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CO-INFECTIONS AND COMORBIDITY (D BHATTACHARYA, SECTION EDITOR)

Undernutrition and HIV Infection in Sub-Saharan Africa: Health Outcomes and Therapeutic Interventions

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Abstract

Purpose of Review Sub-Saharan Africa (SSA) is disproportionately burdened by the twin epidemics of food insecurity and HIV infection, and protein-calorie undernutrition is common among persons with HIV (PWH) initiating antiretroviral therapy (ART) in the region. In this review, we discuss the intersection of HIV infection and undernutrition, health outcomes among undernourished PWH starting ART, and the demonstrated and potential benefits of therapeutic interventions such as micro/macronutrient supplementation and pharmacological agents.

Recent Findings A low body mass index (BMI), used as a general indicator of poor nutrition in most studies, is associated with impaired immune recovery and increased mortality in the early ART period. The increased risk of mortality is multifactorial, and contributors include undernutrition-related immune system dysfunction, increased susceptibility to opportunistic infections, and metabolic and cardiovascular dysregulation. Clinical trials of micro/macronutrient supplementary feeding, appetite stimulants (hormones and anabolic agents), and recombinant adipokines have shown a benefit for weight gain and metabolic health, but there are few data on mortality or immune recovery.

Summary A substantial proportion of PWH in SSA are undernourished, and undernutrition contributes to an increased risk of mortality and other adverse health outcomes. To date, there have been few prospective trials of nutritional supplementation and/or pharmacologic therapy among undernourished PWH in SSA, though findings from other settings suggest a potential benefit in this population.

Keywords Undernutrition · HIV · Body mass index · Immune recovery · Adipokines · Leptin

Introduction

There are an estimated 38 million persons with HIV (PWH) worldwide, two-thirds of who reside in sub-Saharan Africa (SSA) [1]. Access to antiretroviral therapy (ART) for the treatment of HIV infection has expanded worldwide [2–6] and HIV-associated deaths have declined by 45% from 2000 to 2018. Despite this success, an estimated 1.1 million new infections occurred in SSA in 2018, bringing the total to 25.7 million persons with HIV in the region and representing 67% of the global HIV burden [7].

Mortality after ART initiation is higher for PWH in SSA compared to other regions [8, 9]. While the etiology of this survival disparity is multifactorial, one contributor is the overlapping epidemics of chronic food insecurity and undernutrition in many areas of SSA with a high prevalence of HIV [10, 11]. Undernutrition refers to a state of insufficient dietary energy intake leading to low body weight and a low body mass index (BMI) [12], which can be contrasted with the broader condition of malnutrition comprising deviations from a state of optimal

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nutrition, including both undernutrition and over-nutrition, and deficits in specific micro- or macronutrients (e.g., iodine or protein) [13, 14]. The number of undernourished individuals in SSA rose from 181 million in 2010 to 222 million in 2016, accounting for approximately 30% of the global undernutrition burden, despite a decline in other regions over the same period [15]. Here, we review the relationship between undernutrition with mortality risk and immune recovery on ART, discuss mechanisms contributing to adverse outcomes, and review the demonstrated and potential role of therapeutic interventions to improve the health of undernourished PWH.

Low BMI Is Associated with Greater Mortality Among PWH in Sub-Saharan Africa

Quantifying the prevalence of undernutrition, and establishing the diagnosis of adult clinical malnutrition, is complicated in SSA by a lack of appropriate instruments, potential medical confounders (e.g., edema or complex vitamin and micronutrient deficiencies), and large, dispersed rural populations. In resource-limited settings, a low BMI, calculated as weight in kilograms divided by height in meters squared (kg/m^2), is often utilized as a standard measurement of poor macro-nutritional status [15]. The WHO uses BMI to characterize nutritional status as malnourished (BMI < 18.5), well-nourished (BMI 18.5–24.9), and over-nourished (BMI ≥ 25 kg/m^2). Malnutrition can further be divided into three subgroups based on severity: mild (BMI 17.0–18.49), moderate (BMI 16.0–16.9), and severe (BMI < 16.0 kg/m^2) [16]. In the context of food scarcity or specific macronutrient deficiencies, as found in some regions of SSA, a low BMI may be common in PWH at all stages of the infection and in the absence of advanced CD4+ T cell depletion [17]. However, undernutrition per se can also contribute to immunosuppression, including altered innate and adaptive immune function and impaired T cell recovery on ART, as discussed below [18, 19].

A low BMI was recognized early in the HIV epidemic as an indicator of more advanced disease or HIV-associated wasting [20, 21]. According to the 1993 Revised Classification system for AIDS-defining criteria from the Centers for Disease Control and Prevention (CDC), HIV-wasting is characterized by a reduction in an individual's body weight of ≥10% from the pre-infection level in the presence of chronic diarrhea, fever, and/or fatigue [22]. Several factors may contribute to HIV-associated wasting, including increased basal energy expenditure from a persistent antiviral response and inflammation, an accelerated rate of protein (muscle) catabolism and reduced anabolism, decreased energy intake due to anorexia, reduced nutrition absorption, and decreased bowel transit time [23–27]. In resource-limited settings, PWH may present for clinical evaluation after significant unmeasured weight loss, and BMI provides a useful measurement of general nutritional status if more advanced diagnostic tools are unavailable.

Analyses of demographic and health surveys from 11 countries in SSA estimated that approximately 10% of HIV-infected women (age 15–49) have a BMI < 18.5 kg/m^2, but other biomarkers such as CD4 cell counts were not reported [28]. A study of over 40,000 PWH in Lusaka, Zambia, found that 34% of those initiating ART between 2004 and 2008 had a BMI < 18.5 kg/m^2, and of these approximately one-quarter had severe malnutrition, one-quarter moderate malnutrition, and the remainder had mild malnutrition [29]. Those starting ART with a BMI of <16.0 kg/m^2 had significantly higher mortality in the first 90 days on therapy (adjusted hazard ratio [AHR] 2.4; 95% CI 1.8–3.2) when compared to those above this BMI threshold [37••]. In Malawi, patients with pre-treatment BMI <16.0 had a 6-fold increased risk of death after 3 months of ART treatment compared to patients with pre-treatment BMI above 18.5, and those with BMI between 16.0 and 16.9 kg/m^2 had a greater than 2-fold increased mortality [9]. In Tanzania, PWH with a BMI < 16.0 at ART initiation had twice the mortality rate of patients with BMI ≥18.5 kg/m^2 [8]. Similarly, a study from KwaZulu-Natal, South Africa, reported that underweight patients (BMI < 18.5 kg/m^2) had a significantly higher risk of death compared to those in the normal BMI range, irrespective of whether patients also had tuberculosis co-infection [30]. A more recent study from urban (Nairobi) and rural (Maseno) Kenya identified a BMI < 18.5 as a predictor of high mortality compared to participants with a BMI > 18.5 kg/m^2 (AHR 4.99). Additionally, despite similar CD4+ T cell counts among urban and rural located participants, the mortality risk associated with low BMI was greater in rural participants compared to urban participants [31].

Low BMI and CD4$^+$ T Cell Recovery Following ART Initiation

CD4+ and CD8+ T cells are central to the immune response to HIV infection, and CD4+ T cell depletion is a key indicator of HIV disease progression [32–34]. Several reports outside of SSA have demonstrated an association between low BMI and reduced CD4+ T cell recovery after ART initiation. An AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trial (ALLRT) study found men with a BMI above normal (> 25.0 kg/m^2) had higher CD4+ T cells at week 144 on ART compared to men with normal BMI (18.5–24.9 kg/m^2). Furthermore, subjects with a BMI < 18.5 kg/m^2 had a slower recovery of CD4+ T cells relative to subjects with a normal BMI [35]. A report from the multi-site North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) found that PWH with a BMI of 40 kg/m^2 and 30 kg/m^2 had a mean CD4+ count 34% or 22% higher after 5 years on ART, respectively, compared to PWH with a BMI of 22 kg/m^2 [36]. Lastly, a study from China followed 1612 PWH starting ART (11% had a BMI < 18.5 and 18% had a BMI ≥ 25 kg/m^2) and found that baseline

BMI was an independent factor associated with the magnitude of CD4+ increase after 30 months on ART [37••].

There are fewer studies of BMI and immune recovery among PWH in SSA, where undernutrition is more prevalent. In Zambia, an analysis of over 33,000 PWH initiating ART at Lusaka district clinics assessed the relationship between early CD4+ T cell recovery and the subsequent risk of mortality among those with severe, moderate, and mild malnutrition versus a normal BMI. The study found no difference in the magnitude of CD4+ T cell recovery at 6 months according to BMI strata. However, there was an inverse association between baseline BMI and the post 6-month hazard for mortality for PWH who gained less than 100 cells/μL at 6 months. Above this threshold, the risk of mortality for a given CD4+ T cell increase at 6 months did not differ by pre-treatment BMI [17]. However, a few studies have reported no association between low BMI and CD4+ T cell recovery. In a study from Singapore, 394 PWH with a baseline CD4+ T cell count less than 250 cells/μL at the start of ART initiation were followed to determine factors associated with survival. The median CD4+ T cell increase was not significantly between subjects with a BMI <17 compared to subjects with a BMI ≥ 18.5 kg/m^2; however, moderate to severe undernutrition (BMI < 17 kg/m^2) was a significant predictor of death (HR = 2.19) compared with a BMI > 18.5 kg/m^2 [38]. The apparent differences in findings from Zambia and Singapore as compared to other settings could be due to differences in African and Asian diets, secondary infections, or other factors affecting immune function.

The phenotype and functionality of T cells requires further study in undernourished African PWH. A recent study assessed circulating T cells from PWH with a BMI < 18.5 kg/m^2 enrolled in a Zambian clinical trial of lipid-based nutritional supplement (LNS) with or without added vitamins and minerals at ART initiation (n = 181), and after 12 weeks among surviving participants (n = 145). High pre-treatment naïve and low proliferating CD4+ T cells, and high senescent and low proliferating CD8+ T cells, were independently associated with an increased risk of death [39]. These findings suggest that the pre-treatment proliferative capacity of CD4+ and CD8+ T cells, a critical factor in early immune recovery, impacts early survival among undernourished PWH, which the authors hypothesize reflects a more effective response to opportunistic infections common in this group.

Potential Contributors to High Mortality and Poor CD4+ T Cell Recovery in Low BMI PWH

The increased morbidity and mortality among low BMI PWH on ART have been attributed to multiple factors, including metabolic derangements, altered gut mucosa, increased susceptibility and prevalence of opportunistic infections, and impaired innate and cellular immune responses [27, 40]. Additionally, food insecurity, or a deficit of consistent access to enough nutritious food [41], may hinder adherence to ART regimens by posing a barrier to obtaining medications and taking ART at the frequency and dosages indicated [42, 43].

While there are few data on causes of death in the early ART treatment period among low BMI PWH, several studies have identified factors associated with mortality in this group. A study followed 142 PWH initiating ART in Zambia with a BMI <16 kg/m^2 and/or CD4+ count less than 50 cells/μL for 12 weeks. Baseline serum phosphate was significantly higher among participants alive at 12 weeks (median 1.30 mmol/L), compared to those who died (median 1.06 mmol/L; $p < 0.01$), and for each 0.1 mmol/L increase in baseline phosphate, the estimated hazard of death decreased 17% (AHR 0.83; 95% CI 0.72–0.95). In a related study, a pre-treatment serum albumin of 25 g/L was associated with an approximately 50% increased mortality at 12 weeks compared to serum albumin of 30 g/L (AHR = 0.52, 95% CI 0.0.38–0.70) [44, 45] and serum ferritin levels higher than 250 μg/L were associated with a 67% increase in mortality (AHR = 1.67, 95% CI 1.30–2.15) compared to a ferritin of 25 μg/L. Similarly, a baseline high sensitivity CRP (hsCRP) level of 15 mg/L was associated with a nearly twofold increase in the hazard of death compared to a value of 5 mg/L (AHR = 1.96, 95% CI 1.12–3.44) [46]. Taken together, these findings suggest pre-treatment phosphate and protein depletion, and high levels of inflammation, reflect physiologic disturbances in low BMI PWH that may not be readily ameliorated by ART.

Undernutrition leads to changes in the gastrointestinal mucosa, including compromised epithelial cell wall integrity, villous blunting, immune cell activation, and local inflammation. Inflammation, gut wall edema, and reduced villous surface area impair nutrient absorption and utilization [47, 48]. Altered gastrointestinal mucosa and depletion of tissue CD4+ T cells occurs early in the course of HIV infection and exacerbates nutrient malabsorption, impaired gut immune defenses, and inflammation [49, 50]. Despite effective suppression of plasma viremia by ART, changes in the gut immune environment, mucosal defenses, and the microbiome persist, potentially due to chronic viral replication in the gut and/or poor reconstitution of tissue CD4+ T cells [51]. A small study evaluated the relationship of microbial translocation with systemic inflammation among PWH with a BMI <18.5 kg/m^2 starting ART in Zambia. Over the first 12 weeks of ART, the serum level of lipopolysaccharide-binding protein (LBP, a marker of microbial translocation), CRP, and tumor necrosis-α (TNF-α) receptor 1 decreased. Higher serum LBP was associated with higher CRP, while lower endotoxin core IgM (an antibody which scavenges, and falls in proportion to, circulating bacterial endotoxin) was also associated with higher CRP and TNF-α receptor 1 [52]. A separate study in the same cohort demonstrated that a reduction in TNF-α

receptor 1 and CRP over the first 12 weeks of ART was associated with increased peripheral arterial endothelial responsiveness and higher heart rate variability, both potentially reflecting improved cardiovascular health at lower levels of systemic inflammation among low BMI PWH [53].

Opportunistic infections accelerate weight loss in untreated HIV infection and contribute to poor CD4+ reconstitution and increased early mortality in low BMI persons after ART initiation [54]. Malaria is a common infection in SSA and has been shown to increase HIV replication and promote anemia in co-infected persons compared to those with HIV alone [55]. HIV and *Mycobacterium tuberculosis* co-infected persons typically have lower BMI, hemoglobin, and serum albumin levels compared to those with HIV alone [56–59], while syphilis and/or herpes simplex virus co-infections also increase HIV viral load and lower CD4+ T cell counts [60, 61]. Finally, helminth co-infections accelerate HIV disease progression [62, 63], while helminth treatment decreases HIV viral load and improves CD4+ T cell recovery [64, 65].

Undernutrition impairs CD4+ and CD8+ T cell–mediated immunity [18]. Further studies on the effects of undernutrition on T cell development in adults are needed, but a handful of studies conducted in children and adolescents demonstrate that protein-energy malnutrition (PEM), or an energy deficit due to chronic deficiency of both protein and overall macronutrient intake [14, 66], are accompanied by decreased numbers of circulating mature CD4+ T cells and decreased T cell–dependent antibody production [67, 68]. Undernourished children have reduced numbers of CD4+ CD45RO+ memory cells and effector T cells (CD4+ CD62L+ and CD8+ CD28− cells), in addition to lower levels of cytokines required for both T helper 1 (Th1) differentiation and function, but higher levels of Th2-related cytokines [69].

More recent studies demonstrate that nutrient deficiencies and whole-body nutritional status affect immune cell metabolic activity [70, 71]. In a murine model of PEM, lymphocytic choriomeningitis virus (LCMV)–infected mice fed a low protein diet compared to mice fed an adequate diet for 4 weeks had a 2-fold decrease in LCMV-specific memory CD8+ T cells and cell proliferative capacity. A switch from a low to an adequate protein diet resulted in a quantitative rescue of memory CD8+ T cells [12], suggesting that PEM impairs CD8+ T cell maintenance and cell proliferation, but that these defects can be reversed with improved nutrient intake. Nutrient deficiencies may also alter T cell immunometabolism through the glucose sensor AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin serine/threonine kinase complex 1 (mTORc1) [72]. Low nutrient abundance induces AMPK activation to promote cell survival by limiting anabolic metabolism and promoting catabolic metabolism for adenosine triphosphate (ATP) production [73]. Furthermore, mTORc1 signaling can attenuate T cell development in the thymus and suppress naïve T cell differentiation into effector CD4+ Th1, Th2, and Th17 cells as well as cytotoxic CD8+ T cells [74].

Cellular metabolic pathways, including glycolysis as well as mitochondrial membrane potential dynamics, have been shown to regulate cellular metabolism and effector functions [75–77]. Non-proliferating cells rely on a mixture of glucose, lipids, and amino acids for energy, while proliferating and activated cells rely on anabolic metabolism and glycolysis. Since effector cells highly depend on glycolysis to meet their energy requirements, these cells are particularly sensitive to nutrient deficiencies. In mice, CD3/CD28 activated naïve CD4+ T cells from fasted animals were shown to have decreased glucose uptake and glycolysis compared to activated cells from non-fasted animal controls [78]. Furthermore, low glucose levels in fasted or starved mice may contribute to naïve T cell differentiation into regulatory T cells over effector T cells [79].

The glucose transporter 1 (Glut1), a major receptor for glucose uptake and metabolism in immune cells, is expressed on activated CD4+ T cells, CD8+ T cells, and monocytes in PWH and remains elevated even after initiating ART [80] [81]. Glut 1 expression is associated with high mitochondrial membrane potential (MMP) in CD4+ and CD8+ T cells [82••], and production of pro-inflammatory cytokines and reactive oxygen species (ROS) [83]. Further studies in undernourished persons in the general population and among PWH are required to determine the underlying mechanisms by which these cellular bioenergetic pathways influence T cell activation and function in the context of inadequate nutrient intake.

Lastly, adipose tissue produces numerous signaling molecules (adipokines) with a range of metabolic, neuroendocrine, and immunological functions [84]. Adipocytes are the primary site of leptin production, which is expressed roughly in proportion to lipid content, though low levels can be produced by cells in the stomach, lungs, and other organs [85, 86]. Lower serum levels of leptin are associated with poor CD4+ T cell recovery after ART initiation, which may relate to its role as a regulator of T cell function [87–89]. The long-chain isoform of the leptin receptor (OBR) is expressed by various leukocyte populations, including CD4+ and CD8+ T cells [90–92]. In vitro, recombinant leptin treatment of CD4+ T cells is associated with increased Th1 and Th17 cell differentiation, and increased interferon-gamma (IFN-γ) production and cell proliferation [93–95]. Leptin also promotes the upregulation of activation markers (CD69, CD25, TLR2) after antigen stimulation in a dose-dependent manner [96, 97] and pro-inflammatory cytokine production, including ROS, TNF-α, and interleukin (IL)-18 from human macrophages and monocytes [98, 99]. In mice, leptin was essential for activated T cell glucose uptake and metabolism via a cell-intrinsic mechanism specific to activated effector T cells. Additionally, recombinant leptin added to cultured murine T

cells, or leptin injections to mice, enhanced T cell metabolic and functional capabilities [78]. While evidence suggests serum leptin levels could be a critical mediator of immune recovery on ART, further studies are required to determine the role of leptin signaling in the expansion of CD4+ T cells in low BMI PWH starting ART.

Therapeutic Interventions for Undernourished PWH: Supplementary Feeding and Promotion of Weight Grain

Given the observed association between low BMI and early ART mortality in PWH from resource-limited settings, it has been suggested that interventions to promote weight gain at the time of treatment initiation may improve health outcomes [100]. An analysis of over 27,000 PWH initiating ART in Lusaka, Zambia, and remaining in care at 6 months found patients starting treatment in lower BMI strata had greater weight gain compared to those in higher BMI strata. Across every BMI group, PWH with weight loss from ART initiation to 6 months had increased mortality after this time. Among those starting ART with a BMI <16.0 kg/m^2, the risk for mortality after 6 months was inversely related to weight gain in the period from initiation to 6 months [29]. A cohort study of Kenyan and Cambodian PWH found an association between weight gain at 3 and 6 months on ART initiation and subsequent survival. In patients with baseline BMI ≤18.5, weight gain of ≤5% at 3 months was associated with an approximately 5-fold increased risk of death (mortality rate ratio 4.8, 95% CI 2.3–10.1) compared to those with weight gain >10%. In patients with BMI more than 18.5, weight gain was not associated with mortality [101].

The observed association between weight gain and improved survival among low BMI PWH starting ART has led to trials of macronutrient supplementary feeding in this group. A pilot study in Zambia compared ART adherence at 8 government clinics where PWH received World Food Program food assistance with control clinics that had not yet received rations. Food distribution was based on household food security as opposed to poor nutritional status. PWH from the food assistance group were more likely to achieve 95% or greater medical possession ratio (MPR) compared to 48% among control groups (relative risk 1.5). However, there were no differences in weight gain, CD4+ T cell count, or survival between the intervention and control groups [102]. Another study in Zambia also demonstrated significantly higher ART adherence in PWH receiving food assistance compared to non-recipients (98.3% versus 88.8%). However, again there was no difference in weight gain or the change in CD4+ T cell count between groups [103]. A 2018 systematic review found that supplementary feeding in adult PWH increased daily energy and protein consumption more than nutritional counseling alone and initially improved weight gain and/or BMI, but these changes were not maintained long term [104].

A trial among 491 PWH initiating ART with a BMI <18.5 kg/m^2 in Malawi found that participants who received a high-energy peanut-based spread had a greater increase in mean BMI (2.2 ± 1.9 kg/m^2) compared to those who received a corn-soya blend (1.7 ± 1.6 kg/m^2), but there were no significant differences in CD4+ T cell count, HIV viral load, or adherence between groups [105]. In the Democratic Republic of Congo, PWH on ART supplemented with *Moringa oleifera* (M.O.) leaf powder demonstrated a significant increase in mean BMI and albumin levels as compared to those in the nutritional counseling group (CG) after 6 months. However, mean CD4 counts at 6 months compared to baseline did not significantly differ between the MO and CG groups [106]. Finally, a randomized controlled trial was conducted at regional hospitals in Kenya, Uganda, and Zimbabwe to determine the effects of providing ready-to-use supplementary food (RUSF) for 48 weeks to undernourished (BMI 16–18 kg/m^2) adults and children (5–17 years) initiating ART. Adults and teens (age 13+) in the RUSF group had significantly higher weight gain compared to the control group. However, there were no significant differences in CD4 cell counts, viral suppression, and adverse events between the two groups [107]. Together, these findings suggest supplementary feeding of PWH in SSA can improve ART adherence, weight gain, and patient retention.

The *Nutritional Support for Africans Adults Starting Antiretroviral Therapy* (NUSTART) trial randomized 1815 PWH with BMI <18.5 kg/m^2 in Zambia and Tanzania to lipid-based nutritional supplement (LNS) containing multiple vitamins and minerals, including phosphate, potassium, and magnesium, versus LNS alone. At baseline, a lower CD4+ T cell count, BMI, and mid-arm circumference, and higher CRP, were associated with an increased risk of subsequent mortality [108, 109], but no mortality benefit of the fortified compared to unfortified LNS was observed. A sub-study of NUSTART found a greater CRP reduction after ART initiation was associated with higher fat-free mass gain, suggesting reduced inflammation can promote anabolism and recovery of skeletal muscle [110–112]. As earlier studies identified low serum phosphate as a predictor of early mortality in undernourished PWH [44, 45], a separate NUSTART sub-study demonstrated adverse shifts in electrolytes in undernourished PWH may also contribute to mortality in this group [113]. Taken together, trials of macronutrient supplementation in low BMI PWH indicate potential benefits for weight gain and adherence, but no clear reduction in mortality. However, supplementary feeding and promotion of weight gain in low BMI PWH did not improve CD4 recovery nor other virologic and immunologic biomarkers. Further studies are needed to understand the impaired CD4 recovery in low BMI PWH following supplementary feeding.

Pharmacological Therapeutic Interventions: Appetite Stimulants and Anabolic Agents

Cachexia is a common issue in PWH and megestrol acetate, a synthetic progesterone derivative that is approved for treating weight loss, and has been evaluated as a potential therapy for promoting weight gain in PWH [114, 115]. Megestrol acetate administration to persons with advanced HIV initiating ART in a small trial demonstrated that 18 out of the 22 patients showed improved appetite and weight gain (mean weight gain 7.3 kg, range − 4.1 to 17.3) after 72 weeks [116]. Furthermore, a multi-center clinical trial of 100 persons with AIDS reported that participants administered 800 mg megestrol acetate daily had significantly higher mean weight gain and appetite compared to placebo-treated participants (mean weight gain 4.32 kg, range 2.42 to 6.22) after 8 weeks [117, 118]. Another trial with 271 participants also reported that PWH with HIV-associated wasting administered 800 mg of megestrol daily had a mean weight gain of 8.3 lbs compared to − 1.1 lbs in placebo-treated participants ($p < 0.001$) [119].

Dronabinol or Δ-9-tetrahydrocannabinol (THC) is a synthetic derivative that mimics the actions of THC from the naturally occurring *Cannabis sativa* to stimulate appetite [114, 120]. A multi-center clinical trial in 52 PWH initiating ART demonstrated that megestrol acetate treatment alone (750 mg/day) showed the greatest mean weight gain (+6.5 ± 1.1 kg), followed by megestrol acetate and dronabinol (2.5 mg twice daily) in combination (+6.0 ± 1.0 kg). Dronabinol (2.5 mg twice daily) alone or megestrol acetate (250 mg/day) + dronabinol (2.5 mg twice daily) produced poor weight gain (− 2.0 ± 1.3 kg and − 0.3 ± 1.0 kg, respectively) [121]. Together, these findings suggest that megestrol acetate and/or dronabinol are well-tolerated potential therapeutic for stimulating promoting weight gain in PWH.

Trials have assessed whether anabolic agents, including testosterone, testosterone derivatives, and recombinant human growth hormone (rhGH), promote muscle mass gain in PWH [122]. A study of 79 HIV+ men demonstrated that megestrol plus testosterone (MA/TE) or megestrol plus placebo (MA/PL) treatment increased weight gain (median 5.3 and 7.3 kg in MA/TE and MA/PL, respectively), lean body mass (3.3 and 5.3 kg), and fat mass (3.0 and 3.8 kg). Sexual functioning in MA/TE was unchanged but declined in the MA/PL [123]. Testosterone therapy is primarily recommended for untreated or ART-experienced PWH with hypogonadism, low testosterone levels, low libido, and HIV-wasting [124]. In another study, 41 HIV+ men with low testosterone levels (< 400 ng/dL) were treated with testosterone (10 mg over 24-h period) or placebo skin patches. After 12 weeks, a change in lean body mass was observed in testosterone treated group (1.364 ± 0.533 kg, $p = 0.02$) but not the placebo group (0.186 ± 0.470 kg, p = NS [125]). A meta-analysis reported that testosterone supplementation was associated with a significant increase in total body weight, serum total testosterone, and fat mass levels in PWH compared to control groups. Furthermore, supplementation significantly increased lean body mass in male patients, but no difference in lean body mass was observed in women treated with testosterone [126]. A separate study also reported that testosterone replacement therapy did not promote fat-free mass and body weight gain in 52 medically stable HIV+ women [127].

Lastly, recombinant human growth hormones (rhGHs), which promote weight gain by inhibiting the breakdown of protein and depletion of nitrogen, have also been assessed in PWH [128]. One study administered rhGH or placebo daily to 178 PWH with HIV-associated wasting for 12 weeks. Compared to placebo, rhGH treatment significantly increased mean body weight (1.6 ± 3.7 kg, $p < 0.001$), lean body mass (3.0 ± 3.0 kg, $p < 0.001$) and decreased fat mass (− 1.7 ± kg, $p < 0.001$) [129]. In summary, both appetite stimulants and anabolic agents may serve as effective therapeutic options for boosting weight gain among low BMI PWH initiating ART, though additional studies are clearly needed in SSA.

Pharmacological Interventions: Adipokines and Recombinant Leptin Therapy

Loss of adipose tissue, whether from calorie restriction or disease-related wasting, is associated with changes in circulating adipokines, including a reduction in leptin [130]. Several studies have demonstrated that decreased leptin levels in PWH was associated with higher mortality and decreased CD4+ T cell recovery [87, 88, 131–133]. Thus, it has been suggested that human recombinant leptin replacement therapy may potentially benefit low BMI PWH. Recombinant human leptin administered (0.01 mg/kg and 0.03 mg/kg) twice daily for 3 months in eight HIV+ hypoleptinemic men improved insulin sensitivity and dyslipidemia. Serum leptin levels increased from a baseline mean of 7.7 ± 1.9 to 21.3 ± 5.3 ng/ml after 3 months ($p = 0.002$), but there was no effect on CD4+ T cell counts [134]. Another study administered metreleptin, a synthetic analog of the hormone leptin, twice a day (0.02 mg/kg) for 2 months to seven hypoleptinemic ART-treated men. Compared to controls, metreleptin improved insulin resistance but again did not improve CD4+ T cell counts [135]. In these small clinical trials, leptin therapy did not increase CD4+ T cell reconstitution in PWH initiating ART; however, it is possible an effect was not observed because the studies were conducted in PWH with a baseline BMI range of 22–25 kg/m^2. To date, no studies have assessed the use of leptin therapy to promote immune recovery among low BMI PWH initiating ART, or among populations in SSA.

Future Directions

The intersection between HIV infection and endemic undernutrition in SSA, and the association between low BMI at treatment initiation and early ART mortality, has major implications for global health and represents an area of continuing research. While efficacy of modern ART is clear in low BMI PWH, further investigation is needed to understand the immunological factors contributing to poor CD4+ T cell recovery and the subset of individuals most at risk of adverse events. Efforts to improve ART outcomes in resource-limited settings can be aided by improved diagnostic tools and methods for distinguishing between chronic undernutrition from inadequate energy consumption versus HIV-associated wasting syndrome. This distinction may reveal varying metabolic abnormalities and allow for more tailored patient evaluations and treatment. Finally, prospective trials with nutritional supplementation and/or pharmacologic therapy among persons with low BMI at ART initiation are needed to improve the health outcomes of African PWH.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Declarations

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
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