Poster 468

Current Statin Use Reduces Risk of Viral Rebound on Suppressive cART

Henning Drechsler[1,2] Colby Ayers [2] James Cutrell[1,2] Naim Maalouf[1,2] Pablo Tebas[3] Roger Bedimo [1,2]

[1]VA North Texas Health Care System, Dallas, TX, [2]University of Texas Southwestern, Dallas, TX, [3]University of Pennsylvania, Philadelphia, PA

Introduction

Despite compelling evidence for activity against HIV-1 in vitro[1], a virologic effect of statins has not been shown in clinical studies. [2,3] Given their relatively short plasma half-lives, such an effect may be transient and only become apparent during ongoing exposure. Also, given the low rates of lipid-lowering therapy before virologic suppression[4] and the high potency of (current) ART, an incremental effect on initial virologic response may be difficult to detect. We instead analyzed the effect of current and recent statin exposure compared with other cardiovascular medications (CVM) on 1st virologic failure (VF) in patients who had achieved an undetectable HIV viral load (VL) on cART.

Methods

- Data source: VA HIV Clinical Case Registry.
- Inclusion Criteria: cART initiation between 1995-2011 and:
  - ≥ 1 detectable VL >1000 c/mL, *followed by:*
  - ≥ 1 undetectable VL (at any threshold), *and:*
  - ≥ 1 subsequent VL measurement within 13 months
- Definitions: Baseline was the date of the 1st undetectable VL measurement after HAART initiation. Follow-up time ended at the day of VF, or at the last VL measurement. We censored patients if there was no subsequent VL measurements within 13 months. VF was defined as the first VL measurement >1,000 c/mL or the first of two consecutive VL measurements >200 c/mL.
- Outcome: Time to VF
- Stratification: Time period of study inclusion: 1995-2000, 2001-2005, and 2005-2011
- Exposures: Comprehensive exposure model of in- and outpatient medication use incorporating drug accumulation during hospitalization times, early refills, and incompatibility of certain co-exposures (e.g. 2 different statins). We modeled the following drugs:
  - Antiretrovirals (ARV)
  - Statins
  - Non-statin lipid lowering agents (ALP)
  - Antihypertensives (AHT)
  - Cardioprotective Aspirin (ASA)

  We analyzed both current use (within 7 days) and proportion of days covered (PDC) over the past 1 month (CVMs) or 3 months (ARVs).
- Covariates: *Baseline*: age, gender, race, history of drug abuse, time from HIV diagnosis to VS, peak VL, non-HAART ARV use prior to cART. *Time updated*: CD4 counts, ARV class experience, substance abuse, HCV status, and adherence to 6 HAART components (see Table 1)
- Statistical Analysis: We fit both Cox regression models with multivariate adjustment (MVA) and inverse probability weighted (IPW) Cox models. We used SPSS (Version 23, IBM Corporation, Armonk, NY) and the R survival package (Version 3.32, Foundation for Statistical Computing, Vienna).

Results

- 80% of veterans who started HAART 1995-2011 achieved an undetectable VL. Of these, 19,324 met inclusion criteria.
- Median observation time (until last VL measurement) was 5.9 years, inter-quartile range (IQR): 2.6-9.8 years, median follow-up time (until VF or censoring) was 15 months (IQR: 6-40 months).

Table 1. Baseline Characteristics

Median Values (IQR) or % at day of initial VL suppression		Overall	1995-2000	2001-2005	2006-2011
		n=19,324	n=6,678	n=6,240	n=6,406
VL assay detection limit < 50 c/mL		58%	23%	61%	90%
Age		48 (42-54)	46 (40-52)	48 (42-54)	51 (44-57)
Female Gender		3%	2%	3%	3%
Race:	African American	47%	39%	49%	54%
	White	36%	34%	38%	36%
	Unknown	15%	26%	11%	8%
HCV co-infection		26%	31%	27%	19%
Drug Abuse		33%	32%	34%	34%
>30 d non HAART ARV experience		29%	52%	23%	10%
Months since HIV-Dx		31 (9-74)	33 (10-62)	34 (9-85)	28 (8-86)
VL before ART (log)		4.7 (4.0-5.2)	4.6 (4.0-5.2)	4.8 (4.1-5.3)	4.7 (4.0-5.1)
Peak VL (log)		5.0 (4.6-5.5)	5.0 (4.6-5.5)	5.1 (4.7-5.6)	5.0 (4.5-5.5)
CD4 count /mm³		333 (191-505)	321 (180-504)	311 (176-475)	367 (221-531)
ARV class experience*	2 classes	61%	72%	51%	59%
	3 classes	22%	20%	25%	22%
	4 classes	13%	7%	19%	13%
	5 classes	2%	0%	1%	4%
	6 classes	0%	0%	0%	1%
ART use last 3 months: NRTI	3TC/FTC	77%	76%	72%	84%
	TDF	31%	0%	23%	71%
	Other	61%	88%	74%	21%
ART use last 3 months: Anchor	EFV / rDRV / INSTI	36%	14%	38%	57%
	boosted PI**	22%	6%	29%	30%
	unboosted PI, NVP, or other	35%	75%	21%	7%
Native LDL equivalent** mg/dL		114 (89-143)	128 (98-160)	115 (89-145)	109 (87-134)
Body Mass Index		25.1 (22.4-28.3)	24.7 (22.2-27.6)	24.8 (22.2-28.0)	25.5 (22.6-28.9)
Statin use		7%	2%	7%	11%
Non Statin lipid-lowering agent use		4%	4%	6%	4%
Antihypertensive use		26%	20%	27%	32%
Cardiac Aspirin use		6%	5%	6%	7%

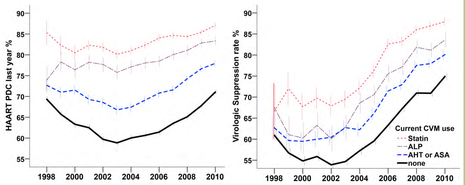
*EFV: efavirenz, rDRV: ritonavir boosted darunavir, INSTI: Integrase Inhibitor, NVP: nevirapine. *boosted PI and unboosted PI counted as separate classes **other than rDRV, ***Maximum of LDL cholesterol or Non-HDL cholesterol minus 30mg/dL when off lipid-lowering therapy.*

Drug Exposure During Follow-Up:

- Ever use rates for CVMs were: AHT: 60%, statins: 34%, ASA: 30%, and ALP: 21%. Ever use rates for statin compounds were: pravastatin: 40%, simvastatin: 23%, fluvastatin: 13%, rosuvastatin: 13%, atorvastatin: 9%, and lovastatin: 2%.
- 91% of all statin users started statins after VL suppression.

Are statin, CVM, and HAART use correlated?

Figure 1. Virologic Suppression Rates and HAART PDC by exposure status to CVM over time (Vertical lines are 95% CI).



- Exposure to statins was associated with higher virologic suppression (VS) rates and higher HAART adherence (PDC) than exposure to ALP, other CVMs, or no CVM exposure. Both HAART PDC and VS increased over time.
- This illustrates the need for rigorous bias correction to isolate any inherent effects on viral suppression.

Is there an independent effect of current statin use on the risk of VF?

Table 2. Association of statin and CVM use with the risk of VF by mode of drug exposure and Bias Correction. Significant associations are color shaded.

Medication Exposure Mode	Bias Correction		Statins	Non-Statin Lipid-lowering Agents	Antihyper-tensives	Cardiac Aspirin
PDC (30/90d)*	None		0.57 (0.53-0.62) p<0.001	0.76 (0.69-0.83) p<0.001	0.79 (0.75-0.83) p<0.001	0.83 (0.76-0.90) p<0.001
	Multivariate Adjustment		0.83 (0.76-0.90) p<0.001	1.03 (0.94-1.14) p=0.5	1.00 (0.95-1.05) p=0.85	1.10 (1.01-1.21) p=0.04
Current Use (within 7 d)	None		0.60 (0.56-0.65) p<0.001	0.76 (0.70-0.83) p<0.001	0.82 (0.79-0.86) p<0.001	0.88 (0.81-0.95) p=0.002
	Multivariate Adjustment		0.81 (0.75-0.88) p<0.001	0.97 (0.89-1.06) p=0.53	1.00 (0.96-1.05) p=0.9	1.13 (1.04-1.23) p=0.004
	IPW	Truncation <5% / >95%	0.76 (0.69-0.83) p<0.001	0.97 (0.88-1.08) p=0.64	0.98 (0.94-1.03) p=0.46	1.01 (0.91-1.12) p=0.86
		<1% / >99%	0.83 (0.75-0.92) p<0.001	1.03 (0.92-1.15) p=0.67	1.02 (0.97-1.07) p=0.57	1.03 (0.92-1.15) p=0.63
		<0.1%/>99.9%	0.90 (0.80-1.01) p=0.08	1.04 (0.93-1.17) p=0.48	1.03 (0.98-1.08) p=0.29	1.04 (0.92-1.16) p=0.57

*Hazard ratios followed by 95% confidence intervals in parenthesis. IPW: Inverse Probability Weighting for treatment and censoring. *PDC interval 30 days for statins and CVMs and 90 days for ARVs. In PDC mode HR is for 100% use.*

- Current statin or CVM use was associated with a decreased risk of VF in univariate analysis,. After MVA, only statin use remained a significant negative predictor: the adjusted HR was 0.83 (CI: 0.76-0.90) in the PDC model, and 0.81 (CI: 0.75-0.88) in the current use model. Using IPW, only statins but not CVMs were associated with lower VF risk. In contrast, current or recent use (PDC model) of cardio-protective aspirin was associated with an increased risk of VF after MVA but not IPW.

How do other factors affect the risk of VF?

Figure 2. Proportion of patients with VF by overall cART adherence since suppression (rows), and time period (columns)

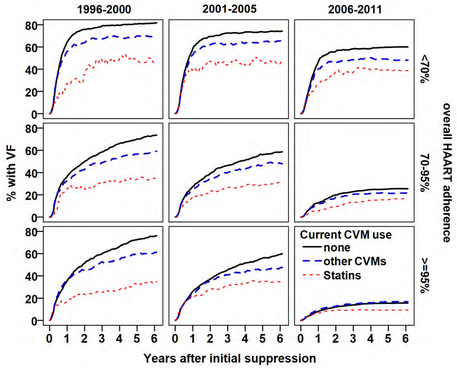


Figure 3. Proportion of patients with VF by predominant anchor drug (rows), and tenofovir exposure status (columns) in past 3 months.

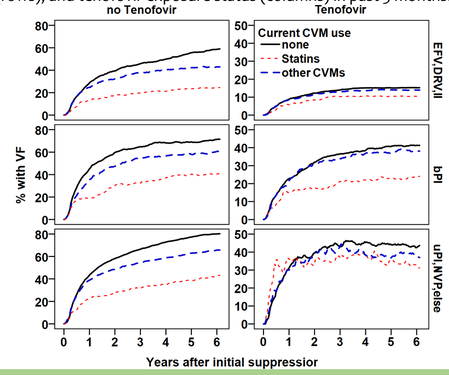
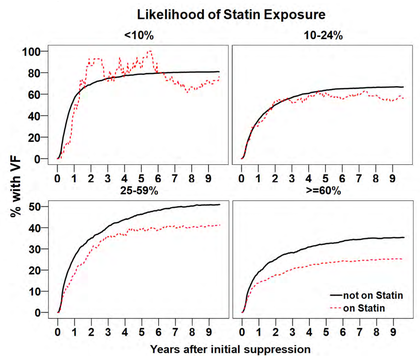


Figure 4. Proportion of patients experiencing VF by likelihood of statin exposure based on propensity score.



- The the negative effect of statins on the risk of VF was present during the entire study period and among all strata of HAART adherence, and types of HAART and most types of statins taken (date not shown); becoming less pronounced after 2005, in patients with optimal HAART adherence, and in those taking 'contemporary' HAART.

Conclusions

- Current statin exposure was independently associated with a lower risk of VF in univariate and multivariate models and after inverse probability weighting. This was not seen with other CVMs, including ALPs, AHTs and ASA.
- To our knowledge, this is the first demonstration of an adjuvant anti-HIV effect for a non-antiretroviral class of medications.
- The mechanism(s) of the protective effect of statins on the chance HIV rebound are unclear.

References

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