Low ART Adherence Is Associated With Higher Inflammation Despite HIV Suppression

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BACKGROUND

- HIV-infected individuals have residual systemic inflammation (even in the setting of suppressed viral replication by conventional assays), which has been linked to non-AIDS adverse events such as cardio-vascular disease, cognitive decline and cancer[1-5].
- Despite its role in preventing HIV-related morbidity and mortality, the non-AIDS consequences associated with variations in ART adherence beyond virologic suppression remain unknown.

OBJECTIVE

- To determine if suboptimal ART adherence is associated with increased inflammation despite viral suppression in HIV-infected men on chronic ART.

METHODS

- Population: Multicenter AIDS Cohort Study (MACS), a cohort study of HIV infection in MSM enrolled in Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; Pittsburgh, PA.
- Data collection: standardized interviews, physical examinations, and phlebotomy for laboratory testing and specimen storage every 6 months.
- Person-visits included in the analysis: (1) available serum biomarker concentrations, (2) reported ART, and (3) HIV RNA <50 copies/ml. Study period from 1998 to 2009.
- Biomarker outcomes (measured in serum)[2]:
  - Soluble (s)CD14, sCD27, sgp130, sIL-2Rα, sIL-6R, sTNF-R2, and B-cell activating factor (BAFF), and CXCL13 were measured using the Luminex x-MAP platform and R&D Systems multiplex immunoassay.
  - IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, and chemokine (C-C motif) ligands (CCL)2, CCL4, CCL11, CCL13, CCL17, CXCL10 measured using the Meso Scale Discovery platform.
  - High sensitivity C-reactive protein (CRP) measured by Quest Diagnostics.

METHODS (cont'd)

- ART adherence (exposure):
  - 6-month self-report dichotomized as <100% vs. 100%
  - 4-day self-report % defined as the minimum (across drugs) of[6]:
    - (∑# times drug taken over 4 days) / (∑# times drug prescribed/day * 4)
    - Categorized as <85%, 85-99%, and 100%
- Biomarker concentrations modeled as generalized gamma (β, σ, λ) with differing β by covariates. Models adjusted for multiple measurements per individual.
- Models adjusted for covariates selected based on associations with both adherence and serum biomarker concentrations: age, HCV infection, hypertension, race, and smoking.
- Adjusted for multiple testing by controlling false discovery rate at 5% using the Benjamini-Hochberg procedure.

RESULTS

Table 1. Demographic and adherence characteristics in 2876 person-visits from 924 MACS participants in the analysis.

CHARACTERISTIC	n	IQR / %
MACS person-visits	2876	
Median # visits per person (IQR)	3	(2, 4)
Median date (IQR) at time of visit	2006	(2003, 2008)
Median age in years (IQR) at time of visit	48.4	(42.6, 54.0)
Median years of HAART use (IQR) at time of visit	5.4	(2.9, 8.0)
PI-based HAART, boosted	984	34%
PI-based HAART, not boosted	446	15%
NNRTI HAART without PI	1345	47%
NRTI/other HAART	101	4%
Nonwhite race	773	27%
Hepatitis C infection	222	8%
Hepatitis B infection	129	4%
Depressive symptoms	697	24%
Smoking	811	28%
Obese	316	11%
Diabetes	307	11%
Hypertension	626	22%
Statin use	843	29%
100% 6-month adherence	2505	87%
100% 4-day adherence	2542	88%
85-99% 4-day adherence	114	4%
<85% 4-day adherence	220	8%

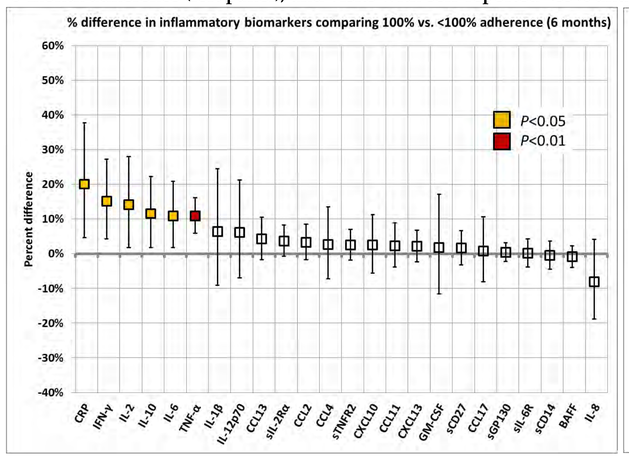
HCV infection was defined by detectable HCV RNA. HBV infection was defined by a positive HBsAg. Depression was defined by a CESD-R score >16. Smoking was yes/no based on self-report. Obesity was defined as a BMI >30 kg/m². Diabetes was defined as HbA1c ≥6.5% or fasting glucose ≥126 mg/dl. Hypertension was defined as either systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Statin use was yes/no based on self-report.

RESULTS (cont'd)

Table 2. Percent difference in serum biomarker concentrations across all percentiles (by adherence category, adjusted for age, HCV infection, hypertension, race, and smoking). Italics: p<0.05; bold: significant after controlling false discovery rate at 5%.

	<100% vs. 100% (6-month)		<85% vs. 100% (4-day)		85-99% vs. 100% (4-day)	
Biomarker	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value
TNF-α	10.9%	***<0.001***	9.1%	*0.002*	9.8%	*0.016*
IFN-γ	15.2%	*0.005*	16.9%	*0.011*	7.7%	0.350
CRP	20.1%	*0.009*	18.4%	*0.047*	17.2%	0.182
IL-2	14.2%	*0.024*	19.4%	*0.014*	-2.9%	0.774
IL-10	11.6%	*0.019*	13.0%	*0.028*	7.9%	0.292
IL-6	10.9%	*0.019*	13.6%	*0.028*	5.2%	0.505

Figure. Estimates from adjusted models: differences in serum biomarker concentrations at visits with self-reported <100% vs. 100% 6-month adherence (left panel); and visits with self-reported <85% and 85-99% compared to 100% 4-day adherence (right panel).



CONCLUSIONS

- Suboptimal self-reported ART adherence was associated with higher concentrations of biomarkers of inflammation and immune activation in virologically suppressed HIV-infected men compared with those who reported 100% adherence, suggesting that ART adherence could have significant biological consequences that are independent of virologic suppression.
- Although the mechanism(s) accounting for this association remains unclear, suboptimal ART adherence could lead to subclinical episodes of viral replication[7] (and persistent inflammation and immune activation) despite apparently virologically suppressive ART.
- The clinical consequences of suboptimal adherence in virally suppressed HIV-infected individuals remain unknown and warrant further study.

Acknowledgments and References

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MACS Multicenter AIDS Cohort Study