Effect of Second Generation Antipsychotics on Metabolic and Vascular Risk Factors in HIV-infected Adults on Long Term Antiretroviral Therapy

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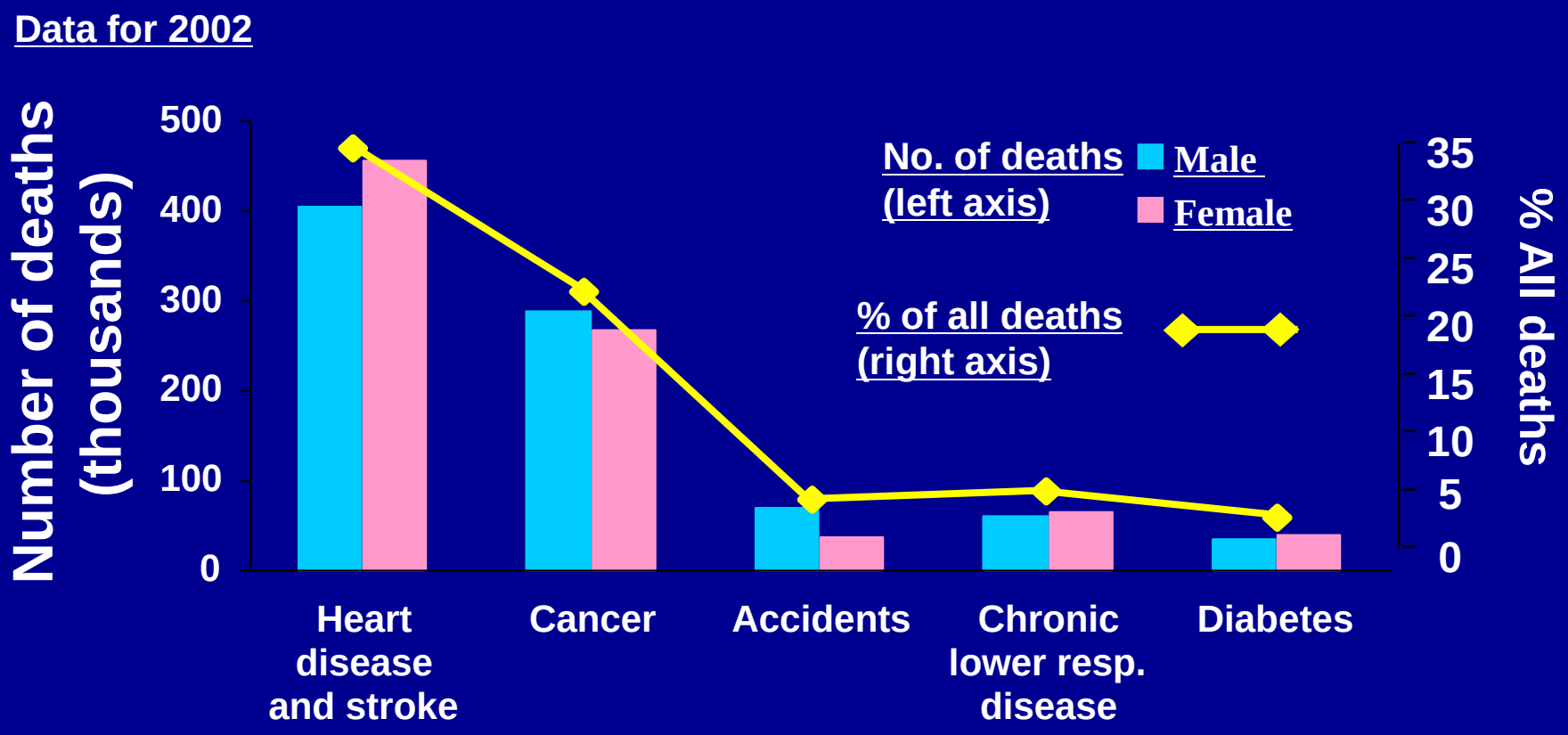
Outline

- Definitions: SGAs, metabolic syndrome and vascular risk factors
- Context: Cardiovascular risk, HIV and antiretroviral therapy
- Cohorts: CHARTER and other HNRP studies
- Methods for ascertaining SGA use and metabolic and vascular risk outcomes
- Results: Increased metabolic/vascular risk with SGAs
- Conclusions and future directions

Despite therapeutic advances, CV disease remains the leading cause of death (USA)



National Center for Health Statistics, 2004

Serious (severe) mental illnesses (SMI): Impact and overlap with HIV

- SMI – mental disorder that substantially interferes with life activities and ability to function
  - » DSM-IV disorders: mood disorders (MDD, BD), anxiety disorders nonaffective psychoses (incl. schizophrenia)
  - » 5.4% of the US adult population
- HIV prevalence 10-fold higher in SMI vs. non-SMI
- 2-3 fold increased risk of dying
- mortality gap widened in recent decades
- 2X increased risk of dying from cardiovascular disease (CVD)

Antipsychotics

Conventional

- perphenazine
- fluphenazine
- haloperidol
- chlorpromazine

Atypical

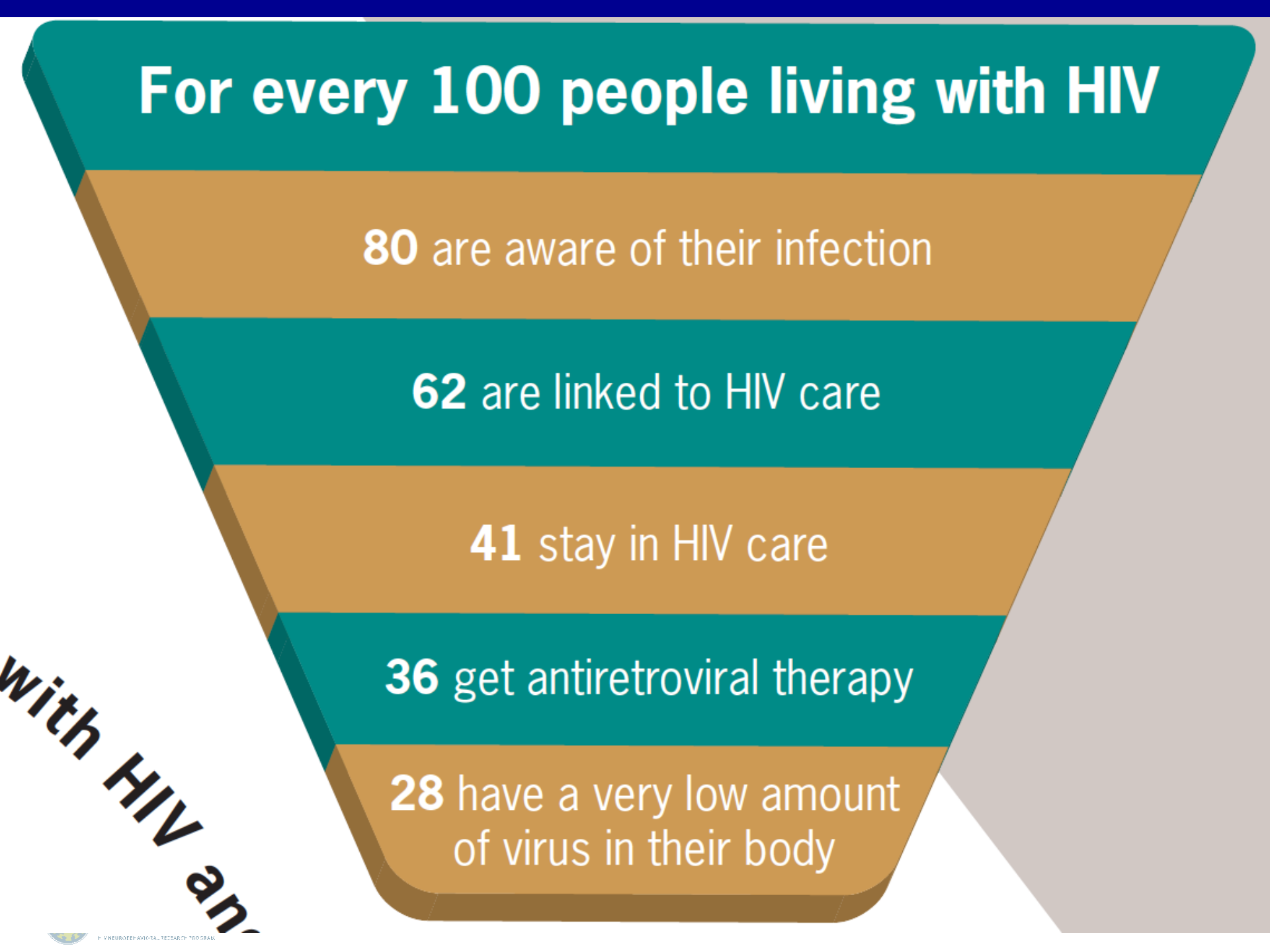
- aripiprazole
- quetiapine
- olanzapine
- risperidone
- ziprasidone
- clozapine

>90% of market share despite being more expensive

Off-label use of SGAs

Maher et al. JAMA. 2011; 306: 1359

- Anxiety disorders
- Bipolar disorders
- Obsessive-compulsive disorder
- Post-traumatic tress disorder
- Behavioral disturbances in dementia


For every 100 people living with HIV
80 are aware of their infection
62 are linked to HIV care
41 stay in HIV care
36 get antiretroviral therapy
28 have a very low amount of virus in their body
with HIV an

Meta-Analysis of CVD in HIV+
Islam et al., HIV Medicine 2012

- Cardiovascular disease = myocardial infarction, ischemic heart disease, cerebrovascular disease and coronary heart disease
- Meta-analysis of 23 studies
  - » 21 observational, 2 randomized trials
  - » 16 cohort studies; average follow-up 5 years
- 3 studies compared HIV+ vs HIV-
- ~80,000 HIV+ vs 1.5M HIV-

Islam et al., HIV Medicine 2012 (cont'd)

- HIV+ vs HIV-
  - » Pooled RR of CVD 1.6 (95% CI 1.4 - 1.8; p<0.001)
- HIV+ on cART vs HIV-
  - » Pooled RR of CVD 2.0 (95% CI 1.7, 2.4; p<0.001)
- cART vs no CART
  - » Pooled RR of CVD 1.5 (95% CI 1.4, 1,7; p<0.001)
- PI-based CART vs no cART
  - » Pooled RR of CVD 1.7 (95% CI 0.86, 3.19; ns)

Metabolic Syndrome Components

- Hypertension: BP. > 140/90
- Dyslipidemia: TG > 150 mg/ dL (1.7 mmol/L)
  - » HDL- C < 35 mg/ dL (0.9 mmol/L)
- Obesity (central): BMI > 30 kg/M2
  - » Waist girth > 94 cm (37 inch)
  - » Waist/Hip ratio > 0.9
- Impaired Glucose Handling: IR , IGT or DM
  - » FPG > 110 mg/dL (6.1mmol/L)
  - » 2hr.PG >200 mg/dL(11.1mmol/L)
- Microalbuninuria (WHO)

Diagnostic Criteria

- **WHO:**
  - » Impaired glucose handling + 2 other criteria
  - » Also requires microalbuminuria - Albumin/ creatinine ratio >30 mg/gm creatinine
- **IDF:**
  - » Central obesity plus two of the other abnormalities
- **NCEP/ATP III:**
  - » Require 3 or more of 5 criteria

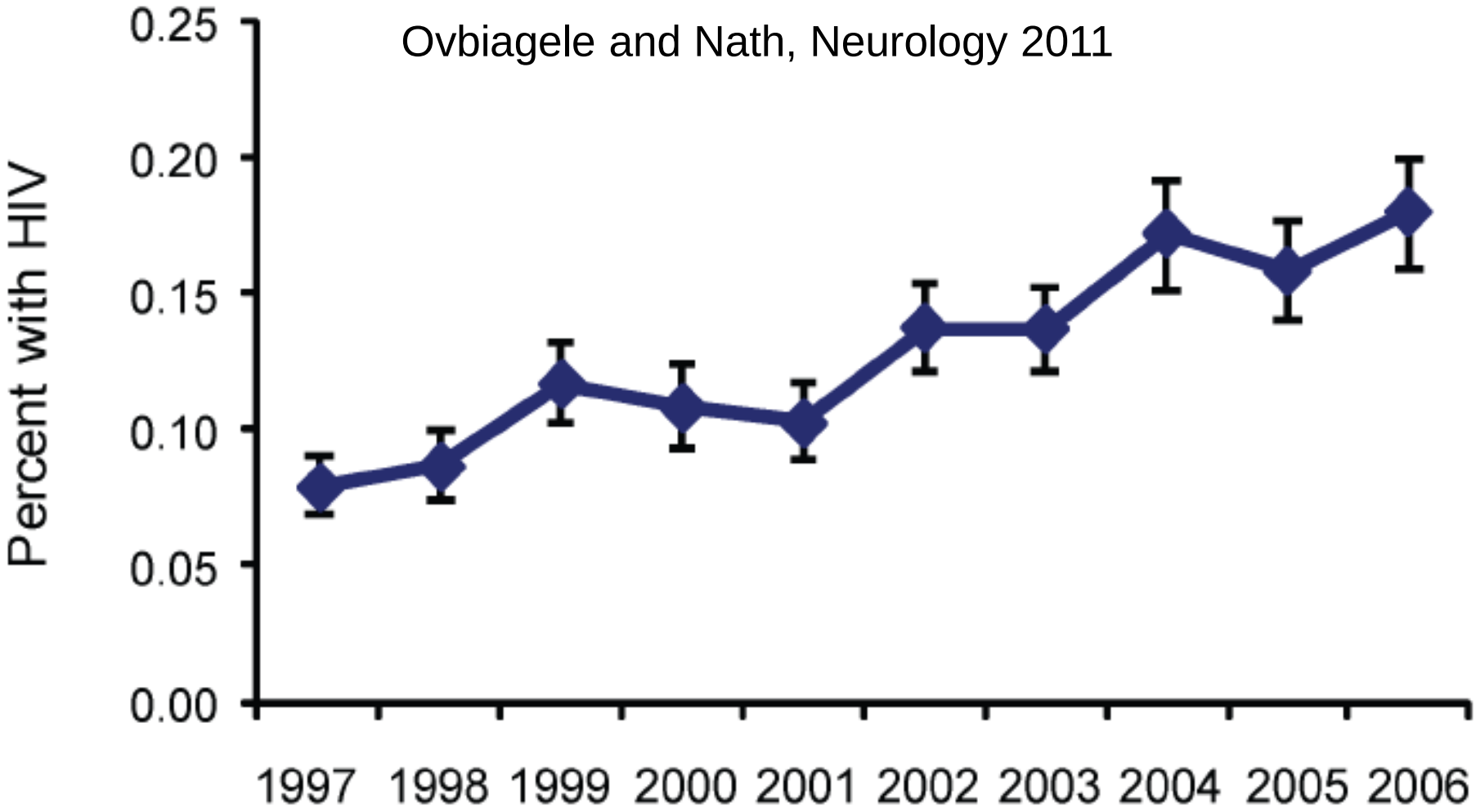
Scope of the Problem

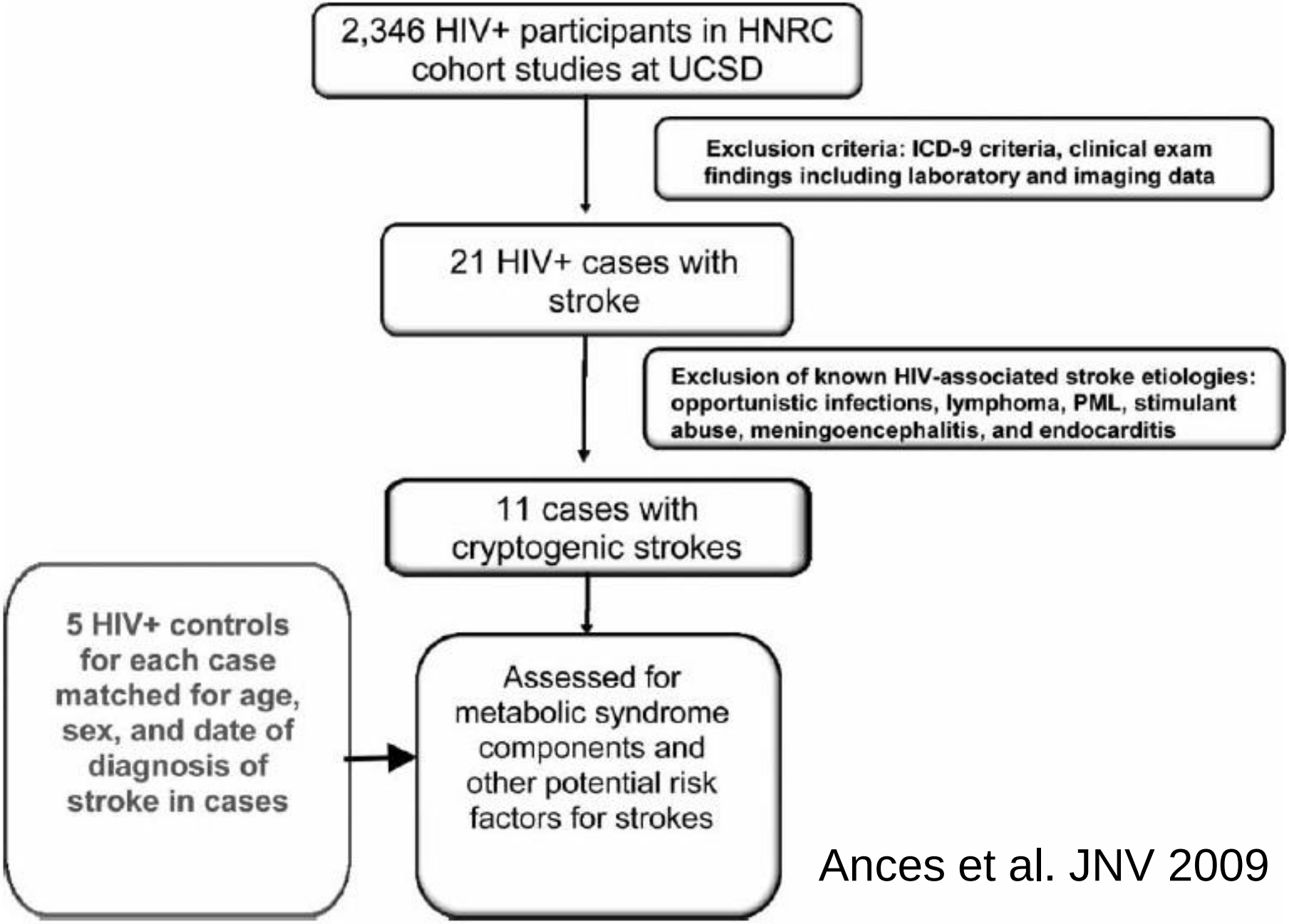
- In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), 1/3 met NCEP criteria for metabolic syndrome at baseline

Untreated metabolic syndrome disturbances:

- 88% of patients with dyslipidaemia
- 62% of hypertensives
- 38% of diabetes mellitus

Percent of coexistent HIV among primary stroke diagnoses in the United States





Ances et al. JNV 2009

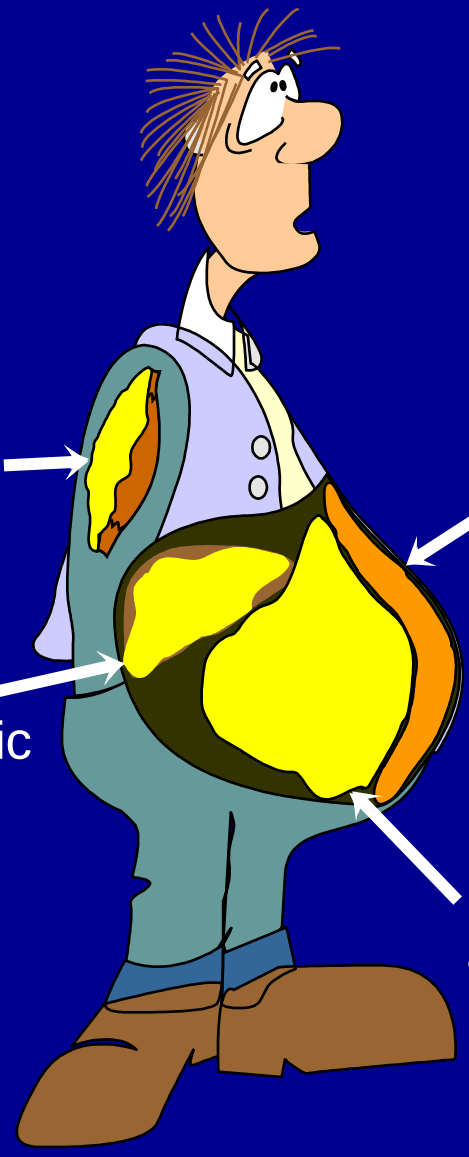
Metabolic Risk Factors in HIV+ Stroke

	HIV+stroke	HIV+control	p	OR (95% CI)	Effect size
(MAP) (mm Hg)	101 ± 11	86 ± 10	0.003	5.9 (1.2, 29.7)	1.46
Random triglycerides (mg/dL)	327 ± 260	217 ± 117	0.460	1.6 (0.76, 3.4)	0.48
BMI (kg/m2)	28.6 ± 7.4	24.7 ± 4.1	0.100	2.0 (1.0, 4.0)	0.73
Random glucose (mg/dL)	115 ± 59	95 ± 19	0.440	1.6 (0.83, 3.1)	0.53
Serum uric acid (mg/dL)	6.3 ± 2.2	4.8 ± 1.2	0.020	2.7 (1.1, 6.7)	0.96

Published studies: Vascular/Metabolic Risk and Neurocognitive Impairment in HIV+

Study	Sample	Subjects	Design	Predictors	Outcome	Key Findings
Valcour 2005, 2006	203 HIV+	82%M 20–76y	X-sect	DM self-report or glucose >125	Learning/memory, SIP, executive, motor, attention	DM assoc with HAD (adj for other vasc risk)
Becker 2009	428 HIV+ 207 HIV-	100% M 40-65y	X-sect	Coronary Ca^{++} cIMT, lipids, DM, GFR	Learning/memory, executive, PM speed	Worse cIMT & GFR assoc → ↓ PM speed
Wright 2010	292 HIV+	58% M 30-50y	X-sect	Prior CVD, HTN, ↑ cholest	PM speed, executive, SIP	CVD, HTN, chol → ↓ cognition
Foley 2010	98 HIV+	81% M 30-65y 70% AA	X-sect	Self-report DM, HTN, MI, CHF	Learning/memory, executive, motor, Attn/WM	CV risk → ↓ processing speed (age adj)
Fabbiani 2012	245 HIV+	76% M 30-60y 94% cART	X-sect	cIMT, vascular comorbid incl obesity, lipids	Learning/memory, executive, PM speed	DM + cIMT → ↓ cognition
McCutchan 2012	130 HIV+	85% M	X-sect	BMI, WC, DM, HTN, lipids	Learning/mem-ory, executive, motor, attention, SIP	↑ WC → ↓ cognition

Fat Topography In Type 2 Diabetic Subjects

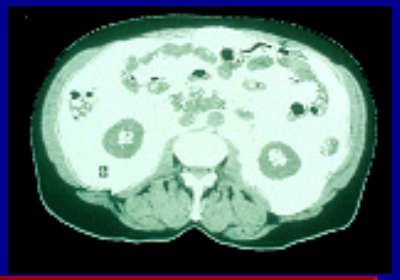


Intramuscular

Subcutaneous

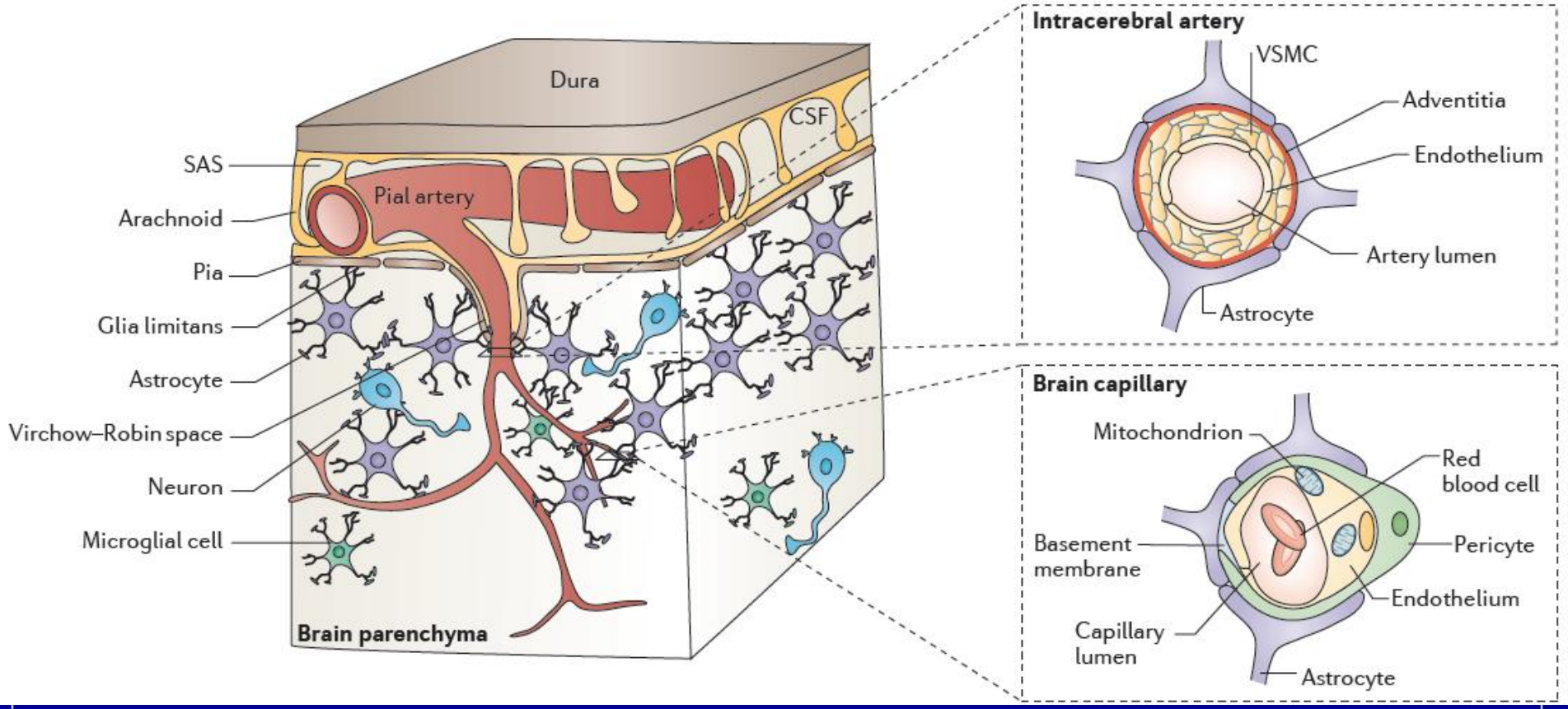
Intrahepatic

Intra-abdominal



FFA*
TNF-alpha*
Leptin*
IL-6 (CRP)*
Tissue Factor*
PAI-1*
Angiotensinogen*

Cerebral microcirculation and the neurovascular unit



Zlokovic BV. Nature Reviews Neuroscience 2011; 12: 723

Metabolic components of the Neurovascular Unit

- Obesity induces functional astrocytic leptin receptors in hypothalamus
- insulin receptors expressed on the surface of BBB endothelial cells
- low-density lipoprotein receptor related protein (LRP) - ApoE and amyloid processing

Objectives

Evaluate the metabolic consequences of concurrent use of ART and second generation antipsychotics (SGAs) in a population of HIV-infected adults

Methods

- Design: Retrospective, cross-sectional multisite study examined of 2229 ARV-treated, HIV+ adults
- SGA+ or SGA- at last visit
- DSM-IV psychiatric diagnoses
  - » Composite International Diagnostic Interview (CIDI)
  - » Psychiatric Research Interview for Substance and Mental Disorders,
  - » Structured Clinical Interview for DSM-IV criteria (SCID)
- Clinical Assessment
- Systolic (SBP), diastolic (DBP) → mean arterial pressure (MAP)
- Height, weight → body mass index (BMI)

Methods, continued

Labs: Plasma total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, serum triglycerides, glucose, HCV sierology

HIV disease: date of infection, current and nadir CD4, Viral load, ARV history, current regimen

Statistical analysis: Linear and logistic multivariable models controlling for demographic and disease covariates

Demographics

		HIV+ on cART SGA- (n=1971)	HIV+ on cART SGA+ (n=258)	p
Age (years)		45.5 (± 9.4)	45.3 (± 8.0)	ns
Gender (male)		1613 (82%)	194 (75%)	0.013*
Ethnicity	Black	619 (31%)	103 (40%)	0.007*
	Hisp	350 (18%)	32 (12%)	0.040*
	White	936 (47%)	114 (44%)	ns
	Other	66 (3%)	9 (4%)	ns

HIV disease and ART

		HIV+ on cART SGA- (n=1971)	HIV+ on cART SGA+ (n=258)	p
HIV disease status	Est. duration HIV (mos)	146.2 (82.5)	148.2 (86.2)	ns
	Nadir CD4	113 (26-232)	146.5(40-226)	ns
	Current CD4	439 (258-644)	425 (258-615)	ns
	Plasma VL (log_{10} c/mL)	1.7 (1.7-2.4)	1.7 (1.7-2.6)	ns
Antiretroviral Therapy	Duration current ART (mos)	15.2 (5.4-34.3)	16.3 (6.9-31.8)	ns
	PI-based (%)	1233 (63%)	170 (66%)	ns

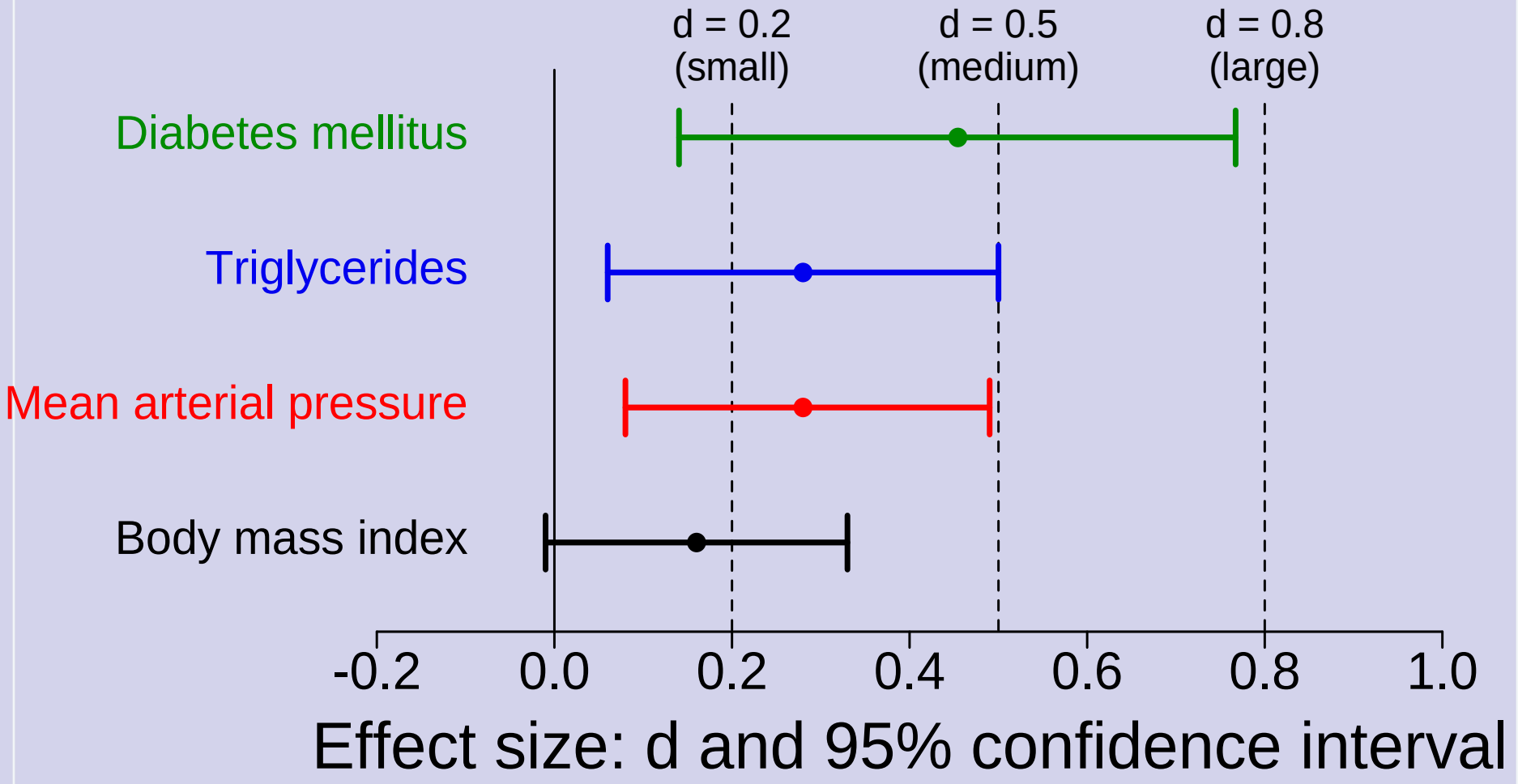
Most commonly used SGAs in 258 CHARTER subjects

Medication	N	Duration Range (mos)
Quetiapine (Seroquel)	125	0.2 – 128
Risperidone (Risperdal)	58	0.16 – 121
Olanzapine (Zyprexa)	48	0.03 – 88
Aripiprazole (Abilify)	29	0.43 – 124
Ziprasidone (Geodon)	13	1.35 – 107
Palimperidone (Invega)*	2	1.02 – 33
Clozapine (Clozaril)*	1	0.46 – 0.46

Psychiatric Diagnoses

	HIV+ on cART SGA- (n=1971)	HIV+ on cART SGA+(n=258)	p
Current substance abuse/dependence[2]	97 (5%)	17 (7%)	ns
Lifetime substance abuse/dependence[2]	1265 (69%)	186 (78%)	0.011*
Alcohol abuse/dependence[2]	944 (52%)	141 (59%)	0.047*
Current major depressive disorder (MDD)[2]	198 (11%)	51 (22%)	<0.001*
Bipolar Disorder[2]	53 (24%)	47 (57%)	<0.001*

Association between SGA and MetS variables



Odds Ratios for association of SGAs with BMI > 30

SGA medication	OR	95% CI	P-value
Aripiprazole (Abilify)	1.61	(0.68, 3.84)	0.283
Olanzapine (Zyprexa)	1.39	(0.68, 2.86)	0.364
Quetiapine (Seroquel)	1.81	(1.19, 2.75)	0.006
Risperidone (Risperdal)	1.84	(1.02, 3.32)	0.043
Ziprasidone (Geodon)	2.63	(0.77, 9.03)	0.125

Relationship of Individual SGAs to Metabolic Syndrome Components

	N	↑BMI	↑MAP	↑Total Cholest	↑Trigly-cerides	↑DM
Quetiapine (Seroquel)	125	✔		✔		✔
Risperidone (Risperdal)	58			✔		
Olanzapine (Zyprexa)	48				✔	
Aripiprazole (Abilify)	29	✔				
Ziprasidone (Geodon)	13		✔			

Conclusions, Limitations

- SGA use common in ART-treated HIV+
- Most frequently used agent quetiapine (Seroquel)
- As in HIV-, SGA use overall associated with significantly worse vascular/metabolic risk (↑ DM, TG, BMI, MAP, but not cholesterol)
- Quetiapine had the largest number of significant associations with vascular/metabolic risk (odds ratios overlapped with those of other SGAs)
- Concomitant SGAs with ART may amplify metabolic disturbances (SGA X ART interaction not studied)

Future Directions

- Consider clinical trials of alternative agents for HIV+ needing antipsychotic therapy
- Assess impact on vascular outcomes directly measured (stroke, myocardial infarction, neurocognitive impairment)
- In vitro and animal model research to assess mechanisms of vascular/metabolic risk associated with SGAs

Intervention strategies:
Targets for vascular/metabolic disease in HIV

- Metabolic syndrome disturbances
  - » Statins, anti-hypertensives, GH
- Insulin resistance – NSAIDs, IGF-1, GH
- Inflammation – cenicriviroc (CCR5/CCR2)
- Physical exercise
- Manipulating the gut microbiome

Effects of Growth Hormone–Releasing Hormone on Cognitive Function in Adults With Mild Cognitive Impairment and Healthy Older Adults

Results of a Controlled Trial

Laura D. Baker, PhD; Suzanne M. Barsness, RN, MSN; Soo Borson, MD; George R. Merriam, MD; Seth D. Friedman, PhD; Suzanne Craft, PhD; Michael V. Vitiello, PhD

Background: Growth hormone–releasing hormone (GHRH), growth hormone, and insulinlike growth factor 1 have potent effects on brain function, their levels

posites reflecting executive function, verbal memory, and visual memory. Executive function was assessed with Stroop Color-Word Interference, Task Switching, the Self-Ordered

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