Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za

Lipids and bone density in HIV-infected people on ART

Joel Dave
UCT/GSH

Global deaths
2012

56 million deaths

38 million (68%) non-communicable diseases (NCDs)

Cardiovascular Dx	17.5 million (46%)
Cancers	8.2 million (22%)
Chronic Lung Dx	4.0 million (11%)
Diabetes	1.5 million (4%)

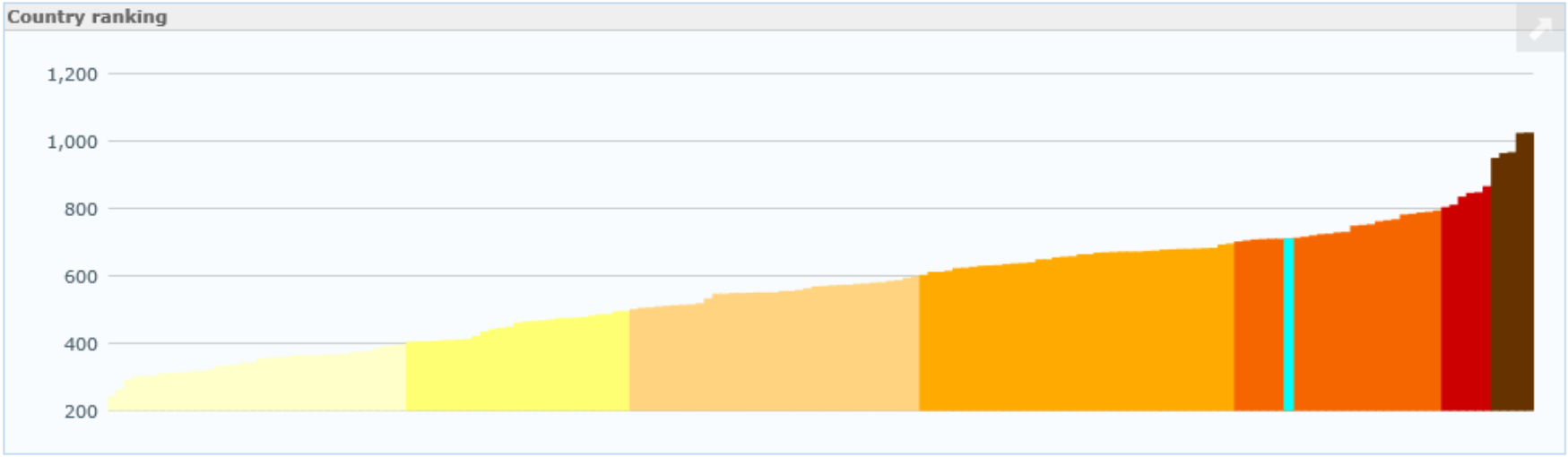
16 million (40%) were in people < 70 years old

Low- and Middle-income countries
28 million of all deaths due to NCDs
13 million (82%) were in people < 70 years old

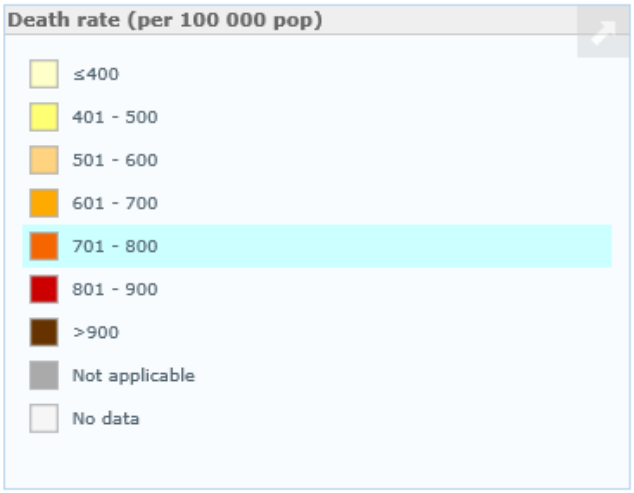
http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf

NCD death rate

2000–2012



Developed countries

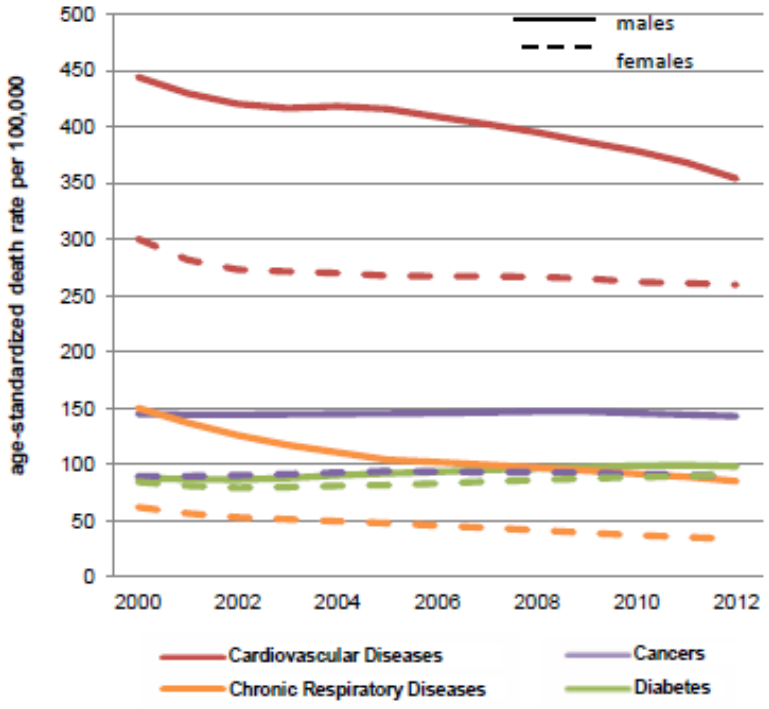


South Africa

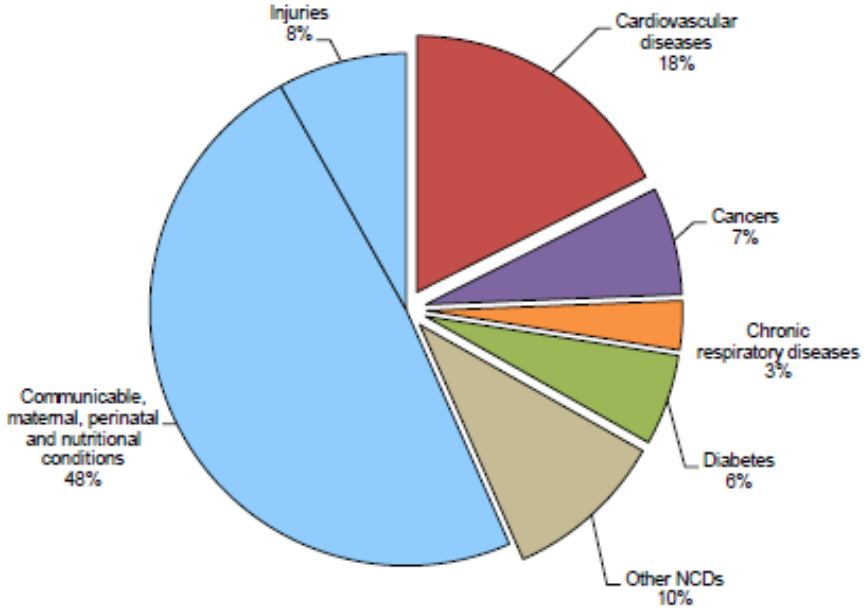
Mortality due to NCDs

South Africa

Age-standardized death rates*



Proportional mortality (% of total deaths, all ages, both sexes)*



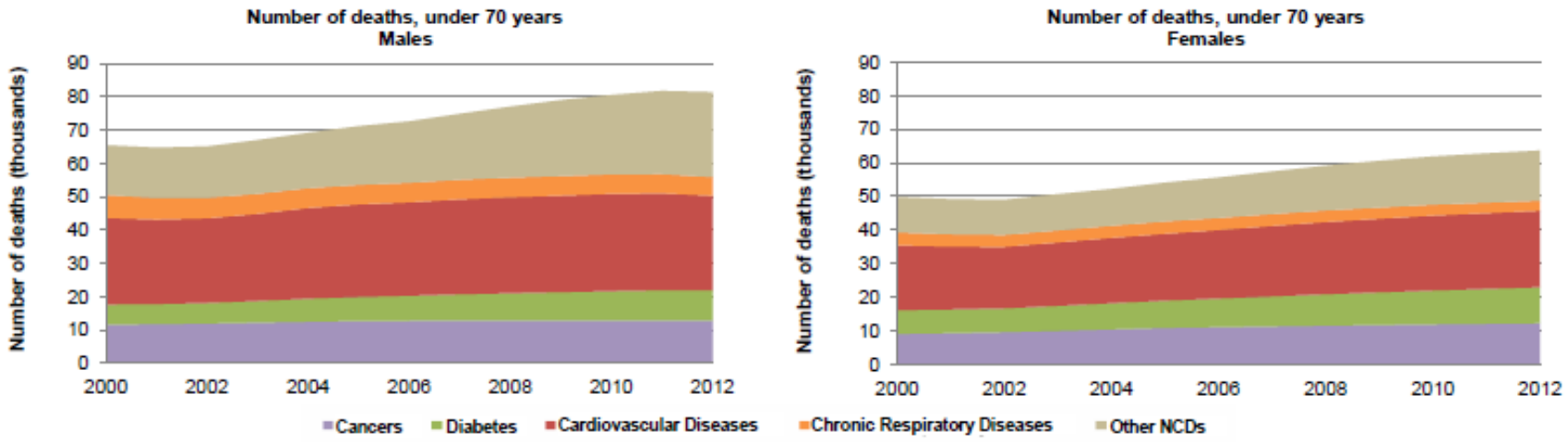
Total deaths: 608,000
NCDs are estimated to account for 43% of total deaths.

http://www.who.int/nmh/countries/zaf_en.pdf

Premature mortality due to NCDs

South Africa

The probability of dying between ages 30 and 70 years from the 4 main NCDs is 27% .

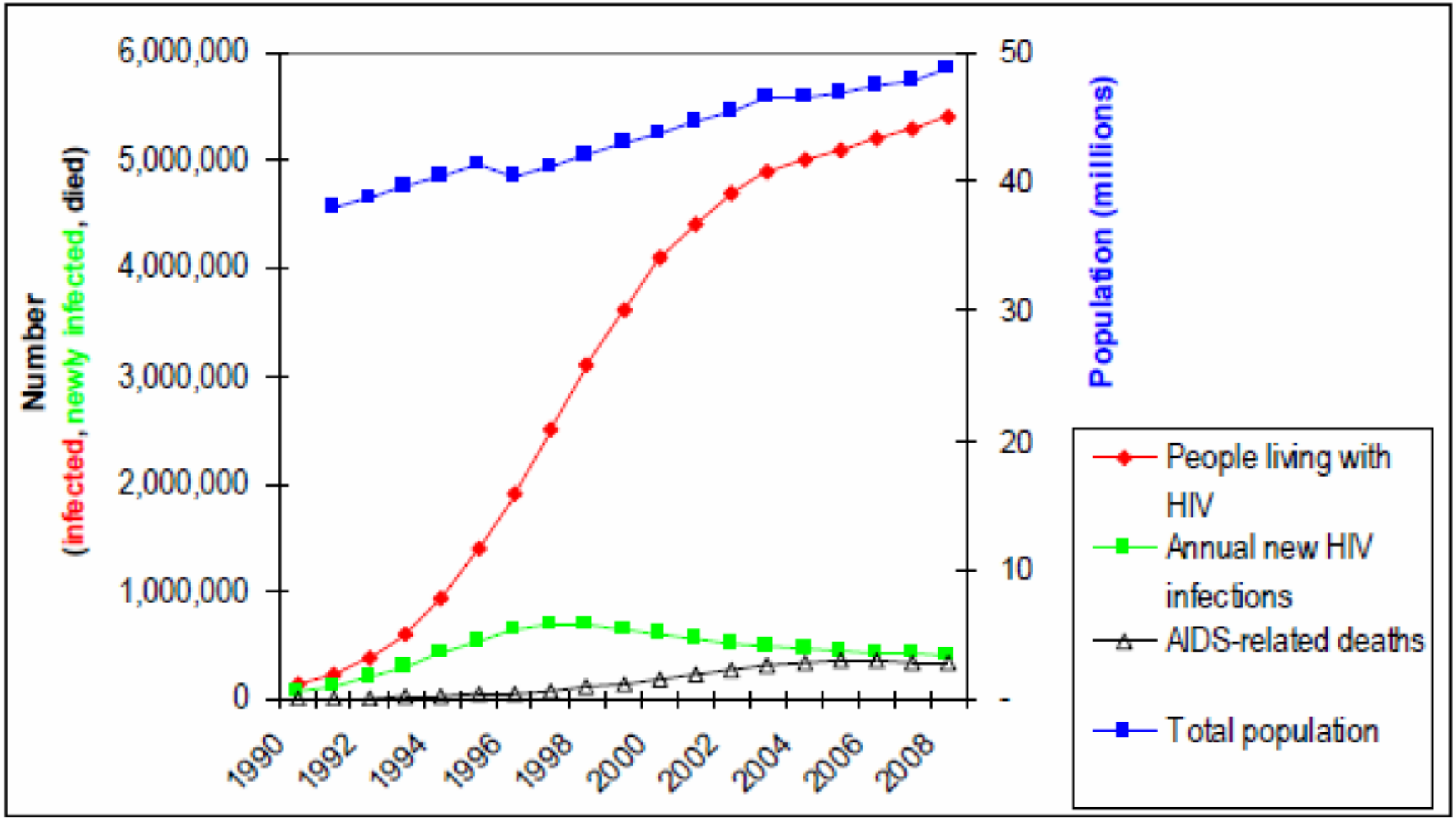


Adult risk factors	males	females	total
Current tobacco smoking (2011)	28%	8%	18%
Total alcohol per capita consumption, in litres of pure alcohol (2010)	18.4	4.2	11.0
Raised blood pressure (2008)	35.2%	32.4%	33.7%
Obesity (2008)	21.0%	41.0%	31.3%

http://www.who.int/nmh/countries/zaf_en.pdf

People living with HIV

Adults Aged 15-49 Years In South Africa (1990-2008)



http://www.unaids.org/sites/default/files/country/documents//ce_ZA_Narrative_Report.pdf

Are HIV-infected people on ART more at risk of premature death from a NCD than HIV-uninfected people?

Increase in NCDs as people age

Premature death from CDs

HIV-infected patients → ART → Healthy aging

Premature death from NCDs

Are HIV-infected people on ART more at risk of premature death from a NCD than HIV-uninfected people?

Dyslipidemia and ischaemic heart disease

HIV-infection causes dyslipidemia

Acute infection[1]

↓ LDL

Chronic infection [2 3]

↓ HDL

↑ TG

[1]Stein JH *et al* (2008). *J Clin Lipidol*. 2(6):464–71; [2]Riddler SA *et al.* (2007). *HIV Med*. 8(5):280–7
[3]Riddler SA *et al* (2003). *JAMA*. 289(22):2978–82

ART can cause dyslipidemia

Effect of protease inhibitors on serum lipids

Table 1
Lipid changes associated with PI use

	Lipids			
PI	Total Cholesterol	HDL-C	LDL-C	Triglycerides
Atazanavir	↔	↔	↔ By 16%	↓ By 12%
Atazanavir + ritonavir and Atazanavir/cobicistat	↔	↔	↑	↑
Darunavir + ritonavir	↔	↔		↑
Fosamprenavir + ritonavir	↑↑	↔		↑↑
Lopinavir/ritonavir (coformulated)	↑↑ (Additional increase over ritonavir alone)	↔ N	al increase over ritonavir alone	↑↑ No additional increase over ritonavir alone
Nelfinavir	↑			↑
Ritonavir (low dose for boosting)	↑ By 10%		↑ By 16%	↑↑ By 26%
Saquinavir + ritonavir	↑↑		↑	↑
Tipranavir + ritonavir	↑↑	ot known	Not known	↑↑↑

Key: ↑, some increase; ↑↑, mod… increase; ↓, some decrease; ↔, no significant change.
Boosting means use as a … another drug.
From Myerson M, Ma… anagement of lipid disorders in patients living with HIV. J Clin Pharmacol 2015. [Epub ahead of print]; with permission.

DEVELOPED COUNTRIES

Myerson M (2016). *Endocrinol Metab Clin N Am.* 45: 141–169

ART can cause dyslipidemia

Effect of NNRTIs on serum lipids

Table 2
Lipid changes associated with NNRTI use

	Lipids				
NNRTI	Total Cholesterol	HDL-C			Triglycerides
Efavirenz	↑	↑			↑
Etravirine	↔	↔		↔	↔
Nevirapine	↑	↑↑ l		↑	↑ Lower increase than with efavirenz
Rilpivrine	↑		wn	↑ Lower increase than with efavirenz	↑ Lower increase than with efavirenz

Key: ↑ , moderate increase; ↑↑↑, large increase; ↓, some decrease; ↔, no signif-
ica

M, Malvestutto C, Aberg JA. Management of lipid disorders in patients living with HIV. armacol 2015. [Epub ahead of print]; with permission.

DEVELOPED COUNTRIES

Myerson M (2016). *Endocrinol Metab Clin N Am.* 45: 141–169

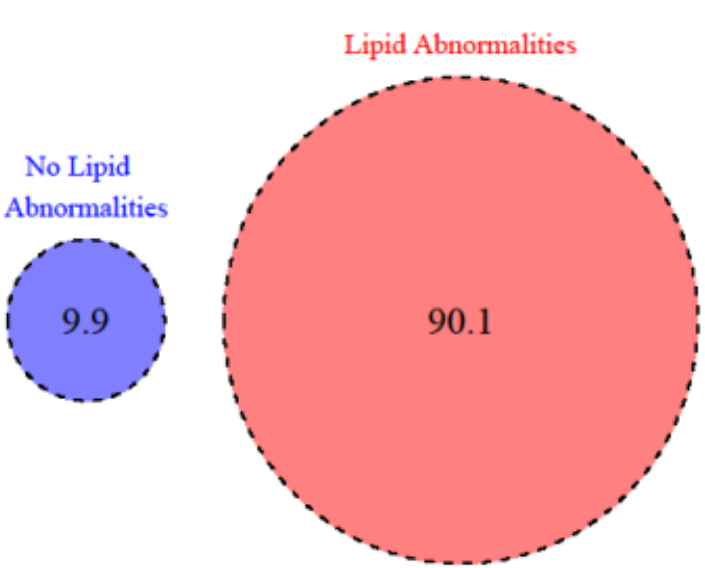
Phenotype of HIV-infected patients

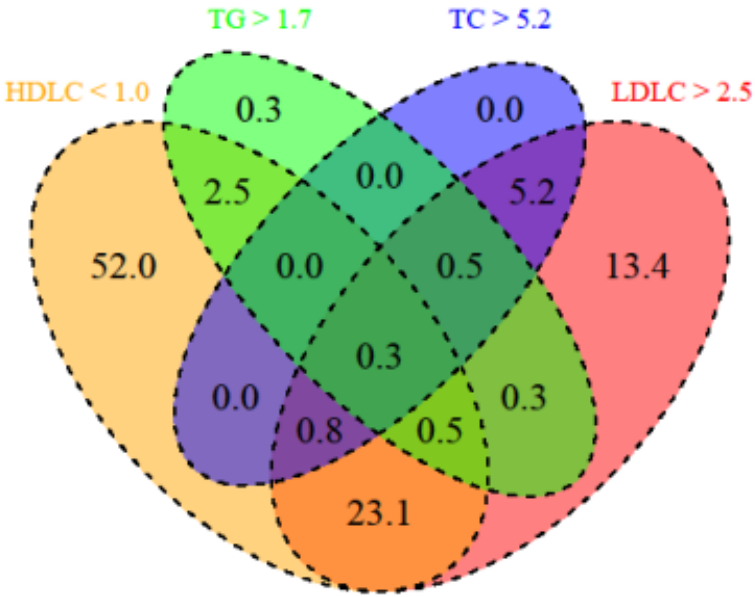
	Developed countries	Sub-Saharan Africa
Phenotype		
Age	45	35
Gender	Male	Female
Race	White	Black
Regimen	**PI-based**	**NRTI-based**

Studies +++++

Distribution of lipid abnormalities in HIV-infected South Africans

Treatment naïve participants (%)

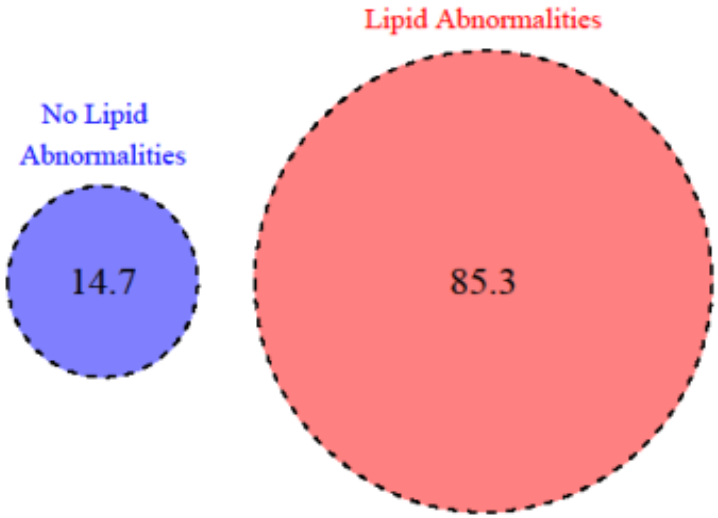


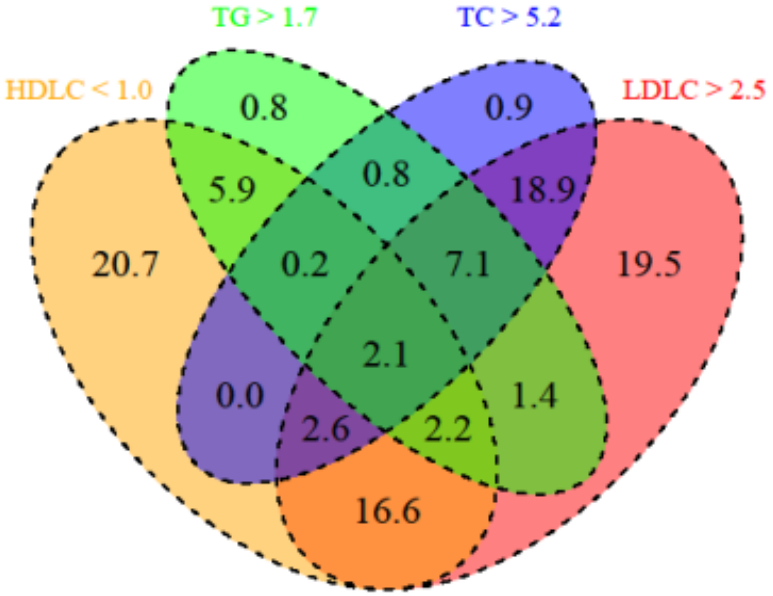


Dave JA *et al* (2016). PLoS One. 11(3):e0151911

Distribution of lipid abnormalities in HIV-infected South Africans

Participants receiving ART (%)





Dave JA *et al* (2016). PLoS One. 11(3):e0151911

Prevalence of dyslipidemia in HIV-infected South Africans

McHAART Study

ART vs ART-naïve

↑ triglycerides (TG), ↑ total cholesterol (TC),
↑ LDL-cholesterol (LDLC) and ↑ HDLC

Severe dyslipidaemia, defined as LDLC >4.9 mmol/l or triglycerides >5.0 mmol/L, was an uncommon finding

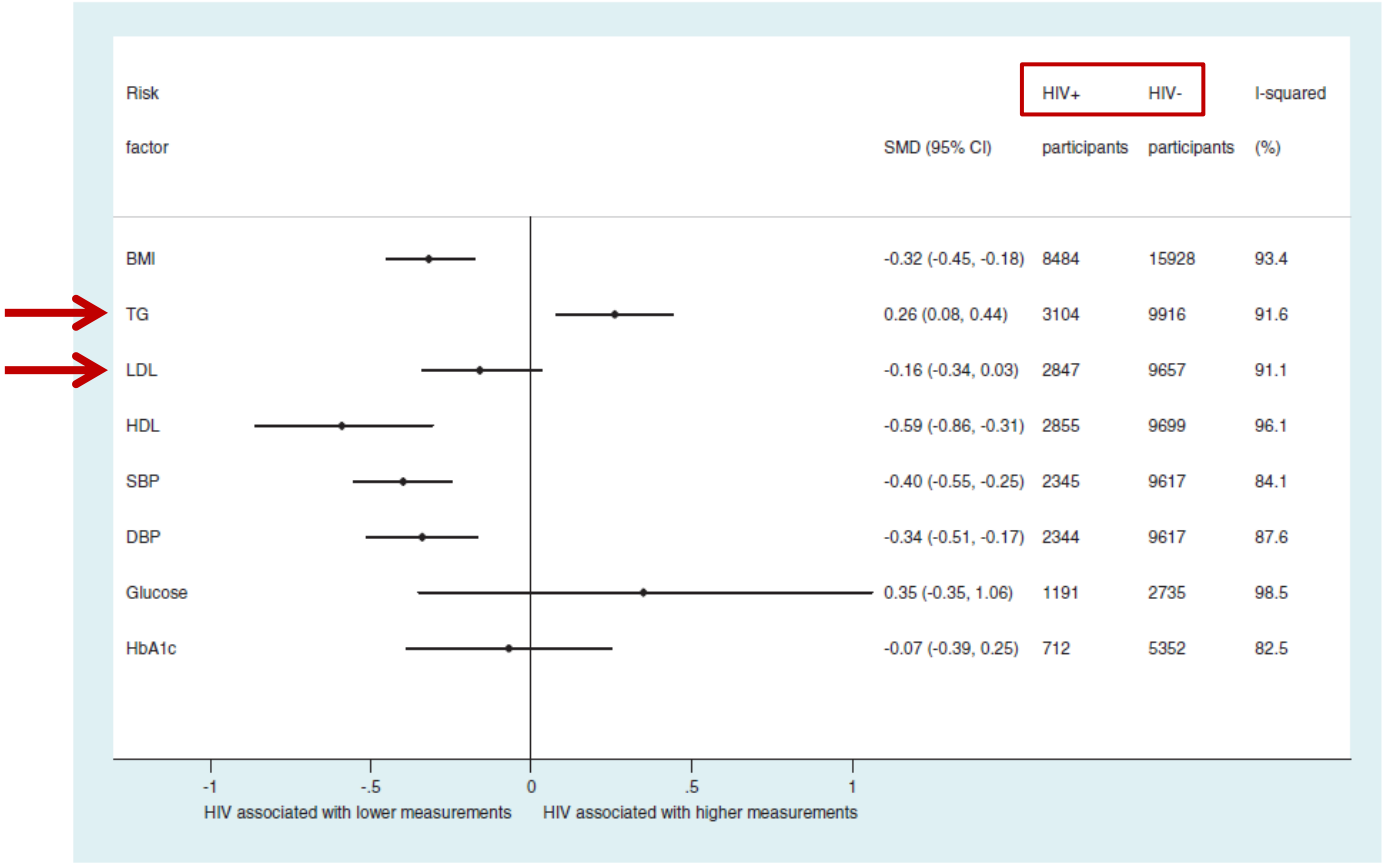
Dave JA *et al* (2016). PLoS One. 11(3):e0151911

Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis

David G Dillon,[1,2] Deepti Gurdasani,[1,2] Johanna Riha,[1,2] Kenneth Ekoru,[1,2,3] Gershim Asiki,[3] Billy N Mayanja,[3] Naomi S Levitt,[4] Nigel J Crowther,[5] Moffat Nyirenda,[6] Marina Njelekela,[7] Kaushik Ramaiya,[8] Ousman Nyan,[9] Olanisun O Adewole,[10] Kathryn Anastos,[11] Livio Azzoni,[12] W Henry Boom,[13] Caterina Compostella,[14] Joel A Dave,[15] Halima Dawood,[16] Christian Erikstrup,[17] Carla M Fourie,[18] Henrik Friis,[19] Annamarie Kruger,[20] John A Idoko,[21] Chris T Longenecker,[22] Suzanne Mbondi,[23] Japheth E Mukaya,[24] Eugene Mutimura,[11] Chiratidzo E Ndhlovu,[25] George Praygod,[26] Eric W Pefura Yone,[27] Mar Pujades-Rodriguez,[28,29] Nyagosya Range,[26] Mahmoud U Sani,[30] Aletta E Schutte,[18] Karen Sliwa,[31] Phyllis C Tien,[32] Este H Vorster,[33] Corinna Walsh,[34] Rutendo Zinyama,[35] Fredirick Mashili,[7] Eugene Sobngwi,[36,37] Clement Adebamowo,[38,39] Anatoli Kamali,[3] Janet Seeley,[3] Elizabeth H Young,[1,2] Liam Smeeth,[40] Ayesha A Motala,[41] Pontiano Kaleebu,[3] Manjinder S Sandhu[1,2]* and on behalf of the African Partnership for Chronic Disease Research (APCDR)

International Journal of Epidemiology 2013;42:1754–1771

Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis



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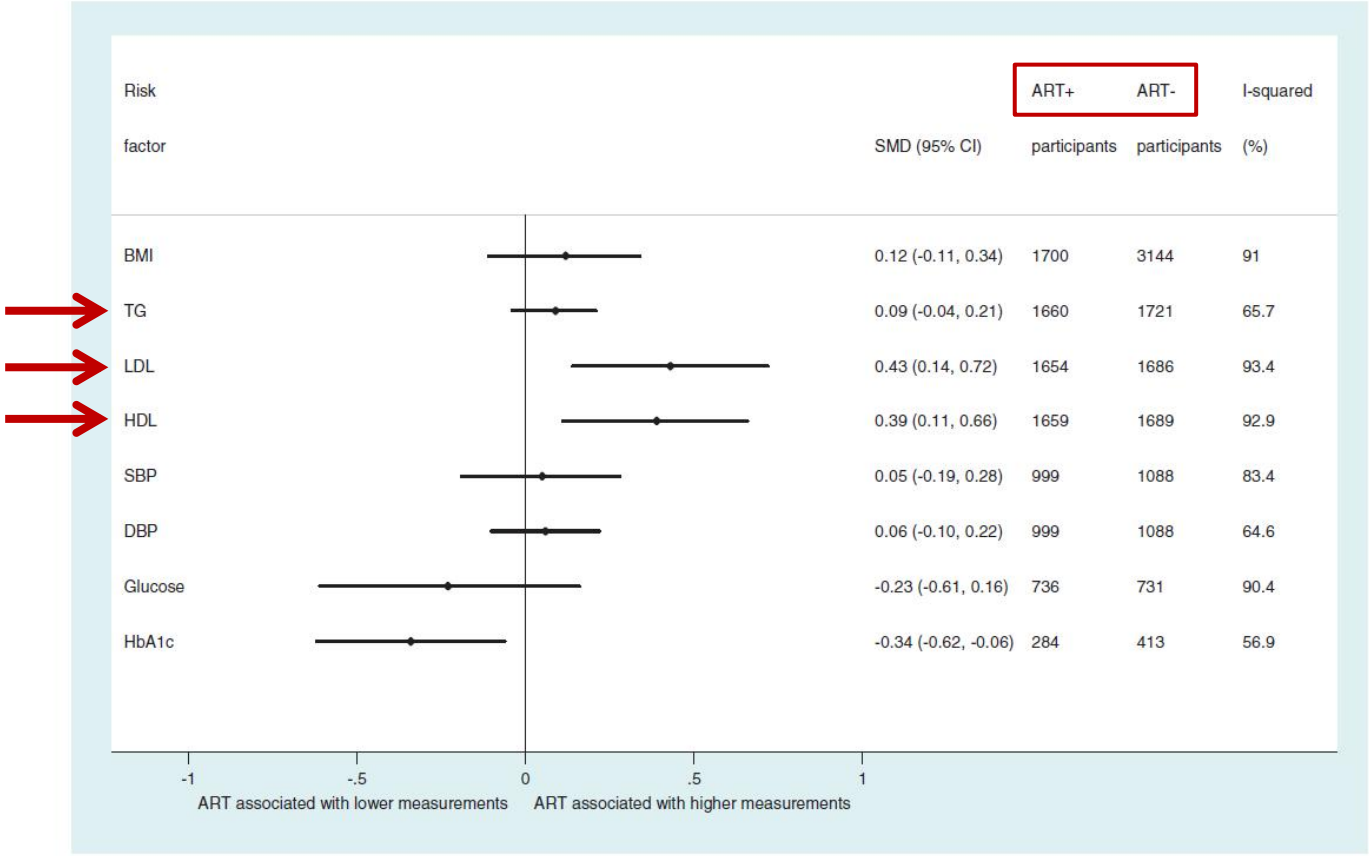


Dillon *et al* (2013). *International Journal of Epidemiology* 2013;42:1754–1771

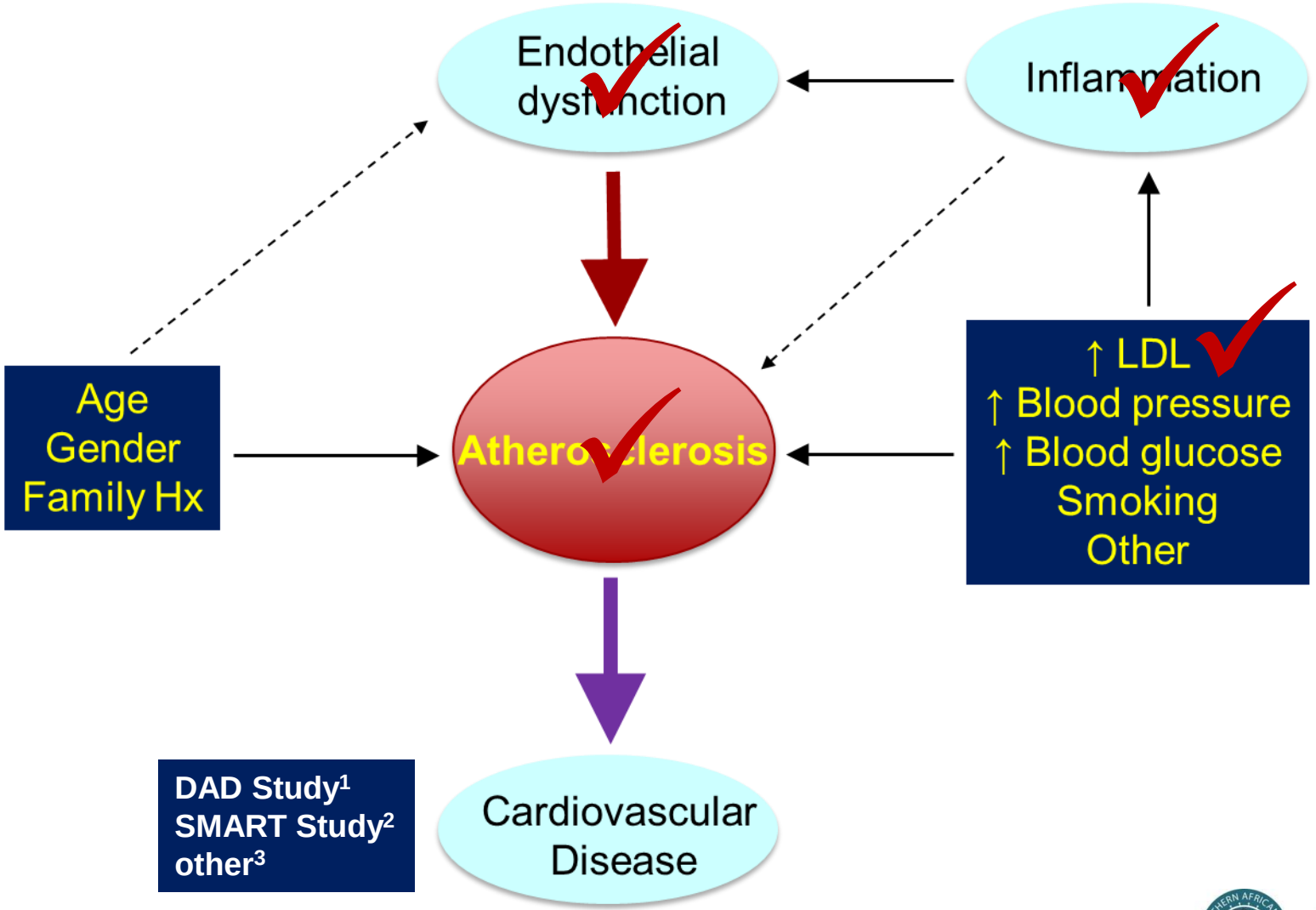
Is the dyslipidemia caused by HIV-infection and ART a risk factor for vascular disease in HIV-infected people?

?

Cardiovascular disease

Causes of Atherosclerosis

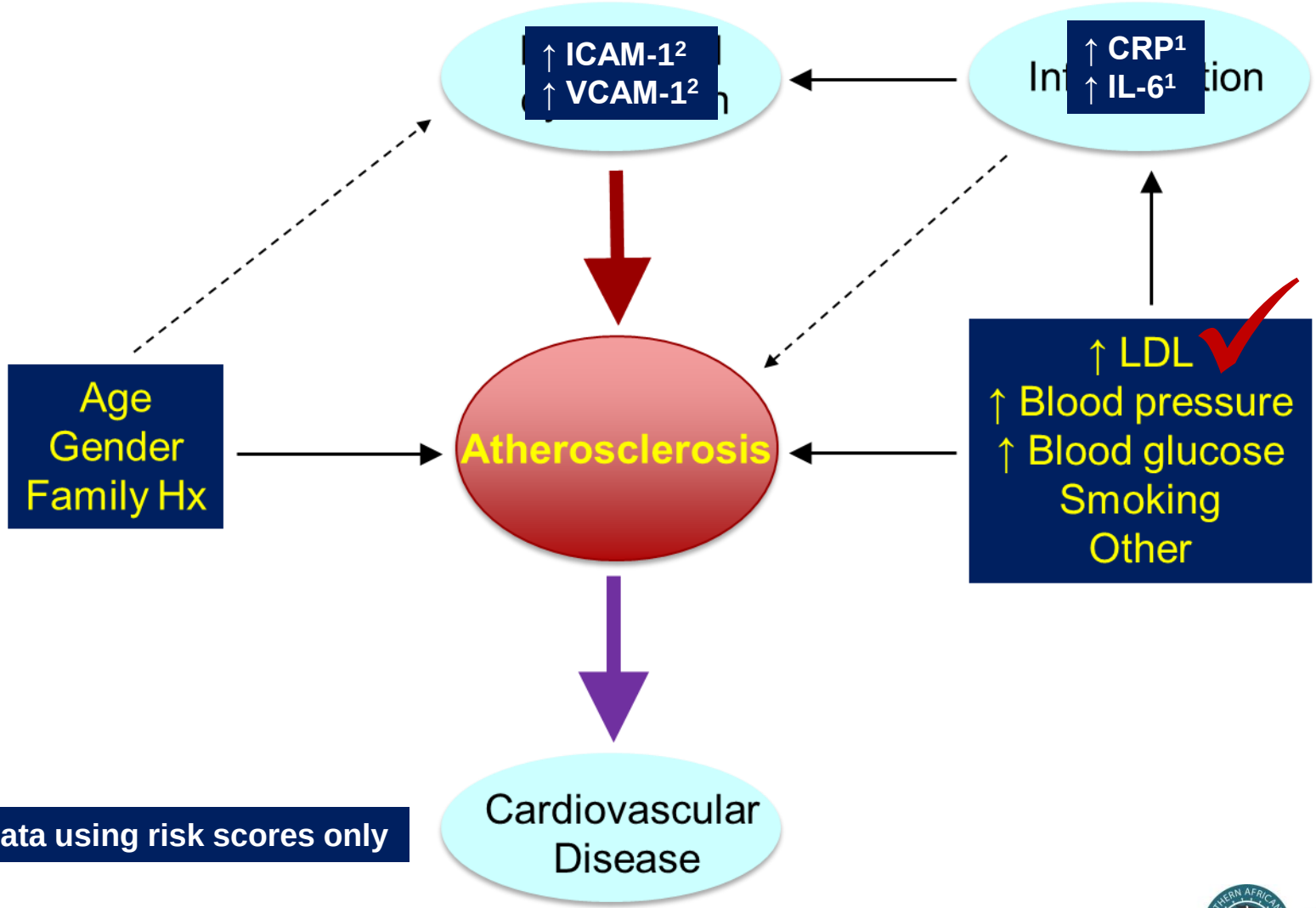
Developed Countries



[1]*N Engl J Med* 2007;356:1723-35; [2]*N Engl J Med* 2006;355:2283-96; [3]*JAMA Intern Med*. 2013 April 22; 173(8): 614–622

Causes of Atherosclerosis

South Africa



Data using risk scores only

[1]Fourie *et al* (2010). Lipids. 45 (1): 73-80; [2]Fourie *et al* (2011). Cardiovasc J Afrci. 22(3): 134-140

Risk stratification of HIV-infected people with dyslipidemia

No validated risk score or stratification scheme currently exists for patients infected with HIV

- Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) Study Group
- VACS Index (includes age, CD4 count, viral load, haemoglobin, AST, ALT, platelets, creatinine, and hepatitis C status)
- Framingham risk score

Diagnosis and management of dyslipidemia in HIV-infected people

There are currently no guidelines specifically for the diagnosis and management of dyslipidemia in patients infected with HIV

Use National Guidelines for the Management of Dyslipidemia in the general population

Guidelines for the Management of HIV-infection in South African Adults

- Fasting cholesterol and triglycerides if requires Lopinavir/Ritonavir (LPV/r)

  To identify those at risk of LPV/r related hyperlipidaemia.
  If above 6 mml/L, consider Atazanavir/Ritonavir instead of LPV/r

- Fasting cholesterol and triglycerides at month 3 if on LPV/r

Interaction of statins with ART

Table 4
Statin interactions with antiretroviral medication

Drug	PI	Effect on PI or Concomitant Drug Concentrations	Recommendation
Atorvastatin	ATV/r ATV	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary
	DRV/r FPV/r FPV SQV/r	DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg administered alone; FPV ± RTV ↑ atorvastatin AUC 130% to 153%; SQV/r ↑ atorvastatin AUC 79%	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary
	TPV/r	↑ atorvastatin AUC 836%	DO NOT COADMINISTER
Pravastatin	DRV/r	Pravastatin AUC ↑ 81%	Use lowest possible starting dose of pravastatin with careful monitoring
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment necessary
	SQV/r	Pravastatin AUC ↓ 47% to 50%	No dose adjustment necessary
Rosuvastatin	ATV/r LPV/r	ATV/r ↑ rosuvastatin AUC 3-fold and C_{max} ↑ 7-fold LPV/r ↑ rosuvastatin AUC 108% and C_{max} ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily
	DRV/r	Rosuvastatin AUC ↑ 48% and C_{max} ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities
	FPV ± RTV	No significant effect on rosuvastatin	No dosage adjustment necessary
	SQV/r	No data available	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities
	TPV/r	Rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	No dose adjustment necessary
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	CONTRAINDICATED, do not coadminister

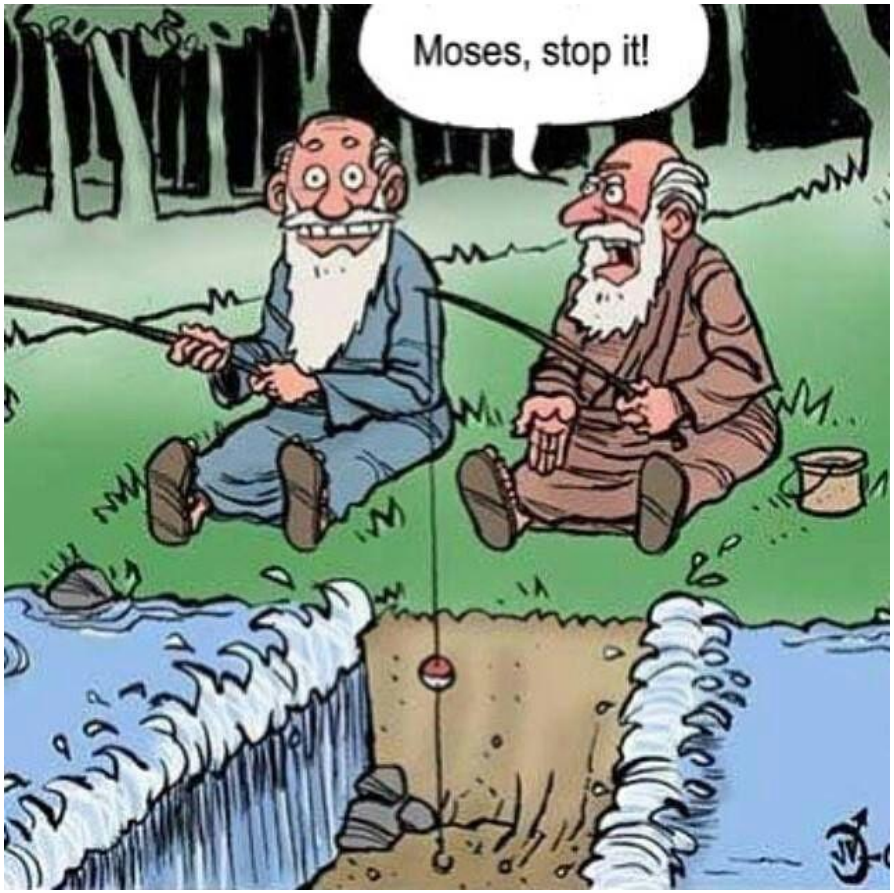
Myerson M (2016). *Endocrinol Metab Clin N Am.* 45: 141–169

SUMMARY

- Development of dyslipidemia in HIV-infected South Africans is a REAL risk with potentially significant consequences

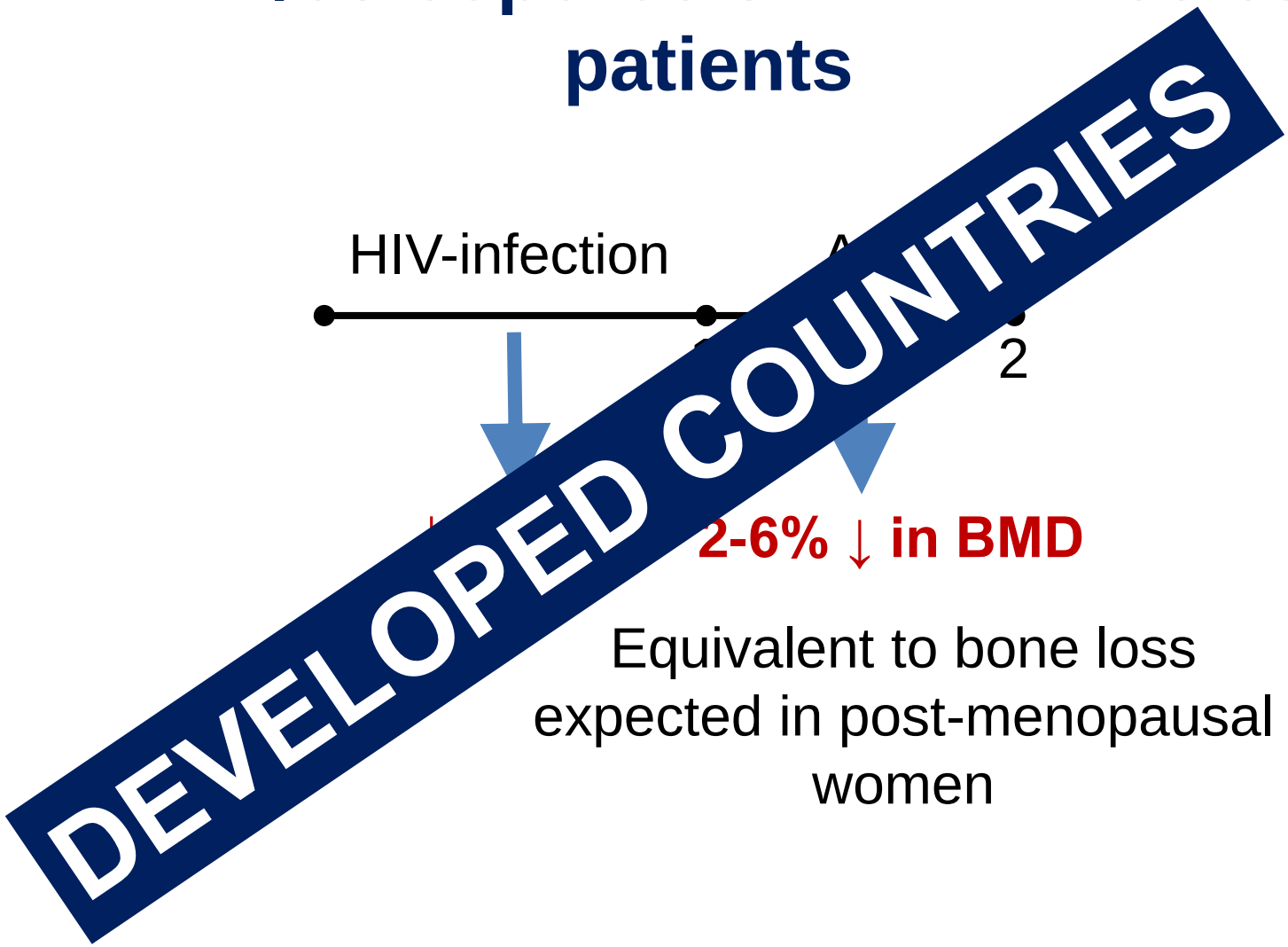
- Maintain a high index of suspicion and use good clinical acumen to decide who should be screened for metabolic complications and treated

- We need large, long-term randomised-controlled/observational studies to determine prevalence of cardiovascular disease and to determine a clinically applicable risk score to identify those needing intensive preventative strategies



Bone density in HIV-infected people

Increased prevalence of reduced BMD/osteoporosis in HIV-infected patients



Brown *et al* (2006). *AIDS*. 20(17):2165-2174

Prevalence of low BMD in HIV-infected South Africans

- **Bone mass, body composition and vitamin D status of ARV-naïve, urban, black South African women with HIV infection, stratified by CD_4 count[1]**

  → **No difference in BMD HIV-positive vs HIV-negative**

- **Antiretroviral Therapy, Especially Efavirenz, Is Associated with Low Bone Mineral Density in HIV-Infected South Africans[2]**

  → **Vitamin D status, use of efavirenz or lopinavir/ritonavir, weight, age and sex are significantly associated with lower BMD**

[1]Hamill *et al* (2013). *Osteoporosis Int*. 24(11):2855-61 [2] Dave *et al* (2015). *PLoS One*. 10(12): e0144286

RCTs comparing BMD in TDF-containing regimens to non-TDF-containing regimens

Study (number randomized)	Regimens	Time point for BMD changes	BMD change in TDF arm	BMD change in comparator arm	*P* value
Studies with nontenofovir alafenamide-containing comparator arm					
Gilead 903 (*n*=602) [24]	EFV/TDF/FTC vs. EFV/d4T/3TC	Week 144	LS: −2.2% TH: −2.8%	LS: −1.0% TH: −2.4%	0.001 0.06
ACTG A5202 substudy A5224s (*n*=269) [25]	ATV/r vs. EFV + TDF/FTC vs. ABC/3TC	Week 96	LS: −3.3% TH: −4.0%	LS: −1.3% TH: −2.6%	0.004 0.024
ASSERT (*n*=385) [26]	EFV/TDF/FTC vs. EFV/ABC/3TC	Week 48	LS: −2.4% TH: −3.6%	LS: −1.6% TH: −1.9%	0.036 <0.001
NEAT substudy (*n*=146) [27▪]	DRV/r/FTC/TDF vs. DRV/r/RAL	Week 48	LS: −2.5% TH: −3.3%	LS: −1.0% TH: −0.7%	0.046 <0.001
PROGRESS (*n*=209) [28]	LPV/r/FTC/TDF vs. LPV/r/RAL	Week 96	Total: −2.5%	Total: +0.7%	<0.001
RADAR (*n*=85) [29]	DRV/r/FTC/TDF vs. DRV/r/RAL	Week 48	Total: −7.0 g/cm2	Total: +9.2 g/cm2	0.002
ACTG A5303 (*n*=262) [30]	DRV/r/FTC/TDF vs. DRV/r/FTC/MVC	Week 48	LS: −2.4% TH: −2.4%	LS: −0.9% TH: −2.4%	
Studies with tenofovir alafenamide-containing comparator arm					
GS-292-0102 (*n*=171) [31]	EVG/COBI/FTC/TDF vs. EVG/COBI/FTC/TAF	Week 48	LS: −3.4% TH: −2.4%	LS: −1.0% TH: −0.6%	<0.001 <0.001
GS-US-292-0104 and GS-US-292–0111 (*n*=1744) [32▪▪]	EVG/COBI/FTC/TDF vs. EVG/COBI/FTC/TAF	Week 48	LS: −2.9% TH: −3.0%	LS: −1.3% TH: −0.7%	<0.001 <0.001
GS-US-299–0102 (*n*=153) [33]	DRV/COBI/FTC/TDF vs. DRV/COBI/FTC/TAF	Week 48	LS: −3.6% TH: −3.8%	LS: −1.6% TH: −0.8	0.003 <0.001

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BMD, bone mineral density; COBI, cobicistat; d4T, stavudine; DRV, darunavir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; LPV, lopinavir; LS, lumbar spine; MVC, Maraviroc; r, low-dose ritonavir (that is, ritonavir boosting); RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TH, total hip.

Grant *et al* (2016). *Curr Opin HIV AIDS*. 11:326–332

Comparative effectiveness of tenofovir in treatment-naïve HIV-infected patients

systematic review and meta-analysis

- 22 RCTs (8297 patients).

- TDF-based regimens significantly reduced:
  total cholesterol (-18.42 mg/dl; -22.80 to -14.0)
  LDL-cholesterol (-9.53 mg/dl; -12.16 to -6.89)
  HDL-cholesterol (-2.97 mg/dl; -4.41 to -1.53)
  triglycerides (-29.77 mg/dl; -38.61 to -20.92)
  bone mineral density (BMD) (hip: -1.41%; -1.87 to -0.94)
  glomerular filtration rate (eGFR) (-3.47 ml/minute; -5.89 to -1.06)

  over 48 weeks of follow-up

Hemkens *et al* (2015). *HIV Clin Trials.* 16(5):178-89

Mechanism of increased bone loss with tenofovir

- Direct effect on bone
- Proximal tubule dysfunction
  - Bicarbonate and phosphate wasting when severe
- Altered vitamin D metabolism.

↓ BMD = ↑ risk of fractures ?

↑ morbidity

↑ mortality

Increased prevalence of fractures in HIV-infected patients

Triant *et al* (2008)[1]
Increased prevalence of fractures in HIV-infe

HIV Outpatient Study[2]
5 826 HIV-infected patients vs HI adults (US general population)
Age-adjusted fractu d higher

Veterans Aging Coh tual Cohort (VASC-VC)[3]
40 115 HIV-infect negative controls
fract 24–32% higher

Wom ncy HIV Study (WIHS)[4]
H atients greater incidence of fragility fractures than HIV-uninfected pati

DEVELOPED COUNTRIES

[1]Triant *et al* (2008). *J Clin Endocrinol Metab.* 93(9): 3499-3504; [2]Young et al (2011). *Clin Infect Dis*. 52:1061–1068; [3]Womack et al (2011). PLoS One. 6:e17217; [4]Sharma et al (2015). *JAIDS*. 70:54–61.

Prevalence of fractures in HIV-infected South Africans

NO DATA FOUND

SUMMARY

- **Developed countries:** significant amount of data showing reduction in BMD and an increase in risk of fractures

- **Developing countries:** increasing data to show a reduction in BMD, no significant data yet on risk of fractures

- We need large, long-term studies to determine prevalence of low BMD and fracture risk as well as a risk score to identify those needing intensive preventative strategies

The End

Thank you for listening !!