Diabetes and Weight gain

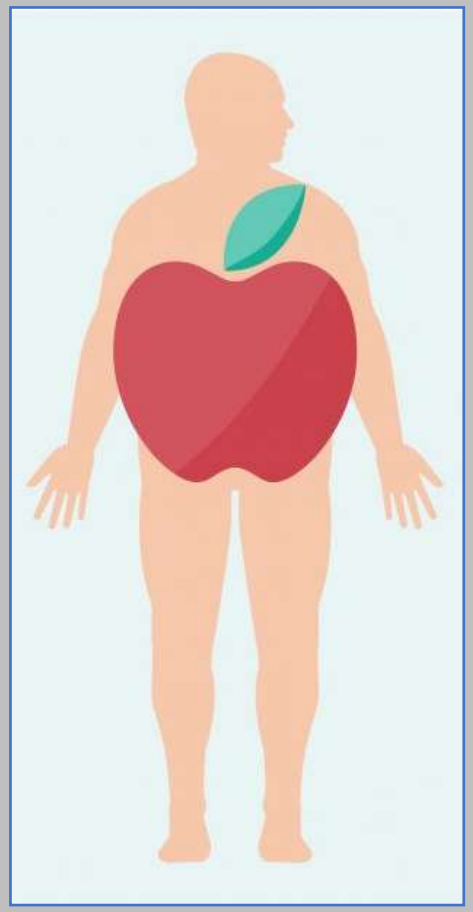
Key Comorbidities in Aging HIV+ Subjects

Dr Graeme Moyle

Chelsea and Westminster Hospital

London, United Kingdom

Obesity is common, with rising prevalence in PLHIV



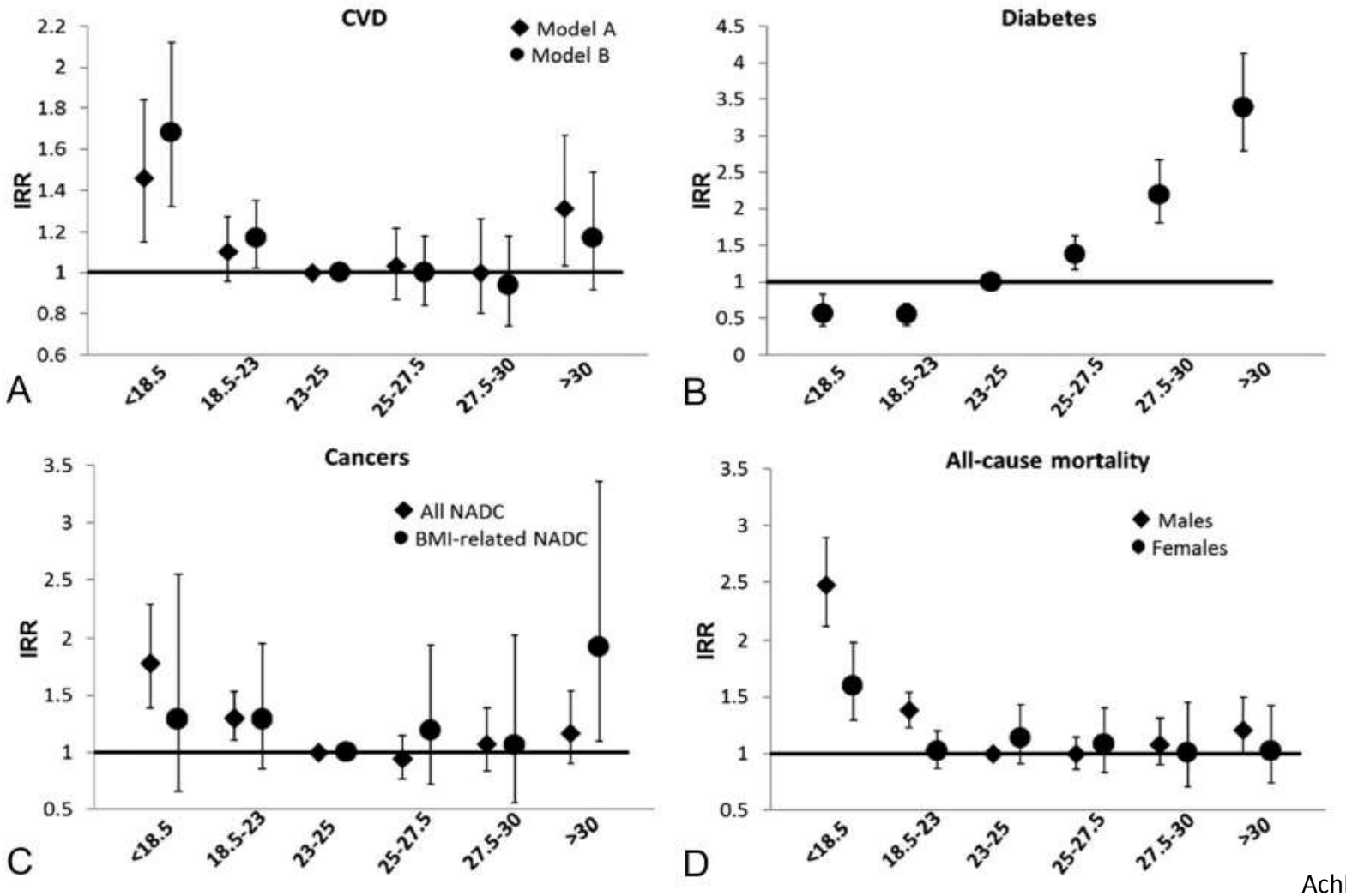
OBESITY

27% of PLHIV in low- and middle- income countries are overweight/obese

Risk factor	Pooled prevalence estimate (%)
Hypertension[a]	21.2
Hypercholesterolemia[b]	22.2
Elevated low-density lipoprotein[c]	23.2
Hypertriglyceridemia[d]	27.2
Low high-density lipoprotein[e]	52.3
Dyslipidemia[f]	72.5
Overweight[g]	21.0
Obese[h]	7.8
Overweight/obese[i]	27.3
Depression[j]	24.4

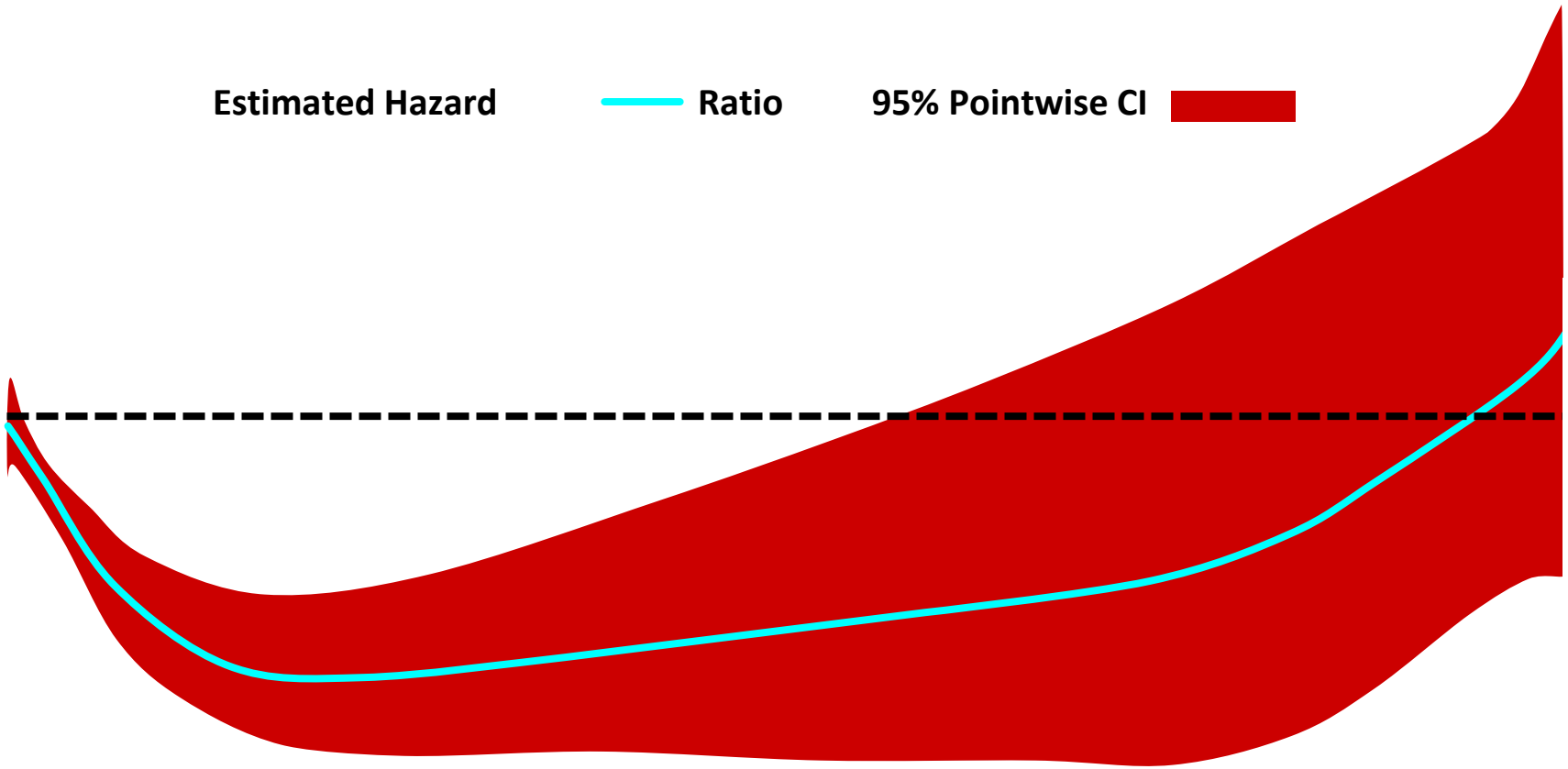
Patel et.al. 2018 AIDS

“U-shaped” relationship between BMI and poor outcomes in PLHIV



Achhra et.al. 2018 JAIDS

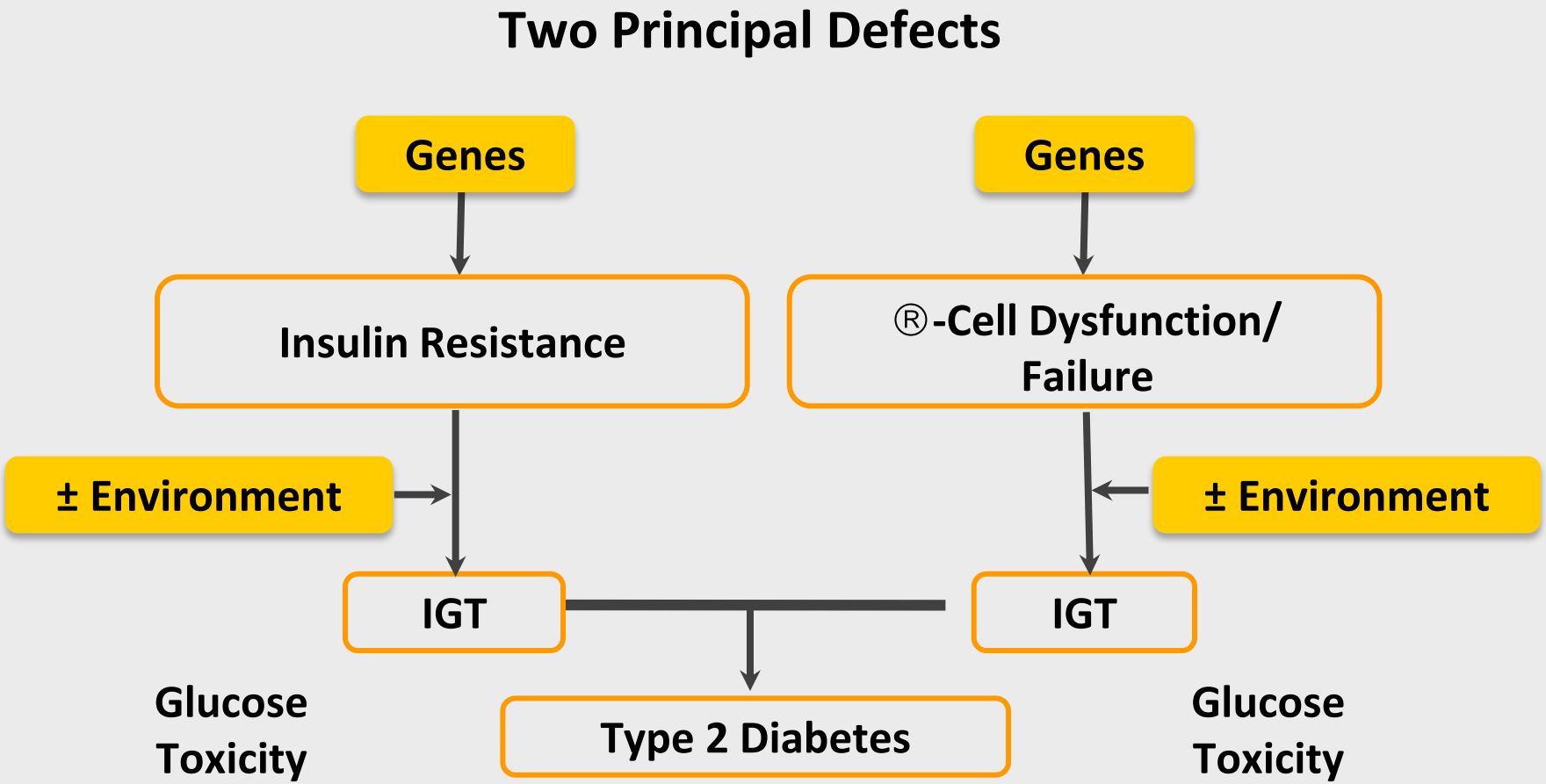
Alcohol is MI protective in Swiss HIV cohort



Wandeler G, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 731.

Insulin Resistance and Diabetes Mellitus in HIV Infection

Type 2 diabetes



IGT = impaired glucose tolerance.

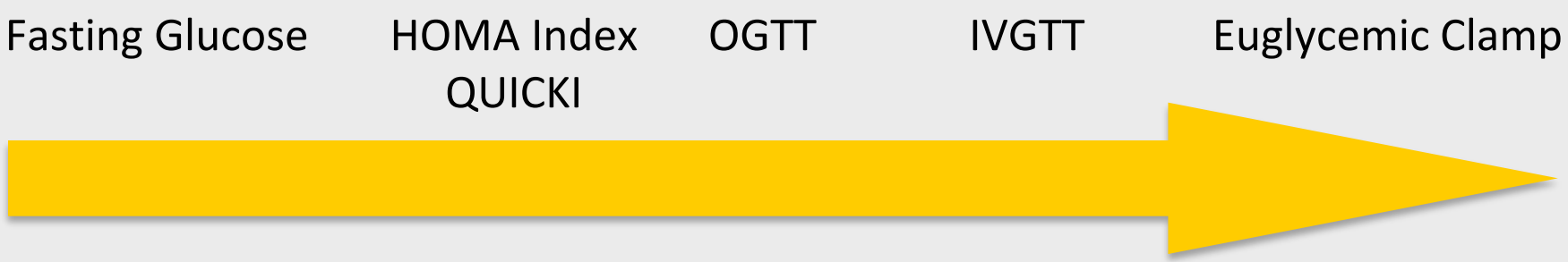
Reaven GM. Physiol Rev. 1995;75:473–486;Polonsky KS. Exp Clin Endocrinol Diabetes. 1999;107(suppl 4):S124–S127.

Major risk factors for type 2 diabetes mellitus

- First Degree relative with type 2 diabetes
- Obesity (>20% over ideal body weight)
- Race/Ethnicity (Hispanics, African, Native Americans, Asian, Pacific Islanders)
- Age > 45 years
- Prior impaired fasting glucose or impaired glucose tolerance
- Hypertension
- Dyslipidemia
- History of gestational diabetes or large-for-gestational-age baby (>9 lbs)

Adapted from American Diabetes Association. Diabetes Care. 2002;25:S35–S49.American

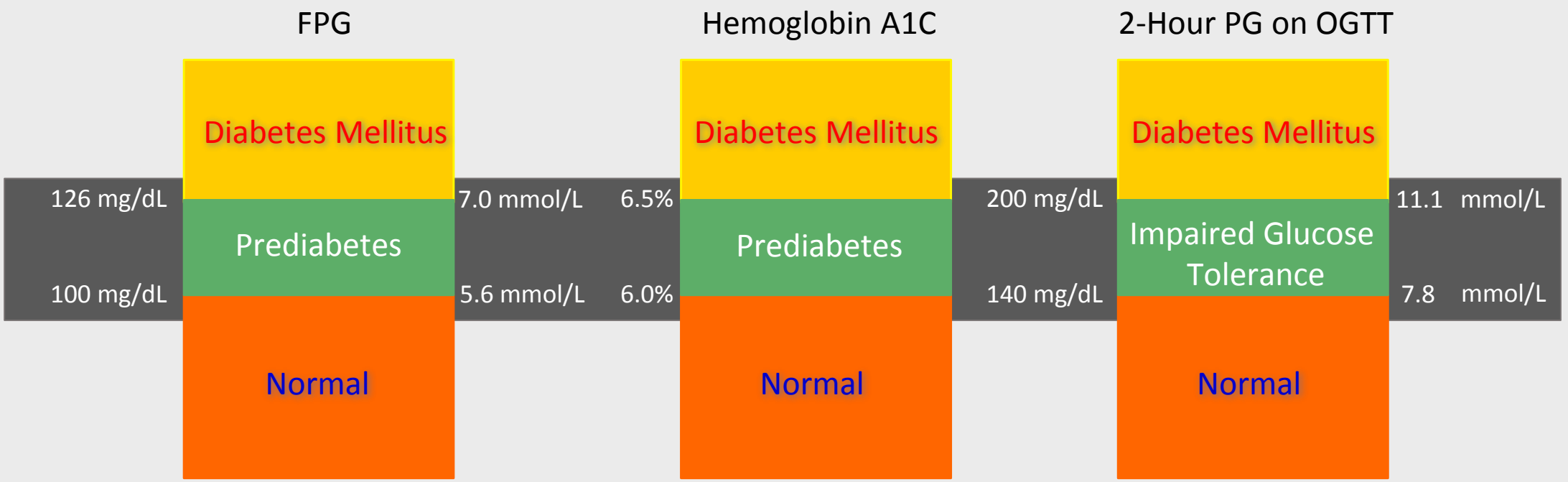
Clinical evaluation of glucose metabolism



HbA1c

- Caution with low MCV e.g. Sickle cell
- Caution with high MCV e.g. ABC
- Fructosamine is alternative

Diagnostic criteria for glycemic abnormalities



To convert mg/dL to mmol/L multiply mg/dl by 0.055

FPG=Fasting plasma glucose, PG=Plasma glucose, OGTT=Oral glucose tolerance test

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2001;24:S5-S20

American Diabetes Association. Diabetes Care 2010;33:S11-61

Insulin resistance, DM and HIV

Classical type 2 diabetes risk factors

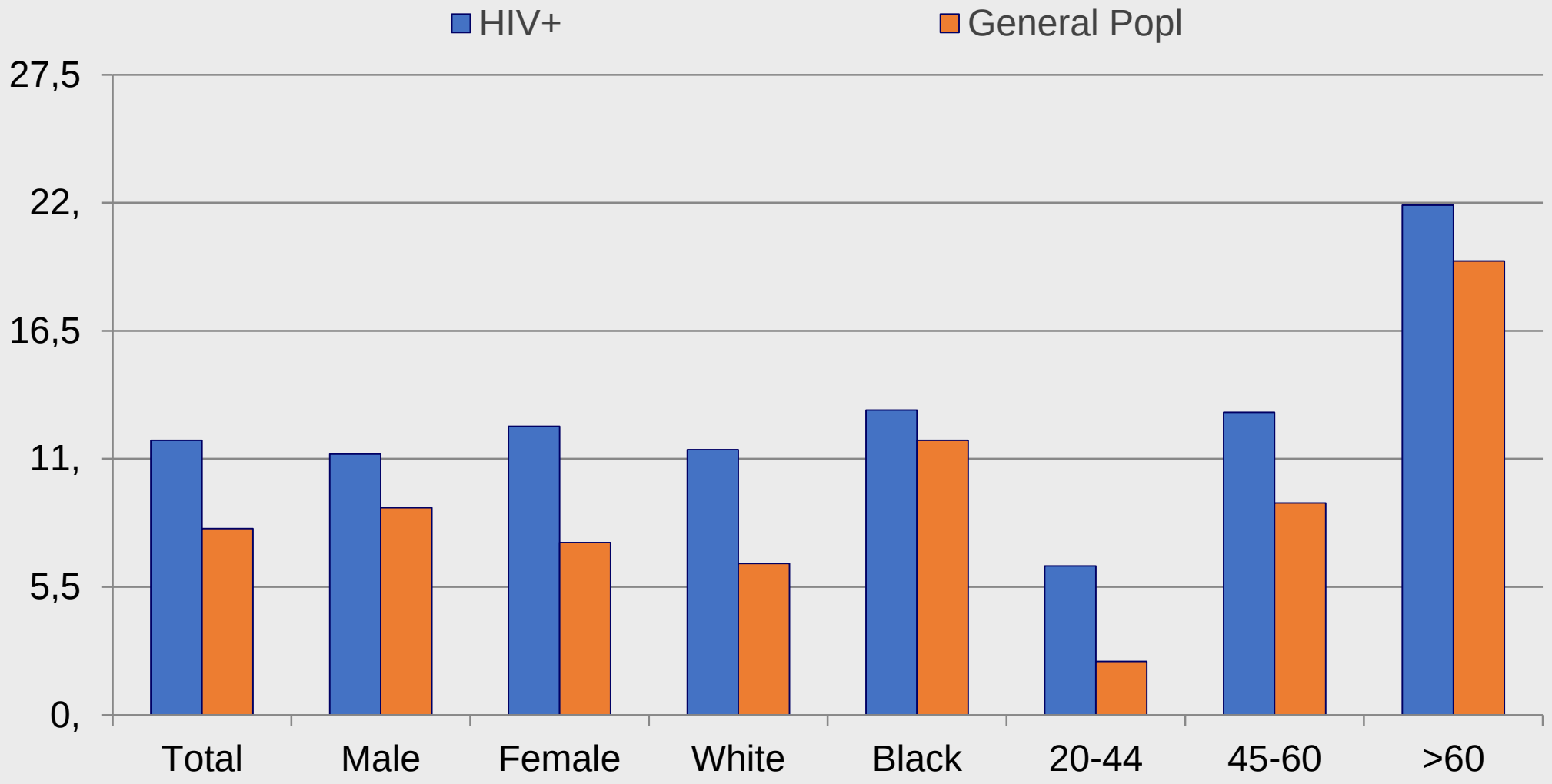
- Obesity (abdominal)
- Physical inactivity
- Genetic
  - Family history
  - Race
- Older age
- Dyslipidemia

HIV-associated risk factors

- NRTI Mitochondrial Toxicity
- PI and GLUT inhibition
- Dyslipidemia
- Peripheral lipoatrophy
- Increased liver or muscle fat
- Inflammatory cytokines
- Low testosterone
- HCV infection

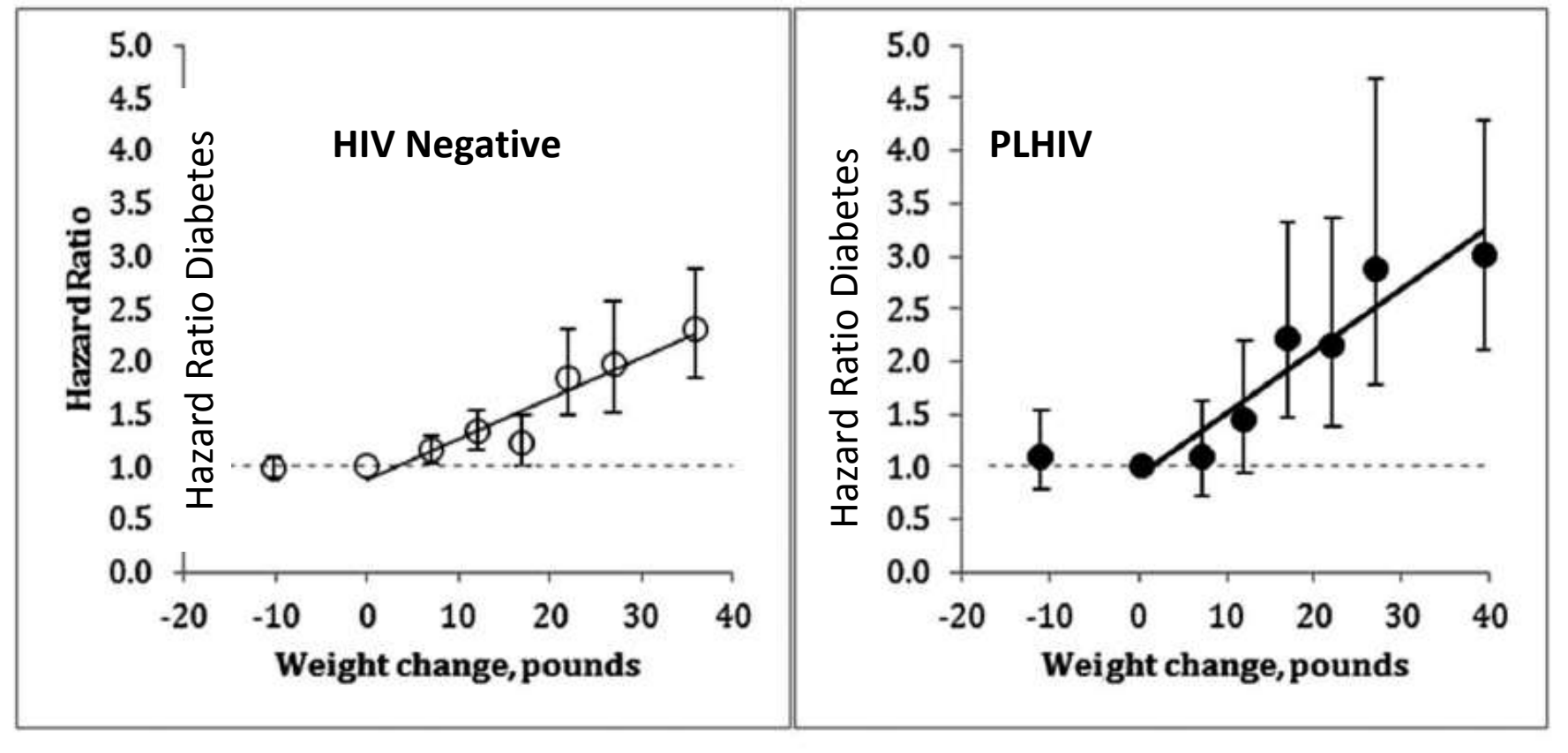
Moyle, G. Personal Communication.

Prevalence comparisons of diagnosed diabetes among HIV-infected adults and general US population adults, MMP and NHANES 2009, 2010



Hernandez-Romeu BMJ Open Diabetes Res Care. 2017; 5(1)

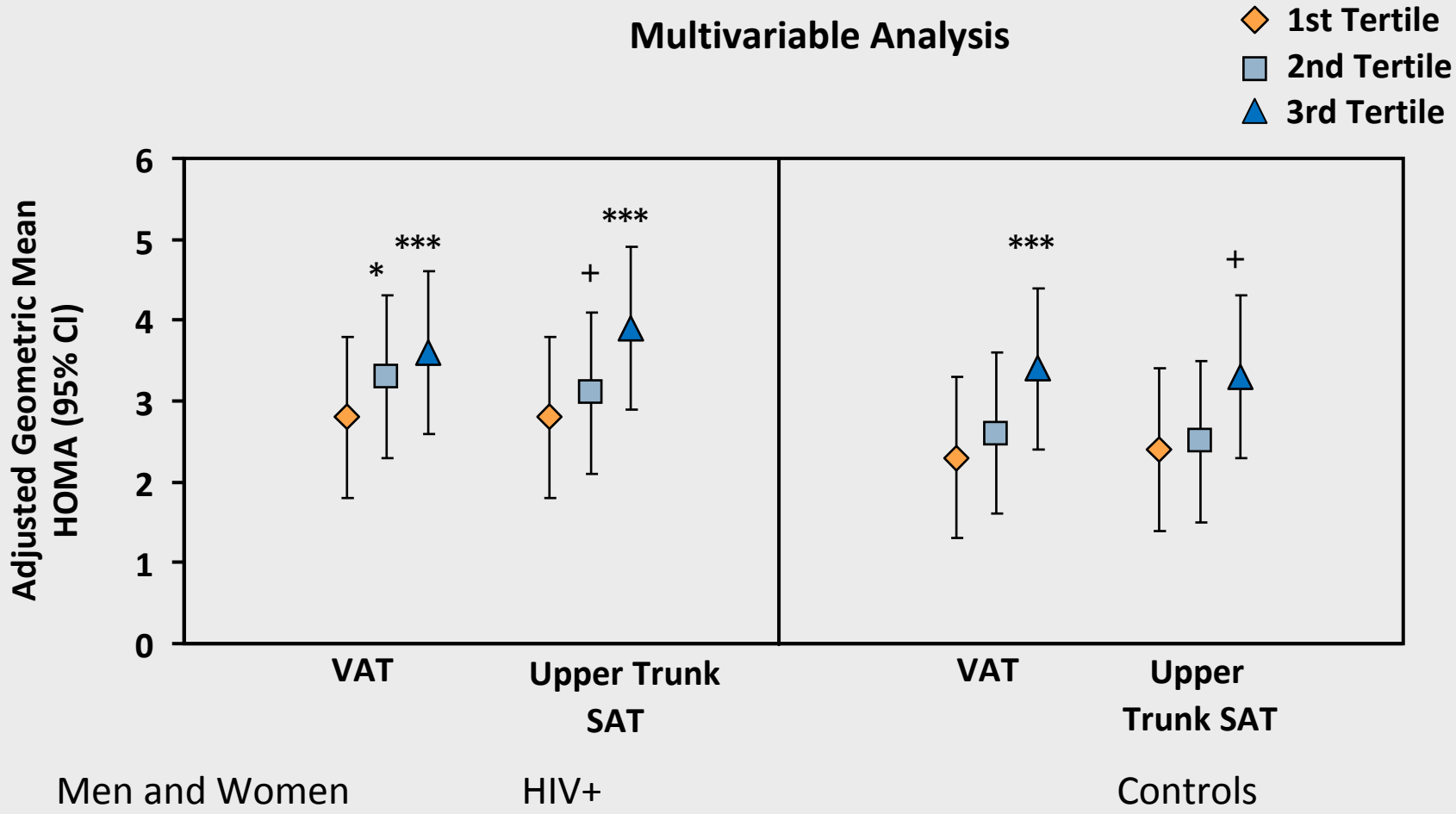
Weight gain in PLHIV is associated with higher risk for diabetes and CVD



Every 2.26 kg weight gained led to 14% increased risk for T2DM in PLHIV but only 8% in HIV negative

Herrin et.al. 2016 JAIDS

FRAM: VAT and upper trunk sat are associated with insulin resistance



Asterisks denote comparison with first tertile: *** p<.0001, ** p <.001, * p < .01, + p<.05

Scherzer R, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 76.

Comparisons in weight increase among ARVs

Prospective randomised clinical trial subsidy of ACTG5257

- 328 patients randomised to ATV/r, RAL or DRV/r1
  - at Week 96, increases in limb fat (13.4%), subcutaneous (19.9%) and visceral abdominal fat (25.8%), trunk fat (18%), and lean mass (1.8%) were apparent ($p<0.001$ for changes within each arm)
  - changes for all fat and lean outcomes were not different between the PI arms or between the RAL and the combined PI arms

Retrospective analysis:

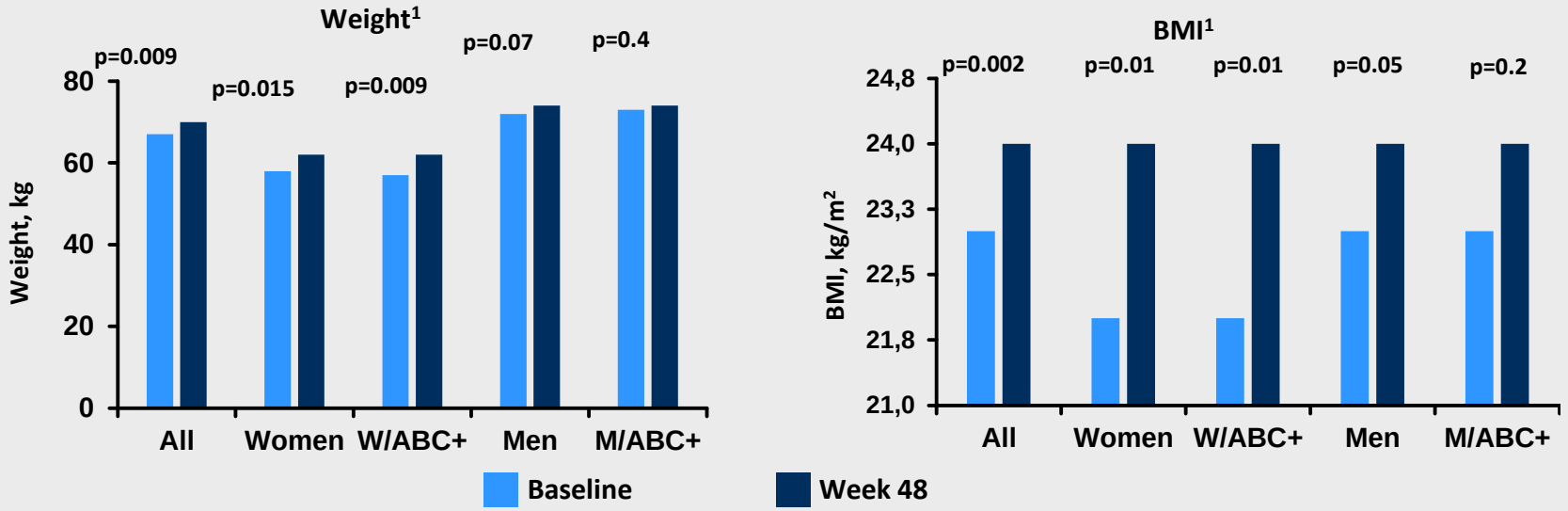
- Study ACTG A5257 (N=1,809 randomised to ATV/r, DRV/r or RAL)2
  - over 96 weeks, average weight increased by 3.8 kg and BMI by 1.3 kg/m2
  - odds of severe weight gain were significantly lower for ATV/r versus RAL (OR: 0.72 [95% CI: 0.53, 0.99]; p=0.043)
  - odds of severe BMI gain were significantly lower for DRV/r versus RAL (OR: 0.73 [95% CI: 0.53, 0.99]; p=0.041)

1. McComsey GA, et al. Clin Infec Dis 2016;62:853–62
2. Bhagwat P, et al. CROI 2017. Abstract 695

Weight increase on INI-based therapy versus baseline

Retrospective analysis:

- 462 patients on DTG-based combination therapy (≥6 months):[1]
  - mean weight gain: 3 kg (p=0.009); mean BMI increase: 1 kg/m^2 (p=0.002) versus baseline
  - increases in weight and BMI were significant for women but not men
  - weight increase particularly significant for women receiving DTG/ABC/3TC, in whom weight increased from 57 to 62 kg (p=0.009) and BMI increased from 22 to 24 kg/m^2 (p=0.01)



Case series:

Five patients using DTG showed evidence of significant weight gain; in two cases weight gain was reversed on discontinuation of DTG[2]

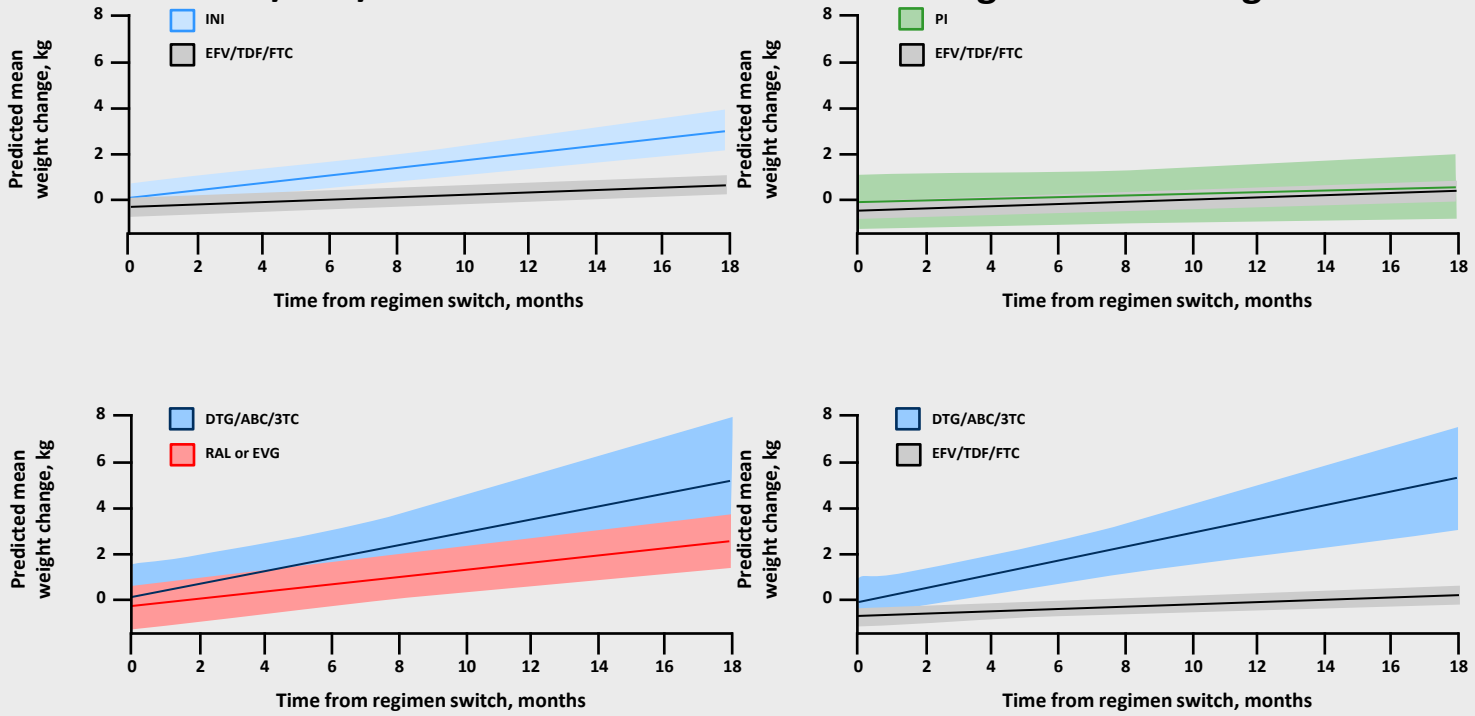
1. Menard A, et al. AIDS 2017;31:1499–500
2. Bhaduri S, et al. HIV Med 2017;18:Abstract P106

Weight gain after switch from EFV/TDF/FTC to INI- or PI- regimens

Retrospective analysis (n=495):

- Patients with sustained virologic suppression switched from EFV/TDF/FTC to an INI- or PI-containing regimen
  - patients who switched to an INI regimen gained a mean 2.9 kg at 18 months vs 0.9 kg in those continuing on EFV/TDF/FTC (p=0.003)
  - patients who switched to a PI regimen gained 0.7 kg (p=0.81)
- Amongst INI regimens, those who switched to DTG/ABC/3TC had gained the most weight at 18 months (5.3 kg, p=0.001 versus EFV/TDF/FTC)

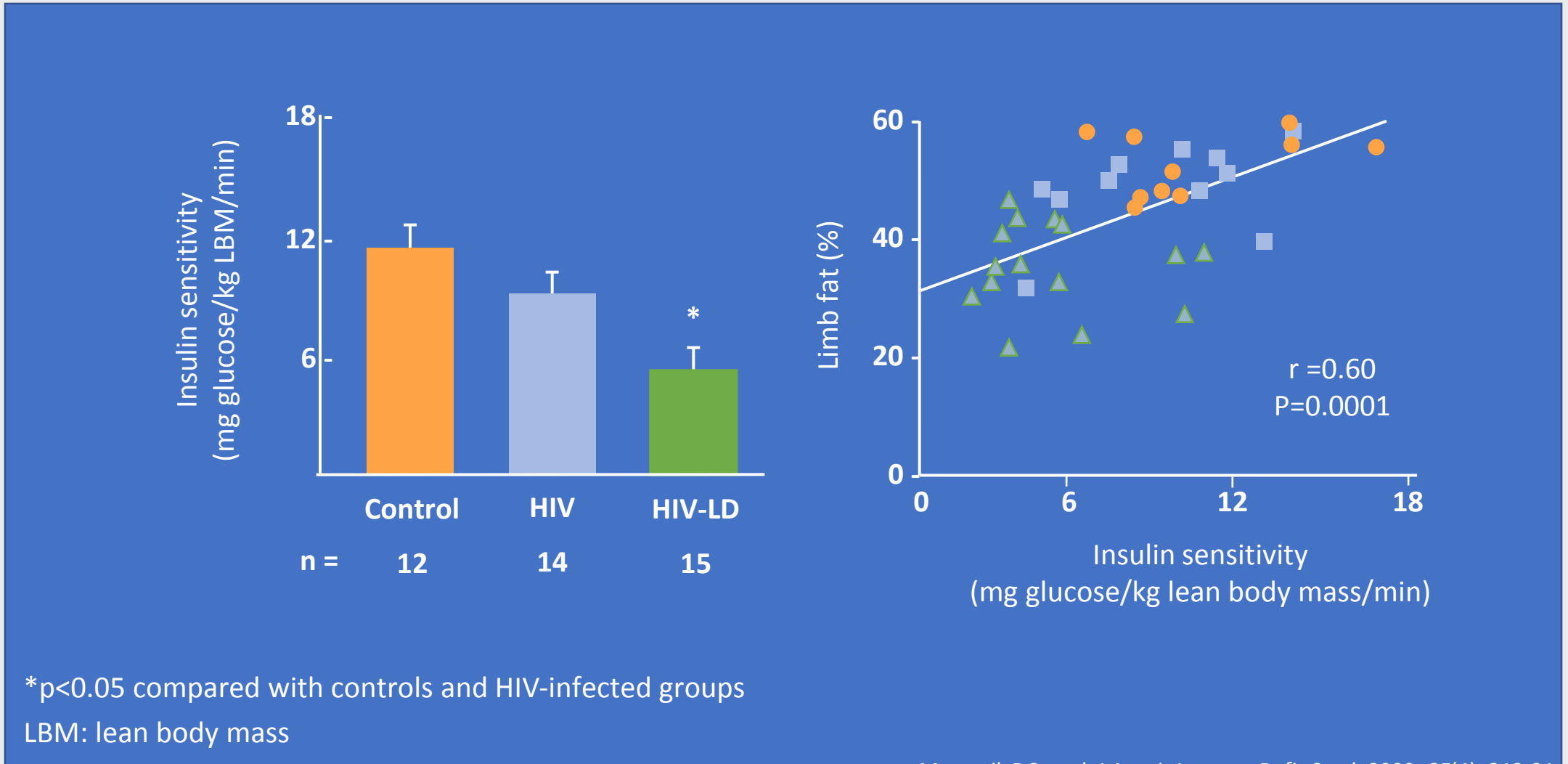
Weight change at 18 months among patients remaining on EFV/TDF/FTC or RAL or EVG versus switching to another regimen



Models adjusted for age, sex, race, total duration of ART, and baseline CD4+ T cell count and weight

Norwood J, et al. J Acquir Immune Defic Syndr 2017;76:527–531

Association between limb fat and insulin resistance in lipoatrophy

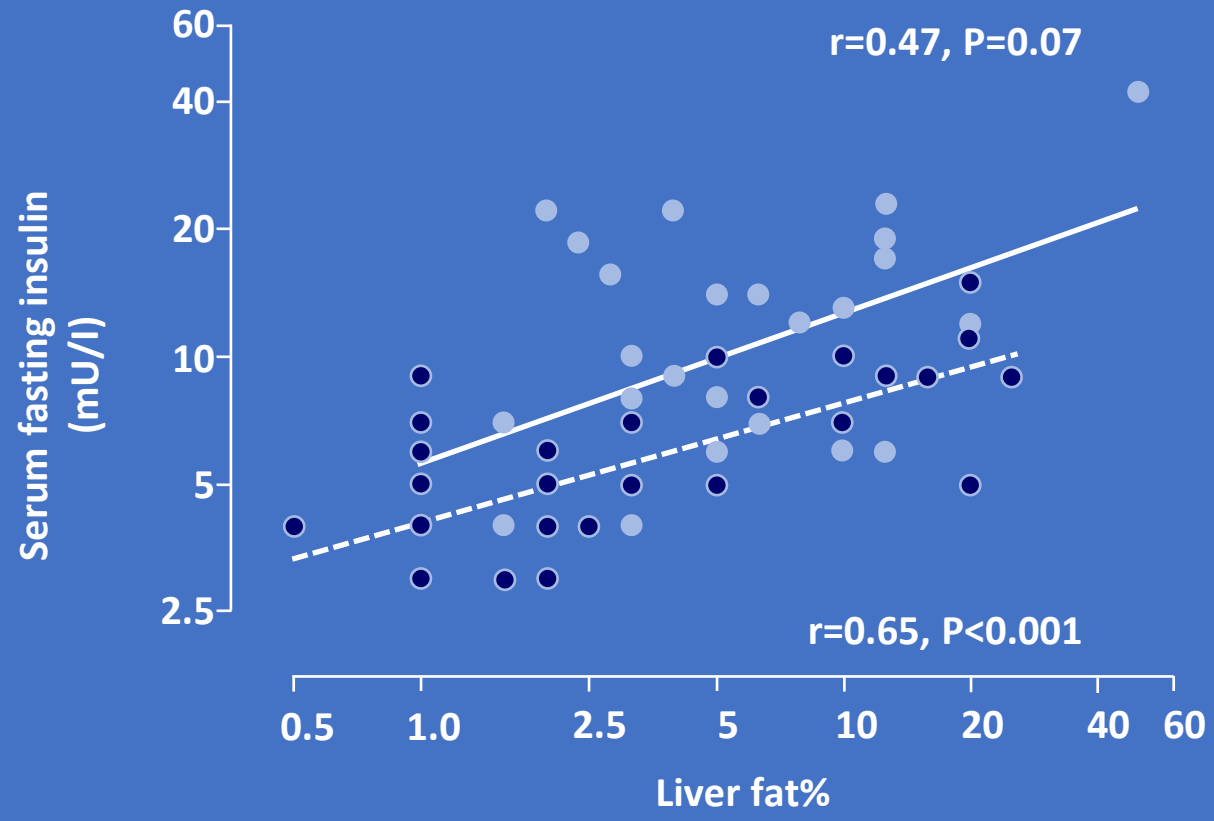


*p<0.05 compared with controls and HIV-infected groups

LBM: lean body mass

Mynarcik DC *et al*. *J Acquir Immune Defic Syndr* 2000; *25*(4): 312-21

Hepatic insulin resistance is associated with hepatic steatosis



Liver fat content (evaluated by proton-MRS) was related to insulin resistance in HIV-LD (○) and control (●) subjects

Sutinen J, et al. *AIDS* 2002, 16:2183–93

D:A:D Relationship Between Exposure to Individuals Drugs and Incidence of DM

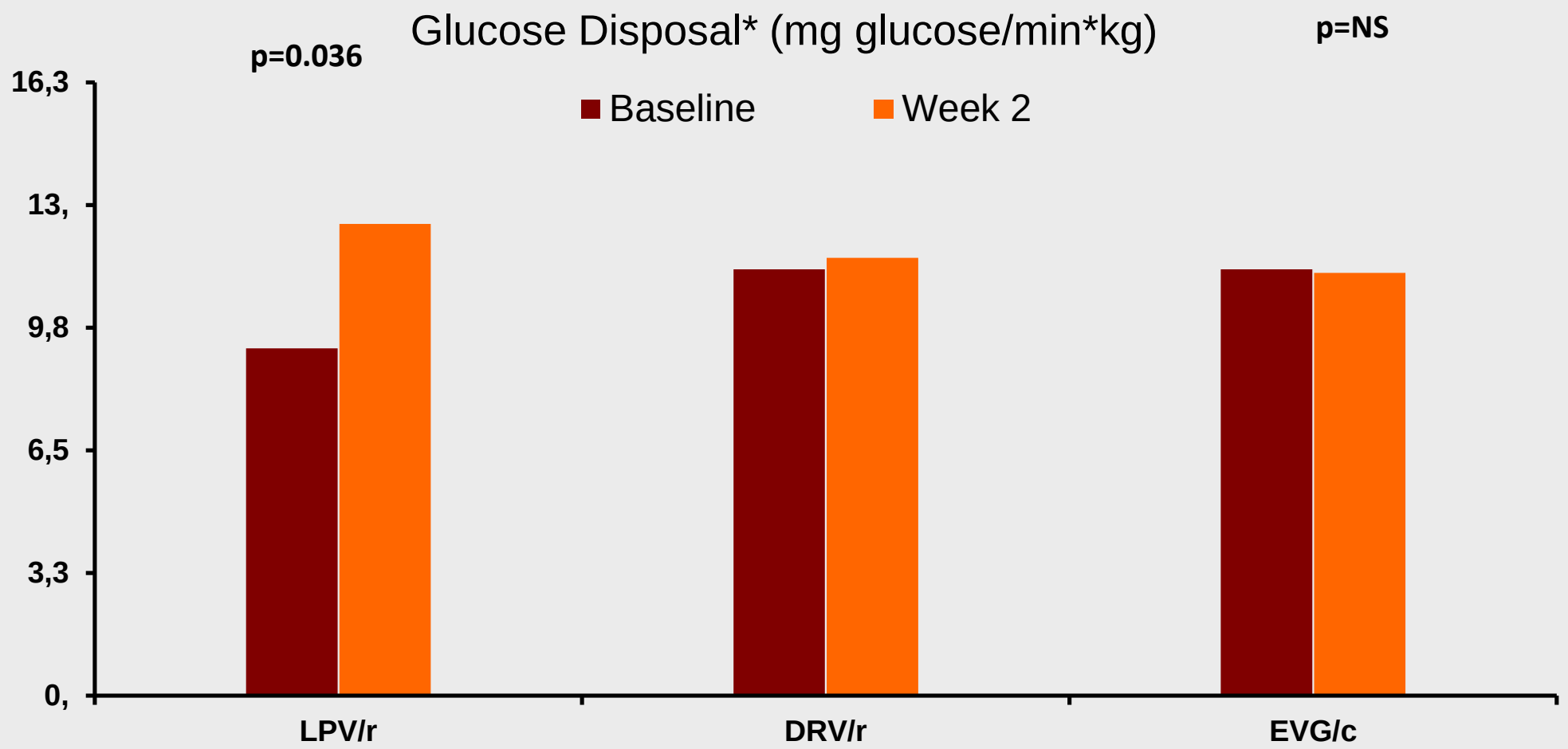
The incidence of DM in D:A:D is 5.72 per 1000 PYFU

Cumulative Exposure	Relative Risk	95% CI	P Value
Stavudine (per year)	1.19	1.15–1.24	0.0001
Zidovudine (per year)	1.06	1.03–1.10	0.0004
Didanosine (per year)	1.06	1.02–1.11	0.01
Ritonavir (per year)	0.94	0.89–0.99	0.01
Nevirapine (per year)	0.89	0.84–0.95	0.0001

Adjusted for age, sex, BMI, race, smoking status, calendar year, and cohort.

De Wit S et al. Diabetes Care. 2008;31:1224 –1229..

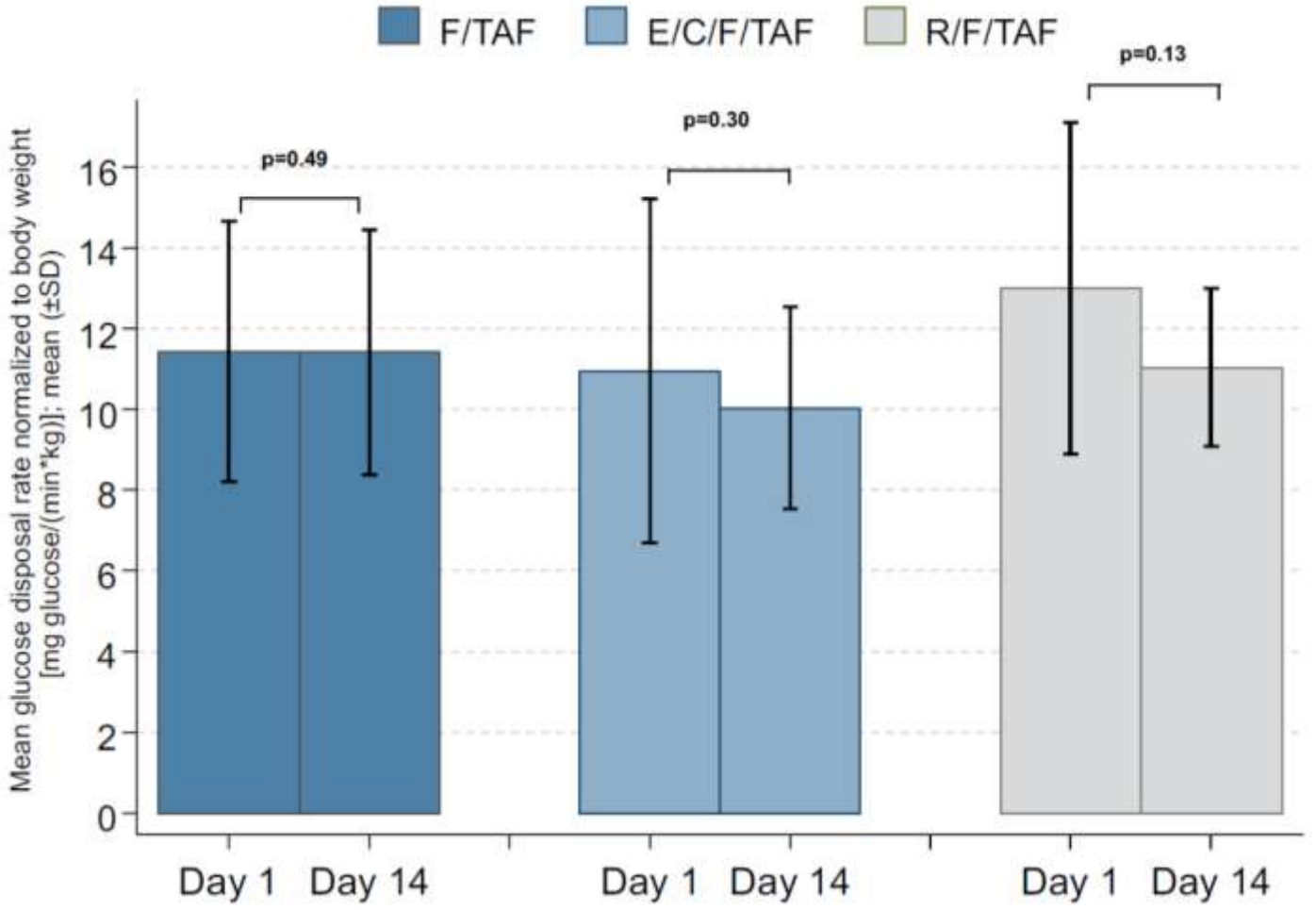
Insulin Resistance with PI/r and EVG/c +TDF/FTC



*Refers to glucose disposal following hyperinsulinemic euglycemic clamp before and 14 days after start of ART

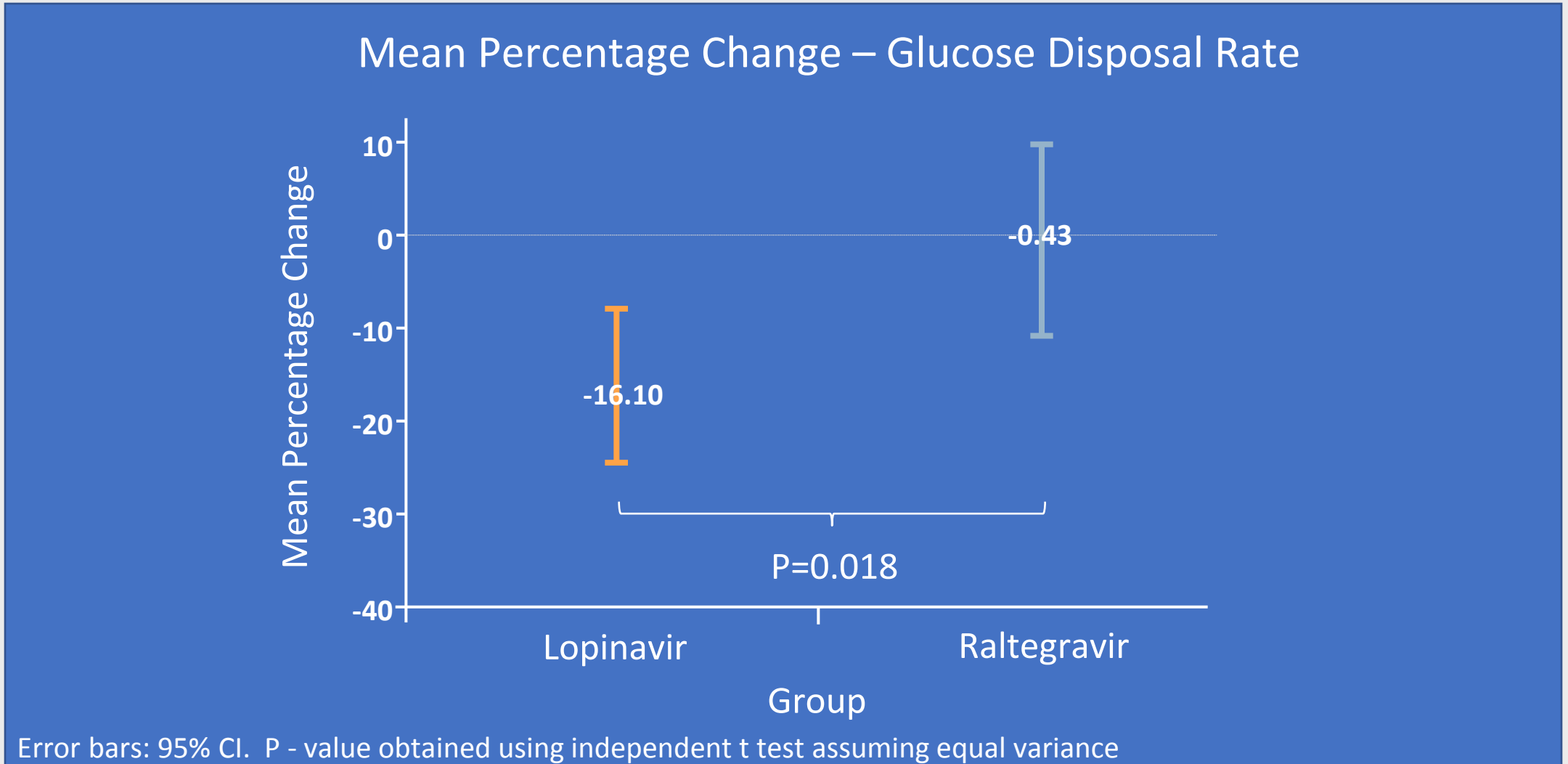
Spinner CD, et al; 8th IAS, Vancouver, Canada, July 19-22, 2015; Abst. TUPEB105.

Changes in BMI adjusted total glucose disposal (m) by TAF regimens



Spinner C, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUPEB126.

No Impact of Raltegravir vs. reduction in Insulin Sensitivity with LPV/r in Healthy Volunteers



Error bars: 95% CI. P - value obtained using independent t test assuming equal variance

Randall P , et al. ADRL London Nov 2008

ACTG5202/5224: Glucose disposal

Multivariate Analyses Examining Effects of Treatment and Clinical Characteristics on Change in Glucose and HOMA-IR Over 96 Weeks

		96-Week Glucose Change (mg/dL)	96-Week HOMA-IR Fold Change
Covariate	**Reference**	***P*-Value**	***P*-Value**
ABC/3TC	TDF/FTC	0.18	0.80
EFV	ATV/r	<0.001	0.61
Baseline HIV-1 RNA	Continuous (per 1 Log_{10} copies/ml higher)	0.047	0.023
96-week BMI Change	Continuous (per 1 kg/m^2 higher)	0.005	

Erlandson K, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 772.

NNT to Harm with MI: ABC in D:A:D

Risk	Underlying 5 year risk (%)	5 year NNH	Underlying 10 year risk (%)	10 year NNH
Low (40 yo non-smoker with good lipids and BP)	0.1	1111	0.3	370
Smoker	0.4	277	1.5	92
Smoker and DM	1.1	101	3.1	35
Smoker and raised lipids	3.1	35	7.5	14
Previous CVD	5	22	10	14

NNT, number needed to harm; MI, myocardial infarction; ABC, abacavir; DM, diabetes mellitus; CVD, cardiovascular disease

Kowalska JD, et al . HIV Med. 2010 Mar;11(3):200-8.

Medical and Surgical Interventions Shown to Delay or Prevent T2D

Lifestyle modification should be used with all pharmacologic or surgical interventions.

Intervention	Follow-up Period	Reduction in Risk of T2D (*P* value vs placebo)
Antihyperglycemic agents		
Metformin[1]	2.8 years	31% (*P*<0.001)
Acarbose[2]	3.3 years	25% (*P*=0.0015)
Pioglitazone[3]	2.4 years	72% (*P*<0.001)
Rosiglitazone[4]	3.0 years	60% (*P*<0.0001)
Weight loss interventions		
Orlistat[5]	4 years	37% (*P*=0.0032)
Phentermine/topiramate[6]	2 years	79% (*P*<0.05)
Bariatric surgery[7]	10 years	75% (*P*<0.001)

T2D, type 2 diabetes.

1. DPP Research Group. *N Engl J Med*. 2002;346:393-403. 2. STOP-NIDDM Trial Research Group. *Lancet*. 2002;359:2072-2077.
3. Defronzo RA, et al. *N Engl J Med.* 2011;364:1104-15. 4. DREAM Trial Investigators. *Lancet*. 2006;368:1096-1105.
5. Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161. 6. Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.
7. Sjostrom L, et al. *N Engl J Med*. 2004;351:2683-2693.

Interventions for pre-DM & DM

- Diet & Exercise, weight reduction, Smoking cessation
- Pharmacological
  - First ine in most cases: Metformin starting at 500-750mg bd
  - Secondline:
    - GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide albiglutide, dulaglutide, semaglutide. Caution: panceatitis
    - SGLT-2 canagliflozin, dapagliflozin, and empagliflozin Caution: glycosuria
  - Others:
  - Sulfonylureas: gliclazide
  - Thiazolidinediones (glitazones): rosiglitazone or pioglitazone
  - Gliptins (DPP-4 inhibitors)
  - Insulin
- ARB or ACE inhibitor for renal protection
- Statin and other lipid lowering agents
- Anticoagulant
- Modification of ART

What happens after DM diagnosis?

New Medication

- Dietary changes
- Metformin
- Statin
- Antihypertensive (ARB or ACE)
- ?anticoagulant

New Monitoring

- Blood sugar
- HBa1c
- Urinary albumin, ACR, eGFR
- BP
- Retinal screens
- Neuropathy screens
- Podiatry

Abstracts of the HIV Drug Therapy Glasgow Congress 2014
Zong J et al. *Journal of the International AIDS Society* 2014, **17(Suppl 3)**:19584
http://www.jiasociety.org/index.php/jias/article/view/19584 | http://dx.doi.org/10.7448/IAS.17.4.19584

JIAS Journal of the International AIDS Society

Poster Sessions – Abstract P052

The effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects

Zong, Jian[1]; Borland, Julie[2]; Jerva, Fred[2]; Wynne, Brian[3]; Choukour, Mike[4] and Song, Ivy[1]

[1]Clinical Pharmacology Modeling & Simulation, GlaxoSmithKline, RTP, USA. [2]CPSSO, GlaxoSmithKline, RTP, USA. [3]Infectious Disease MDD, GlaxoSmithKline, RTP, USA. [4]Biostatistics, Parexel, Sarasota, FL, USA.

Conclusions: Co-administration of DTG and metformin was well tolerated, yet significantly increased metformin plasma exposure; effects were DTG dose dependent. Though metformin has a wide therapeutic index and alone is not associated with hypoglycemia, close monitoring is recommended when co-administering metformin and DTG. Dose adjustments of metformin may be considered.

Table 1. Statistical comparison of metformin PK parameters with and without dolutegravir

Plasma Metformin PK Parameter	GLS mean Metformin Alone (Period 1)	Metformin + DTG (Period 2)	GLS mean ratio (90% CI) Metformin + DTG vs. Metformin Alone
Cohort 1 (DTG 50 mg QD)	n = 15	n = 14	
Cmax (μg/mL)	0.932	1.55	1.66 (1.53, 1.81)
AUC(0-τ) (hr*μg/mL)	6.83	12.2	1.79 (1.65, 1.93)
Cohort 2 (DTG 50 mg BID)	n = 15	n = 14	
Cmax (μg/mL)	0.845	1.878	2.11 (1.91, 2.33)
AUC(0-τ) (hr*μg/mL)	6.49	15.9	2.45 (2.25, 2.66)

Blood pressure treatment target <130, <80

- Employ therapeutic lifestyle modification
  - DASH or other low-salt diet combined with Physical activity
- Select antihypertensive medications based on BP-lowering effects and ability to slow progression of nephropathy and retinopathy
  - ACE inhibitors or ARBs
- Add additional agents when needed to achieve blood pressure targets
  - Calcium channel antagonists
  - Diuretics preferably Indapamide
  - Combined α/β-adrenergic blockers
  - β-adrenergic blockers
  - Do not combine ACE inhibitors with ARBs

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension.>

Statin use

- Should be universally considered
- LDL-C target: <70 mg/dL or 3 mmol/l—for DMs
- Atorvaststin, Rosuvastatin and Pitavastatin
- Watch for ART interactions

- Use a statin regardless of LDL-C level in patients with diabetes who meet the following criteria:
  - >40 years of age
  - ≥1 major ASCVD risk factor
    - Hypertension
    - Family history of CVD
    - Low HDL-C
    - Smoking

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

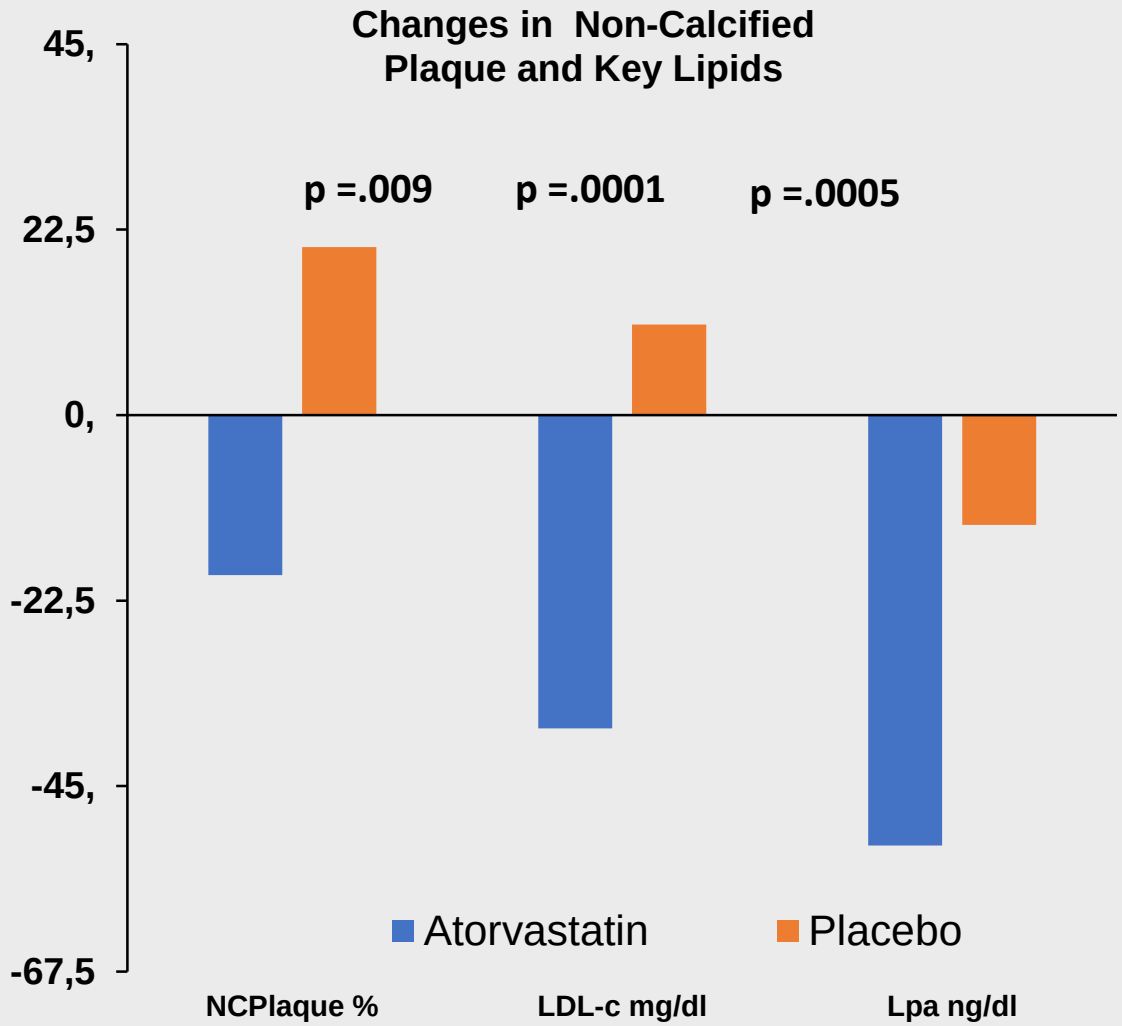
Antiplatelet Agents

- Consider aspirin therapy (75–162 mg/day, weight based)
  - Meta-analysis suggests no/limited benefit in DMs
  - Greater benefits may exist in those who have at least one additional major risk factor
    - Known vascular disease, retinopathy or nephropathy
    - Family history of CVD
    - Hypertension
    - Smoking
    - Dyslipidemia
    - Albuminuria

Adapted from ADA. VI. Prevention, Management of Complications. Diabetes Care 2014;37(suppl 1):S40

Atorvastatin vs Pbo for Non-Ca++ coronary plaques

- 40 HIV-infected pts with subclinical coronary atherosclerosis and low density lipoprotein (LDL) cholesterol <130mg/dL
- Coronary atherosclerotic plaque as assessed by coronary computed tomography angiography
- Statin therapy was well-tolerated, with low incidence of clinical adverse events or laboratory abnormalities



Lo J, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 136.

Assessment of Diabetic Nephropathy

- Annual assessments
  - Serum creatinine to determine eGFR
  - Urine Albumin/Creatinine ratio
- Begin annual screening
  - 5 years after diagnosis of T1D if diagnosed before age 30 years
  - At diagnosis of T2D or T1D in patients diagnosed after age 30 years
- HIV:
  - Caution with DTG, RPV, /r and /c regards effects on eGFR
  - Caution with TDF re renal effects on eGFR and tubular proteins incl albumin
  - Caution with ABC, DRV, LPV due to CV risk in high risk patients
  - Caution with ATV/r and /c due to kidney stones

eGFR = estimated glomerular filtration rate; T1D = type 1 diabetes; T2D = type 2 diabetes.

Key points

- Diet, exercise, & education: foundation of any T2DM therapy program.
- Metformin remains the optimal first-line drug.
- After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable.
- Many patients will require insulin therapy alone or in combination with other agents to maintain BG control.
- Comprehensive CV risk reduction is a major focus of therapy.
- ART choices affect glucose, lipids, CV and renal outcomes