Original Article

Effect of atorvastatin on frailty-related outcomes, body composition and biochemical markers in people living with HIV: A randomized, double-blind, placebo-controlled clinical trial

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Abstract

Frailty is increasingly recognized among people living with human immunodeficiency virus (PLHIV) despite antiretroviral therapy (ART). Statins, including atorvastatin, have pleiotropic metabolic and anti-inflammatory effects that may influence frailty-related pathways, although their impact on frailty in PLHIV remains unclear. The aim of this study was to evaluate the effect of atorvastatin on frailty status, its components, body composition, and related laboratory parameters in PLHIV receiving ART. This randomized, double-blind, placebo-controlled clinical trial included PLHIV with frailty or pre-frailty status at baseline. Participants were assigned to receive atorvastatin 40 mg once daily or placebo for 12 weeks. The primary outcome was frailty incidence, assessed using Cardiovascular Health Study (CHS)-based criteria and the Frailty Index (FI), including combined CHS–FI frailty status and CHS-based frailty components. Secondary outcomes included body composition, total cholesterol, and serum myostatin levels. Statistical analyses were performed using unadjusted and adjusted models. After 12 weeks, FI scores improved significantly within both the placebo (p<0.001) and atorvastatin groups (p=0.009). Serum myostatin levels also decreased significantly within both groups (both p<0.001). However, no significant between-group differences were observed for changes in CHS-based fit status (p=0.201), FI-based fit status (p=0.194), combined CHS–FI fit status (p=0.153), FI score (p=0.292), unintentional weight loss (p=0.225), handgrip strength (p=0.785), exhaustion (p=0.227), gait speed (p=0.333), physical activity limitation (p=0.479), total cholesterol (p=0.586), or serum myostatin levels (p=0.310) in the fully adjusted model. Atorvastatin was significantly associated with reductions in body weight (p=0.029) and BMI (p=0.030), whereas no significant effects were observed on body fat, water mass, muscle mass, or bone mass in the fully adjusted model. In conclusion, atorvastatin did not improve frailty status, frailty-related components, total cholesterol, or serum myostatin levels compared with placebo in PLHIV receiving ART. Although reductions in body weight and BMI were observed, these changes were not accompanied by improvement in frailty outcomes. Future studies with larger sample sizes, longer follow-up periods, and more detailed assessments of physical activity, diet, ART regimens, and inflammatory markers are needed to clarify the role of atorvastatin in frailty-related outcomes among PLHIV.

Keywords: HIV, frailty, statins, body composition, myostatin

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Introduction

People living with human immunodeficiency virus (PLHIV) are at increased risk of developing premature frailty [1,2], a syndrome driven by the convergence of chronic immune activation, metabolic dysregulation, and impaired tissue homeostasis [3,4]. This issue is particularly relevant in Asia, which accounts for a substantial proportion of the global human immunodeficiency virus (HIV) burden, with a rapidly growing population of aging PLHIV due to expanded access to antiretroviral therapy (ART) [5,6]. In Indonesia, one of the countries with the fastest-growing HIV cases in the region, improvements in ART coverage have led to increased survival, thereby shifting the clinical spectrum toward chronic comorbidities and age-related conditions [7,8]. Despite the success of ART in suppressing viral replication and extending life expectancy, residual inflammation persists, reflecting incomplete immune restoration and ongoing exposure to viral antigens and co-infections [9]. This sustained inflammatory milieu promotes a state of accelerated biological aging, characterized by dysregulated cytokine signaling, mitochondrial dysfunction, and altered cellular repair mechanisms, ultimately predisposing PLHIV to early functional decline [10,11].

Frailty represents a systems-level manifestation of impaired physiological resilience, arising from cumulative deficits across multiple organ systems [12]. The Cardiovascular Health Study (CHS) phenotype—encompassing weight loss, exhaustion, muscle weakness, slow gait speed, and reduced physical activity—captures the clinical expression of this vulnerability [13]. At the mechanistic level, skeletal muscle dysfunction is a central determinant of frailty, integrating signals from inflammatory, endocrine, and metabolic pathways [10]. Chronic exposure to pro-inflammatory cytokines, including interleukin (IL)-1β and IL-6, disrupts anabolic signaling and promotes proteolysis, thereby accelerating sarcopenia and functional impairment [14].

Emerging evidence implicates myostatin as a key molecular regulator linking inflammation to muscle atrophy. As a member of the transforming growth factor-β (TGF-β) superfamily, myostatin suppresses myogenesis through activation of suppressor of mother against decapentaplegic (SMAD) signaling pathways, inhibiting muscle protein synthesis and satellite cell proliferation [15]. Increased myostatin expression has been associated with reduced muscle mass and strength, suggesting its role as both a mediator and biomarker of sarcopenia [16]. However, the regulation of myostatin in the context of chronic HIV infection and its responsiveness to therapeutic modulation remain incompletely understood [15].

Persistent inflammation in PLHIV is driven, in part, by activation of innate immune sensors such as the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, which integrates danger-associated molecular patterns and metabolic stress signals to amplify cytokine production [10]. Activation of this pathway leads to caspase-1–dependent maturation of IL-1β and IL-18, reinforcing a feed-forward inflammatory loop that contributes to tissue injury and impaired regeneration [9]. These processes not only exacerbate immune dysfunction but also influence skeletal muscle metabolism, endothelial integrity, and systemic energy balance, thereby linking immune dysregulation to frailty pathogenesis [9,10].

Statins, particularly atorvastatin, have been proposed as potential modulators of interconnected inflammatory, metabolic, endothelial, and skeletal muscle-related pathways involved in HIV-associated frailty [17,18]. Beyond their lipid-lowering effects, statins exert pleiotropic actions, including inhibition of inflammatory signaling, attenuation of oxidative stress, and improvement of endothelial function [18]. A review of experimental and clinical studies suggests that statins can modulate inflammasome activation and downstream cytokine production, thereby potentially influencing muscle metabolism and functional outcomes [17]. In PLHIV, where chronic inflammation and cardiovascular risk coexist, such effects may provide therapeutic benefits that extend beyond lipid control. It is worth noting that atorvastatin is a more suitable option for PLHIV than simvastatin and lovastatin because the latter two are contraindicated with ritonavir- or cobicistat-boosted ART regimens, whereas atorvastatin can still be used with dose adjustment and careful monitoring [19]. Further, atorvastatin was also selected in the present study as a pragmatic option because it is generally more accessible in low- and middle-income countries (LMIC) settings than pitavastatin and rosuvastatin [20].

Regardless, clinical studies evaluating the impact of statins on frailty and its underlying biological determinants in PLHIV remain limited. Importantly, such integrative approaches—linking inflammation, muscle biology, and functional outcomes—are particularly scarce in Asian populations and are rarely conducted in Southeast Asia, including Indonesia, where demographic transitions and HIV-related aging are increasingly relevant [7]. This geographic gap limits the generalizability of existing evidence and highlights the need for region-specific data. Therefore, the aim of this study was to investigate the effect of atorvastatin on frailty status, frailty-related components, anthropometric and body composition outcomes, and related laboratory parameters (total cholesterol and serum myostatin) among PLHIV receiving ART using a randomized, double-blind, placebo-controlled clinical trial.

Methods

Study design and setting

A randomized, double-blind, placebo-controlled clinical trial with a parallel-group design was conducted from January to December 2024 at the outpatient clinic of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. The study recruited adults PLHIV who were receiving routine ART during the study period. Potential participants were screened for eligibility and frailty-related indicators using the CHS criteria and the 40-item Frailty Index (FI). Participants classified as pre-frail or frail by at least one of these instruments were enrolled and randomly assigned to receive either atorvastatin 40 mg once daily or placebo 40 mg once daily for 12 weeks. Frailty-related, anthropometric, body composition, and laboratory outcomes were assessed at baseline and repeated after the 12-week intervention period. The study protocol was prospectively registered in the Thai Clinical Trials Registry (TCTR20240418003).

Participants and criteria

Participants were PLHIV who had received ART for at least six months and were aged ≥18 to <60 years. Potential participants were recruited consecutively. During recruitment, patients underwent initial eligibility screening, followed by interview and clinical assessment, including evaluation of frailty indicators using the CHS criteria and the 40-item FI. Eligible participants were classified as pre-frail or frail based on at least one of the two frailty assessment instruments (the CHS criteria or the 40-item FI). Therefore, some participants could be classified as fit by one instrument at baseline while still meeting the eligibility criteria because they were classified as pre-frail, frail, or non-fit by the other instrument. Patients were excluded if they had acute illness, severe physical or mental limitations affecting assessment, history of statin allergy, pregnancy or breastfeeding, severe renal or hepatic dysfunction, severe heart failure, or severe pulmonary disease. Participants who met all eligibility criteria were subsequently enrolled in the study.

Randomization, allocation concealment, and blinding

Eligible participants were randomly assigned to the atorvastatin or placebo group in a 1:1 ratio. Randomization was performed using a random number table. Eligible participants were first assigned sequential study identification numbers according to the order of enrollment, and the random number table was then used to allocate them to either group. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared by designated pharmacists who were not involved in participant recruitment, clinical assessment, outcome assessment, or data analysis. The allocation sequence and treatment codes were kept exclusively by the pharmacists. Both atorvastatin and placebo were prepared in identical form, appearance, and packaging to maintain blinding. Participants, clinicians, and outcome assessors remained blinded to treatment allocation throughout the study period. Treatment codes were revealed only after completion of data collection and final analysis.

Intervention

Participants in the intervention group received atorvastatin 40 mg once daily for 12 weeks, while participants in the control group received placebo (amilum) 40 mg once daily for 12 weeks, as suggested in a previous trial [21]. Participants were instructed to take the study medication once daily throughout the intervention period. Adherence and safety were monitored regularly during

follow-up. In addition, participants were contacted by telephone every two weeks to assess medication adherence, possible adverse effects, and any clinical complaints. They were also asked to attend monthly follow-up visit for direct clinical evaluation and adherence assessment. At the end of the 12-week intervention period, participants returned for repeat outcome assessment.

Outcome measures

The primary outcomes were: (a) frailty status based on the CHS criteria and the 40-item FI, (b) FI score, and (c) frailty-related components of CHS criteria. Frailty indicators were assessed using two approaches: frailty status based on the CHS criteria and the 40-item FI [22]. Based on the CHS criteria, participants were classified as fit/robust if no frailty component was present, pre-frail if one or two components were present, and frail if three or more components were present. For the 40-item FI, participants were classified as fit/robust if the FI score was <0.08, pre-frail if the FI score was 0.08–0.24, and frail if the FI score was ≥0.24. In addition, a combined frailty status was constructed by integrating both CHS and FI classifications. In this combined categorization, participants were classified as frail or pre-frail/non-fit if at least one of the two instruments indicated frailty or pre-frailty, and as fit only when both CHS and FI indicated fit status. Improvement in binary frailty outcomes was defined as a transition from non-fit at baseline to fit after the intervention, or from "Yes" to "No" for binary CHS components. FI scores for each participant were also measured and treated as the primary outcome.

The frailty-related components based on the CHS criteria included unintentional weight loss, handgrip weakness, exhaustion, gait speed, and low physical activity. Unintentional weight loss was considered positive when participants reported unintentional loss of ≥5 kg in the previous year or ≥5% of body weight since the previous evaluation. Handgrip weakness was assessed using a handgrip dynamometer based on the mean of three measurements; exhaustion was assessed using two items from the Center for Epidemiologic Studies Depression Scale (CES-D); and gait speed was assessed using a 15-foot walking test. All three components were classified using the corresponding CHS cut-offs. Gait speed was assessed using a timed walking test over a fixed distance, with participants instructed to walk at their usual pace; the average of repeated measurements was recorded. Low physical activity was assessed based on self-reported limitation during vigorous activity.

Secondary outcomes included body composition and biochemical markers. Body composition outcomes comprised body weight, body mass index (BMI), body fat, water mass, muscle mass, and bone mass. Body fat, water mass, muscle mass, and bone mass were estimated using bioelectrical impedance analysis under standardized conditions, including resting state and minimal external interference. Biochemical markers included total cholesterol and serum myostatin levels, which were measured using an enzymatic colorimetric method and enzyme-linked immunosorbent assay (ELISA), respectively. All outcomes were assessed at baseline and after 12 weeks of intervention.

Total cholesterol and myostatin measurements

Venous blood samples (3–5 mL) were collected aseptically from the antecubital vein into EDTA-containing tubes. Samples were centrifuged at 1000 rpm for 10–15 minutes, and the plasma fraction was transferred into sterile labeled tubes and stored at −80°C until myostatin analysis. Total cholesterol was measured using an enzymatic colorimetric method with an automated clinical chemistry analyzer according to the manufacturer's instructions. Internal quality controls were included in each assay run to ensure reliability. Serum myostatin levels were measured using a Human MSTN Myostatin ELISA Kit (ELK Biotechnology Co., Ltd., Wuhan, China) according to the manufacturer's instructions. Standards and serum samples were added to antibody-coated wells, followed by incubation, washing, enzyme-linked detection antibody, and substrate solution. After the reaction was stopped, absorbance was measured at 450 nm with wavelength correction at 570 nm. Myostatin concentrations were calculated from a standard curve. All samples were analyzed in duplicate, and mean values were used for analysis.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Within-group pre–post comparisons

were performed separately for the placebo and atorvastatin arms. For continuous variables, normality of the change (Δ = post-intervention minus baseline) was assessed using the Shapiro–Wilk test. If normally distributed, paired t-tests were applied; otherwise, Wilcoxon signed-rank tests were used. Ordinal variables were analyzed using Wilcoxon signed-rank tests. For binary paired outcomes, such as CHS-based fit, FI-based fit, and combined fit status, McNemar tests were used to assess changes between post- and pre-treatment.

Linear regression models were used to estimate mean differences (MDs) of change between post and pre-intervention with 95% confidence intervals (CIs), comparing atorvastatin with placebo. For categorical outcomes, improvement was analyzed using logistic regression to estimate odds ratios (ORs) with 95% CIs. Both unadjusted and adjusted analyses were performed using pre-determined covariates. Adjusted models followed two levels: Model 1 and Model 2. Covariates in each model were selected based on clinical relevance. Model 1 included age, sex, and baseline BMI. Model 2 additionally included HIV-related factors: duration since HIV diagnosis, clinical manifestation, coinfection status, and opportunistic infection (defined as the presence of candidiasis, pulmonary tuberculosis, herpes zoster, or toxoplasmosis). All results were reported with *p*-values, and statistical significance was defined as a two-sided $p<0.05$. All analyses were performed using RStudio version 2025.09.1 (Posit software, PBC, Boston, USA).

Results

Participant recruitment summary

A total of 100 patients attending the outpatient clinic were screened. Of these, 20 were excluded, including 10 who did not meet the inclusion criteria and 10 who declined participation. The remaining 80 patients underwent interview and clinical assessment. Among them, 41 individuals were classified as fit and were not included in the intervention phase. A total of 39 participants were identified as pre-frail or frail, but only 33 participants agreed to participate and were included in the study. During follow-up, six participants were excluded due to discontinuation of the medication. A total of 27 participants completed the study and were included in the final analysis, comprising 14 in the atorvastatin group and 13 in the placebo group. The detailed recruitment process is illustrated in **Figure 1**.

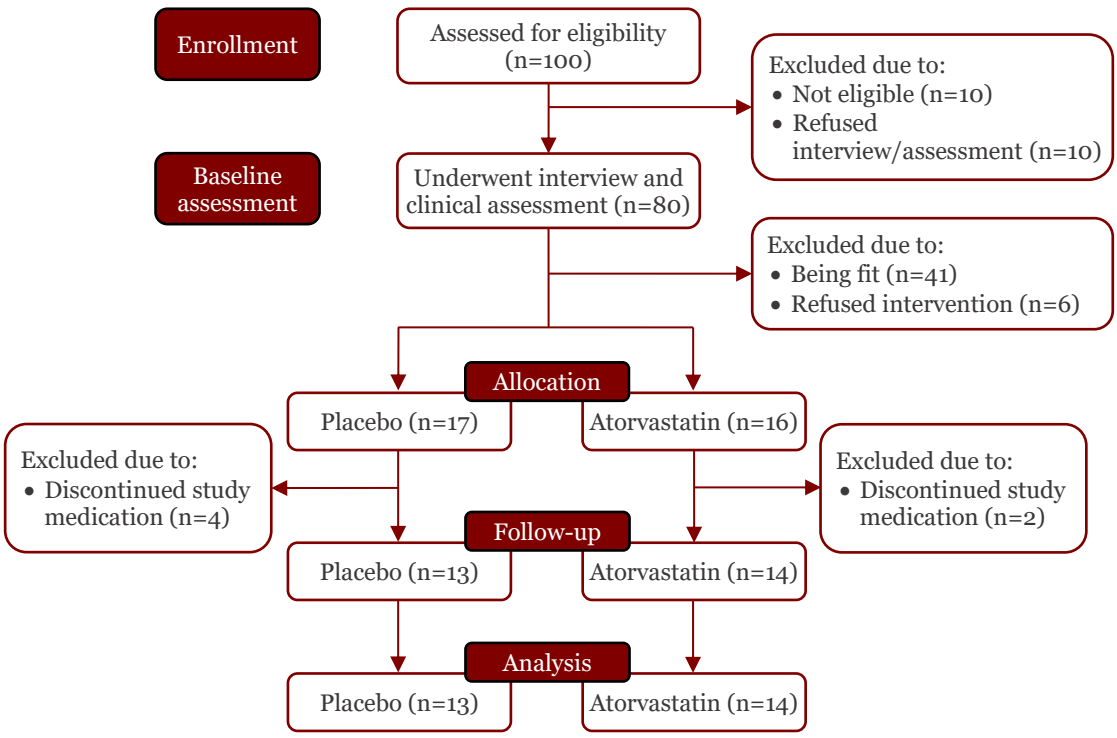

Figure 1. CONSORT diagram describing the flow of the study participant recruitment.

Baseline characteristics

A total of 27 participants were included in the final analysis and their baseline characteristics are presented in **Table 1**. The mean age of participants was 36±9 years, with comparable distributions between the atorvastatin group (37±10 years) and placebo group (35±8 years). The majority of participants were male (n=21, 77.8%), including 71.4% (n=10) in the atorvastatin group and 84.6% (n=11) in the placebo group. Most participants had non-tertiary education (70.4%). In terms of occupation, the formal sector was the most common (n=17, 63.0%), followed by those not working (n=7, 25.9%) and those in the informal sector (n=3, 11.1%).

The mean duration since HIV diagnosis was 4.99±3.48 years, where most participants were in advanced HIV stages, with 66.7% (n=18) classified as stage 3. Fifty-nine percent of participants were homosexual. A history of injection drug use was rare (n=1, 3.7%). Commercial sex contact was reported in 14.8% (n=4) of participants. Approximately one-quarter of participants (25.9%) reported having a partner with HIV. Opportunistic infections were common, with candidiasis present in 37.0% (n=10) of participants, followed by pulmonary tuberculosis (n=9, 33.3%). Co-infection with syphilis was identified in 25.9% (n=7) of participants and was more common in the placebo group (n=5, 38.5%) than in the atorvastatin group (n=2, 14.3%). Clinical manifestations were generally infrequent, including seborrheic dermatitis (n=2, 7.4%), panuveitis (n=2, 7.4%), genital ulcers (n=1, 3.7%), and diarrhea (n=1, 3.7%).

Table 1. Baseline characteristics of participants with non-fit status based on Cardiovascular Health Study (CHS) or Frailty Index (FI) scores

Variable	Total (n=27)	Atorvastatin group (n=14)	Placebo group (n=13)
	n (%)	n (%)	n (%)
Age (years), mean±SD	36±9	37±10	35±8
Sex			
Female	6 (22.2)	4 (28.6)	2 (15.4)
Male	21 (77.8)	10 (71.4)	11 (84.6)
Education			
Tertiary	8 (29.6)	4 (28.6)	4 (30.8)
Non-tertiary	19 (70.4)	10 (71.4)	9 (69.2)
Occupation			
Formal sector	17 (63.0)	8 (57.1)	9 (69.2)
Informal sector	3 (11.1)	2 (14.3)	1 (7.7)
Not working	7 (25.9)	4 (28.6)	3 (23.1)
Marital			
Married	9 (33.3)	4 (28.6)	5 (38.5)
Unmarried	18 (66.7)	10 (71.4)	8 (61.5)
HIV duration (years), mean±SD	4.99±3.48	5.54±3.13	4.44±3.85
HIV stage			
1	1 (3.7)	1 (7.1)	0 (0.0)
2	6 (22.2)	3 (21.4)	3 (23.1)
3	18 (66.7)	10 (71.4)	8 (61.5)
4	2 (7.4)	0 (0.0)	2 (15.4)
Sexual orientation			
Heterosexual	11 (41)	7 (50.0)	4 (30.8)
Homosexual	16 (59)	7 (50.0)	9 (69.2)
People who inject drugs			
Yes	1 (3.7)	0 (0.0)	1 (7.7)
No	26 (96.3)	14 (100.0)	12 (92)
Commercial sex contact			
Yes	4 (14.8)	3 (21.4)	1 (7.7)
No	23 (85.2)	11 (78.6)	12 (92.3)
Partner with HIV			
Yes	7 (25.9)	4 (28.6)	3 (23.1)
No	20 (74.1)	10 (71.4)	10 (76.9)
Opportunistic infection			
Candidiasis	10 (37.0)	6 (42.9)	4 (30.8)
Pulmonary tuberculosis	9 (33.3)	3 (21.4)	6 (46.1)
Herpes zoster	2 (7.4)	0 (0.0)	2 (15.4)
Toxoplasmosis	2 (7.4)	0 (0.0)	2 (15.4)
Co-infection			
Syphilis	7 (25.9)	2 (14.3)	5 (38.5)
Others	3 (11.1)	1 (7.1)	2 (15.4)
Manifestation			

Variable	Total (n=27)	Atorvastatin group (n=14)	Placebo group (n=13)
	n (%)	n (%)	n (%)
Seborrheic dermatitis	2 (7.4)	1 (7.1)	1 (7.7)
Diarrhea	1 (3.7)	0 (0.0)	1 (7.7)
Genital ulcer	1 (3.7)	1 (7.1)	0 (0.0)
Panuveitis	2 (7.4)	0 (0.0)	2 (15.4)
Others	2 (7.4)	2 (14.3)	0 (0.0)

Pre- and post-intervention outcome comparisons

The comparisons of clinical, biochemical, and frailty-related outcomes before and after the intervention are presented in **Table 2**. After the intervention, significant differences in the proportions of participants classified as CHS-based fit (p=0.041) and CHS-FI combination-based fit (p=0.041) were observed only in the placebo group. FI scores decreased significantly in both the placebo (p<0.001) and atorvastatin groups (p=0.009). CHS item on physical activity limitation improved significantly in placebo (p=0.006) and atorvastatin (p=0.011). Myostatin levels were observed to decrease significantly within both the placebo (p<0.001) and atorvastatin groups (p<0.001).

Table 2. Changes in frailty-related outcomes, body composition, and biochemical markers before and after intervention

Variable	Placebo		Atorvastatin	
	Mean±SD	p-value	Mean±SD	p-value
CHS-based fit, n (%)		0.041*		0.371
Before	2 (15.4)		4 (28.6)	
After	8 (61.5)		7 (50)	
FI-based fit, n (%)		0.221		0.134
Before	4 (31)		4 (29)	
After	8 (62)		8 (57)	
CHS-FI combination-based fit, n (%)		0.041*		0.134
Before	0 (0)		0 (0)	
After	6 (46.2)		4 (28.6)	
FI score		<0.001**		0.009**
Before	0.14±0.07		0.13±0.08	
After	0.06±0.04		0.07±0.04	
Unintentional weight loss, n (%)		1.000		NA
Before	5 (38.5)		1 (7.1)	
After	0 (0.0)		0 (0.0)	
Handgrip strength		0.144		0.329
Before	31.05±8.20		25.67±9.19	
After	32.74±7.80		26.88±8.88	
Exhaustion		1.000		0.197
Before	1.08±0.95		0.08±0.28	
After	0.79±0.89		0.21±0.58	
Gait speed (seconds)		0.081		0.188
Before	5.46±1.58		5.09±0.84	
After	4.69±0.68		4.76±0.72	
Physical activity limitation		0.006**		0.011*
Before	1.62±0.51		1.50±0.52	
After	1.00±0.00		0.93±0.27	
Body weight (kg)		0.064		0.322
Before	62.47±10.38		57.07±13.59	
After	64.85±11.33		56.44±12.98	
Body mass index (kg/m²)		0.081		0.333
Before	22.03±2.87		21.65±3.73	
After	22.85±3.26		21.41±3.52	
Body fat (%)		0.552		0.112
Before	18.27±5.77		18.55±8.12	
After	21.14±6.87		21.65±7.48	
Water mass (%)		0.166		0.112
Before	56.81±5.88		56.42±9.01	
After	54.40±5.02		53.26±7.29	
Muscle mass (%)		0.357		0.889
Before	38.71±5.46		35.99±6.39	
After	37.10±4.88		35.76±6.57	
Bone mass (%)		0.589		0.980
Before	2.70±0.39		2.48±0.44	

Variable	Placebo		Atorvastatin	
	Mean±SD	*p*-value	Mean±SD	*p*-value
After	2.74±0.49		2.40±0.51	
Total cholesterol (mg/dL)		0.763		0.805
Before	130.77±22.90		130.46±18.48	
After	132.85±21.43		128.54±20.29	
Myostatin (ng/mL)		<0.001**		<0.001**
Before	49.49±12.06		49.56±11.01	
After	28.06±8.85		24.97±8.06	

CHS: Cardiovascular Health Study; CI: confidence interval; FI: Frailty Index; SD: standard deviation
*Statistically significant at p=0.05
**Statistically significant at p=0.01

Effect of atorvastatin on frailty

The between-group effect of atorvastatin on frailty outcomes is presented in **Table 3**. Compared with placebo, atorvastatin was not significantly associated with improvement in CHS-based fit status (OR: 0.47; 95%CI: 0.09–2.25; p=0.348), FI-based fit status (OR: 0.64; 95%CI: 0.12–3.21; p=0.587), or combined CHS–FI fit status (OR: 0.47; 95%CI: 0.09–2.25; p=0.348). Similarly, no significant between-group difference was observed for the change in FI score (MD: 0.03; 95%CI: −0.02 to 0.08; p=0.182) (**Table 3**).

In the adjusted analyses, no significant between-group differences were observed for any frailty outcome in either model (**Table 3**). In Model 1, atorvastatin was not significantly associated with CHS-based fit status (p=0.395), FI-based fit status (p=0.645), combined CHS–FI fit status (p=0.408), or FI score (p=0.141) (**Table 3**). Similar findings were observed in Model 2, with no significant effects on CHS-based fit status (p=0.201), FI-based fit status (p=0.194), combined CHS–FI fit status (p=0.153), or FI score (p=0.292) (**Table 3**).

Regarding CHS components, no significant between-group differences were observed after atorvastatin treatment (**Table 3**). The changes in unintentional weight loss (p=0.077), handgrip strength (p=0.771), exhaustion (p=0.261), gait speed (p=0.389), and physical activity limitation (p=0.825) were not statistically significant. These findings remained consistent in the adjusted analyses, in which atorvastatin showed no significant effect on any CHS component (**Table 3**).

Effect of atorvastatin on body composition

In the unadjusted analysis, atorvastatin was associated with greater reductions in body weight (MD: −3.00 kg, 95%CI: −5.97 to −0.04; p=0.047) and BMI (MD: −1.06 kg/m², 95%CI: −2.12 to −0.01; p=0.048) compared with placebo (**Table 3**). No significant between-group differences were observed for body fat (p=0.933), water mass (p=0.764), muscle mass (p=0.566), or bone mass (p=0.162). After adjustment in Model 1, the effects on body weight (p=0.058) and BMI (p=0.059) were attenuated and were no longer statistically significant, while all body composition parameters remained non-significant (**Table 3**). In Model 2, atorvastatin was again significantly associated with reductions in body weight (p=0.029) and BMI (p=0.030). However, no significant effects were observed for body fat (p=0.790), water mass (p=0.955), muscle mass (p=0.711), or bone mass (p=0.200) (**Table 3**).

Effect of atorvastatin on total cholesterol and myostatin

The between-group effects of atorvastatin on total cholesterol and myostatin are presented in **Table 3**. In the unadjusted analysis, changes in total cholesterol did not differ significantly between the atorvastatin and placebo groups (MD: −4.00; 95%CI: −24.99 to 16.99; p=0.698). Similarly, no significant between-group difference was observed for myostatin levels (MD: −3.17; 95%CI: −13.40 to 7.07; p=0.530). These findings remained consistent after adjustment. In Model 1, atorvastatin was not significantly associated with changes in total cholesterol (MD: −7.72; 95%CI: −28.74 to 13.30; p=0.454) or myostatin levels (MD: −2.32; 95%CI: −12.88 to 8.24; p=0.653) (**Table 3**). Similar non-significant results were observed in Model 2 for total cholesterol (MD: −5.98; 95%CI: −28.75 to 16.80; p=0.586) and myostatin levels (MD: −5.37; 95%CI: −16.19 to 5.45; p=0.310) (**Table 3**).

Table 3. Effects of atorvastatin on frailty outcomes, frailty-related components, body composition, and laboratory markers in unadjusted and adjusted models

Variable	Δ, mean±SD		Unadjusted		Adjusted Model 1		Adjusted Model 2	
	Placebo	Atorvastatin	Effect (95%CI)[a]	*p*-value	Effect (95%CI)[a]	*p*-value	Effect (95%CI)[a]	*p*-value
Frailty								
CHS-based fit, n (%)	6 (54.5)	3 (30.0)	0.47 (0.09, 2.25)[b]	0.348	0.47 (0.08, 2.6)[b]	0.395	0.23 (0.02, 1.81)[b]	0.201
FI-based fit, n (%)	4 (44.4)	4 (40.0)	0.64 (0.12, 3.21)[b]	0.587	0.67 (0.11, 3.79)[b]	0.645	0.16 (0.01, 1.91)[b]	0.194
CHS-FI combination-based fit, n (%)	6 (46.2)	4 (28.6)	0.47 (0.09, 2.25)[b]	0.348	0.48 (0.08, 2.63)[b]	0.408	0.12 (0.00, 1.57)[b]	0.153
FI score	-0.08±0.05	-0.05±0.06	0.03 (-0.02, 0.08)	0.182	0.03 (-0.01, 0.08)	0.141	0.03 (-0.03, 0.08)	0.292
Unintentional weight loss, n (%)	5 (38.5)	1 (7.1)	0.12 (0.01, 0.95)[b]	0.077	0.07 (0.00, 0.77)[b]	0.068	0.11 (0.00, 2.86)[b]	0.225
Handgrip strength	1.69±3.90	1.21±4.48	-0.48 (-3.82, 2.86)	0.771	-0.35 (-3.94, 3.24)	0.842	-0.56 (-4.78, 3.67)	0.785
Exhaustion	-1.00±0.82	-0.57±1.09	0.43 (-0.34, 1.20)	0.261	0.37 (-0.41, 1.15)	0.338	0.53 (-0.36, 1.42)	0.227
Gait speed (seconds)	-0.77±1.59	-0.33±0.90	0.43 (-0.58, 1.44)	0.389	0.56 (-0.47, 1.6)	0.271	0.52 (-0.58, 1.62)	0.333
Physical activity limitation	-0.62±0.51	-0.57±0.51	0.04 (-0.36, 0.45)	0.825	0.1 (-0.3, 0.51)	0.596	0.16 (-0.31, 0.63)	0.479
Body composition								
Body weight (kg)	2.38±4.85	-0.63±2.28	-3 (-5.97, -0.04)	0.047*	-3.07 (-6.24, 0.11)	0.057	-3.67 (-6.90, -0.43)	0.029*
Body mass index (kg/m²)	0.83±1.69	-0.24±0.88	-1.06 (-2.12, -0.01)	0.048*	-1.09 (-2.22, 0.05)	0.059	-1.31 (-2.47, -0.14)	0.030*
Body fat (%)	2.87±7.24	3.10±6.81	0.23 (-5.34, 5.80)	0.933	0.32 (-5.63, 6.26)	0.913	-0.91 (-8.00, 6.19)	0.790
Water mass (%)	-2.41±5.88	-3.16±6.95	-0.76 (-5.88, 4.37)	0.764	-0.8 (-6.25, 4.65)	0.763	0.17 (-6.20, 6.55)	0.955
Muscle mass (%)	-1.61±6.05	-0.24±6.19	1.37 (-3.49, 6.23)	0.566	1.35 (-3.89, 6.59)	0.598	1.14 (-5.22, 7.49)	0.711
Bone mass (%)	0.04±0.25	-0.08±0.16	-0.12 (-0.28, 0.05)	0.162	-0.11 (-0.29, 0.06)	0.200	-0.12 (-0.31, 0.07)	0.200
Biochemical markers								
Total cholesterol (mg/dL)	2.08±24.25	-1.92±27.51	-4.00 (-24.99, 16.99)	0.698	-7.72 (-28.74, 13.3)	0.454	-5.98 (-28.75, 16.80)	0.586
Myostatin (ng/mL)	-21.43±14.51	-24.59±11.23	-3.17 (-13.4, 7.07)	0.530	-2.32 (-12.88, 8.24)	0.653	-5.37 (-16.19, 5.45)	0.310

CHS: Cardiovascular Health Study; CI: confidence interval; FI: Frailty Index; SD: standard deviation

[a] Effect estimates are reported as mean differences

[b] Effect estimates are odds ratios

* Statistically significant at p=0.05

Discussion

Findings from the present clinical trial indicated that atorvastatin did not have a statistically significant effect on frailty outcomes, including muscle strength, physical performance, and overall frailty status. Similarly, no statistically significant effects were observed in body composition parameters or circulating cholesterol and myostatin levels. Improvements in several outcomes were observed in both the placebo and intervention groups, suggesting that these changes were not attributable to atorvastatin. Instead, the observed improvements may reflect the influence of non-pharmacological factors or general study participation effects that were not specifically measured in this study.

To date, evidence from randomized clinical trials evaluating the effect of atorvastatin on frailty in PLHIV is limited. The closest available evidence comes from the trial of pitavastatin, such as the REPRIEVE study and its ancillary analyses, which demonstrated no significant effect on physical function or frailty-related outcomes [20]. Meanwhile, evidence from observational studies on the relationship between statin use and frailty in PLHIV remains limited and inconsistent [23,24]. Some cross-sectional studies have suggested that statin use may be associated with a lower prevalence or slower progression of frailty; however, these findings are subject to confounding by indication, as statin users are often older and have a higher burden of comorbidities [23,24]. Other studies have reported neutral or even adverse associations, further highlighting the heterogeneity of findings [25].

Furthermore, a statistically significant effect was observed in the present study for body weight and BMI in the unadjusted analysis and in the fully adjusted model. However, these changes were not associated with improvement in frailty status. Therefore, the reductions in body weight and BMI should not be interpreted as beneficial frailty-related effects. Given that participants had a baseline BMI within the normal range, the reduction in body weight and BMI may represent a potentially undesirable effect rather than a beneficial one. The observed reduction in BMI may reflect subtle shifts in energy balance or lipid metabolism, consistent with the known effects of statins on hepatic lipid handling and systemic metabolic regulation [26,27]. However, the absence of corresponding changes in muscle mass, strength, or other frailty-related domains suggests that these weight-related changes do not translate into meaningful or functional improvements in frailty [28].

The dissociation between body weight reduction and muscle-related outcomes may be explained by the complex interplay among inflammation, anabolic signaling, and muscle remodeling in PLHIV. Although statins exert anti-inflammatory effects and have been shown to modulate pathways such as NLRP3 inflammasome activation and downstream cytokine production, these effects may not be sufficient to reverse established sarcopenic processes within the timeframe of this study [29,30]. Skeletal muscle homeostasis is tightly regulated by multiple signaling axes, including myostatin–SMAD, mechanistic target of rapamycin (mTOR), and ubiquitin–proteasome pathways, which may require more targeted or prolonged interventions to achieve measurable changes [31,32]. The lack of significant change in circulating myostatin further supports the notion that atorvastatin does not directly modulate key regulators of muscle growth in this population.

Several limitations should be considered when interpreting findings from the present study. The final sample size was relatively small, which may have reduced the statistical power to detect small to moderate between-group effects, particularly for muscle-related and functional outcomes. The duration of intervention may have been insufficient to capture long-term effects of atorvastatin on muscle metabolism and frailty progression, particularly given the chronic nature of sarcopenia. Residual confounding related to dietary intake, physical activity, and ART regimens cannot be entirely excluded despite adjustment models. Finally, as this study was conducted in a specific population of PLHIV in Indonesia, the generalizability of the findings to other populations may be limited, particularly given potential ethnic and regional differences in body composition and metabolic responses.

Conclusion

Atorvastatin did not demonstrate a statistically significant effect on frailty outcomes in PLHIV receiving ART, including muscle strength, physical performance, and overall frailty status.

Similarly, no significant effects were observed on body composition parameters, including body fat, water mass, muscle mass, and bone mass, or on total cholesterol and circulating myostatin levels. Although reductions in body weight and BMI were observed, these changes were not accompanied by improvements in frailty outcomes. This suggests that the effect of atorvastatin in this population does not extend to the multidimensional pathways underlying frailty. Future studies should evaluate longer intervention durations and focus on PLHIV with elevated cardiovascular risk, in whom statin therapy is clinically indicated, to better understand its potential role in cardiometabolic risk–associated frailty.

Ethics approval

Ethical approval was obtained from the Ethics Committee of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (No. 263/ETIK-RSUDZA/2023). Written informed consent was obtained from all participants prior to enrollment.

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None.

Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

AI-based language model, ChatGPT, was employed for language refinement such as improving grammar, sentence structure, and readability of the manuscript. Authors confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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References

1. Kehler DS, Milic J, Guaraldi G, *et al*. Frailty in older people living with HIV: Current status and clinical management. BMC Geriatr 2022;22(1):919.
2. Tsakona D, Kapetanakis A, Kyrou D, *et al*. Mapping frailty in people living with HIV: A nationwide study in Greece. HIV Med 2023;24(2):170-179.
3. Mir R, Jha CK, Khullar N, *et al*. The role of inflammatory and cytokine biomarkers in the pathogenesis of frailty syndrome. Endocr Metab Immune Disord Drug Targets 2022;22(14):1357-1366.
4. Klotz SA, Egurrola C, Love M, *et al*. Phenotypic frailty in people living with HIV is not correlated with age or immunosenescence. Int J STD AIDS 2022;33(6):597-603.
5. Li J, Xie D-D, Cui H-L, *et al*. Trends in the burden and determinants of HIV in the Asia-Pacific region (1990–2019): An age-period-cohort analysis of the 2019 Global Burden of Disease Study. J Med Virol 2024;96(6):e29724.
6. Payagala S, Pozniak A. The global burden of HIV. Clin Dermatol 2024;42(2):119-127.
7. Jocelyn, Nasution FM, Nasution NA, *et al*. HIV/AIDS in Indonesia: Current treatment landscape, future therapeutic horizons, and herbal approaches. Front Public Health 2024;12:1298297.

8. Merati TP, Yunihastuti E, Wisaksana R, *et al*. A prospective observational cohort study of HIV infection in Indonesia: Baseline characteristics and one-year mortality. BMC Infect Dis 2025;25(1):87.
9. Guerville F, Vialemaringe M, Cognet C, *et al*. Mechanisms of systemic low-grade inflammation in HIV patients on long-term suppressive antiretroviral therapy: The inflammasome hypothesis. AIDS 2023;37(7):1035-1046.
10. Mu W, Patankar V, Kitchen S, *et al*. Examining chronic inflammation, immune metabolism, and T cell dysfunction in HIV infection. Viruses 2024;16(2):219.
11. Obare LM, Temu T, Mallal SA, *et al*. Inflammation in HIV and its impact on atherosclerotic cardiovascular disease. Circ Res 2024;134(11):1515-1545.
12. Inceer M, Mayo N. Health-related quality of life measures provide information on the contributors, components, and consequences of frailty in HIV: A systematic mapping review. Qual Life Res 2024;33(7):1735-1751.
13. Ginanjar E, Rizka A, Ayub AM, *et al*. Diagnostic performance of INA-FRAIL and study of osteoporotic fractures (SOF) index compared to cardiovascular health study (CHS) in diagnosing frailty syndrome in older adults with heart failure. Acta Med Indones 2025;57(2):200-200.
14. Tylutka A, Walas Ł, Zembron-Lacny A. Level of IL-6, TNF, and IL-1β and age-related diseases: A systematic review and meta-analysis. Front Immunol 2024;15:1330386.
15. Dewasi G, Nagda P, Bahl G, *et al*. Myostatin-driven muscle hypertrophy: A double-edged sword in muscle physiology. J Rare Dis 2025;4(1):29.
16. Ishibashi C, Nakanishi K, Nishida M, *et al*. Myostatin as a plausible biomarker for early stage of sarcopenic obesity. Sci Rep 2024;14(1):28629.
17. Khan S, Huda B, Bhurka F, *et al*. Molecular and immunomodulatory mechanisms of statins in inflammation and cancer therapeutics with emphasis on the NF-κB, NLRP3 inflammasome, and cytokine regulatory axes. Int J Mol Sci 2025;26(17):8429.
18. Woźniak E, Broncel M, Niedzielski M, *et al*. The effect of lipid-lowering therapies on the pro-inflammatory and anti-inflammatory properties of vascular endothelial cells. PLoS One 2023;18(2):e0280741.
19. Alagaratnam J, van Bremen K, Behrens GMN, *et al*. Statin use in HIV: European AIDS clinical society guidance for the primary prevention of cardiovascular disease. Lancet HIV 2025;12(5):e382-e392.
20. Erlandson KM, Umbleja T, Ribaudo HJ, *et al*. Pitavastatin is well-tolerated with no detrimental effects on physical function. Clin Infect Dis 2025;80(2):425-433.
21. Zoungas S, Curtis A, Spark S, *et al*. Statins for extension of disability-free survival and primary prevention of cardiovascular events among older people: Protocol for a randomised controlled trial in primary care (STAREE trial). BMJ Open 2023;13(4):e069915.
22. Seto E, Setiati S, Laksmi PW, *et al*. Diagnostic test of a scoring system for frailty syndrome in the elderly according to cardiovascular health study, study of osteoporotic fracture and comprehensive geriatric assessment based frailty index compared with frailty index 40 items. Acta Med Indones 2015;47(3).
23. Milic J, Carobbio A, Menozzi M, *et al*. OC4 statins reduce frailty in people with HIV. Sex Transm Infect 2025;101(Suppl 1):A3-A4.
24. Cárdenas JDG, Oliveira VHF, Borsari AL, *et al*. Statin protects men but not women with HIV against loss of muscle mass, strength, and physical function: A pilot study. Sci Rep 2023;13(1):4693.
25. Mosepele M, Molefe-Baikai OJ, Grinspoon SK, *et al*. Benefits and risks of statin therapy in the HIV-infected population. Curr Infect Dis Rep 2018;20(8):20.
26. Badimon L, Mendieta G, Vilahur G. Statins revisited: Therapeutic applications beyond lipid lowering? Eur Heart J 2023;44(25):2332-2334.
27. Schonewille M, de Boer JF, Mele L, *et al*. Statins increase hepatic cholesterol synthesis and stimulate fecal cholesterol elimination in mice. J Lipid Res 2016;57(8):1455-1464.
28. Bloomfield GS, Watanabe M, McCallum S, *et al*. Heart failure risk and events in people with HIV: The randomized trial to prevent vascular events in HIV (REPRIEVE). Circ Heart Fail 2026;19(4):e013382.
29. Kim D, Morikawa S, Miyawaki M, *et al*. Sarcopenia prevention in older adults: Effectiveness and limitations of non-pharmacological interventions. Osteoporosis Sarcopenia 2025;11(2):65-72.
30. Saleh DO, Abo El Nasr NM, Elbaset MA, *et al*. Role of rosuvastatin and pitavastatin in alleviating diabetic cardiomyopathy in rats: Targeting of RISK, NF-κB/NLRP3 inflammasome and TLR4/NF-κB signaling cascades. PLoS One 2025;20(7):e0325767.
31. Pang X, Zhang P, Chen X, *et al*. Ubiquitin-proteasome pathway in skeletal muscle atrophy. Front Physiol 2023;14:1289537.
32. Ji Y, Li M, Chang M, *et al*. Inflammation: Roles in skeletal muscle atrophy. Antioxidants 2022;11(9):1686.