HIV and Obesity: Approaches to Intervene

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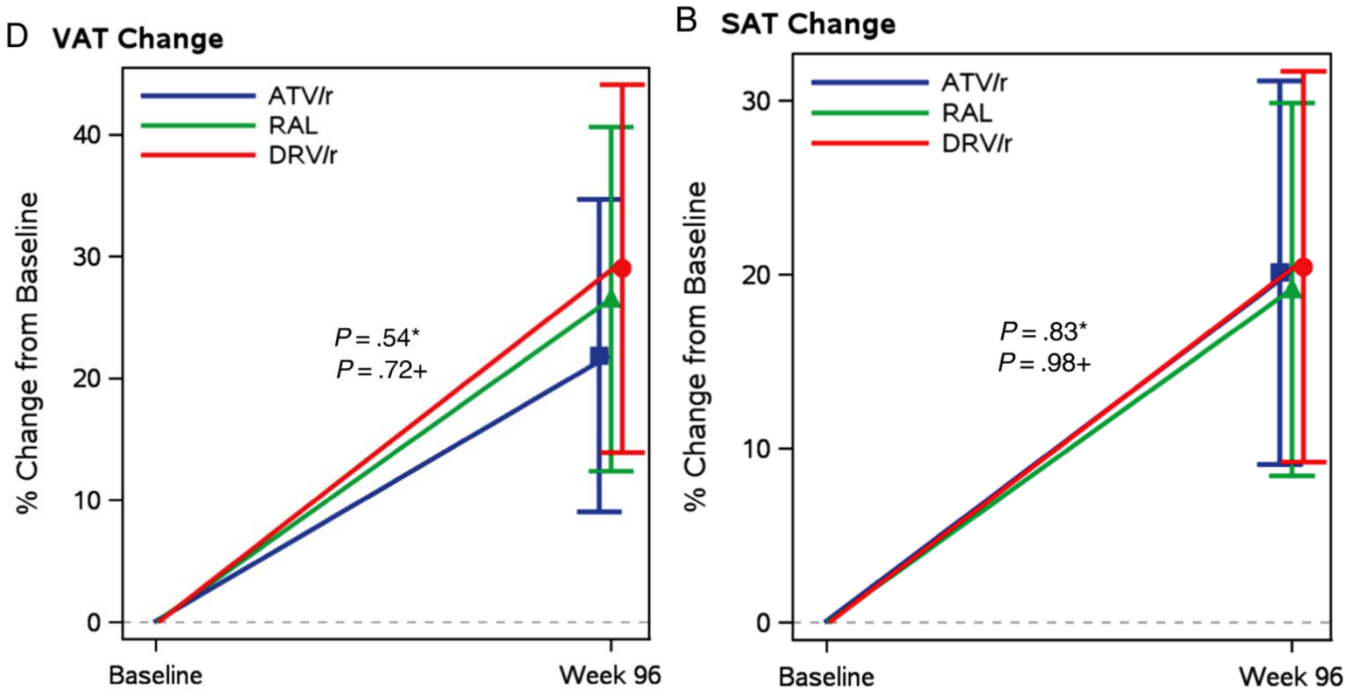
Outline

- Drivers of Obesity in HIV
- Consequences of Excess Adiposity
- Potential Interventions

Body Composition Changes in ACTG A5260s

- 328 ART-naïve participants
  - 109 initiating ATV/rtv + FTC/TDF
  - 113 initiating DRV/rtv + FTC/TDF
  - 106 initiating RAL + FTC/TDF
- Median age 36 years
- 90% male; 10% female
- Median CD4 ct: 349 c/mm^3
- Median VL: 4.6 $\log_{10}$ cp/mL
- Median BMI: 25kg/m^2

- BMI increased 3.8 - 4.7% (p< 0.001)
  - No difference b/t arms

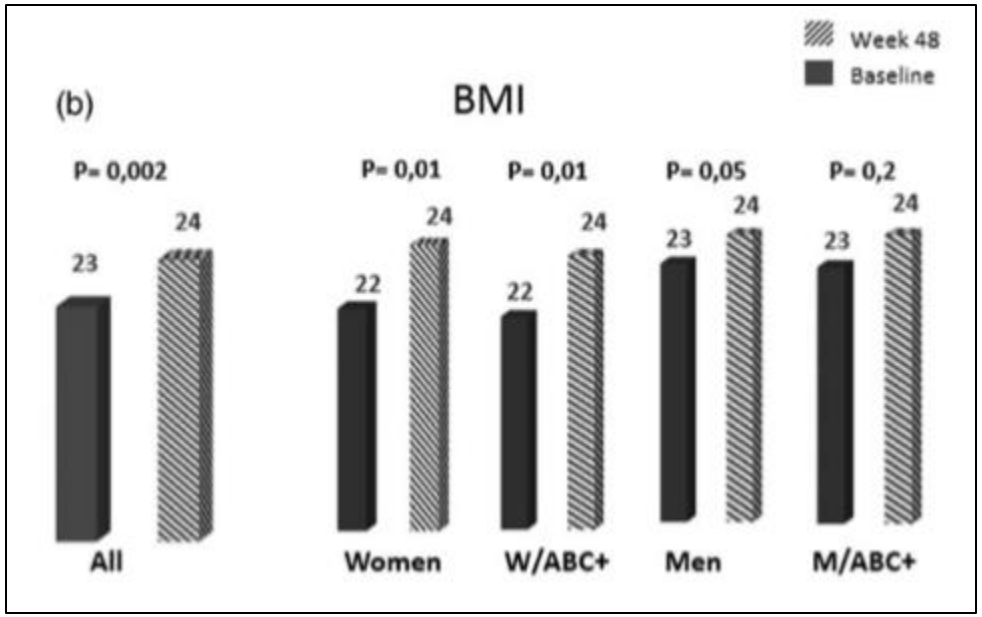


McComsey GA. Clin Infect Dis. 2016;62(7):853-862.

Dolutegravir and Weight Gain

- 462 patients initiating DOL-based ART
  - Mean age 50 years
  - 65% men; 35% women
  - Mean CD4 ct: 591 c/mm^3
  - 92% VL undetectable
- BMI categories
  - 6% underweight (<18kg/m^2)
  - 59% normal weight (18-25kg/m^2)
  - 24% overweight (25-30kg/m^2)
  - 6% obese(>30kg/m^2)

Weight Gain after 1 Year

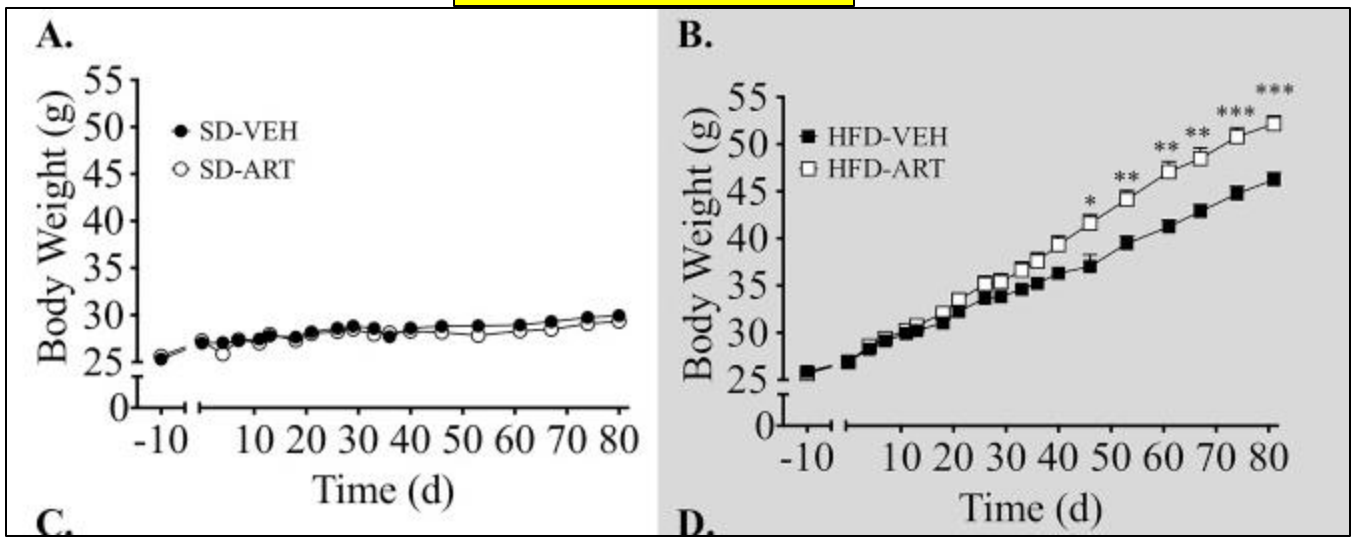


- **1/5 experiences 10% weight gain**

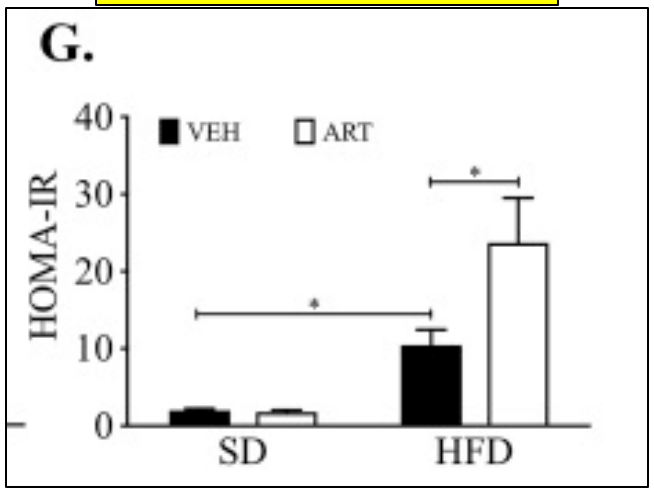
Menard. AIDS 2017, 31: 1499-1502.

ART Exacerbates Diet-Induced Weight Gain

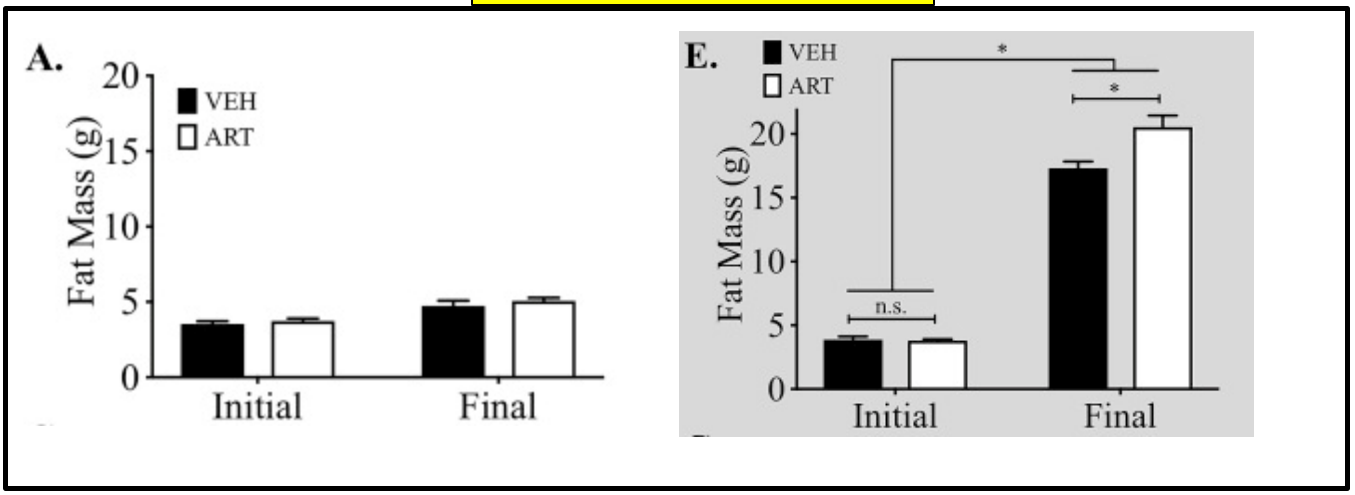
Change in Weight



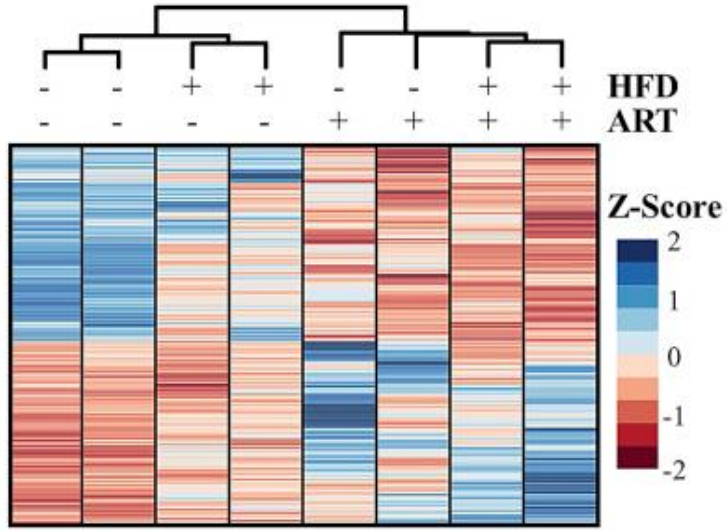
Effect on HOMA-IR



Change in Fat Mass



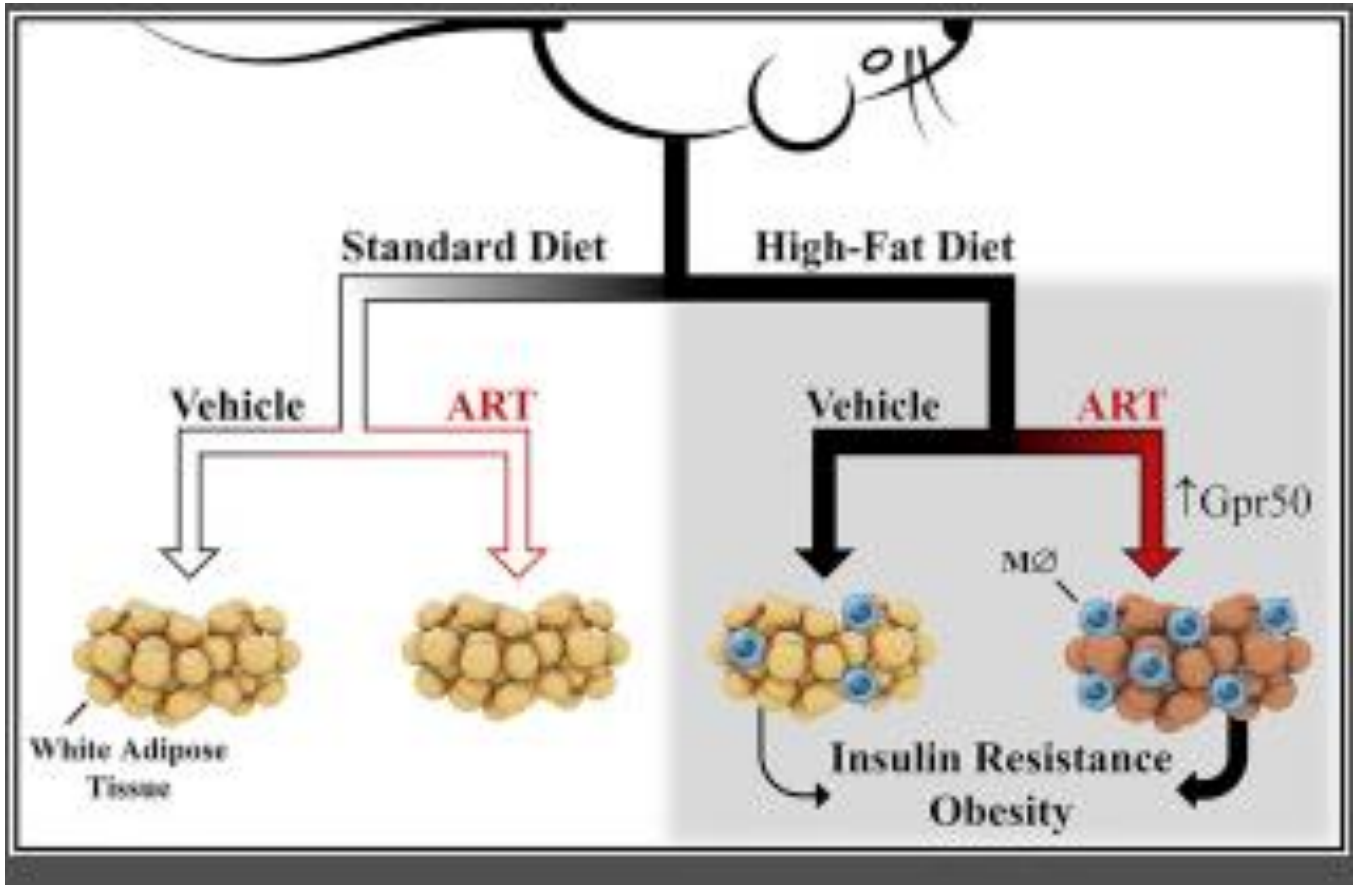
Adipose Tissue Transcriptional Change



Pepin M. Mol Metab. 2018. Epub ahead of print

ART Exacerbates Diet-Induced Weight Gain

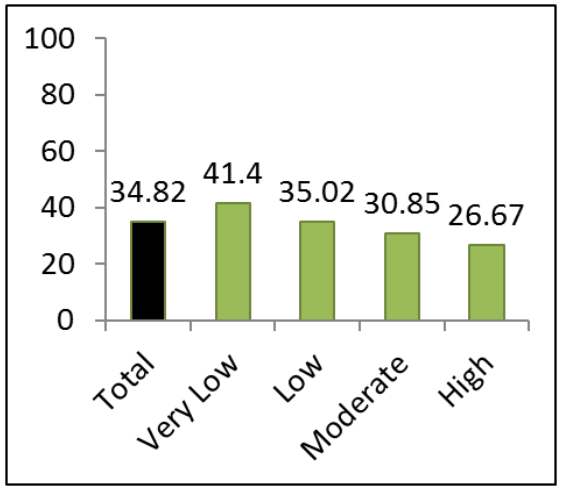
- ↑ Weight gain and adipose tissue
- Alters insulin sensitivity
- Alters gene expression in adipose tissue
- Increased recruitment of macrophages to adipose tissue
- Increase expression of inflammatory cytokines



Pepin M. Mol Metab. 2018. Epub ahead of print

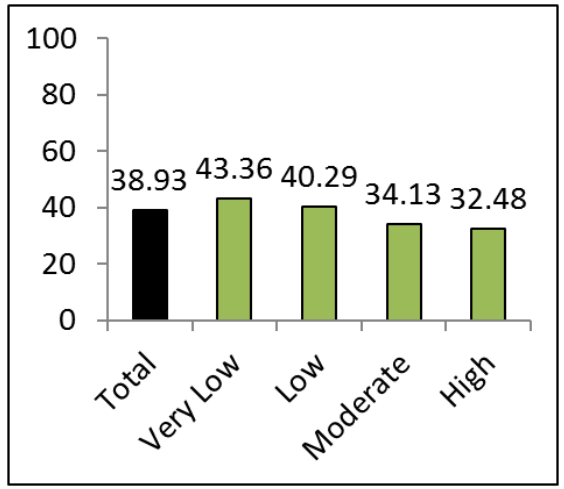
High Prevalence of Obesity and Physical Inactivity Linked to Comorbidity

Obesity



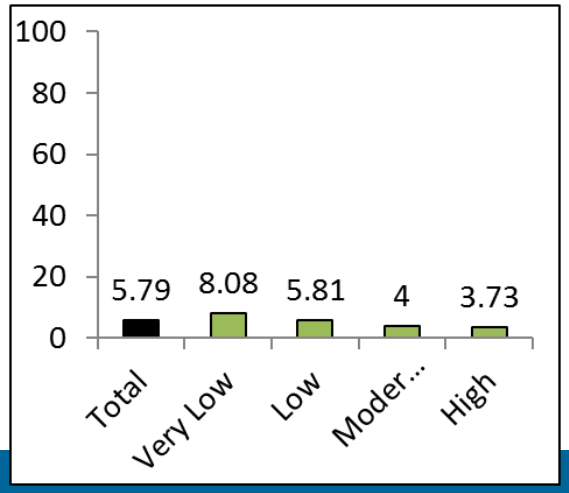
Physical Activity level

Hypertension

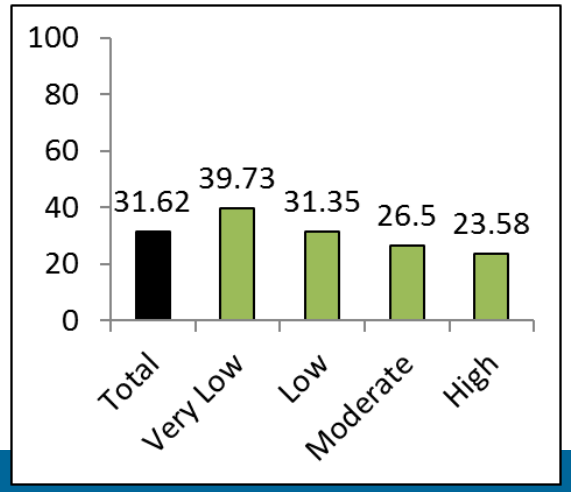


Comorbidity prevalence inversely related to PA level and Obesity.

CVD



Multimorbidity



Willig AL. Manuscript Under Review.

Diet and Food Insecurity

- Dietary Survey of 1917 HIV patients
  - Median Age 54.5 yrs
  - 68% male
  - 80% African American
  - 38% obese
- Failure to Meet Nutritional Recommendations
  - Total estimated caloric intake: 2240 kcal/day
  - Protein 42%
  - **Dietary Fiber 10%**
  - Low micronutrient intake
- **Food Insecurity in 55% of patients surveyed**

Willig AL. Unpublished Data. Puccinelli MT. Poster Presentation. UAB Medical Student Research Day.

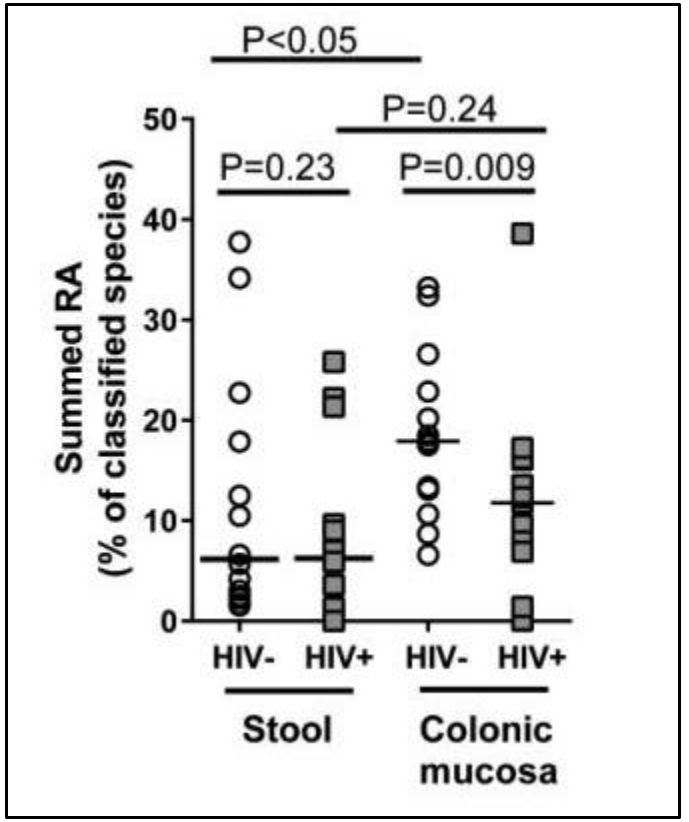
Low abundance of colonic butyrate-producing bacteria in HIV infection is associated with microbial translocation and immune activation

Stephanie M. Dillon[a,*], Jon Kibbie[a,*], Eric J. Lee[a], Kejun Guo[a], Mario L. Santiago[a], Gregory L. Austin[b], Sara Gianella[c], Alan L. Landay[d], Andrew M. Donovan[a], Daniel N. Frank[a,e], Martin D. McCarter[f] and Cara C. Wilson[a]

Study Participant Characteristics

	14 HIV neg	18 HIV pos
Age (yrs)	31 (23-54)	32.5 (22-58)
Male/Female	9/5	13/5
CD4 count (cells/ml)	724 (468-1071)	424.5 (238-782)
HIV VL copies/ml)	-	51350(2880– 207000)
BMI (kg/m^2)	25.3 (18.5-32.3)	25.4 (17.4-34.7)

Percent Butyrate Producing Bacteria



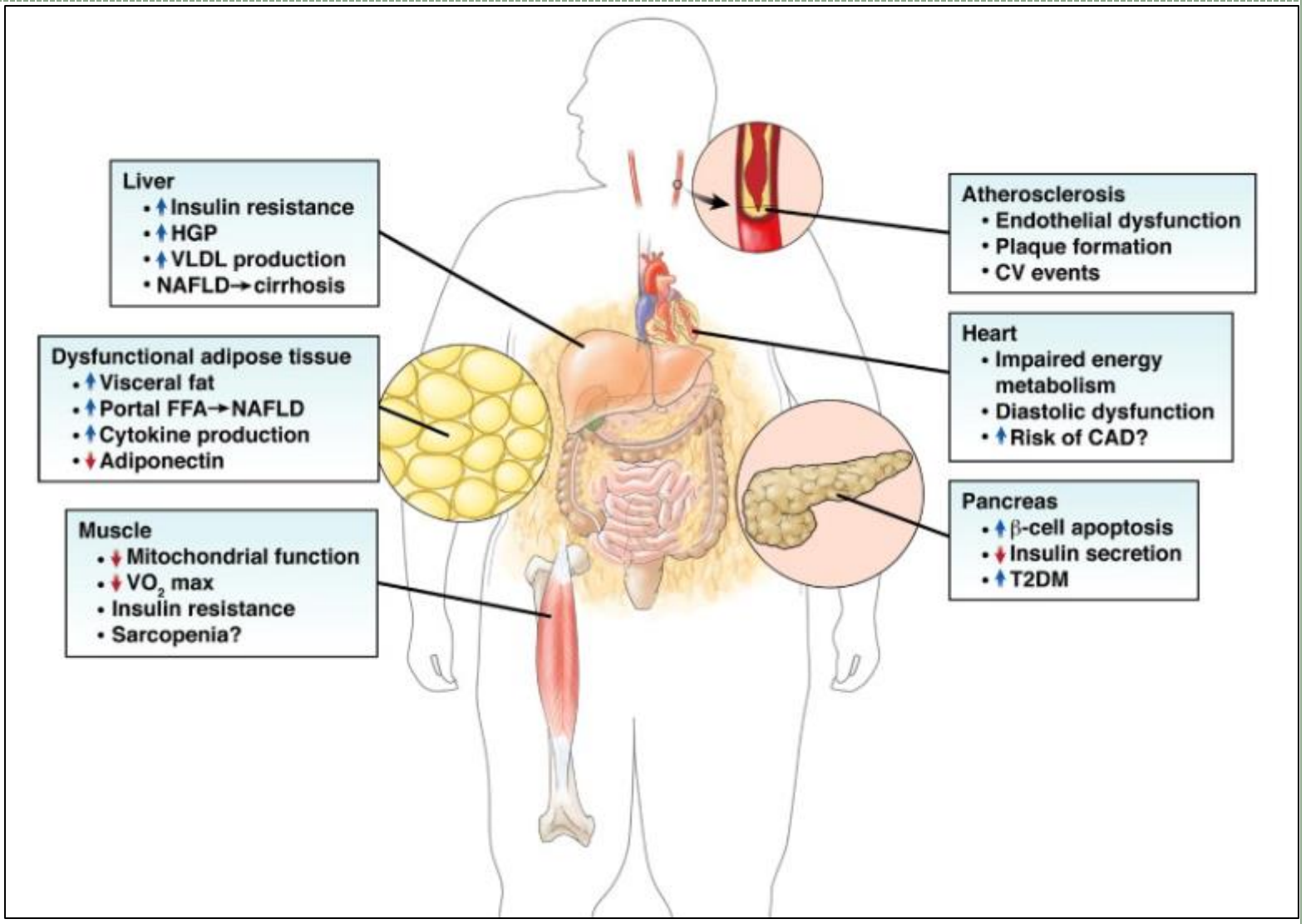
With Supplemental Butyrate

- Decrease in T cell activation
- Decrease in IL-17A and IFN-gamma production

AIDS 2017, 31: 511-21.

Obesity: a state of chronic inflammation mediated in part by alterations to the gut

- ↑ gut permeability
- ↑ bacterial translocation
- Alteration in microbiome
  - ↓ Bifidobacteria
  - ↑ Bacteroidetes
  - ↑ Pathogens
  - ↓ SCFA producers
- Alterations in gut-brain signaling
  - ↑ Appetite
  - ↓ Serotonin production



Curi K. Gastroenterology 2012. 142: 711-25.

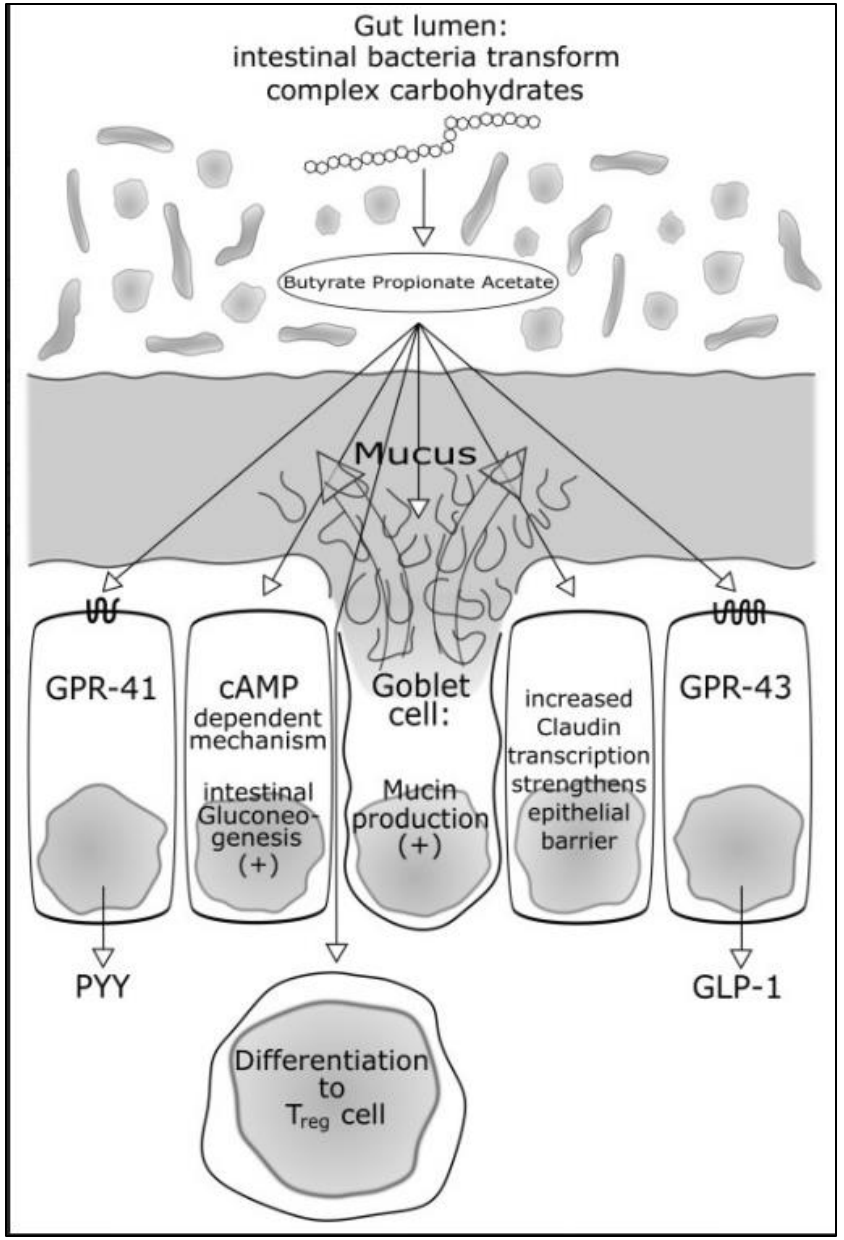
Role and Composition of Gut Microbiota Contribution to Obesity

- Increase energy harvest
- Modulation of free fatty acids
  - Particularly SCFAs
- Modulation of bile acids
- Modulation of GABA
- Impact on TLR expression
- Alter the endocannabinoid system
- Increase potential for metabolic endotoxemia
  - Modulation of LPS and other bacterial products
- Activate innate immune system
- Alter metabolism of amino acids

Harsch IA.. Med Sci. 2018;6:32.

Relevance of Short Chain Fatty Acids

- Butyrate
  - Primary energy source for enterocytes
  - G protein coupled receptors
    - Secretion Protein YY
      - Reduce appetite
    - Secretion GLP-1
  - Expand ILC and T reg populations
  - Enhance Mucus production from Goblet cells

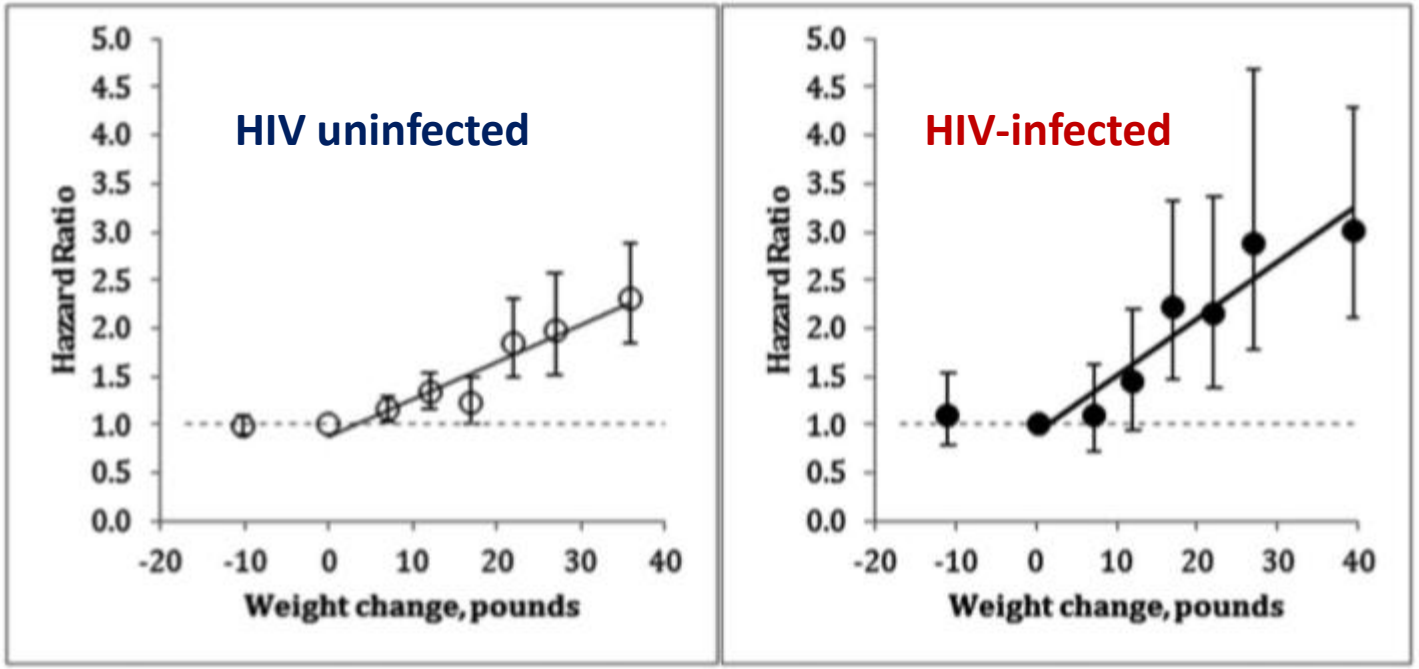


Harsch IA. Med Sci. 2018;6:32.

Are There Any Consequences to Weight Gain?

- VACS cohort
  - 6845 HIV-infected veterans
  - 23,345 HIV negative veterans
- Median age
  - HIV-infected 50 years
  - HIV uninfected 48 years
- Median BMI
  - HIV-infected 25 kg/m^2
  - HIV uninfected 28 kg/m^2
- Median weight change in 1 year
  - HIV-infected 4.3 lbs
  - HIV uninfected 1.0 lbs

Relative Risk of Incident Diabetes by One Year Weight Change



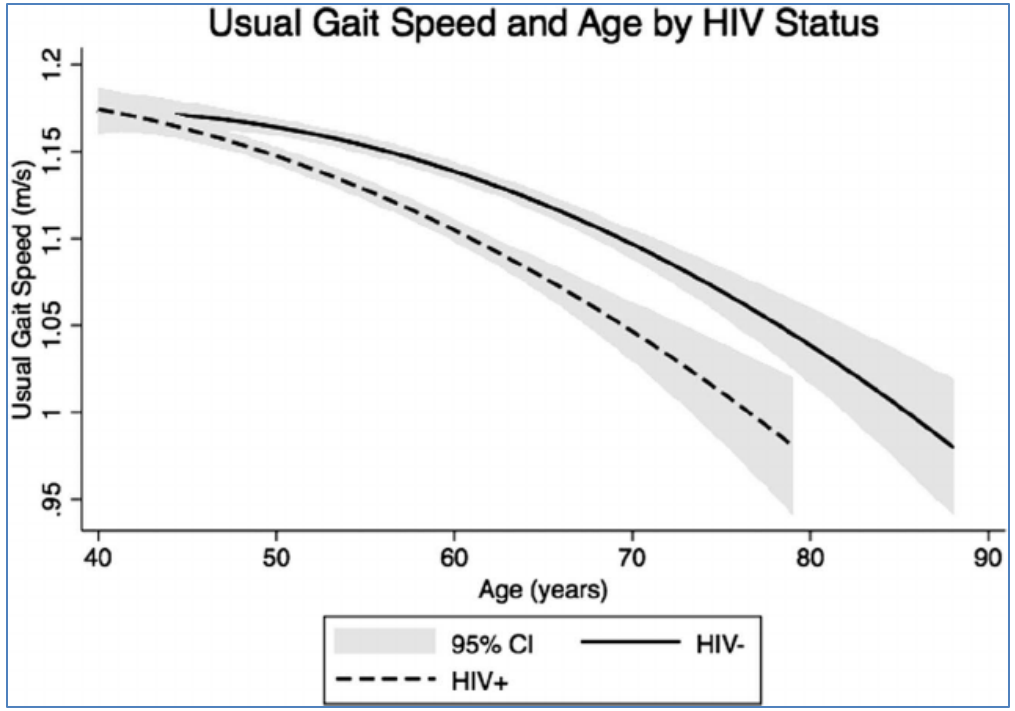
Model adjusted for age, race, sex, baseline BMI, smoking, HCV infection, and calendar year

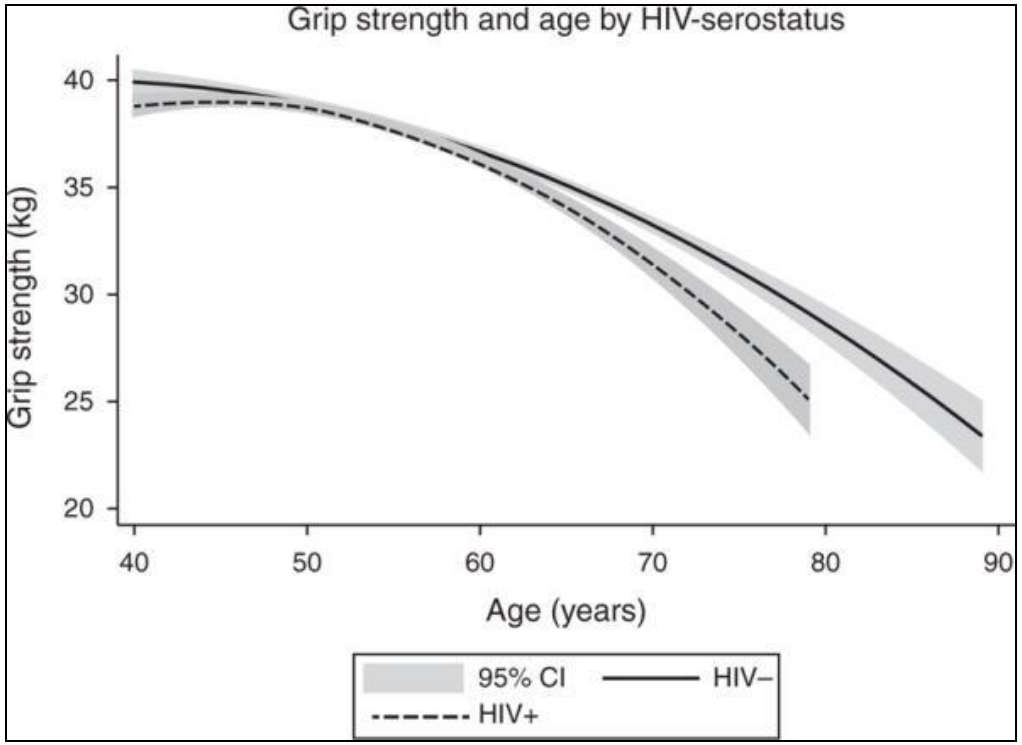
Increased Diabetes Incidence

Herrin M. JAIDS 2016, 73: 228-236.

Are There Any Consequences to Weight Gain?

Measures of Gait Speed and Grip Strength from the MACS Cohort



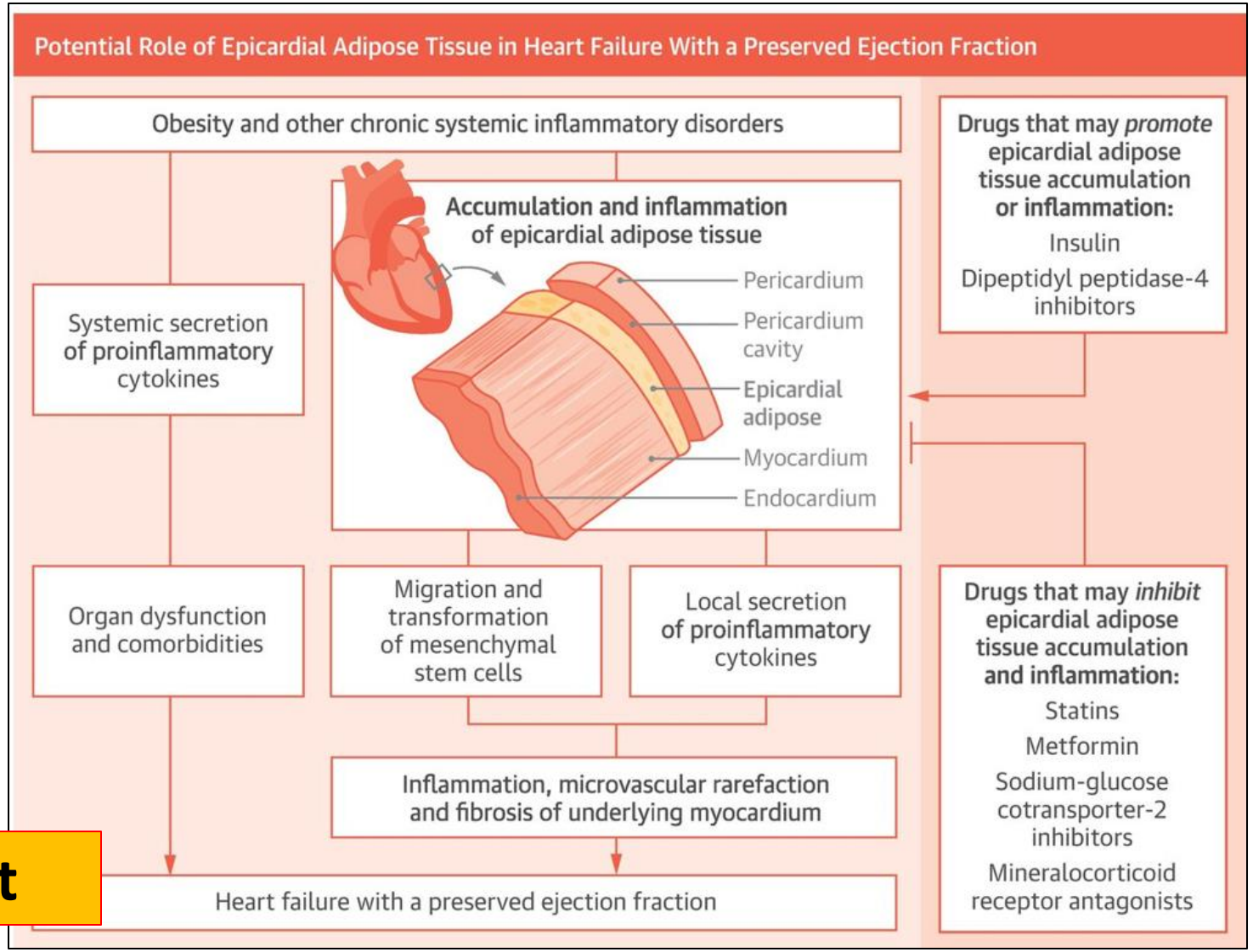


Increased Fatty Infiltration of Muscle

Schrack, et al. JAIDS 2015 and AIDS 2016.

Are There Any Consequences to Weight Gain?

- Epicardial Adipose Tissue
  - Depot of ectopic adipose tissue
  - Similar to VAT
- Increased in HIV
  - Matched for age, race, BMI
- Contributes to atherogenesis
  - Cytokine production
  - Activated macrophages
- Associated with cardiac fibrosis and heart failure with preserved ejection fraction



Increased Epicardial Fat

Lo J. AIDS 2010; 24: 2127-30. Brener M. AIDS. 2014; 28: 1635-44. Srinivasa S.. Antivir Ther. 2018, 23: 1-9. Packer M. JACC. 2018; 71:2360-72.

Pharmacologic/Surgical Intervention

- Specific agents
  - Orlistat: Lipase inhibitor
    - Reduce weight, lipids, BP
    - High prevalence of GI AEs
  - Locaserin: Serotonin agonist
    - Decreases appetite
  - Phentermine: Sympathomimetic agent
    - NA and DA reuptake inhibitor
    - Short term use only
  - Naltrexone/bupropion
  - Antihyperglycemic agents
    - Metformin
    - GLP-1 receptor agonist
    - SGLT-2
  - Teduglutide: GLP-2 for short bowel syndrome
    - Ongoing trial to improve gut permeability in HIV (Lo)

- Treating the consequences
  - Lipid lowering therapy, CVD reduction
    - Statins
    - Fibrates
    - Niacin

- Bariatric Procedures
  - Restrictive procedures
    - Reduce stomach reservoir
    - Decrease appetite
  - Malabsorption
    - Shorten small bowel
    - Metabolic complications
      - Protein calorie malabsorption
      - Micronutrient deficiencies

Drug Therapies Do Not Cure Obesity

New Antihyperglycemic Agents

- Dipeptyl peptidase 4 inhibitors (DPP4 inhibitors)
  - Sitagliptin
- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)
  - **Liraglutide**
  - **Semaglutide**
- Sodium glucose cotransporter 2 inhibitors (SGLT-2 inhibitors)
  - Empagiflozin
  - **Canagliflozin**

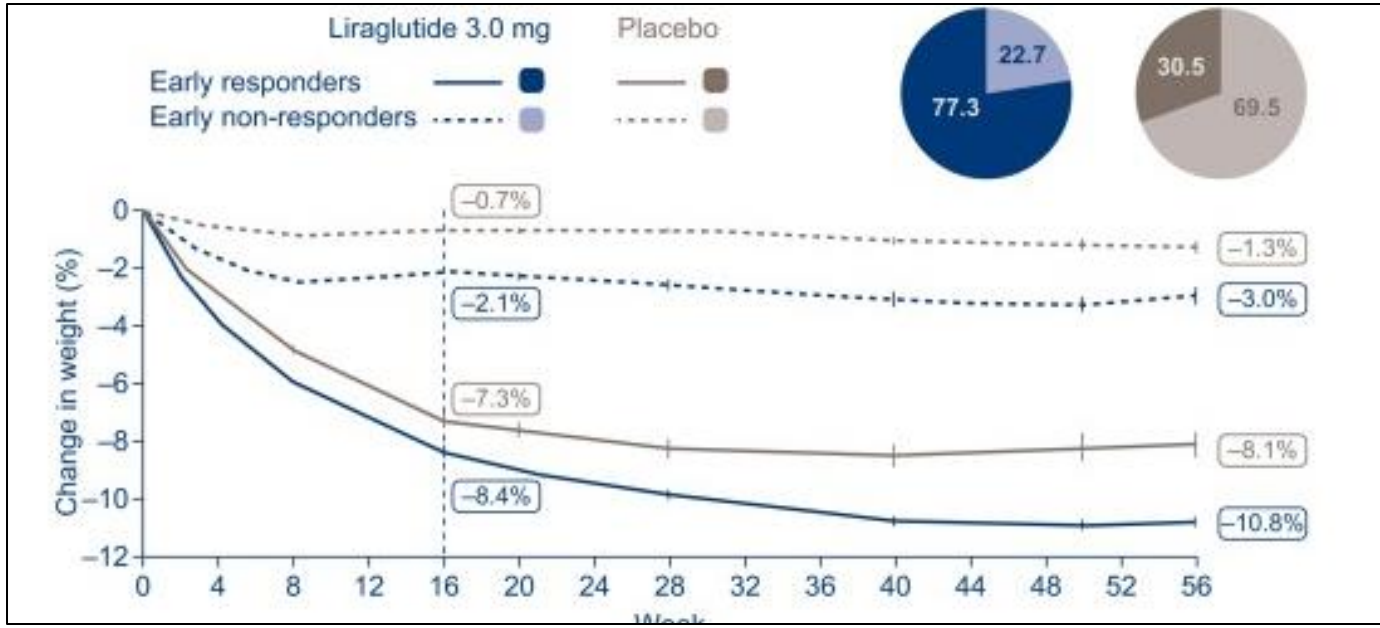
Zheng SL. JAMA. 2018; 39: 1580-91.

Liraglutide

- GLP-1 receptor agonist
  - approved for weight loss

- Actions to decrease weight
  - Increases prandial insulin secretion
  - Decreases prandial glucagon secretion
  - Reduces TG levels
  - Suppresses appetite
  - Improves insulin sensitivity
  - Reduces lipotoxicity

Weight Loss in Obesity and PreDiabetes

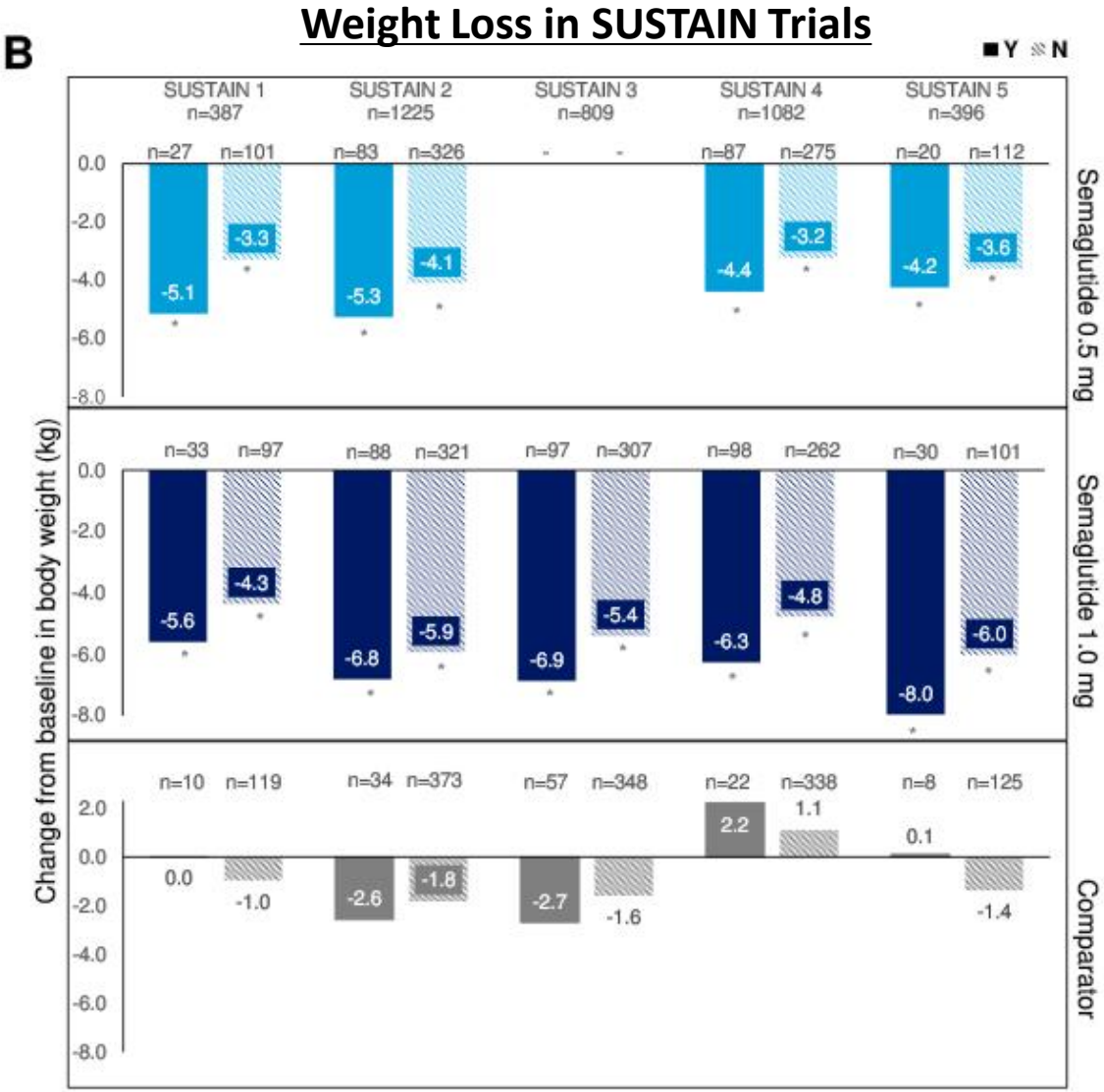


- May be particularly relevant in HIV where microbial translation leads to depletion of GLP-1 secreting neuroendocrine cells
- Reduction in ASCVD events an additional benefit

Armstrong MJ. J Hepatolo. 2016; 64: 399-408. Culha MJ. Medical Hypoth. 2016; 94: 151-53.. Secrest Trends Cardio Med. 2017; 27: 194-202.

Semaglutide

- GLP-1 receptor agonist approved for weight loss
- SUSTAIN 1-5 Trials in Type 2 Diabetes
  - Superior versus several comparators (placebo, sitagliptin exenatide, or insulin)
- Key findings
  - Superior weight loss 2.3-6.3kg
    - better for individuals with higher BMI
  - Better reduction in Hgb A1c
- GI AEs reported more frequently with semaglutide
  - N/V 15-27% versus 6-14% with comparators
- GLP-1 receptor agonists associated with 10% reduction in CVD endpoints
  - Related to improved insulin sensitivity
  - Possibly reduction in EAT

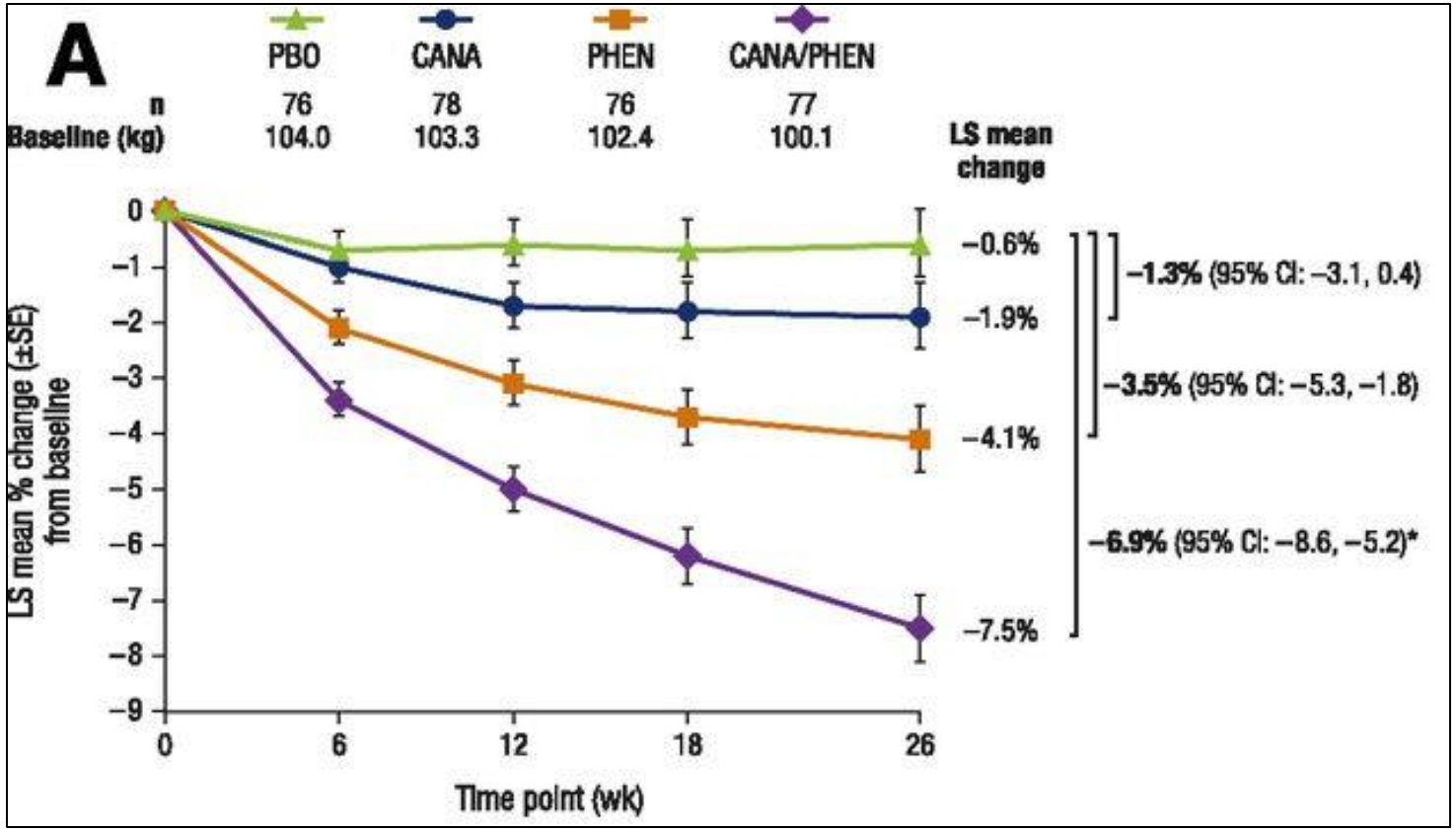


Ahren B. Diabetes Obes Med. 2018. Epub ahead of print. Bethel MA. Lancet Diabetes Endocrin. 2018; 6: 105-13.

Canagliflozin

- Subtype 2 sodium-glucose transport (SGLT-2)
  - Responsible for 90% renal glucose reabsorption
- Mild osmotic diuresis
- Net caloric loss

- RCT, PBO-controlled 4 arm study
  - Overweight/obese without DM
- 4 Arms
  - Placebo
  - Canagliflozin
  - Phentermine
  - CANA + PHEN



Hollander P. Diabetes Care. 2017; 40: 632-39.

Diet and Exercise Can Work-1

- 18 Obese HIV-infected women completed 12 week weight loss program
  - Aerobic and resistance exercise training
  - Diet based on Diabetes Association Exchange Lists (50% carbs, 30% fats, 20% protein)
- Food intake decreased by 27%
- Weight decreased by 6.7 kg (7%) ($p<0.001$)
  - 17% decline in VAT; 14% decline in total adipose tissue ($p<0.001$ for both)
- Improvement in 11/13 domains of QOL testing
- No change in fasting glucose, insulin sensitivity, lipid values

Engelson ES. Metab Clin and Exper. 2006; 55: 1327-36.

Diet and Exercise Can Work-2

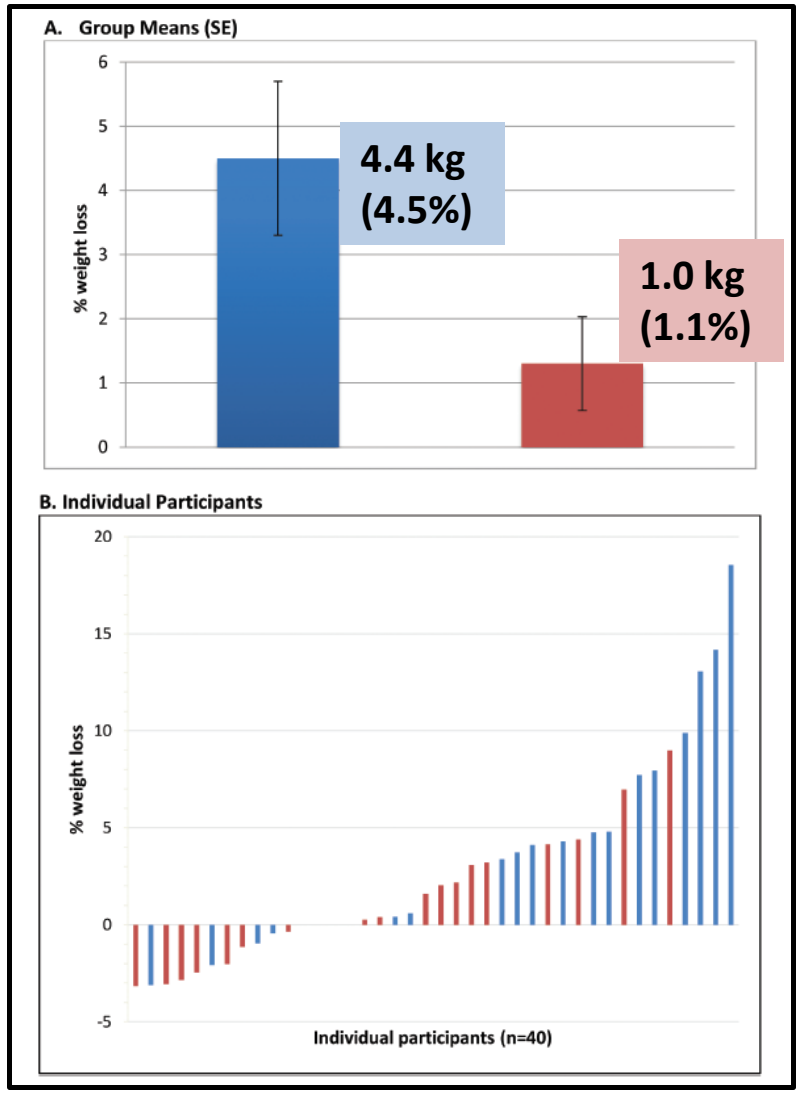
- 20 Obese HIV-infected women and 8 HIV negative women participated in weight loss program targets to facilitate 6-8% weight loss
  - Diet designed to cause 1000 kcal/day energy deficit
  - Meal replacements were provided for 2 meals per day
- Baseline BMI
  - HIV infected 43 kg/m^2
  - HIV negative 39 kg/m^2
- 19/28 achieved desired weight loss correlated to reduction in VAT and IHTG
  - 13 HIV-infected lost 7.7%
  - 6 HIV negative lost 7.3%
- Improvements in blood pressure and glucose levels
- No significant changes in inflammatory biomarkers

Reeds DN. Obesity. 2017. 25: 682-88.

Diet and Exercise Can Work-3

- 60 HIV infected persons on ART
  - 39 female, 21 male
  - Mean BMI 34 kg/m^2
  - Median CD4 ct 743 c/mm3
- Randomized to 12 week program
  - **Interactive Behavioral Program (Multimedia)**
    - **Monitor weight, intake, PA**
    - **Submit data via internet**
    - **Receive real-time feedback**
  - **Weekly Educational lesson posted on website**

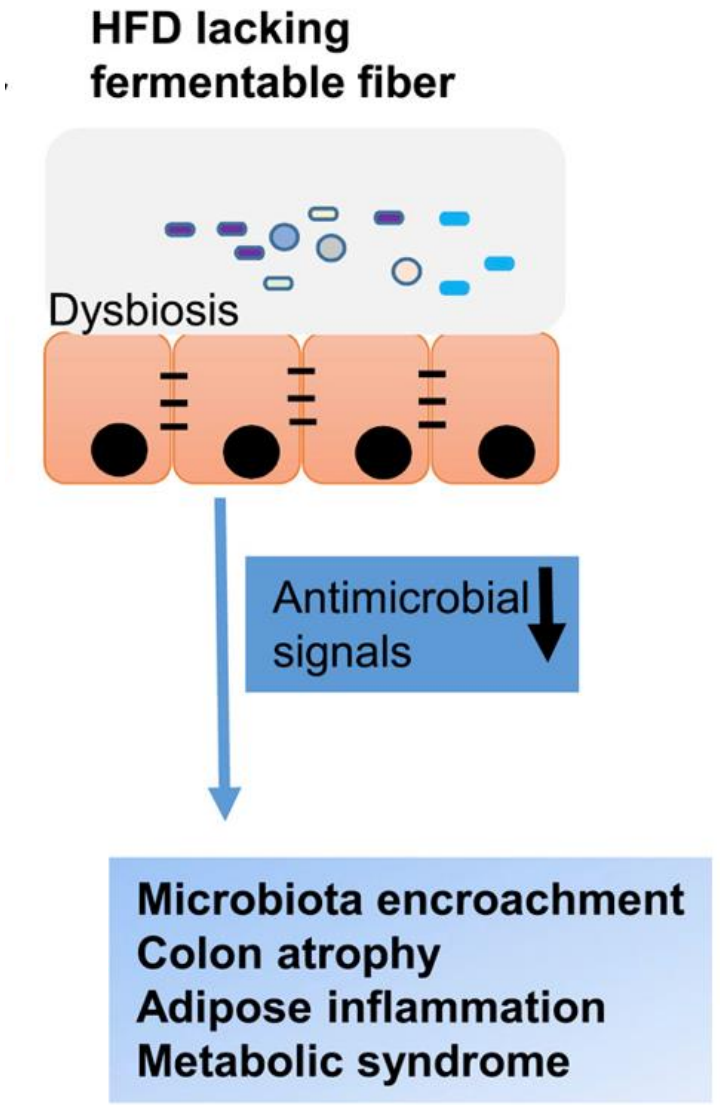
Weight Change After 12 Week Program



Becofsky K. CID. 2017; 65: 154-7.

Diets low in Fiber lead to excess inflammation and weight gain

- High Fat Diet without Fiber
  - Induces Dysbiosis
  - Decreases enterocyte health
  - Increases gut permeability
  - Decreased Immune surveillance
- Subsequent microbial translocation and its consequences



Zou J et al. *Cell Host and Microbe.* 2018;41-53.

Probiotics and Neutraceuticals

- Animal models support these agents
  - Reduction in weight gain
  - Antiatherogenic effects
  - Anti-inflammatory effects
  - Alterations in lipogenic and lipolytic genes in liver
  - Reduction in liver steatosis
  - Improvements in lipid profiles and insulin sensitivity
  - Decreased microbial translocation
- Paucity of data in humans
  - Primarily small, uncontrolled studies
  - Often difficult to control other dietary factors
  - May be challenging to provide sufficient dosing

Nova E. Nutr Clin Pract. 2016; 31: 387-400.

A5350: Effect of Probiotics on Gut Microbiome and Immune Activation Markers

Protocol Co-Chairs: Turner Overton and Adriana Andrade

The trial will randomize 90 HIV-infected adults 18 years of age and older
- On ART, with CD4 count >200 c/mm^3, and HIV VL < **50cp/mL**

Blinded

45 participants on ART + probiotic X 24 weeks

45 participants on ART + placebo X 24 weeks

Followed for an additional 12 weeks off study therapy after completion of probiotic./placebo

ClinicalTrials.gov Identifier:
NCT02706717

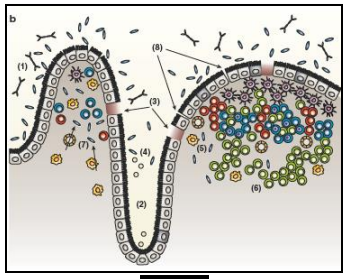
Key Study Objectives

- Assess changes in inflammatory biomarkers
- Assess changes in microbial translocation markers
- Assess changes in T cell phenotypes
- Assess changes in monocyte phenotypes
- Assess changes in microbial diversity
- Assess changes in gut permeability

Relevance to HIV Pathogenesis?

- Potential to increase Th17 T cell population in gut
- Potential to shift monocyte population
- Mediated through improved gut permeability

Microbial translocation



Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Conclusions

- Obesity is highly prevalent among treated HIV-infected patients.
- Drivers of obesity likely augmented by HIV infection.
- Interventions should target the key drivers of Obesity in HIV infection
  - ART
  - Leaky Gut Paradigm (Microbial translocation, Dysbiosis, Gut permeability, Inflammation)
  - Lifestyle/Dietary Factors

- Studies should also evaluate the consequences of obesity
  - Chronic inflammation
  - IR→ Diabetes
  - NAFLD/NASH
  - Other ectopic fat deposition (EAT)
  - Brain: cognition/mood
  - CVD risk: lipids/EAT
  - OSA
  - HIV reservoir

- How to intervene?
  - Behavioral: diet/exercise (caloric restriction, intermittent fasting, ketogenic diet)
  - Pharmacologic