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Authors
Montoya, Jessica L
Henry, Brook
Moore, David J

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Jessica L. Montoya, Brook Henry, and David J. Moore

Contents

Abstract Approximately 30–50% of persons living with HIV manifest some degree of neurocognitive impairment. Even mild-to-moderate forms of HIV-associated neurocognitive disorders (HAND) can result in difficulties with everyday functioning, such as suboptimal medication adherence and impaired driving. Despite the pervasive presence and consequences of HAND, there is a significant unmet need to develop

J. L. Montoya and B. Henry
Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

D. J. Moore (✉)
Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

HIV Neurobehavioral Research Program, San Diego, CA, USA
e-mail: djmoore@ucsd.edu

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effective behavioral strategies to reduce the incidence and consequences of HAND. Although there is an absence of evidence-based behavioral interventions specific to HAND, the literature reviewed in this chapter suggest the following modifiable lifestyle factors as intervention targets: physical activity, diet, sleep, and antiretroviral medication adherence. Adoption and maintenance of these healthy lifestyle factors may reduce inflammation and oxidative stress, which, in turn, may reduce the incidence and/or severity of HAND.

Keywords Antiretroviral therapy adherence · Cognition · Diet · Exercise · Nutrition · Physical activity · Sleep

1 HIV-Associated Neurocognitive Disorders

Approximately 30–50% of persons living with Human Immunodeficiency Virus (HIV) Type-1 manifest some degree of neurocognitive impairment, typically characterized by deficits in executive function, attention, and memory referred to as HIV-associated neurocognitive disorders (HAND) (Heaton et al. 2010). HAND per Frascati diagnostic criteria includes three categories: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), which includes self-reported deficits in everyday functioning, and the most severe of the disorders, HIV-associated dementia (HAD) (Antinori et al. 2007). While HAD prevalence has declined with the use of effective antiretroviral therapy, ANI and MND, marked by impaired performance in at least two neurocognitive domains (greater than one standard deviation below the mean of normative scores), remain a prevalent and significant public health concern. Even mild-to-moderate forms of HAND translate to higher risk of impaired driving, difficulties with instrumental activities of daily living, and poorer antiretroviral therapy adherence (Thames et al. 2011; Vance et al. 2011; Marcotte et al. 2004). Despite the pervasive presence and consequences of HAND, there is a significant unmet need to develop effective behavioral strategies to reduce the incidence and consequences of HAND (Woods et al. 2009b). Among existing behavioral interventions, promotion of physical activity, a healthy diet, improved sleep, and antiretroviral therapy adherence may benefit neurocognitive function.

2 Physical Activity as a Behavioral Intervention for HAND

2.1 Physical Activity Levels Among People Living with HIV

Physical activity, traditionally defined as the movement of skeletal muscles that requires energy expenditure, has been recommended as a safe therapeutic strategy to sustain and maintain the health of persons living with HIV (Botros et al. 2012). Physical activity interventions among people living with HIV are reported to improve body composition, muscle strength, aerobic fitness, and quality of life; however, there are notable barriers to physical activity among people living with HIV, including disease symptoms, antiretroviral therapy side effects, depression, and pain (Henry and Moore 2016; Vancampfort et al. 2018b). Surprisingly, relatively few studies have examined physical activity among people living with HIV. A 2012 review indicated that the diversity and inconsistency of methods used to assess physical activity (typically a variety of self-report questionnaires) precluded any pooled estimate of overall physical activity among people living with HIV, although the range of estimates suggest that 19–73% of people living with HIV are "sedentary," as defined by various criteria (Schuelter-Trevisol et al. 2012). Webel and colleagues reported that an Ohio cohort of persons living with HIV tended to exercise regularly, but the mean level of physical activity was lower in women than men, and below recommended levels (i.e., 150 min per week of moderate-to-vigorous physical activity) (Webel et al. 2015). A sample of 50 African-American females living with HIV from the southern United States exhibited low levels of physical activity, with only one person exceeding 150 min per week of moderate-to-vigorous physical activity (Rehm and Konkle-Parker 2016). In contrast, two-thirds of a cohort of people living with HIV from Vietnam were rated as physically active on the International Physical Activity Questionnaire, although this group did include rural participants with potentially more endogenous physical activity than urban residents (Dang et al. 2018). A recent meta-analysis reviewed physical activity data from 24 studies of people living with HIV conducted across the world (Vancampfort et al. 2018a). To optimize consistency, the authors included physical activity results obtained only through the International Physical Activity Questionnaire or objective measures, such as an accelerometer. The findings from this seminal study showed that approximately 50% of people living with HIV failed to meet suggested physical activity guidelines (i.e., exhibiting less than 150 min per week of moderate-to-vigorous physical activity). Furthermore, average daily steps, when collected, was about 5,800 per day, which is far below the 10,000 steps recommended for adults and close to a sedentary range (typically defined as below 5,000 steps per day). In summary, it is clear that physical activity habits among people living with HIV may vary significantly depending upon geographic and demographic factors, but studies to date suggest that a large proportion of people living with HIV are not sufficiently physically active. As a result, physical activity interventions may be beneficial for numerous persons living with HIV.

2.2 Relationship Between Physical Activity and Neurocognition

Moderate- and vigorous-intensity physical activity has beneficial effects on neurocognitive function (Engeroff et al. 2018). Among healthy individuals and children, physical activity is shown to improve neurocognitive functioning (Davis et al. 2007; Best et al. 2015; Mura et al. 2015; Guiney and Machado 2013; Gill et al. 2015).

Aerobic exercise is associated with improvement in multiple neurocognitive domains, including attention, processing speed, executive function, and memory (Smith et al. 2010). Physical activity may also benefit global neurocognition in patients with mild neurocognitive impairment (Song et al. 2018) or history of stroke (Vanderbeken and Kerckhofs 2017), and may slow neurocognitive decline in Alzheimer's disease (Farina et al. 2014). In the context of HIV, higher engagement in physical activity is associated with better executive function (Ortega et al. 2015) and reduced likelihood of neurocognitive impairment in cross-sectional studies (Dufour et al. 2013; Fazeli et al. 2015). Longitudinally, persons living with HIV who consistently engage in physical activity begin with, and maintain, significantly better neurocognitive function compared to persons living with HIV who do not engage in physical activity or do so inconsistently (Dufour et al. 2018). In a longitudinal Multicenter AIDS Cohort Study, high engagement in physical activity was associated with lower odds of impairment in the domains of learning, memory, and motor function, and these effects were found to be more pronounced among the sample of men living with HIV compared to the pooled sample of men living with HIV and HIV-uninfected men (Monroe et al. 2017). In a scoping review of the effect of physical activity on neurocognitive function among people living with HIV (Quigley et al. 2018), noninterventional studies reported a positive association between physical activity engagement in neurocognitive function, whereas there was a dearth of positive outcomes of aerobic interventions on neurocognition. Null results of interventional studies potentially may be a result of methodological factors (e.g., low prescribed doses of physical activity, recruitment of relatively young people living with HIV who are at lower risk for neurocognitive impairment compared to older people living with HIV, and reliance on self-reported versus objective measures of neurocognitive function). Thus, future randomized controlled trials should prescribe doses of physical activity consistent with current recommendations (150 min per week of moderate-to-vigorous physical activity), recruit participants most likely to benefit from physical activity interventions, and utilize comprehensive neurocognitive assessments.

2.3 Underlying Biologic Mechanisms Linking Physical Activity and Neurocognition

Chronic inflammation is established early in HIV infection and is postulated to contribute to neurocognitive impairment across the age span of persons living with HIV (Sattler et al. 2015; Hong and Banks 2015; Tavazzi et al. 2014; Kapetanovic et al. 2010, 2014; Ancuta et al. 2008; Gannon et al. 2011). Physical activity is known to exert anti-inflammatory effects, which may be a consequence of reduced visceral fat and decreased release of adipokines (d'Ettorre et al. 2014). In addition to reduced inflammation, some of the underlying biologic mechanisms linking physical activity to neurocognition include promotion of cerebral angiogenesis, improved cerebral and peripheral vascular reactivity (i.e., increased maximal oxygen consumption), upregulation of neurotrophins, increased neurogenesis, and decreased hippocampus apoptosis (Stimpson et al. 2018). Imaging studies indicate that engagement in physical activity can increase brain volume, and biomarker studies show that physical activity leads to upregulation of brain-derived neurotrophic factor (BDNF) (Firth et al. 2017). A randomized controlled trial showed that among individuals with schizophrenia, those who participated in an aerobic exercise intervention (compared to treatment as usual) showed improvements in physical fitness and neurocognitive function (Kimhy et al. 2015). Furthermore, enhancement of physical fitness and increases in BDNF accounted for much of the variance in neurocognitive improvement, supporting the hypothesis that physical activity-induced upregulation of BDNF may contribute to improved neurocognitive outcomes.

2.4 Interventions to Increase Physical Activity, Thereby Benefiting Neurocognition

Low-to-moderate intensity walking interventions have demonstrated effectiveness in improving neurocognitive performance in older adults (Rosenberg et al. 2012) and neurocognitively impaired populations (Kemoun et al. 2010). Compared to moderate physical activity, high intensity interval training, which involves short periods of exercise performed at high intensity (greater than 80–85% peak oxygen uptake), may have greater benefits for improving cardiometabolic function (e.g., improved insulin and glucose regulation and reduced inflammation markers, such as interleukin-6 and C-reactive protein) (Tjonna et al. 2009; Munk et al. 2011; Ramos et al. 2015). Interventions employing a combination of aerobic and resistance exercise also show evidence of improving body composition and lipid profile in people living with HIV (Hand et al. 2009; O'Brien et al. 2010). However, the effect of a combined aerobic and resistance exercise regimens on neurocognition has not been investigated as an intervention strategy for HAND.

Limitations of many physical activity interventions are issues of feasibility and scalability. Many intervention studies are conducted at gym facilities, which may not be accessible in nonintervention contexts to many persons living with HIV who may face limited financial resources (Montoya et al. 2015). To date, few studies have specifically examined the effect of a physical activity intervention on neurocognition among people living with HIV. One recent 16-week protocol required participants to attend three aerobic exercise sessions at a gym facility each week, but did not observe any effects of the physical activity intervention on neurocognition relative to a control group (McDermott et al. 2017). However, the sample size was extremely small; only 11 people participated in total (6 control and 5 intervention participants completed the study out of 57 persons living with HIV screened), individuals did not attend 40% of the planned physical activity training sessions, and the neurocognitive assessment was limited, including only the Montreal Cognitive Assessment and

Trail-making A and B tests. These issues highlight some of the challenges involved in conducting physical activity interventions to improve neurocognitive outcomes. Although physical activity that is gym-based may not be feasible for many persons living with HIV, increasing walking/step count may be an appropriate treatment target. Walking may reduce sedentary behavior and improve metabolic function (Healy et al. 2008; Manson et al. 1999). For example, an increase in mean daily step counts by approximately 2,000 improves lipid profile (Sugiura et al. 2002).

In the general population, mobile health interventions have been developed to promote engagement in physical activity, such as walking (Fjeldsoe et al. 2009). An ongoing randomized controlled trial is investigating whether a novel and personalized text messaging intervention (iSTEP) can significantly increase moderate physical activity in people living with HIV (R21MH100968) (Henry and Moore 2016). Second, the iSTEP intervention aims to evaluate the effect of physical activity engagement on neurocognitive performance. Preliminary data supports high text message response rates and positive participant feedback (Henry and Moore 2016).

3 Diet as a Behavioral Intervention for HAND

3.1 Diet and Neurocognitive Function in the General Population

Epidemiological research indicates that a healthy diet, such as the Mediterranean diet and consumption of omega-3 fatty acids (e.g., docosahexaenoic acid, DHA), may help prevent neurocognitive decline (Barak and Aizenberg 2010). The Mediterranean diet is characterized by high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil; moderate intake of fish and alcohol; low-to-moderate intake of dairy products; and low intake of saturated lipids and meat (Loughrey et al. 2017). A recent systematic review indicated a positive, concurrent association between the Mediterranean diet and global neurocognition; however, the association between the Mediterranean diet and specific neurocognitive domains is less established (Knight et al. 2017). Methodological differences in relation to neuropsychological assessment are a likely factor contributing to the lack of consensus among studies on the relationship between the Mediterranean diet and neurocognitive function (Knight et al. 2017). Similar to the Mediterranean diet, diets rich in polyphenols – found in fruits, vegetables, tea, wine, juices, plants, and some herbs – may promote better performance in neurocognitive abilities in a dose-dependent manner (Nurk et al. 2009) and slower rates of neurocognitive decline (Devore et al. 2012) in older persons. Results from the Framingham Heart Study (Schaefer et al. 2006) indicate individuals with higher DHA levels had a relative risk of 0.61 of developing Alzheimer’s disease, compared to individuals with lower

DHA levels, after adjustment for relevant covariates (i.e., sex, apolipoprotein E allele, plasma homocysteine concentration, and education level). Higher DHA levels translated to a mean DHA intake of 180 mg/day and a mean fish intake of 3.0 servings per week.

3.2 Diet and Nutrition Concerns in the Context of HIV

The introduction of effective antiretroviral therapy resulted in improvements in nutritional status and weight gain among people living with HIV (Leyes et al. 2008). However, body composition changes (i.e., lipodystrophy) persist even with effective antiretroviral therapy, particularly among people living with HIV on protease inhibitors (Carr et al. 1998). Body composition changes may include intra-abdominal fat accumulation (Miller et al. 1998), which is of relevance to pathogenesis of HAND given that the HIV CHARTER cohort study has found a link between abdominal obesity and neurocognitive function (Sattler et al. 2015). Multiple studies indicate that cardiometabolic dysfunction (e.g., abdominal obesity, hyperglycemia, dyslipidemia, and hypertension) confers risk for HAND and correlates with imaging markers of neurochemical abnormalities and neuroinflammation among persons living with HIV (Cysique et al. 2013; McCutchan et al. 2012; Saylor et al. 2016; Valcour et al. 2005).

The nutritional status of persons living with HIV can influence body composition changes, but the efficacy of diet interventions to treat metabolic conditions, thereby improving neurocognitive outcomes is limited (Leyes et al. 2008). Despite limitations in the literature to be able to tease apart the various contributors of metabolic changes observed among people living with HIV, cross-sectional studies indicate that diets high in cholesterol and saturated and trans fats play a role in metabolic disturbances (Shah et al. 2005; Hadigan et al. 2001). Although diet and nutrient deficiencies have been extensively documented for persons living with HIV in low-income countries, with a focus on treatment with supplements such as vitamins (Duran et al. 2008), less work has been performed to characterize the diet quality for persons living with HIV in developed countries such as the United States. A couple of reports indicate that youth living with HIV demonstrate a lower Healthy Eating Index score, higher fat intake, and lower micronutrient consumption (including vitamins A, E, calcium, and potassium) compared to an age-matched HIV-seronegative comparison group (Kruzich et al. 2004; Ziegler et al. 2014). Pregnant women living with HIV in their third trimester also exhibited low Healthy Eating Index scores, although individuals born outside the United States had better scores, perhaps indicative of more unhealthy diet practices adopted by people living in the United States (Miller et al. 2017). One cohort of adults living with HIV (53% male) also consumed higher levels of saturated fat and lower amounts of polyunsaturated fat and fiber than recommended by the National Cholesterol Education Program (Capili and Anastasi 2008). While more data needs to be obtained, the existing evidence suggests that interventions that address diet content as well as physical activity may be helpful for people living with HIV in the United States.

3.3 Diet Interventions Specific to People Living with HIV

Current international guidelines recommend dietary intervention as a first-line treatment for HIV-related dyslipidemia (Dube et al. 2003), but the results of clinical trials have been inconsistent. Persons living with HIV who receive macronutrient (protein/carbohydrate) or micronutrient (vitamin) supplements in randomized controlled trials often do not show a significant reduction in morbidity, mortality, or disease progression (e.g., CD4 count and viral load) (Grobler et al. 2013; Visser et al. 2017). Interventions that have promoted low-fat diets are reported to have beneficial but limited effects, such as a reduction in triglycerides but not cholesterol (Stradling et al. 2012). Some nutrition studies have focused on polyunsaturated fatty acids (PUFA) and omega-3 PUFA (n-3 PUFA), which may benefit brain health and function and are emphasized as part of the Mediterranean diet (Poulose et al. 2014). PUFAs may contribute to optimal brain function by reducing oxidative stress and inflammation, maintaining neuronal membrane integrity, and attenuating protein aggregation implicated in neurodegenerative diseases and age-related neurocognitive decline (Poulose et al. 2014). Along these lines, a large 12-month study (PREDIMED) [7 years and 8,000 participants (Zazpe et al. 2008)] indicated that adoption of the Mediterranean diet provided significantly more benefits compared to control or a low-fat diet condition, including a reduction in cardiovascular disease events, decreased markers of oxidative stress, and improved neurocognition (Estruch et al. 2013; Schroder et al. 2014; Fito et al. 2014; Mitjavila et al. 2013; Martinez-Lapiscina et al. 2013). Despite potential neurocognitive benefits, the Mediterranean diet has not been evaluated as a strategy for preventing or treating HAND, although greater Mediterranean diet adherence is associated with improved metabolic function (lower insulin resistance and higher high-density lipoprotein cholesterol) in people living with HIV (Tsiodras et al. 2009). Future studies may examine the effect of the Mediterranean diet on cardiovascular risk and neurocognitive deficits associated with HIV.

4 Sleep as a Behavioral Intervention for HAND

4.1 Sleep Disturbance in the Context of HIV

Sleep disturbance and fatigue are common symptoms reported by persons living with HIV, with up to 75% of people living with HIV experiencing sleep disturbance according to the Pittsburgh Sleep Quality Index (Rubinstein and Selwyn 1998) and up to 88% experience fatigue (Jong et al. 2010). A meta-analysis of sleep disturbances among people living with HIV calculated that the overall prevalence of self-reported sleep disturbance was 58% (Wu et al. 2015). Furthermore, more than half of a sample population of people living with HIV reported symptoms related to sleep disturbance and fatigue, such as lack of energy (65%), drowsiness (57%), and difficulty sleeping (56%) (Lee et al. 2009). In a Taiwanese study, people living with HIV had a 3.74-fold higher risk of sleep disturbances compared to a general population control group (Chen et al. 2017). Among cohorts of people living with HIV, sleep disturbance and/or fatigue severity are associated with depression and anxiety symptoms (Millikin et al. 2003; Jong et al. 2010); antiretroviral therapy medication types and family and social support (Ren et al. 2018); high levels of HIV-RNA (greater than 1,000 copies/mL) (Womack et al. 2017); and substantial night-to-night variability in bedtime and risetime (Taibi et al. 2013).

4.2 *Effect of Sleep Disturbance on Neurocognitive Function*

Studies on the association between self-reported sleep disturbance and neurocognition have been mixed but suggest a link between poor sleep quality and worse neurocognitive outcomes (Yaffe et al. 2014). A meta-analysis of the impact of short-term sleep deprivation on neurocognition indicated that sleep deprivation had the largest effect on simple attention tasks (e.g., Psychomotor Vigilance Test and other simple reaction time tests), with tasks of greater complexity being affected to a lesser degree after sleep deprivation (Lim and Dinges 2010). On the other end of the spectrum, longer total sleep time (e.g., greater than or equal to 10 h of sleep/night) is also reported to significantly influence neurocognition, such as lower scores on the Mini-Mental Status Examination (Faubel et al. 2009) and lower performance on a recall test (Xu et al. 2011). Other measures of sleep disturbance (i.e., lower sleep efficiency, higher levels of wake after sleep onset, and a higher number of long wake episodes) have been related to decline in executive function as measured by the Trails B Test over an average study period of 3.4 years in a community-dwelling cohort of older men (mean age 76.0) (Blackwell et al. 2014). In a cohort of people living with HIV, 63% reported poor sleep quality based on a cutoff point of 5 on the Pittsburgh Sleep Quality Index (Byun et al. 2016). In this same sample, poorer subjective sleep quality, shorter or longer total sleep time measured by actigraphy (i.e., fewer than 7 h or greater than 8 h vs 7–8 h), and greater morning fatigue were associated with self-reported problems with neurocognitive function (e.g., difficulties with reasoning, concentration and thinking, confusion, memory, attention, and psychomotor function), even after controlling for covariates including age, gender, education, and sleep medication use. A study of sleep and neurocognition in a cohort of people living with HIV (75% were neurocognitively impaired based on Frascati criteria) that involved a more comprehensive neurocognitive assessment found that better performance on tasks of attention, frontal/executive function, and psychomotor/motor speed were associated with better polysomnogram sleep parameters, including reduced wake-after sleep, greater sleep efficiency, greater sleep latency, and greater total sleep time (Gamaldo et al. 2013). Thus, these results demonstrate that confounding factors, such as sleep disturbances, might influence the presentation of HAND.

Sleep disturbance may contribute to neurocognitive decline via impaired metabolism and decreased cerebral perfusion. Sleep deprivation may particularly impair metabolism of the prefrontal cortex, a brain region implicated in executive function (Durmer and Dinges 2005). Insufficient sleep duration has been shown to result in decreased cerebral blood flow in the frontal lobes and in worse performance on the Continuous Performance Test and driving performance (i.e., break reaction time in a harsh-braking test) (Miyata et al. 2010). Evidence from epidemiological and experimental studies indicate that sleep disturbance may impair amyloid beta clearance and increase tau phosphorylation, as well as impair synaptic plasticity via disruption of pathways involving gamma-aminobutyric acid (GABA) and cyclin adenosine monophosphate (cAMP) (Yaffe et al. 2014). In a study specific to persons living with HIV, higher inflammation levels (measured by C-reactive protein and interleukin-6) were observed among those with poor sleep characteristics (i.e., later sleep onset and lower total sleep time) and low engagement in moderate-vigorous physical activity (Wirth et al. 2015). These results indicate that disturbances in sleep and low levels of physical activity are associated with inflammation, which is implicated in the pathogenesis of HAND. Thus, improving sleep indices and maintaining regular participation in physical activity may help reduce the risk of inflammation, which, in turn, may reduce the incidence of HAND.

4.3 Behavioral Strategies to Improve Sleep Quality

Cognitive behavioral therapy for insomnia is the first-line treatment for insomnia based on guidelines of the American College of Physicians for management of chronic insomnia (Qaseem et al. 2016). Cognitive behavioral therapy for insomnia is a multimodal cognitive behavioral therapy that can be delivered in individual or group therapy, telephone- or web-based modules, or self-help books, and includes the behavioral strategies of sleep restriction and stimulus control. Although cognitive behavioral therapy for insomnia is associated with robust, long-term improvements in sleep parameters, cognitive behavioral therapy for insomnia has small-to-moderate effects on subjective measures of neurocognitive functioning, and there is insufficient data to determine the effect of cognitive behavioral therapy for insomnia on objective measures of neurocognition in the general population (Herbert et al. 2018).

SystemCHANGE-HIV – a 10-week intervention grounded in a socioecological model that covers different topics of HIV management, including sleep hygiene and behavioral modification strategies – was tested to determine its effectiveness at improving sleep outcomes, including sleep duration, sleep fragmentation index, sleep efficiency, and self-reported sleep quality (Webel et al. 2013). SystemCHANGE-HIV had high levels of engagement (e.g., participants attended 71% of all intervention sessions on average). Although nonsignificant, the pilot study provided preliminary data indicating that SystemCHANGE-HIV leads to improvement in sleep efficiency and sleep fragmentation. A major limitation of the SystemCHANGE-HIV study in regard to its applicability for the treatment of HAND was the absence of neurocognitive assessments. Given the prevalence and association between sleep disturbances and neurocognitive impairment in the context of HIV, a future research direction is to determine whether strategies for improving sleep (e.g., cognitive behavioral therapy for insomnia, SystemCHANGE-HIV) may lead to improvement in subjective and objective measures of neurocognitive functioning among people living with HIV.

5 Promotion of Antiretroviral Therapy Adherence as a Behavioral Intervention for HAND

5.1 Antiretroviral Therapy Adherence and Neurocognitive Performance

Early detection and initiation of antiretroviral therapy is a strategy for preventing significant immune compromise and protecting against neurocognitive decline (D'Antoni et al. 2018). In addition to initiating antiretroviral therapy during acute HIV infection, antiretroviral therapy adherence is crucial for the prevention of HAND (Martin et al. 1999; Suarez et al. 2001). Adherence is generally defined as the extent to which patients take medications as prescribed and is typically reported as the percentage of prescribed doses taken over a specified period, which may include consideration of specific dose timing (Osterberg and Blaschke 2005). Achieving consistently higher levels of antiretroviral therapy adherence in order to derive therapeutic benefit (e.g., sustained viral suppression and immune reconstitution) is a challenge for many people living with HIV (Kirtane et al. 2016). Generally, adherence rates are lower for chronic compared to acute conditions, and even under the controlled settings of clinical trials, average adherence rates range between 43 and 67% (Osterberg and Blaschke 2005).

Higher levels of antiretroviral therapy adherence are predictive of improvements in neurocognitive performance in the domains of information processing speed, attention, executive function, and motor function (Ettenhofer et al. 2010). Among patients who initiate antiretroviral therapy or change to a more effective regimen, improvements in neurocognitive function have been observed after 6 months for patients who achieved successful viral suppression (Parsons et al. 2006). Although antiretroviral therapy may improve neurocognitive function, a major complication is that people living with HIV with neurocognitive impairment, including deficits in prospective memory, are particularly at risk for antiretroviral therapy non-adherence (Hinkin et al. 2002; Woods et al. 2009a). Thus, behavioral strategies to promote antiretroviral therapy adherence among people living with HIV with neurocognitive deficits are particularly pertinent for the treatment of HAND.

5.2 Strategies to Promote Antiretroviral Therapy Adherence

Strategies to promote optimal adherence among people living with HIV include simpler dosing demands (e.g., fewer pills and once-a-day single tablet regiments) (Mohd Salleh et al. 2018). Given the ubiquity of phones, text message interventions have also been developed to prompt people living with HIV to adhere to their antiretroviral therapy regimen (Horvath et al. 2012). Such interventions are particularly effective in promoting antiretroviral therapy adherence in low-resource settings and may be helpful for promoting better antiretroviral therapy dose timing in patients with severe mental illness, such as bipolar disorder (Moore et al. 2015).

Adherence to antiretroviral therapy is influenced by psychosocial stressors, such as the experience of negative life events and depression, as well as individual characteristics like behavioral impulsivity (Salmoirago-Blotcher et al. 2017). Mindfulness training, which may allay distress and lessen impulsivity, is currently being investigated to determine its potential to help persons living with HIV adhere to their antiretroviral therapy regimen (Salmoirago-Blotcher et al. 2017). Given that depression has consistently shown a robust association with poor antiretroviral therapy adherence, several interventions grounded in cognitive behavioral therapy have been developed and evaluated for the treatment of depression and/or to promote medication adherence (Balfour et al. 2006; Safren et al. 2009; Simoni et al. 2007; Olatunji et al. 2006). A small pilot study investigated the effect of one-session behavioral activation treatment for depression designed specifically for people living with HIV (Tull et al. 2018). Although nonsignificant, persons living with HIV who received the one-session of behavioral activation treatment showed improvements in medication adherence of medium effect (Tull et al. 2018). Additional findings indicate that low levels of physical activity were predictive of poor antiretroviral therapy adherence and higher viral load, but importantly, this relationship was mediated by depression symptoms (Blashill et al. 2013). These results highlight the need to develop cost-effective interventions to simultaneously address symptoms of depression and antiretroviral therapy adherence among people living with HIV in order to prevent or treat HAND, and suggest that physical activity may have multifaceted benefits for people living with HIV.

6 Clinical Implications

In this section, intervention approaches to increase engagement in health behaviors (i.e., physical activity, healthy eating, sleep, and antiretroviral therapy adherence) are reviewed. Such approaches have the potential to improve neurocognitive outcomes among people living with HIV by increasing health behaviors that may protect against the development of non-communicable conditions (Lim et al. 2012) that adversely impact neurocognitive outcomes.

Health care providers have a prominent role in integrating health behavior promotion into routine HIV care (Webel et al. 2017). Health care providers can leverage their relationships with patients living with HIV to emphasize a holistic concept of well-being that includes engagement in health behaviors (Webel et al. 2017). Despite evidence supporting the effectiveness of health behavior promotion in primary health care, implementation has been slow (Brotons et al. 2012). One institution-level approach to target health behaviors more effectively and consistently in routine care is to integrate primary care and behavioral health in a single clinic; however, integration requires substantial reengineering of practice (Cifuentes et al. 2015). Another viable solution for targeting health behaviors in routine clinical care has been to train health care providers in Motivational Interviewing, a client-centered, evidence-based behavior change consultation style (Rollnick et al. 2008). Adoption of a Motivational Interviewing approach may be particularly helpful for clinicians providing HIV care, with some evidence indicating the effectiveness of Motivational Interviewing for improving antiretroviral therapy adherence (Golin et al. 2006; Beach et al. 2015).

Beyond the patient–provider relationship, engagement in a health behavior is influenced by a complex system of determinants, including intrapersonal (e.g., cognitive and emotional factors), interpersonal/community, institutional (e.g., access to specialty medical care), environmental (e.g., neighborhood characteristics and employment conditions), cultural, and policy/legislation factors (Dahlgren and Whitehead 2006). For persons living with HIV, readiness to engage in a health behavior is a dynamic and fluctuating construct, which may also be influenced by the episodic nature of HIV and multimorbidity (Simonik et al. 2016). Identification of contextual factors that have a strong relationship with the presence (or absence) of a health behavior is necessary to identify potential modifiable targets of behavioral health interventions (Michie et al. 2011; Wight et al. 2016). Although the field of behavior change research in persons living with HIV acknowledges that interventions need to target more than just factors at the intrapersonal level (Albarracin et al. 2010), there is only a small literature on multi-level models of intervention (Kaufman et al. 2014). Thus, behavior change efforts may be guided by multiple existing theories that, in combination, target various levels of influence (Kaufman et al. 2014).

Ideally, development of behavioral health interventions involves an interdisciplinary group representing relevant expertise (e.g., clinical healthcare, psychology, epidemiology, and policy) and key stakeholders (e.g., patients, caregivers, healthcare professionals, policymakers, and funders) to ensure interventions are evidence-based and acceptable to (1) those for whom the intervention is developed and (2) those involved in the adoption and implementation of the intervention (Eldredge et al. 2016; Witteman et al. 2017; Araújo-Soares et al. 2018). To optimize the effectiveness of a behavioral health intervention, researchers and/or interventionists must consider the appropriateness of various behavior change techniques, mode(s) of intervention delivery, provider(s), location, timing, and dosing of an intervention (Araújo-Soares et al. 2018).

Given the complexity of behavior change interventions, it is important to identify (1) effective behavior change techniques and (2) the processes through which behavior change occurs (i.e., the mechanisms of action) (Connell et al. 2018). For researchers and interventionists, various protocols and taxonomies have been developed to aid in behavior change intervention development. For example, Intervention Mapping describes an iterative process for developing theory- and evidence-based health promotion programs (Kok et al. 2004). In addition, an extensive taxonomy of consensually agreed, distinct behavior change techniques has been developed by a large international network of behavior change experts, which is intended to be used in combination with Intervention Mapping (Michie et al. 2013). Additional research investigating the effectiveness of specific behavior change techniques for promoting the adoption and maintenance of healthy lifestyle factors is needed. Such intervention efforts may reduce inflammation and oxidative stress, which, in turn, may reduce the incidence and/or severity of HAND.

7 Conclusion

Currently, there is no gold-standard treatment for the prevention or treatment of HAND. Although there is an absence of evidence-based neurocognitive interventions for people living with HIV, the literature reviewed in this chapter suggest potential targets for intervention. Modifiable lifestyle factors, such as physical activity, diet, sleep, and antiretroviral therapy adherence, may benefit neurocognitive function among people living with HIV. These healthy lifestyle factors reduce inflammation and oxidative stress, which, in turn, may reduce the incidence of HAND.

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