Statin use during effective ART is not associated with lower biomarkers of HIV persistence or immune activation/inflammation

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Abstract THPEB100

Introduction

Statins exert pleiotropic anti-inflammatory and immune-modulatory effects.
They also have in vitro antiviral effects, and we have shown (Drechsler, PLoS One 2017) that statin use is associated with a reduced risk of virologic rebound in people on suppressive antiretroviral therapy (ART).
This may reflect a statin-induced decreased HIV-reservoir size.

Objective

We evaluated whether statin exposure is associated with lower levels of viral persistence or inflammation/immune activation, or whether these two effects are correlated.

Methods

We analyzed samples from HIV-infected participants of ACTG A5321 who started ART during chronic infection and maintained virologic suppression (HIV-1 RNA levels ≤50 copies/mL) for ≥3 years.

We measured:
1) Three markers of HIV-1 persistence (cell-associated HIV RNA [CA-RNA], CA-DNA, and single copy assay [SCA] plasma HIV RNA) and
2) Soluble markers of immune activation/ inflammation: IL-6, IP-10, neopterin, sCD14, sCD163 and TNF-alpha.

Wilcoxon rank-sum tests compared markers between participants receiving versus not receiving statin therapy at A5321 entry, and regression models adjusted for variables correlated with markers of HIV persistence.

Results

A total of 303 participants who initiated antiretroviral therapy during chronic HIV infection and had maintained virologic suppression for ≥3 years were analyzed.
Characteristics of statin and non-statin recipients are presented in Table 1.

Table 1. Baseline Characteristics

	On Statin at A5321 Entry: Yes (N=72)	No (N=231)	Total (N=303)
Age at A5321 entry (years)			
Median (Q1 - Q3)	53 (49 - 60)	46 (39 - 53)	48 (41 - 54)
Sex (% Male)	61 (85%)	187 (81%)	248 (82%)
Race/Ethnicity			
White Non-Hispanic	46 (64%)	122 (53%)	168 (55%)
Black Non-Hispanic	10 (14%)	51 (22%)	61 (20%)
Hispanic (Regardless of Race)	14 (19%)	52 (23%)	66 (22%)
Other	2 (3%)	6 (3%)	8 (3%)
ARV Regimen at A5321 entry			
NNRTI-based	43 (60%)	113 (49%)	156 (51%)
PI-based	16 (22%)	65 (28%)	81 (27%)
InSTI-based	11 (15%)	50 (22%)	61 (20%)
Other	2 (3%)	3 (1%)	5 (2%)
Years on ART at A5321 entry			
Median (Q1 - Q3)	8.1 (6.6 - 12.3)	7.3 (4.8 - 8.5)	7.3 (6.1 - 10.1)
Pre-ART CD4+ T-cell count (cells/mm³)			
Median (Q1 - Q3)	286 (110 - 414)	254 (114 - 369)	258 (113 - 374)
A5321 entry CD4+ T-cell count (cells/mm³)			
Median (Q1 - Q3)	737 (542 - 935)	665 (505 - 840)	681 (515 - 864)
Pre-ART plasma HIV-1 RNA (log_{10}cps/mL)			
Median (Q1 - Q3)	4.6 (4.3 - 5.0)	4.6 (4.2 - 5.0)	4.6 (4.2 - 5.0)
A5321 entry HIV-1 RNA (cps/mL)			
<40	72 (100%)	231 (100%)	303 (100%)

There were no differences between statin users and non-users in levels of CA-DNA, CA-RNA or SCA (table2).

Table 2. Comparison of Markers of Viral Persistence by Statin Use

	On Statin at A5321 Entry: Yes (N=72)	No (N=231)	P-Value*
Markers of Viral Persistence			
HIV DNA (cps/10^6 CD4+ T-cells)			
Median (Q1 - Q3)	650 (206 - 1,562)	540 (232 - 1,317)	0.58
CA-RNA (cps/10^6 CD4+ T-cells)			
Median (Q1 - Q3)	53 (14 - 198)	37 (14 - 125)	0.12
HIV-1 RNA via iSCA			
< 0.4 cps/mL	31 (46%)	120 (54%)	0.27
If ≥0.4 cps/mL			
Median (Min - Max)	1.1 (0.4 - 22.0)	1.5 (0.4 - 24.9)	

The number of evaluable participants on statins and not on statins is 68 and 224 for HIV DNA and iSCA; 67 and 216 for CA-RNA.
*Exact Wilcoxon test for continuous variables; Fisher's Exact test for iSCA.

Findings with viral persistence markers were unchanged after adjustment for factors including sex of participant, pre-ART CD4 and HIV RNA, CD4 count at study entry, HCV status, ARV regimen and years on ART.

Similarly, there were no significant differences between statin users and non-users in markers of inflammation/activation, except for IP-10 (table3).

Table 3. Comparison of Markers of Inflammation/ Immune Activation by Statin Use

	On Statin at A5321 Entry: Yes (N=72)	No (N=231)	P-Value*
Markers of Inflammation/Immune Activation			
IL-6 (pg/mL)			
Median (Q1 - Q3)	1.5 (1.1 - 2.0)	1.4 (0.9 - 2.3)	0.20
IP-10 (pg/mL)			
Median (Q1 - Q3)	137.2 (93.2 - 183.7)	117.7 (84.3 - 156.3)	0.028
Neopterin (nMol/L)			
Median (Q1 - Q3)	9.4 (7.4 - 11.6)	9.1 (7.1 - 10.9)	0.20
sCD14 (ng/mL)			
Median (Q1 - Q3)	2,036 (1,548 - 2,444)	1,915 (1,459 - 2,444)	0.41
sCD163 (ng/mL)			
Median (Q1 - Q3)	572 (402 - 749)	526 (382 - 776)	0.43
TNF-α (pg/mL)			
Median (Q1 - Q3)	1.9 (1.2 - 3.2)	1.9 (1.1 - 3.3)	0.74

*Exact Wilcoxon test.

Conclusions

- In this cohort of persons on long-term suppressive ART, current statin use was not associated with lower levels of HIV persistence or immune activation/inflammation.
- Association of statin use and high IP-10 could be due to statin-induced repression of dendritic cell (DC) maturation, inducing tolerogenic DCs that secrete high levels of interleukin 10 and IP-10
- These results do not support a major role for statins in reducing HIV persistence although an early transient effect cannot be excluded.
- Prospective, randomized studies are needed to confirm these findings.