Impact of Genetic and Nongenetic Factors on Body Mass Index and Waist-Hip Ratio Change in HIV-Infected Individuals Initiating Antiretroviral Therapy

Catalina Barceló,[1] Monia Guidi,[1,2] Christian W. Thorball,[3,4] Christian Hammer,[5,6] Aziz Chaouch,[2] Alexandra U. Scherrer,[7] Barbara Hasse,[8] Matthias Cavassini,[9] Hansjakob Furrer,[10] Alexandra Calmy,[11] Sebastian Haubitz,[12] Enos Bernasconi,[13] Thierry Buclin,[2] Jacques Fellay,[3,4,14] Philip E. Tarr,[15,a] Chantal Csajka[1,16,a,] , and the Swiss HIV Cohort Study

[1]Center for Research and Innovation in Clinical Pharmaceutical Sciences, Institute of Pharmaceutical Sciences of Western Switzerland, University of Lausanne, Lausanne, Switzerland, [2]Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Switzerland, [3]School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [4]Swiss Institute of Bioinformatics, Lausanne, Switzerland, [5]Department of Cancer Immunology, Genentech, South San Francisco, CA, USA, [6]Department of Human Genetics, Genentech, South San Francisco, CA, USA, [7]Institute of Medical Virology, University of Zurich, Zurich, Switzerland, [8]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Switzerland, [9]Service of Infectious Diseases, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [10]Department of Infectious Diseases, Bern University Hospital, University of Bern, Switzerland, [11]Division of Infectious Diseases, HIV/AIDS Unit, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland, [12]Department of Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Switzerland, [13]Division of Infectious Diseases, Regional Hospital, Lugano, Switzerland, [14]Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [15]University Department of Medicine, Infectious Diseases Service, Kantonsspital Baselland, University of Basel, Switzerland, and [16]School of Pharmaceutical Sciences, Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, Geneva, Switzerland

Objective. There is limited data on abdominal obesity and the influence of genetics on weight change after antiretroviral therapy (ART) initiation. We assessed body mass index (BMI) and waist hip ration (WHR) change over time in the Swiss HIV Cohort study (SHCS).

Methods. Mixed-effects models characterizing BMI and WHR change over time in 1090 SHCS participants initiating ART between 2005 and 2015 were developed and used to quantify the influence of demographics, clinical factors, and genetic background.

Results. Individuals with CD4 nadir <100 cells/μL gained 6.4 times more BMI than individuals with ≥200, and 2.8 times more WHR than individuals with ≥100 ($P < .001$) during the first 1.5 and 2.5 years after ART initiation, respectively. The risk of being overweight or obese after 1.5 years increased with CD4 nadir <100 cells/μL compared to 100–199 (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.63–2.74) and ≥200 (OR, 1.69; 95% CI, 1.26–2.32), persisting after 10 years of ART. The risk of abdominal obesity after 2.5 years increased with CD4 nadir <100 compared to ≥100 (OR, 1.35; 95% CI, 1.17–1.54 [in men]; OR, 1.36; 95% CI, 1.18–1.57 [in women]), persisting after 10 years of ART. No significant differences were found across antiretroviral drug classes or genetic scores.

Conclusions. The risk of general and abdominal obesity increased with CD4 nadir <100 cells/μL. Based on our results, including the genetic background would not improve obesity predictions in HIV-infected individuals.

Key words: abdominal obesity; antiretroviral therapy; body mass index; genetics; nadir CD4 cell count; obesity; waist-hip ratio.

INTRODUCTION

Antiretroviral therapy (ART) has dramatically decreased the incidence of AIDS and HIV-related mortality. However, with the increase in life expectancy for people living with HIV, aging-related complications (such as cardiovascular (CV) disease, liver disease, renal function decline, and certain cancers) have emerged as important causes of morbidity and mortality in HIV [1–3]. Cardiovascular disease remains the second most

common cause of death in the HIV-infected population after malignancies, which has placed care and treatment of CV risk factors, such as obesity, among the primary concerns of current HIV management [4–7].

General [8–10] and abdominal obesity have been steadily increasing in HIV-infected populations over the last decade, and weight gain frequently follows ART initiation [11–13]. Early weight gain during ART has been associated with a higher CV risk [13–15]. Certain ART combinations have been associated with a higher CV risk, perturbations in glucose and lipid metabolism, and metabolic syndrome [16–19]. There is emerging evidence of an association between weight gain and current widely used antiretroviral drugs, such as integrase strand transfer inhibitors (INSTI) and tenofovir alafenamide (TAF) [20–24]. Despite the fact that a genetic basis of general and abdominal obesity is well established, limited information is available in HIV-infected populations [25, 26]. Our hypothesis is that the

genetic determinants of general and abdominal obesity identified in the HIV-negative general population would have a similar impact on the HIV-infected population.

In this study, we selected body mass index (BMI) and waist-hip ratio (WHR) as anthropometric indicators of general and abdominal obesity, respectively. First, we describe obesity trends and concurrent demographic changes in the Swiss HIV Cohort Study (SHCS). Then, we use mixed-effects statistical modelling to describe BMI and WHR changes over time in SHCS participants initiating ART and quantify the relative contribution of clinical, HIV-related, and genetic factors. The assessment of these anthropometric indicators over time and a better understanding of its relationship with traditional and HIV-related risk factors could help identify individuals that could benefit from early interventions to reduce CV risk.

METHODS

Study Population and Longitudinal Data

Participants were enrolled in the SHCS (www.shcs.ch). For the descriptive longitudinal analysis, we included all SHCS participants with ≥1 available measures of BMI (1990–2017) and WHR (2000–2017). For the mixed-effects longitudinal analyses of BMI and WHR gain, we included a subset of SHCS participants that initiated ART between January 1, 2005, and December 31, 2015, with ≥1 BMI and WHR measurement close to ART initiation date (defined as baseline, maximum 18 months before ART initiation) and at least another measurement after January 1, 2011, to ensure the inclusion of contemporary ART regimens. Demographic, clinical, and pharmacological characteristics were extracted from the SHCS database. Local ethics committees approved the study and all participants provided written informed consent for genetic testing.

Body Composition Measures

Body mass index was determined by dividing body weight (kg) by height squared (m^2). Waist-hip ratio was determined by dividing waist circumference (cm) by hip circumference (cm). Individuals were classified according to the World Health Organization (WHO) cut-offs for overweight (BMI ≥ 25 kg/m^2) and abdominal obesity (WHR > 0.9 for men and >0.85 for women) [27, 28].

Descriptive Longitudinal Analysis

At each SHCS semiannual visit, participants undergo a physical examination and provide biological specimens and standardized information on demographics, HIV characteristics, and current ART. Whole body dual-energy X-ray absorptiometry or single slice abdominal computer tomography scans are not routinely performed in the SHCS. Lipodystrophy is assessed clinically at each SHCS semiannual visit based on physician and patient agreement on significant fat loss and/or fat accumulation on physical examination, in any of the following regions:

face, arms, legs, buttocks, abdomen, breasts, and neck. The median BMI and WHR and the percentage of SHCS participants in each obesity category were used to summarize the distribution of BMI (1990–2017) and WHR (2000–2017) following the WHO classification [27, 28].

BMI and WHR Change Models

Piecewise linear mixed-effects models were developed to describe BMI and WHR change over time using natural log-transformed BMI and WHR data (NONMEM v7.4.0, ICON development Solutions, Ellicott City, MD). This approach allows the estimation of average population parameters, between and within-subject variability, and influence of demographic, clinical, pharmacological, and genetic factors.

The parameters estimated by the models were BMI and WHR baseline, corresponding to the BMI or WHR value at ART initiation, and BMI and WHR change per year at different time intervals after ART initiation. Random effects were integrated to describe between and within subject variability of all parameters. Correlations between random effects were included when identifiable and favorable for the model fit.

Model selection was based on diagnostic plots, parameters estimates precision, and log-likelihood ratio test (reduction of the objective function value [OFV] provided by NONMEM). Significant thresholds were fixed at $P < .05$ and $P < .005$ for the stepwise forward inclusion and backwards deletion covariate selection, respectively (ΔOFV between any 2 nested models approximates a χ^2 distribution). Model development, documentation, and evaluation was aided by Perl-speaks-NONMEM (PsN; https://uupharmacometrics.github.io/PsN/) toolkit (version 4.2) and Pirana (Certara, Princeton, NJ, USA) v2.9.2. R v3.3.1 (Rstudio v.1.1.423; Integrated Development for R. RStudio, Inc., Boston, MA, USA) was used for data management, statistical analysis, and graphical output (see Supplementary Data).

Demographic, Clinical, and Pharmacological Factors

We tested the influence of age, gender, self-reported ethnicity, nadir CD4 cell count categories (<100, 100–199 and ≥200 cells/μL), smoking status (current, never, past), intravenous drug use (IDU) as assumed transmission mode, diabetes mellitus, and hepatitis C coinfection on BMI and WHR baseline and change per year. Given the correlation between BMI and WHR, the latter was tested in the BMI model and vice versa. Missing data in continuous covariates were imputed to the population median value, whereas missing data in categorical covariates were first coded as an additional category and then regrouped according to parameter estimates. The impact of antiretroviral drug classes on BMI and WHR gain was studied in patients that maintained the same ART regimen over the time intervals defined by the models.

Genetic Factors

Samples of DNA obtained from peripheral blood mononuclear cells were genotyped with the Infinium CoreExome-24 BeadChip

(Illumina, San Diego, CA) or obtained in the context of previous Genome-wide Association Studies (GWAS) in the SHCS on various platforms, including the HumanCore-12, HumanHap550, Human610, Human1M, and HumanOmniExpress-24 BeadChips (Illumina, San Diego, CA). Each cohort was filtered and imputed separately, with variants first flipped to the correct strand with BCFTOOLS (http://samtools.github.io/bcftools/bcftools.html) (v1.8) according to the human GRCh37 reference genome and filtered based on a <20% deviation from the 1000 genomes phase 3 EUR reference panel. Genotypes were phased with EAGLE2 and missing genotypes were imputed with PBWT; both processes used the 1000 Genomes Project Phase 3 reference panel on the Sanger Imputation Service [29–31]. Imputed variants were filtered by minor allele frequency (>1%), missingness (<10%), deviation from Hardy-Weinberg equilibrium ($P < 1e^{-6}$), and an imputation quality score (INFO>0.8). The filtered genotypes then were combined using PLINK (v1.90b5) prior to analyses [31].

For the present study, we retrieved genetic information for 90 and 46 statistically independent ($r^2 < 0.2$) single nucleotide polymorphisms (SNPs) significantly associated with higher BMI and WHR, respectively, according to recent GWAS meta-analyses conducted in the general population (Supplementary Tables 4 and 5) [32, 33]. Based on these SNPs, we calculated both an additive genetic risk score (GRS) by summing the number of risk alleles (0, 1, 2) carried by the individual for each SNP, and a weighted genetic risk score by summing the product of the number of risk alleles corrected by the effect size of the SNP as reported in the reference papers [32, 33]. Study participants were divided in 4 genetic risk score quartiles (most favorable genetic background = 1st quartile; most unfavorable = 4th quartile). The influence of genetic risk scores was tested in the subpopulation of Caucasian participants as a continuous and as a categorical covariate, using genetic score quartiles.

Model-Based Predictions of BMI and WHR Over Time

Final models including relevant variables influencing BMI and WHR gain over time were validated using standard techniques (ie, nonparametric bootstrap, goodness of fit plots, and prediction-corrected visual predictive check). Model parameter estimates (coefficients and covariates effects) obtained by bootstrapping final models (resampling n = 2000) were used to predict BMI and WHR values over a 10-year period for 10 000 individuals after ART initiation and to estimate the risk of preobesity and abdominal obesity at different time points.

RESULTS

Descriptive Longitudinal BMI and WHR Trends (1990–2017)

Obesity categories and median BMI and WHR trends in the entire SHCS population stratified by calendar year are shown in Figure 1A and 1B. From 1990 to 2017, median BMI and the percentage of overweight and obese participants increas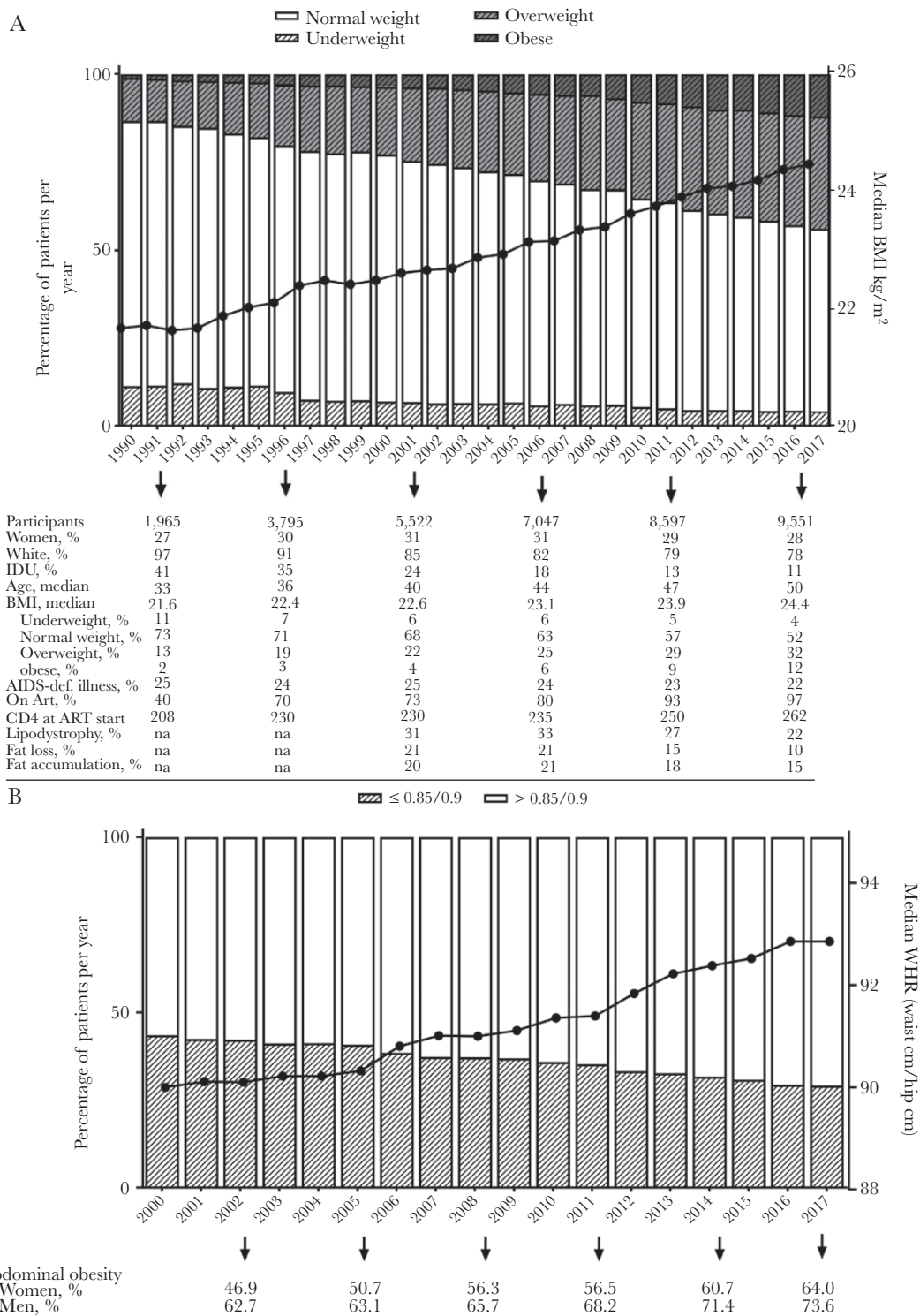ed. From 2000 to 2017, median WHR and the percentage of male and female participants with abdominal obesity increased. In 2017, median BMI was 24.4 kg/m^2 (interquartile range [IQR], 22.0–27.4), median WHR was 92.9 (IQR, 87.6–98.0), and 52% of the population were normal weight, 4% were underweight, 32% were overweight, 12% were obese, and 71% had abdominal obesity. From 1990 to 2017, the percentage of Caucasian participants, IDUs, and participants with AIDS-defining illnesses decreased. The percentage of women, participants on ART, the median CD4 cell count at ART initiation, and the median age of participants increased.

BMI Change Model

One thousand and ninety participants fulfilled the criteria for longitudinal BMI analysis. Median follow-up was 8.2 years (range, 2.6 to 12 years) (Table 1 and Supplementary Table 1). Gain over time for BMI was best described using time intervals, each defining different rates of BMI change per year ($P < .001$, compared to models with 1–2 intervals). The first interval covered the period from ART initiation to 1.5 years of ART and showed a median yearly BMI gain of 0.25 (95% confidence interval [CI], 0.18–0.33) kg/m^2. The second interval covered the period from 1.5 to 3 years of ART and showed a yearly median BMI gain of 0.17 (95% CI, 0.11–0.23) kg/m^2. The third interval covered the period from 3 years of ART until last follow-up and showed a median yearly BMI gain of 0.09 (95% CI, 0.06–0.11) kg/m^2 (Table 2).

Age, WHR, never or past smoking, African ethnicity, and diabetes mellitus were associated with higher baseline BMI. Asian ethnicity and nadir CD4 cell count <200 cells/μL were associated with lower baseline BMI (Table 2). Nadir CD4 cell count was the only covariate showing a significant effect on yearly BMI change after ART initiation. Between initiation and 1.5 years of ART, individuals with nadir CD4 cell count <100 cells/μL and with 100–199 cells/μL gained 6.4 times (95% CI, 4.2–8.5; $P < .001$) and 2.1 times (95% CI, 1.8–2.9; $P < .001$) more BMI per year, respectively, than individuals with nadir CD4 cell count ≥200 cells/μL.

No antiretroviral drug class showed a significant influence on yearly BMI change in the 2 time periods tested (0–1.5 years n = 908 and 1.5–3 years n = 705; $P > .05$; Supplementary Tables 1 and 6). Further analyses on individual drugs thus were not undertaken. Regarding the genetic risk tested in 863 Caucasian participants, the strongest association in univariate analyses was found between the additive genetic risk score (aGRS) and BMI change after 3 years of ART. In univariable analysis, yearly BMI gain was 6.7% higher (95% CI, 1–13%; $P < .05$) with each additional unit of aGRS compared to the median population value (median aGRS = 86). A weaker association was observed with aGRS quartiles and with weighted genetic risk scores (wGRS) in continuous or quartile forms. The impact of the genetic risk was not retained after adjustment for multiple covariates. No effect of genetic risk was found on other model parameters (Supplementary Table 6). Model development steps and validation assessments can be found in the Supplementary Data.

Figure 1. Descriptive Longitudinal Trends for All Swiss HIV Cohort Study Participants. A, descriptive longitudinal BMI trends for all Swiss HIV Cohort Study participants (SHCS), 1990–2017. Obesity classification according to the World Health Organizaiton: underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25–29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Lipodystrophy reflects significant fat loss and/or fat accumulation in face, arms, legs, buttocks, abdomen, breasts, or neck, which was clinically assessed by physician with patient agreement and confirmed over a ≥6-month interval. B, Descriptive longitudinal WHR trends for all SHCS participants, 2000–2017. Longitudinal trends of population abdominal obesity categories and median WHR trajectory, entire Swiss HIV Cohort Study population, 2000–2017. The proportion of SHCS participants with normal WHR (shaded areas) steadily decreased, while the proportion with abdominal obesity (weight areas) increased, among both men and women. Abdominal obesity classification according to the World Health Organization: WHR >0.9 for men and >0.85 for women. Confidence intervals are omitted for visual clarity. AIDS indicates acquired immune deficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; IDU, injection drug user; WHR, waist-hip ratio.

Table 1. Characteristics at Time of Antiretroviral Therapy Initiation of Subpopulation Included the Body Mass Index and Waist-Hip Ratio Models

Characteristics	BMI Change Model (n = 1090)	WHR Change Model (n = 1000)
Sex (male), n (%)	868 (80)	798 (80)
Age (years), median (range)	40 (19–76)	40 (19–75)
BMI (kg/m^2), median (range)	23.3 (14.9–63.4)	23.2 (14.9–63.4)
Underweight, n (%)	56 (5)	50 (5)
Normal weight, n (%)	687 (63)	637 (64)
Overweight, n (%)	282 (26)	255 (25)
Obesity, n (%)[a]	65 (6)	58 (6)
WHR, median (range)	0.89 (0.56–1.13)	0.89 (0.56–1.45)
Missing data, n (%)	90 (8)	
Men >0.9, n (%)	458 (58)	432 (54)
Women >0.85, n (%)	90 (43)	87 (43)
Ethnicity		
Caucasian, n (%)	934 (86)	857 (86)
African	88 (8)	82 (8)
Hispanic, n (%)	36 (3)	31 (3)
Asian, n (%)	32 (3)	30 (3)
Nadir CD4 cell count		
≤99, n (%)	109 (10)	106 (10)
100–199, n (%)	211 (19)	207 (21)
≥200, n (%)	770 (71)	687 (69)
History of AIDS-defining event, n (%)	114 (10)	109 (11)
Injection drug use, n (%)	80 (7)	71 (7)
Hepatitis C coinfection, n (%)	153 (14)	143 (14)
Diabetes mellitus, n (%)	38 (4)	34 (3)
Smoking status		
Current, n (%)	592 (54)	543 (54)
Never, n (%)	447 (41)	416 (42)
Past, n (%)	51 (5)	41 (4)

Abbreviations: BMI, body mass index; WHR, wasit-hip ratio.

[a]Obesity classification according to the World Health Organization: underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25–29.9 kg/m^2), and obesity (BMI ≥ 30 kg/m^2).

WHR Change Model

One thousand participants fulfilled the criteria for longitudinal WHR analysis. Median follow-up was 8.2 years (range 4 to 12 years) (Table 1 and Supplementary Table 1). In line with BMI, WHR gain over time was best described using 3 time intervals, each with different rates of WHR change per year ($P < .001$, compared to models with 1–2 intervals). The first interval covered the period from ART initiation to 2.5 years of ART and showed a median WHR gain of 0.0039 (95% CI, 0.002–0.005) units per year. The second interval covered from 2.5 to 4 years of ART and showed a median WHR gain of 0.0038 (95% CI, 0.002–0.006) units per year. The third interval covered from 4 years of ART until last follow-up and showed a median WHR gain of 0.0029 (95% CI, 0.002–0.004) units per year (Table 2).

Male gender, age, and BMI at baseline were associated with higher baseline WHR. Nadir CD4 cell count was the covariate showing the largest effect on yearly WHR change after ART initiation. Between initiation and 2.5 years of ART, individuals with nadir CD4 cell count <100 cells/μL gained 2.8 times (95% CI, 1.6 –3.9; $P < .001$) more WHR per year than individuals with nadir CD4 cell count ≥100 cells/μL. Between 4 years of ART until end of follow up, African and Hispanic individuals gained 2 times (95% CI, 1.1–2.9; $P < .005$) more WHR per year than other ethnicities.

During the first 2.5 years of ART, individuals with protease inhibitor-based regimens showed less WHR gain per year than other regimens (-58% 95% CI, -109–-8%; $P < .05$) in univariable analysis, but this effect was not significant in multivariate analyses. No antiretroviral drug class showed a significant influence on WHR change at other time intervals. Further analyses of individual drugs thus were not undertaken. No statistically significant association was found between WHR model parameters and genetic risk scores tested in 575 Caucasian participants, neither in continuous ($P > .24$) nor categorical form ($P > .13$) (Supplementary Table 7). Model development steps and validation assessments can be found in the Supplementary Data.

BMI Predictions Over Time

Predictions of BMI at baseline and 1.5, 3, and 10 years after ART initiation are shown in Table 3 and Figure 2. After 1.5 years of ART, individuals with a nadir CD4 cell count <100 cells/μL had a higher risk of being overweight or obese than individuals with a nadir CD4

Table 2. Final Body Mass Index and Waist-Hip Ratio Model Estimates

BMI Model	Estimate (RSE %)	Between-Subject Variability (CV%)
Baseline BMI (kg/m^2)[a]	23.3 (1)	14 (6)
BMI change per year (kg/m^2/y)		
from 0 to 1.5y after ART start	0.25 (14)	344 (12)
from 1.5 to 3y after ART start	0.17 (18)	465 (11)
>3y after ART start	0.09 (14)	388 (10)
Covariate effects on baseline BMI (%)[b]		
70 years old vs 40 years old	+6 (24)	
WHR 1 vs 0.80	+3 (16)	
Past or never smoking	+3 (27)	
Diabetes mellitus	+17 (25)	
African ethnicity	+7 (30)	
Asian ethnicity	-9 (25)	
CD4$_{Nadir}$ < 200 cells/μL vs CD4$_{Nadir}$ ≥ 200 cells/μL	-4 (26)	
Covariate effects on BMI change per year from 0 to 1.5 years (%)[b]		
CD4$_{Nadir}$ < 100 cells/μL vs CD4$_{Nadir}$ ≥ 200 cells/μL	+540 (21)	
CD4$_{Nadir}$ 100-199 cells/μL vs CD4$_{Nadir}$ ≥ 200 cells/μL	+110 (42)	
WHR Model	**Estimate (RSE %)**	**Between-Subject Variability (CV%)**
Baseline WHR [a]	0.84 (0.4)	5.5 (5)
WHR change per year (units/y)		
From 0 to 2.5y after ART start	0.0039 (19)	396 (6)
From 2.5 to 4y after ART start	0.0038 (28)	629 (9)
>4y after ART start	0.0029 (14)	269 (7)
Covariate effects on baseline WHR (%)[b]		
70 years old vs 40 years old	+7 (8)	
BMI 30 vs 25	+3 (7)	
Male gender	+8 (6)	
Covariate effects on WHR change per year from 0 to 2.5 years (%)[b]		
CD4$_{Nadir}$ < 100 cells/μL compared to CD4$_{Nadir}$ ≥ 100 cells/μL	+180 (33)	
Covariate effects on WHR change per year >4 years (%)[b]		
African or Hispanic ethnicity	+100 (46)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; RSE, relative standard error defined as standard error/estimate; WHR, waist-hip ratio.

[a]Baselines of BMI and WHR correspond to the estimated BMI or WHR value at ART initiation.

[b]Relative effects of covariates are expressed as a percentage compared to the reference.

cell count of 100–199 cells/μL (OR = 2.07; 95% CI, 1.63–2.74) or of ≥200 cells/μL (OR = 1.69; 95% CI, 1.26–2.32). After 10 years of ART, the risk of being overweight or obese remained significantly higher in these individuals compared to individuals with a nadir CD4 cell count of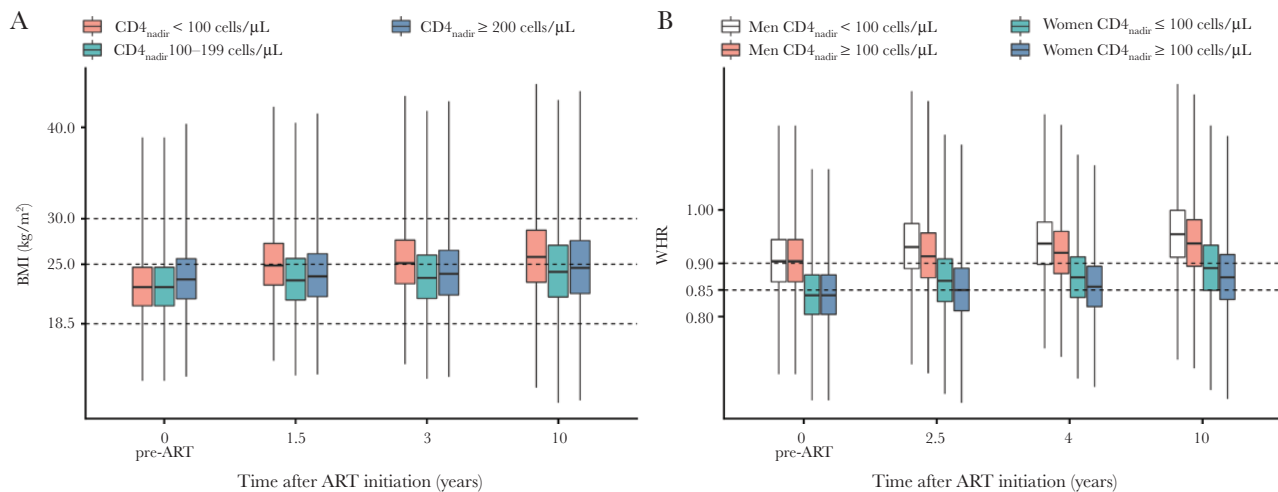 100–199 cells/μL (OR = 1.85; 95% CI, 1.52–2.32) or of ≥200 cells/μL (OR = 1.55; 95% CI, 1.23–2.02). The risk of being overweight or obese was not significantly different between individuals with a nadir CD4 cell count of 100–199 cells/μL and ≥200 cells/μL after 1.5 years (OR = 0.81; 95% CI 0.65–1.00) or 10 years of ART (OR = 0.84; 95% CI, 0.7–1.00).

Table 3. Model-Based Body Mass Index Change Predictions[a]

	Time After ART Initiation (Years)		
BMI Predictions	**1.5**	**3**	**10**
BMI change from ART initiation (kg/m^2)			
CD4$_{Nadir}$ ≥ 200 cells/μL	+0.3 (-0.2, +0.7)	+0.6 (-0.4, +1.4)	+1.3 (-1.3, +3.1)
CD4$_{Nadir}$ 100–199 cells/μL	+0.8 (+0.2, +1.1)	+1.0 (-0.05, +1.8)	+2.2 (-0.9, +3.6)
CD4$_{Nadir}$ < 100 cells/μL	+2.4 (+1.8, +2.8)	+2.7 (+1.5, +3.5)	+3.3 (+0.7, +5.3)
Body weight change from ART initiation (kg, in a typical individual of 1.7 m height)			
CD4$_{Nadir}$ ≥ 200 cells/μL	+1.0 (-0.7, +2.0)	+1.8 (-1.2, +3.9)	+3.7 (-3.7, +9.1)
CD4$_{Nadir}$ 100–199 cells/μL	+2.2 (+0.4, +3.3)	+2.9 (-0.1, +5.2)	+6.4 (-2.7, +10.4)
CD4$_{Nadir}$ < 100 cells/μL	+6.9 (+5.1, +8.1)	+7.7 (+4.5, +10.0)	+9.6 (+2.0, +15.2)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index.

[a]All results are predictive median (95% prediction interval).

Figure 2. Predicted Body Mass Index and Waist-Hip Ratio Values by CD4 nadir Categories at Baseline and Several Years After Antiretroviral Therapy Initiation. ART indicates antiretroviral therapy; BMI, body mass index; WHR, waist-hip ratio.

WHR Predictions Over Time

Predictions of WHR at baseline and 2.5, 4, and 10 years after ART initiation are shown in Figure 2. After 2.5 years of ART, individuals with a nadir CD4 cell count <100 cells/μL had a higher risk of abdominal obesity than individuals with a nadir CD4 cell count ≥100 cells/μL (OR = 1.35; 95% CI, 1.17–1.54 [for men]; OR = 1.36; 95% CI, 1.18–1.57 [for women]). After 10 years of ART, the risk of abdominal obesity remained significantly higher in these individuals compared to individuals with a nadir CD4 cell count of ≥100 cells/μ group (OR = 1.58; 95% CI, 1.28–2.02 [for men]; OR = 1.59; 95% CI, 1.29–2.03 [for women]).

DISCUSSION

Previously, CD4 nadir has been recorded as predictor of weight gain after ART start by us [8] and others [11, 13, 34, 35]. In line with recent studies, our results show that a low nadir CD4 count is a significant risk factor for developing general and abdominal obesity [36, 37]. The approximately 2-fold increased risk of overweight and general obesity and almost 60% increased risk of abdominal obesity associated with CD4 nadir<100 cells/μL was first noted at 1.5 years of ART but persisted at 10 years of ART.

The previously described notion that low CD4 nadir is associated with recovery of weight lost during chronic untreated HIV infection should be extended to include low CD4 nadir as an important risk factor for long term general and abdominal obesity risk, likely in the setting of immunometabolic disturbances [6, 38–40]. Particularly in those with low CD4 nadir, body weight and abdominal fat accumulation after ART initiation may go beyond normal body weight and fat recovery [14]. Our data provide an additional justification for current guidelines recommending early ART initiation beyond well-recorded

benefits in terms of prevention of immunodeficiency, opportunistic complications, and non-AIDS events [41].

We also reveal differences between early and long-term BMI and WHR changes after ART initiation and factors of potential clinical relevance. Consistent with previous data [8, 11, 13], the BMI and WHR models revealed an average continuous gain over the study period, more important during the early years after ART initiation. Despite limited average BMI and WHR increases per year (0.3% to 1.1%, respectively), both our models predicted a substantial increase in general and abdominal obesity after 10 years of ART [10, 42, 43]. To our knowledge, this is the most comprehensive longitudinal assessment of BMI and WHR in a HIV-positive population, showing a stabilization after about 3 and 4 years, respectively, that resembles BMI and WHR changes over time in the general population [11, 44].

Finally, we extend our previous descriptive assessment [8] of the demographic transformation (ie, aging population, fewer IDU, earlier ART start, more complete ART coverage of population) that accompanied the increasing prevalence of obesity in the SHCS population 1990–2012 to the time period 2013–2017. Increasing obesity rates in other HIV cohorts have been described previously [8, 39]. Slightly over 50% of the SHCS population remains normal weight in 2017, similarly to the general population in Switzerland with 42% of overweight or obese [45]. Interestingly, increasing prevalence of abdominal obesity in the SHCS in recent years seems to coincide with a decrease in lipodystrophy prevalence during the same time period, suggesting that our clinical lipodystrophy assessments (physician and patient agreement on abnormal fat loss/fat accumulation, confirmed over a ≥6-month interval) are valid and do not simply capture increasing general and abdominal obesity trends in the SHCS over time.

Traditional risk factors like age, gender, smoking habit, diabetes mellitus, and ethnicity showed a considerable impact on general and abdominal obesity prevalence in this population of HIV patients [46]. These results emphasize the evolution of SHCS participants towards an older population at higher cardiovascular risk.

In line with previous studies, we did not find any impact nor differences among antiretroviral drug classes on BMI and WHR changes, suggesting the necessity to monitor changes in body weight and abdominal fat with all currently recommended ART regimens [12, 47, 48]. The large between-subject variability in BMI and WHR changes over time and the reduced number of participants with the same ART regimen over the first 3 and 4 years, respectively, might have masked this effect. In contrast with some past ART regimens that were frequently associated with marked fat redistribution [49], modern ART regimens usually have a more favorable metabolic profile. However, recent studies have identified an association between INSTI-based regimens and significant increases in body weight, particularly in women and black individuals [23]. In addition, these effects seem to be more pronounced with the use of TAF [23, 24]. Additional studies are needed to clarify the clinical relevance of this association. Due to the observation period covered in our study, we had limited power to detect any influence of integrase inhibitor-based regimens or tenofovir alafenamide on BMI or WHR changes (dolutegravir and tenofovir alafenamide were approved for clinical use in Switzerland in 2015 and 2016, respectively).

Ours represents the largest genetic-obesity study undertaken in HIV-positive persons. However, Swiss HIV-positive persons with an unfavorable genetic predisposition showed only a trend towards a greater BMI increase after 3 years of ART. Accounting for CD4 nadir large effect should allow for other potentially significant effects to be revealed in the multivariate analysis, such as a genetic predisposition effect, if any. This suggests a moderate to small effect of the genetic background on BMI and WHR gain, which is accordance with the literature from the general population [32, 33, 50]. The power to detect any impact of the calculated GRS might have been reduced by constraining our genetic analysis to the Caucasians in our study population ($n_{BMImodel}$ = 863 and $n_{WHRmodel}$ = 575, Supplementary Table 1). Additionally, a modest genetic heterogeneity in our study population (median (range) $aGRS_{BMImodel}$ = 86 (67–103); $wGRS_{BMImodel}$ = 0.013 (0.010–0.016); $aGRS_{WHRmodel}$ = 46 (35–56); $wGRS_{WHRmodel}$ = 0.013 (0.010–0.017); Supplementary Table 1) might have contributed to the lack of significant genetic effect. A recently published meta-analysis of GWAS for body fat distribution in individuals of European ancestry also showed that heritability and variant effects were generally stronger in women than men [51]. Only 20% of our study population were women (Table 1). It also is possible that any genetic effect was masked by other more important factors associated with BMI

and WHR increase. Limitations of our analysis include lack of information on diet, alcohol consumption, physical activity, inflammatory state of participants, and ultimately a comparison with a Swiss HIV-negative cohort.

The present models identified the critical period of 1.5 and 2.5 years after ART initiation where HIV-infected individuals are more prone to increase their BMI and WHR, respectively. These findings support the need to inform individuals starting ART about the likely early-on body composition changes despite the benefits of starting ART that vastly outweigh this risk. Regular monitoring and implementation of early weight management interventions to address body weight and fat gain are to be encouraged, especially in individuals initiating ART with a low nadir CD4 cell count [7, 15, 19, 52, 53]. The present BMI and WHR models also can be applied to test the efficacy of such interventions, either pharmacological or lifestyle modifications, at different time points after ART initiation and further developed into joint models to predict incidence of CV events in the HIV-infected population.

H. Furrer, C.A. Fux, H.F. Günthard (President of the SHCS), D. Haerry (deputy of "Positive Council"), B. Hasse, H.H. Hirsch, M. Hoffmann, I. Hösli, M. Huber, C.R. Kahlert (Chairman of the Mother & Child Substudy), L. Kaiser, O. Keiser, T. Klimkait, R.D. Kouyos, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, C. Marzolini, K.J. Metzner, N. Müller, D. Nicca, P. Paioni, G. Pantaleo, M. Perreau, A. Rauch (Chairman of the Scientific Board), C. Rudin, A.U. Scherrer (Head of Data Centre), P. Schmid, R. Speck, M. Stöckle (Chairman of the Clinical and Laboratory Committee), P. Tarr, A. Trkola, P. Vernazza, G. Wandeler, R. Weber, S. Yerly.

References

1. Rasmussen LD, May MT, Kronborg G, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. Lancet HIV 2015; 2:e288–98.

2. Wong C, Gange SJ, Moore RD, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Multimorbidity among persons living with Human Immunodeficiency Virus in the United States. Clin Infect Dis 2018; 66:1230–8.

3. Feinstein MJ, Bahiru E, Achenbach C, et al. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. Am J Cardiol 2016; 117:214–20.

4. Hanna DB, Jung M, Xue X, et al. Trends in nonlipid cardiovascular disease risk factor management in the women's interagency HIV study and association with adherence to antiretroviral therapy. AIDS Patient Care STDS 2016; 30:445–54.

5. van Zoest RA, van der Valk M, Wit FW, et al; AGEhIV Cohort Study Group. Suboptimal primary and secondary cardiovascular disease prevention in HIV-positive individuals on antiretroviral therapy. Eur J Prev Cardiol 2017; 24:1297–307.

6. Lake JE. The fat of the matter: obesity and visceral adiposity in treated HIV infection. Curr HIV/AIDS Rep 2017; 14:211–9.

7. Lake JE, Stanley TL, Apovian CM, et al. Practical review of recognition and management of obesity and lipohypertrophy in Human Immunodeficiency Virus infection. Clin Infect Dis 2017; 64:1422–9.

8. Hasse B, Iff M, Ledergerber B, et al. Obesity trends and body mass index changes after starting antiretroviral treatment: the Swiss HIV cohort study. Open Forum Infect Dis 2014; 1:ofu040.

9. Mekonnen T, Animaw W, Seyum Y. Overweight/obesity among adults in North-Western Ethiopia: a community-based cross sectional study. Arch Public Health 2018; 76:18.

10. Koethe JR, Jenkins CA, Lau B, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. AIDS Res Hum Retroviruses 2016; 32:50–8.

11. Erlandson KM, Zhang L, Lake JE, et al. Changes in weight and weight distribution across the lifespan among HIV-infected and -uninfected men and women. Medicine (Baltimore) 2016; 95:e5399.

12. Nuvoli S, Caruana G, Babudieri S, et al. Body fat changes in HIV patients on highly active antiretroviral therapy (HAART): a longitudinal DEXA study. Eur Rev Med Pharmacol Sci 2018; 22:1852–9.

13. Achhra AC, Mocroft A, Reiss P, et al; D:A:D Study Group. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. HIV Med 2016; 17:255–68.

14. Yuh B, Tate J, Butt AA, et al. Weight change after antiretroviral therapy and mortality. Clin Infect Dis 2015; 60:1852–9.

15. Kumar S, Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. Front Endocrinol (Lausanne) 2018; 9:705.

16. Nguyen KA, Peer N, Mills EJ, Kengne AP. A meta-analysis of the metabolic syndrome prevalence in the global HIV-infected population. PLOS One 2016; 11:e0150970.

17. Husain NE, Noor SK, Elmadhoun WM, et al. Diabetes, metabolic syndrome and dyslipidemia in people living with HIV in Africa: re-emerging challenges not to be forgotten. HIV AIDS (Auckland) 2017; 9:193–202.

18. Calza L, Colangeli V, Magistrelli E, et al. Prevalence of metabolic syndrome in HIV-infected patients naive to antiretroviral therapy or receiving a first-line treatment. HIV Clin Trials 2017; 18:110–7.

19. Maggi P, Di Biagio A, Rusconi S, et al. Cardiovascular risk and dyslipidemia among persons living with HIV: a review. BMC Infect Dis 2017; 17:551.

20. Bedimo RJ, Mar H, Bosch RJ, et al; A5321 Study Team. Brief report: no evidence for an association between statin use and lower biomarkers of HIV persistence or immune activation/inflammation during effective ART. J Acquir Immune Defic Syndr 2019; 82:e27–31.

21. Bourgi K, CJ, Rebeiro PF, Lake JE, et al. Greater weight gain among treatment-naïve persons starting integrase inhibitors. Paper presented at: Conference on Retroviruses and Opportunistic Infections; March 4–7, 2019; Seattle, Washington. Abstract 670.

22. Kerchberger AM, ANS, Angert CD, Mehta CC, et al. Integrase strand transfer inhibitors are associated with weight gain in women. Paper presented at: Conference on Retroviruses and Opportunistic Infections; March 4–7, 2019; Seattle, Washington. Abstract 672.

23. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad 2019; 5:41–3.

24. Gomez M, Seybold U, Roider J, Harter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015–2017. Infection 2019; 47:95–102.

25. Nunez-Torres R, Macias J, Rivero-Juarez A, et al. Fat mass and obesity-associated gene variations are related to fatty liver disease in HIV-infected patients. HIV Medicine 2017; 18:546–54.

26. Egaña-Gorroño L, Martínez E, Pérez I, et al. Contribution of genetic background and antiretroviral therapy to body fat changes in antiretroviral-naive HIV-infected adults. J Antimicrob Chemother 2014; 69:3076–84.

27. World Health Organization. Obesity and overweight. http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. Published February 16, 2018. Accessed May 5, 2018.

28. World Health Organization. Waist circumference and waist–hip ratio: Report of a WHO expert consultation. http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf. Published December 11, 2008. Accessed May 1, 2018.

29. Durbin R. Efficient haplotype matching and storage using the positional Burrows-Wheeler transform (PBWT). Bioinformatics 2014; 30:1266–72.

30. Loh PR, Danecek P, Palamara PF, et al. Reference-based phasing using the Haplotype Reference Consortium panel. Nat Genet 2016; 48:1443–8.

31. Chang CC, Chow CC, Tellier LC, et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 2015; 4:7.

32. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015; 518:197–206.

33. Shungin D, Winkler TW, Croteau-Chonka DC, et al; ADIPOGen Consortium; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GEFOS Consortium; GENIE Consortium; GLGC; ICBP; International Endogene Consortium; LifeLines Cohort Study; MAGIC Investigators; MuTHER Consortium; PAGE Consortium; ReproGen Consortium. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015; 518:187–96.

34. Grant PM, Kitch D, McComsey GA, et al. Long-term body composition changes in antiretroviral-treated HIV-infected individuals. AIDS 2016; 30:2805–13.

35. Koethe JR, Jenkins CA, Lau B, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Higher time-updated body mass index: association with improved CD4+ cell recovery on HIV treatment. J Acquir Immune Defic Syndr 2016; 73:197–204.

36. 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.

37. Gelpi M, Afzal S, Lundgren J, et al. Higher risk of abdominal obesity, elevated low-density lipoprotein cholesterol, and hypertriglyceridemia, but not of hypertension, in people living with Human Immunodeficiency Virus (HIV): results from the Copenhagen comorbidity in HIV infection study. Clin Infect Dis 2018; 67:579–86.

38. Conley LJ, Bush TJ, Rupert AW, et al; SUN (Study to Understand the Natural History of HIVAIDS in the Era of Effective Therapy) Investigators. Obesity is associated with greater inflammation and monocyte activation among HIV-infected adults receiving antiretroviral therapy. AIDS 2015; 29:2201–7.

39. Mave V, Erlandson KM, Gupte N, et al; ACTG PEARLS and NWCS 319 Study Team. Inflammation and change in body weight with antiretroviral therapy initiation in a multinational cohort of HIV-infected adults. J Infect Dis 2016; 214:65–72.

40. McComsey GA, Moser C, Currier J, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. Clin Infect Dis 2016; 62:853–62.

41. Lundgren JD, Babiker AG, Gordin F, et al; INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015; 373:795–807.

42. Sharma AR, Chakraborty C, Lee SS, et al. Computational biophysical, biochemical, and evolutionary signature of human R-spondin family proteins, the member of canonical Wnt/β-catenin signaling pathway. Biomed Res Int 2014; 2014:974316.

43. Erlandson KM, Taejaroenkul S, Smeaton L, et al. A randomized comparison of anthropomorphic changes with preferred and alternative efavirenz-based antiretroviral regimens in diverse multinational settings. Open Forum Infect Dis 2015; 2:ofv095.

44. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016; 387:1377–96.

45. Federal Statistical Office. Enquête suisse sur la santé 2017: surpoids et obesité. https://www.bfs.admin.ch/bfsstatic/dam/assets/6426303/master. Published 2018. Accessed November 1, 2019.

46. Herrin M, Tate JP, Akgün KM, et al. Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals. J Acquir Immune Defic Syndr 2016; 73:228–36.

47. Taramasso L, Ricci E, Menzaghi B, et al. Weight gain: a possible side effect of all antiretrovirals. Open Forum Infect Dis 2017; 4:ofx239.

48. Erlandson KM, Fiorillo S, Masawi F, et al. Antiretroviral initiation is associated with increased skeletal muscle area and fat content. AIDS 2017; 31:1831–8.

49. Caron-Debarle M, Lagathu C, Boccara F, Vigouroux C, Capeau J. HIV-associated lipodystrophy: from fat injury to premature aging. Trends Mol Med 2010; 16:218–29.

50. Cirulli ET, Guo L, Leon Swisher C, et al. Profound perturbation of the metabolome in obesity is associated with health risk. Cell Metab 2019; 29:488–500.e2.

51. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet 2019; 28:166–74.

52. Becofsky K, Wing EJ, McCaffery J, Boudreau M, Wing RR. A randomized controlled trial of a behavioral weight loss program for Human Immunodeficiency Virus-infected patients. Clin Infect Dis 2017; 65:154–7.

53. Webel AR, Moore SM, Longenecker CT, et al. Randomized controlled trial of the system change intervention on behaviors related to cardiovascular risk in HIV+ adults. J Acquir Immune Defic Syndr 2018; 78:23–33.