Inflammation and Change in Body Weight With Antiretroviral Therapy Initiation in a Multinational Cohort of HIV-Infected Adults

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Background. Both wasting and obesity are associated with inflammation, but the extent to which body weight changes influence inflammation during human immunodeficiency virus infection is unknown.

Methods. Among a random virologically suppressed participants of the Prospective Evaluation of Antiretrovirals in Resource-Limited Settings trial, inflammatory markers were measured at weeks 0, 24, and 48 after antiretroviral therapy (ART) initiation. Associations between both baseline and change in body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) and changes in inflammation markers were assessed using random effects models.

Results. Of 246 participants, 27% were overweight/obese (BMI ≥ 25), and 8% were underweight (BMI < 18.5) at baseline. After 48 weeks, 37% were overweight/obese, and 3% were underweight. While level of many inflammatory markers decreased 48 weeks after ART initiation in the overall group, the decrease in C-reactive protein (CRP) level was smaller in overweight/obese participants (P = .01), and the decreases in both CRP (P = .01) and interleukin 18 (P = .02) levels were smaller in overweight participants. Each 1-unit BMI gain among overweight/obese participants was associated with a 9.32-mg/L decrease in CRP level (P = .001).

Conclusions. Being either overweight or underweight at ART initiation was associated with heightened systemic inflammation. While weight gain among overweight/obese persons predicted increased inflammation, weight gain among underweight persons predicted reduced inflammation.

Keywords. immune activation/inflammation; body mass index; HIV/AIDS; HAART clinical outcomes; noncommunicable diseases.

Globally, there are 36.9 million persons living with human immunodeficiency virus (HIV), and a growing number are noted to be overweight or obese, paralleling the global epidemic of obesity [1–3]. As shown across multiple study populations, the majority of HIV-infected individuals gain weight with antiretroviral therapy (ART) initiation, with the greatest weight gains among individuals with the lowest CD4+ T-cell counts and highest viral loads [4–7]. Weight gain with ART can reflect a slowing resting energy expenditure with suppressed virus level, as well as an improvement in HIV-associated enteropathy, and often signals a return to health [6]. In some settings, obesity is viewed as an external manifestation of health and prosperity and, thus, a desirable outcome of HIV treatment [8–9]. Continued weight gain over time has resulted in an increased prevalence of obesity among HIV-infected persons in both resource-rich and resource-limited settings [2, 3, 10–13]. There is likely a tipping point at which weight gain begins to have a negative influence. Indeed, a recent analysis within the Veterans Aging Cohort found improved survival with weight gain in the first year of ART among underweight or normal-weight participants but not overweight or obese participants [6]. In contrast, weight loss or failure to gain weight with ART initiation is often a poor

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prognostic sign and may be a marker of concomitant infections, such as tuberculosis; severe wasting; or metabolic diseases, such as diabetes or adrenal insufficiency [14].

Both obesity and cachexia (or wasting) are associated with chronic inflammation [15], with heightened levels of multiple inflammatory cytokines, including interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and C-reactive protein (CRP) [15–19]. Although levels of inflammatory markers tend to decrease with suppressive ART, HIV infection is also associated with chronic low-level inflammation, with levels of several markers of inflammation or immune activation elevated even after years of therapy, comparison with levels in HIV-uninfected populations [20, 21]. This persistent, low-grade inflammatory state, even in treated HIV infection, has been associated with an increase in multiple non–AIDS-related comorbidities, including cardiovascular disease, cancer, osteoporosis, weakness, frailty, and death [22–27]. Multiple factors likely contribute to ongoing inflammation, including low-level HIV replication, chronic hepatitis B and C, other viral coinfections, microbial translocation, and lifestyle factors [28].

The degree to which a potentially modifiable and easily measurable condition such as change in body weight, particularly within the first year after ART initiation, influences changes in levels of inflammatory markers is unknown. An understanding of the impact of body weight changes on inflammation across diverse settings with a variety of diets and levels of physical activity may be particularly informative to the early recognition of individuals at increased risk for morbidity and mortality. Furthermore, higher baseline body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) and weight change after ART initiation with a high proportion of both underweight and overweight participants have a higher risk of persistent immune activation and inflammation as compared to normal-weight patients. The Prospective Evaluation of Antiretrovirals in Resource-Limited Settings (PEARLS) trial was a randomized international trial of ART initiation with a high proportion of both overweight and underweight participants and a nearly equal proportion of men and women, many with advanced HIV infection [29]. Using the PEARLS trial, we sought to investigate the association between baseline weight and weight gain with ART initiation on changes in markers of inflammation and immune activation.

**METHODS**

**Study Design and Population**

We used a random sample of persons who experienced virologic suppression within the AIDS Clinical Trials Group (ACTG) PEARLS trial (ClinicalTrials.gov registration NCT00084136) to address our objective. In brief, PEARLS was a randomized trial of ART initiation in 1571 treatment-naive adults from 9 countries (Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, United States, and Zimbabwe) [29]. Enrollment occurred between May 2005 and August 2007, and participants were followed through May 2010, with a primary outcome of HIV disease progression. Eligible participants had a CD4+ T-cell count of <300 cells/mm³ and no history of recent acute illness (ie, pneumonia, gastroenteritis, or pelvic inflammatory disease) or opportunistic infections. Participants were randomized to receive one of the following 3 HIV treatment regimens: (1) efavirenz + lamivudine + zidovudine (EFV+3TC+ZDV), (2) efavirenz+emtricitabine+tenofovir ((EFV+FTC+TDF), or (3) atazanavir+didanosine+emtricitabine (ATV+DDI+FTC). Further details of the PEARLS study design, participant characteristics, and the primary results have been previously published [29]. A New Works Concept Sheet (NWCS-319) was developed as a substudy to PEARLS study that had >80% power to assess the effect of inflammatory and nutritional markers on clinical end points. A sample of 270 individuals from PEARLS comprising 30 randomly selected individuals from each country was included in NWCS-319, and these data were used to assess the effect of BMI on inflammatory markers. We excluded 24 participants (8.9%) who did not achieve virologic suppression at weeks 24 and/or 48.

The human experimentation guidelines of the Department of Health and Human Services were followed, and the institutional review board or ethics committees at each site provided approval. Informed consent, including permission to use biological materials, was obtained from all participants.

**Laboratory Testing**

Serum and plasma specimens were obtained from all participants at weeks 0, 24, and 48 after ART initiation and were stored at −80°C in a repository until the time of testing. Each marker was batch tested at single centralized laboratories [30]. Plasma soluble CD14 (sCD14) and plasma CRP levels were measured using commercially available ELISA kits (R&D Systems, Minneapolis, Minnesota); plasma interferon γ (IFN-γ)–inducible protein 10 (CXCL-10; also referred to as IP-10) was measured using an electrochemiluminescent bridging immunoassay (Meso-Scale Discovery, Gaithersburg, Maryland). Plasma levels of the soluble inflammatory cytokines TNF-α, IL-6, and IFN-γ were measured using the Luminex multiplex cytokine platform (R&D Systems, Minneapolis, Minnesota). IL-18 was performed using ELISA (Platinum ELISA, eBiosciences, San Diego, California).

**Analyses**

Weight was measured at weeks 0, 24, and 48 and height at week 0. BMI was categorized as underweight (<18.5), normal (18.5–24.9), overweight (≥25–29.9), and obese (≥30) [31]. The overweight and obese categories were combined to increase the sample size for many of the analyses. The demographic covariates were summarized and compared between all categories of BMI. Skewed continuous variables were summarized using
medians and interquartile ranges (IQRs) and were compared using a Mann–Whitney test. Nonskewed continuous variables were summarized using means and standard deviations (SDs) and were compared using an unpaired t test. Categorical variables were summarized using frequencies and were compared using a χ² or Fisher exact test when applicable. Heat maps of the log10-transformed values of markers were designed to illustrate the overall trend of data variation according to baseline BMI status and week since ART initiation. Association between baseline BMI and BMI change from weeks 0 to 48 and longitudinal changes in immune activation and inflammatory markers, with adjustment for age, sex, country, study treatment arm [31], screening CD4+ T-cell count, plasma baseline log10 HIV RNA load, and prevalent tuberculosis, was assessed using random effects models. We further assessed the effect of an obese BMI at weeks 0, 24, or 48 on longitudinal changes in immune activation and inflammatory markers, using random effects models. All analyses were conducted in Stata, version 13.1, and JMP 12.0 (SAS Statistics, Cary, North Carolina).

RESULTS

Of the 246 participants, at baseline, 8% were underweight, 65% had a normal BMI, 20% were overweight, and 7% obese (Figure 1A). As shown in Table 1, baseline differences by country and race were seen: India had the highest proportion of underweight participants (31%), and the United States (58%), Brazil (41%), and South Africa (36%) had the highest proportions of overweight/obese participants (P < .001). None of the underweight participants were white (P = .004). Overweight/obese participants tended to be older (38 vs 35 years; P = .03) and underweight participants tended to have a lower hemoglobin level (10.5 vs 12.4 mg/dL; P = .001) and serum albumin level (3.6 vs 4 mg/mL; P = .01).

Baseline BMI and Levels of Inflammatory Markers at Weeks 0, 24, and 48

At week 0 of ART, levels of the inflammatory markers IL-6, INF-γ, CXCL-10, IL-18, and sCD14 were comparable between participants who were either underweight, had a normal BMI, or were overweight/obese, with the exception of baseline TNF-α level (Supplementary Table 1). Compared with participants with a normal BMI at baseline, baseline TNF-α levels were significantly higher among underweight participants and lower among overweight or obese participants (20.6 pg/mL vs 24.6 pg/mL vs 15.9 pg/mL; P = .005).

At weeks 24 and 48 after ART initiation, TNF-α level no longer differed by BMI categories, and levels of the inflammatory markers IL-6, INF-γ, CXCL-10, IL-18, and sCD14 remained comparable between BMI categories, with the exception of week 48 CRP level (Supplementary Table 1). At week 48 of

![Figure 1.](http://jid.oxfordjournals.org/)
ART, compared with participants with a normal BMI, the CRP levels were significantly higher among participants who were overweight/obese at baseline and significantly lower among those who were underweight at baseline (2.61 mg/L vs 5.70 mg/L vs 1.68 mg/L; P < .003).

**Baseline BMI and Change in Levels of Inflammatory Markers Over 48 Weeks**

Figures 1B–D illustrate the changes in all tested markers of inflammation and immune activation after ART initiation, by baseline BMI status. Among all participants, compared with baseline immune markers, TNF-α (P < .001), CXCL-10 (P < .001), and IL-18 (P < .001) levels decreased significantly over 48 weeks. INF-γ, CRP, IL-6, and sCD14 levels did not change significantly.

Among the normal BMI group, compared with baseline immune markers, CXCL-10 (P < .001) and IL-18 (P < .001) levels decreased significantly over 48 weeks; changes in TNF-α, IFN-γ, IL-6, sCD14, and CRP levels, however, did not meet statistical significance. Among individuals in the underweight group, compared with baseline levels, TNF-α (P < .001) and CXCL-10 (P < .001) levels decreased over 48 weeks, while levels of other markers did not change significantly. In the overweight/obese group, TNF-α (P < .001), CXCL-10 (P < .001), and IL-18 (P < .001) levels decreased; IL-6, CRP, sCD14, and IFN-γ levels did not change significantly.

We next assessed the association between baseline BMI and levels of immune markers, using a random effects model adjusted for age, sex, country, study treatment arm, screening CD4+ T-cell count, baseline plasma log_{10} HIV RNA load, and prevalent tuberculosis. In these adjusted analyses (Table 2), compared with individuals of normal weight, the decrease in IL-6, TNF-α, IFN-γ, CXCL-10, IL-18, and CRP levels over 48 weeks was smaller in participants who were overweight/obese at baseline; this only reached statistical significance for CRP (P = .01). Similarly, CRP (P = .02) and IL-18 (P = .02) levels declined significantly among those who were underweight at baseline (Table 2).

**BMI Change and Change in Levels of Inflammatory Markers Over 48 Weeks**

As shown in Figure 1A, between week 0 and week 48 of ART, the proportion of underweight participants decreased >2-fold from 8% to 3%, and the proportion of overweight/obese participants increased from 27% to 37%. A median 14% increase in BMI was observed among underweight participants, compared with a median 5% increase in both normal and overweight groups. We next examined the impact of this change in BMI...
from week 0 to week 48 on the change in inflammatory markers. When adjusted for sex, age, country, screening CD4⁺ T-cell count, baseline log₁₀ plasma HIV RNA load, and study treatment arm in multivariable analyses, each further 1-unit increase in BMI was associated with a decreased CRP level (β = −9.32 mg/L; P = .001). Similar trends were seen among several of the other inflammation/immune activation markers, but none reached statistical significance (P > .05 for all comparisons; Figure 2 and Supplementary Table 2).

**Association Between Obesity and Change in Levels of Inflammatory Markers**

Last, we investigated the impact of an obese BMI (vs a BMI <30) at baseline, week 24, or week 48 on baseline and change in inflammatory markers (Table 3). In multivariable analyses, having an obese BMI at any time point on the study was associated with a 0.19 log₁₀ pg/mL greater sCD14 level, compared with participants who were never obese (P = .02). No significant associations were detected between obesity and other inflammatory markers.

**DISCUSSION**

Within the context of a randomized trial of ART initiation, we have uncovered important differences in the inflammatory/immune activation response to ART based on both the BMI prior to ART initiation and the BMI changes experienced in the first 48 weeks of ART. Similar to data from high-income settings [20, 21], we observed a decrease in many markers of inflammation and immune activation among participants in low- and middle-income settings after ART initiation. However, the
declines in levels of some key markers were not as steep among either baseline underweight or overweight/obese participants. In addition, we observed that further weight gain among overweight and obese participants after ART initiation was associated with an increase in sCD14 level despite adequate virologic suppression, while weight gain among underweight participants was associated with a greater decrease in CRP level. Interestingly, a recent study from the Veterans Aging Cohort demonstrated a reduced mortality with weight gain among underweight patients but not overweight or obese patients in the first year after ART initiation [6]. Furthermore, the study found that each 1-unit gain in BMI among participants with normal BMI resulted in an increase of approximately 18%–20% in the risk of cardiovascular events [33]. These observed associations between clinical events and weight gain with ART initiation emphasize the clinical importance of both the pre-ART BMI and the changes in BMI with ART initiation and support a potential mechanistic link with heightened inflammation.

Another notable finding from our study is that over one third of our participants were overweight or obese after 48 weeks of ART. While the subset in this analysis may not be a truly representative sample from the participating countries, we found a relatively high prevalence of overweight or obese participants (39%) from Brazil and South Africa, while <20% of participants from India, Thailand, and Malawi were overweight or obese. With improved economic conditions, dynamic nutrition transitions to a

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**Table 3. Findings of Unadjusted and Adjusted Random Effects Models of the Effects of Obesity at Weeks 0, 24, or 48 on the Change in Levels of Inflammatory or Immune Activation Markers**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted Analysis</th>
<th>Adjusted Analysis</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (95% CI)</td>
<td>P Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 level in pg/mL</td>
<td>–12.8 (–52.8 to 27.2)</td>
<td>.53</td>
<td>0.2</td>
<td>.009</td>
</tr>
<tr>
<td>TNF-α level in pg/mL</td>
<td>–1.3 (–6.2 to 3.5)</td>
<td>.60</td>
<td></td>
<td>.59</td>
</tr>
<tr>
<td>IFN-γ level in pg/mL</td>
<td>–1.5 (–19.8 to 16.7)</td>
<td>.87</td>
<td></td>
<td>.59</td>
</tr>
<tr>
<td>CXCL-10 level in pg/mL</td>
<td>–57.8 (–593.0 to 477.4)</td>
<td>.83</td>
<td></td>
<td>.47</td>
</tr>
<tr>
<td>IL-18 level in pg/mL</td>
<td>131.0 (2.3–259.7)</td>
<td>.06</td>
<td>0.007</td>
<td>.02</td>
</tr>
<tr>
<td>CRP level in mg/L</td>
<td>–5.7 (–17.7 to 6.3)</td>
<td>.35</td>
<td></td>
<td>.18</td>
</tr>
<tr>
<td>Log10 sCD14 level in pg/mL</td>
<td>0.2 (0.05–1.4)</td>
<td>.009</td>
<td></td>
<td>.02</td>
</tr>
</tbody>
</table>

Obesity was defined as a body mass index (calculated as the weight in kilograms divided by the height in meters squared) of >30.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; CXCL-10, interferon γ-inducible protein 10; HIV, human immunodeficiency virus; IFN-γ, interferon γ; IL-6, interleukin 6; IL-18, interleukin 18; sCD14, soluble CD14; TNF-α, tumor necrosis factor α.

a Adjusted for age, sex, country, study treatment arm, screening CD4+ T-cell count, baseline log10 HIV RNA load, and prevalent tuberculosis.
diet higher in fat and refined carbohydrates, combined with less daily physical activity, obesity is becoming a worldwide public health problem, with the number of overweight individuals exceeding with the number who are underweight [34].

Why levels of sCD14, IL-18, and CRP were elevated in HIV-infected overweight/obese patients instead of IL-6 and TNF-α, as typically seen among HIV-uninfected obese patients, is an intriguing observation that deserves further investigation. It may be that adipocytes that appear to function differently in HIV-infected persons, ongoing microbial translocation, or ongoing coinfections could also account for differences in inflammatory profiles [15, 32, 35, 45, 47]. Notably, a similar association between obesity and both CRP level and sCD14 level has been observed among HIV-infected US adults [47].

sCD14 has been linked to cardiovascular disease risk and mortality among HIV-infected adults [35–38]; thus, the further increase in sCD14 in the overweight/obese groups is of particular relevance. Importantly, some studies have suggested that the level of sCD14 is relatively resistant to therapeutic interventions [28, 39, 40]. Following weight-reduction surgery among HIV-uninfected persons, a significant decrease in sCD14 level was only observed among those with marked weight loss of >30% [41]. Similarly, although sCD14 level was significantly lower among HIV-uninfected men as compared to HIV-infected men, little difference was seen between participants who were and those who were not receiving effective ART [21]. Both IL-18 and CRP have been associated with cardiovascular disease, obesity, and mortality [27, 34, 42–45]. As nonspecific markers of inflammation, elevated CRP and IL-18 levels among underweight participants at baseline may have been markers of coinfection [34, 46]; nearly all underweight participants were enrolled from sites in India or Africa, where the incidence of tuberculosis is among the highest in the world. Similarly, the significant decrease in CRP level among overweight participants who gained weight was suggestive of a return to health. Although weight gain among overweight participants did not exacerbate CRP or IL-18 levels, the lack of reduction despite effective ART may imply an ongoing, heightened cardiovascular disease risk. Importantly, previous studies have demonstrated that similar magnitude of change in sCD14, CRP, and IL-18 levels observed in our study was independently associated with increased mortality, clinical failure, and tuberculosis-associated immune reconstitution inflammatory syndrome, underscoring the clinical relevance of our findings [34, 46, 48].

Our study does have limitations. First, considering the diversity of the population, the sample size is relatively small and limits the number of analyses and adjustments we could perform. Similarly, the proportions of underweight and overweight/obese participants were small and limited the power to detect some associations. Dual-energy absorptiometry or computed tomography findings were not available to further delineate whether changes in BMI were due to changes in subcutaneous fat, visceral fat, or muscle. The distribution of weight gain among these different compartments would be expected to have differing effects on the inflammatory profile. Analyses were not corrected for multiple comparisons; thus, given the marginally significant P values for many comparisons, our findings should be considered exploratory. Although we adjusted for country, we were unable to account for between-country differences in nutrition that may have played a role in weight and inflammatory changes. Last, we did not have measures of low-level HIV replication, chronic hepatitis B virus and hepatitis C virus infection, physical activity, or dietary intake to provide further insight into mechanisms for the weight changes. Despite these limitations, the multiple inflammatory markers before and after randomized ART initiation in a population with diverse ethnic, racial, lifestyle habits, and resources, balanced by sex, adds to the clinical relevance of these data and the generalizability to multiple settings.

In summary, our findings highlight the potential prognostic value in monitoring body weight in the course of ART. Although not applicable to all settings, an inability to gain weight among underweight persons may be a poor prognostic sign and signal a need for nutritional intervention, a need for evaluation of disease progression, or development of an opportunistic infection. In contrast, among those who are already overweight or obese, further weight gain appears to increase inflammation (notably the sCD14 level). Further research is needed to understand the potential barriers to weight maintenance and to test models for effective early nutritional counseling and lifestyle modifications as adjunctive therapy to ART.

Supplementary Data


Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes
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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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