

HIV-AIDS and Aging: Challenges and Management

Abstract

The infection of a healthy person with human immunodeficiency virus type 1 (HIV-1) causing acquired immunodeficiency syndrome (AIDS), is a serious public health threat around the world. In the United States, approximately 80,000 (6 percent) of known cases of HIV are 50 years of age and older and about 11 percent of all US cases of AIDS are in this age group. AIDS has been identified as the 15th leading cause of death in those over 65 years of age in the United States similar to other developed countries of the world. UNAIDS and WHO have estimated that out of the 40 million people living with HIV/AIDS in the world, approximately 2.8 million were 50 years and older. As treated HIV-infected patients live longer and the number of new HIV diagnoses in older patients rise, clinicians need to be aware of these trends and become familiar with the management of HIV infection in the older patients. Long-term treated HIV infected patients remain at higher than expected risk for cardiovascular disease, cancer, osteoporosis, and other diseases along with a number of complications typically associated with aging. However, additional research is needed to generate deeper insights regarding mutual impacts of HIV infection and aging in order to develop and implement effective prevention measures for safe antiretroviral therapy in the older HIV-infected patient. No guidelines are available as on date to specifically address the needs of the elderly HIV-infected patient. This article illustrates the recent updates on current global scenario of HIV-AIDS, aging, complications due to HIV infection and application of antiretroviral treatment (ART), aging and medical management strategies which might be useful for health care agencies and policy makers involved in addressing such issues associated to the older HIV-infected patients.

Keywords: Human immunodeficiency virus type 1; HIV-1; Anti retroviral therapy; Highly active antiretroviral therapy; HAAR; Aging; Inflammation; Immune activation; Management

Review Article

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Bechan Sharma* and Shweta Singh

Department of Biochemistry, University of Allahabad, India

***Corresponding author:** Bechan Sharma, Department of Biochemistry, University of Allahabad, India, Tel: +91-9415715639; Email: sharmabi@yahoo.com

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Abbreviations: HIV-1: Human Immunodeficiency Virus Type 1; AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral Treatment; WHO: World Health Organization; HAART: Highly Active Antiretroviral Therapy; NRTIs: Nucleoside Reverse Transcriptase Inhibitors

Introduction

The Human immunodeficiency virus type 1 (HIV-1) / Acquired Immunodeficiency Disease Syndrome (AIDS) is a devastating worldwide pandemic, which impacts at large including the patient, relatives, the healthcare system, and the socio-political spheres [1]. According to a global estimate presented by World Health Organization (WHO), about 36.7 million people were living with HIV at the end of 2015. Out of this, about 0.8% of adults between the age of 15-49 years worldwide were living with HIV; the Sub-Saharan Africa being the most severely affected (1 in every 25 adults; 4.4%) living with HIV. It alone accounts for nearly 70% of the people living with HIV worldwide. In India the prevalence of HIV is 0.29%. It is seen mainly in the adult population [2], but there are an increasing number of older people infected with HIV, which might be due to increased awareness and the availability of the ART treatment [3,4]. HIV-1 is an enveloped retrovirus belonging to the group of viruses known as *lentiviruses*. It weakens the infected person's immune system by destroying the CD4+ve T lymphocytes, a subpopulation of family of T-cells,

which are responsible for imparting immunity to human body from any pathogenic infection. Normally the CD4+ cells are 1200 per micro liters in males and about 1000 per micro liter in females. During HIV infection, the count of these cells falls to 200 or even at base level i.e. zero bringing the system to completely immune compromised state which is highly vulnerable to many other opportunistic infections [5]. This stage is called acquired immunodeficiency syndrome (AIDS). It shows that not everyone harboring HIV may get AIDS. This disease finally causes the death of the HIV infected individual [5].

HIV-AIDS is no longer a disease of young people. For last one decade, the number of elderly people with HIV infection has increased because of availability of anti retroviral for treatment [6,7]. According to an estimate of about 8 years (2001-2008) in HIV infected population of 50 years of age in USA, the percentage has increased from 17% to about 31%. It was projected that by end of 2015 more than half of all HIV-infected Americans would be over the age of 50. According to an estimate presented by the Joint United Nations Programme on AIDS (UNAIDS), adults have been defined as the people between 15 and 49 years of age and about 7% of the world's HIV positive population (roughly 2.3 million people) is 50 or older. There are significant populations of older adults living with HIV in Kenya, Jamaica, India, and parts of East Asia [8,9].

People contract HIV infection in many ways such as unprotected sex with a partner having HIV/AIDS, through receiving HIV-infected blood or blood products, or by sharing unsterilized needles containing HIV from an infected person and mother to child transmission if mother is HIV infected. However, one cannot contract HIV through shaking hands or hugging a person with HIV/AIDS, using a public telephone, drinking fountain, restroom, swimming pool, whirlpool, or hot tub, sharing a drink or being coughed or sneezed on by a person with HIV/AIDS, from giving blood or from a mosquito bite [10].

It takes more than 10 years for more serious symptoms to appear due to HIV infection. The symptoms may include headache, cough, diarrhea, fevers, and/or sweats, swollen glands, lack of energy, loss of appetite, weight loss, repeated yeast infections, skin rashes, sores in the mouth or genital area, pelvic and abdominal cramps, and short-term memory loss. The clinical indices or biomarkers of HIV infection associated pathology include pro-inflammatory cytokines (IL-6), markers of declining renal function (cystatin C), C-reactive protein (CRP), D-dimer, soluble CD14, CD4 count and viral load, and other acute phase reactants, markers of T-cell activation (CD38, HLA-DR), markers of T-cell senescence (CD28, CD57), markers of B-cell activation (AID, IL10, soluble CD23 (sCD23), sCD27, sCD30), red blood cell indices (hemoglobin, mean corpuscular volume, red cell distribution width), markers of liver injury (FIB-4, AST: platelet ratio index [APRI]), markers of Neuro AIDS (MCP-1, neopterin, osteopontin, ApoE-epsilon4), markers associated with neurodegenerative diseases (amyloid, Abeta42, ApoE, tau, phospho-tau) and markers associated with cardiac disease (Cardiac Troponin and B-Type Natriuretic Peptide) [11,12].

During the course of the disease, the diagnosis of HIV infection in older people has been found to be delayed than the younger people. Therefore in the older people start late treatment which causes more damage to their immune system, poorer prognosis and shorter survival after diagnosis. It is important for HIV infected older people to get to receive proper care and access to mental health. The prolonged infection with HIV and its long term treatment have been shown to augment the aging process in such individuals. It adversely influences brain functions causing depression or psychological distress, dementia, neuro cognitive disorder which may include decrease in attention, language, motor skills, memory, and the overall quality of life of older people [13].

However, detailed studies are required to generate insights as how HIV infection alters the brain function as the information available on the subject is quite meager. The present article encompasses an update of available information on HIV infection, aging, challenges and possible management strategies to address various related issues.

Antiretroviral treatment, co morbidities and aging

The global data available indicates that application of Highly Active Antiretroviral Therapy (HAART) has significantly reduced the HIV induced disease syndrome. HIV infection has been shown not only to cause AIDS but also onset of numerous other disease conditions such as cardiovascular disease, lung disease, infection-related and non-infection-related cancers, HIV-associated neuro

cognitive disorders, neuropsychiatric disorders, osteopenia / osteoporosis, liver cirrhosis, and renal disease. Though it is not very clear whether HIV infection or application of anti retroviral to treat the disease are the causes, but it is evident from the reports published by some authors that it may accelerate the aging process in such individuals. It has been observed that with prolonged HIV infection or receiving treatment for longer duration develop many certain clinical conditions which are reflected so often during aging for example multiple co-morbidities, poly pharmacy, physical and cognitive impairment [14,15], functional decline, alterations in body composition, and increased vulnerability to stressors. The list of co morbidities (diseases or conditions that coexist with a primary disease) associated with HIV includes diseases of the lungs, liver, kidneys and heart and blood vessels, as well as neurological conditions and bone diseases [16,17].

HIV infection and bone diseases

The recent available information indicate that HIV infection negatively impacts the health of the development of bone which includes its formation from very beginning i.e. inception of the child, the birth of the child, the various stages of the growth involving childhood [18,19], adolescence, adult [20,21] and old stages [22,23] resulting into emergence of various bone diseases [24]. However, the tools or techniques towards early detection and prediction of initiation of such bone diseases in HIV infected individuals are still not available [25]. Osteoporotic fracture is a quintessential disease of aging whose incidence increases exponentially after age 65-70 years in the general population. It is also a major cause of morbidity, mortality, reduced quality of life, and healthcare expenditure. The risks of fracture and of osteoporosis among those living with HIV have been found higher than from traditional osteoporosis risk factors alone [26]. Similar to other comorbidities in HIV, the pathogenesis of osteoporosis in HIV-infected persons is complicated and multi factorial, with contributions from certain antiretroviral therapies [20,27-29], other co-infections and co morbidities, behavioral risk factors, and chronic HIV infection, with both HIV infection itself and the associated persistent immune dysfunction having an impact.

In addition, the frailty and falls risk issues that transect both older age and HIV are emerging challenges to those treating people living with HIV [21,22]. Both HIV infection and ART treatment have been shown to be linked with the vitamin D deficiency and fragility of bones, though enough data to support this notion is lacking [30]. Similar observations have been reported to be prevalent in countries with resource-limited settings [31]. In addition, the data obtained from epidemiological studies have reflected that HIV/HCV co infected individuals display 3-fold enhanced fracture incidence in comparison to the uninfected persons. Such patients have been found to exhibit reduced bone mineral density [BMD] [32]. Though the occurrence of osteoporosis is quite common in the people living with HIV [PLWH], not much information is available towards any novel treatment (excepting application of statins) and management of bone diseases in such patients [33].

Complications in HIV infected older people

Further, in the older people the clinical conditions get more complicated due to several other risk factors such as infections with oncogenic viruses (Human Papilloma Virus [HPV], Kaposi-

sarcoma Associated Herpes virus [KSHV/HHV-8], Epstein-Barr virus [EBV], hepatitis B Virus [HBV], and hepatitis C virus [HCV]) [34]. The complications due to HIV infection also include occurrence of proteinuria and renal failure [35-37], the observations including specific psychological challenges in older people suggest that while practicing the management of HIV infected aged people these conditions should be taken into account. In addition, long standing HIV infection may increase the risk factors responsible for induction of chronic inflammation which may be associated to lymphoma, and noninsulin dependent diabetes (type 2 diabetes). However, it is still not clear whether HIV infection related chronic inflammation may induce any other complications in those aging during long treatment with antiretroviral (ART) [21,22,38-39]. The occurrence of diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection have been observed [40].

Antiretroviral treatments and immunologic health

The application of ART, particularly in the late stage of HIV infection does not help improve the immunologic health of the person concerned as it seldom brings back the CD4 counts to normal level. The persistence of immune deficiency and chronic inflammation even after application of ART needs special attention to be paid towards development of new improved antiretroviral regimen which may help increase CD4 counts. Though the applications of inhibitors of HIV-1 RT, proteases and integrate have also been found to act as antitumor agents, some of the nucleoside reverse transcriptase inhibitors (NRTIs) have been found to induce initiation of cancer in humans. These studies indicate that ART may have immune modulator effects, which needs to be further verified by carrying out certain concrete experiments with the reproducible results.

Inflammation and immune activation due to HIV infection and aging

The chronic immune system activation and inflammatory cytokine production are reported to be significant biomarkers of HIV infection [41]. In a review article published in 2012, Dubrow et al. [42] have summarized that mainly three significant immunological events take place due to HIV infection:

- a) Immunodeficiency,
- b) Chronic immune activation of both the innate and adaptive immune systems resulting into chronic inflammation and
- c) Immune dysfunction/senescence.

A sharp depletion of CD4 cells due to HIV infection leads to immunodeficiency. The chronic immune activation might appear due to many factors such as

- a. Immune response to HIV infection,
- b. Activation of lymphocytes and macrophages,
- c. Production of pro inflammatory cytokines,
- d. Immunodeficiency-induced reactivation,
- e. Replication of other viruses [particularly cytomegalovirus and Epstein-Barr virus], and

- f. Translocation of intestinal bacterial flora across the gut wall [43-45].

When an individual is infected with any pathogenic bacteria or viruses (such as HIV), the cells of immune system start producing cytokines, a family of proteins, which act like chemical messengers and help organize the body's immune response. Some of these cytokines are involved in initiation of inflammation [41]. It occurs due to the transport of cells and fluids to the site of the injury. This cascade of events lead to the warmth, redness, swelling and soreness around a cut as it heals. In addition, it has been reported that HIV infection leads to the destruction of massive numbers of immune cells in the gut which results into leakage of intestinal flora into the bloodstream, called as microbial translocation. However, no clear evidences are available to suggest that HIV adversely influences the functions of regulatory T-cells, which are essential to halting immune responses once an infection is eliminated from the body. It appears that the microbial translocation and the dysfunction of regulatory T-cells in an HIV-1 infected individual may jointly trigger immune activation [46]. These factors are expected to contribute towards enhanced aging of such people, though a deeper understanding is needed before reaching to a conclusion [41].

HIV infection, aging and brain related diseases

The development of HIV associated neurodegenerative disorders in the infected individuals has been observed to lead serious negative impacts on their normal activities and the quality of life which may contribute to accelerate the pace of aging processes. In such patients more accumulation of abnormal protein such as amyloid-beta has been observed. In addition, a variety of biological or environmental factors, including genetic factors and chronic substance abuse, may contribute to neurodegenerative processes in aging HIV-positive individuals. In the HIV-1 infected older persons the list of neurologic and neuropsychiatric complications may include dementia, in older adults, onset of diabetes, hypercholesterolemia, stroke, neuro degeneration, mitochondrial dysfunction, autophagy, dendritic degeneration or dyes regulated axonal transport associated to long-term HAART, drastic variations in the status of neurotransmitters, blood-brain barrier.

Advancing age is a significant risk factor for developing frailty, though the mechanisms leading to it are complex, interrelated, and not well understood. Frailty has been defined as a multi-system syndrome of diminished physiologic reserve associated with increased vulnerability to stressors. Like individuals with other chronic diseases, those with long-standing HIV infection are at higher risk of developing frailty than newly-infected or non-infected age-matched controls. However, not much information is available as on date to substantiate this notion and deeper insights are needed to ascertain specific contributors to frailty in older HIV-infected individuals.

The studies related to the cellular and molecular mechanisms of HIV in aging suggest that innate and adaptive immune cells play an important physiological role in eliminating senescent cells and maintaining normal tissue architecture across the lifespan, though the knowledge gaps still do exist in our understanding of long-term changes with treated infection or in the setting of chronic

substance use and abuse. In addition, less is understood about changes in the innate immune system associated with HIV over time. Moreover, most studies evaluate immune function through assays of peripheral blood, which contains only a fraction of the body's immune cells. Further studies are required to investigate status of immune function in brain, bone marrow, gut mucosa, skin, lymph nodes, and other lymphoid tissues in order to reach to a definite conclusion.

HIV infection, aging and nutritional requirement

The application of proper nutritional supplements has been found to reduce malnutrition, morbidity and of HIV infected individuals. Chronic infection burdens the repair and immune functions that are already slowing as a result of aging. [47] Have shown that there is age-related shift in glutathione (an antioxidant) status which helps increase the level of oxidative or pro-oxidant species in the cells. The slower protein assembly during aging plays out as impaired muscle, organ, and bone repair. Impaired protein assembly yields immune senescence-an inability to activate naïve T cells and generate memory T cells. Immune cell activity is sensitive to nutrition deficits; HIV infection alters gut cell structure, impeding all nutrient absorption, even in the HAART era [40]. Increasing dietary protein requirements in elderly people for optimal muscle and bone health are recommended [48]. A positive impact of long-term supplementation with whey proteins on plasma glutathione levels of HIV-infected patients has been observed [49].

Herbal products and aging of AIDS patients

Recent reports have indicated that application of plant based principles may prove to be highly useful, affordable and efficient in order to arrest the HIV-1 progression. Also, the toxicity issues may be easily managed while treating AIDS patients with herbal preparations as these plant-ingredients are suitably metabolized and excreted out of body without much accumulation in human organs. Certain plant extracts such as green tea containing, Brazil nut and Cocoa containing immune potentiators, grapes and red wine containing plenty of antioxidants which mimic oxidative stress induced by intake of antiHIV-1 regimen, *Punica granatum* (pomegranate) and several others have been recently shown to possess properties of intervention in HIV-1 proliferation. However, still only limited information is available regarding existing potential in the natural products isolated from certain medicinal plants to use against HIV-1, which could be relatively more cost effective, safer and easily accessible to the AIDS patients. However, still more efforts are required to be made by researchers in this direction to find out a reliable natural product for blocking the progression of wild type and drug resistant variants of HIV [50-53].

Conclusion

The course of the HIV epidemic has dramatically changed over the past three decades largely as a result of growing awareness, implementation of prevention strategies, and the availability of potent antiretroviral therapy, especially in developed countries. However, current epidemiologic data show changes in the demographics of the HIV population. As the HIV population

ages and the rate of newly detected infections in the elderly rise, clinicians should be aware of the increasing need to balance HIV care and the management of co-morbid conditions commonly associated with aging. The older people are prone to the risk for developing health complications associated with the chronic viral infections, deficiency of vitamin D and development of bone diseases, exposures to such medications with severe side effects and toxicities and reduced level of immunity. The age-related immune senescence which is usually augmented by HIV infection may add to the growing challenges for controlling viral loads and optimizing CD4+ve T-lymphocytes count. Therefore, keeping such immunological events in view the management strategies needs to be adequately developed and modified to get expected results. Application of proper nutrition supplements involving both the macro- and micronutrients may further help improve the cellular functions and hence the effectiveness of the medical treatments. In order to improve the metabolic and cardiovascular functions of HIV infected older people, physical exercise may be useful. However, continued research is needed to develop proper understanding to establish the effects of optimal nutrition and physical activity on the immune system as HIV-infected individuals grow older.

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