Statin Use on HAART is Associated With Greater CD4 Gains in HIV-Infected Veterans

Poster 1118

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Introduction

- Persistent inflammation and immune activation on long-term suppressive HAART is associated with increased mortality and HIV-associated Non-AIDS morbidity[1] as well as incomplete immune reconstitution[2].
- Incomplete immune reconstitution is commonly defined as subnormal CD4 values, i.e. <500 cells/µL but even CD4 values 500-720 cells/µL are associated with increased all-cause mortality[3].
- Many HIV-infected patients never reach these thresholds. HMG-CoA Reductase inhibitors (statins) have been shown to lower markers of immune activation in HIV-infected patients on HAART[4].
- Would statin use impact parameters of immune reconstitution and virologic control in a large retrospective database?

Objectives

- To evaluate whether statin use contributes to immune reconstitution independently of HAART.

Methods

- We used the US Veterans' Cohort (1995-2011) Clinical Case Registry to identify patients with ≥1 viral load (VL) after and ≥1 CD4 count before and after HAART initiation in the VA system.
- Follow-up (f/u) time started at first HAART initiation.
- Accounting for early refills, unused outpatient refills during hospitalizations, inpatient use, and medication switches we computed daily medication use rates, defining:
  - Cumulative **HAART use rate (HUR)**
  - Cumulative **statin use rate (SUR)**

  as the % of follow-up (f/u) time in which patients were in possession of a complete HAART regimen or any statin.
- All covariates related to HIV suppression status, HCV status, and type of HAART were also time-updated.
- Virologic suppression episodes were defined as f/u time between reaching a VL <400 cop/mL and at least 2 consecutive VL > 400 cop/mL or any VL >1000 cop/mL.
- The time-to-loss-of-virologic response (TLOVR) Cox model used only patients reaching a VL <400 within 6 months.
- The Generalized Estimating Equations (GEE) used only patients with non-missing values for its covariates.
- We used SPSS Version 20 for data cleaning, organization, and statistical analyses.

Results

- 36,685 patients started HAART within the VA system and 29,387 met the inclusion criteria.
- 32% used statins during f/u.
- The median cumulative statin exposure was 26 months, the interquartile range (IQR) 10-59 months.
- The median SUR was 35% (IQR: 12-64%).

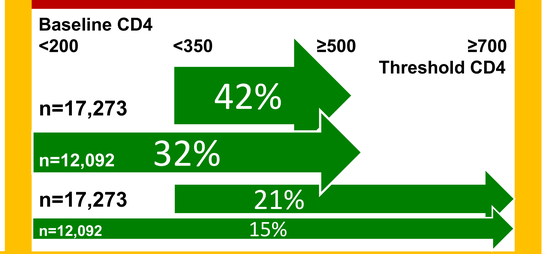
Table 1. Baseline Characteristics

Variable Median (IQR) or %	No statin use on HAART n=19,955	Any Statin use on HAART n=9,417	P*
Years of follow-Up	5.2 (2.2-9.7)	9.2 (5.1-13.2)	<0.0001
Age at HAART initiation	46 (40-52)	49 (43-56)	<0.0001
Males	97%	98%	0.021
African American European American Missing information	44% 29% 25%	41% 46% 12%	<0.0001
Pre HAART (era) ARV experience	33%	33%	0.351
HCV co-infection	33%	16%	<0.0001
Clinical AIDS before HAART	22%	19%	0.476
Baseline CD4 (/µl)	230 (91-384)	282 (140-450)	<0.0001
Baseline CD8 (/µl)	770 (503-1134)	842 (568-1213)	<0.0001
Baseline Hgb <13g/dL	35%	29%	<0.0001
Baseline VL (log) Baseline VL < 400 c/mL	4.4 (3.2-5.1) 16%	4.1 (2.6-5.0) 23%	<0.0001 <0.0001
Ever smoked	52%	51%	0.401
Baseline BMI	24.0 (21.4-27.1)	25.5 (22.8-28.7)	<0.0001

Are statin and HAART use correlated?

- Throughout follow-up statin and HAART use were correlated (R=0.25). However, the correlation coefficients for the time updated medication use variables in the multivariate models did not meet multicollinearity thresholds.

How frequent is immune reconstitution?



Do statins increase the chances of immune reconstitution beyond HAART?

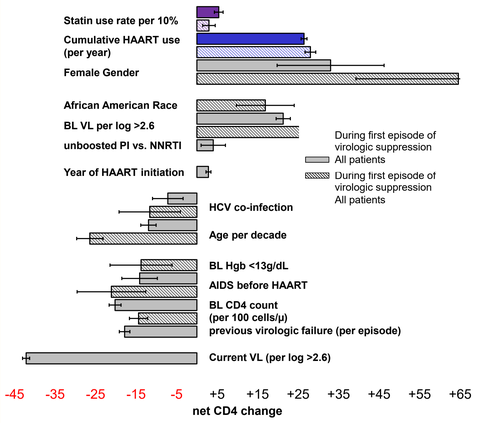
Table 2. Relative contribution of HAART and Statins to immune reconstitution in Cox multivariate models

Model	Median years follow-up (IQR)	Median years to IR (IQR)	Exposure	HR (95% CI) for immune reconstitution for 100% use	per 10% use	p=
<350 → ≥500	6.2 (2.8-10.9)	2.3 (0.9-4.8)	HAART	4.43 (3.97-4.93)	1.16(1.14-1.17)	<0.0001
			Statins	1.22 (1.09-1.37)	1.02 (1.00-1.03)	<0.0001
<200 → ≥500	6.0 (2.6-10.6)	3.8 (2.0-6.4)	HAART	5.00 (4.21-5.93)	1.17 (1.15-1.19)	<0.0001
			Statins	1.20 (0.99-1.45)	1.01 (0.99-1.03)	0.052
<350 → ≥700	6.2 (2.8-10.9)	4.1 (2.1-7.0)	HAART	5.78 (4.93-6.76)	1.19 (1.17-1.21)	<0.0001
			Statins	1.43 (1.23-1.67)	1.03 (1.02-1.05)	<0.0001
<200 → ≥700	6.0 (2.6-10.6)	5.5 (3.2-8.7)	HAART	5.22 (4.04-6.73)	1.17 (1.15-1.21)	<0.0001
			Statins	1.41 (1.09-1.82)	1.03 (1.00-1.06)	0.008

- Statins contribute independently and consistently to the likelihood of immune reconstitution across all models .
- The models control for baseline CD4 and VL(log), age, race, gender, hepatitis C co-infection, clinical AIDS before HAART, and year of HAART initiation as baseline covariates, and virologic suppression status, and time since last detectable VL as time-updated covariates.

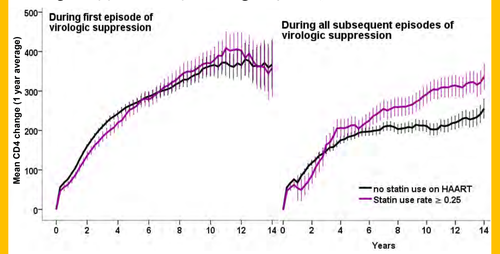
How much CD4 gain is attributable to statin use?

Figure 1. GEE for CD4 changes (±95% CI) in all patients (solid top) and during first virologic suppression (hatched bottom).



- We used GEE for the contribution of statin use to quarterly time-weighted CD4 average changes in 21,029 patients.
- Additionally, we analyzed patients during virologic suppression with ≥6 months f/u:
  - First episode of VL suppression (n= 9,310)
  - All subsequent VL suppression episodes (n=11,202)
- For every 10% ↑ in statin use rate the CD4 gain was 5.4 cells.
- The CD4 gain per year of cumulative HAART was 26.5 cells.
- During first virologic suppression episode the statin effect was smaller: 3 CD4 cells gained per 10%↑ in SUR.
- During subsequent VL suppression episodes, the statin effect was larger: 7.9 CD4 cell gained per 10% ↑ in SUR (not shown in Figure 1, see Figure 2).
- Current and past virologic failure were the strongest negative predictors; female gender and BL VL the strongest positive predictors of CD4 changes.
- Clinical AIDS at baseline and type of HAART backbone were not predictive.

Figure 2: Annual CD4 average changes (±95% CI) updated every 3 months *during* the first (left) and subsequent (right) *virologic suppression episodes* grouped by statin use rate.



Do statins affect virologic control?

Figure 3. Proportion of patients with ≥95% HAART use rate who maintained initial virologic suppression (±95% CI) by statin use rate and current type of anchoring drug used.

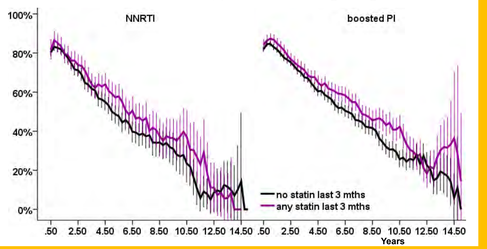
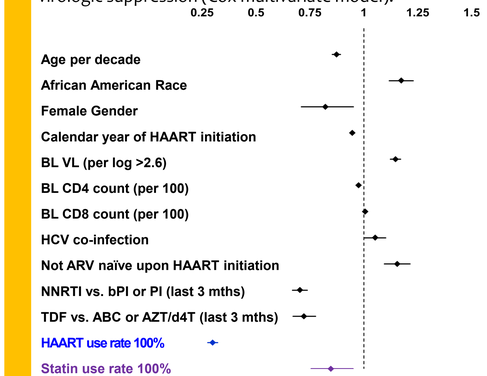


Figure 4. HR (±95% CI) TLOVR during the first episode of virologic suppression (Cox multivariate model).



- The multivariate TLOVR model included 16,226 patients, 56% of whom had subsequent virologic failure. The median f/u was 5.1 y (IQR 1.7-9.8). Loss of f/u or death were not considered failure.
- Statin use was associated with decreased risk of virologic failure (HR 0.85, 95% CI 0.76-0.95 for 100% SUR, p=0.005).
- HAART use rate, type of HAART backbone and anchor last used, older age, and later calendar year of HAART initiation were other negative predictors of virologic failure.

Conclusions

- US veterans who used statins on HAART had accelerated CD4 recovery and delayed time to first virologic failure.
- The statin effect on CD4 recovery was greater after prior virologic failure(s), partially mitigating the known blunting of CD4 gains in this setting[5].
- In the context of substantially decreased mortality rates of statin users in observational studies (HR 0.25-0.41) [6-8], the immunologic consequences of statin use in treated HIV infection may very well be clinically relevant.

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