Changes in bodyweight after initiating antiretroviral therapy close to HIV-1 seroconversion: an international cohort collaboration

*Nikos Pantazis, Caroline A Sabin, Sophie Grabar, Marc Van der Valk, Inma Jarrin, Ard van Sighem, Laurence Meyer, Christina Carlander, John Gill, Alain Volny Anne, Bruno Spire, Shema Tariq, Fiona Burns, Dominique Costagliola, Elisa Ruiz-Burga, Giota Touloumi, Kholoud Porter, for the CASCADE Collaboration**

Summary

Background Understanding the reasons for and consequences of bodyweight change in people living with HIV initiating antiretroviral therapy (ART) is crucial to optimising long-term health and wellbeing. We aimed to examine bodyweight trends and associated factors among individuals with well estimated dates of HIV-1 seroconversion.

Methods In this cohort study, we pooled retrospective data from clinical records of participants in CASCADE aged 16 years and older recruited from clinics in France, Greece, the Netherlands, Spain, Sweden, the UK, and Canada. All participants had well estimated dates of HIV-1 seroconversion, seroconverted between Jan 1, 2007, and Dec 31, 2022 (HIV-1 positive antibody test within 12 months of an HIV-1 negative antibody test, or other laboratory evidence of seroconversion), initiated ART within 1 year of seroconversion, and were previously ART-naive. Participants were followed up to the time of data pooling (May 31, 2023). We modelled bodyweight changes after ART initiation by ART class, BMI categories, and other demographic characteristics using linear mixed models.

Findings Of 15 755 potentially eligible participants, 5698 met inclusion criteria. Of those, 5148 (90·3%) were assigned male at birth, 517 (9·1%) were assigned female at birth, and 33 (0·6%) had sex not known. 2778 (48·8%) participants initiated integrase strand transfer inhibitor (INSTI)-based ART regimens, 1809 (31·7%) initiated protease inhibitor-based regimens, and 1111 (19·5%) initiated non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. The majority of participants were men who have sex with men (MSM; 4519 [79·3%]). Median age at seroconversion was 33·7 years (IQR 26·9–43·2). Bodyweight changes differed significantly by ART class within all baseline BMI categories (BMI <18·5 kg/m² p=0·026, BMI 18·5–24·9 kg/m² p<0·0001, BMI 25·0–29·9 kg/m² p=0·0021, and BMI ≥30·0 kg/m² p=0·0033; ART class and BMI interaction p=0·011). Participants with BMI less than 30 kg/m² on regimens including both INSTI and tenofovir alafenamide gained 4·76 kg (95% CI 4·05–5·46) or more at 3 years. Of those with baseline BMI 18·5–24·9 kg/m², 31·3% (95% CI 29·5–33·1) on INSTI-based regimens, 25·3% (23·0–27·7) on protease inhibitor-based regimens, 20·4% (18·8–22·9) on NNRTI-based regimens, 37·4% (33·9–40·9) on tenofovir alafenamide-based regimens, and 38·4% (34·6–42·1) on tenofovir alafenamide and INSTI-based regimens had gained more than 10% of their baseline bodyweight at 3 years. The greatest 3-year bodyweight gains by individuals on INSTI-based regimens and with BMI 18·5–24·9 kg/m² were in women (5·63 kg [95% CI 4·92–6·35]), and people originating from sub-Saharan African (5·76 kg [5·06–6·46]), compared with MSM (3·82 kg [3·50–4·13]).

Interpretation Our findings suggest a direct effect of INSTIs and tenofovir alafenamide on bodyweight gain, rather than a return to health effect. Given the known risk for cardiometabolic disease, bodyweight management needs to be part of the overall care of individuals prescribed these drugs.

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Introduction

Globally, overweight and obesity are major concerns given their associated negative health consequences.[1] General population studies have shown that longitudinal increases in bodyweight are associated with detrimental changes in cardiometabolic parameters.[2–4]

Excessive weight gain has been reported from studies of people living with HIV-1 on effective antiretroviral therapy (ART), and is one of the most cited unintended consequences of modern HIV therapy,[5] especially in women.[5–7] Integrase strand transfer inhibitors (INSTIs),[8] and the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir alafenamide are the drugs most frequently associated with excessive weight gain.[5,6]

Several HIV-specific reasons have been proposed for this weight gain. First, bodyweight might be expected to increase following discontinuation of some anti-HIV drugs now shown to interfere with weight

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*Members of the CASCADE Collaboration are listed in the appendix (pp 9–11)

Department of Hygiene, Epidemiology, and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece (N Pantazis PhD, Prof G Touloumi PhD); **Institute for Global Health, University College London, London, UK** (Prof C A Sabin PhD, S Tariq PhD, Prof F Burns PhD, E Ruiz-Burga PhD, Prof K Porter PhD); **Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital St Antoine, Paris, France** (S Grabar PhD, Prof D Costagliola PhD); **HIV Monitoring Foundation Amsterdam, Amsterdam, Netherlands** (M Van der Valk PhD, A van Sighem PhD); **Amsterdam University Medical Centers, Division of Infectious Diseases, Amsterdam Institute for Infection and Immunity, University of Amsterdam, Amsterdam, Netherlands** (M Van der Valk); **National Centre of Epidemiology, Carlos III Health Institute, Madrid, Spain** (I Jarrin PhD); **INSERM CESP U1018, APHP Hôpital de Bicêtre, Le Kremlin-Bicêtre, Paris-Saclay University, Gif-sur-Yvette, France** (Prof L Meyer PhD); **Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden** (C Carlander PhD); **Southern Alberta HIV Clinic, Calgary, AB, Canada** (J Gill PhD); **Paris, Île-de-**

France, France (A Volny Anne BA); Inserm, IRD, SESSTIM, ISSPAM, Aix-Marseille Université, Marseille, France (B Spire PhD)

Correspondence to: Dr Nikos Pantazis, Department of Hygiene, Epidemiology, and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens 115 27, Greece
npantaz@med.uoa.gr

See Online for appendix

Research in context

Evidence before this study

Previous studies, both observational and interventional, reported on increases in bodyweight for people prescribed regimens including a drug from the integrase strand transfer inhibitor (INSTI) class or the nucleotide reverse transcriptase inhibitor tenofovir alafenamide. Theories proposed for this gain in bodyweight included it reflecting a return to health effect following prolonged exposure to HIV viraemia, recovery from the bodyweight-reducing effects of previous treatments, or the direct effect of the drugs in the current regimens. As these studies examined data from individuals with unknown duration of HIV infection, who were often switched to INSTI or tenofovir alafenamide regimens, interpretation of these associations was limited. Before conducting the current study, we searched PubMed for English language publications on Oct 2, 2023, using the search terms "HIV seroconversion", "antiretroviral therapy", and "weight gain", without any criteria for study inclusion or exclusion, and found no studies.

Added value of this study

To our knowledge, our study is the first to examine bodyweight changes following initiating therapy soon after HIV acquisition and could, therefore, potentially rule out exposure of prolonged HIV viraemia or use of previous drugs as causes of these changes in bodyweight. Because participants began antiretroviral therapy from naive and within a short interval following seroconversion, the observed bodyweight gains, especially for those on INSTIs, tenofovir alafenamide, or both, suggests a direct impact of these drugs on bodyweight rather than a return to health effect.

Implications of all the available evidence

Whether the gain in bodyweight reported here poses an immediate or long-term health risk is unclear, but these findings call for integrating bodyweight management into clinical care of individuals on these drug regimens.

gain—eg, tenofovir disoproxil fumarate[9] and the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz when used in combination with tenofovir disoproxil fumarate.[10] Second, previously unsuppressed viraemia and the accompanying inflammatory state might lead to weight loss,[11] which is restored on ART initiation. Finally, several of the currently used anti-HIV drugs themselves might have an effect on adipose tissue.[12] Furthermore, similarly to the general population, people living with HIV-1 are exposed to an increasingly obesogenic environment, including increasing fast-food consumption and limited physical activity.[13,14]

For individuals newly initiating ART using drugs implicated in weight gain, we can discount any possible effect of previous therapies. However, the potential catabolic effect of untreated HIV infection remains, with any ensuing weight gain possibly signifying a return to a healthy state. This effect might be difficult to study in the absence of early anthropometric measurements, preferably from before HIV acquisition.

For a minority of people living with HIV-1, the time of HIV seroconversion can be well estimated, mostly through the availability of a previous negative HIV-1 test. We aimed to assess changes in weight gain among individuals initiating ART close to the time of HIV-1 acquisition in order to study the potential contribution of the return to health phenomenon to the reported weight gains attributed to specific ART drugs and classes.

Methods

Study design and participants

In this cohort study, we pooled retrospective clinical and laboratory data from clinical records of participants with well estimated dates of HIV-1 seroconversion in CASCADE, a multinational mixed methods study of HIV-1 cohorts recruiting from clinics in France, the Netherlands, Spain, Sweden, Greece, Canada, and the UK.[15] All CASCADE participants are aged 16 years or older at the time of HIV-1 diagnosis and fulfil at least one of the following criteria: an HIV-1 positive antibody test within 12 months of an HIV-1 negative antibody test, other laboratory evidence of seroconversion (HIV-1 antibody negative with positive RT-PCR, an incident test using a recent incident testing algorithm assay, an equivocal HIV-1 antibody test supported by a repeat test within a 2-week period showing a rising optical density, or p24 antigen positivity supported by neutralisation or PCR), or clinical manifestations of symptomatic HIV seroconversion illness supported by antigen positivity and fewer than four bands positive on western blot.

Eligible individuals for the current study initiated a modern ART regimen (stable for ≥30 days) based on one of the three main classes: INSTI, NNRTI, or boosted (with low-dose ritonavir or cobicistat) protease inhibitors. All included individuals seroconverted between Jan 1, 2007, and Dec 31, 2022, initiated ART within 1 year of seroconversion, were previously ART-naive, and had bodyweight, height, CD4 cell count, and HIV RNA measurements available within 6 months before ART initiation with at least one bodyweight measurement after initiation. Maximum follow-up was to the date of data pooling on May 31, 2023. The closest bodyweight measurement to ART initiation was considered as the baseline value.

The following ethics committees revised and approved the protocols to pool clinical data following signed informed consent from study participants: the Research Ethics Committee H General Universitario Gregorio Marañon on April 20, 2012 (CoRIS cohort); the Research Ethics Committee of the Institute of Health Carlos III

For CASCADE see https://www.cascadestudy.net

(CEI PI 66_2022; CoRIS cohort) on Sept 21, 2022; the Commission Nationale de l'informatique et des Libertés on Nov 27, 1991 (the French Hospital Database on HIV); renewed authorisations were obtained from the Commission Nationale de l'informatique et des Libertés in 2021 (Feb 19 and March 30, 2021; ANRS CO4 French Hospital database on HIV); the Avis Initial du CPP on July 2, 1996 (PRIMO cohort); the Comité de Protection des Personnes Sud-ouest et Outre-Mer III on May 25, 2016 (Cohort Aquitaine); the institutional review board (ATHENA cohort); the Bioethics and Deontology Committee of the Medical School of the National and Kapodistrian University of Athens on Oct 18, 2005 (the Greek cohort); the National Organisation of Medicines on June 5, 2006 (AMACS cohort); the Ethics Review Authority in Sweden on May 23, 2022 (Dnr 2022-00543-01; InfCare cohort), the Yorkshire and the Humber South Yorkshire Research Ethics Committee in the UK on June 20, 2022 (22/YH/0114; UK CASCADE cohort); and the Conjoint Health Research Ethics Board, University of Calgary on July 2, 2020 (Southern Alberta cohort).

Procedures

We transformed repeated bodyweight measurements to bodyweight changes for analysis by subtracting the bodyweight at ART initiation from each measurement. We censored follow-up at the first switch to a different ART class.

We calculated BMI at baseline for each individual and classified into four standard categories: less than 18·5 kg/m², 18·5–24·9 kg/m², 25·0–29·9 kg/m², and 30·0 kg/m² or more. Sex at birth was derived from the following self-identified gender categories: cisgender male, cisgender female, transgender male, transgender female, transgender sex not known, non-binary (assigned male at birth), and non-binary (assigned female at birth). Data on sex and gender were obtained from clinical centres in seven different countries, which use different terminology. In order to try to harmonise the data, we created the aforementioned categories. For the purposes of probable HIV exposure route, we used assigned gender at birth (ie, a transgender female who self-identified as female but who had assigned gender at birth of male was counted as male for the transmission routes). The five categories for probable HIV exposure route were: men who have sex with men (MSM), injecting drug use, men who have sex with women, women who have sex with men, and unknown. Because ethnicity data are not collected in most of the cohorts, including being forbidden by law in some countries, we used country of origin as a proxy, categorised into four regions: Europe and North America, sub-Saharan Africa, Latin America and the Caribbean, and other.

Statistical analysis

We summarised demographic, anthropometric, and clinical characteristics of participants by ART class using standard descriptive statistics (mean and SD or median and IQR for continuous variables, and absolute and relative frequencies for categorical variables). Using ANOVA, Kruskal-Wallis, or χ^2 procedures, we performed corresponding tests for differences between ART classes.

We analysed repeated measurements of bodyweight changes following ART initiation using mixed models. Models did not include fixed or random intercepts as bodyweight changes at baseline were zero by definition (ie, regression through the origin). Exploratory analyses using restricted cubic splines of time since baseline were done to define the required complexity of further models. Following the results of these exploratory analyses (shown in the Results section), all models were simplified assuming a piecewise linear evolution of average bodyweight changes with a knot at 6 months after ART initiation. We entered the resulting time terms into all models as random effects with unstructured variance–covariance matrices, at both the cohort and individual levels. We based model building on standard methods (ie, likelihood ratio tests and information criteria) focusing also on parameter interpretability and clinical relevance.

	INSTIs (n=2778)	Protease inhibitors (n=1809)	NNRTIs (n=1111)	p value
Age at diagnosis, years	33·6 (26·9–43·6)	34·4 (27·2–43·4)	34·1 (27·0–43·2)	0·89
Probable HIV exposure route	..	..	..	<0·0001
Men who have sex with men	2257 (81·2%)	1352 (74·7%)	910 (81·9%)	..
Injecting drug use	14 (0·5%)	14 (0·8%)	3 (0·3%)	..
Men who have sex with women	217 (7·8%)	172 (9·5%)	80 (7·2%)	..
Women who have sex with men	182 (6·6%)	217 (12·0%)	93 (8·4%)	..
Unknown	108 (3·9%)	54 (3·0%)	25 (2·3%)	..
Region of origin	..	..	..	<0·0001
Europe or North America	2096 (75·4%)	1408 (77·8%)	843 (75·9%)	..
Sub-Saharan Africa	170 (6·1%)	214 (11·8%)	90 (8·1%)	..
Latin America or Caribbean	261 (9·4%)	105 (5·8%)	91 (8·2%)	..
Other	251 (9·0%)	82 (4·5%)	87 (7·8%)	..
Year of estimated seroconversion	2017 (2015–2019)	2012 (2011–2014)	2012 (2011–2014)	<0·0001
Time from seroconversion to ART, months	3·5 (1·6–5·5)	3·9 (1·7–6·4)	5·6 (3·6–7·8)	<0·0001
Baseline CD4 count, cells per µL	486 (350–640)	412 (293–570)	464 (334–630)	<0·0001
Baseline HIV RNA, $\log_{10}$ copies per mL	4·9 (4·3–5·6)	5·0 (4·5–5·7)	4·6 (4·1–5·0)	<0·0001
Baseline bodyweight, kg	71 (64–80)	70 (63–77)	72 (65–80)	<0·0001
Baseline BMI, kg/m²	..	..	..	0·037
<18·5	169 (6·1%)	119 (6·6%)	51 (4·6%)	..
18·5–24·9	1936 (69·7%)	1304 (72·1%)	803 (72·3%)	..
25·0–29·9	560 (20·2%)	308 (17·0%)	202 (18·2%)	..
≥30·0	113 (4·1%)	78 (4·3%)	55 (5·0%)	..

Data are n (%) or median (IQR). ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 1: **Demographic, clinical, and anthropometric characteristics of participants by class of main drug in ART regimen**

The fixed part of the models included the two piecewise linear time terms along with their interactions with the categorical covariate representing the ART class and other baseline covariates (BMI category, probable HIV exposure route, region of origin, age at HIV-1 seroconversion, height, square-root-transformed CD4 cell count, and log_{10}-transformed HIV RNA). We also considered for inclusion in the main multivariable model three-way interactions between ART class, time terms, and other covariates. Estimates of weight gain after 6 months and after 3 years following initiation and the corresponding charts produced were based on the fit of an unadjusted and an adjusted model (main models). The unadjusted model included only covariates for ART class, BMI category, and time, and their interactions. The adjusted model additionally included adjustments for probable exposure route, region of origin, age, height, baseline CD4 cell count, and HIV RNA. The inclusion of BMI as a covariate and the presentation of results by BMI strata was due to overall differences in bodyweight evolution between individuals in different BMI categories. Additionally, the association between ART class and bodyweight evolution was substantially modified by initial BMI level. The inclusion of all other covariates in models was guided by the literature. We did not consider calendar time of ART initiation as a potential prognostic factor as it was strongly associated with use of ART class. Furthermore, we considered an independent effect of calendar time on within-subject rate of bodyweight change to be unlikely, except for a potential effect during the COVID-19 pandemic, which, according to recent evidence,[16] had a negligible effect on bodyweight.

We also fitted an additional model, similar to the adjusted one, by replacing the ART class variable with a categorical variable for the most common ART combinations. Finally, we fitted similar adjusted and unadjusted models to subpopulations treated with any regimen that included tenofovir alafenamide or to those treated with a regimen containing tenofovir alafenamide and an INSTI. Using marginal means, we derived from the main adjusted model estimates for specific subpopulations (women who have sex with men, individuals originating from sub-Saharan Africa, and MSM).

We calculated the proportions of individuals with weight gains greater than 5% and greater than 10% after 3 years of ART, relative to their bodyweight at ART initiation, using properties of the normal distribution based on estimates of fixed and random effects of the two main mixed models (given the assumptions of the mixed model the distribution of weight gain at a specific timepoint is normal with the mean depending on the covariate values used as fixed effects and variance depending on the estimated variance components). We took into account uncertainty of these estimates through Monte Carlo methods by drawing samples (5000 replications) from the distribution of the models' estimates and deriving the distribution of the resulting estimates of the aforementioned proportions.[17]

We also fitted the main multivariable model to a subset of the study participants initiating regimens that did not contain tenofovir disoproxil fumarate or efavirenz as these two drugs have been associated with appetite suppression.[10]

We defined an average participant based on the most common participant characteristics in our dataset and the population median measurements as an MSM aged 30–39 years at seroconversion, originating from Europe or North America, with average height, baseline CD4 cell count, and HIV RNA.

For all analyses, we applied a significance level of 5% with two-sided p values. We performed analyses using Stata (release 18).

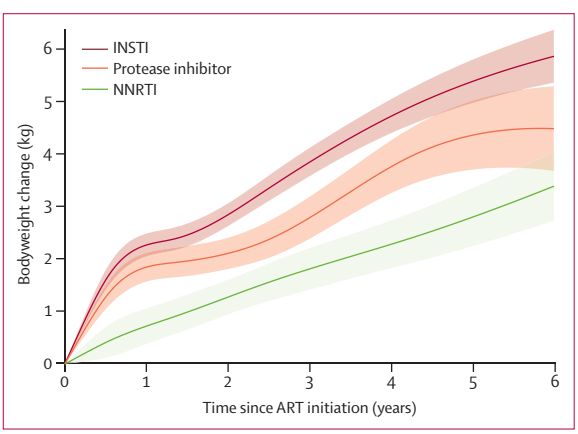

Figure 1: **Estimated bodyweight changes after ART initiation by ART class**
Estimates derived from a mixed model using restricted cubic splines of time since ART initiation to model mean bodyweight changes and shown for up to 6 years after baseline. Shaded areas represent 95% CIs. ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Of 15755 potentially eligible participants, we excluded data from 10057 because ART was initiated more than 12 months after seroconversion (n=5186), ART was not stable for 30 days or longer (n=760), some ART data were missing (n=186), baseline bodyweight or height data were missing (n=2429), baseline CD4 cell count or HIV RNA data were missing (n=549), or bodyweight measurements after ART initiation were missing (n=947; appendix p 2). Individuals excluded due to missing baseline bodyweight or height data had broadly similar demographic and clinical characteristics to included individuals (appendix p 4). Of the 5698 included individuals (5148 [90·3%] assigned male at birth,

517 [9·1%] assigned female at birth, and 33 [0·6%] sex not known), 4519 (79·3%) were MSM and 4347 (76·3%) originated from Europe or North America (table 1). Median age at estimated seroconversion was 33·7 years (IQR 26·9–43·2). Median time to ART initiation was 4·0 months (IQR 1·9–6·3) from estimated seroconversion, with median baseline CD4 count 459 cells per µL (IQR 328–620) and median baseline HIV RNA 4·9 $\log_{10}$ copies per mL (IQR 4·3–5·5). 2778 (48·8%) participants were on INSTI-based regimens, 1809 (31·7%) were on protease inhibitor-based regimens, and 1111 (19·5%) were on NNRTI-based regimens. Dolutegravir was the most prescribed INSTI (1167 [42·0%] of 2778), followed by elvitegravir (728 [26·2%]), bictegravir (558 [20·0%]), and raltegravir (325 [11·7%]). Tenofovir alafenamide was prescribed for 987 (17·3%) participants, mostly in combination with an INSTI (n=878 [89·0%]), particularly bictegravir (n=558 [63·6%]; appendix p 5). During follow-up 1089 (19·1%) participants changed from the initial INSTI drug, tenofovir disoproxil fumarate or tenofovir alafenamide. 368 (33·8%) of these participants replaced tenofovir disoproxil fumarate with tenofovir alafenamide and 271 (24·9%) replaced tenofovir disoproxil fumarate with other NRTIs. Median age at seroconversion was similar across all ART classes but there were noticeable differences in the distribution of all other variables.

Baseline bodyweight data were available within a median 3·5 months (IQR 1·7–5·7) from seroconversion, with a median of 5 measurements (IQR 3–9) during follow-up and 4·7 months (IQR 2·8–7·3) between measurements. Median time of last measurement was at 1·9 years (IQR 0·7–4·0) after ART initiation.

We examined the timing and frequency of bodyweight measurements by ART class and baseline BMI (appendix pp 6–7) along with the potential effects of current bodyweight or weight change (relative to the previous visit) on the time between subsequent visits (appendix p 8). Differences in the frequency of bodyweight measurements by baseline BMI were not significant (p=0·11) and

	Estimated bodyweight change at 6 months, kg (95% CI)	Estimated bodyweight change at 3 years, kg (95% CI)
Unadjusted models		
INSTI		
<18·5 kg/m²	2·50 (1·63 to 3·37)	4·22 (3·14 to 5·30)
18·5–24·9 kg/m²	1·89 (1·60 to 2·19)	3·95 (3·65 to 4·25)
25·0–29·9 kg/m²	1·78 (1·30 to 2·26)	3·43 (2·87 to 3·99)
≥30·0 kg/m²	2·02 (1·01 to 3·04)	2·25 (1·04 to 3·46)
Protease inhibitor		
<18·5 kg/m²	3·03 (2·02 to 4·04)	5·02 (3·67 to 6·38)
18·5–24·9 kg/m²	1·55 (1·20 to 1·90)	2·87 (2·44 to 3·31)
25·0–29·9 kg/m²	1·63 (1·00 to 2·27)	2·18 (1·33 to 3·03)
≥30·0 kg/m²	0·36 (–0·88 to 1·60)	2·32 (0·58 to 4·06)
NNRTI		
<18·5 kg/m²	0·88 (–0·64 to 2·39)	2·74 (0·89 to 4·60)
18·5–24·9 kg/m²	0·90 (0·48 to 1·31)	1·98 (1·54 to 2·41)
25·0–29·9 kg/m²	–0·18 (–0·92 to 0·55)	1·46 (0·63 to 2·29)
≥30·0 kg/m²	–0·97 (–2·39 to 0·44)	1·04 (–0·70 to 2·77)
Tenofovir alafenamide*		
<18·5 kg/m²	3·26 (1·75 to 4·77)	4·94 (2·31 to 7·56)
18·5–24·9 kg/m²	2·23 (1·79 to 2·68)	4·61 (3·96 to 5·27)
25·0–29·9 kg/m²	3·50 (2·67 to 4·33)	5·10 (3·78 to 6·42)
≥30·0 kg/m²	4·66 (2·73 to 6·58)	3·99 (1·13 to 6·85)
Tenofovir alafenamide and INSTI†		
<18·5 kg/m²	3·28 (1·69 to 4·88)	4·78 (2·09 to 7·47)
18·5–24·9 kg/m²	2·39 (1·91 to 2·87)	4·76 (4·05 to 5·46)
25·0–29·9 kg/m²	3·75 (2·84 to 4·66)	4·98 (3·49 to 6·47)
≥30·0 kg/m²	4·56 (2·39 to 6·73)	2·17 (–1·07 to 5·41)
Adjusted models‡		
INSTI		
<18·5 kg/m²	2·63 (1·73 to 3·53)	4·05 (2·92 to 5·17)
18·5–24·9 kg/m²	1·95 (1·58 to 2·32)	3·85 (3·43 to 4·27)
25·0–29·9 kg/m²	1·69 (1·15 to 2·23)	3·34 (2·70 to 3·99)
≥30·0 kg/m²	1·86 (0·82 to 2·90)	2·00 (0·75 to 3·26)
Protease inhibitor		
<18·5 kg/m²	2·97 (1·94 to 4·00)	4·51 (3·12 to 5·90)
18·5–24·9 kg/m²	1·42 (1·01 to 1·83)	2·55 (2·02 to 3·08)
25·0–29·9 kg/m²	1·18 (0·50 to 1·87)	1·63 (0·72 to 2·54)
≥30·0 kg/m²	–0·19 (–1·45 to 1·08)	1·33 (–0·44 to 3·10)
NNRTI		
<18·5 kg/m²	1·02 (–0·51 to 2·54)	2·52 (0·66 to 4·39)
18·5–24·9 kg/m²	1·07 (0·61 to 1·54)	1·98 (1·46 to 2·51)
25·0–29·9 kg/m²	–0·31 (–1·09 to 0·46)	1·28 (0·39 to 2·17)
≥30·0 kg/m²	–1·06 (–2·49 to 0·37)	1·01 (–0·75 to 2·77)
Tenofovir alafenamide*		
<18·5 kg/m²	3·78 (2·13 to 5·43)	4·94 (2·12 to 7·75)
18·5–24·9 kg/m²	2·64 (1·86 to 3·41)	4·47 (3·29 to 5·64)
25·0–29·9 kg/m²	4·02 (2·95 to 5·10)	5·01 (3·32 to 6·71)
≥30·0 kg/m²	5·45 (3·40 to 7·51)	3·60 (0·47 to 6·72)
Tenofovir alafenamide and INSTI†		
<18·5 kg/m²	3·81 (2·06 to 5·56)	4·60 (1·68 to 7·51)
18·5–24·9 kg/m²	2·77 (1·94 to 3·60)	4·61 (3·34 to 5·87)
25·0–29·9 kg/m²	4·23 (3·06 to 5·39)	5·01 (3·15 to 6·88)
≥30·0 kg/m²	5·45 (3·16 to 7·74)	1·74 (–1·77 to 5·25)

(Table 2 continues in next column)

(Continued from previous column))

ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *Tenofovir alafenamide denotes regimens with a tenofovir alafenamide-containing NNRTI backbone (irrespective of main drug). †Tenofovir alafenamide with INSTI denotes only those regimens with tenofovir alafenamide and INSTIs. ‡Estimates shown for men who have sex with men aged 30–39 years at seroconversion, originating from Europe or North America, with average height, baseline CD4 cell count, and HIV RNA.

Table 2: **Estimates of bodyweight change at 6 months and 3 years following ART initiation within 12 months of estimated HIV-1 seroconversion by ART class and baseline BMI category**

the effects of current bodyweight or weight change on the time to the next visit were extremely weak.

The results of the exploratory analyses, using restricted cubic splines of time since baseline, showed that changes in bodyweight were biphasic, with faster increases during the first 6 months of treatment and slower changes thereafter, without indication of a plateau effect for at least 5 years after ART initiation (figure 1).

Among individuals with BMI 18·5–24·9 kg/m², after 3 years on INSTI-based regimens, 53·4% (95% CI 51·4–55·4) were estimated to gain more than 5% of their baseline bodyweight and 31·3% (29·5–33·1) were estimated to gain more than 10% of their baseline bodyweight. After 3 years on protease inhibitor-based regimens, 46·3% (43·4–49·2) were estimated to gain more than 5% of their baseline bodyweight and 25·3% (23·0–27·7) were estimated to gain more than 10% of their baseline bodyweight. After 3 years on NNRTI-based regimens, 40·4% (37·7–43·3) were estimated to gain more than 5% of their baseline bodyweight and 20·4% (18·8–22·9) were estimated to gain more than 10% of their baseline bodyweight. For the subset of individuals on tenofovir alafenamide, 56·8% (53·0–60·3) were estimated to gain more than 5% of their baseline bodyweight and 37·4% (33·9–40·9) were estimated to gain more than 10% of their baseline bodyweight after 3 years. Among those on tenofovir alafenamide with INSTI-based regimens 57·5% (53·5–61·3) were estimated to gain more than 5% of their baseline bodyweight and 38·4% (34·6–42·1) were estimated to gain more than 10% of their baseline bodyweight after 3 years.

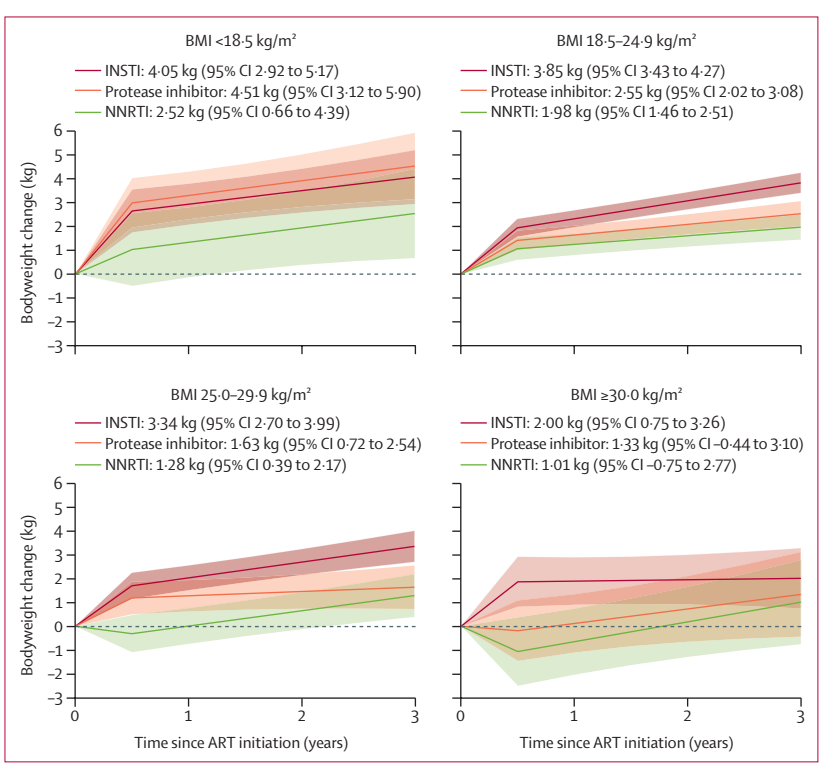

Figure 2: **Estimated bodyweight changes after ART initiation by ART class and baseline BMI**
Estimates shown for men who have sex with men, aged 30–39 years at seroconversion, originating from Europe or North America, with average height, baseline CD4 cell count, and HIV RNA. Shaded areas represent 95% CIs. Data shown in each key are the estimated weight changes at 3 years. ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Overall, bodyweight changes were faster in the first 6 months of treatment and slower thereafter (table 2). Bodyweight trajectories differed significantly by ART class within all baseline BMI categories (BMI <18·5 kg/m² p=0·026, BMI 18·5–24·9 kg/m² p<0·0001, BMI 25·0–29·9 kg/m² p=0·0021, and BMI ≥30·0 kg/m² p=0·0033; ART class and BMI interaction p=0·011). Individuals on tenofovir alafenamide, regardless of the main drug, or on INSTI regimens had the greatest estimated weight gains at 6 months and at 3 years, irrespective of baseline BMI, except for those with baseline BMI less than 18·5 kg/m² who had a slightly higher weight gain after 3 years on protease inhibitor regimens (table 2). In unadjusted models, estimated mean weight gain at 3 years was lowest for those on NNRTI regimens across all BMI categories, and highest for those on tenofovir alafenamide and tenofovir alafenamide with INSTI regimens for baseline BMI 18·5–29·9 kg/m² (table 2).

Considering the average participant in our dataset (ie, MSM aged 30–39 years at seroconversion, originating from Europe or North America, with average height, baseline CD4 cell count, and HIV RNA), estimated weight gains at 3 years for those with baseline BMI 18·5–24·9 kg/m² were lowest for those on NNRTI regimens and highest for those on tenofovir alafenamide and tenofovir alafenamide with INSTI regimens (table 2 adjusted models; trajectories shown in figure 2).

For average participants, regimens including bictegravir combined with tenofovir alafenamide were associated with the highest bodyweight increases in individuals with baseline BMI less than 18·5 kg/m², 18·5–24·9 kg/m², and 25·0–29·9 kg/m², but not in those with baseline BMI 30 kg/m² or more (figure 3). For all BMI categories, elvitegravir was associated with greater weight gains when combined with tenofovir alafenamide rather than with tenofovir disoproxil fumarate (figure 3).

Estimated bodyweight gains after 3 years were higher for women who have sex with men compared with their male counterparts, or compared with MSM (p=0·0003) irrespective of ART class (probable exposure route and ART class interaction p=0·97). Larger bodyweight gains were also observed in individuals originating from sub-Saharan Africa compared with individuals from other regions (p=0·043; ART class and region of origin interaction p=0·18). For every baseline BMI category, people originating from sub-Saharan Africa had the highest bodyweight gain on INSTIs at 3 years, and MSM had the lowest bodyweight gain on INSTIs at 3 years (table 3).

Differences in bodyweight trajectories by age were statistically significant both during the first 6 months

and thereafter (p<0·0001) with no significant interaction with ART class (p=0·43). Older individuals had faster initial bodyweight gains compared with younger individuals but slower increases thereafter, resulting in similar bodyweight gains for all age groups after 3 years of treatment.

Removing individuals on regimens containing tenofovir disoproxil fumarate or efavirenz and refitting the main multivariable model yielded results that were qualitatively similar to those of the main analysis, but with wider confidence intervals due to the substantial reduction in sample size (n=1838; appendix p 3).

Discussion

In this cohort collaboration of 5698 individuals initiating ART within 12 months of estimated seroconversion, we found that bodyweight gain on ART is not restricted to any specific drug or drug class as we observed an increase in bodyweight regardless of prescribed regimen. Overall bodyweight gain at 3 years was at least 2·74 kg for individuals with baseline BMI less than 18·5 kg/m², 1·98 kg for individuals with baseline BMI 18·5–24·9 kg/m², 1·46 kg for individuals with baseline BMI 25·0–29·9 kg/m², and 1·04 kg for individuals with baseline BMI 30 kg/m² or more. These values were remarkably lower than the gains in bodyweight at week 48 reported in the NAMSAL trial[6] (baseline BMI <18·5 kg/m²: 9·0 kg for those on dolutegravir and 6·5 kg for those on efavirenz; baseline BMI 18·5–24·9 kg/m²: 4·0 kg and 3·0 kg; baseline BMI 25·0–29·9 kg/m²: 5·0 kg and 2·0 kg; and baseline BMI ≥30 kg/m²: 4·0 kg and 3·0 kg). However, we found that significant differences exist between classes and specific drugs and drug combinations. Bodyweight gain was highest in those on regimens that include tenofovir alafenamide and INSTI plus tenofovir alafenamide combinations. Of those with baseline BMI 18·5–24·9 kg/m², 37·4% (95% CI 33·9–40·9) of those starting a tenofovir alafenamide regimen and 38·4% (34·6–42·1) of those starting an INSTI plus tenofovir alafenamide combination gained more than 10% of their baseline bodyweight. Of note, these differences remained when we restricted analyses to data from individuals on regimens which did not contain tenofovir disoproxil fumarate or efavirenz, despite the potentially appetite suppressive effects of these two drugs.[10]

Given the proximity of ART initiation to HIV-1 acquisition, the bodyweight gain observed in our cohort is unlikely to be a return to health phenomenon. Reported bodyweight change among people initiating or switching ART regimens is not new. Before the advent of modern ART, bodyweight changes had been reported by cohorts of individuals with unknown HIV-1 infection durations initiating or switching regimens.[18,19]

In our cohort, the highest bodyweight gains at 3 years were observed in individuals starting with a regimen

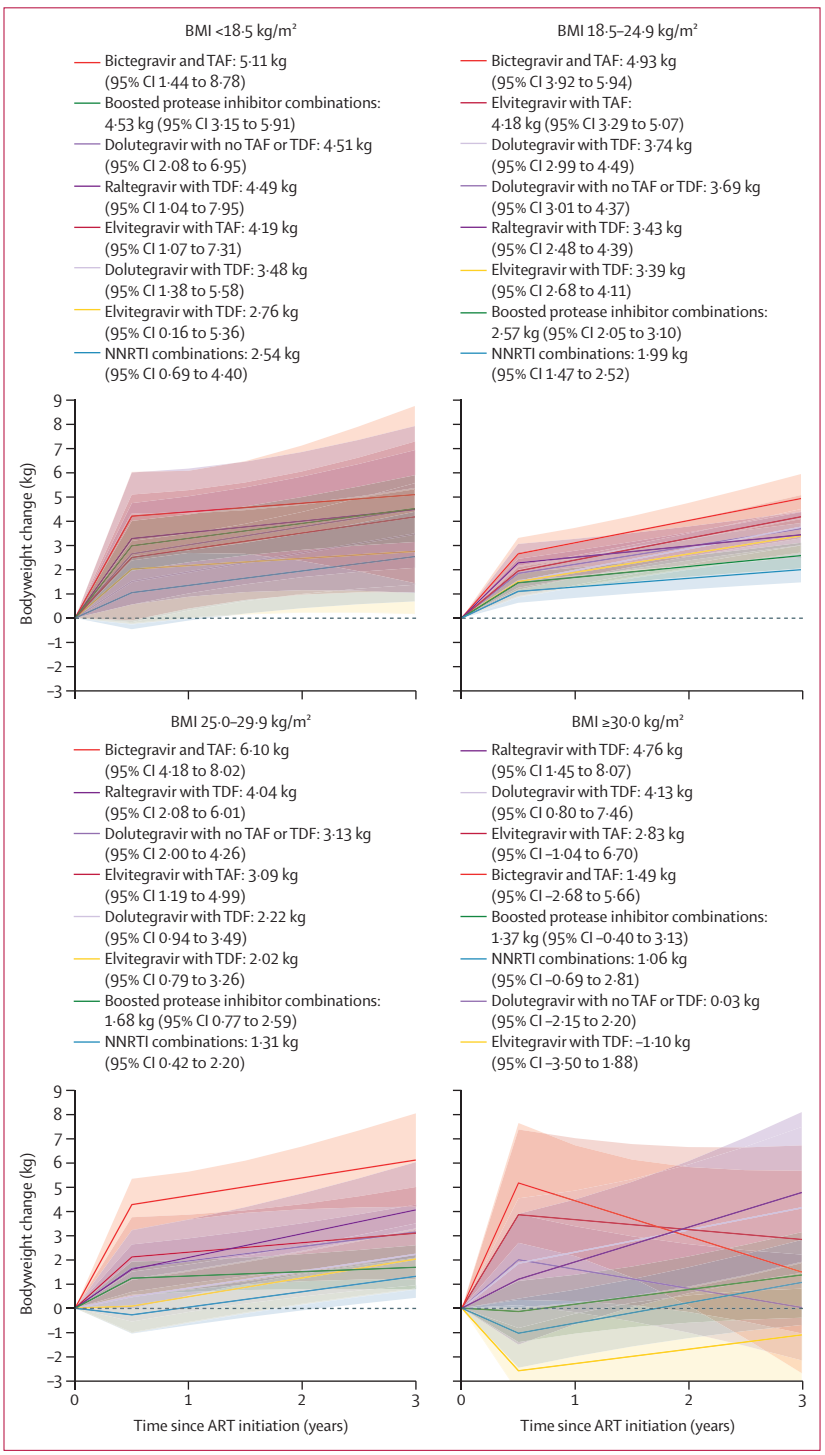

Figure 3: **Estimated bodyweight changes after ART initiation by ART regimen and baseline BMI**
Estimates shown for men who have sex with men, aged 30–39 years at seroconversion, originating from Europe or North America, with average height, baseline CD4 cell count, and HIV RNA. Data shown in each key are the estimated weight changes at 3 years. Shaded areas represent 95% CIs. ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. TAF=tenofovir alafenamide. TDF=tenofovir disoproxil fumarate.

	Estimated bodyweight change at 6 months, kg (95% CI)	Estimated bodyweight change at 3 years, kg (95% CI)
Women who have sex with men		
INSTI		
<18·5 kg/m²	3·59 (2·59 to 4·58)	5·84 (4·57 to 7·10)
18·5–24·9 kg/m²	2·91 (2·34 to 3·48)	5·63 (4·92 to 6·35)
25·0–29·9 kg/m²	2·65 (1·97 to 3·33)	5·13 (4·28 to 5·98)
≥30·0 kg/m²	2·81 (1·73 to 3·90)	3·79 (2·49 to 5·10)
Protease inhibitor		
<18·5 kg/m²	3·92 (2·82 to 5·03)	6·30 (4·82 to 7·78)
18·5–24·9 kg/m²	2·38 (1·79 to 2·97)	4·34 (3·58 to 5·09)
25·0–29·9 kg/m²	2·14 (1·38 to 2·90)	3·42 (2·41 to 4·44)
≥30·0 kg/m²	0·77 (–0·51 to 2·04)	3·12 (1·34 to 4·90)
NNRTI		
<18·5 kg/m²	1·97 (0·40 to 3·54)	4·31 (2·37 to 6·25)
18·5–24·9 kg/m²	2·03 (1·39 to 2·67)	3·77 (2·99 to 4·56)
25·0–29·9 kg/m²	0·64 (–0·22 to 1·51)	3·07 (2·04 to 4·10)
≥30·0 kg/m²	–0·11 (–1·56 to 1·35)	2·80 (0·99 to 4·60)
Individuals originating from sub-Saharan Africa		
INSTI		
<18·5 kg/m²	3·75 (2·75 to 4·75)	5·96 (4·70 to 7·22)
18·5–24·9 kg/m²	3·07 (2·50 to 3·64)	5·76 (5·06 to 6·46)
25·0–29·9 kg/m²	2·81 (2·13 to 3·49)	5·26 (4·42 to 6·09)
≥30·0 kg/m²	2·98 (1·87 to 4·09)	3·92 (2·57 to 5·26)
Protease inhibitor		
<18·5 kg/m²	4·09 (2·98 to 5·20)	6·43 (4·95 to 7·90)
18·5–24·9 kg/m²	2·54 (1·96 to 3·13)	4·46 (3·73 to 5·19)
25·0–29·9 kg/m²	2·30 (1·55 to 3·06)	3·55 (2·56 to 4·53)
≥30·0 kg/m²	0·93 (–0·35 to 2·21)	3·24 (1·45 to 5·04)
NNRTI		
<18·5 kg/m²	2·14 (0·55 to 3·72)	4·44 (2·49 to 6·39)
18·5–24·9 kg/m²	2·19 (1·56 to 2·83)	3·90 (3·14 to 4·65)
25·0–29·9 kg/m²	0·81 (–0·05 to 1·67)	3·19 (2·18 to 4·21)
≥30·0 kg/m²	0·06 (–1·42 to 1·54)	2·92 (1·09 to 4·75)
Men who have sex with men		
INSTI		
<18·5 kg/m²	2·44 (1·57 to 3·31)	4·02 (2·93 to 5·10)
18·5–24·9 kg/m²	1·76 (1·47 to 2·06)	3·82 (3·50 to 4·13)
25·0–29·9 kg/m²	1·50 (1·01 to 1·99)	3·31 (2·73 to 3·89)
≥30·0 kg/m²	1·67 (0·65 to 2·69)	2·44 (1·57 to 3·31)
Protease inhibitor		
<18·5 kg/m²	2·78 (1·77 to 3·79)	4·48 (3·12 to 5·84)
18·5–24·9 kg/m²	1·23 (0·88 to 1·59)	2·52 (2·06 to 2·98)
25·0–29·9 kg/m²	0·99 (0·35 to 1·64)	1·60 (0·73 to 2·47)
≥30·0 kg/m²	–0·38 (–1·63 to 0·87)	2·78 (1·77 to 3·79)
NNRTI		
<18·5 kg/m²	0·83 (–0·68 to 2·34)	2·49 (0·65 to 4·34)
18·5–24·9 kg/m²	0·88 (0·47 to 1·30)	1·95 (1·50 to 2·40)
25·0–29·9 kg/m²	–0·50 (–1·24 to 0·24)	1·25 (0·41 to 2·09)
≥30·0 kg/m²	–1·25 (–2·66 to 0·16)	0·83 (–0·68 to 2·34)

(Table 3 continues in next column)

(Continued from previous column)

Estimates from marginal means based on an adjusted mixed model. ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 3: **Estimates of bodyweight change at 6 months and 3 years following ART initiation by ART class and baseline BMI category for three subpopulations**

containing tenofovir alafenamide, regardless of the main drug in the regimen, as well as those starting tenofovir alafenamide with INSTI regimens. More specifically, regimens including bictegravir and tenofovir alafenamide were associated with the highest weight increases for individuals with baseline BMI less than 18·5 kg/m², 18·5–24·9 kg/m², and 25·0–29·9 kg/m².

With the advent of first and second generation INSTI drugs, cohorts of individuals with unknown HIV-1 infection durations have reported on differential bodyweight gains for those on INSTIs and tenofovir alafenamide,[5,6,20,21] with the first evidence from randomised trials coming from the NAMSAL trial[22] and the ADVANCE trial.[6] The mechanism for these differences is not known, although some have been suggested,[23] including the hypothesis that bodyweight gain on ART might be because of resultant changes in the intestinal microbiome, which might lead to altered gut integrity.[24] Therefore, the potential consequence on food malabsorption might differ by ART class or drug. Dolutegravir is known to suppress the production of adiponectin in fat cells, which is known to be suppressed in individuals with obesity.[25]

Also supporting findings from other studies,[5–7] we found that irrespective of drug class, bodyweight gain was higher for women who have sex with men than for MSM and was higher for individuals originating from sub-Saharan Africa than for people originating from other regions. It is likely that the observed increased risk for women who have sex with men is confounded by the effect of region of origin, which might be related to sex differences in food regulation[26] and fat mass at the same BMI,[27] as well as known differences in levels of HIV viraemia[28] and inflammatory cytokines.[29]

Although high BMI and ART-associated bodyweight gain contribute to cardiometabolic risk,[30,31] findings from the Veterans Aging Cohort Study reported that a 4·5–9·0 kg bodyweight gain for people with BMI 18·5–24·9 kg/m², but not for people with BMI greater than 24·9 kg/m², was associated with a reduced risk of mortality.[32] Furthermore, a meta-analysis of cohorts of individuals without HIV reported in 2020 that the risk of cardiovascular disease mortality was unchanged with weight gain of 0–5 kg.[33]

Although likely to be an undesirable consequence for individuals on ART, at least for those whose BMI is 18·5 kg/m² or more, the increase in bodyweight in our study participants might not present an immediate risk,

although longer term follow-up is required, as well as continual blood pressure monitoring and extra vigilance to guard against further bodyweight gain.

Our study had several limitations. We did not analyse bodyweight data from before ART initiation and have assumed that there had been no substantial change in bodyweight until the bodyweight measurement after HIV diagnosis became available. Therefore, we might have missed any early bodyweight changes, although this is unlikely given that bodyweight information was available within 3·5 months of estimated HIV seroconversion for 50% of our study participants. Additionally, immediate ART initiation was much more likely for those acquiring HIV from 2015 onwards, compared with those acquiring it in earlier time periods, following the publication of the START trial results.[34] The relatively short follow-up for those acquiring HIV from 2015 onwards might have led to a selection bias in modelling bodyweight data from before ART initiation.

We did not exclude data from pregnant women, or from transgender individuals who might be on gender-affirming hormone therapy, known to be associated with bodyweight gain, as we did not collect pregnancy status, and there were only two transgender individuals in our dataset.

Our study participants were mainly MSM originating from Europe or North America and findings might not be generalisable to other populations. However, the data did include a substantial number of women who acquired HIV through sex with men (n=492) and people originating from sub-Saharan Africa (n=474) and we were able to show differences in bodyweight gain between the sexes and regions of origin.

There is potential bias resulting from any differential frequency in bodyweight measurements by baseline BMI. However, we examined frequency of measurements and found no evidence for this (appendix p 6). We also modelled the time between subsequent visits and found that bodyweight at each visit or change in bodyweight (relative to the previous visit) had negligible effects on the time to the next visit. Additionally, if some individuals gain more bodyweight and switch ART class earlier and, therefore, have a shorter series of bodyweight measurements, the missing mechanism would be missing at random—ie, the probability of censoring would depend on already observed bodyweight measurements. Our use of maximum likelihood methods and the inclusion of all available measurements is expected to yield unbiased results.

As with all observational studies, our study might have remaining confounding factors and we cannot rule out differential choice of regimen based on patients' likely bodyweight trajectory. However, given the established literature on bodyweight gain and INSTIs and tenofovir alafenamide, it is unlikely that clinicians would be more likely to prescribe these drugs for people they assess as being at greater risk of bodyweight gain.

Our dataset comprised more than 5000 individuals, allowing us to examine associations between drug classes and specific drug combinations and bodyweight gain. The key strength of our study is the inclusion of individuals with well estimated dates of seroconversion starting ART soon after HIV-1 acquisition, thus ruling out the possible impact of prolonged durations of viraemia and its effect on bodyweight.

Given that participants in CASCADE initiated ART within 12 months of HIV seroconversion, the observed increase in bodyweight, particularly for those on INSTIs, tenofovir alafenamide, and a combination of INSTI and tenofovir alafenamide, is unlikely to be due to a return to health phenomenon and probably signals a direct effect of these drugs on bodyweight. The increased bodyweight might not present an immediate risk to health, but bodyweight management needs to be part of clinical care.

Contributors

Conceptualisation: CAS, NP, and KP. Data curation: SG, MVdV, IJ, AvS, LM, CC, JG, DC, and GT. Formal analysis: NP. Funding acquisition: KP. Methodology: NP. Supervision: KP. Writing the original draft: NP and KP. Reviewing and editing: all authors contributed equally. NP and KP have directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DC reports personal fees from Pfizer (2022) for a lecture outside the submitted work. JG reports advisory board fees from Merck, Gilead, and ViiV. NP has received grants unrelated to this study and paid to his institution from Gilead Sciences Hellas and European Centre for Disease Prevention and Control. All other authors declare no competing interests.

Data sharing

Data collected for the study can be shared under a signed data access agreement with bona fide researchers and only after approval of a proposal by CASCADE's executive and scientific committees. Applications for approval should be sent to the corresponding author.

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