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Review

Obesity, Vascular Disease and Frailty in Aging Women with HIV

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ABSTRACT

Women with chronic HIV infection (WWH) living in the United States, experience a disproportionately high rate of obesity compared to uninfected populations. Both overweight and obesity, particularly central obesity, are major contributors to insulin resistance, hypertension, and dyslipidemia—the major components of metabolic syndromes, including type 2 diabetes, and leading to increased cardiovascular risk, including coronary heart disease, and cerebrovascular diseases. Notably, declining physical performance and frailty co-occur with vascular morbidities as well as changes in bone. These factors tend to exacerbate each other and accelerate the aging trajectory, leading to poorer quality of life, cognitive impairments, dementia, and eventually, death. In WWH, persistent HIV infection, sustained treatment for HIV infection, and concomitant obesity, may accelerate aging-related morbidities and poorer aging outcomes. Furthermore, health disparities factors common among some WWH, are independently associated with obesity and higher vascular risk. The purpose of this review is to describe the constellation of obesity, cardio- and cerebrovascular diseases, bone health and frailty among aging WWH, a 21st century emergence.

KEYWORDS: frailty; HIV; obesity; cardiovascular disease; aging; bone

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ABBREVIATIONS

WWH, women with HIV infection; HIV, human immunodeficiency virus; ART, antiretroviral therapies; kg, kilograms; m, meter; BMI, body mass index; CVD, cardiovascular disease; BMD, bone mineral density; AD, Alzheimer's disease; T2D, type 2 diabetes; ADRD, AD and related dementias; WIHS, Women's Interagency HIV Study; ml, milliliter; INSTI, integrase strand-transfer inhibitor; cm, centimeter; WC, waist

circumference; WHR, waist-to-hip ratio; NHLBI, National Heart, Lung and Blood Institute; FFP, Fried Frailty Phenotype; AIDS, Acquired Immunodeficiency Syndrome; VACS, Veterans Aging Cohort Study; CES-D, Centers for Epidemiologic Studies—Depression; FINDRISC, Finnish Diabetes Risk Score; CaMos, Canadian Multicentre Osteoporosis Study; IGFBG-1, Insulin Like Growth Factor Binding Protein; IGF-1, Insulin Like Growth Factor-1; r, correlation coefficient; OR, odds ratio; 95% CI, 95% Confidence Interval; TBS, trabecular bone score; %, percent; CSVD, Cerebral Small Vessel Disease; WMH, white matter hyperintensities; MRI, magnetic resonance imaging; FSRP, Framingham Stroke Risk Profile; PrEP, Pre-exposure prophylaxis

INTRODUCTION

The HIV epidemic, in its fourth decade, is a treatable chronic condition affecting an increasingly older population [1]. Women with chronic HIV infection (WWH) experience disproportionate obesity and are living longer than ever observed in the history of the HIV epidemic. In the United States, the HIV epidemic began with the first reporting of AIDS in 1981 [2]. Over the last 40 years, advancements in HIV infection treatment regimens have led to a medical 'miracle'—the successful treatment and control of HIV infection. Introduction of antiretroviral therapies (ART) and optimization of ART regimens have led to a growing population of older adults with chronic HIV infection never before observed in human history. However, more effective, newer generations of ART tend to promote body weight gain to obese levels (body mass index (BMI) $\geq$30 kg/m^2), and increase cardiometabolic risk. Observational longitudinal cohorts of WWH report an average BMI that is obese as well as predominant central obesity (waist circumference >88 cm), which is a major risk factor for insulin resistance and cardiovascular disease (CVD) [3,4]. In addition, WWH continue to show lower bone mineral density (BMD) compared to uninfected women [5].

The HIV-aging phenomenon coincides with global aging. Vascular diseases, both cardio- and cerebrovascular diseases, were among the top 10 most common causes of death worldwide in 2019 [6]. Ischemic heart disease is the number one cause of death, followed by stroke (number two, Alzheimer's disease (AD) (number 7, and Type 2 diabetes (number 9). AD is included among the top 10, since it is a neurodegenerative disease with a strong evidence base of vascular risk factors [7,8] and neurovascular etiology [9]. One of the reasons for vascular diseases comprising four of the top 10 causes of death is their association with the evolving pandemic of obesity. Approximately 39% of the world's adult population was overweight and 13% were obese according to 2016 global estimates [10]. Obesity during middle-age is associated with higher risk of several adult life cardiovascular risk factors and events including hypertension, dyslipidaemia, type 2 diabetes (T2D), sleep disorders, atherosclerosis, and overall CVD [3,10]. These CVD risk factors are subsequently associated

with cerebrovascular diseases such as stroke and late-onset, sporadic AD and related dementias (ADRD) [7], including vascular cognitive impairments and vascular dementias [11]. In addition, while higher BMI increases weight-bearing and enhances BMD, at obese levels and with the presence of other chronic conditions and limitations in mobility, this may not be the case, particularly among Black women [12].

Obesity among WWH is not only related to ART, but can also result from health disparities factors that are pervasive among aging WWH. These factors interfere with healthy living practices, and access to public health and health care interventions for obesity, T2D, CVD and cerebrovascular diseases [13–19]. Health disparities arise from variations in sociodemographic variables (age, income, education race/ethnicity and culture); challenging built environments that are common among major urban centers with high population densities and inherent barriers to physical activity promoting sedentary lifestyles; food insecurities; food deserts characteristic of urban environments (areas where access to healthy food is limited and unaffordable); employment and unemployment stresses; dealing with competing interests such as care-giving for children, grandchildren, aging parents, and other family members; and lack of social support. (See Figure 1) Thus, primary prevention of obesity is largely neglected, often followed by poor management of sequelae as secondary and tertiary intervention strategies, and bone health is often ignored.

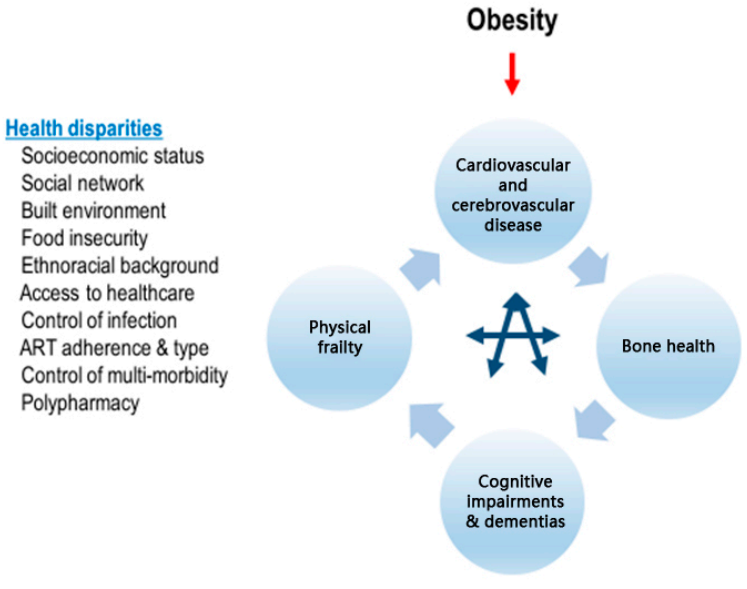

Figure 1. A constellation of obesity, vascular, bone, frailty and brain aging factors against a background of health disparities in aging women with chronic HIV infection.

The importance of multi-morbid HIV infection, obesity, vascular diseases and poor bone health is not only a serious issue for the medical community, but has been echoed in discussions among WWH [20]. A report of the HIV and Aging workgroup, convened by the NIH Office of

AIDS Research, discussed the importance of engaging HIV cohorts, such as the Women's Interagency HIV Study (WIHS) to address issues related to aging and HIV [21]. Longitudinal case-control studies such as the WIHS (now the MACS/WIHS Combined Cohort Study, 27 years old in 2021 and funded through 2026) provide a strong foundation for studying physical, cognitive and biological aging, in health disparities communities.

In this review, we address the obesity that is associated with HIV infection in aging women and its role in vascular diseases, bone health and frailty. Our hypothesis is that WWH experience more obesity, which leads to higher risk for vascular diseases; and that this is concomitant with poor bone health. Together, these factors influence aging frailty characterized by decline in physical functioning, with corresponding cognitive decline and dementia.

OBESITY IN HIV INFECTION

Among WWH, ART must be considered in the evaluation of obesity, CVD risk and frailty. ART was introduced in 1996 and since then, control of HIV infection in geographical areas and health care venues with access to and proactive use of ART, has markedly improved. ART is the first-line of HIV treatment. Adherence to ART reduces HIV viral load to undetectable levels (<40–75 copies/mL) and increases $CD4^+$ counts to desirable levels (>500 cells/mL). It is ideally prescribed within 24 h of HIV infection diagnosis in major urban medical centers serving high-risk populations. ART has increased the probability of longer-term survival that is almost equivalent to those without infection [22]. Despite the success of ART in controlling HIV infection, adherence to several ART increases total and central obesity [23,24], CVD and potentially cerebrovascular disease [25,26]. Integrase strand-transfer inhibitor (INSTI)-based ART in particular, is associated with severe body weight gain [24,27]. In the WIHS for example, over a 2 year average follow-up, women who switched to an INSTI-based ART or added it to their ongoing regimen experienced an average increase of 2.1 kg in body weight; 0.8 kg/m² in BMI; 1.4% in percent body fat; and 2.0, 1.9, 0.6, and 1.0cm in waist, hip, arm, and thigh circumferences, respectively (all $p < 0.05$). There were no differences in magnitude of these changes by INSTI type [27].

Underweight, overweight and obesity are commonly defined anthropometrically among those with and without HIV infection. Measures include BMI, waist circumference (WC), and waist-to-hip ratio (WHR). Generally in adults, either total (based on BMI) or central (based on WC or WHR) obesity indicates higher amounts of adipose tissue *versus* other body tissue types. Table 1 summarizes the National Heart, Lung and Blood Institute (NHLBI) classifications of total and central obesity associated with CVD outcomes and mortality [28].

Table 1. Classification of overweight and obesity by BMI and WC, and disease [1] risk for women [28].

		Disease Risk Relative to Normal BMI and WC [2]		
	BMI (kg/m^2)	**Obesity class**	**Women ≤ 88 cm (35 in)**	**Women > 88 cm (35 in) [3]**
Underweight	<18.5			
Normal	18.5–24.9			
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	1	High	Very high
	35.0–39.9	2	Very high	Very High
Extreme Obesity	≥40	3	Extremely high	Extremely high

[1] Disease risk for type 2 diabetes, hypertension, and CVD.

[2] waist circumference.

[3] Increased WC is a marker for increased risk, even in women of normal weight.

FRAILTY IN HIV INFECTION

Frailty among HIV populations is associated with functional impairment and disability [29]. Published in 2003, the Fried Frailty Index, more accurately termed the Fried Frailty Phenotype (FFP), is a useful construct with which to predict poor quality of life, cognitive impairment, dementias and death [30], particularly in usual aging elderly (65 years and older) [31]. The FFP has been used in studies of HIV as well, and defined using well-described criteria [32]. Using the FFP, frailty is defined as exhibiting at least three of five characteristics: (1) impaired mobility, (2) reduced grip strength, (3) physical exhaustion, (4) unintentional weight loss and (5) low physical activity. In the WIHS, mobility was measured using a 4 meter timed gait test using cut-offs from the Cardiovascular Health Study or from similar, at-risk uninfected adults [32,33]. Grip strength was measured using a dominant hand-held dynamometer with maximum force, using cut-offs from the CHS or from similar, at risk uninfected adults. Physical exhaustion was measured as a "Yes" to the question: "During the past four weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra efforts)"? Low physical activity was a "Yes" to "Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?" Unintentional weight loss was a "Yes" to: "Since your last visit, have you had unintentional weight loss of at least 10 pounds?" Some of these latter three components can be verified to some extent by clinical measurements.

The FFP has been measured in middle-aged WWH who may be at risk for premature aging [29,34]. These studies show that these WWH experience a prevalence of the FFP often greater than that observed in elderly [33,35,36]. The reason for this early manifestation of the FFP may be a consequence of the HIV infection itself, including suboptimal medication and control of infection early on, comorbid diseases (infectious or non-infectious) [35,37] and/or lifestyle and health disparities factors

that may be common among women with HIV infection, such as smoking and substance use and abuse [38].

OBESITY AND FRAILTY

Several published reports suggest a U-shaped relationship between BMI and the FFP in uninfected elderly. This is similar to the well-published U-shaped relationship between BMI and mortality, where both the upper (overweight and obesity) and lower (underweight) ends of the BMI distribution are associated with higher mortality (See Table 1) [39]. Aging with obesity and frailty, sometimes referred to as 'obesity frailty' is induced by sarcopenia [40] or myosteatosis [41] that arises from the combination of obesity and changes in skeletal muscle. This may be especially relevant for WWH compared to men with HIV infection [42]. Obesity frailty accompanies and may precede aging-related physical frailty, which is also accompanied by aging-related changes in skeletal muscle and bone, as well as being associated with health disparities [43].

In WWH to date, a U-shaped relationship between BMI and FFP has not been replicated for two primary reasons. First, adults infected with HIV at the beginning of the epidemic were primarily men and died before the age of 50 years from Acquired Immunodeficiency Syndrome (AIDS) or AIDS-related illnesses and complications that were accompanied by extreme body weight loss and cachexia. Second, comparably aging WWH who are adherent to ART are scarce. Even so, it may be difficult to evaluate given the higher average BMI of these women. While the ability to analyze continuous BMI distributions as part of life and disease course natural histories is not universal, the benefit of long-term monitoring of this phenomenon remain.

At least one report from the WIHS suggested no multivariate-adjusted association between BMI and the FFP in WWH or at risk uninfected women at average age 38 years [33], despite the existence of a univariate association. In this same group of women, the FFP at middle age was predictive of death over approximately 8 years in survival models evaluating a combination of physical frailty (FFP), metabolic (Veterans Aging Cohort Study (VACS) Index) frailty, and mental health (Centers for Epidemiologic Studies-Depression (CES-D)) indices [44]. In all aforementioned analyses there was adjustment for sociodemographic, CVD and aging factors, and BMI.

OBESITY, OSTEOPOROSIS AND CARDIOVASCULAR DISEASE

The association between obesity and CVD has been long-observed, with potential pathophysiological mechanisms based on vascular, inflammatory, endocrine, metabolic, and neurovascular dysregulation [4]. The strong role of obesity in CVD risk is evident based on the inclusion of BMI in diabetes and CVD risk scores such as the American Diabetes Association and Finnish Diabetes Risk Score (FINDRISC) [45], and Framingham CVD risk scores [46].

While seemingly unrelated disorders that increase with age, accumulating evidence indicate a common seed and soil hypothesis and shared pathogenetic mechanisms among obesity, CVD and osteoporosis [47–52]. In 100 obese African-American women (average age, 63 years; average BMI 26.6 kg/m^2), age, hypertension, and low BMD were independent predictors of higher arterial stiffness. Thus, the bone mineral loss leading to lower BMD may increase CVD risk in African-Americans independent of obesogenic effects [49]. Underlying mechanisms postulated for this complex relationship of obesity, osteoporosis and CVD include dyslipidemia, oxidative stress, inflammation, hyperhomocysteinemia, hypertension, and diabetes, all of which have also been associated with higher risk of low BMD or increased bone fragility [48]. Furthermore, nitric oxide, known for its atheroprotective effects, plays a role in osteoblast function and bone turnover. In a randomized controlled trial, nitroglycerine (a nitric oxide donor) was as effective as estrogen in preventing bone loss in women with surgical menopause [53].

OBESITY, OSTEOPOROSIS AND FRAILTY

Accumulating evidence indicates that both obesity and osteoporotic fractures are associated with faster frailty progression [54]. The Canadian Multicentre Osteoporosis Study (CaMos) identified risk factors for frailty progression among over 5500 community-dwelling women age 50 years and older. Rates of change in frailty over 10 years were examined using the 30-item CaMos Frailty Index. Both obesity and new vertebral or hip fractures were associated with frailty progression [54]. Sedentary lifestyle is a possible explanation for this observed association [55]; and/or obesity frailty, a sarcopenic condition.

However, as aforementioned, the relationship between osteoporosis and obesity is complex and obesity is often shown as protective against osteoporosis [56]. Postulated mechanisms for protection in postmenopausal obese women include increased adipose tissue aromatization of androstenedione, secreted from the adrenal glands, into bioactive estrone that maintains or increases bone mass [56,57]; greater weight-bearing concurrent with obesity [56,57]; and the decreased SHBG in obesity that is associated with higher circulating free sex steroids and hyperinsulinemia. This may lead to reduced production of IGFBG-1, an increase in IGF-1, and subsequent osteoblast proliferation and increased BMD [56]. In addition, serum leptin is strongly correlated with BMI, even in WWH (BMI × leptin, $r > 0.70$) [58]. Leptin may exert peripheral effects similar to estrogen, leading to osteoblastic differentiation and increases in BMD [57]. However, it is important to note that leptin has very complex actions on bone, including inhibition of bone formation through actions on the hypothalamus [59] as well as effects on bone resorption through regulation of neural pathways [60], therefore, it controls both aspects of bone remodeling.

Despite biological plausibility, there is inconsistent evidence for a positive association between high BMI and bone health. First, central obesity (higher WC or WHR) increases osteoporosis risk even in non-obese adults [61]. Furthermore, the protective effects of obesity on BMD that have been documented among Whites are not necessarily replicated in other race/ethnic groups [12]. In a study by our group, among over 3000 White and Black women (average age 58 years, average BMI 30.6 kg/m^2), per 1.0 kg/m^2 BMI, the odds of having a BMD one standard deviation below the average peak BMD, was less (OR = 0.90, 95% CI 0.87–0.94, $p < 0.01$) among White women, compared to Black women, among whom a higher odds was observed when compared to Whites (OR 1.015, 95% CI 1.01–1.14, $p < 0.01$). These data indicate a potential race-dependent association of obesity with BMD, perhaps due to genetic background, lower levels of physical activity, or lower circulating vitamin D levels among Black compared to White women [62].

Superimposed upon observations in uninfected women, is HIV infection status and ART adherence, which paints a more complex bone health picture [23]. In the WIHS, among WWH who were on average obese and adherent to ART, one report suggested that older age, White (vs Black) race, prior fracture, history of cocaine use, and history of injection drug use were significant predictors of incident fracture, a marker of low BMD, over 10 years follow-up [63]. However, when these women were evaluated over 5.4 years during premenopause only, there was no association of HIV status with fracture risk; and traditional risk factors such as White (vs Black) race, hepatitis C virus infection, and higher serum creatinine were associated with fracture [64]. In another report from the WIHS, among WWH ($N = 246$) and uninfected women ($N = 219$), average age 45 years and obese, non-Black women experienced greater total hip BMD loss, while Black women experienced greater menopause-associated decline in total hip BMD compared with non-Black women [63]. In addition, among 437 WWH and without infection [5] cross-sectional observations showed that WWH have degraded skeletal microarchitecture (27% vs 9%, $P = 0.001$) and a lower mean lumbar spine (LS) trabecular bone score (TBS) (1.3 ± 0.1 vs 1.4 ± 0.1, $P < 0.001$) than uninfected women, after adjusting for age, race, menopause status, and BMI. However, there were no differences between WWH and uninfected women in the correlation between annual change in TBS and LS BMD change; and mean percent annual change in TBS (−1.0%/year ± 2.9% for WWH vs −0.8%/year ± 1.7% for uninfected women, $P = 0.42$). A plausible explanation that annual changes in TBS and BMD do not vary significantly between infected and uninfected women is that while HIV itself causes bone loss, much of the ART-related bone loss occurs acutely, during the first 1–2 years [65].

Falls, another indicator of low BMD, were associated with the FFP in WWH, but not necessarily HIV status [66]. In the WIHS, the FFP predicted an almost 2-fold higher odds of recurrent, but not single, falls among middle-aged WWH. Of the FFP components, unintentional weight loss and

exhaustion were most informative [67]. Overall, data suggest a multifaceted bone health and frailty risk profile among obese WWH.

OBESITY AND THE BRAIN

Epidemiological studies show that higher midlife BMI and WC are associated with a higher risk of late-onset, sporadic dementias, including AD, which are typically diagnosed at age 65 years or older [68–73]. BMI and central adiposity have also been associated with cognitive impairments in adults aged ≥70 years [74]. Domain-specific associations are also observed. For example, longer exposure to elevated BMI and WC in midlife has been associated with lower memory function at 60–64 years of age [75]; and higher BMI and larger WC at midlife has been associated with lower executive function 10 years later [76].

There is a paucity of comparable reports among WWH, due to the younger age of surviving WWH, the rarity of studies that include cognitive and dementia outcomes, as well as adequate duration of longitudinal follow-up. However, in one multivariable-adjusted cross-sectional analyses, among women with or at-risk for HIV infection in the WIHS, both higher BMI and WC were associated with better cognitive performance at average age 38 years [77]. It was deemed that a higher BMI is a marker for ART adherence, and that these women possess a healthier risk profile.

The higher amounts of adipose tissue accompanying overweight and obesity may contribute to the alterations in peripheral and cerebral circulation that are more pronounced with aging [78]. Adipose tissue and its secretory products (adipokines, cytokines, sex hormones, free fatty acids), contribute to vascular and metabolic effects on human health, and influence function in numerous tissues including the brain [79]. Actions occur both peripherally and centrally, and include inducing atherosclerosis in large carotid and cerebral arteries, and impairing peripheral microvascular function and cerebral microcirculation.

Both cardio- and cerebrovascular disease play key roles in the development of cognitive impairments and dementia [9]. In the brain, outcomes include decreased cerebral blood flow and Cerebral Small Vessel Disease (CSVD). CSVD is comprised of white matter hyperintensities (WMH), lacunes, microbleeds, and neurodegeneration on brain MRI; and obesity has been associated with these CSVD components [80–82]. Alterations in the cerebral circulation may also contribute to Vascular Cognitive Impairments and AD given the essential role of maintaining cerebral blood flow and the neurovascular unit [9]. ‘Every neuron has a capillary’ to maintain normal neuronal function [83]. Practically, the Framingham Stroke Risk Profile (FSRP), while not including BMI in its algorithm, includes sequelae of obesity such as high systolic blood pressure and T2D [84]. Given that WWH present for the first time at older ages when late-life cognitive impairments and dementias occur, with lifetimes of exposure to high vascular and cardiometabolic risk, the threat

of adverse brain events and vascular cognitive impairments with aging is high.

A POTENTIAL GESTALT: STRESS LINKS OBESITY, VASCULAR DISEASES, FRAILTY, BONE AND COGNITION, IN AGING WOMEN WITH HIV INFECTION

Developmental origins hypotheses link brain and bone in earliest and latest life [85]. Small head circumference and low birth weight are associated with age-related cognitive dysfunction in uninfected individuals [86]; and lower birth weights (age-adjusted OR = 1.72; 95% CI 1.29–2.28, $P < 0.001$) and shorter gestational time (age-adjusted OR = 1.13; 95% CI 1.04–1.24, $P = 0.005$) are associated with a higher odds of lifetime depression [87]. In addition, there is evidence for both heart-brain and fat-brain axes [88,89]. Allostasis is a theoretical model suggesting that individual differences in susceptibility to stress over the life course, are linked to behavioral responses to environmental challenges, as well as developmental origins. These behaviors are coupled to physiologic and pathophysiologic responses [90], and there is a process whereby the body responds to stress to maintain homeostasis. Understanding long-term health of WWH requires a life course perspective.

This complex scenario baffles our abilities to tease apart health outcomes among WWH. Thus, the definition of allostasis is extended as the cost of chronic exposure to fluctuating or heightened neuroendocrine responses resulting from repeated or chronic environmental challenges and social burden that an individual reacts to as being particularly stressful [90,91]. Thus, the combination of aging and health disparities directly affect neural mechanisms contributing to cognition and cognitive decline, as well as frailty and depressive symptoms [92]. Considerations for WWH are that HIV infection plus obesity contribute a profound allostatic load comprised of external stressors evoked by health disparities, such as food insecurities and sedentary lifestyles; and internal stressors including enhanced vascular, metabolic and neuronal stress. Repeatedly high stress levels alter the biology of stress and appetite/energy regulation, with both components directly affecting neural mechanisms contributing to stress-induced and food cue-induced motivation that involves encouragement through signals (verbal and non-verbal) and engagement in overeating of foods that enhance risk of weight gain and obesity. While the ‘jolly fat’ hypothesis, which proposed that obesity correlated inversely with depressive symptoms, was first reported in 1976 [93], women in particular, are not observed to be ‘jolly fat’ [94]. However, in the WIHS, there was a null association between obesity and depressive symptom score cross-sectionally at average age 38 years [95]. Yet, for over 20 years, obesity-related stress has been pinpointed as a major factor associated with lack of well-being [96].

Finally, while we described factors related to frailty among HIV-infected women, further research is needed to define effective

interventions to prevent and treat frailty among these vulnerable populations, apart from the traditional life style interventions (diet and exercise) that are deemed insufficient among populations with HIV disease [97].

CONCLUSION

A review of a well-established literature evidences relationships among obesity, CVD, and bone health in physical frailty and brain aging among WWH. When considered against a background of health disparities, there may manifest prevention approaches not considered previously, as illustrated in Figure 2.

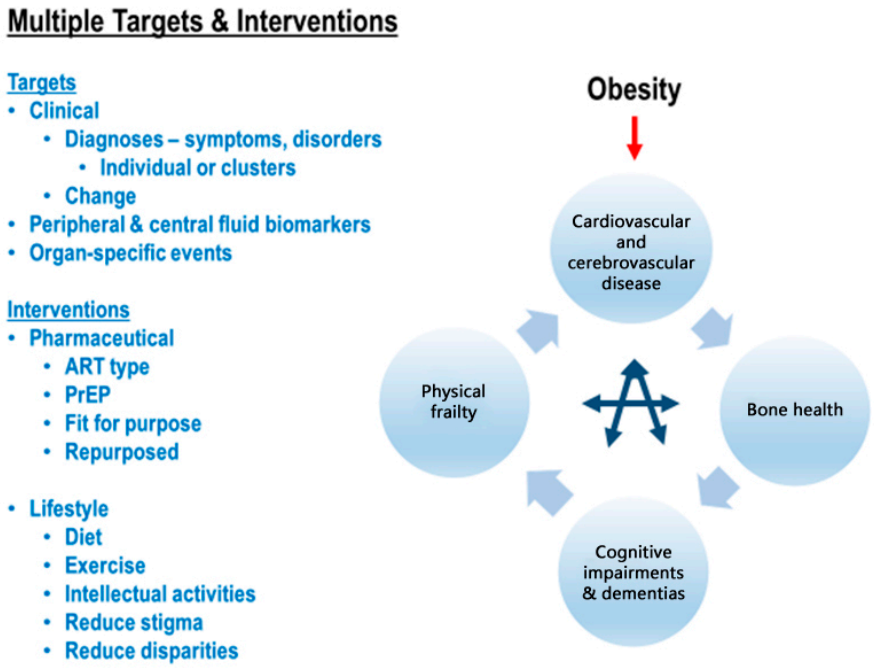

Figure 2. Multiple treatment targets and interventions in aging women with chronic HIV infection. ART, antiretroviral therapies; PrEP, Pre-exposure prophylaxis.

It is unclear whether WWH and obesity experience accelerated and/or aging with excess morbidities, and whether more adverse aging is related to the infection per se, the inflammatory and metabolic effects of the infection and adipose tissue, obesity effects of HIV medications, or an overall HIV + obesity-initiated and/or -mediated increase in allostatic load over the life course [98,99]. Better understanding of this area will propel us forward to a new and novel area of investigation linking brain and periphery in aging HIV [73,79].

DATA AVAILABILITY

No data were generated from the study.

AUTHOR CONTRIBUTIONS

Prof. Gustafson and Dr. McFarlane developed the idea, reviewed the literature, and wrote this review.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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