

Obesity and Fatty Liver Disease in Persons with HIV

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Disclosures

John Koethe receives research funding from Gilead Pharmaceuticals

Outline

- Obesity prevalence and weight gain in persons with HIV
- Obesity and comorbid diseases
 - Metabolic
 - Cardiovascular
 - Neurocognitive
- Fatty liver disease
- Treatment strategies

Learning objectives

- ▶ Describe the prevalence of obesity among persons with HIV and risk factors for weight gain after ART initiation
- ▶ Identify the major co-morbid diseases exacerbated or more prevalent in obese persons with HIV
- ▶ Describe the pathogenesis and risk factors for fatty liver disease in persons with HIV
- ▶ Summarize trials of lifestyle and pharmacologic interventions for obesity and fatty liver disease

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

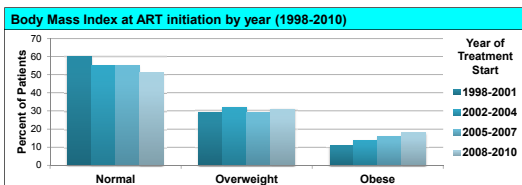
Wasting prevalence in HAART era <8% - Predictors include injection drug use, homeless, food insecurity, and low-income level

With availability of effective ART, maintenance of healthy weight has become a more pressing issue

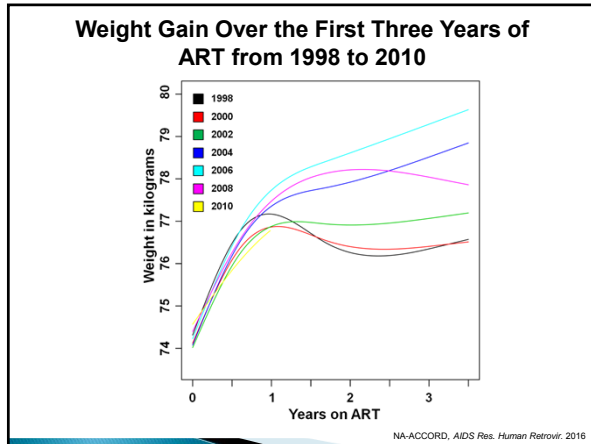
Nahlen BL, et al. AIDS 1993
Siddiqui J, et al. Curr Med Res and Opin 2009

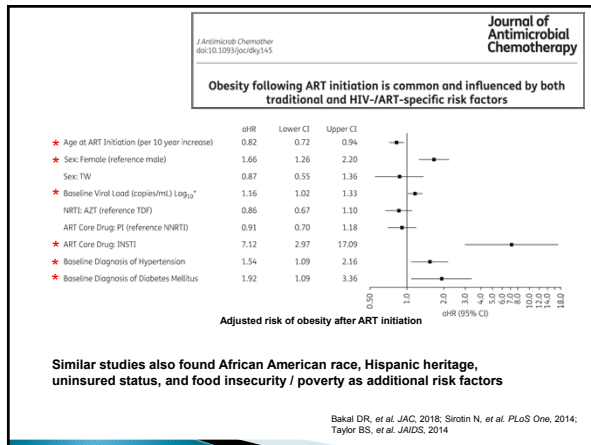
Rising Obesity Prevalence among Adults Starting ART from 1998-2010

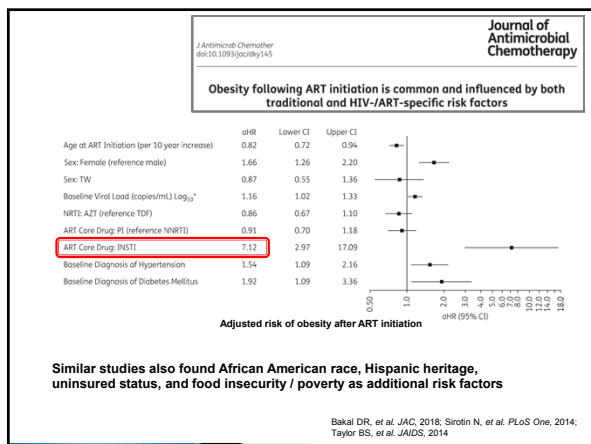
- 9% of HIV+ patients were obese at ART initiation in 1998, which doubled to 18% in 2010
- After 3 years of ART, 22% of normal BMI patients were overweight, and 18% of the overweight were obese



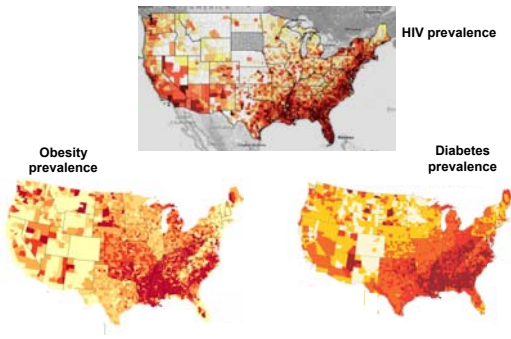
NA-ACCORD, AIDS Res. Human Retrovir. 2016







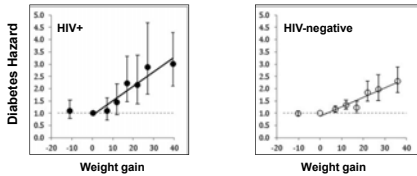
The Southeastern United States is the center of the HIV, obesity, and diabetes epidemics



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



Butt AA, et al. AIDS. 2009; Herrin M, et al. JJAIDS 2016

Waist circumference and neurocognitive impairment in CHARTER

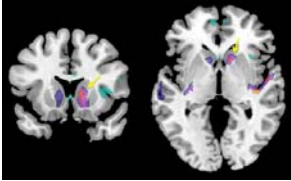
- Mild to severe neurocognitive impairment (NCI) is present in ≈50% patients on ART
- May be due to effects of hyperglycemia, cerebral atherosclerosis, or inflammatory cytokines on local vessels

Predictors of Neurocognitive Impairment		
Variable	Adjusted Odds Ratio	p-value
Advanced immunosuppression	49.6	0.01
Diabetes	17.6	0.07
* Waist circumference	1.34	0.001
Triglycerides, mg/dL	0.32	0.09

McCutchan JA, et al. Neurology 2012

Obesity and neurocognitive impairment in MACS and WIHS cohorts

- Multicenter AIDS Cohort Study: greater brain atrophy associated with higher BMI (light blue) and visceral adipose tissue (purple) in the posterior hippocampus and temporal region



- Women's Interagency HIV Study: higher serum leptin (an adipokine produced by adipose tissue) associated with impaired executive brain function (inference and task-switching)

Gustafson DR, et al. *J Gerontol Geriatr Res*. 2015; Lake JE, et al. *J Neuro-Oncol*. 2017

Obesity and the risk of cardiovascular events in persons with HIV

- Large epidemiologic studies have not found higher BMI independently increases the risk of incident cardiovascular events in persons with HIV
- May reflect the 'washout' of obesity-related risk due to higher baseline CVD risk in persons with HIV
- Interpreting epidemiologic data has been hampered by few studies on how body composition and treated HIV affect cardiovascular parameters.

Womack JA, et al. *J Am Heart Assoc* 2014; Freiberg MS, et al. *JAMA Intern Med* 2013; Friis-Moller N, et al. *N Engl J Med* 2007.

The role of obesity in cardiovascular events is less certain...

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

Friis-Moller N, et al. *N Engl J Med* 2007.

Obesity, visceral fat, and ectopic fat accumulation in persons with HIV

a. HIV- T2DM- b. HIV- T2DM+
 c. HIV+ T2DM- d. HIV+ T2DM+

- Subcutaneous fat
- Visceral fat
- Intramuscular fat
- Skeletal muscle

- Greater proportion of fat surrounding the organs in persons with HIV
- Fatty infiltration of muscle increased in HIV, and a major contributor to diabetes

Visceral fat and ectopic fat accumulation in persons with HIV

Hepatic fat
 Epicardial fat
 Visceral fat

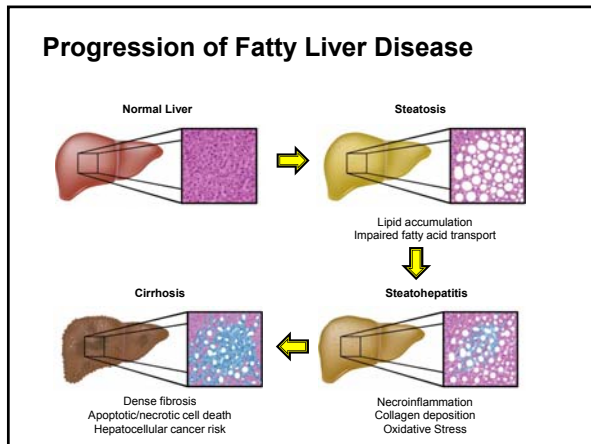
Ectopic adipose tissue deposition in HIV
 Peri-myo cellular and intra-myo cellular fat

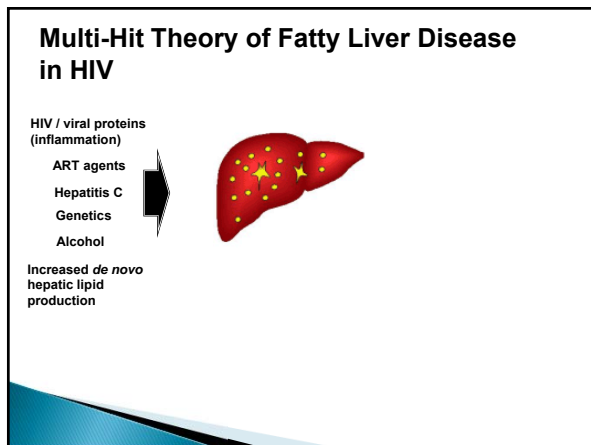
Resulting changes in muscle:
 ↑ Inflammatory gene expression
 ↓ Mitochondrial content
 ↓ Myocellular β-oxidation
 ↓ Insulin receptor and glucose transporter expression
Insulin resistance

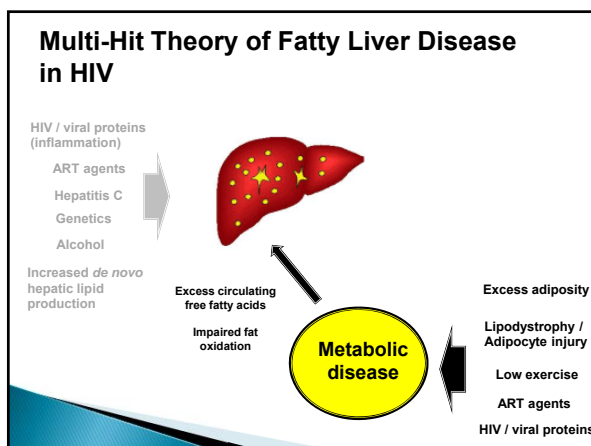
- HIV is often accompanied by an 'energy excess' state due to
 - Increased hepatic lipid production
 - Increased lipid release from subcutaneous fat
 - Reduced sub-Q fat lipid uptake
- This results in fat deposits in liver, muscle, and heart
- These changes mimic obesity in HIV-negative persons, but occur at lower BMI and younger age in HIV+ persons

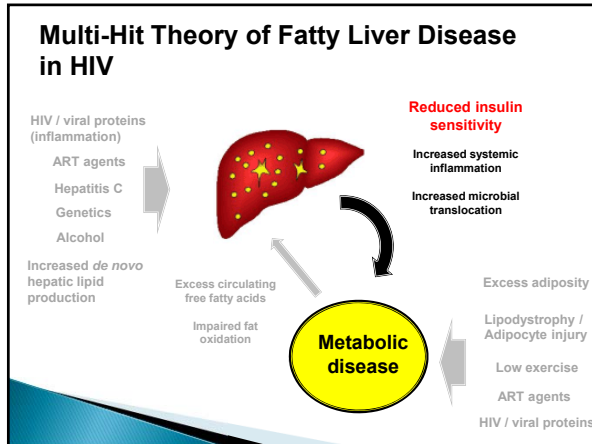
Burden of Fatty Liver Disease in HIV

- 30-40% non-alcoholic fatty liver disease (NAFLD) prevalence in persons with HIV
- The triad of obesity, glucose intolerance, and high TGs is a major risk
- 80-90% of adults with NAFLD have generalized obesity, visceral adiposity, metabolic syndrome or type 2 diabetes
- Cardiovascular disease, not liver failure, accounts for most of the excess morbidity and mortality associated with NAFLD
- NAFLD disease occurs at lower BMI in the HIV population, suggesting other factors are present









Treatment Strategies – Obesity

- Structured exercise with or without diet changes reduced abdominal obesity in most studies in persons with HIV
- A higher fiber diet has been associated with reduced obesity, but not visceral adiposity
- ≥ 30 min of moderate-intensity physical activity most days plus 500 kcal/day reduced intake recommended to attain and sustain significant ($\geq 5\%$) weight loss (AHA/ACC guidelines)
- [Consensus guidelines: Practical Review of Recognition and Management of Obesity and Lipohypertrophy in Human Immunodeficiency Virus Infection](#), Clinical Infectious Diseases, Volume 64, Issue 10, 15 May 2017

Jensen MD, et al. Circulation 2014; Fitch KV, et al. AIDS 2006; Dolan SE, et al. Arch Intern Med 2006; Thori GJ, et al. Diabetes Metab 2002.

Treatment Strategies – Obesity

FDA-approved weight loss medications		
Medication	Mechanism of action	ART / other interactions
Orlistat	Pancreatic/gastric lipase inhibitor	Avoid: Loss of virologic control reported in patients taking ATV/r or EFV.
Phentermine/Topiramate	Norepinephrine releasing agent/ GABA receptor modulation	Caution: sympathomimetic – avoid in hypertension and CVD
Lorcaserin	5HT _{2c} receptor agonist	None
Naltrexone/ Bupropion	Dopamine/norepi-nephine reuptake inhibitor/opioid antagonist	Caution: Bupropion metabolized by CYP2B6 and EFV or RTV may decrease concentrations
Liraglutide	GLP-1 agonist - good choice in patients with diabetes	None

Treatment Strategies – Obesity

- Recombinant human growth hormone (rhGH) reduces visceral fat, but also impairs glucose tolerance. Therefore, rhGH is not FDA-approved for HIV-associated lipodystrophy.
- Tesamorelin, a GH-releasing hormone analog, is approved to reduce excess visceral fat in treated HIV infection.
 - Fixed dose of 2 mg subcutaneously daily, no major ART interactions
 - Approximately 15% visceral fat reduction within 6 months among patients with waist circ. ≥ 95 cm for males or ≥ 94 cm for females
 - Approximately 2/3 of patients respond without decreases in subcutaneous fat
 - Increased fasting glucose is rare and usually transient
 - Unfortunately, visceral fat often accumulates after stopping drug

Lo J, et al. Clin Inf Dis 2004; Lo J, et al. JAMA 2008; Falutz J, et al. NEJM 2007; Falutz J, et al. JCEM 2010.

Treatment Strategies – Obesity

- Metformin accompanied by small (< 1 kg/m²) reductions in BMI, but primarily useful to slow progression of pre-diabetes and potentially NAFLD
- Bariatric surgery highly effective with 60%–70% loss of excess body weight and marked improvements in obesity-related conditions
 - Few small studies in persons with HIV did not show changes in virologic control or ART concentrations
 - Transient fall in TDF concentration reported – requires further study

Flancabaum L, et al. Surg Obes Relat Dis 2005; Fysekidis M, et al. Obes Surg 2015; Muzard L, et al. Obes Res Clin Pract 2016.

Treatment Strategies – NAFLD

- The prevention and treatment of NAFLD in persons with HIV warrants more research
- A 5-10% loss of body weight reduces hepatic fat, but $> 10\%$ may be needed to reduce necroinflammation
- Older thymidine analogues contributed to liver injury but no longer used in US. However, patients susceptible to PI-induced hyperlipidemia may need to switch ART
- Prompt treatment of HCV
- Avoidance of alcohol

Tafesh Z, et al. Curr Opin Inf Dis 2017

Treatment Strategies – NAFLD

- Antioxidant vitamin E is first-line treatment recommendation for non-cirrhotic NAFLD in general population (PIVENS trial – more data still needed)
- Metformin without exercise does not appear to be beneficial
- Tesamorelin shown in early trials to significantly reduce hepatic fat on MRS imaging – larger trials are on-going

Tafesh Z, et al. Curr Opin Inf Dis 2017;
Stanley TL, et al. JAMA 2014

Summary points

- ▶ Persons with HIV on ART have rates of overweight and obesity similar to the US population (>60%).
- ▶ Weight gain on ART is greater in women, minorities, and those with food insecurity/poverty. Some integrase inhibitors may predispose to weight gain (more evidence needed)
- ▶ Obesity predisposes to diabetes, neurocognitive impairment, and fatty liver disease – relationship with CVD less clear

Summary points

- ▶ Visceral obesity more common in HIV and more detrimental than subcutaneous obesity
- ▶ NAFLD present in 30-40% of persons with HIV, occurs at lower BMI, and prevalence rises steeply with generalized obesity, visceral fat accumulation, and insulin resistance / hypertriglyceridemia
- ▶ Exercise and diet effective in reducing metabolic disease in persons with HIV, bariatric surgery appears safe, and tesamorelin reduces visceral fat and hepatic fat