Diabetes, Metabolic Syndrome & HIV

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BOTSWANA-UPENN PARTNERSHIP

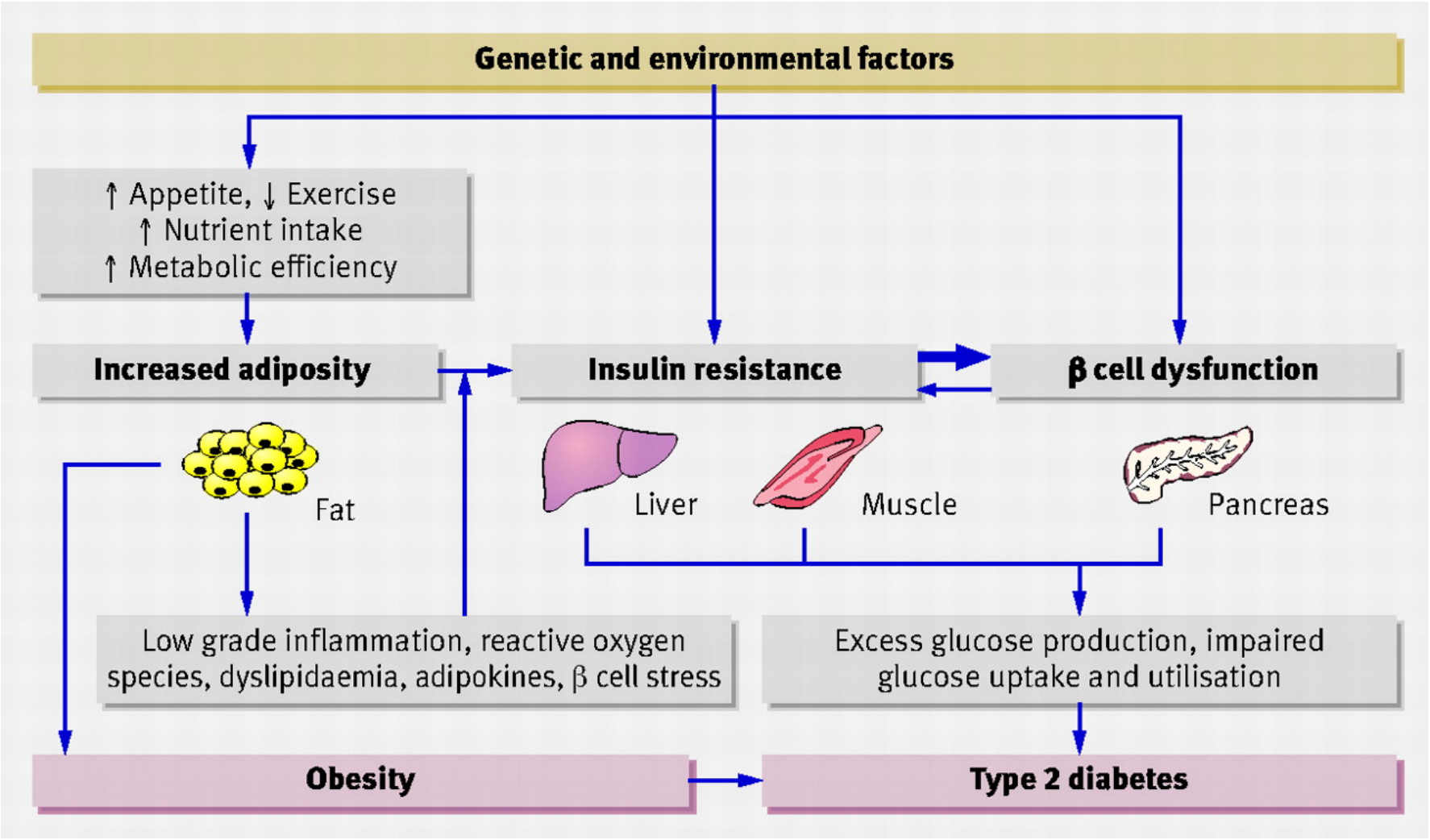
Outline

- Review recent advances in understanding of diabetes in HIV infection
- Describe the impact of HIV and ARVs on pathogenesis of diabetes and diabetic complications
- Discuss importance of prevention, screening and treatment of diabetes in people with HIV in Southern Africa

HIV and DM

DEFINITIONS

Pathogenesis of Diabetes



Bailey C J BMJ 201

BMJ

Diabetes Mellitus: Definitions[1]

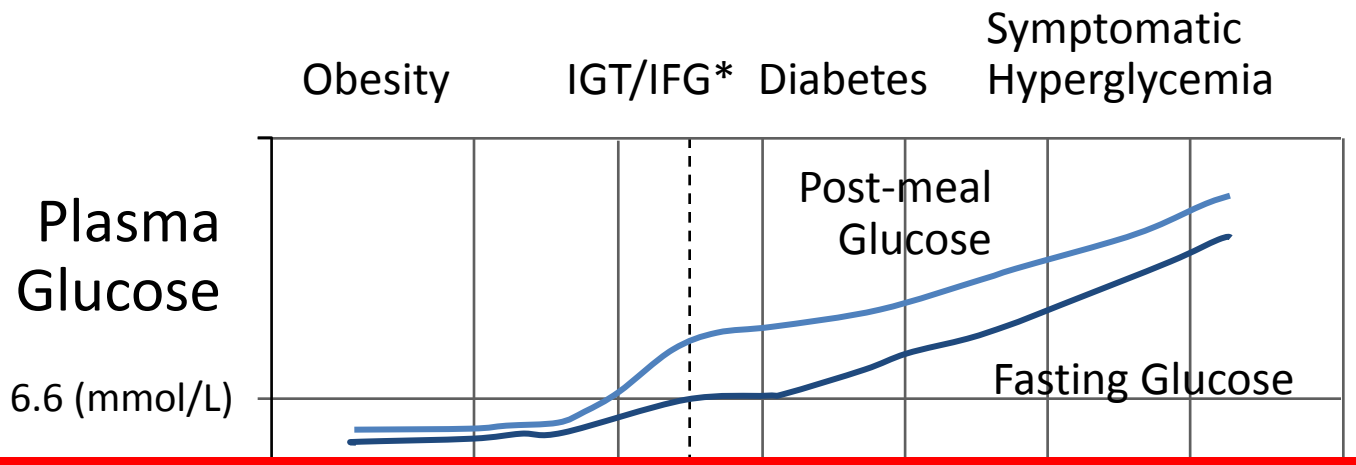
	Fasting plasma glucose (mg/dl)	Oral glucose tolerance test (OGTT) (mg/dl)*	HbA1c
Diabetes	>7.0 OR ➔	>11.1	>6.5%
Impaired Glucose Tolerance (IGT)	<7.0 AND ➔	7.8 -11.0	Pre-diabetes
Impaired fasting glucose (IFG)	6.1 – 6.9 AND ➔	<7.0	5.7-6.4%

OGTT indicated:

- In asymptomatic high-risk individuals
- If FPG is ≥ 5.6 - <7.0 mmol/l
- if random plasma glucose ≥ 5.6 - <11.1† (on screening)

1 WHO, 2009

Pathogenesis of Diabetes



IFG/IGT – Represent prodromal state

- 4-6 times risk of developing DM
- 70% go onto to develop DM
- Associated with increased CV morbidity & mortality

*IGT = impaired glucose tolerance

IFG= impaired fasting glucose

HIV and DM – Part 1

EPIDEMIOLOGY & PATHOGENESIS

Even in Africa, obesity a burgeoning problem – Health – Diet and nutrition | NBC News

THE Sun

Thursday, February 21, 2013

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News

GOT

65% Brit fellas are in fatties epidemic

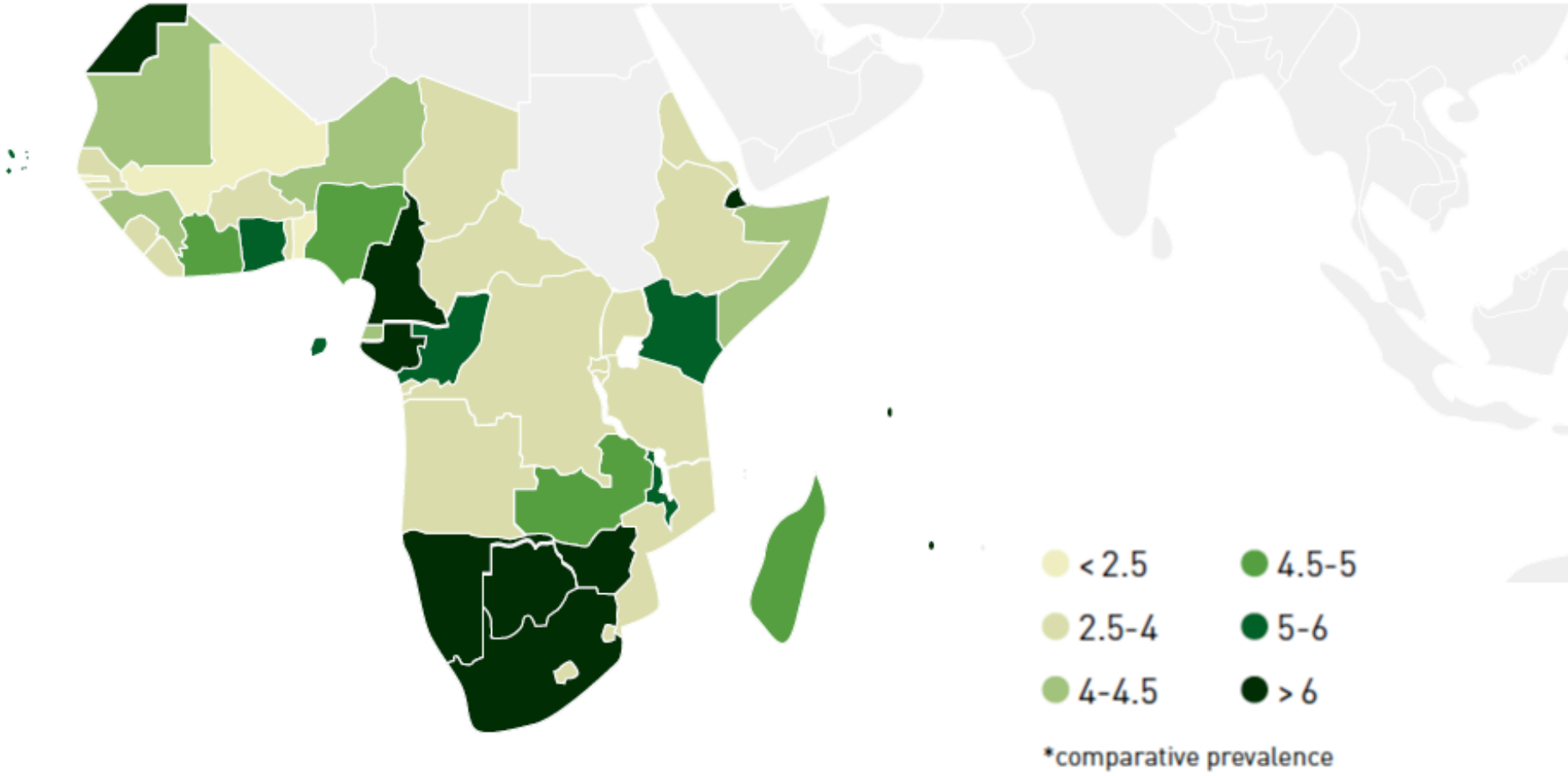
Photograph: Philipp Guelland/AFP/Getty Images

NBC NEWS

GSK study: 61% South Africans overweight

MRC study:
56% of women BMI>25
26% of men BMI>25

Prevalence estimates of diabetes (20-79 years), Africa Region, 2011



International Diabetes Foundation, 2011

Diabetes Prevalence in South Africa

Age-adjusted prevalence of diabetes in South Africa					
Study	**Location**	N	Age (years)	Method	DM
Peer (2012)	58% Increase in DM prevalence between 1998-208				13.1%
Erasmus (2001)	Urban	374	>20	OGTT	4.5%
Omar (1993)	Urban	499	>15	OGTT	5.3%
Levitt (1993)	Urban	729	>30	OGTT	8.0%
Mollentze (1995)	Urban	758	>25	OGTT	6.0%
Motala (2008)	Rural	1021	>15	OGTT	1.5%
Alberts (2005)	Urban	2106	>30	FBG	4.5%

Conservative estimates: **6.5%** of adults have diabetes – but age adjusted prevalence studies from urban populations indicate prevalence >**13%**

6 reasons why DM is on the rise in South Africa

HIV and DM

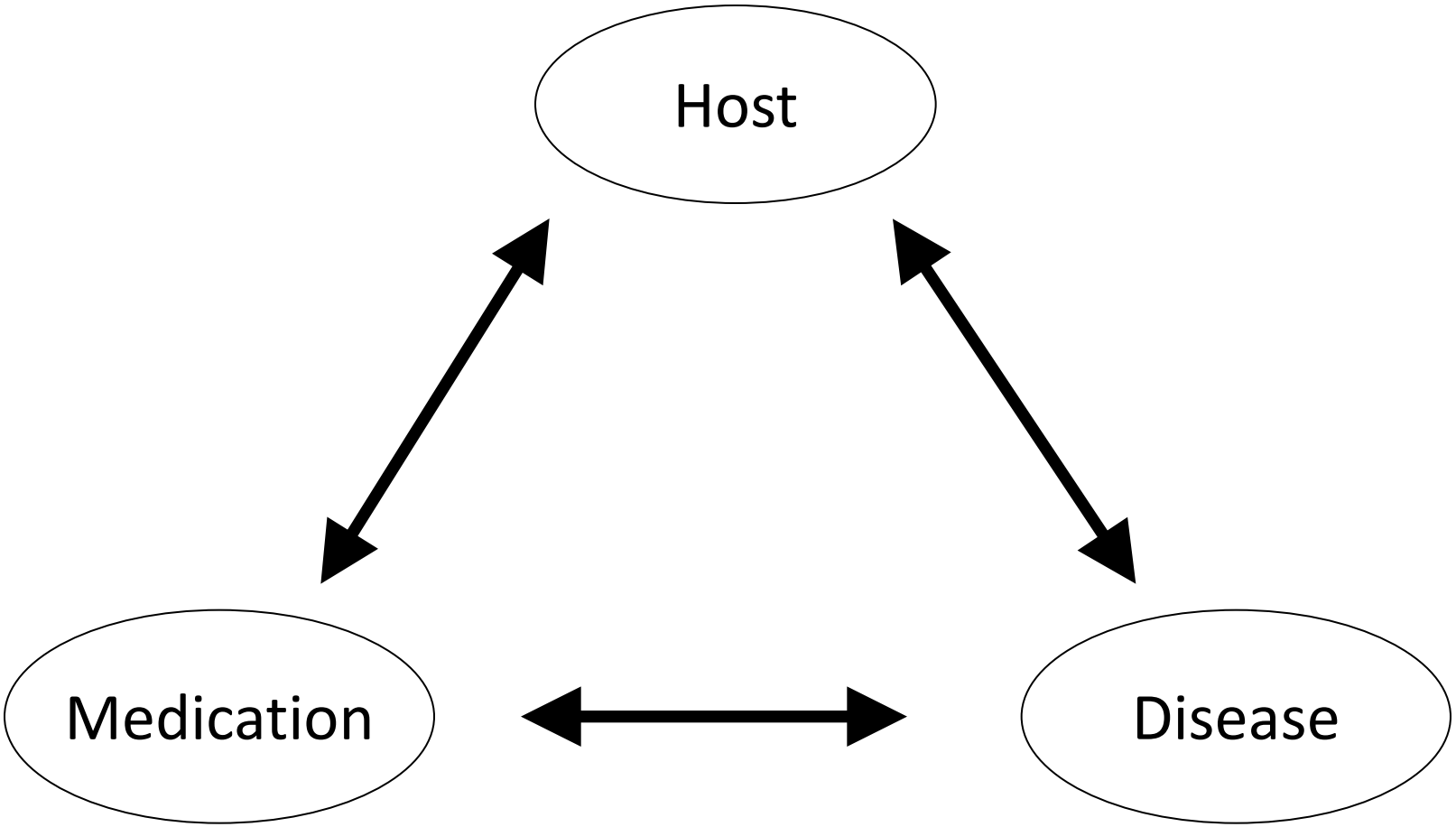
1 Levitt, Am J Clin Nutr, 2011

DM and HIV in Africa

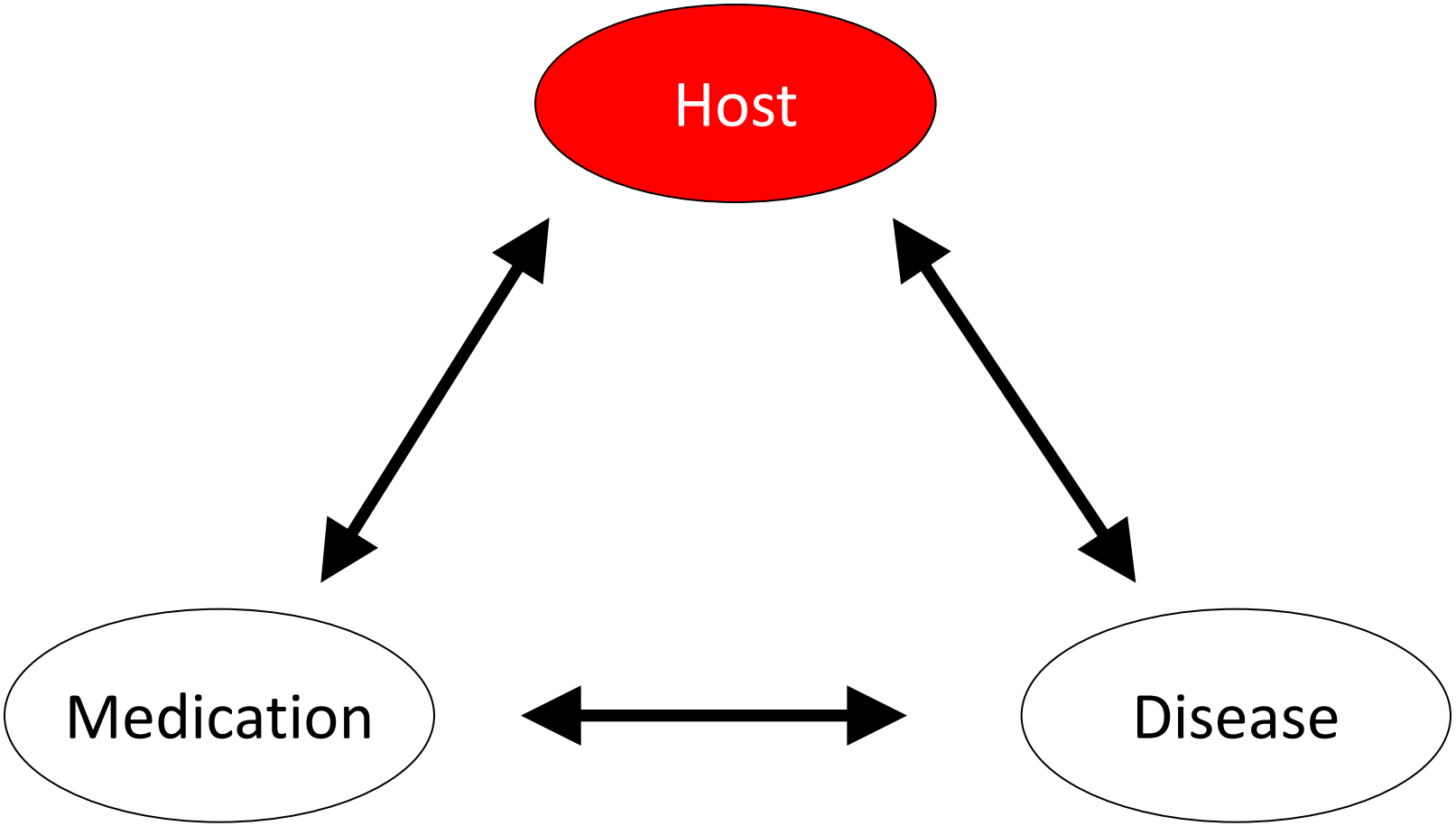
Age-adjusted prevalence of diabetes among PLWH in Southern Africa						
Study	N	Age (years)	On ART? (Y/N)	Years on HAART	DM	IFG
South Africa Dave (2011)	406	34 (mean)	N		3.4%	18.5%
	443	33 (mean)	Y	1.2	2.3%	23.5%
South Africa Julius (2011)	304	18-45	Y	1	1.3%*	
Botswana Hatsu (2009)	610	>15	N	0	4.6%	
		>40	N	0	10%	
Malawi Muronya (2011)	174	>18	Y	1	1.2%	
Rwanda Mutimara (2007)	571	>18	Y	>6 months		16-18%
Kenya Manuthu (2008)	295	>18	Y	>1 yr	1.5%	21.4%
Benin Zannou (2009)	79	>18	Y	>1 yr	1.5%	34-37%

* Young population. Yet >50% had lipid abnormalities

Multifactorial Aetiology of Diabetes in HIV



Multifactorial Aetiology of Diabetes in HIV



Risk Factors – Obesity

D:A:D cohort:[1] (n=33,389) 130,151 person years of patient follow up

Rates of DM:

x2 in overweight (BMI 26-30 kg/m^2)

x4 in obesity (BMI >30kg/m^2)

ANSR-CO8 Cohort[2]

HR for DM 1.91 (CI 1.22-2.99) for overweight participants

HR for DM 2.85 (CI 1.35-6.04) for obese participants

Waist-hip ratio more predictive than BMI

Increased sex-appropriate waist-hip ratio x3.87 risk of DM

1 – De Wit, Diabetes Care, 2008; 2 –Capeau, AIDS, 2012

Risk Factors – Obesity

Many determinant of obesity are same for HIV+ and HIV-

- Genetics –25%[1]
- Intra-uterine and early life influences
- Physical activity[2]
- Education[3]
- Sense of Coherence[4]
- Parity[5]

Implications:

RSA:

56% Women obese or overweight[6]

29% Men obese or overweight [6]

No data available on HIV infected population in RSA

1 – Bouchard, The genetics of obesity, 1994; 2 – Kruger, Nutrition, 2002; 3 Pouane, Obes Res, 2002. 4. Peer, PLOS One, 2012. 5. Weng, J Womens Health, 2004. 6. MRC 2012

Risk Factors – Age

Implications:

Estimated 3 million Africans with HIV > 50 years[3]

In RSA approx 20% of all HIV infected persons are > 50 years[4]

HR 3.6 in patients> 50 years
(95% CI 2.22-5.92)

1 – Hasse, CID, 2011; 2 –Capeau, AIDS, 2012; 3 – Negin, AIDS, 2012, ; 4 –SANAT, 2008

Risk Factors – Sex

- D:A:D study[1]:
  - Male sex associated with **60% higher risk** of diabetes compared to women
- WIHS study[2]:
  - HIV uninfected more obese, yet HIV-infected **x2** as likely to have DM

Take home message: Women on HAART have lower risk of DM compared to men, but DM develops with less adiposity and drug exposure compared to men

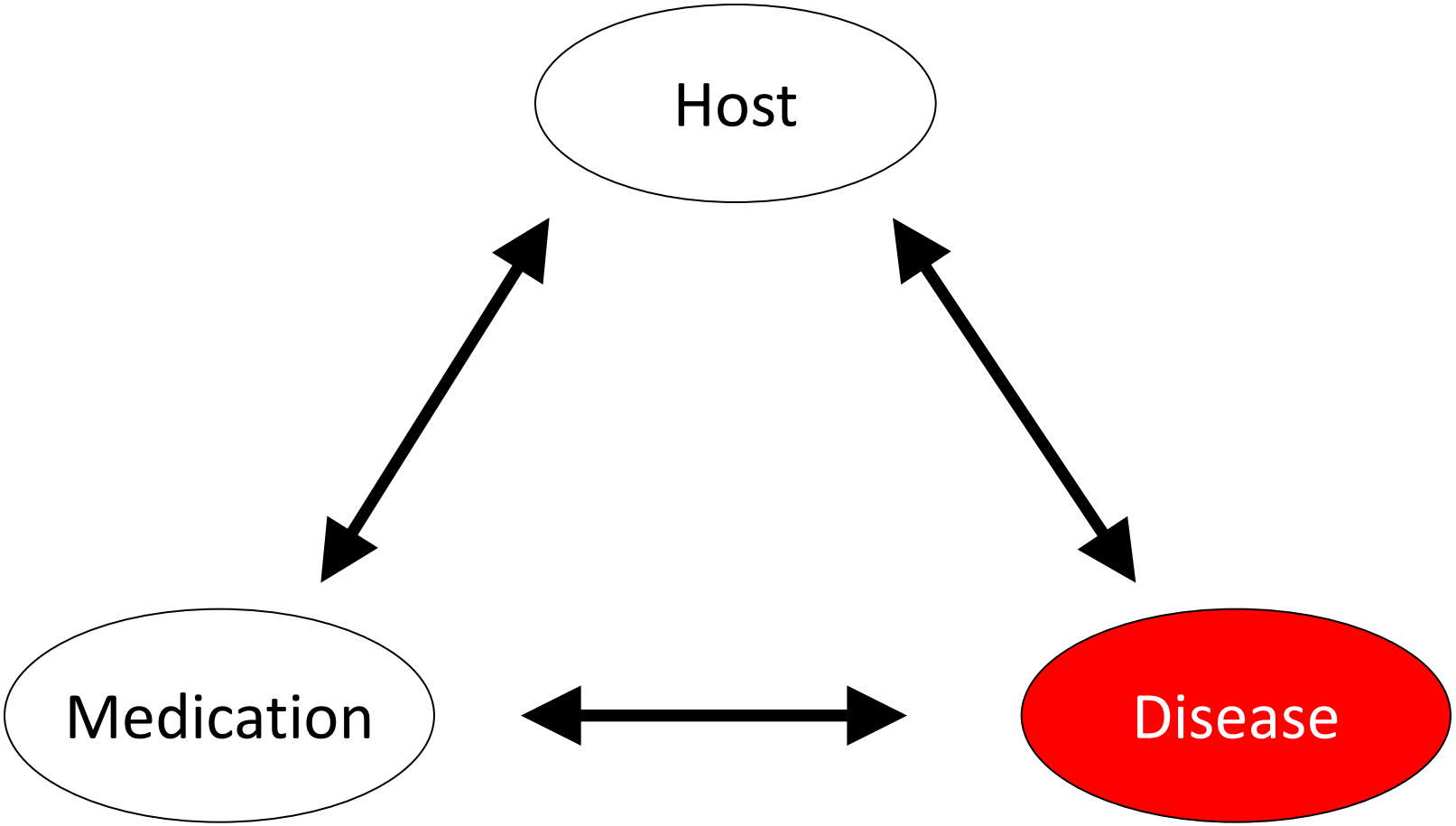
1 – De Wit, Diabetes Care, 2 – Justmann, JAIDS, 2003

Other Risk Factors

- Dyslipidemia[1]
- HCV co-infection[2]
- Vitamin D deficiency[3]
- Sex hormone levels[4]
- Concomitant medications
  - Corticosteroids
  - Pentamidine
  - Atypical antipsychotics

1 – De Wit, Diabetes Care, 2008.. 3 – Milner, Gastroenterology, 2010. 4 – Szep, AIDS, 2011. 5 – Monroe, JAIDS, 2011.

Multifactorial Aetiology of Diabetes in HIV



Risk factors – CD4 nadir

- **MAC Study**[1] (n=710 HIV+): **Lower = Increased risk**

CD4 nadir<300 associated with RR 1.67 (CI 1.0-2.8) compared to CD4 nadir>300

- **Botswana**[2] (54 DM vs 108 non DM): **Higher = Increased risk**

DM associated with higher CD4 nadir (CD4 156 vs CD 118, p<0.05)

- **ANSR-CO8 Cohort**[3] : **No difference in DM risk**

No difference in DM incidence with CD nadir <200 or >200 (p0.67)

1 – Brown, Arch Intern Med 2005; 2– Dumisani, unpublished, 2013. 3–Capeau, AIDS, 2012;

Risk factors –Viral

- Patients with untreated HIV have increased dyslipidemia[1-3]
  - Elevated TG
  - Low HDL-C
  - Low LDL-C (relatively high small dense LDL-C)
- Patients with untreated HIV also have increased bio-inflammatory markers

Do these factors increase risk of insulin resistance or DM in HIV+ not on HAART?

1. G
3. M

Risk factors
HIV duration or Viraemia

- D:A:D Cohort[1]

No association

RR per additional year: 0.98 (CI 0.96-1.00); p=0.09

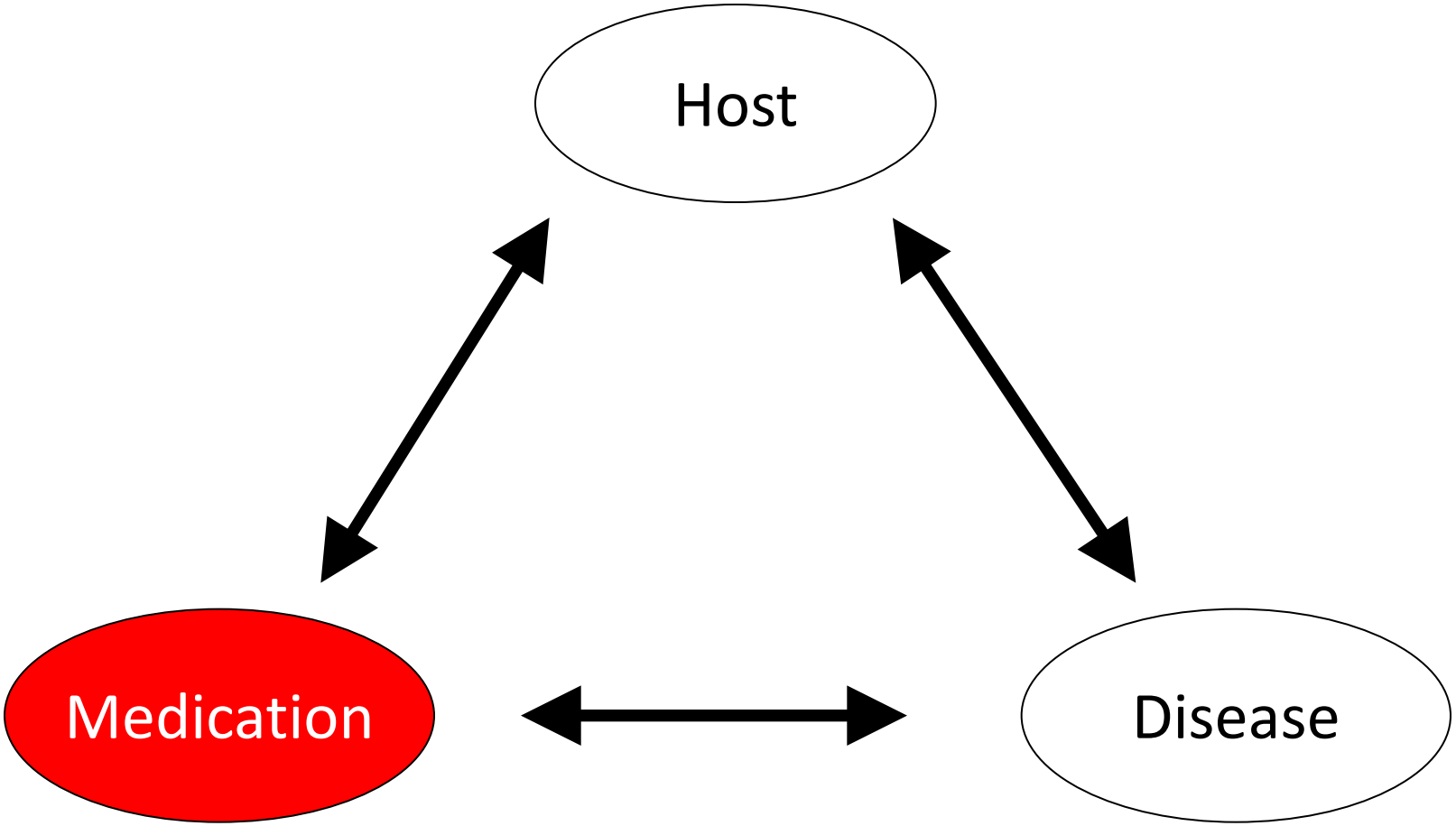
- ANSR-CO8 Cohort[2]

No association between VL and incidence of DM

Incidence 14.3/1000 when VL<5000, 15.2/1000 when VL>100000 (p=0.72)

1- De Wit, Diabetes Care, 2008. 2 –Capeau, AIDS, 2012

Multifactorial Aetiology of Diabetes in HIV



Diabetes Incidence in the Multicenter AIDS Cohort Study

- Incidence analysis on 680 males
  - BL fasting glucose: ≤ 5.44 mmol/L
  - No diabetes history (by self-report)
  - Median follow-up: 2.3 years
- **4-fold increase** in rate of incident diabetes in HAART-treated cohort vs HIV-negative group
  - 4.7 cases/100 person-years for HIV-positive patients on HAART vs 1.4 cases/100 person-years for HIV-negative cohort
  - **RR: 4.11** (95% CI: 1.85-9.16; *P* < .001)

MAC Study Take Home Message:
Initiating HAART significantly increased risk of DM
4 fold increase in DM on HAART cf to HIV negative

HAART – mechanism of diabetogenesis

Indirect effects of the drugs

1. Return to health phenomenon
2. Body Fat Partitioning disorders

Direct effects of specific drugs

1. PIs – inhibiting GLUT4 / reduced β-cell activity
2. NRTIs – mitochondrial toxicity
3. NNRTIs - ?

HAART
Direct Effects

Risk Factor: NRTIs

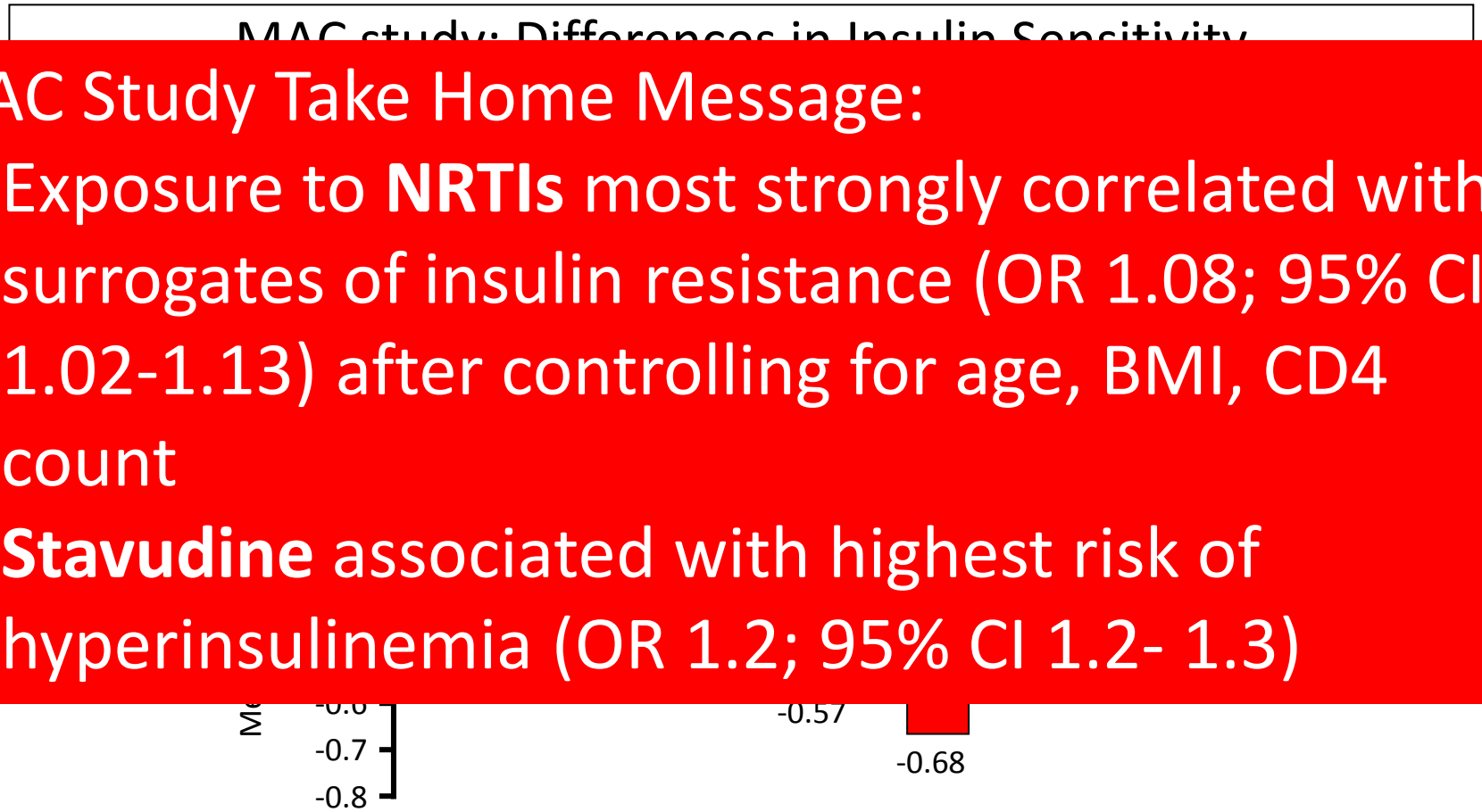
Direct effects

- Potential for mitochondrial toxicity – lipodystrophy syndrome

Indirect effects

- FFA accumulation in muscle and liver (“systemic steatosis”)
  - Effects of inflammatory cytokines

Risk Factor: NRTIs



MAC Study Take Home Message:

- Exposure to **NRTIs** most strongly correlated with surrogates of insulin resistance (OR 1.08; 95% CI 1.02-1.13) after controlling for age, BMI, CD4 count
- **Stavudine** associated with highest risk of hyperinsulinemia (OR 1.2; 95% CI 1.2- 1.3)

1. Brown, AIDS. 2005.

Risk Factor: NRTI

Cohort	# on HAART	Location	Diagnosis	Years of follow up	Incidence (per 1000 person

Summary: NRTI

Risk: d4T>AZT>3TC/FTC

Related to mitochondrial toxicty

Cumulative exposure increases risk of IR

1 – De Wit, Diabetes Care, 2008. 2-Tien, JAIDS, 2008. 3. Hassa, CID, 2011

Risk Factor: Protease Inhibitors

- Insulin resistance: mostly commonly seen with RTV/IDV/NFV[1]

Direct effects of PIs

- Some PIs inhibit GLUT4, the major glucose transporter in fat and muscle (IDV, LPV/RTV)2
- Reduced beta cell function: Ritonavir reported to reduce insulin synthesis between 25-50%[3]
- Inhibition of PPAR-Ɣ activity leading to reduced adipocyte differentiation[4]

Indirect effects

- Increased central obesity +/- lipodystrophy[4]
- Dyslipidemia leading to metabolic syndrome[5]

1. Rudich, Acta Physiol Scand, 2005. 2. Lee, Cur Infect Dis Rep, 2004; 3. Behrens, AIDS, 1999,
4. Noor, MA. Aids, 2001. 5. Pao, AIDS, 2010

Risk Factor: Protease Inhibitors

Hyperinsulinemic Euglycemic Clamp Studies

PI	**N**	**HIV Status**	**Treatment duration**	**Δ in Insulin sensitivity**	**P value**
LPV/r (Noor 2004)	20	-	5 days	-24	0.008
LPV/r (Noor, 2006)	25	-	10 days	-25	>0.001
LPV/r (Randal, 2007)	12	+	4 wks	-0.91	NS
LPV/r (Pao 2010)	8	-	4 wks		NS

Risk Factor: PI

Cohort	# on HAART	Location	Diagnosis	Years of follow up	Incidence (per 1000 person years of FU)

Summary: Protease Inhibitors

Dose dependent risk
Mechanism - dyslipidemia
Withdraw drug and risk of IR drops

1 – De Wit, Diabetes Care, 2008. 2-Tien, JAIDS, 2008. 3. Hassa, CID, 2011

Risk Factor: NNRTIs

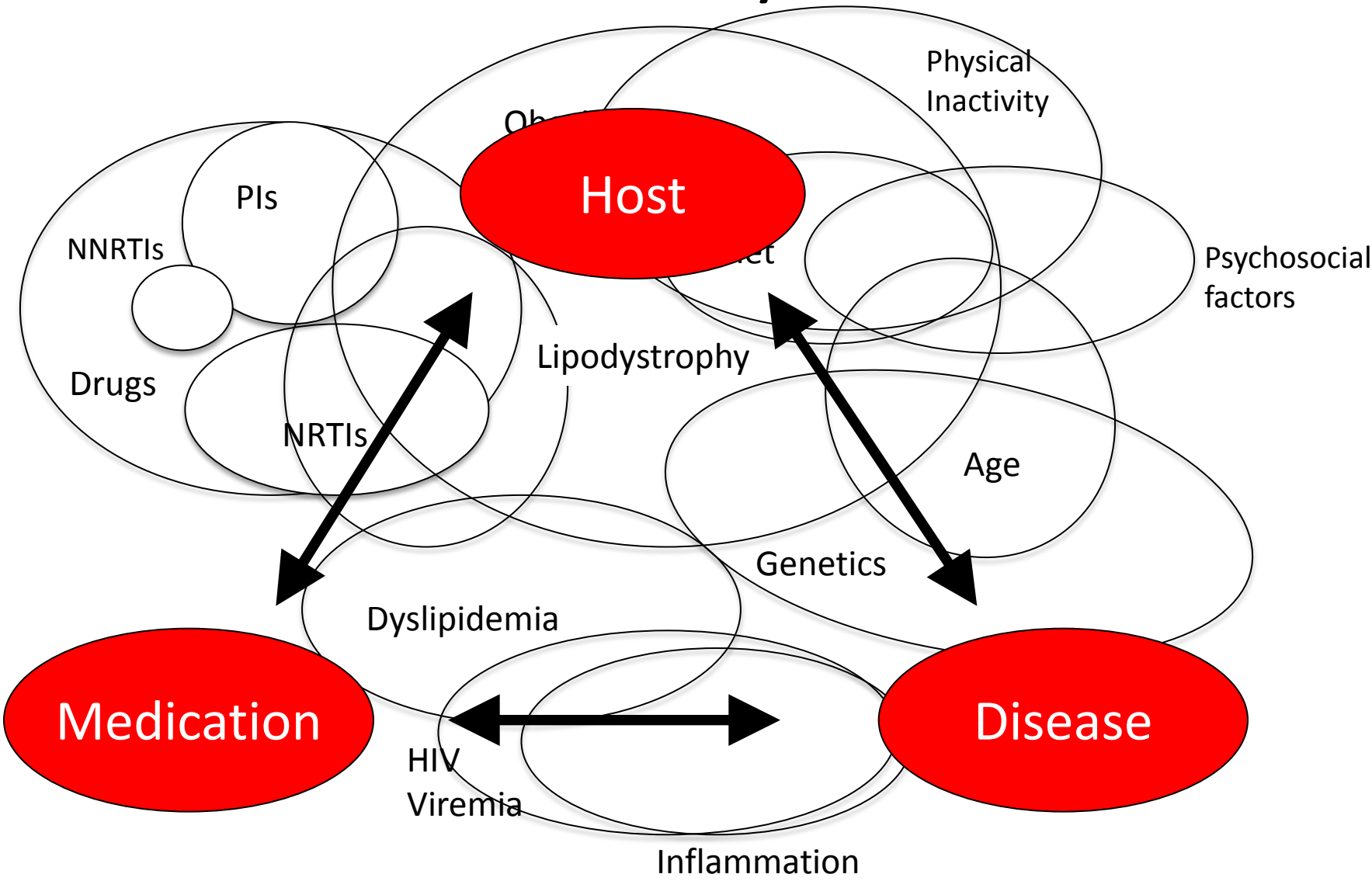
- D:A:D, CO8, MAC – no association between NNRTIs and Insulin Resistance

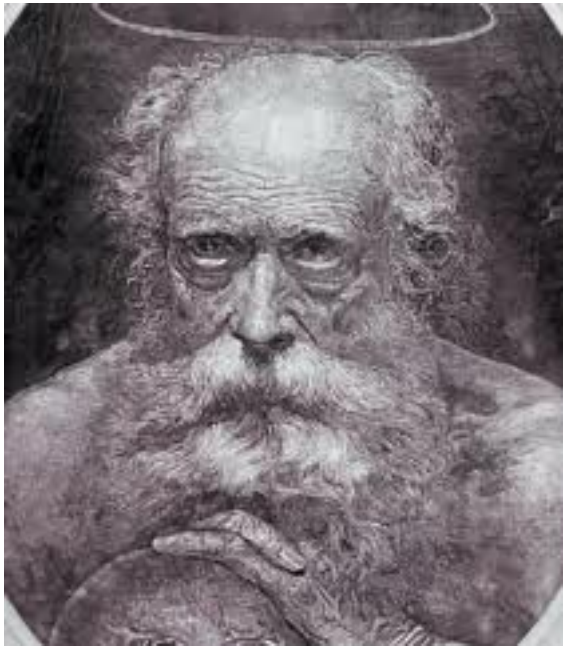
NNRTIs: 2 questions

1. **How do we explain the differences?**
   - African pharmacogenetics
   - Unexplained confounders
     - Lipodystrophy
     - Co-administration with d4T
2. **Clinically meaningful association?**

1 – Dave, JAIDS, 2011. 2–Moyo, unpublished. 3 – Mutimara, JAIDS 2007.

Diabetes Pathogenesis Summary





'Healing is a matter of time, but it is also a matter of opportunity.'

Hippocrates, 460 BC

HIV and DM: Part 2

Treatment & Management

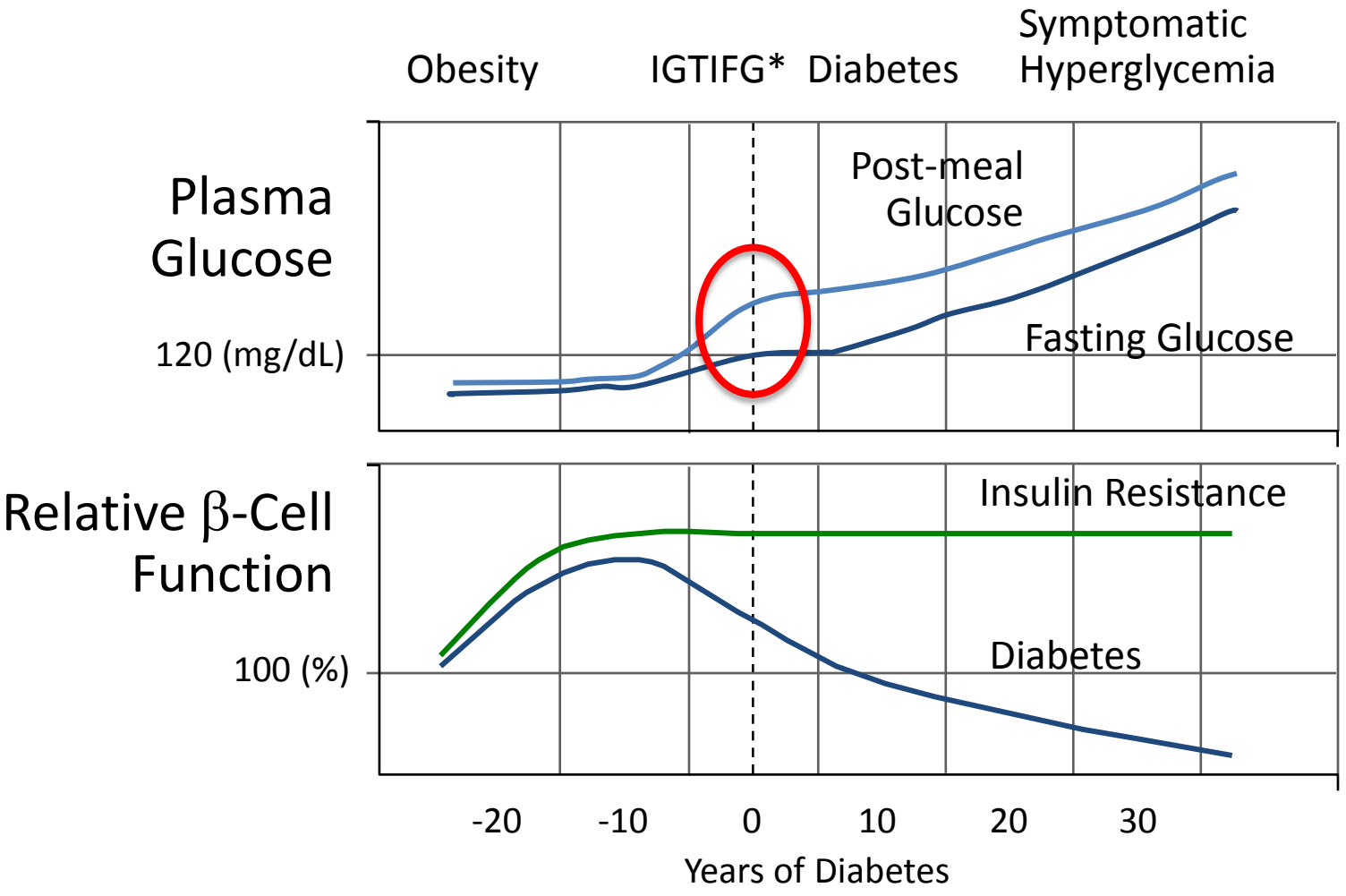
Guidelines for screening

Country	**DM Screening**
SEMDSA (2012)[1]	Every 6 months on ARV treatment
SAHIVSoc (2012)[2]	Glucose should be assessed 'serially.' 3 months after starting PI then annually if normal
United Sates (2011)[3]	Before and after starting ARV 3-6 months after initiation Every 12 months thereafter

Recommendations: At least annually for all patients on HAART and especially those with obesity, lipodsytrophy, FH, on D4T or PIs

1.. Society for Endo and DM of South Africa. 2. Southern African HIV Clinicians Society, 2012. 3. American Diabetes Association, Diabetes Care, 2011

Brief Recap: Pathogenesis of Diabetes



*IGT = impaired glucose tolerance

IFG= impaired fasting glucose

Management of DM/IR in HIV patients

Don't just screen – INTERVENE[1]

1. Lifestyle Modifications
2. Medical management: metformin, TZDs
3. Δ of HAART: D4t, LPV
4. Screen for and manage complications

1. ADA, Diabetes Care, 2011. 2. Reinsch, Eur J Prev Cardiol, 2012. 3. Backus, AIDS Patient Care, 2011

1. Lifestyle Modifications

3234 with IR (IGT):

Prevention program:
150 minutes/week of exercise and

Weight loss of 5-10%:[2]
Reduces HbA1c by 0.5-1%
Increases life expectancy by 2-4 years

Regular exercise:[3]
39-70% reduction in CVD morbidity over a 15 year period

1.Knowler WC, et al. N Engl J Med. 2002. 2. Gregg, Prev Med, 2007. 3. Hu G. Diabetes Care, 2005.

1. Lifestyle Modifications

HIV+ adults (n=62) on ART with confirmed metabolic syndrome

"Those who do not make time for exercise will eventually have to make time for illness"

Earl of Derby 1863

1. Fitch KV, et al. AIDS. 2006

2. Insulin sensitizing agents: metformin, TZDs

Metformin* in pre-diabetes Reduces Lipodystrophy:

Change in Insulin **Change in Waist Circumference**

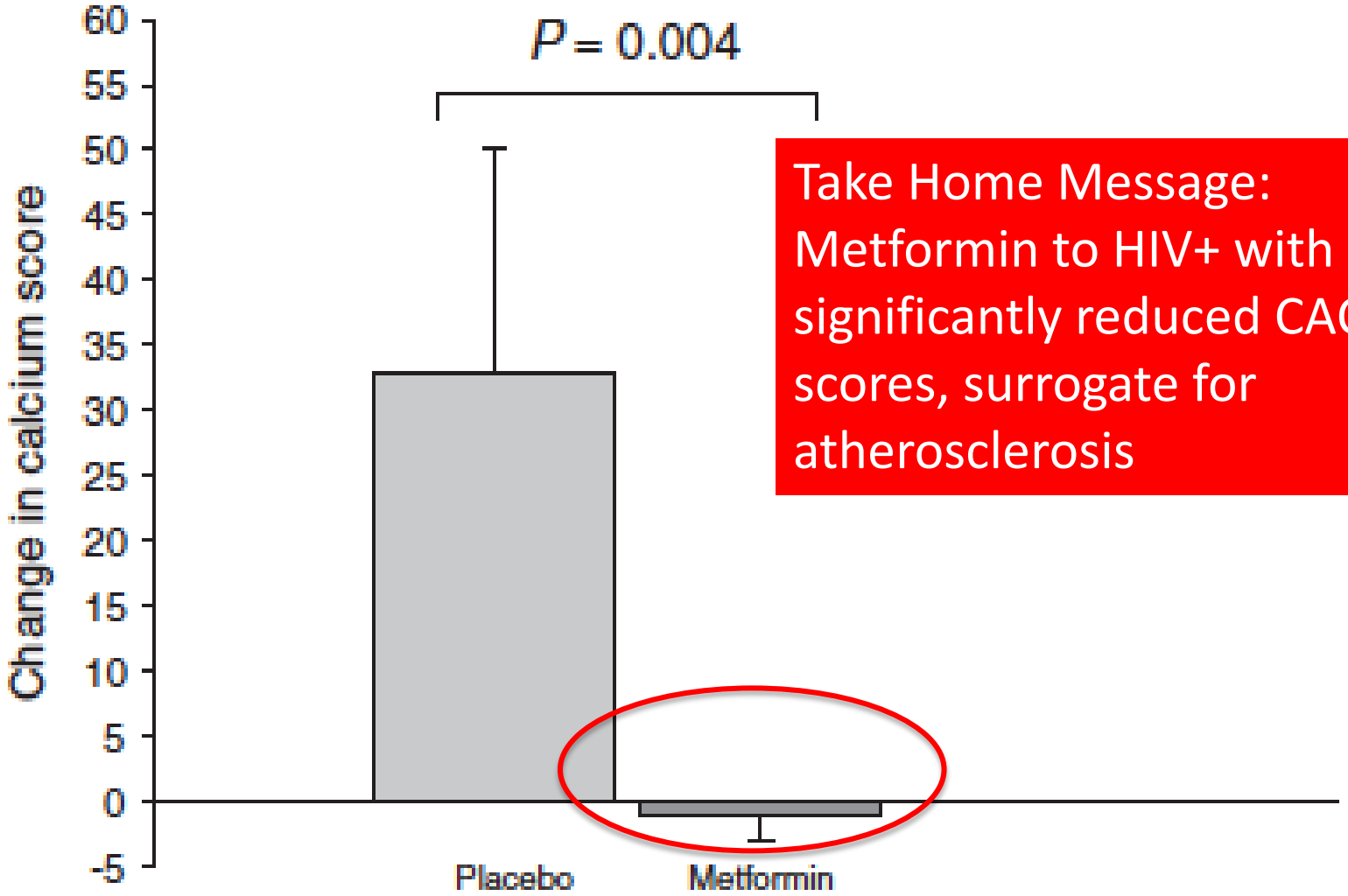
Take Home Message: In patients with pre-diabetes/metabolic syndrome, short term metformin significantly reduced mean insulin levels and visceral abdominal fat

N = 26, 3 month study duration

*500 mg BID

Hadigan C, et al. JAMA, 2000.

Metformin in pre-diabetes Reduces risk cardiovascular risk[1]



Take Home Message: Metformin to HIV+ with MS significantly reduced CAC scores, surrogate for atherosclerosis

Fitch, K, AIDS, 2012

TZDs in pre-diabetes :Impact on lipodystrophy and IR

- ✔ Rosiglitazone associated with increases in fat deposition for patients with lipoatrophy (N = 28) [1,2]
- ✔ Rosiglitazone PLUS Exercise associated with improvements in insulin resistance in HIV+ on HAART (N=44)[3]

Take home message: possible effect in reducing lipoatrophy, but given adverse effects probably best reserved for patients with frank DM and no evidence of CHF

1. Hadigan C, et al. Ann Intern Med, 2004. 2.Schindler, Horm Met Res, 2009. 3. Gervois, Nat Clin Pract Endocrinol Metab. 2007 4. yARASHESKI, Am j Physiol Endo MetaB, 2011

3. Δ of HAART: D4t, LPV

SWITCHING PIs:

Older studies demonstrated that switching from PIs to an NNRTI was associated with significant improvements in fasting insulin resistance index

NVP: decrease of 45%; *P* = .0001[5]

EFV: decrease of 28%; *P* = .03[6]

1. Murphy RL, et al. HIV Clin Trials. 2008. 2. Moyle GJ, et al. AIDS. 2006. 3. Martin A. AIDS 2004. 4. McComsey GA. Clin Infect Dis. 2004. 5. Martinez E. AIDS. 1999.. 6. Martinez E,. Clin Infect Dis. 2000.

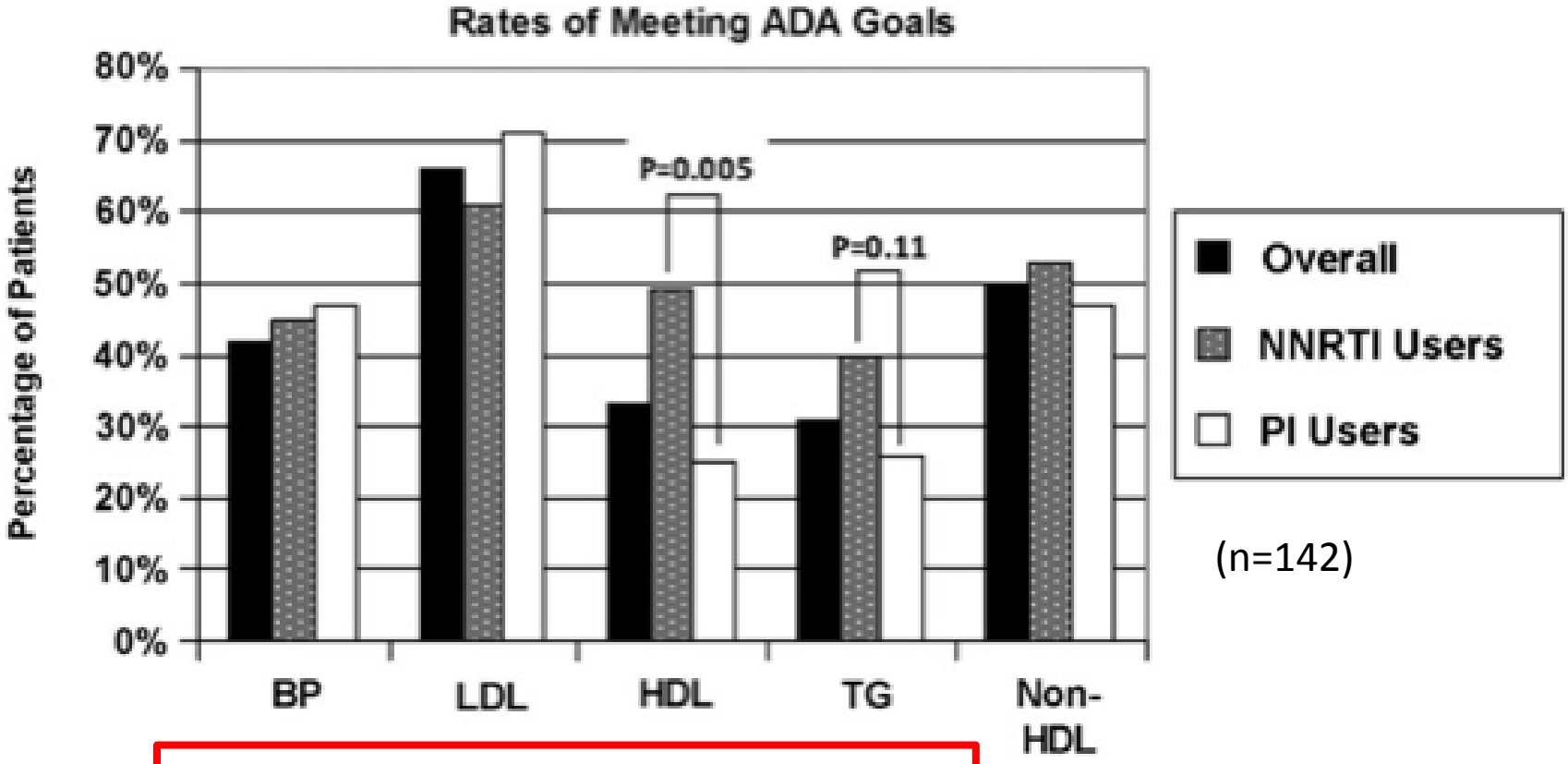
4. Screen for and manage complications

- Nephropathy
  - HIV infected patients with DM: x2 rates of albuminuria to HIV infected non-DM (34% vs 13%, P=0.005)[1]
  - Exposure to ABC associated with increased risk of albuminuria[1]
  - Presence of DM independent risk factor for ESRD in HIV-infected cohort[2]
- Retinopathy
  - Malawi study: retinopathy disease severity not associated with HIV status or VL[3]
- Cardiovascular disease
  - D:A:D – Diabetes associated with x2.4 rates of coronary a disease[4]

1. Kim, PLoS ONE, 2011. 2. Jotwani, Am J Kidney Dis, 2011. 3. Glover, Br J Opth, 2012.
4. Worm, Circulation, 2009

DM and HIV Service Delivery: Quality of Care

Management of DM in HIV patients: 'Ensuring quality care'



(n=142)

Uncontrolled hyperglycemia in 33%,
Suboptimal LDL control in 34%[3]

1. Saitlin, AIDS Patient Care, 2011

Management of DM in HIV patients: 'delivering quality care'

HIV HEART cohort:[1] (n=803;5% diagnosed with DM)

Only 56% (23/41) of patients were on DM meds

41% (42/102) of eligible patients were on anti-platelets

IMPLICATIONS

Implementing standard DM care in HIV infected patients is challenging in settings where treatment barriers are not expected.

Big barrier is **CLINCIAL INTERTIA**[2]

1 Reinsch, Eur J Prev Cardiol, 2012, 2 . Willig, Clin Infect Dis, 2008

DM: the next big challenge for TB control?[1]

1. Harries, IJTLD, 2011

Importance of HIV and DM as risk factors for Tuberculosis[1]

Region	HIV			DM			Smoking			Malnourishment			Alcohol		
	RR	HIV %	PAF %	RR	DM %	PAF %	RR	smoking%	PAF%	RR	Mal't%	PAF %	RR	HD %	PAF %
Afro															
High HIV	**26.7**	7.05	64.4	**3.1**	3.12	6.6	**2.0**	10.1	9.2	**3.2**	29.1		**2.9**	15.6	22.9
Low HIV		1.28	24.7		4.14	8.0		12.1	10.8		21.6			8.22	13.5

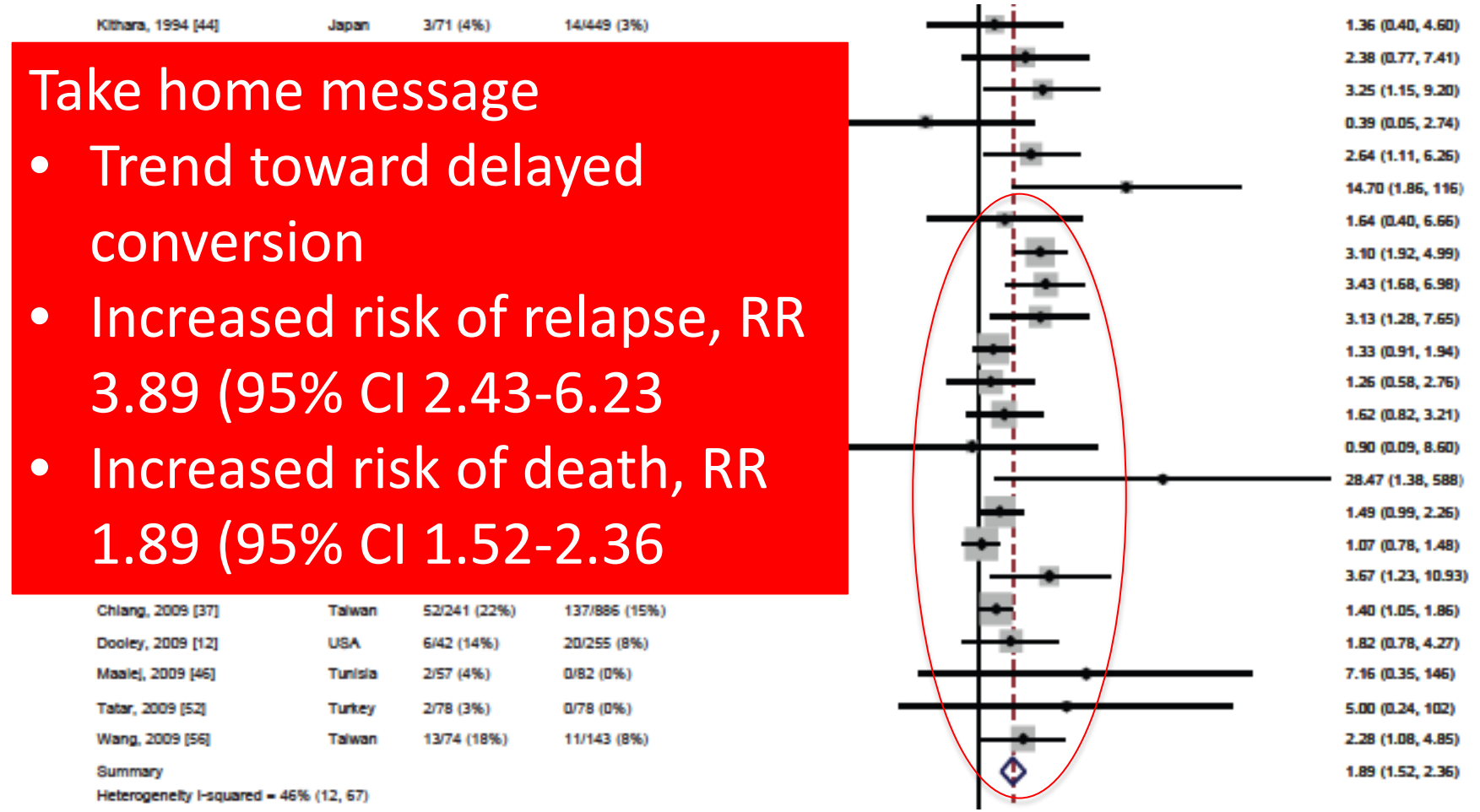
RR – relative risk; PAF – population attributable risk

1 –Cresswell, Eur Respir J, 2011

TB outcomes in DM patients
Systematic Review of 33 studies

Take home message

- Trend toward delayed conversion
- Increased risk of relapse, RR 3.89 (95% CI 2.43-6.23
- Increased risk of death, RR 1.89 (95% CI 1.52-2.36



Baker, BMC Medicine, 2011

Risk of death from TB in patients with DM

Diabetes, HIV and risk of TB Implications

HIV/DM care

Enhanced screening in HIV/DM patients

?IPT for all HIV/DM patients not yet on HAART

?Extended TB treatment – how long?

TB care

Increased screening for DM among TB patients

Tight glycemic control during ATT

‘Unresolved issues’

- Burden of disease?
- Optimal strategies for integration?
- Capacity Building?

1. El Sadr, AIDS, 2010.

Summary

- Diabetes and abnormalities of glucose metabolism are increasing
- Factors related to rising prevalence include ARV therapy and host factors
- Early detection and prevention of DM and metabolic sequelae of HIV infection need to be public health priorities

BOTSWANA-UPENN PARTNERSHIP

Thank You

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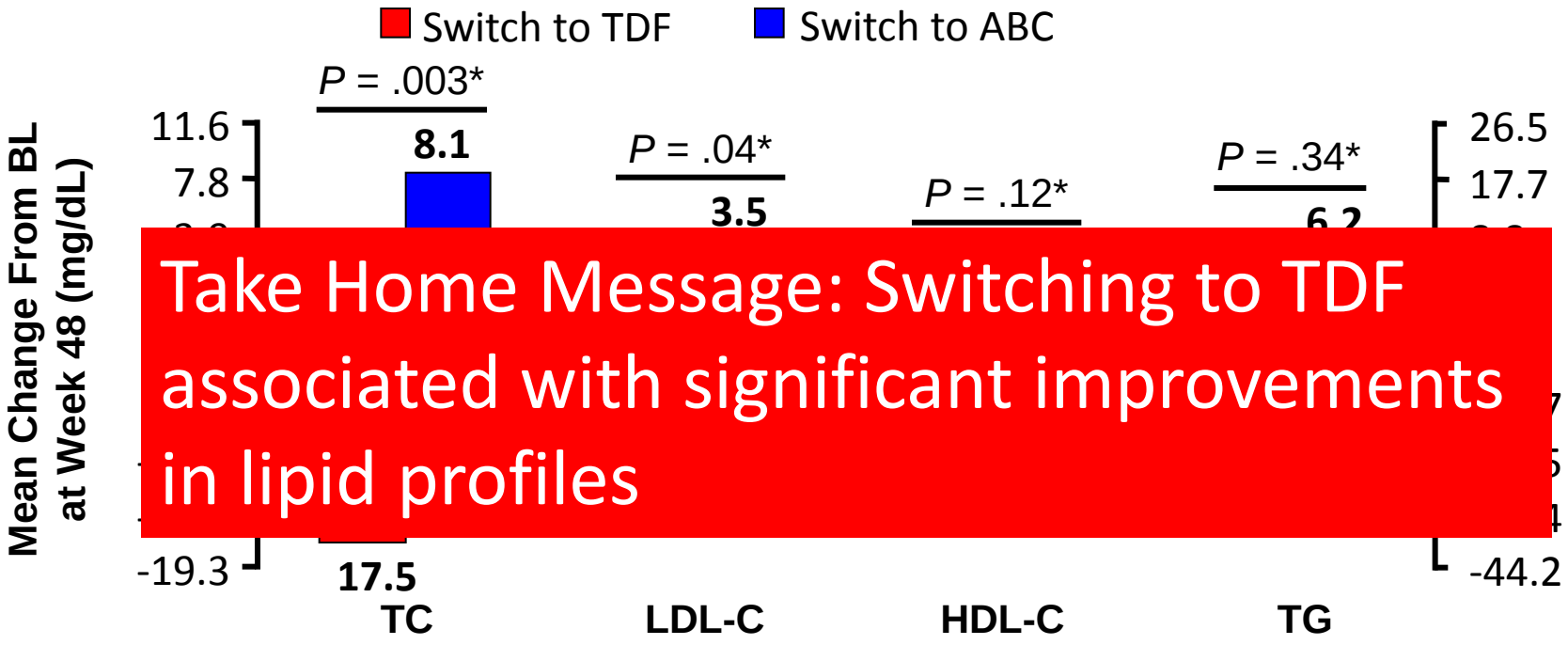
Extra slides

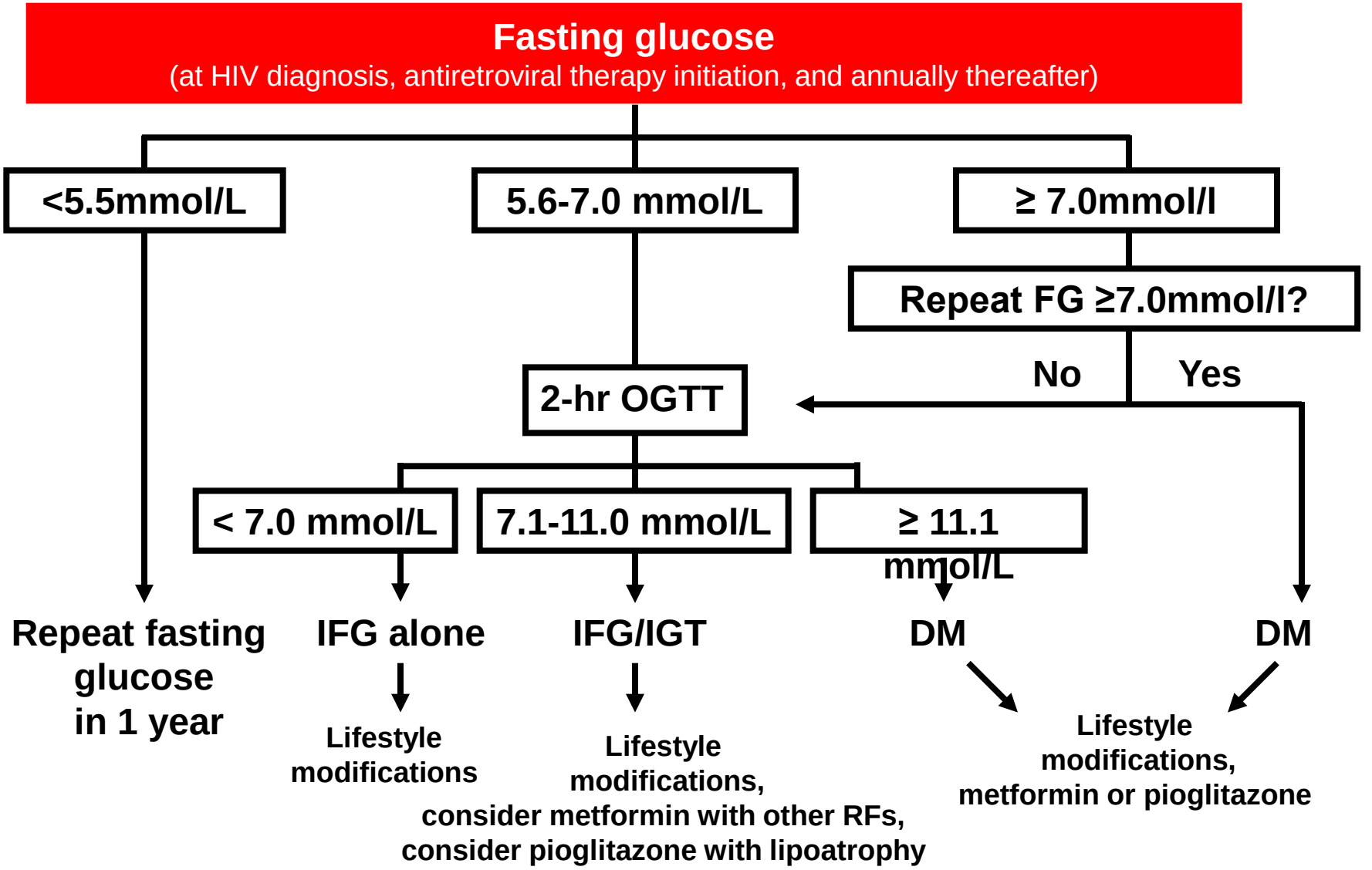
Lipid Effects of Switching Thymidine Analogues to ABC or TDF (RAVE)

Phase IV, open-label, multicenter, randomized, 48-week trial of switching from a thymidine analogue to TDF (n = 52) or ABC (n = 53).

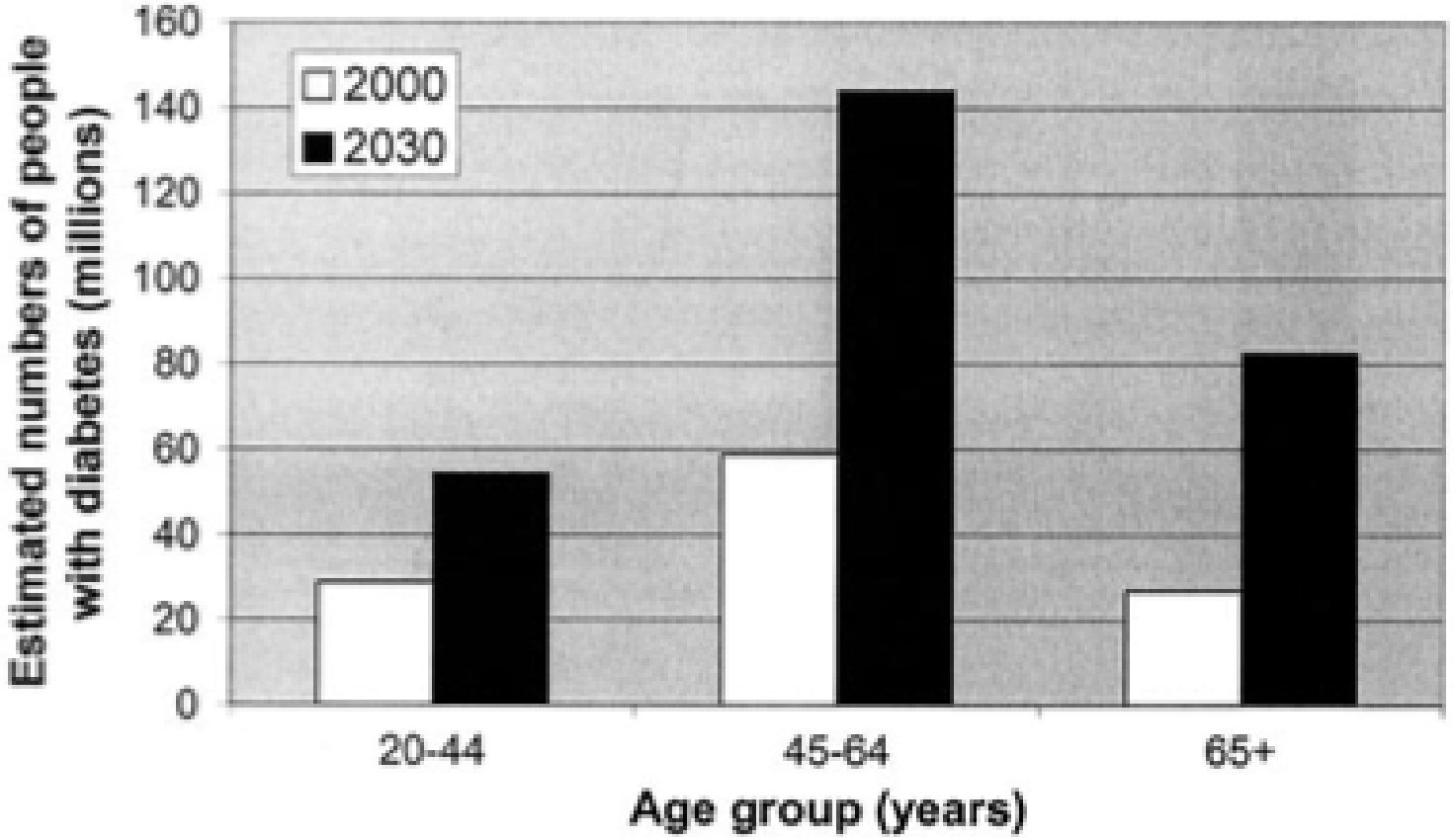


*P values between arm differences.

Moyle GJ, et al. AIDS. 2006.


Fasting glucose
(at HIV diagnosis, antiretroviral therapy initiation, and annually thereafter)
<5.5mmol/L
5.6-7.0 mmol/L
≥ 7.0mmol/l
Repeat FG ≥7.0mmol/l?
No
Yes
2-hr OGTT
< 7.0 mmol/L
7.1-11.0 mmol/L
≥ 11.1 mmol/L
Repeat fasting glucose in 1 year
IFG alone
IFG/IGT
DM
DM
Lifestyle modifications
Lifestyle modifications, consider metformin with other RFs, consider pioglitazone with lipoatrophy
Lifestyle modifications, metformin or pioglitazone

Diabetes 2030 projections[1] Sub Saharan Africa



Wild, Diabetes Care, 2004

Risk Factors – Age

Increasing age = ?longer duration of HIV

Increasing age = ?exposure to older ARVs & > lipodystrophy

Implications:

Estimated 3 million Africans with HIV > 50 years[3]

In RSA approx 20% of all HIV infected persons are > 50 years[4]

1 – Hasse, CID, 2011; 2 –Capeau, AIDS, 2012; 3 – Negin, AIDS, 2012, ; 4 –SANAT, 2008

HAART
Indirect - Body Partitioning

- **Lipodystrophy Case Definition Study:[1]**
  - DM 7% with Lipodsytrophy
  - DM 3% without Lipodystrophy
- **D:A:D study:[2]**
  - Lipohypertrophy
    - HR 1.36 (95% CI 1.09-1.68)
- **ANSR-CO8 Cohort:[3]**
  - Lipoatrophy
    - HR 2.14 (95% CI 1.3-3.44)

Drug specific or all Drugs?

Thymidine Analogues[4,5]
d4T – biggest culprit

NNRTIs
ACTG 5142[6] – EFV associated with >30% fat loss

PIs
ACTG 384[7] – Nelfinavir associated with 13% fat loss on DEXA

Conclusions?
Indirect effect of all drugs
Direct effect of some drugs

1 – Carr, Lancet, 2008. 2- De Wit, Diabetes Care, 2008. 3 –Capeau, AIDS, 2012. 4 – Gallant, JAMA 2004. 5. Mallal, AIDS, 2000. 6. Haubrich, AIDS, 2009. 7. Dube, AIDS, 2005

Metformin: Adverse Effects

Safe!

Recommended as first line for DM by SEMDSA

- Nausea, vomiting, diarrhea
  - Seen in up to 50% of patients
  - Minimized by slow titration and administration with food
- Lactic acidosis
  - Contraindications
    - Renal insufficiency (Cr >132 μmol/L in men, > 123 μmol/L in women)
    - Class III and IV congestive heart failure
    - Hepatic failure
    - Potential for lactic acidosis with antiretrovirals
- May worsen lipoatrophy[1]

1. Kohli R, et al. HIV Med. 2007;8:420-426.

Direct Effect
Measuring Insulin Resistance

Gold standard

- Hyperinsulinemic euglycemic clamp
- Insulin suppression test
- Insulin tolerance test

Fasting markers of insulin resistance

- HOMA-IR = FPG (mmol/L)*FPI (μU/mL)/22.5
- QUICKI = 1/[log(FPG) + log(FPI)]
- Bennets S_1
- McCauley

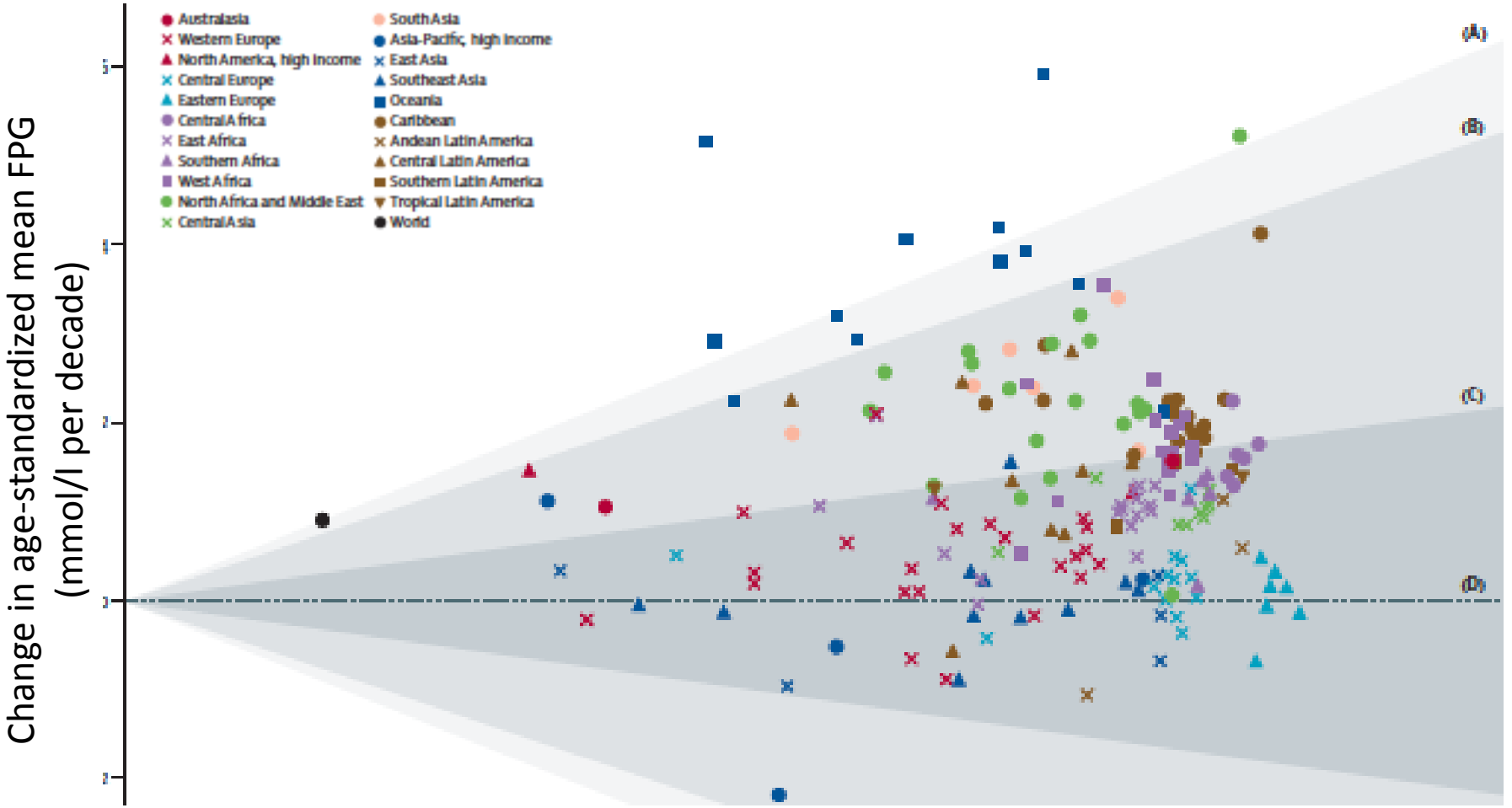
Markers of insulin resistance from OGTT

- Insulin area under the curve
- Insulin sensitivity index (Matsuda)
- Stumvoll ISI_{ogtt}
- Belfiore's ISI

Problems With Measuring Insulin Resistance

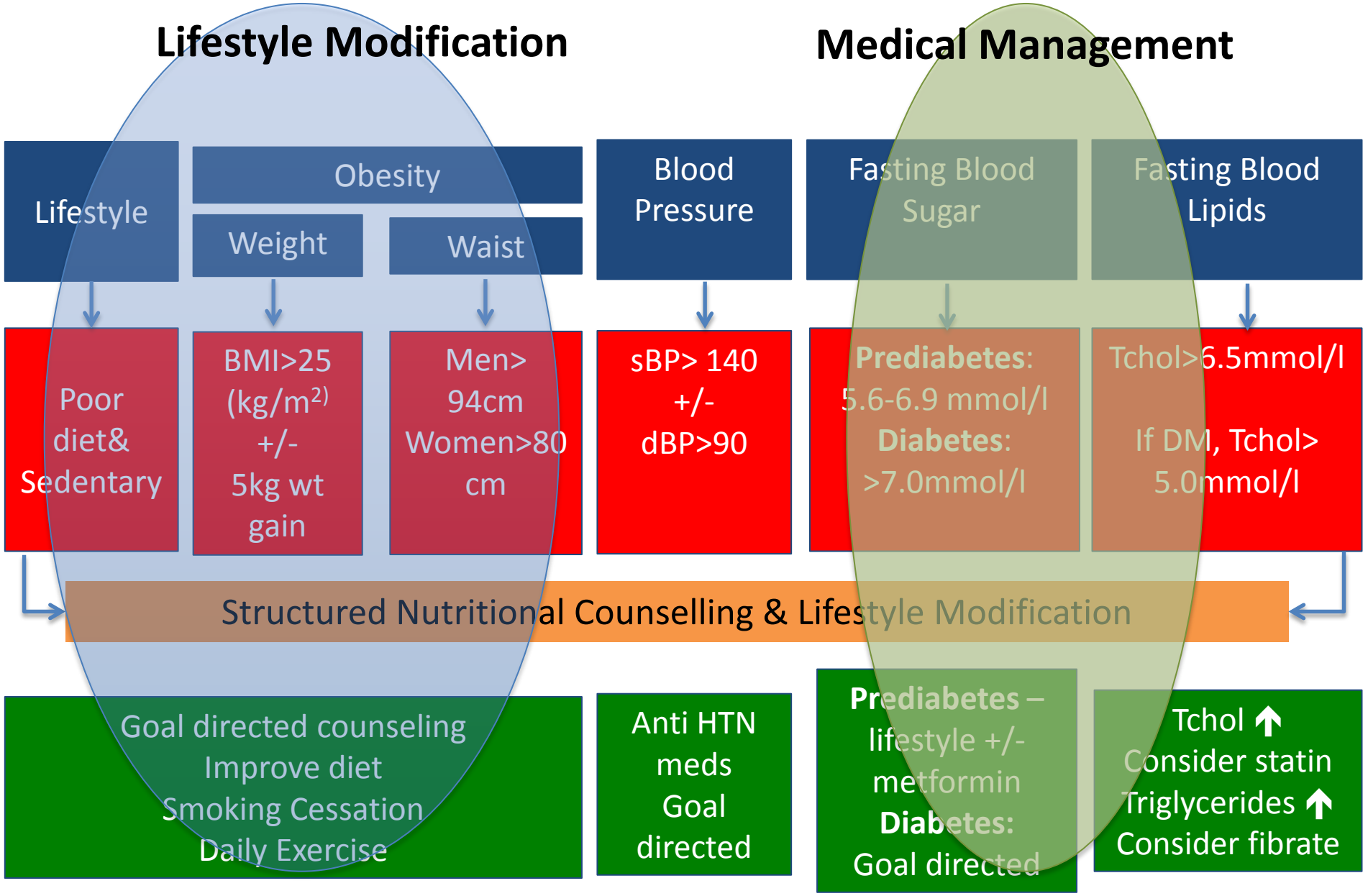
- Gold standard techniques too cumbersome to use clinically
- Insulin resistance markers
  - Useful in populations, not in individual patients
  - Insulin assays not standardized and highly variable
  - No established cutoff points
  - Expensive and difficult to perform

Diabetes - Prevalence 1998-2008
199 Countries[1]



Danaei et al, Lancet 2011

Management of DM/IR in HIV patients



Screening & Diagnosis
Glycated Hemoglobin & HIV

- HbA1c - Underestimates plasma glucose levels in HIV infected patients by 10-15%[1]
  - Discordance associated with NRTI-related macrocytosis[2]
  - Abacavir: increased discordance[2]

- SEMDSA[3] & ADA[4]: HbA1c –for monitoring, not DM diagnosis

1 – Diop, AIDS Res, 2006. 2 – Kim, Diabetes Care, 2009. 3. Soc Endocrinology and DM of SA. 4. ADA, Diabetes Care, 2011

Effects of Antiretroviral Therapy on Lipids

- **LDL** tends to go up modestly with virtually all regimens

- **PIs:** Major effect of most **boosted PI** regimens is increased TG and non–HDL-C, but HDL-C typically increases as well
- **NNRTIs:** Increase HDL-C; also increase in LDL-C and TG with EFV
- **NRTIs:** d4T and ZDV associated with adverse effects on lipids relative to TDF (and ABC)
- **New classes:** MVC and RAL do not appear to adversely affect lipids

Randomized Trial of Lipid-Lowering Therapy vs Switching PI

Take Home Message: Statin more effective in management of hyperlipidemia than switching antiretroviral therapy to an NNRTI

BUT

Lipid drugs have side effects…
Only if virologic suppression can be assured is switch reasonable.

Calza L, et al. AIDS. 2005.

Statins in HIV

Alert!

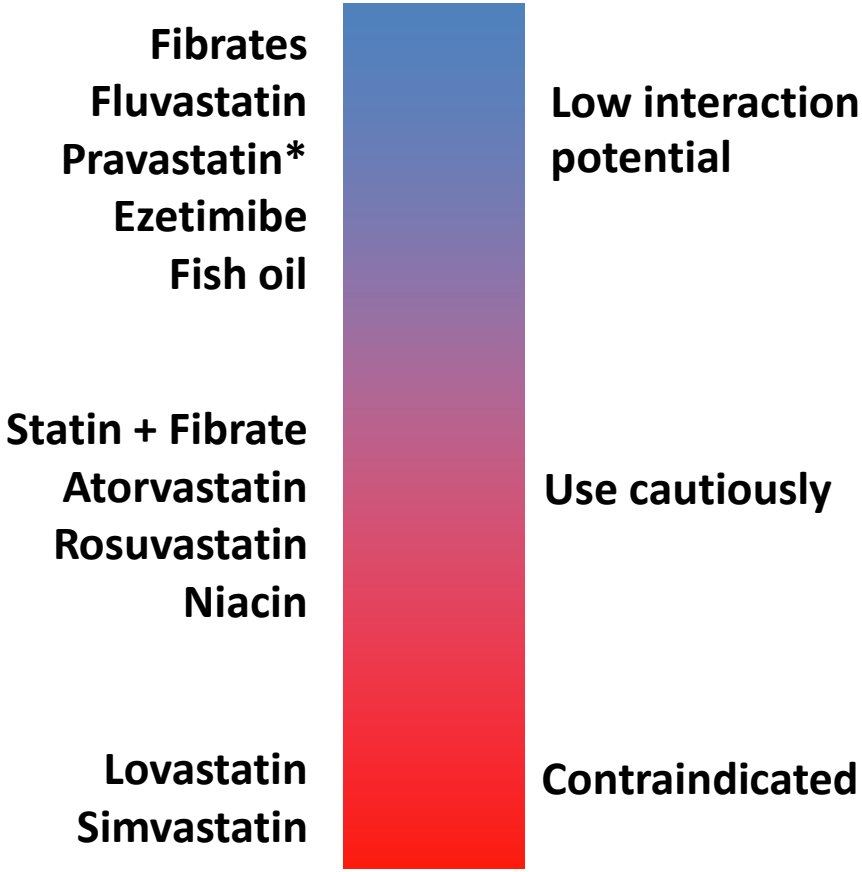
Potential interactions with PIs/NNRTIs

NNRTI – ↓ levels of statins between 40-80%

PIs – ↑ levels of statins to supratherapeutic levels

Simvastatin AUC ↑ 505% with NFV; ↑ 3059% with SQV/RTV
Atorvastatin AUC ↑ 588% to 900% with LPV/RTV

Lipid-Lowering Agents and PIs: Drug-Drug Interactions



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NNRTI Drug Interactions With Statins

- EFV: mixed inducer/inhibitor of CYP450 3A4
  - Simvastatin AUC ↓ 58%
  - Atorvastatin AUC ↓ 43%
  - Pravastatin AUC ↓ 40%
- NVP: inducer of CYP450 3A4
  - Not studied with lipid-lowering therapy
  - Probably the same as EFV

Thomson MICROMEDEX Health Care Series.

Statins: ALLRT study[1]

- HIV infected individuals on HAART, randomized to receive statin, regardless of LDL or total Cholesterol (n=3601)

Statin use-

- Non-significant ↓ decrease in non-AIDS events or death, HR: 0.81 (95% CI: 0.58-1.35)
- Significant ↓ in risk of non-AIDS cancer, HR: 0.43 (95% CI: 0.19-0.94)

1. Overton, CROI, 2012