

# Obesity and Fatty Liver Disease in Persons with HIV

John Koethe MD, MSCI  
Vanderbilt University Medical Center  
Division of Infectious Diseases

---

---

---

---

---

---

---

---

## 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

---

---

---

---

---

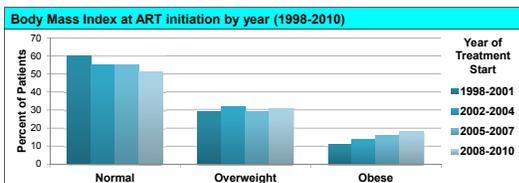
---

---

---

### 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

---

---

---

---

---

---

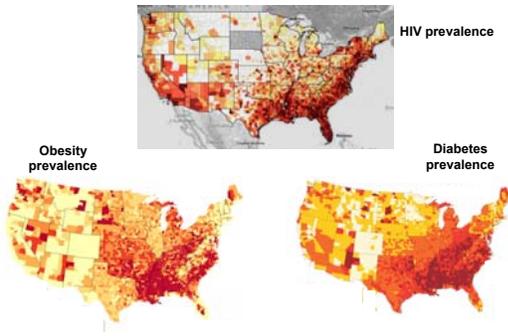
---

---





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




---

---

---

---

---

---

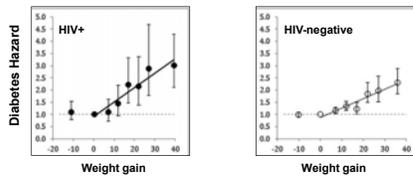
---

---

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 <sup>2</sup>	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

---

---

---

---

---

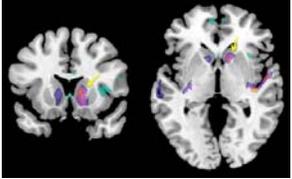
---

---

---

### 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 <sup>2</sup>	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.

---

---

---

---

---

---

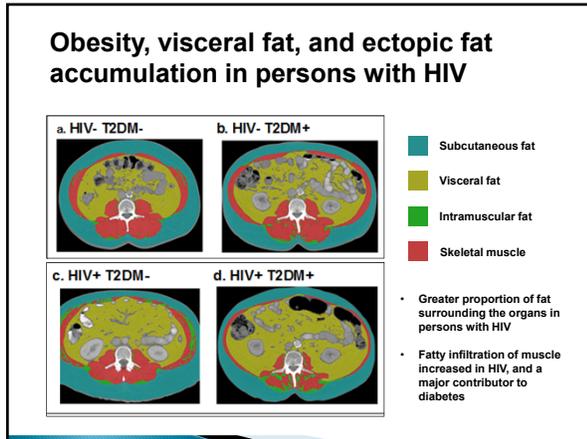
---

---

---

---






---

---

---

---

---

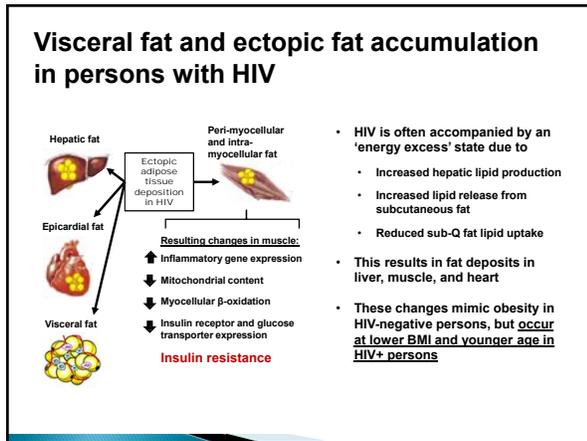
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

### 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

---

---

---

---

---

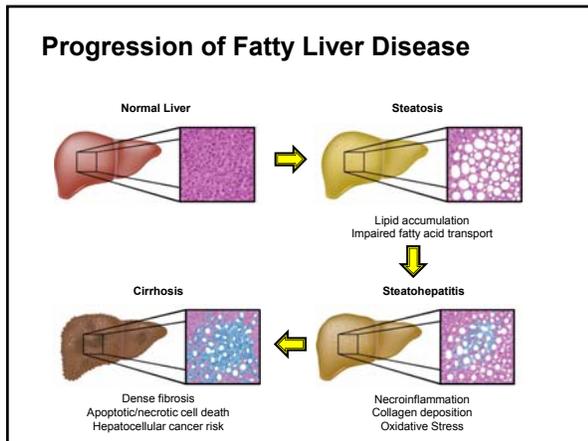
---

---

---

---

---



---

---

---

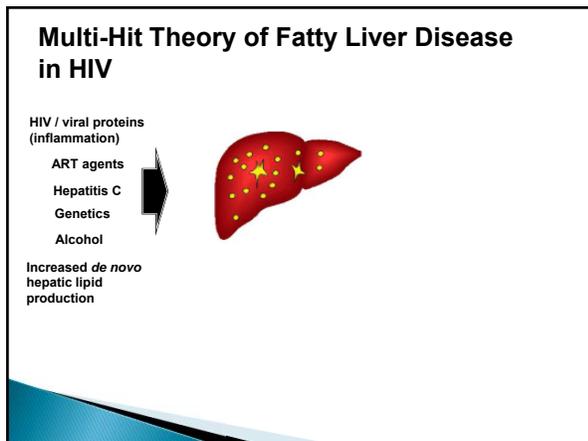
---

---

---

---

---



---

---

---

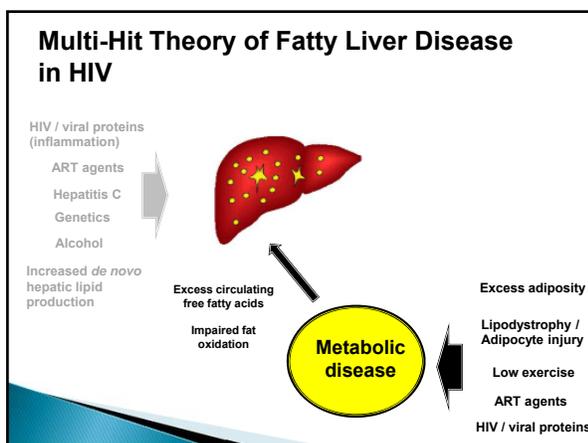
---

---

---

---

---



---

---

---

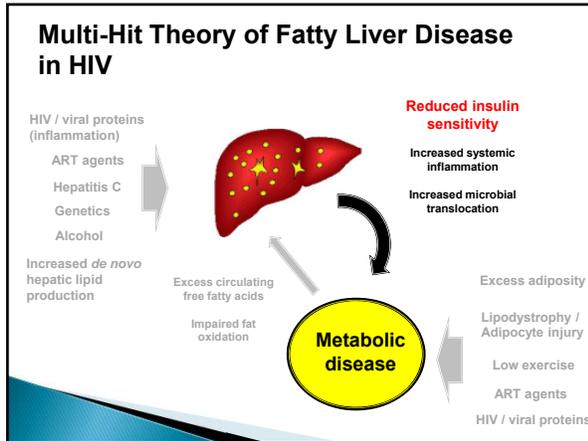
---

---

---

---

---




---

---

---

---

---

---

---

---

### 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
- $\geq 30$  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	<b>Avoid:</b> Loss of virologic control reported in patients taking ATV/r or EFV.
Phentermine/Topiramate	Norepinephrine releasing agent/ GABA receptor modulation	<b>Caution:</b> sympathomimetic – avoid in hypertension and CVD
Lorcaserin	5HT <sub>2c</sub> receptor agonist	None
Naltrexone/ Bupropion	Dopamine/norepi-nephine reuptake inhibitor/opioid antagonist	<b>Caution:</b> 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.  $\geq 95$  cm for males or  $\geq 94$  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/m<sup>2</sup>) 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

---

---

---

---

---

---

---

---

**Thank you!**

VANDERBILT UNIVERSITY  
MEDICAL CENTER



---

---

---

---

---

---

---

---