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No Evidence for an Association Between Statin Use and Lower Biomarkers of HIV Persistence or Immune Activation/Inflammation During Effective ART

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Background: Statins exert pleiotropic anti-inflammatory and immune-modulatory effects, which might translate into antiviral activity. We evaluated whether reported current statin exposure is associated with lower levels of markers of HIV persistence and immune activation/inflammation.

Methods: We compared levels of markers of HIV viral persistence [cell-associated HIV RNA (CA-RNA), CA-DNA, and single copy assay plasma HIV RNA] and immune activation/inflammation (IL-6, IP-10, neopterin, sCD14, sCD163, and TNF-alpha) between statin users and nonusers among participants of ACTG A5321 who initiated antiretroviral therapy (ART) during chronic infection and maintained virologic suppression (HIV-1 RNA levels ≤50 copies/mL) for ≥3 years.

Results: A total of 303 participants were analyzed. Median time on the current statin was 2.9 years (1.2–5.1). There were no differences between statin users and nonusers in levels of CA-DNA (median 650 vs. 540 copies/10^6 $CD4^+$ T cells; $P = 0.58$), CA-RNA (53 vs. 37 copies/10^6 $CD4^+$ T cells; $P = 0.12$), or single copy assay (0.4 vs. 0.4 copies/mL; $P = 0.45$). Similarly, there were no significant differences between statin users and nonusers in markers of inflammation/activation, except for IP-10 (137 vs. 118 pg/mL; $P = 0.028$). Findings were unchanged after adjustment for factors including pre-ART CD4 and HIV RNA, and years on ART.

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. 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.

Key Words: statin, viral persistence, inflammation, immune activation

(*J Acquir Immune Defic Syndr* 2019;82:e27–e31)

INTRODUCTION

HMG-coenzyme A reductase inhibitors (statins) exert pleiotropic anti-inflammatory[1] and immune-modulatory effects.[2] Their inhibition of mevalonate metabolism, which also regulates T-lymphocyte biology, could potentially enhance immune response against invading pathogens,[3] and their inhibition of the induction of major histocompatibility complex class II (MHC-II) expression by interferon-gamma (IFN-γ) leads to reduction of T-cell activation.[2]

Likely as a result of these effects, statins have been found to have in vitro antiviral activity against human cytomegalovirus,[4] dengue virus,[5,6] and HIV-1.[7] Several specific anti-HIV effects of statins have been observed in vitro, including induction of resistance of CD4 T cells to HIV-1 infection through p21 upregulation,[8] inhibition of HIV-1 integrase LEDGF/p75-HIV-1 interaction,[9] and inhibition of viral expression.[7]

We have shown that statin use is associated with a reduced risk of virologic rebound in people on suppressive antiretroviral therapy (ART) in a large cohort of HIV-infected US Veterans.[10] We hypothesized that this finding might reflect anti-inflammatory, immunomodulatory, or direct antiviral effects of statins as described above, resulting in

Received for publication January 30, 2019; accepted June 3, 2019.

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Supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1 AI068634, UM1 AI068636, and UM1 AI106701.

Presented at the International AIDS Society meeting (AIDS 2018); July 23–27, 2018; Amsterdam, the Netherlands.

The authors have no conflicts of interest to disclose.

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decreased HIV reservoir size. We therefore evaluated whether current statin exposure is associated with lower levels of markers of HIV persistence, immune activation, and inflammation.

AIDS Clinical Trials Group study A5321 evaluated longitudinal changes of markers of HIV-1 persistence in relation to inflammation, T-cell activation, and cycling in a large cohort of participants who had initiated ART during chronic HIV-1 infection and had long-term (3–10+ years) sustained suppression of plasma viremia. In that population, we previously showed that high levels of inflammation, immune activation, and T-cell cycling before treatment correlated with high levels during therapy, even after many years of sustained virologic suppression. On the other hand, these inflammatory markers did not correlate with markers of viral persistence (HIV-1 DNA, cell-associated HIV-1 RNA, or plasma HIV-1 RNA) during suppressive therapy, suggesting that HIV-1 persistence is not driving or being driven by inflammation or immune activation.[11]

It therefore remains unclear what drives persistent inflammation and immune activation on ART, and whether any adjunctive therapies could further decrease it. In this study, we used samples from the A5321 cohort to evaluate whether statin exposure is associated with lower levels of viral persistence or inflammation/immune activation, or whether their effects on viral persistence and inflammation/immune activation are correlated.

METHODS

Study Population

All A5321 participants included in this analysis had initiated ART during chronic HIV-1 infection, had achieved virologic suppression (HIV-1 RNA levels ≤50 copies/mL) by year 1 of ART, and maintained suppression with no documented breakthroughs (consecutive HIV-1 RNA >50 copies/mL) in the 3 years before biomarker evaluation.

Participants were censored (excluded) from analyses if they had previous use of an investigational agent that might affect HIV reservoirs or were HCV RNA positive. Participants were classified as statin users if they reported receiving statins at the time of biomarker evaluation.

Paired plasma and peripheral blood mononuclear cell (PBMC) samples were collected at A5321 study entry for virologic and immunologic assays.

Virologic Assays

We measured 3 markers of HIV-1 persistence: unspliced cell-associated HIV RNA (CA-RNA), total CA-DNA, and single copy assay (SCA) plasma HIV RNA. CA-RNA and CA-DNA were measured by quantitative polymerase chain reaction (qPCR) in PBMC samples using methods that have been previously published.[11] Plasma HIV RNA by SCA was measured using previously published methods: Primers and probes used for qPCR of HIV DNA, CA-RNA, and plasma HIV-1 RNA were identical and targeted a conserved region of integrase.[12]

HIV DNA and CA-RNA (per 10^6 $CD4^+$ T cells) were normalized by dividing the total HIV DNA or CA-RNA copies/10^6 PBMC as measured by qPCR by the $CD4^+$ T-cell percentage from the same specimen date or closest specimen date before or after the HIV DNA or CA-RNA results.[12]

Immunologic Assays

Plasma concentrations of interleukin (IL)-6, IFN-γ–inducible protein 10 (IP-10), neopterin, soluble CD14 (sCD14), soluble CD163 (sCD163), and TNF-alpha were quantified using enzyme-linked immunosorbent assay kits, and $CD4^+$ and $CD8^+$ T-cell activation was quantified from PBMCs by multicolor flow cytometry as previously described.[11]

Statistical Analysis

The Wilcoxon rank-sum test compared continuous outcomes between those on a statin versus not on a statin at the time of biomarker measurement, analyzing results below assay limit as the lowest rank. The Fisher exact test compared the dichotomous outcome (SCA ≥ or <0.4 copies/mL) and categorical variables; the signed-rank test evaluated changes in lipids. We performed sensitivity analyses by removing participants with previous statin use reported, but who were not currently taking statins at A5321 entry. In addition, regression models were used to adjust for variables correlated with markers of HIV persistence.

RESULTS

Study Participants

A total of 303 participants who initiated ART during chronic HIV infection and had maintained virologic suppression for ≥3 years were analyzed. The median age was 48 years; 82% were men; and 55% were white. At the time of biomarker measurements, median duration of suppressive ART exposure was 7.3 years (interquartile range: 6.1–10.1); median CD4 count was 681/mm^3 (515–864); 72 (24%) participants reported receiving statins. The median time to biomarker assessment was 2.9 years (1.2–5.1) on the current statin and 4.5 years (2.7–7.4) since first statin use.

Characteristics of statin and nonstatin recipients are presented in Table 1. Of note, statin users were older with greater duration on ART.

A total of 16 participants classified as nonstatin users had previous statin use, but were not taking a statin at time of biomarker measurements. Among these participants, the median time off statins before the measurements (since stop of most recent statin) was 1.8 years (min: 0.1 and max: 12.0).

Markers of Viral Persistence

Median levels of biomarkers of viral persistence are presented in Table 2.

There were no differences between statin users and nonusers in levels of CA-DNA (median 650 vs. 540 copies/10^6 $CD4^+$ T cells; $P = 0.58$), CA-RNA (53 vs. 37 copies/10^6

TABLE 1. Participant Characteristics

	On Statin at A5321 Entry			
	Yes (N = 72)	No (N = 231)	Total (N = 303)	P*
Age at A5321 entry (yr)				
Median (Q1–Q3)	53 (49–60)	46 (39–53)	48 (41–54)	<0.001
Sex (%male)	61 (85%)	187 (81%)	248 (82%)	0.60
Race/ethnicity				
White non-Hispanic	46 (64%)	122 (53%)	168 (55%)	0.34
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%)	
Smoking (%cigarette smoker at A5321 entry)	15 (21%)	55 (24%)	70 (23%)	0.64
Diabetes diagnosis before A5321 entry	10 (14%)	7 (3%)	17 (6%)	0.002
Intravenous drug use at A5321 entry				
Current	0 (0%)	0 (0%)	0 (0%)	0.31
Previous	1 (1%)	11 (5%)	12 (4%)	
Never	71 (99%)	220 (95%)	291 (96%)	
ARV regimen at A532 entry				
NNRTI-based	45 (63%)	113 (49%)	158 (52%)	0.22
PI-Based	16 (22%)	66 (29%)	82 (27%)	
InSTI-based	11 (15%)	51 (22%)	62 (20%)	
Other	0 (0%)	1 (0%)	1 (0%)	
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)	0.002
Pre-ART $CD4^+$ T-cell count (cells/mm^3)				
Median (Q1–Q3)	286 (110–414)	254 (114–369)	258 (113–374)	0.27
A5321 entry $CD4^+$ T-cell count (cells/mm^3)				
Median (Q1–Q3)	737 (542–935)	665 (505–840)	681 (515–864)	0.038
Pre-ART plasma HIV-1 RNA (log_{10} copies/mL)				
Median (Q1–Q3)	4.6 (4.3–5.0)	4.6 (4.2–5.0)	4.6 (4.2–5.0)	0.82
A5321 entry HIV-1 RNA (copies/mL)				
<40	72 (100%)	231 (100%)	303 (100%)	
Statin at A5321 entry				
Simvastatin	5 (7%)	0 (0%)	5 (2%)	
Pravastatin	25 (35%)	0 (0%)	25 (8%)	
Atorvastatin	27 (38%)	0 (0%)	27 (9%)	
Rosuvastatin	14 (19%)	0 (0%)	14 (5%)	
Ezetimibe/simvastatin	1 (1%)	0 (0%)	1 (0%)	

*The Exact Wilcoxon test for continuous variables and the Fisher exact test for categorical variables.
ARV, antiretroviral; InSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

$CD4^+$ T cells; $P = 0.12$), or SCA (46% vs. 54% <0.4 copies/mL; $P = 0.27$). The results were similar in sensitivity analyses excluding the 16 participants with past statin exposure.

Findings with viral persistence were unchanged after adjustment for the following factors: sex of participant, pre-ART CD4 and HIV RNA, CD4 count at study A5321 entry, HCV status, antiretroviral regimen, age, and years on ART ($P \geq 0.28$; $P \geq 0.07$; and $P \geq 0.09$ for CA-DNA, CA-RNA, and SCA, respectively).

Markers of Inflammation/Immune Activation

Median levels of biomarkers of inflammation and immune activation are also presented in Table 2.

There were no significant differences between statin users and nonusers in markers of inflammation/activation, except for IP-10, which had higher values in statin users than nonusers (137 vs. 118 pg/mL, respectively; $P = 0.028$). This association with IP-10 remained ($P < 0.05$) after adjustment for confounders other than age; after adjustment for age, IP-10 levels remained higher, but the effect was attenuated ($P = 0.12$).

Lipid Changes

To address the possibility that the absence of statin effects on viral persistence and inflammation biomarkers was due to nonadherence, changes in fasting low-density lipoprotein (LDL) levels were examined. Among the 49 statin users

TABLE 2. Markers of Viral Persistence and Inflammation by Statin Use

	On Statin at A5321 Entry		
	Yes (N = 72)	No (N = 231)	*P**
Markers of viral persistence			
HIV DNA (cps/10^6 $CD4^+$ T cells)			
Median (Q1–Q3)	650 (206–1562)	540 (232–1317)	0.58
CA-RNA (cps/10^6 $CD4^+$ T cells)			
Median (Q1–Q3)	53 (14–198)	37 (14–125)	0.12
HIV-1 RNA through 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)	
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)	2036 (1548–2444)	1915 (1459–2444)	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
$CD4^+$ T-cell activation (% $CD38^+$/HLA-DR^+)	3.5 (2.9–4.6)	3.9 (2.9–5.5)	0.32
$CD8^+$ T-cell activation (% $CD38^+$/HLA-DR^+)	7.3 (4.4–15.1)	9.4 (5.7–13.9)	0.22

For markers of viral persistence, the number of participants on statins and not on statins is 68 and 224 for HIV DNA and iSCA, and 67 and 216 for CA-RNA. For T-cell activation, the number of participants on statins and not on statins is 24 and 75.

*The Wilcoxon test for continuous variables and the Fisher exact test for iSCA.

CA-RNA, cell-associated RNA; iSCA, SCA plasma HIV RNA.

with measurements before and approximately 1 year after first statin use,[13] fasting LDL levels declined a median 37 mg/dL (Q1, Q3: 18, 58; $P < 0.001$). Comparing levels before first statin use to the latest available measurement (median 4 months before the measurement of biomarkers of viral persistence), fasting LDL levels declined a median 44 mg/dL (Q1, Q3: 15, 68; n = 60, $P < 0.001$) over a median 3.8 years.

DISCUSSION

Despite long-term viral suppression, elevated levels of inflammation and immune activation persist in some ART-treated individuals. Given its association with long-term complications and mortality, and the fact that it might contribute to viral persistence, this residual chronic inflammation and immune activation likely represent an important therapeutic target to improve the long-term prognosis of people living with well-controlled HIV.

In this cohort of participants on long-term suppressive ART, reported current statin use was not associated with lower levels of HIV persistence or immune activation/inflammation. The results failed to validate our hypothesis that the observed in vitro antiviral effect of statins would result in a decrease in HIV-1 reservoir reflected by lower measured levels of viral persistence. They also do not support the hypothesis that a possible effect of decreased HIV reservoir size accounts for our reported statin association with lower risk of virologic rebound.[10] The mechanism of the latter effect of statin use remains unexplained, but likely reflects characteristics of individuals who use statins other than HIV reservoir size.

We also observed a lack of association between statin exposure and most markers of immune activation/inflammation. In the SATURN-HIV study, there was also no statistically significant difference between rosuvastatin recipients and controls in changes in several markers of systemic inflammation and coagulation—except for lipoprotein-associated phospholipase A_2—at week 24.[14] However, contrary to our findings, statin recipients had significantly greater decreases in the monocyte activation marker soluble CD14.[15] Also contrary to our findings are those of the INTREPID study which showed that pitavastatin use was associated with reduction in markers of monocyte activation and arterial inflammation[16] as well as proteins involved in coagulation and oxidative stress.[17] However, our results are in line with other prospective studies that have failed to show a benefit of anti-inflammatory and immune-regulatory measures—including sevelamer,[18] mesalamine,[19] rifaximin,[20] and atorvastatin[21]—on HIV-associated chronic inflammation and immune activation.

Interestingly, we observed significantly higher plasma levels of IP-10 among participants receiving statins. Although this association could have occurred by chance given that we performed multiple comparisons, statins have been shown to repress dendritic cell (DC) maturation thereby inducing tolerogenic DCs that secrete high levels of IL-10 and IP-10 and induce expansion of regulatory T cells which also secrete IL-10.[22] In the presence of IL-10, DCs in the liver, lung, and spleen transform into regulatory DCs, which could be induced to produce both IL-10 and IP-10.[23,24]

Strengths of our study include concomitant analysis of several biomarkers of viral persistence and immune activation and inflammation in a well-characterized cohort of HIV-infected participants. In addition, all participants in the study had consistently maintained virologic suppression, which means they were likely to be adherent to their antiretrovirals; this feature of the cohort reduces the likelihood that difference in antiretroviral adherence between statin users and nonusers might result in spurious associations. One limitation of the study is that biomarker assessments were made after participants had achieved virologic suppression on ART for a median of over 7 years and had received statins for a median of over 4 years. Significant declines in LDL levels after the start of the reported statin use strongly suggests that the absence of statin effect on markers of viral persistence,

inflammation, and immune activation was not likely due to poor adherence. Statins may have had transient effects after their initiation that subsequently waned. Different statins may also differ in their effect(s) on markers of inflammation and immune activation.[25] Also, there could be a dose-dependent effect on the measured markers. We did not record dose of statins received. Furthermore, effect of specific statins and/or doses could not be assessed on such a small sample size. Prospective, randomized studies, such as REPRIEVE (ClinicalTrials.gov Identifier: NCT02344290), could better assess the effect of specific statins on chronic inflammation/immune activation and HIV persistence.

ACKNOWLEDGMENTS

The authors thank all the members of the A5321 team. The authors express their sincere appreciation to the study participants, the ALLRT team who established the original cohort, study staff and the sites for enrolling and following the study participants, the NIAID, and the ACTG. The authors thank Christina Lalama for statistical input and database expertise.

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