Total & Visceral Adiposity in HIV: Effect of ART

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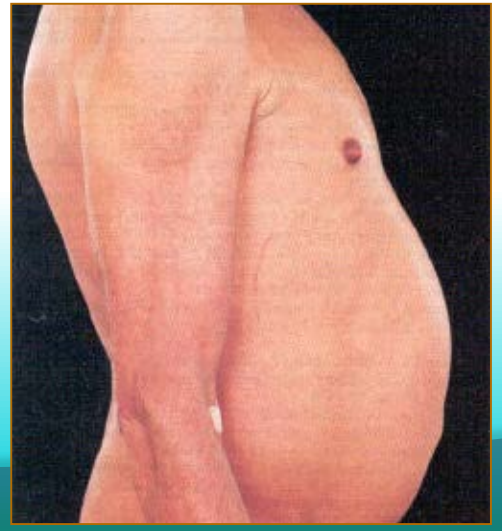
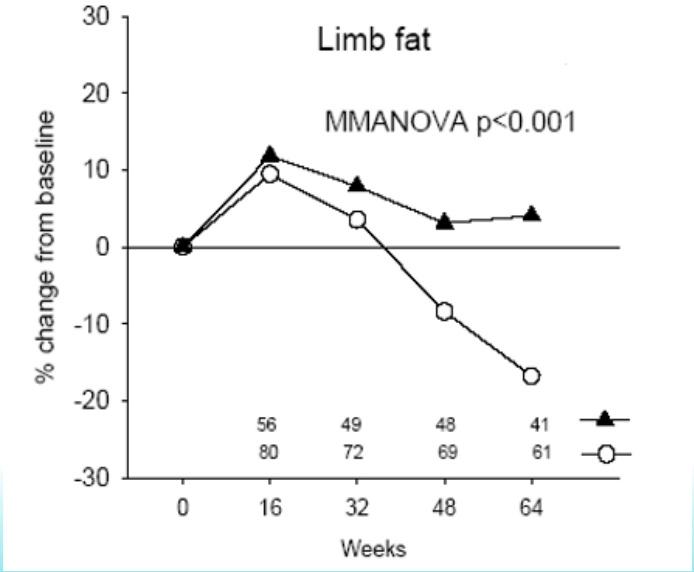
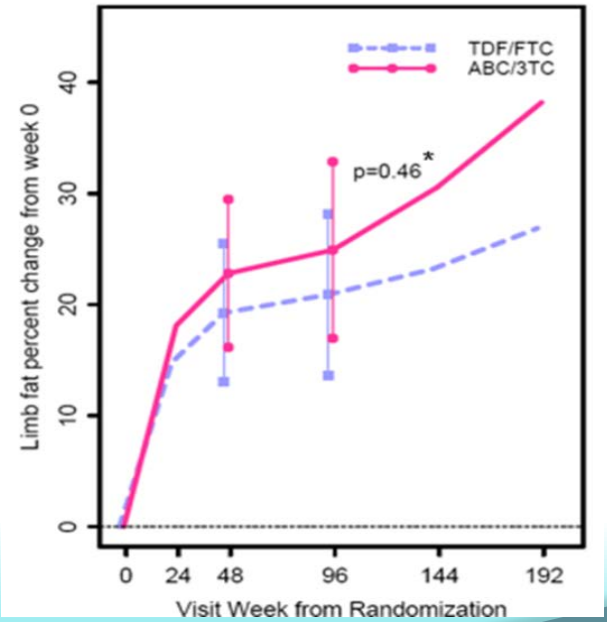
The banned lipodystrophy“ term!



History and Current Knowledge

- Both components of these fat alterations constitute different entities; although may coexist
- Lipoatrophy has been closely linked to mitochondrial toxicity from tNRTI
- Lipoatrophy incidence is now rare, however cases remain from past tNRTIs
- Switching off of tNRTI ↑ limb fat, ↑mtDNA content, ↓ fat apoptosis, but did NOT affect central obesity





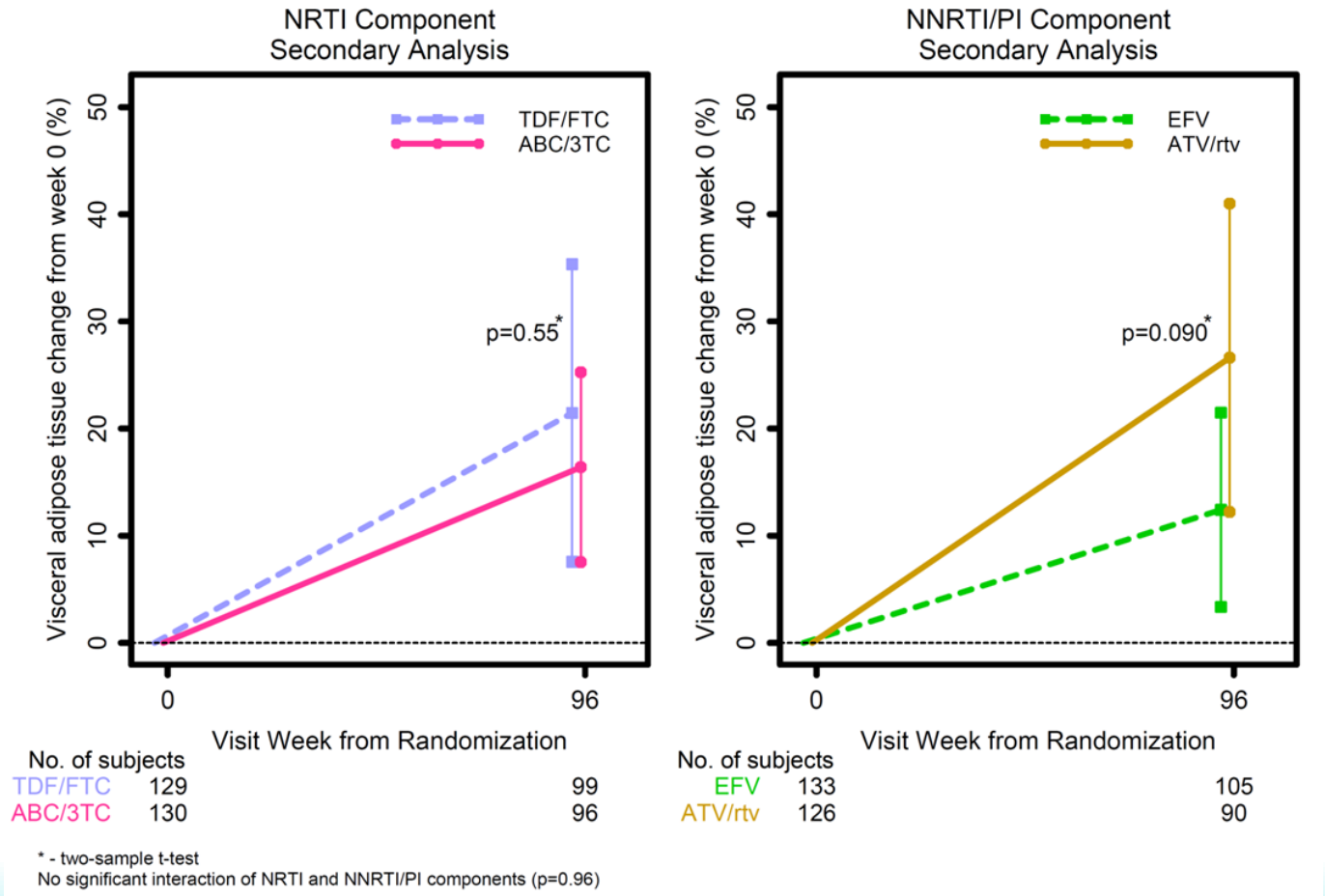
McComsey, Antivir Ther 2008; McComsey AIDS 2005; Joy T, JAIDS 2008; McComsey CID 2011; Dube M, JAIDS 2007, McComsey CID 2016

Changes in Central Adiposity with First-Line ART

- No NRTI effect
  - Similar trunk fat increase with LPV/r monotherapy vs LPV/r + NRTIs
  - Other NRTI sparing strategies also experienced similar increases
- PI type?
  - Similar VAT and weight increases with ATV/r vs. ATV
  - Larger gains fat (SAT, VAT) with ATV/r vs. SQV/r or LPV/r; differences more pronounced in those with low baseline BMI and CD4
  - Similar gains with ATV/r vs. DRV/r in 2 studies

Kolta S,Curr HIV Res. 2011; Haubrich R, AIDS 2009; Shlay J, JAIDS 2007; McComsey G, CID 2009; Vrouenraets S, HIV Med 2011; Moyle G, Clin Drug Investig 2014; Martinez E, CID 2015; McComsey G, CID 2016

VAT Gains on PI/r vs. NNRTI: ACTG 5224s

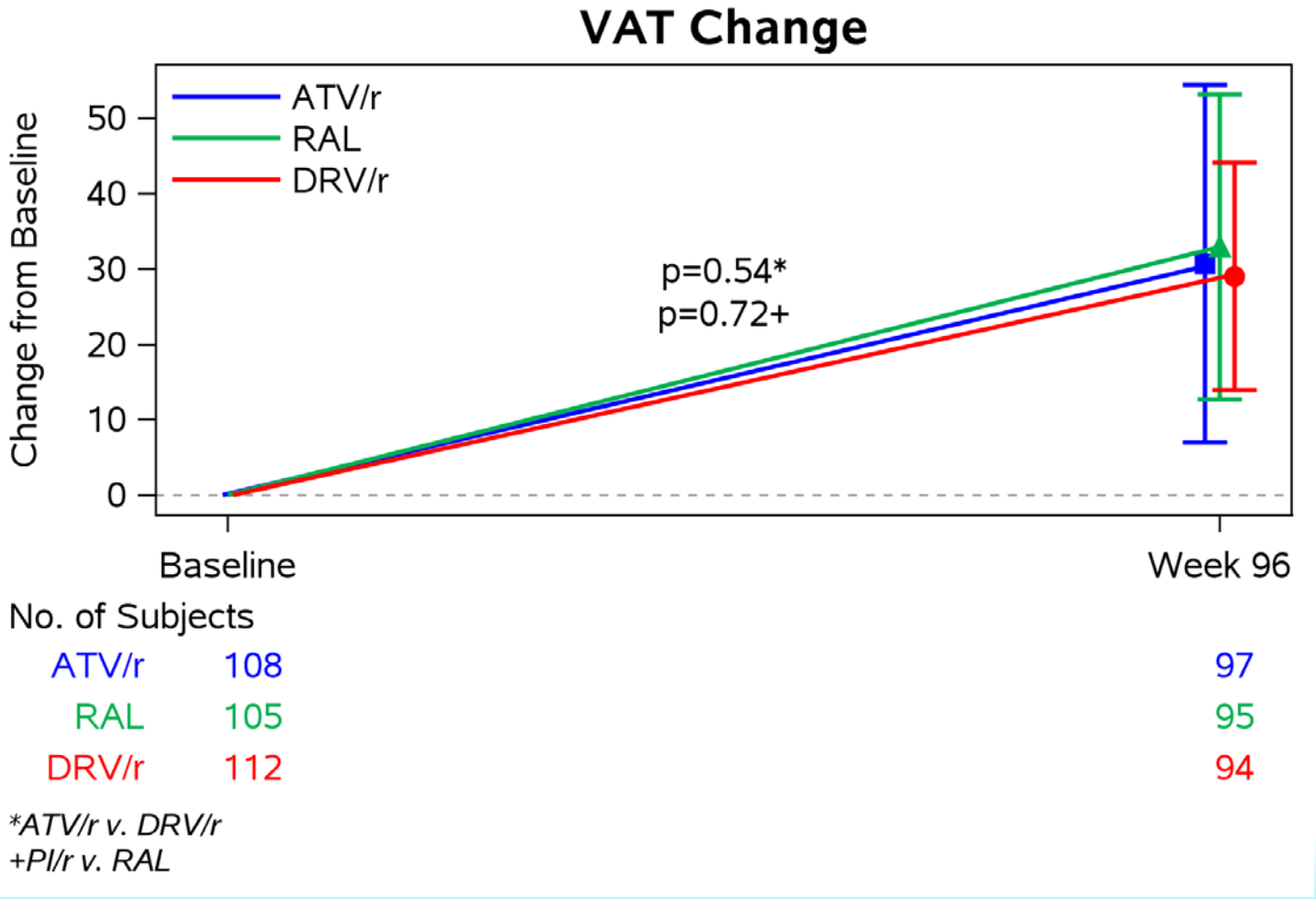


A5142: Similar trunk fat increase (27% at W96) with LPV/r vs. EFV

Jemsek: AZT/3TC with ATV vs. EFV: 33% vs. 25% VAT increase at W48

McComsey G, CID 2011; Haubrich R, AIDS 2009; Jemsek J, CID 2006

VAT Gains on PI/r vs. INSTI: ACTG 5260s

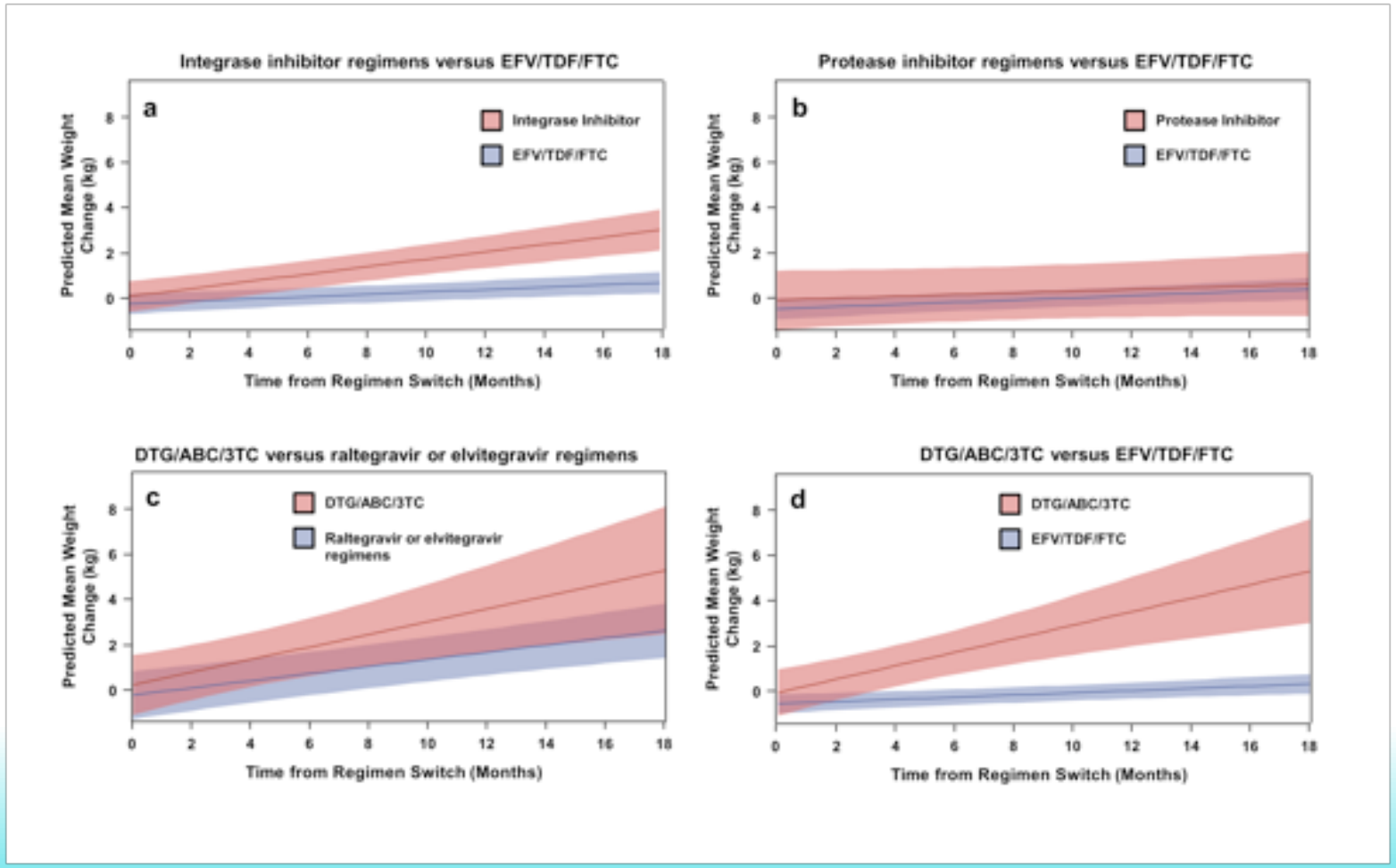


BMI ↑3.8-4.7%

A5257: 23% had >10% wt gain; on RAL vs PI independent predictor

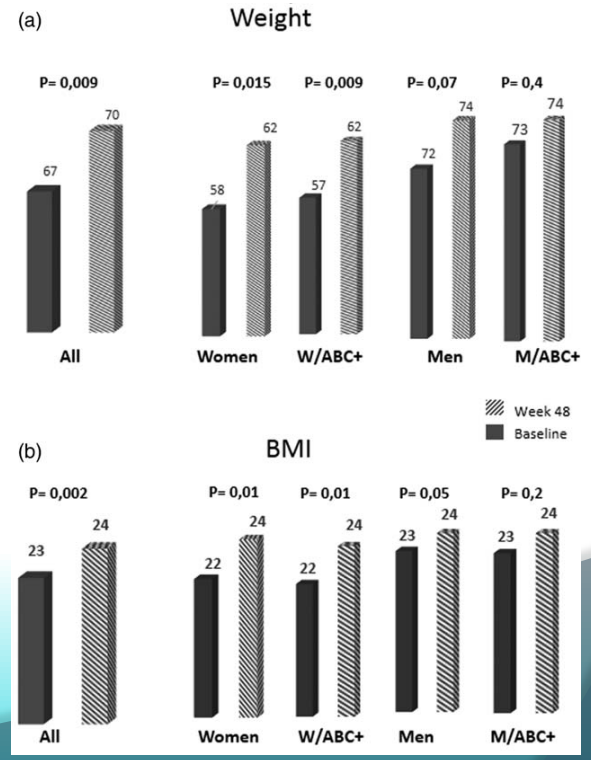
McComsey G, CID 2016; Bhagwat P, CROI 2017

Could INSTI be even Worse than "Older" Classes on Body Composition?



Brazil (n=1794): greatest risk factor for developing obesity was INSTI use

France (Single site): 1 y after Dolutegravir



Norwood J, JAIDS 2017; Bakal DR, J Antimicrob Chemother. 2018; Menard A, AIDS 2017

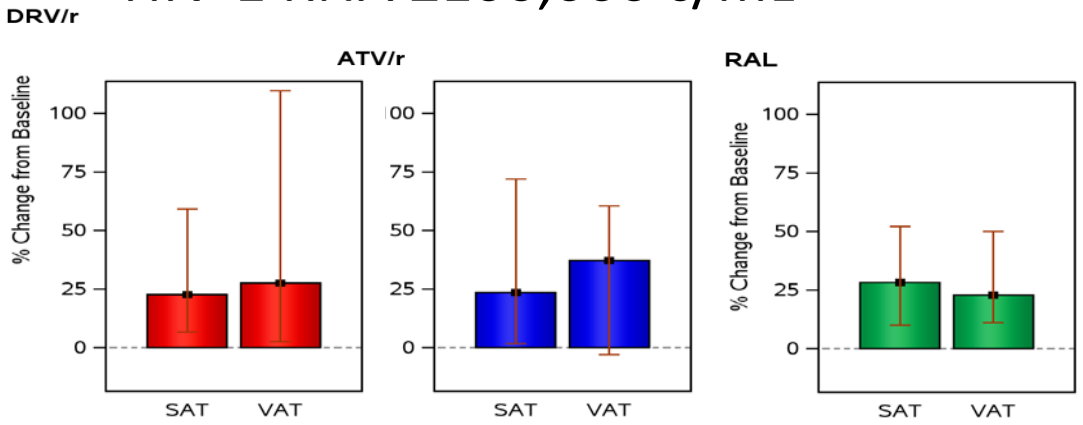
INSTI and Adipose Tissue

- No available data relating to the potential differential accumulation of INSTI in adipose tissue and blood
- Recent study: INSTI do enter adipose tissue while entry of NRTIs is restricted
- In cell culture, elvitegravir (not RAL)
  - Inhibits adipocyte differentiation
  - Inhibits the expression of genes controlling adipogenesis (PPARg, C/EBPa) and lipid accretion (lipoprotein lipase, GLUT4)

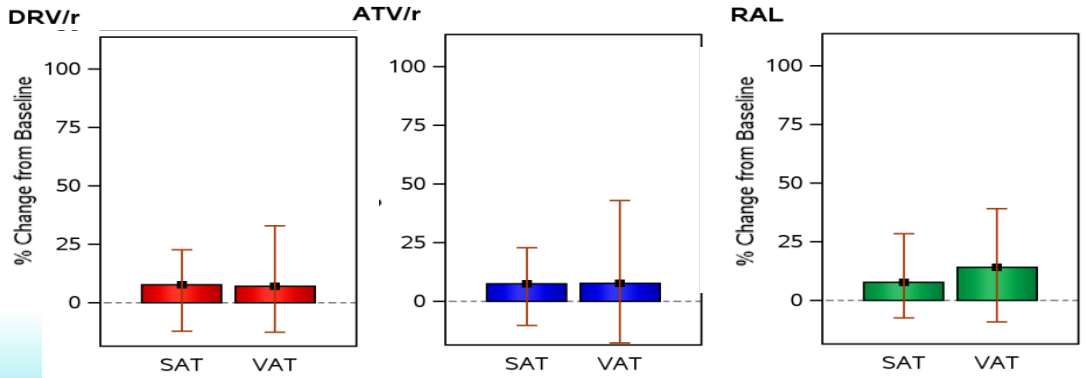
Couturier J, Antiviral Res 2018; Moure R, Antiviral Research 2016

Determinants of VAT Gains on ART

HIV-1 RNA ≥100,000 c/mL



HIV-1 RNA <100,000 c/mL

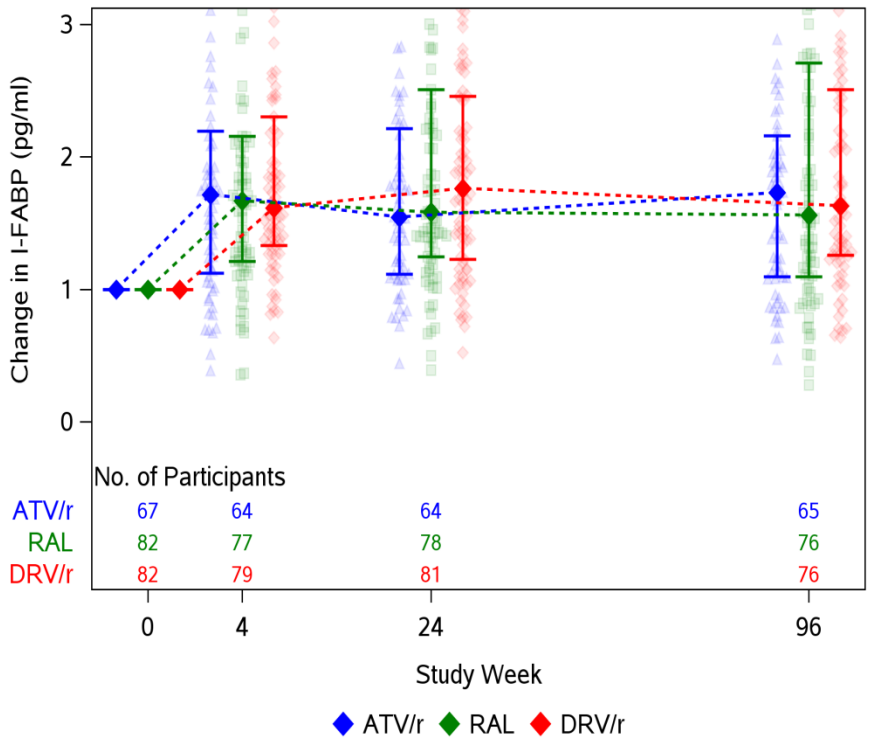


In randomized ART initiation studies:
No consistent patterns for BMI, gender, race, or CD4 in predicting VAT gains

A5260s: subgroup that gained >Q3=43% VAT at 96 weeks had higher baseline HIV-1 RNA, and lower CD4, BMI, and lower marijuana use.

McComsey G, CID 2016; McComsey G, CID 2011; Martinez E, CID 2015

Regardless of ART type, pre-tx IFABP correlate with Fat Gains

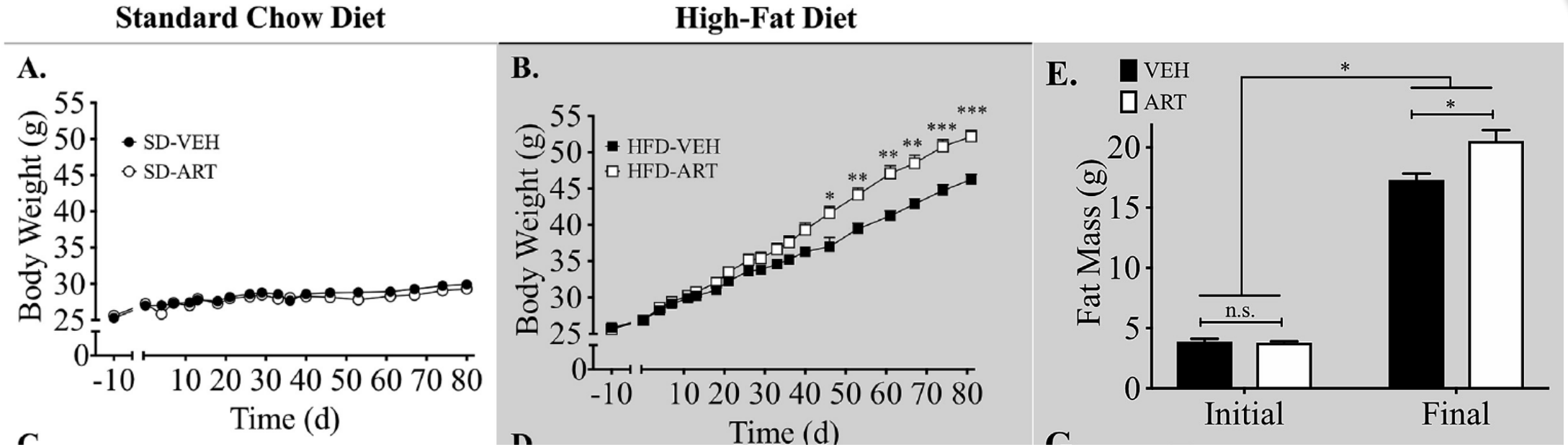


	BMI	VISCERAL ADIPOSE TISSUE	TOTAL ADIPOSE TISSUE
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Unadjusted I-FABP	2.5* (0.8, 4.2)	15.9* (4.5,27.2)	8.6* (0.3, 17.0)
Adjustment			
Age	2.7*(1.0, 4.5)	17.0* (5.4, 28.6)	9.9* (1.4, 18.4)
Sex	2.6* (0.9, 4.3)	16.0* (4.7, 27.3)	8.8* (0.6, 17.0)
Race/Ethnicity	2.1*(0.4, 3.9)	15.5* (3.8, 27.3)	7.5 (-1.0, 16.1)
Smoking history	2.5*(0.8, 4.2)	16.4* (5.0, 27.8)	8.6* (0.3, 17.0)
Alcohol history	2.6*(0.9, 4.2)	18.2** (7.3, 29.1)	9.9* (1.8, 18.1)
Drug history	2.6*(1.0, 4.3)	17.7** (7.0, 28.4)	9.6* (1.6, 17.6)
Physical Activity	2.4*(0.7, 4.1)	14.6* (3.9, 25.3)	7.6 (-0.8, 16.0)
CD4+ cell count	1.5*(-0.1, 3.2)	12.9* (1.4, 24.5)	6.5 (-1.9, 15.0)
HIV-1 RNA	1.9*(0.3, 3.5)	12.5* (1.3, 23.6)	6.0 (-2.2, 14.2)
All covariates	1.6*(0.0, 3.2)	14.7* (4.5, 24.8)	6.7 (-1.4, 14.7)

On ART, IFABP was negatively correlated with BMI

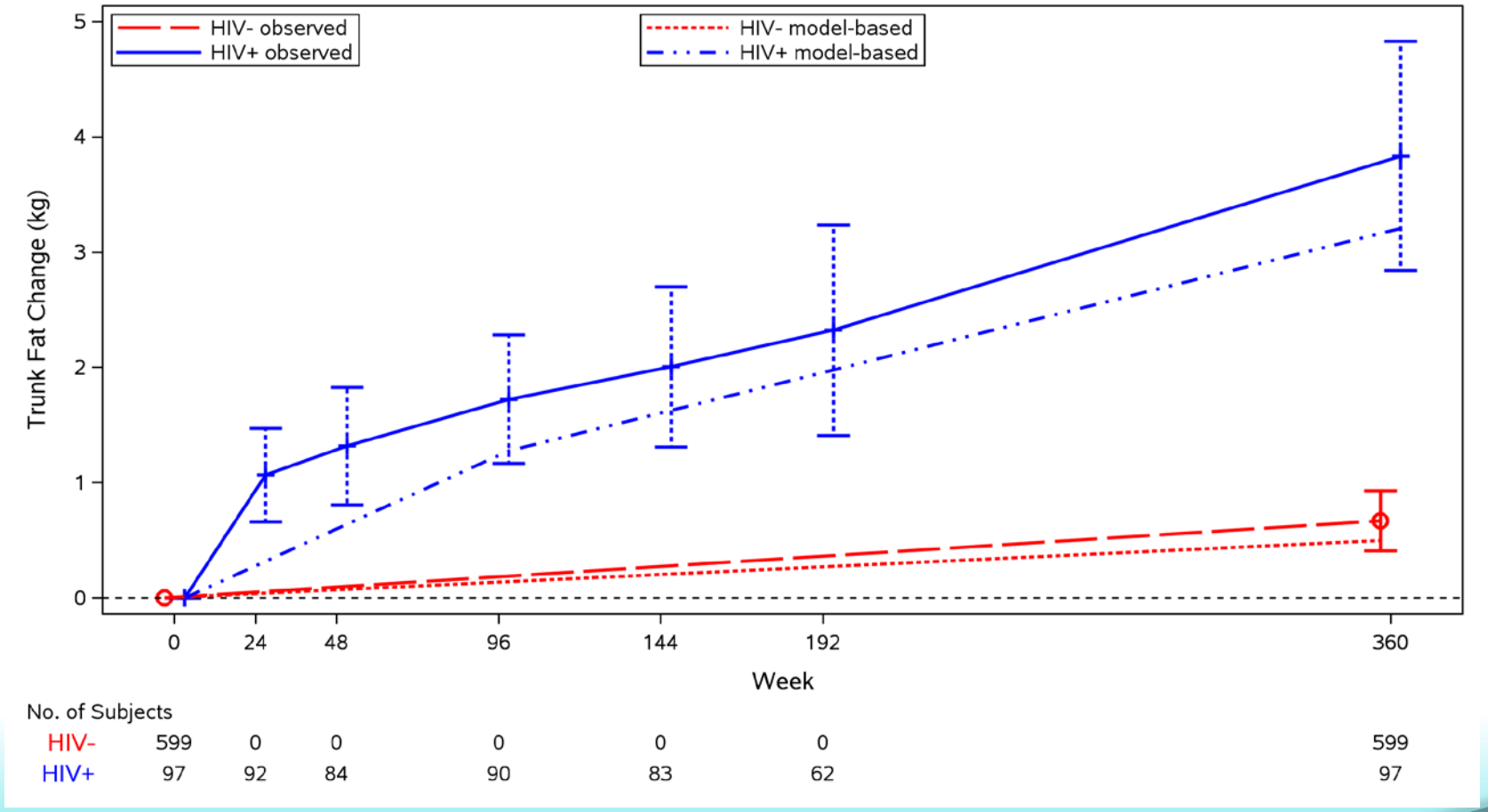
El-Kamary V, CRO 2018

Drug & Diet Effect? High Fat Diet + ART



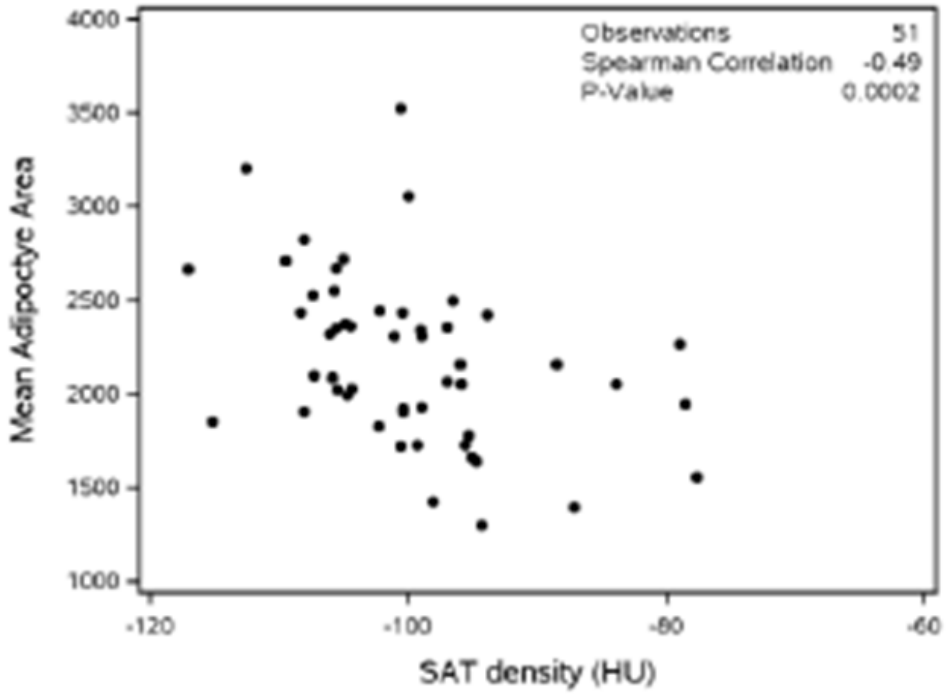
Pepin M; Molecular Metabolism. in press 2018

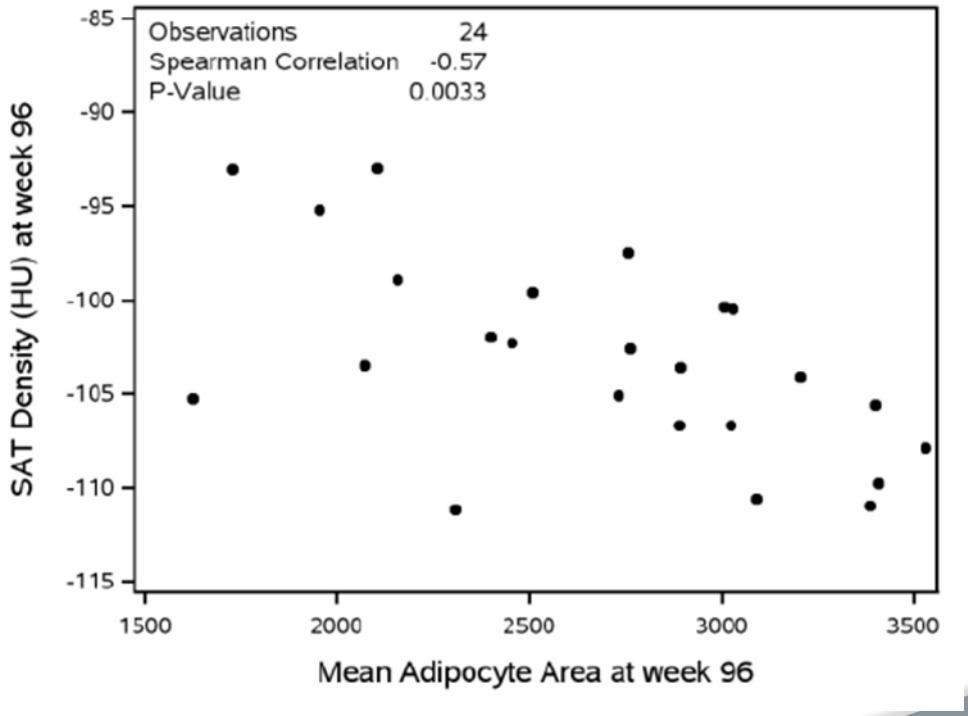
Long Term Changes in Trunk Fat in HIV+ vs. HIV-



Grant P, AIDS 2016; Sharma T, Peds IDJ 2018

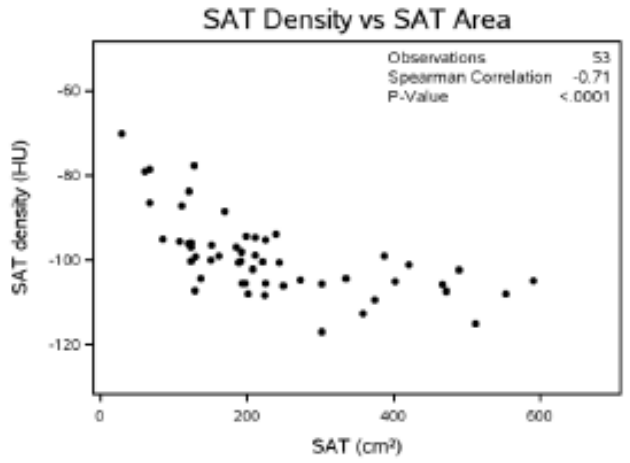
Fat Quality in HIV: pre and post ART

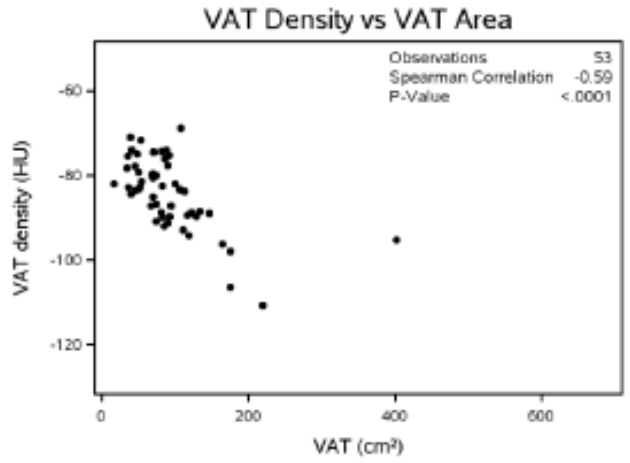


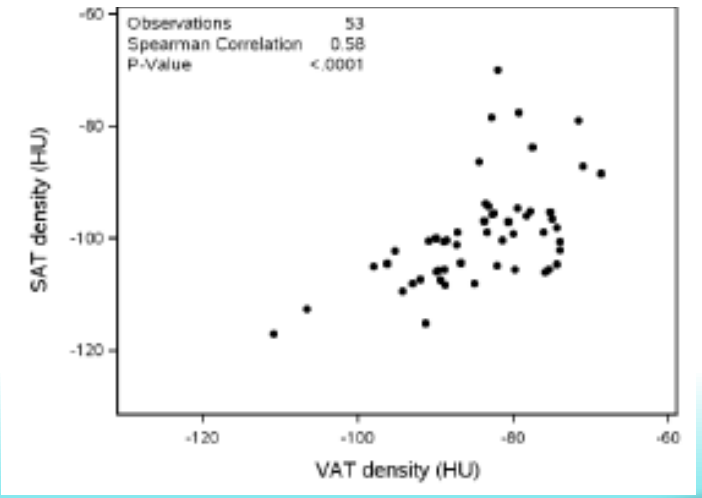


Lake J, CROI 2018

Fat Quality Correlates with Quantity







Lake J, et al. The 18th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV 2016

Does fat Density Change after ART?

Table 1: Participant Characteristics*	Baseline Analyses	On-Treatment Analyses	
	Week 0 (n=54)	Week 0 (n=30)	Week 96 (n=30)
Age (years)	40 (31, 45)	40 (36, 45)	⌘
White, non-Hispanic	67%	73%	73%
Male Sex	89%	93%	93%
Current smoking (%)	26%	23%	20%
BMI (kg/m^2)	26 (22, 30)	26 (24, 30)	27 (25, 30)
BMI ≥30 kg/m^2	26%	27%	27%
Hypertension	13%	20%	⌘
Dyslipidemia	11%	13%	⌘
Chronic viral hepatitis	9%	7%	⌘
CD4$^+$ T lymphocyte count (cells/mm^3)	219 (70, 312)	203 (70, 274)	456 (342, 581)
HIV-1 RNA (log10 copies/mL)	4.8 (4.3, 5.3)	4.8 (4.3, 5.3)	N/A
SAT area (cm^2) *	199 (129, 303)	192 (130, 335)	223 (180, 361)
VAT area (cm^2) *	83 (54, 108)	85 (69, 113)	116 (65, 132)
SAT density (HU)*	-100 (-106, -96)	-100 (-105, -97)	-104 (-107, -100)
VAT density (HU) *	-83 (-90, -78)	-84 (-90, -80)	-90 (-94, -84)
Mean adipocyte area (μm^2)	2156 (1909, 2439)	2098 (1824, 2467)	2759 (2304, 3029)

*Percent or median (interquartile range). ⌘Data not available. *Statistically significant (p<0.05) 96-week change.

Lake J, CROI 2018

VAT/BMI associations with disease in HIV

- Lipohypertrophy associated with lower quality of life, depression, sexual dysfunction
- BMI associated with diabetes, ? CVD
- VAT associated with:
  - 5-year all-cause mortality
  - Presence and progression of coronary calcifications
  - Non calcified plaques
  - Carotid IMT
  - Regional brain atrophy and neurocognitive dysfunction
  - Insulin resistance

- NA-ACCORD: Higher BMI associated with better CD4 recovery

Guaraldi G, AIDS Rev 2008; Scherzer R, AIDS 2011; Orlando G, JAIDS 2012; Guaraldi G, Int J Cardiovasc Imaging. 2012; Palella FJ, OFID 2016, Freitas P, BMC Infect Dis 2014; Hadigan C, Am J Physiol Endocrinol Metab. 2006; Koethe J, HIV Med 2015

ART-switches Studies on Fat Quantity

Do not improve central or total obesity, including:

- Switches off of thymidine NRTI-sparing
- Discontinuing all NRTIs
- PI to NNRTI ineffective
- PI to INSTI ineffective and ?? potentially harmful

Even ART interruption does not improve VAT or BMI

Effect on Fat density unknown

Roubenoff R, AIDS 1999; Dolan S, Arch Intern Med. 2006; Lindegaard B, J Clin Endocrinol Metab 2008; Trøseid M, JAIDS 2014; Valantin MA, HIV Med 2008; Ruiz L, JAIDS 2001; Curran A, AIDS 2012; Lake J, OFID 2015; Martinez E, AIDS 2010

Conclusion

- VAT increases by 25-35% after the initial 2 years of ART, even in the current era of earlier treatment and robust BMI at ART-initiation
- The effect of ART selection appears minimal at best
- However, effect of INSTI remains to be determined
- Little is known about fat quality; it appears to worsen with ART as AT quantity expands

- VAT accumulation is independantly associated with ↑ mortality and CVD in HIV
- ART switches do not work; interventions needed
- Data from obese HIV- subjects should not be extrapolated to HIV-lipohypertrophy; underlying factors (eg gut integrity and immune activation) could affect interventions.