The Journal of Infectious Diseases

MAJOR ARTICLE

Longitudinal Serum Metabolomic Signatures Related to Integrase Strand-Transfer Inhibitors-Associated Weight Gain in Women With HIV Enrolled in the MACS/WIHS Combined Cohort Study

Chin-An Yang,[1] Young-Mi Go,[2] Dean P. Jones,[2] Brahmchetna Bedi,[3] Qian Yang,[3] C. Christina Mehta,[3] Igho Ofotokun,[3] Anandi N. Sheth,[3] Mohammed K. Ali,[4] Sami Teeny,[2] Maria L. Alcaide,[5] Frank J. Palella,[6] Jordan E. Lake,[7] Leah H. Rubin,[8] Elizabeth F. Topper,[8] Julie Schexnayder,[9] Anjali Sharma,[10] Julie B. Dumond,[11] Jennifer Cocohoba,[12] Seble G. Kassaye,[13] Michael Augenbraun,[14] Audrey French,[15] Thomas R. Ziegler,[1,16] Jessica A. Alvarez,[1,16] and Cecile D. Lahiri[3]

[1]Nutrition and Health Sciences Program, Emory University, Laney Graduate School, Atlanta, Georgia, USA; [2]Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University, School of Medicine, Atlanta, Georgia, USA; [3]Department of Medicine, Division of Infectious Diseases, Emory University, School of Medicine, Atlanta, Georgia, USA; [4]Rollins School of Public Health, Emory University, Atlanta, Georgia, USA; [5]Department of Medicine, Division of Infectious Diseases, University of Miami Health, Miller School of Medicine, Miami, Florida, USA; [6]Department of Medicine, Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [7]Department of Internal Medicine, UTHealth, Houston, Texas, USA; [8]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [9]School of Nursing, University of Alabama at Birmingham, Birmingham, Alabama, USA; [10]Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA; [11]Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, North Carolina, USA; [12]Department of Clinical Pharmacy, University of California San Francisco School of Pharmacy, San Francisco, California, USA; [13]Department of Medicine, Georgetown University, Washington, DC, USA; [14]Department of Medicine, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA; [15]Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA; and [16]Department of Medicine, Division of Endocrinology, Metabolism, and Lipids, Emory University School of Medicine, Atlanta, Georgia, USA

Background. Integrase strand-transfer inhibitors (INSTIs) are associated with weight gain in people with HIV, particularly in women with HIV (WWH), but mechanisms remain unclear. We used longitudinal untargeted metabolomics to identify metabolic signatures of INSTI-associated weight gain in WWH.

Methods. Serum samples from 192 Women's Interagency HIV Study participants were analyzed: 38 virologically suppressed WWH who initiated INSTIs, 88 virologically suppressed WWH who remained on their original antiretroviral therapy, and 66 women without HIV. Samples were collected at baseline, 1–6 months post-initiation, and 1–2 years post-initiation, with matched visits for controls. High-resolution metabolomics was performed by liquid chromatography–mass spectrometry. Within each group, linear mixed-effects models adjusted for baseline age and BMI compared longitudinal metabolite changes between weight gainers and maintainers, followed by Mummichog v2.0 pathway enrichment.

Results. Mean age was 45.7 ± 8.9 years and mean BMI 32.4 ± 8.3 kg/m^2. In the INSTI group, differentiating metabolites were enriched in 16 pathways, predominantly lipid-related, including linoleic acid and arachidonic acid metabolism. Comparator groups showed broader pathway patterns, including amino acid metabolism.

Conclusions. INSTI-associated weight gain in WWH is characterized by a lipid- and PUFA-dominated metabolic profile.

Keywords. antiretroviral therapy; polyunsaturated fatty acids; oxylipins; arachidonic acid; linoleic acid.

Integrase strand-transfer inhibitors (INSTIs) have become a cornerstone of antiretroviral therapy (ART) for people living with human immunodeficiency virus (HIV) due to their efficacy, tolerability, and high barrier to resistance [1]. However, accumulating evidence indicates that initiating or switching to INSTI-based regimens can be associated with significant weight gain, particularly in non-White women with HIV (WWH) [2]. INSTI-related weight gain can lead to obesity and related comorbidities, potentially compromising long-term health [3].

Despite the potential clinical significance of this phenomenon, underlying biological mechanisms of INSTI-related weight gain in WWH remain poorly understood, hindered by

Received 11 February 2026; accepted 12 June 2026; published online 29 June 2026

Correspondence: Cecile D. Lahiri, MD, MSc, Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, 341 Ponce de Leon Ave NE, Suite 5024, Atlanta, GA 30308 (cdelill@emory.edu); Jessica A. Alvarez, PhD, RD, Department of Medicine, Division of Endocrinology, Metabolism, and Lipids, Emory University School of Medicine, 101 Woodruff Cr NE, Atlanta, GA 30329 (jessica.alvarez@emory.edu).

© The Author(s) 2026. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

https://doi.org/10.1093/infdis/jiag316

varying individual INSTI molecules, person-to-person variability, and the confounding influence of "return to health" weight gain seen in some ART-naïve individuals initiating first ever ART. Several hypotheses have been proposed, including effects on adipose tissue metabolism, alterations in insulin sensitivity, and changes in inflammatory pathways [3, 4]. However, comprehensive metabolic profiling to identify specific pathways involved in INSTI-related weight gain has been limited.

Based on our previous findings, WWH experience nearly twice the body weight gain compared to men after switching to INSTI-based regimens during 5-year follow-up [5]. In a single-center pilot study utilizing an untargeted, high-resolution metabolomics (HRM) approach to investigate INSTI-related weight gain, we found that neurotransmitter-related metabolism may predict who gains weight, and the mechanisms may involve acute changes in fatty acid-related metabolism [6].

In this study, we performed longitudinal, high-throughput, untargeted HRM to identify metabolic signatures associated with INSTI-related weight gain in virologically suppressed WWH from all sites in the Women's Interagency HIV Study (WIHS), the largest cohort of WWH in the United States which in 2019 merged with the MACS/WIHS Combined Cohort Study (MWCCS). By comparing metabolic profiles across multiple visits among INSTI users, non-INSTI ART users, and demographically similar women without HIV (WWoH), we aimed to elucidate specific metabolic pathways and molecular mechanisms underlying INSTI-related weight gain. Throughout the analysis, all comparisons were stratified by study group, with weight gainers compared to weight maintainers within each group, allowing patterns observed in the INSTI group to be situated against parallel patterns in the non-INSTI ART and WWoH groups.

METHODS

Study Population

The study consisted of 192 participants from WIHS, now part of the MWCCS. The MWCCS follows persons with HIV and demographically similar at-risk persons without HIV across the United States [7]. Recruitment, enrollment, and study procedures for MWCCS have been described in detail previously [7, 8]. Participants attended study visits every 6 months during which clinical data were collected through standardized interviewer-administered surveys, physical examinations, and biological specimen collection. Data for these analyses were contributed by 11 sites: Atlanta, Georgia; Baltimore, Maryland; Birmingham, Alabama/Jackson, Mississippi (combined site); Bronx, New York; Brooklyn, New York; Chapel Hill, North Carolina; Chicago, Illinois; Los Angeles, California; Miami, Florida; San Francisco, California; and Washington, District of Columbia. The MWCCS is approved by the institutional review boards of all participating institutions, and all participants provided written informed consent.

The selection criteria for WWH in this study have been described previously [5]. In brief, for eligible WWH who initiated an INSTI during follow-up, inclusion criteria were (1) documented history of switching from a non-INSTI ART regimen to an INSTI-containing regimen or adding an INSTI to an existing ART regimen; (2) maintained viral suppression (HIV RNA < 200 copies/mL) for 1 year before and after regimen modification; and (3) continuous use of the same INSTI medication for at least 1 year following modification. Participants with reported pregnancy or within 2 years post-partum, tuberculosis diagnosis, or cancer treatment were excluded. For WWoH, visits with reported HIV pre-exposure prophylaxis use were excluded. The current multi-site analysis builds on a prior pilot metabolomics study restricted to women from the Atlanta WIHS site [6]. Thirty women with HIV included in the prior Atlanta pilot study were also included in the present analysis. The visits included in this analysis spanned from October 2009 to August 2019, with a median visit date of February 2015. Consistent with this study period, the INSTI regimens represented in the cohort were primarily elvitegravir (EVG), dolutegravir (DTG), and raltegravir (RAL), with minimal bictegravir (BIC) use because BIC became available later in the study period.

Study Design

Participants were categorized into 3 study groups: women who added or switched to an INSTI-based regimen (INSTI) (n = 38), women who remained on non-INSTI ART (non-INSTI) (n = 88), and women without HIV, WWoH) (n = 66). Henceforth, we refer to timing of INSTI initiation as the first documented visit where women reported either switching to an INSTI from a non-INSTI regimen or adding an INSTI to an existing regimen. For women in the INSTI-group, we used demographic data, clinical data, medical history data, and serum samples at 3 specific time points: (1) baseline (Visit 1): 6–12 months before initiating an INSTI; (2) short-term follow-up (Visit 2): 1–6 months post-INSTI initiation; and (3) long-term follow-up (Visit 3): 1–2 years post-INSTI initiation. For non-INSTI and WWoH groups, samples were collected to align with similar calendar time periods. Participant weight measurements at each time point were analyzed. We further classified participants based on weight change observed over the study period (Visit 3–Visit 1) using a definition of clinically significant weight gain based on prior literature [9]: weight gainers (≥5% increase from baseline) and weight maintainers (<5% change from baseline).

High-Resolution Metabolomics

Untargeted HRM was performed using liquid chromatography–mass spectrometry (LC-MS) with a dual-column

chromatography approach to maximize metabolite feature detection: hydrophilic interaction chromatography (HILIC) in positive ionization mode and C18 in negative ionization mode. This complementary approach enabled comprehensive coverage of both polar and non-polar metabolites. Serum samples were analyzed using standardized HRM methods within the Emory Clinical Biomarkers Laboratory [10]. Samples were treated with acetonitrile and an internal standard mixture prior to analysis. A Thermo Q-Exactive HF high-resolution mass spectrometer operating at 120 000 resolution with a mass-to-charge (m/z) scan range of 85 to 1275 was used [11]. Each sample was analyzed in triplicate. Quality control was maintained using pooled reference plasma from the National Institute of Standards and Technology (Standard Reference Material, SRM, 1950) and Equitech-Bio Inc (SHP45), placed at the beginning, middle, and end of each batch of 25 samples. Raw data processing utilized apLCMS [12] and xMSanalyzer [13] for feature extraction, alignment, and quantification. Metabolic features (metabolites) were annotated using xMSannotator [14], which integrates multiple databases (METLIN, HMDB, and KEGG), based on exact mass matching and MS/MS fragmentation patterns when available.

Data Processing

R (version 4.2.3) was used for data processing, including key steps such as metabolite feature filtering, missing value imputation, and normalization. Features detected in fewer than 20% of samples were excluded to ensure data robustness. To address missing values, a dual imputation strategy was utilized based on the underlying missing data mechanism. The pattern of missingness—classified as either missing not at random (MNAR) or missing at random (MAR)—was inferred using auxiliary features with a Pearson correlation coefficient greater than 0.5 [15]. For MNAR features, quantile regression imputation of left-censored data (QRILC) was applied, while random forest (RF) imputation was used for MAR features, following best practices established in a prior study that systematically evaluated the performance of various imputation algorithms [16]. After imputation, the data were log2-transformed and subjected to quantile normalization to minimize technical variability and enhance comparability across samples.

Statistical Analysis and Bioinformatics

All statistical analyses were conducted in R (version 4.2.3). All analyses were stratified by study group. Continuous characteristics were summarized using mean and standard deviation while categorical characteristics were summarized using count and percentage. Group comparisons of demographic and clinical characteristics between the weight change groups (gainer vs maintainer) were assessed using Fisher's exact test for categorical variables and ANOVA for continuous variables. To evaluate the association between weight change and longitudinal levels of metabolites over time, linear mixed-effects models were performed. These models included fixed effects for time (Visits 1, 2, 3), weight change group, and their interaction (time × weight change group), with a random intercept for each participant to account for within-subject correlation. Baseline age and BMI were included as covariates in all mixed-effects models (Model 1).

Model 1: Linear Mixed-Effects Model for Longitudinal Analysis

Let Y_{ij} denote the normalized metabolite feature for participant i at visit j. The model is as follows:

$$\begin{aligned} Y_{ij} = {} & \beta_0 + \beta_1(\textit{weight change group}_i) + \beta_2(\textit{time}_{i2}) + \beta_3(\textit{time}_{i3}) \\ & + \beta_4(\textit{weight change group}_i * \textit{time}_{i2}) \\ & + \beta_5(\textit{weight change group}_i * \textit{time}_{i3}) \\ & + \beta_6(\textit{Baseline age}) + \beta_7(\textit{Baseline BMI}) + \theta_i + \varepsilon_{ij} \end{aligned}$$

where θ_i is the random intercept and ε_{ij} is the residual. Baseline (Visit 1) is the reference time level.

In this model, the coefficient β_1 reflects baseline differences in metabolite levels between weight gainers and maintainers; β_4 reflects whether the change in metabolite levels from baseline to the short-term follow-up visit (Visit 2) differs between gainers and maintainers; and β_5 reflects the corresponding difference in change from baseline to the long-term follow-up visit (Visit 3). A metabolite feature was considered associated with weight change if any of these 3 coefficients was significant at $P < .05$. Significant features were then analyzed using Mummichog v2.0 [17] to identify metabolic pathways associated with weight change within each ART group.

A subset analysis was conducted using metabolites included in an in-house reference library, consisting of compounds with confirmed identities based on ion dissociation mass spectrometry (MS/MS) spectra and co-elution with authentic chemical standards. These metabolites meet the Level 1 identification criteria defined by the Metabolomics Standards Initiative [18]. Reference standardization was performed by calibrating sample signals against pooled reference standards to generate quantitative estimates based on mass-to-charge ratio (m/z) and ion intensity [19]. The FDR was tested using the BH procedure.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 192 women aged 25–70 years were included in the study, comprising 38 INSTI ART users, 88 non-INSTI ART users, and 66 WWoH. Across the cohort the mean age was 45.7 ± 8.9 years and mean BMI was 32.4 ± 8.3 kg/m^2, with no statistical differences between study groups. In the INSTI group only, the mean age was 46.2 years, and the mean baseline BMI was 32.8 kg/m^2. A total of 18 (47.4%) in the INSTI group were receiving EVG, 15 (39.5%) DTG, 4 (10.5%) RAL, and 1 (2.6%) BIC. Additional baseline clinical and demographic characteristics are presented in Table 1, with comparable characteristics in

Table 1. Baseline Demographic and Clinical Characteristics in WIHS

	Non-INSTI (N = 88)				INSTI (N = 38)				WWoH (N = 66)				
	All (N = 88)	Weight Maintain (N = 67)	Weight Gain (N = 21)	*P* Value Weight Change	All (N = 38)	Weight Maintain (N = 22)	Weight Gain (N = 16)	*P* Value Weight Change	All (N = 66)	Weight Maintain (N = 49)	Weight Gain (N = 17)	*P* Value Weight Change	*P* Value Study Groups
Baseline age													
Mean (SD)	46.45 (8.35)	47.10 (8.81)	44.38 (6.40)	.129	46.24 (9.23)	44.95 (9.46)	48.00 (8.90)	.318	44.26 (9.48)	44.88 (9.86)	42.47 (8.26)	.333	.291
Baseline BMI, kg/m^2													
Mean (SD)	31.18 (7.16)	31.23 (7.42)	31.03 (6.41)	.904	32.81 (7.83)	34.34 (7.31)	30.81 (8.27)	.186	33.75 (9.84)	34.01 (9.61)	33.01 (10.74)	.735	.157
Race													.090
White NH	3 (3.4%)	2 (3.0%)	1 (4.8%)	.396	0 (0%)	0 (0.0%)	0 (0.0%)	*NAN*	4 (6.1%)	3 (6.1%)	1 (5.9%)	1	…
Black NH	55 (62.5%)	40 (59.7%)	15 (71.4%)		28 (73.7%)	16 (72.7%)	12 (75.0%)		51 (77.3%)	38 (77.6%)	13 (76.5%)		…
Else	30 (34.1%)	25 (37.3%)	5 (37.3%)		10 (26.3%)	6 (27.3%)	4 (25.0%)		11 (16.7%)	8 (16.3%)	3 (17.6%)		…
Socioeconomic status													.013
<HS, poverty and/or unemployed	13 (14.8%)	7 (10.4%)	6 (28.6%)	.064	6 (15.8%)	3 (13.6%)	3 (18.8%)	0.228	11 (16.7%)	8 (16.3%)	3 (17.6%)	.819	
1 of <HS, poverty, unemployed	40 (45.5%)	32 (47.8%)	8 (38.1%)		26 (68.4%)	16 (72.7%)	10 (62.5%)		38 (57.6%)	27 (55.1%)	11 (64.7%)		
>HS, not poverty and/or employed	24 (27.3%)	21 (31.3%)	3 (14.3%)		2 (5.3%)	0 (0.0%)	2 (12.5%)		7 (10.6%)	4 (8.2%)	3 (17.6%)		
Missing	11 (12.5%)	7 (10.4%)	4 (19.0%)		4 (10.5%)	3 (13.6%)	1 (6.2%)		10 (15.2%)	10 (20.4%)	0 (0.0%)		
Menopausal status													.069
Premenopausal	34 (38.6%)	25 (37.3%)	9 (42.9%)	.011	12 (31.6%)	8 (36.4%)	4 (25.0%)	.598	28 (42.4%)	20 (40.8%)	8 (47.1%)	.823	…
Perimenopause	13 (14.8%)	6 (9.0%)	7 (33.3%)		3 (7.9%)	1 (4.5%)	2 (12.5%)		16 (24.2%)	13 (26.5%)	3 (17.6%)		…
Post-menopausal (natural or surgical)	39 (44.3%)	34 (50.7%)	5 (23.8%)		23 (60.5%)	13 (59.1%)	10 (62.5%)		22 (33.3%)	16 (32.7%)	6 (35.3%)		…
Missing	2 (2.3%)	2 (3.0%)	0 (0.0%)		0 (0%)	0 (0%)	0 (0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)		…
Current smoker													.239
No	61 (69.3%)	48 (71.6%)	13 (61.9%)	.566	24 (63.2%)	16 (72.7%)	8 (50.0%)	.274	37 (56.1%)	28 (57.1%)	9 (52.9%)	.986	…
Yes	27 (30.7%)	19 (28.4%)	8 (38.1%)		14 (36.8%)	6 (27.3%)	8 (50.0%)		29 (43.9%)	21 (42.9%)	8 (47.1%)		…

Table 1. Continued

	Non-INSTI (N = 88)				INSTI (N = 38)				WWoH (N = 66)				
	All (N = 88)	Weight Maintain (N = 67)	Weight Gain (N = 21)	*P* Value Weight Change	All (N = 38)	Weight Maintain (N = 22)	Weight Gain (N = 16)	*P* Value Weight Change	All (N = 66)	Weight Maintain (N = 49)	Weight Gain (N = 17)	*P* Value Weight Change	*P* Value Study Groups
Heavy alcohol use													.064
No	86 (97.7%)	66 (98.5%)	20 (95.2%)	.422	35 (92.1%)	22 (100.0%)	13 (81.2%)	.132	59 (89.4%)	43 (87.8%)	16 (94.1%)	.667	…
Yes	2 (2.3%)	1 (1.5%)	1 (4.8%)		3 (7.9%)	0 (0.0%)	3 (18.8%)		7 (10.6%)	6 (12.2%)	1 (5.9%)		…
Diabetes													.675
No	77 (87.5%)	58 (86.6%)	19 (90.5%)	1	31 (81.6%)	18 (81.8%)	13 (81.2%)	1	57 (86.4%)	43 (87.8%)	14 (82.4%)	.684	…
Yes	11 (12.5%)	9 (13.4%)	2 (9.5%)		7 (18.4%)	4 (18.2%)	3 (18.8%)		9 (13.6%)	6 (12.2%)	3 (17.6%)		…
Hyperlipidemia													.174
No	68 (77.3%)	51 (76.1%)	17 (81.0%)	.771	25 (65.8%)	13 (59.1%)	12 (75.0%)	.500	54 (81.8%)	39 (79.6%)	15 (88.2%)	.716	…
Yes	20 (22.7%)	16 (23.9%)	4 (19.0%)		13 (34.2%)	9 (40.9%)	4 (25.0%)		12 (18.2%)	10 (20.4%)	2 (11.8%)		…
TAF use													
No	88 (100%)	67 (100.0%)	21 (100.0%)	*NAN*	36 (94.7%)	21 (95.5%)	15 (93.8%)	1	…	…	…	…	…
Yes	0 (0%)	0 (0.0%)	0 (0.0%)		2 (5.3%)	1 (4.5%)	1 (6.2%)		…	…	…	…	…
TDF use													
No	21 (23.9%)	16 (23.9%)	5 (23.8%)	1	8 (21.1%)	4 (18.2%)	4 (25.0%)	.698	…	…	…	…	…
Yes	67 (76.1%)	51 (76.1%)	16 (76.2%)		30 (78.9%)	18 (81.8%)	12 (75.0%)		…	…	…	…	…
NNRTI use													
No	46 (52.3%)	34 (50.7%)	12 (57.1%)	.794	18 (47.4%)	12 (54.5%)	6 (37.5%)	.477	…	…	…	…	…
Yes	42 (47.7%)	33 (49.3%)	9 (42.9%)		20 (52.6%)	10 (45.5%)	10 (62.5%)		…	…	…	…	…
PI use													
No	45 (51.1%)	36 (53.7%)	9 (42.9%)	.536	20 (52.6%)	10 (45.5%)	10 (62.5%)	.477	…	…	…	…	…
Yes	43 (48.9%)	31 (46.3%)	12 (57.1%)		18 (47.4%)	12 (54.5%)	6 (37.5%)		…	…	…	…	…

Values are presented as mean (standard deviation, SD) or n (percentage, %), as indicated. N reflects the number of participants with available data for each characteristic. *P* values were calculated using 1-way ANOVA for continuous variables and χ^2 tests for categorical variables.

BMI, body mass index; NH, non-Hispanic; HS, high school; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand-transfer inhibitor; WWoH, women without HIV.

the non-INSTI and WWoH groups (Table 1). At baseline, there were no significant differences in clinical or demographic characteristics between weight gainers and weight maintainers within the INSTI group. Similar findings were seen in the non-INSTI and WWoH groups (Table 1).

Longitudinal, Metabolome-Wide Associations With INSTI-Related Weight Change

Figure 1 shows the analytical workflow and results of the metabolome-wide association study within each group (INSTI, non-INSTI, WWoH). Pathway enrichment analysis with resulting significant metabolites across time points is shown in Figure 2. Within the INSTI group, 688 and 1187 metabolite features significantly differ by weight change group in the C18 and HILIC modes, respectively, at any of the 3 time points ($P < .05$). Enriched pathways with metabolites differing at baseline were arachidonic acid metabolism, linoleate metabolism, omega-3 fatty acid metabolism, vitamin K metabolism, and vitamin A (retinol) metabolism. Enriched pathways of metabolites significantly differing acutely (1–6 months) were

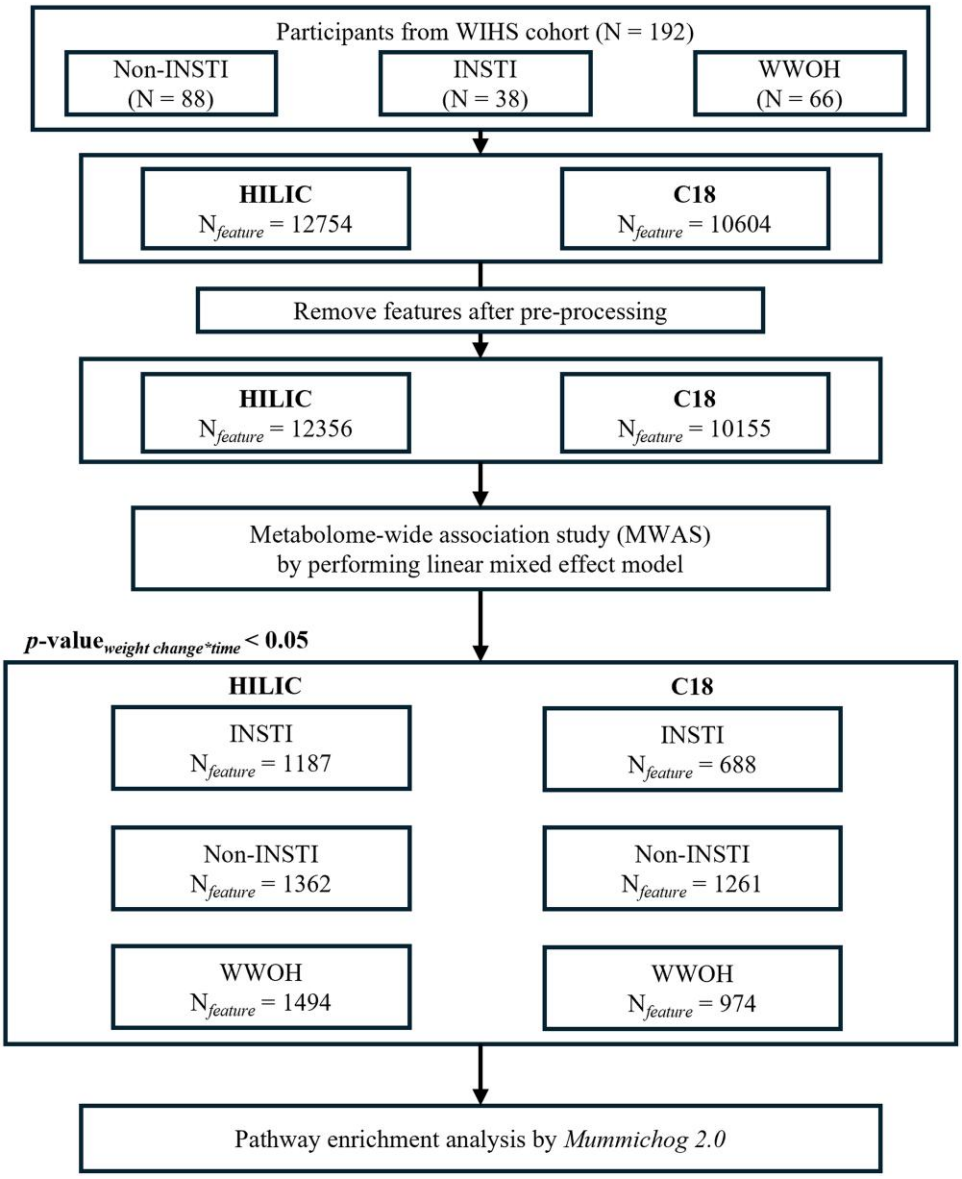


Figure 1. The analytical workflow of metabolome-wide association study (MWAS) and pathway enrichment analysis. Participants from the WIHS cohort (N = 192) were categorized into 3 groups: non-INSTI users (N = 88), INSTI users (N = 38), and WWoH (N = 66). Untargeted metabolomics data were acquired in both HILIC and C18 modes, followed by preprocessing and feature filtering. Linear mixed-effects models were used to evaluate associations between metabolite features and either weight change × time interaction or body weight × time interaction within each group and chromatography mode. Features meeting the significance threshold ($P < .05$) were subsequently subjected to pathway enrichment analysis using *Mummichog* 2.0. WIHS, Women's Interagency HIV Study; INSTI, integrase strand-transfer inhibitor; Non-INSTI, participants not using INSTI-based ART; WWoH, women without HIV; HILIC, hydrophilic interaction chromatography mode; C18, reversed-phase C18 chromatography mode.

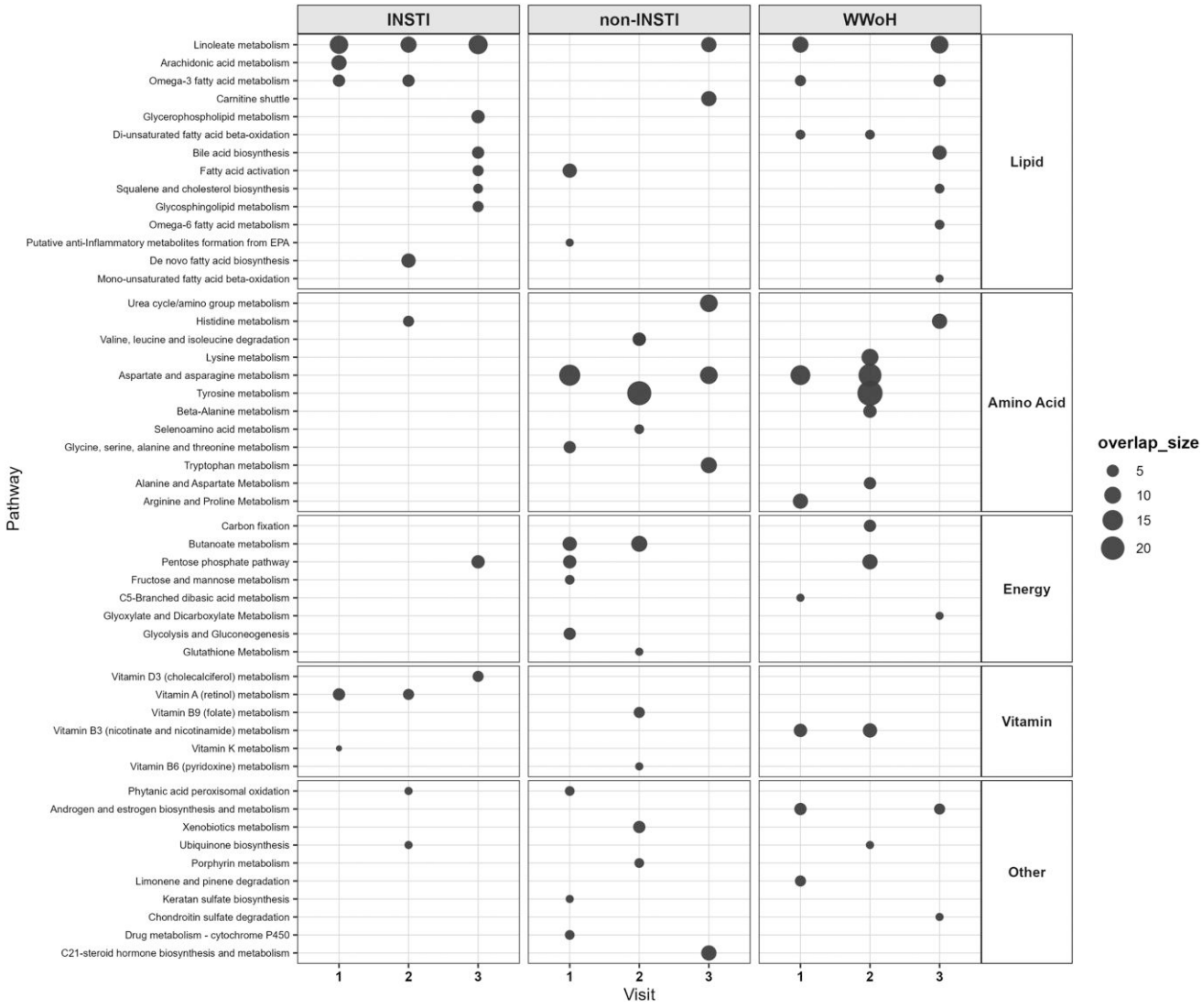


Figure 2. Metabolic pathways associated with the interaction between weight change and time across study groups. Each panel shows significant pathways ($P < .05$) identified in longitudinal analyses for the 3 study groups: INSTI, non-INSTI, and women without HIV (WWoH). The x-axis indicates visit (Visit 1, Visit 2, and Visit 3), and the y-axis lists the identified pathways. Each bubble represents a pathway significantly associated with weight change at a given visit within each group. Bubble size reflects the overlap size, defined as the number of metabolites enriched within that pathway. Pathways are grouped by metabolic category, shown in the right-side blocks: lipid, amino acid, energy metabolism, vitamin, and other pathways.

linoleate metabolism, omega-3 fatty acid metabolism, de novo fatty acid biosynthesis, histidine metabolism, vitamin A (retinol) metabolism, ubiquinone biosynthesis, and phytanic acid peroxisomal oxidation. Enriched pathways of metabolites significantly differing over 1–2 years were bile acid biosynthesis, squalene and cholesterol biosynthesis, glycosphingolipid metabolism, glycerophospholipid metabolism, fatty acid activation, the pentose phosphate pathway, and vitamin D3 (cholecalciferol) metabolism. A subset analysis restricted to Level 1 identified metabolites (Supplementary Tables 1 and 2) revealed several differentiating metabolites at $P < .05$ although they did not meet the FDR threshold. Accordingly, downstream interpretation focused primarily on pathway-level results.

Pathway-level patterns differed across study groups. While metabolites differentiating weight gainers from weight maintainers in the INSTI group were primarily enriched within lipid-related pathways (Figure 2), differentiating metabolites in the non-INSTI and WWoH control groups were enriched within a more diverse set of metabolic pathways, including lipid, amino acid, and energy metabolism pathways. Consistent with prior pilot study findings [6], pathway enrichment analysis revealed associations of omega-6 fatty acid pathways with weight change. Representative polyunsaturated fatty acid

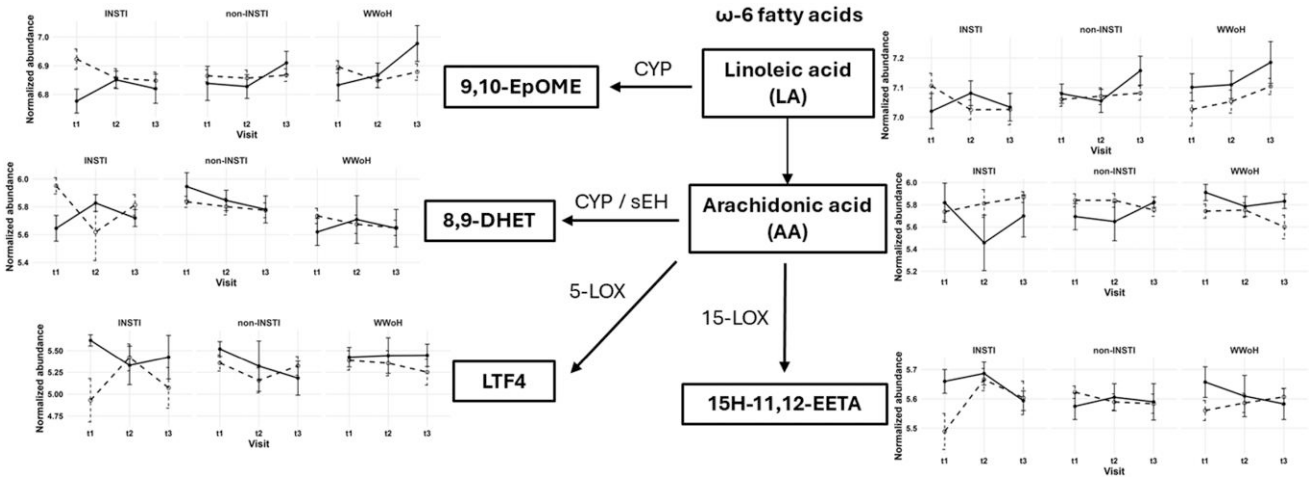


Figure 3. Longitudinal trajectories of selected PUFAs and oxylipins associated with weight change across the INSTI, non-INSTI, and WWoH groups. Each panel shows mean (±SE) normalized metabolite abundance over time by weight change group within each study group. Solid lines represent weight gainers and dashed lines represent weight maintainers. Time points are defined as t1 = baseline (pre-switch), t2 = 1–6 mo post-switch, and t3 = 1–2 y post-switch. CYP, cytochrome P450; sEH, soluble epoxide hydrolase; LOX, lipoxygenase; 15H-11,12-EETA, 15-hydroxy-11,12-epoxyeicosatrienoic acid; 9,10-EpOME, 9,10-epoxyoctadecenoic acid; 8,9-DHET, 8,9-dihydroxyeicosatrienoic acid; LTF4, leukotriene F4.

(PUFA) metabolites from these pathways are shown in Figure 3.

DISCUSSION

This longitudinal, multi-site metabolomics study provides novel insights into the metabolic signatures related to INSTI-associated weight gain in WWH. Through comparisons with non-INSTI ART recipients and WWoH control groups, we identified a predominance of lipid metabolic pathways differentiating weight change groups among INSTI users, including PUFA-related pathways such as LA and AA. These findings highlight potential mechanisms linking INSTI use and weight gain [20]. Our results align with and extend a recent cross-sectional case–control metabolomics study in a Mexican cohort by Ascencio-Anastacio et al in PWH receiving second-generation INSTIs, which identified dysregulated lipid metabolism and mitochondrial dysfunction as key features of INSTI-associated weight gain [21]. Our longitudinal analysis across 3 visits additionally captures the temporal trajectory of lipid pathway perturbations both before and after INSTI exposure, allowing us to distinguish baseline susceptibility from on-treatment metabolic shifts.

In contrast to INSTI users, differentiating metabolites within the non-INSTI WWH were distributed within a broad range of metabolic pathways more similar to that of WWoH, encompassing amino acid, energy, and other metabolic pathways alongside lipid pathways. This broader pattern is consistent with prior population-based metabolomic studies of long-term body-weight change, which have shown that weight gain in the general population is accompanied by coordinated shifts across multiple, interconnected metabolic networks, including lipid, amino acid, insulin-related, and mitochondrial-function pathways [22, 23]. The preponderance of differentiating metabolites within lipid pathways in the INSTI group may reflect a more constrained metabolic phenotype dominated by impaired lipid handling. Such a pattern is consistent with metabolic inflexibility, a diminished capacity to switch fuel substrates in response to nutrient availability, which has been linked to mitochondrial dysfunction, ectopic lipid accumulation, and insulin resistance in cardiometabolic disease [24]. Notably, INSTIs have been directly implicated in adipose tissue mitochondrial dysfunction in mechanistic animal and cellular studies [25, 26]. Together, with the recent findings of Ascencio-Anastacio et al [21], these data suggest that the lipid pathway predominance we observed may reflect mitochondrial and bioenergetic perturbations specific to INSTI exposure, beyond the broader metabolic shifts that accompany weight gain in general populations.

Polyunsaturated fatty acids play important roles in human health and chronic disease. Through enzymatic and non-enzymatic oxidation, PUFAs are converted into oxylipins, which are bioactive lipid mediators that modulate inflammation, vascular function, and energy metabolism [27]. In this study, LA and its downstream oxylipin, 9,10-epoxyoctadecenoic acid (9,10-EpOME), increased from baseline to 1–6 months post-switch among weight gainers in the INSTI group (Figure 3). Elevated EpOMEs have been linked to cardiovascular disease and inflammation [28] and with obesity in a high-fat diet mouse model [29]. The change in LA differed from our pilot study [6]; however, this discordance may reflect the dynamic nature of LA

utilization and diversion to downstream metabolites [30]. The observed increase in 9,10-EpOME may provide a more functionally relevant signal of downstream oxylipin production linked to inflammation and obesity-related metabolic stress. These results suggest that INSTI use may involve acute effects on weight gain through LA-related pathways, although kinetic-based studies will be required to delineate the underlying metabolic fluxes.

Within AA metabolism, several findings point to enzymatically driven shifts in oxylipin production among INSTI users that may reinforce a pro-inflammatory adipose tissue environment. First, weight gainers showed an acute decrease in AA at 1–6 months post-switch with a corresponding increase in 8,9-dihydroxyeicosatrienoic acid (8,9-DHET; Figure 3), consistent with upregulation of soluble epoxide hydroxylase activity, which has been increasingly recognized as a maladaptive feature of obesity and metabolic disease [31, 32]. Second, levels of leukotriene F4 and 15-hydroxy-11,12-epoxyeicosatrienoic acid (15H-11,12-EETA) were generally elevated among weight gainers relative to maintainers in the INSTI group. Their upstream biosynthetic enzymes, 5-LOX [33] and 15-LOX [34], respectively, are overexpressed in adipose tissue in obesity, and the 5-LOX/leukotriene axis has been shown to drive low-grade adipose inflammation and insulin resistance [35, 36]. Taken together, these patterns suggest that INSTI-associated weight gain may involve a coordinated reprogramming of AA metabolism favoring a pro-inflammatory adipose tissue state that promotes weight gain and related metabolic disturbances [37, 38].

Beyond PUFA-related pathways, we also observed enrichment of fat-soluble vitamin pathways with metabolites differentially associated with weight gain only in those who initiated INSTIs. Vitamin A and K metabolism differed between weight change groups at baseline, with vitamin A differences persisting by the second visit. Both vitamins have been linked to adiposity: vitamin A and its active metabolite retinoic acid regulate adipogenesis [39], and higher adiposity is associated with vitamin K sequestration in adipose tissue and lower circulating vitamin K status [40], with dietary intakes of both inversely associated with visceral adiposity [41]. As essential nutrients that must be obtained from the diet, these findings have implications for a role of diet quality in modulating the adipogenic effect of INSTIs. Together, alterations in fat-soluble micronutrient pathways highlight the broader impact of lipid-related dysregulation in INSTI users.

For several pathways and metabolites, differences between women who later gained weight and those who did not were already present at baseline, raising the possibility of a preexisting metabolic susceptibility to weight gain after INSTI initiation, rather than solely treatment-induced changes. At the same time, the divergent directions of change in metabolites between gainers and maintainers support the interpretation that these markers may capture both baseline vulnerability and early metabolic responses to INSTI exposure. Because our study was not designed to formally evaluate predictive performance, this possibility should be considered hypothesis-generating and warrants confirmation in future studies.

In this study, we utilized a large, well-established database to investigate the potential mechanisms of INSTI-associated weight gain among WWH. A strength of this study is the longitudinal study design, enabling us to track the changes of metabolites during follow-up. Furthermore, we compared findings to WWH on non-INSTI ARTs as well as WWoH, reinforcing differences in weight gain specially associated with use of INSTIs. Compared with our prior Atlanta-based pilot study, the present analysis included women recruited across multiple WIHS sites, improving sample size and broader cohort representation, although there was partial overlap between the 2 studies. This broader recruitment enhances generalizability but may also introduce heterogeneity in participant composition, care settings, and other site-level factors. Because site-specific sample sizes were modest, residual heterogeneity across centers may have influenced the observed metabolomic patterns. In addition, the visits included in this analysis spanned an earlier INSTI treatment era, which should be considered when interpreting the findings, as weight gain risk may differ across INSTI agents. While findings from our study were applicable to middle-aged women with well-controlled HIV, caution should be taken when extrapolating to men with HIV, younger or older populations, individuals with advanced HIV, those receiving an INSTI + tenofovir alafenamide or more recent BIC-based regimens, or those from different geographic and clinical settings. Additional limitations were the relatively modest sample size of the INSTI group. Dietary intake information was not available, which could have influenced PUFA levels and metabolism, as well as other metabolic pathways. Menopausal status may also influence both weight-related outcomes and metabolomic profiles through hormonal changes [42]. Although menopausal status defined by STRAW+10 criteria was included in the descriptive characteristics and was not significantly different across study groups or between gainers and maintainers in most comparisons, we did not include it as a covariate in the main models because of the modest sample size. Finally, while we controlled for age and baseline BMI, other potential confounders, such as concurrent medications and comorbidities, may have influenced the results. Additional targeted research is warranted to validate these findings.

In conclusion, in virally suppressed WWH who initiated INSTI-based ART, weight gain over time was associated with a distinct metabolic profile driven primarily by involvement of PUFA and other lipid-related pathways, as compared with WWH on non-INSTI regimens and WWoH whose weight change profiles were distributed within a broad range of metabolic pathways. Differences in PUFA metabolism and downstream oxylipins support a lipid-mediated, pro-inflammatory contribution to INSTI-associated weight gain in WWH.

These findings provide potential insights into INSTI-related metabolic complications and may inform strategies to prevent or mitigate weight gain in this population.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS), now the MACS/WIHS Combined Cohort Study (MWCCS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). MWCCS (Principal Investigators): Atlanta CRS (Cecile Lahiri, Anandi Sheth, and Gina Wingood), U01-HL146241; Baltimore CRS (Todd Brown and Joseph Margolick), U01-HL146201; Bronx CRS (Kathryn Anastos, David Hanna, and Anjali Sharma), U01-HL146204; Brooklyn CRS (Deborah Gustafson and Tracey Wilson), U01-HL146202; Data Analysis and Coordination Center (Gypsyamber D'Souza, Stephen Gange and Elizabeth Topper), U01-HL146193; Chicago-Cook County CRS (Mardge Cohen, Audrey French, and Ryan Ross), U01-HL146245; Chicago-Northwestern CRS (Steven Wolinsky, Frank Palella, and Valentina Stosor), U01-HL146240; Northern California CRS (Bradley Aouizerat, Jennifer Price, and Phyllis Tien), U01-HL146242; Los Angeles CRS (Roger Detels and Matthew Mimiaga), U01-HL146333; Metropolitan Washington CRS (Seble Kassaye and Daniel Merenstein), U01-HL146205; Miami CRS (Maria Alcaide, Claudia Martinez, and Deborah Jones), U01-HL146203; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo), U01-HL146208; UAB-MS CRS (Mirjam-Colette Kempf, James B. Brock, and Emily Levitan), U01-HL146192; and UNC CRS (M. Bradley Drummond and Michelle Floris-Moore), U01-HL146194.

Author Contributions. C.-A. Y., C. D. L., and J. A. A. conceived and designed the study. C. C. M., Q. Y., Y.-M. G., and D. P. J. created the database. C.-A. Y. analyzed the data. C.-A. Y., C. D. L., and J. A. A. wrote the manuscript. C.-A. Y. created all tables and figures. C.-A. Y., Y.-M. G., D. P. J., B. B., Q. Y., C. C. M., I. O., A. N. S., M. K. A., S. T., M. L. A., F. J. P., J. E. L., L. H. R., E. F. T., J. S., A. S., J. B. D., J. W. M., J. C., S. G. K., M. A., S. W., A. F., T. R. Z., C. D. L., and J. A. A. reviewed, edited, and approved the manuscript and all figures and tables.

Statement. C. C. M. holds the position of Statistical Editor for JID and has not peer reviewed or made any editorial decisions for this paper.

Financial support. The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), with additional co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD), National Institute on Aging (NIA), National Institute of Dental & Craniofacial Research (NIDCR), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), National Institute of Nursing Research (NINR), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Institute on Minority Health and Health Disparities (NIMHD) and in coordination and alignment with the research priorities of the National Institutes of Health, Office of AIDS Research (OAR). MWCCS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR003098 (JHU ICTR), UL1-TR001881 (UCLA CTSI), P30-AI-050409 (Atlanta CFAR), P30-AI-073961 (Miami CFAR), P30-AI-050410 (UNC CFAR), P30-AI-027767 (UAB CFAR), P30-AI-124414 (ERC-CFAR), P30-MH-116867 (Miami CHARM), UL1-TR001409 (DC CTSA), KL2-TR001432 (DC CTSA), and TL1-TR001431 (DC CTSA). The data underlying this article will be shared on reasonable request to the corresponding author. This work also included support from NIH/NIDDK R01 DK125246 (C. D. L., J. A. A., A. N. S., M. K. A., C. C. M.) and NIH/NHLBI K24 HL176324 (C. D. L.).

Potential conflicts of interest. C. D. L. receives grant funding from NIH and Merck Pharmaceuticals and serves as an advisory board member and consultant for Theratechnologies, Inc. M. L. A. receives grant funding from NIH and AbbVie, serves on a Gilead advisory board, and has a fiduciary role with Discidium Biosciences. M. K. A. receives grant funding from NIH and serves on advisory boards for Bayer and Eli Lilly. J. E. L. receives grant funding from Gilead Sciences and serves as a consultant for Gilead Sciences and Theratechnologies. F. J. P. serves as a consultant and on the speakers bureau for ViiV, Gilead, and EMG/Serono. J. C. received grants from ViiV Healthcare, Janssen Pharmaceuticals, and Genentech; served as a symposium speaker for Clinical Care Options; served as a webinar speaker for the American Conference for the Treatment of HIV; and is a data and safety monitoring board (DSMB) member for the BFTAF Study. S. G. K. receives grants from NIH, developed HIV materials for Vindico Medical Education, and is a DSMB member for the WE RISE study. I. O. and L. H. R. received grants from

NIH. All other authors report no conflicts of interest. All other authors report no conflicts of interest.

References

1. *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV*, D.o.H.a.H. Services, Editor. 2023, Panel on Antiretroviral Guidelines for Adults and Adolescents.
2. Lake JE, Wu K, Bares SH, et al. Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy. Clin Infect Dis **2020**; 71:e471–7.
3. Summers NA, Lahiri CD, Angert CD, et al. Metabolic changes associated with the use of integrase strand transfer inhibitors among virally controlled women. J Acquir Immune Defic Syndr **2020**; 85:355–62.
4. Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. J Antimicrob Chemother **2018**; 73:2177–85.
5. Lahiri CD, Mehta CC, Yang Q, et al. Short and long-term body weight change following the switch to or the addition of integrase inhibitors in persons with HIV differs by sex. Clin Infect Dis **2024**; 80:575–84.
6. Alvarez JA, Teeny S, Yang CA, et al. Altered lipid and neurotransmitter metabolism as potential mechanisms of weight gain in women with HIV initiating INSTIs in a pilot study. J Acquir Immune Defic Syndr **2026**; 101:325.
7. D'Souza G, Bhondoekhan F, et al. Characteristics of the MACS/WIHS combined cohort study: opportunities for research on aging with HIV in the longest US observational study of HIV. Am J Epidemiol **2021**; 190:1457–75.
8. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's interagency HIV study. WIHS collaborative study group. Epidemiology **1998**; 9:117–25.
9. Galdamez R, García JA, Fernández M, et al. Short-term increase in risk of overweight and concomitant systolic blood pressure elevation in treatment-naive persons starting INSTI-based antiretroviral therapy. Open Forum Infect Dis **2019**; 6:ofz491.
10. Park YH, Lee K, Soltow QA, et al. High-performance metabolic profiling of plasma from seven mammalian species for simultaneous environmental chemical surveillance and bioeffect monitoring. Toxicology **2012**; 295:47–55.
11. Go YM, Walker DI, Liang Y, et al. Reference standardization for mass spectrometry and high-resolution metabolomics applications to exposome research. Toxicol Sci **2015**; 148:531–43.
12. Yu T, Park Y, Johnson JM, et al. apLCMS–adaptive processing of high-resolution LC/MS data. Bioinformatics **2009**; 25:1930–6.
13. Uppal K, Soltow QA, Strobel FH, et al. xMSanalyzer: automated pipeline for improved feature detection and downstream analysis of large-scale, non-targeted metabolomics data. BMC Bioinformatics **2013**; 14:15.
14. Uppal K, Walker DI, Jones DP. xMSannotator: an R package for network-based annotation of high-resolution metabolomics data. Anal Chem **2017**; 89:1063–7.
15. Curnow E, Cornish RP, Heron JE, et al. Multiple imputation using auxiliary imputation variables that only predict missingness can increase bias due to data missing not at random. BMC Med Res Methodol **2024**; 24:231.
16. Wei R, Wang J, Su M, et al. Missing value imputation approach for mass spectrometry-based metabolomics data. Sci Rep **2018**; 8:663.
17. Li S, Park Y, Duraisingham S, et al. Predicting network activity from high throughput metabolomics. PLoS Comput Biol **2013**; 9:e1003123.
18. Sumner LW, Amberg A, Barrett D, et al. Proposed minimum reporting standards for chemical analysis chemical analysis working group (CAWG) metabolomics standards initiative (MSI). Metabolomics **2007**; 3:211–21.
19. Liu KH, Nellis M, Uppal K, et al. Reference standardization for quantification and harmonization of large-scale metabolomics. Anal Chem **2020**; 92:8836–44.
20. Alvarez JA, Yang C-A, Ojuri V, et al. Sex differences in metabolic disorders of aging and obesity in people with HIV. Curr HIV/AIDS Rep **2024**; 22:3.
21. Ascencio-Anastacio AM, Larios-Serrato V, Mata-Marín JA, et al. Metabolomic profile of weight gain of people living with HIV treated with integrase strand transfer inhibitor regimens reveals dysregulated lipid metabolism and mitochondrial dysfunction. Metabolites **2025**; 15:695.
22. Zhao H, Shen J, Djukovic D, et al. Metabolomics-identified metabolites associated with body mass index and prospective weight gain among Mexican American women. Obes Sci Pract **2016**; 2:309–17.
23. Murthy VL, Mosley JD, Perry AS, et al. Metabolic liability for weight gain in early adulthood. Cell Rep Med **2024**; 5: 101548.
24. Ang JC, Sun L, Foo S-YR, et al. Perspectives on whole body and tissue-specific metabolic flexibility and implications in cardiometabolic diseases. Cell Rep Med **2025**; 6:102354.
25. Jung I, Tu-Sekine B, Jin S, et al. Dolutegravir suppresses thermogenesis via disrupting uncoupling protein 1 expression and mitochondrial function in brown/beige adipocytes in preclinical models. J Infect Dis **2022**; 226:1626–36.
26. Gorwood J, Bourgeois C, Pourcher V, et al. The integrase inhibitors dolutegravir and raltegravir exert proadipogenic and profibrotic effects and induce insulin resistance in human/simian adipose tissue and human adipocytes. Clin Infect Dis **2020**; 71:e549–60.
27. Gabbs M, Leng S, Devassy JG, et al. Advances in our understanding of oxylipins derived from dietary PUFAs. Adv Nutr **2015**; 6:513–40.

28. Hildreth K, Kodani SD, Hammock BD, et al. Cytochrome P450-derived linoleic acid metabolites EpOMEs and DiHOMEs: a review of recent studies. J Nutr Biochem **2020**; 86:108484.
29. Wang W, Yang J, Yang H, et al. Effects of high-fat diet on plasma profiles of eicosanoid metabolites in mice. Prostaglandins Other Lipid Mediat **2016**; 127:9–13.
30. Whelan J, Fritsche K. Linoleic acid. Adv Nutr **2013**; 4: 311–2.
31. Khadir A, Kavalakatt S, Madhu D, et al. Soluble epoxide hydrolase 2 expression is elevated in obese humans and decreased by physical activity. Int J Mol Sci **2020**; 21:2056.
32. Lopez-Vicario C, Alcaraz-Quiles J, García-Alonso V, et al. Inhibition of soluble epoxide hydrolase modulates inflammation and autophagy in obese adipose tissue and liver: role for omega-3 epoxides. Proc Natl Acad Sci U S A **2015**; 112:536–41.
33. Radmark O, Werz O, Steinhilber D, et al. 5-Lipoxygenase, a key enzyme for leukotriene biosynthesis in health and disease. Biochim Biophys Acta **2015**; 1851:331–9.
34. Chawengsub Y, Aggarwal NT, Nithipatikom K, et al. Identification of 15-hydroxy-11,12-epoxyeicosatrienoic acid as a vasoactive 15-lipoxygenase metabolite in rabbit aorta. Am J Physiol Heart Circ Physiol **2008**; 294:H1348–56.
35. Martinez-Clemente M, Claria J, Titos E. The 5-lipoxygenase/leukotriene pathway in obesity, insulin resistance, and fatty liver disease. Curr Opin Clin Nutr Metab Care **2011**; 14:347–53.
36. Mothe-Satney I, Filloux C, Amghar H, et al. Adipocytes secrete leukotrienes: contribution to obesity-associated inflammation and insulin resistance in mice. Diabetes **2012**; 61:2311–9.
37. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature **2017**; 542:177–85.
38. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest **2017**; 127:1–4.
39. Blaner WS. Vitamin A signaling and homeostasis in obesity, diabetes, and metabolic disorders. Pharmacol Ther **2019**; 197:153–78.
40. Shea MK, Booth SL, Gundberg CM, et al. Adulthood obesity is positively associated with adipose tissue concentrations of vitamin K and inversely associated with circulating indicators of vitamin K status in men and women. J Nutr **2010**; 140:1029–34.
41. Villa THC, Ruiz-Vivanco G, Porchia LM, et al. Dietary vitamins A and K are inversely associated with visceral adiposity in US adults: NHANES 2011-2018. Nutr Res **2026**; 146:26–39.
42. Abelman RA, Ma Y, Mehta CC, et al. Switch to integrase strand transfer inhibitors during the menopausal transition is associated with accelerated body composition change in women with HIV. Clin Infect Dis **2025**; 80:1125–32.