PE9/80

Low Body Mass Index (BMI) in ART naïve HIV-positive subjects and risk of virologic failure and drug discontinuation: data from the ICONA Foundation cohort.

Roberto Rossotti[1], Giovanni Guaraldi[2], Alessandro Cozzi Lepri[3], Vincenzo Spagnuolo[4], Stefania Cicalini[5], Jacopo Vecchiet[6], Eugenia Quiros Roldan[7], Giordano Madeddu[8], Sergio Lo Caputo[9], Andrea Antinori[5], Massimo Puoti[1], Antonella d'Arminio Monforte[10] on behalf of the ICONA Foundation Study Group.

1 ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy ~ 2 University of Modena and Reggio Emilia, Modena, Italy ~ 3 University College, London, UK ~ 4 San Raffaele Scientific Institute, Milan, Italy ~ 5 INMI L. Spallanzani, Rome, Italy ~ 6 G. D'Annunzio University, Chieti, Italy ~ 7 University of Brescia, Brescia, Italy ~ 8 University of Sassari Sassari, Italy ~ 9 University of Bari, Bari, Italy ~ 10 University of Milan - San Paolo Hospital, Milan, Italy.

Fondazione Icona – Italian Cohort Naive Antiretrovirals – Conceived by Professor Mauro Moroni

EACS European AIDS Clinical Society – 17th EUROPEAN AIDS CONFERENCE – November 6–9, 2019 | Basel, Switzerland

BACKGROUND

- In recent published literature, a low Body Mass Index (BMI) condition, defined as a value <18.5, is mostly evaluated in low/middle-income settings while in Western Countries it was frequently evaluated in the pre- or early antiretroviral treatment (ART) era.
  - Nevertheless, in recent years BMI and weight gain returned to be investigational issues especially for the observed excessive weight increase under integrase strand-transfer inhibitors (INSTI) treatment, especially with dolutegravir (DTG) and raltegravir (RAL) use.
- A BMI <18.5 cumulatively affects about 5% of HIV-infected population and might be related not only to complex clinical conditions but also to socio-economic issues.
- A BMI <18.5 is associated with an increased risk of death for both cardiovascular and neoplastic disease (with an OR 2.47 for males and 1.60 for females).
- An excessive weight gain in the first year of treatment has a strong impact on the development of cardiovascular disease and diabetes.
- However, a low BMI at baseline could have different meaning and diverse consequences compared to a persisting low BMI after ART start; additionally, few data are available on BMI normalization (expression of general conditions improvement) in terms of virologic and immunologic recovery, especially with the availability of modern ART drugs.

AIMS

- Aims of present Study are:
  - Define the proportion of subjects who start any ART with a low BMI <18.5;
    - Describe their demographic, clinical and socio-economic characteristics.
  - Evaluate the proportion of subjects who increase their weight to reach normal, overweight or obesity condition within 48 weeks after ART start.
  - Assess the consequences in terms of virologic and immunologic recovery, virologic failure, treatment switch, overall survival and clinical events (either AIDS or non-AIDS related) after BMI increase

STUDY DESIGN AND METHODS

STUDY POPULATION

- ICONA Foundation Cohort is an observational Study that enrolls HIV positive subjects naïve to antiretroviral treatment from more than 50 Centers operating throughout Italy. Since 1997, more than 16,500 individuals have been included in the ICONA Study.
- Subjects enrolled in ICONA from 2008 to 2018 with a BMI value available before ART start and a further assessment after 48 weeks of treatment were included in the analysis.
- Demographic, clinical, socio-economic and behavioral features were collected;
  - Study population was grouped according to the WHO classification of weight status:
    - BMI below 18.5: underweight;
    - BMI between 18.5 and 25: normal weight;
    - BMI between 25 and 30: overweight;
    - BMI above 30: obesity.

STATISTICAL ANALYSIS

- Descriptive statistics and non-parametric (Chi-square and Kruskal-Wallis) tests were used.
- KM probability curves and multivariable Cox regression models for virologic failure, treatment discontinuation and clinical events were used.
- Mean changes in CD4 and CD8 cell count from fitting a linear mixed model after ART start were estimated.

RESULTS (1)

- 8,556 subjects were included: 6,858 (80.2%) males, mainly born in Italy (6,351, 74.2%) and with comparable distribution among MSM (3,996, 46.7%) and heterosexuals (3,353, 39.2%; **Table 1**).
- Baseline BMI value was missing in 2,635 individuals (30.8%), while the stratification for the others was:
  - **Underweight: 315 (3.7%)**;
  - Normal weight: 3,926 (45.8%);
  - Overweight: 1,374 (16.1%);
  - Obese: 306 (3.6%).
- The majority received FTC/TDF or TAF as backbone (81.3%), while the most prescribed third agents were rilpivirine (15.5%) and DTG (14.4%).

RESULTS (2)

Table 1 – Main characteristics of patients by baseline BMI group (Chi-square and Kruskal-Wallis tests, as appropriate).

		BMI <18.5 (N=315)	BMI 18.5-25 (N=3926)	BMI 25-30 (N=1374)	BMI >30 (N=306)	Unknown (N=2635)	p-value
Female gender, n(%)		141 (44.8)	753 (19.2)	206 (15.0%)	75 (24.5)	523 (19.8%)	<0.001
Mode of HIV transmission, n(%)	IVDU	33 (10.5)	296 (7.5)	110 (8.0)	19 (6.2)	151 (5.7)	<0.001
	MSM	191 (32.1)	2029 (51.7)	645 (46.9)	107 (35.0)	1114 (42.3)	
	Heterosexual	159 (50.5)	1416 (36.1)	553 (40.2)	166 (54.2)	1059 (40.2)	
	Other	22 (7.0)	185 (4.7)	66 (4.8)	14 (4.6)	311 (11.8)	
Not Italian Nationality, n(%)		94 (29.8)	949 (24.2)	309 (22.5)	65 (21.2)	788 (29.9)	0.019
AIDS diagnosis, n(%)		42 (13.3)	194 (4.9)	54 (3.9)	10 (3.3)	196 (7.4)	<0.001
Age (years), median (IQR)		35 (28-42)	37 (30-44)	39 (33-47)	40 (35-50)	38 (31-45)	<0.001
CD4 count (cell/mmc), median (IQR)		218 (47-400)	344 (204-480)	370 (240-507)	399 (242-545)	314 (149-481)	<0.001
CD8 count (cell/mmc), median (IQR)		752 (474-1083)	888 (620-1257)	945 (660-1320)	997 (748-1420)	888 (588-1279)	<0.001
HIV RNA (log_{10} cp/mL), median (IQR)		4.97 (4.25-5.53)	4.65 (4.02-5.22)	4.58 (3.90-5.11)	4.51 (3.76-5.03)	4.66 (3.93-5.23)	<0.001
Diabetes, n(%)		2 (0.6)	49 (1.2)	48 (3.5)	19 (6.2)	48 (1.8)	<0.001
Smoking, n(%)	No	158 (50.2)	1929 (49.1)	701 (51.0)	174 (59.6)	689 (26.1)	<0.001
	Yes	133 (42.2)	1610 (41.0)	504 (36.7)	103 (33.7)	574 (21.8)	
	Unknown	24 (7.6)	387 (9.9)	169 (12.3)	29 (9.5)	1372 (52.1)	
Total cholesterol (mg/dL), median (IQR)		152 (128-178)	160 (135-184)	166 (142-193)	167 (143-190)	156 (134-182)	<0.001
HDL cholesterol (mg/dL), median (IQR)		39 (31-51)	40 (32-48)	38 (31-46)	37 (31-46)	38 (31-48)	<0.001
Education, n(%)	Primary	31 (9.8)	216 (5.5)	75 (5.5)	23 (7.5)	81 (3.1)	<0.001
	Secondary	69 (21.9)	745 (19.0)	272 (19.8)	57 (18.6)	291 (11.0)	
	College	103 (32.7)	1352 (34.4)	450 (32.8)	96 (31.4)	570 (21.6)	
	University	28 (8.9)	587 (15.0)	173 (12.6)	21 (6.9)	235 (8.9)	
	Unknown	84 (26.7)	1026 (26.1)	404 (29.4)	109 (35.6)	1458 (55.3)	
Employment, n(%)	Unemployed	74 (26.7)	559 (16.2)	179 (14.9)	41 (16.0)	244 (15.2)	<0.001
	Employed	116 (41.9)	1766 (51.2)	587 (49.0)	136 (52.9)	761 (47.5)	
	Self-employed	35 (12.6)	553 (16.0)	235 (19.6)	37 (14.4)	258 (16.1)	
	Occasional	8 (2.9)	160 (4.6)	38 (3.2)	9 (3.5)	48 (3.0)	
	Student	16 (5.8)	169 (4.9)	28 (2.3)	4 (1.6)	58 (3.6)	
	Retired	9 (3.2)	76 (2.2)	57 (4.8)	14 (5.4)	60 (3.7)	
	Invalid	--	7 (0.2)	4 (0.3)	1 (0.4)	4 (0.2)	
	Housewife	14 (5.1)	77 (2.2)	26 (2.2)	10 (3.9)	37 (2.3)	
	Other	5 (1.8)	85 (2.5)	44 (3.7)	5 (1.9)	131 (8.2)	

- After 48 weeks of treatment, among those starting from a low BMI 21.9% remained within the Underweight group, 30.5% entered the Normal weight, 1.9% passed in the Overweight/Obese groups (of note, 45.7% had no BMI value in the 48 week period).
- In the unadjusted analysis, baseline BMI class was associated with a significantly different risk of virologic failure and treatment discontinuation, while no correlations with clinical events were observed (**Figure 1** and **Table 3**).
- The difference in risk of virologic failure and treatment discontinuation was attenuated after controlling for key confounding factors (age and CD4 count, **Table 2**). CD4 count and CD4/CD8 ratio trend over time had no correlation with BMI, while CD8 count showed a steeper slope of decrease during ART in low and obese BMI classes (**Figure 2** and **Table 4**).

Figure 1 - KM estimates for virologic failure (A), drug discontinuation (B), AIDS and severe non-AIDS clinical events, including death.

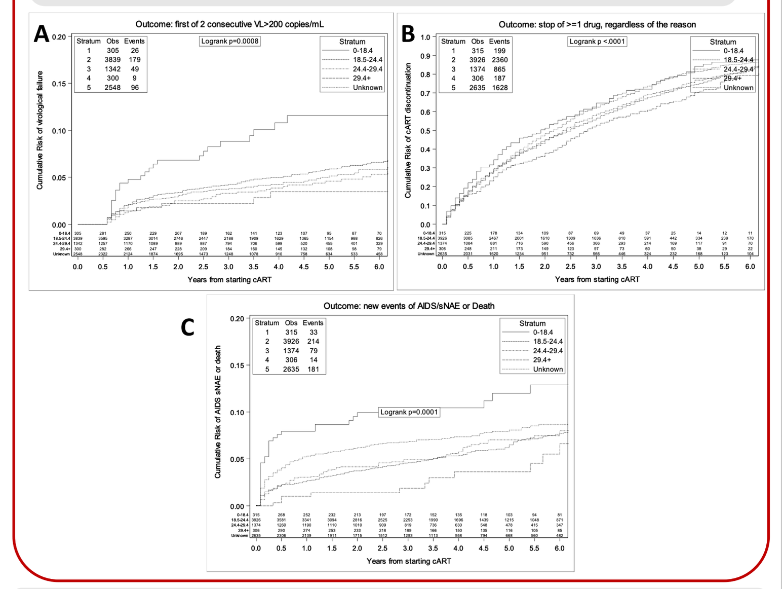

Table 2 – Relative hazards of virologic failure, treatment discontinuation and clinical events from fitting a Cox regression model.

Outcomes		Crude RH (95%CI)	p	Adjusted* RH (95%CI)	p
Virologic failure					
BMI	<18.5	1.90 (1.26-2.86)	**0.002**	1.41 (0.84-2.36)	0.189
	18.5-25	1.00		1.00	
	25-30	0.76 (0.55-1.04)	**0.082**	0.82 (0.57-1.18)	0.295
	>30	0.60 (0.31-1.16)	0.130	0.70 (0.35-1.38)	0.303
	Unknown	0.87 (0.68-1.12)	0.280	0.97 (0.69-1.36)	0.854
Treatment discontinuation					
BMI	<18.5	1.20 (1.04-1.39)	**0.012**	1.14 (0.95-1.37)	0.151
	18.5-25	1.00		1.00	
	25-30	1.02 (0.94-1.10)	0.672	1.01 (0.92-1.11)	0.777
	>30	0.88 (0.76-1.02)	**0.087**	0.93 (0.78-1.10)	0.365
	Unknown	1.12 (1.05-1.20)	**<0.001**	1.08 (0.99-1.18)	0.099
AIDS and Serious non-AIDS clinical events					
BMI	<18.5	1.98 (1.37-2.86)	**<0.001**	1.36 (0.86-2.16)	0.189
	18.5-25	1.00		1.00	
	25-30	1.02 (0.79-1.32)	0.202	0.99 (0.74-1.33)	0.949
	>30	0.78 (0.46-1.34)	0.950	0.65 (0.34-1.24)	0.194
	Unknown	1.36 (1.12-1.66)	**0.022**	0.97 (0.73-1.30)	0.853

*adjusted for age, gender, mode of HIV transmission, AIDS diagnosis, nadir CD4 count, year of starting ART, type of anchr drug in first combination.

Table 3 – Clinical and viro-immunologic outcomes of subjects starting from BMI<18.5.

Week 48 outcome	BMI at week 48 in those with baseline BMI<18.5 (N=315): BMI<18.5 (N=69, 22%)	BMI 18.5-25 (N=96, 31%)	Missing (N=144, 46%)	Total (N=309*, 100%)
Deaths (%)	1 (0.3%)	1 (0.3%)	7 (2.3%)	9 (2.9%)
Serious Non-AIDS events (%)	--	3 (1.0%)	3 (1.0%)	6 (1.9%)
AIDS (%)	--	7 (2.3%)	11 (3.6%)	18 (5.8%)
% with clinical endpoint (95% CI) ^	--	8% (3%-14%)	12% (6%-18%)	8% (5%-11%)
% with ART discontinuation (95% CI) ^	28% (17%-39%)	42% (32%-52%)	32% (23%-40%)	34% (28%-40%)
CD4 count, cells/mm^3	N=69	N=95	N=96	N=260
Absolute mean (SD)	536 (274)	480 (342)	590 (376)	535 (341)
Mean change from pre-ART (SD)	+229 (149)	+276 (236)	+262 (268)	+258 (228)
CD4/CD8	N=59	N=86	N=92	N=237
Absolute mean (SD)	0.74 (0.50)	0.76 (1.64)	0.80 (0.60)	0.77 (1.09)
Mean change from pre-ART(SD)	+0.34 (0.33)	+0.53 (1.82)	+0.39 (0.36)	+0.43 (1.09)

*six patients (1.9%) with a BMI>25 were excluded. ^ KM estimates.

Table 4 – Mean changes in CD8 cell count from fitting a linear mixed model.

Estimated from fitting the linear mixed model for Underweight

BMI	Baseline CD8 count	Difference in baseline	CD8 count change/year	Difference in change/year	Adjusted* CD8 count change/year	Adjusted* difference in change/year
18.5-25	991.8 (977.3, 1006)		-31.6 (-35.1, -28.1)		-32.4 (-37.0, -27.8)	
<18.5	905.4 (853.9, 956.8)	-86.4 (-140, -32.9)	-14.9 (-27.3, -2.49)	16.68 (3.79, 29.57)	-3.87 (-21.4, 13.71)	28.53 (10.36, 46.70)
p		**0.002**		**0.011**		**0.002**

Estimated from fitting the linear mixed model for Obese

BMI	Baseline CD8 count	Difference in baseline	CD8 count change/year	Difference in change/year	Adjusted* CD8 count change/year	Adjusted* difference in change/year
18.5-25	992.5 (977.1, 1008)		-32.4 (-36.5, -28.4)		-33.3 (-38.9, -27.7)	
>30	1128 (1073, 1183)	135.8 (78.70, 192.9)	-61.1 (-74.9, -47.4)	-28.7 (-43.0, -14.4)	-69.0 (-88.5, -49.5)	-35.7 (-56.0, -15.4)
p		**<.001**		**<.001**		**<.001**

*adjusted for age, gender, mode of HIV transmission, AIDS diagnosis, nadir CD4 count, CD8 at cART, year of starting ART, type of anchor drug in first cART (NNRTI,PI/r,INSTI), level of education and employement

CONCLUSIONS

- **Underweight in an uncommon condition in ART naïve subjects and reflects worse immunologic and virologic conditions, as well as social-economic issues (younger patients, especially females and not born in Italy, mostly intravenous drug users and smokers, with lower education and more modest employment state). Hence, low BMI might be a manifestation of advanced disease but also of social marginalisation.**
- **After 48 weeks of treatment only a minority failed to improve the BMI although a large proportion on enrolled subjects was missing the observation at this time point.**
- **A low BMI is related to virologic failure and treatment discontinuation, although age and pre-ART CD4 count played the pivotal role. Overall, it does not seem to have a role for the development of AIDS and serious non-AIDS clinical events.**
- **CD4 and CD4/CD8 ratio were not influenced by baseline BMI, while CD8 decreased more in Underweight and Obese, thus reflecting an inflammatory reduction mainly evident in the two extreme classes.**
- **Nevertheless, low baseline BMI could be an indicator of vulnerability and might be considered as a predictor of treatment failure.**

Acknowledgments – Icona Foundation Study Group

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Funding

ICONA Foundation is supported by unrestricted grants from BMS, Gilead Sciences, Janssen, MSD and ViiV Healthcare. This study has been supported by an unrestricted Medical Grant from Gilead Sciences.

Contact Information

Mail: Roberto.rossotti@ospedaleniguarda.it

Address: ASST Grande Ospedale Metropolitano Niguarda, piazza Ospedale Maggiore 3, 20162, Milan, Italy.