Incomplete ART Adherence is Associated with Higher Interleukin-6 in Individuals with HIV who Achieved Virologic Suppression in the Immediate Arm of the Strategic Timing of Antiretroviral Treatment (START) Study

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Background

- People living with HIV infection (PLWH) exhibit a phenotype of chronic residual inflammation, immune activation and coagulopathy that persists despite sustained viral suppression, and is associated with severe non-AIDS events (SNAEs) and all-cause mortality[1].
- Recent studies (including SMART) have demonstrated that suboptimal (i.e., less than 100%) ART adherence, even if it is sufficient to achieve and sustain plasma viral suppression, could be a contributor of inflammation, immune activation and coagulopathy in PLWH with advanced disease[2-4].
- Whether variations in ART adherence, in the setting of suppression, are also associated with these findings in early treated HIV infection remains unknown and was the aim of this study.

Methods

- ART-naïve participants with CD4$^+$ T-cells >500 cells/mm^3 were included in the analysis if they: a) were randomized to the immediate treatment arm of START[5]; b) achieved viral suppression (<50 copies/mL) while on ART at the 8-month visit, and; c) had concomitant adherence data and plasma biomarkers available at the 8-month visit.
- ART adherence was measured by self-report at 1, 4 and 8 months after treatment initiation using the Terry Beirn CPCRA Form 065-BAS-2, which uses a 7-day global recall, where participants respond whether they took "all", "most", "about one-half", "very few", or "none" of their pills for each specific pill in their ART regimen. Adherence at the 8-month visit was labeled as "incomplete" if a participant reported not taking "all" pills in the preceding 7-days for at least one antiretroviral medication.
- Plasma biomarker concentrations (measured at baseline and at the 8-month visit using ELISA or chemiluminiscence [MesoScale, MSD]) included: interleukin (IL)-6, high-sensitivity C-reactive protein (hsCRP), serum amyloid A protein (SAA), IL-27, soluble intercellular adhesion molecule-1 (sICAM), soluble vascular adhesion molecule-1 (sVCAM) and D-dimer[6]. CD4$^+$ and CD8$^+$ T-cell subsets were determined by flow cytometry.
- Biomarker concentrations (except the CD4$^+$/CD8$^+$ T-cell ratio) were ln-transformed and analyzed using univariable and multivariable linear regression to assess their association with ART adherence at the 8-month visit adjusting for covariates.
- Data are presented as fold differences in biomarker concentrations and in the CD4$^+$/CD8$^+$ T-cell ratio in individuals who reported incomplete vs. 100% adherence at the 8-month visit.

Results

Table 1. Demographic characteristics of study participants (N=1,627).

Characteristic	Incomplete Adherence n=109	100% Adherence n=1,518
	n(%) or median (IQR)	
Female	24 (22)	398 (26)
Age (years)	32 (27, 40)	36 (29, 44)
Time since diagnosis (years)	1.1 (0.4, 3.0)	0.9 (0.3, 2.8)
Race		
Black	31 (28)	448 (30)
Hispanic	24 (22)	191 (13)
Asian	10 (9)	139 (9)
White	35 (32)	683 (45)
Other	9 (8)	57 (4)
ART class at 8-month visit*		
NNRTI-based	77 (71)	1,086 (72)
b/PI-based	22 (20)	337 (22)
INSTI-based	9 (8)	76 (5)
Other/Multiclass	1 (<1)	19 (1)
Education level		
Less than high school	33 (30)	448 (30)
High school or equivalent	22 (20)	334 (22)
Completed vocational training	11 (10)	145 (10)
Some college/some university	18 (17)	262 (17)
Bachelor's/university	20 (18)	248 (16)
Any post-graduate education	5 (5)	81 (5)
HIV exposure		
IDU	1 (1)	22 (1)
MSM	73 (67)	844 (56)
Heterosexual	33 (30)	572 (38)
Other	2 (2)	80 (5)
Region		
Africa	16 (15)	341 (22)
Latin America	37 (34)	382 (25)
Europe/Israel	26 (24)	511 (34)
United States	19 (17)	123 (8)
Australia	2 (2)	36 (2)
Asia	9 (8)	125 (8)
HBV infection	0 (0)	44 (3)
HCV infection	4 (4)	51 (3)
BMI at baseline (Kg/m^2)	24.4 (22.3, 29.3)	24.5 (22.0, 27.8)
Current smoker (baseline)	43 (39)	476 (32)
CD4$^+$ T-cells at baseline (cells/mm^3)	658 (596, 760)	649 (585, 769)
HIV RNA at baseline (copies/mL)	9,803 (3,017, 34,178)	13,411 (3,382, 42,717)

* All participants received a dual nucleoside/nucleotide reverse transcriptase inhibitor backbone. ART: antiretroviral therapy. IQR; inter-quartile range. VL: viral load. MSM: men who have sex with men. IDU: injection drug users. PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor. INSTI: integrase strand-transfer inhibitor. BMI: body mass index. HBV: hepatitis B virus. HCV: hepatitis C virus.

Results (continued)

Table 2. Adjusted fold difference in biomarker plasma concentrations and CD4$^+$/CD8$^+$ ratio according to adherence category in participants who achieved HIV viral load <50 copies/mL at the 8-month visit in the immediate arm of START.

Biomarker	Incomplete Adherence		100% Adherence[a]		Adjusted[b]		
	n	Median (IQR)	n	Median (IQR)	Fold difference	95% CI	p value
Biomarkers for which there was a pre-specified hypothesis based on previous data							
IL-6 (pg/mL)	109	1.34 (0.95, 2.10)	1,518	1.23 (0.84, 1.92)	1.13	1.00-1.27	*0.047*
D-dimer (μg/mL)	109	0.25 (0.18, 0.38)	1,513	0.28 (0.19, 0.43)	1.04	0.94-1.15	0.47
Exploratory analyses of other biomarkers[c]							
hsCRP (μg/mL)	109	2.32 (0.75, 5.65)	1,518	1.81 (0.74, 4.58)	1.19	0.96-1.49	0.11
SAA (mg/L)	109	4.59 (2.72, 9.71)	1,518	3.72 (2.07, 7.73)	1.30	1.04-1.62	*0.02*
IL-27 (pg/mL)	109	265 (109, 546)	1,518	239 (111, 533)	1.00	0.84-1.18	0.98
sICAM (ng/mL)	109	487 (366, 625)	1,518	476 (370, 610)	1.01	0.94-1.08	0.86
sVCAM (ng/mL)	109	535 (452, 690)	1,518	556 (437, 690)	1.00	0.93-1.07	0.97
CD4$^+$/CD8$^+$ ratio	109	0.94 (0.71, 1.25)	1,512	0.98 (0.74, 1.29)	0.96	0.90-1.02	0.22

[a]100% adherence defined as no report of any missed doses for any drug in the preceding 7-day period. [b]Models were adjusted for covariates including gender, age, race, baseline biomarker concentrations (or CD4$^+$/CD8$^+$ ratio), level of education, HIV risk factor, region of enrollment, viral hepatitis co-infection, BMI, and smoking. [c]O'Brien test overall p=0.35. IQR: interquartile range; IL-6: interleukin 6; hsCRP: high-sensitivity C-reactive protein; SAA: serum amyloid A protein; sVCAM: soluble vascular adhesion molecule-1; sICAM: soluble intercellular adhesion molecule-1; IL-27: interleukin 27.

Discussion and Conclusions

- Our results confirm prior findings where incomplete adherence was associated with higher concentrations of IL-6[2-4], and expand this association to individuals who initiated ART early in the course of their disease. These findings are contrasting to other studies where variable ART adherence (i.e., alternative less-than-daily dosing) have not demonstrated any impact in biomarkers of inflammation or coagulopathy[7,8].
- A novel association between incomplete ART adherence and SAA was identified. SAA was previously correlated with biomarkers of vascular inflammation in START[6]. This association is biologically consistent with the IL-6 findings and suggests that variable ART adherence may be most impactful through a unified inflammatory pathway that involves these biomarkers (and could possibly include CRP), in comparison to other networks of inflammation or defective adaptive immunity.
- Possible explanatory mechanisms for this association include:
  a) Subclinical viral replication below the limit of detection of conventional assays as a driver of inflammation.
  b) Intermittent episodes of measurable (but missed) viremia that are not identified between visits.
  c) Higher adherence to non-HIV medications with an anti-inflammatory effect (i.e., statins or aspirin) and/or healthier behaviors (i.e., exercise, less smoking) among participants who were 100% adherent to their ART.
- Whether an improvement in ART adherence (through behavioral interventions or easier dosing such as long-acting injectable ART) translates into a reduction in inflammation in the setting of virologic suppression remains unknown, but should be evaluated.

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