Obesity at antiretroviral therapy initiation and long-term risk of cardiovascular disease, cancer, or death in people with HIV in Italy: a prospective cohort study

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Summary

Background **Altered adipose tissue biology plays a key role in the development of cardiovascular disease (CVD) and cancer and contributes to mortality. We assessed the association between obesity in people with HIV (PWH) at antiretroviral therapy (ART) initiation and the risk of clinical events.**

Methods **In this prospective cohort study, we included ART-naïve adults PWH enrolled in the Italian Cohort Naive Antiretrovirals (Icona) Foundation study cohort in Italy across 96 sites between January 1997 and July 2025. Participants were included if they initiated ART, had body mass index (BMI) > 18.5 kg/m^2, and were free from AIDS, CVD, and cancer at ART initiation. Participants were classified as having obesity, defined as BMI ≥ 30 kg/m^2, or not having obesity, defined as BMI 18.5–29.9 kg/m^2, at ART initiation. The primary outcome was the first occurrence of CVD, cancer, or death. We performed a standard survival analysis with time-fixed covariates at baseline with a composite outcome of CVD/cancer/death. We hypothesized that age may be an effect measure modifier: results are presented after stratification by age (young [18–30], middle aged [31–60] and older [>60 years]).**

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Findings A total of 11,652 PWH (20.7% females, median age 38 years [Inter Quartile Range (IQR): 31, 46]) were included: 11,005 (94.4%) were people without obesity and 647 (5.6%) people with obesity. A total of 837 events were recorded: 122 CVD, 374 cancers and 341 deaths. By 15 years from ART initiation, the risk of CVD/cancer/death was 19.1% in people with obesity (95% Confidence Interval [CI]: 14.1–24.9%) vs. 12.4% in people without obesity (95% CI:11.3–13.4%, log-rank p = 0.0029). After controlling for confounding, the difference was attenuated (adjusted hazard ratio [aHR] 1.28 [95% CI:0.98–1.67], p = 0.073). Although we did not find evidence for interaction (p-value = 0.758) there was a trend for a larger effect among younger PWH: young (aHR 1.83 [95% CI 0.74, 4.56]), middle aged (aHR 1.49 [95% CI 1.11, 2.00]) and older (aHR 1.20 [95% CI 0.60, 2.41]).

Interpretation Obesity at ART initiation may be associated with a clinically meaningful increase in the risk of CVD, cancer, and death. We found weak evidence of a possible age-related gradient, with larger effect size in PWH under 60 years of age, which warrants further investigation.

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Keywords: HIV; Obesity; Cardiovascular disease; Cancer; Death

Research in context

Evidence before this study

We searched PubMed from database inception to 3 July 2026 for studies published in English using the terms "HIV", "obesity", "body mass index", "cardiovascular disease", "cancer", "mortality", and "antiretroviral therapy". A total of 14,245 studies were identified. Body weight abnormalities have long been recognized as clinically relevant in people with HIV (PWH). While underweight was historically linked to advanced disease and mortality, recent data suggest a growing epidemic of obesity among PWH. Adipose tissue plays a key role in chronic inflammation, immune activation, and viral persistence, potentially contributing to non-AIDS comorbidities. Observational studies in PWH have shown an association between body mass index (BMI) and diabetes, and cardiovascular disease (CVD), but causal link has been limited by confounding and study design. To date, no study has evaluated whether obesity at antiretroviral therapy (ART) initiation affects the long-term risk of CVD, cancer, or death in PWH.

Added value of this study

Our analysis of over 11,000 ART-naïve PWH receiving care in Italy identified an association between obesity at ART initiation and a higher subsequent risk of CVD, cancer, and death. Notably, this association was not consistent across age groups: the excess risk was more pronounced in younger and middle-aged individuals, suggesting potential age-related heterogeneity in the clinical consequences of obesity. Together with emerging evidence on the metabolic and anti-inflammatory benefits of novel weight-reducing therapies, these findings underscore the need to formally evaluate whether treating obesity at the time of ART initiation can improve long-term health outcomes in PWH. This may be particularly relevant at earlier stages of adult life.

Implications of all the available evidence

These findings provide new insight into the complex relationship between obesity and the development of age-related comorbidities in PWH, highlighting the importance of early metabolic risk assessment and prevention strategies at ART initiation. Obesity at ART initiation may be associated with a worse long-term clinical prognosis in PWH. We found weak evidence that there may be an age-related gradient, with higher risk among those younger than 60 years, which would be of clinical relevance if true and warrants further investigation.

Introduction

Body weight has long been a central concern in epidemiology and medical science in general. Obesity (defined as body mass index [BMI]>30) is a complex chronic disease associated with a markedly increased risk of serious clinical events. A causal link between obesity and the risk of morbidity, such as cardiovascular disease (CVD) and some types of cancers, has been reported in the general population.[1,2] The recent Lancet Commission on obesity further emphasized that obesity should be understood as a chronic, relapsing disease characterized not only by excess adiposity but also by evidence of organ dysfunction or substantial health impairment attributable to adipose tissue dysfunction.[3]

Recently, obesity has fallen under the spotlight in HIV research, as it has grown to be an epidemic within the community of people with HIV (PWH).[4] A single

centre study conducted in the US found a prevalence of obesity of around 28% among PWH.[5] However, the burden of obesity in PWH varies across settings and largely reflects the prevalence of obesity in those settings, underscoring the importance of contextual and population-level determinants.

The Copenhagen Comorbidity in HIV Infection Study reported that for a given BMI, PWH showed an independent almost two-fold higher risk of abdominal obesity compared to people without HIV,[6] highlighting a disproportionate burden of central adiposity and altered fat distribution in this population. The impact of obesity has previously been reported in antiretroviral therapy (ART)- experienced PWH. Data from the D:A:D study found an association between BMI and the risk of diabetes during ART, but there was insufficient evidence to support an association with the risk of CVD.[7]

Several mechanisms of association between obesity and morbidity and/or death have been postulated. Altered adipose tissue biology is a well-recognized driver of systemic inflammation and immune dysfunction.[8] Indeed, the co-existence of HIV infection and obesity seems to exponentially increase inflammation and create a substrate for the early onset of clinical complications during ART.[9]

Whether obesity at ART initiation influences long-term risk of major clinical outcomes in PWH remains unclear. In particular, it is unknown whether the association between baseline obesity and subsequent clinical events differ across age groups or by sex assigned at birth.

We aimed to assess the association between obesity at ART initiation and the risk of developing CVD, cancer, or death in PWH, and to investigate whether this association is modified by age and sex assigned at birth.

Methods

Study design

We included PWH enrolled in a prospective observational cohort of ART-naïve adults. Enrolment in the Italian Cohort Naive Antiretrovirals (Icona) Foundation study cohort began in 1st January 1997 and is still ongoing.[10] More than 20,000 Italian PWH have been enrolled so far across 96 centres. Collected data includes laboratory parameters (CD4 count, HIV-RNA), dates of ART initiation and interruption, and clinical events.[11,12]

The inclusion criteria for the present study specified PWH enrolled prior to 31 July 2025 and at ART initiation (i) were free from AIDS and any CVD or cancer, and (ii) BMI > 18.5. Underweight (BMI < 18.5) PWH were excluded.

The primary analysis is the composite outcome of CVD (myocardial infarction, coronary revascularization, cerebral hemorrhage and cerebral ischemia), cancer or death, as has been reported in meta-analyses of Mendelian randomization studies in the general population.[13] In line with previous studies, we excluded non-melanoma skin cancers from the endpoint.[14]

The secondary endpoints were: i) CVD + cancer (censoring persons' follow-up at time of death), ii) CVD + BMI-related cancers (hepatocellular, breast, colorectal, pancreatic, kidney, esophageal, gallbladder and corpus uteri) + death.[15]

Participants were grouped according to their BMI measured at ART initiation in people with obesity (≥30 kg/m^2) vs. people without obesity (18.5–29.9 kg/m^2).

Ethics

The institutional review boards of all participating centres approved the Icona Foundation Study. Each participant signed an informed consent according to committees' ethical standards and the Helsinki Declaration (October 2013). Patient engagement was sought at the annual Icona Foundation Study meeting (June 2025). The latest amendment of the Icona Foundation Study was approved centrally in July 2024 (Lazio Area 4 Territorial Ethics Committee approval 158 no. 83–2024). Reporting of the study follows the strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines.

Statistical analysis

Main participants' characteristics at ART initiation were described overall and stratified by BMI exposure groups (people with obesity vs. people without obesity).

Individuals with overweight were included in the reference group because BMI ≥30 kg/m^2 represents the established clinical threshold for obesity and associated adipose tissue dysfunction. In addition, previous HIV cohort studies have not consistently demonstrated excess risk among individuals with overweight compared with those of normal weight. A sensitivity analysis using three BMI categories (normal weight, overweight, and obesity) was conducted to explore potential differences across strata.[6]

Hypothesis testing was conducted by means of chi-square test for categorical variables and Mann–Whitney test for numerical variables. We also described the prevalence of obesity at ART initiation over time.

We performed a standard survival analysis with time-fixed covariates at baseline with the primary composite outcome described above. Follow-up started at ART initiation and ended at the first occurrence of the outcome of interest, last available clinical visit, or administrative censoring, whichever occurred first. Specifically, we performed unweighted and weighted (controlled for baseline confounding) Kaplan–Meier (KM) curves (up to 15 years follow-up). KM curves were compared with the log-rank test. Weighted

Kaplan–Meier curves were generated to provide a graphical representation of cumulative outcome risk after accounting for measured baseline differences between exposure groups. We used inverse probability of treatment weighting based on the estimated probability of obesity at ART initiation conditional on baseline covariates included in the adjusted Cox model: year of ART initiation, age, sex assigned at birth, mode of HIV acquisition, HIV-RNA and CD4 count at ART initiation, hepatitis co-infection, smoking, diabetes, level of education, and employment status. Covariate balance before and after weighting was assessed using absolute standardised mean differences, with values < 0.1 considered indicative of good balance. We did not use inverse probability of censoring weight as the analysis essentially uses cause-specific hazards. A standard proportional hazard Cox regression analysis conditioned on baseline covariates was conducted. We tabulated unadjusted and adjusted hazard ratios (HR) of the exposure. Adjusted HR (aHR) was controlled for by a set of confounders including a list of a priori variables identified as important predictors of outcome, exposure or both: year of ART initiation, age, sex assigned at birth, mode of HIV acquisition, HIV-RNA and CD4 count at ART initiation, hepatitis co-infection, smoking, diabetes, level of education and employment status. Blood pressure and lipid levels were not included in the primary adjustment set because they may represent intermediate factors in the pathway linking obesity to cardiovascular events and mortality.

We performed a sensitivity analysis using a 3-way categorization of the exposure of normal weight (BMI 18.5–24.9) and PWH with overweight into distinct groups. As an additional sensitivity analysis for the CVD/cancer endpoint, we fitted Fine–Gray subdistribution hazard models treating death as a competing event. Models were adjusted for the same baseline covariates as the main Cox regression models.

We also hypothesised at the outset that the effect of obesity on the risk of developing the clinical endpoint may differ according to sex and age. To evaluate effect-measure modification we stratified age using the cut-off of young (18–30), middle aged (31–60) and older (>60 years) and formally tested the interaction between exposure and age fitted as continuous. The age groups were set to maximize the statistical power of the proportions of PWH in the cohort at ART initiation (a very low proportion of participants aged 65+ were people with obesity). Because the analysis had low power to detect interactions, regardless of the p-value, we chose to present the results after stratification by age group. A specular analysis was conducted to investigate effect measure modification by sex assigned at birth.

All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and Stata (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Role of funding source

The Icona Foundation Study is supported by unrestricted grants from Gilead Sciences, ViiV Healthcare, Merck Sharpe & Dohme. The funders had no involvement in study design, data collection, data analyses, data interpretation, or the writing of the report.

Results

A total of 11,652 PWH (20.7% females, median age 38 years [Inter Quartile Range (IQR): 31, 46]) were included: 647 (5.6%) were people with obesity and 11,005 (94.4%) were people without obesity (8157 normal weight; 2848 overweight). Compared to PWH with obesity, PWH without obesity were younger (38 [IQR: 31, 45] vs. 41 [IQR: 35, 50] years, $p < 0.001$) and more frequently men who have sex with men (44.8% vs. 31.7%, $p < 0.001$). At ART initiation, PWH without obesity also had lower baseline CD4 count (349 [IQR: 221, 494] vs. 389 [IQR: 249, 556] cells/mm^3, $p < 0.001$) and lower prevalence of diabetes (1.5% vs. 6.8%, $p < 0.001$) (Tables 1 and 2). Supplementary Fig. S1 shows absolute standardised mean difference in factors comparing PWH with and without obesity before and after weighting. The prevalence and distribution of obesity at ART initiation over time is depicted in Supplementary Fig. S2. This figure shows that the prevalence of obesity has remained stable and close to the average estimate of 6% over time.

A total of 837 events were recorded: 122 CVD, 374 cancers and 341 deaths. Table 3 shows the breakdown of the components of the main composite outcome by exposure group. Individual cancer diagnoses and type of CVD events are reported in Supplementary Table S1. The breakdown of the components of the main composite outcome by age strata in people with obesity and people without obesity is reported in Supplementary Table S2.

Main composite endpoint analysis

The KM analysis estimated that up to 15 years from ART initiation, the risk of CVD, cancer or death was higher in people with obesity (19.1%; 95% Confidence Interval [CI]: 14.1–24.9%) vs. people without obesity (12.4%; 95% CI:11.3–13.4%, log-rank $p = 0.0029$) (Fig. 1A). Median follow-up, calculated as the arithmetic median of the survival time was 84 months (IQR 32–135). In the unadjusted Cox model, obesity at ART initiation was associated with a higher risk of CVD/cancer/death (HR 1.47, 95% CI 1.14–1.90, $p = 0.003$). However, after controlling for confounding, the difference in risk was attenuated, as shown by the weighted KM results (Fig. 1B). In the Cox regression model, after adjustment for baseline confounders, the point estimate remained compatible with a clinically relevant increase in risk (aHR 1.28, 95% CI 0.98–1.67, $p = 0.073$) (Table 4). Results were similar, although the magnitude

Characteristics	PWH without obesity	PWH with obesity	p-value[a]	Total
	N = 11,005	N = 647		N = 11,652
Baseline characteristics				
Sex at birth, n (%)			<0.001	
Female	2241 (20.4%)	171 (26.4%)		2412 (20.7%)
Male	8764 (79.6%)	476 (73.6%)		
Age, years			<0.001	
Median (IQR)	38 (31, 45)	41 (35, 50)		38 (31, 46)
Nationality, n (%)			0.126	
Not born in Italy	1999 (18.2%)	133 (20.6%)		2132 (18.3%)
Highest education level, n (%)			<0.001	
Primary school	628 (5.7%)	47 (7.3%)		675 (5.8%)
Middle school	2436 (22.1%)	145 (22.4%)		2581 (22.2%)
High school	3361 (30.5%)	181 (28.0%)		3542 (30.4%)
University	1377 (12.5%)	50 (7.7%)		1427 (12.2%)
Other/Unknown	3203 (29.1%)	224 (34.6%)		3427 (29.4%)
Employment, n (%)			<0.001	
Unemployed	1591 (14.5%)	91 (14.1%)		1682 (14.4%)
Employed	5025 (45.7%)	276 (42.7%)		5301 (45.5%)
Self-employed	1732 (15.7%)	97 (15.0%)		1829 (15.7%)
Occasional	347 (3.2%)	24 (3.7%)		371 (3.2%)
Student	395 (3.6%)	8 (1.2%)		403 (3.5%)
Retired	250 (2.3%)	20 (3.1%)		270 (2.3%)
Housewife	333 (3.0%)	26 (4.0%)		359 (3.1%)
Other/unknown	1312 (11.9%)	103 (15.9%)		1415 (12.1%)
Mode of HIV acquisition, n (%)			<0.001	
PWID	1685 (15.3%)	86 (13.3%)		1771 (15.2%)
MSM	4926 (44.8%)	205 (31.7%)		5131 (44.0%)
Heterosexual contacts	3995 (36.3%)	332 (51.3%)		4327 (37.1%)
Other/Unknown	399 (3.6%)	24 (3.7%)		423 (3.6%)
Hepatitis co-infection, n (%)			0.434	
HCV-Ab				
No	5726 (52%)	353 (54.6%)		6079 (52.2%)
Yes	1328 (12.1%)	69 (10.7%)		1397 (12%)
Not tested	3951 (35.9%)	225 (34.8%)		4176 (35.8%)
HBsAg			0.247	
No	6916 (62.8%)	422 (65.2%)		7338 (63)
Yes	58 (0.5%)	4 (0.6%)		62 (0.5%)
Not tested	4031 (36.6%)	221 (34.2%)		4252 (36.5%)
Psychiatric diagnosis, n (%)			0.279	
Yes	326 (3.0%)	24 (3.7%)		350 (3.0%)
Diabetes, n (%)			<0.001	
Yes	165 (1.5%)	44 (6.8%)		209 (1.8%)
Active injecting drug use, n (%)			0.356	
Yes	389 (4.2%)	27 (5.0%)		416 (4.2%)
Alcohol use, n (%)			0.816	
Abstain	2135 (19.4%)	133 (20.6%)		2268 (19.5%)
Social use	1651 (15.0%)	95 (14.7%)		1746 (15.0%)
Abuse	492 (4.5%)	32 (4.9%)		524 (4.5%)
Unknown	6727 (61.1%)	387 (59.8%)		7114 (61.1%)
Smoking, n (%)			0.001	
No	3179 (28.9%)	230 (35.5%)		3409 (29.3%)
Yes	3008 (27.3%)	160 (24.7%)		3168 (27.2%)
Characteristics at ART initiation				
Time from HIV diagnosis to ART initiation, months			0.268	
Median (IQR)	3 (1, 42)	4 (1, 46)		3 (1, 42)
Calendar year of ART initiation			0.002	
Median (IQR)	2013 (2004, 2017)	2014 (2008, 2018)		2013 (2004, 2017)

(Table 1 continues on next page)

Characteristics	PWH without obesity	PWH with obesity	p-value[a]	Total
	N = 11,005	N = 647		N = 11,652
(Continued from previous page)				
Type of first ART regimen, n (%)			0.033	
3TC + DTG	311 (2.8%)	32 (4.9%)		343 (2.9%)
PI/r	2980 (27.1%)	172 (26.6%)		3152 (27.1%)
NNRTI	2764 (25.1%)	153 (23.6%)		2917 (25.0%)
INSTI	3063 (27.8%)	173 (26.7%)		3236 (27.8%)
Other	1887 (17.1%)	117 (18.1%)		2004 (17.2%)
CD4 count, cells/mmc			<0.001	
Median (IQR)	349 (221, 494)	389 (249, 556)		351 (223, 498)
0–200 cells/mm^3, n (%)	2314 (21.9%)	113 (18.1%)		2427 (21.7%)
Viral load, log_{10} copies/mL			<0.001	
Median (IQR)	4.71 (4.15, 5.24)	4.58 (3.95, 5.04)		4.71 (4.14, 5.23)
Follow-up, months			0.634	
Median (IQR)	84 (32, 135)	83 (32, 132)		84 (32, 135)

PWH, people with HIV; *With obesity*, BMI >30; *without obesity*, BMI 18.5–29.9; *n*, number; *IQR*, Inter Quartile Range; *PWID*, people who inject drugs; *MSM*, men who have sex with men; 3TC, lamivudine; *DTG*, dolutegravir; *PI/r*, boosted protease inhibitor; *NNRTI*, non-nucleoside reverse transcriptase inhibitor; *INSTI*, integrase inhibitors; *BMI*, body mass index. [a]Chi-square or Kruskal–Wallis test as appropriate.

Table 1: **Main characteristics of people with HIV (PWH) at antiretroviral therapy (ART) initiation, stratified by exposure group (PWH with obesity and without obesity): Sociodemographic characteristics and lifestyle behaviours.**

of the association was attenuated, when we analysed the endpoint considering only comorbidities (aHR 1.08 [95% CI 0.75, 1.55], p = 0.67) and after restricting cancers to BMI-related cancers (aHR 1.17 [95% CI 0.86, 1.60], p = 0.31) (Supplementary Table S3).

Sensitivity analysis

In the sensitivity analysis using three BMI categories (normal weight [reference group], overweight and obesity], overweight was not associated with the composite endpoint after adjustment for baseline confounders (aHR 0.92 [95% CI 0.78–1.08], p = 0.307). The adjusted estimate for obesity vs. normal weight was consistent with that of the primary analysis comparing obesity with non-obesity (aHR 1.26, 95% CI 0.96–1.66, p = 0.098) (Supplementary Table S3).

Effect measure modification by age and sex

Overall, there was no formal evidence for an interaction with age (p = 0.758). However, KM curves stratified by age suggested that the risk of developing a clinical event associated with obesity at ART initiation was higher among the young and middle aged compared to the older PWH (Supplementary Fig. S3A–C). These findings persisted after adjustment for confounding factors, with a trend toward larger effect sizes in younger participants (aHR 1.83 [95% CI 0.74–4.56]), more modest estimates in middle-aged individuals (aHR 1.49 [95% CI 1.11–2.00]), and smaller estimates in older participants (aHR 1.20 [95% CI 0.60–2.41]) (Table 5). However, the limited number of events within each stratum reduced the precision of these estimates.

Finally, data carried no formal evidence for an interaction between obesity and sex assigned at birth after controlling for confounding with similar magnitude of aHR among males (aHR 1.38 [95% CI 1.04, 1.84]) and females (aHR 1.42 [95% CI 0.77, 2.62], p = 0.93, Supplementary Fig. S4A and B and Table 6).

Discussion

Our analysis shows that, when compared to PWH without obesity, PWH with obesity at ART initiation have a 28% higher risk of developing CVD, cancer or death after controlling for confounding. Although the magnitude of the association was attenuated after multivariable adjustment, its consistency across analyses and overall size suggests a clinically meaningful increase in risk. Of note, the point estimates were larger among young and middle aged PWH with obesity. In particular, we found weak evidence of a possible age-related gradient, with larger effect size in PWH under 60 years of age. Indeed, the interaction test did not formally provide statistical evidence of effect modification, and the estimates were uncertain due to the low number of events per age strata. Nevertheless, if confirmed in other studies, this finding has potential clinical relevance, identifying PWH under the age of 60 who have obesity at ART initiation as a group at higher risk of developing serious clinical outcomes.

At baseline, the prevalence of obesity in our cohort was 5.6% and remained stable over time. These data are consistent with national prevalence estimates in the general population in Italy, suggesting that obesity in PWH is not HIV-specific. The observed prevalence of obesity appears lower than expected, although it should be interpreted in the context of estimates from ART-naïve populations. Indeed, the discrepancy when

Characteristics	Total	PWH without obesity	PWH with obesity	p-value[a]
	N = 11,652	N = 11,005	N = 647	
Baseline characteristics				
Hepatitis co-infection, n (%)				0.434
HCV-Ab				
No	6079 (52.2%)	5726 (52%)	353 (54.6%)	
Yes	1397 (12%)	1328 (12.1%)	69 (10.7%)	
Not tested	4176 (35.8%)	3951 (35.9%)	225 (34.8%)	
HBsAg				0.247
No	7338 (63%)	6916 (62.8%)	422 (65.2%)	
Yes	62 (0.5%)	58 (0.5%)	4 (0.6%)	
Not tested	4252 (36.5%)	4031 (36.6%)	221 (34.2%)	
Psychiatric diagnosis, n (%)				0.279
Yes	350 (3.0%)	326 (3.0%)	24 (3.7%)	
Diabetes, n (%)				<0.001
Yes	209 (1.8%)	165 (1.5%)	44 (6.8%)	
Characteristics at ART initiation				
Time from HIV diagnosis to ART initiation, months				0.268
Median (IQR)	3 (1, 42)	3 (1, 42)	4 (1, 46)	
Calendar year of ART initiation				0.002
Median (IQR)	2013 (2004, 2017)	2013 (2004, 2017)	2014 (2008, 2018)	
Type of first ART regimen, n (%)				0.033
3TC + DTG	343 (2.9%)	311 (2.8%)	32 (4.9%)	
PI/r	3152 (27.1%)	2980 (27.1%)	172 (26.6%)	
NNRTI	2917 (25.0%)	2764 (25.1%)	153 (23.6%)	
INSTI	3236 (27.8%)	3063 (27.8%)	173 (26.7%)	
Other	2004 (17.2%)	1887 (17.1%)	117 (18.1%)	
CD4 count, cells/mmc				<0.001
Median (IQR)	351 (223, 498)	349 (221, 494)	389 (249, 556)	
0–200 cells/mm^3, n (%)	2427 (21.7%)	2314 (21.9%)	113 (18.1%)	
Viral load, $\log_{10}$ copies/mL				<0.001
Median (IQR)	4.71 (4.14, 5.23)	4.71 (4.15, 5.24)	4.58 (3.95, 5.04)	
Follow-up, months				0.634
Median (IQR)	84 (32, 135)	84 (32, 135)	83 (32, 132)	

With obesity, BMI >30; *without obesity*, BMI 18.5–29.9; *n*, number; *IQR*, Inter Quartile Range; 3TC, lamivudine; *DTG*, dolutegravir; *PI/r*, boosted protease inhibitor; *NNRTI*, non-nucleoside reverse transcriptase inhibitor; *INSTI*, integrase inhibitors. [a]Chi-square test for categorical variables and Wilcoxon rank-sum test for numerical variables.

Table 2: **Main characteristics of people with HIV (PWH) at antiretroviral therapy (ART) initiation, stratified by exposure group (PWH with obesity and without obesity): clinical characteristics.**

comparing with higher prevalences reported in other studies, may be explained by differences in duration of ART exposure or by other factors, such as population-specific characteristics including diet or genetic background. In ART-naïve or early ART, other European/Mediterranean cohorts have reported similar obesity prevalence to our study, with approximately 5.0% in AMACS in Greece[16] and 6.4% in the CAPOTA study in Southern Spain.[17] A Brazilian cohort reported an estimate of 7.9% but by contrast,[18] North American cohorts

Clinical events, n (%)	PWH without obesity	PWH with obesity	Total	p value
CVD	112 (14.5%)	10 (15.6%)	122 (14.6%)	0.794
Cancer	348 (45.0%)	26 (40.6%)	374 (44.7%)	
BMI related	114 (14.7%)	5 (7.8%)	119 (14.2%)	
Non-BMI related	234 (30.3%)	21 (32.8%)	255 (30.5%)	
Death	313 (40.5%)	28 (43.8%)	341 (40.7%)	
Total	**773 (100%)**	**64 (100%)**	**837 (100%)**	

With obesity, Body mass index (BMI) > 30; *without obesity*, BMI 18.5–29.9; *CVD*, cardiovascular disease.

Table 3: **Clinical events observed throughout follow-up.**

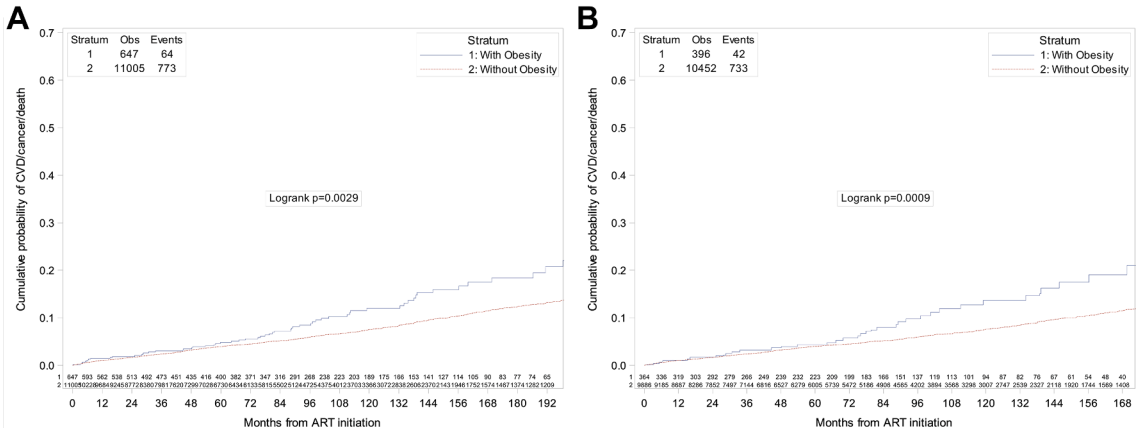

Fig. 1: Unweighted (A) and weighted (B) Kaplan–Meier curves of the main outcome: risk of cardiovascular disease (CVD), cancer or death according to the exposure. p values were calculated using the log-rank test. Numbers below the curves indicate the number of participants at risk at each time point. ART, antiretroviral therapy; CVD, cardiovascular disease.

have reported substantially higher baseline obesity prevalence, ranging between 15% and 20%.[19,20] These differences probably reflect geographical variation in background obesity prevalence, case-mix, calendar period, baseline immune status, and BMI ascertainment methods. Therefore, our estimate appears plausible for an Italian ART-naïve cohort, but in countries with higher baseline obesity prevalence, the population-attributable burden of obesity-related complications in PWH may be substantially greater.

In the general population, both overweight and obesity are associated with an increasing risk of all-cause mortality.[21] In the D:A:D study including PWH, the highest risk of all-cause mortality was among those with obesity or underweight.[7] Despite differences in the selection of study populations and timing of BMI assessment, our study confirmed obesity as an important determinant of long-term outcome.

Despite a lack of significance in the interaction test our adjusted estimates suggest that the risk of developing CVD, cancer or death varied by age with a trend for a larger effect size of obesity in younger age groups. When ordered by magnitude of effect, the association was strongest among individuals aged 18–30 years, intermediate among those aged 31–60 years, and weakest among those older than 60 years. The higher risk among young PWH with obesity may be due to the early development of co-morbidities (premature ageing) observed in PWH compared to people without HIV, and obesity may further accelerate this process.[22] The inflammatory effect of obesity becomes less dominant with increasing age due to age-related immune modifications; the so-called immunosenescence. This may explain the smaller difference in risk in PWH with or without obesity among the older PWH.[23] Although age-specific estimates may reflect a true biological effect, age-dependent biases may have also played a role, including differential misclassification of adiposity (e.g., BMI poorly reflects metabolic risk in older adults due to sarcopenia) as well as selective survival (older participants with obesity may represent a selected group more resilient to severe clinical events) and competing risks (older people are at higher risk of dying for other causes).[24]

Our study did not find any evidence that sex at birth was an effect measure modifier for the association of interest. It was shown that sex-related differences in adipose tissue distribution, hormonal milieu, and metabolic regulation can lead to distinct obesity trajectories and cardiometabolic consequences. In the general population, women accumulate more subcutaneous adipose tissue, while men show greater

	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
CVD/cancer/death				
PWH without obesity	1		1	
PWH with obesity	1.47 (1.14, 1.90)	0.003	1.28 (0.98, 1.67)	0.073

Multivariable models included year of antiretroviral therapy (ART) initiation, age, sex assigned at birth, mode of HIV acquisition, HIV-RNA and CD4 at ART, hepatitis co-infection, smoking, diabetes, level of education and employment status as covariates.

Table 4: **Risk of cardiovascular disease (CVD)/cancer/death by exposure group (Hazard Ratio (HR)–standard Cox proportional hazard regression models): overall risk.**

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Interaction p-value
CVD/cancer/death by age strata			
Young (18–30 years)			
PWH without obesity	1	1	
PWH with obesity	1.76 (0.71, 4.35)	1.83 (0.74, 4.56)	
Middle age (31–60 years)			p = 0.76
PWH without obesity	1	1	
PWH with obesity	1.37 (1.03, 1.83)	1.49 (1.11, 2.00)	
Older (> 60 years)			
PWH without obesity	1	1	
PWH with obesity	1.16 (0.58, 2.30)	1.20 (0.60, 2.41)	

Multivariable model included year of ART initiation, sex assigned at birth, mode of HIV acquisition, HIV-RNA and CD4 at ART, hepatitis co-infection, smoking, diabetes, level of education and employment status as covariates.

Table 5: **Risk of cardiovascular disease (CVD)/cancer/death by exposure group (Hazard Ratio (HR)–standard Cox proportional hazard regression models): risk stratified by age group.**

visceral fat deposition, conferring higher cardiometabolic risk.[25] BMI is likely to be unable to capture differences in adipose tissue distribution. General data on the interaction between sex at birth and obesity for predicting clinical outcome are conflicting. The Women's Interagency HIV Study did not find an increased risk of mortality among women classified as overweight or with obesity.[26] A cross-sectional study showed that higher BMI and excessive ectopic fat burden among PWH on ART were associated with circulating markers of systemic inflammation.[27]

Following the adoption of integrase inhibitors as the preferred ART regimen, several studies have reported weight gain during treatment.[28] In light of our findings suggesting an association between obesity at ART initiation and poorer clinical outcomes in PWH, clinicians should be encouraged to address obesity from the time of starting therapy.

With the introduction of glucagon-like peptide (GLP)-1 receptor-agonists, the objective of reducing excessive weight seems more clinically achievable.[29] In the general population, short term data suggest that GLP-1 receptor-agonists reduce CVD event risk.[30] Data in PWH are limited, but it has been hypothesized that a positive effect on metabolic-dysfunction-associated steatohepatitis may contribute to reducing CVD and cancer risks.[31] A randomized double-blinded study in PWH showed that once-weekly semaglutide reduces visceral fat by 30.6%. Sub-analysis data suggest that inflammation decreases, offering a further protective effect.[32] Our results raise the hypothesis that earlier identification and treatment of obesity, particularly among younger PWH, could modify long-term risk trajectories. Nevertheless, access to GLP-1 receptor agonists remains uneven, and reimbursement is often restricted to individuals with diabetes, raising concerns about socioeconomic disparities in preventive care. Compared to people without HIV, PWH are at higher risk of CVD and several cancers, mostly due to chronic low-grade inflammation.[33] In the Icona cohort, soluble markers of inflammation are not routinely collected, thus we could not include them in our analysis, and therefore further studies are needed.

Our study has several limitations. In observational studies, BMI as an exposure has been the target of controversies in epidemiology, mainly in establishing associations or causal links between BMI (or a change in BMI) and clinical outcome.[2] The relatively low prevalence of obesity at ART initiation in our cohort limited the precision of subgroup analyses and restrict generalisability to populations with higher baseline obesity prevalence or larger studies. Smoking status

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Interaction p-value
CVD/cancer/death by sex at birth			
Male			
PWH without obesity	1	1	
PWH with obesity	1.59 (1.20, 2.10)	1.38 (1.04, 1.84)	
Female			p = 0.93
PWH without obesity	1	1	
PWH with obesity	1.10 (0.60, 2.02)	1.42 (0.77, 2.62)	

Multivariable models included year of ART initiation, age, mode of HIV acquisition, HIV-RNA and CD4 at ART, hepatitis co-infection, smoking, diabetes, level of education and employment status as covariates. *PWH*, people with HIV; *ART*, antiretroviral treatment; *HR*, hazard ratio; *CI*, confidence interval.

Table 6: **Risk of cardiovascular disease (CVD)/cancer/death by exposure group (Hazard Ratio (HR)–standard Cox proportional hazard regression models): risk stratified by sex at birth.**

and alcohol use had a high proportion of missing or unknown values which may have introduced bias in our "missing indicator" analysis. Several factors considered common causes of obesity and risk of clinical progression are not typically measured in HIV studies (i.e., diet, physical activity, asymptomatic clinical diseases and complex genetic factors or interactions of genetic and environmental factors) so unmeasured confounding cannot be ruled out. Nevertheless, in sophisticated analyses in which unmeasured confounding is expected to be minimal, such as Mendelian randomisation studies, a causal link between BMI and clinical risk has been reported.[13] Besides the issue of unmeasured confounding, there was also a potential issue with information bias and misclassification of the outcome as some events may not have been precisely documented (e.g., for cancers). However, a large effort has recently been carried out by Icona investigators to improve the quality of data.[12] Also, our analysis was likely underpowered for single events (CVD, cancer or death). Reassuringly, secondary analysis of alternative end points, including CVD and cancer with death as non-informative censoring or treated as a competing risk, reported similar results to those of our primary analyses. With regards to the exposure, BMI was the sole anthropometric measure available. Incorporating measures of central obesity or body composition would likely provide a more precise risk stratification. Despite the intrinsic limitations of BMI, as we showed that obesity at ART-initiation may be a marker of increased long-term clinical vulnerability, our study provides actionable information for early risk stratification in routine HIV care. Finally, regarding potential mechanisms underlying our findings, it is known that PWH are at increased risk of CVD and several cancers, largely driven by chronic low-grade inflammation.[30] However, in the Icona cohort, soluble markers of inflammation are not routinely collected and therefore could not be included in our analysis.

In conclusion, our analysis suggests that obesity at ART initiation may be associated with a worse long-term clinical prognosis in PWH. Obesity at ART initiation may not only be a peripheral metabolic comorbidity but also an early marker of long-term clinical vulnerability. We found weak evidence that there may be an age-related gradient, with higher risk among those younger than 60 years, which would be of clinical relevance if true and warrants further investigation.

Contributors

CM conceptualisation, writing—original draft, and writing—review & editing, A Gi writing—original draft, and writing—review & editing, GL investigation and writing—review & editing, ADB investigation and writing—review & editing, AGo investigation and writing—review & editing, GO investigation and writing—review & editing, EQR investigation and writing—review & editing, AC investigation and writing—review & editing, GMad investigation and writing—review & editing, VM investigation and writing—review & editing, RR investigation and writing—review & editing, SLC investigation and writing—review & editing, GMar investigation and writing—review & editing, JC writing—original draft, and writing—review & editing, AdM investigation and writing—review & editing, GG investigation and writing—review & editing and ACL accessed and verified data and formal analysis and methodology. ACL and AGi accessed and verified the underlying data. Icona Foundation Study Group investigation. All authors read and approved the final version of the manuscript.

Data sharing statement

The datasets generated during the current study are not publicly available because they contain sensitive data to be treated under data protection laws and regulations. Appropriate agreement of data sharing can be arranged after a reasonable request to the corresponding author.

Declaration of interests

CM has received research grants from Gilead Sciences, Speaker honoraria from Gilead Sciences, ViiV Healthcare, MSD, Johnson & Johnson, travel grants from Gilead.

AGi received consultancy fees from ViiV Healthcare, Gilead Sciences, MSD and Janssen travel grant from Gilead Sciences and research grant from ViiV and Gilead.

GL received fees for consultations from ViiV Healthcare, Insmed and Pfizer srl.

ADB served as a consultant or attended advisory board meetings for Gilead Sciences, ViiV Healthcare, MSD, and received research grants from Gilead Sciences and ViiV Healthcare.

AGo served as consultant and received research grants from Janssen, ViiV Healthcare, MSD, BMS, ABBVIE, Gilead Sciences, Novartis, Pfizer, Astellas, Astrazeneca, Angelini, Moderna, Novavax, Shionogi.

GO has nothing to declare.

EQR received travel Grant from Gilead Sciences and ViiV Healthcare, received a research grant from Gilead Sciences.

GMad has received consultancy and/or speakers' fees from Gilead Sciences, Janssen, Merck Sharp & Dohme, ViiV and Advanz Pharma.

AC received consultant fees from Gilead and ViiV Healthcare.

GMar has received consultancy and/or speakers' fees from Gilead Sciences, Merck Sharp & Dohme, ViiV and Advanz Pharma.

VM has served as a paid consultant for Gilead Sciences and ViiV Healthcare and has received institutional research funding from these companies.

RR received consultancy fees from ViiV Healthcare, Gilead Sciences, MSD and Johnson&Johnson, travel and research grant from Gilead Sciences.

SLC received research grant from Gilead Sciences, ViiV Healthcare, MSD.

GM is Advisory board member for Gilead Sciences, Viiv Healthcare and received travel grants from Gilead Sciences.

JC has nothing to declare.

GG received research grant and speaker honorarium from Gilead Sciences, ViiV Healthcare, MSD, Jansen and attended advisory boards of Gilead, ViiV and MERCK.

AdM has nothing to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.104150.

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