

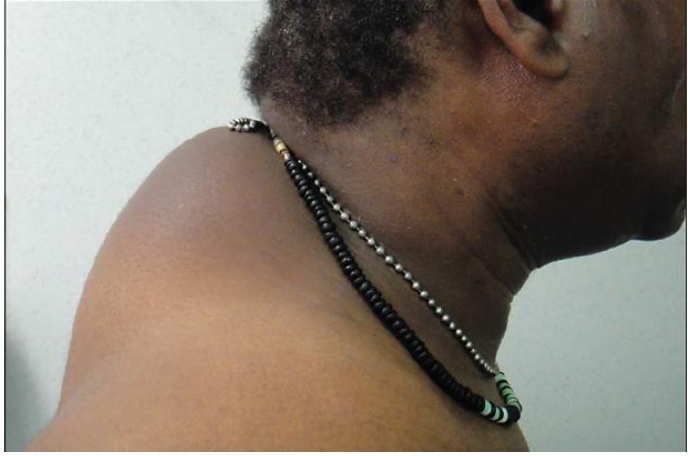

# Metabolic Complications over a lifetime

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*Cape Town, South Africa*

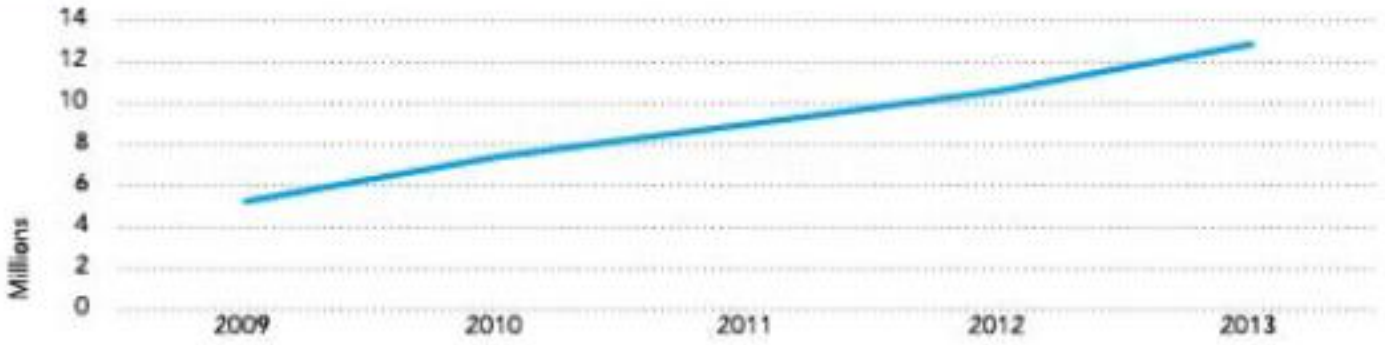
# Disclosures

- I receive grant funding from the
  - US NIH (NIAID, NICHD, Fogarty, CFAR)
  - US CDC
  - Indian Department of Biotechnology and Indian Council of Medical Research
  - Foundations (Gilead, Wyncote, Ujala, Gates)
  - Mylan
- Any opinions expressed are my own and not of any of my sponsors.

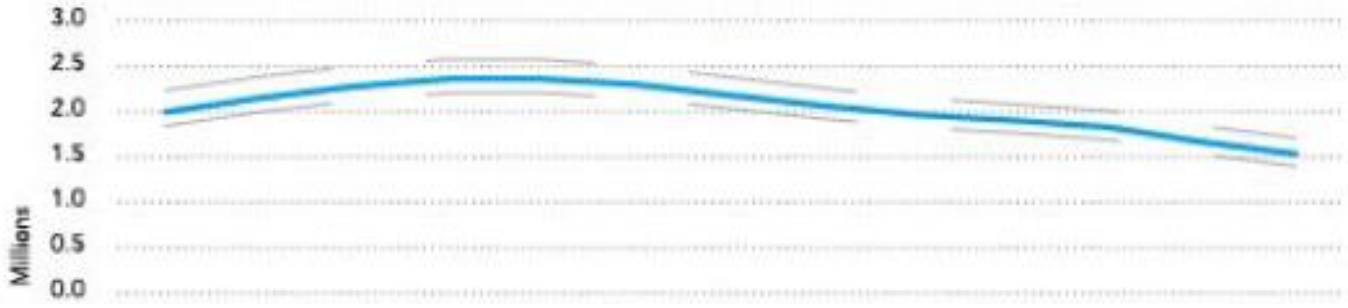
# Roadmap

- Burden of chronic diseases
- Body Composition Changes
- Cardiometabolic
  - Insulin resistance and diabetes mellitus
  - Dyslipidemia
- Inflammation

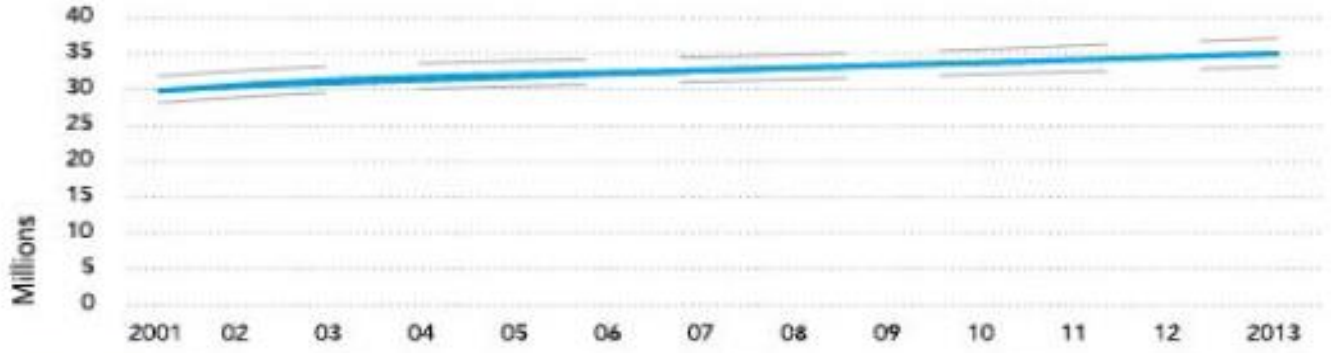
# Increasing ART, Living Longer




Number of people receiving ART – global




Number of AIDS-related deaths – global



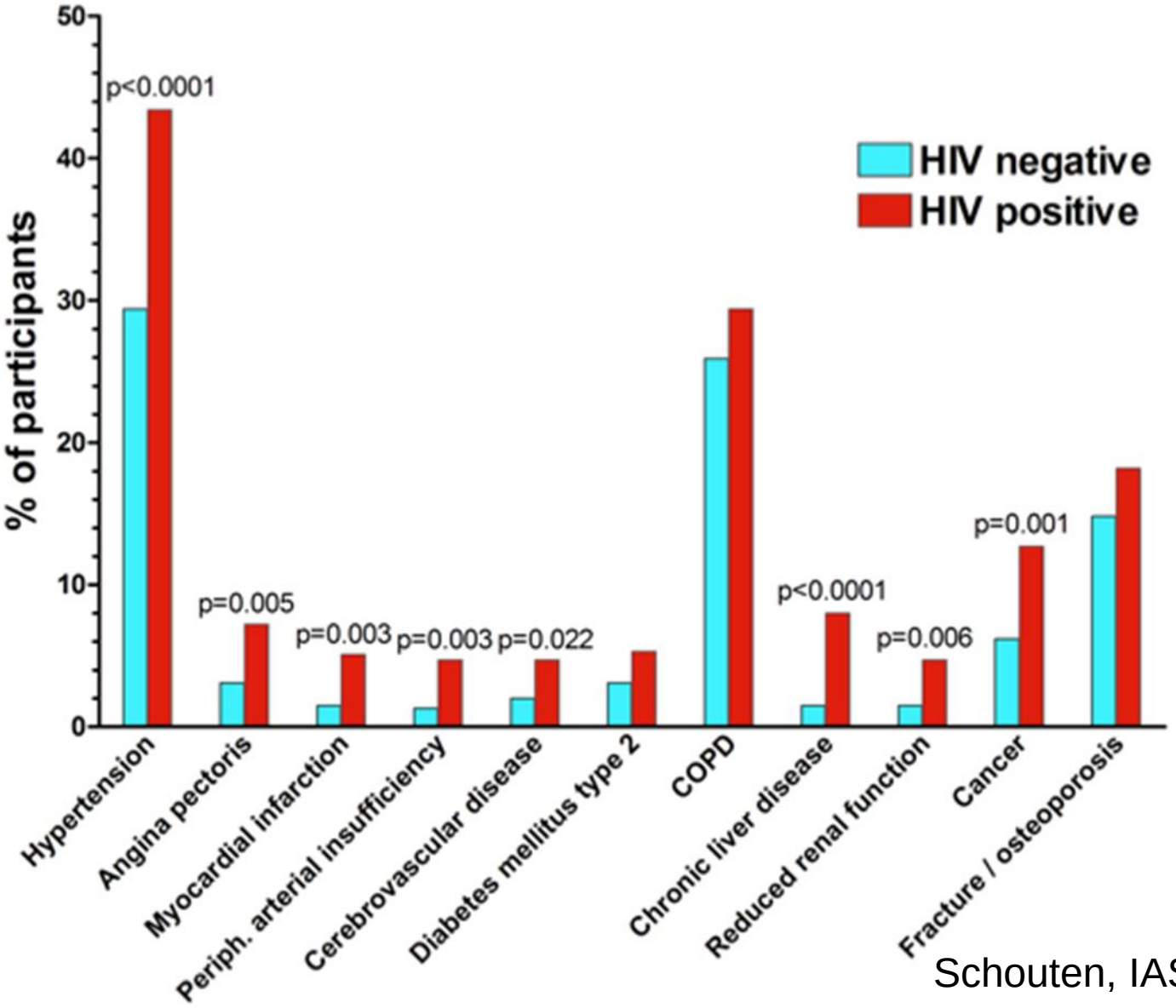

Number of peop living with HIV –

UNAIDS 2014

# Diseases more Common Among HIV-infected Persons in High-Income Settings

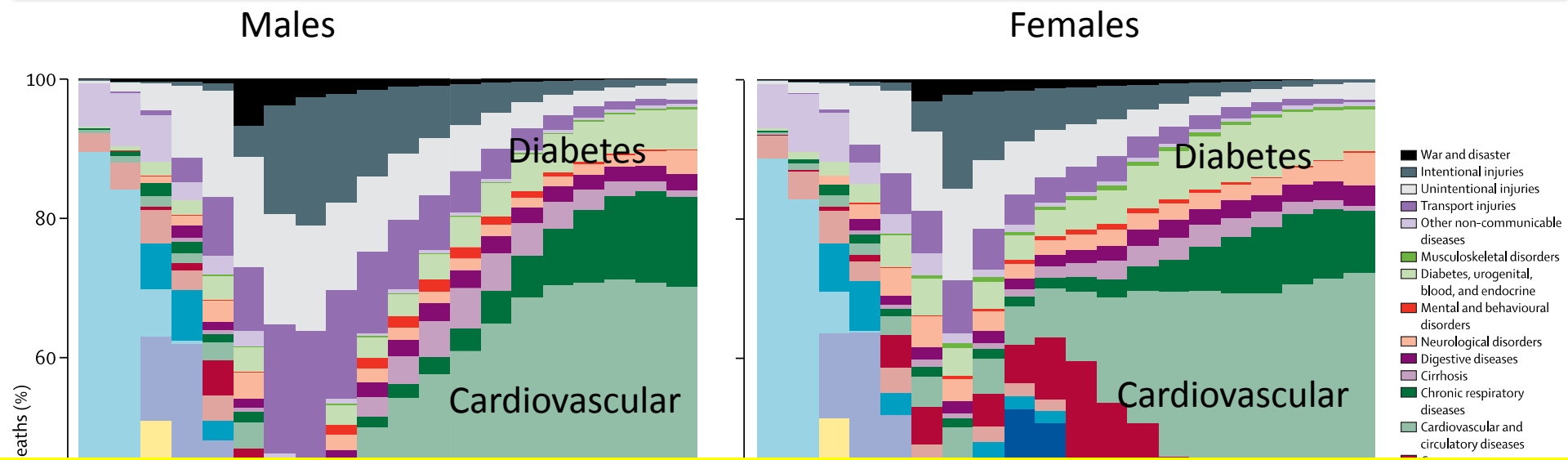
- **Lipodystrophy**
- **Cardiovascular Disease**
  - **(1.8 fold increased risk MI- Triant JCEM 2007)**
- **Diabetes Mellitus**
  - **(4-fold increased risk Brown Arch Int Med 2005)**
- Cancer
- Kidney Problems
- Cognitive Problems
- Osteoporosis
- Low Testosterone
- Fraility

# Comorbidity distribution




Schouten, IAS, 2012

# WHO Global Burden



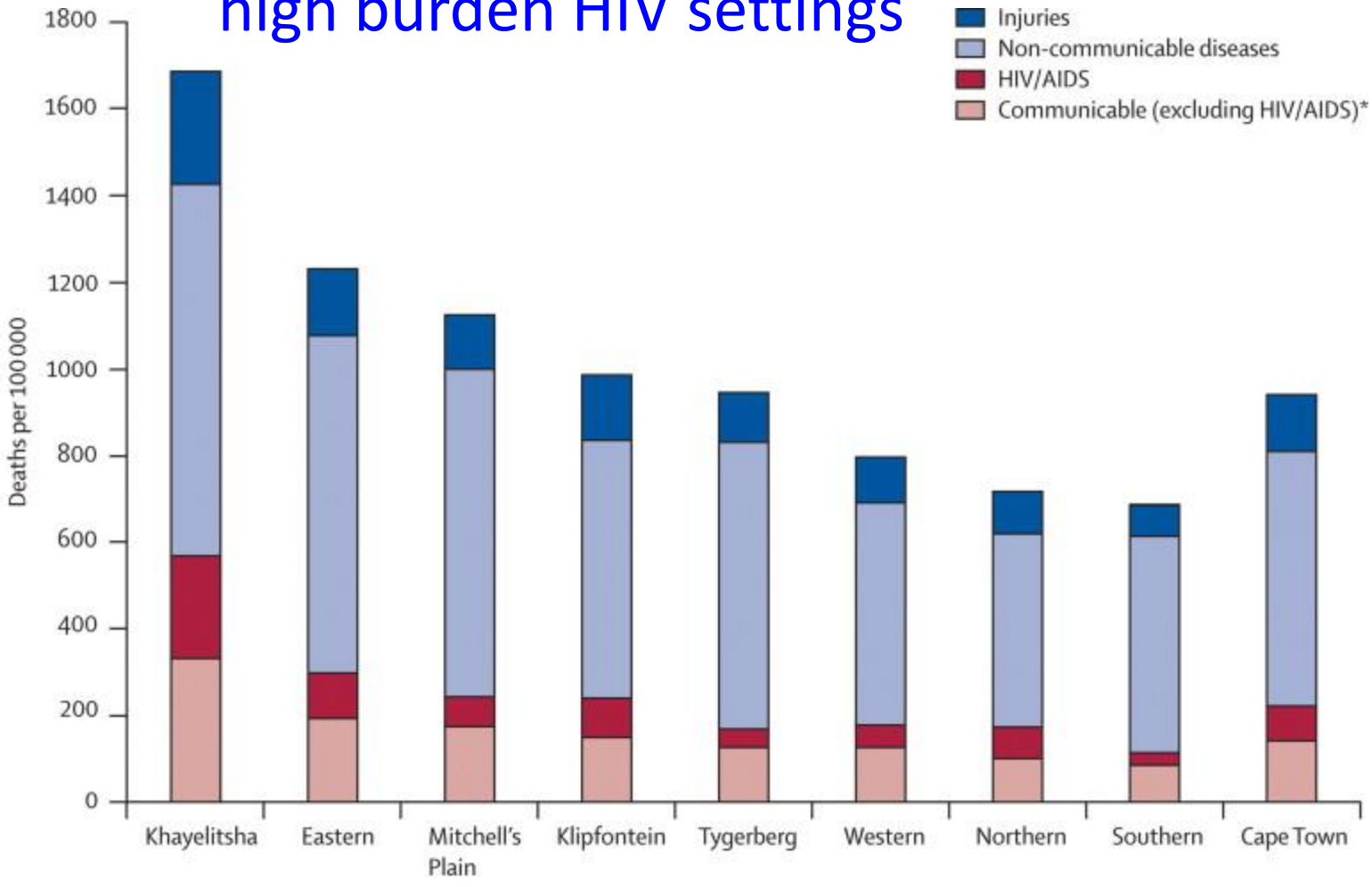

Non-communicable diseases (NCDs) cause about two-thirds (or 36 million of the 57 million deaths annually in the world.

About 80 percent of the NCDs deaths occur in low- and middle-income countries.

Nearly 30 percent of those deaths are in people under age 60.

Lozano Lancet 2012

# Non-communicable deaths are important even in high burden HIV settings




| | Khayelitsha | Eastern | Mitchell's Plain | Klipfontein | Tygerberg | Western | Northern | Southern | Cape Town |
|---|---|---|---|---|---|---|---|---|---|
| Injuries | 259·6 | 152·7 | 126·1 | 150·6 | 113·3 | 150·6 | 98·2 | 70·5 | 128·9 |
| Non-communicable diseases | 856·4 | 781·1 | 755·7 | 594·9 | 662·1 | 512·7 | 445·8 | 501·3 | 590·2 |
| HIV/AIDS | 238·5 | 103·2 | 69·3 | 90·2 | 43·0 | 50·2 | 69·6 | 25·6 | 76·1 |
| Communicable (excluding HIV/AIDS)* | 330·3 | 193·8 | 174·2 | 149·4 | 125·5 | 127·4 | 103·2 | 87·7 | 144·3 |

Mayosi et al Lancet 2009

# Population-based prevalence of Diabetes in Africa

Kengne AP, *et al*. *Heart* 2013;**99**:979–983. doi:10.1136/heartjnl-2012-303316

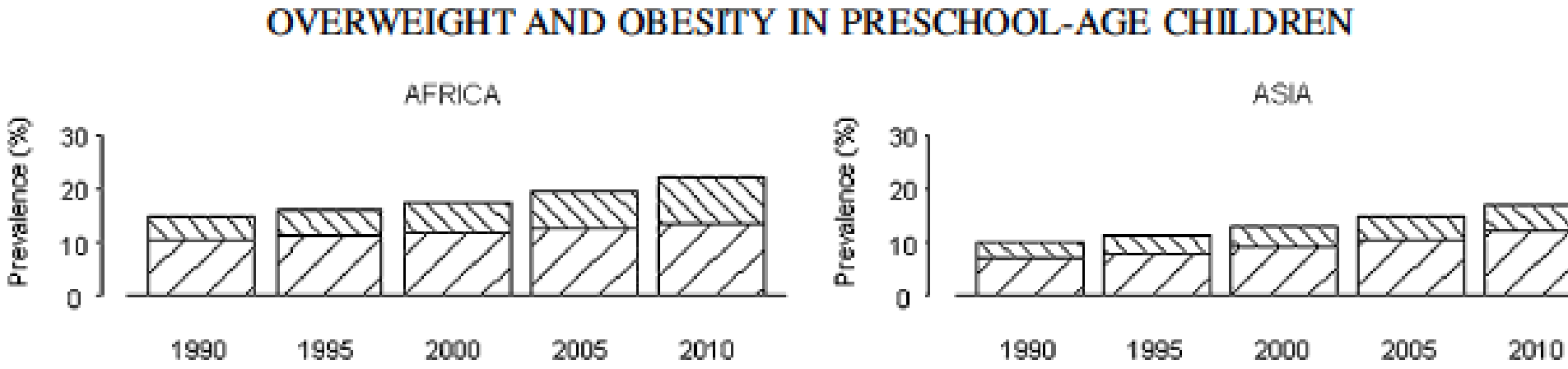
**Table 1** Selected population-based prevalence studies on diabetes in Africa, 2002–2012

| | | | | | | | Prevalence of diabetes (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Country** | **Sample** | **Sampling** | **Setting** | **Age (years)** | **Diagnosis** | **Overall** | **Men** | **Women** | **Undiagnosed** |
| Evaristo-Neto[11] | Angola | 421 | Random | Rural | 30–69 | OGTT | 2.8 | 3.2 | 2.7 | – |
| Echouffo-Tcheugui[15] | Cameroon | 1591 | Self-selected | Urban | 43.7 | FBG | 15.3 | 13.7 | 17.0 | 6.3 |
| Katchunga[17] | DRC | 424 | Random | Urban | 53.3 | RBG | 4.7 | – | – | 1.0 |
| Katchunga[17] | DRC | 245 | Random | Rural | 58.5 | RBG | 2.9 | – | – | 1.6 |
| Ploubidis[18] | Kenya | 2959 | Random | Rural | 64.7 | RBG | 5.1 | – | – | – |
| Ploubidis[18] | Kenya | 1437 | Random | Urban | 60.8 | RBG | 10.1 | – | – | – |
| Ejim[13] | Nigeria | 858 | Random | Rural | 59.8 | FBG | 4.4 | 7.3 | 3.3 | – |
| Duboz[12] | Senegal | 600 | Random | Urban | >20 | FBG | 17.9 | 14.0 | 21.8 | 16.2 |
| Peer[10] | South Africa | 1099 | Random | Urban | 43.3 | OGTT | 12.1 (13.1) | 10.2 (11.3) | 13.8 (14.7) | 4.9 |
| Erasmus[9] | South Africa | 642 | Random | Urban | 50.9 | OGTT | 28.2 (26.3) | | | 18.1 |
| Baragou[16] | Togo | 2000 | Random | Urban | 39 | 2 FBG | 7.3 | 6.9 | 7.3 | – |
| Nsakashalo-Senkwe[54] | Zambia | 1928 | Random | Urban | ≥25 | FBG | 2.7 | – | – | – |
| Hammami[14] | Tunisia | 598 | Random | Urban and rural | 72.3 | RBG | 27.4 | 29.2 | 26.5 | – |
| Chamie[20] | Uganda | 2283 | Self-selected | Urban | 35 | RBG | 3.5 | – | – | 0.8 |

Figures within parenthesis are age-adjusted.
FBG, fasting blood glucose; OGTT, oral glucose tolerance test; RBG, random blood glucose.

Diabetes Prevalence 3-28%

# Obesity not just a CVD risk factor in the West




8.5% Children in Africa Overweight/Obese

# Obesity not just a CVD risk factor in the West

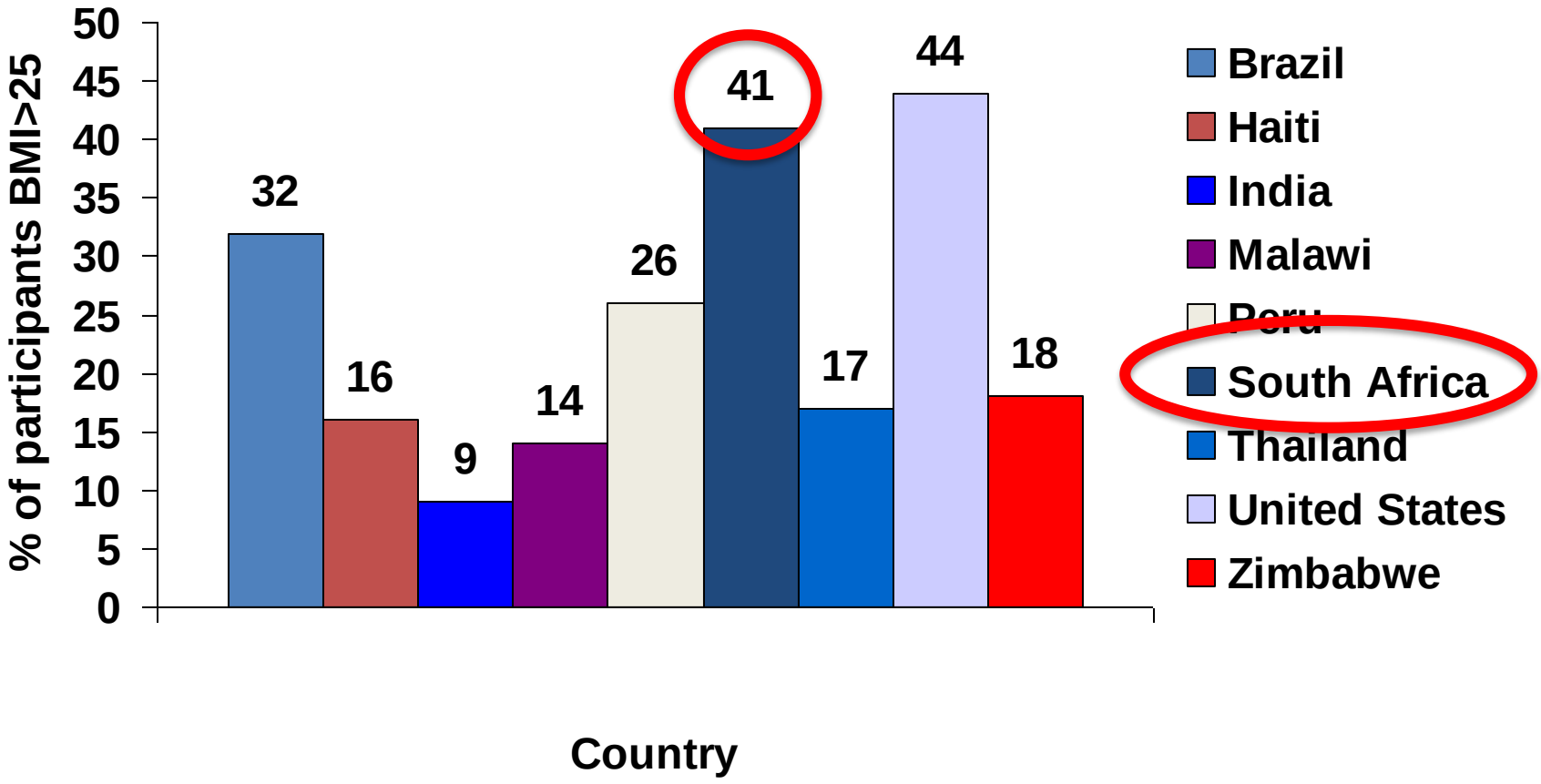
Kengne AP, *et al*. *Heart* 2013;**99**:979–983. doi:10.1136/heartjnl-2012-303316

**Table 2** Population-based prevalence studies on overweight and obesity in Africa

| | | | | | | Obesity (%) | | | Overweight (%) | | | Abdominal obesity (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Country** | **Sample** | **Sampling** | **Setting** | **Age (years)** | **Overall** | **Men** | **Women** | **Overall** | **Men** | **Women** | **Overall** | **Men** | **Women** |
| Fouda[55] | Cameroon | 552 | Random | Urban | 34.5 | 23.4 | 17.8 | 36.1 | 49.1 | 51.7 | 43.2 | 35.2 | 19.8 | 69.8 |
| Sani[56] | Nigeria | 300 | Convenient | Urban | 37.6 | 21.3 | 10.9 | 29.2 | 32 | – | – | 43.7 | 12.4 | 67.3 |
| Ejike[28] | Nigeria | 1584 | Random | Urban | 21.8 | 1.3 | 0.4 | 2.5 | 19.4 | 17.1 | 22.3 | 7.5 | 1.3 | 16.1 |
| Ejim[13] | Nigeria | 858 | Random | Rural | 59.8 | 30 | 21.1 | 33.6 | – | – | – | 31 | 2.4 | 42.6 |
| Wahab[57] | Nigeria | 300 | Convenient | Urban | – | 21 | 9.3 | 29.8 | 53.3 | 41.9 | 62 | – | – | – |
| Okafor[29] | Nigeria | 898 | Random | Urban | 48.7 | 21.2 | – | – | 40.4 | – | – | 66.5 | – | – |
| Mkhonto[58] | South Africa | 532 | Convenient | Rural | 45.9 | 24.4 | 9.6 | 29.6 | 26.1 | 17.7 | 29.0 | – | – | – |
| Malaza[41] | South Africa | 14 198 | Convenient | Rural | >15 | 45.7 | 15.9 | 45.7 | 23.3 | 31.3 | 4.9 | – | – | – |
| Baragou[16] | Togo | 2000 | Random | Urban | 39 | 25.2 | 16.7 | 32.2 | – | – | – | – | – | – |
| Mayega[27] | Uganda | 1656 | Random | Rural | 44 | 5.3 | 2.2 | 8.2 | 12.3 | 7.5 | 16.9 | 13.8 | 1.4 | 24.5 |
| Rudatsikira[59] | Zambia | 1928 | Random | Urban | – | 14.3 | 5.1 | 18.6 | – | – | – | – | – | – |

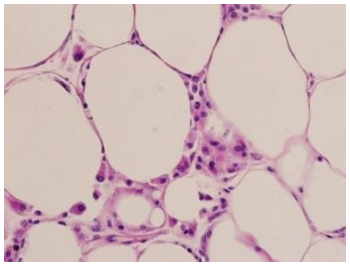
Obesity 1-46% Overweight 12-53% Abdominal Obesity 14-66%

# ACTG 5175: Proportion of HIV infected adults initiating ART who were overweight or obese (BMI>25) by country

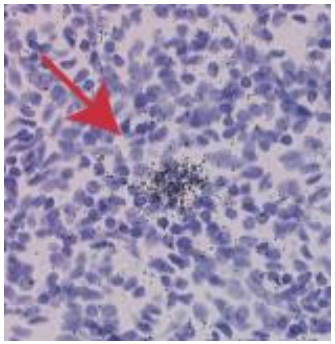



*Unpublished data*
*Campbell PLOS Med 2011*

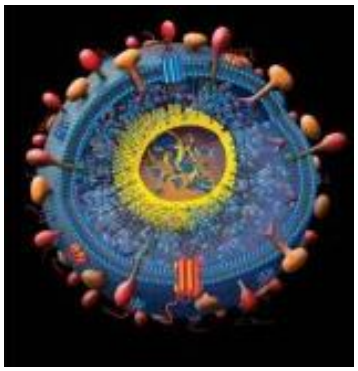
## HIV-associated fat
## Metabolic syndrome



## HIV production
## HIV replication



## CMV
## Excess pathogens



## Inflammation

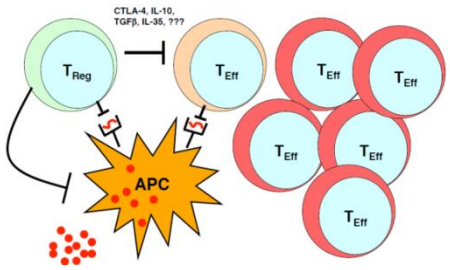
↑ Monocyte activation

↑ T cell activation

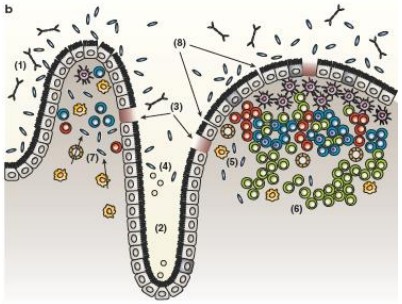
Dyslipidemia

Hypercoagulation

## Loss of regulatory cells




## Microbial translocation



## Co-morbidities
## Aging

S. Deeks, 2013

# HIV-associated Metabolic Syndrome
# Body Composition

Lipoatrophy

Lipodystrophy

Mixed Lipodystrophy

# Lipoatrophy

## Children

Sawawiboon Int J STD&AIDS 2012

## Adults


Brown Nat Rev Endocrin 2012

# Lipohypertrophy

## Children

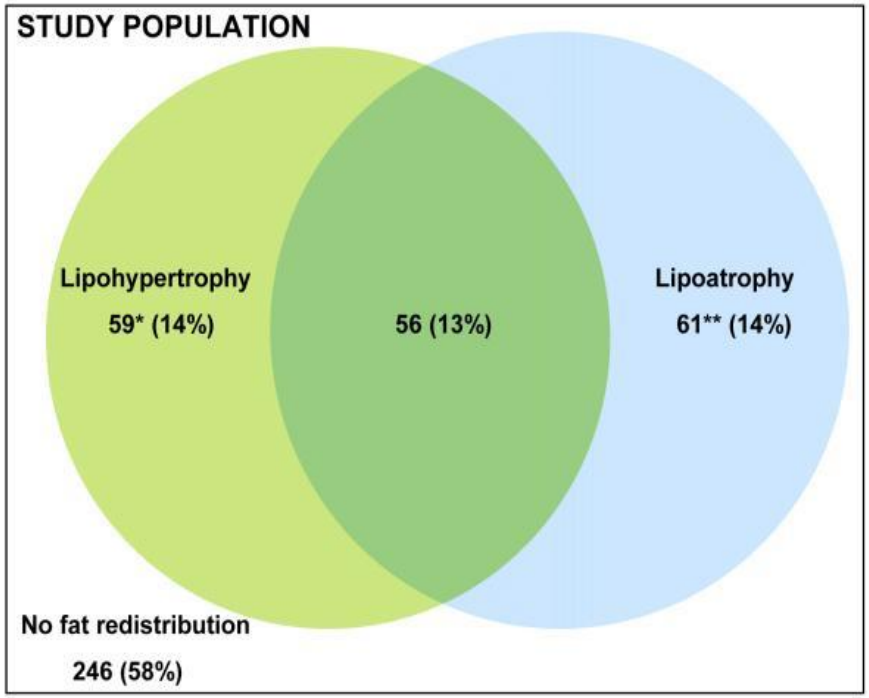
Chokephaibukit, IAS 2013

## Adults

Brown Nat Rev Endocrin 2012

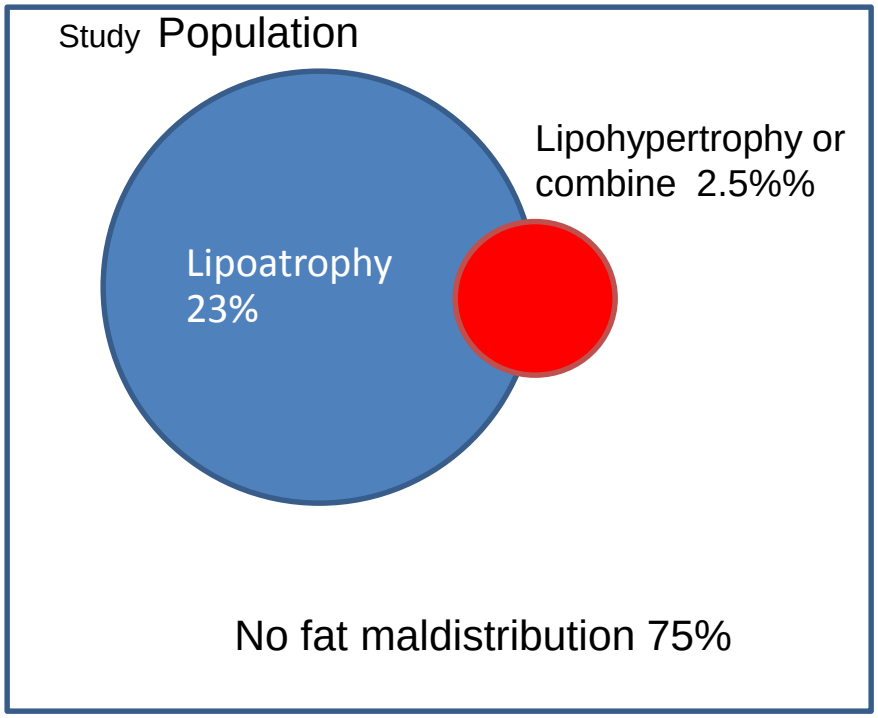
| | Lipoatrophy | Lipodystrophy |
|---|---|---|
| Adipose tissue | Subcutaneous loss | Abnormal visceral gain |
| Affected areas | Face, buttock, leg, arms | Abdomen,dorsocervical, liver, muscle |
| Social sequalae | Stigma, ↓ QOL, ↓Adherence | |
| Clinical Sequalae | Insulin resistance, dyslipidemia, inflammation | |
| ART Risk factors | tNRTIs d4T>AZT cumulative/dose<br>Older PIs (nelfinavir) | PIs |
| Other risk factors | Puberty, genetics, age, male sex, advanced HIV | Age, male sex, more advanced HIV |
| Pathogenesis | Mitochondrial toxicity<br>Adipocyte apoptosis | Dysregulaton of free fatty acid metabolism |

# Body fat abnormality in HIV-infected children and adolescents: *The difference of regions*




Europe (N= 426, LD = 42%
Receiving PI 60%,
Received d4T 10%

*Alam NM. J Acquir Immune Defic Syndr. 2012 March 1; 59(3): 314–324*




Thailand, N=202, LD = 25%
Receiving PI 41%,
Received d4T 60%

*Sawawiboon N. International Journal of STD & AIDS 2012; 23: 497–501*

*Courtesy of Chokephaibukit, IAS 2013*

# Facial lipoatrophy
# Is it reversible?


Figure 1 The serial photos of two children who had improvement of facial lipoatrophy after stopping stavudine (d4T)

## Facial Lipoatrophy may improve after stopping d4T

**Improvement found in 23%, at mean duration of 45 months after stopping d4T, around early adolescence**

Need to stop d4T before reaching adolescence

*Sawawiboon N. International Journal of STD & AIDS 2012; 23: 497–501*

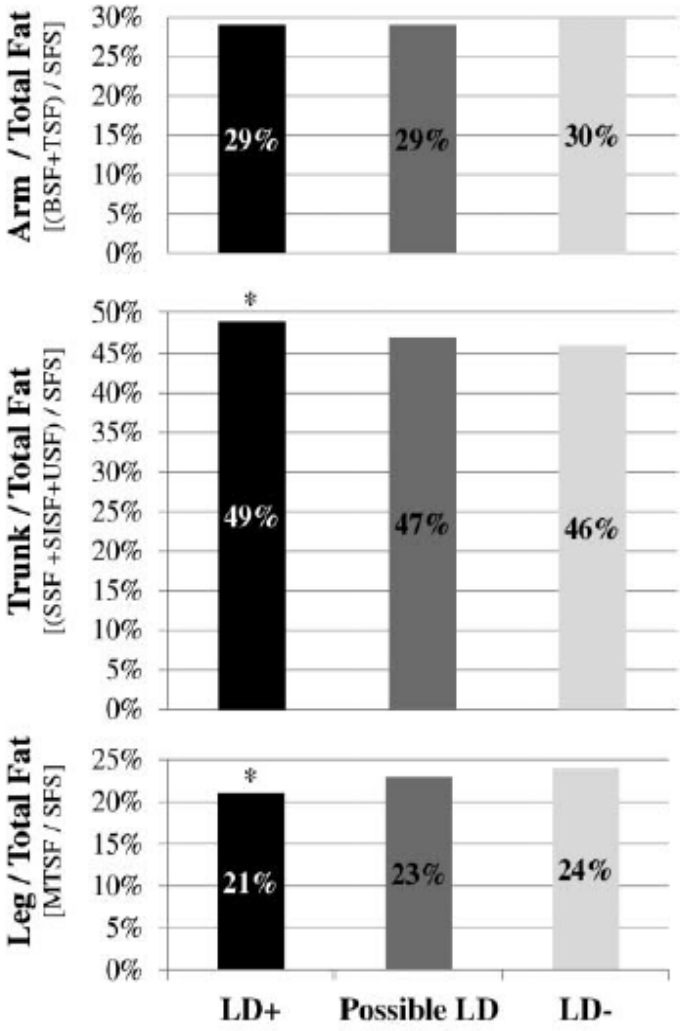
*Courtesy of Chokephaibukit, IAS 2013*

# Lipodystrophy prevalence

**NEVEREST trial (South Africa)**

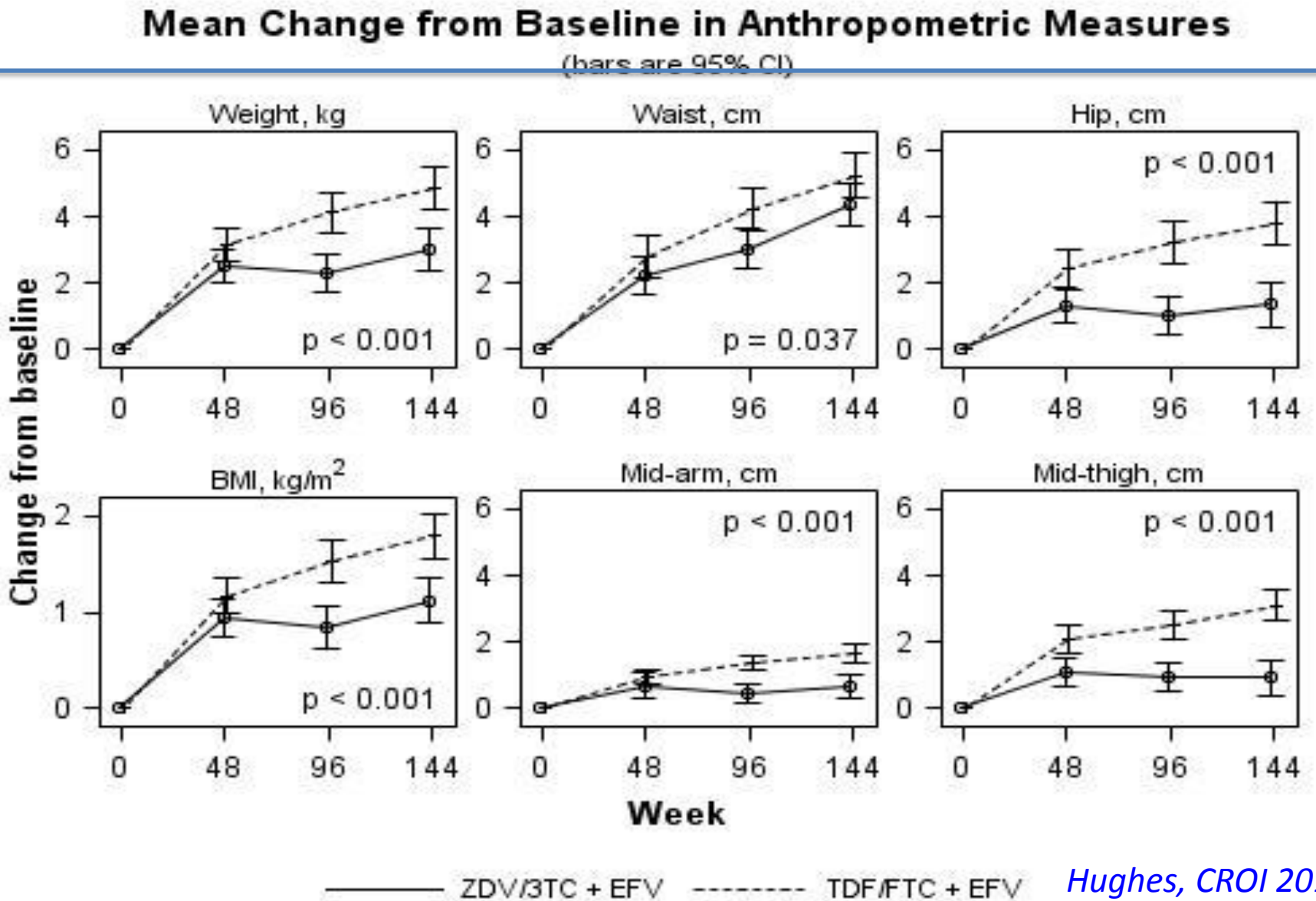
- Suppressed on LPV/r then randomized to stay on LPV/r or switch to NVP
- Mean age 5 years at assessment
- mean time on ART: 4 years
- Lipids, anthropometrics, markers

- Higher Lipids (TC, LDL, TG) with LPV/r
- 8.4% had lipodystrophy




Arpadi, Kuhn Arch Dis Child 2013

# A5175 Treatment effects
# AZT vs TDF




*Hughes, CROI 2014*

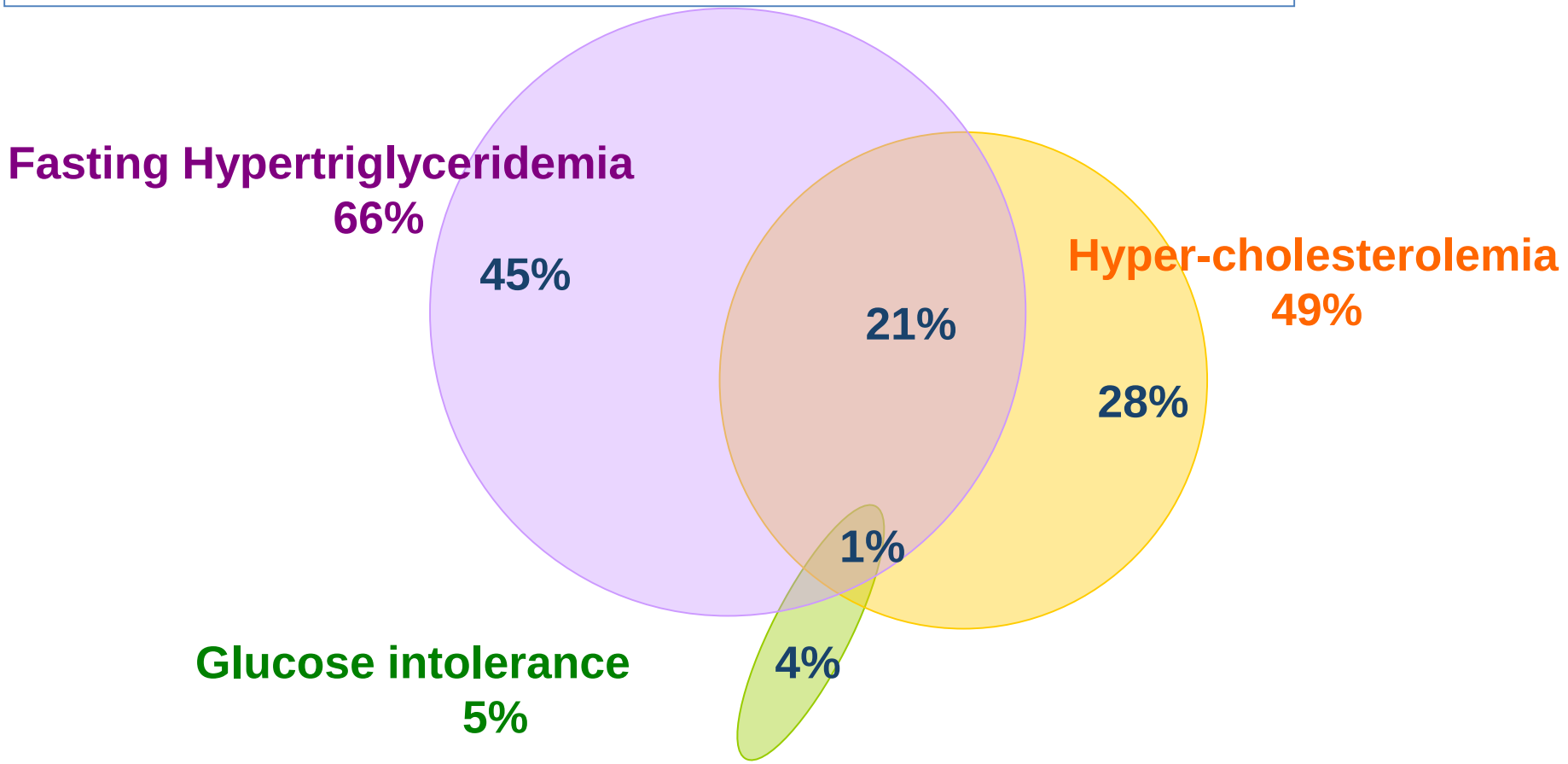
**Table 1** | Treatment strategies for adipose tissue changes in HIV-infected individuals

| Strategy | Effect | Comments |
|---|---|---|
| ***Lipoatrophy*** | | |
| Switching antiretroviral therapy | Modest effect | Switching from stavudine or zidovudine to abacavir or tenfovir disoproxil fumarate; best available strategy for lipoatrophy |
| Thiazolidinediones | Modest effect | Effect not clinically significant; availability of rosiglitazone limited due to increased risk of cardiovascular disease; pioglitazone associated with decreased levels of triglycerides, increased levels of HDL cholesterol, slight increased levels of LDL cholesterol |
| Pravastatin | No effect | NA |
| Uridine | No effect | NA |
| Facial fillers | Clinically significant effect | Potential adverse effects include fat hypertophy with autotransplatation, skin nodules with resorbable fillers and local infections with permanent fillers |
| Leptin | Unclear | No effect on peripheral adipose tissue, but may improve insulin resistance and dyslipidemia |
| ***Lipohypertrophy*** | | |
| Switching antiretroviral therapy | No effect | Overall, no benefit except for switching from lopinavir plus ritonavir to atazanavir plus ritonavir in one small study |
| Lifestyle changes | Modest effect | NA |
| Metformin | Modest effect | May worsen lipoatrophy |
| Growth hormone | Clinically significant effect | Rejected by FDA because of safety concerns |
| Tesamorelin | Clinically significant effect | FDA-approved in 2010; long-term benefits and risks unclear |
| Liposuction (dorsocervical fat pad) | Clinically significant effect | Can reaccumulate |

# Dyslipidemia

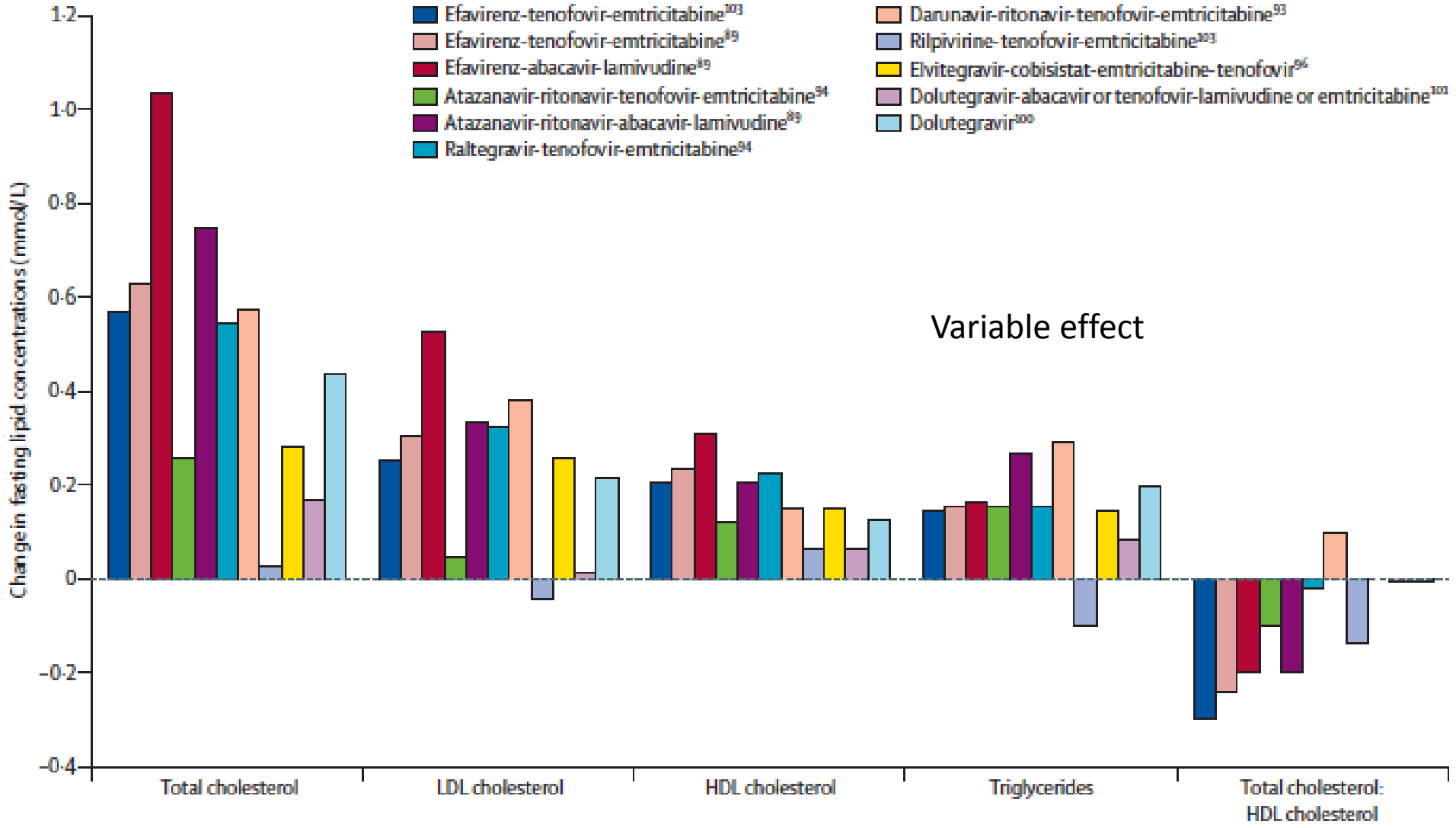
# Dyslipidemia found 40%-80% in children, associated with receiving PI and lipodystrophy[1-3]

**Prevalence of Dyslipidemia in a European cohort of HIV-infected children and adolescents (N=426), 60% receiving PI[4]**




*1.Lapphra K. J Med Assoc Thai. 2005. 2. Taylor P. Pediatrics 2004. 3. Amaya RA. Pediatr Infect Dis J. 2002, 4. Alam NM. J Acquir Immune Defic Syndr. 2012 March 1; 59(3): 314–324*

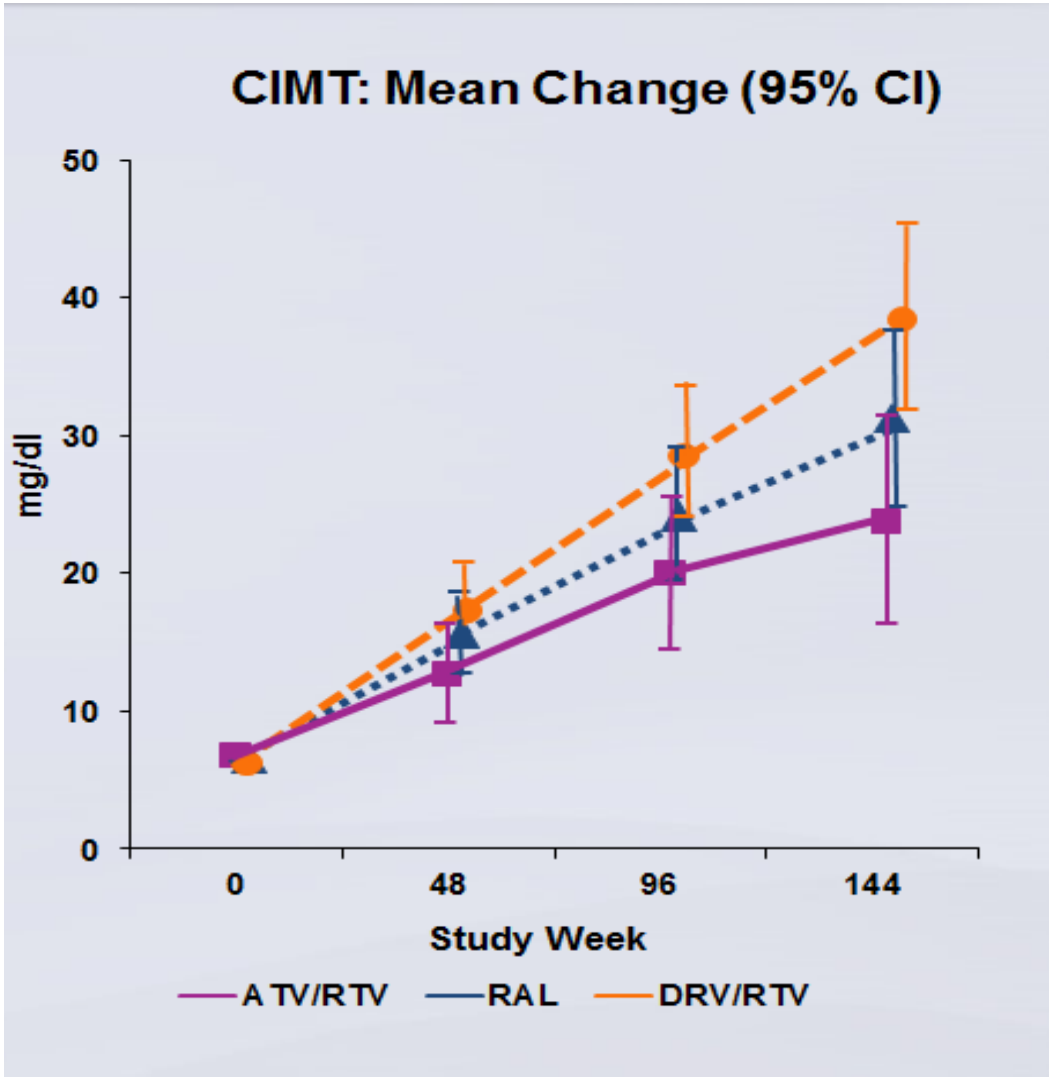
# ART Effect on Lipids




Variable effect

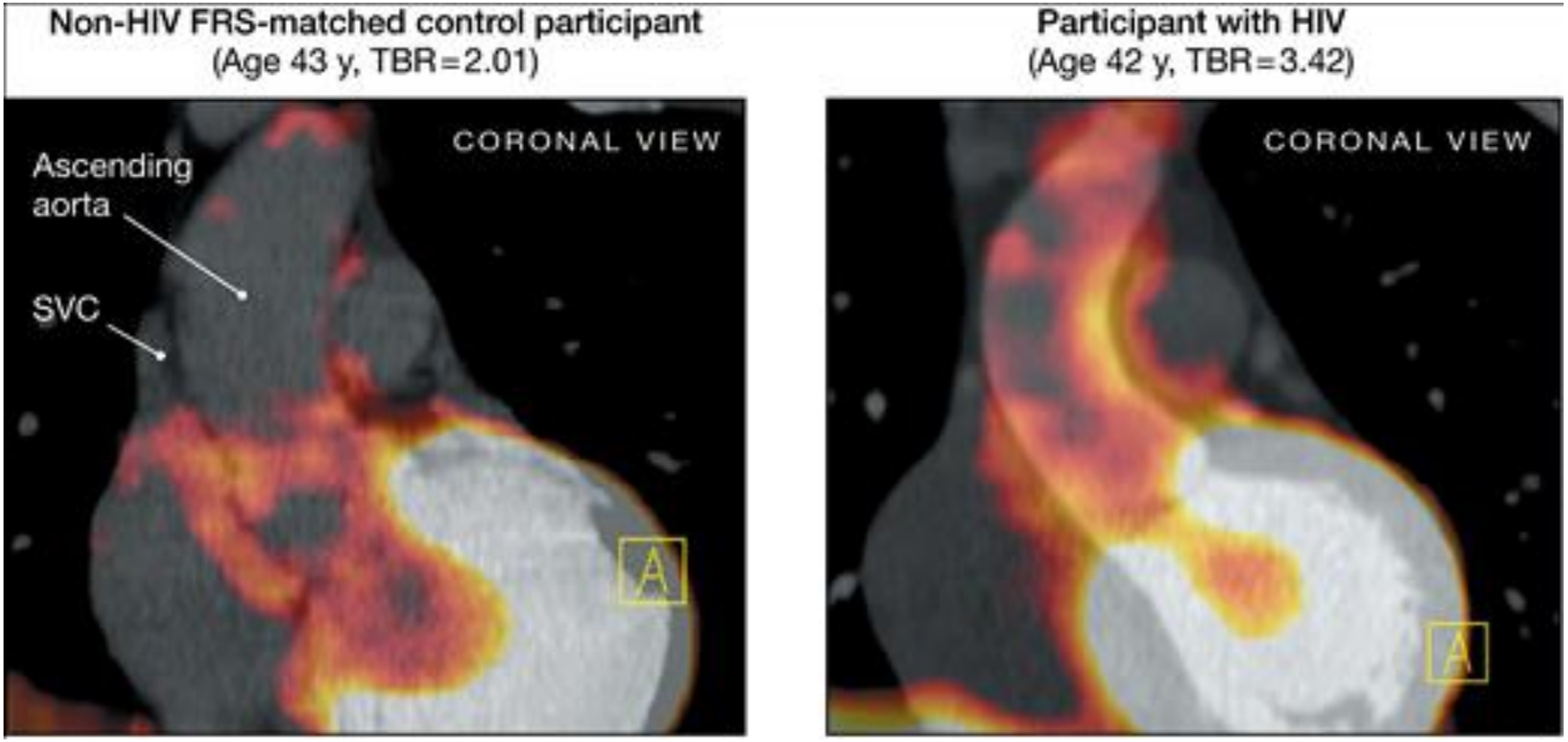
Lake, Lancet ID 2013

# Carotid Intima-Media Thickening (IMT) increases on ART




Stein J et al, *J Am Coll Cardiol*. 2014;63(12_S): CROI 2014;Abstract A1322

# Blood Vessel Inflammation in HIV




Subramanian, JAMA, 2012

# Dyslipidemia Management

- Lifestyle modifications
- Switch ART  (e.g. LPV/r to ATV/r)
- Lipid Lowering drugs
  - Statins for low LDL
  - Fenofibrates, fish oil, niacin for elevated TGs
  - May be less effective in HIV *(Silverberg Ann Int Med 2009)*

# Insulin resistance

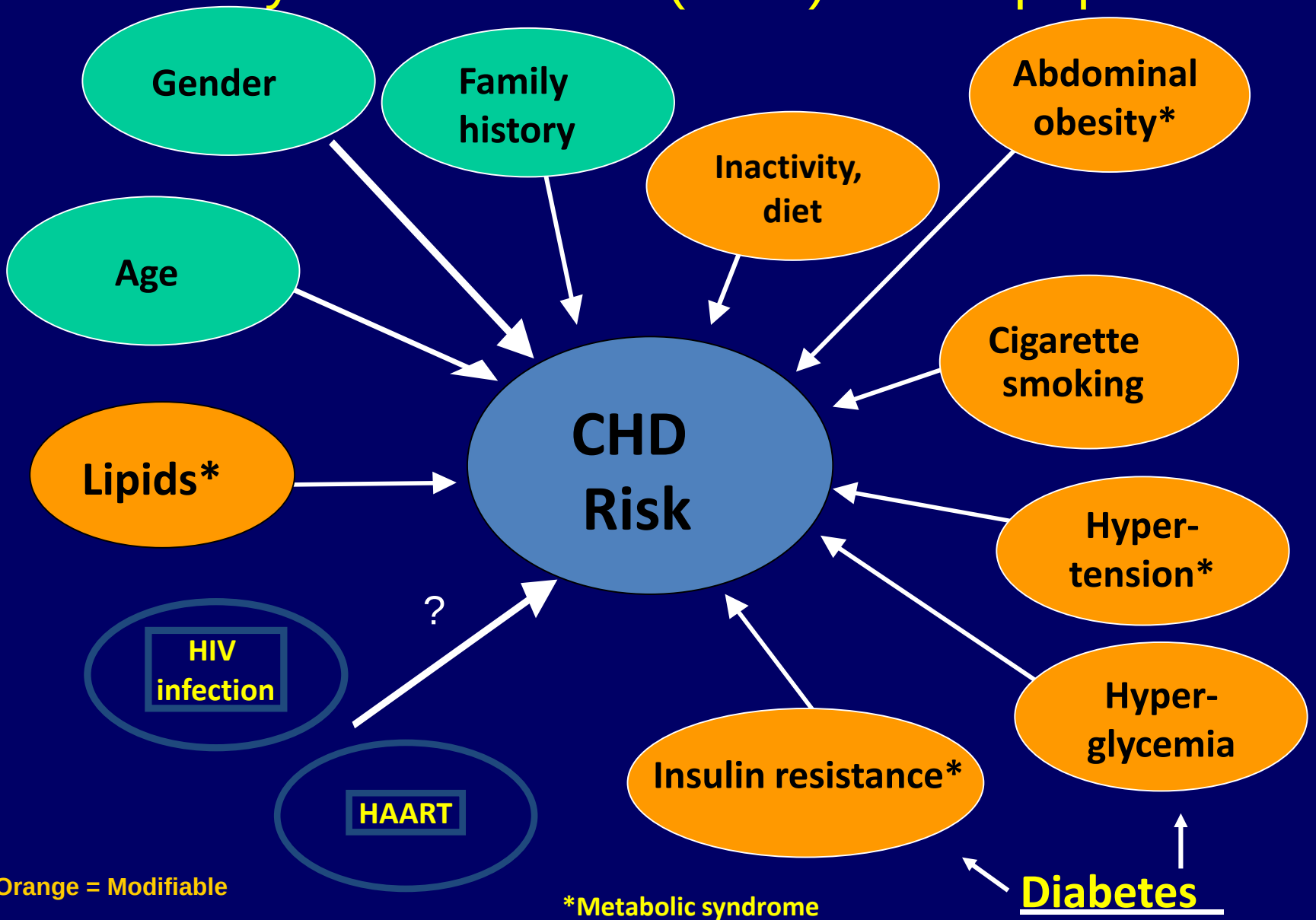
- Increased incidence in untreated HIV
- ART direct and indirect
  - PIs (via inhibition of glucose transporter GLUT4)
  - tNRTIs via mitochondrial toxicity
  - via regional adipose tissue changes
  - inflammation, adipose FFA dysregulation
- HbA1c may underestimate DM in HIV
- Manage like HIV-uninfected
  - lifestyle, metformin

# Insulin Resistance and Type 2 Diabetes in HIV-Infected Children

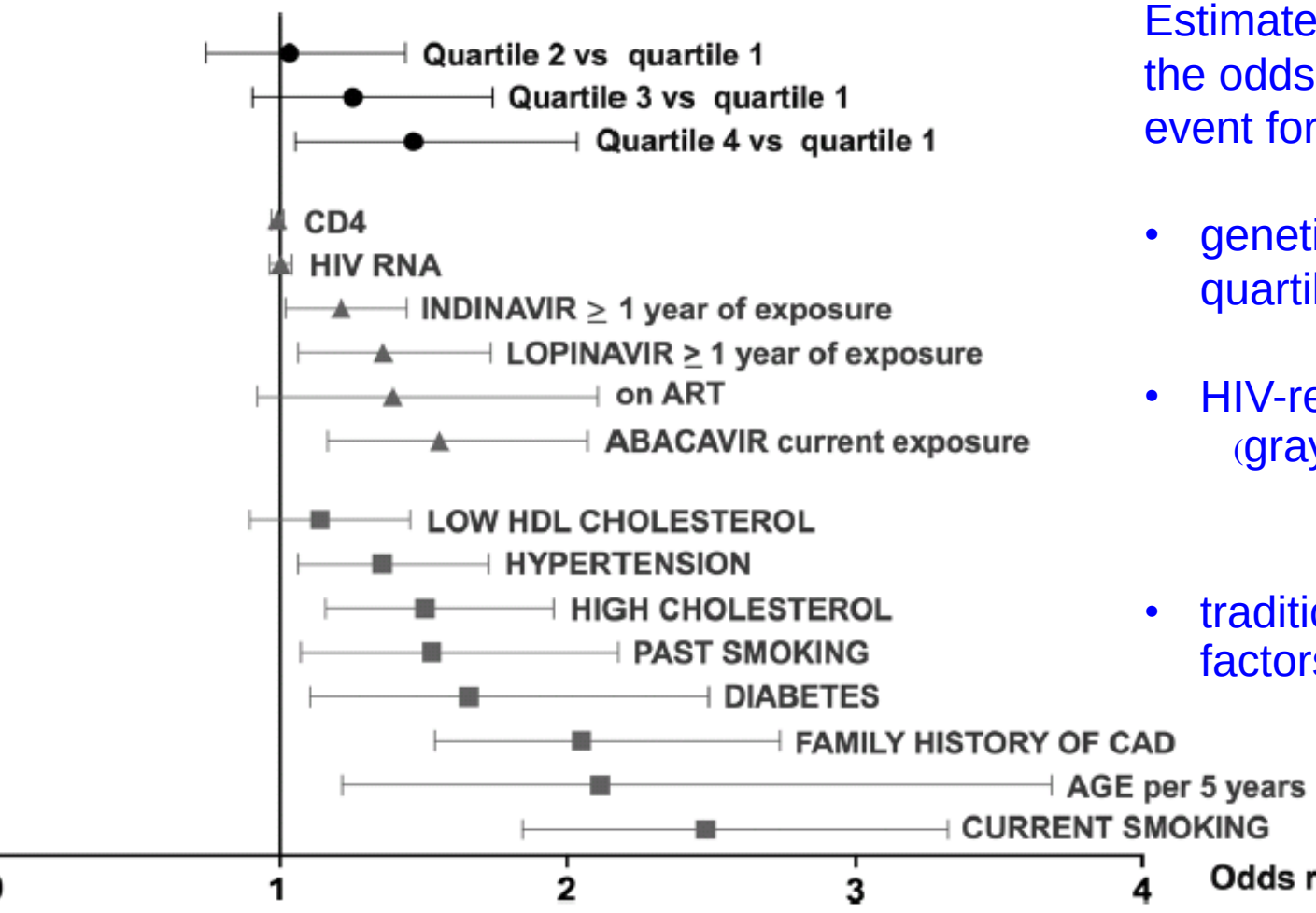
- **Prevalence in adults 10-20%**
  - **Increase prevalence in patients receiving HAART with lipodystrophy[1]**
- **Incidence in children is much lower**
- **However, 19% of children receiving PI had impair OGTT[2]**

*1.Vigouroux C. Diabetes & Metabolism 1999*
*2. Bitnun A. J Clin Endocrinol Metab 2005*

# Traditional factors important are contributors to coronary heart disease (CHD) in HIV populations



# Contribution of risks factors for CAD in HIV-Positive Persons




Estimated effect (95%CI) on the odds ratio of a first CAD event for:

- genetic risk score quartile (black dots),
- HIV-related variables (gray triangles)
- traditional CAD risk factors (gray squares).

*Rotger M. CID 2013 Jul;57(1):112-21.*

# Kenya CVD/HIV Integration Pilot

## *Biological CVD Risk Factors and Length on ART*

| Variable | | Length on ART | | |
|---|---|---|---|---|
| | | <1 year | 1 – 3 years | > 4 years |
| **Blood pressure** | | **(n=92)** | **(n=198)** | **(n=115)** |
| | Normal | 87% | 74% | 76% |
| | High | 13% | 26% | 24% |
| **BMI** | | **(n=92)** | **(n=198)** | **(n=115)** |
| | Normal | 78% | 74% | 78% |
| | High | 22% | 26% | 22% |
| **Waist Circumference** | | **(n=92)** | **(n=198)** | **(n=115)** |
| | Normal | 84% | 86% | 79% |
| | High | 16% | 14% | 21% |
| **Random blood sugar (RBS)** | | **(n=43)** | **(n=117)** | **(n=80)** |
| | Normal | 98% | 98% | 99% |
| | High | 2% | 2% | 1% |
| **Total cholesterol** | | **(n=39)** | **(n=118)** | **(n=76)** |
| | Normal | 90% | 68% | 72% |
| | High | 10% | 32% | 28% |

# Nigeria CVD/HIV Integration
## *Pilot Findings*

- Most common risk factors were:
  - age >40years (25.7%)
  - male sex (25.9%)
  - overweight/obese (21.8%)
  - blood pressure >140/90 mmHg (15.2%)

- Linear relationship found between the mean levels of serum total cholesterol and duration on ART

| Total Cholesterol | | | |
|---|---|---|---|
| **Duration on ART** | **N** | **Mean** | **p value** |
| < 1Yr | 33 | 3.93 | 0.02 |
| 1-<3Yrs | 52 | 4.49 | |
| >=3Yrs | 67 | 4.54 | |

GHAIN
Global HIV/AIDS Initiative Nigeria

# Non-AIDS defining events similar or possibly higher in non-US settings

| | Gabarone, Botswana | | Nashville, TN, USA |
|---|---|---|---|
| | Crude/ 1000 PY | Standardized age, sex/ 1000 PY | |
| NADE | 10 | 18.7 | 12.4 |
| CVD | 5 | 8.4 | 5 |
| Renal | 2.2 | 2.4 | 3 |
| Hepatic | 0 | 0 | 4 |
| Malignancy | 2.8 | 8 | 0.5 |
| NADE Mortality | 12/18 (67%) | | 3/25 (12%) |

Wester AIDS 2011

# Unanswered Questions

- What role does HIV-associated metabolic syndromes have in causing co-morbidities?
- Will HIV-infected children have increased, premature atherogenesis and CVD?
- Are persons in LMIC are similar, or higher risk?
- Do HIV-infected patients need more aggressive management of their chronic inflammation, CVD risk?


US Populations are not the only ones inflamed!

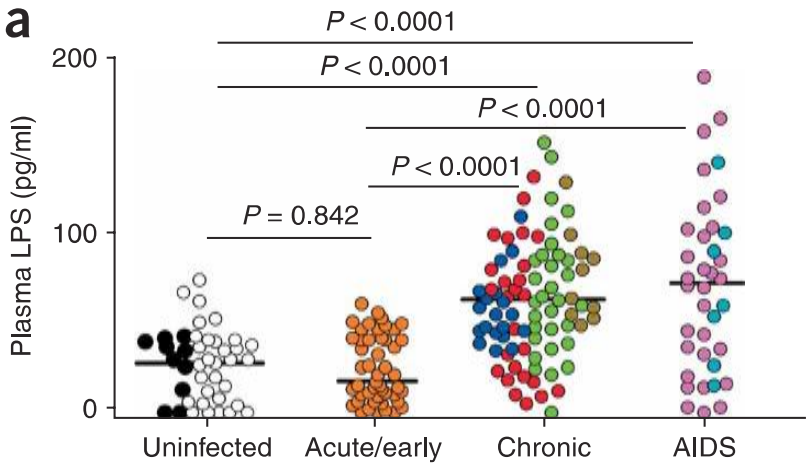
# HIV AND INFLAMMATION IN NON-US SETTINGS

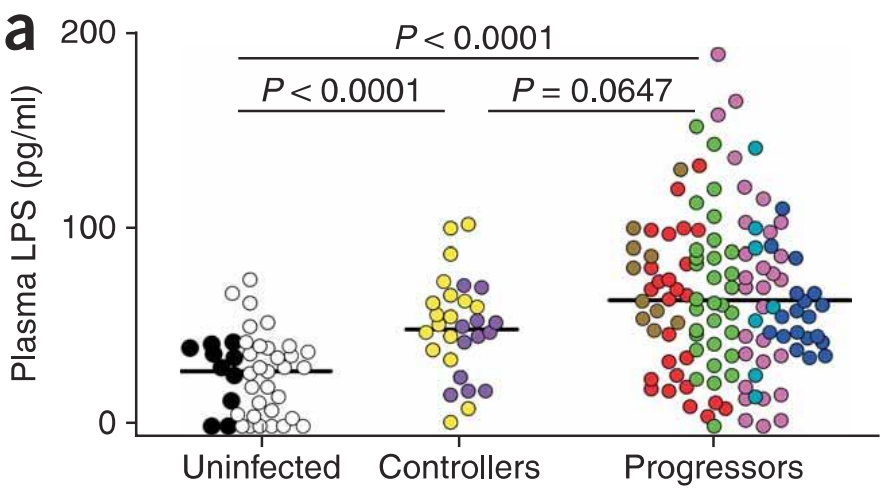
# Markers of inflammation: mixed results

# Association of inflammatory markers and HIV outcomes- data largely from high income settings

- Treated HIV-infected 50-100% higher IL-6 than matched HIV-uninfected adults (Neuhaus JID 2010)
- IL-6 independently associated with all-cause mortality (INSIGHT SMART- Kuller PLOS Med 2008)
- sCD14 associated with all-cause mortality (INSIGHT SMART Sandler JID 2011)
- sCD163 associated with coronary artery inflammation/athersclorosis (Burdo JID 2011)
- Activated T cells associated with morbidity and mortality but less so than soluble markers (Hunt AIDS 2011)

# Microbial Translocation and HIV progression



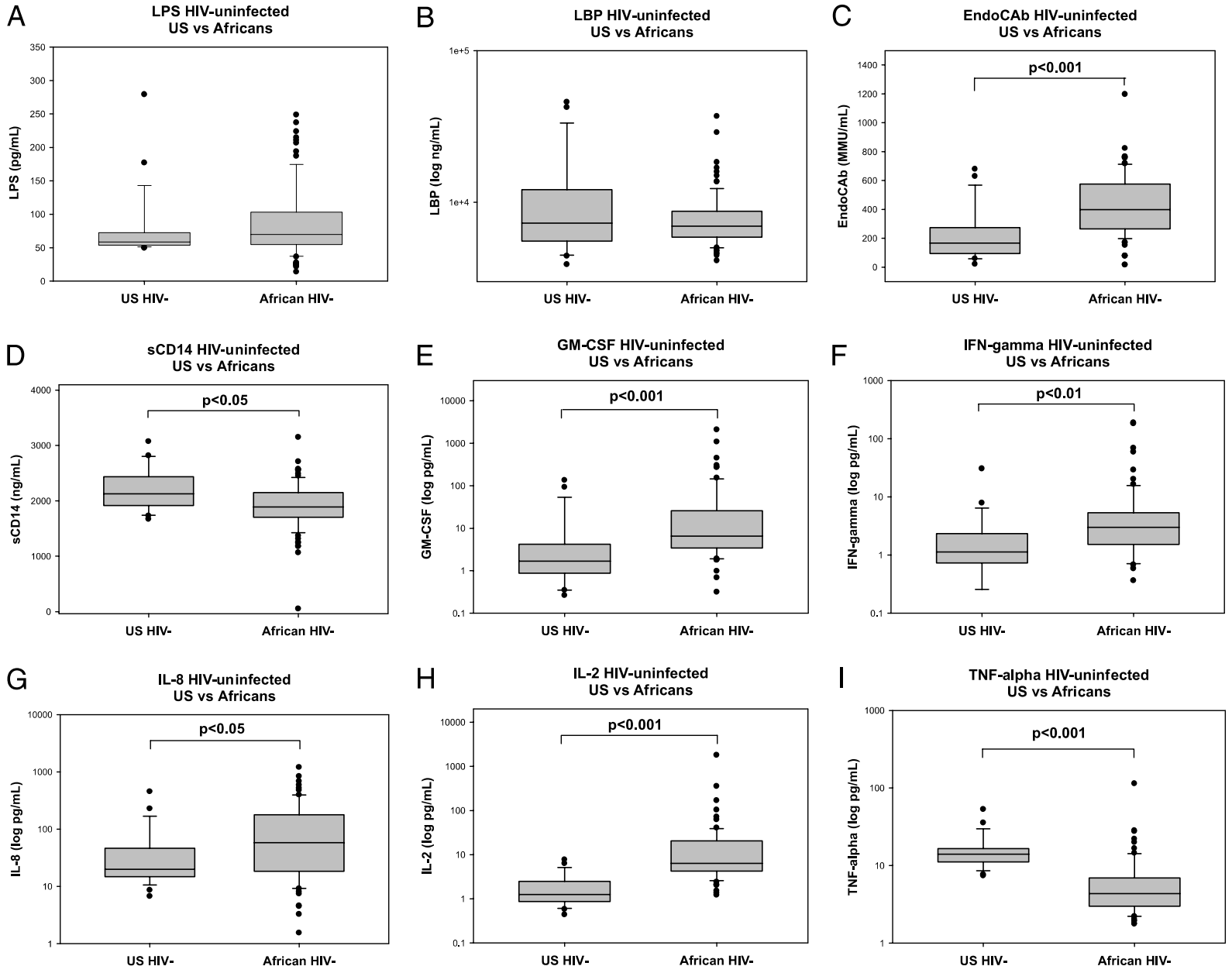




Study suggesting markers of microbial translocation (LPS, endoCAB, sCD14) associated with HIV disease progression

Small Sample Size, US population, cross-sectional study, not adjusted for any covariates

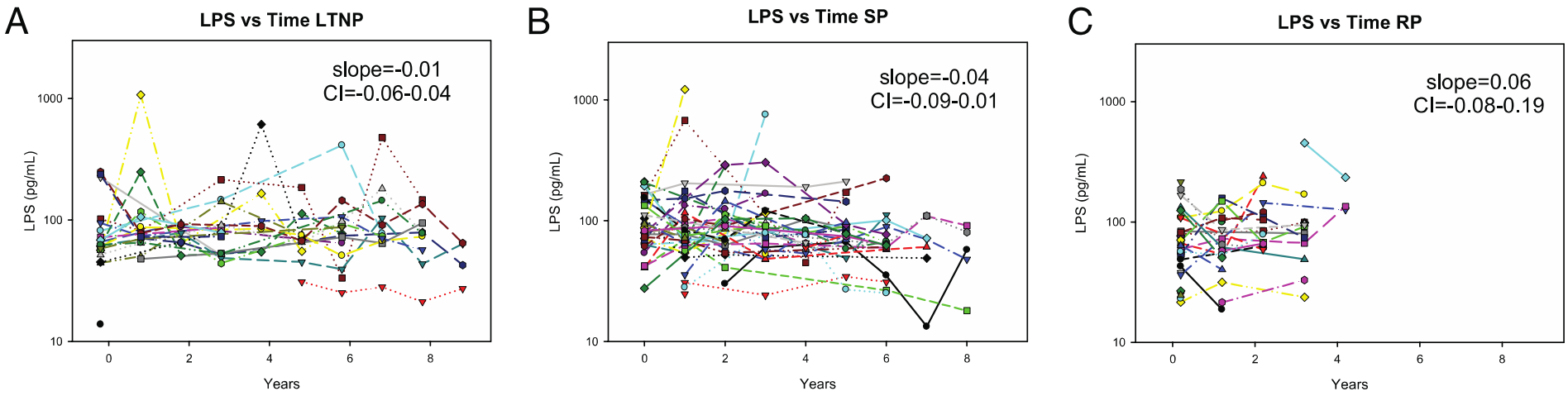
Brenchley et al., *Nat Med*, 2006

# Baseline Levels of Microbial Translocation Markers Differ Between African and U.S. HIV-Uninfected Subjects




Redd et al., *PNAS*, 2009

# Microbial Translocation and HIV in Uganda




No significant relationship of markers to HIV disease progression among LTNP, SP, RP

Redd et al., *PNAS*, 2009

# NWCS 319: The Association between Nutritional Status, Microbial Translocation, Inflammation and Soluble and Cellular Immune Activation Biomarkers and Highly Active Anti-retroviral Therapy (HAART) Outcomes in Resource-Limited Settings using A5175 data

NIH R01 AI 080417

# NWCS319 Methods

- Nested case-cohort study within ACTG PEARLS randomized trial of 1575 HIV-infected treatment-naïve adults in 9 countries (PLoS Med 2011).
  - Malawi, South Africa, Zimbabwe, Haiti, Peru, Brazil, Thailand, India and US
- A random sub-cohort sample of 30 HIV infected treatment-naïve adults were selected from each country (sub-cohort size: 270)
- Primary endpoint (cases): WHO stage 3/4 event or death by 96 weeks

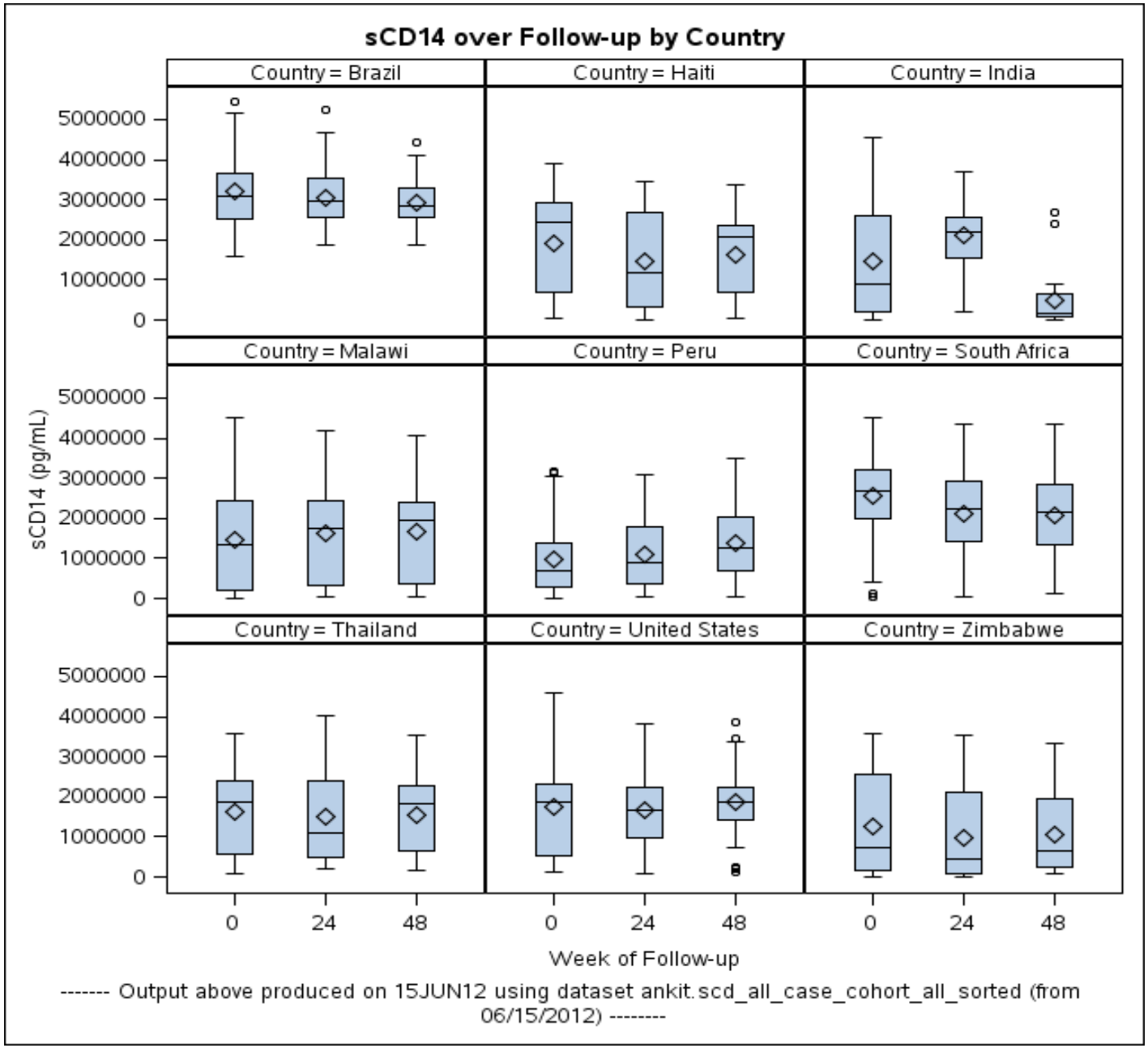
# Biomarkers analyzed in NWCS319

Markers of infection/inflammation
- C-Reactive Protein

Microbial translocation markers
- Soluble CD14 (sCD14)
- EndoCab (IgM)
- Lipopolysaccharide (LPS)

Plasma cytokines
- Interferon-gamma (INF-Gamma)
- Tumor necrosis factor alpha (TNF-alpha)
- IL-6
- IP-10
- IL-18

Activated T-Cell Markers
- CD4+/DR+/38+
- CD8+/DR+/38+




NWCS319 Study Team Balagopal CROI 2012

# Novel therapeutic agents need study in non-US settings

- Phase I

Sevelemer (antiLPS), anti PD1 Ab, anti IL-6 Ab, anti IFN alpha AB, sirolimus

- Phase II

Statins, ASA, Cox-2 inhibitor, methotrexate, chloroquine/hydroxychloroquine, probiotics, rifaximin, acyclovir, ACE/ARBs, mesalazine, IL7

# Many unanswered questions

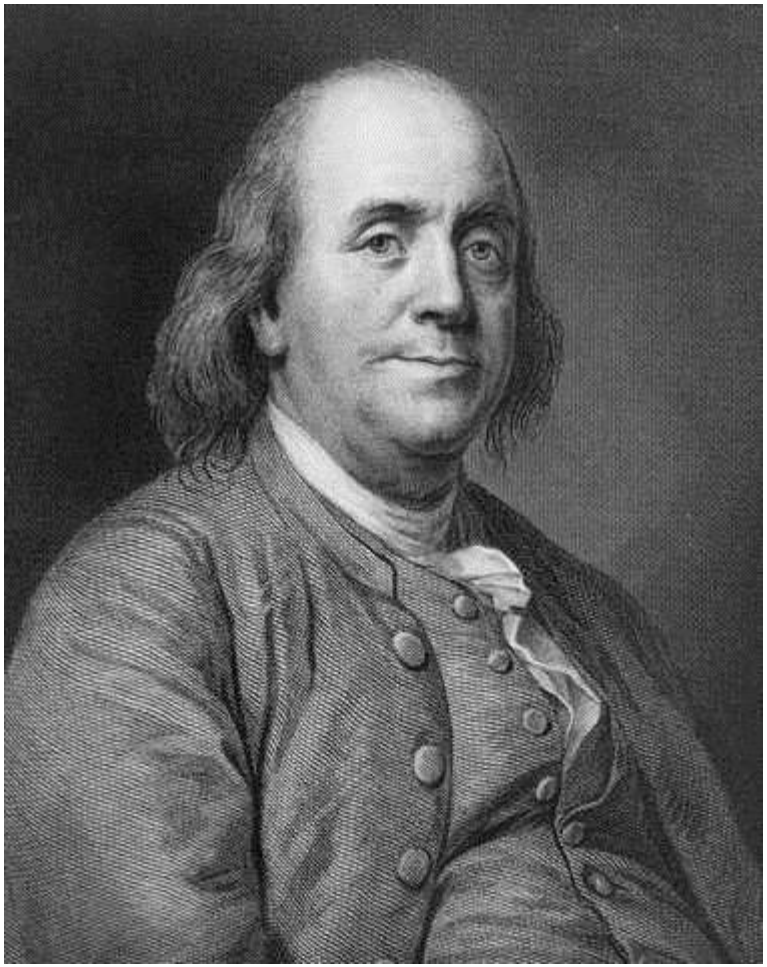
- What are the best approaches to manage HIV-associated metabolic complications and CVD risk in non-US settings
- What is the safety and efficacy of therapies that reduce inflammation and/or are immunomodulatory in the diverse non-US settings
  - Trials of Statins, ASA, anti-inflammatory not just pertinent to US/high income settings

# How to Beat Metabolic Complications & Inflammation

- Use ARVs that have less metabolic complications
- Continue HIV medications. Stay undetectable
- Don’t start smoking, Stop smoking if you do
- Maintain normal weight
- If overweight, lose at least 5-10% of body weight
- Exercise
- Have a healthy diet
- Cut down on alcohol, avoid drugs

“An ounce of prevention is worth a pound of cure”

Benjamin Franklin



# Acknowledgments





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