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Sarcopenia in persons living with HIV under antiretroviral therapy: Literature review

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Abstract

The epidemiological profile of people living with HIV (PLWH) has expressively changed since the introduction of antiretroviral therapy (ART), from a high mortality rate to a profile similar to those living with chronic diseases. Despite the advances and effectiveness of ART, there are still various challenges to overcome, and we highlight the increased risk of sarcopenia in PLWH. This review study aims to (i) explore the pathophysiological background of sarcopenia in PLWH under the different existing ART and (ii) develop a mini-systematic review searching epidemiological studies investigating sarcopenia prevalence in PLWH. As our main findings: we established the risk of sarcopenia development, under a sequential path involving HIV, ART, immune activation, low-grade systemic inflammation, metabolic disorders, and changes in protein synthesis and breakdown in skeletal muscle tissue; some ART drugs, mainly reverse transcriptase inhibitors and protease inhibitors, contribute to critical metabolic changes, lowering the autophagy, increasing mitochondrial dysfunction and insulin resistance, which favor the development of inflammation and muscle protein breakdown. There is still insufficient data to discuss the effects of the new generation drugs, namely integrase inhibitors and fusion inhibitors, on skeletal muscle. More studies are needed to better clarify these relationships.

Keywords

HIV. Skeletal muscle. Sarcopenia. Skeletal muscle. Low-grade systemic inflammation. Antiretroviral therapy.

Introduction

Throughout the last decades, the development and improvements of HIV antiretroviral therapies (ART) enormously changed the epidemiological course of the persons living with HIV (PLWH) by lowering the viral load and consequently reducing AIDS-related mortality[1]. However, despite the important benefits of ARTs, many side effects of these drugs have been observed, contributing to the development of non-AIDS-related chronic diseases. Several physiological responses to ART can explain these effects, particularly a chronic immune activation with a consequent low-grade systemic inflammation (LGSI)[2]. One of the relevant outcomes of this is the increased risk of developing muscle disorders such as sarcopenia.

Sarcopenia is a progressive and generalized skeletal muscle disorder, now recognized as a disease (ICD-10-CM - M62.84)[3]. Its definition changed throughout the years, from emphasizing the reduced muscle mass to poor muscle strength and low muscle mass. This disease is generally associated with aging (primary sarcopenia), but its development can begin earlier in

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life due to many contributing causes beyond aging (secondary sarcopenia); it increases the likelihood of adverse outcomes such as physical frailty, disabilities, and mortality[3].

Many authors have identified a high prevalence of sarcopenia, or low muscle mass, in PLWH[4], reinforcing the importance of understanding this issue. Despite this, studies discussing the different ART-related effects on muscle are still scarce. This manuscript aims to explore the pathophysiological background of sarcopenia in PLWH and the association with the current ARTs. To achieve this aim, we divided the study into two parts: (i) a narrative review of physiological mechanisms to understand the relationship between HIV, ART, and sarcopenia (ii) a mini-systematic review searching epidemiological studies investigating sarcopenia in PLWH. Considering that the definition of sarcopenia changed very recently, we will include in this review, besides studies with the new definition, studies with the oldest ones, most of them focusing only on muscle mass.

Part 1. Physiological relationship between HIV, ART, and skeletal muscle disorders

Skeletal muscle is the body's most abundant tissue and is involved in several functions. Skeletal muscle is a primary target for glucose and lipid uptake, plays a vital role in immunoregulation, and is determinant for physical performance; these factors are associated with functionality, cardiorespiratory capacity, quality of life, and longevity[5]. It has been demonstrated that greater muscle mass at midlife is associated with successful aging in men[6].

The body muscle mass decreases approximately 1-2% per year after 50 years old in HIV-uninfected people. The nadir of muscle mass occurs at about the age of 80 years old[5]. Notably, the loss of muscle strength, so-called dynapenia, occurs between 2 and 5 times faster than muscle mass loss[5]. Both muscle mass and strength losses have been associated with several metabolic disorders and raise the odds of diseases, incapacities, and mortality[5]. Several factors are associated with muscle changes, such as physical exercise (type, intensity, and frequency), dietary and sleep patterns, illnesses, licit and illicit drugs, and neuronal disorders[5]. Imbalances in skeletal muscle turnover, namely, blunted muscle protein synthesis and increased protein breakdown, are reported in aging and pathological conditions[7].

Moreover, the motor unit (a primary functional component of the neuromuscular system for generating strength and movement) and satellite cells decrease with aging. The myosin heavy chain isoform IIa, shortening of sarcomere length, and high fat infiltration in muscle tissue appear to be contributors or parallel factors to muscle atrophy[5]. Interestingly, muscle-related changes especially occur in type II fibers, mainly responsible for muscle strength[5].

Aging, systemic inflammation, and skeletal muscle: similarities between normal aging and HIV infection

Aging is characterized by an LGSI status, a process named *inflammaging*[8]; it is part of the immunosenescence and includes organs with immunometabolic activity, such as adipose tissue and gut[8]. In turn, PLWH presents a persistent residual HIV infection, together with the ART effects, responsible for a persistent immune activation and, consequently, an LGSI. Some authors named this process "InflammAIDS[8]," and a hypothesis of anticipated aging in PLWH has been commonly accepted. Below, we will describe some features of inflammaging and the correspondent aspects of HIV infection.

Aged (senescent) cells

An essential characteristic of aging, both chronological and pathological, is cell senescence. Among various features, senescent cells reduce the capacity of dealing with antigenic molecules, metabolites, apoptotic cells, and other so-called danger-associated molecular patterns (DAMPs). In response to these patterns, the cells activate the inflammasomes[8]. Inflammasomes are multiprotein complexes capable of activating intracellular pathways and consequently nuclear factors (such as the nuclear factor kappa-beta [NF-κB]), increasing the expression and secretion of inflammatory cytokines (for instance, interleukin [IL]-6, IL-8, and Il-1α and tumor necrosis factor [TNF-α])[8]. Notably, the increase in TNF-α gene expression interacts negatively with proteins related to muscle protein synthesis (protein kinase B)[8]. In addition, NF-κB activates a proteasome-dependent pathway for protein degradation (through binding to a molecule represented by MuRF1)[9]. This process is accompanied by reactive oxygen species production that increases the muscle protein breakdown. Furthermore, the inflammasome activation reduces the expression of genes involved in autophagy, constituting, therefore, a vicious cycle which, among other consequences, fuels oxidative stress, and muscle protein breakdown[8].

Comparatively, PLWH presents a reduction in autophagy and impairs cellular removal of debris (DAMPs). Furthermore, the persistence of HIV in some cells can constitute a so-called pathogen-associated molecular pattern (PAMP); thus, DAMPs and PAMPs in PLWH's cells lead to a senescent phenotype[10].

Increased body fat

Another concept included in inflammaging is an increase and redistribution of body fat. The high-fat content of adipose tissue leads to the recruitment of M1-type macrophages[11], changing the adipocytokines secretion; there is a decrease of the anti-inflammatory molecules (i.e., adiponectin and IL-10) and an increase in the pro-inflammatory ones (i.e., IL-1β, IL-6, TNF-α, C-reactive protein [CRP], and among others)[11].

In PLWH, some ART drugs, such as protease inhibitors (PIs) and reverse transcriptase inhibitors, and some of the newest generation drugs (integrase inhibitors [IIs]) increase the body fat content[12]. The increased body fat leads to the LGSI, enhancing the risk of developing insulin resistance and diabetes, increasing the risk of reducing muscle strength and quality[13]. Therefore, fat accumulation in PLWH creates an inflammatory environment similar to the aging process[12].

Leaky gut

The aging process changes the bacterial profile of gut microbiota and enhances the immune activation, changing tolerance of gut-associated lymphoid tissue (GALT). These changes weaken the gut epithelium's barrier function, which increases intestinal permeability, allowing the passage of bacterial fragments to the bloodstream[14]. The most studied bacterial fragment from the intestine is lipopolysaccharide (LPS), from Gram-negative bacteria's outer membrane[14]. Similarly, in PLWH, the primary HIV infection and replication occur in GALT, leading the intestinal epithelial cells to be compromised, increasing gut permeability with consequent LPS translocation. Although the ART drugs improve gut immune activation, they cannot return to basal (pre-infection) levels[14].

Once in the circulation, LPS binds to specific pattern-recognizing receptors in different body tissues. Skeletal muscle has both receptors for LPS and cytokines (i.e., toll-like receptor-4 and TNF-a receptor, respectively); the signaling pathway of these receptors activates protein kinases, which can phosphorylate the insulin receptor substrate-1 (IRS-1), decreasing insulin signal transduction, impairing, among many metabolic pathways, the protein synthesis[15]. Furthermore, activation of both receptors can trigger the inflammatory cascade mediated by the NF-κB, leading to the above-described responses. Furthermore, metabolic endotoxemia provoked by LPS is associated with high body fat, glucose intolerance, raised pro-inflammatory mediators, and macrophages' infiltration in adipose tissue, constituting, therefore, a vicious cycle[14].

We can put together, at this point, immune activation, gut permeability, increased adiposity, insulin resistance, reduced protein synthesis, and increased protein degradation. In skeletal muscle cells, these interrelated processes are explanations for the reduced quantity and quality of muscle mass, or sarcopenia. Recently, Natsag et al. (2017)[16] verified, in a multicenter cross-sectional study, that PLWH presented low muscle density, accompanied by a high fat infiltration; these changes were related to insulin resistance and low activity of enzymes involved in lipid metabolism[13]. Therefore, ectopic fat accumulation in muscle can be a crucial factor for muscle-related disorders, mainly due to the increased inflammatory process[13].

Immune activation, inflammatory environment, and skeletal muscle in PLWH

Erlandson et al. (2013)[17] showed in PLWH that low $CD4^+/CD8^+$ T-cells ratio, the high CD38/HLA-DR expression on $CD8^+$ T-cells, and the high IL-6 levels were associated with increased odds of low functional status (odds ratio [OR], ≥ 1.1 for all analyses). The same authors found that reduced levels of IGF-1 (OR 5.0; 95% confidence interval [CI]: 1.4-20.0) and IGF-1 binding protein-3 (OR 3.3; 95% CI: 1.7-9.9) were associated with low functional capacity, and both were associated with increased inflammatory status[18]. In contrast, other authors verified that although inflammatory mediators (i.e., soluble CD14, CRP, and IL-6) and immunosenescent phenotype (by $CD57^+$) were high in PLWH than HIV-uninfected subjects, none of these biomarkers were associated with physical performance in 21 years old (54-69 years) PLWH under ART[19].

Langkilde et al. (2015)[20] verified that IL-6 and soluble urokinase plasminogen activator receptor were significantly associated with low muscle mass index. Recently, de Almeida et al.[21] pointed out that high CRP levels were associated with sarcopenia in PLWH, reinforcing the relationship between inflammation and sarcopenia.

Inflammaging and hormones related to skeletal muscle metabolism

High blood levels of inflammatory molecules promote the reduction of the action of anabolic hormones such as IGF-1 and reduction in myoblast determination protein-1 (MyoD-1), both molecules necessary for proliferation and differentiation of satellite cells[22]. Therefore, we can infer that both aged persons without HIV and PLWH present hormonal disturbances related to compromised muscle maintenance.

The statements above clarify that muscle disorders, including sarcopenia, are shared by aging and HIV infection under ART. Discussions about muscle mass disorders in PLWH began before ART development when AIDS-associated cachexia was frequently identified. HIV infection was recognized as a wasting disease, which can directly affect the functionality, leading to a risk of physical dependency and anticipation of death[23].

Participation of the ART on some deleterious effects in skeletal muscle

At present, there are six classes of drugs used in ART, developed according to the stages of viral replication. Briefly, the nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) compete with natural deoxynucleotides for incorporation into a growing viral DNA chain, preventing viral DNA formation[24]. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit the reverse transcriptase after binding and form a hydrophobic pocket proximal to the active site, leading to a change in the substrate-binding site structure and reducing the polymerase activity[24]. Integrase inhitors (IIs) act negatively on the enzyme integrase, whose function is to catalyze the viral DNA and transfer the strand from the 3' end of the final processing; they bind to the specific complex between integrase and viral DNA, blocking the viral replication process[24]. Protease inhibitors (PIs) inhibit the HIV-1 protease enzyme responsible for breaking down the gag and viral gag-pol polyprotein precursors during the maturation of the virus. The entry inhibitors are subdivided into fusion inhibitors (FIs), which binds to gp41 and disrupts membrane attachment, and chemokine Receptor-5 (CCR-5) antagonists, which block the CCR receptor on the T-Cell to prevent viral attachment[24]. It is recommended to combine different drug classes in the ART, and the more common combinations include two NRTIs and another drug that can be NNRTIs, PIs, or IIs. Furthermore, according to the individual's responsiveness to ART, it is possible to use one entry inhibitor[24].

The different ART categories are pointed to reduce the amount and function of proteins and enzymes that regulate muscle tissue's metabolism, consequently decreasing muscle functionality. These risks assume particulars importance in PLWH facing concomitant disorders related to the aging process[25]. The effects of ARTs on mitochondrial functioning are associated with muscle metabolism. For instance, The PIs, especially the early generation (i.e., indinavir and full-dose ritonavir), can inhibit essential proteins of energy metabolism and promote several negative metabolic changes, culminating in ART-associated chronic diseases. Adverse changes in the gene expression of several proteins responsible for mitochondrial biogenesis and the lower mitochondria efficiency led to increased intramuscular metabolites such as reactive oxygen species, increasing the senescent feature of the cells. Besides, excessive accumulation of intramuscular triacylglycerol can compromise oxidative efficiency and increase the inflammatory status and insulin resistance[16].

Moreover, reduced autophagy mediated by ARTs and the consequent accumulation of DAMPs triggers systemic inflammation. Likewise, ART-related effects on gut microbiota could increase leaky gut and inflammatory status. Together, these alterations are suggested to mitigate, by several pathways, muscle protein synthesis and, in parallel, increase the activity of muscle protein breakdown. Table 1 presents a summary of studies evaluating the relationship between ART's and disorders potentially associated with skeletal muscle diseases, mainly sarcopenia. Moreover, in figure 1, we summarize the mechanisms explaining sarcopenia risk in PLWH.

Part 2. Studies investigating the prevalence of sarcopenia in PLWH

In the last decade, HIV-associated sarcopenia has been described more frequently by researchers in the field. The understanding of sarcopenia-related parameters in PLWH under ART has increased in the last decade, showing that insufficient muscle mass and strength contribute to other conditions. However, the disagreements between the appropriate methods to evaluate and diagnose this disease turn it challenging to compare the different studies, both in HIV-infected and non-infected persons. This issue is highlighted by

Table 1. Studies investigating the ART's effect on indicators of sarcopenia

ART Class	Drug	Mechanism of action	Outcome	Sample	Reference
NRTI	AZT	Changes in mitochondria quality and mitochondria complex I and III activity	Negatively affect mitochondria electron transport chain	*In vitro/ in vivo*	26
		mtDNA depletion and autophagy decreases	Accumulation of dysfunctional mitochondria and increase in ROS production	*In vitro*	27
		Decreased muscle mtDNA	Reduction of oxidative efficiency	*In vivo*	28
		Blunted cytochrome oxidase activity and mtDNA	Decrease 40% of mitochondrial volume fraction	*In vivo*	29
		AZT induces mitochondrial defects primarily in muscles with the highest oxidative capacities	Decrease muscle performance during a contractile activity at 2 and 5 Hz	*In vivo*	30
		AZT affect muscle mtDNA	AZT decreases muscle mtDNA by DNA polymerase gamma in vitro	Humans	31
PI	IDV	PI negatively affect proteins involved in MPS and MBP	Indinavir decreased MPS (42%) compared with control and reduced eIF4F complex	*In vitro*	32
		Effect of PI on glucose uptake	Indinavir decreases GLUT-4 on the cell surface	*In vivo*	33
		Insulin resistance and low MPS	High glucose levels, insulinemia and HOMA, low testosterone levels, and basal MPS	*In vivo*	34
		Indinavir induces insulin resistance in HIV-noninfected subjects	Indinavir increases fasting glucose, insulin, insulin:glucose ratio and HOMA index	Humans	35
	SQV, r, IDV, nelfinavir or combinations	--	Gain in fat mass without changes in LBM	Humans	36
	LPV/r or ATV/r	Lopinavir induces insulin resistance	ATV/r reduced visceral fat, improved muscle glucose uptake and lipid profile	Humans	37
	r, ATV, LPV e DRV	Lower expression of CD-36 and CPT-1	Less oxidation of fatty acids and increased fatty acids in the blood and accumulation in the liver and muscle	Humans	38
	RAL + ATV/r or DRV/r	Atazanavir improves insulin sensitivity	DRV/r reduced muscle density	Humans	39

(Continues)

Table 1. Studies investigating the ART's effect on indicators of sarcopenia

PI + NRTI	IDV; SQV; r, and 3TC	PI and NRTI, glycemic and lipid profile, and body composition	PI, not 3TC, worsens glycemic and lipid profile regardless of body composition changes	Humans	40
PI only; PI + NRTI + PI; PI +NNRTI	Two protease inhibitors or 2 NRTI + 1 protease inhibitor, or 2 NRTIs + 1 nonnucleoside NNRTI	--	HAART was associated with LBM increases in men, without differences in women	Humans	41
PI vs. NNRT vs. PI plus NRTI	Nelfinavir; IDV; EFZ; NVP; delavirdine; AZT + 3TC; d4T + 3TC; ABC + 3TC; ABC + d4T	Verify the effect of ART on body composition after 4-month and 5-year follow-up	PI, NNRTI, or PI plus NNRTI increases FFM, without differences between groupsw	Humans	42
PI or NNRTI plus NRTI or only NNRTI	ATV/r or EFZ + TDF /FTC or ABC/3TC	Speculate increased chronic inflammatory process	Increase in LBM in the first 96 weeks ART use with consequent reduction after 96 weeks	Humans	43
NRTI, INTI, and PI	TDF/FTC plus ATV/r or DRV/r and RAL	Limited data on the effect of integrase inhibitors and NRTI has been linked with lipoatrophy, while PI has been linked with hyperlipotrophy	ATZ/r, RAL, and DRV/r increases LBM, without differences between groups	Humans	44

LATV: atazanavir; AZT: zidovudine; r: ritonavir; DRV: darunavir; TDF: tenofovir; 3TC: lamivudine; ABC: abacavir; FTC: emtricitabine; EFZ: efavirenz; IDV: indinavir; LPV: lopinavir; SQV: saquinavir; NVP: nevirapine; ROS: reactive oxygen species; mtDNA: mitochondrial DNA; eIF4F: eukaryotic initiation factor 4F; GLUT-4: glucose transporter type 4; HOMA: homeostasis model assessment; LBM: lean body mass; HAART: highly active antiretroviral therapy; FFM: fat-free mass.

the experts responsible for the last updated consensus about sarcopenia, the European Working Group on Sarcopenia in Older People (EWGSOP2)[3].

Previous studies verified that PLWH under ART presents less muscle strength[45], although others have seen no difference compared with HIV-uninfected subjects[46]. The loss of muscle strength has shown an association with several muscle-related disorders, and EWGSOP2 considers as the primary parameter to be assessed for sarcopenia diagnosis[3]. Functionality analysis is crucial since systematic reviews and meta-analyses found that in PLWH, muscle strength and aerobic capacity are lower than in non-infected controls[47].

Due to biochemical changes in muscle tissues, poor muscle strength and reduced aerobic capacity are commonly found simultaneously. In this context, Ortmeyer et al. (2016)[13] described that the activity of some enzymes responsible for energy metabolism, namely B-HAD and Citrate Synthase, and peak oxygen consumption (VO_{2peak}) was lower in PLWH compared to healthy counterparts. Moreover, lower muscle plasticity commonly observed in older adults seems to occur in PLWH, as demonstrated by Jankowski et al. (2020)[48]. The authors evaluated aged PLWH after 24 weeks of physical exercise (n = 18; ART > 2 years) and compared with HIV-uninfected subjects (n = 21); they observed that adaptations promoted by training are much more relevant in HIV-uninfected subjects[48]. Considering the lower responsiveness to exogenous stimuli promoted to maintain muscle functionality even in ART subjects, understanding these changes is essential.

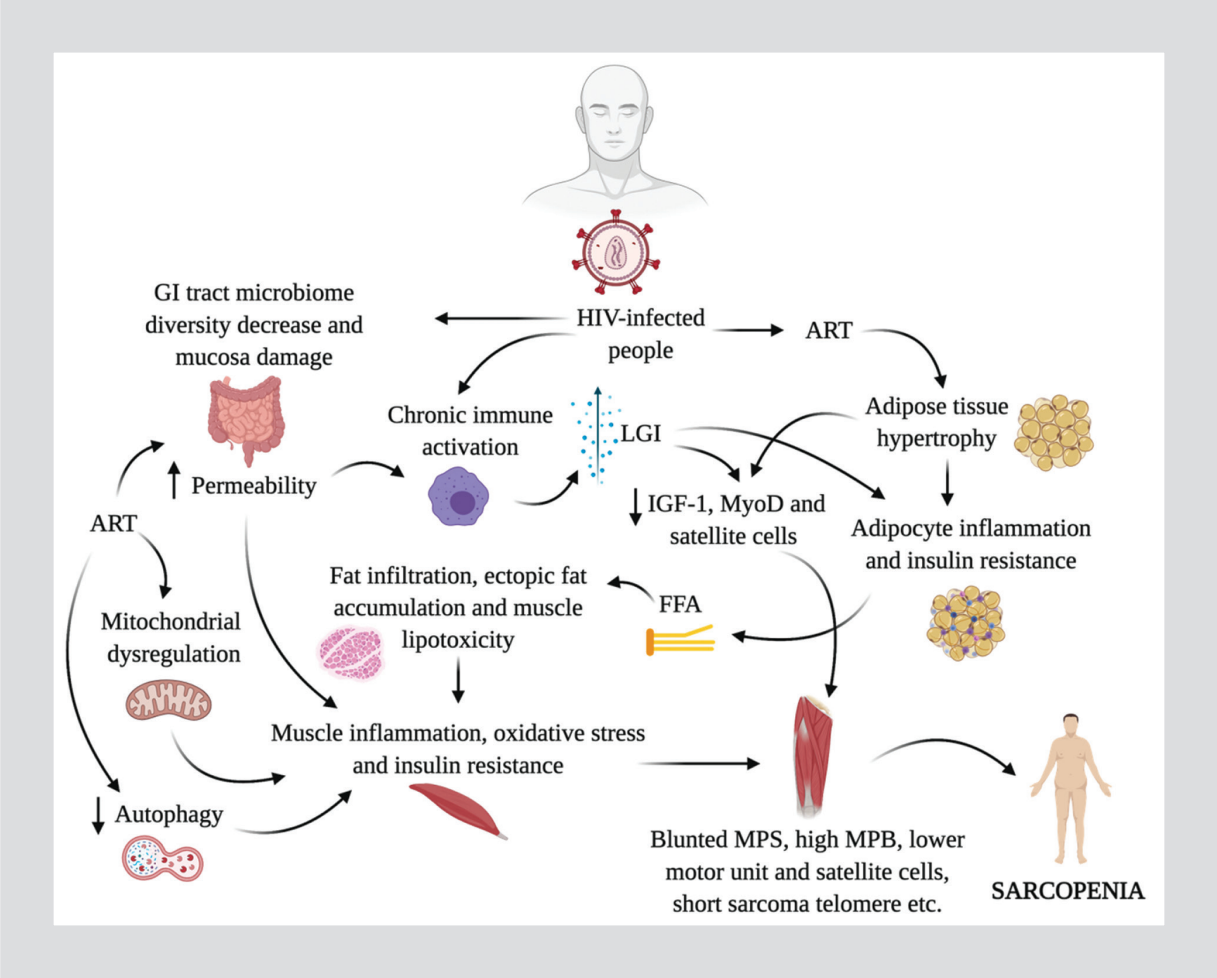

Figure 1. *Potential mechanisms of action to explain sarcopenia in PLWH.*
Created with BioRender.com. 1. HIV promotes changes in the gut microbiota shape and intestinal epithelial cells, increasing the leaky gut process. The translocation of metabolites (i.e., LPS) promotes immune activation in immune and non-immune cells, such as skeletal muscle. Inflammation in muscle tissue increases oxidative stress and insulin resistance (with bidirectional interface), which may reduce MPS. 2. Chronic immune activation increases LGSI, which can decrease the activity of substances responsible for MPS (i.e., IGF-1, MyoD, and Satellite Cells). 3. LGSI and ART modify adipose tissue functionality, which can lead to insulin resistance and increase the circulation of FFA, which act as inflammatory triggers, creating a vicious cycle. 4. Ectopic fat accumulation due to adipose tissue dysfunction can promote muscle protein turnover changes, increasing MPB. 5. ART promotes mitochondrial damage (i.e., toxicity, less efficiency, and less mitophagy) by increasing muscle tissue inflammation.

Trying to identify studies investigating the prevalence of sarcopenia in PLWH, we performed a literature search exclusively in the PubMed database, adopting MeSH terms for HIV and sarcopenia respective entry terms; the search included articles published up to January 2021, without the previous restriction of date. Sixty-two studies were found, and after analyzing the title and summary, 20 studies were selected for reading in full. After this step, we choose the studies that took sarcopenia (regardless of the diagnostic criteria) as a primary or secondary outcome, which resulted in 13 studies described in table 2. Below, we highlight the main features of these studies.

Several criteria were used to diagnose pre-sarcopenia and sarcopenia, being (i) European Working Group on Sarcopenia in Older People 1 (EWGSOP 1); (ii) European Working Group on Sarcopenia in Older People 2 (EWGSOP 2); (iii) Foundation of the National Institutes of Health Sarcopenia Project (FNIH); (iv) Sarcopenia Definitions and Outcomes Consortium (SDOC); (v) Asian Working Group for Sarcopenia (AWGS); (vi) and Baumgartner's criteria. It is important to note that numerous factors can modify the prevalence of sarcopenia. For instance, lean mass can be assessed by electrical bioimpedance (BIA) and energy X-ray absorptiometry (DXA). Muscle strength can be assessed by the grip strength or chair stand test.

Table 2. Studies investigating sarcopenia, or sarcopenia-related outcomes, in PLWH.

Author (year)	Location	Sample (n)	Age (years)	Current therapy	HIV-1 RNA and CD4	Duration of HIV infection (Years)	Sarcopenia related results	Method of sarcopenia diagnosis
Buehring et al. (2012)[49]	USA	66	41.5 (23-68)	Treatment naive PI + NNRTI NRTI	Viral load: 136.68 Nadir CD4: 233	7 (1-19)	Sarcopenia (21.9%)	Muscle strength:- LBM: DXA Muscle function:- < 2 standard deviations ALM/m^2 (< 7.26 kg/m^2) Baumgartner's criteria
Erlandson et al. (2013)[18]	USA	359	52.1 ± 0.3	When stratified by low and high-functioning subjects Low function Tenofovir (24; 80%) Protease inhibitor (n = 24; 80%) High function Tenofovir (41; 85%) Protease inhibitor (n = 32; 67%)	Current CD4+ T-cells/μL 600 (16) Detectable HIV-1 RNA (≥ 48 copies/mL) 18 (5)	Not reported	27 (35%) met the criteria for low muscle mass 15 (50%) of the low muscle function subjects were classified as sarcopenic	Muscle strength:- LBM: DXA Muscle function: SPPB and the 400-m walk Low muscle mass was defined as ASMI < 5.45 kg/m^2 for women and < 7.26 kg/m^2 for men Baumgartner's criteria
Wasserman; Segal-Maurer; Rubim (2014)[50]	USA	80	54 (50-60)	NRTI + NNRTI + INSTI or NRTI + NNRTI + PI	Indetectable viral load and CD4 cells/mm^3 > 500	15.5 (10-19)	Sarcopenia (5%) Pre-sarcopenia (20%) No sarcopenia (75%)	Muscle strength: HGD LBM: BIA Muscle function: gait speed EWGSOP 1 criteria
Neto et al. (2015)[51]	Brazil	33	59 ± 7	Lamivudine + Zidovudine (n = 17) Lamivudine + Tenofovir (n = 16) Efavirenz (n = 13)	Undetectable viral load (90.9%)	7.15 ± 3.74	Sarcopenia: HIV^+ = 24.2%; n = 8 Pre-sarcopenia: HIV^+ = 12.1%; n = 4 No sarcopenia: HIV^+ = 63.6%; n = 21	Muscle strength: HGD LBM: BIA Muscle function: gait speed EWGSOP 1 criteria
Dutta et al. (2017)[52]	Indian	103	35 (32-41)	n = 94 NRTI n = 88 NNRTI n = 6 PI	HIV-1 RNA < 50 c/mL not reported CD4 = 460 (365-640)	4.75 (2.1-8.1)	PSMM in controls and males with HIV was 67.08 ± 4.11% and 63.74 ± 10.66%, respectively	Muscle strength:- LBM: DXA Muscle function:- PSMM (total LM/weight x 100) < 2 SD below

(Continues)

Table 2. Studies investigating sarcopenia, or sarcopenia-related outcomes, in PLWH *(Continued)*.

Echeverría et al. (2018)[53]	Spain	860	52 (47-57)	Not reported	HIV-1 RNA < 50 c/mL (n = 94%) CD4 = 552 (377-728)	8 (3-15)	Sarcopenia in whole sample = 25.7% Female 57 % Male 27 % Sarcopenia in the age ≥ 50 years Female (n = 55; 43%) Male (n = 33; 8.8%)	Muscle strength: - LBM: DXA Muscle function: - The cut-off point used was two SD below the mean SMI Baumgartner's criteria
Hawkins et al. (2018)[54]	USA	199	60.1 (54.4-63.8)	Cumulative years on ART 12.5 (9.1–15.3) Cumulative years on TDF 5.5 (1.2–8.7) Cumulative years on PI 7.6 (1.7–13) Cumulative years on ZDV or D4T 6.9 (3.3–11.2)	HIV-1 RNA < 50 c/mL n = 179 (90%) CD4 = 641 (500-843)	Not reported	Sarcopenia HIV+ (n = 32; 17%	Muscle strength: HGD LBM: DXA Muscle function: gait speed (4-meter course Sarcopenia criteria-only ASMI
Abdul Aziz et al. (2018)[55]	Malaysia	315	43 (37-51)	Not reported	HIV-1 RNA < 50 c/mL n = 179 (90%) CD4 = 550 (394-760)	Not reported	HIV+ (n = 15; 10%)	Muscle strength: HGD LBM: BIA Muscle function: Gait speed (4-m course Sarcopenia using definitions adapted from the AWGS
Oursler et al. (2019)[56]	USA	31	62.1 ± 6.6	Tenofovir (n = 17) NNRTI (n = 10) Protease inhibitor (n = 4) ISTI (n = 20)	HIV-1 RNA < 20 c/mL (n = 27) CD4 = 683.9 (293.4)	20.4 (8.3)	n = 4 (13%) ASMI cut-off values. None of these cases of sarcopenia had low grip strength	Muscle strength: HGD LBM: DXA Muscle function: - Baumgartner's criteria and Grip strength (EWGSOP)
Debroy et al. (2019)[57]	Italy	169	56.8 ± 5.9	Not reported	HIV-1 RNA < 50 c/mL (n = 90%) CD4 = 628 (479-792)	18.9 (6.5)	n = 42 (27.8%)	Muscle strength: HGD LBM: DXA Muscle function: - Baumgartner's criteria

(Continued)

Table 2. Studies investigating sarcopenia, or sarcopenia-related outcomes, in PLWH *(Continued)*.

de Almeida et al. (2020)[21]	Brazil	83	Sarcopenia = 62.4 ± 8.1 Pre-sarcopenia = 56.4 ± 5.2 No sarcopenia 57.0 ± 6.0	Not described	HIV-1 RNA Sarcopenia = 363.6 (1046.4) Pre-sarcopenia = 35.1 (75.4) No sarcopenia = 289.5 (1542.7) CD4 cells/mm^3 Sarcopenia = 609.3 (283.7) Pre-sarcopenia = 513 (176.2) No sarcopenia = 614.8 (251.9)	Not described	Sarcopenia (n = 10) Pre-sarcopenia (n = 14) No sarcopenia (n = 59)	Muscle strength: HGD LBM: DXA Muscle function: - EWGSOP 2 Sarcopenia was defined as low ALMI) and altered muscle strength
Oliveira et al. (2020)[58]	Brazil	302	51.7 ± 9.0	NRTI + PI (n = 134; 44.4%) NRTI + NNRTI (n = 92; 30.5%) NRTI + INSTI (n = 43; 14.2%) NRTI + PI + INSTI (n = 14; 4.6%)	75% had an undetectable HIV-1 RNA (< 40 copies/mm^3) CD4 cells/mm^3 > 500 173 (57.9%)	11.2 ± 7.7	EWGSOP 1 = 4.3% EWGSOP 2 = 1.0%	Muscle strength: HGD and chair stand LBM: BIA and DXA Muscle function: Gait speed and static balance EWGSOP 1 and 2
Erlandson et al. (2020)[46]	USA	645	Men HIV$^+$ = 59 ± 5 HIV$^-$ = 60 ± 5 Women HIV$^+$ = 50 ± 5 HIV$^-$ = 49 ± 6	Not described	HIV-1 RNA < 50 copies/mL n = 179 (Men) n = 103 (Women) CD4 + T-cells < 500 cells/uL n = 48 (men) n = 62 (women)	Not described	EWGSOP 1 Men: HIV$^+$ = 12% Women: HIV$^+$ = 3% FNIH Men: HIV$^+$ = 11% Women: HIV$^+$ = 3%	Muscle strength: HGD LBM: DXA Muscle function: Gait speed (4-m course) EWGSOP 1 FNIH

HGD: handgrip dynamometry; LBM: lean body mass; AWGS: Asian Working Group for Sarcopenia; RNA: ribonucleic acid; DXA: dual-energy X-ray absorptiometry; ALMI: appendicular lean mass; NNRTI: non-nucleoside reverse-transcriptase inhibitors; PI: protease inhibitors; NRTI: nucleoside reverse-transcriptase inhibitors; INSTI: integrase inhibitors; CD4: cluster of differentiation 4; EWGSOP: European Working Group on Sarcopenia in Older People; FNIH: Foundation of the National Institutes of Health Sarcopenia Project; BIA: bioelectrical impedance analysis; ASMI: appendicular skeletal muscle mass; SDOC: Sarcopenia Definitions and Outcomes Consortium; PSMM: percentage skeletal muscle mass (total LM/weight x 100); SPPB: Short Physical Performance Battery.

Finally, physical performance can be assessed by Gait speed and Short Physical Performance Battery (SPPB). Several studies use only one parameter (i.e., lean body mass) to define sarcopenia; others added muscle strength or muscle function. Still, parameter sequence can change pre-sarcopenia and sarcopenia definitions. For example, EWGSOP1 considered lean body mass as a primary outcome, while EWGSOP2, a revised definition of sarcopenia, recommends low muscle strength as the primary outcome, making the prevalence of sarcopenia heterogeneous across studies. EWGSOP2 has resulted in a lower sarcopenia prevalence in HIV-uninfected subjects[59].

Buehring et al. (2012)[49] found in PLWH a prevalence of sarcopenia of 21%, considering only Baumgartner's criteria. Erlandson et al. (2013)[18] evaluated body composition by DXA and functionality by Short Physical Performance Battery and the 400-m walk. The authors found that using appendicular skeletal muscle index cut points, 27 (35%) of all subjects met the criteria for low muscle mass, and 15 (50%) of the low function subjects were classified as sarcopenic. Still, the authors found higher odds for lower lean mass in subjects with low function (OR 2.5; 95% CI: 1.0-6.1).

Wasserman; Segal-Maurer; Rubim (2014)[50] verified 20% (95% CI: 12.5-31.9%) and 5% (95% CI: 1.4-12.3%) of pre-sarcopenia and sarcopenia prevalence, respectively. Pre-sarcopenia was defined operationally as low skeletal muscle index only, and sarcopenia was defined operationally as low skeletal muscle index and low muscle strength or performance. Furthermore, considering EWGSOP1 criteria, other authors found 24.2% (n = 8) and 6.7% (n = 4) of sarcopenia prevalence in PLWH and HIV-uninfected subjects, respectively[51]. Thus, studies that consider only muscle mass as a criterion for defining sarcopenia found higher prevalences[52].

Echeverría et al. (2018)[53] observed that the prevalence of sarcopenia (definition based only on low appendicular muscle mass) was 25.7% (95% CI 22.8-28.7) in PLWH. The authors also showed that the higher time that lasted from the HIV diagnosis (> 5 years) increased the risk of sarcopenia (1.78; 95% CI 1.31-2.41; $p < 0.001$).

Hawkins et al. (2018)[54] defined sarcopenia as appendicular skeletal muscle index ≤ 7.26 kg/m^2 using DXA scan. In contrast, considering only Baumgartner's criteria, sarcopenia prevalence was higher in HIV-uninfected subjects (21%) versus PLWH (17%). Interestingly, when stratified by visceral adipose tissue > 130 cm^2, sarcopenia prevalence was higher in PLWH (n = 25; 14%) versus HIV-uninfected (n = 15; 8%), suggesting that high visceral adiposity with a more inflammatory status could increase sarcopenia prevalence. Similarly, Abdul Aziz et al. (2018)[55], using the AWGS as definition criteria, verified that HIV-uninfected individuals had lower muscle mass than the infected individuals 9.56 (8.46-10.64) kg/m^2 and 10.08 (8.28-11.24) kg/m^2, respectively. When stratified by < 50 years old, 7 (7%) PLWH and 7 (7%) HIV-uninfected subjects presented sarcopenia, but when stratified by 50 years or older, 8 (17%) PLWH and only 2 (4%) HIV-uninfected presented sarcopenia.

Considering Baumgartner's criteria, some studies found that 27.8% of PLWH met the definition of sarcopenia[57], while others found only 13% prevalence of sarcopenia[56]. Interestingly, EWGSOP 2 appears to reduce the prevalence of sarcopenia, being verified that 16% and 12% met the criteria for pre-sarcopenia and sarcopenia, respectively[21]. Likewise, Oliveira et al. (2020)[58], using EWGSOP1 and EWGSOP2, evaluated sarcopenia prevalence in PLWH. The prevalence of pre-sarcopenia was 9.6% and 5.6% for EWGSOP1 and EWGSOP2, respectively. Sarcopenia prevalence was 4.3% and 1% considering EWGSOP1 and EWGSOP2, respectively.

Erlandson et al. (2020)[46] found no differences in strength and gait speed between people without HIV. Applying EWGSOP1 criteria, the prevalence of sarcopenia in men and women with HIV was 12 and 3%, respectively. In HIV-uninfected subjects, the prevalence of sarcopenia in men and women was 7 and 3%, respectively. According to the FNIH criteria, the prevalence of sarcopenia in men and women with HIV was 11 and 3%, respectively. In HIV-uninfected subjects, the prevalence of sarcopenia in men and women was 8 and 1%, respectively.

A recent systematic review and meta-analysis observed 24.1% (95% CI: 17.8-31%) prevalence of sarcopenia in PLWH. The authors also found that the prevalence was higher when considering only muscle mass (28.8%; 95% CI: 24-34.1%), while studies that defined sarcopenia by reducing muscle mass and function found an average prevalence of 13.2% (95% CI: 5.2-22.9%). Finally, studies considered to be of high methodological quality have a lower average prevalence (18%; 95% CI: 5.4-33.2%) versus moderate (27.6%; 95% CI: 20.3-35.5%) and low quality (27.5%; 95% CI: 22-33.5%). From the studies that compared the prevalence of sarcopenia in people with or without HIV, it can be seen that the prevalence of sarcopenia in HIV-uninfected subjects is 11.1% (95% CI: 1.4-26.5%); therefore, PLWH has 2.4 higher odds for sarcopenia (95% CI: 1.1-5.3)[60]. Another recent systematic review and meta-analysis assessing the prevalence of

sarcopenia in PLWH verified that the frequency of sarcopenia defined by low muscle mass (Baumgartner's operational definition) alone was 30.3% (95% CI: 24.3-37.1%) and the frequency of sarcopenia defined by low muscle mass with low muscle strength (EWGSOP definition) was 4.5% (95% CI: 1.3-13.9%)[61].

In vitro *studies*

In vitro studies that evaluated the potential effects of ARTs (especially NRTIs and PIs) on muscle tissue identified mitochondrial damage[26], reduced complex I and III activity in the electron transport chain[28], impairment autophagy[27], an increase of reactive oxygen species, and blunted of muscle protein synthesis[32].

In vivo *non-human studies*

In vivo studies also evaluated ART's effect. Several metabolic alterations were verified, such as anabolic muscle resistance[29], smaller mitochondrial biogenesis[30], insulin resistance[33,34], and lower testosterone levels[29].

Figure 2 presents the potential ART's mechanisms that could affect the skeletal muscle.

Human studies

Human studies did not directly assess the relationship between ARTs and sarcopenia (considering the combined criteria); they only associated with sarcopenia-isolated parameters (i.e., lean body mass, muscle strength, or physical function). Therefore, studies are needed for more specific associations between ARTs and sarcopenia.

One of the initial studies investigating ART's effect on muscle mass was published in 1991[31]. The authors evaluated the muscle (removed by biopsy) of 9 PLWH treated with AZT for 9-18 months and 2 PLWH who did not receive the therapy. The authors pointed that PLWH treated with AZT reduced their mtDNA. First-generation ARTs, mainly NRTI (zidovudine, zalcitabine, didanosine, and stavudine), generated mitochondrial dysfunction, impairing oxidative capacity leading to clinical manifestations such as exercise intolerance, H^+ accumulation, and muscle acidosis[62].

Silva et al. (1998)[36] evaluated PIs (saquinavir, ritonavir, indinavir, nelfinavir, or combinations) effect on the lean body mass of adult subjects. The authors found an increase in fat mass without changes in lean body mass. It is believed that changes in fat mass can be attributed to insulin resistance. The same adverse effects on glucose metabolism were seen *in vitro* and *in vivo* studies using indinavir in humans[35].

Mulligan et al. (1999)[40] compared groups treated with PIs (n = 20; 16 indinavir; 2 saquinavir; 2 ritonavir), NRTIs (n = 9; lamivudine plus other NRTI), and control group (n = 12; stable ART's other than PIs or lamivudine 3TC). The intervention time was 3.4 ± 0.5 and 4.8 ± 1.2 months in PIs and 3TC, respectively. Regarding LBM, the authors observed changes of +1.1 ± 0.6, +0.1 ± 0.6, and −0.1 ± 0.5 in the PIs, 3TC, and control groups, respectively, with no statistical difference between the groups. In addition, the authors found insulin (+12.2 ± 4.9 μU/mL), triacylglycerol (+53 ± 17 mg/dL), and LDL-cholesterol (+18 ± 5 mg/dL) increases in the PIs group, with no difference in the other groups. Thus, they conclude that the use of PIs worsened the metabolic profile, regardless of changes in body composition.

Similarly, other authors have found that PLWH PI users (ritonavir, atazanavir, lopinavir, and darunavir) had lower expression of proteins responsible for lipids' metabolism, such as CD-36 and carnitine palmitoyl transferase-1, essential for skeletal muscle fatty acid oxidation. The lower efficiency in lipid oxidation has been associated with lipolysis, high free fatty acids circulation, intrahepatic, and muscular fat accumulation[38].

Moreover, obesity prevalence's increased in recent years in PLWH. Weight gain involves subcutaneous and visceral fat depot increases[63]. High adiposity is attributed, at least in part, to adverse-related ART regimens[63]. For instance, INSTI-based regimens were associated with weight gain; however, mechanisms are unclear, speculating effects on thermogenesis, appetite, energy regulation, or direct effects on adipose tissue[63]. Katlama et al. (2020)[64] verified in 165 PLWH with viral suppression that PI switch for raltegravir and etravirine increased by 12% total, trunk and limb fat mass after 96 weeks. High adiposity can lead to ectopic fat accumulation, including muscle tissue. Intramuscular fat accumulation incurs muscle-related dysfunctions (i.e., increased inflammation, insulin resistance, and mitochondrial damage). The interaction between obesity and sarcopenia is widely discussed, with several suggested mechanisms, mainly related to the effects of inflammation, insulin resistance, and lower IGF-1 levels, stimulating muscle protein degradation and reducing muscle protein synthesis[10,16].

Few studies verified the effect of ART on lean mass, being observed a positive association between the trunk and leg lean mass and ART, especially in men[41]. Shlay et al. (2007)[42] evaluated 422 antiretroviral-naive

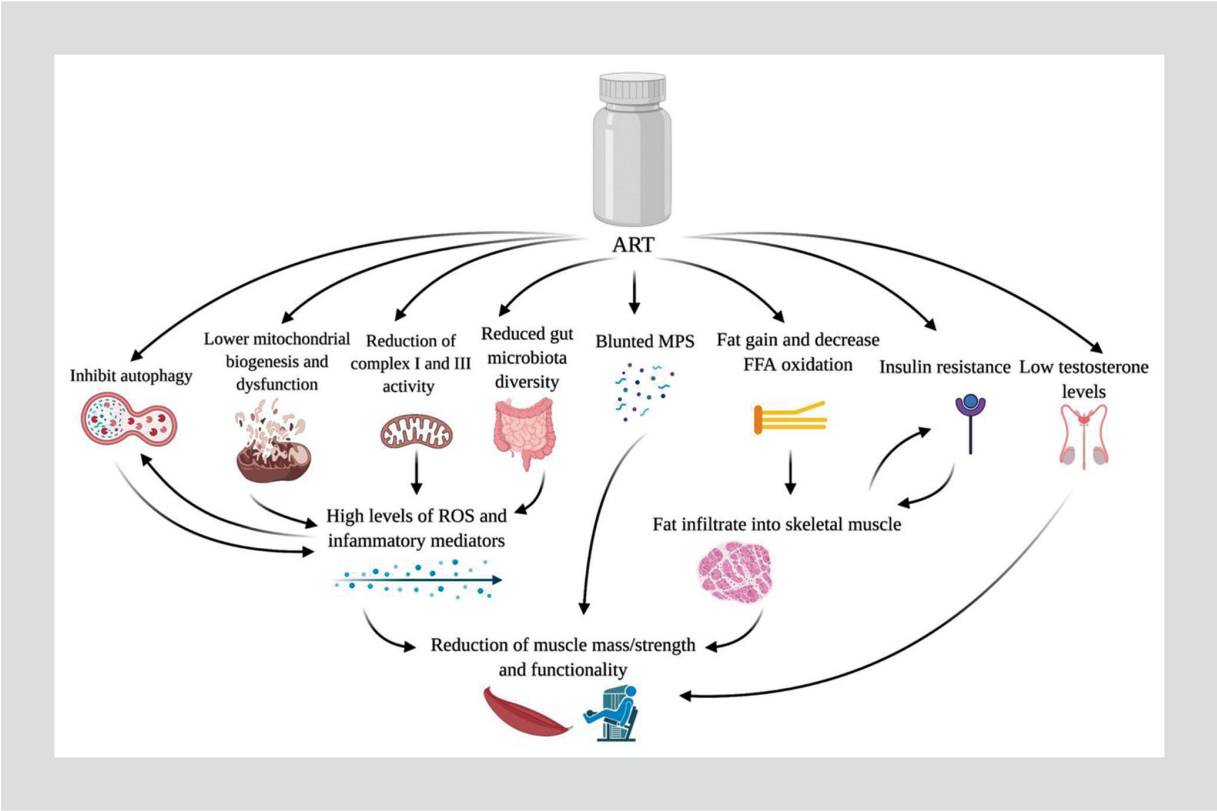

Figure 2. *Potential mechanisms of ART's drugs associated with muscle metabolism. Created with BioRender.com.*
Over the years, several ART's and combinations have been proposed to reduce viral replication and restore the immune system. It is not clear how these drugs have modified and still modify substances responsible for muscle protein turnover. 1. ART appears to reduce autophagy, increasing the accumulation of damaged molecules (DAMPs), which can maximize the inflammatory process. 2. The mitochondrial inefficiency generated by ART can contribute to the accumulation of intramuscular lipids responsible for insulin resistance and inflammation in muscle tissue. 3. ART increases the production of ROS, contributing to oxidative stress. 4. Directly, ART can reduce the gene expression of proteins involved in MPS. 5. The lower uptake and oxidation of peripheral lipids explains, at least in part, LGSI and the increase in fat infiltrate in the muscle. 6. ART, mainly protease inhibitors, are associated with insulin resistance, a crucial factor for MPB. 7. There is evidence that ART also negatively affects testosterone, an essential hormone for MPS. 8. The reduction in functionality can occur from these various changes mentioned, leading to less muscle tissue use, culminating in a muscle catabolic environment.

patients who were randomized into three groups, being: PI (n = 141; nelfinavir; indinavir; ritonavir-boosted PI); NNRTI (n = 141; efavirenz; nevirapine; delavirdine); or some PI (described above) + combination of NNRTI (n = 140; AZT +3TC; stavudine [d4T] +3TC; abacavir +3TC; abacavir + d4t). After 4 months, the authors found an increase in FFM in the PI group (1.2 kg) in the NNRTI group (1.43 kg) and the PI + NNRTI group (1.04 kg) with no statistical difference between groups. After 5 years, the authors observed an increase in FFM of 1.92, 2.02, and 1.79 kg in the PI, NNRTI, and PI + NNRTI groups, respectively, without statistical difference.

Previous studies verified metabolic parameters after switching from lopinavir/ritonavir to atazanavir/ritonavir (ATV/r). The combination of ATV/r reduced visceral fat, improved muscle glucose uptake and lipid profile[37]. These findings were confirmed more recently, ATV/r improved glucose metabolism and reduced insulin resistance, suggesting more negative effects on lopinavir use[65]. Thus, it is not possible to infer that all PIs have the same effects on body composition and metabolism.

Adrian et al. (2020)[39] found that darunavir/ritonavir (DRV/r) were associated with low lateralis muscle density (−2.43; SE =1.07; p = 0.024) and high intermuscular lateralis fat area (1.64; SE =0.80; p = 0.041). This finding suggests negative effects of DRV/r combination on muscle mass and fat mass. Still, muscle density (psoas and paraspinal) was positively associated with short physical performance physical battery (SPPB) and grip strength evaluation in men. Paraspinal muscle density was positively associated with SPPB and of women.

Therefore, it is possible to infer that the different combinations of PIs have different effects on the

muscle. While ATV/r improves glucose metabolism, DRV/r is associated with lower muscle density. This effect may be due to DRV only. Finally, raltegravir use was negatively associated with intermuscular psoas fat area. Raltegravir, an IIs, is still little explored despite the effects on body composition.

In Grant et al. (2016)[43] study, ART-naïve subjects were randomized to ATV/r or efavirenz (EFV) combined with either tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC). During the first phase of the intervention, HIV-infected subjects increased LBM (0.53 vs. 0.06 kg/year; 95% CI for difference: 0.12, 0.82 kg/year; p = 0.008) versus non-infected subjects. In the second phase (> 96 weeks), however, HIV-infected individuals lost LBM in comparison to HIV-uninfected controls (–0.28 vs. 0.06 kg/year; 95% CI for difference: –0.51, –0.18 kg/year $P < 0.001$). These data suggest that chronically, ART appears to have negative effects on LBM. In addition, the authors found no relationship between the ART type and changes in skeletal muscle. These findings are confirmed in other studies, being verified an increase in FFM in ATZ/r (2 ± 5.8%), raltegravir (2 ± 6%), and DRV/r (1.2 ± 6.4%) groups; however, they did not observe differences in LBM between groups over 96 weeks[44].

Conclusion

Living with HIV and the aging process share similar metabolic and inflammatory changes that, by themselves, could justify the increased risk of sarcopenia in PLHW. Besides, PLWH in ART, despite the numerous benefits on the immune system and survival, have to live with the side effects of the treatment, including chronic diseases and skeletal muscle changes. However, there is still a lack of studies investigating the effects of the virus with ART on skeletal muscle metabolism. For now, it is possible to infer that living with HIV under ART is associated with persistent metabolic changes, such as lower efficiency in autophagy, insulin resistance, and mitochondrial dysfunction, increasing inflammation, and muscle protein breakdown. The inflammaging (and inflammAIDs) anticipate the aging process changes, and the adipose tissue, the gut microbiota, and some ART-drugs (NRTI, especially AZT and PIs) are involved in those processes. Concerning the new generations of drugs, mainly INIs and FIs, there is still insufficient data to assess skeletal muscle effects. More targeted studies to confirm antiretroviral drugs' effect on skeletal muscle mass, strength, and functionality, are needed to clarify the relationship between HIV, ART, and sarcopenia.

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References

1. Abaasa AM, Todd J, Ekoru K, Kalyango JN, Levin J, Odeke E, et al. Good adherence to HAART and improved survival in a community HIV/AIDS treatment and care programme: the experience of The AIDS Support Organization (TASO), Kampala, Uganda. BMC Health Serv Res. 2008;8:241.
2. Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, Page-Shafer K, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J Infect Dis. 2008;197:126-33.
3. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16-31.
4. Scherzer R, Heymsfield SB, Lee D, Powderly WG, Tien PC, Bacchetti P, et al. Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection. AIDS. 2011; 25:1405-14.
5. Siparsky PN, Kirkendall DT, Garrett WE Jr. Muscle changes in aging: understanding sarcopenia. Sports Health. 2014;6:36-40.
6. Jyvakorpi SK, Urtamo A, Kivimaki M, Salomaa V, Strandberg TE. Association of midlife body composition with old-age health-related quality of life, mortality, and reaching 90 years of age: a 32-year follow-up of a male cohort. Am J Clin Nutr. 2020;112:1287-94.
7. Bauer J, Morley JE, Schols A, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: a time for action. An SCWD position paper. J Cachexia Sarcopenia Muscle. 2019;10:956-61.
8. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14:576-90.
9. Wyke SM, Russell ST, Tisdale MJ. Induction of proteasome expression in skeletal muscle is attenuated by inhibitors of NF-kappaB activation. Br J Cancer. 2004;91:1742-50.
10. Zembron-Lacny A, Dziubek W, Wolny-Rokicka E, Dabrowska G, Wozniewski M. The relation of inflammaging with skeletal muscle properties in elderly men. Am J Mens Health. 2019;13:1557988319841934.
11. Mau T, Yung R. Adipose tissue inflammation in aging. Exp Gerontol. 2018;105:27-31.
12. McCann K, Shah S, Hindley L, Hill A, Qavi A, Simmons B, et al. Implications of weight gain with newer antiretrovirals: 10-year predictions of cardiovascular disease and diabetes. AIDS. 2021;2021:2930.
13. Ortmeyer HK, Ryan AS, Hafer-Macko C, Oursler KK. Skeletal muscle cellular metabolism in older HIV-infected men. Physiol Rep. 2016;4:e12794.
14. d'Ettorre G, Paiardini M, Zaffiri L, Andreotti M, Ceccarelli G, Rizza C, et al. HIV persistence in the gut mucosa of HIV-infected subjects undergoing antiretroviral therapy correlates with immune activation and increased levels of LPS. Curr HIV Res. 2011;9:148-53.
15. Brown J, Wang H, Hajishengallis GN, Martin M. TLR-signaling networks: an integration of adaptor molecules, kinases, and cross-talk. J Dent Res. 2011;90:417-27.
16. Natsag J, Erlandson KM, Sellmeyer DE, Haberlen SA, Margolick J, Jacobson LP, et al. HIV infection is associated with increased fatty infiltration of the thigh muscle with aging independent of fat distribution. PLoS One. 2017;12:e0169184.
17. Erlandson KM, Allshouse AA, Jankowski CM, Lee EJ, Rufner KM, Palmer BE, 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;208:249-59.

18. Erlandson KM, Allshouse AA, Jankowski CM, MaWhinney S, Kohrt WM, Campbell TB, et al. Functional impairment is associated with low bone and muscle mass among persons aging with HIV infection. J Acquir Immune Defic Syndr. 2013;63:209-15.
19. Wallet MA, Buford TW, Joseph AM, Sankuratri M, Leeuwenburgh C, Pahor M, et al. Increased inflammation but similar physical composition and function in older-aged, HIV-1 infected subjects. BMC Immunol. 2015;16:43.
20. Langkilde A, Petersen J, Henriksen JH, Sankuratri M, Leeuwenburgh C, Pahor M, 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.
21. de Almeida LL, Ilha T, de Carvalho JA, Stein C, Caeran G, Comim FV, et al. Sarcopenia and its association with vertebral fractures in people living with HIV. Calcif Tissue Int. 2020;107:249-56.
22. Langen RC, Van Der Velden JL, Schols AM, Kelders MC, Wouters EF, Janssen-Heininger YM, et al. Tumor necrosis factor-alpha inhibits myogenic differentiation through MyoD protein destabilization. FASEB J. 2004;18:227-37.
23. Dudgeon WD, Phillips KD, Carson JA, Brewer RB, Durstine JL, Hand GA, et al. Counteracting muscle wasting in HIV-infected individuals. HIV Med. 2006;7:299-310.
24. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. Cold Spring Harb Perspect Med. 2012;2:a007161.
25. Guaraldi G, Pintassilgo I, Milic J, Mussini C. Managing antiretroviral therapy in the elderly HIV patient. Expert Rev Clin Pharmacol. 2018; 11:1171-81.
26. Lamperth L, Dalakas MC, Dagani F, Anderson J, Ferrari R. Abnormal skeletal and cardiac muscle mitochondria induced by zidovudine (AZT) in human muscle *in vitro* and in an animal model. Lab Invest. 1991; 65:742-51.
27. Lin H, Stankov MV, Hegermann J, Budida R, Panayotova-Dimitrova D, Schmidt RE, et al. Zidovudine-mediated autophagy inhibition enhances mitochondrial toxicity in muscle cells. Antimicrob Agents Chemother. 2019;63:e01443-18.
28. Lewis W, Gonzalez B, Chomyn A, Papoian T. Zidovudine induces molecular, biochemical, and ultrastructural changes in rat skeletal muscle mitochondria. J Clin Invest. 1992;89:1354-60.
29. McCurdy DT 3rd, Kennedy JM. Skeletal muscle mitochondria from AZT-treated rats have a diminished response to chronic electrical stimulation. J Appl Physiol. 1996;81:326-34.
30. Freyssenet D, DiCarlo M, Escobar P, Grey J, Schneider J, Hood DA. Zidovudine (AZT) induced alterations in mitochondrial biogenesis in rat striated muscles. Can J Physiol Pharmacol. 1999;77:29-35.
31. Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA, et al. Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy. Lancet. 1991;337:508-10.
32. Hong-Brown LQ, Brown CR, Lang CH. Indinavir impairs protein synthesis and phosphorylations of MAPKs in mouse C2C12 myocytes. Am J Physiol Cell Physiol. 2004;287:C1482-92.
33. Nolte LA, Yarasheski KE, Kawanaka K, Fisher J, Le N, Holloszy JO, et al. The HIV protease inhibitor indinavir decreases insulin- and contraction-stimulated glucose transport in skeletal muscle. Diabetes. 2001;50:1397-401.
34. Hong-Brown LQ, Pruznak AM, Frost RA, Vary TC, Lang CH. Indinavir alters regulators of protein anabolism and catabolism in skeletal muscle. Am J Physiol Endocrinol Metab. 2005;289:E382-90.
35. Noor MA, Lo JC, Mulligan K, Schwarz JM, Halvorsen RA, Schambelan M, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. AIDS. 2001;15:F11-8.
36. Silva M, Skolnik PR, Gorbach SL, Spiegelman D, Wilson IB, Fernández-DiFranco MG, et al. The effect of protease inhibitors on weight and body composition in HIV-infected patients. AIDS. 1998;12:1645-51.
37. Stanley TL, Joy T, Hadigan CM, Liebau JG, Makimura H, Chen CY, et al. Effects of switching from lopinavir/ritonavir to atazanavir/ritonavir on muscle glucose uptake and visceral fat in HIV-infected patients. AIDS. 2009;23:1349-57.
38. Richmond SR, Carper MJ, Lei X, Zhang S, Yarasheski KE, Ramanadham S, et al. HIV-protease inhibitors suppress skeletal muscle fatty acid oxidation by reducing CD36 and CPT1 fatty acid transporters. Biochim Biophys Acta. 2010;1801:559-66.
39. Adrian S, Miao H, Feng H, Scherzinger A, Nardini G, Beghetto B, et al. Effects of atazanavir, darunavir, and raltegravir on fat and muscle among persons living with HIV. HIV Res Clin Pract. 2020;21:91-8.
40. Mulligan K, Grunfeld C, Tai VW, Algren H, Pang M, Chernoff DN, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. J Acquir Immune Defic Syndr. 2000;23:35-43.
41. McDermott AY, Shevitz A, Knox T, Roubenoff R, Kehayias J, Gorbach S, et al. Effect of highly active antiretroviral therapy on fat, lean, and bone mass in HIV-seropositive men and women. Am J Clin Nutr. 2001; 74:679-86.
42. Shlay JC, Bartsch G, Peng G, Wang J, Grunfeld C, Gibert CL, et al. Long-term body composition and metabolic changes in antiretroviral naive persons randomized to protease inhibitor-, nonnucleoside reverse transcriptase inhibitor-, or protease inhibitor plus nonnucleoside reverse transcriptase inhibitor-based strategy. J Acquir Immune Defic Syndr. 2007;44:506-17.
43. Grant PM, Kitch D, McComsey GA, Collier AC, Bartali B, Koletar SL, et al. Long-term body composition changes in antiretroviral-treated HIV-infected individuals. AIDS. 2016;30:2805-13.
44. McComsey GA, Moser C, Currier J, Ribaudo HJ, Paczuski P, Dubé MP, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. Clin Infect Dis. 2016;62:853-62.
45. Oliveira VH, Wiechmann SL, Narciso AM, Webel AR, Deminice R. Muscle strength is impaired in men but not in women living with HIV taking antiretroviral therapy. Antivir Ther. 2018;23:11-9.
46. Erlandson KM, Travison TG, Zhu H, Magaziner J, Correa-de-Araujo R, Cawthon PM, 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;75:1338-45.
47. Gomes-Neto M, Rodriguez I, Ledo AP, Vieira JP, Brites C. Muscle strength and aerobic capacity in HIV-infected patients: a systematic review and meta-analysis. J Acquir Immune Defic Syndr 2018;79:491-500.
48. Jankowski CM, Wilson MP, MaWhinney S, Reusch J, Knaub L, Hull S, et al. Blunted muscle mitochondrial responses to exercise training in older adults with HIV. J Infect Dis. 2020;2020:jiaa799.
49. Buehring B, Kirchner E, Sun Z, Calabrese L. The frequency of low muscle mass and its overlap with low bone mineral density and lipodystrophy in individuals with HIV--a pilot study using DXA total body composition analysis. J Clin Densitom. 2012;15:224-32.
50. Wasserman P, Segal-Maurer S, Rubin DS. High prevalence of low skeletal muscle mass associated with male gender in midlife and older HIV-infected persons despite CD4 cell reconstitution and viral suppression. J Int Assoc Provid AIDS Care. 2014;13:145-52.
51. Pinto Neto LF, Sales MC, Scaramussa ES, da Paz CJ, Morelato RL. Human immunodeficiency virus infection and its association with sarcopenia. Braz J Infect Dis. 2016;20:99-102.
52. Dutta D, Sharma M, Bansal R, Sharma N, Garga UC, Anand A, et al. Low skeletal mass is an important predictor of osteoporosis in HIV-infected men in India. Endokrynol Pol. 2017;68:642-51.
53. Echeverria P, Bonjoch A, Puig J, Estany C, Ornelas A, Clotet B, et al. High prevalence of sarcopenia in HIV-infected individuals. Biomed Res Int. 2018;2018:5074923.
54. Hawkins KL, Zhang L, Ng DK, Althoff KN, Palella FJ Jr., Kingsley LA, et al. Abdominal obesity, sarcopenia, and osteoporosis are associated with frailty in men living with and without HIV. AIDS. 2018;32:1257-66.
55. Aziz SA, McStea M, Bashah NS, Chong ML, Ponnampalavanar S, Omar SF, et al. Assessment of sarcopenia in virally suppressed HIV-infected Asians receiving treatment. AIDS. 2018;32:1025-34.
56. Oursler KK, Iranmanesh A, Jain C, Birkett KL, Briggs BC, Garner DC, et al. Short communication: low muscle mass is associated with osteoporosis in older adults living with HIV. AIDS Res Hum Retroviruses. 2020;36:300-2.
57. Debroy P, Lake JE, Malagoli A, Guaraldi G. Relationship between grip strength and nonalcoholic fatty liver disease in men living with HIV referred to a metabolic clinic. J Frailty Aging. 2019;8:150-3.
58. Oliveira VH, Borsari AL, Cardenas JD, Junior CM, Castro NF, Marinello PC, et al. Low Agreement Between Initial and Revised European Consensus on Definition and Diagnosis of Sarcopenia Applied to People Living With HIV. J Acquir Immune Defic Syndr. 2021;86:e106-e113.
59. Phu S, Vogrin S, Zanker J, Hassan EB, Al Saedi A, Duque G, et al. Agreement between initial and revised European working group on sarcopenia in older people definitions. J Am Med Dir Assoc. 2019;20:382-3.
60. Oliveira VH, Borsari AL, Webel AR, Erlandson KM, Deminice R. Sarcopenia in people living with the human immunodeficiency virus: a systematic review and meta-analysis. Eur J Clin Nutr. 2020;74:1009-21.
61. Guimaraes NS, Raposo MA, Greco D, Tupinambas U, Premaor MO. People living with HIV, lean mass, and sarcopenia: a systematic review and meta-analysis. J Clin Densitom. 2021;2021:22-6.
62. Duong M, Dumas JP, Buisson M, Martha B, Piroth L, Grappin M, et al. Limitation of exercise capacity in nucleoside-treated HIV-infected patients with hyperlactataemia. HIV Med. 2007;8:105-11.
63. Koethe JR, Lagathu C, Lake JE, Domingo P, Calmy A, Falutz J, et al. HIV and antiretroviral therapy-related fat alterations. Nat Rev Dis Primers. 2020;6:48.
64. Katlama C, Assoumou L, Valantin MA, Soulié C, Martinez E, Béniguel L, et al. Dual therapy combining raltegravir with etravirine maintains a high level of viral suppression over 96 weeks in long-term experienced HIV-infected individuals over 45 years on a PI-based regimen: results from the Phase II ANRS 163 ETRAL study-authors' response. J Antimicrob Chemother. 2020;75:3699-700.
65. d'Ettorre G, Ceccarelli G, Zaccarelli M, Ascoli-Bartoli T, Bianchi L, Bellelli V, et al. Impact of switching from lopinavir/ritonavir to boosted and un-boosted atazanavir on glucose metabolism: the ATAzanavir and GLUcose metabolism (ATAGLU) study. Int J STD AIDS. 2016;27:638-43.