Comorbidities in the Setting of Antiretroviral Therapy

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Bedimo has received grants and research support awarded to the Veterans Affairs North Texas Healthcare System from Merck & Co. He has served as a scientific advisor for ViiV Healthcare, Merck & Co, Inc, Gilead Sciences, Janssen, and Theratechnologies. (Updated 12/14/22)

Slide 2

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Learning Objectives

After attending this presentation, learners will be able to:

1. Review the trends in comorbidities and their impact in survival of people with HIV
2. Identify predictors of weight gain and cardiometabolic risk of ART and list potential mechanisms
3. Apply best practices in prevention and management of cardiometabolic risk in PWH

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Outline

1. Trends in Co-morbidities and impact on survival of PWH
2. Magnitude and predictors of weight gain associated with antiretroviral use.
   - ART-Naïve
   - ART switch
   - PrEP
3. Potential mechanism(s) of weight gain and cardiometabolic complications during antiretroviral therapy.
4. Prevention and management of weight gain and mitigation of ARV-related cardiometabolic risk

Slide 4

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ARS Question 1: Case #1: Weight Gain on ART Initiation

- M.J. is a 30 y/o Hispanic female who was diagnosed with HIV disease in 2017 on routine screening. She had no history of opportunistic infections. Her baseline CD4 count was 159 and viral load was 857,000. She was HBV immune and HCV antibody negative. She weighed 160 pounds (BMI: 27). She initiated antiretroviral therapy with BIC/FTC/TAF. Over the following 2 years, she reported a 20-pound weight gain (BMI is now 30). She denies any change in diet or exercise level.
- Which of the following is CORRECT regarding the weight gain observed in this patient?

A. Weight gain on antiretroviral therapy is more likely to occur in men than in women
B. Weight gain is more likely to occur with NNRTI than with INSTI-based regimens
C. Weight gain is more likely to occur with TAF- than with TDF-based regimens
D. Exposure to FTC/TAF would not have been associated with weight gain if taken for PrEP rather than antiretroviral therapy.
E. All of the above are correct.

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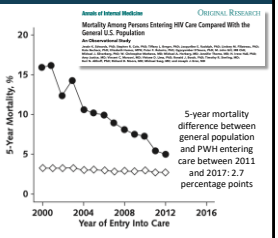
Dramatic Decline in Mortality Among People Entering HIV Care

- Adults entering HIV care in the US between 1999 and 2017 (n=82,766)
- Difference in 5-year mortality between people with HIV (PWH) and general population decreased over time
- Likely because of earlier initiation of therapy, improved treatment



Edwards JK et al, Ann Int Med, 2021

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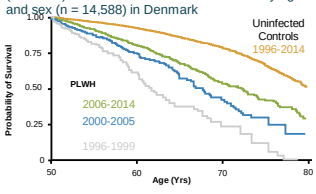
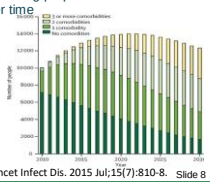
Narrowing Survival Gap in Older Adults with HIV in Modern ART Era; Persistent Gap Driven by NCDs

Population-based cohort study of survival in PLWH (n = 2440) and uninfected controls matched by age and sex (n = 14,588) in Denmark



Legarth RA, et al. J Acquir Immune Defic Syndr. 2016;71:213-218.

Predicted burden of non-communicable diseases (NCDs) in HIV patients modeled for 2010-2030
Increasing proportion with more NCDs over time



Smit. Lancet Infect Dis. 2015 Jul;15(7):810-8.

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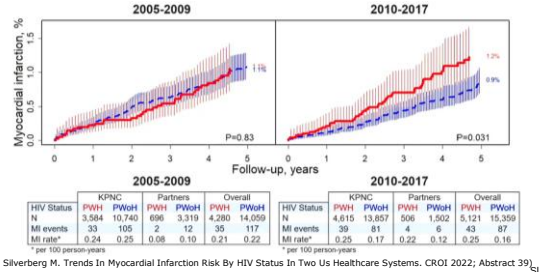
8

Cumulative incidence of MI by HIV status:



2005-2009

	KPNC		Partners		Overall	
HIV Status	PWH	PWoH	PWH	PWoH	PWH	PWoH
N	3,584	10,740	696	3,319	4,280	14,059
MI events	33	105	2	12	35	117
MI rate*	0.24	0.25	0.08	0.10	0.21	0.22

per 100 person-years

2010-2017

	KPNC		Partners		Overall	
HIV Status	PWH	PWoH	PWH	PWoH	PWH	PWoH
N	4,615	13,857	506	1,502	5,121	15,359
MI events	39	81	4	6	43	87
MI rate*	0.25	0.17	0.22	0.12	0.25	0.16

per 100 person-years

Silverberg M. Trends In Myocardial Infarction Risk By HIV Status In Two Us Healthcare Systems. CROI 2022; Abstract 39)

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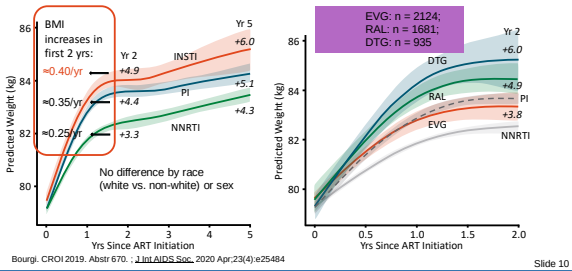
Weight Gain by Class or Specific INSTI: NA-ACCORD



Bourgi. CROI 2019. Abstr 670. ; J Int AIDS Soc. 2020 Apr;23(4):e25484

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Obesity Risk in PWH Initiating INSTI or TAF: Analysis of 3 African Trials

Trial	Arm	Clinical obesity (probability)		
		Men	Women	Overall
ADVANCE (Week 192)	TAF/FTC/DTG	11%	42%	29%
	TDF/FTC/DTG	8%	28%	18%
	TDF/FTC/EFV	3%	20%	11%
NAMSAL (Week 192)	TDF/3TC/DTG	28%	25%	26%
	TDF/3TC/EFV	9%	20%	16%
VISEND BL<1,000 cp/mL (Week 96)	TAF/FTC/DTG	2%	22%	13%
	TDF/FTC/DTG	3%	14%	10%
VISEND BL≥1,000 cp/mL (Week 96)	TAF/FTC/DTG	6%	14%	11%
	TDF/FTC/DTG	1%	19%	12%
	ZDV/3TC/LPVr	4%	14%	11%
	ZDV/3TC/ATVr	7%	21%	15%

Venter. HIV Drug Therapy Glasgow, October 23-26, 2022.

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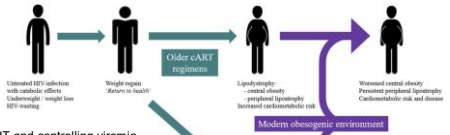
Weight Gain with ART Initiation: Return to Health Versus Obesity?



Hypothesis:

- Starting "modern" ART and controlling viremia decreases inflammation and reduces the catabolic effects of HIV infection
- The better and faster viremia is controlled (e.g. with INSTI) the more "return to health" gain.
- Greater gain with higher baseline viremia
- Calorie intake might improve with better clinical status, healthcare services, etc…

Kumar S, et al. *Front Endocrinol.* 2018;9:705.

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ARS Question 2: Case #2: Weight Gain with ART Switch

- M.S. is a 35 y/o while male on EFV/3TC/TDF for the past 10 years. He has been very reluctant to change a regimen that "saved his life". However, willing to consider, due to persistent insomnia, depressive disorder. CD4 count is 700, VL<20 copies/mL. He's HCV negative and HBV immune. A switch to DTG + FTC/TAF will likely result in:

a. No change in weight, as patient was already virologically suppressed.
b. Weight loss, since TAF is associated with fewer metabolic complications.
c. Weight gain because of switch from TDF to TAF
d. Weight gain because of switch from EFV to DTG
e. Both c and d.

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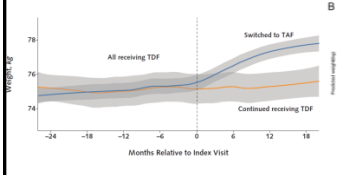
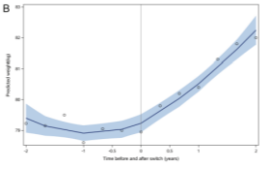
Weight Gain after Switch from TDF to TAF, or Switch to INSTi

Swiss Cohort: 4375 adults living with HIV who received TDF-containing ART for 6 months or longer.



Surial. Ann Intern Med 2021 Jun;174(6):758-767

Pre/post-INSTI weight changes from AIDS Clinical Trials Group participants (A5001 and A5322)



Lake. Clin Infect Dis. 2020 Dec 3;71(9):e471-e477

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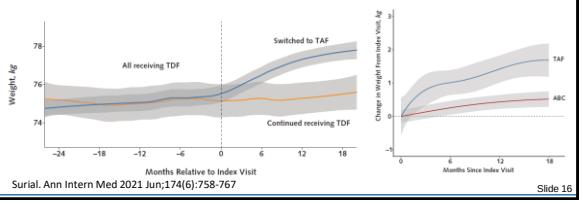
Weight Gain after Switch from TDF to TAF, or ABC to TAF

Swiss Cohort: 4375 adults living with HIV who received TDF-containing ART for 6 months or longer.

Patients who received ABC and continued ABC (n = 2560) or switched to TAF(n = 427).



Surial. Ann Intern Med 2021 Jun;174(6):758-767

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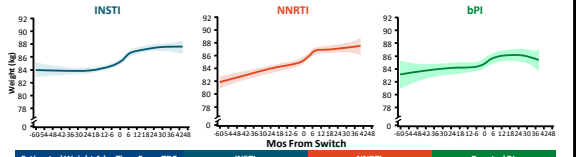
OPERA: Weight Change With Switch From TDF to TAF While Maintaining Other ARVs by Class of Anchor Agent



Estimated Weight Δ by Time From TDF to TAF Switch, kg/yr (95% CI)	INSTI (n = 3281)	NNRTI (n = 1452)	Boosted PI (n = 746)
-60 to 0 mos	0.42 (0.26 to 0.59)	0.66 (0.51 to 0.81)	0.31 (-0.02 to 0.64)
0 to 9 mos	2.64 (2.26 to 3.01)	2.25 (1.78 to 2.71)	1.98 (1.13 to 2.83)
9+ mos	0.29 (0.08 to 0.51)	0.20 (-0.14 to 0.54)	-0.11 (-0.57 to -0.35)

Mallon. AIDS 2020. Abstr OAB0604. Reproduced with permission.

Slide credit: clinicaloptions.com

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Examining Weight Gain in the Context of Pathogenesis of Chronic Complications of HIV Infection

#1: THE PATIENT
- **Individual and social factors**
- **Higher rate of traditional risk factors: smoking, dyslipidemia, HTN, diabetes, obesity**

Metabolic Complications:
Cardiovascular Disease
Renal Disease
Osteoporosis
Non-AIDS Cancers

#2: THE VIRUS(ES)
- **HIV infection itself**
- **Inflammation and immune activation**
- **Coinfections: HCV**

#3: THE TREATMENT
- **ART and toxicity**

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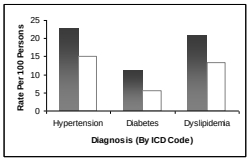
#1: The patient: Traditional CVD risk factors are very common among PLWH



Smoking
- High prevalence
  - 56% (D:A:D)
  - 54% (SFGH)
  - 47% (US cohort)
  - 69% (French cohort)
- 85% lifetime history
- More life years lost through smoking than through HIV

Dyslipidemia
- Distinctive pattern of low HDL and high TG
- May be impacted by PIs

Triant JCEM 2007; Burkhalter Nicotine Tob Res 2005; Friis-Moller AIDS 2003; Mamary AIDS Pt Care STDs 2002; Gritz Nicotine Tob Res 2004; Vittecoq AIDS 2003; Savès CID 2003; Lifson AJPH 2010; Helleberg, CID 2013.

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#1: The Patient: Intersection of HIV and Obesity Epidemics:

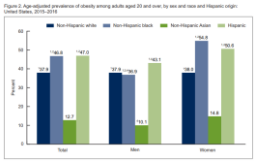
Obesity in the World:

- Worldwide obesity has nearly tripled since 1975.
- In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.
- 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese.

WHO. Health topics. https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight

Obesity in the US:

- The prevalence of 39.8% in 2016. Affected mostly Blacks and Hispanics



https://www.cdc.gov/nchs/data/databriefs/db288.pdf

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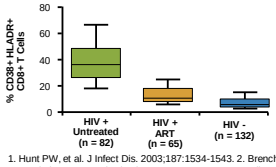
#2: The Virus: Inflammation Persists in the Setting of Treated HIV Infection; VL and CD4 assoc. with AMI risk

T-cell activation higher in treated HIV vs controls[1]
LPS higher in treated HIV vs controls[2]
Tissue factor elevated in treated HIV vs controls[3]



HIV RNA≥500 and CD4<200 each associated with increased AMI risk
AMI risk persists in patients achieving viral suppression or immune reconstitution[4]

Table 4. Time-Updated Analyses Assessing the Association of HIV-1 RNA and CD4 Cell Count Values and the Risk of AMI in Separate Models[a]

Category	HR (95% CI)	P Value[b]
HIV-1 RNA		
Uninfected	1 [Reference]	
≥500	1.75 (1.40-2.18)	.05
<500	1.39 (1.17-1.66)	
CD4 cell count		
Uninfected	1 [Reference]	
<200	1.88 (1.46-2.40)	.04
≥200	1.43 (1.21-169)	

1. Hunt PW, et al. J Infect Dis. 2003;187:1534-1543. 2. Brenchley JM, et al. Nat Med. 2006;12:1365-1371.
3. Funderburg NT, et al. Blood. 2010;115:161-167.; 4. Freiberg. JAMA Intern Med. 2013

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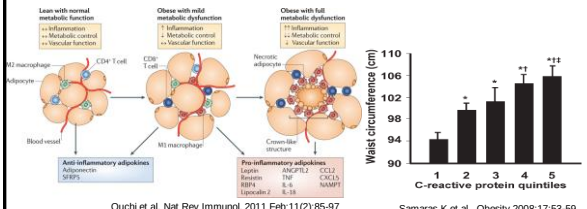
Obesity-Induced Inflammatory Changes in Adipose Tissue – Phenotypic Modulation



Ouchi et al. Nat Rev Immunol. 2011 Feb;11(2):85-97

Samaras K et al. Obesity 2008;17:53-59

Need to understand mechanisms and metabolic implications of weight gain in HIV

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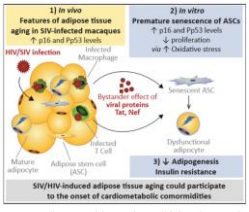
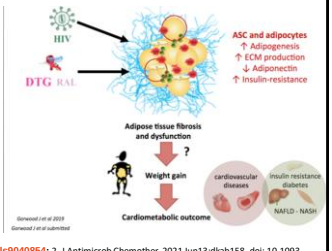
#2: The Virus and #3: The Treatment: HIV Induces Adipocyte Dysfunction; Likely worsened by Integrase Inhibitors





Gorwood. *Cells* **2020**, *9*(4), 854; https://doi.org/10.3390/cells9040854; 2. J Antimicrob Chemother. 2021 Jun13;dkab158. doi: 10.1093

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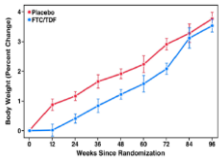
#3: The Treatment: Weight Gain on PrEP Studies: iPrEX: FTC/TDF vs. Placebo HPTN 083

- Placebo (n=1225)
- TDF/FTC (n=1226)
- Delayed weight gain in treatment group



Grant. NEJM 2010;363: 2587-99

- Overall, significantly greater median weight increase from BL with CAB vs FTC/TDF ($P < .001$)
  - CAB: +1.30 kg/yr (95% CI: 0.99-1.60)
  - FTC/TDF: +0.31 kg/yr (95% CI: -0.12 to -0.49)

Landowitz. AIDS 2020. Abstr OAXLB0101

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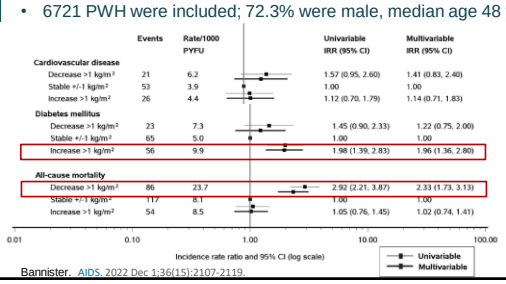
Change in BMI and Cinical Outcomes - EuroSIDA

- 6721 PWH were included; 72.3% were male, median age 48 years



Bannister. AIDS. 2022 Dec 1;36(15):2107-2119.

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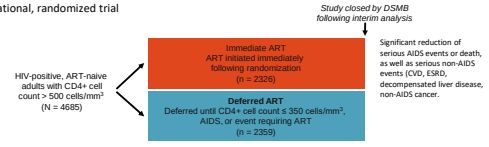
START: Immediate vs Deferred Therapy in ART-Naïve

- International, randomized trial



Mean percent change in weight from baseline:
Immediate: 1.1% (95% CI: 0.9 – 1.5)
Deferred: 1.9% (95% CI: 1.7 – 2.2)

Important to note:
Most patients (80%) are on NNRTI; <4% on INSTI
Very high median CD4 count (650), and rather low median viremia (12.7K).

INSIGHT START Group. N Engl J Med. 2015;373:795-807. Lundgren J, et al. IAS 2015. Abstract MOSY0302.; Moestrup. EACS 2019

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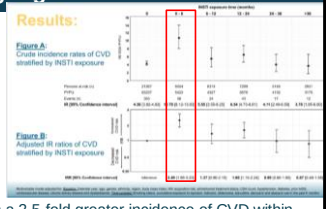
RESPOND: INSTIs and CVD Risk: Is it driven by weight gain???

- International collaboration of 17 cohorts
- Composite endpoint of MI, stroke and invasive cardiovascular procedure; adjudicated events
- N=21267 (46% exposed to INSTI)
- 517 CVD events, 4.9/1000 PY
- Could not specifically examine ART-naive



- INSTI exposure associated with a 2.5-fold greater incidence of CVD within first 6 months of exposure compared to no exposure in adjusted analyses

Neesgaard et al. vCROI 2021, abstract 488; *Lancet HIV* 2022 Jun 7; [e-pub].

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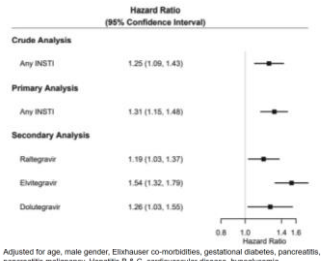
DM and INSTI Initiation

- Data from IBM MarketScan databases
- Adults with commercial insurance and Medicaid on ARVs
- Outcomes ascertained by ICD and CPT codes
- HR for new-onset DM/Hyperglycemia in PWH initiating ART ('07 to '19)
- Bictegravir: HR: 1.45 (0.84–2.51; P = .182)
- Sensitivity analysis with TAF: HR: 1.28 (0.99–1.64; P = .06)
  - <5% were on concurrent TAF



Adjusted for age, male gender, Elixhauser co-morbidities, gestational diabetes, pancreatitis, pancreatitis malignancy, Hepatitis B & C, cardiovascular disease, hypoglycemia

O'Halloran et al. Clin Infect Dis. 2022 May 6:ciac355.

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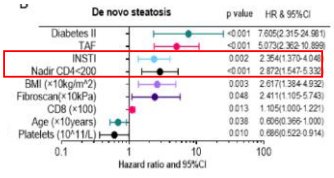
De-Novo Hepatic Steatosis with Weight Gain After ART Initiation

- Exposure to TAF and INSTIs associated with de-novo steatosis.
- Prospective cohort of 319 HIV mono-infected on ART;
  - 155 (52%) with no b/l steatosis → 69 (45%) developed steatosis on f/u
- BMI of >23 kg/m^2 for males is significantly associated with development of de novo steatosis (68% risk vs. 25% for females)
- TDF associated with lower risk of de-novo steatosis.
  - Regardless of weight trajectory…



Bischoff. EClinicalMedicine 2021 Sept 5;40:101116

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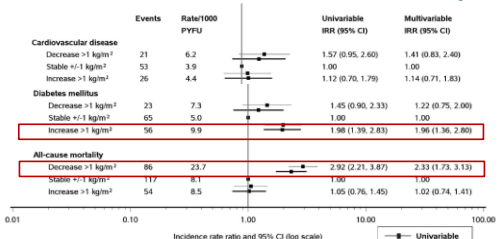

Bannister. AIDS. 2022 Dec 1;36(15):2107-2119.

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Management of Weight Gain on ART

- Antiretroviral Switch
  - Reversal of weight gain with switch to non-INSTI or non-TAF regimen still uncertain.
- Weight Loss Medications
  - Interesting new data from GLP-1 analogues [1]; Being explored in HIV
- Lifestyle Modification
  - Diet and exercise have been reported to work. Ancillary benefit in PLWH include prevention/mitigation of non-AIDS complications
  - IAS-USA: Counseling regarding possibility of weight gain and potential cardiometabolic complications is recommended for people with HIV initiating or switching ART (evidence rating: AIII).[2]

1. Wilding. N Engl J Med 2021;384:989-1002; 2. Gandhi. *JAMA*. Published online December 1, 2022. doi:10.1001/jama.2022.22246

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Management of Diabetes in PLWH

- Moderate intensity aerobic exercise *plus* nutritional optimization
- No evidence for ARV switch
- Metformin is the first-line medication recommended by the ADA, if there is no contraindication:
- ≥ 150 min of moderate intensity aerobic exercise over ≥ 3 days a week[1]
- Calorie guideline options for weight loss.[2,3]
  1. 1200–1500 calories/day for women or 1500–1800 calories/day for men
  2. An energy deficit of 500-750 calories per day
  3. An evidence-based diet that restricts a certain food type (e.g., high-carbohydrate foods) to create an energy deficit
- IAS-USA: Yearly diabetes screening and assessment of cardiovascular risk score of patients receiving InSTI-based ART is recommended (evidence rating: BIII) [4]

1. ADA. Diabetes Care. 2020;43(Suppl 1):S48-s65; 2. Knowler et al, NEJM, 2002; 3. Monroe et all, CID, 2014
4. Gandhi. *JAMA*. Published online December 1, 2022. doi:10.1001/jama.2022.22246

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Weight Gain and Metabolic Complications While Receiving Antiretroviral Therapy (ART)

- Documentation of weight and BMI at baseline and every 6 months is recommended for people with HIV initiating or switching regimens to identify those with excessive weight gain (evidence rating: AIIa)
- Counseling regarding possibility of weight gain and potential cardiometabolic complications is recommended for people with HIV initiating or switching ART (evidence rating: AIII)
- Yearly diabetes screening and assessment of cardiovascular risk score of patients receiving InSTI-based ART is recommended (evidence rating: BIII)
- Lifestyle changes (exercise and diet) are recommended to support people with HIV who gain greater than 5% body weight (evidence rating: AIII)

Gandhi. *JAMA*. Published online December 1, 2022. doi:10.1001/jama.2022.22246

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