Contribution of INSTI, BMI, physical activity or caloric intake to weight gain in PWH

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Background

Weight gain in people living with HIV (PWH) is a multifactorial phenomenon in which the relative contribution of traditional and HIV specific modifiable risk factors is still to be investigated. A well-known epidemiological approach is the population attributable fraction (PAF) tool to quantify the proportion of a specific health condition that could be avoided if particular risk factors were not present .

The aim of this study was to assess the population attributable fractions (PAFs) of modifiable lifestyles and INSTI regimens in ART experienced PWH who had at least a 5% weight gain over 4 years follow up.

Methods

Study design and inclusion criteria

This was an observational retrospective longitudinal study that included virally suppressed ART-experienced PWH attending Modena HIV Metabolic Clinic (MHMC) from January 2007 to July 2019.

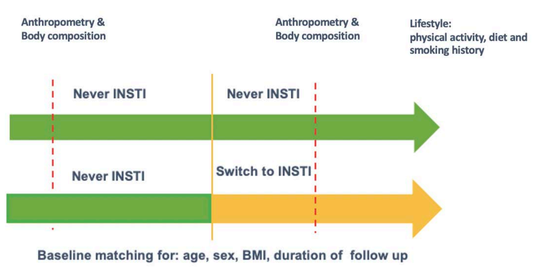

Figure 1. *At the beginning of observation period all participants were INSTI-naive (INSTI-n). During follow-up, they were divided in two groups: INSTI-n vs INSTI-switchers (INSTI-s) with no further change in ART. Groups were matched for sex, age, BMI at a first visit and follow-up duration. Patients were eligible for analyses if lifestyles data were available at last observation.*

Outcome measure

Significant weight gain was defined as an increase of ≥5% from 1st visit weight over a mean 4 years follow-up.

Covariates

Physical activity was assessed with International Physical Activity Questionnaire (IPAQ) as metabolic equivalent of task (MET). Daily caloric intake (DCI) was evaluated with a 3 day food diary.

Statistical analysis and PAF calculations

We calculated the crude hazard ratio allowing some risk factors (nadir CD4 cell count, CD4/CD8 ratio, high daily caloric intake, low physical activity, smoke pack year) to vary with time. PAFs and 95% CIs were estimated to quantify the proportion of outcomes that could be avoided if the risk factor was prevented, using the following dichotomic variables: BMI >25 kg/m2 vs <25 kg/m2, DCI above cut-off are indicated according to *2015–2020 Dietary Guidelines Estimated Calorie Needs*, IPAQ MET <600 vs MET>600, quitting vs continuing smoking, INSTI vs no-INSTI regimens, and CD4/CD8 ratio <1 vs >1. In addition to the prevalence of the risk factors, PAF is influenced by the risk of the outcome associated with each preventable or modifiable risk factor.

Results and discussion

Of 281 PWH (74% males), mean follow-up was 4.2 years ,age 54.3 (7.8 SD) years, median duration since HIV diagnosis 22.3 years (IQR 15.5-27.5), CD4 cell count 714 cells/microL (IQR 561.5-892); 98.9% had undetectable HIV-1 RNA.

Table 1 *shows the anthropometric and clinical characteristics of PWH who remained INSTI naïve and PWH who switched to an INSTI-based regimen. It can be noticed that PWH who switched to INSTI have a more pronounced immunological scar depicted by nadir CD4 cell count, lower median CD4 cell count, longer duration of HIV infection and higher burden of multimorbidity.*

	INSTI-n (N=163)	INSTI-s (N=118)	p
Age, years, mean (±SD)	49.9 (8.7)	50.7 (6.5)	0.13
Males (%)	118 (72.4%)	91 (77.1%)	0.45
Moderate physical activity (%)	65 (39.9%)	47 (39.8%)	0.64
Intense physical activity (%)	14 (8.6%)	14 (11.9%)	0.64
BMI, kg/m2, mean (±SD)	23.7 (3.45)	23.46 (3.3)	0.79
BMI, 18.5-25 kg/m2, %	111 (68.1%)	79 (67%)	0.85
BMI, 25-30 kg/m2, %	46 (28.2%)	33 (28%)	0.85
Obesity (%)	12 (7.4%)	6 (5.1%)	0.60
Waist circumference, cm, mean (±SD)	87.6 (9.9)	86.9 (9.6)	0.63
VAT, cm3, mean (±SD)	143 (84.8)	137.6 (77.2)	0.73
SAT, cm3, mean (±SD)	154.4 (123.6)	140.6 (85.6)	0.57
Nadir CD4 cell count, cell/microL, median (IQR)	220 (118-310)	158 (64-269)	0.002
CD4/CD8 ratio, mean (±SD)	0.92 (0.46)	0.79 (0.44)	0.04
Current CD4 cell count, cell/microL, median (IQR)	653 (537-866)	578 (445.5-780)	0.009
HIV duration, months, median (IQR)	189 (121-261.6)	244 (188.5-300)	<0.001
Undetectable HIV viral load (%)	145 (89%)	112 (94.9%)	0.12
Multimorbidity (%)	41 (25.2%)	44 (37.3%)	0.04

	<5% weight gain N=206			≥5% weight gain N=75			p
	Baseline	Follow-up	p	Baseline	Follow-up	p	
Age, years, mean (±SD)	50.9 (7.8)	54.8 (8)	<0.001	48.6 (7.7)	53.3	<0.001	0.09
Males (%)	162 (78.6%)	162 (78.6%)	NA	47 (62.7%)	47 (62.7%)	NA	0.01
Moderate physical activity (%)	84 (40.8%)	84 (40.8%)	0.87	28 (37.3%)	27 (36%)	0.64	0.63
Intense physical activity (%)	20 (9.7%)	17 (8.3%)	0.87	8 (10.7%)	5 (6.7%)	0.64	0.63
Pack year, years, mean (±SD)	16 (1.9-28.5)	16 (1.9-28.5)	NA	14 (1.2-28.5)	14.5 (1.2-31)	0.57	0.82
Weight, kg, mean (±SD)	69.2 (11.8)	68.4 (11.2)	0.54	67 (13.4)	74.2 (14.7)	0.002	0.002
Delta weight, kg, mean (±SD)	NA	-0.9 (2.9)	NA	NA	10.8 (6.0)	NA	<0.001
BMI, kg/m2, mean (±SD)	23.7 (3.4)	23.5 (3.2)	0.61	23.3 (3.5)	25.8 (2.9)	<0.001	<0.001
BMI, 18.5-25 kg/m2, %	135 (65.3%)	136 (66.7%)	0.81	55 (73.3%)	30 (40%)	<0.001	<0.001
BMI, 25-30 kg/m2, %	63 (30.6%)	58 (28.4%)	0.81	16 (21.3%)	44 (58.7%)	<0.001	<0.001
Obesity (%)	13 (6.3%)	9 (4.4%)	0.53	5 (6.7%)	12 (16%)	0.12	0.003
Waist circumference, cm, mean (±SD)	87.6 (9.6)	91.7 (5.2)	0.70	86.1 (10.1)	94.7 (11.1)	<0.001	<0.001
VAT, cm3, mean (±SD)	144.1 (86.1)	158 (230.9)	0.90	131.5 (65.4)	176.3 (90.7)	0.001	0.002
SAT, cm3, mean (±SD)	147.8 (114.8)	155.6 (142.9)	0.42	150.8 (93.2)	213.1 (105.9)	<0.001	<0.001
Liver to spleen ratio, mean (±SD)	1.17 (0.18)	1.20 (0.21)	0.07	1.24 (0.15)	1.21 (0.18)	0.45	0.74
IPAQ score, MET, mean (±SD)	NA	964 (944)	NA	NA	656.2 (663.4)	NA	0.005
Daily caloric intake, kcal, mean (±SD)	NA	1962.9 (549.4)	NA	NA	1947.3 (503.3)	NA	0.96
Use of statins (%)	38 (18.5%)	43 (20.9%)	0.62	14 (18.7%)	19 (25.3%)	0.43	0.53
Nadir CD4 cell count, cell/microL, median (IQR)	200 (100-310)	200 (100-310)	NA	159 (89-264)	159 (89-264)	NA	0.09
CD4/CD8 ratio, mean (±SD)	0.83 (0.47)	0.92 (0.5)	0.07	0.93 (0.37)	1.07 (0.48)	0.15	0.003
Current CD4 cell count, cell/microL, median (IQR)	603 (488-836)	705 (544-844)	0.005	666.5 (474-827)	794 (595-1042)	0.02	0.02
HIV duration, years, median (IQR)	220 (149-280)	268 (199-333)	<0.001	208 (117.5-270)	262 (168.5-334)	<0.001	0.37
Undetectable HIV viral load (%)	188 (91.3%)	204 (99%)	<0.001	69 (92%)	74 (98.7%)	0.12	0.99
Multimorbidity (%)	62 (30.1%)	95 (46.1%)	0.001	23 (30.7%)	33 (44%)	0.13	0.85
Hypertension (%)	92 (44.7%)	116 (56.3%)	0.02	25 (33.3%)	43 (57.3%)	0.005	0.98
Cardiovascular disease (%)	7 (3.4%)	10 (4.9%)	0.62	2 (2.7%)	4 (5.3%)	0.68	0.99
Diabetes mellitus (%)	21 (10.2%)	29 (14.1%)	0.29	5 (6.7%)	10 (13.3%)	0.28	0.99
Chronic kidney disease (%)	19 (9.2%)	37 (18%)	0.01	9 (12%)	12 (16%)	0.64	0.84
Osteoporosis (%)	44 (21.4%)	58 (28.2%)	0.14	21 (28%)	27 (36%)	0.38	0.26
Dyslipidemia (%)	177 (85.9%)	194 (94.2%)	0.008	66 (88%)	70 (93.3%)	0.40	0.99
Liver cirrhosis (%)	13 (6.3%)	20 (9.7%)	0.28	5 (6.7%)	9 (12%)	0.40	0.74

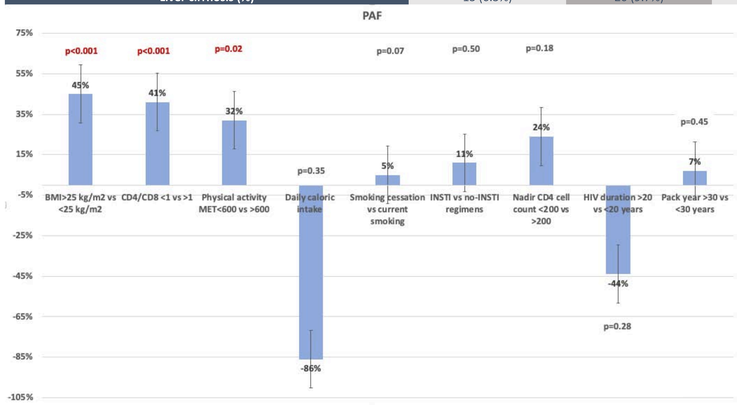

Table 2. *First panel on the left shows anthropometric and clinical characteristics in PWH that did not get weight between baseline and follow-up. It can be observed that prevalence of dyslipidaemia incresed between two time points. Second panel on the right shows the same variables in PWH that experienced weight gain. Burden of multimorbidity remained the same, while body composition changed, as depicted by visceral and subcutaneous adipose tissue. The last column shows the differences in PWH in two groups between baseline and follow—up.*

Figure 2. *PAF for WG was the greatest for BMI (45%, p<0.001), followed by CD4/CD8 ratio (41%, p<0.001) and physical activity (32%, p<0.02).*

Conclusion

Our findings suggest that WG is mostly influenced by pre-existing weight, low physical activity and immunological status:

- ✓ The most relevant risk factor for WG was baseline BMI>25. Not only obesity, but even overweight at baseline should be avoided in order to prevent WG during follow up.
- ✓ The second most relevant risk factor for WG was MET<600 at baseline. At a clinical level, these data suggest that a dedicated counselling should be offered in all ART experienced PWH that recommends a moderate to intense physical activity (MET>600) to prevent WG, for example suggesting:
  - 3 or more days of vigorous intensity activity and/or walking of at least 30 minutes per day , OR
  - 5 or more days of moderate intensity activity and/or walking of at least 30 minutes per day , OR
  - 5 or more days of any combination of walking, moderate intensity or vigorous intensity activities
- ✓ High CD4/CD8 ratio suggests potential immunologic mechanisms linked to weight gain.

This study was not powered to address clinical significance of WG, but we did not observe that the already high proportion of co-morbidities at baseline changed over time in weight gainers.

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