The Converging Epidemics of HIV and Obesity

Southeast AETC Webcast Wednesday Series
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Objectives

- Describe changes in obesity prevalence among HIV-infected individuals over the past decade and the groups most affected
- Identify the effects of obesity on cardiometabolic disease risk factors in HIV patients and the major non-infectious comorbidities exacerbated by obesity
- Summarize the disease screening and major cardiometabolic disease treatment considerations in obese HIV patients

From pre-ART to HAART: The Nutrition Transition

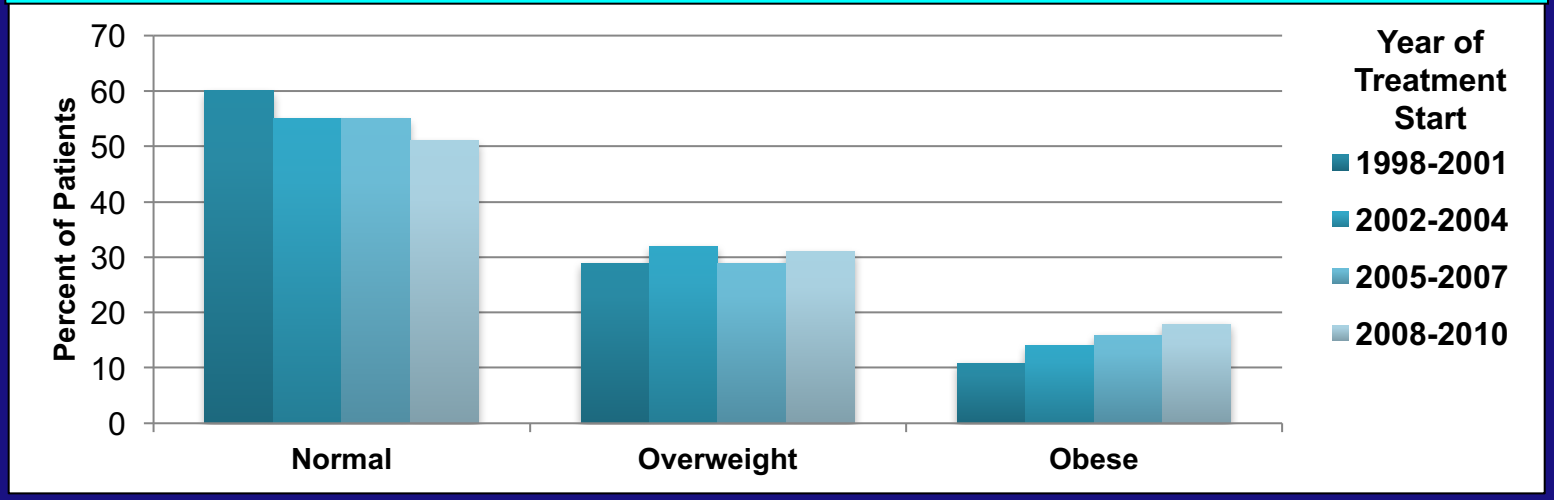
- HIV-wasting (>10% involuntary weight loss) seen in >30% of patients in pre-ART era and often signaled accelerated disease progression
- Wasting prevalence in HAART era <8% - Predictors include injection drug use, homeless, food insecurity, and low-income level
- With availability of effective ART, maintenance of healthy weight has become a more pressing issue

Nahlen BL. *AIDS* (2)1993
Siddiqui J. *Curr Med Res and Opin* (25) 2009

Overweight/Obesity Prevalence among Adults Starting ART in 1998-2010

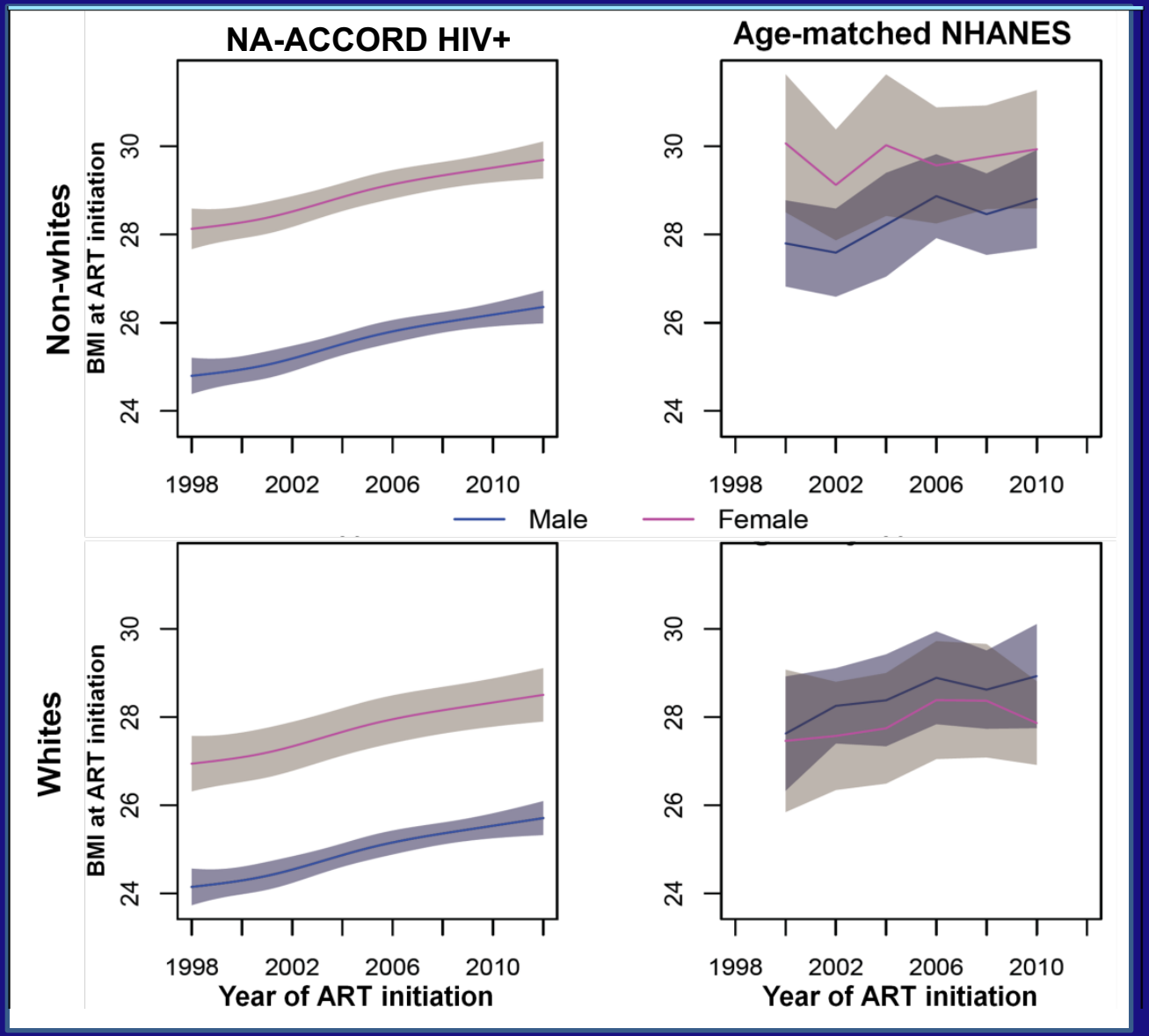
- 9% of HIV+ patients were obese at ART initiation in 1998, which doubled to 18% in 2010
- After 3 years of ART, 22% of normal BMI patients were overweight, and 18% of the overweight were obese

BMI category at ART initiation by year (1998-2010)



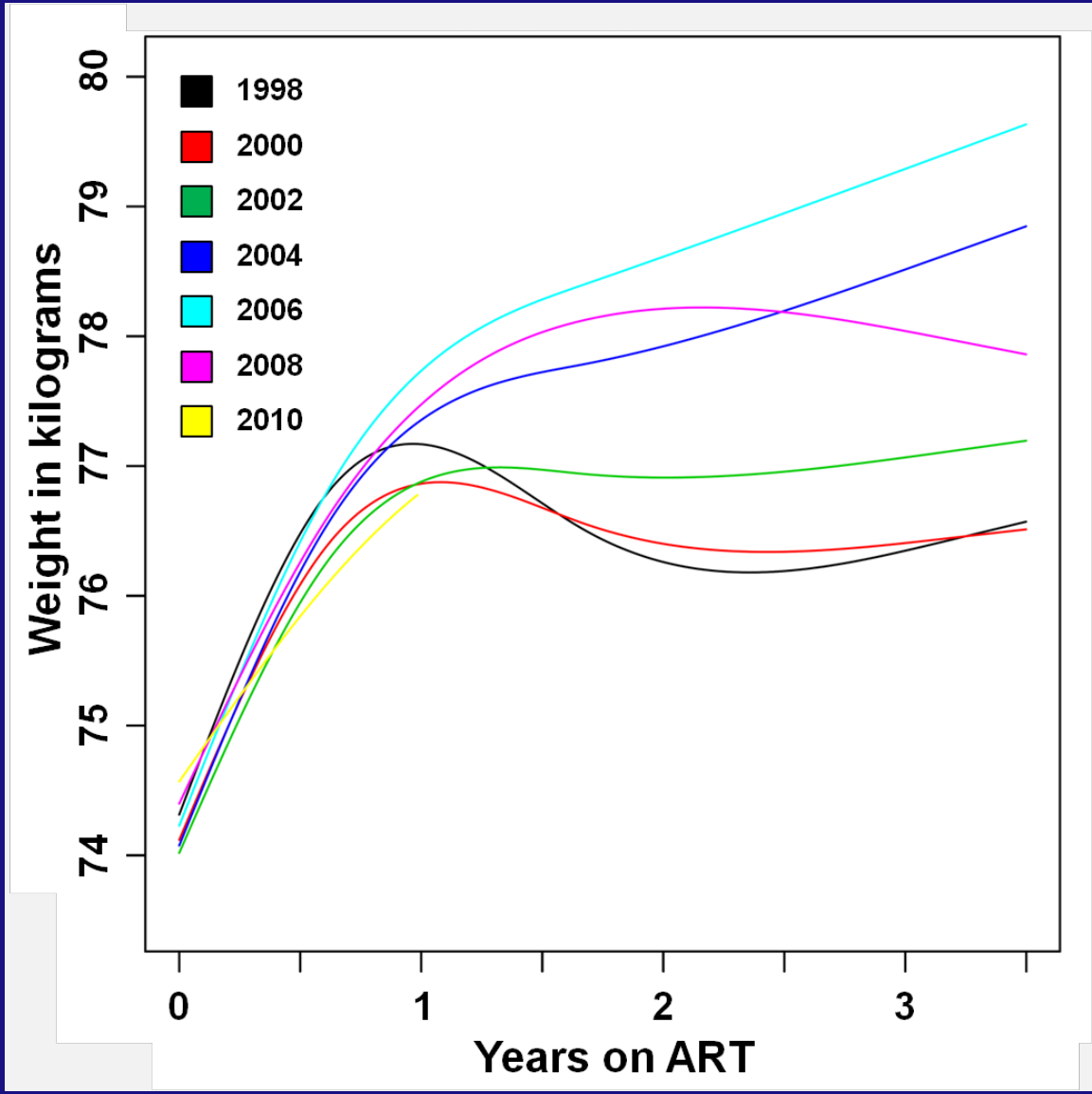
NA-ACCORD, *AIDS Res. Human Retrovir*. 2016

BMI at ART Initiation in Persons with HIV Compared to the General US Population



NA-ACCORD, *AIDS Res. Human Retrovir*. 2016

Weight Gain Over the First Three Years of ART in 1998 to 2010

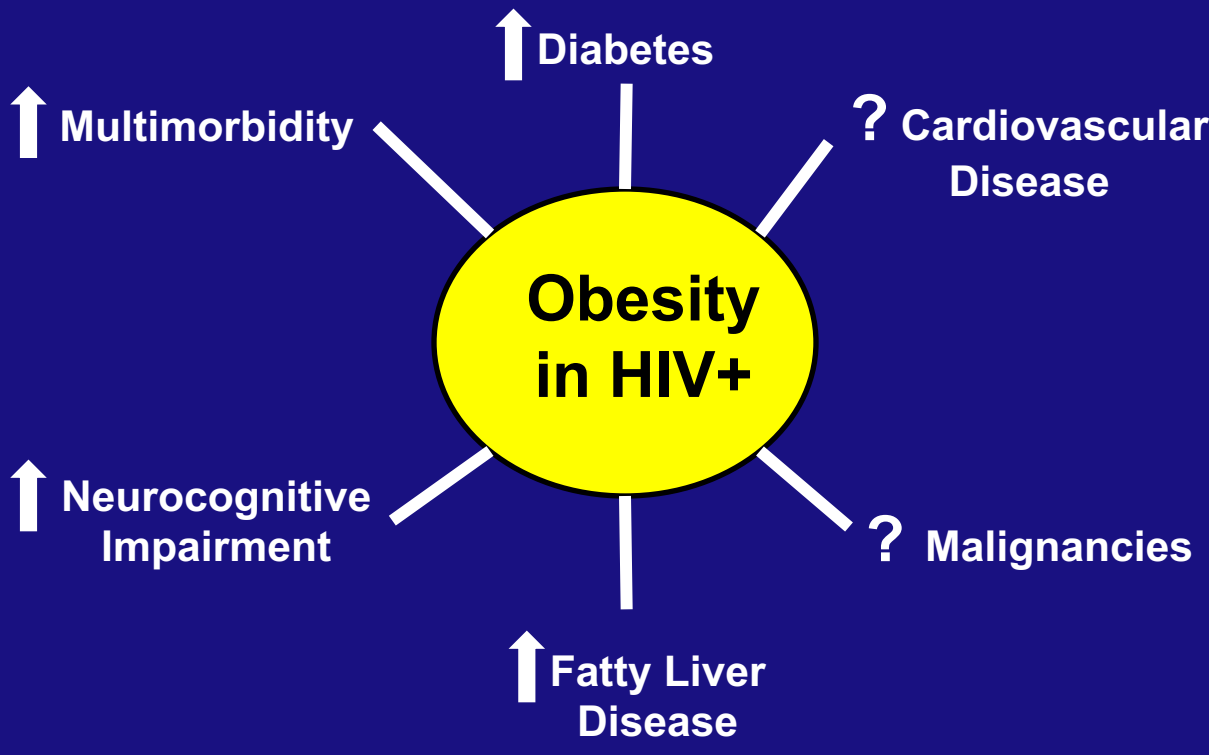


NA-ACCORD, *AIDS Res. Human Retrovir*. 2016

Summary: Weight Gain among Patients Starting ART in the United States

- On average, over 80% of total 3-year weight gain occurred in first 12 months
- Overall weight gain was greatest among white men and non-white women
- In the first 3 years of ART:
  - One-quarter of US patients with a normal BMI became overweight
  - One-fifth of those previously overweight became obese
- After 3 years of ART, the average BMI of patients with HIV approaches parity with age-, sex-, and race-matched members of the HIV-negative population

Non-communicable Diseases Associated with Obesity in HIV+ Persons



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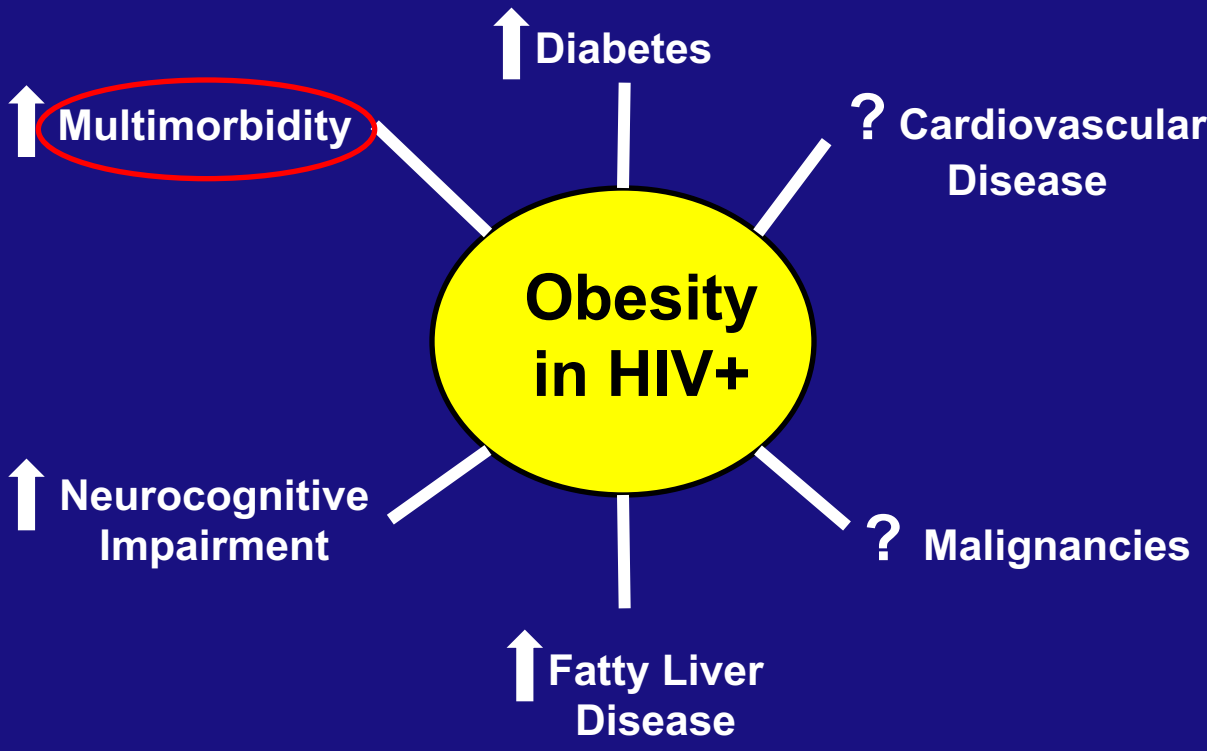
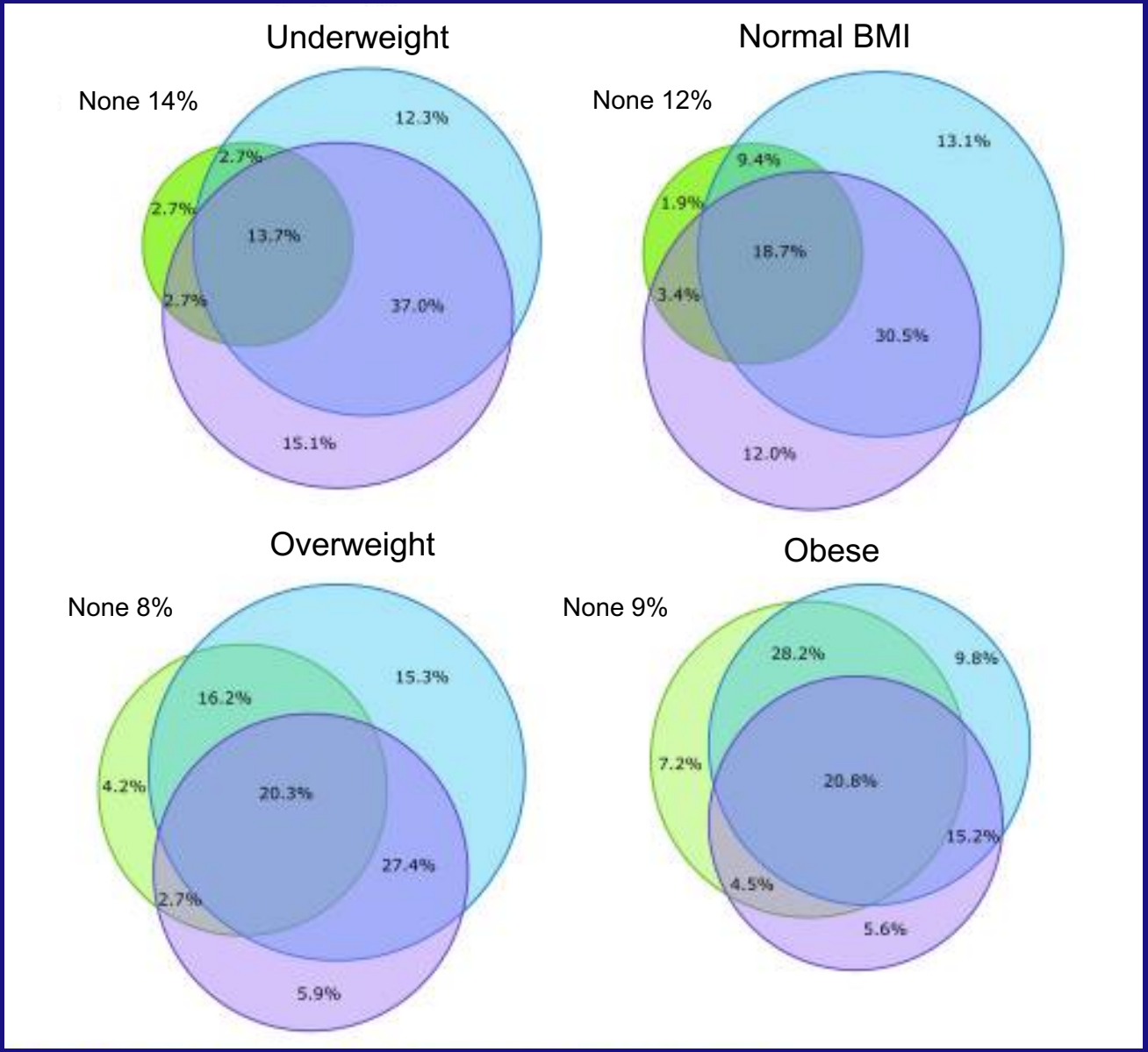


A High BMI in Patients on ART is Accompanied by More Multimorbidity

Cluster 1: HTN, diabetes, renal disease

Cluster 2: Dyslipidemia, CVD, sleep apnea, others

Cluster 3: Substance abuse, hepatitis C



Kim DJ. *JAIDS*. 2012.

A High BMI in Patients on ART is Accompanied by more Multimorbidity

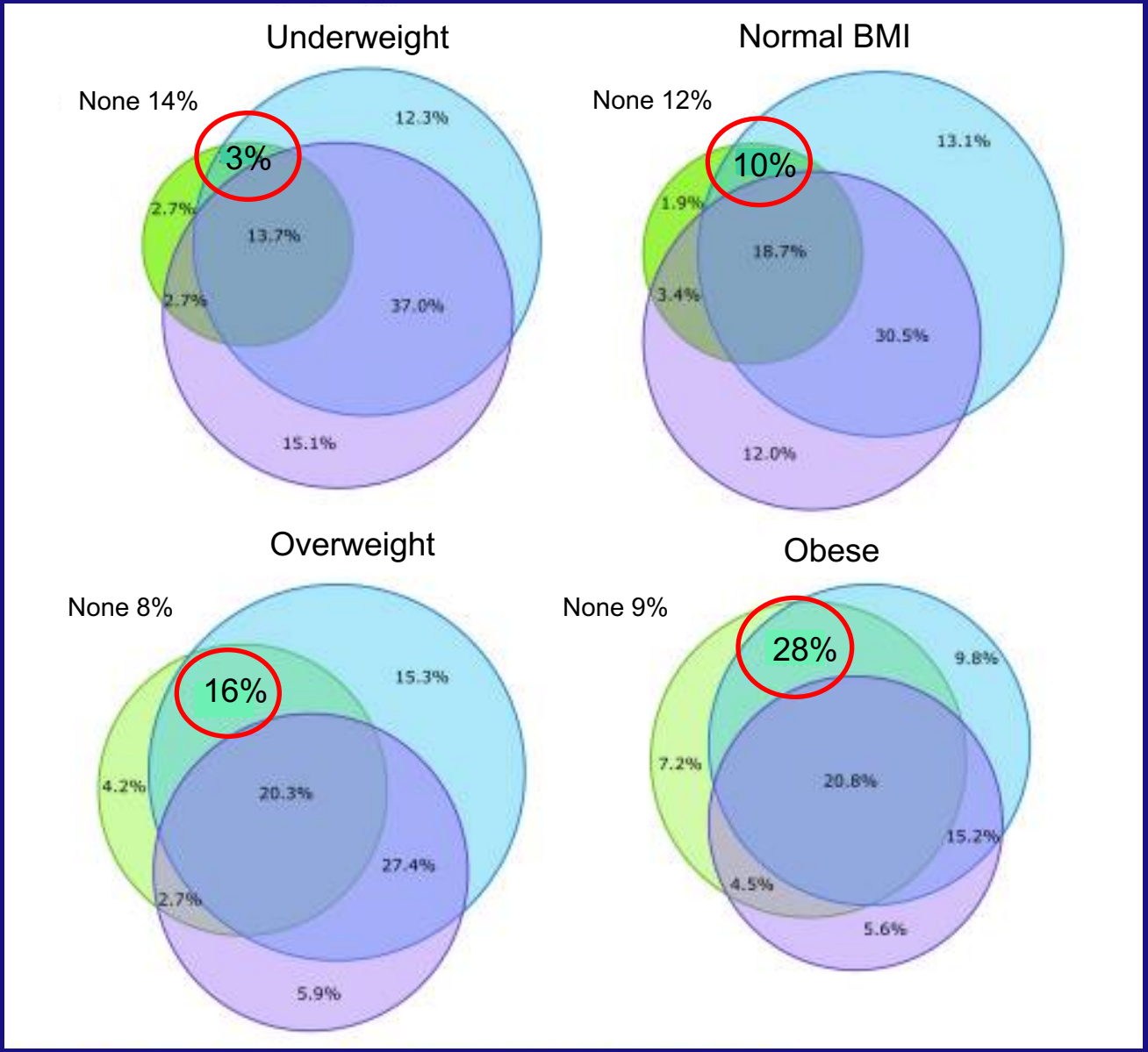
Cluster 1: HTN, diabetes, renal disease

Cluster 2: Dyslipidemia, CVD, sleep apnea, others

Cluster 3: Substance abuse, hepatitis C

Combined prevalence of cluster 1 *and/or* 2 disorders:

- **Underweight: 17%**
- **Normal BMI: 29%**
- **Overweight: 36%**
- **Obese 49%**



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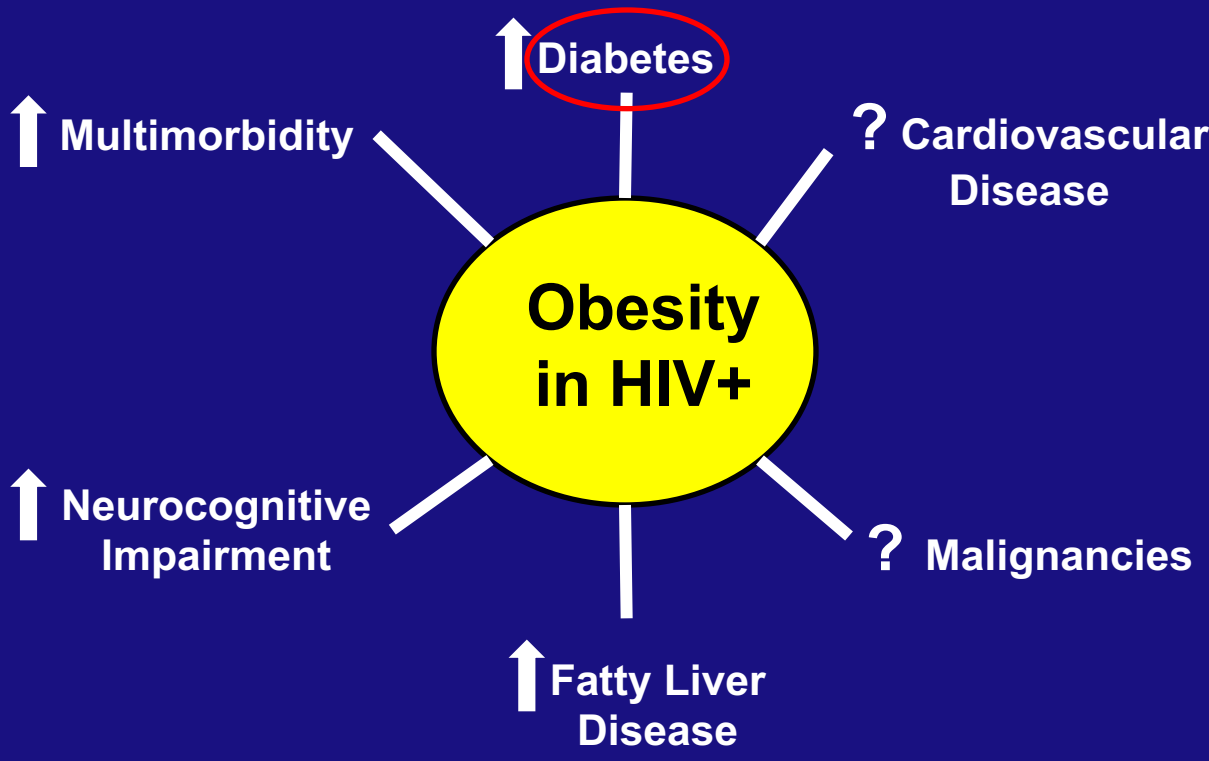
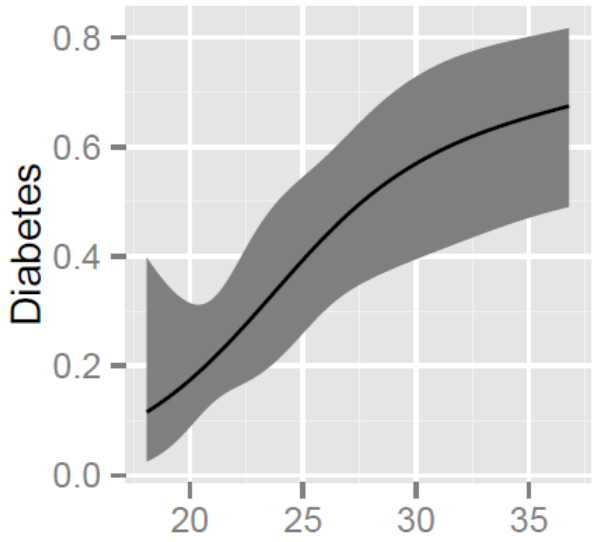


Effect of Obesity on Diabetes Risk in Patients on ART

Risk of Incident Diabetes Diagnosis after ART Initiation in French APROCO-COPILOTE cohort*	
	Multivariate Analysis HR
<25 kg/m²	1.0 (ref)
BMI 25-30	1.9
* **BMI >30**	2.9
Waist-to-hip ratio ≥0.97 (men) or ≥0.92 (women)	3.9

Probability of Incident Diabetes after ART initiation in the Vanderbilt HIV Cohort

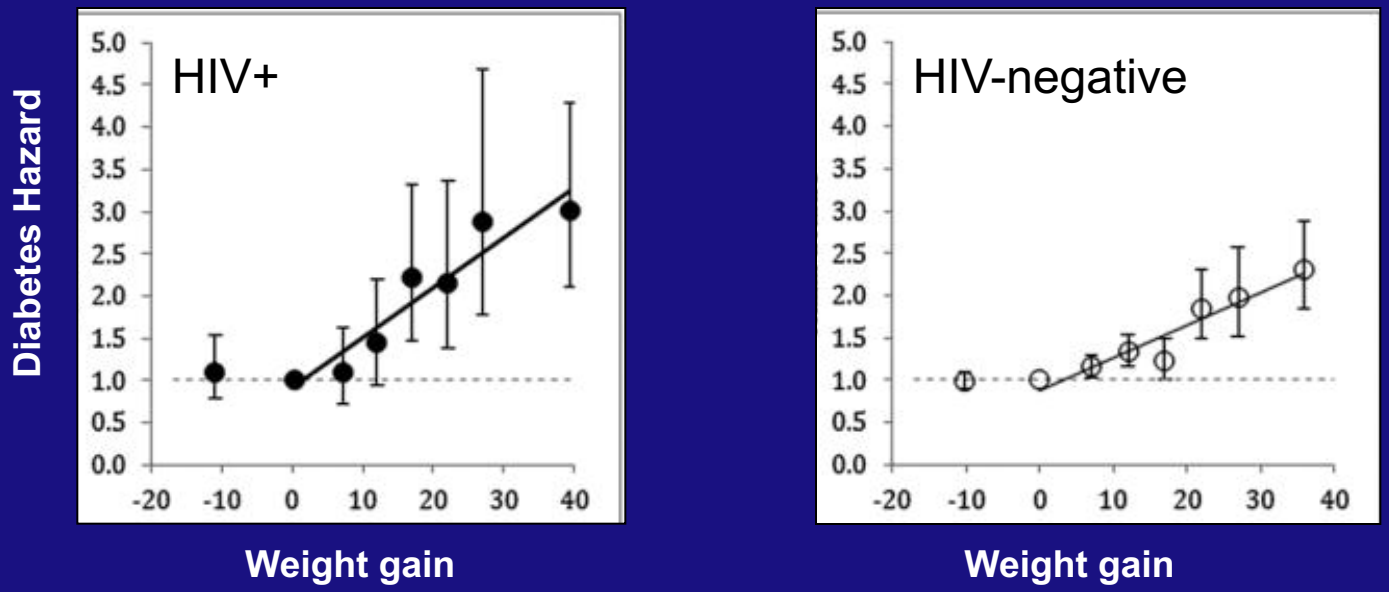


Capeau J, et al. *AIDS* 2012, De Wit S, et al. Diabetes Care 2008, Koethe J, et al. *HIV Medicine* 2015.

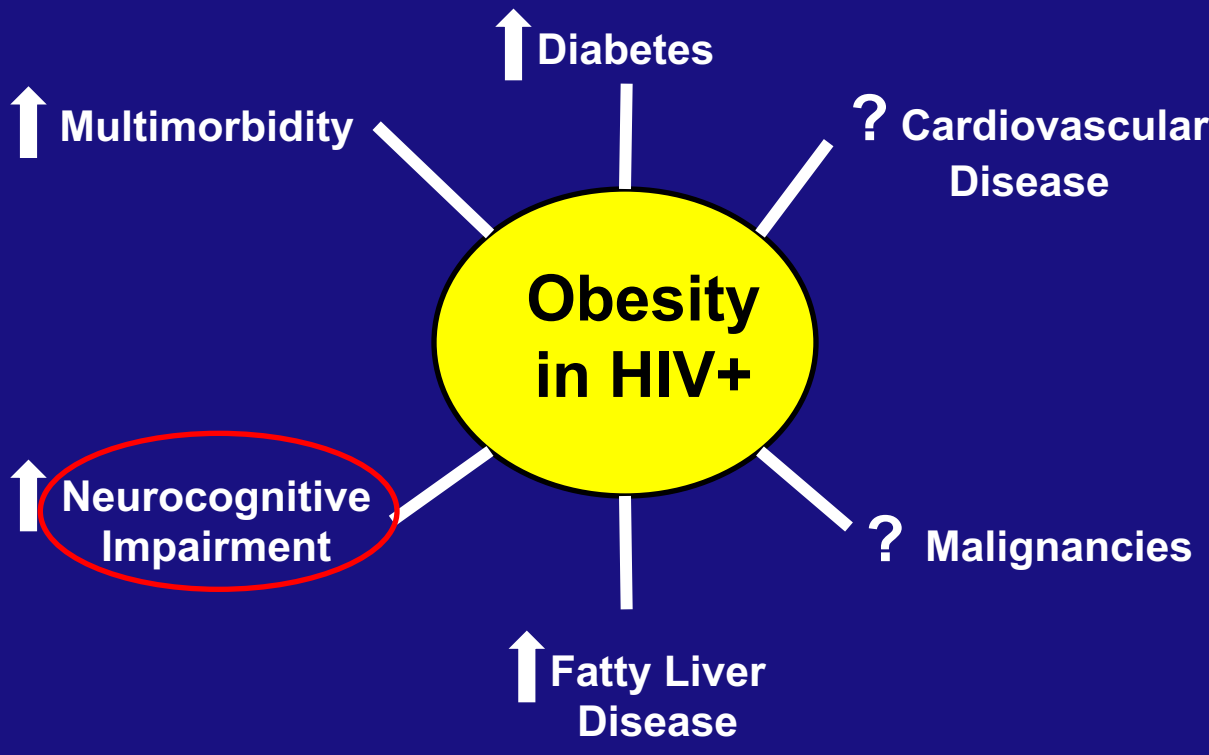
Diabetes prevalence in persons with HIV rises more steeply at higher BMI compared to HIV-negative….

BMI category	Diabetes Odds HIV+	Diabetes Odds HIV-negative
<20 kg/m^2	1.0	1.0
20-24.9	1.68	1.20
25-29.9	2.30	1.70
≥ 30	5.35	3.25

…and incidence rises more steeply with weight gain



Non-communicable Diseases Associated with Obesity in HIV+ Persons



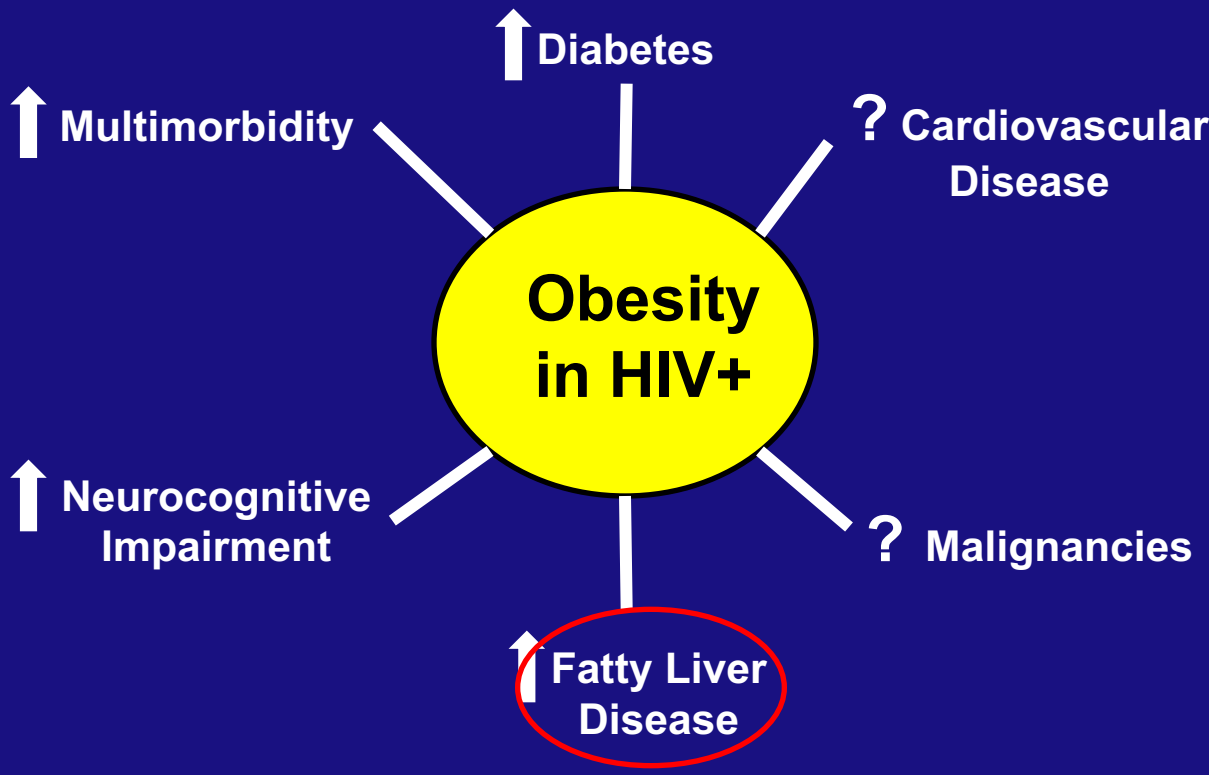
Effect of Waist Circumference on Neurocognitive Impairment

- Mild to severe neurocognitive impairment (NCI) is present in ≈50% patients on ART
- May be due to effects of hyperglycemia, cerebral atherosclerosis, or inflammatory cytokines on local vessels

Predictors of Neurocognitive Impairment (n=55)		
Variable	**Adjusted Odds Ratio**	**p-value**
AIDS	49.6	0.01
Diabetes	17.6	0.07
* Waist circ., cm	1.34	0.001
Triglycerides, mg/dL	0.32	0.09

McCutchan JA, et al. Neurology 2012

Non-communicable Diseases Associated with Obesity in HIV+ Persons

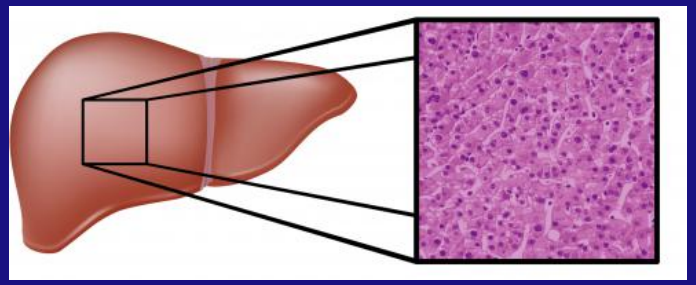


Burden of Fatty Liver Disease in HIV

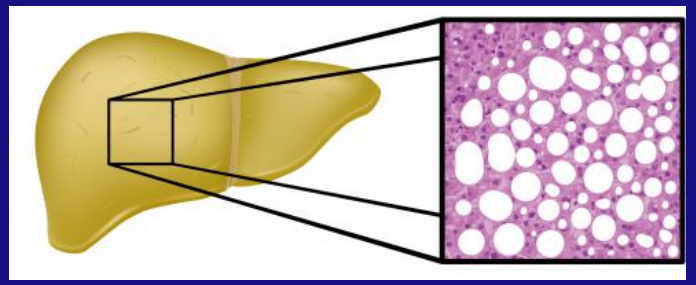
- Hepatic disease is the second leading cause of non-AIDS death in the D:A:D cohort
- 30-40% fatty liver disease (FLD) prevalence in the HIV+
- The triad of obesity, glucose intolerance, and high TGs is a major risk, though FLD appears to occur at lower BMI in the HIV population, suggesting other factors are at play.
- These may include damage to hepatocytes by ART or viral proteins, and effects on adipocytes leading to higher lipolysis and reduced ability to store fatty acids.
- Even moderate alcohol intake likely contributes to FLD in patients with other risk factors

Multi-Hit Theory of Fatty Liver Disease in HIV

Normal Liver

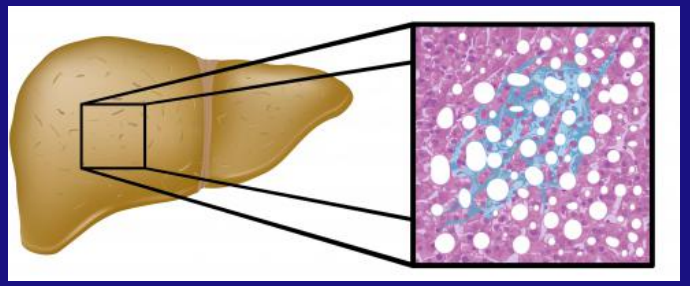


Steatosis



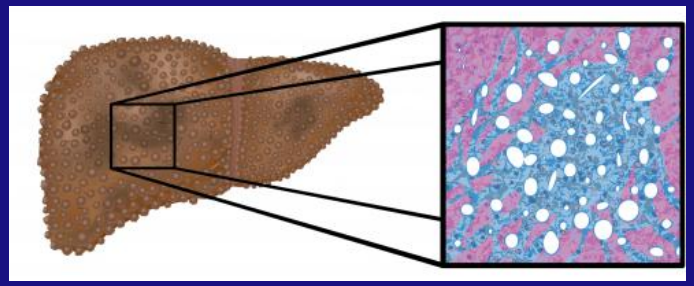
Lipid accumulation
Impaired fatty acid transport

Steatohepatitis



Necroinflammation
Collagen deposition
Oxidative Stress

Cirrhosis



Dense fibrosis
Apoptotic/necrotic cell death
Hepatocellular cancer risk

Multi-Hit Theory of Fatty Liver Disease in HIV

HIV / viral proteins

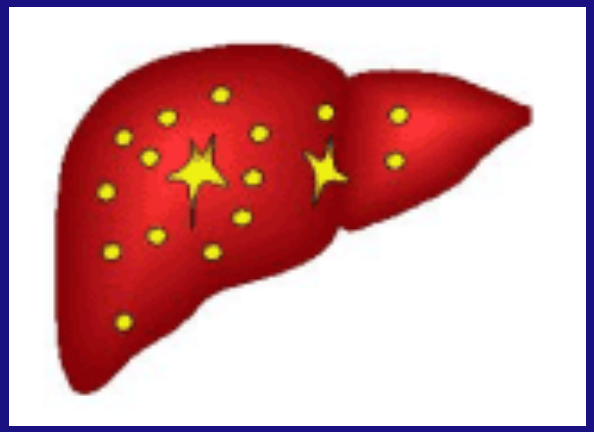
ART agents

HCV

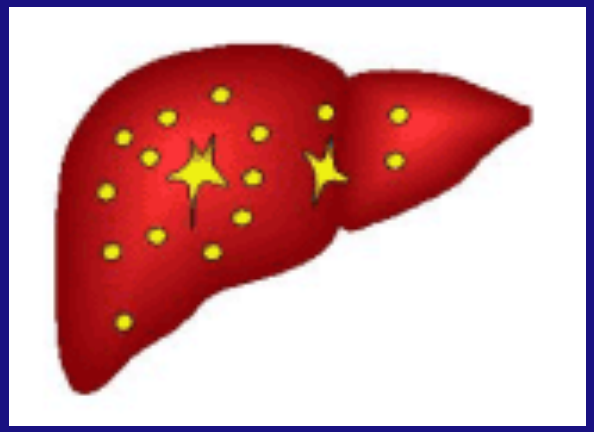
Genetics

Alcohol

(Direct hepatic effects)



Multi-Hit Theory of Fatty Liver Disease in HIV



Increased free fatty acids

Impaired fat oxidation

Metabolic Dysfunction

Excess adiposity

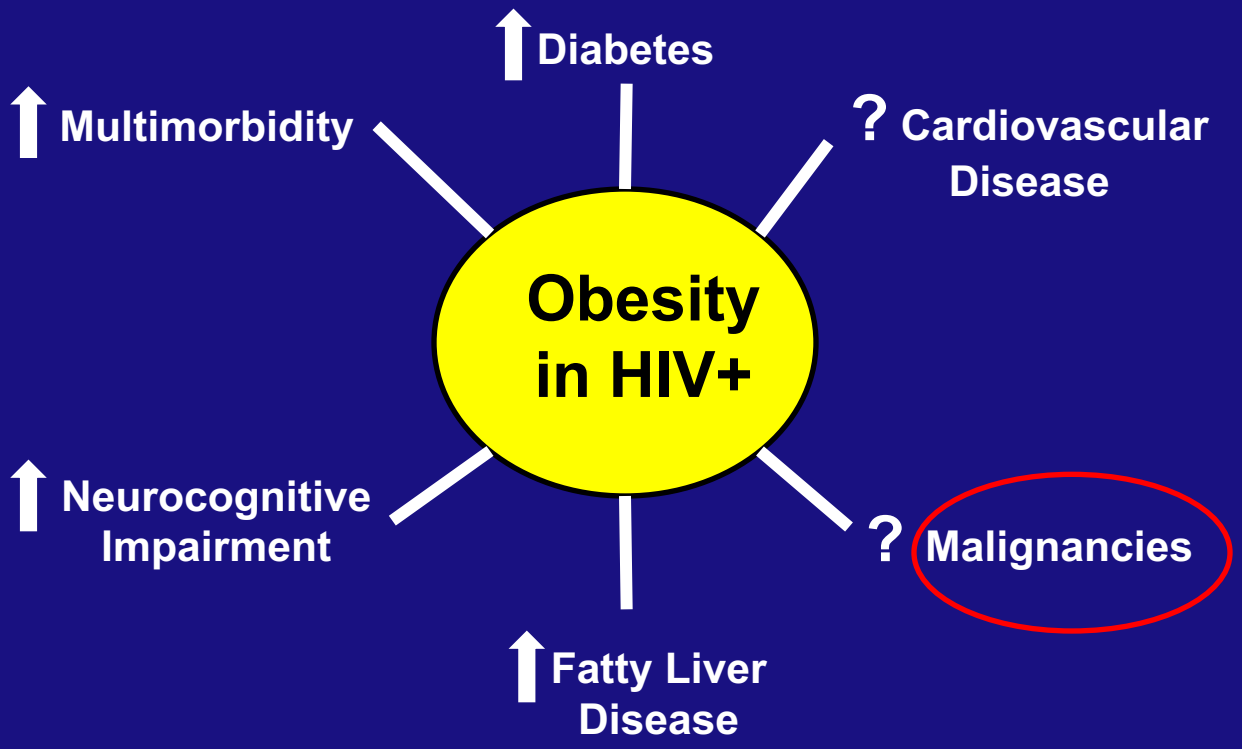
Lipodystrophy / Adipocyte injury

Low exercise

ART agents

HIV / viral proteins

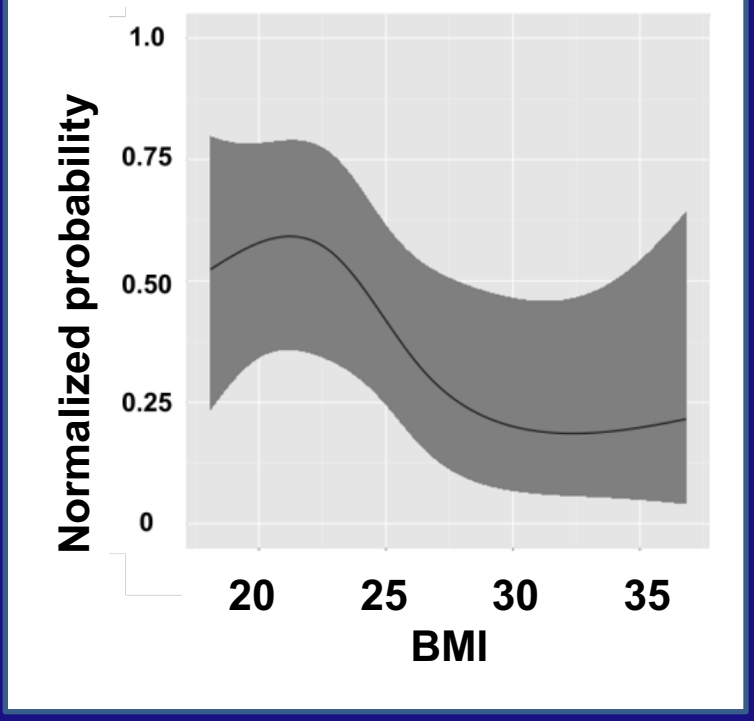
Non-communicable Diseases Associated with Obesity in HIV+ Persons



Fewer Data on Risk of Malignancies in Obese Persons with HIV

- Obesity expected to increase risk of ovarian, breast, colorectal, and some other cancers as in general population
- At present there are insufficient data on whether this is true
- Differing health habits and behavioral risk factors may also be important

BMI at ART and Probability of a New Oncologic Diagnoses in VUMC HIV Cohort



Koethe J, et al. *HIV Medicine* 2015

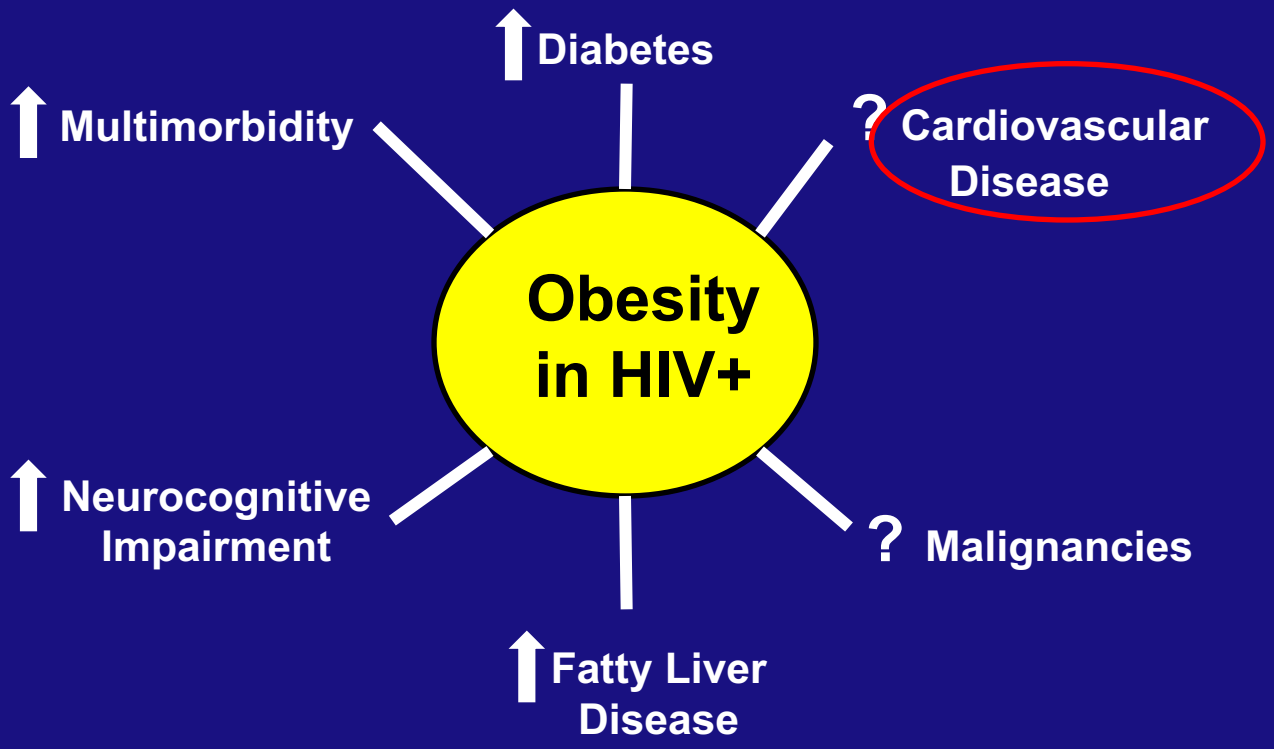
Behavioral Risk Reduction: Obesity and Substance Use

Substance use in the Women's Interagency HIV Study (WIHS)		
	Total	**Relationship to $\log_{10}$ BMI (95% CI)**
Current smoker	51%	-1.1 (-2.1, 0)
Moderate-heavy alcohol	22%	-1.3 (-2.4, -0.2)
Marijuana use	12%	-0.8 (-2.2, 0.5)
Other illicit drug use	23%	-4.0 (-5.2, -2.8)

Substance use in the Vanderbilt Cohort				
	Normal BMI	**Overweight**	**Obese**	**p-value**
Current smoker	51%	38%	36%	<0.01
Heavy alcohol use	10%	11%	5%	0.28
Marijuana use	20%	17%	10%	0.01
Other illicit drug use	6%	6%	5%	0.78

Boodram B, et al. *AIDS Pat. Care STDs.* 2009

Non-communicable Diseases Associated with Obesity in HIV+ Persons



Obesity Does Not Appear to Contribute Much to the Risk of Cardiovascular Events

- **Large epidemiologic studies have not found that a higher BMI increases the risk of incident cardiovascular events in HIV-infected persons.**

- **Interpreting these findings has been hampered by a paucity of clinical data on how body composition and ART-treated HIV infection interact to affect cardiovascular parameters.**

The Role of Obesity in Cardiovascular Outcomes is Uncertain…

Risk Factors for Myocardial Infarction in the D:A:D Cohort		
	Relative Rate (95% CI)	P Value
Exposure to PIs (per year)	1.10 (1.04-1.18)	0.002
Age (per 5 yr)	1.32 (1.23-1.41)	<0.001
Male sex	2.13 (1.29-3.52)	0.003
BMI >30 kg/m^2	1.34 (0.77-2.34)	0.31
Family history of CHD	1.40 (0.96-2.05)	0.08
Current smoker	2.92 (2.04-4.18)	<0.001
Former smoker	1.63 (1.07-2.48)	0.02
Previous cardiovascular event	4.64 (3.22-6.69)	<0.001
Diabetes mellitus	1.86 (1.31-2.65)	<0.001
Hypertension	1.30 (0.99-1.72)	0.06
Total cholesterol (per mmol/liter increase)	1.26 (1.19-1.35)	<0.001
HDL cholesterol (per mmol/liter increase)	0.72 (0.52-0.99)	0.05

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Obesity Appears to have Minimal Effects on several CVD Risk Factors in Persons with HIV

Comparison of CV parameters between non-obese and obese HIV+ persons			
Outcome variable	**Non-obese (n=35)**	**Obese (n=35)**	**p-value**
HOMA2 insulin sensitivity, %	130 (74, 191)	58 (41, 89)	**<0.001**
HDL, mg/dl	46 (35, 64)	44 (39, 49)	0.28
LDL, mg/dl	101 (85, 122)	111 (88, 129)	0.50
Triglycerides, mg/dl	94 (66, 131)	104 (85, 152)	0.12
Carotid bulb intima-media thickness, cm	0.06 (0.05, 0.07)	0.06 (0.06, 0.08)	0.25
Common carotid IMT, cm	0.057 (0.05, 0.06)	0.062 (0.05, 0.07)	0.11
Internal carotid IMT, cm	0.056 (0.05, 0.07)	0.053 (0.04, 0.07)	0.97
Brachial artery dilation (FMD), %	9.0 (5.9, 11.6)	8.4 (4.8, 10.6)	0.31

Getting to Goal with Primary Prevention

Proportion of HIV patients with CV risk factors not at goal in HIV-HEART Study	
Hypertriglyceridemia	39%
Low HDL	28%
Hypertension	21%
High LDL (patients with Moderate Framingham CHD Risk)	50%
High LDL (patients with High Framingham CHD Risk)	30%
No antiplatelet Therapy (CHD / CHD equivalent only)	59%
Uncontrolled Diabetes Mellitus	44%

Reinsch N, et al. *Eur J Prev Cardiol.* 2012 Apr 19(2)

Reducing Comorbid Disease Risk in Obese, HIV-infected Adults

- Weight loss: Goal BMI <25 kg/m^2 and waist circumference <94cm (males) or <80cm (females)
- Prevention of weight gain after ART initiation: <5kg or <5cm in waist circ.
- Nutrition counselling:
  - Aim for <25% calories from fat
  - Reduce/eliminate energy-dense snacks
  - Reduce/eliminate soft drinks and high-sugar juices
  - Increase soluble fiber intake
- Physical activity:
  - 30 minutes of walking daily
  - 10,000 steps (digital pedometer – Fit Bit)

Reducing Comorbid Disease Risk in Obese, HIV-infected Adults

- Who is most at risk of diabetes:
  - Overweight: 2x increased risk of developing diabetes on ART
  - Obese: 3-4x higher risk
  - Waist hip ratio: more predictive of diabetes than BMI (estimates central obesity)
  - Metabolic syndrome (central obesity, HTN, dyslipidemia, elevated fasting glucose): 5-9x risk of developing diabetes
  - *Possibly* exposure to AZT, d4T, older generation PIs; case reports with Dolutegravir
  - Diabetes dyslipidemia: High triglycerides with low HDL, 80% increased risk in the D:A:D cohort

Reducing Comorbid Disease Risk in Obese, HIV-infected Adults

- Who is most at risk of fatty liver:
  - Triad of obesity, glucose intolerance, and high triglycerides
  - Concomitant moderate-heavy alcohol use or Hep C
- Screening (DM and FLD)
  - Perform yearly HbA1c or fasting glucose, fasting triglycerides and HDL at minimum in non-diabetics
  - Perform yearly AST/ALT, consider US or fibroscan if persistently elevated

Summary Points

- **Proportion of overweight and obese HIV-infected individuals is reaching parity with the general population**
- **Comorbid obesity and HIV is a strong risk factor for diabetes, neurocognitive decline, and fatty liver disease**
- **Central obesity appears to be far worse than peripheral fat**

Summary Points

- **There may be an ‘obesity paradox’ for malignancies in persons with HIV, but likely due in part to differences in smoking, alcohol, and drug use**
- **While obesity does not appear to increase CVD event risk in persons with HIV, CV risk factors are often not at goal in HIV patients**
- **Emphasis on nutrition and exercise counselling, routine diabetes and CVD screening and treatment, and prevention of weight gain can improve health outcomes for obese persons with HIV**

Thank you!

VANDERBILT UNIVERSITY
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TENNESSEE CENTER FOR AIDS RESEARCH