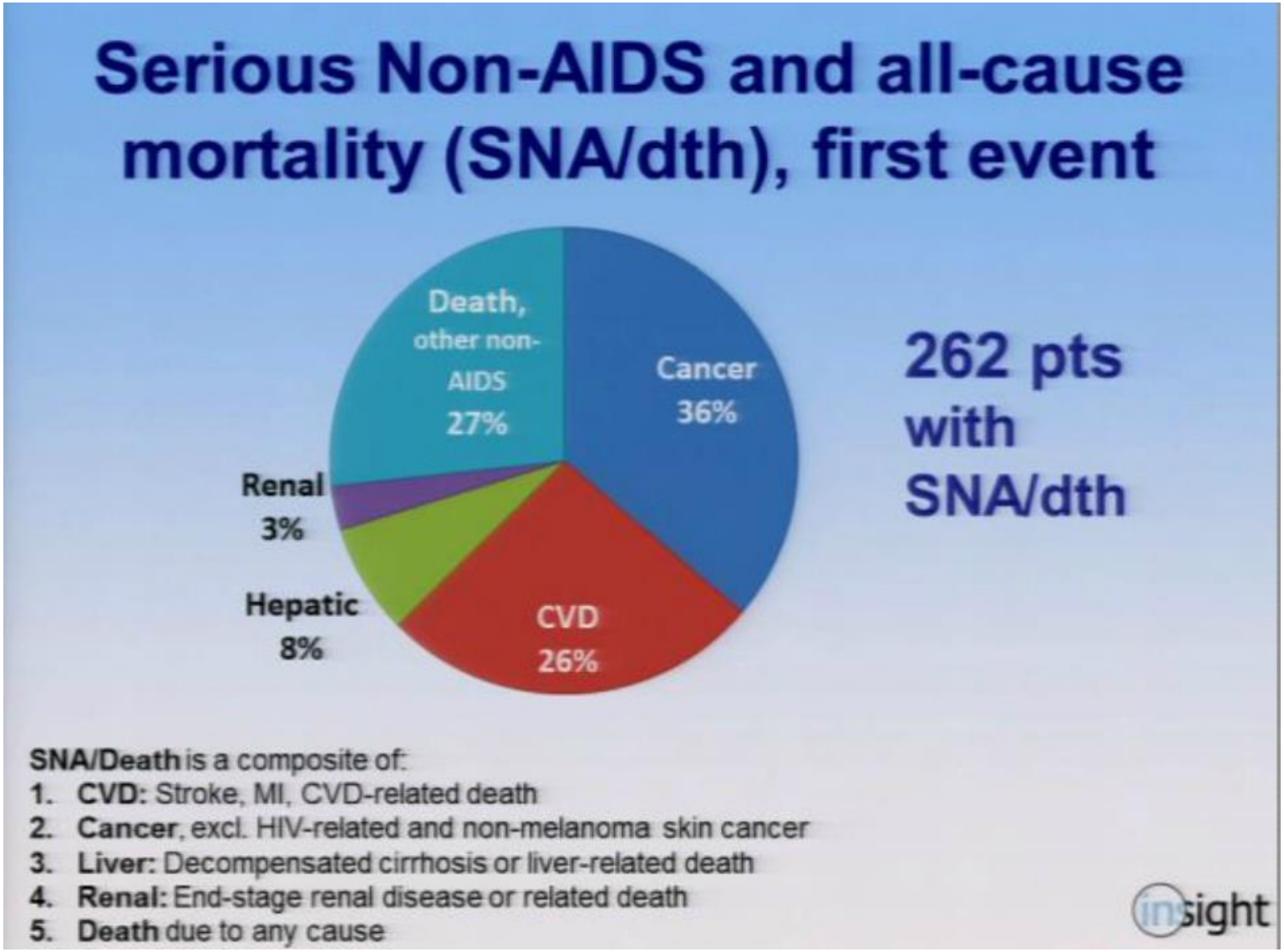
# Inflammation and serious non-AIDS events

| | CV disease [1,2] | Cancer [3,4] | Bone disease [5] | HAND [6,7] | Liver disease: HCV [8,9] | Liver disease: HBV [9] |
|---|---|---|---|---|---|---|
| **T cell activation** | ✔ | | ✔ | ✔ | | |
| **CRP** | ✔ | ✔ | ✔ | | | |
| **IL-6** | ✔ | ✔ | ✔ | | ✔ | ✔ |
| **sCD168** | ✔ | | | ✔ | | |
| **Cystatin C** | | | | ✔ | | |
| **sCD14** | ✔ | ✔ | | ✔ | ✔ | ✔ |
| **LPS** | ✔ | ✔ | | ✔ | ✔ | |
| **D-dimer** | ✔ | | | | | ✔ |

[1] Hsue et al *Journal of American Heart Asso* 2012; 2 Burdo et al., *J Infect Dis* 2011; 204:154; [3] Marks et al., *AIDS* 2013, 27(3):469-74; [4]Borges et al., AIDS 2013 (in press) [5] Morse CG et al., *AIDS*.2013;27; [6] Ancuta P, *et al*. *PLoS One* 2008;3:e2516; [7] Lyons et al., *J Acquir Immune Defic Syndr*. 2011 Aug 15;57(5):371-9(4):591-5; [8] Balagopal A, *et al*. *Gastroenterology* 2008;135:226–233 [9] Sereti et al., *J Infect Dis* 2013 (epub)

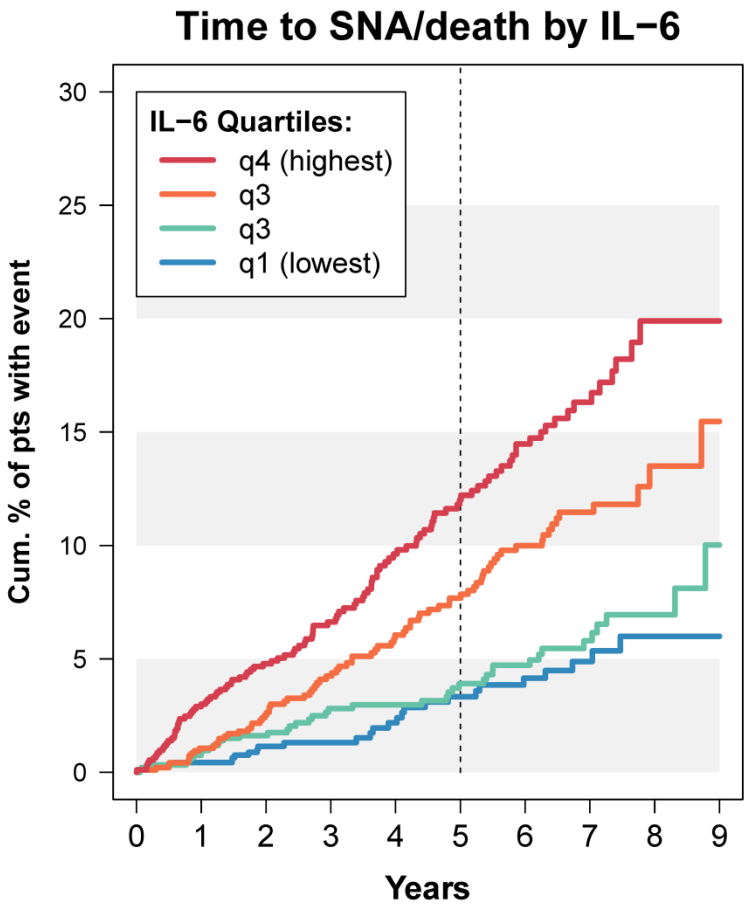
*S Lewin CROI2013*

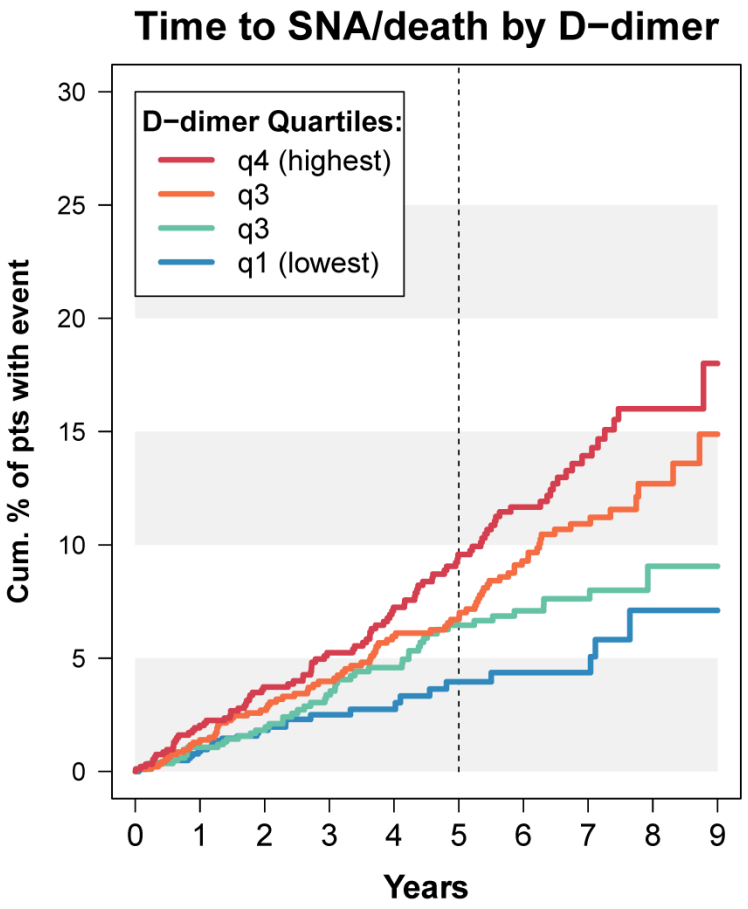
# Results from 3 large randomized trials of controlled patients: ESPRIT, SILCAAT, SMART




*Grund #60 CROI 2013*

# Time to SNAE/death associated with IL-6 and D-dimer



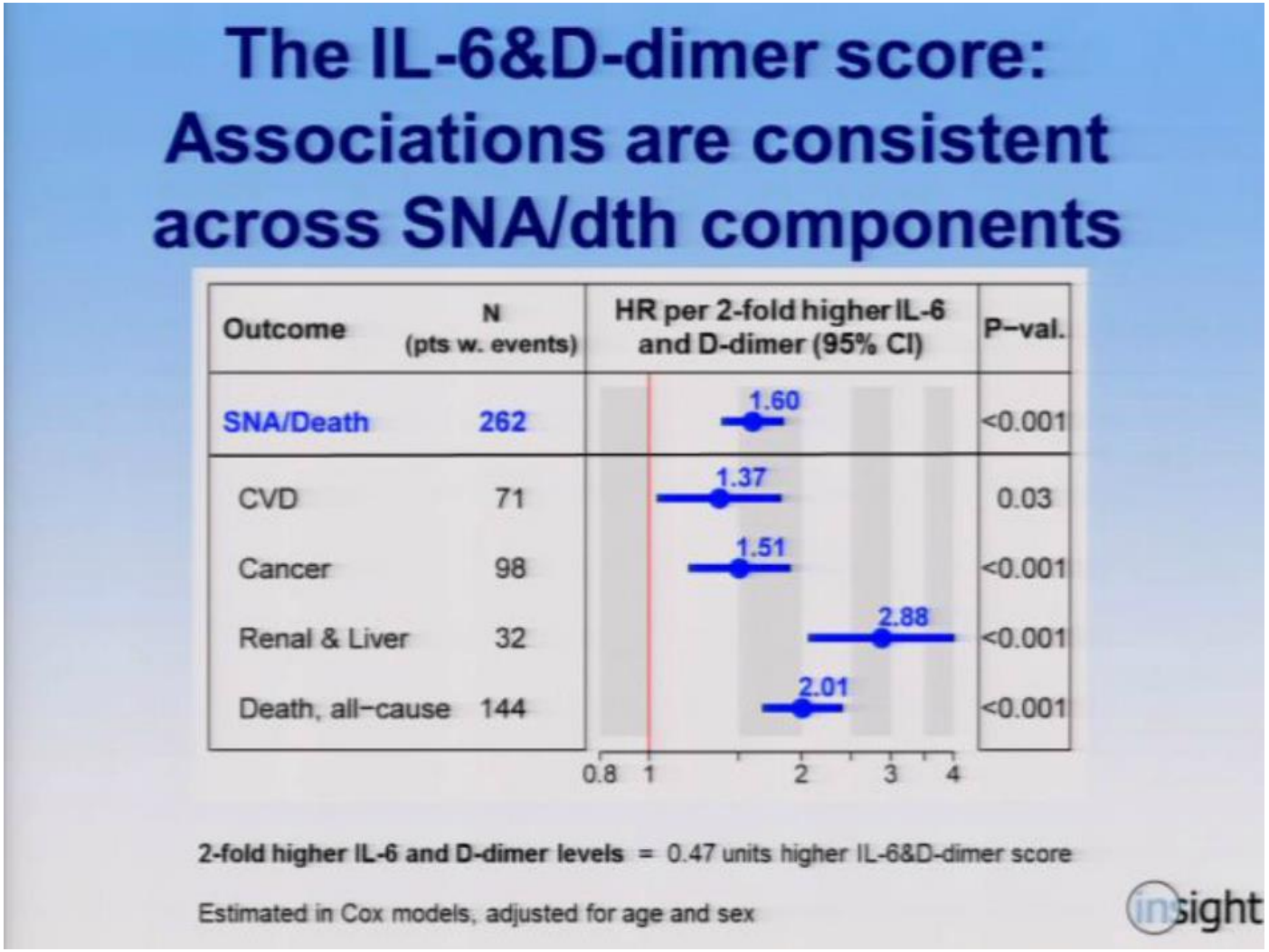




N= 3766, control arms of the SMART, ESPRIT and SILCAAT trials, all on ART
Mean CD4=500cells/ul; mean follow up for 5 years

*S Lewin CROI2013*

Grund et al., 20th CROI, Atlanta, GA, Abstract 60

# IL-6 and D-dimers and non-AIDS defining morbidity/mortality




$$0.33 \times \log_2 \text{IL-6} + 0.14 \times \log_2 \text{D-dimer}$$

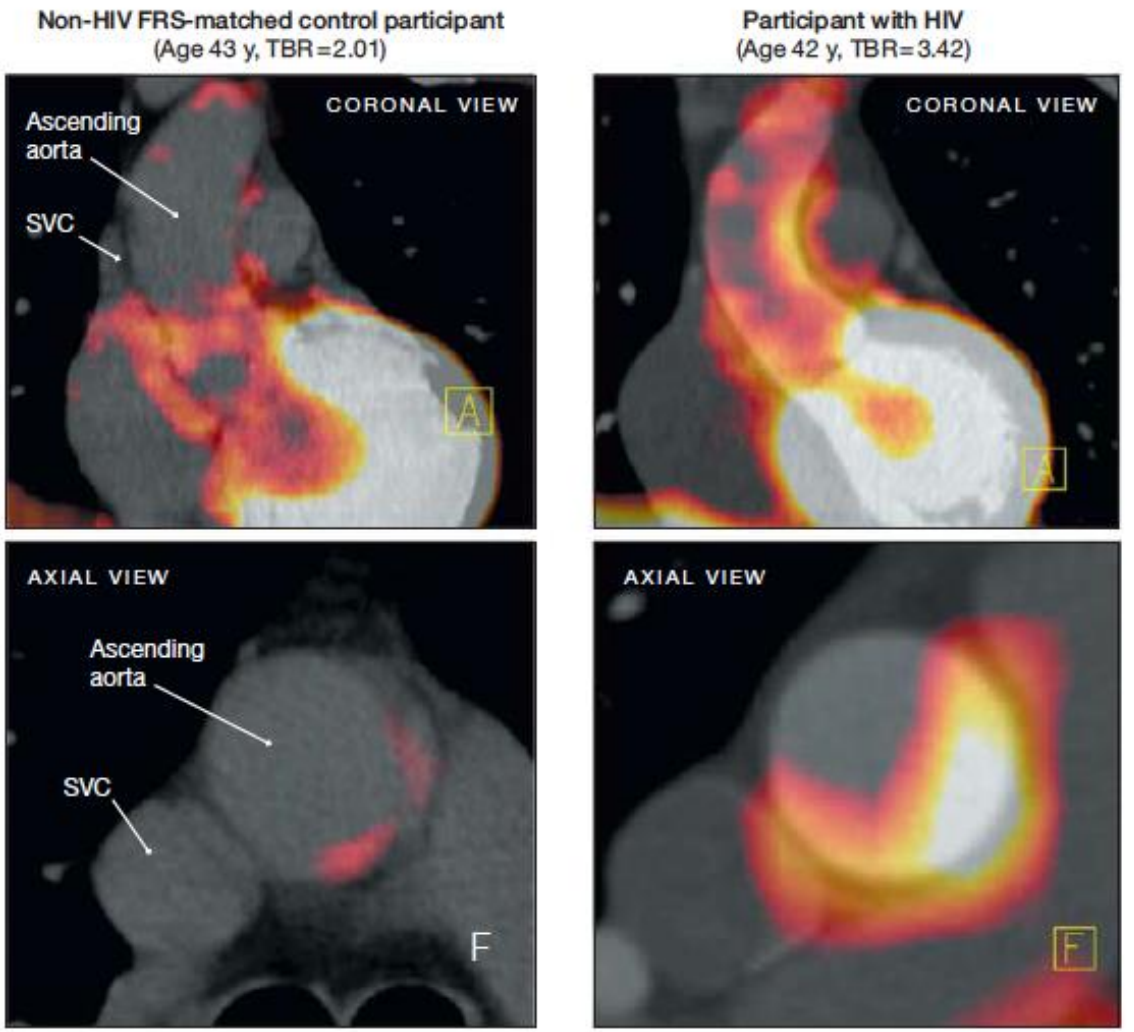
*Grund #60 CROI 2013*

# Arterial Inflammation in Patients With HIV

Arterial inflammation as measured by PET-scan is increased in HIV-infected patients as compared to VIH- subjects with the same FRS

*Subramanian S, JAMA 2012*

**Figure 2.** Representative $^{18}$F-FDG-PET/CT Imaging of the Aorta

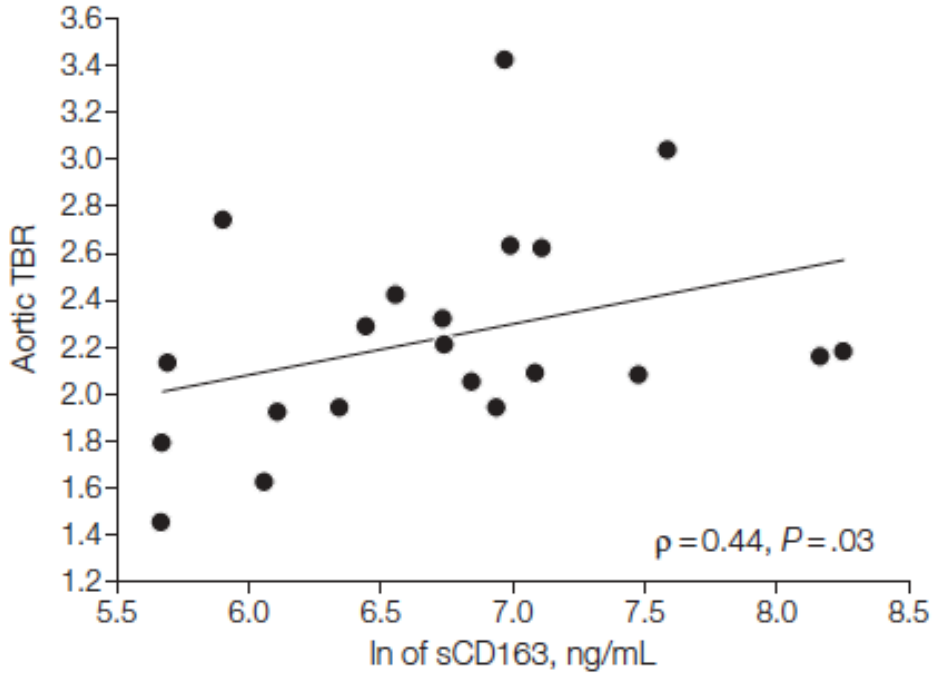



$^{18}$F-FDG-PET indicates $^{18}$fluorine-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; FRS, Framingham risk score; HIV, human immunodeficiency virus; SVC, superior vena cava; TBR, target-to-background ratio. There is increased aortic PET-FDG uptake (red coloration) in a participant infected with HIV compared with a non-HIV FRS-matched control participant. Neither participant had known heart disease. For each participant, the FRS was low with a score of 2 and calcium was not present on the cardiac CT scan. Neither participant was receiving a statin. A indicates anterior-posterior orientation and F, foot-head orientation.

# Arterial Inflammation in Patients With HIV

Arterial inflammation is related to the level of the macrophage activation marker sCD163

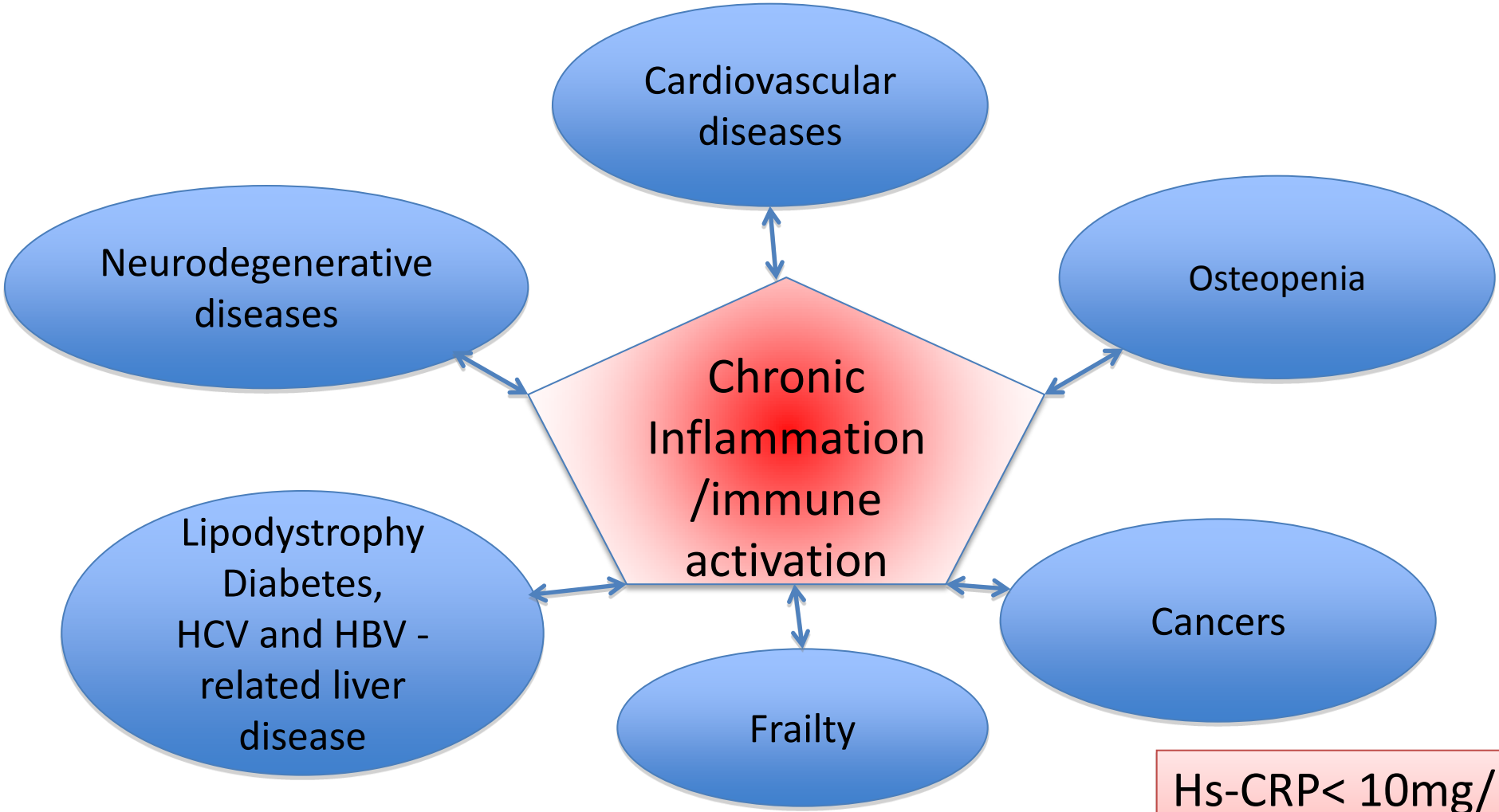
**Figure 3.** Linear Regression of Aortic Target-to-Background Ratio (TBR) vs ln of sCD163 in 21 Patients With HIV With Undetectable Viral Load




HIV indicates human immunodeficiency virus; ln, natural logarithm; sCD163, soluble CD163. Solid line represents the linear regression fit across all 21 patients (aortic TBR = 0.8 + 0.22 × ln sCD163). A sCD163 level of more than 800 ng/mL corresponds with a ln of more than 6.7 and an aortic TBR of more than 2.3.

*Subramanian S, JAMA 2012*

# In HIV-infected patients, most age-related comorbidities are associated with a chronic low-grade inflammation/immune activation

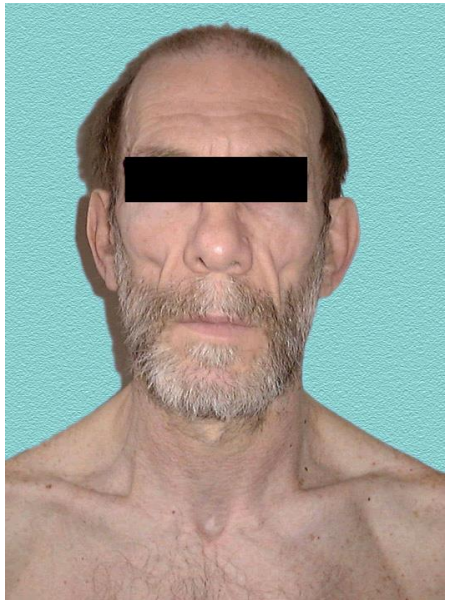


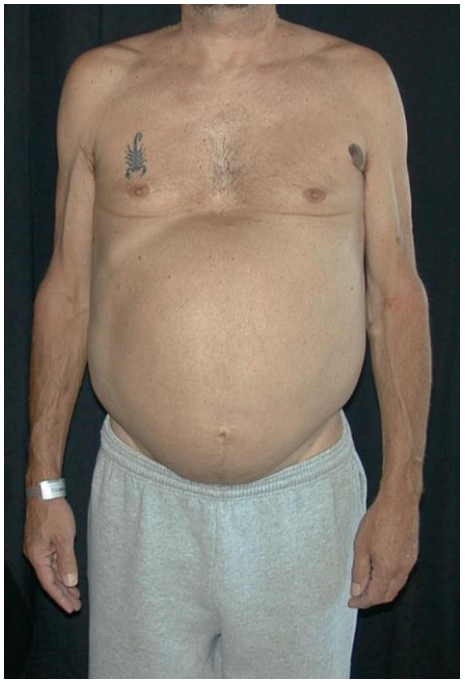

Hs-CRP< 10mg/l
Hs-IL6

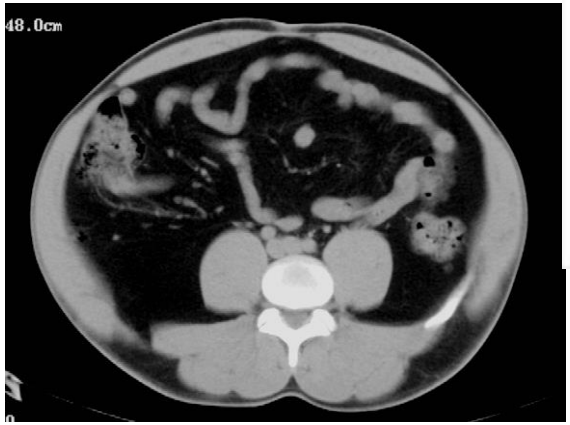
*From A Freund Trends Molecular Med 2010*

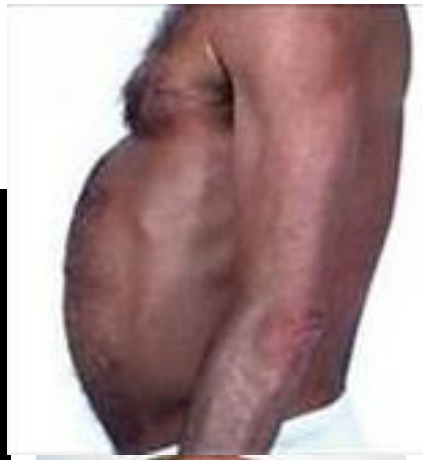
1. Pathogenesis of low-grade inflammation/immune activation
2. Impact of aging
3. Consequences on mortality and morbidity in HIV-infected patients
4. Impact of HIV drugs on metabolic parameters

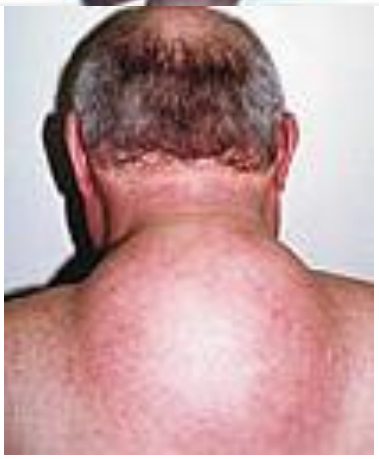
# Lipodystrophy is related in priority to ART
# « First generation lipodystrophy »





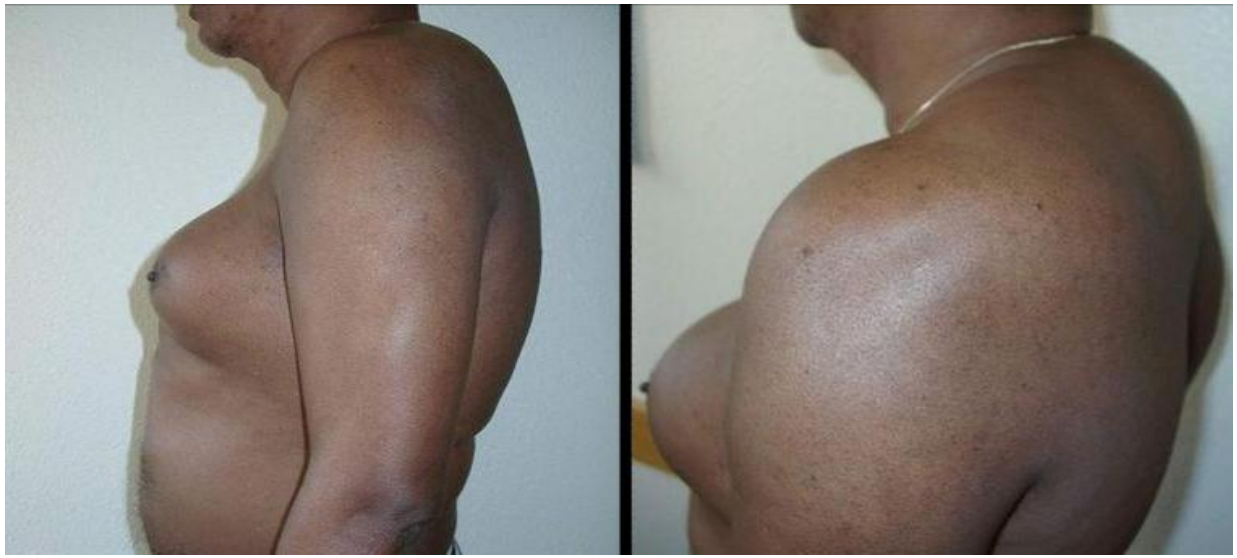


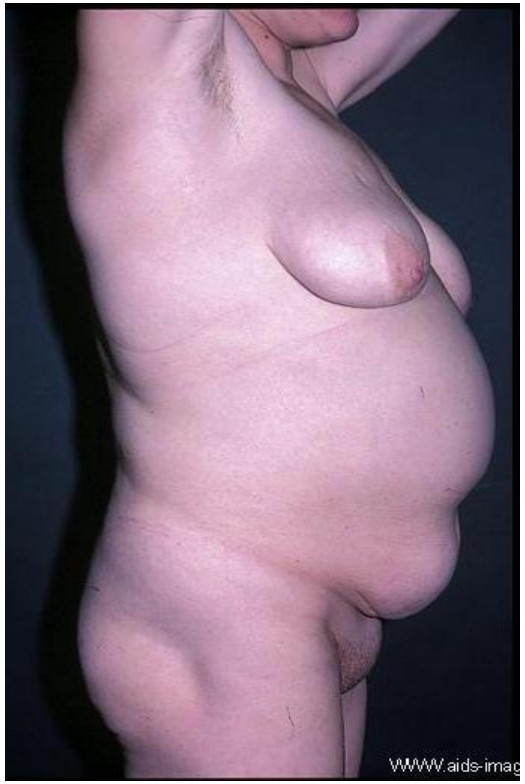





Lipoatrophy mainly linked to tNRTI: stavudine and zidovudine
Role of PI in lipohypertrophy

# « Second generation lipodystrophy »






Lipodystrophy worsen inflammatory state and metabolic disorders

# ART-induced metabolic alterations and lipodystrophy in the clinics

**Table 1. Antiretrovirals drugs and their effects on fat and metabolism***

| Class | Molecule | Abbreviation | Lipoatrophy | Lipohypertrophy | Dyslipidemia | Insulin resistance |
|---|---|---|---|---|---|---|
| NRTI | Stavudine | D4T | +++ | ++ | ++ | ++ |
| | Zidovudine | AZT, ZDV | ++ | + | + | ++ |
| | Didanosine | ddI | +/– | +/– | + | + |
| | Lamivudine | 3TC | 0 | 0 | + | 0 |
| | Abacavir | ABC | 0 | 0 | + | 0 |
| | Tenofovir | TDF | 0 | 0 | 0 | 0 |
| | Emtricitabine | FTC | 0 | 0 | 0 | 0 |
| NNRTI | Efavirenz | EFV | +/– | +/– | ++ increased HDL | + |
| | Nevirapine | NVP | 0 | 0 | + increased HDL | 0 |
| PI | Ritonavir | RTV | +/– | + | +++ | ++ |
| | Indinavir | IDV | +/– | + | + | +++ |
| | Nelfinavir | NFV | +/– | + | ++ | + |
| | Lopinavir | LPV | +/– | + | ++ | ++ |
| | Amprenavir Fosamprenavir | APV FPV | +/– | + | + | +/– |
| | Saquinavir | SQV | +/– | + | +/– | +/– |
| | Atazanavir | ATV | 0 | ++ | +/– | 0 |
| | Darunavir | DRV | 0 | + | +/– | +/– |
| Fusion inhibitor | Enfuvirtide | T20 | ? | ? | 0 | 0 |
| CCR5 inhibitor | Maraviroc | MVC | ? | ? | 0 | 0 |
| Integrase inhibitor | Raltegravir | RAL | ? | ? | 0 | 0 |

Mild or no dysmetabolic effect of the newer NNRTI : etravirine and rilpivirine

*M Caron-Debarle TMM 2010*

## Integrase inhibitors

**Table 1. Integrated safety data from prospective clinical trials (phase 2–4) for raltegravir, elvitegravir and dolutegravir**

| | Raltegravir | Elvitegravir/Cobicistat | Dolutegravir |
|---|---|---|---|
| Numbers exposed to INSTI | 3178 | 1318 | 206 |
| Serious adverse events | 7–14% | 4–7% | 5% |
| Discontinuation rates due to adverse events | 1–4% | 4% | 1% |
| Deaths | 2% | 1% | No deaths reported |
| Gastrointestinal events (nausea/vomiting, diarrhoea) | 3–20% | 17–23% | 8–12% |
| Headache, nervous system & neuropsychiatric effects | 1–26% | 15–17% | 6% |
| Grade 3/4 dyslipidaemia rates and effect on plasma lipids | Total cholesterol – 8% | Total cholesterol – 3% | No grade 3/4 dyslipidaemia reported |
| | LDL cholesterol – 8% | No impact on TC and LDL compared with atazanavir/ ritonavir | |
| | Triglycerides – 6% | Triglycerides – 9% | |
| Lower impact on all plasma lipid measurements compared with efavirenz (statistically significant) | Less impact on TG, LDL and TC compared with efavirenz (statistically significant); change in TC:HDL ratio similar to efavirenz | Favourable impact on TC and LDL compared with efavirenz | |

# Lipodystrophy and ART predicts diabetes in HIV-infected patients

| | HR |
|---|---|
| Age 40-50 vs <40 y | 2.1 |
| >50 vs <40 y | 3.6 |
| BMI 25-30 vs <25 kg/m$^2$ | 1.9 |
| >30 vs <25 kg/m$^2$ | 2.8 |
| WHR | 3.9 |
| Lipoatrophy | 2.1 |
| stavudine | 2.6 |
| indinavir | 2.5 |
| didanosine | 3.2 |

*J Capeau AIDS 2012*

# Lipodystrophy and ART predict atherosclerosis lesions in HIV-infected patients

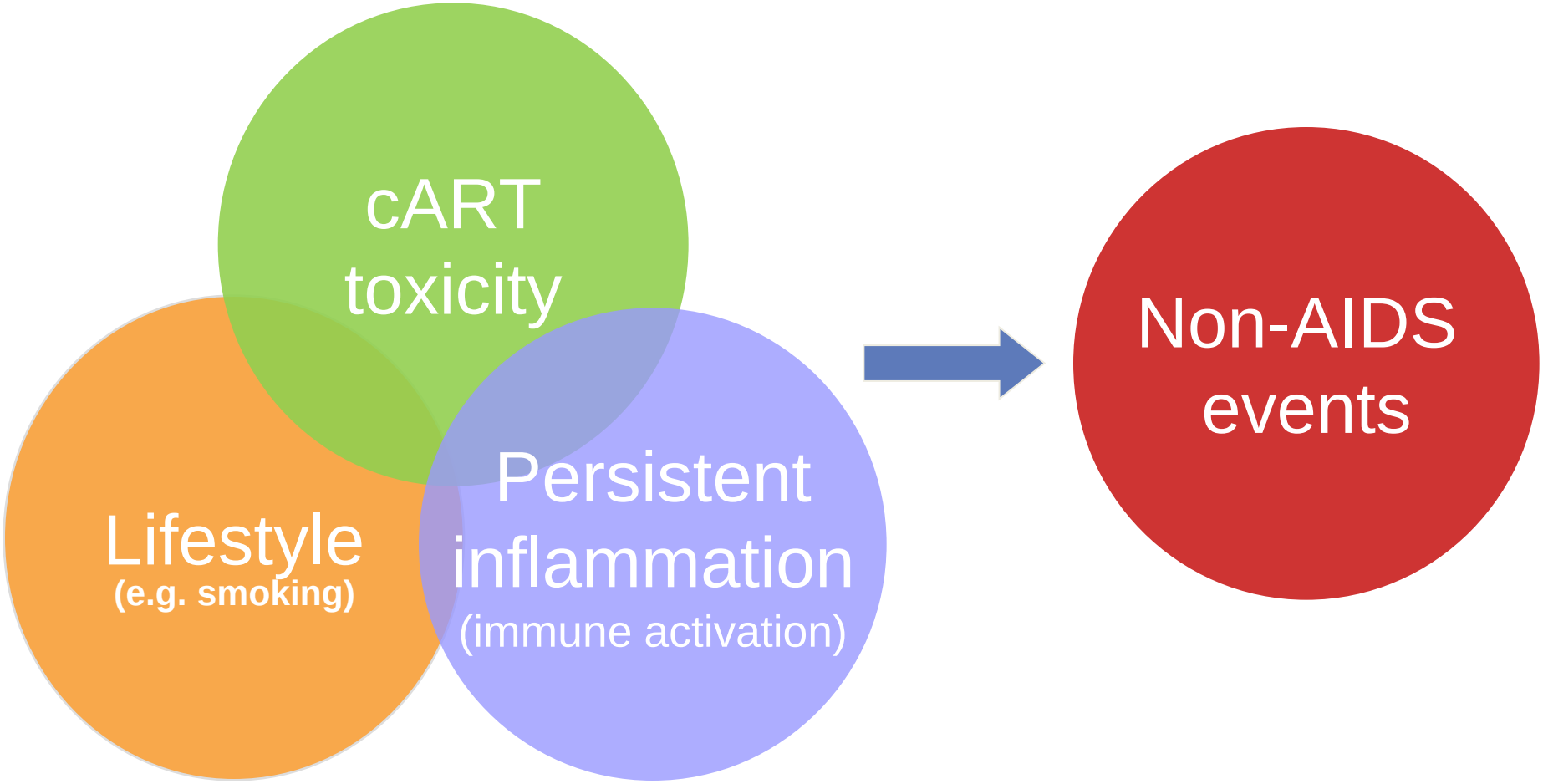
| | OR | Confidence interval | P-value |
|---|---|---|---|
| Male sex | 2.8 | 1.3-6.1 | 0.009 |
| Age per 1 year | 1.12 | 1.07-1.17 | <0.001 |
| BMI | 1.09 | 0.98-1.21 | NS |
| Chol T | 0.99 | 0.99-1.01 | NS |
| HDL C | 1.00 | 0.98-1.03 | NS |
| Hypertension | 2.09 | 1.13-3.88 | 0.018 |
| Exposure to ART, per 1 y | 1.21 | 1.07-1.37 | 0.002 |
| No lipodystrophy | 1 ref | | |
| Lipoatrophy | 3.82 | 1.11-13.1 | 0.033 |
| Lipohypertrophy | 7.65 | 1.71-37.17 | 0.008 |
| Mixed form | 4.36 | 1.26-15.01 | 0.02 |

Multivariable logistic analysis for independent predictors of coronary artery calcium

*G Guaraldi Atherosclerosis 2010*

# Etiology of non-AIDS-related events

Non-AIDS-related events are more common in HIV disease, even after adjustment for age, cART exposure and traditional risk factors




*S Lewin CROI 2013*

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

# Hot topics in September 2013
# Interventions for “inflammation”??

| | Statins | aspirin |
|---|---|---|
| **Number of trials** | **12** | **1*** |
| **T cell activation** | ↓/↑ | ↓ |
| **CRP** | ↓/↔ | |
| **IL-6** | | |
| **sCD14** | | ↓ |
| **Platelet func** | | ↓ agg |
| **D-dimer** | | |
| **Clinical endpoint** | **↓malig ↓mortality** | **ND** |

*O’Brian et al., J Acquir Immune Defic Syndr. 2013 Feb 12

# Hot topics in September 2013
# : HIV-related dysbiosis

## Dysbiosis of the Gut Microbiota Is Associated with HIV Disease Progression and Tryptophan Catabolism

bacterial community profiling, we identified a dysbiotic mucosal-adherent community enriched in Proteobacteria and depleted of Bacteroidia members that was associated with markers of mucosal immune disruption, T cell activation, and chronic inflammation in HIV-infected subjects. Furthermore, this dysbiosis was evident among HIV-infected subjects undergoing HAART, and the extent of dysbiosis correlated with activity of the kynurenine pathway of tryptophan catabolism and plasma concentrations of the inflammatory cytokine interleukin-6 (IL-6),

**Prebiotics/probiotics ?**

*I Vujkovic-Cvijin Science Translational Medicine 2013*

# Long-term glucose tolerance in highly experienced HIV-infected patients receiving nucleoside analogue-sparing regimens

Thirty-nine HIV-1-infected patients treated for 156 weeks with a new nucleoside analogue-sparing regimen [raltegravir, etravirine and maraviroc (REM) or raltegravir, etravirine and darunavir/ritonavir (RED)] showed a uniform increase in fasting glucose levels and a uniform decrease in insulin secretory capacity. Diabetes mellitus occurred in one RED-treated and four REM-treated patients. A worsening glucose tolerance was observed in highly treatment-experienced HIV-infected patients receiving effective antiretroviral therapy after virological failure.

*A Bigoloni AIDS 2012*

# HIV infection and glycemic response to newly initiated diabetic medical therapy

HIV-infected patients achieved significantly smaller reductions in HbA1c, with an absolute mean difference of −0.17% (95% CI −0.28 to −0.06; $P = 0.003$). On subanalyses, HIV-infected patients on a protease inhibitor-based regimen had significantly smaller reductions in HbA1c compared to HIV-uninfected patients (adjusted absolute difference −0.21%, 95% CI −0.35 to −0.08; $P = 0.002$).

**Conclusion:** Patients with HIV infection who initiate diabetic medical therapy achieve smaller reductions in HbA1c than patients without HIV infection in the course of routine clinical care. This less robust response may in part be related to use of antiretrovirals that exacerbate insulin resistance, specifically protease inhibitors.

*JH Han AIDS 2012*