What data remain about weight and ART?

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Disclosures

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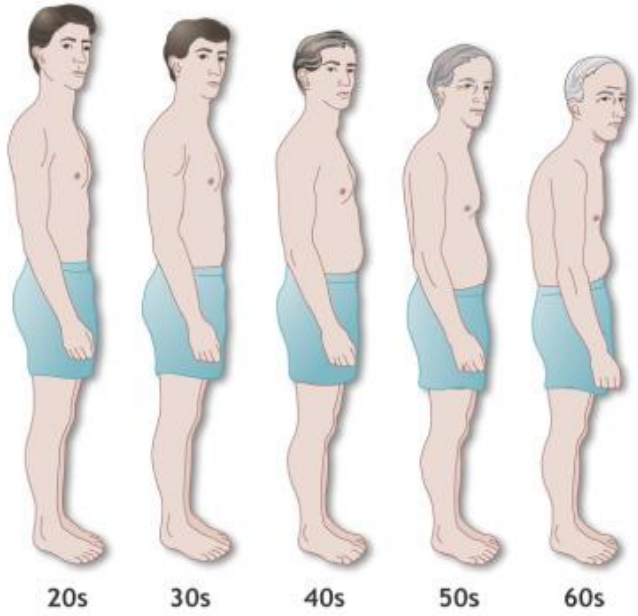
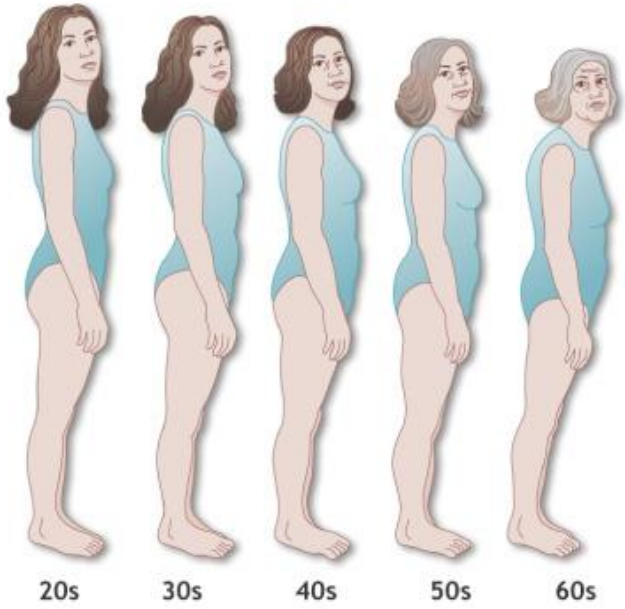
Obesity & Weight gain determinants

Are PWH different regarding weight gain and obesity?



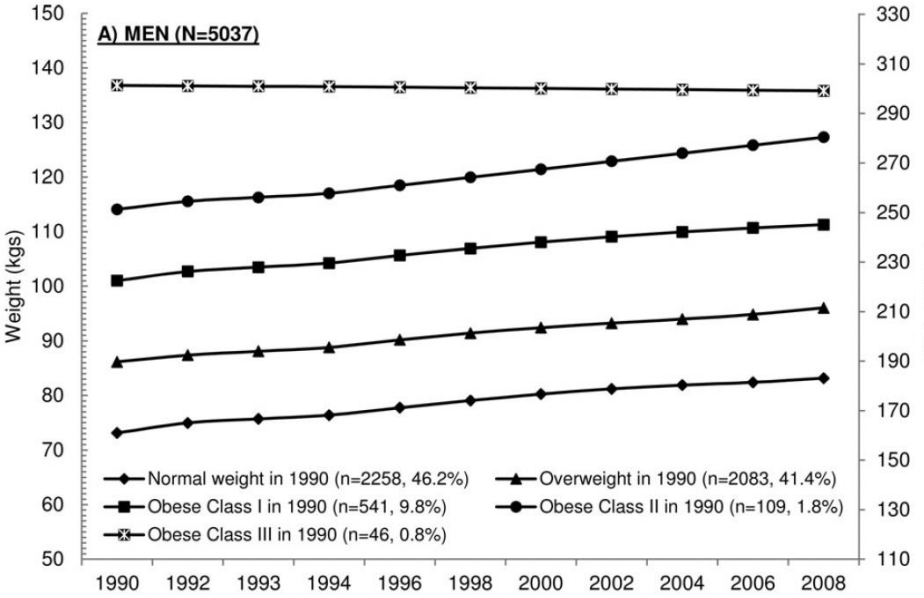


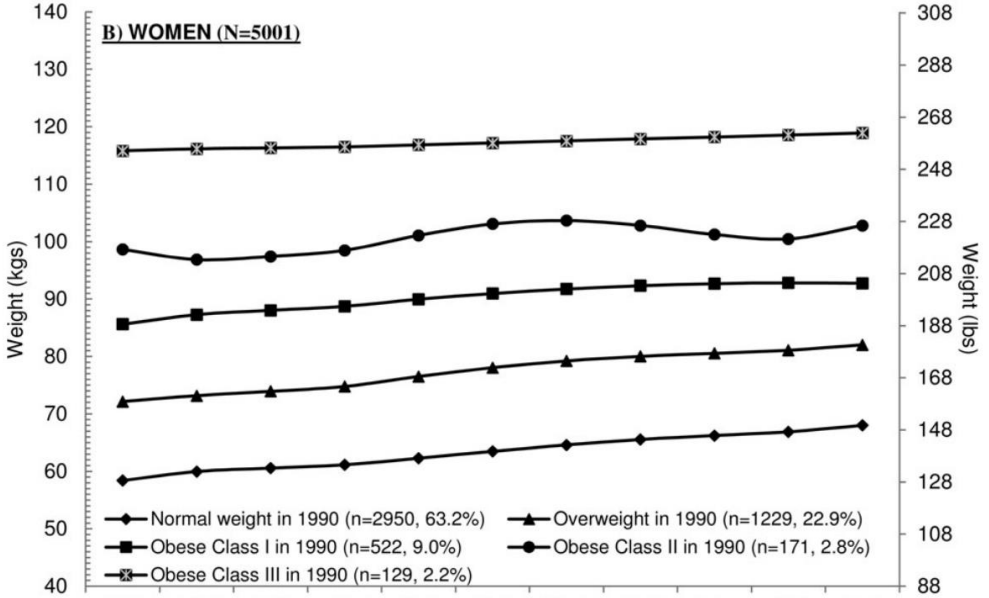
20 y

30 y

47 y

Young adult weight trajectories through midlife





In general population, weight gain is commonly observed during aging:

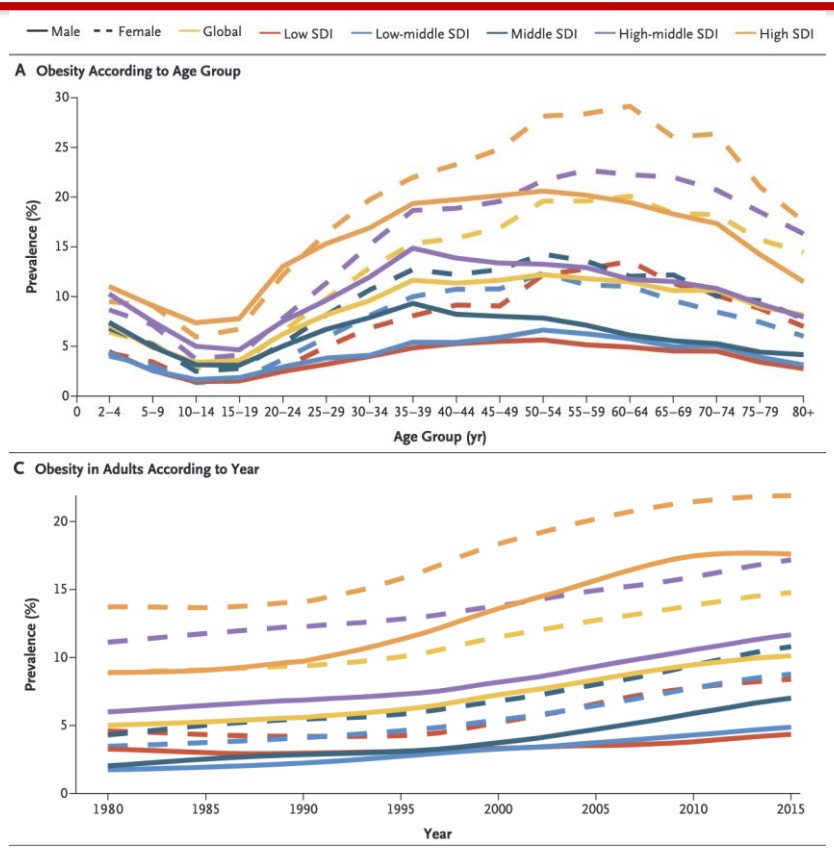
0.2-0.5 Kg/year Europe

0.5-1 Kg/year North America

Malhotra K et al. Obesity 2013; 21: 1823-1934. doi:10.1002/oby.20318. Haftenberger M et al. Eur J Clin Nutr 2016; 70:300-306.

Trends in weight in the general population

- Obesity prevalence has risen steadily across the globe for the last 50 years.
- Age-standardized mean BMI increased from 1974 and 2014 from 21.7 to 24.2 in men 22.1 to 24.4 in women
- In 2016, 39% of adults worldwide were overweight and 13% were obese
- Global prevalence of obesity tripled in men and doubled in women



World Health Organization. Noncommunicable diseases country profiles 2018. Geneva: World Health Organization; 2018. https://apps.who.int/iris/handle/10665/274512. (accessed Oct 5, 2021). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016:Lancet 2017; 390: 2627–42. The GBD 2015 Obesity collaborators. N Engl J Med 2017; 377: 13-27

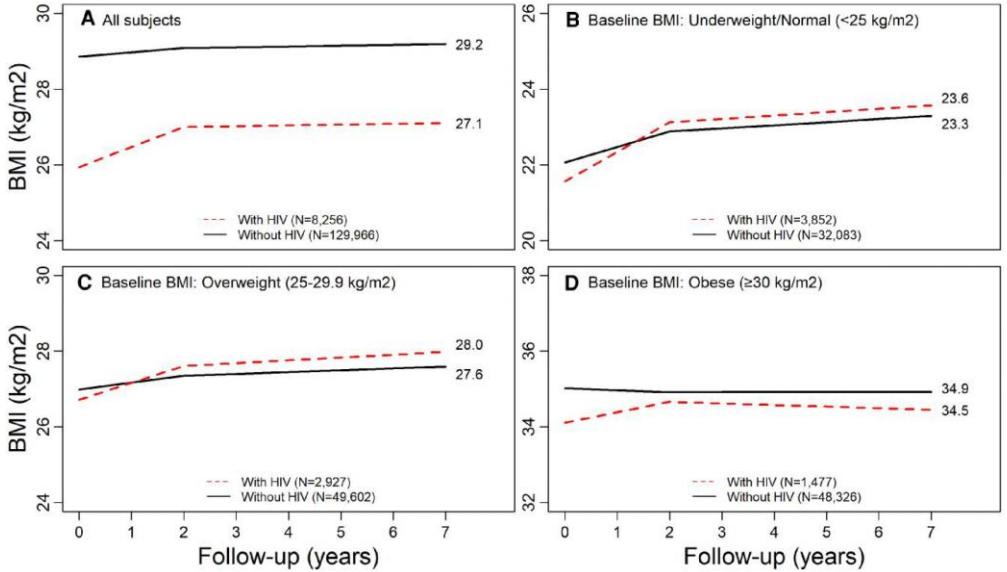
Weight gain and obesity in PWH

- PWH have increases in BMI over 5 year compared to HIV-ve.

  (0.02 average annual increase)

- Similar prevalence in obesity in PWH compared negative controls (BMI) but higher abdominal obesity (waist/hip ratio)

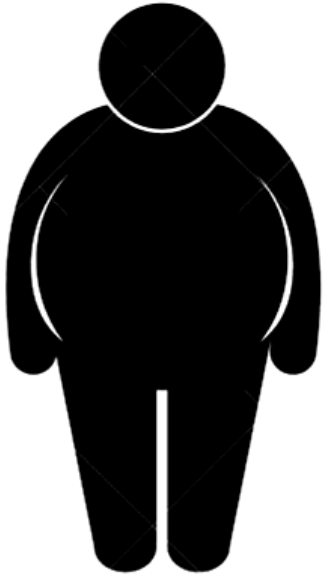
- Higher in females, older, longer ART duration and certain ethnicities



Savinelli S. AIDS 2022; 36:1477-1491. Talathi R. Curr Opin HIV AIDS 2024; 19:1-5. Bailin SS. Curr Opin HIV AIDS 2024; 19:6-13 Gelpi M Clin Infec Dis 2018;67: 579-586. Lam JO et al. Open Forum Infec Dis 2024; Feb 6;11(2):ofad611. doi: 10.1093/ofid/ofad611.

Contributors to metabolic disease in PWH

Antiretrovirals& HIV
- Inflammation
- Microbial translocation
- Energy absorption
- Lipid trafficking
- Adipose tissue distribution



Diet
- Food preferences
- Food insecurity
- Access to healthy foods (food deserts)

Activity
- Regular exercise
- Opportunities for physical activity
- Safety, walkability

Environment
Sociocultural knowledge, economic resources
Attitudes, beliefs, & practices regarding diet, nutrition, exercise
Conceptions of 'health'

Host
- Race/ethnicity
- Sex
- Genetics
- Comorbidities
- Other medications

Habits
- Smoking
- Alcohol
- Drugs

Mental Health
- Depression
- Stress
- Poverty
- Stigma

Slide courtesy of J R Koethe

What weight gain is clinically relevant?

Data driven definition of WG is lacking

Guaraldi et al. BMC Infectious Diseases (2023) 23:230
https://doi.org/10.1186/s12879-023-08174-3

BMC Infectious Diseases

RESEARCH Open Access

Evidence gaps on weight gain in people living with HIV: a scoping review to define a research agenda

Giovanni Guaraldi[1], Paolo Bonfanti[2,3], Antonio Di Biagio[4], Andrea Gori[5,6*], Jovana Milić[1], Paola Saltini[5,6], Francesco V. Segala[7], Nicola Squillace[2], Lucia Taramasso[4] and Antonella Cingolani[7]

Current literature regarding WG in PLWH suggests a definition criterion evaluating either a continuous measure of weight or an arbitrary cut-off such as a 5% weight increase or a body mass index (BMI) increase of 7%. The former cut-off of 5% is derived from recommended lifestyle interventions for weight loss as treatment of cardiometabolic conditions in the general population

A weight increase by 1% reduced the protective effect of INSTI in insulin resistance by 21% over 1 year

Guaraldi G. BMC Infec Dis 2023; 23:230. Milic J. AIDS. 2022. https://doi.org/10.1097/ QAD.0000000000003289.

Limitations of BMI in predictive metabolic disease

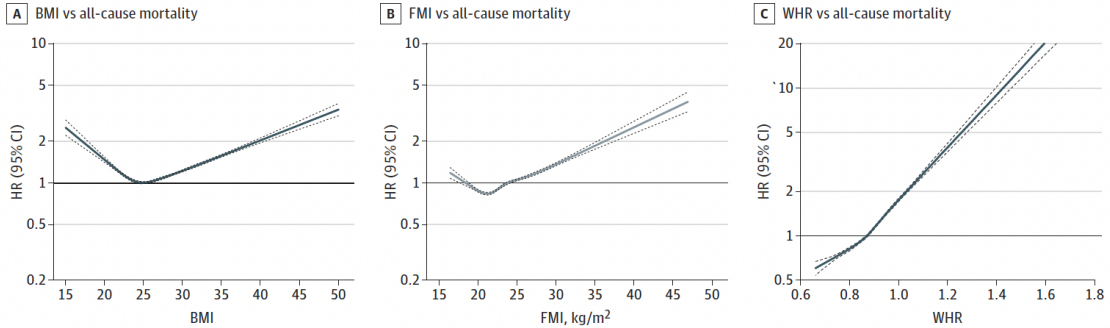
Metabolically Healthy

BMI: 30.0 kg/m²
Waist Circ: 92 cm
VAT Volume: 100 cm³
HOMA-IR: 0.5

Metabolically Unhealthy

BMI: 30.0 kg/m²
Waist Circ: 106 cm
VAT Volume: 366 cm³
HOMA-IR: 5.0

Figure 1. Association of Body Mass Index (BMI), Fat Mass Index (FMI), and Waist-to-Hip Ratio (WHR) With All-Cause Mortality Among 387 672 Participants from the UK Biobank



BMI calculated as weight in kilograms divided by height in meters squared.

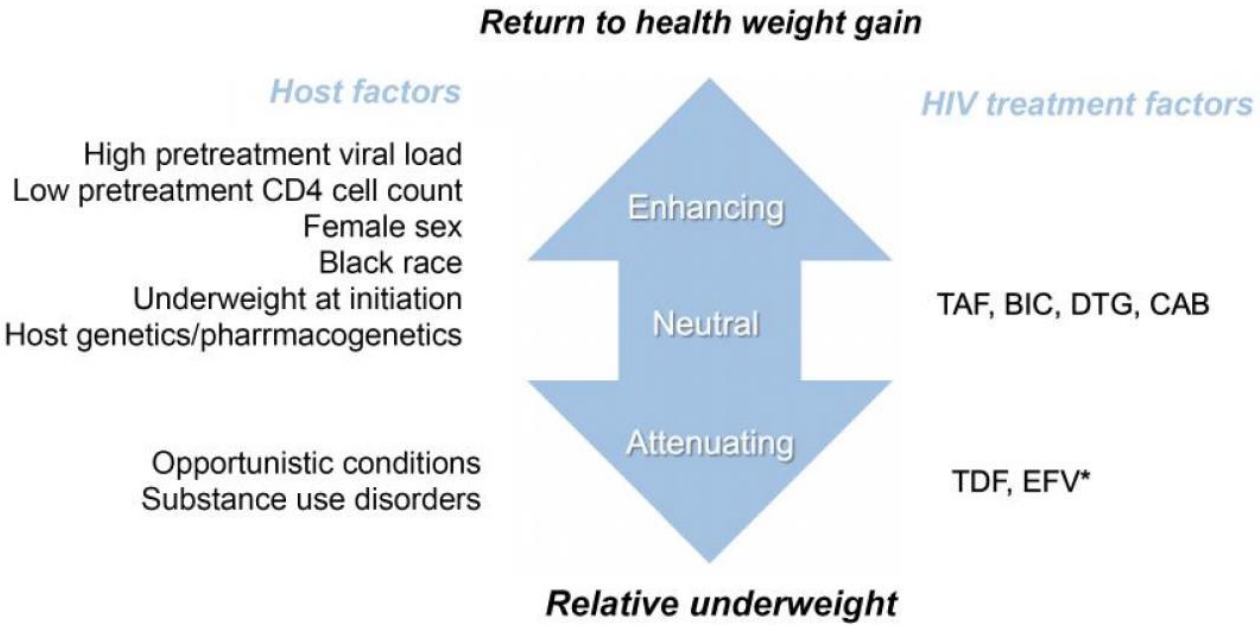
Bailin SS: Infec Dis Clin N Am 2024; 38:499-515. Khan I. JAMA Network Open 2023; 6(9):*e2334836*

Specific issues in PWH

Has ART any role in weight gain?

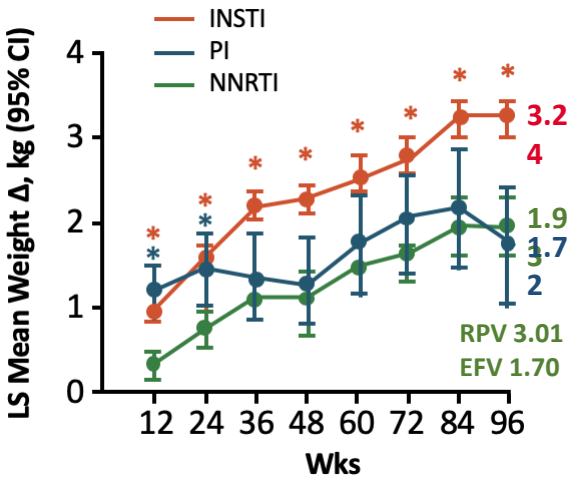
Data on naïve and suppressed PWH

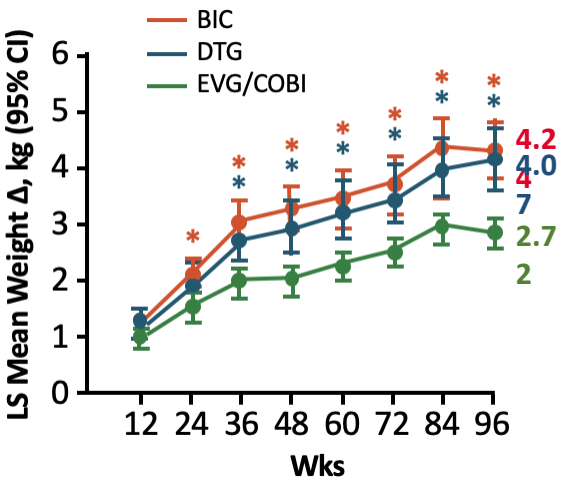
Propose model ART & weight gain

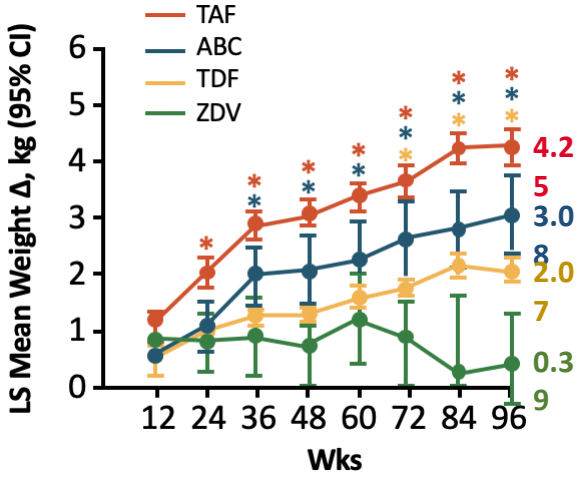


Wohl D. Clin Infec Dis 2024; ahead pub of print https://doi.org/10.1093/cid/ciae191

Modern ART and weight gain. Naïve clinical trials



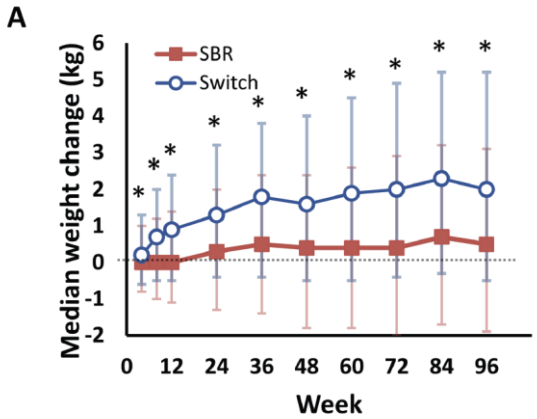




	Host	HIV (return to health)	ART
Risk factors for Weight gain	▪ Women ▪ Black ▪ No IDU	▪ ↓ CD4 (<200 ↑~3 kg vs >200) ▪ ↑ VL (>100K ↑~1 kg vs <100K) ▪ Low or normo weight ▪ Symptomatic HIV infection	▪ INSTI: DTG/BIC vs EVG ▪ NNRTI: RPV vs EFV ▪ NRTI: TAF

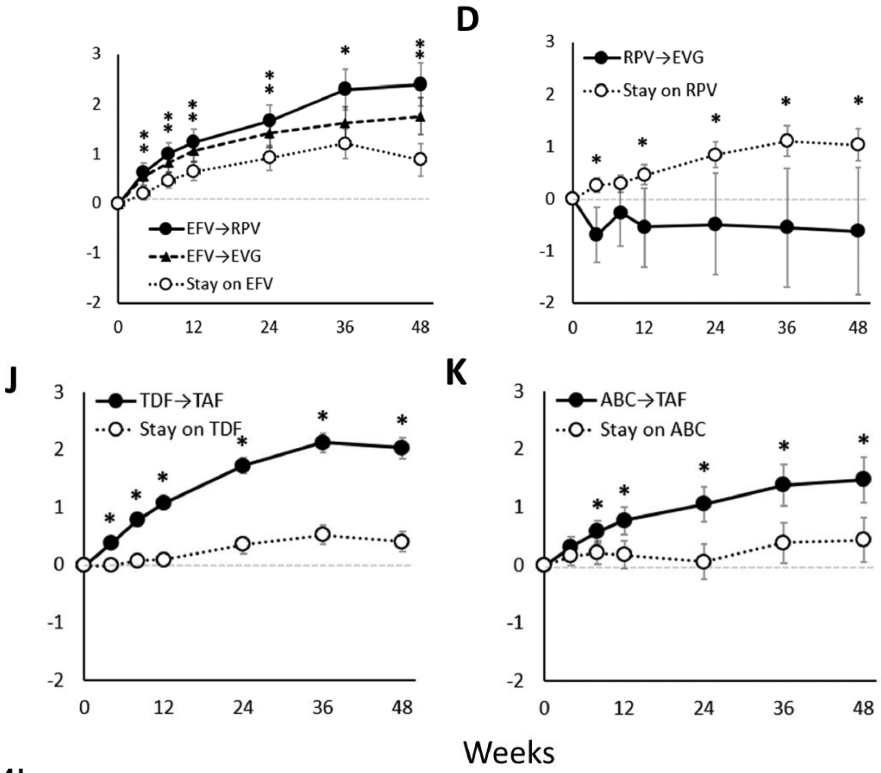
Sax PE, et al. Clin Infec Dis 2020;71:1379-1389

Modern ART and weight gain. Switch clinical trials



Median 1.6Kg (IQR -0.5 to 4.0) 48w
Median 2.0Kg (IQR -0.5 to 5.2) 96w

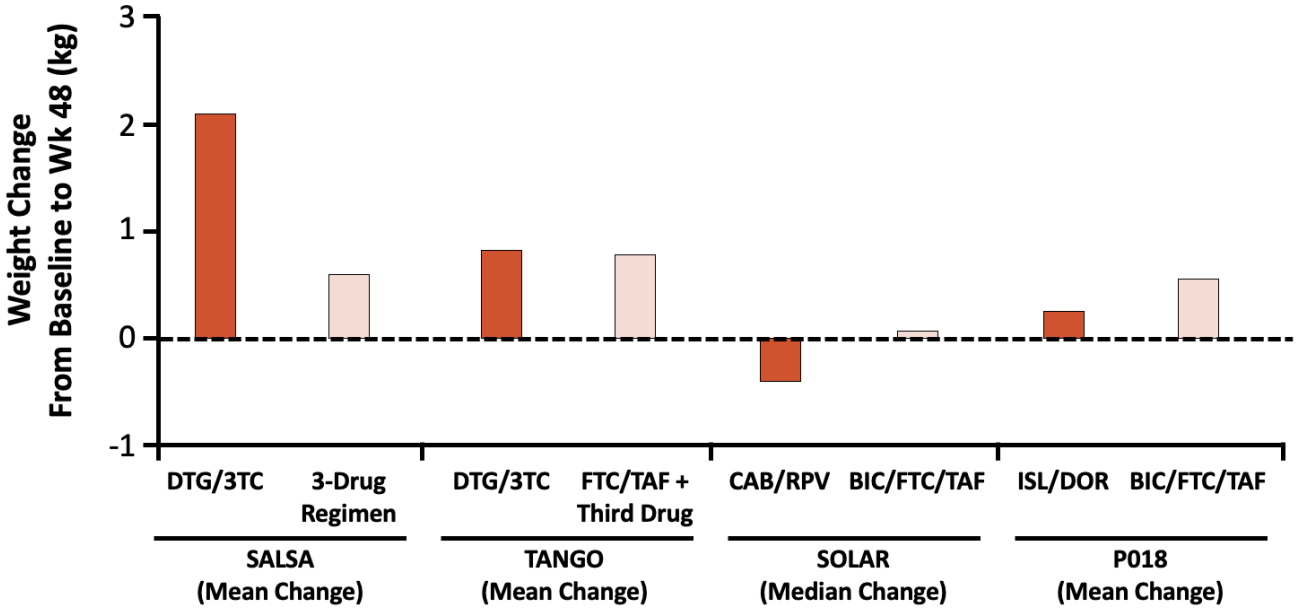
Plateau reached between 24w and 36w



Risk factors for weight gain: Younger age & lower BMI

Erlandson KM, et al. Clin Infect Dis 2021; 73(8):1440-51

Separate Studies of Switches to 2-Drug Regimens: Weight Changes

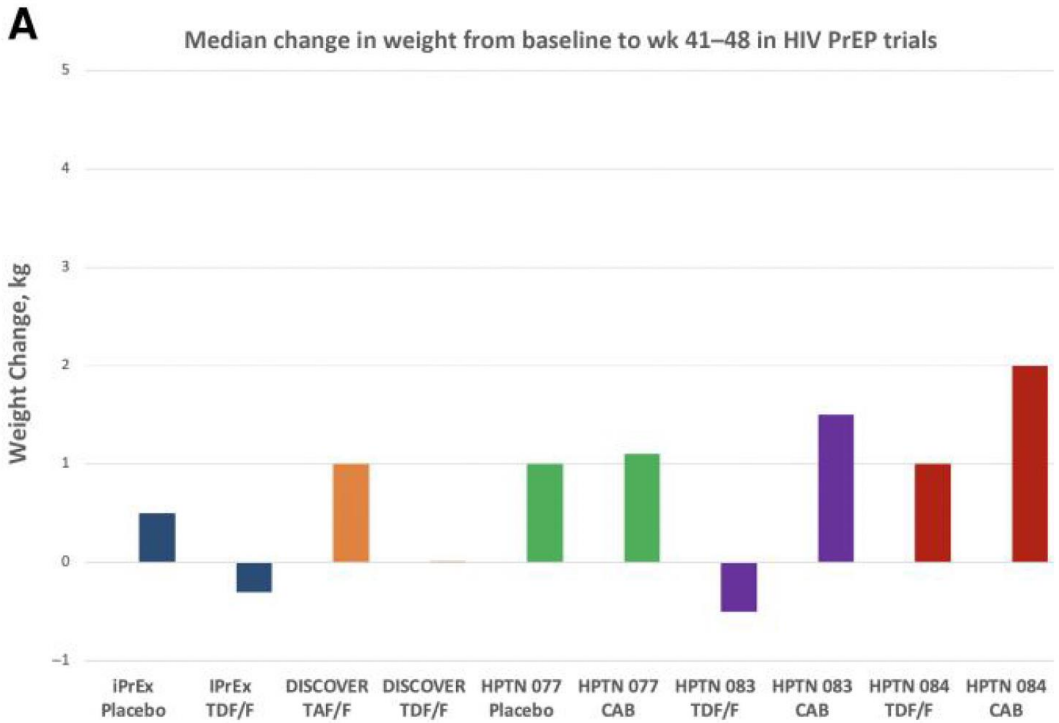


- In separate studies, switches to **2-drug regimens** that exclude TAF **did not** consistently lead to clinically important reversal of weight gain

Wohl. Clin Infect Dis. 2024:ciae191.

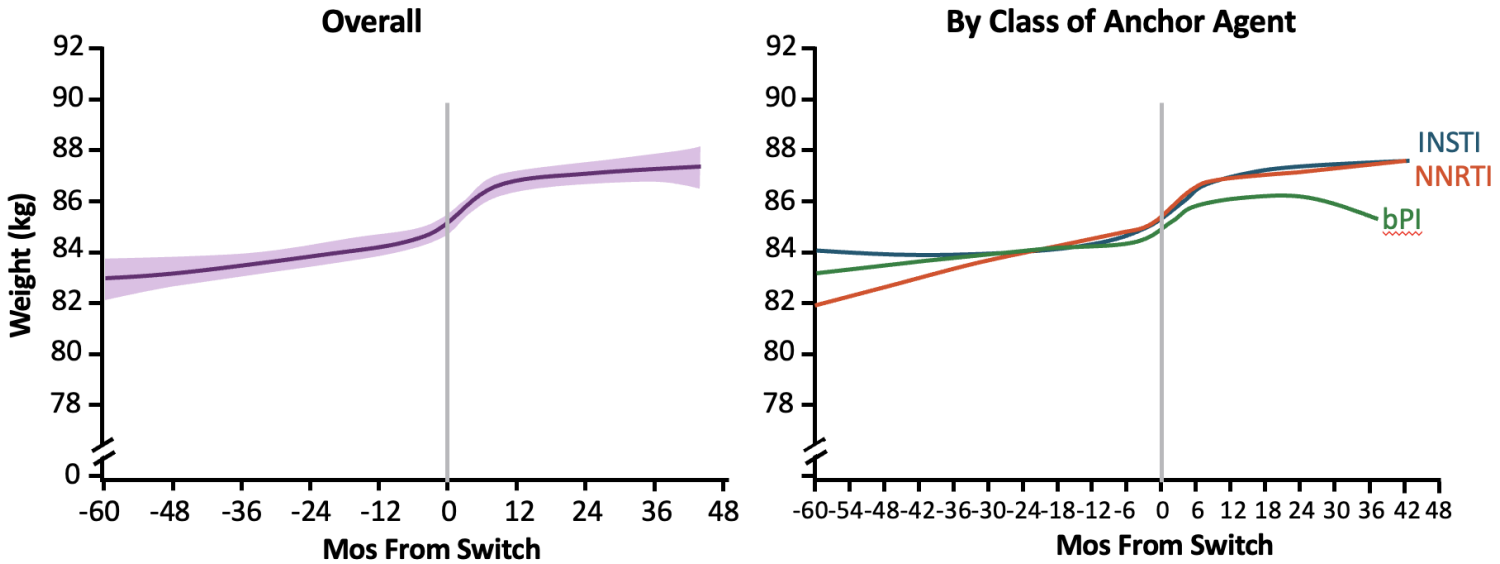
Slide credit: clinicaloptions.com

PreP studies suggest TDF has a weight suppresive effect



Wohl D. Clin Infec Dis 2024; ahead pub of print https://doi.org/10.1093/cid/ciae191

OPERA: Weight Change With Switch From TDF to TAF While Maintaining Other ARVs

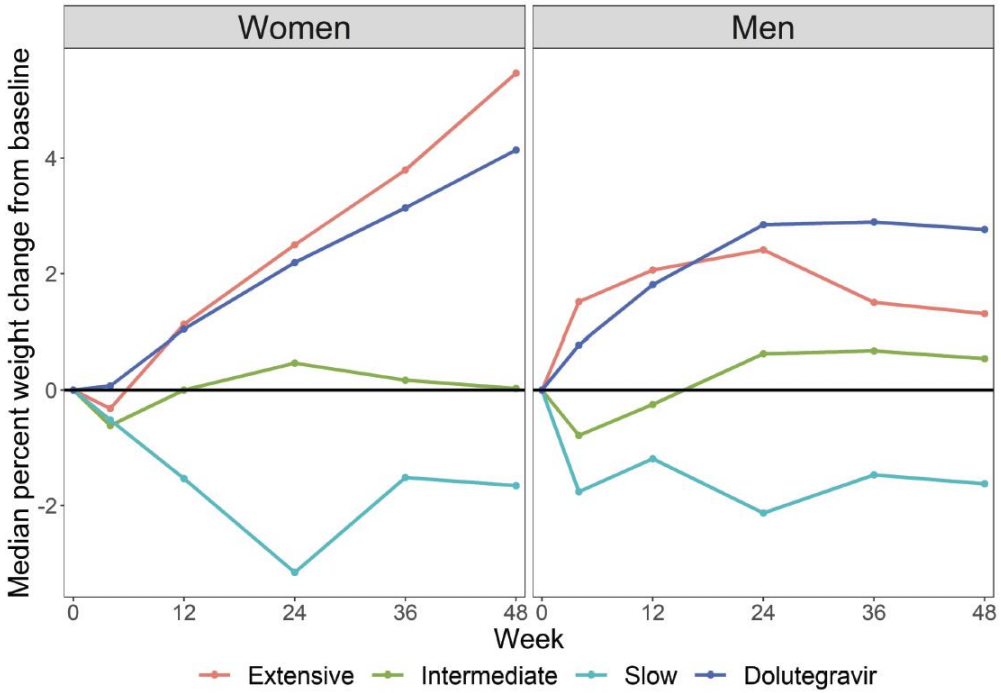


Referent patient (mean or lower-risk category): 45-yr-old nonblack male, BMI 27, CD4+ cell count 700 cells/mm^3, no endocrine disorders or prescriptions associated with weight modification

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

Slide credit: clinicaloptions.com

CYP2B6 genotype associated with EFV-weigh gain



Griesel R et al. Clin Infec Dis 2021; 73: e3902-e3909

Weight gain after seroconversion. CASCADE cohort

10% weight gain in BMI 19-25 Kg/m^2

- 31 % on INSTI
- 25 % on bPI
- 20 % on NNRTI
- 37 % on TAF
- 38% on TAF + INSTI

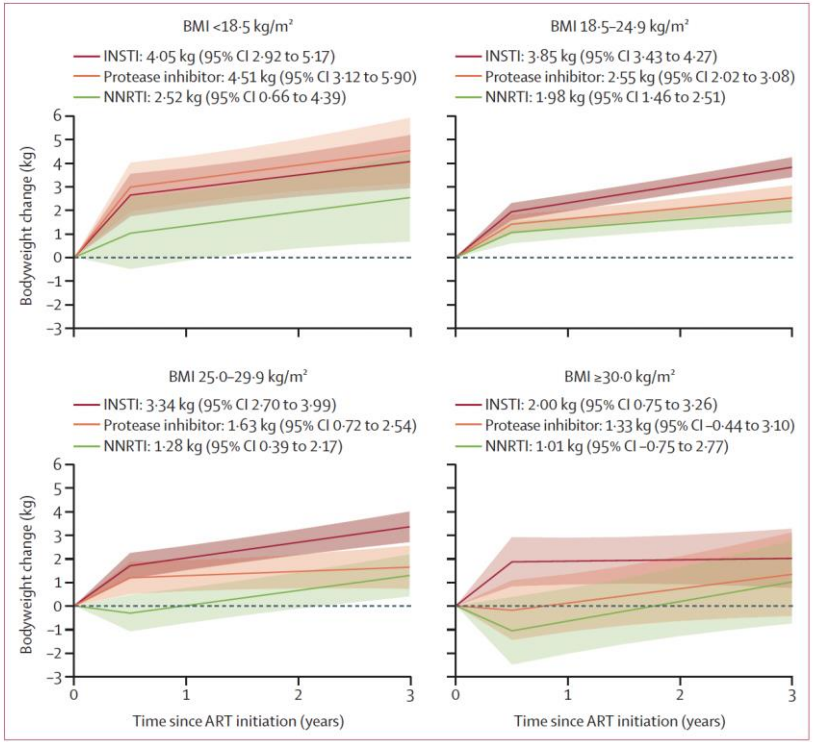


Figure 2: **Estimated bodyweight changes after ART initiation by ART class and baseline BMI**
Estimates shown for men who have sex with men, aged 30–39 years at seroconversion, originating from Europe or North America, with average height, baseline CD4 cell count, and HIV RNA. Shaded areas represent 95% CIs. Data shown in each key are the estimated weight changes at 3 years. ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Pantazis N et al. Lancet HIV 2024; Published Online August 23, 2024 https://doi.org/10.1016/S2352-3018(24)00183-8

AIDS 2024

PASO-DOBLE study: Design

Phase IV, open-label, multicentre, randomised clinical trial[1]

30 sites across Spain

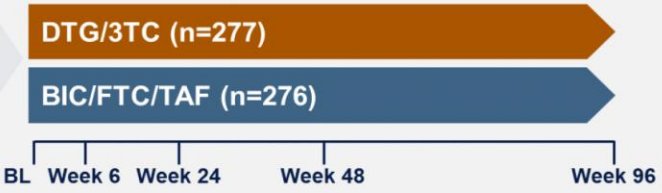
Collaborative study between **Fundación SEIMC-GeSIDA** and ViiV Healthcare

Screening

- HIV-1 RNA <50 c/mL for ≥24 weeks
- Current ART containing >1 pill/day, cobi booster, EFV or TDF
- No prior VF or known/suspected resistance
- No prior DTG or BIC
- No chronic hepatitis B

Randomised 1:1

Stratified by BL TAF use and sex at birth



Primary endpoint: Participants with plasma HIV-1 RNA ≥50 c/mL (FDA Snapshot; non-inferiority margin 4%)
Key secondary endpoint: Weight change (study was powered to assess differences)

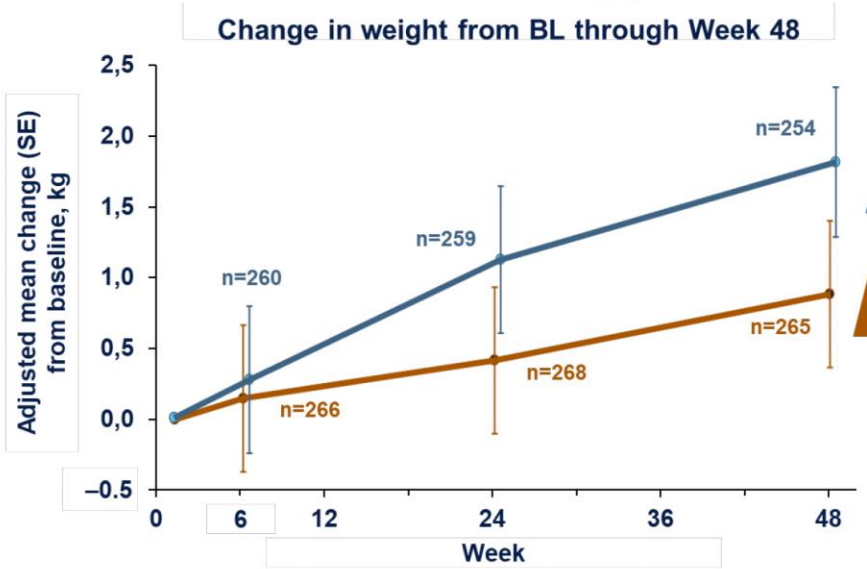
Other secondary endpoints include efficacy, safety, tolerability, immune recovery, metabolic parameters, kidney function, blood pressure, body composition and bone mineral density, PROs, and genotypic resistance analysis in case of virological failure

Four sub-studies: Omics | Senescence | Fat biopsies | Liver steatosis

1. PASO DOBLE. Available at: https://clinicaltrials.gov/ct2/show/NCT04884139.

AIDS 2024

PASO-DOBLE study: Weight change



+1.81 kg on BIC/FTC/TAF

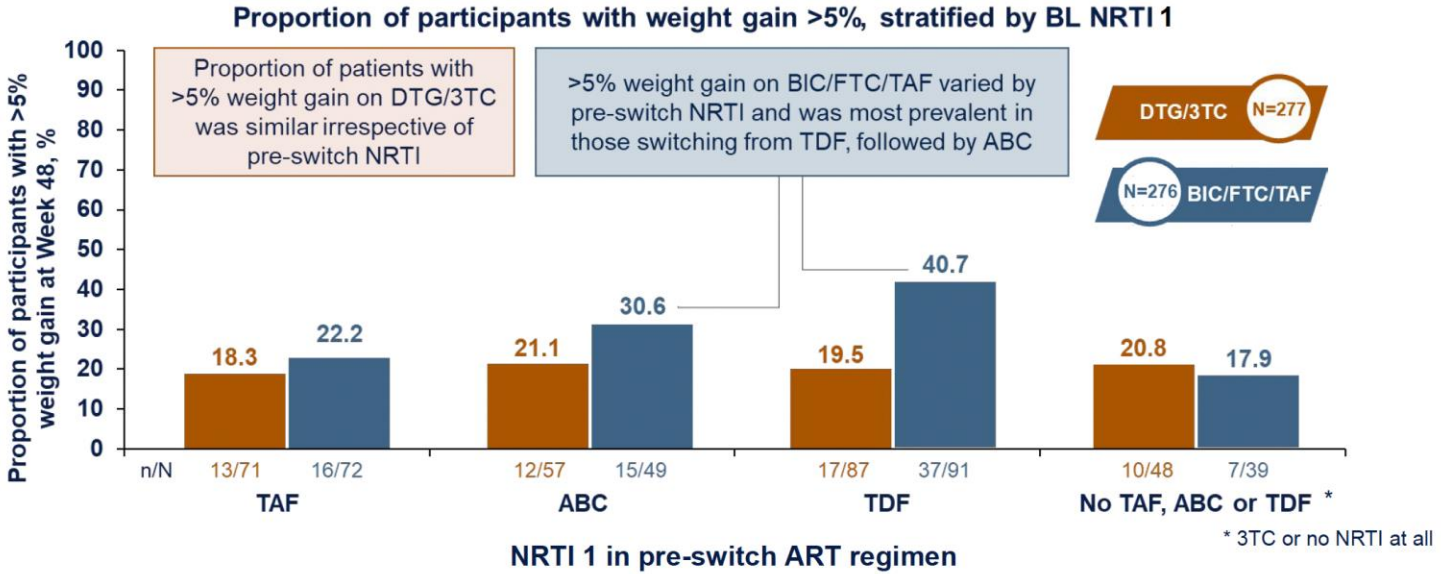
+0.89 kg on DTG/3TC

Mean adjusted difference:
+0.92 kg
(95% CI: 0.17, 1.66)
P=0.016

Adjusted by baseline value, sex, presence of TAF in previous ART, age and ethnicity. The only association that was statistically significant in the model was treatment group

AIDS 2024

PASO-DOBLE study: Weight gain >5% by pre-switch NRTI 1



Is there any biological plausibility?

Adipose tissue & INSTI

Adipose tissue & TAF

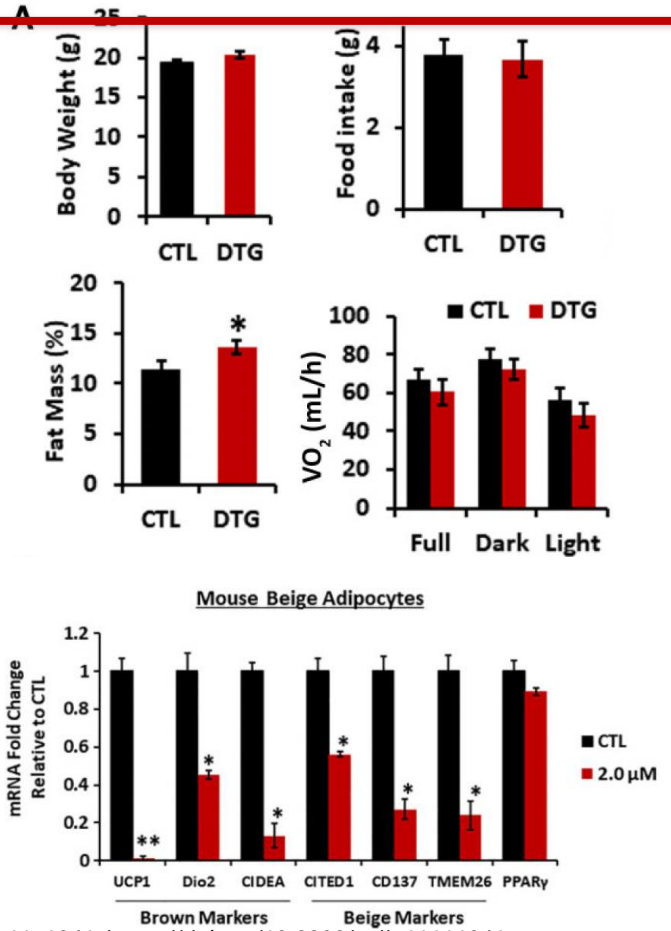
INSTI and weight gain. Mechanisms

In vitro studies demonstrate INSTI promote gene expression lipid synthesis and adipocyte differentiation

Increased periadipocyte fibrosis in adipose tissue from INSTI treated PWH (Bariatric surgery studies)

Adipose hypertrophy, fibrosis, and insuline resistance effect of INSTI

DTG suppress UCP1expression and mitochondrial functions (respiratory chain and glucose uptake) in brown and beige adipocytes impairing energy expenditure



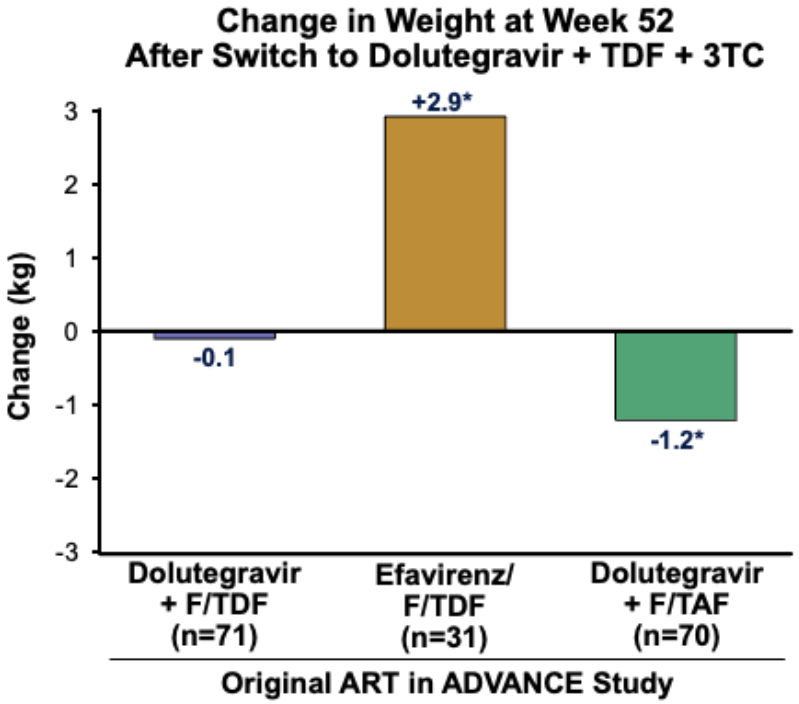
Gorwood J Clin Infec Dis 2020; 71:e549-560. Jung I, et al. J Infec Dis 2022;226:1626-1636 Ayissi KN, et al. Cells 2022 11, 1841. https://doi.org/10.3390/cells11111841

ART strategies to reduce weight gain

Will switching ART help to weight loss in PWH?

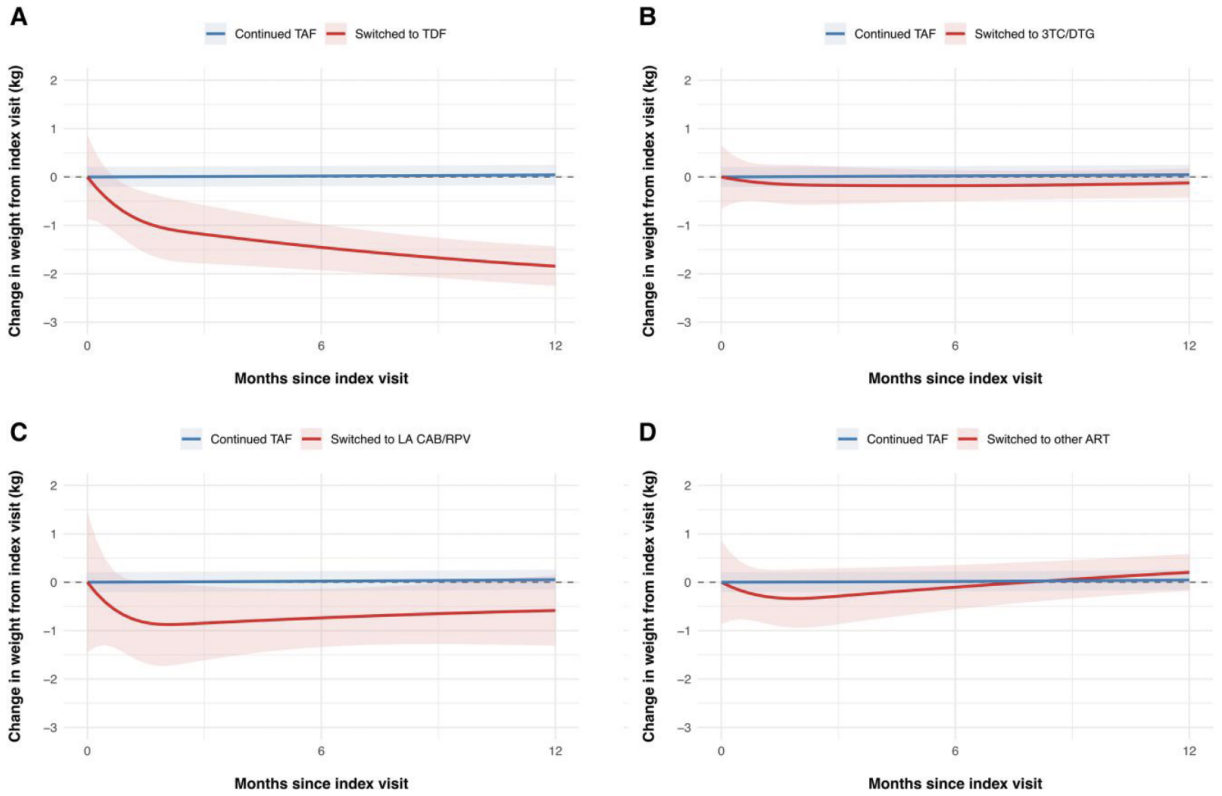
CHARACTERISE Study: Weight and Metabolic Changes at Week 52 After Switching to Dolutegravir + TDF + 3TC

- Residents of inner-city Johannesburg who had previously been part of ADVANCE study (n=172)
  - Before switch, received either dolutegravir + F/TAF, dolutegravir + TDF + 3TC, or efavirenz/F/TDF
    - HIV RNA <50 copies/mL before switch (98%)
- Results at week 52 after switch to/continuing on dolutegravir + TDF + 3TC
  - Rate of HIV RNA <50 copies/mL: unchanged
  - Weight loss in those switching from dolutegravir + F/TAF (women/men: -1.6/-0.2 kg)
  - Weight gain in those switching from efavirenz/F/TDF



Bosch B Clin Infec Dis 2023;76; 1492-5

Few data about TAF discontinuation on weight gain



Damas J et al. Clin Infec Dis 2024; Apr12:ciae189. https://doi.org/10.1093/cid/ciae189

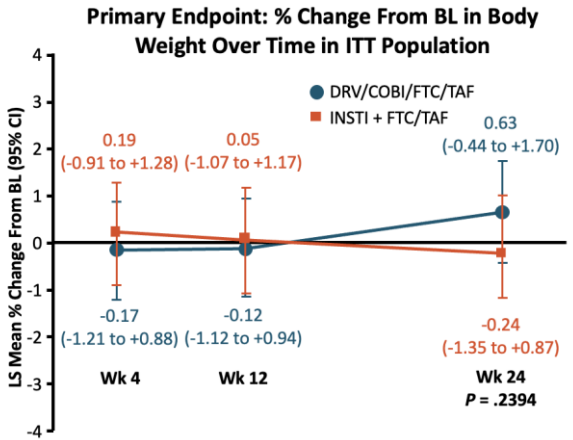
DEFINE Study: Switch to DRV/c/F/TAF Due to Weight Gain From INSTI-Based ART

- Prospective phase 4 study
  - Virologically suppressed with ≥10% weight gain with INSTI + F/TAF
- Switch to darunavir/c/F/TAF or continue INSTI + F/TAF
- At 24 weeks, there was no significant difference in percent body weight gain among the 2 arms
  - Results consistent among key subgroups
- Most patients remained within baseline BMI and waist circumference categories
- Body composition and DEXA was stable over time in both study arms
- Both arms were well tolerated

Results at Week 24

	Switch to Darunavir/c/F/TAF (n=53)	Continue INST + F/TAF (n=50)
Change in body weight (%)	**+0.63***	-0.24
HIV RNA (%)		
<50 copies/mL	91	80
≥50 copies/mL	0	10

**P*<0.05 versus continue INS + F/TAF.



Short WR, et al. IAS 2023. Abstract OALBB0502.

Will new clinical trials give us the answer?

- **DeLITE: (NCT04665375)** Switch from **INSTI** to **DOR/3TC/TDF**
  - More than 10% weight gain since INSTI initiation

- **ACTG (NCT04636437**) Switch from **INSTI and TAF** to **TDF/XTC/DOR or TAF/XTC + DOR**
  - More than 10% weight gain in the 1-3 years after INSTI initiation with at least 1 year of TAF

Points for discussion

- Tiny amounts of weight gain in a worldwide obesogenic enviroment. Is it relevant enough?
- ART-linked excessive weight gain is uncommon (affects a minority of PWH)
- Casualty assessment is very tricky
- Most of the weight gain is observed in the initial 12-m period.
- TDF and efavirenz have a weight-suppressant effect
- The reversibility of weight gain when stopping INSTI and/or TAF appears limited. So, what's the role of ART?
- Need a standardised clinically validated definition of weight gain