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Higher ART Adherence is Associated with Lower Systemic Inflammation in Treatment-naïve Ugandans who Achieve Virologic Suppression

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Conflicts of interest

There are no conflicts of interest.

Supplemental Digital Content

UARTO_Adherence_Inflammation_Suppl_Tables_Revision.doc

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Abstract

Background—Residual systemic inflammation persists despite suppressive antiretroviral therapy (ART) and is associated with non-AIDS clinical outcomes. We aimed to evaluate the association between ART adherence and inflammation in Ugandans living with HIV who were predominantly receiving nevirapine-based ART with a thymidine analog backbone and were virologically suppressed by conventional assays.

Methods—Plasma concentrations of interleukin-6 (IL-6), D-dimer, soluble (s)CD14, sCD163, the kynurenine/tryptophan (K/T) ratio, in addition to $CD8^+$ T-cell activation, were measured at baseline and 6 months after ART initiation in treatment-naïve adults who achieved an undetectable plasma HIV RNA (<400 copies/mL) at their 6-month visit. Adherence was measured through medication event monitoring system (MEMS) and calculated as the ratio of observed/prescribed device openings per participant. We fit adjusted linear regression models to estimate the association between ART adherence and the log-transformed plasma concentrations of inflammatory biomarkers.

Results—We evaluated 282 participants, median age 35 years, 70% women. The median (IQR) adherence was 93 (84, 98) %. In the adjusted analyses, for every 10% increase in average ART adherence, we found a 15% (P<0.0001, 95% CI −21.0, −7.9), 11% (P=0.017, −18.3, −2.0) and 3% (P=0.028, −5.0, −0.3) decrease in IL-6, D-dimer and sCD14, respectively.

Conclusions—Higher ART adherence was associated with lower levels of biomarkers of inflammation, immune activation and coagulopathy among Ugandans living with HIV who achieved viral suppression shortly after ART initiation. This suggests that ART adherence could have biological consequences beyond viral suppression. Whether ART adherence optimization in virologically-suppressed individuals could reduce residual inflammation remains unknown.

Keywords

adherence; inflammation; antiretroviral therapy; Uganda

Introduction

Antiretroviral therapy (ART) prevents AIDS-related morbidity and mortality[1–3] and reduces HIV transmission[4]. In addition, ART reduces systemic inflammation[5–7], immune activation[8] and coagulopathy[9] by achieving and sustaining viral suppression, but only partially to levels observed in HIV-negative individuals[6,10,11]. This chronic residual inflammation and coagulopathy have been linked to the development of non-AIDS complications including cardiovascular disease, cancer and death[12–19]. While multiple interventions aimed at improving residual inflammation have been evaluated (e.g., ART intensification, anti-inflammatories, treating co-infections)[20–25], most have shown modest or no beneficial effect. Thus, effective strategies to reduce residual inflammation in treated HIV infection are needed[26].

Sustained ART adherence is required to achieve durable virological suppression, yet the relationship between adherence and viral suppression is complex and dynamic[27–30]. Perfect (i.e., 100%) adherence is not required to achieve or sustain viral suppression, and viral suppression is not necessarily a perfect surrogate for complete adherence (i.e., ART can be interrupted for short periods of time without the development of viremia using conventional assays)[31–35]. However, the consequences of suboptimal adherence, beyond suppression, are unknown. Recently, low self-reported adherence was associated with higher levels of residual inflammation and immune activation in chronically-suppressed men living with HIV[36]. This association has not been replicated, nor has been evaluated in women, treatment-naïve individuals, or in cohorts utilizing objective measures of ART adherence. To address this gap, we aimed to determine whether ART adherence, measured by electronic monitoring, is associated with biomarkers of systemic inflammation and coagulopathy among treatment-naïve individuals living with HIV who initiate non-nucleoside reverse transcriptase inhibitors (NNRTI) and thymidine analog-based ART.

Methods

Participants

We evaluated treatment-naïve adults living with HIV who initiated first-line ART between 2005 and 2010 and were enrolled in the Uganda AIDS Rural Treatment Outcomes cohort (UARTO, NCT01596322) at a regional referral hospital in Mbarara, Uganda[37–39]. In UARTO, participants were followed every 3-4 months; blood was collected for plasma and cell isolation, including $CD4^+$ T-cell count and HIV viral load (VL; Amplicor HIV Monitor 1.5 test, Roche, Branchburg, NJ), at baseline and subsequent visits. For this analysis, we evaluated participants who: a) had available biomarker levels at baseline and after 6 (±1) months of ART; b) had HIV VL <400 copies/mL at the 6-month visit, and; c) had available ART adherence data for at least 3 months in the 6-month period.

Adherence measurement

ART adherence (across the 6-month study period) was measured using the medication event monitoring system (MEMS) electronic pill bottle (Aardex Group, Switzerland), which recorded the date and time for each bottle opening. Average ART adherence was calculated based on the number of observed cap openings divided by the number of prescribed doses/day in the 6-month period (capped at 100%).

Biomarkers of inflammation, coagulopathy and $CD8^+$ T-cell activation

Plasma was centrifuged and stored at −80°C until analysis. Most (95%) samples were stored in acid citrate dextrose (ACD), while the remaining in ethylenediaminetetraacetic acid; to account for this difference, an adjustment factor of 1.276 was used for biomarkers tested from ACD tubes[39]. D-dimer (Diagnostico Stago), interleukin 6 (IL-6; Human IL-6 Ultra-Sensitive Kit, Meso Scale Diagnostics), soluble (s)CD14 (sCD14; R&D Systems), sCD163 (sCD163; Trillium Diagnostics), and the kynurenine/tryptophan ratio (K/T ratio) were measured in thawed plasma samples as previously reported[38,39]. The percentage of human leukocyte antigen-D related $(HLA\text{-}DR)^+/CD38^+$ $CD8^+$ T-cells was measured in fresh whole-blood specimens processed on the day of collection, as previously described[37].

Statistical Analysis

Demographic and baseline cohort characteristics were summarized. Biomarker concentrations were log-transformed, except the proportion of HLA-DR$^+$/CD38$^+$/CD8$^+$ T-cells, which was analyzed as an absolute value. The crude change in biomarkers and CD8$^+$ T-cell activation between baseline and the 6-month visit was analyzed using paired t-tests. Average ART adherence was considered to be continuous. We used scatterplots to graphically evaluate the relationship between average ART adherence and the outcomes of interest at the 6-month visit, assessing for a linear relationship between the explanatory and outcome variables. We then fit linear regression models to estimate the change in biomarkers and CD8$^+$ T-cell activation after 6-months on ART with changes in ART adherence, adjusting for baseline biomarker values. We initially evaluated a model where average ART adherence was the primary predictor of interest. We then used a model that adjusted for potential confounders including age, gender, CD4$^+$ T-cell count, baseline HIV VL, depression (using the Hopkins Symptoms Checklist Score[40,41]), and heavy alcohol use (using the AUDIT-C questionnaire[42]). Variables excluded from the unadjusted model due to missing data and/or collection later during the study included smoking status, illicit drug use, food security, BMI, and anemia. Since biomarkers of inflammation and CD8$^+$ T-cell activation were analyzed as related and complementary outcomes, we did not correct for multiple comparisons[43]. We also performed sensitivity analyses, limiting our sample to participants with an HIV VL <40 copies/mL at the 6-month visit (as the HIV VL assay evolved throughout the course of the study) and removing high influence observations with DFBETA values outside the range of ±2/sqrt(n) or a Cook's D value >1.0. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). A P value <0.05 was considered to be statistically-significant.

Ethical Considerations

Study procedures were reviewed and approved by the institutional review boards of Mbarara University of Science and Technology and Partners Healthcare/Massachusetts General Hospital, as well as the Ugandan National Council of Science and Technology. All participants provided written informed consent.

Results

Study population

Of a total of 546 participants enrolled in the UARTO cohort during the study period, 282 met our evaluation criteria for at least one outcome and were included in the unadjusted analysis. Reasons for exclusion comprised: baseline visit only (24%), no 6-month visit within study window (8%), <3 month MEMS data (8%), no ART initiation within study window (8%), and no HIV VL or HIV VL >400 copies/mL at 6-month visit (4%). The median age was 35 years (IQR 30, 40), and 196 (70%) of the participants were women. Heavy alcohol use and depression where reported at least once in 39 (15%) and 92 (34%) of participants, respectively. Most ART regimens were NNRTI-based (244 [89%] nevirapine and 21 [7%] efavirenz), with an NRTI-backbone consisting of zidovudine/lamivudine (68%), stavudine/lamivudine (28%) or other (4%). Median CD4$^+$ T-cell count was 134 cells/mm^3 (IQR 80, 198), and 54% of participants had a baseline HIV VL >100,000 copies/mL.

Baseline characteristics of virologically-suppressed participants who were included in the adjusted analysis vs. those excluded due to missing data are presented in Table 1.

ART adherence and biomarkers of inflammation and coagulopathy

The median ART adherence was 93% (IQR 84, 98); 13 (5%) participants had mean 6-month adherence of 100%, 194 (68%) had adherence 85-100%, and 75 (27%) had adherence <85%. We observed a significant decrease in all biomarkers between the pre-ART and 6-month visits (P<0.0001 for all biomarkers, except sCD14 P=0.003). In the analyses adjusted for baseline values of biomarkers only, we identified a statistically-significant inverse linear relationship between average ART adherence and biomarkers of inflammation and coagulopathy (Supplementary Table 1, Figure 1). After additionally adjusting for age, gender, a positive depression screen, heavy alcohol use, and baseline $CD4^+$ T-cell count and HIV viral load (Table 2), these relationships remained statistically significant for IL-6 (15% decrease; P<0.0001), D-dimer (10% decrease; P =0.017) and sCD14 (3% decrease; P=0.028) in participants who achieved virologic suppression to <400 copies/mL at the 6-month visit. In the adjusted model for participants who achieved virologic suppression to <40 copies/mL, IL-6 (11% decrease; P=0.040) and sCD163 (7% decrease; P=0.009) remained statistically significant, despite a smaller sample size (Table 2). These findings were similar (and the slopes in all biomarkers remained negative) when removing highly influential observations (Supplementary Table 2). A sensitivity analysis adjusting for the most prevalent ART regimens (limited to participants on 3TC/AZT/NVP or 3TC/d4T/NVP, which corresponded to 88% of the ART regimens in this cohort) did not show any additional effect on biomarker levels (data not shown).

Discussion

We demonstrated an inverse relationship between ART adherence, measured using electronic monitoring, and plasma concentrations of biomarkers of inflammation and coagulopathy in treatment-naïve Ugandan adults who achieved virologic suppression after 6 months of ART. These relationships remained significant for IL-6, D-dimer and sCD14 after adjusting for several covariates, including pre-ART $CD4^+$ T-cell count and VL, with decreases of 3-15% in each biomarker for each 10% increase in average adherence. Interestingly, our observations were the strongest for IL-6, which has also been found to be the strongest predictor of adverse outcomes in comparison with other markers[16], and could have been influenced by our overall low CD4-T cell at baseline, as has been previously proposed[44]. To our knowledge, this study is the first to demonstrate a relationship between electronically-monitored adherence using MEMS, inflammation and coagulopathy among virologically-suppressed patients. Collectively, these findings suggest that variations in ART adherence could have biological consequences that extend beyond achieving and sustaining virologic suppression.

Our findings are consistent with previous observations, where <100% ART adherence (measured subjectively through self-report) was associated with higher levels of inflammatory biomarkers in virologically-suppressed men on ART in the US[36]. Among the possible explanations for our findings is that suboptimal ART adherence could lead to low-

level viral replication below the limit of detection of most clinically-available assays[45–47], which may result in spurts of inflammation and immune activation[48,49]. Likewise, incomplete ART adherence could also be associated with intermittent episodes of viremia that are not captured between visits. Further research to evaluate these and other possible mechanisms is needed.

The findings in this study could have clinical implications that deserve further evaluation. Given the relationship between low ART adherence and higher levels of IL-6, which has been associated with higher morbidity and mortality in HIV[12,15,16], suboptimal ART adherence could conceivably also be associated with worse clinical outcomes that extend beyond those prevented by sustained virologic control, although this relationship remains unknown. It is also unclear whether strategies to improve ART adherence can reduce chronic residual inflammation and its downstream consequences in treated HIV infection. Interestingly, in a recent clinical trial of ART intensification among individuals maintaining plasma HIV RNA levels <40 copies/mL, a significant reduction of at least one biomarker of immune activation (activated $CD4^+$ T-cells) was observed in the placebo arm[23]. This was coupled with an early reduction in low-level viremia using a highly sensitive single-copy assay[23], which was also reported in the placebo arm of a second intensification study[24]. Though the mechanisms behind these findings in the participants randomized to placebo remain unclear, it is plausible that they could have been mediated, at least partially, by an improvement in ART adherence after enrollment in a clinical trial (i.e., Hawthorne effect). While any single intervention is unlikely to completely reverse residual inflammation and its clinical consequences, ART adherence could play a significant synergistic role to achieve this goal. Future studies evaluating the impact of adherence optimization beyond virologic suppression are necessary to corroborate these hypotheses.

Among the strengths of our study are the inclusion of a diverse population with a large proportion of women in resource-limited settings, the use of an objective adherence measure that is more informative than self-report[50], and the inclusion of multiple biomarkers of systemic inflammation, innate and acquired immune activation, and coagulopathy. The main limitations include the use of a relatively high viral load cutoff (<400 copies/mL), the evaluation of primarily older NNRTI-based ART regimens, and the potential influence of unmeasured confounders (i.e., smoking and diet). Further studies to determine if these findings persist with even lower VL thresholds and during long term virologic control are needed. In addition, these findings should be replicated in the era of modern ART, to determine if the relationships between adherence and inflammation in suppressed patients are generalizable to those taking more forgiving antiretrovirals, such as the integrase strand transfer inhibitors.

In summary, we demonstrated that lower ART adherence is associated with higher inflammation and coagulopathy in treatment-naïve Ugandans who achieved virologic suppression after 6 months of therapy. These findings confirm previous observations and suggest that optimal adherence may be required to maximize the biological benefit or ART.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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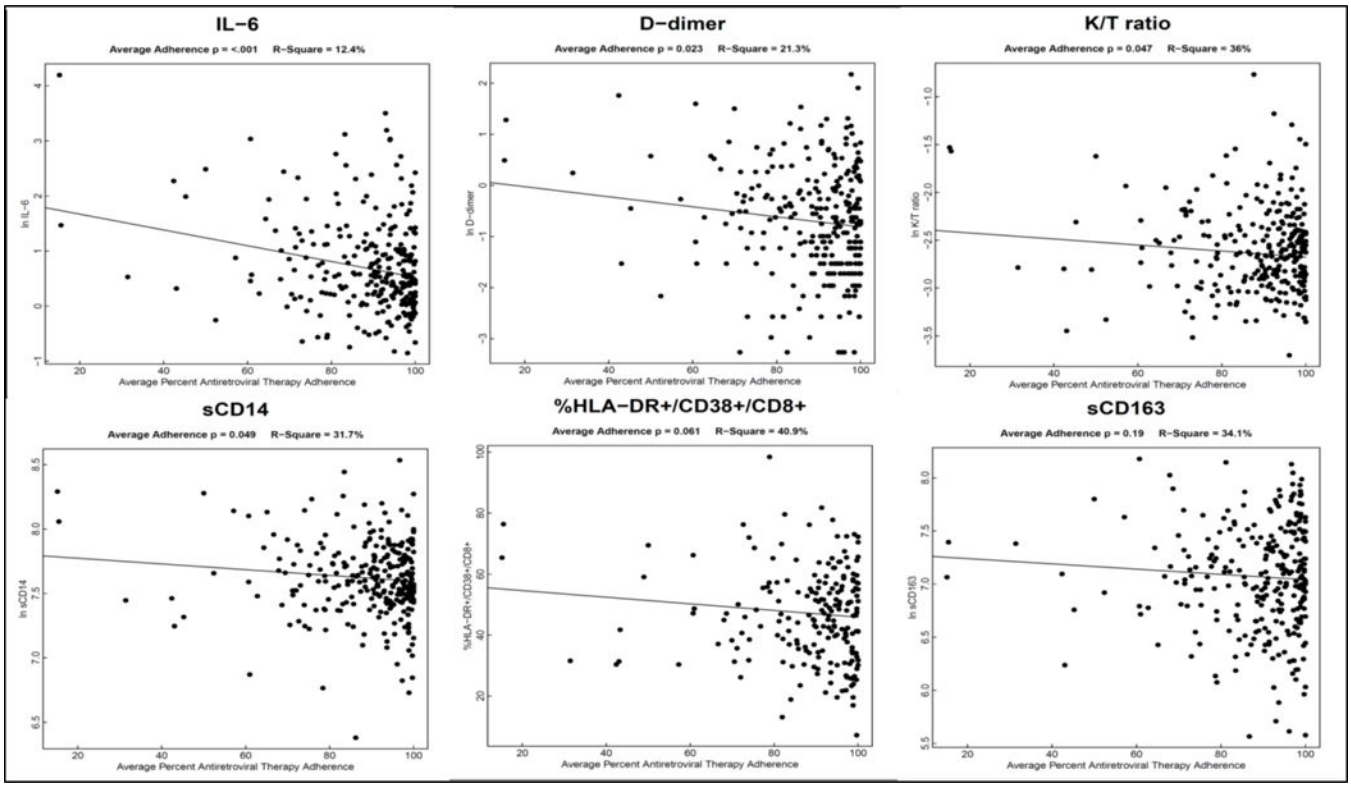

Figure 1. Antiretroviral adherence and biomarkers of inflammation, coagulopathy and CD8+ T-cell activation in virologically-suppressed Ugandans living with HIV six months after treatment initiation

Scatter plots represent biomarkers values at the 6 month visit by average antiretroviral adherence. IL-6: interleukin 6; K/T ratio: kynurenine/tryptophan ratio; sCD14: soluble CD14; sCD163: soluble CD163.

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Table 1

Baseline characteristic of participants who achieved virologic suppression (<400 copies/mL) at the 6-month visit and were included in the multivariate analysis vs. those who achieved virologic suppression (<400 copies/mL) and were excluded from the multivariate analysis due to missing data (i.e., missing MEMS and/or covariates such as age, baseline $CD4^+$ T-cells, baseline HIV viral load, depression score[b] and alcohol use[c]).

Characteristic	Full Model	n[a]	Excluded from multivariate analysis	n[a]	*P*-value[*]
Number of subjects	261		66		
Female, n(%)	182 (70%)	261	46 (70%)	66	1.0
Age, mean (SD)	35 (7.6)	261	36 (8.5)	65	0.692
Baseline $CD4^+$ T-cells (cells/mm^3), geometric mean (95% CI)	116 (105, 128)	261	109 (83, 144)	60	0.687
Baseline HIV viral load >100,000 copies/mL, n(%)	141 (54%)	261	34 (57%)	60	0.821
Depression[b], n(%)	86 (33%)	261	24 (44%)	54	0.145
Heavy alcohol use[c], n(%)	39 (15%)	261	24 (13%)	48	0.827
Baseline Biomarker concentrations, mean(log) (SD(log))					
IL-6	1.24 (0.95)	247	0.99 (1.02)	62	0.084
D-dimer	−0.05 (0.99)	251	−0.18 (0.89)	63	0.314
K/T ratio	−2.00 (0.55)	250	−2.10 (0.57)	62	0.229
sCD14	7.67 (0.30)	251	7.56 (0.35)	60	*0.029*
HLA-DR^+/$CD38^+$ $CD8^+$ T-cells, mean (SD)	66 (14)	184	67 (12)	55	0.667
sCD163	7.58 (0.45)	251	7.36 (0.50)	60	*0.003*
Regimen		255		65	*0.0002*[**]
EFV-based, n(%)	20 (8%)		17 (26%)		
NVP-based, n(%)	225 (88%)		48 (74%)		
Other, n(%)	10 (4%)		0 (0%)		

[a] Participants for whom baseline data were available.

[b] (Yes/No) according to the Hopkins Symptom Checklist Score (score >1.75).

[c] (Yes/No) according to the AUDIT-C questionnaire (>4 in men and >3 in women).

[*] t-tests for independent samples or chi-square, as appropriate.

** Fisher's exact test, represents distribution across all types. SD: Standard Deviation; IL-6: interleukin 6; K/T: Kynurenine/tryptophan; sCD14: soluble CD14; sCD163: soluble CD163; EFV: efavirenz, NVP: nevirapine; 95% CI: 95% confidence interval.

Table 2

Antiretroviral adherence and biomarkers of inflammation, coagulopathy and $CD8^+$ T-cell activation six months after treatment initiation in study participants who achieved an HIV viral load of <400 copies/mL and <40 copies/mL.

	Full Model for <400 copies/mL[a]				Full Model for <40 copies/mL[a]			
Biomarker	**Number of Participants**	**Percent reduction for each 10% increase in adherence[b]**	**95% CI**	***P*-value**	**Number of Participants**	**Percent reduction for each 10% increase in adherence[b]**	**95% CI**	***P*-value**
IL-6	247	−14.7	(−21.0, −7.9)	*<0.0001*	121	−11.3	(−20.9, −0.6)	*0.040*
D-dimer	251	−10.5	(−18.3, −2.0)	*0.017*	125	−11.0	(−21.5, 1.0)	0.070
K/T ratio	250	−3.0	(−6.0, 0.3)	0.070	122	−2.6	(−6.9, 1.9)	0.247
sCD14	251	−2.7	(−5.0, −0.3)	*0.028*	124	−1.5	(−4.6, 1.9)	0.382
% $HLA\text{-}DR^+/CD38^+$ $CD8^+$[c]	184	−1.2	(−2.5, 0.03)	0.056	92	−1.1	(−3.1, 0.9)	0.272
sCD163	251	−3.1	(−6.8, 0.8)	0.119	124	−7.4	(−12.4, −2.0)	*0.009*

[a] Adjusted for baseline biomarkers, age, gender, and baseline values of $CD4^+$ T cell count, HIV viral load, depression (Yes/No) and alcoholism (Yes/No).

[b] Percent change from baseline after 6 months of therapy.

[c] Absolute decrease in proportion of $CD8^+$ T-cells that co-express $HLA\text{-}DR^+/CD38^+$ (not percent decrease). IL-6: interleukin 6; K/T: Kynurenine/tryptophan; sCD14: soluble CD14; sCD163: soluble CD163; 95% CI: 95% confidence interval.

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