Obesity measured at ART initiation and the risk of cardiovascular disease, cancer and death in people with HIV

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BACKGROUND

- A causal link between obesity and morbidity (e.g. cardiovascular disease [CVD]) and cancers has been reported in the general population.
- In people with HIV (PWH), there is a suggested association between BMI and risk of diabetes, but there is insufficient evidence to support an association with the risk of CVD.
- If obesity at time of ART initiation is associated with long-term higher risk of morbidity and mortality in PWH is missing.

AIMS

Primary Aim
To evaluate the long-term risk of clinical events (defined as a composite outcome of cancer, CVD and death) associated with starting first-line ART with a **BMI≥30 (obese) vs. a BMI of 18.5-29.9 (non-obese)**

Secondary Aim
To test whether **age** may be effect measure modifiers of the association of interest (BMI at ART initiation and long-term clinical risk)

METHODS

- **Study Population:** PWH of the Icona Foundation Study cohort who initiated ART (Jan 1997-July 2025) and (i) were free from AIDS and any CVD and cancer at baseline, and (ii) baseline BMI >18.5. Underweight (BMI<18.5) PWH were excluded.
- **Exposure:** Participants were grouped according to BMI measured at ART initiation - obese (≥30 kg/m^2) vs. non-obese (18.5-29.9 kg/m^2).
- **Outcomes:** The primary outcome was composite cancer/CVD(myocardial infarction, angioplasty, coronary by-pass, cerebral hemorrhage and cerebral ischemia)/death. The secondary endpoints were: i) cancer + CVD (censoring persons' follow-up at time of death), ii) BMI-related cancers (liver, breast, colorectal, pancreatic, kidney, esophageal, gallbladder and thyroid) + CVD + death.
- **Potential effect measure modifiers:** age (18-30; 31-60; 61+ years)

Statistical Analysis

- Participants' main characteristics at ART initiation (baseline) were described overall stratified by BMI exposure groups (obese vs. non-obese).
- Hypothesis testing: chi-square test (categorical variables) and Mann-Whitney (numerical variables).
- Standard survival analysis with time-fixed covariates at baseline. KM curves were compared with log-rank test. A standard proportional hazard Cox regression analysis conditioned on baseline covariates was conducted.
- Adjusted HR was controlled for confounders: 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.
- We formally tested for interaction between exposure and age (fitted as continuous).
- Because the analysis was likely to be underpowered to verify interactions, regardless of p-value for interaction, we showed results stratified by age

In PWH, obesity at ART initiation is an important determinant of CVD, cancer or death. The size of the effect was larger with younger age.
This novel finding profiles obese PWH at ART initiation as a group of individuals at higher risk of developing serious clinical outcomes

RESULTS

A total of 11,652 PWH (20.7% females, median age 38 years [IQR: 31, 46]) were included: 11,005 (94.4%) were non-obese and 647 (5.6%) obese. 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 obese (95% CI: 14.1-24.9%) vs. 12.4% in non-obese (95% CI:11.3-13.4%, log-rank p=0.006). After controlling for confounding, the difference was attenuated (adjusted hazard ratio [aHR] 1.28 [95% CI:0.98-1.67], p=0.073). No evidence for interaction was found (p-value=0.758) but there was a clear trend for a larger effect in 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]).

Table 1. Main characteristics of PWH at ART initiation, stratified by exposure group (non-obese vs obese)

Characteristics	Non-obese	Obese	p-value*	Total
Sex at birth, n(%)			<.001	
Female	2241 (20.4%)	171 (26.4%)		2412 (20.7%)
Age, years			<.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%)
Mode of HIV acquisition, n(%)			<.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(%)			0.247	
No	5439 (49.4%)	341 (52.7%)		5780 (49.6%)
Yes	1368 (12.4%)	72 (11.1%)		1440 (12.4%)
Not tested	4198 (38.1%)	234 (36.2%)		4432 (38.0%)
Diabetes, n(%)			<.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%)
Healthy	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)
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			<.001	
Median (IQR)	349 (221, 494)	389 (249, 556)		351 (223, 498)
0-200 cells/mm3, n(%)	2314 (21.9%)	113 (18.1%)		2427 (21.7%)
Viral load, $\log_{10}$ copies/mL			<.001	
Median (IQR)	4.71 (4.15, 5.24)	4.58 (3.95, 5.04)		4.71 (4.14, 5.23)

Table 2. Clinical events observed throughout follow-up

Clinical events, n (%)	Non-obese	Obese	Total
CVD	112 (14.5%)	10 (15.6%)	122 (14.6%)
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%)

Figure 1. Kaplan-Meier estimate of the time to CVD/cancer/death by exposure group (non-obese vs obese)

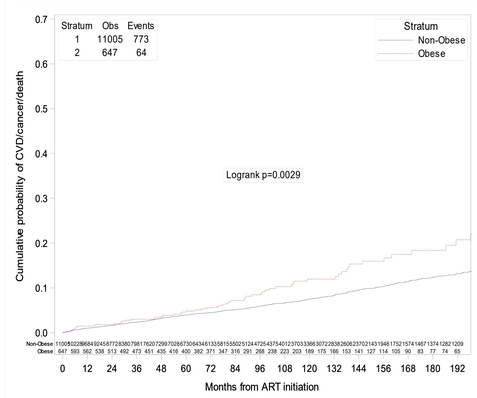

Table 3. Hazard ratios (HR) from fitting a Cox regression model stratified by age groups

	Unadjusted HR (95%CI)	Adjusted*HR (95%CI)	p-value
	Young (18-30 years)		
Non-Obese	1	1	
Obese	1.76 (0.71, 4.35)	1.83 (0.74, 4.56)	
	Middle age (31-60 years)		p=0.76
Non-Obese	1	1	
Obese	1.37 (1.03, 1.83)	1.49 (1.11, 2.00)	
	Older (> 60 years)		
Non-Obese	1	1	
Obese	1.16 (0.58, 2.30)	1.20 (0.60, 2.41)	

*for 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.

CONCLUSIONS

- **Obesity at ART initiation is an important determinant of long-term clinical prognosis in PWH**
- **Age-stratified analyses showed larger effect size per younger age groups**
- **Although survivor bias cannot be ruled out, the observation that the magnitude of the effect is bigger in younger individuals suggests a complex interplay between ageing, immune-senescence, and metabolic dysfunction**
- **Our findings underscore the need to address obesity in PWH at ART initiation**
- **Given the emerging data on metabolic and anti-inflammatory benefits of novel weight-reducing therapies, further studies on its effect on long-term prognosis in PWH are warranted**

PLAIN LANGUAGE SUMMARY

Obesity at the time of starting HIV treatment is linked to a higher long-term risk of cardiovascular disease, cancer, or death. Younger people with HIV are at greater risk. These findings suggest that addressing excess weight early in HIV care could improve long-term health outcomes