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

NA-ACCORD HIV+

Age-matched NHANES

Non-whites

Year of ART initiation

Whites

Year of ART initiation

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

- Diabetes
- Multimorbidity
- Neurocognitive Impairment
- Fatty Liver Disease
- Cardiovascular Disease
- Malignancies
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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%

Kim DJ. JAIDS. 2012.
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**Effect of Obesity on Diabetes Risk in Patients on ART**

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

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

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

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Diabetes Odds HIV+</th>
<th>Diabetes Odds HIV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 kg/m²</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>20-24.9</td>
<td>1.68</td>
<td>1.20</td>
</tr>
<tr>
<td>25-29.9</td>
<td>2.30</td>
<td>1.70</td>
</tr>
<tr>
<td>≥ 30</td>
<td>5.35</td>
<td>3.25</td>
</tr>
</tbody>
</table>

...and incidence rises more steeply with weight gain

HIV+  

HIV-negative
Non-communicable Diseases Associated with Obesity in HIV+ Persons

- Diabetes
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- ? Cardiovascular Disease
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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)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>49.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Waist circ., cm</td>
<td>1.34</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>0.32</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*McCutchan JA, et al. Neurology 2012*
Non-communicable Diseases Associated with Obesity in HIV+ Persons

- Multimorbidity
- Diabetes
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- Fatty Liver Disease
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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

Cirrhosis
- Dense fibrosis
- Apoptotic/necrotic cell death
- Hepatocellular cancer risk

Steatohepatitis
- Necroinflammation
- Collagen deposition
- Oxidative Stress
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

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- Cardiovascular Disease
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- Fatty Liver Disease
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.

Behavioral Risk Reduction: Obesity and Substance Use

### Substance use in the Women’s Interagency HIV Study (WIHS)

<table>
<thead>
<tr>
<th>Substance use</th>
<th>Total</th>
<th>Relationship to $\log_{10} BMI$ (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Current smoker</td>
<td>51%</td>
<td>-1.1 (-2.1, 0)</td>
</tr>
<tr>
<td>Moderate-heavy alcohol</td>
<td>22%</td>
<td>-1.3 (-2.4, -0.2)</td>
</tr>
<tr>
<td>Marijuana use</td>
<td>12%</td>
<td>-0.8 (-2.2, 0.5)</td>
</tr>
<tr>
<td>Other illicit drug use</td>
<td>23%</td>
<td>-4.0 (-5.2, -2.8)</td>
</tr>
</tbody>
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### Substance use in the Vanderbilt Cohort

<table>
<thead>
<tr>
<th>Substance use</th>
<th>Normal BMI</th>
<th>Overweight</th>
<th>Obese</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>51%</td>
<td>38%</td>
<td>36%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>10%</td>
<td>11%</td>
<td>5%</td>
<td>0.28</td>
</tr>
<tr>
<td>Marijuana use</td>
<td>20%</td>
<td>17%</td>
<td>10%</td>
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<tr>
<td>Other illicit drug use</td>
<td>6%</td>
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<td>5%</td>
<td>0.78</td>
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Non-communicable Diseases Associated with Obesity in HIV+ Persons

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• 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…

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<th>Risk Factor</th>
<th>Relative Rate (95% CI)</th>
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<td>Exposure to PIs (per year)</td>
<td>1.10 (1.04-1.18)</td>
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<td>Age (per 5 yr)</td>
<td>1.32 (1.23-1.41)</td>
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<td>Male sex</td>
<td>2.13 (1.29-3.52)</td>
<td>0.003</td>
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<tr>
<td>BMI &gt;30 kg/m²</td>
<td>1.34 (0.77-2.34)</td>
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<tr>
<td>Family history of CHD</td>
<td>1.40 (0.96-2.05)</td>
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<tr>
<td>Previous cardiovascular event</td>
<td>4.64 (3.22-6.69)</td>
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<td>Diabetes mellitus</td>
<td>1.86 (1.31-2.65)</td>
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<td>Hypertension</td>
<td>1.30 (0.99-1.72)</td>
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<td>Total cholesterol (per mmol/liter increase)</td>
<td>1.26 (1.19-1.35)</td>
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<td>HDL cholesterol (per mmol/liter increase)</td>
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Obesity Appears to have Minimal Effects on several CVD Risk Factors in Persons with HIV

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<th>Outcome variable</th>
<th>Non-obese (n=35)</th>
<th>Obese (n=35)</th>
<th>p-value</th>
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</thead>
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<tr>
<td>HOMA2 insulin sensitivity, %</td>
<td>130 (74, 191)</td>
<td>58 (41, 89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>46 (35, 64)</td>
<td>44 (39, 49)</td>
<td>0.28</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>101 (85, 122)</td>
<td>111 (88, 129)</td>
<td>0.50</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>94 (66, 131)</td>
<td>104 (85, 152)</td>
<td>0.12</td>
</tr>
<tr>
<td>Carotid bulb intima-media thickness, cm</td>
<td>0.06 (0.05, 0.07)</td>
<td>0.06 (0.06, 0.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Common carotid IMT, cm</td>
<td>0.057 (0.05, 0.06)</td>
<td>0.062 (0.05, 0.07)</td>
<td>0.11</td>
</tr>
<tr>
<td>Internal carotid IMT, cm</td>
<td>0.056 (0.05, 0.07)</td>
<td>0.053 (0.04, 0.07)</td>
<td>0.97</td>
</tr>
<tr>
<td>Brachial artery dilation (FMD), %</td>
<td>9.0 (5.9, 11.6)</td>
<td>8.4 (4.8, 10.6)</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Proportion of HIV patients with CV risk factors not at goal in HIV-HEART Study

<table>
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<th>Risk Factor</th>
<th>Percentage</th>
</tr>
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<tr>
<td>Hypertriglyceridemia</td>
<td>39%</td>
</tr>
<tr>
<td>Low HDL</td>
<td>28%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21%</td>
</tr>
<tr>
<td>High LDL (patients with Moderate Framingham CHD Risk)</td>
<td>50%</td>
</tr>
<tr>
<td>High LDL (patients with High Framingham CHD Risk)</td>
<td>30%</td>
</tr>
<tr>
<td>No antiplatelet Therapy (CHD / CHD equivalent only)</td>
<td>59%</td>
</tr>
<tr>
<td>Uncontrolled Diabetes Mellitus</td>
<td>44%</td>
</tr>
</tbody>
</table>

Reducing Comorbid Disease Risk in Obese, HIV-infected Adults

- Weight loss: Goal BMI <25 kg/m² 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!