Full Title: Lower antiretroviral therapy adherence is associated with residual systemic inflammation among African persons with HIV undergoing real-time adherence monitoring

Running Title: ART adherence and inflammation in Africa

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Abstract

Background: Lower antiretroviral therapy (ART) adherence is associated with higher systemic inflammation in virally suppressed persons with HIV (PWH); however, prior studies have mostly relied on subjective adherence measures and have not assessed this association by disease stage upon ART initiation.

Methods: In the Monitoring Early Treatment Adherence study, adherence was monitored electronically in real-time among adult, treatment-naïve PWH in Uganda and South Africa who initiated tenofovir disoproxil fumarate/emtricitabine/efavirenz during early ($CD4^+$ >350 cells/mm^3) or late ($CD4^+$ <200 cells/mm^3) stage disease. Participants who achieved viral suppression (<400 copies/mL) at 6 months and remained suppressed after 12 months were analyzed. The association between average ART adherence and plasma concentrations of interleukin 6 (IL-6), soluble CD14 (sCD14) and D-dimer was evaluated using adjusted multivariable linear regression, stratified by disease stage.

Results: Four hundred eighty-eight PWH (61% women, mean age 35 years) were included in the analysis. Median ART adherence overall was 87%. In adjusted models, every 10% increase in average adherence was associated with a 3.0% decrease in IL-6 (95%CI, -5.9, -0.01; p=0.05) at 12 months. This relationship was both observed in PWH with early- (5.9%; 95%CI, -10.1, -1.6; p=0.009) and late-stage disease (3.7%; 95%CI, -7.2, -0.2; p=0.039).). No significant associations were found with sCD14 and D-dimer.

Conclusions: Objective ART adherence measurement was inversely associated with systemic inflammation in PWH who achieved viral suppression after ART initiation in sub-Saharan Africa, with a greater association in those with early-stage HIV. This finding underscores the importance of ART adherence beyond establishing viral suppression.

Keywords: adherence; antiretroviral therapy; residual inflammation; viral suppression

Introduction

The main goal of antiretroviral therapy (ART) is to achieve and sustain an undetectable HIV viral load (VL), in order to prevent disease progression to AIDS(1), HIV transmission(2), and decrease non-AIDS comorbidities(3, 4). While early studies suggested that >95% ART adherence was required to reach viral suppression(5), the increasing potency of modern ART has allowed for lower levels of adherence (~80-85% in more recent reports)(6, 7) to attain this goal. The greater forgiveness for missed doses with modern ART regimens is advantageous to persons with HIV (PWH) given the numerous challenges faced across their socio-ecological spectrum(8, 9) and to public health by supporting the undetectable=untransmittable (U=U) premise(10). However, the clinical consequences of suboptimal – although suppressive– ART adherence remain understudied.

Previous research has established that <100% (and in particular <85%) ART adherence, while potentially sufficient to sustain viral suppression, has been associated with a 10-20% increase in biomarkers of residual systemic inflammation, immune activation, and coagulopathy(11-13) and with overall mortality(14) in diverse populations, including PWH in sub-Saharan Africa(15, 16). However, in most of these studies ART adherence was quantified using self-report (which usually overestimates adherence(17)). Notably, one previous study conducted by our group utilized the Medication Event Monitoring System (MEMS)(15, 16) –which captures pill bottle openings– to quantify adherence. While MEMS is more objective, data are downloaded retrospectively at periodic intervals; the measure is therefore vulnerable to device loss, technical failures, and/or non-use that may go undetected for weeks to months, all of which may limit accuracy.

Additionally, the impact of HIV disease stage at ART initiation on the association with residual inflammation is unknown. This question is of particular importance given the higher residual inflammation, immune activation and coagulopathy (i.e., quantified using interleukin-6 [IL-6], soluble CD14 [sCD14] and D-dimer) that has been observed in virologically-suppressed PWH who initiate ART at an advanced stage when compared to those who initiate ART early(18-20).

To address these gaps in the literature, we evaluated whether real-time ART adherence monitoring is associated with biomarkers of inflammation, immune activation and coagulopathy within the Measuring Early Treatment Adherence (META, NTC02419066) study, a longitudinal cohort study of ART adherence conducted in Uganda and South Africa(21). We hypothesized that lower ART adherence, measured using real-time electronic monitoring, would be associated with higher levels of inflammation, immune activation, and coagulopathy in META participants who achieved and sustained viral suppression at 6 and 12 months. We also aimed to explore any potential differences in this association in PWH who initiated ART during early or late HIV infection.

Methods

Study setting and participants

META was an observational study of ART adherence conducted in Mbarara, Uganda and Cape Town, South Africa, as previously reported(21). The study enrolled treatment-naïve PWH between March 2015 and September 2016 who were ≥18 years old and initiating ART (tenofovir disoproxil fumarate/emtricitabine/efavirenz [TDF/FTC/EFV] as a single tablet regimen) into one of three groups: a) early stage (asymptomatic with $CD4^+$ T-cells >350 cells/mm^3) men and non-pregnant women; b) early stage pregnant women (asymptomatic with $CD4^+$ T-cells >350 cells/mm^3), and; c) late stage ($CD4^+$ T-cells <200 cells/mm^3) men and non-pregnant women(21). This analysis focuses on the first and third groups.

Study and laboratory procedures

Study participants received care at their routine local clinics and attended study visits at 6 and 12 months for completion of socio-behavioral questionnaires and sample collection. Blood was collected in EDTA for HIV VL, $CD4^+$ T-cell count and biomarkers of inflammation, immune activation, and coagulopathy (biomarkers were only obtained in the early and late stage participants due to resource

constraints)(22). HIV VL was quantified using the Cobas Taqman test in Uganda and Roche CAP/CTM HIV-1 v2 in South Africa(21). For biomarkers, plasma was obtained by centrifugation and stored frozen at -80ºC until analysis at the Laboratory for Clinical Biochemistry Research at the University of Vermont(22). Concentrations of IL-6 were quantified using the MesoScale Discovery Platform (Rockville, MD, USA), sCD14 was quantified using the R&D Systems (Minneapolis, MN, USA), and D-dimer was quantified using Diagnostica Stago (Parsippany, NY, USA)(22). Depression was assessed using the Hopkins Symptom Checklist (probable depression indicated by a score of >1.75)(23), and alcohol use was assessed using the AUDIT-C screening test(24).

Adherence was monitored using a real-time electronic real-time monitoring pill container (Wisepill Technologies, South Africa), which recorded the date and time when the container was opened as a surrogate of medication ingestion and transmitted it over the cellular network for data storage(21). Participants were asked to only open the device at the time of ingestion and to only remove one dose at a time.

Statistical analysis

To focus specifically on benefits of adherence beyond suppression, we limited our analysis to the study participants who achieved virologic suppression (HIV VL <400 copies/mL) at both the 6- and 12-month visits and had biomarkers of inflammation available. Each biomarker was log transformed prior to fitting a multivariable linear regression model with Huber White robust standard errors. We fit models on the full cohort dataset, as well as stratified by country and study group (i.e., early- vs late-stage disease). For each model, we controlled for determinants of systemic inflammation, including age, gender, baseline biomarker concentrations, $CD4^+$ T-cells, having depression, alcohol use, baseline log viral load, and smoking(18, 25-27). For analyses of the full cohort dataset, we also controlled for country. For all models, our primary exposure of interest was ART adherence, which was defined separately in models as either 12-month average percentage adherence and number of 72-hour interruptions, given that sporadic

and sustained treatment interruptions are associated with distinct likelihoods of viral rebound(15, 28). Model coefficients were exponentiated from log using the formula (exp(β)-1)*100 (where β is the coefficient for the dependent variable) and are presented as the percentage change in the geometric mean of the biomarker for a unit change in the covariate. Data are presented as mean (standard deviation), number (percentage), or median (interquartile range). Statistical analysis was performed using Stata version 13 (StataCorp, LP; College Station, TX).

Ethics Statement

Prior to any study procedures, all participants provided written informed consent. The study was approved by the institutional review boards from MassGeneral Brigham, the Mbarara University of Science and Technology, the Uganda National Council for Science and Technology, the University of Cape Town, and the Western Cape Provincial Department of Health in South Africa.

Results

Study population

A total of 904 study participants (483 in Uganda and 421 in South Africa) were enrolled in the META study between March 2015 and September 2016, as previously described(21). From these participants, 269 in Uganda and 219 in South Africa achieved virologic suppression (<400 copies/mL) at both 6 and 12 months. While pregnant women were also included in META, biomarkers of inflammation, immune activation and coagulopathy were not performed in this population due to funding limitations. The baseline characteristics of the study population included in this analysis (N=488) are shown in **Table 1**. The mean age of the study population was 35 years, and 296 (61%) study participants were women. The early and late-stage disease groups included 257 (53%) and 231 (47%) participants, respectively, with similar distribution between both sites (**Table 1**). Median (IQR) baseline HIV VL in the study population overall was 34,523 (4,828, 120,832) copies/mL, with higher HIV VL in South Africa than in

Uganda (**Table 1**). Depression and alcohol use were documented in 36% and 18% of the overall study population, respectively, with a higher proportion in South Africa for both; 18% of the study population reported smoking (**Table 1**).

ART adherence and biomarkers of inflammation, immune activation, and coagulopathy

Table 2 shows the distribution of biomarkers of inflammation, immune activation, and coagulopathy at baseline and at the 12-month visit among the study participants who achieved virologic suppression at the 6- and 12-month visit. Both IL-6 and D-dimer showed a statistically significant decrease from baseline to 12 months, while sCD14 showed an increase in this same study interval, as previously reported(29).

The overall median (IQR) adherence in the study population was 87% (71%, 95%), with higher adherence in Uganda than in South Africa (90% vs. 78%, **Table 1**). Upon initial evaluation using scatter plots, we did not observe a linear relationship between individual ART adherence and the biomarkers analyzed (**Supplemental Figure 1**). **Figure 1** shows the biomarkers according to different categories of average adherence(6, 7, 11) in the study population. When assessed in relation to average ART adherence among all study participants in the adjusted models, D-dimer and IL-6 showed a 3.4% (95% CI, -7.1%, 0.3%; p=0.074) and 3.0 (95% CI, -5.9, -0.01; p=0.05) decrease in plasma concentrations at the 12-month visit for every 10% increase in ART adherence, respectively (**Table 3a**). According to stage at ART initiation, IL-6 showed a 5.9% (95% CI, -10.1%, -1.6%; p=0.009) decrease in plasma concentrations in the early-stage group, and a 3.7% (95% CI, -7.2%, -0.2%; p=0.039) decrease in plasma concentrations in the late-stage group for every 10% increase in average ART adherence, respectively (**Table 3b**). In an analysis categorized by specific country, the association of D-dimer was not observed in Uganda, but was strengthened in South Africa, where the plasma concentrations of D-dimer decreased by 5.8% (95% CI, -10.1%, -1.2%; p=0.015) for every 10% increase in average ART adherence (**Table 3c**). The association between ART adherence and sCD14 was not found to be statistically significant in any of the analyses,

with point estimates that ranged between a 0.5% and a 1.4% increase in this biomarker for every 10% increase in average ART adherence (p>0.14, **Tables 3a, 3b** and **3c**).

The total number of 72-hour interruption episodes was 2774 (1359 in the early ART initiation group and 1415 in the late initiation group). We evaluated the association of plasma biomarkers with the number of 72-hour ART interruptions adjusting for the same covariates as for average adherence. In this analysis, there was a 0.5% (-1.0%, -0.03%; p=0.064) decrease in the plasma concentrations of sCD14 for every 72-hour interruption among all study participants (**Table 3a**). This association had a similar magnitude and significance in participants with both early- (-0.6% [95% CI, -1.3%, 0.05%; p=0.067]) and late- (-0.7% [95% CI, -1.5%, 0.1%; p=0.065]) stage disease and in participants from Uganda (-0.5% [95% CI, -1.1%, 0.06%; p=0.076]; **Table 3b** and **3c**). For D-dimer, every 72-hour interruption was associated with a 0.2% (-1.0%, 1.4%; p=0.722) increase in this biomarker concentration in the overall population, with variable results by disease stage and site (**Tables 3a, 3b** and **3c**). Lastly, every 72-hour ART interruption was associated with IL-6 increases that ranged between a 0.1% to 1.4% across all study groups (p>0.11, **Tables 3a, 3b** and **3c**).

Discussion

In this analysis, we demonstrated that higher ART adherence, measured using electronic real-time monitoring, was associated with lower residual systemic inflammation in PWH who initiated ART in sub-Saharan Africa and achieved and sustained viral suppression after 6 months and 12 months of therapy, respectively. We also observed a trend towards lower coagulopathy with higher adherence, in particular in patients from South Africa. These findings are consistent with our previous observations in PWH in diverse settings(11-13), including Uganda(15, 16). This study adds to the literature the use of an objective, real-time adherence measure, and observation of PWH who initiated ART at both early- (i.e., $CD4^+$ T-cells >350 cells/mm^3) and late- (i.e., $CD4^+$ T-cells <200 cells/mm^3) stage of infection. Collectively, our findings provide additional support to the importance of ART adherence beyond viral

suppression, and on the deleterious consequences that low adherence could have in PWH even though they are adherent enough to achieve and sustain viral suppression.

In comparison with our previous study of PWH in late-stage disease in Uganda (the Uganda ART Outcomes study; UARTO), where nevirapine was the predominant non-nucleoside reverse transcriptase inhibitor(15), 72-hour ART interruptions were not associated with higher concentrations of biomarkers in this study. While this finding was unexpected, it could be explained by the longer half-life of efavirenz (40-55 hours after multiple dosing)(30) compared to nevirapine (10-20 hours)(31), and also by the differences in ART adherence data in META, where median ART adherence was 87% compared to 93% in UARTO(15, 16). In addition, the association between ART adherence and coagulopathy that we identified in PWH from South Africa only trended to significance in the overall population and was not observed patients from Uganda. This is an interesting finding that will require further characterization but suggests that environmental and other unmeasured differences in each region of our study could be relevant. Future studies to further elucidate these discrepant results are required.

While the association between low ART adherence and high inflammation has been established, the mechanisms behind it have yet to be elucidated. A potential explanation could be derived from previous observations where incomplete ART adherence has been associated with residual viral replication(32, 33), and where residual viral replication has been linked to heightened systemic inflammation(34-36); however, other studies have not confirmed these findings(37, 38). Another possible driver of this association is that PWH who are not fully adherent to ART are more likely to accumulate risk factors and/or comorbidities that are also associated with high inflammation, immune activation, and/or coagulopathy such as diabetes mellitus or chronic infections. However, data on chronic disease other than HIV were not systematically assessed in META. Despite this, our analysis (and previous studies) controlled for some of these potential confounders, such as age, gender, and smoking. Future studies to elucidate whether these –and other potential mechanisms– explain this association are needed.

The possible clinical implications of our findings should be highlighted. First, they emphasize the continued importance that ART adherence could have not only to achieve and sustain viral

suppression, but to potentially reduce the overall burden of non-AIDS disease and mortality(14, 39, 40). Second, given the limited efficacy of existing interventions aimed and reducing systemic residual inflammation in virologically-suppressed PWH(18), medication adherence could become the focus of future study as a clinically-relevant intervention to reduce inflammation. This was recently suggested in an analysis derived from the Multicenter AIDS Cohort study in the US, were PWH who reported 100% adherence had concentrations of IL-6 that were similar to persons without HIV(41). In this context, the 3% to 6% reductions in IL-6 and D-dimer that we observed in META could be extrapolated into a potential reduction of 5% to 10% in the risk of severe non-AIDS events and death based on previous observations in three large international cohorts(40). Third, the association between ART adherence and residual inflammation was observed in both PWH who initiated treatment during early- vs. late-stage disease. This supports the concept that ART is equally important throughout all stages of HIV infection. Together, all these possible clinical implications reinforce the critical relevance that ART has –and should continue to have– for patients and providers when prescribing and taking ART. Additional randomized studies could help establish whether effective adherence interventions could help reduce residual inflammation, immune activation, and coagulopathy in PWH on ART.

Our study has several strengths. For instance, we evaluated a large, binational cohort in sub-Saharan Africa where over half of the cohort were women. These data allow for potential generalizability of our findings in low- and middle-income countries. In addition, our study utilized an electronic objective adherence measure in real-time that is known to be feasible in this setting(21, 42). An additional advantage of assessing the association between ART adherence and residual inflammation in the META study was that this cohort consisted of PWH taking a uniform ART regimen who had both early- and late-stage disease. This suggests that the contribution of high adherence to the reduction in residual inflammation would be relevant in both PWH with early-stage infection, in comparison with PWH with more advanced stage in whom non-AIDS comorbidities may have already established(18). Such comparisons could not be achieved in our previous analysis in the UARTO cohort in sub-Saharan Africa(15, 16), where all study participants initiated ART during late-stage disease. Weaknesses of our

study include the lack of participants on an integrase-based regimen, which should be included in future similar analyses. We also do not have documented proof of drug ingestion from our electronic adherence monitoring; however, this modality has been shown to be adequately sensitive to detect suboptimal ART adherence prior to the development of viremia in sub-Saharan Africa(42). Furthermore, our viral suppression threshold of <400 copies/mL is relatively insensitive and could have misclassified some PWH as virally suppressed when they were not. Finally, we were limited to a small number of biomarkers and did not include pregnant women in this analysis (due to funding limitations), in whom ART adherence is of critical importance. Further research in the field including broader populations of PWH taking modern ART should help address these remaining gaps.

In conclusion, this study established an inverse association between ART adherence and residual systemic inflammation in treatment naïve PWH who achieved and sustained viral suppression in sub-Saharan Africa. Our findings confirmed previous observations and demonstrated that this association can be identified in PWH who initiate ART at early- and late-stage disease. As the population of PWH on ART expands in the region, and the burden of non-AIDS comorbidities increase, future research is needed to assess the role of ART adherence interventions to reduce residual inflammation and coagulopathy beyond viral suppression in PWH on modern ART regimens.

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Potential conflicts of interest

JEH reports consulting fees from Merck and owns stock in Natera. All other authors report no potential conflicts of interest.

Author contributions

J.R.C.M. led the conception and design of this analysis, the result interpretation, wrote the first manuscript draft, and performed all the edits for all the subsequent drafts. N.M. assisted with study design, performed data and statistical analysis and interpretation, generated the tables, and made substantial edits and critical revision of the manuscript. C.O. led the Cape Town site in the parent META study, performed data acquisition and quality control, and reviewed and edited the manuscript. S.A assisted with study oversight and data collection at Kabwohe site. D.R.B. helped design the parent META study and performed manuscript editing and revision. M.J.S. led the study design concepts related to assessment of inflammatory biomarkers, participated in data analysis and interpretation, and made

substantial edits and critical revision of the manuscript. J.E.H. was the principal investigator and developer of the META study. She performed data acquisition, assisted with the adherence data interpretation, and performed manuscript editing and revision.

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