Statins reduce frailty in people with HIV

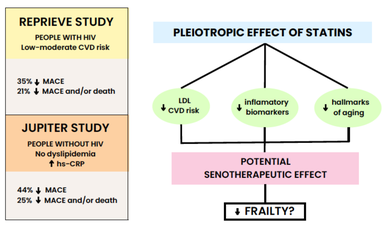
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Background

Statins have pleiotropic effects beyond lowering LDL cholesterol, offering benefits in multiple cardiometabolic conditions and reducing chronic inflammation. Two landmark prevention studies, JUPITER and REPRIEVE, may inform geroprotective strategies – because CVD tends to be a comorbid condition (accelerated/accentuated by HIV infection) with advancing age that is potentially driven by a finite set of common aging-related pathways, e.g., hallmarks (Figure 1).



Reduction in LDL within REPRIEVE and reduction in inflammatory biomarkers in JUPITER trial may have common antecedent molecular drivers. These effects have the potential to also influence biological aging trajectories, reflected by frailty (Figure 1).

Figure 1. *Pleiotropic effects of statins and potential of frailty reduction.*

The objective of this study was to compare frailty trajectories, in people with HIV (PWH) who used statins for primary cardiovascular prevention with those who did not.

Methods

- This was an observational longitudinal study including antiretroviral therapy (ART)-experienced PWH attending the Modena HIV Metabolic Clinic (Italy) who had no prior statin exposure at baseline (BL) and with at least 3 frailty assessments during follow-up.
- BL was defined as the first visit with available FI, and follow-up was defined as the last visit with available FI.
- Statin users and non-users were matched based on median time between BL and initiation of the statin therapy in the first group.
- Time 0 was defined as the initiation of the statin therapy.
- Frailty was assessed using a validated 37-item frailty index (FI), ranging from 0 to 1.
- Frailty trajectories were analysed using a linear mixed model (LMM) adjusted for statin use, age, sex, follow-up time, diabetes, hypertension, smoking (pack year), and BL LDL cholesterol.

Results

A total of 3,544 PWH were included, 1,100 (31%) were women. Median age at BL was 44.7 yrs, time since HIV diagnosis was 14 yrs, current CD4 cell count was 558.5/microL, undetectable HIV viral load was 88.6%. The median follow-up was 5 years (Q1,Q3: 1.1-9.1). PWH who switched to statins had a higher cardiometabolic burden (Table 1).

Statin use reduces frailty by 2.33% per year, whereas statins prescribed for secondary prevention increase it by 2.8% per year.

Statins can modify the trajectory of frailty over time.

Table 1 *shows characteristics of PWH at time 0 (i.e. initiation of the statin therapy) according to statin use. For non-statin users, time 0 accounted for a wash-out period of 3.37 years, calculated as a median time to start statins from baseline.*

	No statins (N = 2581)	Statins (N=963)	p
Female sex, N (%)	870 (33.7%)	230 (23.9%)	**<0.001**
Age, years, median (Q1,Q3)	43.6 (39.3-48.2)	48.4 (43.3-54.5)	**<0.001**
BMI, kg/m2, median (Q1,Q3)	23.0 (20.9-25.4)	23.9 (21.7-26.3)	**<0.001**
Waist circumference, cm, median (Q1,Q3)	85.0 (79.0-92.0)	88.0 (82.0-95.5)	**<0.001**
Current smoking, N (%)	1135 (44.5%)	382 (39.7%)	**<0.001**
Pack year, median (Q1,Q3)	16.0 (8.1-27.0)	21.8 (11.7-31.9)	**<0.001**
Total cholesterol, mg/dL, median (Q1, Q3)	183.0 (156.0-211.0)	208.0 (176.0-239.0)	**<0.001**
LDL cholesterol, mg/dL, median (Q1, Q3)	109.0 (88.0-134.0)	129.0 (103.0-156.0)	**<0.001**
Current CD4 cell count, c/microL, median (Q1, Q3)	550.0 (388.0-740.0)	586.0 (420.0-779.0)	**0.001**
Nadir CD4 cell count, c/microL, median (Q1, Q3)	198.0 (80.0-300.0)	186.5 (80.0-290.0)	0.16
Years since HIV diagnosis, median (Q1, Q3)	13.8 (7.7-19.4)	13.9 (9.3-19.9)	0.85
CD4/CD8 ratio, median (Q1, Q3)	0.8 (0.5-1.1)	0.7 (0.5-1.1)	0.67
Current exposure to INSTI, N (%)	271 (10.5%)	149 (15.5%)	**<0.001**
Current exposure to NNRTI, N (%)	879 (34.1%)	338 (35.0%)	0.62
Current exposure to PI, N (%)	1,140 (44.2%)	460 (47.8%)	0.06
Diabetes, N (%)	120 (4.7%)	111 (11.5%)	**<0.001**
Dyslipidemia, N (%)	1,422 (55.1%)	717 (74.5%)	**<0.001**
Hypertension, N (%)	398 (15.4%)	306 (31.8%)	**<0.001**
Metabolic syndrome, N (%)	341 (13.2%)	236 (24.5%)	**<0.001**
Frailty index, median (Q1, Q3)	0.3 (0.2-0.3)	0.3 (0.2-0.3)	0.67
Sarcopenia, N (%)	225 (26.4%)	88 (23.8%)	0.33
Dominant hand grip, kg, median (Q1, Q3)	38.5 (29.2-44.0)	37.2 (28.9-44.3)	0.67

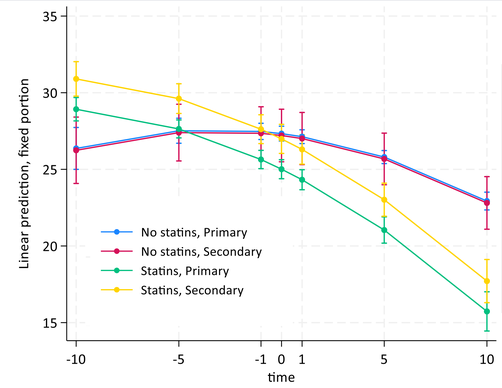


Figure 2 *shows linear predictions of frailty index with predictive margin of statins according to its use for primary and secondary prevention.*

Table 2 *shows linear mixed model for frailty with beta estimates and 95% confidence intervals. Statins and female sex significantly reduce frailty over time, while age, diabetes and hypertension increase risk of frailty.*

Covariate	Beta estimate	[95% conf. interval]		p
Age	-0.061	-0.114	-0.008	**0.025**
Sex (female)	-0.785	-1.552	-0.018	**0.045**
Follow-up time	-0.182	-0.256	-0.108	**<0.001**
Statins	-0.661	-0.114	0.010	0.052
Interaction statins*time	-2.333	-5.254	-0.588	**0.017**
Pack year (smoking)	0.053	-0.032	0.074	0.223
Diabetes	3.939	3.187	4.690	**<0.001**
Hypertension	3.552	3.057	4.049	**<0.001**
Total cholesterol	0.033	-0.028	0.038	0.088
HDL cholesterol	-0.101	-0.116	0.085	0.143
CD4 cell count	-0.005	-0.005	0.004	0.187
Undetectable HIV RNA viral load	-0.722	-1.089	-0.354	**<0.001**
Secondary prevention (vs. primary)	2.796	0.523	5.068	**0.016**
High CV risk (vs. moderate)	0.117	-0.404	0.638	0.661
Very high CV risk (vs. moderate)	1.044	-0.123	2.212	0.079
Reached LDL target	0.073	-0.510	0.656	0.806

Discussion and conclusions

- Statins used for primary prevention significantly reduces frailty over time, suggesting potential geroprotective effect of statins.
- Statins used for secondary prevention appear to increase frailty, as they are prescribed to vulnerable PWH who have already experienced a CV event.
- The protective effect of statins on frailty is independent of achieving target LDL cholesterol levels or quantifying cardiovascular risk with standard algorithms. This implies the involvement of an additional mechanism, potentially HIV-related chronic inflammation, in mediating statins' protective role against frailty.

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