Persistent Inflammation on ART is Associated with Poor Nutritional Recovery in Zambia and Tanzania

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INTRODUCTION

- In sub-Saharan Africa, weight loss prior to HIV diagnosis and antiretroviral therapy (ART) remains a problem. A third of HIV-infected adults are malnourished (body mass index [BMI] <18.5 kg/m^2) at the time of ART initiation, which is a major risk factor for early ART mortality.[1, 2]
- Prior studies in Africa investigating the effects of nutritional supplementation in the early ART period have not shown a mortality benefit, and some supplements may produce a disproportionate increase in fat mass.[3, 4]
- A greater recovery of lean mass during the early ART period may improve survival and reduce the long-term risk of developing chronic diseases, but the factors influencing lean mass gains among malnourished adults are poorly understood.[5]
- Malnutrition and HIV infection are accompanied by high levels of systemic inflammation, due in part to impaired mucosal defenses and the presence of opportunistic infections.[6-9]
- We hypothesized that a failure to normalize systemic inflammation after starting ART impairs recovery of lean mass while biasing weight gain towards adipose tissue deposition.

METHODS

- This study was conducted as part of the Nutritional Support for African Adults Starting Antiretroviral Therapy (NUSTART, PACTR201106000300631) trial, a randomized, double blind, controlled trial of a lipid-based nutritional supplement (LNS) for malnourished patients starting ART in Mwanza, Tanzania and Lusaka, Zambia.[10]
- NUSTART participants were randomized to receive either the LNS alone (control arm) or fortified with additional vitamins and minerals (intervention arm) in a two-stage nutritional intervention. From recruitment until 2 weeks after starting ART, participants received a low calorie (30 g or ~170 kcal/d) LNS, and during weeks 2-6 of ART participants received a high calorie (250 g or ~1400 kcal/d) LNS.
- Trial inclusion criteria were 18 years of age or older, ART-naive, BMI < 18.5 kg/m^2, and a CD4 count < 350 cells/µl or WHO stage 3 or 4 disease.
- The primary analysis assessed the relationship between change in C-reactive protein (CRP) from baseline (pre-ART) to 6 weeks post-ART and change in anthropometry and body composition over the same period. Models were adjusted for age, sex, CD4+ count, hemoglobin, treatment arm, country, and whether the subject was receiving treatment for tuberculosis before starting ART. Continuous variables were modeled using restricted cubic splines with 4 knots.
- A second analysis assessed the effect of changes in CRP at 6 weeks with body composition at 12 weeks to determine whether CRP measurements during the LNS intervention predicted longer term nutritional status after the intervention ended.

RESULTS

Clinical and demographic characteristics of patients surviving more than 6 weeks on antiretroviral therapy (n=838)

Female, n (%)	462 (55%)	**Study site, n (%)**	
Age, years	36 (30, 42)	**Zambia**	494 (59%)
CD4+ count, cells/µl	135 (63, 225)	**Tanzania**	344 (41%)
BMI, kg/m^2	16.8 (15.9, 17.6)	**TB treatment prior to ART, n (%)**	227 (27%)
Hemoglobin, g/L	98 (83, 113)	**Time from recruitment to ART initiation, days**	21 (15, 29)
Intervention arm, n (%)	431 (51%)		

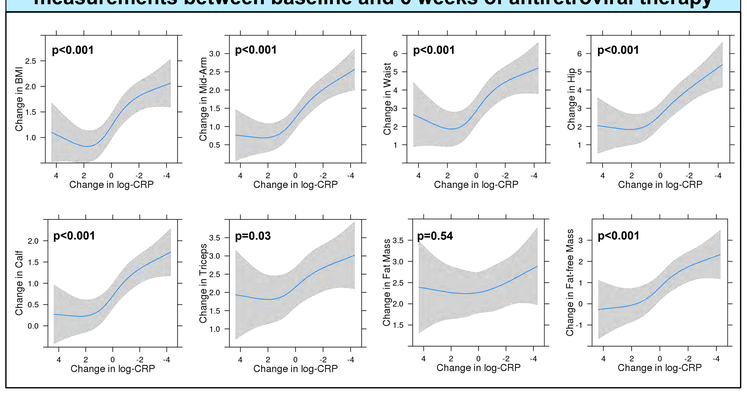
Values expressed as percentages or median with interquartile range. Abbreviations: ART, antiretroviral therapy; BMI, body mass index; TB, tuberculosis

Median serum C-reactive protein, anthropometric, and bioelectric impedance measurements at study time points

	N	Baseline	N	Week 6	N	Week 12
Serum CRP, mg/l	838	38.2 (8.9, 124)	838	34.8 (12.2, 94.5)†		NA
Body mass index, kg/m^2	838	16.8 (15.9, 17.6)	836	18.0 (16.8, 19.1)*	664	18.5 (17.4, 19.6)*
Mid-upper arm circ., cm	833	21.7 (20.4, 23.1)	832	23.1 (21.4, 24.4)*	653	23.8 (22.3, 25.1)*
Waist circumference, cm	833	66.8 (63.5, 69.5)	832	70.5 (66.7, 74.8)*	652	71.9 (68.1, 75.5)*
Hip circumference, cm	833	79.6 (77.0, 82.5)	830	82.6 (79.6, 86.0)*	651	84.3 (81.0, 87.5)*
Calf circumference, cm	833	28.6 (27.4, 30.1)	832	29.6 (28.2, 31.1)*	653	30.0 (28.6, 31.5)*
Triceps skinfold, mm	489	5.8 (4.6, 8.0)	488	7.0 (5.2, 9.8)*	396	7.8 (5.8, 10.4)*
Scapular skinfold, mm	489	6.6 (5.8, 7.8)	489	7.6 (6.2, 9.0)*	397	8.0 (6.8, 9.8)*
BIA fat mass, kg	721	5.0 (3.3, 7.1)	766	6.8 (4.6, 9.1)*	630	7.5 (5.2, 10.0)*
BIA fat-free mass, kg	721	38.3 (35.0, 44.1)	766	40.0 (36.3, 46.7)*	630	40.2 (36.9, 46.9)*

Values expressed as median with (interquartile range) Triceps and scapular skinfold are collected only from patients in Zambia.
Wilcoxon signed-rank test used for pairwise comparisons. Abbreviations: BIA, bioelectric impedance; BMI, body mass index; CRP, C-reactive protein
†p-value=0.91 for the change in CRP from 0 to 6 weeks
*p-value<0.01 for the change from 0 to 6 weeks and from 6 to 12 weeks for all anthropometric and BIA measurements

Relationship of the change in C-reactive protein and body composition measurements between baseline and 6 weeks of antiretroviral therapy



RESULTS CONTINUED

Associations of baseline and week 6 serum C-reactive protein with 12 week body composition measurements

	Baseline CRP*		Week 6 CRP†	
	Effect (95% CI)	p-value	Effect (95% CI)	p-value
Body mass index, kg/m^2	-0.13 (-0.40, 0.14)	0.09	-0.69 (-1.03, -0.35)	<0.001
Mid-upper arm circ., cm	-0.33 (-0.65, -0.01)	0.003	-0.91 (-1.31, -0.51)	<0.001
Waist circumference, cm	-0.03 (-0.77, 0.71)	0.02	-2.10 (-3.03, -1.17)	<0.001
Hip circumference, cm	-0.71 (-1.44, 0.02)	0.05	-1.64 (-2.56, -0.72)	<0.001
Calf circumference, cm	-0.05 (-0.36, 0.25)	0.26	-0.69 (-1.08, -0.30)	<0.001
Triceps skinfold, mm	-0.80 (-1.49, -0.12)	0.05	-0.68 (-1.53, 0.17)	0.01
Scapular skinfold, mm	-0.34 (-0.85, 0.18)	0.42	-0.64 (-1.28, 0.00)	0.10
BIA fat mass, kg	-0.55 (-1.05, -0.04)	0.34	-0.84 (-1.51, -0.16)	0.26
BIA fat-free mass, kg	0.07 (-0.54, 0.69)	0.76	-0.96 (-1.79, -0.14)	0.06

Models are adjusted for age, sex, treatment arm, country, time from enrollment to ART, and CD4+ count, hemoglobin, and anti-TB therapy at treatment initiation.
*Model is adjusted to a median baseline log-CRP of 3.5 mg/l. The effect size estimate represents the average difference in 12 week body composition for two individuals with 4.0 versus 3.0 log-CRP at baseline (i.e., a one log-CRP increase around the median).
†Model is adjusted to a median week 6 log-CRP of 3.6 mg/l. The effect size estimate represents the average difference in 12 week body composition for two individuals with 4.1 versus 3.1 log-CRP at week 6 (i.e., a one log-CRP increase around the median).

CONCLUSIONS

- Restoring individuals with advanced HIV disease and malnutrition to health requires both the recovery of effective immune protection and the rebuilding of adequate stores of metabolically active muscle and other lean tissues.[11]
- We found that a failure to reduce excessively high levels of CRP in the weeks following ART initiation is associated with failure to accrue lean mass as measured by both anthropometry and BIA.
- Our findings may explain why some patients gained no weight or primarily fat mass during early ART in prior nutritional supplementation trials, which has also been reported in patients with other inflammatory states such as tuberculosis and severe trauma. [12, 13]
- Our study could not assess the long-term implications of early changes in body composition on ART.
- Future trials should consider interventions addressing both nutritional recovery and inflammation.

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