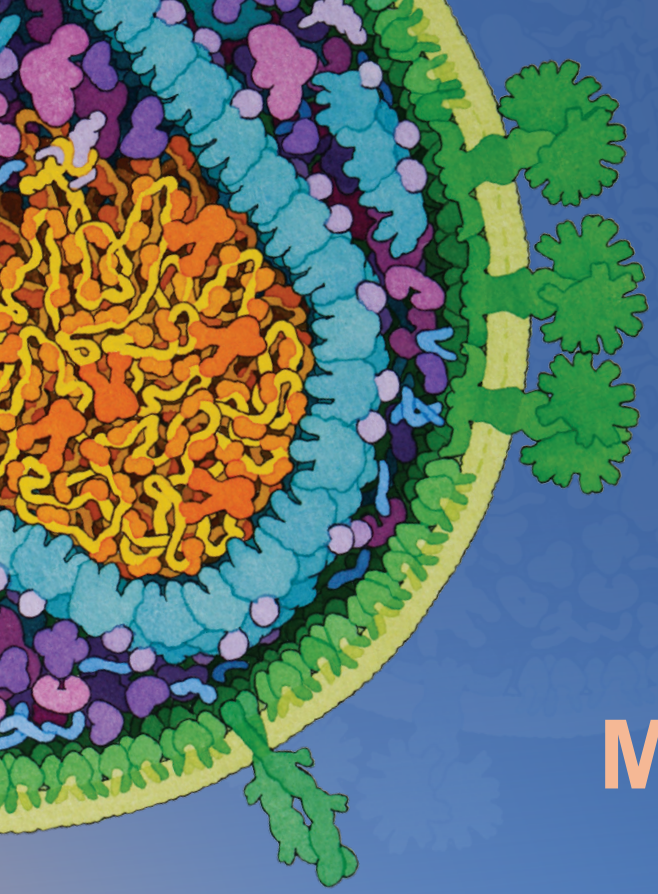

SCIENCE SPOTLIGHT™

ASSESSMENT OF OBESITY AND METABOLIC PROFILE BY INTERGRASE INHIBITOR USE IN REPRIEVE

Janet Lo, MD, MMSc

Massachusetts General Hospital
Boston, MA / United States

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BACKGROUND AND STUDY OBJECTIVE

Introduction

- INSTI-based regimens are highly effective in suppressing the HIV virus and are now first line therapy in most countries.

- Epidemiologic data suggest significant weight gain associated with INSTIs, long-term cardiometabolic health consequences of weight gain associated with INSTI-use remain largely unknown.

Study Objective

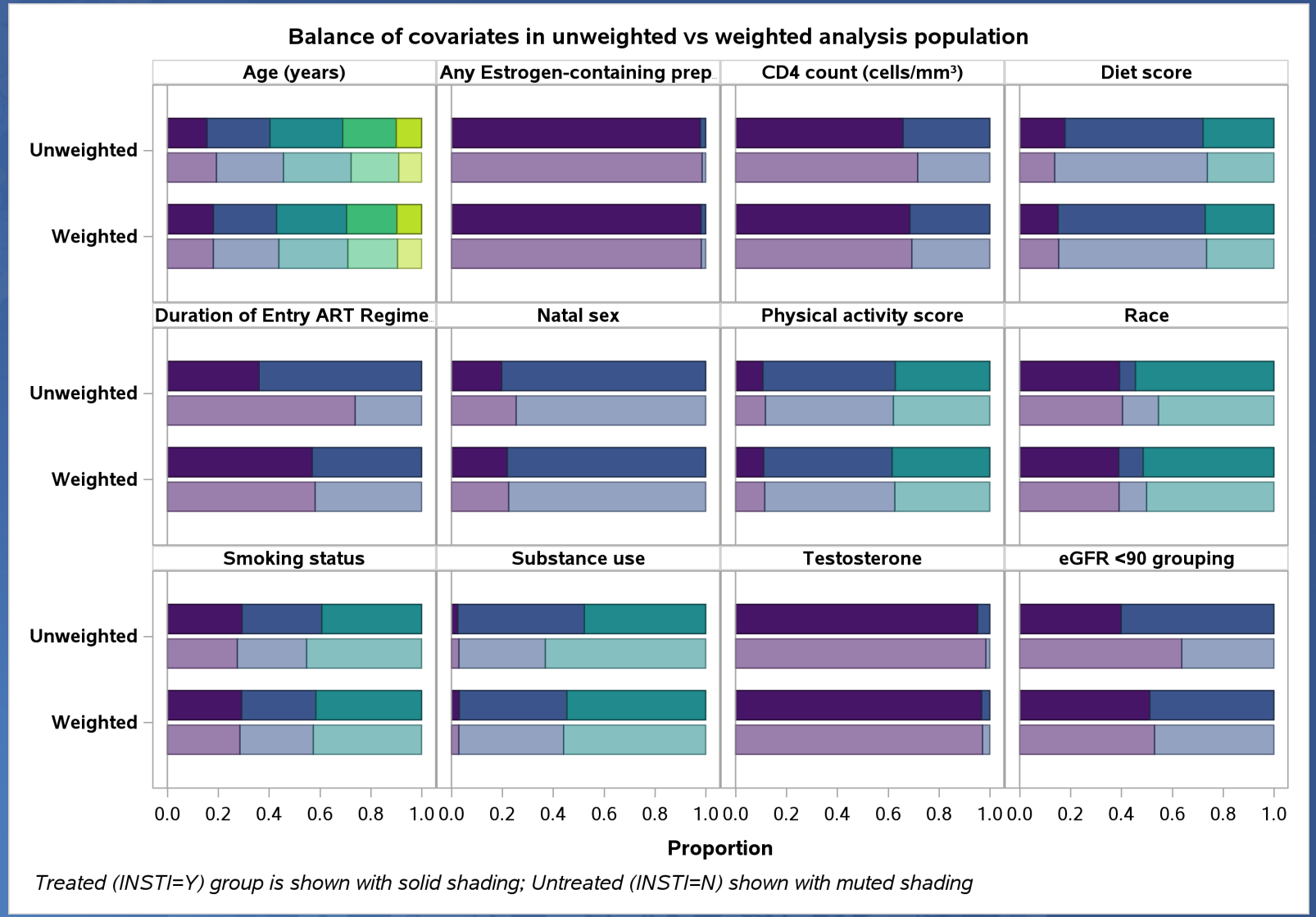
- Effects of INSTI-based ART regimens vs non-INSTI based ART regimens on weight and associated clinically relevant cardiometabolic parameters at REPRIEVE entry:
  - Fasting glucose, LDL-cholesterol, hypertension, and metabolic syndrome

Hypothesis

- Although use of INSTI-based regimens may be associated with greater weight, these agents will be associated with neutral or less adverse cardiometabolic outcomes compared to use of non-INSTI based regimens.

METHODS

- REPRIEVE enrolled a global cohort of 7770 ART-treated PWH, aged 40-75 years between 2015-2019 with low-to-moderate traditional CVD risk.
- Cross-sectional analysis
- INSTI-use of least 6 months
- Regions where at least 5% of the enrolled population were using INSTI based regimens.
- Characteristics of INSTI users vs Non-INSTI were balanced by inverse-probability-of-treatment-weights (IPTW).
- Primary analyses used linear and logistic regressions, secondary analyses used quantile regressions



Treated (INSTI=Y) group is shown with solid shading; Untreated (INSTI=N) shown with muted shading

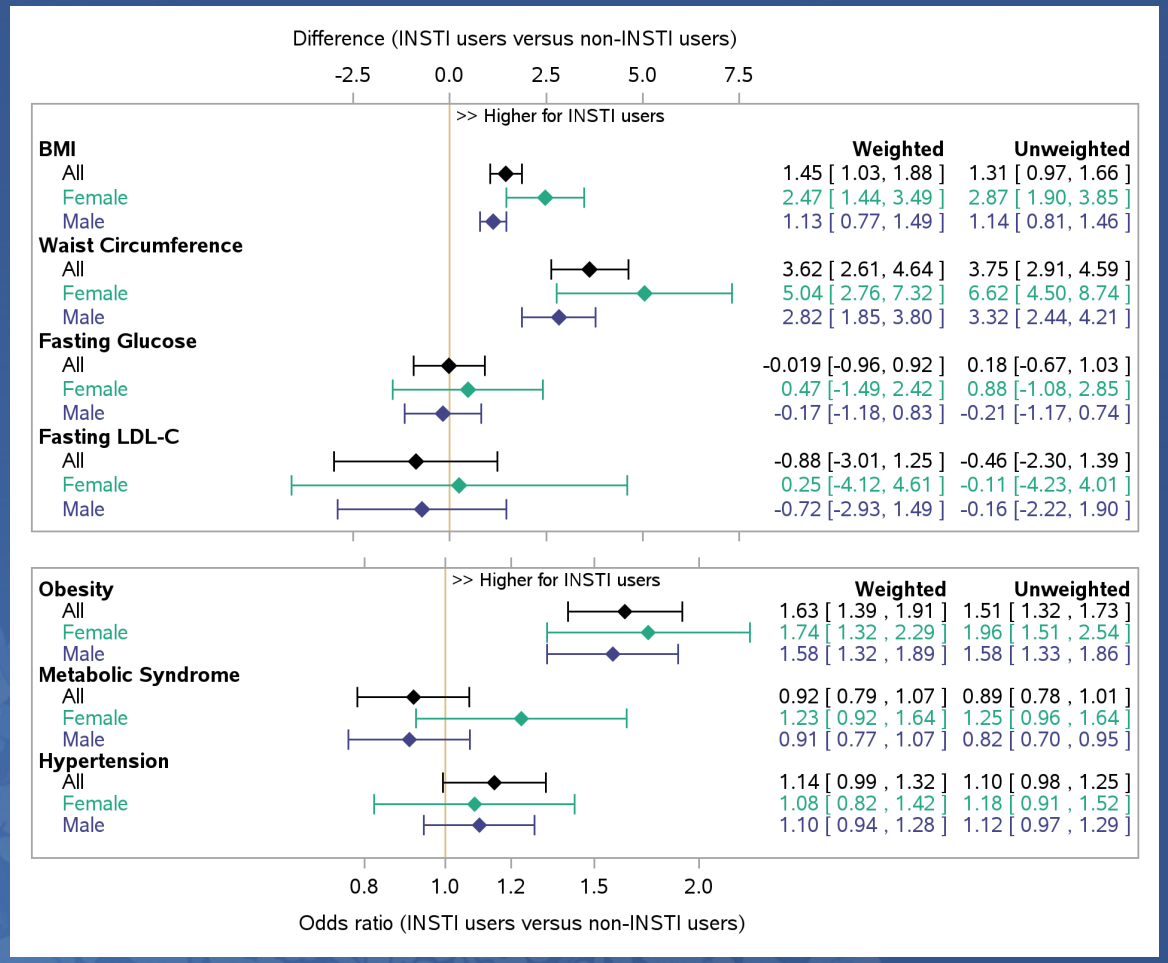
RESULTS

- 63% higher odds of obesity associated with INSTI based regimens vs non
- Higher mean WC of 3.6cm associated with INSTI based regimens vs non
- Associations most pronounced among females
- No difference in fasting glucose, LDL-C, HTN, or metabolic syndrome.
- Results remained consistent in a sensitivity analysis that balanced TDF/TAF use between INSTI users vs non

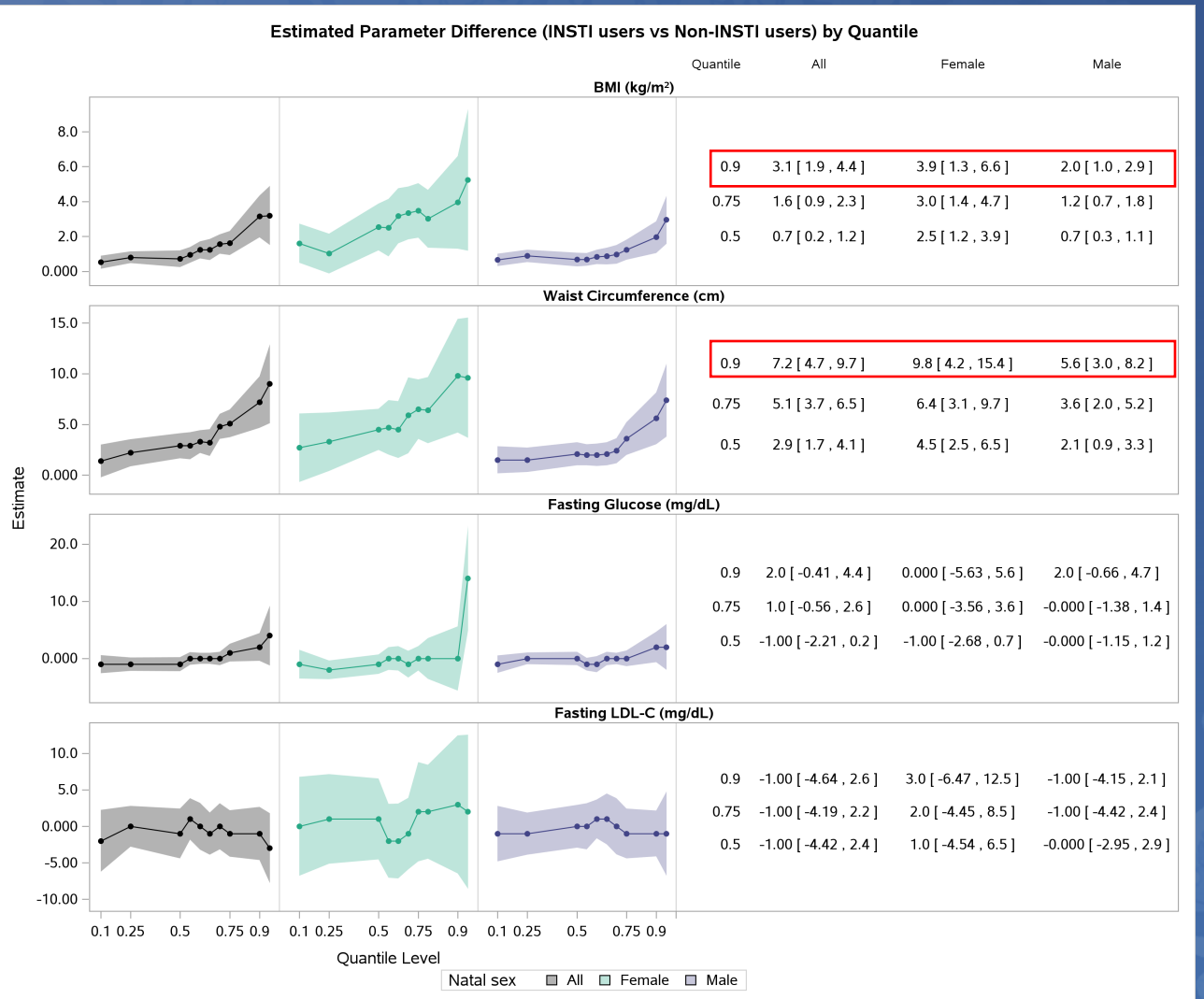
Baseline characteristics

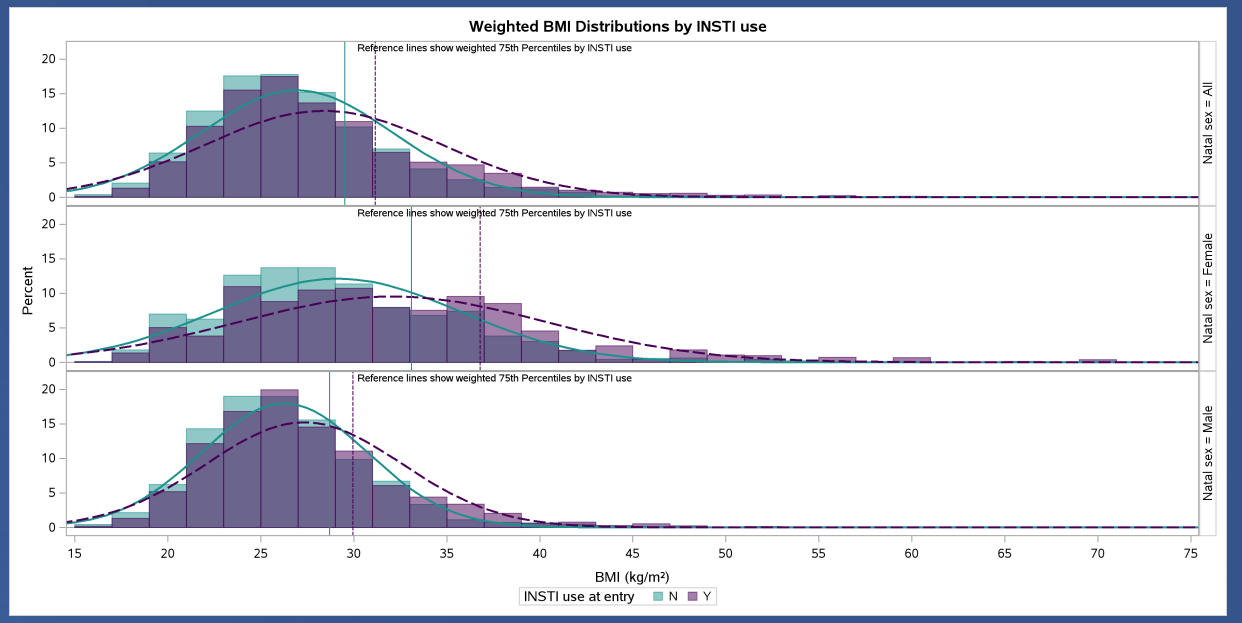
	Overall (n=4500)	INSTI users at entry (n=1848)	Non-INSTI users at entry (n=2652)
Age (years)	51 (46, 55)	51 (47, 56)	50 (46, 55)
Female sex	1040 (23%)	365 (20%)	675 (25%)
BMI (kg/m2)	27.5 (±5.7)	28.2 (±6.1)	26.9 (±5.3)
Waist Circumference (cm)	95.5 (±13.8)	97.7 (±14.8)	94 (±12.8)
Fasting Glucose (mg/dL)	93.0 (±14)	93..1 (±14.1)	93.0 (±14)
Fasting LDL-C (mg/dL)	108 (±31)	108 (±30)	108 (±31)
Metabolic Syndrome (yes)	28%	27%	29%
Hypertension (yes)	37%	39%	36%
Duration of entry ART regimen (years)	4 (±3)	2 (±2)	5 (±4)
CD4 count <500 (cells/mm3)	31%	34%	28%

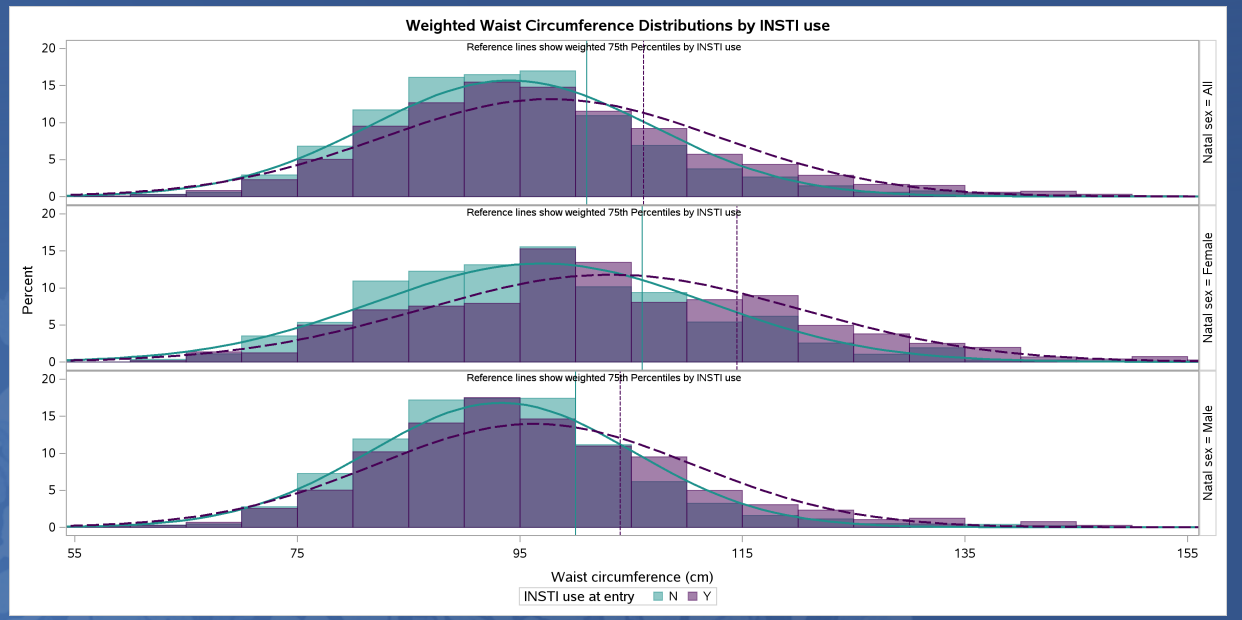
Age is presented as median (Q1, Q3). All other continuous variables, including BMI, WC, fasting Glucose, LDL-C, and duration of entry regimen are presented as mean (+/- sd).



RESULTS


Estimated Parameter Difference (INSTI users vs Non-INSTI users) by Quantile
Quantile
All
Female
Male
BMI (kg/m²)
0.9 3.1 [1.9 , 4.4] 3.9 [1.3 , 6.6] 2.0 [1.0 , 2.9]
0.75 1.6 [0.9 , 2.3] 3.0 [1.4 , 4.7] 1.2 [0.7 , 1.8]
0.5 0.7 [0.2 , 1.2] 2.5 [1.2 , 3.9] 0.7 [0.3 , 1.1]
Waist Circumference (cm)
0.9 7.2 [4.7 , 9.7] 9.8 [4.2 , 15.4] 5.6 [3.0 , 8.2]
0.75 5.1 [3.7 , 6.5] 6.4 [3.1 , 9.7] 3.6 [2.0 , 5.2]
0.5 2.9 [1.7 , 4.1] 4.5 [2.5 , 6.5] 2.1 [0.9 , 3.3]
Fasting Glucose (mg/dL)
0.9 2.0 [-0.41 , 4.4] 0.000 [-5.63 , 5.6] 2.0 [-0.66 , 4.7]
0.75 1.0 [-0.56 , 2.6] 0.000 [-3.56 , 3.6] -0.000 [-1.38 , 1.4]
0.5 -1.00 [-2.21 , 0.2] -1.00 [-2.68 , 0.7] -0.000 [-1.15 , 1.2]
Fasting LDL-C (mg/dL)
0.9 -1.00 [-4.64 , 2.6] 3.0 [-6.47 , 12.5] -1.00 [-4.15 , 2.1]
0.75 -1.00 [-4.19 , 2.2] 2.0 [-4.45 , 8.5] -1.00 [-4.42 , 2.4]
0.5 -1.00 [-4.42 , 2.4] 1.0 [-4.54 , 6.5] -0.000 [-2.95 , 2.9]
Estimate
Quantile Level
Natal sex All Female Male


Weighted BMI Distributions by INSTI use
Reference lines show weighted 75th Percentiles by INSTI use
Natal sex = All
Natal sex = Female
Natal sex = Male
Percent
BMI (kg/m²)
INSTI use at entry N Y


Weighted Waist Circumference Distributions by INSTI use
Reference lines show weighted 75th Percentiles by INSTI use
Natal sex = All
Natal sex = Female
Natal sex = Male
Percent
Waist circumference (cm)
INSTI use at entry N Y

CONCLUSIONS

- Using IPTW analyses, INSTI-based regimens were associated with higher BMI, higher odds of obesity and higher waist circumference, but not with increased fasting glucose, LDL-C, HTN, or metabolic syndrome.
- Differences in BMI and WC are more consistent and concerning among females, in whom they may be more likely to be related to metabolic risk.
- The greatest differences were seen in the tails of the BMI and WC distributions: at the 90^{th} quantile INSTI-use was associated with higher BMI of 3.2kg/m^2 (2.0, 4.3) and a higher WC of 7.2cm (4.7, 9.7).
- These data provide a degree of reassurance that, in general, higher weights associated with INSTI use are not associated with increased cardiometabolic risk, but highlight the subgroups for whom such changes may be very concerning. Further longitudinal studies are necessary to confirm these results.

ACKNOWLEDGMENTS

REPRIEVE

Study Teams & Participants

Coauthors: Emma M. Kileel, Carlos Malvestutto, Markella V. Zanni, Kathleen V. Fitch, Carl J Fichtenbaum, Edgar T. Overton, Nwora Lance Okeke, Princy Kumar, Essau Joao, Pamela S. Douglas, Judith A. Aberg, Heather Ribaudo, and Steven K. Grinspoon

NIH National Heart, Lung, and Blood Institute

NIH National Institute of Allergy and Infectious Diseases

ACTG AIDS CLINICAL TRIALS GROUP

Kowa

GILEAD

ViiV Healthcare