Title

Poorer Muscle Quality and Quantity With ART Initiation Is Associated With Greater Inflammation and Immune Activation

Journal

JAIDS Journal of Acquired Immune Deficiency Syndromes, 88(4)

ISSN

1525-4135

Authors

Kousari, Arianna
Moser, Carlee
Olefsky, Maxine
et al.

Publication Date

2021-12-01

DOI

10.1097/qai.0000000000002776

Peer reviewed

HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2021 December 01; 88(4): 399–405. doi:10.1097/QAI.0000000000002776.

Poorer Muscle Quality and Quantity with ART Initiation is Associated with Greater Inflammation and Immune Activation

Arianna Kousari, MD[1], **Carlee Moser, PhD**[2], **Maxine Olefsky, MS**[2], **Todd T. Brown, MD, PhD**[3], **Judith S. Currier, MD**[4], **Grace A. McComsey, MD**[5], **Ann Scherzinger, PhD**[1], **James H. Stein, MD**[6], **Jordan E. Lake, MD, MSc**[7], **Kristine M. Erlandson, MD, MS**[1]

[1]University of Colorado Anschutz Medical Campus; Aurora, CO

[2]Harvard T.H. Chan School of Public Health; Boston, MA

[3]Johns Hopkins; Baltimore, MD

[4]University of California Los Angeles; Los Angeles, CA

[5]Case Western Reserve; Cleveland, OH

[6]University of Wisconsin; Madison, WI

[7]University of Texas Houston; Houston, TX

Abstract

Background: We have previously shown that initiation of antiretroviral therapy (ART) is associated with a decrease in skeletal muscle density (greater fat accumulation), suggesting that gains in lean body mass seen in many ART studies may reflect gains in low quality, fatty muscle. Here we explore whether skeletal muscle density and area are associated with markers of inflammation and immune activation.

Methods: ART-naïve PWH were randomized to raltegravir or ritonavir-boosted atazanavir or darunavir, each with tenofovir disoproxil fumarate/emtricitabine. Abdominal Computed Tomography (CT) scans from baseline and week 96 were re-analyzed for psoas density and area and correlations explored with inflammation (IL-6, hs-CRP) and immune activation (sCD14, sCD163, %CD38+HLADR+ on CD4+ or CD8+ T-cells).

Results: 222 participants had available inflammation/immune activation markers and paired CT scans. At baseline, lower psoas density (greater fat) correlated with higher IL-6 (r −0.26, $p<0.001$) and sCD163 (r −0.15, $p=0.03$) and lower lean psoas area correlated with higher IL-6, hs-CRP, sCD14, sCD163, and %CD38+HLADR+ on CD4+ T-cells (r= −0.30 to 0.13); all $p\leq0.05$). From baseline to week 96, greater % decrease in total psoas density (more fat) correlated with greater increase in IL-6 (r −0.14; $p=0.04$); greater % decrease in lean psoas area correlated greater increases in IL-6, sCD14, sCD163, and %CD38+HLADR+ on CD8+ T-cells (r −0.15 to −0.18; all $p<0.04$).

Correspondence: Kristine M. Erlandson, MD, 12700 E. 19th Avenue, Mail Stop B168, Aurora, CO 80045, 303-724-4941; fax 303-724-4926, Kristine.Erlandson@cuanschutz.edu.

Meetings:

This research was presented in part at the HIV/Aging International Workshop 10/10/2019, New York, New York (Abstract #40)

Conclusions: Greater fat infiltration within the psoas muscle (lower density) and greater loss in lean psoas muscle area were associated with higher inflammation and immune activation, which may portend important effects on muscle function and cardiometabolic risk.

Keywords

Inflammation; Immune Activation; Muscle; HIV; Antiretroviral Therapy; ectopic fat

Introduction

Both HIV infection and antiretroviral therapy (ART) for treatment of HIV are associated with alterations in adipose tissue and skeletal muscle. Prior to the advent of ART, weight loss and wasting were common AIDS-defining illnesses[1]; however, newer generations of ART are now associated with weight gain[2,3]. Studies suggest that this weight gain is associated with negative metabolic consequences, including increased risk for diabetes[4]. Less is known about the effects of newer ART on extra-visceral sites of fat deposition, such as skeletal muscle.

Visceral adipose tissue (VAT) accumulation and accumulation of adipose tissue in other extra-visceral sites has been associated with increased inflammation[5] and immune activation[6], and likely contributes to the higher levels of inflammation observed among PWH even with a suppressed HIV-1 viral load, in comparison to HIV-uninfected controls[7,8]. Whether accumulation of extra-visceral fat in skeletal muscle is similarly associated with greater inflammation, particularly in the setting of weight gain experienced with ART initiation, is unknown.

In addition to fat within muscle, people with HIV may have greater loss of muscle mass and function, or sarcopenia[9–11]. Sarcopenia has been described in HIV infection, either as a result of HIV infection itself or due to effects of ART on muscle[12]. Inflammation has been implicated in the development of sarcopenia in PWH[13]. Thus, sarcopenia remains a clinical target of interest given its associated risk for accelerated aging in PWH and subsequent morbidity.

In the AIDS Clinical Trials Group (ACTG) study, A5260s, we have previously shown that ART initiation is associated with decreases in visceral and subcutaneous adipose tissue density, regardless of initial ART regimen[14]. Furthermore, we have shown that weight gain with ART initiation attenuates a decrease in markers of inflammation and immune activation, particularly among women[15], and that lower adipose tissue density following ART correlates with higher inflammatory markers, even with effective viral suppression[14]. We similarly found that ART initiation was associated with an increase in lean mass (an estimate of skeletal muscle mass by DEXA) and psoas muscle volume (by CT), but with lower muscle density, suggesting that gains were primarily of lower quality, fatty skeletal muscle[16]. Here, our goal was to explore the relationships between inflammation and immune activation and changes in psoas muscle density and area following ART initiation. We hypothesized that after 96 weeks of ART, those with persistent inflammation and immune activation would have poorer muscle quality (less fat within the muscle) and smaller muscle area, changes that may have longer-term effects on physical function.

Methods

Study Design

ACTG A5260s was the observational metabolic substudy of A5257[17,18]. In A5257, ART-naïve PWH were randomized to tenofovir-emtricitabine (TDF/FTC) plus atazanavir (ATV)/ritonavir(r), darunavir (DRV)/r, or raltegravir (RAL) for at least 96 weeks[17]. The A5260s primary objectives were to compare atherosclerosis progression and endothelial function between the randomized regimens[18]. Secondary objectives included assessing changes in cardiovascular disease burden, fat composition (as measured by abdominal CT scans for SAT (subcutaneous AT) and VAT (visceral AT) quantity assessment (i.e., AT area)), soluble inflammation and cellular immune activation biomarkers, and bone mineral density. All participants provided written, informed consent and the institutional review boards at each institution provided approvals for the studies.

Body Composition Measures

Computed Tomography (CT) has been validated as a tool to measure skeletal muscle area (quantity) and fatty infiltration (quality)[19,20]. A cross-sectional measure of psoas muscle area at the L4-L5 level[21] or at mid-thigh[22] has been used to estimate total body skeletal muscle volume. CT can also provide a measure of skeletal muscle quality through the density, or intramuscular fat, as measured by Hounsfield Units (HU), a radiographic distinction between tissues densities such as water, muscle, fat, or bone[23]. CT estimates of muscle density are strongly associated with increased muscle fiber lipid content i*n vivo*[23] and with clinical measures of physical function[24]. For this study, CTs at week 0 and 96 were re-interpreted for psoas density (HU), psoas lean density (HU), psoas area (cm^2), and psoas lean area (cm^2) at the University of Colorado Anschutz Medical Center by a reader blinded to clinical data using specialized body composition software (Excelis Visual Information Systems; Boulder, CO). The lean density and lean area were determined by excluding muscle with a density <30 HU.

Laboratory Assessment

Blood samples (fasting for > 8 hours) were collected at study entry prior to ART initiation and at 96 weeks. All blood samples were sent to core laboratories without prior thaw for processing. Biomarkers were measured at the University of Vermont Laboratory for Clinical Biochemistry Research (Burlington, VA) on batched plasma stored at −70°C. Tests included high-sensitivity C-reactive protein (hs-CRP) by nephelometry (Siemens BNII Nephelometer; Siemens Healthcare, Indianapolis, Indiana, USA), interleukin-6 (IL-6) using enzyme linked immunosorbent assay. Measures of immune activation were measured including soluble CD14, soluble CD163, %CD4+:CD38+HLA-DR+, and %CD8+:CD38+HLA-DR+[25].

Statistical Methods

This exploratory, retrospective analysis included all participants enrolled in A5260s, who had paired CT scans (at week 0 and 96), who were virologically suppressed at week 96, and had inflammation or immune activation biomarker data available.

Total psoas density and area were calculated as the sum of the right and left psoas measures. All biomarker outcomes were log-10 transformed prior to analysis. Percent change in psoas density and area and absolute change in biomarker levels were calculated from baseline to week 96.

Spearman's rank-based correlations were used to assess associations between psoas density and psoas lean area, and biomarkers cross-sectionally at baseline and week 96 and as change from baseline. Partial Spearman's correlations were used to evaluate associations adjusting for BMI, psoas area, and ART regimen. Spearman's rho and p-values are used to describe all associations, with p-values compared with a 5% type-I error rate. No adjustments for multiple comparisons were made; however, interpretations emphasized magnitudes and consistency of effect sizes (Spearman's rho). All analyses were done in SAS 9.4.

Results

Baseline Characteristics

Of the 328 participants enrolled in A5260s, 239 (73%) had paired CT scans that could be re-read for muscle endpoints and were virologically suppressed at week 96, and among those 222 (67%) had available inflammation or immune activation marker data. As shown in Table 1, the median baseline age of participants was 36 (IQR 28, 45) years; the majority were male (90%). 44% were white non-Hispanic, 30% black non-Hispanic, and 21% Hispanic. Baseline median (IQR) CD4 was 345 (185, 454) cells/μL, HIV-1 RNA was 4.6 (4.1, 5.1) $\log_{10}$ copies/mL, and BMI was 24.5 (22. 3, 27.8) kg/m^2.

Cross-Sectional Inflammation and Immune Activation and Psoas Muscle Density and Area

Correlations between markers of inflammation with psoas density and area were first examined at baseline. As shown in Figure 1, panel A, we found weak to moderate associations ($r=-0.15$ to -0.30). The strongest associations were observed between IL-6 and psoas density, psoas lean density, psoas area, and psoas lean area ($r= -0.23$ to -0.30, $p<0.001$), and sCD14 and psoas area and psoas lean area ($r= -0.26$ to -0.30, $p<0.001$). Modest associations were observed between sCD163 and %CD4:CD38+HLADR+ with psoas area and psoas lean area ($r=-0.18$ to -0.21, $p<0.01$). In analyses adjusting for baseline BMI, IL-6 and sCD163 remained independently associated with psoas density, and higher levels of inflammation and immune activation remained independently correlated with lower baseline psoas lean area (Table 2).

We next examined associations between inflammation and immune activation biomarkers with psoas density or area at week 96 (post-ART initiation) (Figure 1, panel B). The strongest associations were observed between IL-6 and hs-CRP and psoas density and lean density ($r=-0.22$ to -0.28, $p<0.001$), with higher levels of inflammatory markers associated with lower density. We found modest correlations ($r=-0.24$ to $r=-0.28$, $p<0.001$) between higher IL-6 and hs-CRP with lower psoas total and lean density (Figure 1, panel B).
In analyses adjusting for baseline BMI, baseline psoas area and ART regimen, IL-6 and hs-CRP remained independently correlated with psoas density; adjusting for baseline BMI and ART, hs-CRP remained correlated with psoas lean area (Table 3).

Change in Inflammation and Immune Activation and Psoas Density and Area

Correlations between absolute change in inflammatory and immune activation biomarkers with percent change in psoas density and area are shown in Figure 1, panel C. The strongest associations were observed for IL-6, sCD14, and sCD163, with a greater decrease in these markers associated with a greater increase in psoas density, psoas area, and psoas lean area (r=−0.07 to −.18). %CD8+:CD38+HLA-DR+ was weakly correlated with psoas lean area (r=0.17, P=0.015) while no significant associations were observed between psoas density or area and %CD4+:CD38+HLA-DR+.

In partial correlations adjusted for change in BMI, change in psoas area, or ART regimen (Table 4), greater decreases in IL-6 remained independently associated with greater increase in psoas density. Similarly, in partial correlations adjusted for change in BMI and ART, greater decrease in IL-6, %CD8+:CD38+HLA-DR+, sCD14, and sCD163 all remained independently associated with greater increase in psoas lean area.

Discussion

In the setting of ART initiation, we observed that prior to ART initiation, higher inflammation (IL-6, hs-CRP) was associated (albeit weakly) with lower psoas density and area, while higher immune activation correlated only with lower psoas area. With 96 weeks of ART, greater decreases in inflammation were associated with greater increases in psoas density and area and decreases in immune activation associated only with increases in psoas muscle area, most prominently with the lean muscle area.

We observed that higher baseline levels of IL-6 were associated with decreased psoas area and lean area. In HIV-uninfected populations, high levels of inflammation are associated with muscle atrophy due to signaling pathways resulting in decreased protein synthesis or increased muscle degradation. These effects are particularly prominent in cancer, where high systemic inflammation is associated with cancer associated cachexia[26]. Notably, the median serum IL-6 level in cancer patients from 72 separate studies was 6.95 pg/mL (range: 0.23–78.5 pg/mL)[27] compared to the median value (1.6 pg/mL) in our study, emphasizing the comparatively low level of inflammation even prior to ART. In murine models, increased IL-6 levels activate the STAT3 pathway with subsequent downstream activation of the ubiquitin proteasome system (UPS)[28]. This creates muscle degradation by breaking down myofibrillar proteins[29]. Additionally, in murine models, higher systemic IL-6 induced skeletal muscle protein degradation and skeletal muscle atrophy[30]. Among adults with cancer, higher IL-6 is associated with increased ubiquitin protein levels (UPS activity) in skeletal muscle[31]. In older adults, higher IL-6 was associated with smaller muscle area and less appendicular muscle mass[32].

IL-6 also influences muscle through modulation of the insulin-like growth factor (IGF)-1 pathway. IGF-1 activates a common signaling pathway with the end result of activation of mTOR, resulting in protein synthesis and inhibition of muscle degradation[33,34]. IL-6 has several effects on this pathway that can lead to muscle atrophy. First, in a rat model,

treatment with IL-6 resulted in skeletal muscle atrophy[35]. IL-6 inhibits mTOR, the main transcriptional regulator of protein synthesis[36]. In a mouse model, overexpression of IL-6 decreases IGF-1 levels[37]. We have previously shown that in PWH, administration of tesamorelin, a growth hormone analog, resulted in increases in muscle density and lean area. The increases in lean area seen with tesamorelin were suggested to be due to IGF-1 effects rather than reduction in visceral adipose tissue[38].

We also found associations between greater decreases in immune activation (sCD14, sCD163, and %CD4+:CD38+DR+ T-cells) and increased psoas lean area at week 96. After one year of ART, markers of inflammation and immune activation decrease; however, certain markers including sCD14 can remain elevated despite virologic suppression[8]. Adipose tissue can act as a reservoir for persistent inflammation and immune activation, which may explain this occurrence in PWH with virologic suppression[39,40]. Adipose tissue harbors latent HIV infected CD4+ cells, T cell activation and IL-6 mediated inflammation[41,42]. Adipose tissue deposits within muscle, may therefore act similarly to perpetuate systemic inflammation and immune activation, which may have negative effects on muscle function. Obesity is another well-described inflammatory state in which adipose tissue can similarly act as a reservoir for pro-inflammatory cells and function to secrete pro-inflammatory cytokines[43]. In a murine obesity model, increased systemic inflammation was associated with increased deposition of extramyocellular adipose tissue in skeletal muscle, however, addition of Baricitinib, a JAK1/2 inhibitor, was shown to decrease the number and expression of CD8+ T cells in skeletal muscle[44]. In an uninfected population of patients on hemodialysis, higher serum sCD14 levels were associated with lower lean body mass, BMI, hand grip strength, but not with fat body mass, and higher sCD14 level correlated with more severe muscle atrophy[45]. Similarly, in PWH, higher plasma levels of sCD14 were associated with greater odds of physical function impairment[46]. Relatively little is known regarding the association of immune activation markers and muscle function in PWH. These adipose tissue reservoirs may act to perpetuate systemic inflammation and immune activation, and secondarily promote fat deposition within skeletal muscle, leading to overall poorer muscle quality (density). Fatty deposition within skeletal muscle can also secondarily lead to decreased lean area (good muscle) but overall increased total muscle area due to expansion from fatty infiltrates. Therefore, overall improvement in the local inflammatory and immune activation milieu, either in AT or intramuscular AT could explain the improvements in psoas muscle lean area we observed.

Whether associations between muscle and ART initiation are indirect effects of inflammation or a direct result of ART penetrance into the tissue is unknown. This is in contrast to associations between ART and visceral adipose tissue, where variable ART penetrance into adipose tissue is described[47,48]. In this same cohort, we have previously shown a greater increase in visceral adipose tissue density with RAL than ATV/r or DRV/r[14]. In a separate cohort, we have shown that DRV/r was associated with greater visceral fat area and lower visceral fat and muscle density when compared to ATV/r and RAL[45]. Variable ART penetrance into intramuscular, intermuscular or myocellular lipid deposits could account for varying changes in suppression of inflammation or immune activation, given these AT deposits are well known to be reservoirs of persistent inflammation despite virologic suppression[39,40] . More studies examining the effects of different classes of

ART on intramuscular AT, and consequently changes in these inflammatory and immune activation markers could further fill in the gaps in this knowledge.

Our study had several limitations. First, this was a correlational study, thus we cannot draw conclusions about causality or effects between the variables we studied. Additionally, analyses within ART treatment group were limited due to small sample sizes. No data was collected on physical activity, which may impact adiposity overall and in muscle. However, the study was strengthened by inclusion of both men and women with robust data prior to and following initiation of ART.

In summary, we observed that decreases in inflammation and immune activation with ART initiation were associated with increases in psoas muscle area and density, largely independent of changes in BMI. These findings provide a link between ongoing, low-level inflammation and immune activation following ART initiation with poor muscle quality and quantity, which may have a long-term effect on physical function. Whether these changes have clinical implications on muscle cannot be determined from this existing study, as physical function measures were not obtained. However, we can draw inferences based on prior studies. Among older adults without HIV, lower psoas quality and/or quantity has been associated with frailty and falls[49–51]. We have previously shown greater odds of lower functional status associated with the immune activation biomarker CD8+CD38/HLA-DR and increased levels of IL-6 in PWH[46]. And, we have found that higher density (less fat) psoas and paraspinal muscle were associated with better physical function[45]. Interventions to minimize inflammation and immune activation may have additional benefit on muscle area and density, which ultimately may result in improvements in physical function and mobility.

Funding:

This research was supported by grants from the National Institutes of Health (grant numbers HL095132, HL095126, AI069501, AI068636, AI110532). The project was also supported by awards UM1 AI068634, UM1 AI068636, and UM1 AI106701 from the National Institute of Allergy and Infectious Diseases. KME was supported in part by the National Institutes of Health, National Institute on Aging Grants R01AG066562 and R01AG054366. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

Conflicts of Interest:

KME has received research funding from Gilead Sciences (paid to the University of Colorado), and consulting fees from ViiV Pharmaceuticals and Theratechnologies (paid to the University of Colorado)

References

1. Wanke CA, Silva M, Knox TA, Forrester J, Speigelman D, Gorbach SL. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. Clin Infect Dis. 2000;31(3):803–805. [PubMed: 11017833]
2. Koethe JR, Jenkins CA, Lau B, et al. Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada. AIDS Res Hum Retroviruses. 2016;32(1):50–58. [PubMed: 26352511]
3. Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2020;71(6):1379–1389. [PubMed: 31606734]

4. Herrin M, Tate JP, Akgun KM, et al. Weight Gain and Incident Diabetes Among HIV-Infected Veterans Initiating Antiretroviral Therapy Compared With Uninfected Individuals. J Acquir Immune Defic Syndr. 2016;73(2):228–236. [PubMed: 27171741]
5. Unamuno X, Gómez-Ambrosi J, Rodríguez A, Becerril S, Frühbeck G, Catalán V. Adipokine dysregulation and adipose tissue inflammation in human obesity. Eur J Clin Invest. 2018;48(9):e12997. [PubMed: 29995306]
6. Ferrante AW Jr., The immune cells in adipose tissue. Diabetes Obes Metab. 2013;15 Suppl 3(0 3):34–38. [PubMed: 24003919]
7. Neuhaus J, Jacobs DR Jr., Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis. 2010;201(12):1788–1795. [PubMed: 20446848]
8. Wada NI, Jacobson LP, Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. Aids. 2015;29(4):463–471. [PubMed: 25630041]
9. Rolland Y, Czerwinski S, Abellan Van Kan G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging. 2008;12(7):433–450. [PubMed: 18615225]
10. Oliveira VHF, Borsari AL, Webel AR, Erlandson KM, Deminice R. Sarcopenia in people living with the Human Immunodeficiency Virus: a systematic review and meta-analysis. European journal of clinical nutrition. 2020;74(7):1009–1021. [PubMed: 32341489]
11. Erlandson KM, Travison TG, Zhu H, et al. Application of Selected Muscle Strength and Body Mass Cut Points for the Diagnosis of Sarcopenia in Men and Women With or at Risk for HIV Infection. J Gerontol A Biol Sci Med Sci. 2020;75(7):1338–1345. [PubMed: 32301484]
12. Hawkins KL, Brown TT, Margolick JB, Erlandson KM. Geriatric syndromes: new frontiers in HIV and sarcopenia. Aids. 2017;31 Suppl 2(Suppl 2):S137–s146. [PubMed: 28471944]
13. Langkilde A, Petersen J, Henriksen JH, et al. Leptin, IL-6, and suPAR reflect distinct inflammatory changes associated with adiposity, lipodystrophy and low muscle mass in HIV-infected patients and controls. Immun Ageing. 2015;12:9. [PubMed: 26244048]
14. Debroy P, Lake JE, Moser C, et al. Antiretroviral therapy initiation is associated with decreased visceral and subcutaneous adipose tissue density in people living with HIV. Clin Infect Dis. 2020.
15. Sara H Bares LMS, Vincent Vu, Zavoda-Smith Beth A., Scott Sarah E., Godfrey Catherine, McComsey Grace A.. The Impact of Weight Gain and Sex on Immune Activation Following Initiation of ART Poster presented at Conference on Retroviruses and Opportunistic Infections 3 4, 2019 2019; Seattle, Washington
16. Erlandson KM, Fiorillo S, Masawi F, et al. Antiretroviral initiation is associated with increased skeletal muscle area and fat content. Aids. 2017;31(13):1831–1838. [PubMed: 28590329]
17. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. Ann Intern Med. 2011;154(7):445–456. [PubMed: 21320923]
18. McComsey GA, Moser C, Currier J, et al. Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors: ACTG A5260s. Clin Infect Dis. 2016;62(7):853–862. [PubMed: 26797215]
19. Visser M, Fuerst T, Lang T, Salamone L, Harris TB. Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass. Health, Aging, and Body Composition Study--Dual-Energy X-ray Absorptiometry and Body Composition Working Group. J Appl Physiol (1985). 1999;87(4):1513–1520. [PubMed: 10517786]
20. Goodpaster BH, Thaete FL, Kelley DE. Composition of skeletal muscle evaluated with computed tomography. Ann N Y Acad Sci. 2000;904:18–24. [PubMed: 10865705]
21. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. Journal of Applied Physiology. 2004;97(6):2333–2338. [PubMed: 15310748]
22. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. Journal of applied physiology (Bethesda, Md : 1985). 1998;85(1):115–122.

23. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol (1985). 2000;89(1):104–110. [PubMed: 10904041]
24. Farsijani S, Santanasto AJ, Miljkovic I, et al. The Relationship between Inter-muscular Fat and Physical Performance Is Moderated by Muscle Area in Older Adults. J Gerontol A Biol Sci Med Sci. 2020.
25. Kelesidis T, Tran TT, Stein JH, et al. Changes in Inflammation and Immune Activation With Atazanavir-, Raltegravir-, Darunavir-Based Initial Antiviral Therapy: ACTG 5260s. Clin Infect Dis. 2015;61(4):651–660. [PubMed: 25904376]
26. Cole CL, Kleckner IR, Jatoi A, Schwarz EM, Dunne RF. The Role of Systemic Inflammation in Cancer-Associated Muscle Wasting and Rationale for Exercise as a Therapeutic Intervention. JCSM Clin Rep. 2018;3(2).
27. Lippitz BE, Harris RA. Cytokine patterns in cancer patients: A review of the correlation between interleukin 6 and prognosis. OncoImmunology. 2016;5(5):e1093722. [PubMed: 27467926]
28. White J, Puppa M, Sato S, Baynes J, Welle S, Carson J. IL-6 inhibition attenuates activation of ubiquitin proteasome-dependent degradation in cachectic muscle. The FASEB Journal. 2011;25(S1):1105.1112–1105.1112.
29. Roy B, Curtis ME, Fears LS, Nahashon SN, Fentress HM. Molecular Mechanisms of Obesity-Induced Osteoporosis and Muscle Atrophy. Front Physiol. 2016;7:439. [PubMed: 27746742]
30. Muñoz-Cánoves P, Scheele C, Pedersen BK, Serrano AL. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? Febs j. 2013;280(17):4131–4148. [PubMed: 23663276]
31. DeJong CH, Busquets S, Moses AG, et al. Systemic inflammation correlates with increased expression of skeletal muscle ubiquitin but not uncoupling proteins in cancer cachexia. Oncol Rep. 2005;14(1):257–263. [PubMed: 15944798]
32. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A Biol Sci Med Sci. 2002;57(5):M326–332. [PubMed: 11983728]
33. Bakker AD, Jaspers RT. IL-6 and IGF-1 Signaling Within and Between Muscle and Bone: How Important is the mTOR Pathway for Bone Metabolism? Curr Osteoporos Rep. 2015;13(3):131–139. [PubMed: 25712618]
34. Schiaffino S, Mammucari C. Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. Skelet Muscle. 2011;1(1):4. [PubMed: 21798082]
35. Goodman MN. Interleukin-6 induces skeletal muscle protein breakdown in rats. Proc Soc Exp Biol Med. 1994;205(2):182–185. [PubMed: 8108469]
36. Bolster DR, Crozier SJ, Kimball SR, Jefferson LS. AMP-activated protein kinase suppresses protein synthesis in rat skeletal muscle through down-regulated mammalian target of rapamycin (mTOR) signaling. J Biol Chem. 2002;277(27):23977–23980. [PubMed: 11997383]
37. De Benedetti F, Meazza C, Oliveri M, et al. Effect of IL-6 on IGF binding protein-3: a study in IL-6 transgenic mice and in patients with systemic juvenile idiopathic arthritis. Endocrinology. 2001;142(11):4818–4826. [PubMed: 11606449]
38. Adrian S, Scherzinger A, Sanyal A, et al. The Growth Hormone Releasing Hormone Analogue, Tesamorelin, Decreases Muscle Fat and Increases Muscle Area in Adults with HIV. J Frailty Aging. 2019;8(3):154–159. [PubMed: 31237318]
39. Koethe JR. Adipose Tissue in HIV Infection. Compr Physiol. 2017;7(4):1339–1357. [PubMed: 28915327]
40. Couturier J, Lewis DE. HIV Persistence in Adipose Tissue Reservoirs. Curr HIV/AIDS Rep. 2018;15(1):60–71. [PubMed: 29423731]
41. Couturier J, Suliburk JW, Brown JM, et al. Human adipose tissue as a reservoir for memory CD4+ T cells and HIV. Aids. 2015;29(6):667–674. [PubMed: 25849830]
42. Chen Y, Tian J, Tian X, et al. Adipose tissue dendritic cells enhances inflammation by prompting the generation of Th17 cells. PLoS One. 2014;9(3):e92450. [PubMed: 24642966]
43. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021;320(3):C375–c391. [PubMed: 33356944]

44. Khan IM, Perrard XY, Brunner G, et al. Intermuscular and perimuscular fat expansion in obesity correlates with skeletal muscle T cell and macrophage infiltration and insulin resistance. Int J Obes (Lond). 2015;39(11):1607–1618. [PubMed: 26041698]
45. Adrian S, Miao H, Feng H, et al. Effects of atazanavir, darunavir, and raltegravir on fat and muscle among persons living with HIV. HIV Res Clin Pract. 2020;21(4):91–98. [PubMed: 32878571]
46. Erlandson KM, Allshouse AA, Jankowski CM, et al. Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral therapy. J Infect Dis. 2013;208(2):249–259. [PubMed: 23559466]
47. Couturier J, Winchester LC, Suliburk JW, et al. Adipocytes impair efficacy of antiretroviral therapy. Antiviral Res. 2018;154:140–148. [PubMed: 29630975]
48. Dupin N, Buffet M, Marcelin AG, et al. HIV and antiretroviral drug distribution in plasma and fat tissue of HIV-infected patients with lipodystrophy. Aids. 2002;16(18):2419–2424. [PubMed: 12461415]
49. Chiang PL, Chen YS, Lin AW. Altered Body Composition of Psoas and Thigh Muscles in Relation to Frailty and Severity of Parkinson's Disease. Int J Environ Res Public Health. 2019;16(19).
50. Koizia L, Naik M, Peck G, et al. The Utility of Psoas Muscle Assessment in Predicting Frailty in Patients Undergoing Transcatheter Aortic Valve Replacement. Curr Gerontol Geriatr Res. 2020;2020:5783107. [PubMed: 32684927]
51. Idoate F, Cadore EL, Casas-Herrero A, et al. Adipose tissue compartments, muscle mass, muscle fat infiltration, and coronary calcium in institutionalized frail nonagenarians. Eur Radiol. 2015;25(7):2163–2175. [PubMed: 25510447]

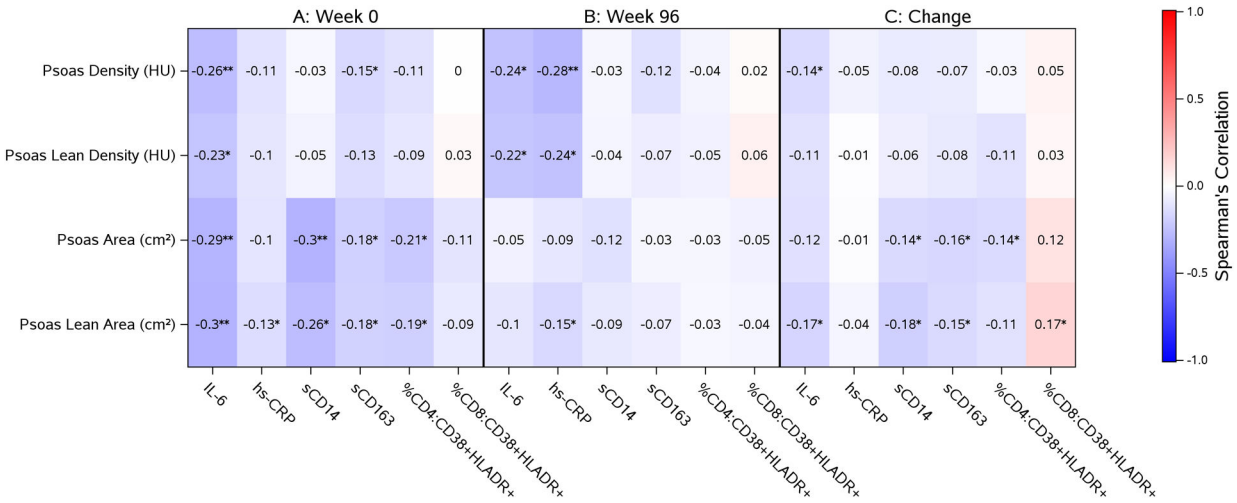

Figure 1.

Changes in psoas density, lean density, area and lean area at week 0 baseline (Panel A), week 96 post ART-initiation (Panel B), and Percent Change (Panel C) and correlations with inflammatory and immune activation markers. Partial Spearman's correlations are represented by color gradients indicating strength of correlation. Significant correlations are indicated with * or **. Abbreviations: Interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), soluble CD14 (sCD14) and soluble CD163 (sCD163).

Table 1.

Baseline Characteristics

Values reported represent median (1st and 3rd quartile) or frequency (percentage).

Characteristics	N=222
Age (years)	36 (28,45)
Baseline $CD4^+$ T cell count (cells/μL)	345 (185, 454)
HIV-1 RNA (log_{10} copies/mL)	4.6 (4.1, 5.1)
BMI (kg/m^2)	24.5 (22.3, 27.8)
Race/Ethnicity	
White, non-Hispanic	97 (44%)
Black, non-Hispanic	67 (30%)
Hispanic (regardless of race)	46 (21%)
Other	12 (5%)
Female Sex	23 (10%)
ART Regimen	
Atazanavir/Ritonavir	74 (33%)
Raltegravir	76 (34%)
Darunavir/Ritonavir	72 (32%)
Psoas Measures	
Total psoas area (cm^2)	37.36 (32.17, 41.77)
Total psoas density (HU)	94.79 (88.40, 101.59)
Lean psoas area (cm^2)	31.79 (26.74, 36.20)
Lean psoas density (HU)	108.41 (103.83, 113.16)
Biomarkers	
IL-6 (pg/mL)	1.61 (1.12, 2.75)
hs-CRP (ug/mL)	1.29 (0.66, 2.81)
sCD14 (ng/ml)	1684.01 (1453.88, 1977.13)
sCD163 (ng/ml)	1078.11 (770.87, 1563.83)
%CD4+: CD38+HLADR+	19.1 (11.9, 31.4)
%CD8+: CD38+HLADR+	42.5 (34, 54.8)

Abbreviations: Body Mass Index (BMI), Hounsfield Units (HU), Interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), soluble CD14 (sCD14) and soluble CD163 (sCD163).

Table 2.

Partial Spearman Correlations: *Baseline* Psoas Density (HU) and Psoas Lean Area (cm^2) with *Baseline* Biomarker Levels

Biomarker	**Adjusted for Baseline BMI**		**Adjusted for baseline psoas area**	
Baseline Psoas Density (HU)				
	Correlation	*p-value*	*Correlation*	*p-value*
IL-6 (log_{10} pg/mL)	−0.27	**<0.001**	−0.17	**0.01**
hs-CRP (log_{10} ug/mL)	−0.09	0.18	−0.08	0.24
sCD14 (log_{10} ng/mL)	−0.08	0.22	0.08	0.21
sCD163 (log_{10} ng/mL)	−0.14	**0.04**	−0.09	0.19
%CD4:CD38+HLADR+ (log_{10})	−0.15	**0.029**	−0.04	0.52
%CD8:CD38+HLADR+ (log_{10})	−0.01	0.89	0.03	0.61
Baseline Psoas Lean Area (cm^2)				
IL-6 (log_{10} pg/mL)	−0.29	**<0.001**		
hs-CRP (log_{10} ug/mL)	−0.15	**0.02**		
sCD14 (log_{10} ng/mL)	−0.23	**0.0005**		
sCD163 (log_{10} ng/mL)	−0.18	**0.0073**		
%CD4:CD38+HLADR+ (log_{10})	−0.16	**0.02**		
%CD8:CD38+HLADR+ (log_{10})	−0.08	0.24		

Abbreviations: Body Mass Index (BMI), Hounsfield Units (HU), Interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), soluble CD14 (sCD14) and soluble CD163 (sCD163).

Table 3.

Partial Spearman Correlations between *Week 96* Psoas Density (HU) and Psoas Lean Area (cm^2) and *Week 96* Biomarker Levels

Biomarker	**Adjusted for baseline BMI**		**Adjusted for baseline Psoas Area**		**Adjusted for ART Regimen**[1]	
Week 96 Psoas Density (HU)						
	Correlation	*p-value*	*Correlation*	*p-value*	*Correlation*	*p-value*
IL-6 (log_{10} pg/mL)	−0.22	**0.0008**	−0.22	**0.0012**	−0.25	**0.0002**
hs-CRP (log_{10} ug/mL)	−0.25	**0.0002**	−0.24	**0.0003**	−0.29	**<0.0001**
sCD14 (log_{10} ng/mL)	−0.06	0.42	0.02	0.81	−0.04	0.52
sCD163 (log_{10} ng/mL)	−0.11	0.09	−0.08	0.26	−0.12	0.078
%CD4:CD38+HLADR+ (log_{10})	−0.06	0.37	−0.01	0.87	−0.04	0.55
%CD8:CD38+HLADR+ (log_{10})	−0.002	0.98	0.08	0.24	0.02	0.76
Week 96 Psoas Lean Area (cm^2)						
IL-6 (log_{10} pg/mL)	−0.11	0.12			−0.10	0.13
hs-CRP (log_{10} ug/mL)	−0.17	**0.011**			−0.16	**0.019**
sCD14 (log_{10} ng/mL)	−0.08	0.25			−0.10	0.13
sCD163 (log_{10} ng/mL)	−0.07	0.27			−0.07	0.31
%CD4:CD38+HLADR+ (log_{10})	−0.02	0.82			−0.03	0.71
%CD8:CD38+HLADR+ (log_{10})	−0.02	0.80			−0.03	0.62

[1]Protease Inhibitors were pooled together.

Abbreviations: Hounsfield Units (HU), Interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), soluble CD14 (sCD14) and soluble CD163 (sCD163).

Table 4.

Partial Spearman Correlations between *Percent Change* in Psoas Density (HU) and Psoas Lean Area (cm^2) and *Absolute Change* in Biomarker Levels (Changes from Baseline to Week 96)

Biomarker	**Adjusted for Change in BMI**		**Adjusted for Change in Psoas Area**		**Adjusted for ART Regimen**[1]	
Percent Change in Psoas Density (HU)						
	Correlation	*p-value*	*Correlation*	*p-value*	*Correlation*	*p-value*
IL-6 (log_{10} pg/mL)	−0.13	0.06	−0.15	**0.02**	−0.14	**0.04**
hs-CRP (log_{10} ug/mL)	−0.04	0.57	−0.04	0.55	−0.05	0.49
sCD14 (log_{10} ng/mL)	−0.07	0.31	−0.09	0.17	−0.08	0.24
sCD163 (log_{10} ng/mL)	−0.07	0.31	−0.08	0.27	−0.07	0.29
%CD4:CD38+HLADR+ (log_{10})	−0.02	0.77	−0.05	0.48	−0.03	0.67
%CD8:CD38+HLADR+ (log_{10})	0.04	0.61	0.06	0.42	0.05	0.49
Percent Change in Psoas Lean Area (cm^2)						
IL-6 (log_{10} pg/mL)	−0.14	**0.043**			−0.17	**0.0121**
hs-CRP (log_{10} ug/mL)	−0.008	0.90			−0.04	0.5384
sCD14 (log_{10} ng/mL)	−0.16	**0.019**			−0.2	**0.0033**
sCD163 (log_{10} ng/mL)	−0.14	**0.04**			−0.14	**0.038**
%CD4:CD38+HLADR+ (log_{10})	−0.09	0.19			−0.11	0.10
%CD8:CD38+HLADR+ (log_{10})	0.14	**0.044**			0.17	**0.016**

[1]Protease Inhibitors were pooled together.

Abbreviations: Body Mass Index (BMI), Hounsfield Units (HU), Antiretroviral Therapy (ART), Interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), soluble CD14 (sCD14) and soluble CD163 (sCD163).