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Genetic contribution to weight gain after initiation of antiretroviral therapy in treatment naïve patients with HIV

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Background & Aim

- Overweight and obesity are growing problems in PWH, among whom ART initiation is often associated with weight gain [1-7].
- Weight gain after the onset of ART can be partly explained by a return-to-health phenomenon. Other factors associated with higher weight gain include black race, female gender, high viral load, low CD4 count, and use of regimens including INSTI and TAF [8-13].
- To the best of our knowledge, the role of genetic factors in weight gain after ART initiation in naïve PWH has not been analyzed so far.
- Our objective was to study the association of polymorphisms of genes potentially involved in obesity with weight gain in this clinical scenario.

1) Crum-Cianflone N. AIDS Patient Care STDS 2008; 22: 925. 2) Tate T. Antivir Ther 2012; 17: 1281. 3) Lakey W. AIDS Res Hum Retroviruses 2013; 29: 435. 4) Yuh B. Clin Infect Dis 2015; 60: 1852. 5) Achhra AC. HIV Med 2016; 17: 255. 6) Koethe JR. AIDS Res Hum Retroviruses 2016; 32: 50. 7) Bakal DR. J Antimicrob Chemother 2018; 73: 2177. 8) Kumar S. Front Endocrinol (Lausanne) 2018; 9: 705. 9) McCormick CL. Front Immunol 2014; 5: 507. 10) Bhagwat P. Open Forum Infect Dis 2018; 5: ofy201. 11) Venter WDF. N Engl J Med 2019; 381: 803. 12) Group NAS. N Engl J Med 2019; 381: 816. 13) Sax PE. Clin Infect Dis 2020; 71: 1379.14) McCann K. AIDS 2021; 35: 1657.

Design, eligibility criteria, and variables

Study Design

- Retrospective observational study.

Key inclusion criteria

- PWH included in CoRIS, which started ART as of January 1, 2014,
- Weight & height information within the 24 wk before and at 96 (± 24) wk after the beginning of ART
- At least one blood or DNA sample deposited in the CoRIS Biobank.

Variables

- **Outcomes:** The primary outcome was weight change at 96 wk after starting ART. Secondary outcomes: change in BMI and 10% weight gain at 96 wk.
- **Exposure variables:** 14 obesity-related SNPs selected from a meta-analysis of genome-wide association study (GWAS) BMI loci [1].
- **Adjustment variables:** Sex, age, baseline BMI, world region of birth, HIV transmission category, level of education, baseline CD4+ counts & HIV-RNA load, prior AIDS-defining conditions, serological status against HCV & HBV, ART anchor drug, NRTI backbone, and underlying comorbidities.

1. Locke AE. Nature 2015; 518(7538): 197-206.

Obesity-related SNPs genotyped selected from a meta-analysis of GWAS BMI loci in European people*

SNP	Chromosome:Position (GRCh38)	Notable gene(s)	Alleles	P value
rs1558902	16:53,769,662	FTO	A/T	7.51E-153
rs6567160	18:60,161,902	MC4R	C/T	3.93E-53
rs13021737	12:632,348	TMEM18	G/A	1.11E-50
rs10938397	4:45,180,510	GNPDA2; GABRG1	G/A	3.21E-38
rs543874	1:177,920,345	SEC16B	G/A	2.62E-35
rs2207139	6:50,877,777	TFAP2B	G/A	4.13E-29
rs11030104	11:27,662,970	BDAF	A/G	5.56E-28
rs3101336	1:72,285,502	NEGR1	C/T	2.66E-26
rs7138803	12:49,853,685	BCDIN3D; FAIM2 (D)	A/G	8.15E-24
rs3888190	16:28,878,165	ATXN2L; SBK1; SULT1A2; TUFM	A/C	3.14E-23
rs12446632	16:19,924,067	GPRC5B; IQCK	G/A	1.48E-18
rs2112347	5:75719417	POC5; HMGCR; COL4A3BP	T/G	6.19E-17
rs3810291	19:47,065,746	ZC3H4	A/G	4.81E-15
rs12429545	13:53,528,071	OLFM4	A/G	1.09E-12

* Locke AE. Nature 2015; 518: 197-206.

Laboratory methods: Genomic DNA was extracted from peripheral blood with the Qiagen kit (QIAamp DNA Blood Midi / Maxi; Qiagen, Hilden, Germany). DNA genotyping was performed in the Spanish National Genotyping Center (CeGen; http://www.cegen.org/) using the iPLEX® Gold technology and Agena Bioscience's MassARRAY platform (San Diego, CA, USA).

Abbreviations: **SNP**, single nucleotide polymorphism; **HW (*P*)**; *P*-value Hardy-Weinberg equilibrium. ***FTO***, Fat Mass and Obesity Associated; ***MC4R***, Melanocortin 4 Receptor; ***TMEM18***, Transmembrane Protein 18; ***GNPDA2***, Glucosamine-6-Phosphate Deaminase 2; ***GABRG1***, Gamma-Aminobutyric Acid Type A Receptor Subunit Gamma1, ***SEC16B***, SEC16 Homolog B Endoplasmic Reticulum Export Factor; ***TFAP2B***, Transcription Factor AP-2 Beta; ***BDNF***, *Brain Derived Neurotrophic Factor*; ***NEGR1***, Neuronal Growth Regulator 1; ***BCDIN3D***, BCDIN3 Domain Containing RNA Methyltransferase; ***FAIM2***, Fas Apoptotic Inhibitory Molecule 2; ***ATXN2L***, Ataxin-2-like protein; ***SBK1***, SH3 Domain Binding Kinase 1; ***SULT1A2***, Sulfotransferase Family 1A Member 2; ***TUFM***, Elongation Factor Tu, Mitochondrial; ***GPRC5B***, G Protein-Coupled Receptor Class C Group 5 Member B; ***IQCK***, Motif Containing K; ***POC5***, POC5 centriolar protein; ***HMGCR***, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; ***COL4A3BP***, Collagen type IV alpha-3-binding protein; ***ZC3H4***, Zinc Finger CCCH-Type Containing 4; ***OLFM4***, Olfactomedin 4.

Study analysis

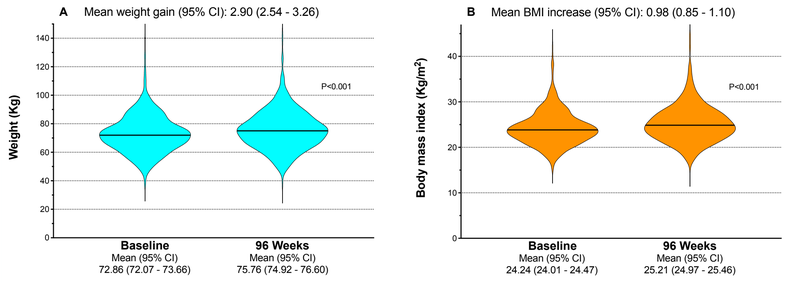
- Identification of baseline characteristics associated with weight gain
  - Multivariable linear regression analysis.
- Genetic association analysis
  - The Hardy-Weinberg equilibrium (HWE) was evaluated by the Chi-square test, considering the equilibrium when *P*>0.05.
  - Adjusted linear or logistic regressions were conducted as appropriate to assess the influence of SNPs on the variables of interest.
    - Different inheritance models (dominant, recessive, and additive) were tested, selecting the model that best fitted the data.
  - Unadjusted and adjusted linear mixed models for longitudinal data were used to account for repeated measures of weight and BMI, with SNPs and time, and their interaction was taken as fixed effects and the patient as a random effect.

Patients characteristics

Characteristic	Total (No.=1,021)
Demographics	
Male Sex – No. (%)	900 (88.15)
Age Median (IQR) – yr.	35.76 (29.59 – 43.23)
BMI at baseline	
< 18.5 (low weight)	41 (4.02)
18.5 – 24.9 (normal weight)	626 (61.31)
25 – 29.9 (overweight)	287 (28.11)
≥ 30 (obesity)	67 (6.56)
HIV transmission mechanism – No. (%)	
Men who have sex with men	728 (71.30)
Heterosexual sex	239 (23.41)
Injection drug use	25 (2.45)
Other/Unknown	29 (2.84)
Level of education – No. (%)	
None/Compulsory	219 (21.45)
Upper secondary/University	611 (59.84)
Other/Unknown	191 (18.71)
Region of birth – No. (%)	
Spain	666 (65.23)
Western Europe	24 (2.35)
Eastern Europe	22 (2.15)
Sub Saharan Africa	30 (2.94)
Northern Africa	14 (1.37)
Latin America	259 (25.37)
Other	5 (0.49)
Unknown	1 (0.10)
HIV data at baseline	
Prior AIDS defining conditions – No. (%)	60 (5.88)
CD4+ cell count Median (IQR), cells/uL	426 (274 – 591)
HIV RNA Median (IQR), copies/mL	45,986 (14,900 – 160,216)

Characteristic	Total (No.=1,021)
Antiretroviral therapy	
Regimen according to anchor drug – No. (%)	
2 NRTI + 1 INSTI	643 (62.98)
2 NRTI + 1 NNRTI	183 (17.92)
2 NRTI + 1 bPI	120 (11.75)
Other regimens	21 (2.06)
Unknown	54 (5.29)
Type of NRTI backbone – No. (%)	
TDF/FTC	452 (44.27)
ABC/3TC	344 (33.69)
TAF/FTC	160 (15.67)
Other	11 (1.08)
Unknown	54 (5.29)
Hepatitis C virus antibodies	
Negative	698 (68.36)
Positive	51 (5.00)
Unknown	272 (26.64)
Hepatitis B surface antigen	
Negative	754 (73.85)
Positive	22 (2.15)
Unknown	245 (24.00)
Comorbid conditions – No./with data (%)	
Arterial hypertension	152 (14.89)
Non-AIDS non-liver related cancer (active)	11 (1.08)
Cardiovascular disease	6 (0.59)
Diabetes mellitus	6 (0.59)
Chronic renal failure	2 (0.20)

Baseline and 96 wk distribution of weight & BMI



Factors associated with weight gain at 96 wks after ART initiation (multivariable linear regression analysis)

	Mean difference weight gain (kg)	95%CI Lower	95% CI Upper	P
Gender				
Male	Ref.			
Female	1.339	0.058	2.620	0.041
Age - years				
<30	Ref.			
30-39	-0.046	-0.886	0.795	0.915
40-49	-0.431	-1.413	0.550	0.388
50-59	0.353	-1.007	1.713	0.610
≥60	-0.164	-2.637	2.308	0.896
BMI at baseline				
< 18.5 (low weight)	0.660	-1.029	2.349	0.443
18.5 – 24.9 (normal weight)	Ref.			
25 – 29.9 (overweight)	0.104	-0.670	0.870	0.792
> 30 (obesity)	-1.692	-3.083	-0.302	0.017
HIV transmission mechanism				
Men who have sex with men	Ref.			
Injection drug use	1.577	-0.940	4.093	0.219
Heterosexual sex	-0.187	-1.214	0.840	0.721
Other/Unknown	-0.143	-2.178	1.892	0.890
Level of education				
None/Compulsory	Ref.			
Upper secondary/University	0.286	-0.575	1.147	0.515
Other/Unknown	0.248	-0.803	1.300	0.643
Region of birth				
Spain	Ref.			
Western Europe	0.222	-2.004	2.448	0.845
Eastern Europe	-0.495	-2.793	1.803	0.673
Sub Saharan Africa	2.684	0.609	4.758	0.011
Northern Africa	-1.007	-3.839	1.824	0.485
Latin America	0.231	-0.564	1.026	0.568
Other	0.649	-4.065	5.363	0.787
Unknown	4.250	-6.732	15.232	0.448
Prior AIDS defining conditions				
No	Ref.			
Yes	4.164	2.586	5.741	<0.001
CD4+ cells/uL				
< 200	Ref.			
200 – 349	-3.593	-4.804	-2.383	<0.001
350 – 499	-3.640	-4.876	-2.404	<0.001
≥ 500	-3.514	-4.703	-2.326	<0.001
Unknown	-0.247	-3.871	3.378	0.894

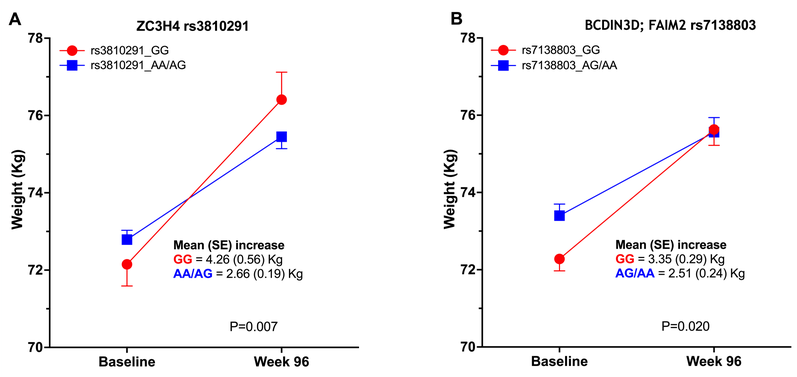
	Mean difference weight gain (kg)	95%CI Lower	95% CI Upper	P
HIV RNA copies/mL				
< 10,000	Ref.			
10,000 – 100,000	0.286	-0.643	1.215	0.546
> 100,000	1.346	0.310	2.382	0.011
Unknown	-1.266	-4.495	1.964	0.442
Hepatitis C virus antibodies				
Negative	Ref.			
Positive	-2.060	-3.828	-0.291	0.023
Unknown	0.414	-0.470	1.298	0.358
Hepatitis B surface antigen				
Negative	Ref.			
Positive	-2.166	-4.460	0.128	0.064
Unknown	-0.736	-1.659	0.186	0.118
ART type of regimen				
2 NRTI + 1 NNRTI	Ref.			
2 NRTI + 1 bPI	-0.131	-1.394	1.131	0.838
2 NRTI + 1 INSTI	0.490	-0.523	1.503	0.343
Other regimens	0.241	-2.984	3.467	0.883
Unknown	0.345	-1.283	1.972	0.678
ART type of NRTI backbone				
TDF/FTC	Ref.			
TAF/FTC	1.076	0.018	2.135	0.046
ABC/3TC	-0.668	-1.538	0.202	0.132
Other	0.470	-3.869	4.810	0.832
Unknown	-			
Comorbid conditions				
Diabetes mellitus				
No	Ref.			
Yes	-2.218	-6.785	2.349	0.341
Arterial hypertension				
No	Ref.			
Yes	-0.485	-1.444	0.473	0.321
Cardiovascular disease				
No	Ref.			
Yes	-1.375	-5.991	3.240	0.559
NANL-related cancer				
No	Ref.			
Yes	-1.521	-4.708	1.667	0.349

Distribution of polymorphisms among the 1,021 PWH for the 14 obesity-related SNPs and their association with weight & BMI changes by unadjusted linear mixed model analysis

					Weight (P-value)				BMI (P-value)	
Gene	SNP	Alleles (%)		HW (P)	Dominant	Recessive	Additive	Dominant	Recessive	Additive
FTO	rs1558902	T (64.8)	A (35.2)	0.063	0.086	0.629	0.221	0.063	0.545	0.174
MC4R	rs6567160	T (83.2)	C (16.8)	0.946	0.946	0.851	0.977	0.928	0.947	0.992
TMEM18	rs13021737	G (84.4)	A (15.7)	0.718	0.875	0.163	0.322	0.943	0.140	0.297
GNPDA2; GABRG1	rs10938397	A (59.4)	G (40.6)	0.253	0.951	0.430	0.694	0.946	0.360	0.639
SEC16B	rs543874	A (81.8)	G (18.2)	0.130	0.262	0.378	0.171	0.270	0.396	0.185
TFAP2B	rs2207139	A (82.0)	G (18.0)	0.005	0.679	0.392	0.506	0.745	0.333	0.475
BDNF	rs11030104	A (80.6)	G (19.4)	0.001	0.264	0.316	0.125	0.224	0.378	0.128
NEGR1	rs3101336	C (64.4)	T (35.6)	0.789	0.398	0.452	0.616	0.357	0.383	0.544
BCDIN3D; FAIM2	rs7138803	G (68.4)	A (31.6)	0.011	0.018	0.125	0.046	0.016	0.146	0.046
ATXN2L; SBK1; SULT1A2; TUFM	rs3888190	C (61.9)	A (38.1)	0.123	0.197	0.242	0.140	0.144	0.227	0.101
GPRC5B; IQCK	rs12446632	G (86.4)	A (13.6)	0.826	0.507	0.475	0.671	0.603	0.556	0.770
POC5; HMGCR; COL4A3BP	rs2112347	T (63.3)	G (36.7)	0.187	0.537	0.310	0.366	0.608	0.261	0.351
ZC3H4	rs3810291	A (61.5)	G (38.5)	0.106	0.103	0.008	0.026	0.109	0.009	0.029
OLFM4	rs12429545	G (84.7)	A (15.3)	<0.001	0.284	0.464	0.519	0.302	0.457	0.536

Abbreviations: **SNP**, single nucleotide polymorphism; **HW (*P*)**; *P*-value Hardy-Weinberg equilibrium. ***FTO***, Fat Mass and Obesity Associated; ***MC4R***, Melanocortin 4 Receptor; ***TMEM18***, Transmembrane Protein 18; ***GNPDA2***, Glucosamine-6-Phosphate Deaminase 2; ***GABRG1***, Gamma-Aminobutyric Acid Type A Receptor Subunit Gamma1, ***SEC16B***, SEC16 Homolog B Endoplasmic Reticulum Export Factor; ***TFAP2B***, Transcription Factor AP-2 Beta; ***BDNF***, *Brain Derived Neurotrophic Factor*; ***NEGR1***, Neuronal Growth Regulator 1; ***BCDIN3D***, BCDIN3 Domain Containing RNA Methyltransferase; ***FAIM2***, Fas Apoptotic Inhibitory Molecule 2; ***ATXN2L***, Ataxin-2-like protein; ***SBK1***, SH3 Domain Binding Kinase 1; ***SULT1A2***, Sulfotransferase Family 1A Member 2; ***TUFM***, Elongation Factor Tu, Mitochondrial; ***GPRC5B***, G Protein-Coupled Receptor Class C Group 5 Member B; ***IQCK***, Motif Containing K; ***POC5***, POC5 centriolar protein; ***HMGCR***, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; ***COL4A3BP***, Collagen type IV alpha-3-binding protein; ***ZC3H4***, Zinc Finger CCCH-Type Containing 4; ***OLFM4***, Olfactomedin 4.

Association of SNPs with weight change at 96 wk by adjusted linear mixed models



Adjusted by age, sex, BMI at baseline, country of birth, prior AIDS-defining conditions, CD4+ cell count, HIV-RNA viral load, type of ART anchor drug, and NRTI backbone

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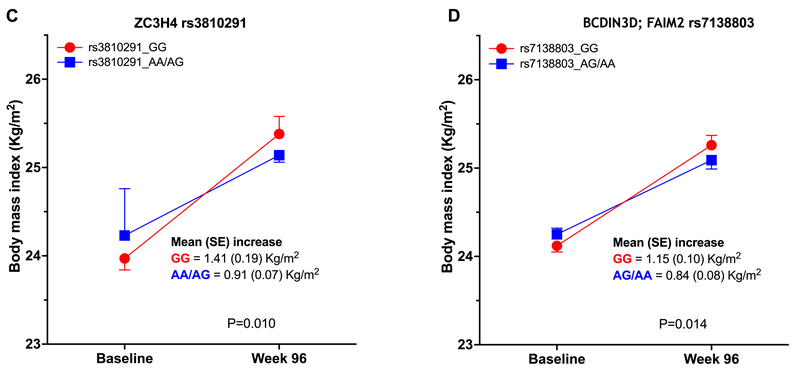
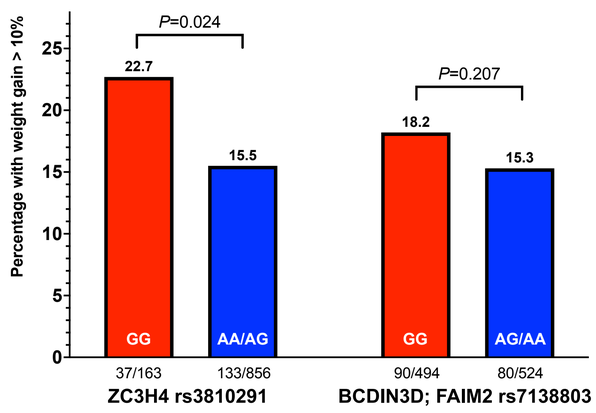


Adjusted by age, sex, BMI at baseline, country of birth, prior AIDS-defining conditions, CD4+ cell count, HIV-RNA viral load, type of ART anchor drug, and NRTI backbone

Frequency of 10% weight gain at 96 wks



Discussion

- *ZC3H4* rs3810291 A allele has been associated with BMI in the general population (1). Variants in/near *ZC3H4* have been found to be positively associated with emotional eating and uncontrolled eating, suggesting that its link to obesity may, in part, be mediated by eating behaviors (2).
- Large-scale GWAS have identified associations between *BCDIN3D*/*FAIM2* rs7138803 with BMI and obesity (1, 3). The underlying mechanisms are poorly understood.
- We used the GTEx (Genotype-Tissue Expression) Portal (4) and we found.
  - rs3810291 polymorphism may contribute to the expression of *SUMO-Activating Enzyme Subunit 1*, a regulatory gene in metabolic homeostasis and obesity (5).
  - An association between rs7138803 A allele with higher expression of *C1QL4/CTRP11* (Complement C1q Like 4/C1q/Tumor Necrosis Factor-related Protein 11) in the thyroid (4). In animal models, *C1QL4/CTRP11* expression has been found to modulate food intake, energy expenditure, and insulin sensitivity (6).

1) Speliotes EK et al. Nat Genet. 2010;42(11):937-48. 2) Cornelis MC et al. Obesity (Silver Spring). 2014;22(5):E135-41. 3) Thorleifsson G et al. Nat Genet. 2009;41(1):18-24. 4) The Genotype-Tissue Expression (GTEx) Project GTExPortal : https://gtexportal.org/home/. 5) Kamynina E et al. Adv Exp Med Biol. 2017;963:143-68. 6) Sarver DC, et al. FASEB J. 2022;36(6):e22347.

Conclusions

- Our findings suggest that genetic factors play a role in weight gain after ART initiation.
- Further work is needed to understand how the polymorphisms in/near *ZC3H4* and *BCDIN3D/FAIM2* lead to higher weight gain in this clinical context.

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