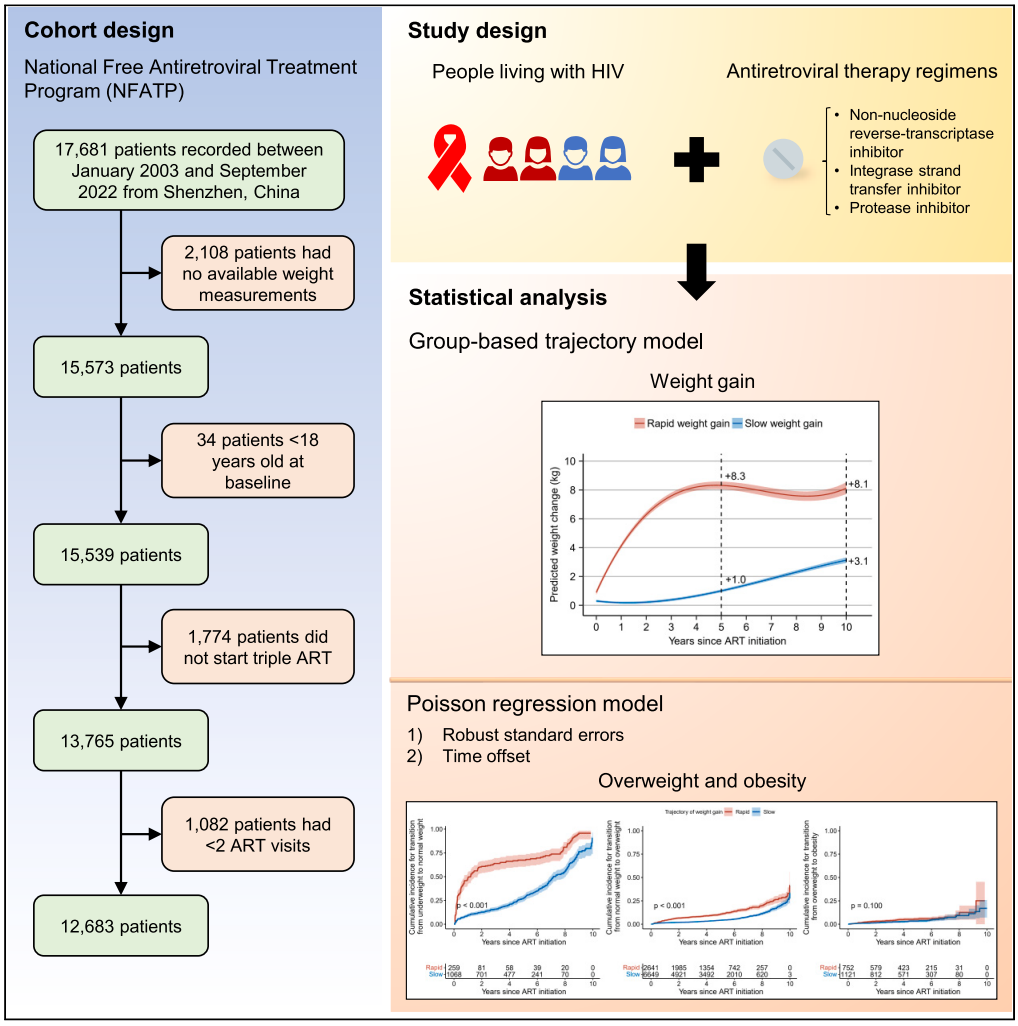
iScience

CellPress
OPEN ACCESS

Article

Longitudinal trajectories of weight changes among people living with HIV on antiretroviral therapy: A group-based study



Xinsheng Wu, Lukun Zhang, Zhen Lu, ..., Xinyi Zhou, Hui Wang, Huachun Zou

huiwang98@szsy.sustech.edu.cn (H.W.)
zouhuachun@fudan.edu.cn (H.Z.)

Highlights

PLHIV initiating DTG, RAL, or LPV-based ART showed higher risks of rapid weight gain

PLHIV on ART showed rapid and slow weight gain trajectories

Weight gain of PLHIV who initiated PI-based ART should not be ignored

Wu et al., iScience 26, 108259
November 17, 2023
https://doi.org/10.1016/j.isci.2023.108259

iScience

CellPress
OPEN ACCESS

Article

Longitudinal trajectories of weight changes among people living with HIV on antiretroviral therapy: A group-based study

Xinsheng Wu,[1,6] Lukun Zhang,[2,6] Zhen Lu,[1] Yuwei Li,[1] Yun He,[2] Fang Zhao,[2] Qiaoli Peng,[2] Xinyi Zhou,[1] Hui Wang,[2,*] and Huachun Zou[3,4,5,7,*]

SUMMARY

Weight changes vary among people living with HIV (PLHIV) on different antiretroviral therapy (ART) regimens. Here, we performed multi-trajectory modeling fitting growth mixture models (GMM) to identify longitudinal weight change trajectories of PLHIV. Multiple logistic regression was used to assess correlates of rapid weight gains; 12,683 PLHIV (median age: 34 years [interquartile range 29–42], 91.1% male) who initiated ART at the Third People's Hospital of Shenzhen, China, between January 2003 and September 2022 were included. We identified two trajectories: slow (70.5%) and rapid weight gains (29.5%). PLHIV who initiated ART with dolutegravir- (adjusted odds ratio [aOR] 2.46, 1.92–3.15), raltegravir- (2.74, 1.96–3.82), and lopinavir (1.62, 1.36–1.94)-based regimens were more likely to have rapid weight gains compared with efavirenz-based regimen. The monitoring of nutritional status should be strengthened for PLHIV who initiated these regimens during regular ART follow-ups.

INTRODUCTION

Antiretroviral therapy (ART) has revolutionized the management of and clinical outcomes in people living with HIV (PLHIV). Over the past few decades, the introduction and implementation of ART has been demonstrated to contribute to a reduction in HIV-related morbidity and mortality.[1,2]

In recent years, the utilization of integrase strand transfer inhibitor (INSTI) class drugs, particularly dolutegravir (DTG), as the modern first-line treatment for PLHIV has been widely recommended not only in the treatment-naive but also the treatment-switching settings since its global introduction.[3,4] However, despite their established favorable efficacy and superior safety profile compared to other drug classes according to randomized trials,[5–7] there have been some emerging concerns regarding the use of INSTIs in routine clinical care for PLHIV.[8,9] As the population continues to age, the incidence of non-AIDS comorbidities and associated risk factors is becoming more prevalent.[10] Over the past 20 years, weight gain or obesity has been observed in several PLHIV on ART.[11,12] Increasing data suggest that PLHIV who started INSTI or protease-inhibitor (PI)-based first-line ART experience more substantial weight gain compared with those who initiated non-nucleoside reverse-transcriptase inhibitor (NNRTI).[13–15] Practitioners must now take it into account a post-marketing safety signal when making clinical decisions because obesity is proven a significant risk factor for several critical comorbidities, such as cardiovascular disease, diabetes, and cognitive impairment.[16] A recent multicentre prospective study among 29,340 PLHIV[17] found that INSTIs initiation was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure, after accounting for known cardiovascular disease risk factors.

This post-approval observation of weight gains in PLHIV has presented a clinical conundrum. However, existing studies on this topic have some limitations. First, almost all studies have assumed a differential impact of different ART class use on PLHIV weight changes and then conducted subsequent verification, rather than conducting an exploratory analysis of the effects of different drugs based on differences in patient weight changes. Moreover, existing studies have not elucidated the impact of the nucleotide reverse-transcriptase inhibitors (NRTIs), such as tenofovir alafenamide fumarate (TAF) and tenofovir disoproxil fumarate (TDF), on PLHIV weight changes in combination with the third drug.[18–20] Finally, although some existing studies provide evidence on this topic partly, longer-term studies would yield results that are more practical and clinically relevant for PLHIV, given that HIV/AIDS has gradually become a chronic disease.

[1]School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, China
[2]National Clinical Research Centre for Infectious Diseases, The Third People's Hospital of Shenzhen and The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen, China
[3]School of Public Health, Fudan University, Shanghai, China
[4]School of Public Health, Southwest Medical University, Luzhou, China
[5]Kirby Institute, University of New South Wales, Sydney, NSW, Australia
[6]These authors contributed equally
[7]Lead contact
*Correspondence: huiwang98@szsy.sustech.edu.cn (H.W.), zouhuachun@fudan.edu.cn (H.Z.)
https://doi.org/10.1016/j.isci.2023.108259

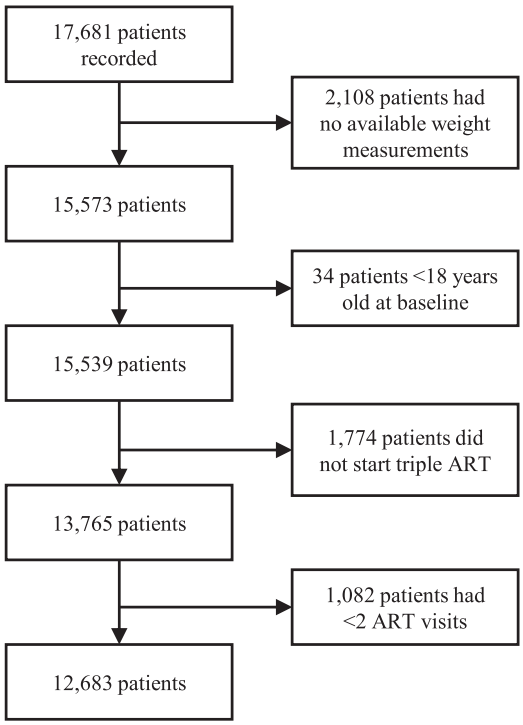


Figure 1. Patient flowchart

ART, antiretroviral therapy. Overall, 2,108 patients were excluded because they had no available weight measurements, 34 were excluded because they were <18 years old at baseline, 1,774 were excluded because they did not start triple ART, and 1082 were excluded because they had <2 ART visits.

In this study, we introduced a novel statistical method. We used multi-trajectory modeling[21] fitting growth mixture models (GMM)[22] to characterize how weight of PLHIV changes over time in Shenzhen, China. We further examined the factors of different weight gain groups, focusing on the regimens at ART initiation

RESULTS

Patient characteristics

We obtained 433,108 ART collection data for 17,681 PLHIV in the Third People's Hospital of Shenzhen, China between January 2003 and September 2022. After accounting for the inclusion and exclusion criteria, 60,935 observations for 12,683 patients were included in the analysis (Figure 1). Overall, 11,555 patients were male (91.1%), and the median age at enrollment into HIV care (baseline) was 34 years (IQR 29–42) (Table 1). The median observation time for each individual was 5.0 years (2.8–7.1).

Description of trajectory groups

The model identifying two trajectory groups had the most optimal data fit according to the Bayes Information Criteria (BIC) (Figure 2). The first trajectory group was individuals with rapid weight gain ("rapid gain" group, an average gain of 8.1 kg after 10 years) and was predicted to account for 29.5% of the population. And the second trajectory group was patients with slow weight gain ("slow gain" group, an average gain of 3.1 kg after 10 years) and was predicted to account for 70.5% of the population. Table S1 showed diagnostic metrics for the final model, indicating that it had a good data fit and an excellent separation of trajectory groups based on well-established metrics.

Incidence of transition to a higher BMI category by trajectory group membership

There were significantly different risks of incidence of transition to a higher BMI category by trajectory group membership (Figure 3 and Table 2). In the adjusted Poisson regression model, the rapid gain group had significantly increased rates of incidence of transition from underweight to normal weight (adjusted incidence rate ratio [aIRR] 4.08, 3.24–5.14), from normal weight to overweight (3.71, 3.14–4.38), and from overweight to obesity (3.24, 1.99–5.29) as compared with the slow weight gain group (Table 2). For PLHIV who had baseline CD4 $\leq$ 200, the rapid gain group had significantly increased rates of incidence of transition from underweight to normal weight (4.21, 3.08–5.74), from normal weight to overweight (3.79, 3.09–4.66), and from overweight to obesity (4.00, 2.18–7.32) as compared with the slow weight gain group. For PLHIV who had baseline CD4 >200, the rapid gain group had significantly increased rates of incidence of transition from underweight to normal weight (3.98, 2.82–5.62) and from normal weight to overweight (3.53, 2.67–4.67) as compared with the slow weight gain group.

Table 1. Baseline and follow-up characteristics of patients included in the study

Characteristic	Value	Value in trajectories		p value
		Rapid gain	Slow gain	
Total	12683	3742	8941	
Baseline age (%)				0.153
Median (IQR)	34(29–42)	34(29–41)	34(29–42)	
18-24	949(7.5)	232 (6.2)	717 (8.0)	
25-34	5580(44.0)	1752 (46.8)	3828 (42.8)	
35+	6154(48.5)	1758 (47.0)	4396 (49.2)	
Risk group (%)				<0.001
MSM	8444(66.6)	2480 (66.3)	5964 (66.7)	
Heterosexual male	3111(24.5)	992 (26.5)	2119 (23.7)	
Female	1128(8.9)	270 (7.2)	858 (9.6)	
Baseline height (cm)	170(165–174)	170(167–175)	170(165–174)	<0.001
Baseline weight (kg)	60(55–68)	60(55–67)	61(55–68)	<0.001
Baseline BMI status (%)				<0.001
Underweight	1327(10.5)	259 (6.9)	1068 (11.9)	
Normal weight	9290(73.2)	2641 (70.6)	6649 (74.4)	
Overweight	1873(14.8)	752 (20.1)	1121 (12.5)	
Obesity	193(1.5)	90 (2.4)	103 (1.2)	
Regimen at ART initiation (%)				<0.001
EFV	9973 (78.6)	2714 (72.5)	7259 (81.2)	
NVP	598 (4.7)	160 (4.3)	438 (4.9)	
Other NNRTIs	44 (0.3)	5 (0.1)	39 (0.4)	
DTG	301 (2.4)	166 (4.4)	135 (1.5)	
RAL	160 (1.3)	94 (2.5)	66 (0.7)	
EVG	606 (4.8)	268 (7.2)	338 (3.8)	
BIC	402 (3.2)	100 (2.7)	302 (3.4)	
LPV	599 (4.7)	235 (6.3)	364 (4.1)	
NRTI backbone (%)				<0.001
TAF-containing	1039 (8.2)	384 (10.3)	655 (7.3)	
TDF-containing	9403 (74.1)	2719 (72.7)	6684 (74.8)	
Others	2241 (17.7)	639 (17.1)	1602 (17.9)	
Virological failure during follow-up[a] (%)	787(6.2)	254 (6.8)	533 (6.0)	0.086
Year of ART initiation (%)				0.999
After 2016	8743(68.9)	2579 (68.9)	6164 (68.9)	
CD4 at ART initiation (cells/μL)				<0.001
Median (IQR)	248(176–365)	237(109–340)	263(196–376)	
HIV viral load at ART initiation (copies/mL log10-transformed)				<0.001
Median (IQR)	5.1(4.8–5.2)	5.1(5.0–5.3)	5.1(4.7–5.2)	

ART, antiretroviral therapy; IQR, interquartile range; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; EFV, efavirenz; NVP, nevirapine; Other NNRTIs: rilpivirine, doravirine, ainuovirine; DTG, dolutegravir; RAL, raltegravir; EVG, elvitegravir; BIC, bictegravir; LPV, lopinavir; NRTI, nucleotide reverse-transcriptase inhibitor; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

[a]Subjects were censored on the date when virological failure was confirmed.

Characteristics associated with trajectory group membership

The characteristics of PLHIV in different trajectory groups were shown in Table 1. Multiple logistic regression showed that using efavirenz (EFV)-based regimen at ART initiation as the reference, participants who initiated DTG- (adjusted odds ratio [aOR] 2.46, 1.92–3.15; Table 3),

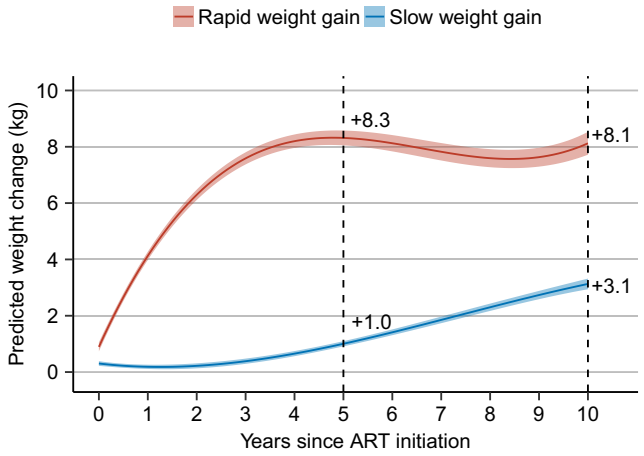


Figure 2. Trajectories of weight change among people living with HIV after antiretroviral therapy initiation

The figure shows trajectories of weight change among people living with HIV after ART initiation from 12,683 individuals. Shading around the lines represents confidence bands for the calculated trajectory.

raltegravir (RAL)- (2.74, 1.96–3.82), and lopinavir (LPV) (1.62, 1.36–1.94)-based regimens were more likely to be in the rapid weight gain group. Other factors associated with the increased risk of being in the rapid weight gain group included baseline age group (25–34: 1.42, 1.20–1.67; 35+: 1.27, 1.07–1.50), baseline height (1.05, 1.04–1.06), baseline weight (0.98, 0.97–0.98), baseline CD4 (0.94, 0.93–0.95), and baseline HIV viral load (1.14, 1.07–1.22).

Sensitivity analyses

Sensitivity analysis using Bolck-Croon-Hagenaars (BCH) method showed that the results were about consistent with the primary analyses (Table S2). However, compared with initiating ART regimens containing TAF, PLHIV who initiate ART regimens without both TAF and TDF have a lower risk of being in the rapid weight gain group (0.42, 0.20–0.92). Sensitivity analysis redefining the criteria for transition to a higher BMI category showed that the results were about consistent with the primary analyses (Table 2).

DISCUSSION

In this study, we identified two trajectories of weight change of PLHIV on ART: slow (70.5%) and rapid weight gains (29.5%). The rapid gain group had significantly increased rates of incidence of transition from underweight to normal weight (+308%), from normal weight to overweight (+271%), and from overweight to obesity (+224%), as compared with the slow gain group. PLHIV who initiated ART with DTG- (+146%), RAL- (+174%), and LPV (+62%)-based regimens were more likely to have rapid weight gains compared with EFV-based regimen. Our study highlights the need to strengthen nutritional status monitoring for PLHIV who initiated these regimens during regular ART collections.

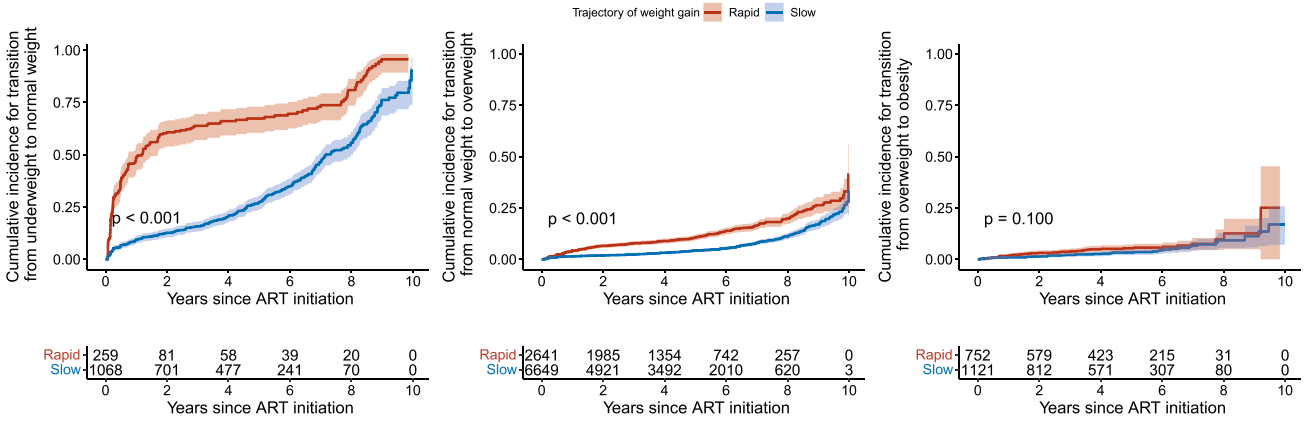


Figure 3. Kaplan–Meier estimates of the cumulative incidence for transition to a higher BMI category by trajectory group with bootstrapped 95% confidence intervals

ART, antiretroviral therapy. Underweight = BMI <18.5 kg/m^2. Normal weight = BMI from 18.5 to 24.9 kg/m^2. Overweight = BMI from 25 to 29.9 kg/m^2. Obesity = BMI ≥30 kg/m^2. p-values were calculated using the log-rank test.

Table 2. Poisson regression model for transition to a higher BMI category by trajectory of weight gain

	Underweight to normal weight		Normal weight to overweight		Overweight to obesity	
Trajectory of weight gain	aIRR (95% CI)	p	aIRR (95% CI)	p	aIRR (95% CI)	p
Total						
Slow weight gain	Ref.		Ref.		Ref.	
Rapid weight gain	4.08(3.24–5.14)	<0.001	3.71(3.14–4.38)	<0.001	3.24(1.99–5.29)	<0.001
Baseline CD4 $\leq$ 200						
Slow weight gain	Ref.		Ref.		Ref.	
Rapid weight gain	4.21(3.08–5.74)	<0.001	3.79(3.09–4.66)	<0.001	4.00(2.18–7.32)	<0.001
Baseline CD4 > 200						
Slow weight gain	Ref.		Ref.		Ref.	
Rapid weight gain	3.98(2.82–5.62)	<0.001	3.53(2.67–4.67)	<0.001	2.16(0.97–4.83)	0.059
Sensitivity analysis						
Slow weight gain	Ref.		Ref.		Ref.	
Rapid weight gain	4.38(3.55–5.41)	<0.001	3.33(2.73–4.07)	<0.001	3.28(1.78–6.06)	<0.001

IRR, adjusted incidence rate ratio; aIRR, adjusted incidence rate ratio.
Poisson regression model adjusted for baseline age group, risk group, height, weight, year of ART initiation, initial ART regimen, NRTI backbone, $CD4^+$ T cell count (square-root transformed), and HIV viral load (log10 transformed).

We adopted a different strategy from previous research by using the multi-trajectory modeling to identify distinct, latent subpopulations with different behavioral phenotypes.[21,22] This approach assumes that the overall population is consist of these subpopulations.[21,22] Within subgroups, individuals share similar trajectories of a single or multiple variables of interest. We did not presuppose any patterns of weight change but instead objectively classifies the heterogeneous latent subgroups based on the participants' response values. This strategy helps to more accurately distinguish PLHIV subgroups at risk of weight gain than grouping them based on ART regimen at ART initiation. Multi-trajectory modeling fitting GMM is a widely used method in longitudinal cohort-based studies, including studies of HIV disease progression,[23,24] study of depressive symptoms and dementia risk,[25] etc. Studies using multivariate linear mixed models showed similar sizes of weight gain to our study.

Based on our strategy, we were able to conduct a comprehensive analysis of real-world data and provide further evidence for the association between initial ART regimen and weight gain of PLHIV. In line with existing studies, we found an increased risk of rapid weight gain (an average gain of 8.1 kg after 10 years) with PLHIV who initiated DTG- (2.46, 1.92–3.15), RAL- (2.74, 1.96–3.82), and LPV (1.62, 1.36–1.94)-based regimens. In 2017, a short research letter of 2,260 PLHIV in France[26] reported that of 517 patients, 55 (10.6%) discontinued dolutegravir-based ART due to adverse effects, of which 7% of these adverse effects were abnormal weight gain (ranged between 4 and 12 kg). Since then, increasing data have found weight gain or obesity in PLHIV appears to be associated with the use of ART regimen. In 2020, a large observational cohort study using multivariate linear mixed effects models in the United States and Canada[27] found that PLHIV starting INSTI-based regimens had mean estimated five-year weight change of +5.9 kg, compared with +3.7 kg for NNRTI and +5.5 kg for PI. The exact underlying mechanisms are still to be identified but may include more rapidly reducing HIV-related inflammation and basal energy expenditure due to faster viral load suppression,[28] direct off-target effects of INSTIs,[14] and the effect of CYPB26 genotype.[29] We also found that low baseline weight was a risk factor for rapid weight gain. Potential reasons have been reported in previous studies.[30–34]

After accounting for bias caused by misclassification of trajectory group membership using the BCH method, we found that compared with initiating ART regimens containing TAF, PLHIV who initiate ART regimens without both TAF and TDF have a lower risk of being in the rapid weight gain group (0.42, 0.20–0.92). Our results once again demonstrate the promotive effect of ART regimens containing TAF on weight gain in PLHIV. A phase 3 randomized trial in South Africa[35] found that weight increase (both lean and fat mass) was greatest in the TAF-based group (mean increase, 6.4 kg in the TAF-based group, 3.2 kg in the TDF-based group). Pooled analyses including 8 Gilead-Sciences-sponsored trials of participants initiating ART between 2003 and 2015[15] found that among NRTIs, TAF was associated with more weight gain than TDF. In our analyses, although the point estimate for the TDF group was 0.58, we did not observe a significant protective effect due to the limited sample size.

The rapid gain group had significantly increased rates of incidence of transition from underweight to normal weight (aIRR 4.08, 3.24–5.14), from normal weight to overweight (3.71, 3.14–4.38), and from overweight to obesity (3.24, 1.99–5.29) as compared with the slow gain group. Obesity is proven a significant risk factor for many comorbidities, such as diabetes and cardiovascular disease, among others.[16] Obesity is also associated with decreased life expectancy.[36] Over the past four decades, China has experienced significant changes in society and economics.[37] Presently, China has the highest number of people with overweight and obesity.[38,39] However, regular weight measurement of PLHIV on ART has not received sufficient attention, mostly once a year. Recently, a large study assessed weight and BMI trajectories among PLHIV initiating ART across five countries in Latin America and the Caribbean, and the US[40] found that weight gain and obesity were prevalent

Table 3. Multiple logistic analysis of characteristics associated with being in the "rapid increase" trajectory group

	Model 1		Model 2	
Variables	OR (95% CI)	p value	aOR (95% CI)	p value
Baseline age group				
18–24	Ref.		Ref.	
25–34	1.41(1.21–1.66)	<0.001	1.42(1.20–1.67)	<0.001
35+	1.24(1.06–1.45)	0.009	1.27(1.07–1.50)	0.005
Risk group				
MSM	Ref.		Ref.	
Heterosexual male	1.13(1.03–1.23)	0.009	1.03(0.93–1.13)	0.582
Female	0.76(0.65–0.87)	<0.001	0.95(0.79–1.13)	0.554
Baseline height (cm)	1.02(1.02–1.03)	<0.001	1.05(1.04–1.06)	<0.001
Baseline weight (kg)	0.99(0.98–0.99)	<0.001	0.98(0.97–0.98)	<0.001
Regimen at ART initiation				
EFV	Ref.		Ref.	
NVP	0.98(0.81–1.18)	0.807	0.89(0.72–1.09)	0.265
Other NNRTIs	0.34(0.14–0.87)	0.024	0.40(0.16–1.04)	0.059
DTG	3.29(2.61–4.15)	<0.001	2.46(1.92–3.15)	<0.001
RAL	3.81(2.77–5.23)	<0.001	2.74(1.96–3.82)	<0.001
EVG	2.12(1.80–2.50)	<0.001	1.27(0.58–2.82)	0.550
BIC	0.89(0.70–1.12)	0.302	0.47(0.21–1.05)	0.066
LPV	1.73(1.46–2.05)	<0.001	1.62(1.36–1.94)	<0.001
NRTI backbone				
TAF-containing	Ref.		Ref.	
TDF-containing	0.69(0.61–0.79)	<0.001	0.58(0.27–1.26)	0.169
Others	0.68(0.58–0.80)	<0.001	0.54(0.25–1.19)	0.126
Year of ART initiation				
Before 2016	Ref.		Ref.	
After 2016	1.00(0.92–1.08)	0.982	1.00(0.90–1.10)	0.921
CD4 at ART initiation (cells/μl square-root transformed)	0.93(0.93–0.94)	<0.001	0.94(0.93–0.95)	<0.001
HIV viral load at ART initiation (copies/mL log10-transformed)	1.30(1.21–1.39)	<0.001	1.14(1.07–1.22)	<0.001

ART, antiretroviral therapy; NNRTI, non-nucleoside reverse-transcriptase inhibitor; EFV, efavirenz; NVP, nevirapine; Other NNRTIs: rilpivirine, doravirine, ainuovirine; DTG, dolutegravir; RAL, raltegravir; EVG, elvitegravir; BIC, bictegravir; LPV, lopinavir; NRTI, nucleotide reverse-transcriptase inhibitor; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

Model 1 was unadjusted; Model 2 was adjusted for individuals' demographic and clinical characteristics, including baseline age group, risk group, height, weight, year of ART initiation, initial ART regimen, NRTI backbone, $CD4^+$ T cell count (square-root transformed), and HIV viral load (log10 transformed).

in different countries and ethnicities. Our study provided a comprehensive analysis of real-world data. Given that the regimen at ART initiation, duration of ART use, and switching patterns of different ART drugs mostly increase the risk of rapid weight gain, HIV care providers should include monitoring of more nutritional indicators in PLHIV follow-up. The frequency of weight measurement of PLHIV on ART should be increased, and accessible prevention and treatment measures should be made available. A history and family history of obesity and its associated comorbidities should be taken into account on ART.

Our study suggested that LPV-based regimen use at ART initiation was associated with rapid weight gain of PLHIV. As revealed by nearly 20 years of research, PI have profound effect on serum and hepatic triglycerides, insulin signaling, body fat composition, and adipokine levels both in humans and mice.[41–43] However, most existing studies focused on the relationship between INSTI-based ART use and weight gain of PLHIV, whereas the impact of PI has not received sufficient attention. This may be due to the favorable efficacy, safety profile, and wide use of INSTI compared with other drug classes. Additionally, due to variations in the level of development and healthcare across different countries, commonly used ART regimens also vary. It was reported that NNRTI- and PI-based ART regimens were used mostly in low- and middle-income countries.[44,45] Therefore, weight gain of PLHIV who initiated PI-based ART should not be ignored in areas where PI use is common.

Limitations of the study

The key strength of our study lies in the identification of an association between weight gain in PLHIV and the initial ART regimens over a long period in China. Given that HIV/AIDS has gradually become a chronic disease, studies conducted over longer time spans will have more practical implications. Other strengths of our study include its population-based setting, long follow-up, and robust and novel analytic strategy. However, our study also has some limitations. Firstly, the trajectory groups we identified should be interpreted as an attempt to characterize and classify individuals based on the data available. The data were collected through a reporting system and thus may not accurately reflect the true picture, leading to the possibility of survivor effect bias. A few newly introduced ART drugs have a relatively short duration of use. Nonetheless, model diagnostics showed good data fit and clear distinctions between trajectory groups with relatively high average posterior probabilities. A sensitivity analysis considering the uncertainty associated with assigning trajectory group membership produced similar results. Additionally, we implemented a restricted cubic spline adjustment for the duration of individual observation to minimize bias. Overall, we successfully identified weight change trajectory groups in PLHIV that may be associated with the phenotype and classified patients into these groups. Secondly, our study was based on real-world data and therefore reflects the situation in the region, which may limit the generalizability of our findings. Finally, the study used HIV collection data from 2003 to 2022, a period during which China adjusted its ART standards several times.[46] The global COVID-19 pandemic and associated non-pharmacological interventions (NPIs) in 2020 have also significantly impacted the HIV care continuum and accurate reporting.[47,48] However, the good model fit suggested that this was unlikely to affect the general conclusions.

In conclusion, we identified different PLHIV weight trajectories and found that initial DTG-, RAL-, and LPV-based regimens and TAF-containing regimens were risk factors for rapid weight gain of PLHIV, which highlights the need to strengthen nutritional status monitoring during regularly ART follow-ups. Weight gain of PLHIV who initiated PI-based ART should not be ignored in areas where PI use is common (mainly low- and middle-income countries). Future studies are necessary to reveal the underlying mechanisms of these associations, as well as to guide clinical decision-making.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND SUBJECT DETAILS
  - Study design
- METHOD DETAILS
  - Outcomes and variables
  - Ethical statement
- QUANTIFICATION AND STATISTICAL ANALYSIS
  - Group-based trajectory model
  - Incidence of transition to a higher BMI category by trajectory group membership
  - Characteristics associated with trajectory group membership
  - Sensitivity analyses

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.108259.

ACKNOWLEDGMENTS

This study was supported by the Shenzhen Science and Technology Innovation Commission Basic Research Program [JCYJ20190807155409373], the Natural Science Foundation of China Excellent Young Scientists Fund [82022064], Natural Science Foundation of China International/Regional Research Collaboration Project [72061137001], the Sanming Project of Medicine in Shenzhen [SZSM201811071], the High Level Project of Medicine in Longhua, Shenzhen [HLPM201907020105], Special Support Plan for High-Level Talents of Guangdong Province [2019TQ05Y230], the Fundamental Research Funds for the Central Universities [58000-31620005], and the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences [2020-JKCS-030]. All funding parties did not have any role in the design of the study or in the explanation of the data. We thank all co-authors for their contributions and support for this study. We thank the editors and reviewer for their valuable insights and feedback.

AUTHOR CONTRIBUTIONS

X.W. conceived and designed the study in consultation with H.Z., H.W., and L.Z. H.Z., H.W., and L.Z. contributed to data collection. X.W. and L.Z. contributed to data analysis and presentation. X.W. and L.Z. drafted the manuscript with all authors critically reviewing the paper. All authors saw and approved the final report.

DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Received: June 26, 2023
Revised: August 7, 2023
Accepted: October 16, 2023
Published: October 20, 2023

REFERENCES

1. Antiretroviral Therapy Cohort Collaboration (2017). Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet. HIV *4*, e349–e356. https://doi.org/10.1016/S2352-3018(17)30066-8.
2. Fauci, A.S., and Lane, H.C. (2020). Four Decades of HIV/AIDS - Much Accomplished, Much to Do. N. Engl. J. Med. *383*, 1–4. https://doi.org/10.1056/NEJMp1916753.
3. Gandhi, R.T., Bedimo, R., Hoy, J.F., Landovitz, R.J., Smith, D.M., Eaton, E.F., Lehmann, C., Springer, S.A., Sax, P.E., Thompson, M.A., et al. (2023). Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society-USA Panel. JAMA *329*, 63–84. https://doi.org/10.1001/jama.2022.22246.
4. Ryom, L., Cotter, A., De Miguel, R., Béguelin, C., Podlekareva, D., Arribas, J.R., Marzolini, C., Mallon, P., Rauch, A., Kirk, O., et al. (2020). 2019 update of the European AIDS Clinical Society Guidelines for treatment of people living with HIV version 10.0. HIV Med. *21*, 617–624. https://doi.org/10.1111/hiv.12878.
5. Stellbrink, H.-J., Reynes, J., Lazzarin, A., Voronin, E., Pulido, F., Felizarta, F., Almond, S., St Clair, M., Flack, N., and Min, S.; SPRING-1 Team (2013). Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS *27*, 1771–1778. https://doi.org/10.1097/QAD.0b013e3283612419.
6. Walmsley, S.L., Antela, A., Clumeck, N., Duiculescu, D., Eberhard, A., Gutiérrez, F., Hocqueloux, L., Maggiolo, F., Sandkovsky, U., Granier, C., et al. (2013). Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N. Engl. J. Med. *369*, 1807–1818. https://doi.org/10.1056/NEJMoa1215541.
7. Zolopa, A., Sax, P.E., DeJesus, E., Mills, A., Cohen, C., Wohl, D., Gallant, J.E., Liu, H.C., Plummer, A., White, K.L., et al. (2013). A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. J. Acquir. Immune Defic. Syndr. *63*, 96–100. https://doi.org/10.1097/QAI.0b013e318289545c.
8. Trickey, A., Zhang, L., Gill, M.J., Bonnet, F., Burkholder, G., Castagna, A., Cavassini, M., Cichon, P., Crane, H., Domingo, P., et al. (2022). Associations of modern initial antiretroviral drug regimens with all-cause mortality in adults with HIV in Europe and North America: a cohort study. Lancet. HIV *9*, e404–e413. https://doi.org/10.1016/S2352-3018(22)00046-7.
9. Wu, X., Wu, G., Ma, P., Wang, R., Li, L., Chen, Y., Xu, J., Li, Y., Li, Q., Yang, Y., et al. (2023). Associations of modern initial antiretroviral therapy regimens with all-cause mortality in people living with HIV in resource-limited settings: a retrospective multicenter cohort study in China. Nat. Commun. *14*, 5334. https://doi.org/10.1038/s41467-023-41051-w.
10. Pelchen-Matthews, A., Ryom, L., Borges, Á.H., Edwards, S., Duvivier, C., Stephan, C., Sambatakou, H., Maciejewska, K., Portu, J.J., Weber, J., et al. (2018). Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. AIDS *32*, 2405–2416. https://doi.org/10.1097/QAD.0000000000001967.
11. Crum-Cianflone, N., Roediger, M.P., Eberly, L., Headd, M., Marconi, V., Ganesan, A., Weintrob, A., Barthel, R.V., Fraser, S., and Agan, B.K.; Infectious Disease Clinical Research Program HIV Working Group (2010). Increasing rates of obesity among HIV-infected persons during the HIV epidemic. PLoS One *5*, e10106. https://doi.org/10.1371/journal.pone.0010106.
12. Koethe, J.R., Jenkins, C.A., Lau, B., Shepherd, B.E., Justice, A.C., Tate, J.P., Buchacz, K., Napravnik, S., Mayor, A.M., Horberg, M.A., et al. (2016). Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada. AIDS Res. Hum. Retroviruses *32*, 50–58. https://doi.org/10.1089/aid.2015.0147.
13. Rebeiro, P.F., Jenkins, C.A., Bian, A., Lake, J.E., Bourgi, K., Moore, R.D., Horberg, M.A., Matthews, W.C., Silverberg, M.J., Thorne, J., et al. (2021). Risk of Incident Diabetes Mellitus, Weight Gain, and Their Relationships With Integrase Inhibitor-Based Initial Antiretroviral Therapy Among Persons With Human Immunodeficiency Virus in the United States and Canada. Clin. Infect. Dis. *73*, e2234–e2242. https://doi.org/10.1093/cid/ciaa1403.
14. Bourgi, K., Rebeiro, P.F., Turner, M., Castilho, J.L., Hulgan, T., Raffanti, S.P., Koethe, J.R., and Sterling, T.R. (2020). Greater Weight Gain in Treatment-naive Persons Starting Dolutegravir-based Antiretroviral Therapy. Clin. Infect. Dis. *70*, 1267–1274. https://doi.org/10.1093/cid/ciz407.
15. Sax, P.E., Erlandson, K.M., Lake, J.E., McComsey, G.A., Orkin, C., Esser, S., Brown, T.T., Rockstroh, J.K., Wei, X., Carter, C.C., et al. (2020). Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin. Infect. Dis. *71*, 1379–1389. https://doi.org/10.1093/cid/ciz999.
16. Kyrou, I., Randeva, H.S., Tsigos, C., Kaltsas, G., and Weickert, M.O. (2000). Clinical Problems Caused by Obesity. In Endotext, K.R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, W.W. de Herder, K. Dhatariya, K. Dungan, J.M. Hershman, J. Hofland, and S. Kalra, et al., eds. (MDText.com, Inc), pp. 5–25. Copyright © 2000-2022, MDText.com, Inc.
17. Neesgaard, B., Greenberg, L., Miró, J.M., Grabmeier-Pfistershammer, K., Wandeler, G., Smith, C., De Wit, S., Wit, F., Pelchen-Matthews, A., Mussini, C., et al. (2022). Associations between integrase strand-transfer inhibitors and cardiovascular disease in people living with HIV: a multicentre prospective study from the RESPOND cohort consortium. Lancet. HIV *9*, e474–e485. https://doi.org/10.1016/S2352-3018(22)00094-7.
18. Lake, J.E., Wu, K., Bares, S.H., Debroy, P., Godfrey, C., Koethe, J.R., McComsey, G.A., Palella, F.J., Tassiopoulos, K., and Erlandson, K.M. (2020). Risk Factors for Weight Gain Following Switch to Integrase Inhibitor-Based Antiretroviral Therapy. Clin. Infect. Dis. *71*, e471–e477. https://doi.org/10.1093/cid/ciaa177.
19. Kuo, P.-H., Sun, H.-Y., Chuang, Y.-C., Wu, P.-Y., Liu, W.-C., and Hung, C.-C. (2020). Weight gain and dyslipidemia among virally suppressed HIV-positive patients switching to co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Int. J. Infect. Dis. *92*, 71–77. https://doi.org/10.1016/j.ijid.2019.12.029.
20. Palella, F.J., Hou, Q., Li, J., Mahnken, J., Carlson, K.J., Durham, M., Ward, D., Fuhrer, J., Tedaldi, E., Novak, R., and Buchacz, K. (2023). Weight gain and metabolic effects in persons with HIV who switch to ART regimens containing integrase inhibitors or tenofovir alafenamide. J. Acquir. Immune Defic. Syndr. *92*, 67–75. https://doi.org/10.1097/QAI.0000000000003101.
21. Nagin, D.S., Jones, B.L., Passos, V.L., and Tremblay, R.E. (2018). Group-based multi-trajectory modeling. Stat. Methods Med. Res. *27*, 2015–2023. https://doi.org/10.1177/0962280216673085.
22. Nagin, D.S., and Odgers, C.L. (2010). Group-based trajectory modeling in clinical research. Annu. Rev. Clin. Psychol. *6*, 109–138. https://doi.org/10.1146/annurev.clinpsy.121208.131413.
23. Mody, A., Eshun-Wilson, I., Sikombe, K., Schwartz, S.R., Beres, L.K., Simbeza, S., Mukamba, N., Somwe, P., Bolton-Moore, C., Padian, N., et al. (2019). Longitudinal engagement trajectories and risk of death among new ART starters in Zambia: A group-based multi-trajectory analysis. PLoS Med. *16*, e1002959. https://doi.org/10.1371/journal.pmed.1002959.
24. Boussari, O., Subtil, F., Genolini, C., Bastard, M., Iwaz, J., Fonton, N., Etard, J.-F., and Ecochard, R.; ANRS 1215 study group (2015). Impact of variability in adherence to HIV antiretroviral therapy on the

immunovirological response and mortality. BMC Med. Res. Methodol. *15*, 10. https://doi.org/10.1186/1471-2288-15-10.

25. Mirza, S.S., Wolters, F.J., Swanson, S.A., Koudstaal, P.J., Hofman, A., Tiemeier, H., and Ikram, M.A. (2016). 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. Lancet Psychiatr. *3*, 628–635. https://doi.org/10.1016/S2215-0366(16)00097-3.
26. Menard, A., Meddeb, L., Tissot-Dupont, H., Ravaux, I., Dhiver, C., Mokhtari, S., Tomei, C., Brouqui, P., Colson, P., and Stein, A. (2017). Dolutegravir and weight gain: an unexpected bothering side effect? AIDS *31*, 1499–1500. https://doi.org/10.1097/QAD.0000000000001495.
27. Bourgi, K., Jenkins, C.A., Rebeiro, P.F., Palella, F., Moore, R.D., Altoff, K.N., Gill, J., Rabkin, C.S., Gange, S.J., Horberg, M.A., et al. (2020). Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J. Int. AIDS Soc. *23*, e25484. https://doi.org/10.1002/jia2.25484.
28. Bakal, D.R., Coelho, L.E., Luz, P.M., Clark, J.L., De Boni, R.B., Cardoso, S.W., Veloso, V.G., Lake, J.E., and Grinsztejn, B. (2018). Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. J. Antimicrob. Chemother. *73*, 2177–2185. https://doi.org/10.1093/jac/dky145.
29. Leonard, M.A., Cindi, Z., Bradford, Y., Bourgi, K., Koethe, J., Turner, M., Norwood, J., Woodward, B., Erdem, H., Basham, R., et al. (2021). Efavirenz Pharmacogenetics and Weight Gain Following Switch to Integrase Inhibitor-Containing Regimens. Clin. Infect. Dis. *73*, e2153–e2163. https://doi.org/10.1093/cid/ciaa1219.
30. Yuh, B., Tate, J., Butt, A.A., Crothers, K., Freiberg, M., Leaf, D., Logeais, M., Rimland, D., Rodriguez-Barradas, M.C., Ruser, C., et al. (2015). Weight change after antiretroviral therapy and mortality. Clin. Infect. Dis. *60*, 1852–1859. https://doi.org/10.1093/cid/civ192.
31. Madec, Y., Szumilin, E., Genevier, C., Ferradini, L., Balkan, S., Pujades, M., and Fontanet, A. (2009). Weight gain at 3 months of antiretroviral therapy is strongly associated with survival: evidence from two developing countries. AIDS *23*, 853–861. https://doi.org/10.1097/QAD.0b013e32832913ee.
32. Koethe, J.R., Lukusa, A., Giganti, M.J., Chi, B.H., Nyirenda, C.K., Limbada, M.I., Banda, Y., and Stringer, J.S.A. (2010). Association between weight gain and clinical outcomes among malnourished adults initiating antiretroviral therapy in Lusaka, Zambia. J. Acquir. Immune Defic. Syndr. *53*, 507–513. https://doi.org/10.1097/QAI.0b013e3181b32baf.
33. Maia Leite, L.H., and De Mattos Marinho Sampaio, A.B. (2010). Progression to overweight, obesity and associated factors after antiretroviral therapy initiation among Brazilian persons with HIV/AIDS. Nutr. Hosp. *25*, 635–640.
34. Mave, V., Erlandson, K.M., Gupte, N., Balagopal, A., Asmuth, D.M., Campbell, T.B., Smeaton, L., Kumarasamy, N., Hakim, J., Santos, B., et al. (2016). Inflammation and Change in Body Weight With Antiretroviral Therapy Initiation in a Multinational Cohort of HIV-Infected Adults. J. Infect. Dis. *214*, 65–72. https://doi.org/10.1093/infdis/jiw096.
35. Venter, W.D.F., Moorhouse, M., Sokhela, S., Fairlie, L., Mashabane, N., Masenya, M., Serenata, C., Akpomiemie, G., Qavi, A., Chandiwana, N., et al. (2019). Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N. Engl. J. Med. *381*, 803–815. https://doi.org/10.1056/NEJMoa1902824.
36. Fontaine, K.R., Redden, D.T., Wang, C., Westfall, A.O., and Allison, D.B. (2003). Years of life lost due to obesity. JAMA *289*, 187–193.
37. Wu, Y., Xue, H., Wang, H., Su, C., Du, S., and Wang, Y. (2017). The impact of urbanization on the community food environment in China. Asia Pac. J. Clin. Nutr. *26*, 504–513. https://doi.org/10.6133/apjcn.032016.09.
38. Wang, Y., Wang, L., and Qu, W. (2017). New national data show alarming increase in obesity and noncommunicable chronic diseases in China. Eur. J. Clin. Nutr. *71*, 149–150. https://doi.org/10.1038/ejcn.2016.171.
39. Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Mullany, E.C., Biryukov, S., Abbafati, C., Abera, S.F., et al. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet *384*, 766–781. https://doi.org/10.1016/S0140-6736(14)60460-8.
40. Coelho, L.E., Jenkins, C.A., Shepherd, B.E., Pape, J.W., Mejia Cordero, F., Padgett, D., Crabtree Ramirez, B., Grinsztejn, B., Althoff, K.N., Koethe, J.R., et al. (2022). Weight gain post-ART in HIV+ Latinos/as differs in the USA, Haiti, and Latin America. Lancet Reg. Health. Am. *8*, 100173. https://doi.org/10.1016/j.lana.2021.100173.
41. Pistell, P.J., Gupta, S., Knight, A.G., Domingue, M., Uranga, R.M., Ingram, D.K., Kheterpal, I., Ruiz, C., Keller, J.N., and Bruce-Keller, A.J. (2010). Metabolic and neurologic consequences of chronic lopinavir/ritonavir administration to C57BL/6 mice. Antiviral Res. *88*, 334–342. https://doi.org/10.1016/j.antiviral.2010.10.006.
42. Lenhard, J.M., Croom, D.K., Weiel, J.E., Spaltenstein, A., Reynolds, D.J., and Furfine, E.S. (2000). Dietary fat alters HIV protease inhibitor-induced metabolic changes in mice. J. Nutr. *130*, 2361–2366.
43. Tsiodras, S., Mantzoros, C., Hammer, S., and Samore, M. (2000). Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. Arch. Intern. Med. *160*, 2050–2056.
44. Mbhele, N., Chimukangara, B., and Gordon, M. (2021). HIV-1 integrase strand transfer inhibitors: a review of current drugs, recent advances and drug resistance. Int. J. Antimicrob. Agents *57*, 106343. https://doi.org/10.1016/j.ijantimicag.2021.106343.
45. Steegen, K., van Zyl, G., Letsoalo, E., Claassen, M., Hans, L., and Carmona, S. (2019). Resistance in patients failing integrase strand transfer inhibitors: a call to replace raltegravir with dolutegravir in third-line treatment in South Africa. Open Forum Infect. Dis. *6*, ofz377. https://doi.org/10.1093/ofid/ofz377.
46. Wu, X., Wu, G., Ma, P., Wang, R., Li, L., Sun, Y., Xu, J., Li, Y., Zhang, T., Li, Q., et al. (2023). Immediate and long-term outcomes after treat-all among people living with HIV in China: an interrupted time series analysis. Infect. Dis. Poverty *12*, 73. https://doi.org/10.1186/s40249-023-01119-7.
47. Zhao, T., Liu, H., Bulloch, G., Jiang, Z., Cao, Z., and Wu, Z. (2023). The influence of the COVID-19 pandemic on identifying HIV/AIDS cases in China: an interrupted time series study. Lancet Reg. Health. West. Pac. *36*, 100755. https://doi.org/10.1016/j.lanwpc.2023.100755.
48. Wu, X., Wu, G., Ma, Y., Huang, X., Yang, Y., Cai, Y., Luo, G., Ma, P., Qiao, Y., Chen, Y., et al. (2022). The impact of COVID-19 non-pharmaceutical interventions on HIV care continuum in China: An interrupted time series analysis. Lancet Reg. Health. West. Pac. *29*, 100569. https://doi.org/10.1016/j.lanwpc.2022.100569.
49. Zhang, F., Dou, Z., Ma, Y., Zhang, Y., Zhao, Y., Zhao, D., Zhou, S., Bulterys, M., Zhu, H., and Chen, R.Y. (2011). Effect of earlier initiation of antiretroviral treatment and increased treatment coverage on HIV-related mortality in China: a national observational cohort study. Lancet Infect. Dis. *11*, 516–524. https://doi.org/10.1016/S1473-3099(11)70097-4.
50. Ma, Y., Zhang, F., Zhao, Y., Zang, C., Zhao, D., Dou, Z., Yu, L., Fang, H., Zhu, T.Y., and Chen, R.Y. (2010). Cohort profile: the Chinese national free antiretroviral treatment cohort. Int. J. Epidemiol. *39*, 973–979. https://doi.org/10.1093/ije/dyp233.
51. Bray, B.C., Lanza, S.T., and Tan, X. (2015). Eliminating Bias in Classify-Analyze Approaches for Latent Class Analysis. Struct. Equ. Modeling. *22*, 1–11.
52. Proust-Lima, C., Letenneur, L., and Jacqmin-Gadda, H. (2007). A nonlinear latent class model for joint analysis of multivariate longitudinal data and a binary outcome. Stat. Med. *26*, 2229–2245.
53. Muthén, B., and Shedden, K. (1999). Finite mixture modeling with mixture outcomes using the EM algorithm. Biometrics *55*, 463–469.
54. World Health Organization-Regional Office for Europe. Body Mass Index-BMI. https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi.
55. Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. Am. J. Epidemiol. *159*, 702–706.
56. Zou, G.Y., and Donner, A. (2013). Extension of the modified Poisson regression model to prospective studies with correlated binary data. Stat. Methods Med. Res. *22*, 661–670. https://doi.org/10.1177/0962280211427759.
57. Bakk, Z., Tekle, F.B., and Vermunt, J.K. (2013). Estimating the Association between Latent Class Membership and External Variables Using Bias-adjusted Three-step Approaches. Socio. Methodol. *43*, 272–311. https://doi.org/10.1177/0081175012470644.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
HIV data in Shenzhen	Own data	NA
Software and algorithms		
R	https://www.r-project.org	NA

RESOURCE AVAILABILITY

Lead contact

Further information and requests for the processed data should be directed to and will be fulfilled by the lead contact, Huachun Zou (zouhuachun@fudan.edu.cn).

Materials availability

The study did not generate any new materials.

Data and code availability

- The raw data that support the findings of this study are not publicly available for confidentiality reasons, since these patients may be re-identified through various techniques. The processed data are available on reasonable request to the lead contact, with each request subject to ethical and legislative review from the data source.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Study design

We performed a group-based study using data retrieved from the National Free Antiretroviral Treatment Program database, which is managed by the National Center for AIDS/STD Control and Prevention, China Center for Disease Control and Prevention (China CDC). Further details on this database have been provided elsewhere.[49] Anonymized programmatic data on clinical testing and ART collection in PLHIV between January 2003 and September 2022 were collected from the Third People's Hospital of Shenzhen, China, which is the only designated hospital for HIV care in Shenzhen. We included all subjects who >18 years, started triple ART, had ≥2 ART visits, and had available weight measurements.

Method details

METHOD DETAILS

Outcomes and variables

We obtained baseline and follow-up data, including demographic, clinical information (exposures and outcomes), and laboratory test data from National Free Antiretroviral Treatment Program database. Additional information regarding data collection can be found elsewhere.[50] The outcome of interest was body weight change after ART initiation, initial ART regimen, and NRTI backbone. We defined weight change as the difference between each follow-up weight with measurement and the weight at baseline for each PLHIV. Baseline measures were those at ART initiation. The primary variables were the regimen at ART initiation, including NNRTI (EFV, nevirapine [NVP] and other NNRTIs [rilpivirine, doravirine, ainuovirine]), INSTI (DTG, RAL, elvitegravir [EVG] and bictegravir [BIC]) and PI (LPV) based ART. The NRTI backbone pairs were stratified as TAF-containing, TDF-containing, and others.

Ethical statement

No ethical approval is required for this study as no identifiable data has been analyzed.

QUANTIFICATION AND STATISTICAL ANALYSIS

Group-based trajectory model

We conducted a descriptive analysis to evaluate the baseline and clinical characteristics of PLHIV, using median (IQR) or percent with frequency, as appropriate. To identify the longitudinal patterns of weight change of PLHIV over time, we conducted a multi-trajectory modeling

fitting GMM, where the model parameters were estimated using the maximum likelihood method.[21,22] We tested multiple models with two to five trajectory groups and various polynomials of linear, quadratic, and cubic using the "forward" classification approach to determine the optimal number of trajectories and polynomials, and used the "backward" removal of non-significant higher-order trends to establish the form of each trajectory. We assigned individuals to the most likely trajectory group based on estimated maximum posterior probabilities.[51] Finally, we used the BIC and the interpretability of the model to determine the number of trajectories and polynomial orders.[52] The criterion for determining the best-fitting, most parsimonious model was that any given trajectory must contain at least 5% of the study population, and the posterior probability of randomly selected members of the population belonging to the corresponding group must be > 0.70.[53] Individuals were censored at the time of settling in new areas, or at the time of the first instance of virologic failure, or when changed their first-line ART regimen. We defined virologic failure as a plasma HIV-1 RNA level greater than 1000 (copies/mL), or the first of two consecutive detectable HIV-1 RNA measurements equal to or greater than 400 after having previous viral suppression. To address the collinearity of sex and transmission routes, we divided risk group into MSM, heterosexual male and female. To ease the linearity assumptions, we modeled baseline height, weight, CD4 and HIV viral load using restricted cubic splines with five knots. To facilitate interpretability, we assigned labels to the trajectories on the basis of their modeled graphic patterns.

Incidence of transition to a higher BMI category by trajectory group membership

Kaplan-Meier curves were employed to determine the cumulative incidences of transition from underweight to normal weight, from normal weight to overweight, and from overweight to obesity. We used the WHO classification,[54] which defines normal weight as a BMI of 18.5 to 24.9 kg/m^2, overweight as a BMI of 25 to 29.9 kg/m^2, and obesity as a BMI of $\geq$30 kg/m^2. We used a Poisson regression model with robust variances and a time offset adjusting for individuals' demographic and clinical characteristics, including baseline age group, risk group, height, weight, year of ART initiation, initial ART regimen, NRTI backbone, CD4$^+$ T cell count (square-root transformed) and HIV viral load (log10 transformed) to estimate incidence rate ratios of incidences of transition by trajectory group.[55,56] To explore the differences in weight gains among PLHIV with different baseline CD4 levels, we conducted a stratified analysis based on 200 cells/μl.

Characteristics associated with trajectory group membership

We characterized the sociodemographic and clinical characteristics of patients in each group by tabulating baseline individual information based on their assigned group according to their posterior probabilities. We used Kruskal-Wallis tests to assess the associations of continuous variables with the trajectory group and Pearson's chi-squared tests to examine the association between categorical variables and trajectory group. We conducted a multiple logistic regression to assess the factors of weight change patterns, focusing on regimen at ART initiation. We fitted two models: model 1 that was unadjusted; and model 2 that was adjusted for the same covariates described above.

Sensitivity analyses

We conducted two sensitivity analyses. Firstly, we used the modified BCH method, an alternative approach for assigning trajectory group membership.[51,57] We repeated analyses for factors associated with trajectory group membership using multiple logistic regression. This approach allowed us to examine the influence of the any uncertainties that arose from assigning group membership using maximum posterior probability assignment rule. Secondly, to minimize potential errors in determining the cumulative incidences of transition to a higher BMI category, we conducted a sensitivity analysis by redefining the criteria for transition to require two consecutive BMI results.

All statistical tests were two sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).