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Mechanisms of Cognitive Aging in the HIV-Positive Adult

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Abstract

Purpose of Review—As of the year 2016, an estimated 50% of the United States' HIV-Positive population is aged 50 years or older. Due to a combination of increased rates of infection in older adults, and successful anti-retroviral (ART) regimens allowing HIV-positive adults to survive for decades with the disease, we are now faced with a steadily graying HIV-positive population, with only limited knowledge of how the cognitive and physiological effects of aging intersect with those of chronic HIV-infection.

Recent Findings—Age-related changes to mood, cognition, and neurological health may be experienced differently in those living with HIV, and research concerning quality of life, mental health, and cognitive aging needs to account for and explore these factors more carefully in the coming years.

Summary—This review will explore the topic of cognitive aging with HIV: 1. Central nervous system (CNS) infection of HIV and how the virus affects brain integrity and function; 2. Cognitive and behavioral symptoms of HIV-Associated Neurocognitive Disorders (HAND); 3. Neurobiological theories of Cognitive Aging and how these processes may be exacerbated by HIV-infection; 4: Clinical implications and complications of aging with HIV and factors that may result in poorer cognitive outcomes.

Keywords

Aging; HIV-1; HIV-Associated Neurocognitive Disorders; Cholinergic; Dopaminergic

Introduction

Human Immunodeficiency Virus (HIV-1) affects more than 1 million people in the US [1]. Though it is still a life-threatening diagnosis, many HIV-positive adults have survived the initial epidemic in the early 1980's and continue to live relatively stable, healthy lives with the disease. As the HIV-positive population survives with the disease, management of the

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added complications of age-related changes to their physical, mental and cognitive health becomes a more significant challenge. As the face of the HIV-positive population changes, so too should the considerations of clinicians who treat them. Older age is associated with cognitive and motor changes as well as the development of brain pathologies. Cognitive functioning is additionally vulnerable to HIV-related damage, particularly if the individual is infected late in life, goes undiagnosed or untreated for some time after exposure, or if they have lived with the disease for more than a decade.

The combination of pathological processes may interact, resulting in an HIV-positive population that may experience significant impairments earlier than their HIV-negative counterparts. Current estimates indicate that roughly 50% of the US HIV-positive population is currently aged 50 years or older [1, 2], which makes understanding the unique nuances of aging with HIV a concern for researchers, clinicians, and patients alike. This review will discuss the cognitive, clinical, and behavioral considerations facing a “greying” HIV-positive population, and factors that may contribute to better outcomes for older adults living with this disease.

I. Pathology of Central Nervous System (CNS) HIV Infection

In most HIV-positive adults, strict compliance with an anti-retroviral therapy (ART) regimen results in low systemic viral loads and high T-Cell counts[3]. However the HIV virus is able to enter and infect cells that express the CD4 co-receptor, in addition to either the CCR5 or CXCR4 receptor, via the envelope glycoprotein 120 (gp120). The virus thus travels to the brain via monocytes, where it can cross the blood brain barrier by infecting vascular epithelial cells, allowing it to access to the brain parenchyma. Once in the brain, the virus can directly infect astrocytes and oligodendrites, which replicate the virus and subsequently die, releasing a host of neurotoxic chemokines including Tnf, Tat-1, Vpr, interleukin 6, nitric oxide, and quinolinic and arachidonic acids [4].

CNS infection by the HIV-virus adds an additional complication because many existing ART medications cannot cross the blood-brain-barrier, turning the central nervous system into a viral “reservoir” where the virus can continue to replicate without being affected by medication [5]. The time between initial infection and initiation of treatment has been shown to have an effect on extent of CNS damage [6], essentially the less time the virus is able to replicate unchecked peripherally, the better cognitive outcomes, and lower risk of developing cognitive impairments.

The resulting inflammatory cascades from these chemokines trigger the persistent recruitment and activation of microglia, which attempt to clear the brain of the dead and dying cells [7-9]. Excessive neuroinflammation leads to the progressive death of glia (oligodendrocytes and astrocytes) leaving local neurons vulnerable to glutamate excitotoxicity, resulting in diffuse, progressively worsening neurodegeneration [10, 11].

Once introduced to the brain tissue, HIV-related damage follows a selective “sub-cortical” pattern, accelerating deterioration of connectivity, processing, and association areas [12]. Damage typically affects fronto-striatal structures and both structural and functional

connectivity [13, 14] as well as hippocampal tissue [15] and motor areas [16, 17]. Abnormal fMRI pre-frontal activation during working memory tasks [18], increased measures of inflammation and diffusivity [19], and reduced resting state functional connectivity within the lateral occipital network [20], and overall cortical thinning [21, 22] have all been observed in HIV-positive adults relative to HIV-negative controls, and in many of these studies the structural changes were in excess of that to be expected given participant age.

There is also evidence that in HIV-positive adults, risk biomarkers related to Alzheimer's disease confer an additional burden; HIV-positive adults with at least one APOE-e4 gene have been found to have more severe markers of brain atrophy [23], higher risk of developing the most severe form of HAND [24], and higher deposition of damaging brain amyloid [25].

II. HIV-Associated Neurocognitive Disorders (HAND)

Central Nervous system (CNS) viral load, and subsequently the extent of resulting neurodegeneration processes, is thought to be responsible for the symptoms of the cognitive impairments known collectively as HIV-Associated Neurocognitive Disorders, or HAND [26]. HAND is identified diagnostically by neurocognitive performance at least 1 standard deviation below the mean (normalized for age and education) in at least 2 of the following domains of cognition: language, attention, working memory, learning, information processing, sensory perception, and motor skills [27]. HAND ranges from the mildest form, asymptomatic neurocognitive impairment (ANI), to the most commonly found mild neurocognitive disorder (MND), to the most severe, HIV associated dementia (HAD). Symptoms tend to progress from ANI to MND with longer infection time, though early ART medication has reduced prevalence of HAD [28]. Despite the success of antiretroviral medications to keep CD4+ cell counts high, it has been hypothesized that the inability of these medications to cross the blood brain barrier turns the brain into a ‘viral reservoir’, where the virus can continue to replicate, leading to continuing neurological damage over time [29].

HAND severity over time can be predicted by CD4+ cell count at treatment initiation, with decreased chance of cognitive impairment if antiretroviral treatment is initiated as soon as possible after exposure, while CD4+ counts are still high and viral load is still relatively low [26]. The impaired immune response caused by HIV leads to a premature, persistent inflammatory state, when this is combined with the neurological and cognitive changes associated with aging, presumably physiological and cognitive changes may occur more rapidly [30].

HAND is a common late-stage outcome of the HIV-1 virus infection, affecting more than 50% of seropositive individuals. HAND symptoms result from neurodegeneration caused by the infiltration of the virus into the brain, and is characterized by a number of cognitive deficits [31]: one study found that cognitively asymptomatic HIV-positive individuals displayed abnormal visual spatial attention processing compared to HIV-negative controls [32], another found that HIV-positive individuals showed significant deficits in verbal working memory storage and processing [33], and another group characterized immediate,

delayed (auditory/visual), and working memory deficits in HIV-positive males compared to controls, which they attributed to subcortical gray and white matter damage due to HIV infection [34].

There has also been investigation into biomarkers for cognitive outcomes in adults with HIV. One study found subtle frontal grey matter changes in older HIV-positive men when compared to younger and HIV-negative men, despite no significant differences in cognition [35]. In another study comparing HIV- individuals and HIV+ individuals with and without cognitive deficits, it was found that while asymptomatic HIV-positive individuals showed increased BOLD activation in regions necessary for bottom-up (exogenous) and top-down (endogenous) attention control compared to HIV-negative individuals as the task difficulty increased, implying higher cognitive effort and use of cognitive reserve, HIV-positive individuals meeting HAND criteria showed no increase in activity, and impaired performance even at the moderate difficulty, which they interpreted as the virus diminishing the capacity of cognitive reserve [36].

Less is known about the cognitive consequences of aging with HIV compared to normal aging. One study found that in HIV-positive individuals, age over 50 years increased the risk of developing a cognitive disorder three-fold compared to HIV-negatve controls [37], and another found that aging and positive HIV status had an adverse, additive impact on learning and executive functioning [38]. In contrast, large cohort studies evaluating the effects age and HIV status on neuropsychological performance, found no evidence for increased impairment of performance [39, 40].

Perhaps because of advances in ART medication, the milder cognitive impairments of HAND (ANI and MND) are becoming more common, and HAD is becoming less common [41], so understanding the mechanisms of these impairments as well as any interaction with age has implications for long-term treatment and quality of life as the HIV-positive population lives longer. As research into the aging HIV population continues, it may be useful in this population to study cell and receptor populations in the brain that have already been associated with the cognitive aging process, such as the cholinergic and dopaminergic receptor system. Existing knowledge of age-related changes to these systems, the cognitive impairment associated with dysfunction, and how they may overlap with cognitive symptoms seen in HIV-positive individuals, could provide useful insight into how mechanisms of the cognitive aging process are altered by the presence of HIV, and how neurotransmitter-based treatments may be beneficial.

III. Normal Cognitive Aging

Normal cognitive aging is the progressive changes to cognitive abilities such as memory, attention, psychomotor functioning, that progressively worsen as an individual ages, starting in the 50's and 60's in the normal population [42, 43]. Neuronal loss, loss of connectivity, and alterations in task-related activation patterns within the brain all contribute to outward symptoms of cognitive aging [44-47], particularly the dopaminergic and cholinergic neurotransmitter systems. The functioning of the cholinergic and dopaminergic systems, and cognitive performance are affected by advancing age [48] which may lead to effects on

cognitive abilities such as attention and executive control. These domains and other cognitive functions rely on adequate functioning of projections of the cholinergic neurotransmitter system [49, 50], which modulate other neurotransmitter systems via nicotinic and muscarinic acetylcholinergic receptors [51]. The dopaminergic system primarily controls reward processing [52, 53] but is also associated with spatial and verbal working memory [54, 55] and cognitive flexibility [56]. All these functions are similarly vulnerable to neuronal and connectivity loss with advancing age, particularly loss of functioning of D2 receptors [57] and the dopamine transporter [57, 58], in conjunction with modulatory changes from the cholinergic system [59]. Both the cholinergic and dopaminergic systems lose necessary receptor density and connectivity, with aging associated with cognitive changes in performance [60, 61].

Cholinergic System

The functioning of the cholinergic system related to cognitive performance was first explained using temporary blockade studies; cholinergic antagonist drugs such as mecamylamine or scopolamine result in deficits of learning, memory, psychomotor speed, and attention [62, 63, 50, 64]. This effect is more pronounced in older individuals, and this increase in sensitivity with age has been associated with fewer available cholinergic receptors and/or projections. The similarity between symptoms of cholinergic blockade and the cognitive impairments seen with advancing age are described by the cholinergic theory of cognitive aging [50], which suggests that the progressive decline of cholinergic receptor activity has a negative impact on cognition, which may be rescued by cholinergic agonists.

Cognitive aging may be partly due to a decline in cholinergic system function and the progressive loss of cholinergic projections from the basal forebrain nuclei [65]. Decrease in projections, and decrease in expression of nicotinic and muscarinic acetylcholinesterase receptors (nAChRs and mAChRs) with age results in an increase in sensitivity to cholinergic blockade [66]. In particular, impairment of the nAChR system is associated with deficits of attention and working memory, and thought to be involved in the cognitive symptoms seen in Alzheimer's disease, Parkinson's disease, and others, such as slowed reaction time, sustained attention deficits, sensory gating and working memory problems [67]. It has been shown that availability of nAChRs decreases with age, and this loss is more profound in individuals suffering from cognitive disorders [68]. In these cases, as nAChRs are lost, exogenous activation of the remaining receptors may be a useful strategy to maintain or improve cognitive performance impaired by these or other disorders.

Dopaminergic System

The presence of catecholamine neurotransmitters, specifically dopamine, is necessary for normal functioning of complex neurological and cognitive functioning [69]. Originating in the basal ganglia (nucleus accumbens, ventral tegmental area, substantia nigra, striatum) and heavily enervating the frontal cortices, dopamine availability is involved in attention, decision making, learning and reward processing [63]. In the context of cognition, dopamine activity is important for reward and decision processing [53, 70], visuospatial working memory [55], as well as attention and working memory, with modulation from the cholinergic system as well [69, 59].

Dopamine acts through two main receptor subtypes, the D1DR and D2DR, and the two receptors modulate slightly different cognitive functions [71-73]. Dopamine activity at D2 receptors is associated with memory function, and loss of these receptors with age has been associated with poorer memory functional connectivity between the hippocampus and caudate [74] The release of dopamine is closely modulated by cholinergic receptors, allowing for fine tuning of working memory [59].

Aging has demonstrable effects on the ability of dopamine to regulate cognitive functions, particularly as receptors and dopaminergic cells are lost in cases of pathological aging. Older age is associated with lower dopaminergic activity in the ventral striatum and pre-frontal cortex, resulting in poorer ability to process reward [70]. Dopamine has also been shown to be involved in the process of memory dedifferentiation (the loss of distinct neural representations of information), and reduced dopamine availability is associated with poorer memory specificity in older adults [75]Older adults also show decreases in dopamine mediated measures of cognitive flexibility, Loss of D1DR density in the caudate and dorsolateral pre-frontal cortex in older adults is associated with poorer working memory performance and higher blood-oxygen level dependent (BOLD) neural activation variability (a measure of lower task attention) [76]. Decreased connectivity has been found between the locus coeruleus (another dopaminergic region), with parahippocampal cortex in older adults [77], consistent with other studies that have linked this loss of connectivity to working memory, attention and executive control impairments of mild cognitive impairment.

Genetically, polymorphisms in the catechol-o-methyltransferase (COMT) gene, necessary for dopamine metabolism, also have distinct effects on stability of cognitive functions with age. The Val158Met polymorphism is the most common, and has been assessed in multiple studies of dopamine availability and the subsequent impact on cognitive ability. Presence of the Met amino acid at this position confers a “low activity” phenotype (slower degradation of dopamine and other catecholamines), versus the Val amino acid which confers a “high activity” phenotype, resulting in different rates of loss of synaptic dopamine after release.

One study found that older adults homozygous for the COMT*Val allele performed significantly more poorly on both working memory and episodic memory tasks compared to heterozygous or homozygous COMT*Met adults [78].

Potential Roles of Cholinergic and Dopaminergic Systems in HIV-Associated Cognitive Changes

Some early work has been done to evaluate changes to the dopamine and cholinergic system in the HIV-positive brain, particularly in older adults, though much of it is in the context of the effects of stimulant drug use (methamphetamines, cocaine, etc). One study found a number of structural and connectivity differences in brain regions heavily innervated by dopaminergic and cholinergic inputs, associated with HIV-status: decreased connectivity within the resting state fronto-striatal network (FSN), between FSN and caudate, and between the caudate and parietal regions relative to controls [14]. Diminished capacity for dopamine-mediated attention and reward processing, has also been shown in HIV-positive adults; researchers found reduced ability to ignore irrelevant information while processing a reward [79]. Neurological vulnerabilities in these systems may indicate that HIV virus

preferentially targets these dopaminergic and cholinergic regions, and that they may deteriorate faster in HIV positive adults than in HIV-negative adults.

HIV-related proteins, specifically HIV-tat and gp120, have been shown to interact with both cholinergic and dopaminergic receptors, facilitating cell death and subsequent cognitive impairment. The gp120 molecule, a surface protein of the HIV virus capsule, has been shown to bind to the highly calcium permeable homomeric α7-nAChR [80], upregulating receptor production, leading to astrocyte death, and subsequent apoptosis of nearby neurons, particularly in the striatum [81]. Another group also showed that gp120 may facilitate the production of reactive oxygen species that increase apoptotic loss of dopamine neurons in the substantia nigra, causing some of the Parkinsonian-like motor impairments that are present in HAND [82]. HIV-tat has been shown to be toxic to both cholinergic and dopaminergic cell populations, particularly in the hypothalamus and the hippocampus, where the protein can more readily cross the blood brain barrier and damage cells in those regions [83]. Indeed, the extra-pyramidal symptoms of HAND do resemble those in Parkinson's disease, resulting from HIV-related damage to the caudate, putamen, substantia nigra, and basal ganglia [84-87].

Co-Morbid Neurodegeneration

HIV-positive older adults may have to face the combined symptoms of HAND and Alzheimer's Disease [88], while others may instead experience the combination of HAND and Parkinson's Disease [89]. These disease combinations may present additional complications of slightly differing symptom profiles. One study evaluated deficit pattern differences between Older HIV positive adults, adults with Parkinsons, and adults with Alzheimer's, finding that while there was some symptom overlap between aging with HIV and each of these age-related disorders, aging with HIV is somewhere in between a “cortical” and “subcortical” cognitive disorder [90].

Mood Disorders in an Aging HIV-Positive Population

Cognitive health and mental health have been shown to be closely linked, particularly in older adults. Somatic symptoms of depression and anxiety can contribute to poorer cognitive outcomes, and vice versa [91]. The added complication of aging with HIV, a disorder with a well-documented high incidence of mood disorders, in particular major depression, poses a significant risk for worsening of cognitive outcomes compared to the HIV-negative population. Not only are older persons more vulnerable to more persistent depressive symptoms despite treatment [92], but depression in this older population is associated with cognitive impairments in and of itself: in the domains of executive functioning, processing speed, episodic memory, all of which are already impaired by the process of cognitive aging [93, 94]. In HIV-positive adults, this higher incidence of cognitive and mood disorders [95] can also exacerbate risk of substance abuse, relative to younger HIV-positive adults or older HIV-negative adults [96] and the combination of these factors may impact quality of life [97, 98]. Treating mood symptoms without addressing cognitive impairments may be one reason that depression symptoms are less responsive to treatment in older and HIV-positive persons, and more consistent monitoring and treatment of both may lead to better outcomes.

IV. Clinical Implications, Comorbidities, and Management for Aging with HIV

Assessing and Monitoring Cognitive Symptoms in HIV-Positive Older Adults

With the knowledge that a substantial proportion of the HIV-positive population will develop some degree of cognitive impairment over the course of their life, it is important that cognitive evaluations become more widespread within HIV clinics. There currently isn't a consensus as to which measures are appropriate and sensitive to accurately detect individual cognitive changes over time. Many HIV clinics routinely provide biological, physiological, sociological and psychiatric monitoring of their HIV patient's well-being, in many cases combining a number of these various follow-ups into a single, comprehensive visit. Cognitive monitoring however, is a relatively new concept, and as this field continues expanding, clinicians and researchers alike should consider how best to address on-going cognitive assessment, particularly in patients over the age of 40. Like many other facets of HIV-related health care, such as CD4 count, detectable vs. undetectable viral load, educating the patient on their risk for cognitive changes, what to expect, and when to alert their caregivers to changes, may be helpful to identify when further assessment and monitoring is warranted.

In order to better identify and monitor symptoms as efficiently as possible, it is important to evaluate which cognitive measures are sensitive enough, easily administered, and correlate well with objective deficits in cognitive function. In the cognitive aging literature, subjective cognitive impairment, or the patient's own appraisal of how their memory is functioning, has shown some success in adults with age-related cognitive disorders, such as mild cognitive impairment (MCI) and early stages of Alzheimer's disease [99-101], though not as reliably in cognitively normal older adults. One study has shown that the Montreal Cognitive Assessment (MoCA) was able to detect cognitive impairments in aging HIV-positive veterans [102]. Another study also recently showed that scores on the subjective Memory Functioning Questionnaire (MFQ) significantly correlated with an objective verbal memory performance in HIV-positive middle aged adults, but not HIV-negative adults [103], suggesting that in cognitively vulnerable or impaired HIV-positive adults, comprehensive subjective measures of memory may be a salient and useful monitoring tool to identify those who may be developing objective cognitive impairments.

Potential for Cognitive Enhancers for HAND and Age-Related Cognitive Impairment in HIV

Acetylcholinesterase inhibitors (AChEIs), which target and inhibit the metabolism of endogenous acetylcholine, have been used for years as treatment for the cognitive symptoms of Alzheimer's disease. With prior evidence that HIV-positive adults with the APOE-e4 allele (one of the primary risk genes for developing AD) suffer significantly greater impairments in executive functioning, memory fluency, attention and working memory than HIV-negative or non-APOE-e4 carriers [104], it has been suggested that AChEIs may provide improvement in HAND symptoms, similar to their efficacy in AD [reviewed by 105]. Galantamine has been shown to work synergistically with nicotine to attenuate the over activation of microglia that trigger inflammatory cascades in the HIV-infected CNS [106]. However, rivastigmine was found to only have an effect on psychomotor speed, while Alzheimers Disease Assessment Scale – Cognitive (ADAS-Cog) scores were unchanged

compared to placebo [107]. Pyridostigmine has also been shown to alleviate the over activity of acetylcholine mediated over-activity of T-Cells compared to placebo [108], and though this drug does not cross into the CNS, it may be beneficial to control peripheral viral activity, helping to prevent additional viral particles from crossing into the brain.

With the only moderate efficacy of AChEIs, nicotinic agonists may be a worthwhile therapeutic alternative to target the cholinergic system, Nicotinic agonists function in the brain by enhancing the flux of ions primarily through the two major ionotropic nicotinic receptor subtypes, the heteromeric α4β2*-n AChR and the homomeric α7-nAChR [109]. In the CNS, nAChRs are distributed widely in the cerebral cortex and hippocampus, and a significant portion of these receptors are located on the axon terminals of neurons that release glutamate, GABA, serotonin, dopamine, etc. [110], allowing nAChR activity to directly modulate the activity of other CNS transmitters [111]. Treatment with nicotinic agonists therefore may be beneficial to help support cognitive ability and neurological function of necessary neurotransmitter systems.

Nicotine itself is the most readily available agonist, available in the form of transdermal patches. It has also been suggested that the high incidence of cigarette smoking in the HIV-positive population (up to 70% by some estimates) may be a form of cognitive self-medication [112, 113]. A number of cholinergic (nicotinic and muscarinic) therapies are in development or in clinical trials to treat the cognitive symptoms of Alzheimer's [114] and these may have similarly beneficial effects on cognitive deficits associated with HAND, by targeting similarly impaired neurobiological targets.

As far as dopaminergic treatment options, only one study has evaluated a dopaminergic stimulant drug (methylphenidate) and its effect on cognitive ability in HIV-positive older adults, finding that cognitively symptomatic adults showed improvement in choice reaction time scores, though there was no effect in the asymptomatic participants [115]. Additional studies with dopaminergic drugs, such as other stimulant medications should be explored, to assess whether there is any definitive evidence of cognitive benefit for the portion of HIV-related cognitive deficits that can be attributed to dopaminergic system dysfunction.

V. Conclusions

There are numerous factors that complicate brain aging in the HIV-positive population. Early CNS infiltration of the HIV virus leads to an ongoing inflammatory and neurodegenerative process that is closely linked to the cognitive impairments of HAND, which may affect older HIV-positive adults more significantly than their younger or HIV-negative counterparts. Damage to the dopaminergic and cholinergic neurotransmitter systems in particular may contribute to the particular collection of symptoms that are seen in older HIV-positive adults. Investigating and leveraging these systems individually or synergistically may lead to treatment opportunities to improve quality of life as these individuals survive into old age, by supporting their functioning for longer before impairments are noticeable. Furthermore, understanding how dopaminergic and cholinergic systems are affected, may indicate that treatments targeted at maintaining function, or

perhaps protection of these regions, may lead to better cognitive outcomes as HIV-positive individuals age.

Understanding both cognitive and psychomotor elements of cognitive aging with HIV may lead to more concrete approaches to both identification of symptoms, and treatments to manage those symptoms, by stimulating these underlying systems to improve cognitive outcomes as HIV-positive individuals age. In HIV positive adults, these approaches may also need to take into account how ART needs may change when administered to an older or more cognitively impaired patient. Age-related changes in blood brain barrier integrity may alter how well established ART regimens can penetrate the CNS, though how that may affect cognition is not yet known.

Early identification, monitoring, and management of cognitive impairments and symptoms are worthwhile additions to comprehensive HIV disease management, particularly in patients who are aging into their 60's, 70's and beyond. Regular cognitive screening, particularly as the HIV-positive patient population ages, may allow both patients and caregivers time to adjust, or to consider options to remediate symptoms, before they have progressed significantly. Treatments targeting the cholinergic or dopaminergic systems are worthwhile considerations for many reasons, one in particular being that regardless of the underlying cause of cognitive impairments, they still are effective at improving cognitive performance. Age-related impairments in HIV-positive adults may respond similarly, especially in a population already at higher risk for cognitive problems. Overall, better understanding of the nuances of aging with HIV versus normal aging, will allow this vulnerable population to not only survive into old age, but thrive.

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•• Of major importance

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