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Switch to Raltegravir Decreases Soluble CD14 in Virologically Suppressed Overweight Women: The Women, Integrase, and Fat Accumulation Trial

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Abstract

Objectives—Soluble CD14 (sCD14) is a monocyte activation marker associated with increased mortality in HIV. We assessed 48-week changes in sCD14 and other inflammatory biomarkers in virologically suppressed, HIV-infected women switching to raltegravir (RAL) from PI or NNRTI.

Methods—HIV-infected women with central adiposity and HIV-1 RNA <50 copies/mL continued their thymidine-sparing NRTI backbone and were randomized to switch to open-label RAL at week 0 (immediate) or 24 (delayed). In an exploratory analysis, inflammatory biomarkers were measured on stored fasting plasma.

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CONFLICTS OF INTEREST

S.A. Stramotas has no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

J.E. Lake was the primary author, served as Co-Principal Investigator for the protocol, aided in protocol revisions and contributed to study oversight and data analysis. G.A. McComsey developed the original study design and protocol with J.S. Currier, served as Co-Principal Investigator for the protocol and contributed to the analytic plan and manuscript preparation. T. Hulgan, C.A. Wanke, A. Mangili and S.L. Walmsley were Co-Investigators, enrolled participants and contributed to manuscript preparation and review. S.A. Stramotas assisted with data analysis and contributed to manuscript preparation. R. Tracy was responsible for biomarker assay oversight, provided scientific consultation and assisted with manuscript preparation. J.S. Currier developed the original study design and protocol with G.A. McComsey, was Co-Principal Investigator of the protocol and contributed to manuscript development.

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Results—Thirty-seven evaluable subjects were 78% non-White and had median age 43 years, BMI 32 kg/m^2 and CD4+ T cell count 558 cells/μL. At baseline, biomarker values were similar between groups. After 24 weeks, median sCD14 significantly declined in subjects switching to RAL (−21% ($p<0.001$) vs. PI/NNRTI −5% ($p=0.49$), between group $p<0.01$). After 48 weeks, immediate switch subjects maintained this decline and delayed switch subjects experienced a similar decline following switch to RAL (−10%, within-group $p<0.01$). Immediate switch subjects also experienced an initial increase in TNF-α that was neither maintained after 48 weeks nor seen in delayed switch subjects. After adjustment for multiple testing, only declines in sCD14 remained significant.

Conclusions—In this randomized trial of women with central adiposity, switch to RAL from PI or NNRTI was associated with a statistically significant decline in sCD14. Further studies are needed to determine whether integrase inhibitors have improved monocyte activation profiles compared to PIs and/or NNRTIs, and whether measured differences between antiretroviral agents translate to demonstrable clinical benefit.

Keywords

raltegravir; sCD14; monocyte activation; inflammation; women

INTRODUCTION

HIV infection is characterized by a state of inflammation and immune activation that may not normalize with suppressive antiretroviral therapy (ART),(1–5) and may contribute to the development of end-organ disease in HIV-infected persons. Recently, circulating markers of inflammation [including interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) and soluble CD14 (sCD14)] have been shown to predict all-cause mortality in HIV infection,(6–8) enhancing interest in biomarkers as predictors of morbidity and mortality in this patient population.

CD14 is a monocyte/macrophage surface marker that recognizes pathogen-associated molecular patterns and is a co-receptor for lipopolysaccharide.(9) CD14 may be membrane bound or exist as sCD14 when shed or secreted from activated monocytes/macrophages or secreted by hepatic Kupffer cells.(10, 11) sCD14 is elevated in the setting of HIV infection and does not normalize with ART initiation.(12–14) Similarly, significant declines in sCD14 have not previously been documented in virologically-suppressed patients switching or intensifying ART. The associations between higher sCD14 levels, increased all-cause mortality(7, 15, 16) and progression of HIV disease(15, 17) emphasize the need to both understand the mechanism of sCD14 elevation in HIV infection and determine whether interventions to normalize sCD14 levels/monocyte activation improve clinical outcomes.

Persistent immune activation in HIV-infected persons on ART may be the result of one or more stimuli such as concomitant infections and/or co-morbidities, enterocyte damage leading to microbial translocation, or medication-specific toxicities. Determining how sCD14 changes with other markers of monocyte activation, microbial translocation and inflammation [including soluble CD163 (sCD163), intestinal-type fatty acid binding protein

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(I-FABP), tumor necrosis factor-α (TNF-α) and soluble TNF receptor II (sTNF-RII)] could help define the mechanism driving changes in sCD14 following ART initiation or switch.

This analysis describes changes in biomarkers of inflammation, immune activation and microbial translocation in a 48-week trial of virologically-suppressed, HIV-infected women with central adiposity on protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART who continued their thymidine-sparing nucleoside reverse transcriptase inhibitor (NRTI) backbone and were randomized to switch to raltegravir (RAL) immediately or after 24 weeks.

METHODS

Study design

Complete methods for the parent study have previously been published.(18) Briefly, HIV-infected women with central adiposity (defined as waist circumference >94 cm or waist-to-hip ratio >0.88) and HIV-1 RNA <50 copies/mL on a regimen of tenofovir or abacavir *and* emtricitabine or lamivudine *plus* a PI or NNRTI were randomized 1:1 to substitute PI or NNRTI for RAL 400 mg po bid at week 0 (immediate switch) or week 24 (delayed switch). Subjects randomized to delayed switch provided an internal control group of subjects on continued PI/NNRTI therapy for the first 24 weeks. During weeks 24–48, all subjects received RAL. The study was not blinded, as randomization required switching to RAL vs. continued standard of care.

Subjects were recruited from five centers in North America between September 2008 and July 2010. Inclusion criteria included: Age 18 years, documented HIV-1 infection, central adiposity, continuous virologic suppression since ART initiation and current HIV-1 RNA <50 copies/mL, current ART with a compatible NRTI backbone plus a PI or NNRTI (as above), no change in ART for 12 weeks prior to screening and ability and willingness to provide informed consent.

The parent study hypothesized that, in women experiencing central fat gain on PI/NNRTI, switch to a more metabolically neutral agent (RAL) might prevent ongoing fat gain or allow partial reversal of lipohypertrophy. As such, the study was powered to observe a 10% difference in computed tomography-quantified visceral fat between RAL- and PI/NNRTI-treated subjects over 24 weeks. While anticipated reductions in total and LDL cholesterol were observed in RAL-treated subjects, only a 5.4% between group difference in visceral fat was observed (RAL −3.6% visceral fat, PI/NNRTI +1.9%).(18)

A protocol-defined, exploratory analysis of changes in inflammatory biomarkers was performed on stored plasma samples. The institutional review boards/ethics committees of the participating institutions approved all study documents and procedures, and all subjects provided written informed consent prior to initiation of study procedures.

Assessments

Biomarker Assessments—Complete parent study assessments have previously been published.(18) For this analysis, blood for plasma isolation was obtained in EDTA tubes at

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weeks 0, 24 and 48 and centrifuged for 15 minutes at 2000 rpm's and 20–22 °C within 30 minutes of collection. Samples were stored at the sites in 1cc aliquots at −80 °C until the end of the study, when they were sent to the University of California, Los Angeles for sorting and cataloging prior to shipment to the Laboratory for Clinical Biochemistry Research at the University of Vermont, where all assays were performed under the supervision of Dr. Russell Tracy.

sCD14, sCD163, IL-6, sTNF-RII and soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured via R&D Systems Human Quantikine® ELISA, TNF-α via Millipore Human Adipokine Panel B multiplex assay, I-FABP via R&D Systems Human FABP-2 DuoSet® ELISA, d-dimer via StagoSTA®-Liatest® assay, C-telopeptide (CTP) via Immunodiagnostic Systems (IDS) UniQ™ ICTP ELISA and pro-collagen type 1 N-terminal pro-peptide (P1NP) via IDS UniQ™P1NP radioimmunoassay. All assays had coefficients of variation of ten percent or less.

Statistical Analyses

Baseline characteristics were compared between treatment groups using the Mann-Whitney U test for continuous variables and the Fisher's exact test for categorical variables. Median values and interquartile ranges (IQR) are reported for continuous variables, and percentages for categorical data.

Median, between group, 24-week change scores for all biomarkers were compared using the Wilcoxon sign-rank test. Additionally, 48-week change scores were calculated for the immediate switch group, and a pooled analysis of biomarker changes in the 24 weeks following switch to RAL was performed for all subjects. Spearman or Kendall tau rank correlation coefficients were calculated to assess relationships between 1) changes in biomarkers and 2) changes in biomarkers and clinical parameters. All analyses were as-treated, excluding subjects who did not remain on the study regimen and/or did not have an observed primary end point. A supplemental intent-to-treat analysis and analyses of log-transformed mean values were also performed and produced similar results (data not shown).

Sample size was determined by the parent study (n=37). All biomarker analyses were exploratory. However, 37 subjects provided 80% power to see a minimum between-group effect size of: sCD14 453.0 ng/mL, sCD163 372.0 ng/mL, I-FABP 1501.0 pg/mL, IL-6 13.0 pg/mL, d dimer 0.4 μg/mL, TNF-α 2.1 pg/mL, sTNF-RII 842.0 pg/mL, sVCAM-1 536.0 ng/mL, CTP 2.3 μg/L, and P1NP 43.0 μg/L. All statistical tests were two-sided with a nominal alpha level of 0.05. Analyses were exploratory and were performed with and without adjustment for multiple testing. Data analysis and management was performed using SAS 9.2 or 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient population

Sixty-one subjects screened and 39 enrolled. Eighteen subjects were randomized to immediate switch, and 21 to delayed switch. Thirty-seven subjects completed the week 24

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primary endpoint, and 36 completed the week 48 endpoint. No study withdrawals were RAL-related. Complete demographic and baseline clinical characteristics of the 37 participants included in the as-treated analysis are provided in Table 1. At baseline, randomization groups were well balanced, although the delayed switch group had a higher rate of current tobacco use (24% vs. 58%). The median age was 43 years, BMI 32 kg/m^2, and 75% of subjects self-identified as Black or Hispanic. Sixty-two percent of subjects were on a PI at entry (vs. 38% NNRTI), and the most commonly reported NRTIs were tenofovir (78%) and emtricitabine (68%).

Baseline Biomarker Characteristics

At baseline, no significant differences in median sCD14, sCD163, I-FABP, IL-6, d-dimer, TNF-α, sTNF-RII, sVCAM-1, CTP or P1NP were observed between subjects randomized to the immediate vs. delayed switch arms (Table 2).

Changes in Biomarkers Between Weeks 0 and 24

Changes in biomarkers for both randomization groups are presented in Table 3. After 24 weeks, a significant median decline in sCD14 was observed in RAL-treated subjects (−461.9 ng/mL, −21%, IQR (−704.0, −253.7), $p<0.001$) compared to subjects remaining on PI or NNRTI (−102.6 ng/mL, −5%, IQR (−277.4, 107.6), $p=0.28$; between group $p<0.01$). This decline in sCD14 occurred regardless of whether subjects switched off PI or NNRTI, and was accompanied by an increase in TNF-α (RAL: 0.3 pg/mL, 7%, IQR (−0.2, 0.6), $p=0.05$; PI/NNRTI: −0.1 pg/mL, −2%, IQR (−0.9, 0.3), $p=0.28$; between group $p=0.05$). Subjects experiencing sCD14 declines below the median drove the increase in TNF-α among RAL-treated subjects. An insignificant increase in sTNF-RII (16.5 pg/mL, 0.6%, IQR (−76.4, 236.1), $p=0.55$) that was statistically different than the change seen in PI-/NNRTI-treated subjects (−195.7 pg/mL, −6%, IQR (−333.6, −47.9), within group $p<0.001$, between group $p<0.01$) was also observed. sTNF-RII did not change significantly in any sCD14 subgroup. Changes in sCD14, TNF-α, and sTNF-RII are illustrated in Figure 1. No statistically significant within or between group changes in other biomarkers were observed between weeks 0 and 24.

Changes in Biomarkers Between Weeks 24 and 48

Changes in biomarkers for both randomization groups are presented in Table 3. After 48 weeks, subjects randomized to immediate switch maintained a reduction in sCD14 (total 48-week change −494.1 ng/mL, −23%, IQR (−764.8, −269.4), $p<0.0001$). Subjects randomized to delayed switch saw a significant decline in sCD14 following switch to RAL at week 24 (−217.6 ng/mL, −10%, IQR (−498.8, 14.35), $p<0.01$; Figure 2). Following switch to RAL, both groups achieved similar sCD14 declines (week 48 between group p value=0.48).

In the delayed switch group only, switch to RAL was also associated with an increase in sCD163 (70.6 ng/mL, 12%, IQR (−7.0, 165.7), $p=0.05$). No other statistically significant changes in biomarkers were observed in either randomization group after 48 weeks. Of note, upon switch to RAL, no significant increase in TNF-α or sTNF-RII was observed in subjects in the delayed switch arm. Additionally, at week 48, the small increases in TNF-α and

sTNF-RII initially observed in immediate switch subjects no longer retained statistical significance.

Pooled Changes in Biomarkers for All Subjects Following Switch to RAL

When 24-week post-switch data from all subjects (weeks 0–24 for immediate switch, weeks 24–48 for delayed switch) was pooled to improve power, the median sCD14 decline remained significant (−308.9 ng/mL, −14%, IQR (−704.0, −97.0), p<0.0001). Pooled analysis also detected significant increases in sCD163 (previously observed in both groups but only significant in the delayed switch group; median 49.8 ng/mL, 8%, IQR (−26.7, 125.4), p=0.05) and TNF-α (previously observed in both groups but only significant in the immediate switch group; median 0.3 pg/mL, 6%, IQR (−0.15, 0.79), p=0.01). No other statistically significant changes in biomarkers were observed in the pooled analysis, including sTNF-RII.

Adjustment for Multiple Testing

After adjustment for multiple testing, significance for biomarker change scores was defined as p<0.001. While the decline in sCD14 in individual study arms approached but did not reach statistical significance (immediate switch weeks 0–24, p=0.003; delayed switch weeks 24–48, p=0.006), declines in sCD14 were significant for the 48-week change in the immediate switch group and in the pooled 24-week analysis (both p<0.0001).

Correlations Between Changes in Biomarkers and Clinical Parameters

At baseline, sCD14 correlated with sCD163 (r=0.40, p=0.01) and I-FABP (r=0.34, p=0.04), and sCD163 correlated strongly with sVCAM-1 (r=0.82, p<0.0001), TNF-α (r=0.68, p<0.0001), sTNF-RII (r=0.74, p<0.0001), and low-density lipoprotein cholesterol (LDL; r=−0.41, p=0.01). I-FABP correlated positively with sTNF-RII (r=0.38, p=0.02), visceral fat volume (r=0.50, p<0.01) and high-density lipoprotein cholesterol (HDL; r=0.43, <0.01), and negatively with current CD4+ T cell count (r=−0.36, p=0.03).

In the immediate switch group, 24-week changes in sCD14 correlated only with changes in hs-CRP (although no significant change in hs-CRP was observed (data previously published(18); r=0.55, p=0.03). Correlations between changes in sCD163 and visceral fat (r=0.56, p=0.05), I-FABP and d-dimer (r=−0.56, p=0.02) and TNF-α and CD4+ T cell count (r=−0.53, p=0.03) were also present. In the delayed switch group, significant correlations were observed between 24-week changes in sCD14 and d-dimer (r=0.48, p=0.03); TNF-α and sTNF-RII (r=0.59, p<0.01), CD4+ T cell count (r=−0.44, p=0.05), and sVCAM-1 (r=0.47, p=0.04); and sTNF-RII and sVCAM-1 (r=0.59, p<0.01).

In analysis of pooled 24-week changes following switch to RAL, changes in CTP correlated with changes in sCD163 (r=0.51, p=0.001) and waist circumference (r=−0.44, p=0.01), and changes in I-FABP correlated with changes in BMI (r=−0.35, p=0.04).

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DISCUSSION

In this randomized trial of HIV-infected women with central adiposity, switch to RAL was associated with statistically significant within and between group declines in sCD14 compared to subjects remaining on PI or NNRTI. While RAL was associated with greater declines in sCD14 than NNRTI-based regimens in a small study of treatment-naïve subjects,(19) to our knowledge a decline in sCD14 in virologically-suppressed patients switching ART has not previously been described. This finding may have important clinical implications, as sCD14 has been associated with all-cause mortality in HIV infection.(7, 15, 16)

In the SMART study, a gradient effect of sCD14 quartile on mortality was observed, with an OR for mortality of 2.3 per increase in sCD14 IQR.(7) Setting the SMART overall mortality rate (1.55%) as the median mortality rate and using the per sCD14 IQR increase in OR for mortality (2.3) as a basis to calculate the OR for a one quartile change, it can be hypothesized that a one quartile increase in sCD14 might translate to a 52% increase in mortality among SMART subjects. The limitations of extrapolating this data to different patient populations are significant, and include the fact that an intervention to lower sCD14 may not have the same mortality benefit as initiating ART with a lower baseline sCD14 level; however, baseline sCD14 values in our study were similar to those in SMART, and, if the SMART data can be generalized to other patient populations, it is possible that the 21% decline in sCD14 we observed over 24 weeks in women switching to RAL might translate to an estimated 44% reduction in mortality. Or, for a similar mean follow-up time (16 months), approximately 200 subjects would need to switch to RAL to save one life.

Additionally, higher circulating levels of sCD14 and other markers of monocyte activation and/or microbial translocation have been associated with end-organ diseases including cardiovascular disease (sCD14,(20–22) sCD163(23) and lipopolysaccharide (LPS)(21, 24)), neurocognitive decline (sCD14,(25) sCD163(26) and LPS(27)), and non-alcoholic steatohepatitis,(11) suggesting that, if a true benefit of RAL on sCD14 exists, its long-term use could be associated with a smaller burden of comorbid disease than other antiretroviral agents.

Although the mechanism of sCD14 decline in subjects switching to RAL is unknown, one possibility is that increased RAL penetration into the gut (vs. PI/NNRTI) promotes local control of viral replication and inflammation and decreased microbial translocation. In a small study of HIV-uninfected men, Patterson et al reported rapid penetration of RAL into gastrointestinal tissue, with levels throughout the colon 160–650 fold greater than plasma levels. Additionally, RAL achieved higher levels in gastrointestinal tissue than other antiretroviral agents.(28)

A similar potential mechanism is reduced viremia and/or viral replication in areas other than the gut. However, prior RAL switch and intensification studies have not consistently demonstrated improved residual viremia or low-level viral replication (defined as decreased HIV-1 viral load via ultra-sensitive assay or increased 2-long-term repeat (2-LTR) circles) with RAL initiation.(29–34) Additionally, studies demonstrating increased 2-LTR circles

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with RAL intensification saw effects predominately in PI-treated subjects.(29, 30) While measurement of 2-LTR circles and HIV-1 viral load via ultra-sensitive assay were beyond the scope of this study, sCD14 decline following switch to RAL was not restricted to PI-treated subjects. RAL intensification has also demonstrated inconsistent improvements in T cell activation,(29, 30, 35, 36) and improved D dimer (29) and lipopolysaccharide(33) but not sCD14 levels.(33, 35, 36)

Finally, the observed decline in sCD14 might be attributable to RAL's known, beneficial effects on lipid levels.(18, 37) For example, reduction in circulating lipid levels could lead to reduced hepatic inflammation and steatosis (leading to decreased sCD14 secretion from the liver), as has been observed with statin use.(38) Although we did not detect correlations between changes in monocyte activation markers and lipids or directly measure oxidized lipid levels in our study, oxidized LDL stimulates CD14 expression on circulating monocytes,(39) and oxidized HDL activates monocytes in vitro.(40) Thus, is reasonable to hypothesize that oxidized lipids may be a mediator of monocyte activation in HIV-infected patients.

It is important to note that, although we did not observe statistically significant changes in I-FABP or sCD163 following switch to RAL (vs. continued PI/NNRTI), we were not powered for these endpoints, and decreased microbial translocation and/or monocyte activation could contribute to the observed decline in sCD14 levels. Additionally, although I-FABP is a known marker of enterocyte damage,(41) its utility as a marker of microbial translocation in virologically-suppressed, HIV-infected patients has recently been challenged.(42). Similarly, the lack of statistically significant changes in markers of vascular function (sVCAM-1) and bone metabolism (CTP and P1NP) was likely heavily influenced by both our lack of power to observe these exploratory endpoints and the large observed physiologic variability. As such, these results should be interpreted as neutral rather than the lack of an effect of RAL on vascular function and/or bone turnover.

Although physiologic variability was large, a significant 24-week increase in TNF-α was observed in the immediate switch group. sTNF-RII also increased in the immediate switch group (although not significantly). Both increases were statistically different from the stable TNF-α and decreased sTNF-RII values observed in subjects remaining on PI or NNRTI; however, after 48 weeks the increase in TNF-α was no longer significant in the immediate switch group, and no significant changes in TNF-α or sTNF-RII were observed in delayed switch subjects following switch to RAL. The increase in sTNF-RII also was not significant in the pooled analysis. Additionally, the observed changes in TNF-α and sTNF-RII were small in magnitude compared to sCD14 (7% TNF-α, 0.6% sTNF-RII, −21% sCD14), are of unknown clinical significance and did not vary significantly by entry regimen. This latter finding is in contrast to the SPIRAL study, in which subjects switching from PI to RAL experienced significant declines in TNF-α.(43) Most importantly, only changes in sCD14 retained significance after adjustment for multiple testing. Further studies are needed to assess whether these findings can be replicated in larger cohorts, and to determine the mechanism of sCD14 decline in patients switching to RAL.

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Finally, the study of sex differences in markers of immune activation is critically important, and documenting changes in biomarkers in HIV-infected women who are virologically suppressed is needed. For example, recent studies demonstrating associations between HIV infection and increased sCD14 and sCD163 were not designed to assess sex differences.(44–46) Complicating this is the observation that healthy HIV-infected women may have lower sCD14 and higher sCD163 levels than age-matched men.(45) The contribution of age to HIV infection and sex is also important: although sCD163 levels increase with age, Martin and colleagues recently reported sCD163 levels in HIV-infected women (87% on ART) that were similar to HIV-uninfected women 14.5 years older,(44) a finding previously described in HIV-infected men.(47) Thus, understanding the contribution of sex to immune activation is necessary in order to optimize care for women living with HIV.

Limitations

This study has several limitations. First, the sample size is small, biomarker measurements were exploratory in nature and physiologic variability was high. While the likelihood of types I and II error exist in this exploratory analysis, the magnitude of sCD14 improvement, its reproducibility across treatment arms and its significance after adjustment for multiple testing lead us to believe that the observed improvement in sCD14 represents a true finding. The fact that observed correlations between biomarkers (for example, positive correlations between baseline sCD14, sCD163 and I-FABP, and the negative correlation between change in sTNF-RII and CD4 count) were in keeping with physiologic expectations supports this conclusion.

Next, the high prevalence of generalized obesity in this cohort (median BMI 32 kg/m^2) likely confounds any effect of RAL on biomarkers of inflammation. For example, sCD163 may be elevated in obese subjects,(48) and Koethe et al described the loss of incremental BMI effect on sCD14 in obese HIV-infected subjects.(49) Finally, we are unable to determine the mechanism of sCD14 decline in women switching to RAL, including whether the decrease arises from switch to RAL or switch away from PI or NNRTI. Thus, a larger study designed to provide mechanistic insight and powered to detect clinically significant effect sizes for changes in biomarkers is needed.

Conclusions

In this randomized trial of virologically-suppressed, HIV-infected women with central adiposity, switch to RAL from PI or NNRTI was associated with a statistically significant decline in sCD14. This is the first study to demonstrate significant changes in sCD14 following ART switch in subjects well controlled on ART, and may have important implications for mortality and/or the development of comorbidities in treated HIV-infected patients. Further studies are needed to assess whether this finding can be replicated in larger cohorts and to determine the mechanism of this decline.

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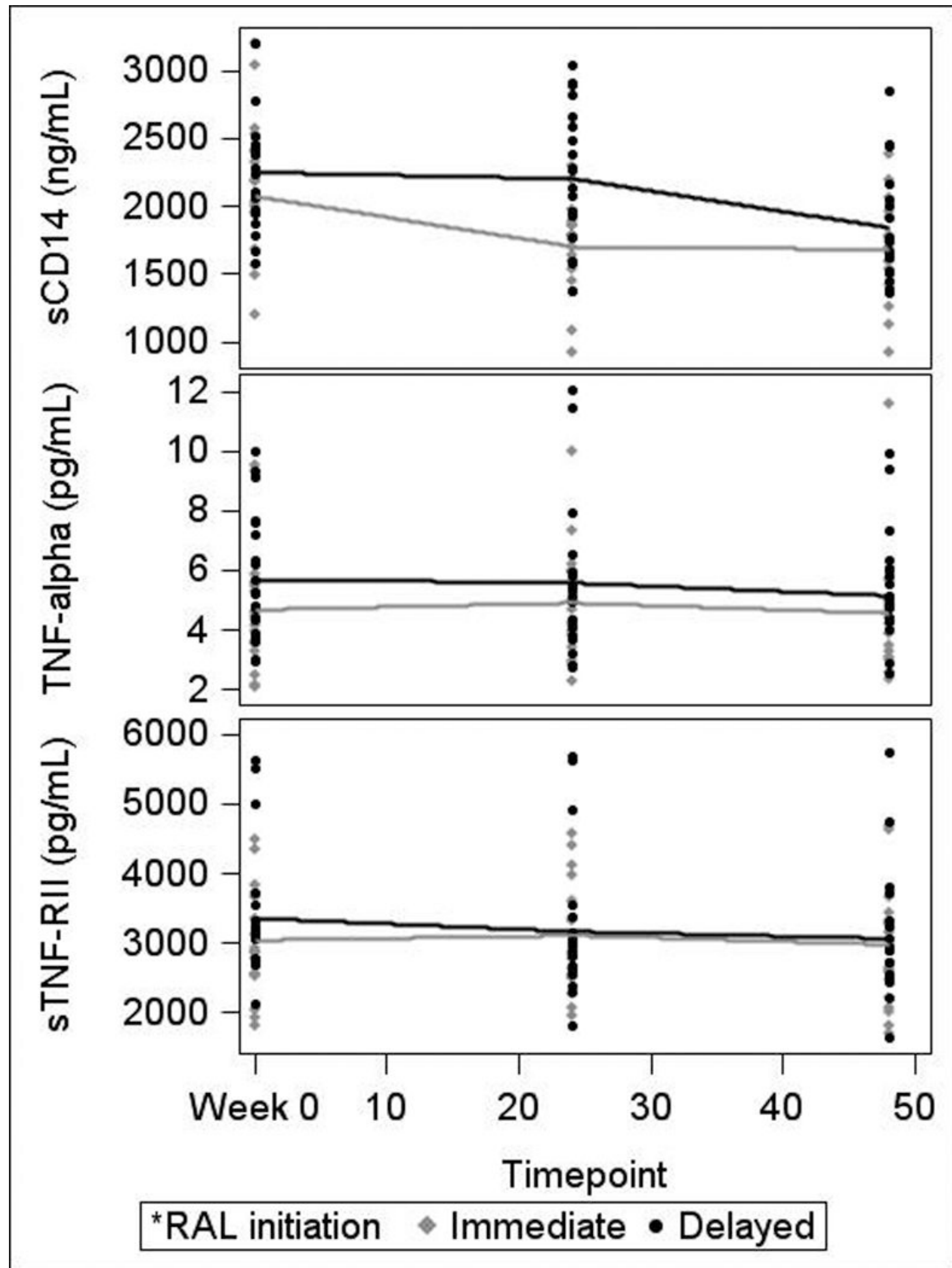

Figure 1. 48-Week Changes in sCD14, TNF-α and sTNR-RII

sCD14=soluble CD14; TNF-α=tumor necrosis factor-α; sTNF-RII=soluble tumor necrosis factor receptor II; RAL=raltegravir

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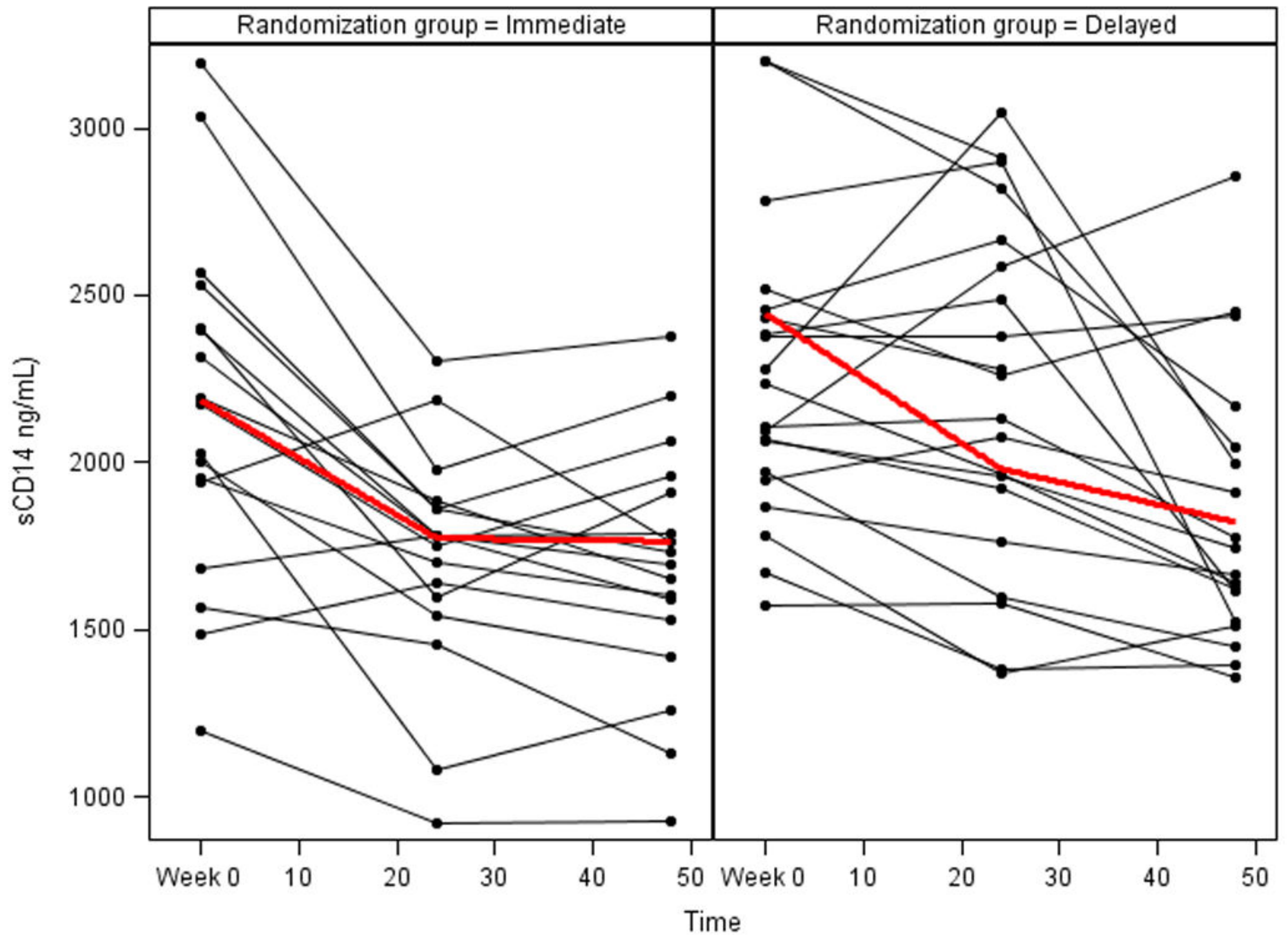

Figure 2. Individual Level Changes in sCD14 Over 48 Weeks
sCD14=soluble CD14

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Table 1

Baseline Demographic and Clinical Characteristics[a]

	Immediate	Delayed	Overall
Ethnicity	n=17	n=20	n=37
African American	53%	65%	59%
Hispanic	23%	10%	16%
White	18%	25%	22%
Asian	6%	0%	3%
Age (years)	41 (39, 47)	46 (36, 51)	43 (37, 49)
BMI (kg/m^2)	34.7 (28.8, 37.6)	30.4 (27.7, 35.4)	32.0 (28.0, 36.5)
Tobacco use (current)[b]	24%	60%	43%
CD4 count (cells/μL)	563 (447, 747)	554 (354, 770)	558 (422, 747)
Time on ART (years)	5.1 (3.1, 7.1)	2.7 (1.6, 6.3)	3.7 (2.4, 7.1)
PI	n=11 (65%)	n=12 (60%)	n=23 (62%)
Atazanavir/ritonavir	35%	30%	32%
Atazanavir	6%	15%	11%
Fosamprenavir/ritonavir	0%	5%	3%
Fosamprenavir	0%	5%	3%
Lopinavir/ritonavir	18%	5%	11%
Nelfinavir	6%	0%	3%
NNRTI	n=6 (35%)	n=8 (40%)	n=14 (38%)
Efavirenz	18%	30%	24%
Etravirine	6%	0%	3%
Nevirapine	12%	10%	11%
NRTI	n=17 (100%)	n=20 (100%)	n=37 (100%)
Abacavir	18%	25%	22%
Lamivudine	29%	35%	32%
Emtricitabine	71%	65%	68%
Tenofovir	82%	75%	78%
Waist circumference (cm)	106.0 (102.0, 121.0)	102.4 (99.2, 113.0)	105.5 (99.5, 118.0)
Hip circumference (cm)	117.5 (102.1, 127.0)	106.5 (102.2, 124.4)	115.5 (102.1, 127.0)
Waist:hip ratio	0.96 (0.90, 0.99)	0.97 (0.93, 1.02)	0.96 (0.92, 1.00)
Glucose (mg/dL)	84.0 (78.0, 93.0)	88.5 (80.0, 97.5)	87.0 (78.0, 94.0)
Total cholesterol (mg/dL)	179.0 (162.0, 206.0)	199.0 (164.5, 221.5)	188.0 (162.0, 214.0)
Triglycerides (mg/dL)	116.0 (85.0, 144.0)	129.0 (101.0, 176.0)	118.0 (92.0, 152.0)
LDL (mg/dL)	113.0 (103.0, 123.0)	116 (89.0, 138.1)	115.8 (93.0, 128.0)
HDL (mg/dL)	47.6 (40.2, 57.0)	49.1 (39.0, 55.0)	49.0 (40.0, 57.0)
hs-CRP (mg/dL)	2.7 (0.6, 6.0)	4.7 (0.8, 7.5)	3.2 (0.6, 6.5)
Diabetes[c]	0%	0%	0%
Hyperlipidemia[c]	18%	25%	22%

[a]Percent or median with interquartile range. Mann-Whitney U or Fisher's exact tests used to test statistical significance for continuous and categorical variables, respectively.

[b]p=0.05. Otherwise, no statistically significant association between-arm differences.

[c]Defined as self-reported diagnosis or on-therapy at baseline.

BMI, body mass index; ART, antiretroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

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Table 2

Median (IQR) Baseline Biomarker Distributions

	Immediate	Delayed	Overall	Between Group p value
N	**17**	**20**	**37**	
sCD14 (ng/mL)	2175.7 (1940.1, 2403.9)	2170.9 (1958.7, 2444.8)	2175.7 (1948.1, 2432.6)	0.62
sCD163 (ng/mL)	629.0 (405.1, 723.4)	606.1 (514.7, 753.0)	613.2 (480.3, 749.6)	0.49
I-FABP (pg/mL)	1840.0 (1224.0, 2163.9)	1755.7 (1288.7, 2245.7)	1793.7 (1224.0, 2195.1)	0.87
IL-6 (pg/mL)	3.8 (2.3, 6.1)	3.8 (3.1, 6.9)	3.8 (2.6, 6.6)	0.81
D dimer (μg/mL)	0.3 (0.1, 0.3)	0.2 (0.1, 0.4)	0.3 (0.1, 0.4)	0.68
TNF-α (pg/mL)	4.3 (3.6, 5.5)	5.2 (4.1, 7.4)	4.7 (3.7, 6.2)	0.12
sTNF-RII (pg/mL)	2862.2 (2543.0, 3669.7)	3149.4 (2739.5, 3432.7)	3067.6 (2690.3, 3542.0)	0.34
sVCAM-1 (ng/mL)	870.2 (644.8, 938.6)	859.4 (751.8, 962.9)	870.2 (686.9, 938.6)	0.57
CTP (μg/L)	3.2 (3.1, 3.4)	3.7 (2.8, 4.9)	3.2 (2.9, 3.8)	0.20
P1NP (μg/L)	48.6 (37.4, 72.0)	55.6 (42.5, 83.6)	53.1 (39.5, 75.8)	0.28

Median baseline values shown with interquartile range (IQR). Wilcoxon rank sum test used for determination of statistical significance. Two-sided α=0.05. sCD14=soluble CD14; sCD163=soluble CD163; I-FABP=intestinal-type fatty acid binding protein; IL-6=interleukin-6; TNF-α=tumor necrosis factor-α; sTNF-RII=soluble tumor necrosis factor receptor II; sVCAM-1=soluble vascular cell adhesion molecule-1; CTP=C-telopeptide; P1NP=pro-collagen type 1 N-terminal pro-peptide.

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Table 3

Median (IQR) Changes in Biomarkers

	Week 0–24 Changes			Week 0–48 Changes		Week 24–48 Changes		Pooled 24-week Changes	
	Immediate	**Delayed**	**Between Group p**	**Immediate**	**Within Group p**	**Delayed**	**Within Group p**	**Immediate 0–24 weeks Delayed 24–48 weeks**	**Within Group p**
N	**17**	**20**		**17**					
sCD14 (ng/mL)	−461.9 (−704.0, −253.7)*	−102.6 (−277.4, 107.6)	**0.003**	−494.1 (−764.8, −269.4)	**<0.0001**	−217.6 (−498.8, 14.4)	**0.006**	−308.9 (−704.0, −97.0)	**<0.0001**
sCD163 (ng/mL)	29.4 (−71.6, 98.0)	−27.5 (−44.8, 36.8)	0.34	3.0 (−84.2, 94.0)	1.00	70.6 (−7.0, 165.7)	**0.05**	49.8 (−26.7, 125.4)	**0.05**
I-FABP (pg/mL)	−150.1 (−380.4, 173.3)	250.2 (−379.7, 948.9)	0.16	−93.5 (−347.9, 227.3)	0.75	261.2 (−110.6, 1341.2)	0.08	149.7 (−380.4, 885.9)	0.37
IL-6 (pg/mL)	0.5 (−0.9, 1.3)	−0.5 (−2.0, 0.3)	0.16	−0.2 (−0.4, 0.7)	0.67	0.0 (−0.6, 1.0)	0.77	0.3 (−0.9, 1.1)	0.48
D dimer (μg/mL)	−0.1 (−0.2, 0.0)	0.0 (−0.1, 0.1)	0.29	0.0 (−0.1, 0.1)	0.87	0.1 (−0.1, 0.2)	0.31	0.0 (−0.1, 0.1)	0.80
TNF-α (pg/mL)	0.3 (−0.2, 0.6)*	−0.1 (−0.9, 0.3)	**0.05**	0.1 (−0.9, 0.9)	0.81	0.2 (−0.1, 0.9)	0.15	0.3 (−0.2, 0.8)	**0.01**
sTNF-RII (pg/mL)	16.5 (−76.4, 236.1)	−195.7 (−333.6, −47.9)*	**0.005**	12.8 (−415.8, 195.4)	0. 46	73.9 (−197.8, 207.2)	1.00	59.2 (−172.4, 218.4)	0.66
sVCAM-1 (ng/mL)	−1.5 (−170.2, 30.8)	−46.0 (−173.2, 76.9)	0.99	−2.7 (−169.9, 39.1)	0.16	−1.9 (−41.0, 61.1)	1.00	−1.8 (−95.0, 59.7)	0.38
CTP (μg/L)	0.1 (−0.6, 0.8)	0.1 (−0.3, 0.4)	0.84	−0.0 (−0.7, 0.6)	0.91	0.3 (−0.5, 0.7)	0.44	0.2 (−0.6, 0.7)	0.47
P1NP (μg/L)	4.0 (−7.6, 12.9)	−4.0 (−15.1, 4.8)	0.31	−2.5 (−18,9, 1.8)	0.08	0.0 (−23.8, 4.5)	0.46	0.6 (−13.9, 9.4)	0.90

Median within-person change scores shown with interquartile range. Wilcoxon rank sum test used for determination of statistical significance. Two-sided α=0.05. sCD14=soluble CD14; sCD163=soluble CD163; I-FABP=intestinal-type fatty acid binding protein; IL-6=interleukin-6; TNF-α=tumor necrosis factor-α; sTNF-RII=soluble tumor necrosis factor receptor II; sVCAM-1=soluble vascular cell adhesion molecule-1; CTP=C-telopeptide; P1NP=pro-collagen type 1 N-terminal pro-peptide.

*Within group p<0.05.