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Frailty and HIV: Moving from Characterization to Intervention

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Abstract

Purpose of Review: While the characteristics associated with frailty in people with HIV (PWH) have been well-described, little is known regarding interventions to slow or reverse frailty. Here we review interventions to prevent or treat frailty in the general population and in people with HIV (PWH).

Recent Findings: Frailty interventions have primarily relied on non-pharmacologic interventions (e.g., exercise, nutrition). Although few have addressed frailty, many of these therapies have shown benefit on components of frailty including gait speed, strength, and low activity among PWH. When non-pharmacologic interventions are insufficient, pharmacologic interventions may be necessary. Many interventions have been tested in preclinical models, but few have been tested or shown benefit among older adults with or without HIV.

Summary: Ultimately, pharmacologic and non-pharmacologic interventions have the potential to improve vulnerability that underlies frailty in PWH, though clinical data is currently sparse.

Keywords

Frailty interventions; mobility; HIV and aging; senolytics; pillars of aging

Introduction

With early initiation and consistent use of antiretroviral therapy (ART), HIV has been transformed from a progressive disease of wasting and immune compromise, to a chronically managed condition. With advances in treatment, more than 50% of those living in the US are now over the age of 50[1]. However, even with effective and consistent ART, people with HIV appear to have alterations in the underlying “pillars of aging”, including inflammation, immune senescence, metabolism, and mitochondrial function[2]. These

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alterations in combination with lifestyle factors (smoking, sedentary behavior, substance use), contribute to an accelerated or accentuated occurrence of many comorbidities, including cardiovascular disease, osteoporosis, lung and liver diseases, and cognitive impairment. Furthermore, the combined effects of aging and comorbidity burden have led to a state of vulnerability, or frailty, identified among people with HIV (PWH) at a younger age than typically seen among people aging without HIV[3, 4]. This phenotype of frailty has been described by Fried et al. as encompassing low levels of activity, fatigue, slowness, weakness, and weight loss[5]. As a state of vulnerability, frailty represents an opportunity to intervene and prevent transition to disability, institutionalization, or death. While the epidemiology and factors associated with frailty in PWH have been previously well described in the literature, relatively little is known regarding non-pharmacologic and pharmacologic interventions to slow or reverse frailty. Here we review what is known regarding treatment of frailty in the general population and how these interventions may apply or have been applied to PWH (Table 1). For nearly all of the interventions described below, early recognition of frailty or a pre-frail state and early introduction of interventions may provide the greatest benefit[6].

Non-Pharmacologic Interventions

Exercise and Physical Activity

With aging, self-initiated physical activity tends to decline (low activity). Decreased physical activity contributes to decreased strength (weakness) from lack of use, decreased exercise tolerance (gait speed), and easy fatigability with activity (fatigue)[7]. This lack of physical activity may be accompanied by decreased caloric intake and/or accompanied by decreased caloric expenditure, manifest by either a state of weight loss[7], or with weight gain[6], thus overlapping with components of the frailty phenotype[8]. While interventions of structured physical activity (i.e., exercise) may improve frailty through multiple pathways, mechanistically, physical activity decreases catabolism and muscle protein breakdown, improves mitochondrial function, and increases anabolic effects and muscle protein synthesis[6, 9]. Interventions incorporating physical activity or structured exercise target several components of the frailty phenotype, hence are the most effective interventions to prevent and reverse frailty in older adults with and without HIV[6, 9–11]. Many interventions in older adults focus on the effects of exercise on components of the frailty phenotype and less on the overall presence of frailty or frailty score. Cardiovascular exercise interventions can improve endurance (measured by V02 peak), improve muscle oxidative capacity to decrease fatigability, and may help to preserve lean mass during weight loss. The loss of muscle strength and quality that are synonymous with aging are counteracted with resistance exercise. Although muscle responses to resistance exercise may be attenuated with aging, even frail elderly can experience marked improvements in strength with resistance exercise[12].

The importance of physical activity in health of older adults is reflected in the recently updated recommendations by the U.S. Department of Health and Human Services recommendations[13] and the World Health Organization[14]. Both organizations recommend at least 150–300 weekly minutes of moderate-intensity aerobic physical activity,

as well as functional balance and strength training 3 or more days per week, and a new recommendation (from the World Health Organization) focused on reducing sedentary time[14]. A recent example of the benefits of regular exercise is seen through the LIFE Study, a large randomized intervention among older adults at risk for mobility impairment. The LIFE intervention included walking, resistance, and flexibility training compared to educational control, and yielded improvements in physical frailty components: 400-m walk time (endurance); a Short Physical Performance Battery including gait speed, lower extremity strength, and balance[15]; and cognitive frailty[16, 17], with greater improvements observed with higher "doses" of physical activity[18]. The effects of physical activity or structured exercise interventions on frailty or components of frailty in other populations have been recently reviewed[6, 8, 9].

Similar to literature in the older adult population, research on the benefits of physical activity and exercise on frailty in PWH can be extrapolated from the effect on components of frailty, with limited literature on improvement in the frailty phenotype or other measures of frailty. Most exercise interventions in PWH have focused on strength and endurance outcomes among younger PWH,[19] with few studies representative of the now majority of PWH aged 50 and older experiencing multimorbidity and impairments in physical function. Two excellent Cochrane reviews of endurance and resistance exercise interventions among PWH[20, 21] highlighted the benefits of exercise on strength, endurance, body composition and quality of life, but no frailty or physical function outcomes were assessed in the included studies, and studies almost exclusively included younger PWH.

In a recently completed study, we found significant improvements in measures of strength, endurance, and activity with a 24-week combined cardiovascular and resistance exercise intervention[22, 23]. Although no frail participants joined the study, the number of PWH with pre-frailty decreased with exercise[22]. In one of the few studies focused on older adults,[24] a 12-month supervised, twice weekly resistance exercise intervention among adults 60 years or older with or without HIV demonstrated improvements in many functional measures in both groups.[24] A multidimensional physiotherapy program including endurance and resistance exercise, stretching, and goal setting, found significantly improved physical function among 37 middle and older-aged PWH (mean age 51 years)[25]. Potential benefits of high-intensity interval training (HIIT) compared to continuous, high-intensity exercise among older adults with HIV (mean age 62 years) was also recently demonstrated: both the HIIT and continuous exercise groups experienced significant improvements in V02 peak, exercise endurance and strength[26]. Lower intensity or home-based interventions have also demonstrated benefit in improving gait speed and chair rise time (frailty components of gait and strength)[27], but generally to a lesser degree than center-based exercise interventions. The benefits of physical activity or exercise from observational and interventional studies on numerous endpoints, including frailty components, have also been recently summarized by our group[28]. Ongoing studies will further investigate the benefits of mHEALTH (NCT03708640, NCT04550676), high intensity interval training (NCT04550676), and community based exercise[29] among older adults with HIV, with frailty or frailty components as outcomes.

In addition to the direct benefits of exercise on components of frailty, physical activity and structured exercise may have added indirect benefits. For example, greater physical activity has been strongly associated with decreased fatigue among PWH in a cross-sectional study[30]. Physical activity or exercise is associated with improvement in sleep efficiency and decreased sleep disorders in some[31] but not all[32] studies of PWH, which may lead to decreased fatigability, a component of the frailty phenotype.

Nutritional Interventions

Exercise interventions are often combined with a nutritional component when targeting frailty in older populations. While nutritional replacement may stabilize or reverse weight loss, few studies have convincingly demonstrated a benefit of nutritional supplementation alone on frailty[33]. Nutritional interventions may include ensuring adequate dietary protein or providing supplemental protein, leucine, amino acids, beta-hydroxy-beta-methylbutyrate, vitamin replacement (vitamin D especially), ensuring greater caloric intake by removing dietary restrictions, or may target weight loss in frail or pre-frail individuals with obesity. In a recent systematic review, the benefit of multi-domain (nutrition, vitamins, counseling, exercise, pharmacologic) interventions on frailty were compared to mono-domain interventions[34]. Frailty tended to improve to a greater extent in the multi-domain vs mono-domain intervention, and in many studies, larger improvements were also maintained over time when an exercise intervention was included. The review also explored the benefit on the individual frailty domains, where the benefit of nutritional supplementation was seen primarily in the “weight loss” component of frailty. Very few studies demonstrated added benefit of nutrition beyond exercise for strength or activity[34]. However, the combination of exercise with nutritional interventions when focused on weight loss in obese older adults has been shown to preserve lean mass and result in greater gains in physical function than exercise or dietary weight loss alone[6, 35].

Nutritional supplementation in PWH was a mainstay of treatment for the profound wasting prior to the introduction of ART. Many interventional studies in the early AIDS era provided combinations of vitamins, supplements, total parenteral nutrition, and oral supplemental nutrition to improve weight and fatigue[36], sometimes in combination with exercise[37]. Although these studies have not been replicated in older adults specifically with frailty-related weight loss, one could assume that results may be similar, with an exercise stimulus providing improvement in lean mass and muscle function. Food security, or access to sufficient, safe, and nutritious food should also be a key consideration for older PWH. In older adults, financial constraints, transportation, and mobility may further impact access or ability to prepare food[38]. Food insecurity is associated with frailty in older adults with [39, 40] and without HIV[41], and food insecurity is six times more common among PWH compared to people without HIV[42]. Ensuring adequate and regular access to food should be a key component of nutritional interventions to reduce frailty in PWH.

While AIDS wasting is now uncommon, obesity has significantly increased[43], related to a multitude of factors[44, 45]. Obesity among PWH is associated with frailty in several different cohorts[46–48], and, similar to older adults without HIV, effective interventions to reduce frailty in PWH may need to target weight reduction through high quality diet in

combination with exercise[44]. Among PWH, a behavioral weight loss intervention incorporating physical activity counseling with nutritional education led to significant decreases in weight, and improvement in self-reported physical function although frailty or objective measures of physical function were not obtained[49]. Although we did not specifically target weight loss, we observed significant reductions in overall weight and central adiposity in conjunction with improvements in pre-frailty and physical function in our 24-week exercise intervention in older PWH[50].

Polypharmacy

As frailty often overlaps with comorbidity[51], frailty is inevitably accompanied by the use of multiple medications. Similarly, as frailty may manifest as underlying diseases are poorly controlled, interventions to optimize management of underlying comorbidities may result in the prescription of additional medications or higher doses of existing medications. Frailty itself may also alter the pharmacokinetics and pharmacodynamics of medications[52], and individuals with frailty are more likely to experience adverse drug effects, including falls[53]. Polypharmacy, often defined as 5 or more medications, is common in frailty, and associated with prolonged hospitalizations and risk for readmission[54], compared to patients without frailty and polypharmacy. Furthermore, each additional medication increases the risk of drug-drug interactions, adverse reactions, frailty, falls, and mortality[54]. Despite the perceived necessity of many medications to manage underlying disease, additional medications are often associated with more risk than benefit[54]. Many studies have explored the economic benefits and the ability to decrease medications in patients with polypharmacy, or whether de-prescribing can improve upon clinical outcomes such as medication-related adverse events and greater adherence[55, 56]. Although few studies have addressed the benefit of de-prescribing directly on frailty [56–59], the reduction in adverse reactions due to polypharmacy (fatigue, dizziness, cognitive slowing), may improve frailty or components of frailty.

Polypharmacy is even more common among older PWH, with the addition of at least two ART agents to routine medications, often with numerous drug-drug interactions. The link between polypharmacy and poor outcomes is similarly strong among PWH, including associations between polypharmacy and frailty[60], components of frailty[60], and increased fall risk[61, 62]. Although several studies have explored the frequency and clinical effects of polypharmacy, only one study has tested a de-prescribing intervention. In a pharmacist-led intervention among older PWH, 69% of patients had at least one medication discontinued, and almost 10% had six or more medications discontinued[63], many contraindicated for older adults[64]. In addition to targeting non-ART medications, newer studies in PWH support the efficacy and safety of two-drug ART regimens rather than the traditional three-drug regimens[65]. Decreasing the number of ART agents while maintaining viral suppression can decrease side effects and additional drug interactions for older or frail adults, particularly when the discontinued third agent may have known toxicity.

Combining de-escalation with non-pharmacologic interventions to manage symptoms may result in the most effective outcomes. For example, weight loss interventions decrease the need for blood pressure or diabetes medications, cognitive behavioral therapy may decrease

the need for psychiatric medications, and sleep hygiene and treatment of sleep apnea with continuous positive airway pressure may decrease night time sleeping aids or daytime stimulants.

Reduction in Fall Risk

Although falls are not a component of the frailty phenotype, there is significant overlap between those identified as frail and those at high risk for falls[66]. Frail individuals, due to weakness and mobility impairments, are more likely to fear falling or sustain a fall[67, 68], and a fall in a frail individual may precipitate a decline in frailty, particularly if the fall leads to injury[69]. Similarly, interventions targeting a decrease in fall risk, such as de-prescribing, balance training, or physical therapy[70], may also lead to improvements in frailty[71]. In PWH, falls occur at a similar frequency among middle-aged adults (aged 45–65 years) as observed among uninfected controls aged 65 or older[61, 62, 72, 73]. Similar to populations without HIV, falls are also strongly associated with frailty or components of frailty[61, 73–76]. While no specific interventions have targeted PWH with a high risk for or history of recurrent falls, some studies have shown improvement in balance[77]. Studies in PWH have included interventions that are often used for falls (Tai Chi, Qigong, yoga), but did not specifically look at an effect on falls[78, 79]. In an exercise intervention by our group[22], 10 of our 69 participants reported any fall in the 6 months prior to the intervention. During 24 weeks of exercise, 7 of the 10 fallers had no subsequent falls, while 3 reported another fall, and 2 initial non-fallers sustained a fall (unpublished data). Prevention of falls is an important component of functional independence, and future studies should explore the impact of frailty interventions on falls or fear of falling.

Mood and Cognition

As the components of the frailty phenotype closely align with symptoms of depression[80], distinguishing depression from frailty can be difficult. Depression and other mood disorders often co-occur with frailty in populations of both middle-age and older adults[80]. Mood disorders, including depression, can also masquerade as cognitive impairment among older adults, and evaluation of mood is one of the first components in an evaluation of dementia. Furthermore, cognitive impairment is often found hand-in-hand with frailty, in populations both with and without HIV. Thus, frailty, mood disorders, and cognition are closely related conditions[81, 82]. Complicating the association is the adverse effect profile of many medications used for mental health conditions, with drug-drug interactions or anticholinergic effects, particularly among older adults. These associations have been observed among PWH, where cognitive impairment and mood disorders are risk factors for frailty[48, 83–85], and use of medications for mood disorders are associated with frailty or components of frailty (gait)[86]. Ensuring that mood disorders and cognitive impairment are both identified and treated, as possible, is an important component to preventing further declines in frailty.

Multi-Modal Approaches

Frailty is caused by decline across multiple organ systems, thus interventions appear to be most effective when combined in a multimodal approach, whether in the context of specific interventions targeting frailty, or through coordination and implementation of medical care, as achieved through a comprehensive geriatric assessment. For example, in a large

interventional trial combining nutrition, cognitive training, physical training, the combination, or a control, the odds of improved frailty score were significantly greater in the combination group (Odds Ratio [OR] 5) compared to a control intervention, with a lower effect observed (OR ~2–3) for all single interventions[87]. Other multicomponent interventions have similarly demonstrated benefit, either in comparison to a control group or to single interventions[88, 89]. A comprehensive geriatric assessment individualizes care by incorporating physical, cognitive, and psychological function, environment and support, medications, and other health needs of each patient to maximize independence and preserve quality of life through a coordinated, interdisciplinary approach.

Many HIV clinics with Ryan White support have incorporated a multi-disciplinary approach to patient care, with onsite resources including social workers, pharmacists, nutritionists, and mental health care providers, though few have focused on aging-specific outcomes. Over the last 10 years, several clinics have established geriatric consultative services with additional multidisciplinary aging resources[90]. The Silver Clinic, a multidisciplinary clinic in Brighton, England, includes a once per month visit with a multidisciplinary team where older, at risk PWH are provided with coordinated and individualized referrals to specialists, social services, or other services. Of 52 initial referrals, 65% were frail by the FRAIL Scale at baseline. Although there was no change in FRAIL scale with the program, the authors note that frailty is usually progressive, thus the program may have prevented progression of frailty[91]. Other clinics in San Francisco and New York have published on satisfaction[92] and adherence to geriatrician recommendations[93], but improvement in frailty or components of frailty have not been published. Other healthcare systems have emphasized physical rehabilitation[94] as a multidimensional intervention that incorporates physical, social, and psychological health and could improve frailty[95].

Pharmacologic Interventions

Understanding Frailty Biology is Key to the Development of Pharmacologic Frailty Interventions

Some older adults may be unable to exercise to the extent necessary to reverse frailty, or frailty may persist despite interventions described above, and pharmacologic interventions may be necessary. Understanding the biological pathways that underlie frailty is critical to the development of pharmacologic interventions to prevent frailty onset, ameliorate frailty progression, and promote potential reversal or recovery to a non-frail state, all key to mitigating the adverse morbidity and mortality consequent to frailty. The state of vulnerability and loss of resilience inherent to frailty has been considered to be driven by the dysregulation of multiple physiologic systems, including those that disrupt homeostasis, energy balance, body composition, and the body’s response to internal and external stressor[96].

Frailty and Hallmarks of Aging

As mentioned above, the biological hallmarks of aging as reviewed by Lopez-Otin et al constitute primary pillars characterizing disruption of the biological pathways that may precipitate frailty[2]. These aberrant pathways include genomic instability, telomere

attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication[2]. Modulated by both genetic and environmental factors, these pathways have been active targets for the development of putative pharmacological agents to combat frailty and other key adverse aging syndromes. Multiple of these investigational agents have been examined in preclinical and clinical phases as potential therapeutics for promoting both the duration of healthy life (healthspan) and survival (lifespan). These include pharmacological agents targeting growth factor pathways involved in nutrient sensing such as the mammalian target of rapamycin (mTOR) inhibitors, insulin signaling and metabolic pathways including metformin, the nicotinamide adenine dinucleotide (NAD) reduction-oxidation stress response pathways including resveratrol, autophagy related cellular homeostatic pathways such as polyamines, and pathways to cellular senescence including a range of senolytic agents[96, 97]. Studies of several of these agents in preclinical and clinical phases have investigated their role as putative interventions for frailty or key aspects of the frailty phenotype in the general population. Several of these agents or pathways intersect with HIV pathophysiology.

Frailty and mTOR Inhibitors

The mammalian target of rapamycin (mTOR) signaling pathway is a master regulator of cell growth and metabolism[98]. mTOR is a conserved protein kinase that exists in 2 distinct complexes known as mTORC1 and mTORC2, that combined promote cellular growth, proliferation and survival through integration of energy, nutrient and growth factor inputs, and stressors[98, 99]. mTOR inhibitors include the therapeutic agent rapamycin, first identified as an antifungal metabolite and initially approved as an immunosuppressive agent for use in acute renal allograft rejection[98]. In preclinical studies, mTOR inhibitors have been found to increase both lifespan and healthspan[97, 100]. Rapamycin also has been found to improve frailty parameters in murine models. Intraperitoneal injection of rapamycin for 3 months was found to improve grip strength and stride length in middle-aged mice[100]. Rapamycin also was found to decrease a physiologic frailty index measure in male but not female mice[101].

Several relationships of HIV infection with the mTOR signaling pathway have been identified: HIV has been associated with modulation of mTOR signaling, enhancing mTORC1 activity [102, 103]. Studies have suggested relationships of mTOR dysregulation to HIV pathogenesis including HIV-associated nephropathy and malignancies, with amelioration of pathologic lesions with the mTOR inhibitor rapamycin in several studies[104, 105]. mTOR inhibitors also have been found to suppress HIV viremia in a humanized mouse model[106]. In HIV cure research, rapamycin has been found to reduce proinflammatory cytokine toxicity in the setting of use of anti-CD3/anti-CD28 antibodies for T cell activation to promote reactivation of the latent HIV reservoir[107]. The role of rapamycin or other mTOR inhibitors as a therapeutic intervention for frailty in HIV remains to be explored.

Frailty and NAD Pathways: Resveratrol and Other Sirtuin Activating Compounds

Nicotinamide adenine dinucleotide (NAD) is a key co-enzyme in reduction-oxidation reactions, metabolism and stress response pathways[97]. NAD^+ availability decreases with age, potentially related to decrease in the balance between NAD biosynthesis and consumption[108]. Loss of NAD^+ has been associated with age-associated muscle decline and loss of muscle strength and endurance in mice.[109] Molecules with potential to boost NAD^+ biosynthesis include precursors such as nicotinamide mononucleotide and nicotinamide riboside. Administration of NAD precursors reduce aging-related NAD^+ decline and have been associated with improved muscle mass and function in murine models[109, 110]. Such NAD precursors have been found to extend both healthspan and lifespan in other animal models such as Drosophila and yeast[111, 112].

Sirtuins or silent information regulator 2 (Sir2) proteins are protein deacetylases dependent on NAD and considered to play a key role in aging, longevity and cellular homeostasis, with roles in inflammation, mitochondrial dysfunction, energy metabolism and autophagy[113–117]. Resveratrol is a naturally occurring polyphenol found in the skin of red grapes and other natural products that exerts potential beneficial health effects via the sirtuin pathway[118]. Data on the impact of resveratrol on frailty parameters remains mixed[96, 117, 118]. In preclinical models, dietary supplementation with resveratrol has been found to extend both the healthspan and lifespan in multiple animal models in a sirtuin pathway dependent manner[119–130]. Resveratrol has been associated with improved frailty-related parameters in preclinical studies as well. In 1 year old mice fed a high calorie diet, supplementation with resveratrol for 6 months shifted performance on measures of function and endurance compared to that of mice fed a standard diet[130]. Three to four week trials of resveratrol were found to increase limb grip strength and reduce exercise induced exhaustion (improve endurance) in mice[131, 132]. In a mouse model of frailty based on deficit accumulation, 6 months of resveratrol was associated with a significant reduction in frailty index scores[133]. Resveratrol also has been shown to improve insulin sensitivity and reduce tissue inflammation in monkeys[134].

In a prospective longitudinal human study of 769 participants, aged 65 years and older, Rabassa and colleagues examined the association between habitual dietary resveratrol exposure with the development of frailty[135]. Total dietary resveratrol intake was assessed using a food-frequency questionnaire and total urinary resveratrol was assessed via liquid chromatography – tandem mass spectroscopy. The combination of higher habitual dietary resveratrol exposure and total urinary resveratrol was associated with a lower risk of frailty onset over 3 years. In a double-blind crossover, randomized controlled study, 11 obese men were treated with 150mg/day resveratrol for 30 days or placebo. Resveratrol induced metabolic changes that mirrored the effects of calorie restriction, with reduced resting metabolic rate, reduced systolic blood pressure and improved Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [136]. However, in a separate randomized controlled trial of 24 healthy, obese men, resveratrol had no effect on metabolic physiologic parameters.[137] In a recent randomized clinical trial of adults 65 years and older with peripheral arterial disease treated with resveratrol supplementation for 6 months vs. placebo, participants randomized to 125 mg/day resveratrol had a statistically significant but not

clinically meaningful improvement in 6 minute walk, while those randomized to 500 mg/day resveratrol demonstrated no improvement.[138]

A role for resveratrol in inhibiting HIV-1 replication in resting CD4+ T cells and in protecting against protease inhibitor-induced reactive oxygen species production has been suggested.[139, 140] However, very little data exist on the role of resveratrol in aging pathophysiology in HIV. More data on the role of resveratrol as a therapeutic agent for frailty in populations with and without HIV is needed.

Other sirtuin-activating compounds (STACs) with higher *in vitro* potency than resveratrol have been found to have positive impact on healthspan and lifespan in animal models.[117, 141–145] Beneficial effects on muscle mass, a key frailty parameter, have been observed for these compounds in preclinical studies.[143] In humans, several observational studies have demonstrated associations of the sirtuin pathway with frailty. In the Concord Health and Ageing in Men Project (CHAMP) cohort of community dwelling men 70 years and older, participants in the lowest quintile of SIRT1 protein expression were less likely to be frail.[146] In a cross-sectional study of 119 non-frail and 81 frail individuals characterized by the physical frailty phenotype, serum SIRT1, SIRT2 and SIRT3 levels were significantly lower among frail participants compared to non-frail.[147] Several sirtuin activating compounds are being tested in human clinical trials targeting aging-related conditions and inflammation in the general population.[96, 117] In simian immunodeficiency virus (SIV) models, SIRT-1 levels were decreased in neural tissue microglia and myeloid cells of infected macaques, with studies suggesting a role for SIRT1 binding in regulating neuroinflammation in SIV infection.[148] Data for the role of these pathways in PWH remain limited. Ultimately, the role of NAD and sirtuin pathways on frailty in populations with and without HIV requires further study.

Frailty and Insulin Signaling Pathways: Metformin and Other Metabolic Regulators

Hormonal pathways play a key role in homeostatic regulation in response to internal and external signals and in the body's response to stress. Regulation of metabolic pathways, particularly insulin signaling, are a key component of the homeostatic response. Metformin is an oral hypoglycemic with demonstrated effects on insulin signaling and glucose metabolism currently used for the treatment of type 2 diabetes and pre-diabetes. Increasing data suggest a pleiotropic role for metformin in combating adverse aging-related phenotypes beyond insulin signaling, through action on many of the biological pillars of aging including reduction in inflammation and senescence, amino acid restriction, modulation of mTOR and sirtuin pathways, enhanced DNA repair, increased autophagy, reduced mitochondrial oxidative stress, reduced telomere attrition, and reduced stem cell exhaustion.[149–159] Shifts in gut microbiome composition by metformin has also been proposed to precipitate some of its effects.[160, 161] In the setting of the proposed effects on these multiple key aging-related pathways, metformin has been demonstrated to improve both healthspan and lifespan in preclinical models.[162–164] Metformin also has been associated with improvements in frailty-related parameters in preclinical studies including enhanced motor speed, limb strength and endurance.[162, 165] In a cross-sectional study, among veterans 65 years and older with type 2 diabetes, exposure to metformin was associated with a

significant lower risk for frailty, using a 44-item frailty index.[166] In another cross-sectional observational study of 2415 veterans aged 65–89 years with type 2 diabetes mellitus maintained on metformin or a sulfonylurea for at least 6 months, metformin use was associated with a significantly decreased odds of frailty.[167]

Considering the multiple aforementioned biological roles, metformin is of interest to target adverse aging-related phenotypes, beyond its role as an oral glycemic agent. In particular, several ongoing human trials are exploring the role of metformin as a therapeutic target for frailty or frailty-related parameters in the general population. In one study of 120 pre-frail, non-diabetic adults 60 years and older randomized to metformin or placebo for 16 weeks, a significant improvement in mean gait speed but not grip strength was observed in the metformin group.[168] Other ongoing randomized controlled studies include a double-blinded, clinical trial targeting enrollment of 120 adults 65 years and older with prediabetes randomized to metformin or placebo, to be followed for 2 years with frailty as the primary outcome.[169] The TAME trial with a planned enrollment of 3000 older adults without diabetes mellitus will examine the effect of metformin on the incidence of new aging-related diseases, including frailty.[170, 171]

Among PWH, in a small study (n=12) of virologically suppressed PWH without diabetes mellitus randomized to 24 weeks of metformin vs. observation, metformin was associated with reduced CD4+ T cell exhaustion, as reflected in decreased expression of negative immune checkpoint receptors on CD4+ T cells.[172] As in the general population, it has been postulated that effects of metformin in PWH may be through effects on the gut microbiota and subsequent reductions in inflammation, thereby modulating aging phenotypes such as frailty.[173, 174] In a trial of 23 PWH on ART for over 2 years, 12 weeks of metformin treatment was associated with increased abundance of butyrate-producing species and *Akkermansia muciniphila* in the gut microbiota, known to have anti-inflammatory properties, though plasma levels of IL-6 and TNFα were unchanged.[175] Other metformin trials among PWH without diabetes are ongoing. These include a single-arm pilot trial to determine whether metformin supplementation might reduce the size of the HIV reservoir, an investigation with potential applicability to HIV cure research and residual HIV biological effects which may impact frailty.[176]

Other agents postulated to have a role in targeting insulin and other related metabolic signaling pathways in the context of aging pathways include the oral hypoglycemic acarbose and the endogenous steroidal estrogen, 17α-Estradiol.[96] 17α-Estradiol has been associated with increased lifespan and reduced inflammation in male mice.[177] Little current data exist for the role of 17α-Estradiol in frailty in adults with or without HIV. Acarbose has been associated with enhanced healthspan and lifespan in animal models, preferentially in male mice.[178] These observed effects of acarbose have been associated with significant increases in fibroblast growth factor 21 (FGF21),[178] a key hormone produced in response to fasting that has been identified as playing a key role in regulation of metabolic pathways.[179] FGF21 also has been shown to extend lifespan when overexpressed in mice, and to modulate growth hormone and insulin-like growth factor (IGF)-1 signaling.[180, 181] While a postulated role for FGF21 in modulating muscle mass and function has been proposed, limited data exist on its relationship to frailty in older

adults[182], and few studies have examined the role of FGF21 in HIV. In observational studies, serum FGF21 was associated with fatigue in PWH[183], and FGF21 expression in muscle was increased among men with HIV and lipodystrophy compared to age-matched, HIV-uninfected controls.[184] Conversely, serum FGF21 levels among PWH (29–71 years of age) significantly correlated with both current CD4+ count and total CD4+ count gain since ART initiation, suggesting an association with immune recovery.[185] The relevance of these findings to aging-related phenotypes in PWH require further investigation.

Frailty and Senolytics

Cellular senescence is characterized by cell cycle arrest in response to stressors, and can block proliferation of damaged cells. Accumulation of senescent cells in tissues with age can lead to impaired tissue function, stem cell exhaustion, and a proinflammatory phenotype that may precipitate aging-related disease and adverse aging phenotypes.[2, 186] In murine models, clearance of senescent cells has been shown to delay onset of aging-related phenotypes and pathologies and to reduce progression of already established aging-related disorders.[187]

Senolytics are compounds capable of selective clearance of senescent cells through induction of apoptosis.[188] Senolytic agents include the anticancer agents quercetin, dasatinib and navitoclax, other BCL-XL inhibitors, and heat shock protein 90 inhibitors. Senolytic administration has been shown to improve physical function in both senescent cell-transplanted young mice and naturally aged mice, resulting in improved gait speed, grip strength, endurance, daily activity, and survival, changes associated with reductions in pro-inflammatory cytokines.[189–191] Administration of senolytics also decreases senescent cell burden in humans.[192] In an open label study of dasatinib with quercetin administered 3 days per week over 3 weeks to 14 patients with idiopathic pulmonary fibrosis, there was significant improvement observed in the 6 minute walk, 4 meter gait speed, and chair stands, but no change in a laboratory-based frailty index.[193]

Little data exist on the role of senolytics in PWH. A role for dasatinib has been recently proposed as a potential agent for reducing the HIV latent reservoir, with the question of its potential dual role in addressing frailty and other aging-related phenotypes.[194] Whether senolytics may serve as a frailty-targeted intervention in HIV remains to be determined.

Other Pharmacologic Targets for Frailty Intervention in Human Clinical Trials

Several other investigational human clinical trials of pharmacologic interventions with frailty or frailty-related parameters as a substantive outcome have been recently reviewed.[195] Several studies have examined the role for the anabolic steroid testosterone in the management of frailty or frailty related parameters in both people with and without HIV. Travison et al. randomized men aged 65 years and older with baseline mobility limitations and low testosterone to 6 months of daily testosterone gel or placebo.[196] Testosterone treatment was associated with greater improvements in strength (leg and chest press), stair climbing power, and muscle mass compared to placebo. No change in physical activity, gait speed, or fatigue was observed, and an increased frequency of adverse events in the testosterone arm led to cessation of enrollment.[197] Kenny et al. randomized men ≥50

years with a hip fracture, or men ≥60 years with or at high risk of a hip fracture to testosterone or placebo for 12–24 months.[198] Men receiving testosterone had increased testosterone levels and lean mass, and decreased fat mass but no differences in strength or physical performance compared to placebo. Gharahdaghi et al. randomized non-hypogonadal men 65 to 75 years of age to 6 weeks of biweekly testosterone injections or placebo in combination with resistance exercise; testosterone was associated with increased muscle mass and strength.[199] Lastly, Liu et al. randomized men 60 years and older with low testosterone levels to 3 months of twice weekly subcutaneous recombinant human chorionic gonadotropin (hCG) or placebo.[200] hCG treatment was associated with increased lean body mass and reduced fat mass, but no change in muscle strength or physical function.

Testosterone is one of the most studied pharmacologic interventions among PWH for numerous outcomes, including frailty or frailty-related parameters among PWH. In a study of 155 frail men with HIV matched to 141 non-frail men with HIV and 150 HIV-uninfected men, matched by age, calendar year and ART use, frailty (by physical frailty phenotype) was associated with lower free testosterone levels.[201] Rochira et al. found an association between low serum total testosterone and frailty by a frailty index.[202] In a cross-sectional study, Pencina et al. found that testosterone was associated with gait speed via accelerometry but not a 6 minute walk test.[203] In a study of 25 women with HIV and free testosterone levels below the median of the normal female range, randomization to transdermal testosterone twice weekly for 18 months was associated with a greater increase in lean mass and hip and trochanter bone mineral density compared to placebo.[204] Among men with HIV and weight loss randomized to weekly intramuscular 300mg injections of testosterone or placebo for 16 weeks, testosterone administration increased lean mass and leg press strength but not gait speed or stair climbing power.[205] Additionally among men with HIV aged 18–50 years with low testosterone levels and weight loss in the previous 6 months randomized to testosterone, exercise, both or placebo for 16 weeks, testosterone, exercise, or testosterone + exercise led to significant increases in muscle strength while testosterone or testosterone + exercise resulted in increased lean mass.[206] Overall, testosterone treatment has been associated with improvements in muscle strength, function and body composition though with potential adverse effects. Further investigation of the role of testosterone as a therapeutic for frailty in populations with or without HIV may be warranted, both relative to safety and efficacy considerations.

Other clinical trials of pharmacologic interventions for frailty or frailty-related parameters have included the vitamin D analog alfacalcidol, the anabolic parathyroid hormone teriparatide, the growth hormone secretagogue capromorelin, and the nonsteroidal anti-inflammatory drug piroxicam.[195] In a randomized, placebo- controlled trial of women 60 years and older, randomization to 0.5μg/day alfacalcidol for 90 days was associated with significant improvement in handgrip strength and the timed-up-and-go test.[207] In a study of teriparatide, participants were randomized to 20μg/day of teriparatide or 35mg/week of risedronate following peritrochanteric hip fracture fixation; those in the teriparatide group experienced significantly faster completion of the timed-up-and-go test, a secondary endpoint, at 6, 12, 18 and 26 weeks.[208] For capromorelin, adults 65 to 84 years of age were randomized to treatment with capromorelin at 4 different treatment doses or placebo. A

significant increase in lean mass, tandem walk, and stair climb was observed for all capromorelin treatment groups.[209] In a randomized controlled trial of 30 patients hospitalized with acute infection and C-reactive protein >10, patients randomized to 10 days of 10mg piroxicam vs. placebo experienced increased mobility and greater measured fatigue resistance, but no change in grip strength.[210]

Beyond testosterone, there have been little data on the specific role of these agents in frailty or other aging-related syndromes among PWH. In a secondary analysis of a randomized controlled trial of the growth hormone releasing hormone analogue tesamorelin among PWH and abdominal obesity, tesamorelin administered for 26 weeks was associated with significant increases in skeletal muscle area and density compared to placebo.[211]

HIV Specific Pharmacologic Interventions: Frailty and ART

Frailty has been strongly associated with poorly controlled HIV infection,[212] and attaining HIV virologic suppression through ART is associated with reduced frailty progression and increased frailty recovery.[213] These findings suggest the role of ART itself as a critical pharmacologic intervention for frailty in PWH. As an estimated 32% of the 38 million PWH worldwide are still not receiving ART[214], enhanced efforts to improve the HIV cascade of care will remain key in prevention or amelioration of frailty among PWH globally.

Additional HIV Related Factors: Frailty and Inflammation

Heightened chronic inflammation has been centrally associated with multiple of the biologic pillars of aging detailed above and has been significantly associated with frailty in multiple studies of older HIV-uninfected adults.[215] Even with ART-mediated virologic suppression in HIV, inflammation persists. Persistent inflammation in HIV has been implicated in the pathophysiology of aging-related disease and syndromes increasingly prevalent in the aging HIV-infected population. In cross-sectional studies across multiple HIV cohorts, frailty is strongly associated with heightened inflammation.[201, 215, 216] In longitudinal studies in PWH, reduced inflammation has been significantly associated with reduced frailty progression and improved frailty recovery.[213] Multiple putative precursor pathways to heightened chronic inflammation in HIV have been characterized as previously reviewed.[174, 215] Further elucidation and targeting of upstream inflammatory precursors in HIV will be key to the development of effective therapeutic interventions for frailty in this population.

Addressing Social Determinants

Health equity has been defined as the state in which everyone has the opportunity to attain full health potential and no one is disadvantaged from achieving this potential because of social position or any other socially defined circumstance.[217] The struggle to achieve health equity has long been stymied by disparate experiences across a range of social determinants, namely the conditions in the social, economic, and physical environment in which people are born, live, work, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks.[218, 219] Multiple studies have demonstrated that

frailty and HIV both disproportionately impact socioeconomically challenged populations and racial/ethnic groups known to be long more vulnerable to poor health.[220–233]

In the National Health and Aging Trends Study, a nationally representative sample of adults 65 years and older in the U.S., frailty prevalence was found to be significantly higher among the Hispanic/Latino population (24.6%) and the African American/Black population (22.9%) relative to the White non-Hispanic population (13.8%).[234] This frailty disparity persisted across income quartiles and was independent of the number of other co-existing chronic disease conditions.[233] In both populations with and without HIV, frailty also has been significantly associated with greater socioeconomic challenges including low income, unemployment, occupation, and low educational attainment.[212, 230, 234, 235] In longitudinal studies among PWH, less socioeconomic challenge has been significantly associated with a lower likelihood of frailty progression and an increased likelihood of frailty recovery.[213] These findings suggest a double hit, namely a lower physiologic resilience to stress existing among those with potentially simultaneous heightened stress exposure.

Interventions for these factors in the frailty pathway likely will require both efforts to minimize social stressors and their impact, conjoined with systematic macro-level structural interventions directed at upstream social determinants to promote equitable health outcomes for all older adults.[236, 237] Several multimodal, tailored interventions have been found to be effective in reducing stressors for older adults so as to improve function and reduce institutionalization.[238, 239] Further elucidation of the pathways by which social determinants precipitate the marked frailty disparities extant in populations both with and without HIV will be critical to the identification and design of the requisite programs, policies, and societal prescriptions to reduce the marked vulnerability and ensure optimal health for all.

Conclusions

In summary, several non-pharmacologic interventions have been shown to reduce components for populations with and without HIV, with exercise as one of the most effective interventions. Clinical trials of putative pharmacologic interventions have begun to emerge for translation of preclinical findings into human trials, though specific trials of pharmacologic agents with frailty as the primary focus remain sparse, particularly among PWH. Further identification of the novel biological pathways underlying progression to frailty in HIV remains critical to reverse or delay frailty and consequently to mitigate the substantial frailty associated morbidity and mortality in the HIV-infected population. Furthermore, including frailty or components of frailty as endpoints in clinical trials among PWH can advance understanding of therapies regardless of the primary target (such as studies focused on HIV cure or HIV reservoir). Ultimately, addressing the social determinants that underlie frailty will be critical to ensuring that pharmacologic and non-pharmacologic interventions can improve the vulnerability that underlies frailty and support optimal health for older adults with HIV.

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Table 1.

Proposed and/or Tested Interventions to Prevent or Treat Frailty in Populations with or without HIV

Non-Pharmacologic Interventions	Pharmacologic Interventions
Unstructured physical activity and exercise • Endurance training • Strength training • Higher intensity or high-intensity interval training	mTOR pathway • Rapamycin
Nutritional • Supplements • Protein • Obesity management	Sirtuin/NAD pathway • Nicotinamide • Resveratrol
Polypharmacy • De-escalation • Non-pharmacologic interventions when possible	Insulin-signaling/metabolic regulators • Metformin • Acarbose • 17α-Estradiol • Fibroblast growth factor 21
Reduce fall risk • Balance training • Physical therapy • Medical de-escalation	Senolytics • Dasatinib • Quercetin • Navitoclax
Evaluate/treat mood disorders and cognitive impairment	Testosterone
Multimodal approaches • Combination of above interventions • Geriatric consultative clinics • Comprehensive geriatric assessment	Other therapies • Antiretroviral therapy (for populations with HIV) • Alfacalcidol • Capromorelin • Piroxicam • Teriparatide • Tesamorelin
Address social determinants of health that underlie risk of frailty and access to treatment and care for frailty-associated aging-related conditions • Economic opportunity (e.g. income, employment, housing, food security) • Educational opportunity • Social and community factors (e.g. addressing precipitants of racial/ethnic disparities) • Neighborhood and built environment • Access to health/health care (e.g. health promotion, disease prevention and care)	

mTOR, mechanistic target of rapamycin; NAD, Nicotinamide adenine dinucleotide (NAD)